Chemistry, Design, and Structure–Activity Relationship of Cocaine Antagonists

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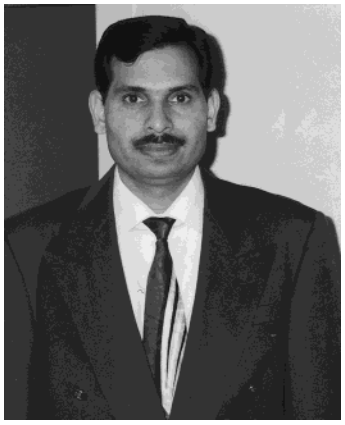
I. Introduction

Cocaine (Figure 1) abuse is growing at an alarming rate in the United States. Currently, we are experiencing its third epidemic. The two prior epidemics occurred in the 1890's and in the late 1920s.[1] A recent survey for the United States indicated that more than 23 million people have tried cocaine, nearly 400 000 use it daily, and 5000 new users are added each day.[2] It should, however, be remembered that not all users become drug addicts. Three main factors contribute to the addiction of cocaine: (1) availability, (2) repeated use, and (3) individual susceptibility.

Cocaine or crack when sniffed, smoked, swallowed, or applied to mucus membrane is absorbed from all sites of exposure. It is also taken intravenously. The onset of action of cocaine depends on the mode of its intake, e.g., approximately 30 min for snorting or inhalation and 1−2 min for an intravenous injection. The elimination half-life of cocaine is approximately 40−60 min, except at very high doses. It is metabolized by plasma and liver cholinesterases to water-soluble metabolites that are excreted in the urine.[3] These metabolites of cocaine in urine serve as useful markers of cocaine use and can be detected up to 24−36 h after the first use of cocaine, depending on the route of its administration and cholinesterase activity.[3,4] It is important to note that only *R*-isomer of cocaine (Figure 1) is addictive. Its *S*-isomer is nonaddictive because of its significantly low potency (155-fold less compared to *R*-cocaine)[5] and faster rate of metabolism.[6]

The abuse liabilities of cocaine result from its euphorigenic and reinforcing properties, i.e., increase in the probability of repeated use of cocaine.[4,7] Repeated administration of cocaine produces enhanced psychostimulant actions, and this hypersensitization (or sensitization) has been believed to be the cause of addiction. According to the incentive-sensitization theory of addiction,[8] in some individuals, the repeated use of cocaine produces increased neuroadaptation in the dopaminergic system, rendering it increasingly and possibly permanently sensitized to cocaine and cocaine-associated stimuli. This sensitization of the neural system is gated by associative learning, which causes excessive incentive salience attributable to the act of cocaine use and to stimuli associated with it. Incentive salience is hypothesized to be the psychological process by which stimuli become "wanted" or imbued with salience; their perception is altered. This psychological process is hypothesized to occur independent of changes in neural systems that mediate withdrawal. Thus, sensitization of incentive salience produces addictive behavior despite diminished expectation of pleasure from the drug, even in the face of strong disincentives, including loss of reputation, employment, family, and home.



Satendra Singh was born to Radhey Shyam and Dropadi in June 1960 at Kanaura, U.P., India. He obtained both his B.S. and M.S. degrees from the D. S. College, Aligarh, India in 1979 and 1981, respectively. After working at Central Avian Research Center, Izatnagar, and Camphor and Allied Products Limited, Bareilly, he joined Malti-Chem Research Center, Baroda, in 1983. He earned his Ph.D. degree in Organic Chemistry from the Malti-Chem Research Center, Baroda, India, in 1988 under the supervision of Dr. Sukh Dev. From 1989 to 1992, he worked with Professor Glenn Dryhurst at the University of Oklahoma, Norman. Then he worked with Professors Robert Magarian and Garo Basmadjian at the University Health Sciences Center, Oklahoma City. From 1996 to 1998, he worked as Assistant Professor of Research in the Department of Medicinal Chemistry and Pharmaceutics at the University of Oklahoma Health Sciences Center, Oklahoma City, OK. During this period he was awarded research grants from the NIH, Presbyterian Health Foundation, Oklahoma Board of Regents for Higher Education, and Oklahoma Center for the Advancement of Science and Technology. After working at ZymeTx, Inc., Oklahoma City, for some time, he joined Peninsula Laboratories, Inc. in 1999, where he is presently working as a Scientist. He is an author/coauthor of 22 research papers, one patent, one book chapter, and seven presentations. His research interests include developing new and efficient synthetic strategies and reagents. His hobbies include sports, yoga, and reading.

Neurochemical studies on cocaine's effects have shown that the mesolimbic and mesocortical dopamine systems, which project from the ventral tegmental area to the nucleus accumbens and frontal cortex, respectively, are involved in psycholomotor stimulant reward function.[9] Volkow et al.[10] found that normal circuitry that involved the orbitofrontal cortex, cingulate gyrus, thalamus, and striatum was abnormal in cocaine addicts. It was postulated that its activation by cocaine perpetuated the compulsive administration of the drug and was perceived by the cocaine abuser as an intense desire resulting in the loss of control over the drive to take more cocaine.

Pharmacologically, drug-seeking (drug-craving) behaviors, induction of stereotypies, and stimulation of locomotor activity by cocaine share a common mediation by dopamine (DA) (Figure 1).[11−18] The current view, termed "dopamine hypothesis", is that behaviors associated with cocaine addiction result, to a large extent, not from a direct message elicited by the binding of cocaine but rather from the accumulation of dopamine in the synapse and its actions at one or more of the D_1−D_5 dopamine receptors.[19]

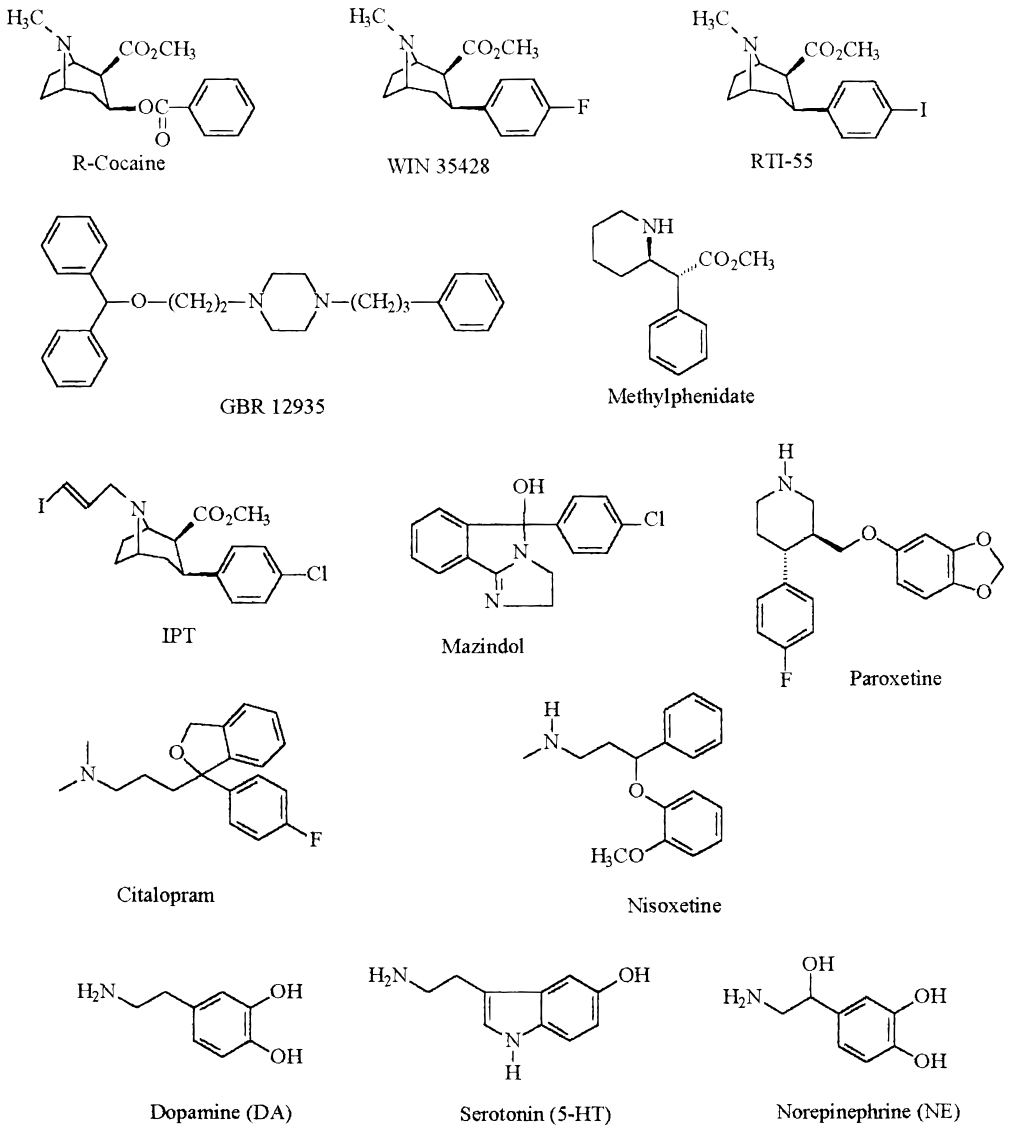


Figure 1. Structures of the ligands used for evaluating cocaine antagonists.

Furthermore, in recent experiments involving knock out mice genetically lacking dopamine transporter (DAT), cocaine had no stimulant effect. This finding also supported the role of the DAT in cocaine action.[20] It should, however, be noted that although the dopamine hypothesis explains the process of cocaine addiction, additional understanding is needed because the activity of neurons is not simply related to reward but related to salience or novelty as well.[21]

The DAT plays an important role in the regulation of dopaminergic transmission.[22,23] The human DAT has been cloned, and its primary structure has been elucidated.[24,25] No crystallographic data on the DAT or, for that matter, any other member of the family of neurotransmitter transporters have been obtained to date. However, site-directed mutagenesis studies have revealed that aspartate and serine residues lying within the first and seventh hydrophobic putative transmembrane regions are crucial for cocaine binding and DA uptake.[26] These findings suggested that the carboxyl group of the aspartic acid residue 79 engages in an ionic interaction either with DA's protonated amino group or with the protonated nitrogen of cocaine in binding to the transporter.

It was originally proposed that cocaine was a competitive inhibitor of DA uptake, coincident with cocaine and DA having common binding domains on the DAT.[27−29] However, the idea of separability of the binding sites for DA and cocaine on the transporter was first proposed by Rothman in 1990 based on two types of DA reuptake inhibitors: type 1 blockers, which produce euphoria (e.g., cocaine), and type 2 blockers, which are not euphorigenic (e.g., bupropion, nomifensine, benztropine, and mazindol).[30] The most direct evidence, however, for two distinct binding sites for DA and cocaine on the DAT has come from site-directed mutagenesis studies. For example, Kitayama et al.[26] were able to produce mutants using cloned DAT, which were more deficient in translocating [^{3}H]DA than in binding a cocaine analogue, WIN 35428 (Figure 1). Conversely, DAT mutants were obtained, which translocated DA normally but were impaired in cocaine binding. Studies employing transporter chimera have supported these results. Chimeric dopamine−norepinephrine transporters were constructed which completely lacked cocaine binding but maintained uptake properties, suggesting that the determinants for cocaine binding existed inde-

pendent of the substrate.[31,32] In addition to these molecular biology studies, several biochemical lines of evidence have suggested that the DA transport and cocaine binding domains on the DAT are distinct. For instance, DA offers substantially less protection than cocaine against the alkylation of [^{3}H]mazindol binding sites by *N*-ethylmaleimide.[33] Furthermore, thermodynamic analysis suggested that the binding of DAT substrates is entropy-driven (hydrophobic) while the binding of the inhibitors is enthalpy-driven (conformational change).[34] Taken together, these observations clearly suggest that cocaine and DA have distinct recognition sites on the DAT.

If cocaine and dopamine do, in fact, have distinct binding sites on the DAT, then it should be possible to develop a small molecule cocaine antagonist which would specifically inhibit cocaine recognition by the DAT while permitting the transporter to maintain all or most of its functions. Such a selective compound may have clinical utility because it would block the physiological effects of cocaine but leave normal DA transmission within the brain intact.

Different mechanisms appear to account for other actions of cocaine. For example, induction of seizures/convulsions are primarily mediated by cocaine binding to serotonin (5-HT$_2$) receptors.[18,35−37] Dopaminergic receptor sites are responsible for the fatal effects of cocaine, including death.[35,36,38,39] Discriminative stimulus properties of cocaine are believed to be modulated by dopamine D$_1$ and D$_2$ receptors in the mesocorticolimbic DA systems.[40,41] In addition to its DAT blocking action, cocaine possesses the ability to inhibit serotonin transporter (5-HTT)[18,42−44] and norepinephrine transporter (NET),[42,45] has local anesthetic activity via its action on sodium channels,[46−48] and binds to muscarinic M$_2$[49] and sigma sites.[50]

Despite improved knowledge of the neuropharmacological mechanisms underlying the addictive action of cocaine, no competitive cocaine antagonist has been reported to date.[51,52] There are two main strategies that are being actively pursued to fight cocaine addiction: (1) pharmacotherapeutical and (2) immunological. The pharmacotherapeutic agents that are currently available to treat cocaine addiction are divided into three major classes: (1) drugs that treat premorbid coexisting psychiatric disorders (e.g., antidepressant desipramine; stimulants, methylphenidate or pemoline), (2) drugs that treat cocaine withdrawl and craving (e.g., dopamimetic agents, L-dopa/carbidopa; amino acids, tyrosine and tryptophan; the antidepressants; and the anticonvulsant medication, carbmazepine), and (3) drugs that produce an aversion reaction when taken with cocaine (e.g., phenelzine).[53,54] For recent reviews on the development of pharmacotherapies for the treatment of cocaine abuse, see Carroll et al.[55] and Smith et al.[56] The pharmacological agents that do not directly act on the DAT but elicit potentially exploitable behavioral effects on cocaine responsiveness include the following: (1) excitatory amino acid receptor antagonists,[57,58] 5-HT$_3$ receptor antagonists,[59,60] dopamine receptor agonists/antagonists,[61−66] sigma receptor antagonists,[67,68] and kappa[69] and delta[70,71] opioid receptor ligands. The immunological approach involves the development of catalytic/noncatalytic cocaine antibodies. It is important to state that pharmacotherapeutic agents are functional antagonists which inhibit binding of cocaine to the DAT. Cocaine antibodies, on the other hand, are chemical antagonists which bind to cocaine and degrade it.

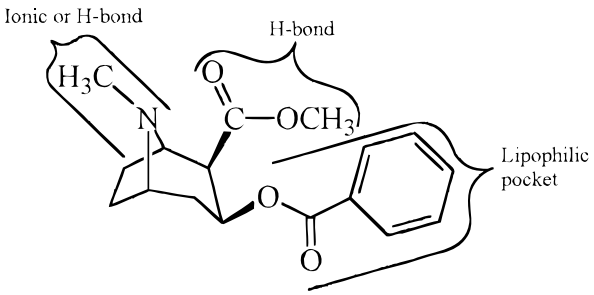


Figure 2. Schematic representation of putative interactions of cocaine with its receptor at the dopamine transporter (DAT).

On the basis of the structure−activity relationship (SAR) data and preliminary molecular modeling studies, a pharmacophore model for the cocaine recognition site was proposed by Carroll et al.[72] The model consists of an electrostatic or hydrogen-bond site on the DAT to interact with the basic amino function (i.e., N8) of cocaine. The presence of at least one or perhaps two additional hydrogen-bond sites has been speculated in the vicinity of the two oxygen atoms of the 2β-carbomethoxy group of cocaine. A hydrophobic pocket, which is believed to accommodate the benzoyl/phenyl group of cocaine, has been suggested. A schematic representation of the putative interactions of cocaine with its receptor at the DAT is shown in Figure 2. It has, however, been discovered that the requirement for a basic nitrogen[73,74] or even a nitrogen[75−78] is not essential for potent activity. Investigation of the necessity of a hydrogen bond between the 2β-carbomethoxy ester function of cocaine and the receptor revealed that hydrogen bonding between analogues and the receptor is not a prerequisite.[79−81] It should also be noted that an *R*-configuration of the tropane ring is required for potent activity of cocaine analogues,[5,82] but in some cases the *S*-enantiomers were more active[83] or only slightly less active than the structurally related *R*-tropanes,[84,85] suggesting that the requirement for an *R*-configuration is not absolute and depends on the substitution pattern. Furthermore, a piperidine ring can be exchanged for the tropane ring without any significant loss in potency.[86]

Since 1990, a large number of compounds have been synthesized. A variety of radioligands, including [^{3}H]WIN 35428,[87−89] [^{125}I]RTI-55,[90] [^{3}H]mazindol,[91] [^{3}H]GBR 12935,[92,93] [^{3}H]methylphenidate,[94] [^{3}H]-cocaine,[87−89] and [^{3}H]nomifensine,[95] have been used. However, inhibition of the [^{3}H]WIN 35428[87−89] binding to the DAT is the current standard due to reasonable specificity to the DAT. It labels both the high- and low-affinity binding sites, just like cocaine, and is resistant to metabolic and chemical degradation. It also has a high specific-to-nonspecific ratio.[96−98] Other radioligands, e.g., paroxetine, citalopram, and nisoxetine, are used to study the actions of cocaine

analogues at other transporters, 5-HTT and NET. The structures of these ligands are shown in Figure 1.

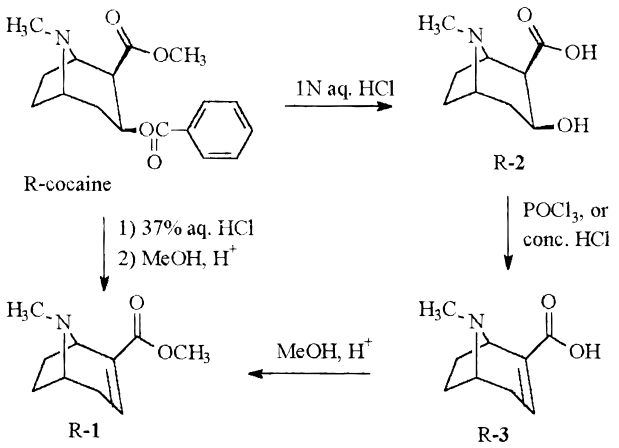
The present review discusses synthetic methodologies employed for a systematic procurement of the desired compound for biological evaluation as well as the rationale for the design of such compounds. Minor variations in basic synthetic methods have not been included. Throughout the review the selection of compounds for inclusion of their transporter-binding potencies is restricted to chemically well-defined compounds. The transporter-binding potencies are combined in tables in accordance with the classes of compounds. Efforts have been made to include only those transporter-binding potencies that have been obtained against standard radioligands in accordance with the NIDA protocol.[99] This restriction allows, in many cases, an approximate comparison of transporter potencies within one class and among different classes of compounds. In addition, in some cases, where important, other transporter-binding potencies are included in tables. In most of the cases the transporter-binding potencies are reported as IC_{50} and uptake inhibition values as K_i. However, some researchers have determined only IC_{50} values or vice versa. It is important to note that the IC_{50} values change with experimental conditions. Several factors play roles, e.g., type and amount of radioligand, fresh or frozen tissue, buffer, incubation time, region of brain, and protein content.[100−102] It is recommended that K_i values rather than IC_{50} values should be determined for both binding and uptake[103] under identical conditions (i.e., uptake conditions).[104,105] In vivo behavioral studies are not discussed in this review.

Furthermore, in this review the emphasis is on the synthetic and SAR aspects of potential compounds of the cocaine/tropane, GBR, methylphenidate, and mazindol, and their transporter-binding potencies, although another topic, which deals with the immunological approach of combating cocaine addiction, is also discussed. An attempt is made to cover the material as comprehensively as possible, but not necessarily exhaustively, because of an overwhelming amount of literature. Nevertheless, it is believed that all important original contributions are critically appraised and included.

Cocaine chemistry was conceived in the late 1800s. The first synthesis of cocaine was reported by Willstatter in 1923.[106] Although much was learned in those early years, interest in the pharmacological effects of cocaine remained low until the middle part of this century. Much of the analogue design and synthesis involved isomeric cocaine studies,[107] modifications of the tropane moiety at the bridge nitrogen (N8),[108] or modification at the C2 position.[109] The chemistry of tropanes is reviewed by Lounasmaa.[110]

The goal of designing cocaine analogues is mainly 3-fold: (1) to modify the chemical structure of cocaine in such a way as to retain or reinforce its useful stimulant or antidepressant pharmacological effects and to minimize its high toxicity and dependence liability, (2) to use high-affinity analogues as pharmacological probes to gain greater insight into the structural requirements for binding to the DAT, and (3) to obtain a competitive cocaine antagonist which can selectively inhibit cocaine binding to the DAT but which itself is devoid of transporter-inhibiting actions and is free from toxic effects. While there has been some success in accomplishing the first two goals, a true cocaine antagonist, which does not elicit stimulant and euphoric behavioral attributes of cocaine, is not known at the present time. The synthesis and biological evaluation of hundreds of compounds has enormously broadened our knowledge of the neuropharmacological mechanisms underlying the addictive action of cocaine and its binding site and has resulted in the design of more selective ligands for the DAT.

Scheme 1



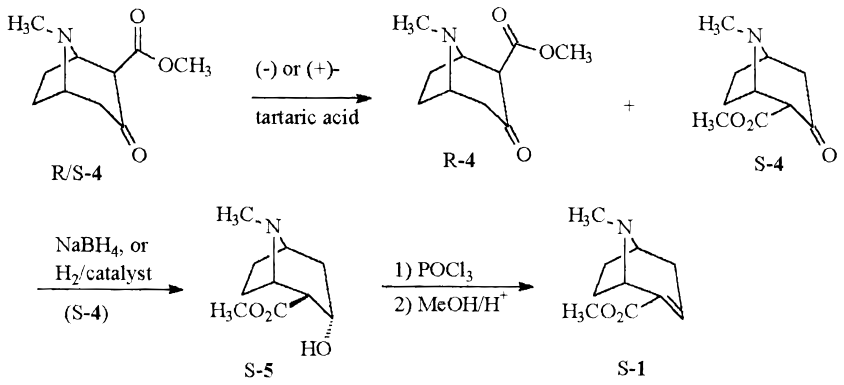
II. Phenyltropanes

The main structural feature of phenyltropanes (WIN-type of compounds) is that they lack the 3β-benzoyl ester functionality present in cocaine. The phenyl ring is directly attached to the tropane ring. The phenyltropanes were first designed by Clarke et al.[111] with the intention of obtaining a useful stimulant or antidepressant with reduced toxicity. The biological activities were determined. The studies were later reviewed by Clarke in 1977.[112] More recently, the inhibition of radioligand binding and DA uptake at the DAT including synthesis of some 3β-(substituted phenyl)tropanes is reviewed by Carroll et al.[113] The phenyltropanes are discussed in several subgroups.

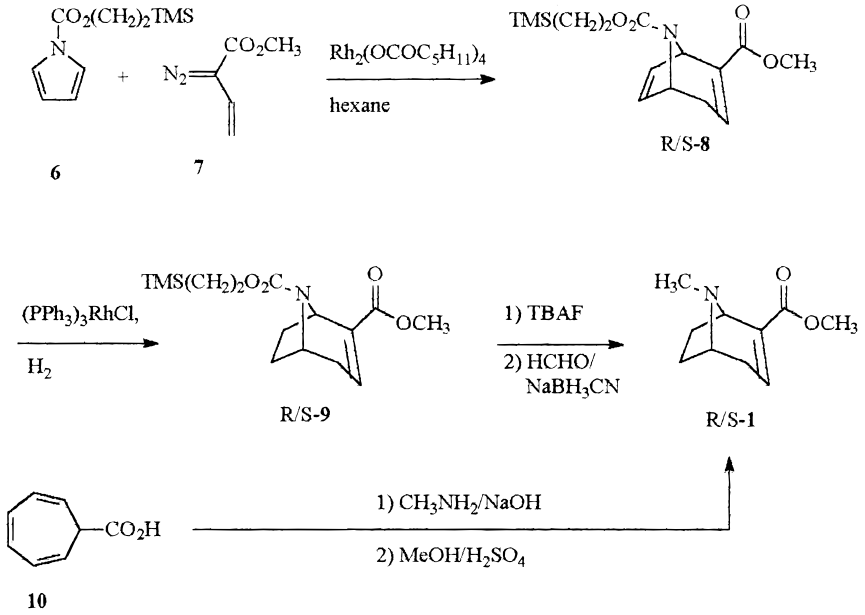
A. Phenyl Ring Substituted Phenyltropanes

The synthesis of phenyltropanes was carried out from (1*R*,5*S*)-anhydroecgonine methyl ester (*R*-**1**), which was prepared from *R*-cocaine in three steps: (1) hydrolysis,[114] (2) dehydration,[115] and (3) esterification,[116] as shown in Scheme 1. In addition, *R*- or *S*-anhydroecgonine methyl ester (*R*-**1** or *S*-**1**) was obtained from 2-carbomethoxy-3-tropinone (*R*/*S*-**4**).[117,118] Resolution of *R*/*S*-**4** using (−) or (+)-tartaric acid provided *R*-2-carbomethoxy-3-tropinone (*R*-**4**) or *S*-2-carbomethoxy-3-tropinone (*S*-**4**).[111,117−120] Reduction of the individual ketone *R*-**4** or *S*-**4** with sodium borohydride or hydrogenation over a catalyst provided an alcohol *R*-**5** or *S*-**5**,[5,111] which was dehy-

Scheme 2



Scheme 3



drated with phosphorus oxychloride and esterified with methanol as shown in Scheme 2. Anhydroecgonine (*R*-**3**) was also prepared in one step by refluxing *R*-cocaine in concentrated hydrochloric acid (Scheme 2).[121]

Davies et al. synthesized *R*/*S*-**1** by a tandem cyclopropanation/Cope rearrangement.[122,123] Thus, reaction of methyldiazobutenoate (**7**) with 5 equiv of *N*-((2-(TMS)ethoxy)carbonyl)pyrrole (**6**) in the presence of rhodium(II) hexanoate/hexane gave the [3.2.1]-azabicyclic system *R*/*S*-**8** in 62% yield. The unsubstituted double bond was selectively reduced using Wilkinson's catalyst to provide *N*-protected anhydroecgonine methyl ester (*R*/*S*-**9**). Following deprotection of N8 nitrogen with TBAF and reductive methylation with formaldehyde and sodium cyanoborohydride, *R*/*S*-**1** was obtained in overall good yield (Scheme 3). Kline et al. have synthesized *R*/*S*-**1** from the reaction of 2,4,6-cycloheptatriene-7-carboxylic acid (**10**) with methylamine (Scheme 3).[124]

1. 3β-(4′-Substituted Phenyl)tropanes

The first synthesis of 2*β*-carbomethoxy-3*β*-phenyltropanes, as reported by Clarke et al.,[111] involved the conjugate addition of an appropriately substituted phenylmagnesium bromide to anhydroecgonine methyl ester (*R*-**1**) in ether at −20 °C. A 75% yield of a 1:3 mixture of 2*β*-carboxylate (**11**) and 2-α-carboxylate (**12**) was obtained (Scheme 4). The structural assignments were based upon NMR data and reduction to the corresponding alcohols **13** (2*β*) and **14** (2α), one of which; i.e., **13** showed intramolecular hydrogen bonding. Another observation was that 2*β*-carboxylate **11** quaternized more slowly compared to 2α-carboxylate **12** due to an electron-rich carbomethoxy group in the *axial* position interfering with the electrophile accessing the tropane nitrogen. This difference in the rates of quaternization was found to be helpful in separating the two isomers. The strategy was utilized by Clarke et al.[111] and Milius et al.[125] to obtain 2*β*-carbomethoxy-3*β*-(substituted phenyl)tropanes. Subsequent studies have shown that the stereoselectivity for the 2*β*-isomer (**11**) could be significantly improved by adjusting the reaction temperature and/or performing a low-temperature quench of the reaction as summarized in Table 1. It should be noted that the substituents in the Grignard reagent affect the yield and the ratio of the products.[128]

The structures of 4′-substituted phenyltropanes are shown in Figure 3. The key step in the synthesis of these compounds was the 1,4-conjugate addition of

Scheme 4

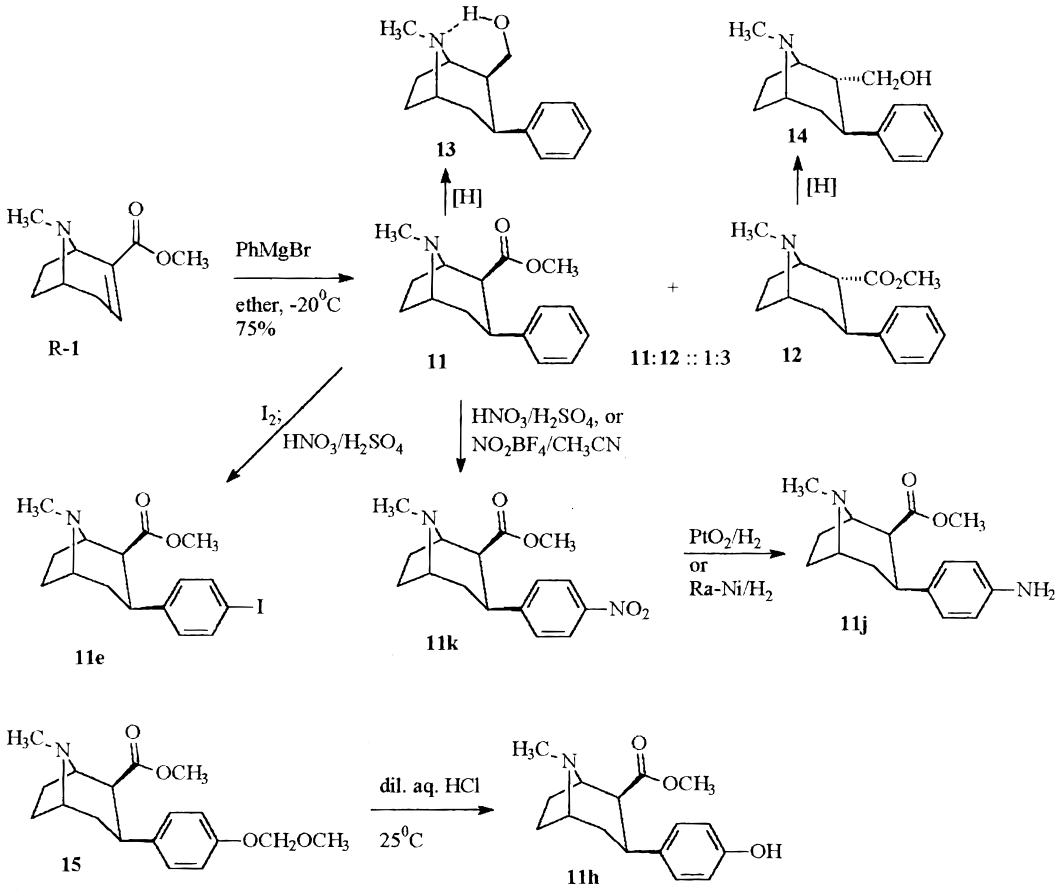


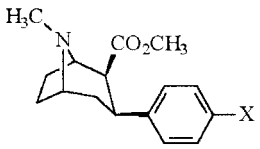
Table 1. Stereoselectivity of 1,4-Conjugate Addition of Grignard Reagent (PhMgBr) to Anhydroecgonine Methyl Ester (*R*-1)

reaction conditions	quenching	yield (%)	ratio[a] **11:12**	ref
Et_2O, −20 °C	ice	75	1:3	111
Et_2O, −40 °C	TFA, −78 °C	79	1.6:1	126
Et_2O, −20 °C	HCl/Et_2O/ice	80	1.8:1	127
Et_2O/DCM, −40 °C	TFA/DCM, −78 °C	84	5:1	128

[a] Isomers ratio was determined by ^1H NMR. Structures of **11** and **12** are shown in Scheme 4.

an appropriately substituted Grignard reagent as shown in Scheme 4. Further modifications were made in the adduct to afford the target compound. A nitro group in the phenyl ring at the 4′-position was directly introduced by treating 2β-carbomethoxy-3β-phenyltropane (**11a**; Scheme 4) with nitrating mixture (HNO_3/H_2SO_4)[124] or with nitronium tetrafluoroborate[126] to afford 4′-nitrophenyltropane (**11k**). The nitro group in the latter compound was easily reduced with hydrogen over a catalyst, PtO_2,[124] or Ra-Ni[126] to give 4′-aminophenyltropane (**11j**; Scheme 4). Compound **11j** was either diazotized and substituted with a nucleophile or acylated. The 4′-iodophenyltropane (**11e**; Scheme 4) was synthesized via diazotization or direct iodination[82,129] or stannylation.[130] The 4′-hydroxy analogue (**11h**) was obtained by selectively hydrolyzing the MOM protecting group of 4′-methoxymethylphenyltropane (**15**; Scheme 4).[131]

Synthesis of 3β-(4′alkyl-, 4′-alkenyl- and 4′-alkynylphenyl)tropane-2β-carboxylic methyl esters **11r−z**

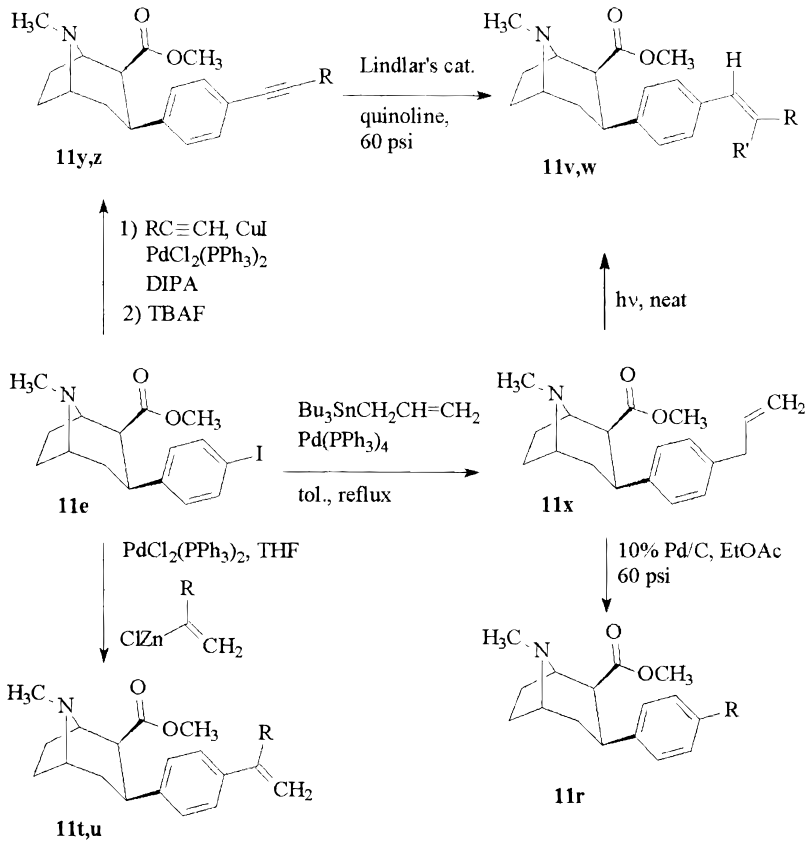


11a; X= H (WIN 35065-2)
11b; X= F (WIN 35428)
11c; X= Cl
11d; X= Br
11e; X= I (RTI-55)
11f; X= CH_3
11g; X= C_2H_5
11h; X= OH
11i; X= OCH_3
11j; X= NH_2
11k; X= NO_2
11l; X= N_3
11m; X= CF_3
11n; X= $NHCOCH_3$
11o; X= $NHCOC_2H_5$
11p; X= $NHCO_2C_2H_5$
11q; X= $Sn(CH_3)_3$
11r; X= n-C_3H_7
11s; X= $CH(CH_3)_2$
11t; X= $CH=CH_2$
11u; X= $C(=CH_2)CH_3$
11v; X= trans-$CH=CHCH_3$
11w; X= cis-$CH=CHCH_3$
11x; X= $CH_2CH=CH_2$
11y; X= $C\equiv CH$
11z; X= $C\equiv CCH_3$
11aa; X= Ph
11bb; 3β-2-naphthyl

Figure 3. Structures of 2β-carbomethoxy-3β-(4′-substituted phenyl)tropanes.

(Figure 3) was conducted using Castro−Stevens and Stille-type palladium-catalyzed coupling of the organometallic reagents to the 4′-iodophenyltropane analogue (**11e**).[132,133] As shown in Scheme 5, a Castro−Stevens coupling of a terminal acetylene was utilized to obtain 3β-(4′-alkynylphenyl)tropane derivatives, **11y** and **11z**. Thus, reaction of **11e** with trimethylsilyl acetylene in the presence of a catalytic amount of copper(I) iodide and bis(triphenylphosphine)palladium(II) chloride in degassed diisopropylamine

Scheme 5



(DIPA) followed by removal of the silyl group with TBAF in THF gave **11y** in 98% yield. The 3β-(4′-allylphenyl)tropane analogue (**11x**) was synthesized via a Stille coupling of allylbutyltin with **11e** using tetrakis(triphenylphosphine)palladium as the catalyst in refluxing toluene.[134] The isomerization of the terminal C=C double bond of **11x** occurred upon standing at room temperature for 6 months, affording *trans*-3β-(4′-propenylphenyl)tropane (**11v**). The *cis* analogue (**11w**) was obtained from 4′-propynylphenyltropane (**11z**) by hydrogenation over Lindlar's catalyst. To prepare 4′-alkenylphenyltropanes, Stille-type coupling between an alkenylzinc chloride and **11e** was exploited. Thus, reaction of **11e** and vinylzinc chloride solution, generated by the addition of zinc chloride to a solution of vinylmagesium bromide in THF, in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride afforded the 4′-vinyl analogue (**11t**). It is important to note that the coupling of tributylvinyltin or tributylisopropenyltin with **11e** in the presence of bis(triphenylphosphine)palladium(II) chloride or tetrakis(triphenylphosphine)palladium catalyst was unsuccessful. Perhaps, either the palladium intermediate was unstable or the heating in the presence of vinylstannate reagent caused the decomposition of the tropane ring. The 4′-ethyl- (**11g**), 4′-*n*-propyl- (**11r**), and 4′-isopropylphenyltropane (**11s**) analogues were obtained from **11t**, **11x**, and **11u**, respectively, by catalytic hydrogenation over Pd/C in ethyl acetate at 60 psi.[133] The 4′-phenyl (**11aa**) and 3β-2-naphthyl phenyltropane (**11bb**) derivatives were prepared using standard Grignard reaction.[135]

Table 2 summarizes the binding potencies of the 4′-substituted phenyltropanes for inhibition of [^{3}H]-WIN 35428, [^{3}H]paroxetine, and [^{3}H]nisoxetine at the DA, 5-HT, and NE transporters, respectively. The phenyltropanes exhibited much greater affinity for the DAT compared to cocaine and some selectivity at other transporters. The binding affinity of **11a** (WIN 35065-2) was 4.4 times greater than cocaine. To explain the higher binding potency of **11a**, the interatomic distances between the bridgehead nitrogen (N8) and the centroid of the aromatic ring in **11a** and cocaine were measured. These interatomic distances in **11a** and cocaine were 5.6 and 7.7 Å, respectively, suggesting that the aromatic ring of **11a** lied in a more favorable binding region.[126] It is also apparent from Table 2 that substitution in the 3β-phenyl ring profoundly influenced the ligand affinity and binding site selectivity. The comparative molecular field analysis (CoMFA) of 25 3β-phenyltropane analogues, demonstrated that the increased electron density around the 3β-phenyl ring was correlated with high ligand potency at the dopamine transporter.[126,131] For example, substitution at the 4′-position of **11a** with a chloro (**11c**), bromo (**11d**), iodo (**11e**), or methyl (**11f**) group provided a compound with an IC_{50} value less than 2 nM. 4′-Substitution with an electron-withdrawing group, e.g., nitro (**11k**) or trifluoromethyl (**11m**), or electron-donating amino (**11j**), methoxy (**11i**), or hydroxy group (**11h**) provided a compound with a similar IC_{50} value but 1 order of magnitude less potent than **11c**, **11d**, **11e**, or **11f**. Large 4′-substituents such as acetylamino (**11n**), propionylamino (**11o**), ethoxycarbonylamino (**11p**),

Table 2. Transporter Binding Potencies of 2β-Carbomethoxy-3β-(4′-substituted phenyl)tropanes

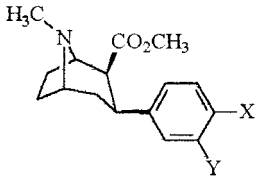
	IC$_{50}$(nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]paroxetine	NET [^{3}H]nisoxetine	5-HTT/DAT	NET/DAT
cocaine	102 ± 12	1045 ± 89	3298 ± 293	10.2	32.3
	241 ± 18[a]	112 ± 2[b]	160 ± 15[c]	0.5[d]	0.7[e]
11a	23.0 ± 5.0	1962 ± 61	920 ± 73	85.3	40.0
(WIN 35065-2)	49.8 ± 2.2[a]	173 ± 13[b]	37.2 ± 5.2[c]	3.5[d]	0.7[e]
11b	15.7 ± 1.4	810 ± 59	835 ± 45	51.6	53.2
(WIN 35428)	22.9 ± 0.4[a]	100 ± 13[b]	38.6 ± 9.9[c]	4.4[d]	1.7[e]
11c	1.12 ± 0.06	44.5 ± 1.3	37 ± 2.1	39.7	33.0
	3.68 ± 0.09[a]	5.00 ± 0.05[b]	5.86 ± 0.67[c]	1.3[d]	1.7[e]
11d	1.81 ± 0.30	10.6 ± 0.24	37.4 ± 5.2	5.8	20.7
11e (RTI-55)	1.26 ± 0.04	4.21 ± 0.3	36 ± 2.7	3.3	28.6
	1.96 ± 0.09[a]	1.74 ± 0.23[b]	7.51 ± 0.82[c]	0.9[d]	3.8[e]
11f	1.71 ± 0.30	240 ± 27	60 ± 0.53[e]	140	35.1
	7.02 ± 0.30[a]	19.38 ± 0.65[b]	8.42 ± 1.53[c]	2.8[d]	1.2[e]
11g	55 ± 2.1	28.4 ± 3.8	4030 ± 381	0.5	73.3
11h	12.1 ± 0.86				
11i	8.14 ± 1.3				
11j	24.8 ± 1.3				
11k	10.1 ± 0.10				
11l	2.12 ± 0.13				
11m	13.1 ± 2.2				
11n	64.2 ± 2.6				
11o	121 ± 2.7				
11p	316 ± 48				
11q	144 ± 37				
11r	68.5 ± 7.1	70.4 ± 4.1	3920 ± 130	1.0	57.2
11s	597 ± 52	191 ± 9.5	75000 ± 5820	0.3	126
11t	1.24 ± 0.2	9.5 ± 0.8	78 ± 4.1	7.7	62.9
11u	14.4 ± 0.3	3.13 ± 0.16	1330 ± 333	0.2	92.4
11v	5.29 ± 0.53	11.4 ± 0.28	1590 ± 93	2.1	300
11w	15 ± 1.2	7.09 ± 0.71	28000 ± 300	0.5	1867
11x	32.8 ± 3.1	28.4 ± 2.4	2480 ± 229	0.9	75.6
11y	1.2 ± 0.1	4.4 ± 0.4	83.2 ± 2.8	3.7	69.3
11z	2.37 ± 0.2	15.7 ± 1.5	820 ± 46	6.6	346
11aa	10.3 ± 2.6[f]				
	29.4 ± 3.8[a]				
11bb	3.32 ± 0.08[f]				
	3.53 ± 0.09[a]				

[a] K_i value for displacement of [^{3}H]DA uptake. [b] K_i value for displacement of [^{3}H]5-HT uptake. [c] K_i value for displacement of [^{3}H]NE uptake. [d] [^{3}H]5-HT uptake to [^{3}H]DA uptake ratio. [e] [^{3}H]NE uptake to [^{3}H]DA uptake ratio. [f] IC$_{50}$ value for the displacement of [^{3}H]cocaine.

and trimethylstannyl (**11q**) resulted in compounds with low affinity for the DAT.[126,131] Among the 4′-alkyl-substituted analogues (**11g**, **11r**−**z**; Figure 3), 4′-ethyl analogue (**11g**), which was only slightly larger than 4′-methyl analogue (**11f**), was 32 times less potent. Replacement of the 4′-alkyl group larger than the ethyl group, e.g., *n*-propyl (**11r**) and isopropyl (**11s**), resulted in further loss of potency both at the DAT as well as 5-HTT. Two carbon unsaturated groups containing analogues, 4′-alkenyl (**11t**) and 4′-alkynyl (**11y**), exhibited IC$_{50}$ less than 2 nM. Three carbon unsaturated groups containing analogues, 4′-alkenyl and 4′-alkynyl analogues, displayed somewhat lower binding potencies.[133]

2. 3β-(3′-Substituted or 3′,4′-Disubstituted Phenyl)-tropanes

These compounds (**16a**−**e**, **17a**−**f**; Figure 4) were synthesized by conjugate addition of an appropriately substituted phenylmagnesium iodide or phenylmagnesium bromide to *R*-**1** as described in Scheme 4. Two methods have been employed to prepare 3′-bromophenyltropane (**16c**) and 3′-iodophenyltropane (**16d**). 4′-Aminophenyltropane (**11j**) as prepared above



16a; X= H Y= F
16b; X=H, Y= Cl
16c; X= H, Y= Br
16d; X= H, Y= I
16e; X= H, Y= $SnBu_3$

17a; X= F, Y= CH_3
17b; X= Cl, Y= CH_3
17c; X= Cl, Y= Cl
17d; X= NH_2, Y= Br
17e; X= NH_2, Y= I
17f; X= N_3, Y= I

Figure 4. Structures of 2β-carbomethoxy-3β-(3′,4′-substituted phenyl)tropanes.

(Scheme 4) was brominated with NBS or iodinated with iodine chloride in acetic acid to give 3′-bromo-4′-amino- (**17d**) or 3′-iodo-4′-aminophenyltropane (**17e**) derivative.[131,136] Diazotization of **17d** or **17e** followed by treatment of the diazonium salt with hypophosphorus acid resulted in 3′-bromo- (**16c**) or 3′-iodophenyltropane (**16d**) analogue (Scheme 6). Also the treatment of the diazonium salt generated from **17e** with sodium azide gave 4′-azido-3′-iodophenyltropane

Scheme 6

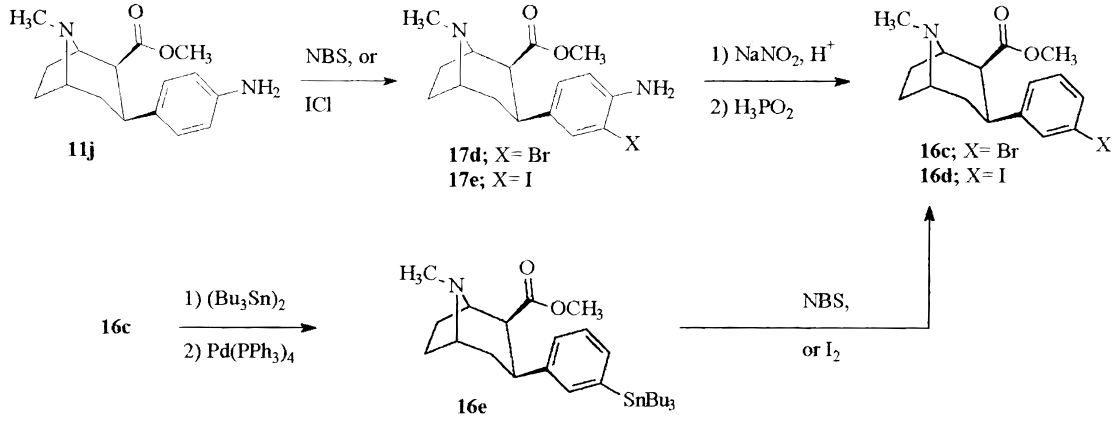


Table 3. Transporter Binding Potencies of 2*β*-Carbomethoxy-3*β*-(3′-substituted or 3′,4′-disubstituted phenyl)tropanes

	IC$_{50}$ (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]paroxetine	NET [^{3}H]nisoxetine	5-HTT/DAT	NET/DAT
16a	23 ± 7.8				
16b	10.6 ± 1.8				
16c	7.93 ± 0.08[a]				
16d	26.1 ± 1.7				
16e	1100 ± 170				
17a	2.95 ± 0.58				
17b	0.81 ± 0.05	10.5 ± 0.05	36.2 ± 1.0	13.0	44.7
17c	0.79 ± 0.08	3.13 ± 0.36	18.0 ± 0.8	4.0	22.8
17d	3.91 ± 0.59				
17e	1.35 ± 0.11	120 ± 4	1329 ± 124	88.9	984
17f	4.93 ± 0.32				

[a] IC$_{50}$ value was determined in Cynomolgous monkey caudate-putamen.

17f.[137] Compounds **16c** and **16d** could also be synthesized via 3′-tributylstannylphenyltropane (**16e**). *R*-**1** was reacted with the mono-Grignard reagent generated from 1,3-dibromobenzene to give 3′-bromophenyltropane (**16c**) in 27% yield.[138] The latter compound was stannylated to obtain 3′-tributyltin analogue **16e**, which was treated with NBS or iodine to afford 3′-bromo (**16c**) or 3′-iodo (**16d**) analogue in 85% or 56% yield, respectively, Scheme 6.[127]

Substitution at the 3′-position of the 2*β*-carbomethoxy-3*β*-phenyltropanes had somewhat inconsistent results as described in Table 3. For example, 3′-substitution of **11a** resulted in analogues **16a**−**e** (Figure 4) with lower affinities than their corresponding 4′-substituted counterparts.[131]

Among 3′,4′-disubstituted 2*β*-carbomethoxy-3*β*-phenyltropanes, addition of a 3′-chloro or 3′-methyl group to the 4′-chloro analogue (**11c**) to give 3′,4′-dichloro (**17c**) or 4′-chloro-3′-methyl (**17b**) analogue, respectively, had only a minor effect on potency (Table 3). Strikingly, addition of a 3′-methyl group to the 4′-fluoro analogue (i.e., **17a**) or a 3′-bromo or 3′-iodo group to the 4′-amino analogue (compound **17d** or **17e**, respectively) increased potency relative to the 4′-substituted analogue.[131]

3. 3α-(4′-Substituted Phenyl)tropanes

Recently, other stereoisomers of **11a** (Figure 5) and some of its 4′-substituted analogues were prepared to compare the binding potencies and selectivities at the DA, 5-HT, and NE transports.[139] The synthesis of 2*β*-carbomethoxy-3α-(4′-substituted phenyl)tropanes (**20a**−**e**; Figure 5) is shown in Scheme 7. Thus, reaction of *R*-**1** with acetamide oxime in the presence of sodium hydride at 60 °C in dry THF afforded (1*R*,5*S*)-2-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)-8-methyl azabicyclo[3.2.1]oct-2-ene (**18**). Conjugate addition of an appropriately substituted aryllithium in THF or ether at −28 °C followed by quenching with TFA at −78 °C mainly gave 3α-(substituted phenyl)-2α-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropane (**19**). In some cases (X = I, CH_3), the 2α,3*β*-isomer was also formed, which was either removed by flash chromatography or carried through the next reaction. Reduction of **19** with either samarium iodide/methanol[140] or nickel boride/HCl in refluxing methanol provided the 2*β*-carbomethoxy-3α-(4′-substituted phenyl)tropanes (**20a**−**e**).[139] Under these reaction conditions, complete epimerization at C2 occurred forming the 2*β*,3α-stereoisomer. This was facilitated by the ability of the piperidine ring to adopt an *equatorial*-substituted twist−boat conformation.

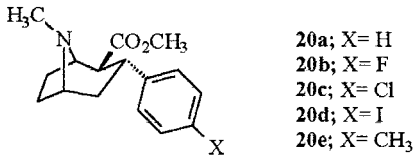
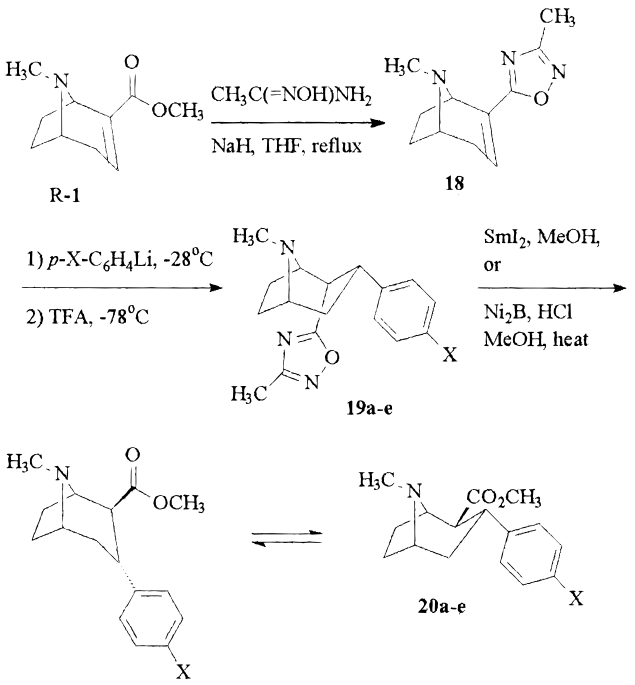


Figure 5. Structures of 2*β*-carbomethoxy-3α-(4′-substituted phenyl)tropanes.

Table 4. Transporter Binding Potencies of 2β,3α-Phenyltropanes

	IC_{50} (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]paroxetine	NET [^{3}H]nisoxetine	5-HTT/DAT	NET/DAT
allococaine	6160 ± 900				
20a	101 ± 16	5700 ± 721	2080 ± 285	56.4	20.6
20b	21 ± 0.57	5060 ± 485	1230 ± 91	241	58.6
20c	2.4 ± 0.2	998 ± 120	60.1 ± 2.4	416	25.0
20d	2.85 ± 0.16	64.9 ± 1.97	52.4 ± 4.9	22.8	18.4
20e	10.2 ± 0.08	4250 ± 422	275 ± 24	417	27.0

Scheme 7



As shown in Table 4, the 2β,3α-isomers were 1.5−5.9 times less potent at the DAT than the analogous 2β,3β-isomers. These results, however, differed sharply with allococaine, the 2β,3α-stereoisomer of *R*-cocaine, which was 60 times less potent than cocaine at the DAT.[5] Furthermore, 2β,3α-stereoisomers (**20a**−**e**) were more selective for the DAT relative to the 5-HTT than their respective 2β,3β-counterparts. It appeared that the 2β,3α-stereoisomers (**20a**−**e**; Figure 5) preferred to exist in the twist−boat conformation, thus allowing the tropane amine (N8), phenyl, and carbomethoxy groups (pharmacophores) to adopt similar positions as to the corresponding pharmacophores in 2β,3β-stereoisomers. Consequently, 2β,3α-phenyltropanes exhibited relatively high DA binding affinities compared to allococaine. It is also interesting to note that the 2β-carbomethoxy-3α-iodophenyl analogue (**20d**) was only slightly less potent than the 2β-carbomethoxy-3β-iodophenyl analogue (**11e**) but 7 times more selective for the DAT compared to 5-HTT.[139]

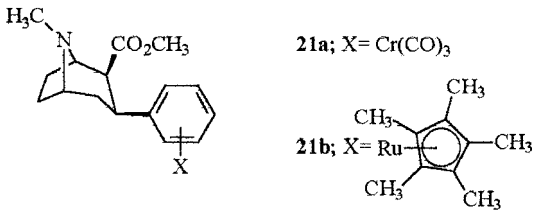


Figure 6. Structures of 2β-carbomethoxy-3β-(transition metal complexed phenyl)tropanes.

4. η^6-3β-(Transition Metal Complexed Phenyl)tropanes

Recently, transition metal complexes of 2β-carbomethoxy-3β-phenyltropane (**11a**) were synthesized (**21a,b**; Figure 6).[141] The rationale to synthesize such complexes was (1) η^6-coordinated transition metal

Scheme 8

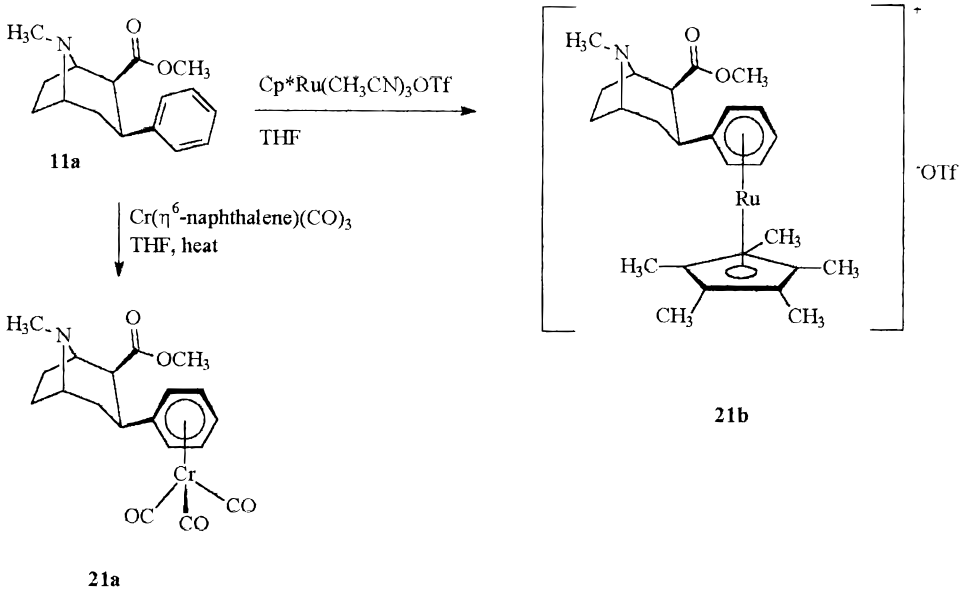


Table 5. Displacement of Receptor-Bound [^{3}H]WIN 35428 and Inhibition of [^{3}H]DA Uptake by Transition Metal Complexes of 3β-Phenyltropanes

compound no.	K_i (nM)[a]	IC_{50} (nM)	selectivity uptake/binding
cocaine	32 ± 5 388 ± 221	405	12.6
11a	33 ± 17 314 ± 222	373	11.3
21a	17 ± 15[b] 224 ± 83	418	24.6
21b	2280 ± 183	3890	1.7

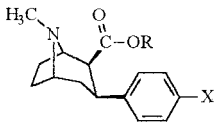
[a] The binding data fit a two-site model better than a one-site model. [b] The K_i value for the one-site model was 124 ± 10 nM.

moiety has been shown to dramatically alter the electronic character and reactivity of the arene unit of the ligand, and (2) selective η^6-coordination of the transition metal moiety to either the α- or β-face of the arene has served to introduce an element of asymmetrical molecular volume to the otherwise planar arene unit.

As shown in Scheme 8, the 2β-carbomethoxy-3β-phenyltropane (**11a**) was treated with Cr(η^6-naphthalene)$(CO)_3$ in refluxing THF to afford the [η^6-(2β-carbomethoxy-3β-phenyl)tropane]tricarbonylchromium (**21a**) in 85% yield.[142] Similarly, treatment of **11a** with Cp*Ru$(CH_3CN)_3$OTf in dry THF at ambient temperature gave [η^5-(pentamethylcyclopentadienyl)]-[η^6-(2β-carbomethoxy-3β-phenyl)tropane]ruthenium-(II) triflate (**21b**) in 80% yield.[143] The ^{1}H and ^{13}C NMR data of **21a,b** showed that the transition metal moiety was coordinated to the less hindered external phase of the phenyl ring to give a single diastereomer of each complex.

Table 5 summarizes the biological activity of transition metal complexes of 2β-carbomethoxy-3β-phenyltropanes. It is interesting to note that $Cr(CO)_3$ complex **21a** was 2-fold more potent than cocaine and free ligand **11a** in the inhibition of [^{3}H]WIN 35428. The complex **21a** exhibited both high- and low-affinity K_i values similar to cocaine as well as 2β-carbomethoxy-3β-phenyltropane (**11a**).[144] In addition, **21a** was equipotent to cocaine and free ligand **11a** for inhibition of DA uptake. On the other hand, Cp*Ru(II) complex **21b** exhibited a 100-fold decrease in the inhibition of high-affinity binding relative to cocaine and **11a** and a 10-fold decrease in DA uptake potency.[141] Such a large difference in the binding potencies of the two complexes **21a** and **21b** appeared to be due to electrostatic differences rather than steric bulk because tricarbonyl moiety is generally considered to be equivalent to the cyclopentadienyl ligand (Cp). Comparison of the solid cone angles (θ, steric parameter) of Cp (θ = 131°) and Cp* (θ = 187°) indicated that Cp*Ru was roughly only 30% larger than $Cr(CO)_3$ moiety.[145]

Thus, evaluation of a large number of phenyl ring substituted phenyltropanes clearly demonstrated that increased electron density in the phenyl ring was favorable for binding and that the region that interacted with the phenyl ring of **11a** (WIN 35065-2) was sufficiently large to accommodate large bulky lipophilic substituents.



23a; R= CH$(CH_3)_2$, X= H
23b; R= C_6H_5, X= H

24a; R= CH$(CH_3)_2$, X= Cl
24b; R= cyclopropyl, X= Cl
24c; R= C_6H_5, X= Cl
24d; R= C_6H_4-4-I, X= Cl
24e; R= C_6H_4-3-CH_3, X= Cl
24f; R= C_6H_4-4-CH_3, X= Cl
24g; R= C_6H_4-2-CH_3, X= Cl
24h; R= C_6H_4-4-Cl, X= Cl
24i; R= C_6H_4-4-OCH_3, X= Cl
24j; R= $(CH_2)_2C_6H_4$-4-NO_2, X= Cl
24k; R= $(CH)_2C_6H_4$-4-NH_2, X= Cl
24l; R= $(CH_2)_2C_6H_3$-3-I-4-NH_2, X= Cl
24m; R= $(CH_2)_2C_6H_3$-3-I-4-N_3, X= Cl
24n; R= $(CH_2)_2C_6H_4$-4-N_3, X= Cl
24o; R= $(CH_2)_2C_6H_4$-4-NCS, X= Cl
24p; R= $(CH_2)_2C_6H_4$-4-$NHCOCH_2Br$, X= Cl

25a; R= CH$(CH_3)_2$, X= I
25b; R= cyclopropyl, X= I
25c; R= C_6H_5, X= I

26a; R= CH$(CH_3)_2$, X= CH_3
26b; R= CH$(C_2H_5)_2$, X= CH_3
26c; R= cyclopropyl, X= CH_3
26d; R= cyclobutyl, X= CH_3
26e; R= cyclopentyl, X= CH_3
26f; R= C_6H_5, X= CH_3
26g; R= C_6H_4-3-CH_3, X= CH_3
26h; R= C_6H_4-4-CH_3, X= CH_3
26i; R= C_6H_4-2-CH_3, X= CH_3
26j; R= C_6H_4-4-Cl, X= CH_3
26k; R= C_6H_4-4-OCH_3, X= CH_3

Figure 7. Structures of 2β-ester-3β-phenyltropanes.

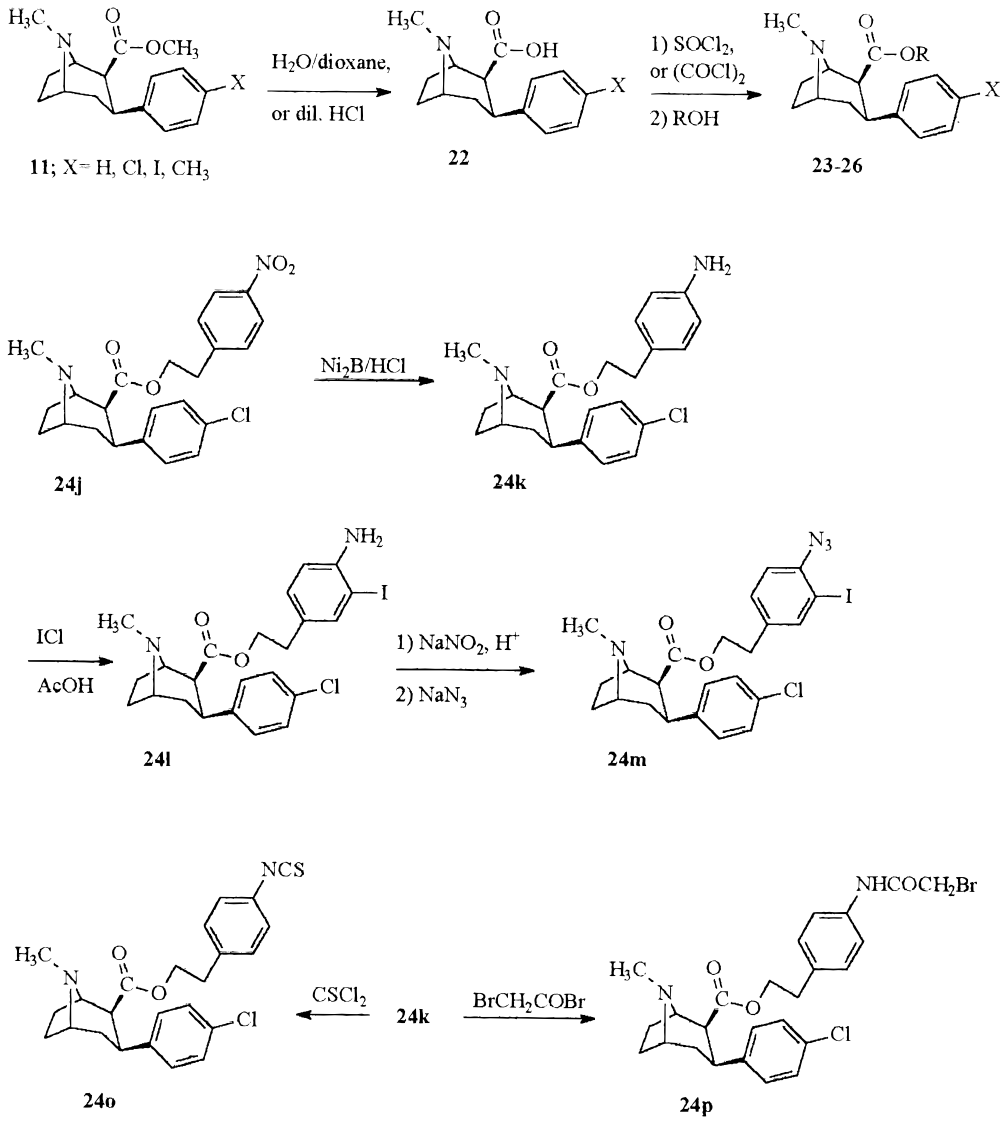
B. 2β-Substituted-3β-phenyltropanes

The 2β-substituted phenylpropanes were designed with mainly two goals in mind: (1) to explore the nature of interaction between the cocaine binding site and the high-affinity ligands, because the 2β-carbomethoxy pharmacophore in cocaine is believed to contribute to binding via hydrogen bonding on the DAT,[146] and (2) to obtain cocaine analogues with distinct selectivities at the monoamine transporter sites, because cocaine has moderately high affinity for 5-HTT and NET. A large number of compounds have been synthesized by incorporating mainly two kinds of substituents at the C2 position: (1) hydrogen bonding and (2) nonhydrogen bonding (lipophilic). The hydrogen-bonding pharmacophores (groups) at the C2-position are of the following types: (a) esters, (b) carboxamides, (c) isosteric heterocyclics, and (d) ketones. The non-hydrogen-bonding pharmacophores include (a) alkanes, (b) alkenes, (c) alkanes/alkenes with a terminal hydrogen-bonding functional group, e.g., ester, ketone, halide, or ether, and (d) aryls.

1. 2β-Ester-3β-phenyltropanes

In these phenyltropanes the methyl group of the 2β-ester function is replaced with other alkyl, aryl, or alkylaryl groups. A large number of compounds have been prepared as depicted in Figure 7. The synthetic strategy used to yield these compounds is shown in Scheme 9. The appropriately substituted 2β-carbomethoxy-3β-phenyltropane was hydrolyzed in water/dioxane or HCl/water and subsequently converted into acid chloride by treatment with either thionyl chloride or oxalyl chloride. The acid chloride was then reacted with an appropriate alcohol to obtain the 2β-ester-3β-phenyltropane. The substituted phenyl ring containing esters were prepared from the amino analogue **24k**, which in turn was obtained from the nitro analogue **24j** by reduction over nickel boride. Direct alkylation or nucleophilic substitution via diazotization of **24k** gave the esters **24l**−**p**, Scheme 9.[146,147]

Scheme 9



The binding potencies of C2-ester phenyltropanes are presented in Table 6. The binding affinities as well as selectivities of these compounds depended upon the substituent in the 3β-phenyl ring. For example, 2β-esters of unsubstituted 3β-phenyltropane (**23a,b**) were less potent than the parent methyl ester (**11a**; Table 2) at all the transporters. Among 3β-4′-chlorophenyltropanes, only 2β-isopropyl ester (**24a**) was slightly more potent than the parent compound (**11c**; Table 2). Other esters were less potent. The 2β-esters of 3β-4′-iodophenyltropane (**25a**−**c**) were more potent than the parent methyl ester (**11e**; Table 2) except for the 2β-phenyl ester (**25c**). However, among 3β-4′-methylphenyltropanes (**26a**−**k**), the 2β-esters were generally less potent than the parent methyl ester (**11f**; Table 2) except for the 2β-cyclopropyl ester (**26c**), which was equipotent.

The interesting finding from this series of compounds was that the isopropyl ester (**23a, 24a, 25a, 26a**) and phenyl ester (**23b, 24c, 25c, 26f**) analogues of each of the 3β-substituted phenyltropane-2β-carboxylic acids possessed high selectivity for the DAT. The esters combining the highest selectivity and potency for the DAT were 3β-(4′-methylphenyl)- and 3β-(4′-chlorophenyl)tropane-2β-carboxylic acid phenyl esters (**26f** and **24c**), respectively, and 3β-(4′-chlorophenyl)- and 3β-(4′-iodophenyl)tropane-2β-carboxylic acid isopropyl esters (**24a** and **25a**).[146,147] It is also important to note that bulky ester groups at the 2-position were well tolerated without any significant loss in potency (e.g., **24p**).

2. 2β-Carboxamide-3β-phenyltropanes

To gain further insight into the effects of the 2β-substituent on the binding affinities at the monoamine transporters, several 3β-substituted phenyl 2β-carboxamides were synthesized and evaluated, Figure 8.

The 2β-carboxamide analogues were prepared by treating benzoylecgonine (**22**) with oxalyl chloride in DCM followed by reaction of the resultant acid chloride with an appropriately substituted amine (Scheme 10).[147] The 2β-methanolamide analogue (**27d**) was prepared by treating a THF solution of **27a** with 37% aqueous formaldehyde in the presence of potassium carbonate (Scheme 10).[147]

Table 6. Binding Affinities and Inhibition of Monoamine Transport by 2β-Ester-3β-phenyltropanes

	IC_{50} (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]paroxetine	NET [^{3}H]nisoxetine	5-HTT/DAT	NET/DAT
23a	85.1 ± 2.5	23121 ± 3976	32047 ± 1491	272	376
23b	76.7 ± 3.6	106149 ± 7256	19262 ± 593	1384	251
24a	1.4 ± 0.13	1400 ± 7	778 ± 21	1000	556
	6.04 ± 0.31[a]	128 ± 15[b]	250 ± 0.9[c]	21.2[d]	41.4[e]
24b	0.96 ± 0.10	168 ± 1.8	235 ± 8.39	175	245
24c	1.99 ± 0.05	2340 ± 27	2960 ± 220	1176	1.3
	5.25 ± 0.76[a]	390 ± 34[b]	242 ± 30[c]	74.3[d]	41.6[e]
24d	32.6 ± 3.9	1227 ± 176	967.6 ± 26.3	37.6	29.7
24e	9.37 ± 0.52	2153 ± 143	2744 ± 140	230	293
24f	27.4 ± 1.5	1203 ± 42	1277 ± 118	43.9	46.6
24g	3.91 ± 0.23	3772 ± 384	4783 ± 387	965	1223
24h	55 ± 2.3	16914 ± 1056	4883 ± 288	307	88.8
24i	71 ± 5.6	19689 ± 1843	1522 ± 94	277	21.4
24j	2.71 ± 0.13				
24k	2.16 ± 0.25				
24l	2.51 ± 0.25				
24m	14.5 ± 0.94				
24n	6.17 ± 0.57				
24o	5.3 ± 0.6				
24p	1.73 ± 0.06				
25a	0.43 ± 0.05	66.8 ± 6.53	285 ± 7.6	155	663
	2.79 ± 0.13[a]	12.5 ± 1.0[b]	41.2 ± 3.0[c]	4.5[d]	14.8[e]
25b	0.61 ± 0.08	15.5 ± 0.72	102 ± 11	25.4	167
25c	1.51 ± 0.34	184 ± 22	3791 ± 149	122	2510
	6.85 ± 0.93[a]	51.6 ± 6.2[b]	32.7 ± 4.4[c]	7.5[d]	4.8[e]
26a	6.45 ± 0.85	6090 ± 488	1926 ± 38	944	299
	15.3 ± 2.08[a]	917 ± 54[b]	73.4 ± 11.6[c]	59.9[d]	4.8[e]
26b	19.1 ± 1	4499 ± 557	3444 ± 44	235	180
26e	17.8 ± 0.76	485 ± 21	2628 ± 252	27.2	148
26d	3.74 ± 0.52	2019 ± 133	4738 ± 322	540	1267
26c	1.68 ± 0.14	1066 ± 109	644 ± 28	634	383
26f	3.27 ± 0.06	24500 ± 1526	5830 ± 370	7492	1783
	9.13 ± 0.79[a]	1537 ± 101[b]	277 ± 23[c]	168[d]	30.3[e]
26g	8.19 ± 0.90	5237 ± 453	2136 ± 208	639	261
26h	81.2 ± 16	15954 ± 614	4096 ± 121	196	50.4
26i	23.2 ± 0.97	11040 ± 504	25695 ± 1394	476	1107
26j	117 ± 7.9	42761 ± 2399	9519 ± 864	365	81.3
26k	95.6 ± 8.8	82316 ± 7852	3151 ± 282	861	33.0

[a] K_i value for displacement of [^{3}H]DA uptake. [b] K_i value for displacement of [^{3}H]5-HT uptake. [c] K_i value for displacement of [^{3}H]NE uptake. [d] [^{3}H]5-HT uptake to [^{3}H]DA uptake ratio. [e] [^{3}H]NE uptake to [^{3}H]DA uptake ratio.

An amide group can undergo hydrogen bonding, though weaker than an ester function depending upon its substitution pattern. The 2β-carboxamides, particularly with oxygen-bearing substituents (e.g., **27g,j, 28c, 29c**), were more potent within the same series of compounds, Table 7. Furthermore, *N*,*N*-dimethyl tertiary amide **27e** and *N*-pyrrolidine analogues **27i** and **28a** were more potent and significantly more selective than their parent methyl esters **11c** and **11e** (Table 2). The most potent and the most selective analogues among carboxamides were 3β-(4′-iodophenyl)tropane-2β-*N*-pyrrolidino carboxamide (**28a**) and 3β-(4′-chlorophenyl)tropane-2β-*N*-morpholino carboxamide (**27l**), respectively.[147,148]

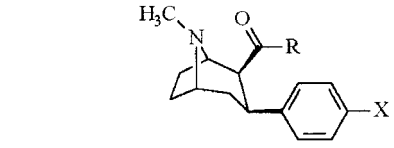
3. 2β-Heterocyclic-3β-phenyltropanes

The 3β-(substituted phenyl)-2β-(3′-substituted 1′,-2′,4′-oxadiazol-5′-yl)tropanes (**31**, **32a**−**f**, **33**; Figure 9) were designed because the 1,2,4-oxadiazole ring is a bioisostere of the carbomethoxy group and also stable to chemical and enzymatic degradation.[149,150] The 1′,2′,4′-oxadiazol-5′-yltropanes (**32a**−**f**) were synthesized by reacting an acid chloride with an appropriately substituted amide oxime in pyridine/chloroform (3:1) mixture at ambient temperature via a β-ketoxime amide, which underwent cyclodehydration in situ, Scheme 11.

Synthesis of other five-membered heterocyclic ring containing analogues, such as isoxazole, 1,3,4-oxadiazole, and oxazole in the 2β-position (**32g**−**i**; Figure 9), is outlined in Scheme 11. An isoxazole containing analogue **32g** was prepared via a β-ketoxime generated from the reaction of dilithium salt of acetophenone oxime with 3β-(4′-chlorophenyl)tropane-2β-carboxylic acid methyl ester (**11c**) in THF at 0−25 °C. The β-ketoxime was not isolated but cyclized in situ by refluxing in THF containing sulfuric acid. Dehydration occurred under the reaction conditions to give isoxazole (**32g**). Cyclodehydration of the β-ketoxime has also been effected by heating in 5 N aqueous HCl at 90−95 °C for 2−3 h.[151] The 1′,3′,4′-oxadiazole analogue (**32h**) was obtained by treatment of the acid **22** with benzoic acid hydrazide in $POCl_3$. Similarly, treatment of the acid **22** with oxalyl chloride followed by condensation with 2-aminoacetophenone gave the amide (**30**), which upon cyclization in the presence of phosphorus oxychloride gave the oxazole derivative **32i**.[152]

Table 7. Binding Affinities and Inhibition of Monoamine Transport by 2β-Carboxamide Phenyltropanes

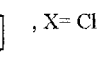
	IC_{50} (nm)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
27a	11.5 ± 1.6	1621 ± 110	4270 ± 359	141	371
27b	12.4 ± 1.17	1313 ± 46	1584 ± 62	106	128
27c	10.7 ± 1.25	43700 ± 1960	9907 ± 632	4084	926
27d	2.05 ± 0.23	97.8 ± 10	144 ± 3	47.7	70.2
27e	1.38 ± 0.1	1079 ± 102	942 ± 48	792	683
27f	5.48 ± 0.19	9433 ± 770	5532 ± 299	1721	1009
27g	0.85 ± 0.06	724 ± 94	549 ± 18.5	852	646
27h	6.57 ± 0.67	814 ± 57	990 ± 4.8	124	151
27i	1.38 ± 0.03	12400 ± 1207	3950 ± 72	8985	2862
27j	1.47 ± 0.13	2470 ± 56	1083 ± 76	1680	737
27k	6.95 ± 1.21	3470 ± 226	1752 ± 202	499	252
27l	2.90 ± 0.3	88769 ± 1855	8545 ± 206	30610	2946
27m	45.5 ± 3	23610 ± 2128	2202 ± 495	519	48.4
28a	0.37 ± 0.04	1728 ± 39	991 ± 21	4670	2678
28b	1.08 ± 0.15	73.9 ± 8.1	103 ± 6.2	68.4	95.4
28c	0.75 ± 0.02	130 ± 15.8	357 ± 42	173	476
29a	41.8 ± 2.45	6371 ± 374	4398 ± 271	152	105
29b	24.7 ± 1.93	33928 ± 2192	6222 ± 729	1374	252
29c	2.55 ± 0.43	3402 ± 353	422 ± 26	1334	165
29d	11.7 ± 0.87	>100000	23601 ± 1156	>8547	2017



27a; R= NH_2, X= Cl
27b; R= $NHCH_3$, X= Cl
27c; R= $NHOCH_3$, X= Cl
27d; R= $NHCH_2OH$, X= Cl
27e; R= $N(CH_3)_2$, X= Cl
27f; R= $N(C_2H_5)_2$, X= Cl
27g; R= $N(OCH_3)CH_3$, X= Cl

27h; R=  , X= Cl

27i; R=  , X= Cl

27j; R=  , X= Cl

27k; R=  , X= Cl

27l; R=  , X= Cl

27m; R= $N(CH_3)C_6H_5$, X= Cl

28a; R=  , X= I

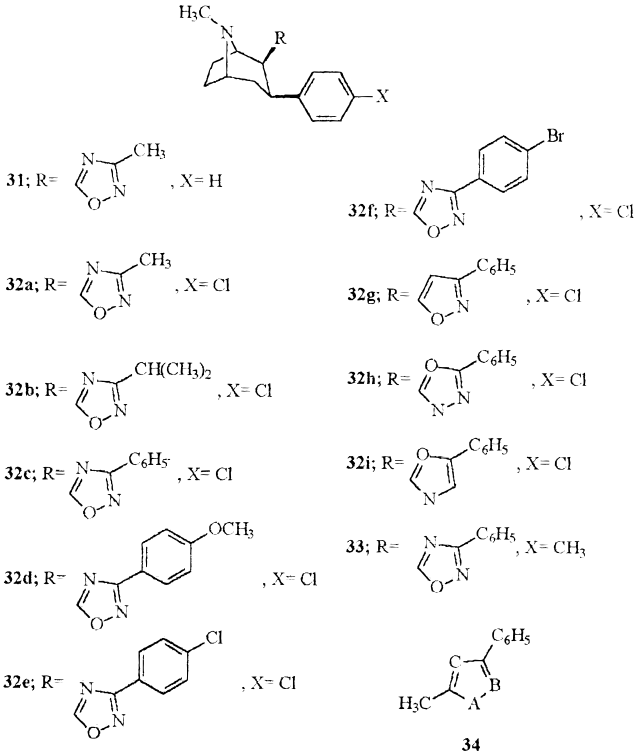
28b; R= $N(OCH_3)CH_3$, X= I

28c; R=  , X= I

29a; R= NH_2, X= CH_3
29b; R= $N(CH_2CH_3)_2$, X= CH_3
29c; R= $N(OCH_3)CH_3$, X= CH_3

29d; R=  , X= CH_3

Figure 8. Structures of 2β-carboxamide-3β-phenyltropanes.



31; R= , X= H

32a; R= , X= Cl

32b; R= , X= Cl

32c; R= , X= Cl

32d; R= , X= Cl

32e; R= , X= Cl

32f; R= , X= Cl

32g; R= , X= Cl

32h; R= , X= Cl

32i; R= , X= Cl

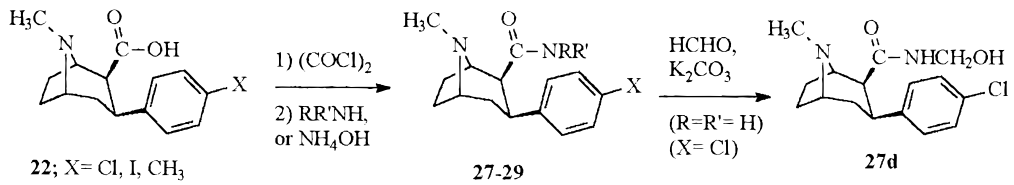
33; R= , X= CH_3

34

Figure 9. Structures of 2β-heterocyclic-3β-phenyltropanes.

As seen from Table 8, 3β-(4′-chlorophenyl)-2β-(3′-phenyl-1′,2′,4′-oxadiazol-5′-yl)tropane (**32c**) was the most potent analogue (IC_{50} 1.62 nM) and 3β-(4′-chlorophenyl)-2β′(3′-methoxyphenyl-1′,2′,4′-oxadiazol-5′-yl)tropane (**32d**) with an IC_{50} of 1.81 nM was the most selective analogue for the DAT with 5-HTT/DAT and NET/DAT ratios of 186 and 461, respectively.[149] Other five-membered heterocyclic ring containing analogues, **32g**−**i** possessed nearly equal molecular shapes and volumes but with variations in the

Scheme 10



22; X= Cl, I, CH_3 **27-29** **27d**

Scheme 11

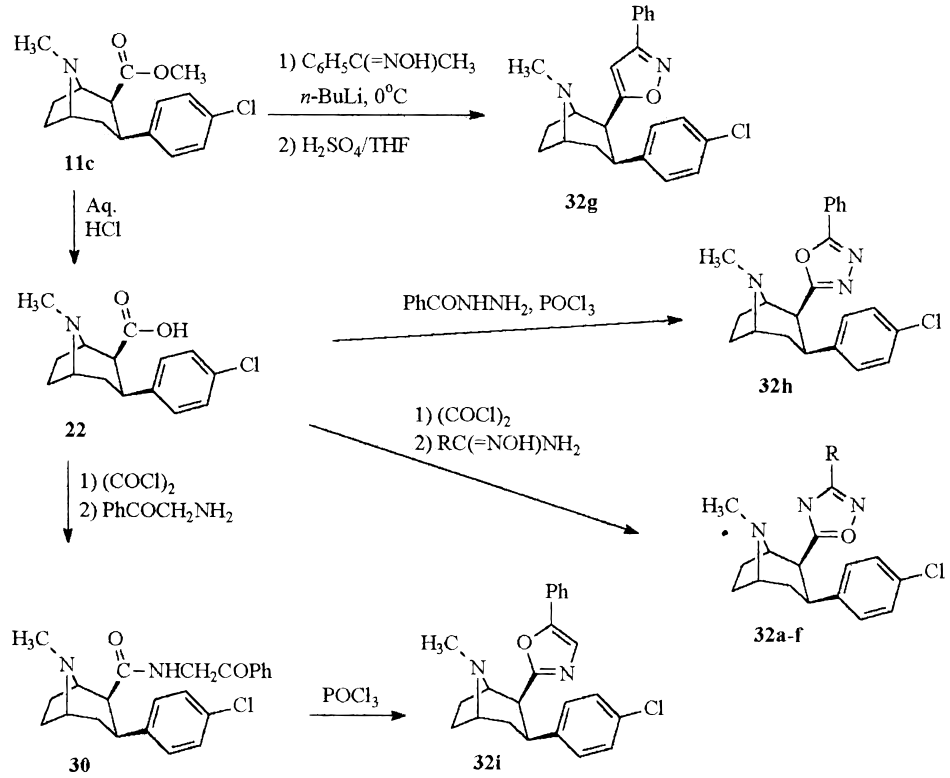


Table 8. Binding Affinities and Inhibition of Monoamine Transport by 2β-Heterocyclic-3β-phenyltropanes

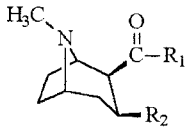
	IC$_{50}$ (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
31	100 ± 6	3830 ± 420	7880 ± 551	38.3	788
32a	4.05 ± 0.57	2580 ± 800	363± 36	637	89.6
32b	6.00 ± 0.55	3460 ± 250	135 ± 13	577	22.5
32c	1.62 ± 0.02	195 ± 5	245 ± 13	120	151
32d	1.81 ± 0.19	337 ± 40	835 ± 8	186	461
32e	4.06 ± 0.22	404 ± 56	40270 ± 180	99.5	9919
32f	3.44 ± 0.36	106 ± 10	1830 ± 170	30.8	532
32g	1.28 ± 0.18	2420 ± 136	504 ± 29	1891	394
32h	12.6 ± 10.3	330 ± 196	929 ± 88	262	73.7
32i	19.7 ± 1.98	1120 ± 107	496 ± 42	56.8	25.5
33	2.33 ± 0.26	1070 ± 130	60 ± 2	459	25.7

location and, in some cases, the number of heteroatoms and are considered bioisosteres of the ester function. The oxadiazoles **32c** and **32h** contained the same number and types of heteroatoms in the 2β-substituent but the binding potencies were 8-fold different. Similarly, **32g** and **32i** both had one nitrogen and one oxygen in the 2β-substituent, but **32g** was 15 times more potent at the DAT compared to **32i**.[152]

To explore the possibility that the differences in binding potencies of the 2β-heterocyclic phenyltropanes were due to electrostatic interactions, molecular electrostatic potentials (MEP) in the vicinity of the atoms at positions A−C in the model compound (**34**; Figure 9) were examined. In this model, phenyltropane moiety was replaced by a methyl group. The differences in the electrostatic potential minima near position A (ΔV_{min}(A)) were calculated using semiempirical (AM1) quantum mechanics calculations after superimposing the heterocyclic and the phenyl rings to minimize steric and conformational effects. A strong correlation between ΔV_{min}(A) and affinity at the DAT was obtained. The ΔV_{min}(A) values for **32c**, **32g**, **32h**, and **32i** were 0, −4, −50, and −63 kcal/mol, respectively.[153] It should be noted that an increasingly negative ΔV_{min} in the vicinity of hydrogen-bond acceptor atoms is correlated with an increase in the strength of associated hydrogen bonds.[154] Thus, higher affinity at the DAT appeared to be associated with relatively less negative ΔV_{min} values. In other words, the observed correlation was against the hydrogen-bond interaction in the heterocyclic analogues.[152] Thus, it can be stated that the binding of analogues possessing 2β-substituents, which are capable of participating in electrostatic interactions, may be dominated by electrostatic factors rather than hydrogen bonding.[155]

4. 2β-Acyl-3β-phenyltropanes

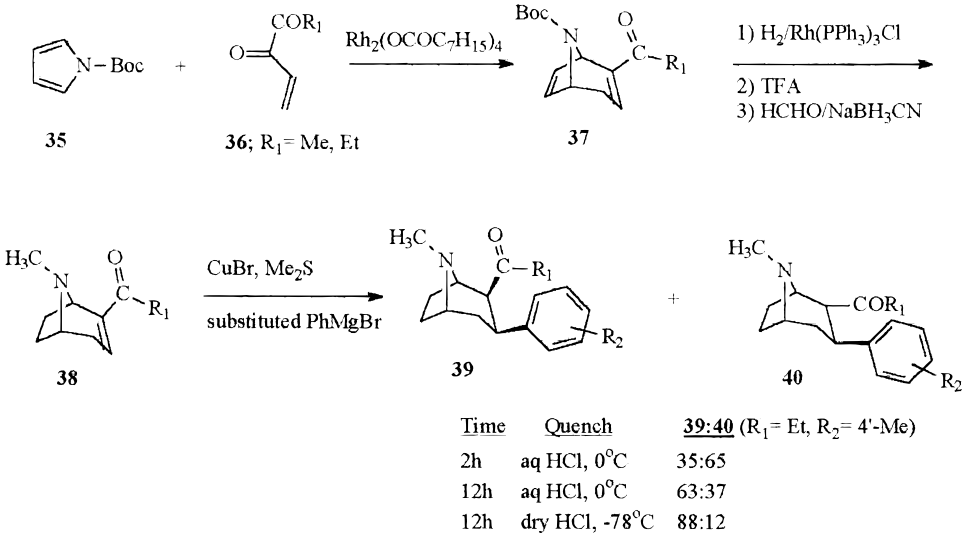
Davies et al.[156,157] synthesized diversely substituted phenyltropanes by replacing the 2β-carbomethoxy



39a; R_1= C_2H_5, R_2= C_6H_5
39b; R_1= CH_3, R_2= C_6H_5
39c; R_1= C_2H_5, R_2= C_6H_4-4-F
39d; R_1= CH_3, R_2= C_6H_4-4-F
39e; R_1= C_2H_5, R_2= C_6H_4-4-CH_3
39f; R_1= CH_3, R_2= C_6H_4-4-CH_3
39g; R_1= CH_3, R_2= C_6H_4-4-C_2H_5
39h; R_1= C_2H_5, R_2= C_6H_4-4-$CH(CH_3)_2$
39i; R_1= C_2H_5, R_2= C_6H_4-4-$C(CH_3)_3$
39j; R_1= C_2H_5, R_2= C_6H_4-4-C_6H_5
39k; R_1= C_2H_5, R_2= C_6H_4-2-CH_3
39l; R_1= C_2H_5, R_2= 1-naphthyl
39m; R_1= CH_3, R_2= 1-naphthyl
39n; R_1= C_2H_5, R_2= 2-naphthyl
39o; R_1= CH_3, R_2= 2-naphthyl
39p; R_1= C_2H_5, R_2= C_6H_4-4-$CH(C_2H_5)_2$
39q; R_1= C_2H_5, R_2= C_6H_4-4-C_6H_{11}
39r; R_1= C_2H_5, R_2= C_6H_4-4-$CH=CH_2$
39s; R_1= C_2H_5, R_2= C_6H_4-4-$C(=CH_2)CH_3$

Figure 10. Structures of 2β-acyl-3β-phenyltropanes.

Scheme 12



Time	Quench	39:40 (R_1= Et, R_2= 4'-Me)
2h	aq HCl, 0°C	35:65
12h	aq HCl, 0°C	63:37
12h	dry HCl, -78°C	88:12

group with a ketone functionality. The structures of these compounds are shown in Figure 10.

The synthesis of 2β-acyl-3β-phenyltropanes involved the reaction between rhodium(II)-stabilized vinyl carbenoids (**36**) and *N*-Boc pyrrole (**35**) similar to the synthesis of (±)-anhydroecgonine.[122] Azabicyclo-[3.2.1]oct-2-ene (**38**) thus obtained was reacted with appropriately substituted phenylmagnesium bromide in the presence of cuprous bromide as a catalyst to give a mixture of 2β- and 2α-acyl-3β-phenyltropanes (**39** and **40**). It is noteworthy that the stereochemistry at the 2-position was dependent upon the reaction time and quenching conditions. Long reaction times followed by a low-temperature quench strongly favored the formation of the desired 2β-isomer **39** as delineated in Scheme 12. The 2β-isomer **39** was readily separated from its 2α-isomer **40** by column chromatography.

The compounds containing a 2β-ethanoyl or propanoyl pharmacophore (Figure 10) instead of a 2β-carbomethoxy pharmacophore were tested for their binding potencies at the DAT and 5-HTT as summarized in Table 9. The analogues containing a 2-naphthyl group at the 3β-position (**39n,o**) were the most potent (K_i values < 1 nM) in binding to both DAT and 5-HTT. Other compounds, particularly containing a relatively smaller substituent in the aromatic moiety (such as Me or F; **39c**−**f**), were relatively selective for the DAT, while a 4′-isopropylphenyl derivative (**39h**) was more selective for the 5-HTT sites.[156]

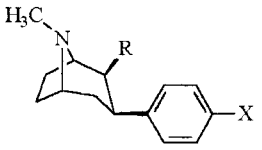
Since 3β-4′-isopropylphenyl-2β-propanoyl (**39h**) was quite selective for the 5-HTT, other compounds were synthesized by retaining the 2β-ethyl ketone functionality and modifying the 4′-isopropyl substituent of the aromatic ring (**39p**−**s**). The choice of unsaturated substituents on the aromatic ring was based on the observation that extended sp^2 functionality in the 3β-aryl ring, as seen with 2-naphthyl (**39n,o**) or biphenyl (**39j**), resulted in potent compounds.[156,158] Some of these compounds (**39r,s**) were more potent at the 5-HTT than **39h**; however, they also retained high affinity for the DAT.

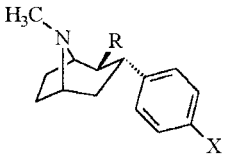
5. 2-Alkane/Alkene-3-phenyltropanes

It has been proposed above that the 2β-carbomethoxy function of cocaine engages with hydrogen-bond donor groups at the DAT. This hypothesis was, however, called into question when a C2 vinyl analogue of cocaine displayed a 10-fold greater potency for the displacement of (^{3}H)mazindol at the DAT.[80] Subsequently, substituted alkyl groups inca-

Table 9. Binding Affinities of the 2β-Acyl-3β-phenyltropanes

compound no.	IC_{50} (nM) DAT [^{125}I]RTI-55	K_i (nM) 5-HTT [^{3}H]Paroxetine	selectivity 5-HTT/DAT
cocaine	173 ± 19		
11a (WIN 35065-2)	98.8 ± 12.2		
39a	48.3 ± 2.8	1005 ± 112	20.8
39b	114 ± 22	1364 ± 616	12.0
39c	15.3 ± 2.8	630 ± 67	41.2
39d	70.8 ± 13	857 ± 187	12.1
39e	8.2 ± 1.6	131 ± 1	16.0
(+)-**39e**	4.21 ± 0.05	74 ± 12	17.6
(−)-**39e**	1337 ± 122	>10000	
39f	9.8 ± 0.5	122 ± 22	12.4
39g	152 ± 24	78.2 ± 22	0.5
39h	436 ± 41	35.8 ± 4.4	0.08
39i	2120 ± 630	1771 ± 474	0.8
39j	2.29 ± 1.08	4.31 ± 0.01	1.9
39k	1287 ± 322	710000	>7.8
39l	5.43 ± 1.27	20.9 ± 2.9	3.8
39m	10.1 ± 2.2	25.6 ± 5.1	2.5
39n	0.115 ± 0.021	0.394 ± 0.074	3.5
39o	0.28 ± 0.11	1.06 ± 0.36	3.8
39p	270 ± 38	540 ± 51	2.0
39q	320 ± 55	97 ± 12	0.30
39r	0.90 ± 0.34	3.2 ± 1.3	3.5
39s	7.2 ± 2.1	0.82 ± 0.38	0.1





41a; R= $(CH_2)_2CH_3$, X= H
41b; R= $(CH_2)_3C_6H_5$, X= H

42; R= $(CH_2)_2CH_3$, X= F

43a; R= $CH{=}CH_2$, X= Cl
43b; R= E-CH=CHCl, X= Cl
43c; R= Z-CH=CHCl, X= Cl
43d; R= E-CH=CHC_6H_5, X= Cl
43e; R= Z-CH=CHC_6H_5, X= Cl
43f; R= CH_2CH_3, X= Cl
43g; R= $(CH_2)_2CH_3$, X= Cl
43h; R= $(CH_2)_3CH_3$, X= Cl
43i; R= $(CH_2)_5CH_3$, X= Cl
43j; R= $(CH_2)_2C_6H_5$, X= Cl

44a; R= $(CH_2)_2CH_3$, X= CH_3
44b; R= $(CH_2)_3CH_3$, X= CH_3

45; R= $(CH_2)_2CH_3$, X= H

46; R= $(CH_2)_2CH_3$, X= F

47a; R= $(CH_2)_2CH_3$, X= CH_3
47b; R= $(CH_2)_3CH_3$, X= CH_3

Figure 11. Structures of 2-alkane/alkene-3-phenyltropanes.

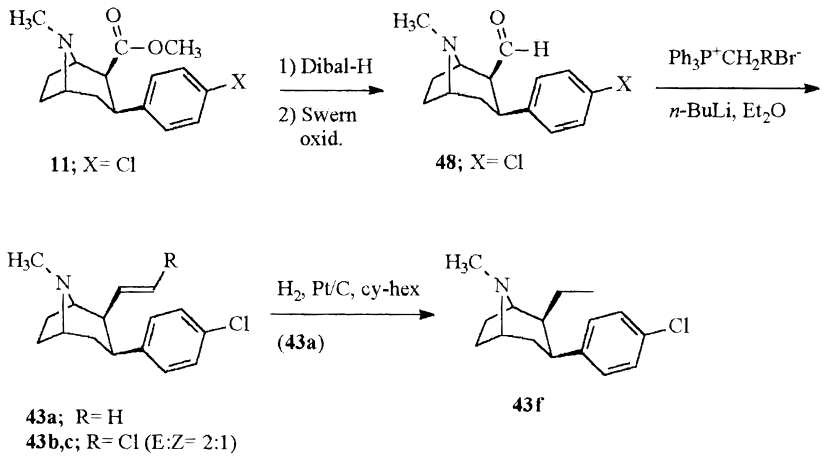
pable of forming hydrogen bonds were introduced in phenyltropanes to further delineate structure−activity relationships for phenyltropanes in an effort to identify a possible cocaine antagonist.[81,159,160] As depicted in Figure 11, both the 2β,3β- and 2α,3β-isomers have been synthesized and tested.

The 2-alkane/alkene-3-phenyltropanes were synthesized using two strategies. The 4′-chlorophenyltropane (**43a**−**j**; Figure 11) were synthesized using a Wittig reaction as illustrated in Scheme 13. The C2 aldehyde **48** was prepared from **11** in two steps by reduction of the C2 ester with Dibal-H in toluene at −78 °C followed by Swern oxidation with oxalyl chloride/DMSO in DCM at −78 °C.[161] It should be emphasized that the single-step transformation of the C2 ester into an aldehyde (**48**) using a mild and bulky reducing agent, such as lithium tri-*tert*-butoxyaluminum hydride,[162] diisobutylaluminum hydride,[163] sodium aluminum hydride,[164] bis(4-methyl-1-piperazinyl)aluminum hydride,[165] or $LiAlH_4-NHCl_2$,[166] was unsuccessful. In all cases, either the ester was reduced directly to the alcohol or it was recovered unchanged with only traces of aldehyde. Since **48** was unstable as well stereochemically sensitive, it was subjected to the Wittig olefination reaction without isolation and purification. The yield in the Wittig reaction was 35.6%, and the ratio of the *cis*/*trans* isomers was 20:80 in favor of the *trans* isomer.

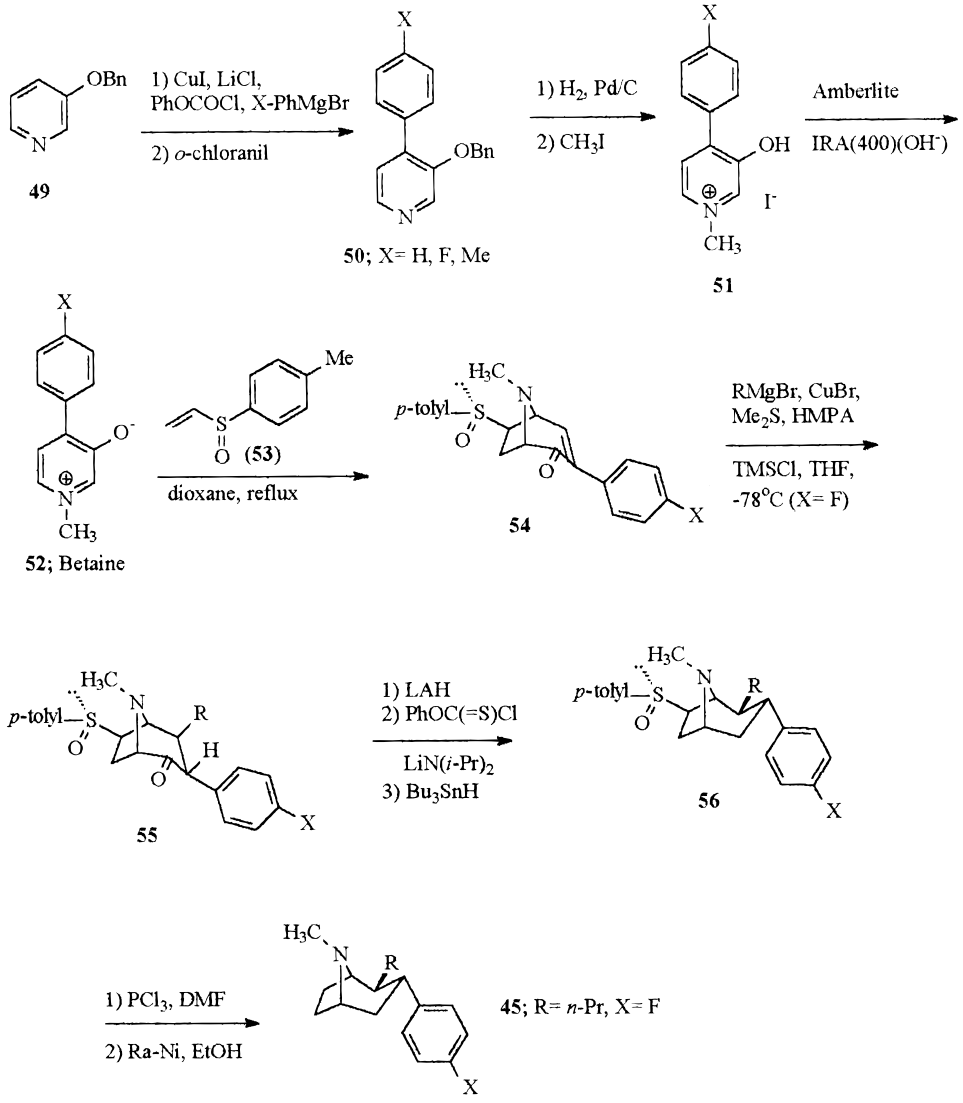
It is also noteworthy that the attempts to improve the yield of the Wittig reaction by modifying the reaction conditions, e.g., lower temperature, variations in the order of addition, stoichiometry, counterion, and reaction time, were not successful. In some cases, the reaction was slow but no change in the isomer ratio was observed. However, the reaction of *o*-(methoxymethoxy)phenyl-armed ylide with **48** gave solely the *cis*-olefin[167] but with epimerization at C2 possibly due to the basisity of phosphorane, which promoted the formation of the more stable α-isomer through enolate formation. To prepare 2β-alkyl analogues, the C=C double bond of the vinyl analogues was reduced with hydrogen over Pt/C as a catalyst at 40 psi in cyclohexane.[168] Use of Pd/C under similar conditions resulted in hydrogenolysis to some extent.

The 2β,3β-analogues containing a 4′-fluoro or 4′-methyl in the 3-aryl moiety (**42, 44**; Figure 11) could also be synthesized using a Wittig reaction as illustrated in Scheme 13. The 2β,3α-isomers (**45**−**47**; Figure 11) were synthesized using a 1,3-dipolar cycloaddition of a dipolarophile to a betaine followed by a Grignard reaction. Since Grignard reaction is not compatible with 4′-chlorophenyltropanes, synthesis of 2β,3α-isomers of only 4′-hydrogen, 4′-fluoro-,

Scheme 13



Scheme 14



or 4′-methylphenyltropanes employed a Grignard reaction.

As illustrated in Scheme 14, the addition of phenylmagnesium bromide to 3-benzyloxypyridine was performed using a known procedure[169] but with some modifications; i.e., CuI·2LiCl was used in place of CuI/Me_2S.[170] Following dehydrogenation of the dihydropyridine intermediate with *o*-chloranil, the product **50** was hydrogenolyzed and treated with methyliodide in acetone at reflux. Finally, the resulting hydroxyyridinium salt **51** was treated with resin (OH^-) to afford betaine **52** in quantitative yield. The oxidopyridinium betaine **52** was reacted with optically pure (*R*)-(+)-*p*-tolyl vinyl sulfone (**53**) to give

Scheme 15

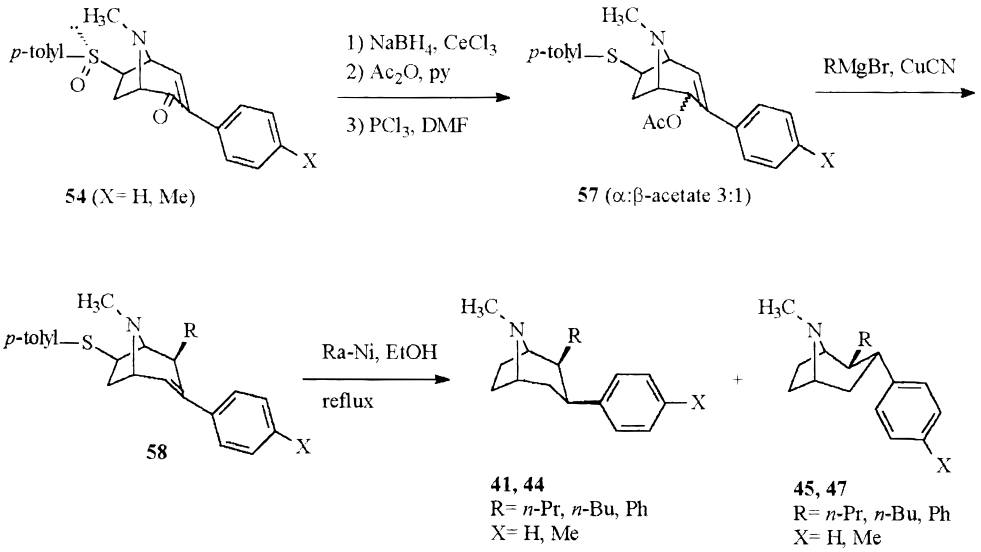


Table 10. Binding Affinities and Inhibition of Monoamine Transport by 2-Alkane/Alkene-3-phenyltropanes

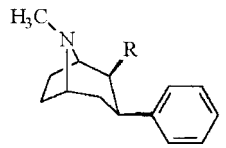
	K_i (nM)			selectivity
compound no.	DAT [^{3}H]mazindol	[^{3}H]DA uptake	[^{3}H]5-HT uptake	DA uptake/ DAT binding
11a (WIN 35065-2)	89.4	53.7	186	0.6
11c	0.83 ± 0.07	28.5 ± 0.9		34.3
11f	5.76	6.92	23.2	1.2
41a	12.2	6.89	86.8	0.6
41b	16 ± 2[a]	43 ± 13[b]		2.7
42	5.28	1.99	21.7	0.4
43a	0.59 ± 0.15	2.47 ± 0.5		4.2
43b	0.42 ± 0.04	1.13 ± 0.27		2.7
43c	0.22 ± 0.02	0.88 ± 0.05		4.0
43d	0.31 ± 0.04	0.66 ± 0.01		2.1
43e	0.14 ± 0.07	0.31 ± 0.09		2.2
43f	2.17 ± 0.20	2.35 ± 0.52		1.1
43g	0.94 ± 0.08	1.08 ± 0.05		1.1
43h	1.21 ± 0.18	0.84 ± 0.05		0.7
43i	156 ± 15	271 ± 3		1.7
43j	1.46 ± 0.03	1.54 ± 0.08		1.0
44a	1.57	1.10	10.3	0.7
44b	1.82	1.31	15.1	0.7
45	74.9	30.2	389	0.4
46	21.1	12.1	99.6	0.6
47a	8.91	11.8	50.1	1.3
47b	11.4	10.1	51.0	0.9

[a] K_i value for displacement of [^{3}H]WIN 35428. [b] IC_{50} value.

nonracemic tropenone **54**.[171] The copper-catalyzed conjugate addition reaction of a Grignard reagent to the tropenone **54** gave intermediate **55**, in which introduction of the proton and the alkyl group occurred from the β-face.[103] The ketone group in **55** was removed in a series of steps involving reduction followed by Barton-type deoxygenation of the resulting alcohol. The sulfoxide group of **56** was removed after reductive deoxygenation to sulfide with phosphorus trichloride followed by desulfurization with Raney nickel (Ra-Ni) to give **45**.

To obtain compounds **41, 44,** and **45, 47,** the tropenone **54** was first subjected to Luche reduction followed by acetylation to allylic acetates and reductive deoxygenation of the sulfoxide with phosphorus trichloride to give sulfide **57**. The copper cyanide catalyzed cross-coupling reaction with a Grignard reagent followed by Ra-Ni catalyzed hydrodesulfurization gave a mixture of 2β,3β- and 2β,3α-isomers (1:1), which were separated by column chromatography, Scheme 15.

The 2-alkane/alkene-substituted phenyltropanes were synthesized to eliminate the possibility of a hydrogen bonding at the DAT. As apparent from Table 10, these compounds exhibited increased binding potencies at the DAT as well as inhibited DA uptake. The magnitude of change in their affinities strongly depended upon the conformation of the tropane ring and the 3-phenyl ring substituent. For example, **41a** was more than 7-fold potent than parent compound **11a** whereas its boat isomer **45** was only 1.2-fold more potent. A similar trend was observed for **42** vs **46** and **44** vs **47**.[103] Among 3β-(4′-chlorophenyl)tropanes, the 2β-vinyl analogue **43a** was slightly more potent than the parent 2β-methyl ester **11c** for displacement of [^{3}H]mazindol binding



59a; R= $CH{=}CHCO_2CH_3$
59b; R= $CH_2CH_2CO_2CH_3$
59c; R= $(CH_2)_2CH{=}CHCO_2CH_3$
59d; R= $(CH_2)_4CO_2CH_3$
59e; R= $CH{=}CHCH_2OH$
59f; R= $CH_2CH_2CH_2OH$
59g; R= $CH_2CH_2COC_6H_5$

Figure 12. Structures of 2β-alkyl ester-3β-phenyltropanes.

(0.59 vs 0.83 nM).[160] Kozikowski et al. then synthesized C2 saturated alkyl analogues in order to eliminate the possibility of weak interactions between the double bond of the vinyl group at C2 and hydrogen donor at the DAT, because an unsubstituted vinyl group could still participate in weak interactions, though hydrogen bonding was beyond question. To further explore, the *Z* and *E* stereoisomers of the vinyl analogues were synthesized.[159] As seen in Table 10, *Z*-isomers were more potent than their *E*-isomer counterparts (**43b**−**e**). The saturated analogues (**43f**−**j**) in this series were only slightly less potent than the vinyl analogue **43a**. However, a large alkyl group, e.g., hexyl (**43i**), was detrimental for potency.

6. 2β-Alkyl Ester-3β-phenyltropanes

Another series of 2β-substituted-3β-phenyltropanes was designed to further explore the nature of the interaction between cocaine binding site at the DAT and to identify the proximal effects of electron-rich/unsaturated 2β-subtituents on binding affinity and DA uptake, Figure 12.[172,173]

As illustrated in Scheme 16, the α,β-unsaturated esters were prepared from aldehyde **48** according to the Masamune−Rousch olefination procedure in 65% overall yield.[174] The aldehyde **48** was obtained by LAH reduction of the methyl ester **11a** (Figure 3) followed by Swern oxidation. It is important to mention that although **48** was prone to epimerization, the mild conditions of the Masamune−Rousch olefination procedure afforded ester **59a** as a single crystalline isomer.[175] With the stereochemistry at the 2-position no longer susceptible to epimerization, the other derivatives **59b**−**f** were prepared in a straightforward fashion from the unsaturated ester **59a**. Hydrogenation of **59a** afforded saturated ester, **59b**, in quantitative yield, while reduction with LAH gave alcohol **59e** in 95% yield. The higher homologues were synthesized in a similar fashion by reduction, Swern oxidation, and olefination. The phenyl ketone **59g** was synthesized from **59b** by 1,2-addition of phenylmagnesium bromide.

Table 11. Binding Affinities and DA Uptake Inhibition by 2β-Alkyl Ester Phenyltropanes

compound no.	K_i (nM) DAT [^{3}H]WIN 35428	IC_{50} (nM) [^{3}H]DA uptake	selectivity uptake/binding
59a	22 ± 2	123 ± 65	5.6
59b	23 ± 2	166 ± 68	7.2
59c	20 ± 2	203 ± 77	10.1
59d	30 ± 2	130 ± 7	4.3
59e	26 ± 3	159 ± 43	6.1
59f	11 ± 1	64 ± 32	5.8
59g	28 ± 2	47 ± 15	1.7

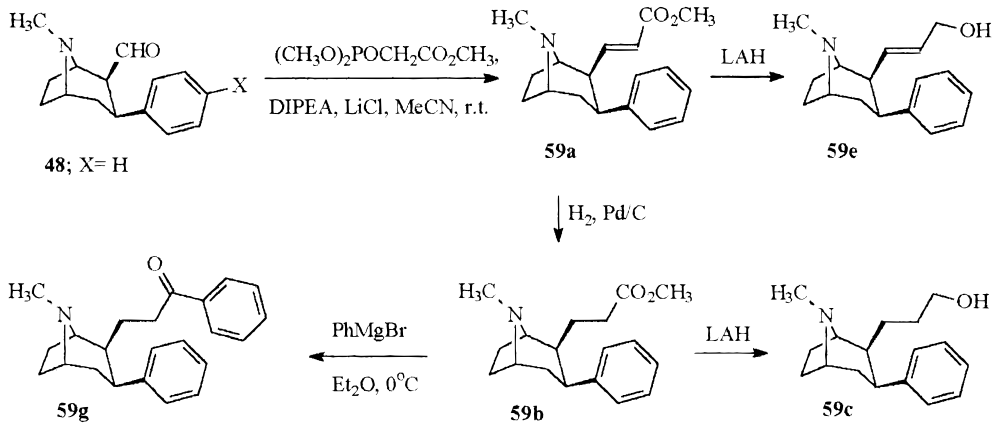
The binding potencies of 2β-alkyl esters are presented in Table 11. These compounds retained strong affinities for the DAT. The high affinity of the saturated analogue **59f** suggested that the flexible nature of the side chain allowed the ligand to better conform to the structural constraints imposed by this region of the cocaine binding site. However, this trend was not obvious in other saturated analogues and the unsaturated analogues were either equipotent or slightly more potent (e.g., **59a** vs **59b** and **59c** vs **59d**).

From this study it was proposed that a large lipophilic pocket was present at the binding site, which was capable of accommodating large substituents at the C2 position of the ligand.[172] Another finding from this study was that while electrostatic or hydrogen-bonding interactions may be significant at the α-carbon atom of some 2β-substituents,[152] they appeared to be of lesser importance when electron-rich groups were removed from the proximity of the tropane nucleus.

7. 2-Alkyl Ether-3-phenyltropanes

Several lines of evidence suggest that the inhibition of serotonin reuptake modulates the reinforcing properties of cocaine.[176−180] Furthermore, cocaine inhibits 5-HT reuptake with greater potency compared to DA reuptake (see Table 2)[181] and influences 5-HT neurotransmission. Thus, the goal of designing these compounds was to improve upon their binding

Scheme 16



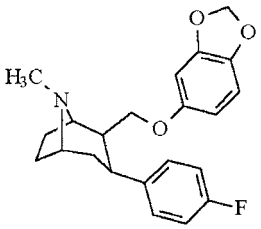


Figure 13. Structures of 2-alkyl ester-3-phenyltropanes.

potencies at the 5-HTT. The choice of a 3,4-(methylenedioxy)phenoxymethyl substituent at C2 position was based upon a 5-HT reuptake inhibitor, paroxetine, (3*S*,4*R*)-4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine, Figure 1.[182] Six of the eight possible isomers were synthesized containing a 3,4-(methylenedioxy)phenoxymethyl at C2 and a 4-fluorophenyl group at C3. The latter functionalities were also present in paroxetine in equivalent positions. The structures of these compounds are shown in Figure 13.

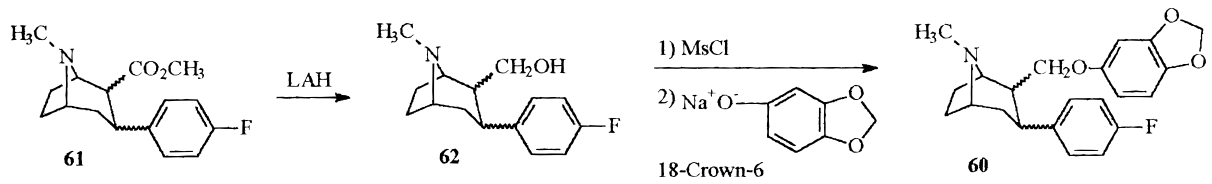
The synthesis of tropane analogues **60a**−**f** involved LAH reduction of the appropriate 3-(4-fluorophenyl)-tropane-2-carboxylic methyl ester isomer **61** to give 2-(hydroxymethyl)tropane **62**. The latter compound (i.e., **62**) was mesylated and treated with sesamol in the presence of a phase-transfer catalyst to give 3-(4-fluorophenyl)-2-[[3, 4-methylenedioxy)phenoxy]methyl]tropane **60** as illustrated in Scheme 17.[183]

The three *R*-configuration possessing 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl esters *R*-**61** were synthesized from anhydroecgonine (*R*-**1**) as shown in Scheme 18. Addition of (*p*-fluorophenyl)-magnesium bromide gave a mixture of (*R*)-2*β*,3*β*-**61a** and (*R*)-2α,3*β*-**61b**.[126] However, the latter isomer, i.e., (*R*)-2α,3*β*-**61b**, could also be prepared by simple isomerization of (*R*)-2*β*,3*β*-**61a** with sodium methoxide in methanol. The (*R*)-2*β*,3α-**61c** isomer was prepared by *cis*-addition of (*p*-fluorophenyl)lithium to the α,*β*-unsaturated 1′,2′,4′-oxadiazole **63** to give **64**, which upon reduction over nickel boride afforded the required isomer.[139] It should be emphasized here that modifications in the reductive opening of the oxadiazole ring to 2*β*-methyl ester resulted in isomerization of the 2α-group to the 2*β*-isomer, Scheme 18.

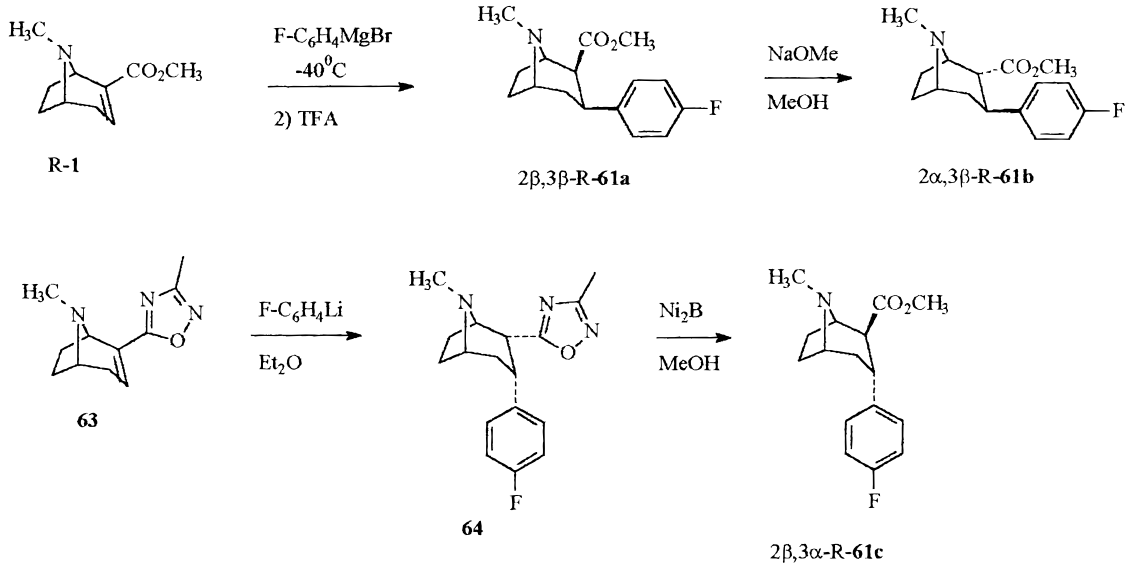
Three of the *S*-isomers of 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl esters were prepared by routes shown in Scheme 19.[183] A triflate **65** was first prepared from (*S*)-2-carbomethoxy-3-tropinone (*S*-**4**), which upon reaction with (4-fluorophenyl)-boronic acid in refluxing diethoxymethane using $Pd_2(dba)_3$ as a catalyst, followed by chromatographic purification, gave the (4-fluorophenyl)tropene (**66**).[140] Reduction of **66** with samarium iodide at −78 °C using methanol as the proton source, followed by quenching with TFA at 0 °C, gave a mixture of (*S*)-2*β*,3α-**61f** as the major product and (*S*)-2*β*,3*β*-**61d** as a minor product, which were separated. The latter compound upon base-catalyzed isomerization gave (*S*)-2α,3*β*-**61e** isomer. The (*S*)-2*β*,3*β*-**61d** could also be prepared from *S*-**1** by Grignard reaction with 4-fluorophenylmagnesium bromide. The *S*-**1** on the other hand was prepared from the same triflate **65** by treatment with TEA, formic acid, triphenylphosphine, and palladium catalyst as shown in Scheme 19.

Extensive NMR studies were conducted to determine the structures of the above isomers. In general,

Scheme 17



Scheme 18



Scheme 19

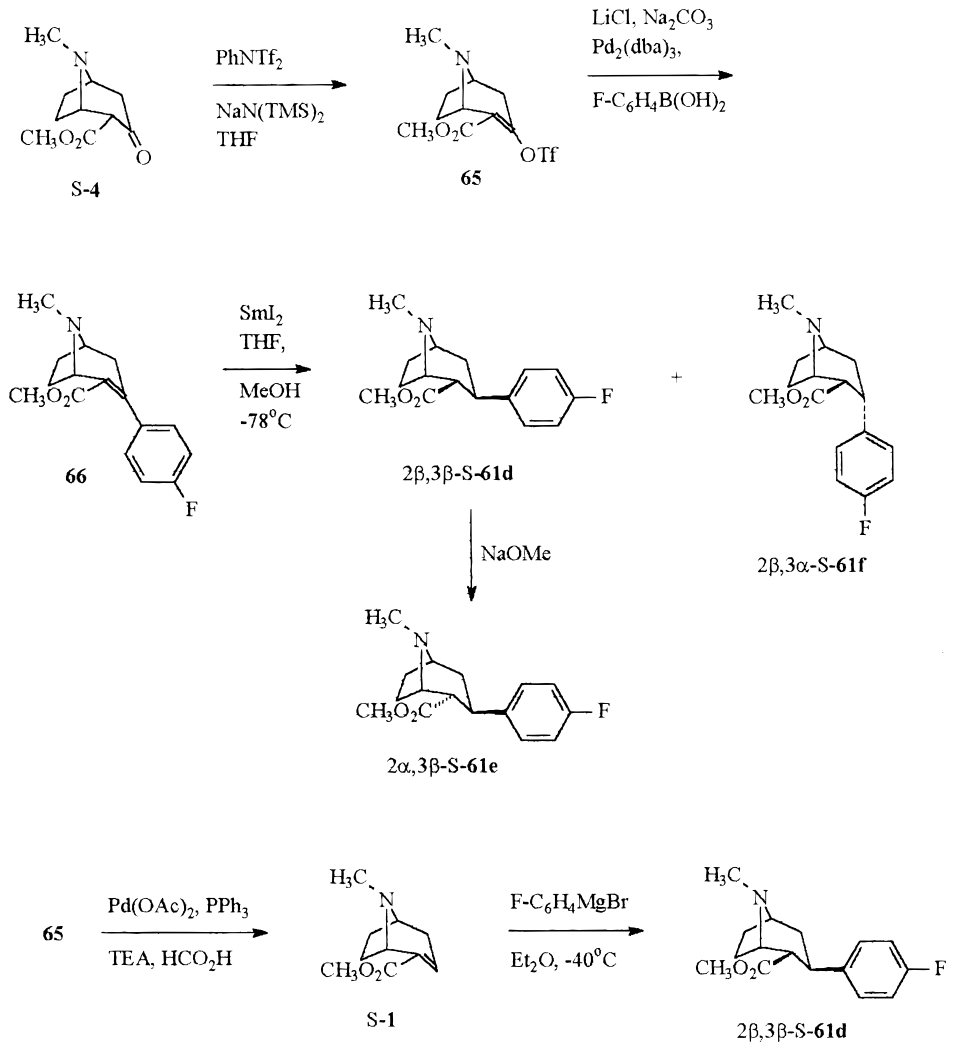


Table 12. Binding Potencies of 2-Alkyl Ether Phenyltropanes

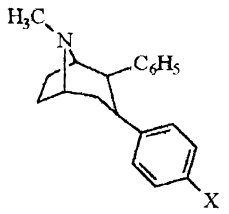
	IC_{50} (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
paroxetine	623 ± 25	0.28 ± 0.02	535 ± 15	0.0004	0.8
R-**60a**	308 ± 20	294 ± 18	5300 ± 450	0.9	17.2
R-**60b**	172 ± 8.8	52.9 ± 3.6	26600 ± 1200	0.3	155
R-**60c**	3.01 ± 0.2	42.2 ± 16	123 ± 9.5	14.1	40.9
S-**60d**	1050 ± 45	88.1 ± 2.8	27600 ± 1100	0.08	26.3
S-**60e**	1500 ± 74	447 ± 47	2916 ± 1950	0.3	1.9
S-**60f**	298 ± 17	178 ± 13	12400 ± 720	0.6	41.6

the coupling constants were measured for H2, H3, and H4 protons. These protons were, in turn, characterized by COSY, NOESY, and HQMC experiments. The *axial*−*axial* couplings were larger (10−12 Hz) than the *axial*−*equatorial* or *equatorial*−*equatorial* coupling constants.

The binding affinity data of 2-alkyl ether phenyltropanes are presented in Table 12. The potencies of these compounds depended upon their relative configurations of the C2/C3 substituents and the tropane ring. In *R*-configuration, 2β,3α-isomer, *R*-**60c** was the most potent compound both at the DAT and the 5-HTT. It was also the most selective isomer at the DAT. The 2α,3β-isomer *R*-**60b** was more selective at the 5-HTT. In the *S*-series, compounds were generally more potent at 5-HTT than DAT. The most selective and potent compound at 5-HTT was *S*-**60d** (2β,3β). It is also interesting to note that isomers with *R*-configuration were more potent at both DAT as well as 5-HTT than their *S*-counterparts.[183]

8. 2-Phenyl-3-phenyltropanes

Recently, 2-phenyl-3-phenyltropanes were synthesized to further evaluate the structural requirements for a high-affinity ligand for the cocaine binding site at the DAT.[184,185,103] The structures of these compounds are shown in Figure 14. Two synthetic strategies were adopted to prepare these compounds. The synthesis of **67a,c** and **69a,c** is delineated in Scheme 20. The target compounds were synthesized



67a; 2β,3β; X= H
67b; 2β,3α;X= H
67c; 2α,3α; X= H

68; 2β,3α; X= F

69a; 2β,3β; X= CH_3
69b; 2β,3α; X= CH_3
69c; 2α,3α; X= CH_3

Figure 14. Structures of 2-phenyl-3-phenyltropanes.

from intermediate (±)-**70**, which in turn was prepared in five steps from 3-tropinone.[186] Thus, treatment of (±)-**70** with phenylmagnesium bromide produced *t*-alcohol ((−)-**71**), which was dehydrated to produce tropene (±)-**72**. Hydrogenation of the latter compound over Pd/C followed by separation and reduction with LAH gave 2*β*,3*β*-diphenyl (±)-**67a, 69a** and 2α,3α-diphenyl (±)-**67c, 69c** isomers, which were resolved.[184,185] Compounds **67a,b** and **69a,b** were also prepared using a 1,3-dipolar cycloaddition reaction to oxidopyridinium betaine as depicted in Scheme 15.[103]

The binding potencies and monoamine transport inhibition values are presented in Table 13. It is apparent that 2α,3α-diphenyl isomers **67c, 69c** were significantly less potent at both the DAT and 5-HTT. The 2*β*,3*β*- and 2*β*,3α-isomers were more potent than their parent 2*β*-methyl esters **11a** and **11f** (K_i = 89.5 and 5.76 nM for displacement of [^{3}H]mazindol, respectively, Table 10). As observed earlier, 4′-methylphenyltropane analogues were more potent. The interesting finding from this series of compounds was that the 2*β*,3α-isomer (boat conformer) was more selective in inhibiting DA uptake compared to its 2*β*,3*β*-isomer (cf. **67a** vs **67b** and **69a** vs **69b**).[103]

9. 2*β*-Transition Metal Chelated 3*β*-Phenyltropanes

As discussed above, phenyltropanes exhibited much greater affinity and selectivity for the DAT (**11a**−**f**; Table 3) than cocaine. Some of these compounds have been radiolabeled and are useful as positron emission tomography (PET) and single-photon emission-computed tomography (SPECT) imaging agents.[187,188] Following SAR data on the 2*β*-substituted-3-phenyltropanes that a large substituent including a lipophilic group can be readily accommodated, Meegalla et al. prepared technetium-99m ($t_{1/2}$ = 6 h, 140 keV) chelated ligand TRODAT-1 (**73**; [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]methyl]-(2-mercaptoethyl)amino]ethyl]amino]ethanethiolato-(3−)-N2, N2′, S2, S2′]oxo-[1*R*-(*exo*, *exo*)]-[99mTc]technetium; Figure 15).[189]

TRODAT-1 (**73**) was prepared by ligand-exchange reaction between free ligand and Tc−glucoheptanoate at acidic pH. Ligand **73** existed as a diastereomer with diasterotopy at the quaternary nitrogen chiral center of the bisaminodithiol skeleton. The diastereomers of TRODAT-1 (**73**) were separated on a chiral HPLC.[190] The low polarity isomer was assigned the *R* configuration, while the other the *S* configuration

Scheme 20

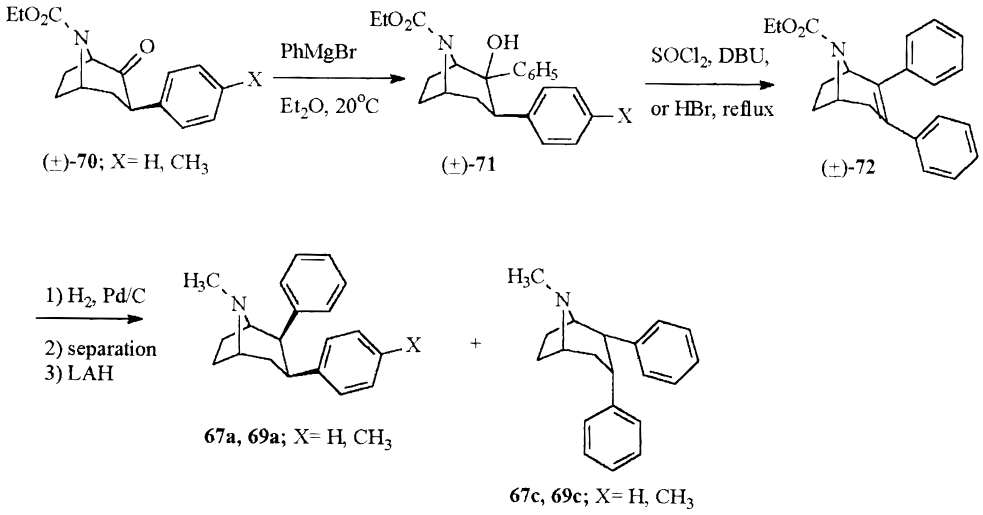
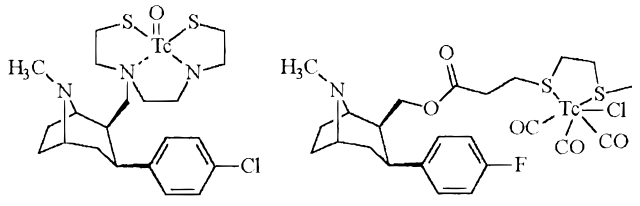


Table 13. Binding Affinities and Inhibition of DA and 5-HT Uptake by 2-Phenyl-3-phenyltropanes

	DAT		5-HTT	[^{3}H]DA[b] uptake	[^{3}H]5-HT[b] uptake	selectivity [^{3}H]5-HT/
compound no.	IC_{50} (nM) [^{3}H]WIN 35428[a]	K_i (nM) [^{3}H]mazindol[b]	IC_{50} (nM) [^{3}H]paroxetine[a]	K_i (nM)	K_i (nM)	[^{3}H]DA
cocaine	89 ± 4.8	281	1050 ± 89	423	155	0.4
67a	12.6 ± 1.8	14.9	21000 ± 3320	28.9	1100	38.1
67b		13.8		11.7	753	64.3
67c	690 ± 37		41300 ± 5300			
68		6.00		4.58	122	26.6
69a	1.96 ± 0.08	2.58	11000 ± 83	2.87	73.8	25.7
69b		2.87		4.16	287	69.0
69c	429 ± 59		15800 ± 3740			

[a] Data from ref 185. [b] Data from ref 103.



73; TRODAT-1 **74**; TROTEC-1

Figure 15. 2β-Transition metal chelated 3β-phenyltropanes.

at the quaternary nitrogen center. The K_i values of the *R*- and *S*-isomers of rhenium (Re) complexed ligand (instead of Tc) were 13.9 and 8.42 nM, respectively, for the displacement of [^{125}I]IPT.

Recently, Hoepping et al.[191] developed a tricarbonyltechnitium complexed ligand, TROTEC-1 (**74**; Figure 15). The binding affinity (IC_{50}) of the ligand Re−TROTEC-1 (Re in place of Tc) for displacement of [^{3}H]WIN 35428 was 0.15 ± 0.04 and 20.3 ± 16.1 nM for high- and low-affinity binding sites (cf. IC_{50} 2.62 ± 1.06 and 139 ± 72 nM for WIN 35428). The higher binding affinity of TROTEC-1 (**74**) was attributed to a combination of hydrogen bonding and lipophilic interaction exerted by the sulfur atoms of the dithioether.

The results of C2 substituents have demonstrated that a wide variety of groups can be accommodated at C2 position. Srivastava and Crippen[192] performed an analysis of the cocaine binding site by three-dimensional Voronoi site modeling. It was proposed that the cocaine binding site comprised of four regions, r_{1-4}. The 2β-carbomethoxy group, 3β-benzoate/phenyl, tropane ring, and *N*-methyl group positioned in the r_1, r_2, r_3, and r_4 regions of this model, respectively. With a limited number of compounds in the training set, these researchers found that the phenyl substituent at the 3-position of the tropane ring of cocaine was the most significant functionality for activity while moderate contributions resulted from the hydrogen interactions of the tropane ring with the binding regions. These researchers also postulated that the C2 substituent does not impart significant activity to cocaine analogues. However, above studies have shown that C2 substituents do impart significant activity. To explain the differences in the binding potencies of cocaine, WIN 35065-2 (**11a**), and vinyl analogue (**43a**), Yang et al.[193] invoked the solvation effects. Thus, cocaine containing two 2β,3β-ester groups was calculated to be more solvated than the WIN compounds. The calculations also predicted higher pK_as of the tropane nitrogen in the WIN compounds than in cocaine. The pK_as of cocaine, WIN 35065-2, and **43a** are 8.65, 9.55, and 11.95, respectively. Thus, decreased conformational flexibility, decreased aqueous solvation, and increased pK_as of the WIN compounds were correlated to their increased binding affinity at the cocaine binding site.

In the case of vinyl analogue (**43a**), however, it has been argued that the difference in [^{3}H]DA uptake values for **43a** and **11c** should be larger than 4-fold (Table 10) if only a solvation effect was the contributing factor in inhibition studies. Therefore, other factors may be playing a significant role in the binding affinities of these compounds. For example, Carroll et al. found that in the absence of a strong H-bond acceptor/donor substituent at C2, electrostatic interactions dominated in C2β-heterocyclic analogues.[155] Searle and William[194,195] have proposed that the total free energy for association of a ligand to its binding site via a hydrogen bond is partitioned among four separate energy terms. Thus, in the case of *Z*-vinyl chloride analogue (**43c**), the vinyl chloride function would contribute to binding through hydrophobic component of the hydrogen bonding. However, the above suggestion has been argued since the compounds **41b**, **43f**, **43g**, and **43h**, which lack a functional group able to act as a H-bond donor and/or acceptor, still retained high potency.[159]

In conclusion, a 2β-substituent is required for high potency at the DAT. The SAR data showed that a wide range of substituents can be accommodated at the C2 position. While the β-orientation of the C2 group is required, C2 substituents are capable of interacting with the cocaine binding site via a hydrogen bond, electrostatic, hydrophobic, or some other process depending on the nature of the C2 pharmacophore.

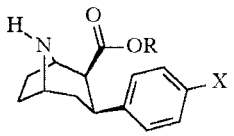
C. *N*-Modified Phenyltropanes

Developing selective ligands for one of the three transporters, DAT, 5-HTT, NET, to which cocaine is known to interact, is important for delineating these receptors as well as drug development. For example, 5-HT agonists lacking dopaminergic activity have been found not to produce reward or euphoria. However, some evidence has suggested that inhibition of 5-HT reuptake modulates the reinforcing properties of cocaine.[176−180,196] If 5-HT synapses on the cell body of DA neurons regulate reward threshold levels, then cocaine inhibition of 5-HT reuptake could enhance or reduce cocaine-induced effects in the dopaminergic system. Even though the importance of the 5-HTT in mediating the neurochemical and behavioral actions of cocaine is now recognized, the biochemical mechanism of action and regulation of this transporter is not well understood. This has led to the design and synthesis of cocaine analogues which would bind selectively to the 5-HTT site. One of the strategies to obtain 5-HTT-selective cocaine analogues is by *N*-demethylation.[197,198] The following sections discuss the synthesis and biological evaluation of N8-nor, N8-substituted, 8-oxa, and 8-carba analogues of phenyltropanes.

1. N-Nor-2β-ester-3β-phenyltropanes

The most important feature of these compounds is that the N8 methyl group of the tropane ring is replaced with a hydrogen atom. In addition, the 2β-ester function is either a methyl or an isopropyl ester and the 3β-phenyl ring is also substituted with a variety of functional groups at the 4′-position.

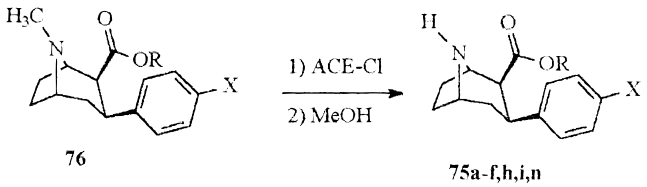
The design of *N*-norphenyltropanes was important for two reasons: (1) *N*-norphenyltropanes can be considered as metabolites of their *N*-methyl phenyltropane precursors because norcocaine is an *N*-demethylated metabolite of cocaine, and (2) *N*-nor-



75a; R= CH_3; X= H
75b; R= CH_3; X= F
75c; R= CH_3; X= Cl
75d; R= CH_3; X= I
75e; R= $CH(CH_3)_2$; X= I
75f; R= CH_3; X= C_2H_5
75g; R= CH_3; X= *n*-C_3H_7
75h; R= CH_3; X= $CH(CH_3)_2$
75i; R= CH_3; X= $CH{=}CH_2$
75j; R= CH_3; X= $C(=CH_2)-CH_3$
75k; R= CH_3; X= trans-$CH{=}CHCH_3$
75l; R= CH_3; X= cis-$CH{=}CHCH_3$
75m; R= CH_3; X= $CH_2CH{=}CH_2$
75n; R= CH_3; X= $C{\equiv}CH$
75o; R= CH_3; X= $C{\equiv}CCH_3$
75p; R= CH_3; X= 3, 4-Cl_2

Figure 16. Structures of *N*-nor-2β-ester-3β-phenyltropanes.

Scheme 21



76 75a-f,h,i,n

R= CH_3, $CH(CH_3)_2$
X= H, F, Cl, I, C_2H_5, $CH(CH_3)_2$, $CH{=}CH_2$, $C{\equiv}CH$

phenyltropanes were expected to possess improved potencies for the 5-HTT similar to norcocaine.[72] The structures of these norphenyltropanes are depicted in Figure 16.

Two methods have been employed to obtain *N*-nor analogues of phenyltropanes. The compounds **75a**−**f,h,i,n** (Figure 16) were prepared by treating the corresponding 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid ester analogue (**76**) with α-chloroethyl chloroformate (ACE-Cl) to give the α-chloro ethyl urethane intermediate, which was converted to the *N*-nor analogue by solvolysis in methanol (Scheme 21).[199]

The above method of *N*-demethylation failed to afford 3β-(4′-isopropenyl)tropane-2β-carboxylic acid methyl ester (**75j**) and resulted in the loss of the isopropenyl moiety. Therefore, 2,2,2-trichloroethyl carbamate (Troc) protected intermediate *N*-(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-iodophenyl)nortropane-2β-carboxylic acid methyl ester (**77**) was used to obtain **75g,j,k,m,o**. Thus, reaction of 4′-iodophenyltropane (**11e**) with *N*-2,2,2-trichloroethyl chloroformate (Troc-Cl) in refluxing DCM gave **77** in 96% yield. The isopropenyl analogue was then synthesized by reaction of **77** with isopropenyl zinc chloride and bis(triphenylphosphine)palladium(II) chloride. The *N*-Troc group was also compatible with the Castro−Stevens coupling reaction to form **78b**. Removal of the *N*-Troc group was effected by using either 2 N acetic acid or 10% lead oxide/cadmiun[200] in THF/ammonium acetate providing 3β-(4′-substituted phenyl)nortropane-2β-carboxylic acid methyl ester analogues **75j** and **75o**. Reduction of **75o** using either Pd/C or Lindlar's catalyst afforded **75g** or **75l**, respectively. Isomerization of the allyl group in **78c** using $RhCl_3$ in refluxing ethanol followed by removal of the Troc group afforded **75k**. Reaction of 3β-(4′-allylphenyl)tropane-2β-carboxylic acid methyl ester (**11x**) with Troc-Cl in refluxing DCM afforded **78c** in 72% yield. The *N*-Troc group was then removed with 10% lead oxide/cadmium producing **75m** as described in Scheme 22.[133]

The IC_{50} values of *N*-norphenyltropanes are shown in Table 14. Norcocaine possessed nearly equal potency at the 5-HTT and NET.[72,133] However, it was

Scheme 22

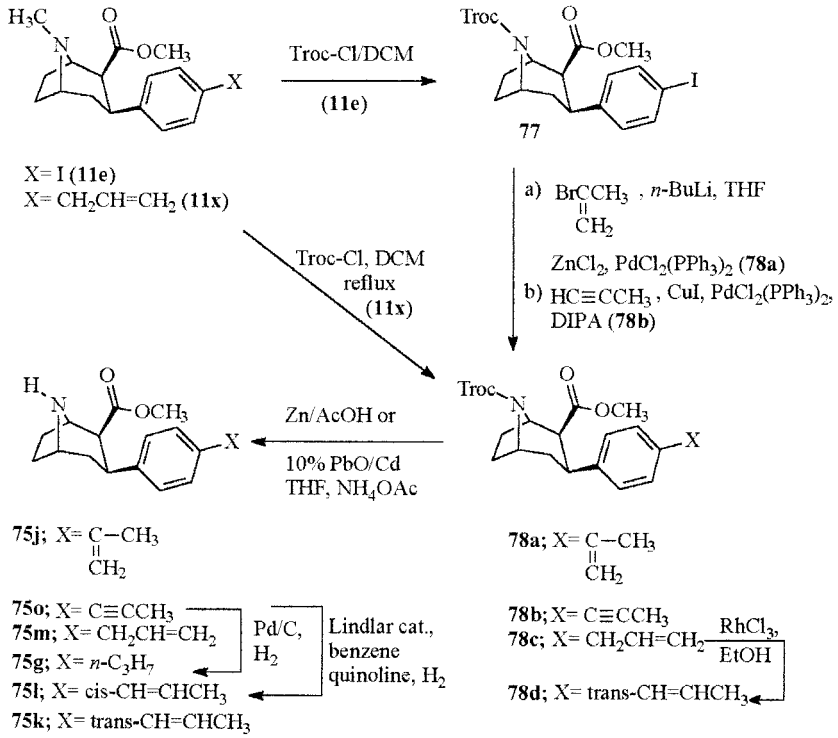


Table 14. Binding Affinities of the *N*-Norphenyltropane Analogues

	IC_{50} (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
norcocaine	206 ± 29	127 ± 13	139 ± 9	0.6	0.7
75a	30.8 ± 2.3	156 ± 8	84.5 ± 7.5	5.1	2.7
75b	4.39 ± 0.20	68.6 ± 2.0	18.8 ± 0.7	15.6	4.3
75c	0.62 ± 0.09	4.13 ± 0.62	5.45 ± 0.21	6.7	8.8
75d	0.69 ± 0.2	0.36 ± 0.05	7.54 ± 3.19	0.5	10.9
75e	1.06 ± 0.12	3.59 ± 0.27	132 ± 5	3.4	124
75f	49.9 ± 7.3	8.13 ± 0.30	122 ± 12	0.2	2.4
75g	212 ± 17	26 ± 1.3	532 ± 8.1	0.1	2.5
75h	310 ± 21	15.1 ± 0.97		0.05	
75i	1.73 ± 0.05	2.25 ± 0.17	14.9 ± 1.18	1.3	8.6
75j	23 ± 0.9	0.6 ± 0.06	144 ± 12	0.03	6.3
75k	28.6 ± 3.1	1.3 ± 0.1	54 ± 16	0.04	1.9
75l	31.6 ± 2.2	1.15 ± 0.1	147 ± 4.3	0.04	4.6
75m	56.5 ± 56	6.2 ± 0.3	89.7 ± 9.6	0.1	1.6
75n	1.24 ± 0.11	1.59 ± 0.2	21.8 ± 1.0	1.3	17.6
75o	6.11 ± 0.67	3.16 ± 0.33	116 ± 5.1	0.5	19.0
75p[a]	0.66 ± 0.24	1.4		2.1	

[a] These values were determined in Cynomolgus monkey caudate-putamen. The radioligand used for 5-HTT was [^{3}H]Citalopram.

Table 15. Binding Affinities of 2β-Propanoyl-*N*-norphenyltropanes

	IC_{50} (nM)	K_i (nM)		selectivity	
compound no.	DAT [^{125}I]RTT-55	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
79a	0.07 ± 0.01	0.22 ± 0.16	2.0 ± 0.09	3.1	28.6
79b	4.7 ± 0.58	19 ± 1.4	5.5 ± 2.0	4.0	1.2
79c	380 ± 110	5.3 ± 1.0	3400 ± 270	0.01	8.9
79d	190 ± 17	150 ± 50	5100 ± 220	0.8	26.8
79e	490 ± 120	85 ± 16	4300 ± 1100	0.1	8.8
79f	1.5 ± 1.1	0.32 ± 0.06	10.9 ± 1.5	0.2	7.3
79g	16 ± 4.9	0.11 ± 0.02	94 ± 18	0.07	5.9

much less potent at the DAT compared to cocaine (Table 14). As seen with norcocaine, *N*-norphenyltropane analogues exhibited improved potencies for the 5-HTT.

The synthesis of 4′-alkyl-, 4′-alkenyl-, and 4′-alkynyl-substituted analogues was inspired by the observation that 3β-4′-ethylphenyltropane (**75f**) possessed relatively enhanced potency at the serotonin transporter.[201] As seen in Table 14, compounds containing extended sp^2 functionality were more potent at the 5-HTT (e.g., **75j,l**) with 5-HTT/DAT ratios of 0.03−0.04 nM.[133] The 3β-3′,4′-dichlorophenyl nortropane analogue was nearly twice as potent at the DAT compared to 5-HTT.[127]

2. N-Nor-2β-propanoyl-3β-phenyltropanes

The *N*-desmethyl-2-propanoyltropane analogues were synthesized to enhance their selectivity for the 5-HTT. Furthermore, the choice of the unsaturated functional groups (sp^2 hybridization) was based on the observation that 3β-2-naphthyl (**79a**) was very potent at the monoamine transporters. The structures of 2β-propanoyl-3β-phenyltropanes are presented in Figure 17.[157] The synthesis of these analogues proceeded from the common 2-propanoyl-8-azabicyclo[3.2.1]oct-2-ene (**80**).

The synthesis of *N*-methylated **80** has been described above (Scheme 12). Two approaches were pursued to obtain *N*-demethylated analogues (**79a**−**g**). First, the more common approach of *N*-demethylation of *N*-methylated analogues of **79a**−**g** was tried, which either did not work or resulted in epimerization at C2 in addition to demethylation. The second approach involved copper-catalyzed 1,4-addition of Grignard reagent directly to the *N*-demethylated derivative **80**. Excess of Grignard reagent was used due to an abstractable proton (N−H). Quenching of the 1,4-adduct at low temperature led to good control over the stereochemistry, and 2β,3β-derivatives were obtained in 40−60% yield as shown in Scheme 23.[157]

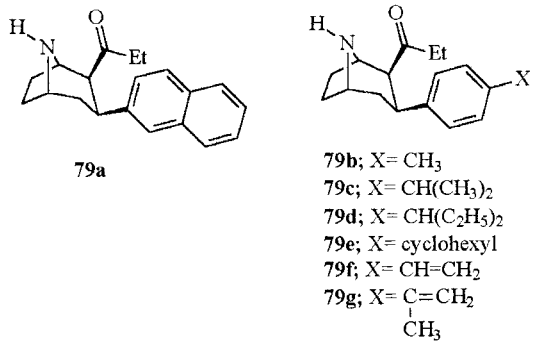
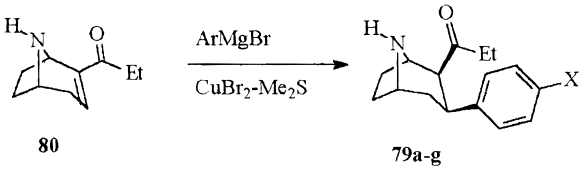


Figure 17. 2β-Propanoyl-*N*-norphenyltropanes.

As presented in Table 15, *N*-demethylation of 2β-acyl-3β-phenyltropanes caused an increase in selectivity for 5-HTT (cf., Table 9) similar to norphenyltropanes.[201] The most potent and selective compound in this series was 4′-isopropenylphenyltropane (**79g**) with 145 times more potency at the 5-HTT vs DAT

Scheme 23



and 854 times more potency at the 5-HTT vs NET (Table 15).[157]

3. N-Nor-2-[3,4-(methylenedioxy)phenoxymethyl]-3-phenyltropanes

These compounds were modeled after paroxetine (Figure 1) and share some structural features, e.g., substituents at C2 and C3 and piperidine ring. The major difference between paroxetine and these compounds is the presence of an ethylene bridge in nortropane analogues, which leads to reduced conformational heterogeneity. For example, the piperidine ring in paroxetine (3*R*,4*S*) can interconvert between the chair conformations; the piperidine ring in analogous nortropane analogues can only interconvert between the chair and boat conformations but not between two chair conformations. The structures and conformations of these compounds are illustrated in Figure 18.[183]

The 2-phenoxymethyl nortropane analogues **81a**−**f** (Figure 18) were synthesized by treating their *N*-methylated precursors **60a**−**f** (Figure 13) with either ACE-Cl/MeOH or Troc-Cl/Zn−AcOH as illustrated in Schemes 21 and 22.[183]

Among 2-phenoxymethyl nortropane (**81a**−**f**) analogues, the most potent isomer was *R*-**81c** (2β,3α) suggesting that its conformation best mimicked the conformation of paroxetine, which was recognized by the 5-HT receptor (Table 16). Furthermore, since the preferred conformation of the piperidine ring of *R*-**81c** was a substantially flattened boat (Figure 18), it appeared that a relatively flat conformation may be required for binding at the 5-HTT. Such a conformation could resemble both the *R*- and *S*-isomers of **81c**, and indeed, the potency of *R*-**81c** was only 3.4 times greater than that of the *S*-isomer. The more than 1 order of magnitude lower potency of *R*-**81c** (IC_{50} = 5.60 nM) relative to paroxetine (IC_{50} = 0.28 nM) could be due to steric inhibition of binding by the ethylene bridge in *R*-**81c**. It is also important to note that while *N*-demethylation has led to increased potency for 5-HT, DA, and NE transporters (e.g., *N*-Nor analogue of WIN 35428),[201] *N*-demethylation in 2-phenoxymethyltropane analogues led to increased potency at 5HTT only for those isomers, which preferentially existed in the boat conformation; the effect on potency at the DAT and NET appeared to be random.[183]

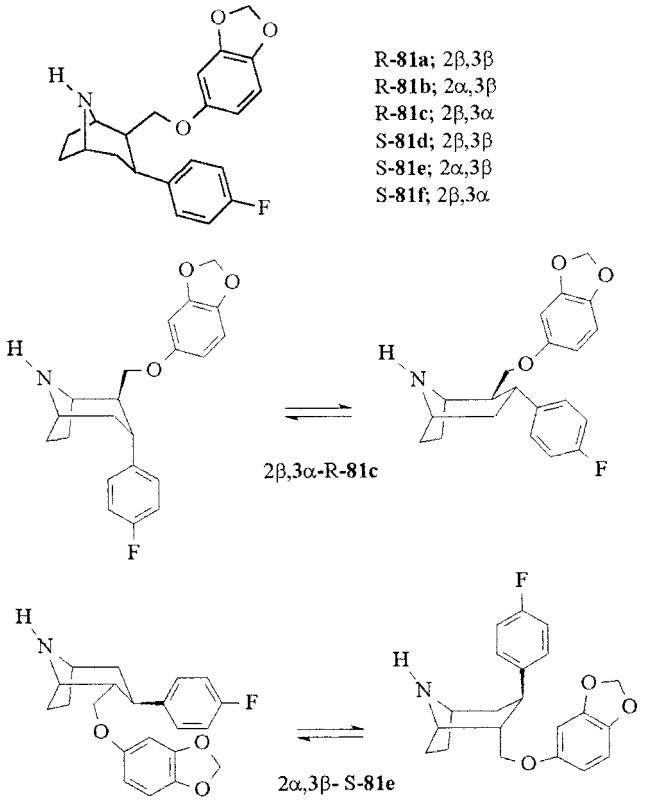


Figure 18. Structures and conformations of 2-[[3,4-(methylenedioxy)phenoxy]methyl]norphenyltropanes.

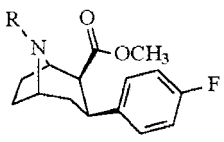
4. N-Alkyl-3β-phenyltropanes

It has been reported above that modifications at the C2-position lead to significant changes in the potency/selectivity of such analogues, e.g., 2-propanoyl- and 2-(3,4-(methylenedioxy)phenoxy)methylphenyltropanes.[156,183] It has also been demonstrated that the nature of the substituent on the aromatic ring directly attached at the 3β-position strongly affects the dopamine transporter−ligand recognition interaction. Furthermore, *N*-demethylation improved selectivity for the 5-HTT.

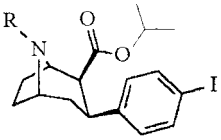
Further studies on the structure−activity relationship led to the exploration of the influence of different substituents on N8 of phenyltropanes. As seen in Figure 19, a large number of functionalities have been introduced in WIN 35428 and RTI-55 (**11b** and **11e**, Figure 3), because these have already been

Table 16. Binding Potencies of 2-(3,4-(Methylenedioxy)phenoxy)methylnorphenyltropanes

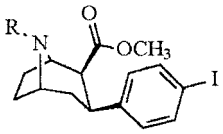
	IC_{50} (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
paroxetine	623 ± 25	0.28 ± 0.02	535 ± 15	0.0004	0.8
R-**81a**	835 ± 90	480 ± 21	37400 ± 1400	0.6	44.8
R-**81b**	142 ± 13	90 ± 3.4	2500 ± 250	0.6	17.6
R-**81c**	3.86 ± 0.2	5.62 ± 0.2	14.4 ± 1.3	1.4	3.7
S-**81d**	1210 ± 33	424 ± 15	17300 ± 1800	0.3	14.3
S-**81e**	27.6 ± 2.4	55.8 ± 5.73	1690 ± 150	2.0	61.2
S-**81f**	407 ± 33	19 ± 1.8	1990 ± 176	0.05	4.9



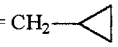
82a; R= $CH_2CH=CH_2$
82b; R= $CH_2CH_2CH_3$
82c; R= $CH_2C_6H_5$
82d; R= $(CH_2)_3C_6H_5$
82e; R= $(CH_2)_5C_6H_5$



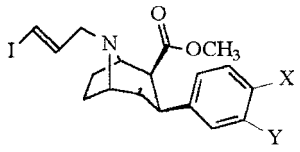
83a; R= $CH_2CH_2CH_2F$
83b; R= CH_2CH_2F



84a; R= $CH_2CH_2CH_2F$
84b; R= CH_2CH_2F
84c; R= CH_2CHF_2
84d; R= $CH_2CH_2CH_2Cl$
84e; R= $CH_2CH_2CH_2Br$
84f; R= $CH_2CH_2CH_2I$

84g; R= CH_2— 

84h; R= $CH_2CH_2CH_2OH$
84i; R= $CH_2CH_2(OCH_3)_2$
84j; R= $CH_2CO_2CH_3$
84k; R= $CH_2CON(CH_3)_2$
84l; R= $CH_2CH_2CH_2OMs$
84m; R= $COCH(CH_3)_2$
84n; R= $(CH_2)_2Pht$
84o; R= $(CH_2)_3Pht$
84p; R= $(CH_2)_4Pht$
84q; R= $(CH_2)_5Pht$
84r; R= $(CH_2)_8Pht$
84s; R= $CH_2CH=CH-CH_3$
84t; R= $CH_2C(Br)=CH_2$
84u; R= $CH_2CH=CH_2I(E)$
84v; R= $CH_2C\equiv CH$
84w; R= $CH_2C_6H_5$
84x; R= $CH_2C_6H_4$-2-CH_3



85a; X= Y= H
85b; X= Y= Cl
85c; X= CH_3, Y= H
85d; X= $CH(CH_3)_2$, Y= H
85e; X= n-C_3H_7, Y= H

Figure 19. Structures of *N*-alkyl analogues of phenyltropanes.

shown to be potent analogues for the DAT.[202−205] Therefore, the aim of synthesizing these *N*-substituted phenyltropanes was to obtain compounds with improved potency and selectivity at the DAT.

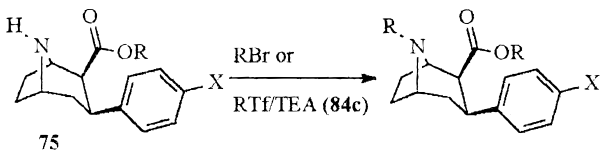
The main strategy to obtain *N*-substituted phenyltropanes was to first synthesize appropriately functionalized 3β-phenylnortropane (**75**). Next, the reaction of nortropane with an alkyl bromide or alkyl triflate resulted in *N*-substituted phenyltropane, Scheme 24. As described above in Schemes 21 and 22, both the reagents, ACE-Cl and Troc-Cl, were employed for *N*-demethylation.

Compound **84h** was used as the starting material for the preparation of **84d−f,l**. Treatment of **84l** with methane sulfonyl chloride in the presence of 2,6-lutidine for 48 h gave *N*-(chloropropyl)nor-β-CIT (**84d**). Chloride generated from the reaction of mesyl chloride was sufficient to chlorinate the mesyl intermediate. Therefore, mesylate (**84l**) was prepared by treatment of the alcohol **84h** with methane sulfonic anhydride. The *N*-bromopropyl analogue (**84e**) was prepared from **84h** by treatment with Br_2/PPh_3 at 0−5 °C. Displacement of the mesyl group of **84l** with iodine gave the corresponding *N*-(iodopropyl)nor-β-CIT (**84f**), Scheme 25.[203]

N-(3-Iodoprop-(2*E*)-enyl)nortropane derivatives **84u** and **85a−e** were obtained by iododestannylation of *N*-(3-tributyltinprop-(2*E*)-enyl)nortropane intermediate (**88**) by treatment with iodine in chloroform (Scheme 26).[204,205] The intermediate **88** was prepared from their respective *N*-nortropane derivative **86** by reacting with 3-(tributylstannyl)prop-(2*E*)-enyl chloride (**87**). The alkylation agent **87** was prepared by chlorination of pure 3-(tri-*n*-butyl stannyl)prop-(2*E*)-en-1-ol with triphenylphosphine and carbon tetrachloride.[206] The pure (*E*)-stannyl alcohol was obtained by hydrostannylation of propargyl alcohol.[207] The tributyltin precursors (**88a−f**) could also be prepared from *N*-prop-2-ynylnortropane derivatives by adding Lipshutz reagent ($Bu_3SnCuBuCNLi_2$) at −78 °C.[208] However, this method gave poor yields and a mixture of *E*/*Z* isomers.

The IC_{50} values of the *N*-alkylphenyltropanes are shown in Table 17. *N*-Allyl, *N*-propyl, and *N*-benzyl nor β-CFT (**82a,b,c**) were less potent than β-CFT (**11b**).[125] However, *N*-phenylpropyl (**82d**) and *N*-phenylpentyl (**82e**) were significantly more potent than β-CFT, which indicated that the sterically bulky groups in this part of the molecule could be tolerated at the DAT sites.[209] This encouraged the evaluation of several *N*-substituted phenyltropane derivatives. Most of these modifications were carried out in β-CIT (**11e**) molecule and tested for all three transporters (DA, 5-HT, NE). As shown in Table 17, the *N*-fluo-

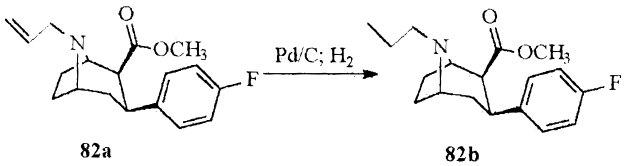
Scheme 24



75

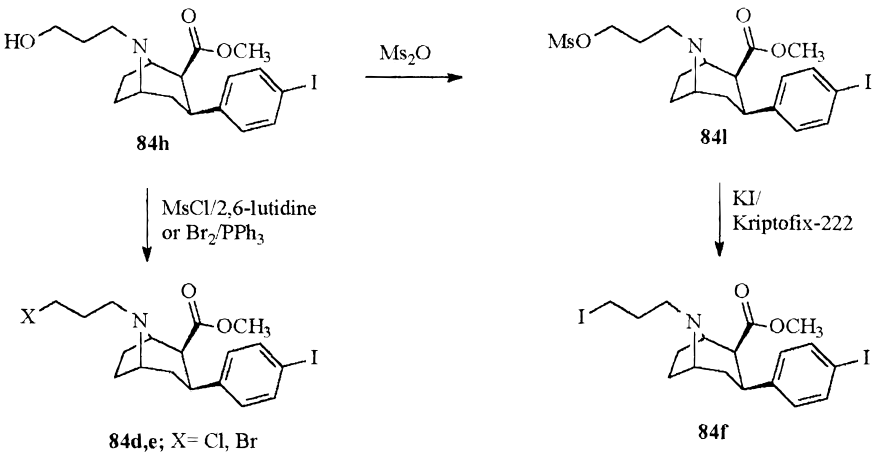
R= Me or $CH(CH_3)_2$
X= F or I

82a, 83a,b, 84a-c,g-k,m-t,v-x

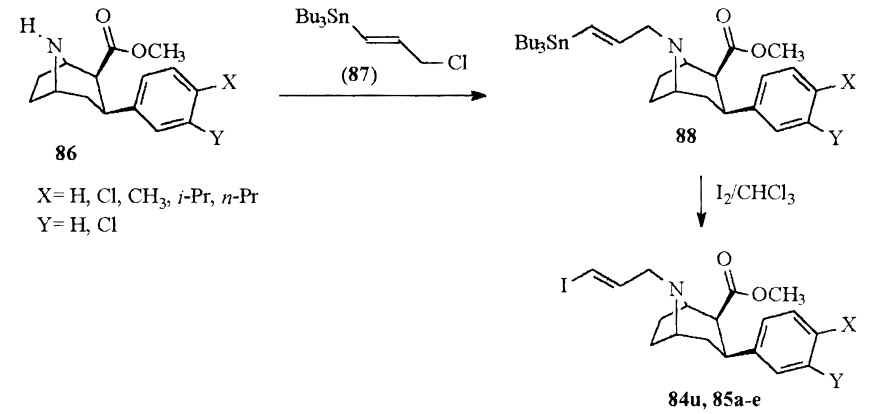


82a **82b**

Scheme 25



Scheme 26



ropropyl-2β-carboisopropyloxy analogue of β-CIT (**83a**) was the most DAT selective agent over both NET (8300-fold) and 5-HTT (41-fold). It was even more potent than β-CIT. This selectivity and potency appeared to be due to the 2β-carboisopropyloxy group and not essentially due to the *N*-fluoropropyl group (cf. **83a** vs **84a**). Nevertheless, the C2 fluoropropyl group did contribute to a higher binding potency (cf. **83a** vs **83b**; **84a** vs **84b**). In other *N*-haloalkyl-substituted phenyltropanes (**84a**−**f**), the compounds exhibited relatively poor affinities for the DAT but relatively higher potencies for the 5-HTT.

An interesting finding was the significant loss of DAT affinity (by a factor of ca. 1500 vs β-CIT) with **84m**, which contained an electron-withdrawing group, 2′-methylpropionyl, directly attached to N-8. However, it is also important to note that other compounds, in which the electron-withdrawing groups were at least separated by one carbon atom (e.g., **84c,j,k**), did not show a sharp reduction in DAT binding affinity. Small losses in DAT affinity in these compounds could have been due to other factors, such as lipophilicity or steric effects. In fact, a nonpolar cyclopropyl methyl group (**84g**) provided a similar steric feature as the polar hydroxypropyl group (**84h**), with only minor reduction in DAT affinity (K_i = 4.3 vs 5.4 nM).[203]

Another intriguing result was observed with rather bulky *N*-phthalimidoalkyl analogues of β-CIT (**84n**−**r**). These substituents showed moderate to strong affinity for the DAT, with an increase in affinity for 5-HTT when the spacer was ≥4 carbon atoms long. The 8-carbon derivative (*N*-[8-phthalimidooctyl]-2β-carbomethoxy-2β-[4′-iodophenyl]nortropane (**84r**)) showed a particularly high affinity and selectivity for the 5-HTT.[204]

Other compounds included *N*-alkenyl-, *N*-alkynyl-, and *N*-benzyltropane derivatives of nor-β-CIT. The *N*-benzyl analogues (**84w,x**) were less potent, but *N*-alkenyl (**84s**−**u**) and *N*-alkynyl (**84v**) were nearly equipotent to β-CIT (15−30 vs 27 nM, respectively).[205] Since the compound **84u** was the most selective in this series, other derivatives were designed by modifying substituents on the aromatic ring while retaining *N*-3-iodoprop-(2*E*)-ene moiety. One of these compounds (**85c**) showed comparable binding affinity for the DAT. These results suggested that the tropane nitrogen could be substituted with large substituted alkyl moieties without loss of affinity or selectivity for the amine transporters.

5. N-Chelated-3-phenyltropanes

The transition metal complexes of phenyltropanes are excellent ligands for the DAT sites in the brain. The transition metal, usually rhenium (Rh), can be exchanged with a radioactive transition metal ^{99m}Tc. The radiolabeled transition metal chelates can then be used as SPECT agents. The transition metal chelates, like any other ligand, have to have good binding affinity and selectivity for the monoamine transporter sites. The major hurdle in designing these chelates is the steric bulk of the ^{99m}Tc chelating

Table 17. In Vitro Binding Affinities of *N*-Substituted 3β-Phenylnortropanes for DA, 5-HT, and NE Transporters in Rat Forebrain Tissue

	K_i (nM)			selectivity	
compound no.	DAT [^{3}H]GBR 12935	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
cocaine	350 ± 80	>10000	>30000	>28.6	
GBR 12909	0.06 ± 0.02	52.8 ± 4.4	>20000	880	
11b (WIN 35428)	14.7 ± 2.9	181 ± 21	635 ± 110	12.3	43.2
11e (RTI-55)	1.40 ± 0.20	0.46 ± 0.06	2.80 ± 0.40	0.3	2
82a	22.6 ± 2.9[a]				
82b	43.0 ± 17.7[a]				
82c	58.9 ± 1.65[b]	1073[c]		18.2	
82d	1.4 ± 0.2[b]	133 ± 7[c]		95.0	
82e	3.4 ± 0.83[b]	49.9 ± 10.2[c]		14.7	
83a	1.20 ± 0.29	48.7 ± 8.4	10000	40.6	8333
83b	4.40 ± 0.35	21.7 ± 8.3	>10000	4.9	
84a	3.50 ± 0.39	0.110 ± 0.02	63.0 ± 4.0	0.03	18
84b	4.00 ± 0.73	0.140 ± 0.02	93.0 ± 17.0	0.03	23.2
84c	15.1 ± 3.7	9.6 ± 1.5	>5000	0.6	
84d	3.10 ± 0.57	0.32 ± 0.06	96.0 ± 29.0	0.1	31.0
84e	2.56 ± 0.57	0.35 ± 0.08	164 ± 47	0.1	64.1
84f	38.9 ± 6.3	8.84 ± 0.53	5000	0.2	128
84g	4.30 ± 0.87	1.30 ± 0.25	198 ± 9.6	0.3	46.0
84h	5.39 ± 0.21	2.50 ± 0.20	217 ± 19	0.5	40.2
84i	6.80 ± 1.10	1.69 ± 0.09	110 ± 7.7	0.2	16.2
84j	11.9 ± 1.4	0.81 ± 0.10	29.1 ± 1.0	0.07	2.4
84k	12.2 ± 3.8	6.40 ± 1.70	522 ± 145	0.5	42.8
84l	36.3 ± 2.1	17.3 ± 1.2	5000	0.5	138
84m	2100 ± 140	102 ± 23	>10000	0.05	
84n	4.23 ± 0.48	0.84 ± 0.02	441 ± 66.0	0.2	104
84o	9.10 ± 1.10	0.59 ± 0.07	74.0 ± 11.6	0.06	8.1
84p	2.38 ± 0.22	0.21 ± 0.02	190 ± 18.0	0.09	79.8
84q	2.40 ± 0.17	0.34 ± 0.03	60.0 ± 3.10	0.1	25.0
84r	2.98 ± 0.30	0.20 ± 0.02	75.0 ± 3.6	0.07	25.2
84s[d]	15 ± 1	75 ± 5	400 ± 80	5.0	26.7
84t[d]	30 ± 5	200 ± 40	>1000	6.7	
84u[d]	30 ± 5	960 ± 60	295 ± 33	32.0	9.8
84v[d]	14 ± 1	100 ± 30	>1000	7.1	
84w[d]	42 ± 12	100 ± 17	600 ± 100	2.4	14.3
84x[d]	93 ± 19	225 ± 40	>1000	2.4	
85a[d]	113 ± 41	100 ± 20	>1000	0.9	
85b[d]	29 ± 4	50 ± 6	500 ± 120	1.7	17.2
85c[d]	17 ± 7	500 ± 30	>1000	29.4	
85d[d]	500 ± 120	450 ± 80	>1000	0.9	
85e[d]	500 ± 100	300 ± 12	750 ± 160	0.6	1.5

[a] IC_{50} for displacement of [^{3}H]cocaine. IC_{50} for cocaine = 67.8 ± 8.7 (nM). [b] IC_{50} values for displacement of [^{3}H]WIN 35428. [c] IC_{50} values for displacement of [^{3}H]citalopram. [d] The standard K_i value for the displacement of [^{3}H]GBR 12935, [^{3}H]paroxetine, and [^{3}H]nisoxetine were 27 ± 2, 3 ± 0.2, and 80 ± 28 nM, respectively, for these experiments.

unit. In addition, a ligand (or the guiding ligand) has to be carefully selected. It must possess both potency and selectivity. The point of attachment is the next consideration. The ligand must have demonstrated ability to tolerate wide molecular modifications. A tether (or spacer) has to be carefully chosen based upon the SAR data. Furthermore, the chelating unit (the chelator) has to be carefully selected. It must have enough lipophilicity and be of neutral character in order to cross the blood brain barrier. The following N8-chelated phenyltropanes have been synthesized as shown in Figure 20.[209,210]

Synthesis of these chelates followed standard procedures.[209,210] The binding potencies and selectivities of *N*-chelated phenyltropanes were indeed interesting and are presented in Table 18. The chelate **89a** (Technepine) was more potent and selective than parent *N*-methyl compound, WIN 35428. While the low potency of **89b** (2α-CO_2CH_3) was expected, the reduced potency of **89c** was unwarranted. The IC_{50} values for the parent *N*-methyl analogue of **89c** were 1.09 ± 0.02 and 2.47 ± 0.14 nM for the DAT and 5-HTT, respectively. It has been suggested that the presence of a large group at the N8 position forces the molecule to protrude more toward the acceptor site at which the C3-aryl group binds, causing a reduction in potency. Decreasing the length of the N8-tether from three carbon to two carbon led to enhanced potency (compound **89d**). This suggested that three-dimensional molecular shape is more important than specific functionality at either the N8- or the C3- positions.[77]

6. 2-Carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes

N-Modified phenyltropanes discussed above include *N*-demethylated and *N*-substituted derivatives. These compounds or, for that matter, all of the phenyltropanes synthesized thus far contain a tropane nucleus bearing a nitrogen at the N8-position. It is believed that the nitrogen atom plays a pivotal role in anchoring the ligand with its acceptor site at the monoamine transporter. Furthermore, it is as-

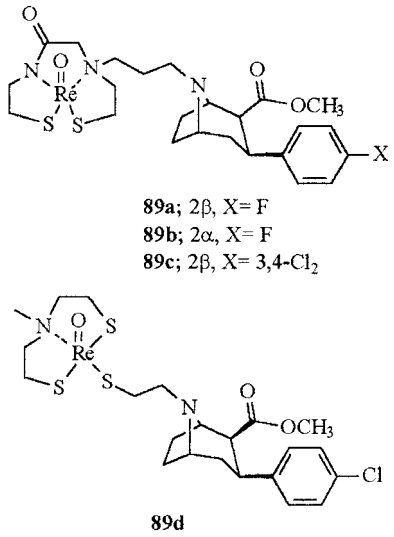


Figure 20. *N*-Chelated-3-phenyltropanes.

Table 18. Affinities of *N*-Chelated Phenyltropanes

	IC_{50} (nM)		
	DAT	5-HTT	selectivity
compound no.	[^{3}H]WIN 35428	[^{3}H]Citalopram	5-HTT/DAT
WIN 35428	11.0 ± 1.0	160 ± 20	14.5
89a	5.99 ± 0.81	124 ± 17	20.7
89b	2960 ± 157	5020 ± 1880	1.7
89c	37.2 ± 3.4	264 ± 16	7.1
89d	0.31 ± 0.03[a]		

[a] K_i value for displacement of [^{125}I]IPT radioligand.

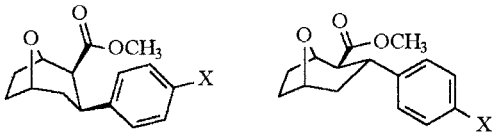


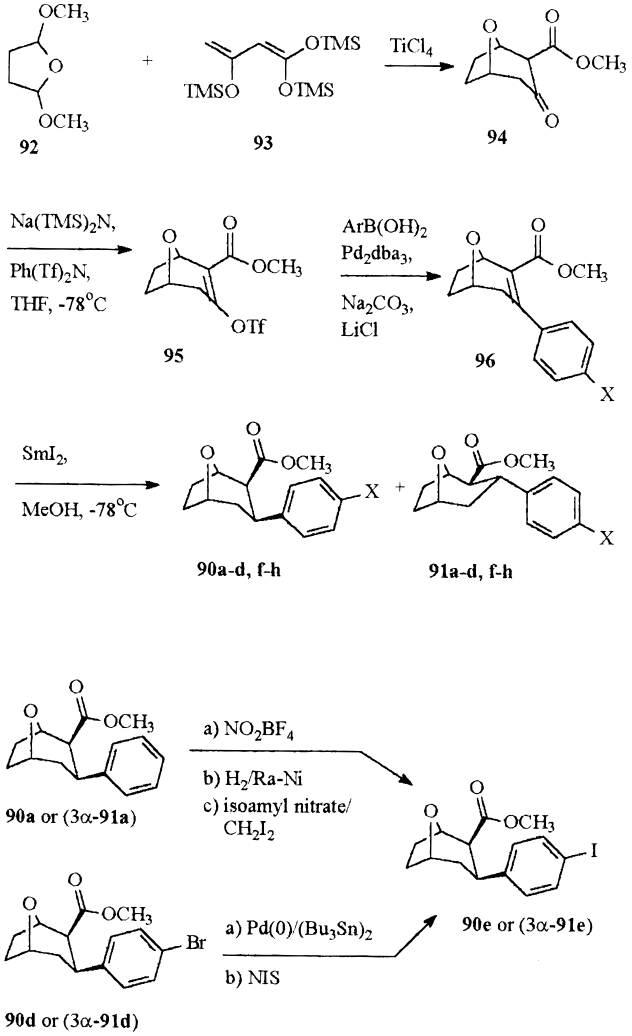
Figure 21. Structures of 3-aryl-8-oxanortropanes.

sumed that binding is effected by an ionic bond between the protonated amine and an acceptor site on the transporter (i.e., aspartic acid).[26] However, since quaternary cocaine methiodide lacks any significant binding to the DAT, it is presumed that the protonation of the N8-amine occurs at the transporter itself.[211]

Meltzer et al.[76] recently prepared 8-oxaphenyltropane analogues (Figure 21) to reexamine the importance of an ionic interaction of the N8 amine with the transporter. It was suggested that while an ionic interaction may play some role, the N8 amine may also engage in hydrogen bonding with the H-donor at the transporter. The fact that *N*-sulfonyl cocaine analogues, which can only partake in hydrogen bonding, further supported the design of 8-oxaphenyltropanes.

Synthesis of 8-oxa analogues of phenyltropanes (**90a**−**h, 91a**−**h**) was carried out from the 8-oxa keto

Scheme 27



ester **94** by suitable modifications. Compound **94** could be prepared by Lewis acid catalyzed [4 + 3] annulations[212,213] or organometallic-mediated annulations.[214−216] Thus, 2,5-dimethoxytetrahydrofuran (**92**) was reacted with 1,3-bis(trimethoxysiloxy)-1-methoxybuta-1,3-diene (**93**)[217,218] and 2 equiv of titanium tetrachloride to give the keto ester in 45% yield (Scheme 27). The ketone **94** was converted to enol triflate (**95**), which was then coupled with an appropriate aryl boronic acid[219] by Suzuki coupling[220] in the presence of lithium chloride, sodium carbonate, and tris(dibenzylidene acetone)dipalladium ($Pd_2(dba)_3$) to afford aryloctenes **96** in good yield. The octenes were reduced with samarium oxide to provide 3*β*- and 3α-diastereoisomers.[140] It should be remarked that the ratio of 2*β*,3*β* to 2*β*,3α depended upon the quenching agent. For example, when TFA was used to quench the reaction, the major product was 2*β*,3α. However, with water as a quenching agent, a 1:1 mixture of 3*β*- and 3α-diastereoisomers was obtained.

Since 4-iodophenyl boronic acid was not available, the analogues **90e/91e** were synthesized following the previously reported method as discussed above,[126] Scheme 27. Some of the analogues (**90g,h** and **91g,h**) were also prepared in enantiomerically pure forms. This required enantiomeric resolution of *R*/*S*-**94** by

Scheme 28

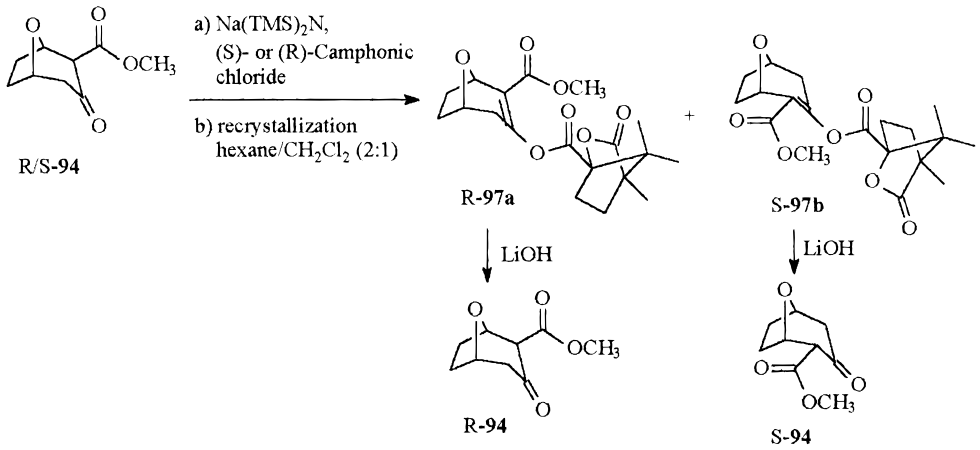


Table 19. Inhibition of Binding by 8-Oxanortropanes in Monkey Caudate-Putamen

	IC_{50} (nM)		
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]citalopram	selectivity 5-HTT/DAT
R/S-**90a**	>1000	>1000	
R/S-**90b**	546	2580	4.7
R/S-**90c**	10	107	10.7
R/S-**90d**	22	30	1.4
R/S-**90e**	7	12	1.7
R/S-**90f**	3.35	6.52	1.9
R-**90g**	3.27	4.67	1.4
S-**90h**	47	58	1.2
R/S-**91a**	1990	11440	5.7
R/S-**91b**	>1000	>10000	
R/S-**91c**	28.5	816	28.6
R/S-**91d**	9	276	30.7
R/S-**91e**	42	72	1.7
R/S-**91f**	3.08	64.5	20.9
R-**91g**	2.34	31	13.2
S-**91h**	56	2860	51.1

converting it into a diastereomeric mixture of enol comphanates **97** with (*S*)-(−)- or (*R*)-(+)-comphanic chloride as illustrated in Scheme 28. After recrystallization, *R*-**94** and *S*-**94** were regenerated by treatment with lithium hydroxide.[76]

The configurational assignments of 2β,3β- and 2β,3α-diastereomers were based upon sequential decoupling and NOE experiments. While 2β,3β-isomers preferably existed in the chair conformation, the 2β,3α-isomers favored the boat conformation. Consistent with the boat conformation, the 2-carbomethoxy occupied β-configuration and the 3-phenyl ring the α-configuration in **91**. This conformation allowed observable NOEs between protons located on the same face (α) of the molecule, e.g., H2 and H4(α) and H2 and H7(α). In addition, the methyl protons in camphanate diastereomers resonated at slightly different chemical shifts (δ 1.06 and 1.04 ppm for *R*-**97a** and *S*-**97b**, respectively).

The binding potencies of 8-oxa analogues are shown in Table 19. The 2β,3β compounds (**90a**−**h**) had a rank order of 3,4-Cl_2 > Cl ∼ I > Br > F > H, while 2β,3α diastereomers (**91a**−**h**) had a rank order of 3,4-Cl_2 > Br > Cl > I > F > H. In both series 3,4-Cl_2 compounds (**90g, 91g**) were the most potent at the dopamine transporter. The *S*-isomers **90h** and **91h** in both series were much less potent compared to the *R*-isomers (**90g, 91g**). The 3α-series of compounds were also more selective than 3β-isomers.

The above data supported the notion that the 8-amine functionality of the tropanes was indeed not a prerequisite for potency. Formation of an ionic bond was not possible for these compounds, and yet many interacted with both the DAT and 5-HTT with potencies similar to that of their nitrogen containing counterparts. The data also supported the fact that hydrogen-bond formation was likely between the aspartic acid or other amino acid and the heteroatom of the ligand. Molecular modeling studies of 8-oxa derivatives and 8-aza compounds revealed that the interatomic distances between potential binding points (8-heteroatom, 2β-ester, and the centroid of the 3-aryl ring) were almost identical. The variations in binding potencies of these analogues compared to 8-aza analogues then could be due to differences in the strength of the H-bond formed between, on one hand, the 8-oxygen and amino acid and, on the other, the 8-nitrogen and amino acid. Hydrogen bonds formed to nitrogen are generally weaker than those formed to oxygen since oxygen is more electronegative of the two (3.0 vs 3.5 on Pauling scale, respectively). Consequently, for similar compounds, the $R_2O\cdots H-X$ bond could be expected to be shorter than the $R_3N\cdots H-X$ bond. This difference in length could influence the placement of the remote 3-aryl ring in relation to its acceptor site. Therefore, in the case of the aza analogues, the 3-aryl ring will probe a greater distance into the site, while in the oxa analogues the controlling H···O bond will allow placement of the 3-aryl ring at a lesser distance. This suggested that the deeper placement of the 3-aryl substituent into the acceptor site at the DAT was important for higher potency.[76]

The intriguing biological profile of 8-oxa analogues has indeed opened up new possibilities for developing selective ligands. Such compounds could also possess a unique kinetic profile, biological transport, metabolism, and elimination compared to 8-aza analogues. Extensive research on these compounds might result in the development of some drugs of therapeutic value.

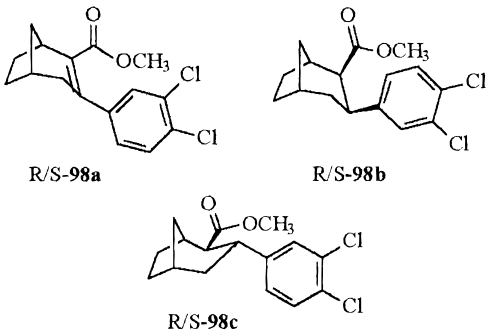


Figure 22. Structures of 3-aryl bicyclo[3.2.1]octanes.

7. 2-Carbomethoxy-3-aryl Bicyclo[3.2.1]octanes

Having demonstrated that the nitrogen in the phenyltropanes can be exchanged for an oxygen without loss in binding potency,[76] Meltzer et al. recently synthesized 8-carbaphenyltropanes, Figure 22.[221] In these compounds, the heteroatom (N or O) was replaced with a methylene group (−CH_2−). The main goal of the study was to explore if a heteroatom at position-8 was indeed necessary. The functional role of a heteroatom is to engage in hydrogen bonding with the acceptor site at the transporter. The 8-carba analogues cannot participate in hydrogen bonding.

The 8-carba analogues (**98a**−**c,** Figure 22) were prepared by the reaction of 3-chlorobicyclo[3.2.1]oct-2-ene (**99**) with sulfuric acid and subsequent introduction of the 2-carbomethoxy group by reaction with methyl cyanoformate in the presence of LDA to provide racemic keto ester **101** in 65% yield as illustrated in Scheme 29. The keto ester **101** was converted to 8-carba analogues **98b** and **98c** analogous to the route previously reported for synthesis of the 8-oxa compounds in Scheme 27, via an enol triflate followed by Suzuki coupling and reduction.

The IC_{50} values of 8-carba analogues are shown in Table 20. It is very interesting that these analogues retained significant binding to the DAT and 5-HTT, albeit 3- to 4-fold less potent at the DAT (cf. **90f** and **91f**, Table 19). Their potency at the 5-HTT was also lower than their 8-oxa counterparts (Table 19). The 2,3-unsaturated compound was particularly selective for the DAT.[77,221]

Table 20. Inhibition of Binding by 3-Aryl Bicyclo[3.2.1]octanes

	IC_{50} (nM)		
	DAT	5-HTT	selectivity
compound no.	[^{3}H]WIN 35428	[^{3}H]citalopram	5-HTT/DAT
R/S-**98a**	7.1 ± 1.7	5160 ± 580	726
R/S-**98b**	9.6 ± 1.8	33.4 ± 0.6	3.5
R/S-**98c**	14.3 ± 1.1	180 ± 65	12.6

An important finding from the above study was that the DAT was considerably more flexible and that a functional anchor at position-8 of the tropane ring is not necessary for binding at the DAT.

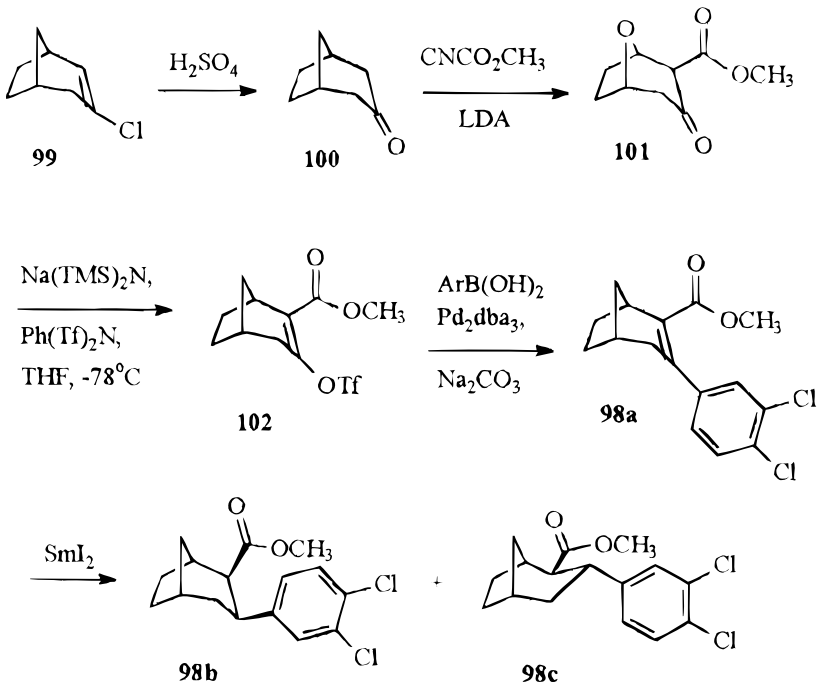
D. 6/7-Substituted Phenyltropanes

In the phenyltropanes, it has been shown that various modifications in the cocaine structure lead to high-affinity ligands. To further explore the importance of the tropane ring, a diverse group of substituents were introduced in the two-carbon bridge (C6−C7) of phenyltropanes. The synthesis of 6- or 7-substituted phenyltropanes was further substantiated by the fact that 7-methoxylation of pseudococaine (**225e,** Figure 36) produced a weak cocaine antagonist (discussed later).[222]

1. 6/7-Substituted 2-Carbomethoxy-3-phenyltropanes

The strategy to obtain 6- or 7-hydroxy/methoxy-3-phenyltropanes was based upon a classical Mannich-type of condensation reaction.[223] In this way 6/7-hydroxy- or methoxy-2-carbomethoxy-3-tropinone was

Scheme 29



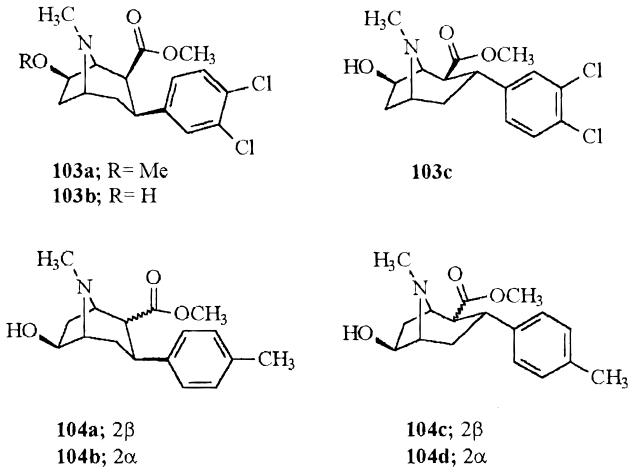


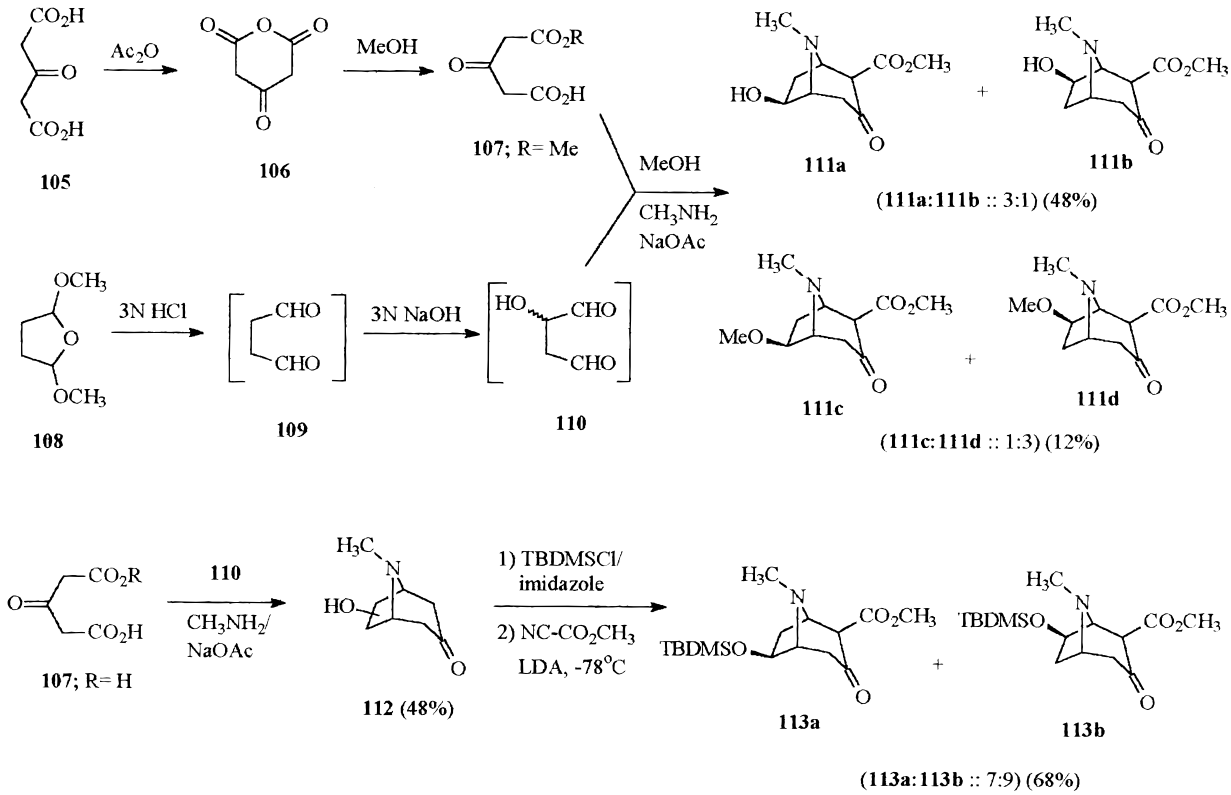
Figure 23. 6/7-Substituted 2-carbomethoxy-3-phenyltropanes.

obtained in a single step, which was further modified to obtain either analogues of cocaine or phenyltropanes. Of these analogues, 7β-hydroxyphenyltropane analogue was the most interesting compound because it could undergo intramolecular hydrogen bonding and thus reduce the basicity of the bridgehead tropane nitrogen. The structures of 6/7-methoxy/hydroxy-2-carbomethoxy phenyltropanes are depicted in Figure 23.

Synthesis of 6/7-hydroxy/methoxy phenyltropanes is shown in Schemes 30 and 31. First, 6/7-substituted-2-carbomethoxy-3-tropinone (**111, 113**) was prepared, which was then converted into the required phenyltropane derivative. As shown in Scheme 30, dimethoxy dihydropyran (**108**) in 3 N HCl was stirred for 12 h at ambient temperature and then neutralized by addition of aqueous sodium hydroxide solution. To this mixture, methylamine hydrochloride in water and acetone dicarboxylic acid anhydride **106** in methanol were added. The pH of the reaction was maintained at about 4.5 by addition of sodium acetate.[224] This biomimetic reaction after separation gave **111a** and **111b** (**111a:111b**, 3:1) and **111c** and **111d** (**111c:111d**, 1:3) in 48% and 12% yields, respectively. The *exo*(β) stereochemistry of the hydroxy/methoxy group was confirmed by NMR experiments. Most importantly, a coupling constant (J) of 0 Hz between H5 and H6 (δ = 4.05 ppm) in **111a** and between H1 and H7 (δ = 4.1 ppm) in **111b** was observed, confirming a dihedral angle of 90° for both compounds. Such a dihedral angle was only possible if the hydroxyl group in **111a** and **111b** was β-oriented.

In another synthesis, 6/7-hydroxy-3-tropinone was prepared as above using a Mannich-type condensation reaction. The 6/7-hydroxyl group was protected as TBDMS ether and subsequently methoxycarbonylated with methyl cyanoformate to yield a mixture **113a** and **113b** (7:9) as shown in Scheme 30.[225] The latter reaction has also been performed using dimethyl carbonate. The hydroxyl group in **111** was protected as a MOM ether and subsequently converted into a vinyl triflate (**115**). Phenyl-substituted alkenes **116** were obtained by Suzuki coupling. Reduction with samarium iodide then afforded **117** and **119** in 61% and 20% yields, respectively. Other reagents, e.g., PtO_2/H_2, led to loss of the chlorine atom in the phenyl ring, and with TFA as a quenching agent, the MOM group was lost and the ratio of **119:120** was 1:1. However, reduction of **116** (R = TBDMS, X = Me) with samarium iodide gave a mixture of three

Scheme 30



Scheme 31

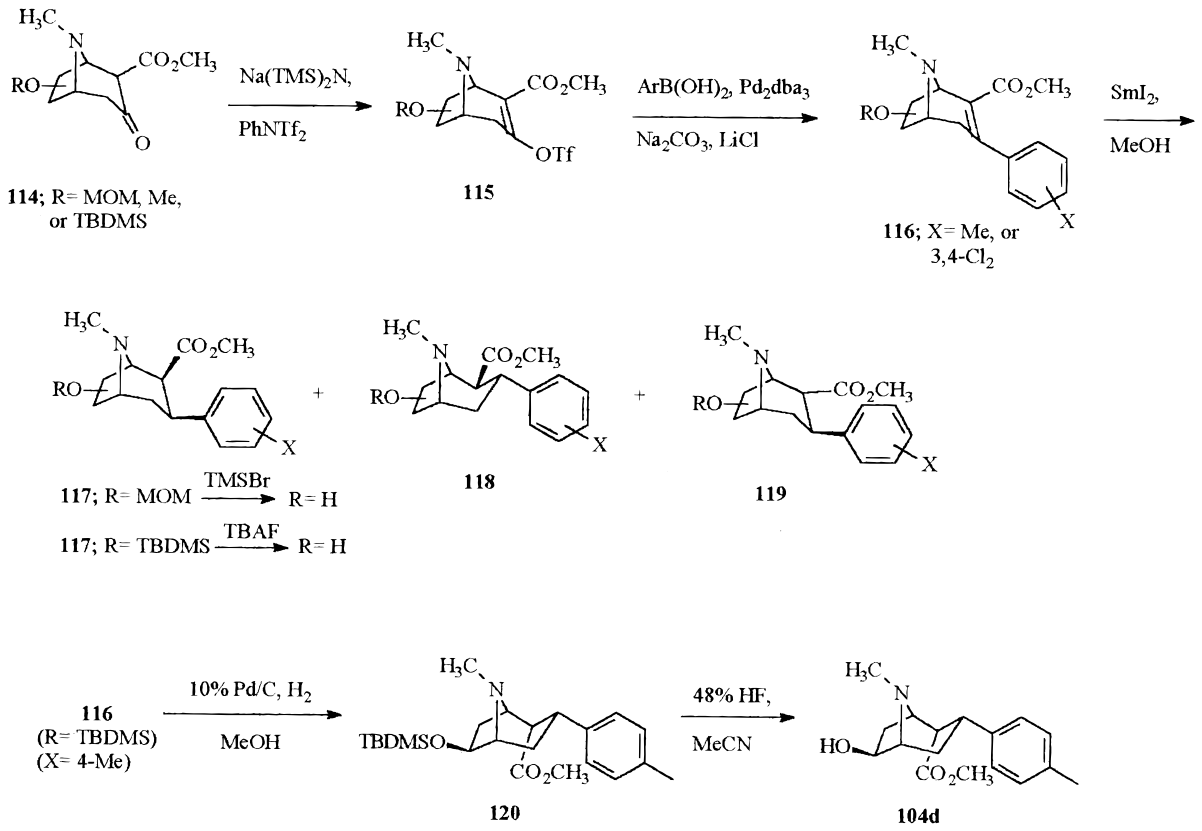


Table 21. IC_{50} Values of 6/7-Substituted 2-Carbomethoxyphenyltropanes

	IC_{50} (nM)		
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]citalopram	selectivity 5-HTT/DAT
cocaine	65 ± 12		
103a	86 ± 4.7	884 ± 100	10.3
103b	1.42 ± 0.03	28.6 ± 7.8	20.1
103c	1.19 ± 0.16	1390 ± 56	1168
104a	215[a]		
104b	15310[a]		
104c	930[a]		
104d	7860[a]		

[a] IC_{50} value for displacement of [^{3}H]mazindol. IC_{50} for cocaine 288 nM for displacement of [^{3}H]mazindol.

tropane analogues, **117, 118,** and **119** in 38%, 48%, and 5.2% yields, respectively; hydrogenation with 10% Pd/C as a catalyst provided 2α,3α-substituted isomer **120** exclusively. Compound **117** was shown by ^{1}H NMR to exist in a twist−chair conformation, while **118** assumed a twist−boat conformation. The MOM group was removed using trimethylsilyl bromide at 0 °C, and the TBDMS group was removed using TBAF or HF as shown in Scheme 31. The 6- and 7-methoxy β-keto esters **111c** and **111d** were analogously transformed to their methoxy tropane analogues.

The binding affinity data for 6/7-substituted phenyltropanes are shown in Table 21. Among 7β-hydroxyphenyltropanes, both 3β- as well as 3α-phenyltropane (**103b,c**) were significantly more potent at the DAT compared to cocaine and only slightly less potent than the parent compound **17c** (Table 3). The most striking observation was that 3α-phenyltropane **103c** was 1168-fold more selective at the DAT than at the 5-HTT while **103b** was only 20-fold selective. The 7β-methoxy analogue **103a** was significantly less potent and selective compared to hydroxylated phenyltropanes.[77]

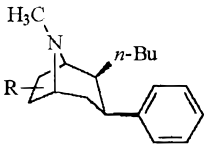
Among 6β-hydroxylated phenyltropanes, only 2β-isomer **104a** was more potent than cocaine. The twist−boat isomer **104c** was the next most active compound, while the other two isomers having an α-oriented carbomethoxy group showed only micromolar binding activity.[225]

2. 6/7-Substitued 2-n-Butyl-3-phenyltropanes

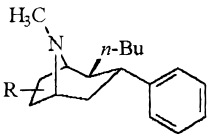
These compounds were synthesized by exploiting pyridinium betaine-based dipolar cycloaddition strategy.[226] The *n*-butyl group at the C2-position and a phenyl group at the C3-positon was chosen to facilitate chemistry. The structures of these compounds are presented in Figure 24.

The synthesis of oxidopyridinium betaine **52** is shown in Scheme 14. The 1,3-dipolar cycloaddition reaction of **52** with an appropriate dipolarophile gave the tropenones **122**, Scheme 32. The tropenones **122e−j** were obtained by refluxing the reactants in dry acetonitrile, but in the case of **122a−d**, an excess of acrylonitrile was used as the solvent. Furthermore, all four possible isomers were obtained with acrylonitrile, whereas with phenyl vinyl sulfone and phenyl fluorovinyl sulfone, only three products were isolated (the 7α-isomers were not formed in these cases).[227]

The α,β-unsaturated ketone intermediates **122a,-b,e−h** were selectively reduced with $NaBH_4/CeCl_3$



121a; R= 7β-CN
121b; R= 6β-CN
121c; R= 7β-SO_2Ph
121d; R= 6β-SO_2Ph
121e; R= 7α-OH



121f; R= H
121g; R= 7β-CN
121h; R= 6β-CN
121i; R= 7β-SO_2Ph
121j; R= 6β-SO_2Ph
121k; R= 7α-SO_2Ph
121l; R= 7β-SO_2Ph, 7α-F
121m; R= 7α-F
121n; R= 7β-F

Figure 24. 6/7-Substituted 2-butyl-3-phenyltropanes.

to allylic alcohols,[228] followed by acetylation with Ac_2O to give allylic acetates **123** in the ratio of 76:21; 2α:2*β*. Both isomerically pure α- and *β*-acetates underwent the copper(I)-catalyzed cross-coupling reaction with *n*-BuMgBr as the nucleophile to afford the olefin **124** derived by an S_N2'-type mechanism and having the *n*-butyl group in the *β*-orientation.[229] The attack of the butyl group from the *β*-face was facilitated by complexation of the nitrogen atom with the organocopper intermediate. Hydrogenation of the olefin intermediate **124** gave a mixture of *cis* and *trans* (2*β*,3*β* and 2*β*,3α) isomers, the ratio of which depended on the 6/7-substituent. A representative synthesis is shown in Scheme 33. The 6/7-nitrile-2-*n*-Bu-3-phenyltropanes **121a,b** and **121g,h** were also obtained by an alternative method.[227]

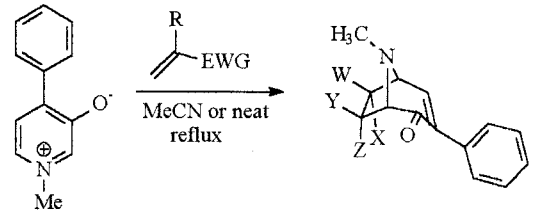
Desulfonylation of compound **121l** was conducted with sodium amalgam in MeOH to afford **121m,n** in a ratio of 9:1 (7α:7*β*).[230] A similar result was obtained when olefin **122h** was first desulfonylated to give 7α- and 7*β*-fluoro isomers (**125a,b**) in a 9:1 ratio, which upon hydrogenation afforded **121m,n**, respectively, as shown in Scheme 34.

To introduce a hydroxyl substituent at the C7-position, the 7-phenylsulfonyl tropane **122e** was oxidized to **126** using MoOPH,[231] followed by Dibal-H reduction to give exclusively the 7α-hydroxy isomer **127.** Hydrogenation of the C=C double bond over PtO_2 as a catalyst gave the *cis*-isomer **121e**, exclusively. Hydrogenation from the *endo* side was favored by coordination of the α-hydroxy group with the catalyst.[232]

As is apparent from Table 22, introduction of a substituent at the C6/7 position in the 2-*n*-Bu series of compounds **121a**−**n** led to reduction in potency for displacement of [^{3}H]mazindol at the DAT. In particular, a cyano group at the 6/7-position caused approximately 20−240-fold reduction in potency compared to the 6/7-unsubstituted congener, **121f** (compounds **121a,b,g,h**). A phenylsulfonyl group, on the other hand, decreased the binding affinity by 34−77-fold compared to **121f**. Compounds with a smaller polar group, e.g., OH and F, were only 2−8-fold less potent than **121f**.

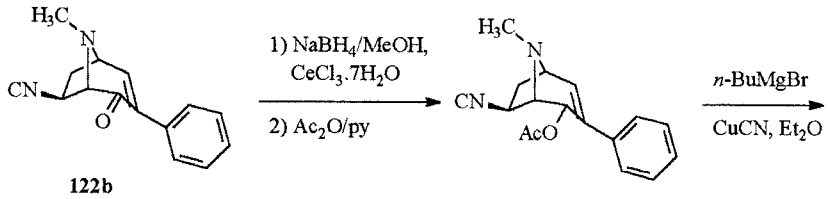
It is also interesting to note that 7α-isomers (*endo*), **121k** and **121m**, were nearly 2-fold more potent than the corresponding 7*β*-isomers, **121i** and **121n**, respectively. These results indicated that the receptor

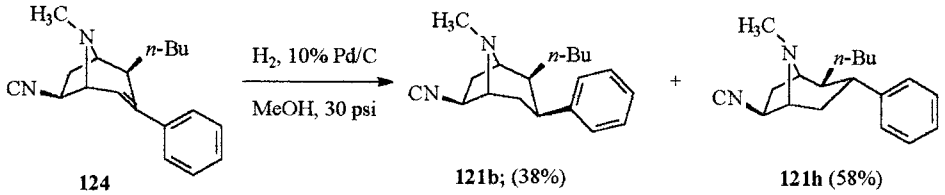
Scheme 32



(±)-**122a**; X= Y= Z= H, W= CN
(±)-**122b**; X= W= Z= H, Y= CN
(±)-**122c**; W= Y= Z= H, X= CN
(±)-**122d**; W= X= Y= H, Z= CN
(±)-**122e**; X= Y= Z= H, W= SO_2Ph
(±)-**122f**; X= W= Z= H, Y= SO_2Ph
(±)-**122g**; W= Y= Z= H, X= SO_2Ph
(±)-**122h**; Y= Z= H, W= SO_2Ph, X= F
(±)-**122i**; Y= Z= H, X= SO_2Ph, W= F
(±)-**122j**; W= X= H, Y= SO_2Ph, Z= F

Scheme 33





Scheme 34

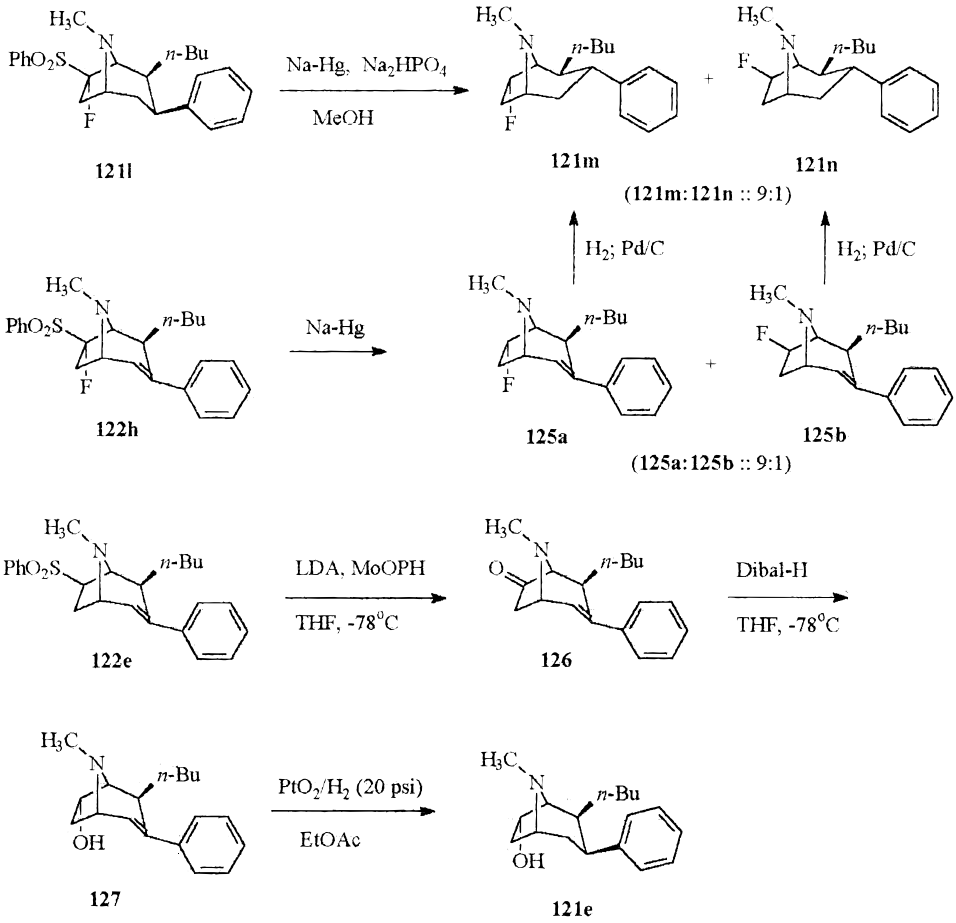


Table 22. Inhibition of Binding and Uptake by 6/7-Substituted 3-Butyl Phenyltropanes

	K_i (nM)		selectivity
compound no.	[^{3}H]mazindol binding	[^{3}H]DA uptake	uptake/binding
cocaine	270 ± 0.03	400 ± 20	1.5
121a	2020 ± 10	710 ± 40	0.3
121b	3040 ± 480	6030 ± 880	2.0
121c	4010 ± 310	8280 ± 1340	2.1
121d	4450 ± 430	8270 ± 690	1.8
121e	830 ± 40	780 ± 60	0.9
121f	100 ± 10	61 ± 10	0.6
121g	24000 ± 3420	32100 ± 8540	1.3
121h	11300 ± 1540	26600 ± 3330	2.3
121i	7690 ± 2770	7050 ± 450	0.9
121j	4190 ± 700	8590 ± 1360	2.0
121k	3420 ± 1100		
121l	840 ± 260	2520 ± 290	3.0
121m	200 ± 10	680 ± 10	3.4
121n	500 ± 10	550 ± 140	1.1

pocket was more able to accommodate substituents in the α-orientation compared to the β-position of the two-carbon bridge.

Furthermore, consistent with earlier observation,[139] 3β-phenyl derivatives were more potent that their 3α-phenyl counterparts. These compounds also displayed some discrepancy in binding and DA uptake. For example, the K_i value for binding of the compound **121m** was about 3.4 times smaller that its K_i for the inhibition of DA reuptake. However, compound **121a** showed a 3 times smaller K_i for the inhibition of DA reuptake than for binding.

E. Bridged Phenyltropanes

The rigid tricyclic (bridged) phenyltropanes were designed to determine the spatial requirements of the nitrogen lone pair. In these analogues, the conformation of the nitrogen lone pair was fixed by means of a tether to either the 3- or 2-carbon bridge of the tropane moiety.[233,234] The following analogues were designed as shown in Figure 25.

Synthesis of front-bridged analogues of phenyltropanes is shown in Scheme 35. The synthetic strategy utilized 1,3-dipolar cycloaddition of 3-hydroxypyridinium betaine with eletron-deficient olefin to create a tropenone moiety as discussed above in Scheme 32.[226,227] Thus, *N*-alkylation of 3-hydroxy-4-(4-tolyl)-pyridine (**134**) with 2,3-dibromopropene in THF afforded pyridinium bromide **135**, which upon cycloaddition with phenylvinyl sulfone produced a mixture of 6- and 7-*exo*-phenylsulfonyl regioisomers **136** in 21% yield. Radical cyclization of **136** afforded the tricyclic (front bridged) ketone **137** in 75% yield, which was reduced to an alcohol **138**. Reductive desulfonylation of **138** to alcohol **139** followed by two-step deoxygenation of **139** gave the rigid analogue **128** in 16% yield. Tricyclic **128** was also resolved by crystallization with (1*S*)-(+)-10-camphorsulfonic acid.

The tricyclic analogue **129** bearing a benzo-tether to the 2β-position of the tropane moiety was similarly prepared as shown in Scheme 35. 3-Hydroxy-4-(4-tolyl)pyridine (**134**) was reacted with 2-bromobenzylbromide to give *N*-alkylated pyridine, which was then transformed into compound **129**.

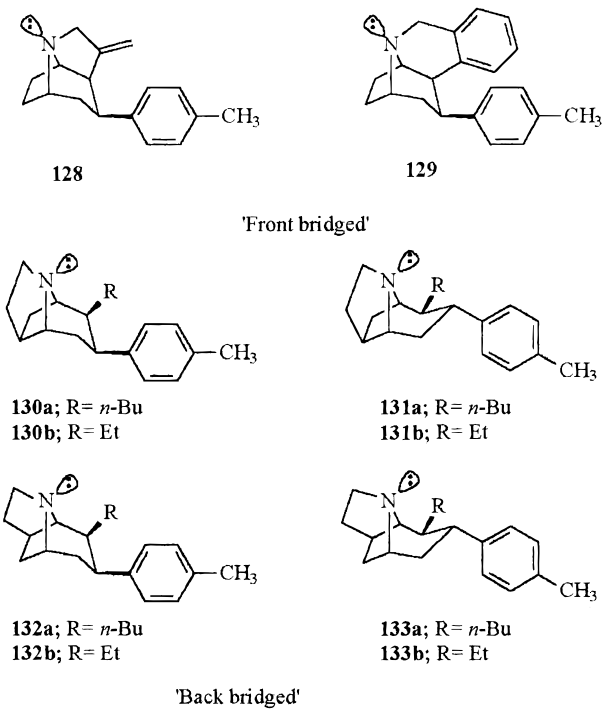


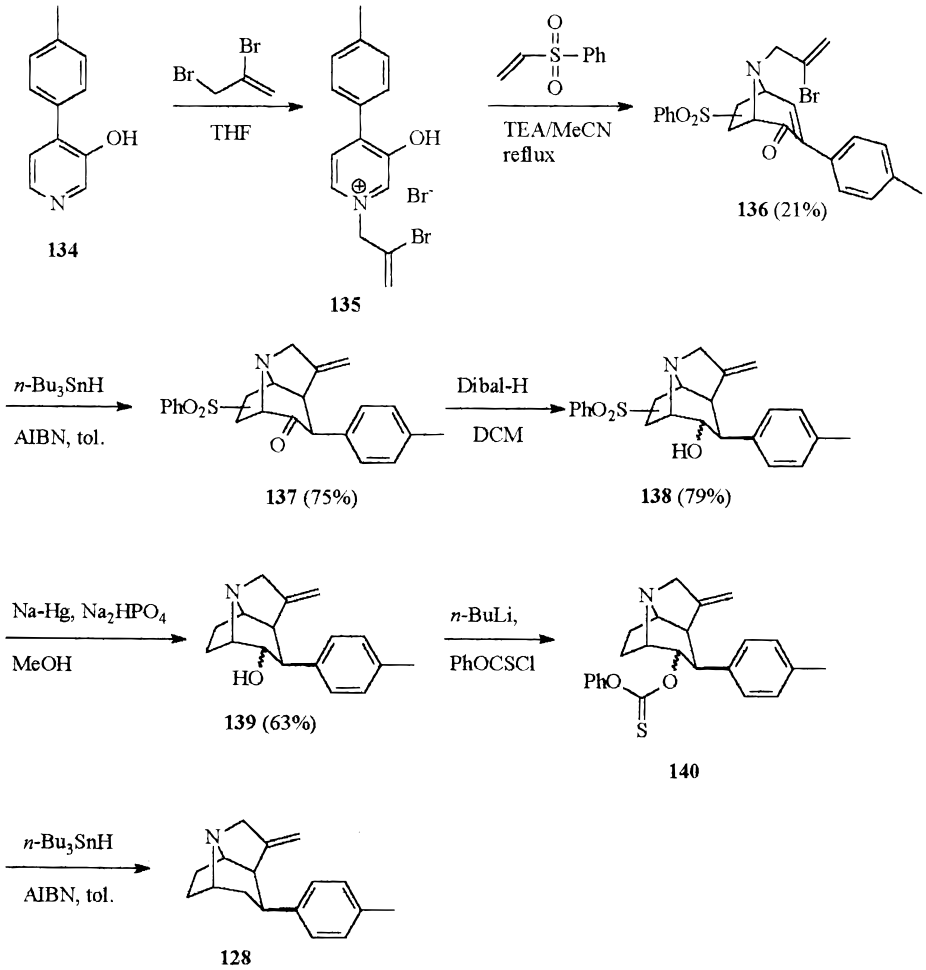
Figure 25. Bridged analogues of phenyltropanes.

Synthesis of back-bridged analogues is illustrated in Scheme 36. An intramolecular dipolar cycloaddition of betaine **141** gave the 6-bridged tropenone isomer **142** as the only cycloadduct in 36% yield.[233] Reduction of **142** followed by acetylation afforded epimeric allyl acetates **143**. Copper(I) cyanide catalyzed cross coupling of *n*-butyl- or ethylmagnesium bromide with **143** afforded a mixture of all four possible isomeric products, from which **144** and **145** were isolated in 42% and 20% yields, respectively. Reduction of **144** and **145** under acidic conditions gave the back-bridge analogues **130**, **131** and **132**, **133**, respectively.[233,234]

The biological data for the rigid phenyltropane analogues are presented in Table 23. In the front-bridged analogues (**128, 129**), the direction of the nitrogen lone pair is fixed so as to point toward the two-carbon bridge of the tropane nucleus, i.e., lone pair resides in the *equatorial* position of the piperidine ring of the tropane nucleus. However, in the back-bridged phenyltropanes, the lone pair of nitrogen occupies an *axial* position. It is important to note that the nitrogen lone pair in cocaine and phenyltropanes prefers to occupy an *axial* position[118,235] and consequently should mimic back-bridged phenyltropanes at the DAT, 5-HTT, and NET rather than front-bridged analogues.

All the compounds tested showed a higher binding affinity at the DAT than cocaine (2.5−104-fold). In addition, these analogues were generally more potent in inhibition of monoamine reuptake at the DAT,

Scheme 35



Scheme 36

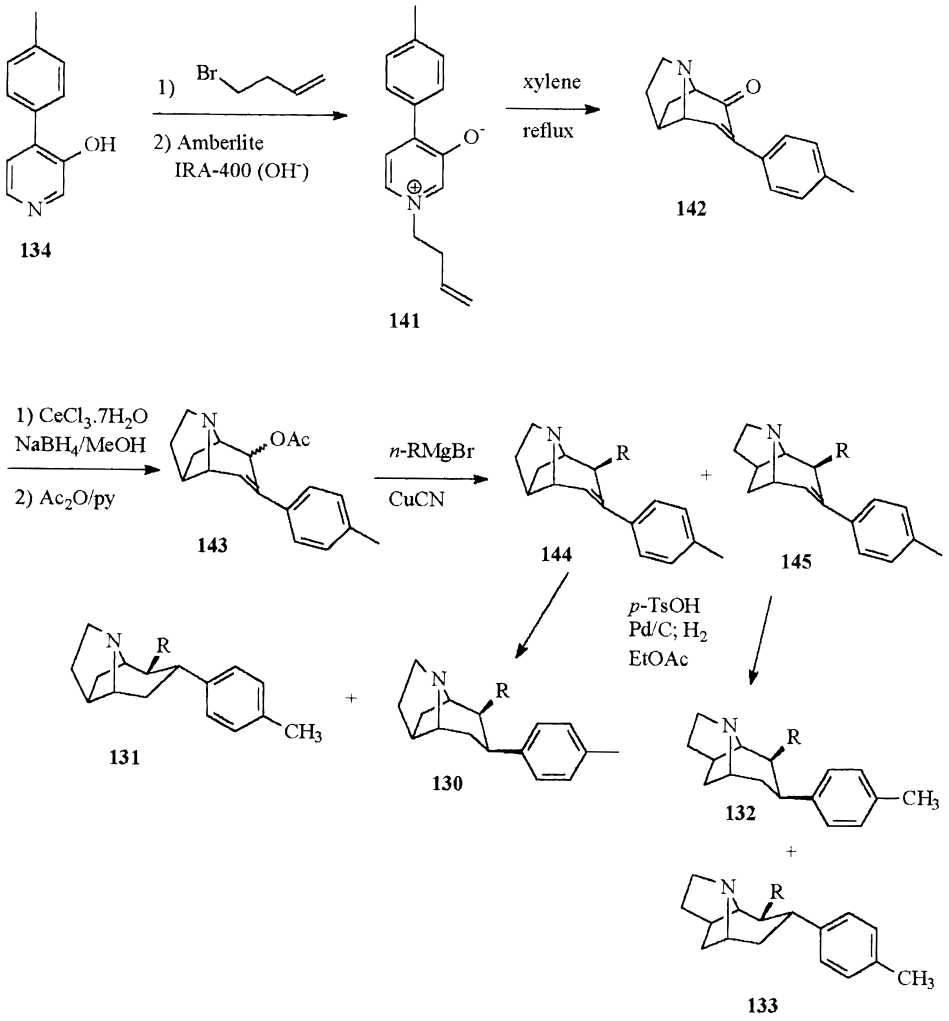


Table 23. Binding Affinities and Monoamine Transport Inhibition by Bridged Phenyltropane Analogues

	K_i (nM)				
compound no.	[^{3}H]mazindol binding	[^{3}H]DA uptake	[^{3}H]5-HT uptake	[^{3}H]NE uptake	selectivity [^{3}H]5-HT/[^{3}H]DA
cocaine	375 ± 68	423 ± 147	155 ± 40	83.3 ± 1.5	0.4
(−)-**128**	54.3 ± 10.2	60.3 ± 0.4	1.76 ± 0.23	5.24 ± 0.07	0.03
(+)-**128**	79 ± 19	114 ± 28	1.48 ± 0.07	4.62 ± 0.31	0.01
(±)-**128**	61.7 ± 8.5	60.3 ± 0.4	2.32 ± 0.23	2.69 ± 0.12	0.04
129	6.86 ± 0.43	24.0 ± 1.3	1.77 ± 0.04	1.06 ± 0.03	0.07
130a	17.2 ± 1.13	10.2 ± 1.4	78.9 ± 0.9	15.0 ± 0.4	7.8
131a	4.00 ± 0.07	2.23 ± 0.12	14.0 ± 0.6	2.99 ± 0.17	6.3
131b	3.61 ± 0.43	11.3 ± 1.1	25.7 ± 4.3	4.43 ± 0.01	2.3
132a	13.7 ± 0.8	14.2 ± 0.1	618 ± 87	3.84 ± 0.35	43.5
133a	149 ± 6	149 ± 2	810 ± 80	51.7 ± 12	5.4

5-HTT, and NET compared to cocaine. This increased potency was most evident at the DAT, where the bridged analogues were 2.8−190-fold more active than cocaine. A somewhat smaller spread in activities was noted at the NET with 1.6−78-fold increase in activity. The potency at the 5-HTT was 100-fold greater for (+)-**128** while 4−5.2-fold weaker for **132a** and **133a**, respectively.

The most interesting finding of this study was the significant difference in the 5-HT/DA reuptake ratio. While front-bridged analogues (**128, 129**) exhibited greater potency at the 5-HTT, the back-bridged analogues (**130**−**133**) preferably interacted at the DAT. This effect has been attributed to the stereochemistry of the lone pair of the nitrogen atom (N8).

F. 3-Phenyl-9-azabicyclo[3.3.1]nonane Derivatives

The rationale behind designing these compounds was to explore the effect of structural modification of the C6−C7 ethylene bridge of the phenyltropanes. The idea was supported by the fact that 6/7-methoxycocaine and pseudococaine analogues were weak cocaine antagonists.[222] These compounds could also be considered as homologues of WIN 35065-2. The following compounds were synthesized as shown in Figure 26.[236]

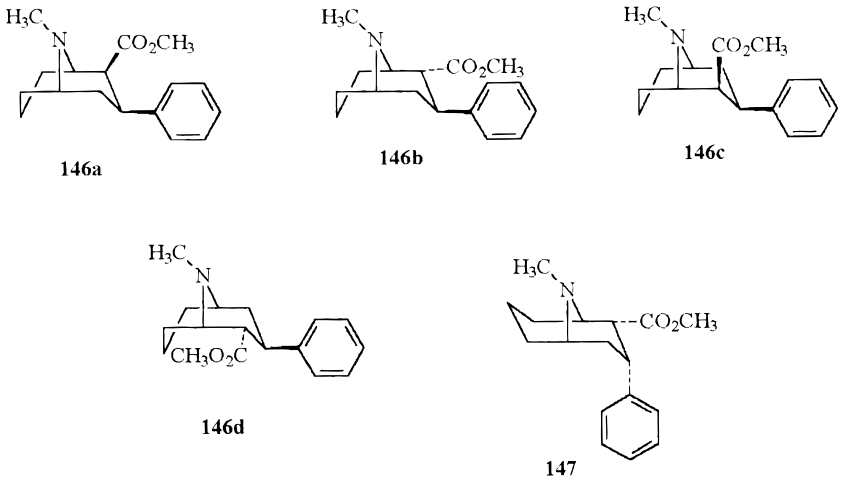
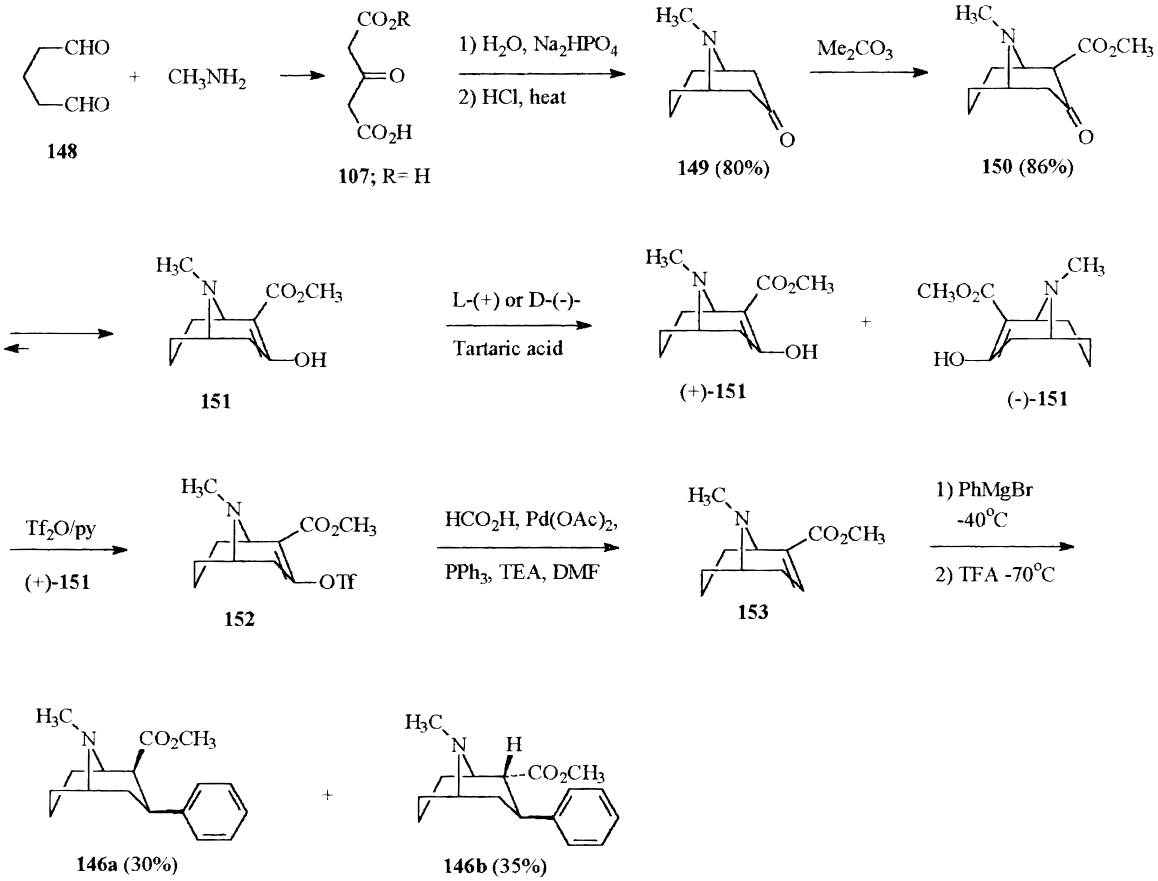


Figure 26. [3.3.1]Azanonane analogues of phenyltropanes.

Scheme 37



As illustrated in Scheme 37, the 9-azabicyclo[3.3.1]-nonane ring was constructed using a modified Robinson's procedure to give ketone **149**,[237] which upon carbomethoxylation with dimethyl carbonate afforded *β*-keto ester **150**.[120] The *β*-keto ester **150** was, however, found to exist almost entirely in the enol tautomeric form **151** as suggested by NMR data. The racemic mixture of **151** was resolved using L-(+)- and D-(−) tartaric acid to afford (+)-**151** and (−)-**151** enantiomers, respectively. The enantiomer (+)-**151** was then hydrodehydroxylated into alkene **153** via vinyl triflate **152**[238] using Cacchi's procedure.[239] Conjugate addition of 1 equiv of phenylmagnesium bromide to (+)-**153** provided **146a** and **146b** in 30% and 35% yields, respectively, after chromatography. The enantiomers **146c** and **146d** were analogously prepared from (−)-**151**.

Compound **147** was prepared from the enol triflate **152** via Pd(0)-catalyzed coupling of phenylboronic acid. Thus, a mixture of vinyl triflate **152** and phenyl boronic acid was refluxed in dimethoxyethane (DME) in the presence of $Pd_2(dba)_3$ as a catalyst to provide **156** in 80% yield.[240] Hydrogenation (50 psi) of alkene **154** over platinum oxide provided **147** as the major product (30%) and trace amounts of other isomers, Scheme 38.

The binding affinities for 9-azabicyclo[3.3.1]nonane derivatives **146a**−**d, 147** are shown in Table 24. It

Scheme 38

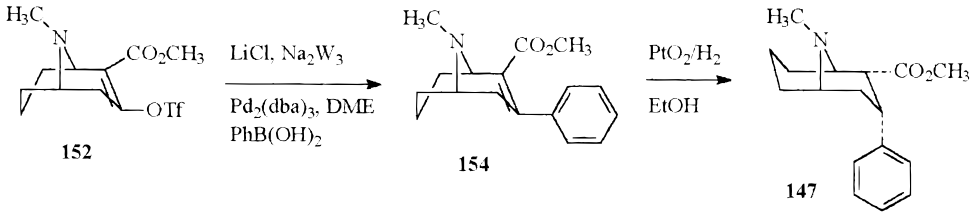


Table 24. K_i Values for Displacement of Bound [^{3}H]WIN 35428 by [3.3.1]Azanonane Analogues of Phenyltropanes

compound no.	K_i (nM)
cocaine	32 ± 5
	390 ± 220
WIN 35065-2	33 ± 17
	310 ± 220
146a	4600 ± 510
146b	5730 ± 570
146c	3450 ± 310
146d	3470 ± 350
147	13900 ± 2010

is noteworthy that C2-stereoisomers (**146a** vs **146b** and **146c** vs **146d**) as well as enantiomers (**146a** vs **146c** and **146b** vs **146d**) did not have any significant differences in potencies. The most important finding from this study was that the addition of a single methylene unit in the tropane ring system caused more than 100-fold decrease in binding affinity. While compound **146a** could be considered a homologue of WIN 35065-2, such a drastic loss in potency inferred that the cocaine binding site at the DAT was very sensitive to structural modifications of the unsubstituted methylene bridge [C6−C7] of cocaine and cocaine-like compounds.

G. 3-Phenyl-7-azabicyclo[2.2.1]heptane Analogues of Phenyltropanes

Continuing their efforts to address the importance of the topology imparted by the tropane ring of cocaine and phenyltropanes for molecular recognition at the cocaine binding site on the DAT, Zhang et al.[241] recently synthesized ring-contracted analogues of cocaine. It was envisaged that incorporation of the basic structural features of phenyltropanes into the rigid 7-azabicyclo[2.2.1]heptane ring system would provide additional insight into topological requirements of the DAT pharmacophore. The following four stereoisomers of (±)-2-(methoxycarbonyl)-7-methyl-3-phenyl-7-azabicyclo[2.2.1]heptane (**155a**−**d**) were synthesized and evaluated as shown in Figure 27.

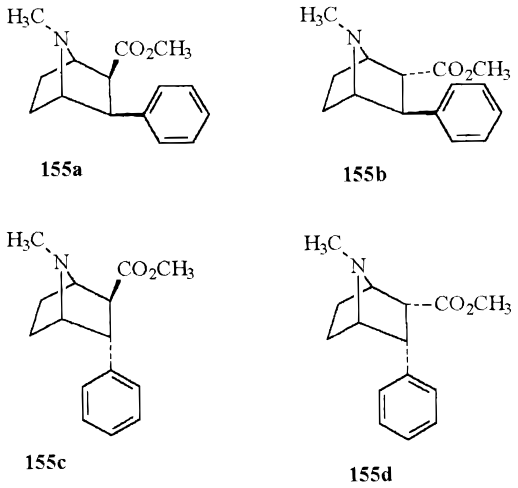


Figure 27. [2.2.1]Azabornane analogues of phenyltropanes.

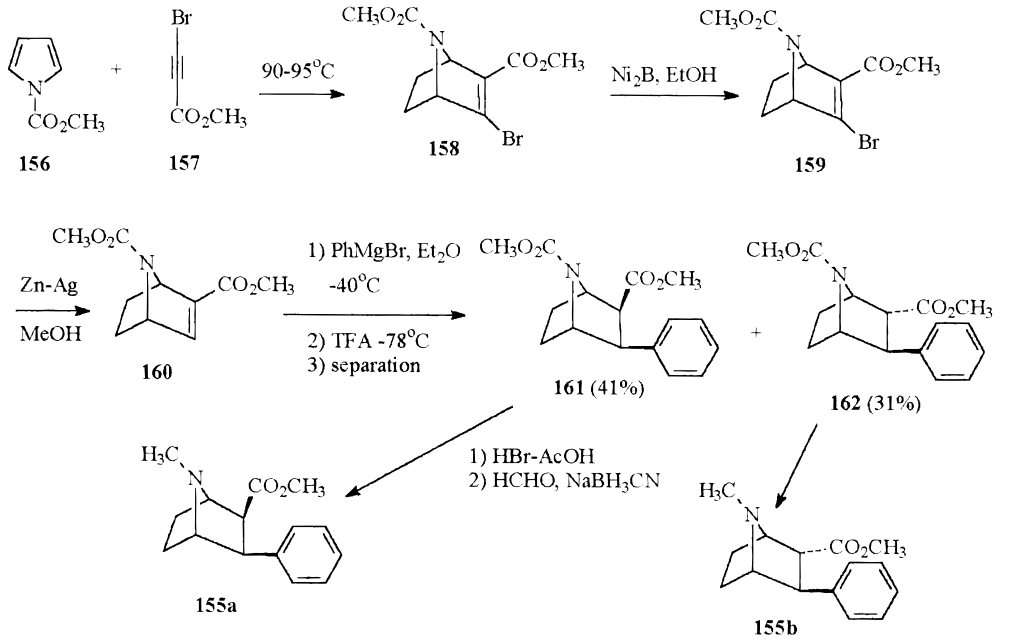
The synthesis of ring-contracted phenyltropanes **155a**−**d** required the construction of the 7-azabicyclo-[2.2.1]heptene ring system, which was achieved by a Diels−Alder reaction. Thus, heating methyl-3-bromopropiolate (**157**)[242] with 4-fold excess of *N*-(methoxycarbonyl)pyrrole (**156**)[243] at 90−95 °C for 33 h furnished the cycloadduct **158** in 56% yield.[244] Other methods for the construction of 7-azabornane have been reviewed by Chen and Trudell.[245] The unsubstituted double bond was reduced using nickel boride as catalyst to give **159**. This has also been achieved using palladium catalyst.[246] Hydrodehalogentation of **159** with Zn−Ag couple afforded **160**,[247] which upon Grignard reaction with phenylmagnesium bromide afforded 2β- and 2α-isomers, **161** and **162**, respectively. After separation, **161** and **162** were deprotected and *N*-methylated with formaldehyde and sodium cyanoborohydride as illustrated in Scheme 39.

Synthesis of **155c** and **155d** involved Suzuki reaction between 7-azabicyclo[2.2.1]heptene derivative **159** and phenyl boronic acid in the presence of a palladium(0) catalyst to give intermediate **163**.[248] Reduction of **163** with magnesium in methanol gave 2β,3α-isomer **164** as the major product (51%) along with **162** (32%).[249] The 2α,3α-isomer **155d** was prepared by hydrogenation (40 psi) of **163** over 5% Pd/C in methanol to give 95% of the *endo* product **165** as depicted in Scheme 40. Both **164** and **165** were then converted into *N*-methyl derivatives, **155c** and **155d**, respectively, as illustrated above in Scheme 40.

As shown in Table 25, the binding affinities for the ring-contracted tropane derivative **155a**−**d** were very low (100−3000-fold). The interesting feature of this series of compounds was that 3α-phenyl derivatives **155c** and **155d** were more potent than their 3β-phenyl counterparts, **155a** and **155b**, respectively.[241]

Molecular modeling studies were performed using a SYBYL 6.0 molecular modeling software. The intramolecular distances were measured, and the geometry-optimized structures were aligned by least-squares fitting of C1, C5, C6, C7, and N8 of WIN 35065-2 (**11a**; Figure 3) and **20a** (Figure 5) with C1, C4, C5, C6, and N7 of **155a** and **155c** using the FIT option of SYBYL 6.0. The most striking difference between the four molecules (**155a**−**d**) was the intramolecular distance between the phenyl group

Scheme 39



Scheme 40

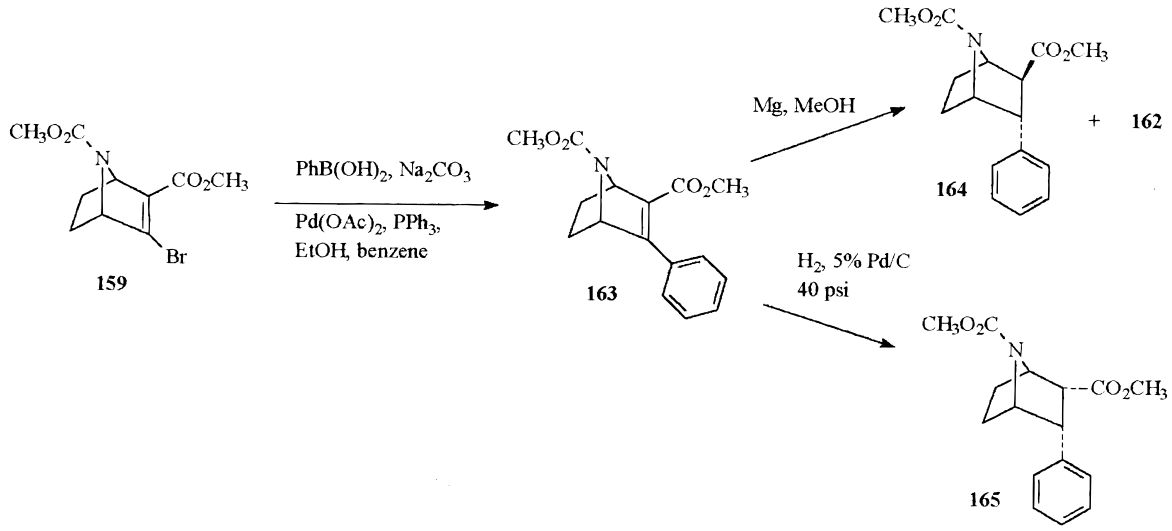


Table 25. K_i Values of 7-Azabicyclo[2.2.1]heptane Derivatives for the Inhibition of Bound [^{3}H]WIN 35428

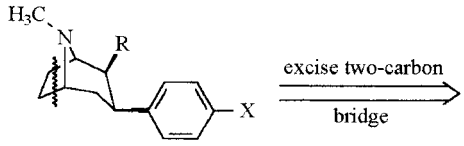
compound no.	K_i (nM)
cocaine	32 ± 5
	390 ± 220
WIN 35065-2	33 ± 17
	310 ± 220
155a	60,400 ± 4,800
155b	96,500 ± 42
155c	5,620 ± 390
155d	18,900 ± 1700

(centroid) and the nitrogen atom. From the geometry-optimized structures, the calculated N−Ph$_{(Centroid)}$ distance for **155a** was 4.2 Å and for **155c** was 5.0 Å, while the N−Ph$_{(Centroid)}$ distances for WIN 35065-2 (**11a**) and **20a** were 5.6 Å and 5.5 Å, respectively. In addition, the spatial orientation of the phenyl groups in **155a** and **155c** were significantly different relative to WIN 35065-2 and **20a**. The phenyl groups in **155a** and **155c** were displaced from the molecular plane, which passed through the nitrogen atom and C3 and the middle of C6−C7 ethylene bridge.

In summary, the compressed topologies of **155a** and **155c** did not permit sufficient penetration of the phenyl ring into the binding site to elicit similar potencies compared to phenyltropanes, WIN 35065-2 and **20a**. Therefore, a tropane ring system is important for imparting a molecular topology among phenyltropane derivatives. However, piperidine homologues of phenyltropanes have displayed potencies comparable to phenyltropanes at the DAT as discussed below.

H. Piperidine Analogues of Phenyltropanes

Kozikowski et al. have recently synthesized piperidine analogues of 3-(4-chlorophenyl)-2-carbomethoxy tropane.[86] These compounds could be viewed as truncated versions of the WIN series of compounds, i.e., they lack the two-carbon bridge (C6−C7) of the tropane ring system as illustrated in Figure 28. The



WIN series

(±)-**166a**; R= β-CO_2CH_3; X= Cl
(±)-**166b**; R= α-CO_2CH_3; X= Cl
(-)-**166a**; R= β-CO_2CH_3; X= Cl
(+)-**166a**; R= β-CO_2CH_3; X= Cl
(-)-**167a**; R= β-CH_2OH; X= Cl
(+)-**167a**; R= β-CH_2OH; X= Cl
(-)-**168a**; R= β-CH_2OAc; X= Cl
(+)-**168a**; R= β-CH_2OAc; X= Cl
(-)-**169a**; R= β-*n*-Pr; X= Cl
(-)-**170a**; R= β-CO_2CH_3; X= H
(+)-**166b**; R= α-CO_2CH_3; X= Cl
(-)-**166b**; R= α-CO_2CH_3; X= Cl
(+)-**167b**; R= α-CH_2OH; X= Cl
(+)-**168b**; R= α-CH_2OAc; X= Cl
(+)-**169b**; R= α-*n*-Pr; X= Cl

Figure 28. Structures of the piperidine analogues of phenyltropanes.

piperidine analogues were of interest for two reasons: (1) the molecular size was smaller compared to tropanes and (2) they embodied cocaine's pharmacophores.

The synthesis of piperidine analogues is illustrated in Scheme 41. The racemic piperidines (±)-**166a,b** were prepared from arecoline hydrobromide (**171**) after neutralization followed by Grignard reaction.[250] The *cis* and *trans* isomers were separated and subjected to resolution using (+)- and (−)-dibenzoyltartaric acid to provide pure enantiomers (−)-**166a** and (+)-**166a**.[251] The absolute stereochemistry conformed to WIN series of structures. The optically pure (−)- and (+)-*cis* esters were converted into their respective alcohols (−)-**167a** and (+)-**167a** by LAH reduction, and these, in turn, were converted into their acetate derivatives (−)-**168a** and (+)-**168a** by acetylation.

To explore the effect of a less polar, nonhydrolyzable group at the C3 position, the ester group at C3 was converted into a *n*-propyl group (compound (−)-**169a**). This was accomplished by converting ester into aldehyde by way of alcohol intermediate (−)-**167a**, Wittig reaction, and hydrogenation to provide (−)-**169a**. The *p*-chloro substituent was hydrogenolyzed (compound (−)-**170a**) to examine its effect on binding affinity, Scheme 41.

The *trans* isomers of piperidine analogues (**166b, 167b, 168b, 169b,** Figure 28) were also synthesized. These analogues could have been obtained from (±)-**166b** but its resolution was unsuccessful. Therefore, (−)-**166a** and (+)-**166a** were subjected to base-catalyzed epimerization to give pure *trans*-configured products (+)-**166b** and (−)-**166b,** respectively. The more active (+)-**166b** was also converted to its alcohol (+)-**167b**, acetate (+)-**168b**, and *n*-propyl (+)-**169b** derivative as described above, Scheme 41.

The binding affinity data for piperidine analogues is presented in Table 26. It is indeed very interesting to note that whereas earlier reports on replacement of the basic tropane ring structure with piperidine,[252]

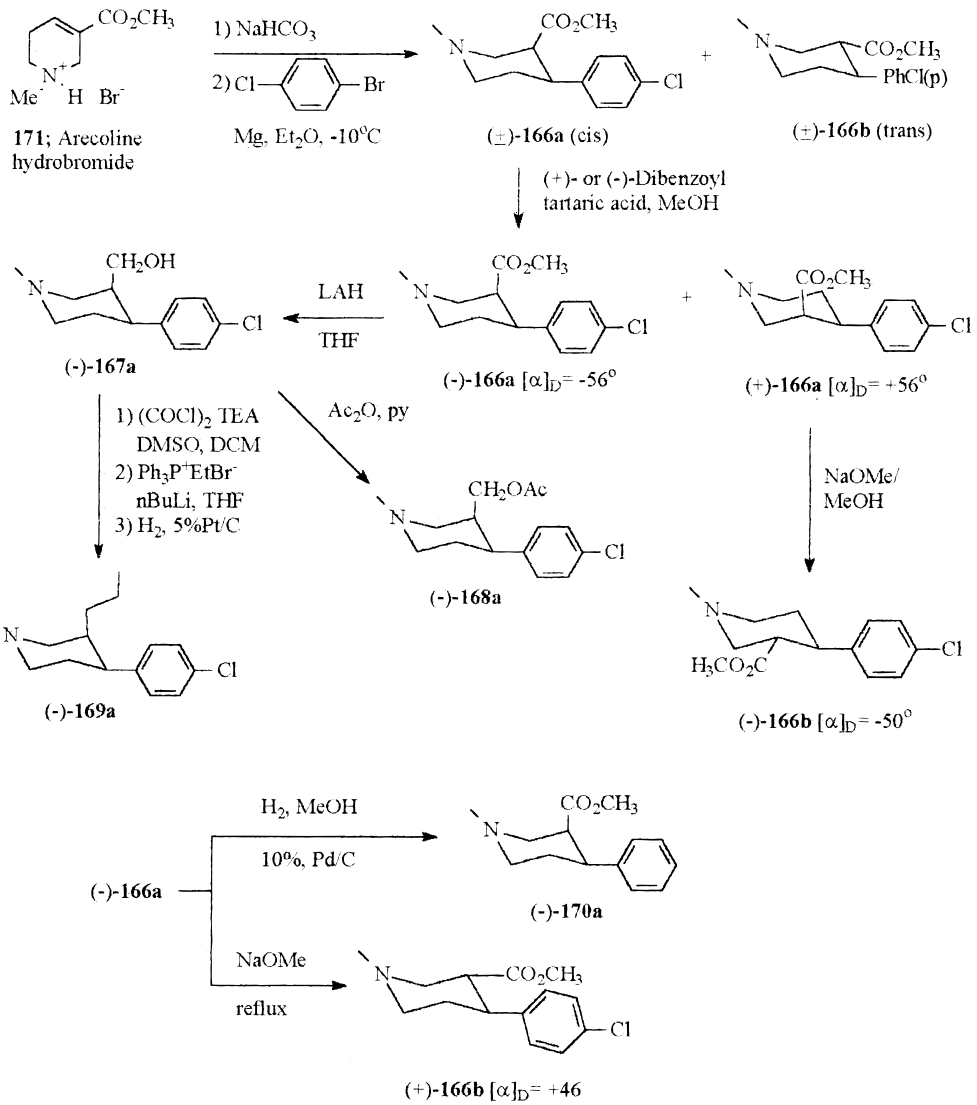
Table 26. IC_{50} Values of Piperidine Analogues of Phenyltropanes for DAT and DA Uptake

	IC_{50} (nM)		selectivity
compound no.	[^{3}H]WIN 35428 binding	[^{3}H]DA uptake	uptake/binding
cocaine	102 ± 9	239 ± 1	2.3
(±)-**166a**	53.7 ± 1.9	37.8 ± 7.9	0.7
(±)-**166b**	197 ± 8		
(−)-**166a**	24.8 ± 1.6	85.2 ± 2.6	3.4
(+)-**166a**	1360 ± 125	5090 ± 172	3.7
(−)-**167a**	75.3 ± 6.2	49.0 ± 3.0	0.6
(+)-**167a**	442 ± 32		
(−)-**168a**	44.7 ± 10.5	62.9 ± 2.7	1.4
(+)-**168a**	928 ± 43	2023 ± 82	2.2
(−)-**169a**	3.0 ± 0.5	8.3 ± 0.6	2.8
(−)-**170a**	769 ± 19		
(+)-**166b**	57.3 ± 8.1	34.6 ± 3.2	0.6
(−)-**166b**	653 ± 38	195 ± 8	0.3
(+)-**167b**	240 ± 18	683 ± 47	2.8
(+)-**168b**	461 ± 11		
(+)-**169b**	17.2 ± 0.5	23.2 ± 2.2	1.3

7-azabornane,[241] or azabicyclo[3.3.1]nonane[236] led to significant reductions in potency of these cocaine analogues, the present series of compounds showed significantly high binding affinities for the DAT.

Of all the compounds synthesized, the 3-*n*-propyl derivative (−)-**169a** was the most potent with a binding affinity of 3 nM. It was 34-fold more potent than cocaine in inhibiting [^{3}H]WIN 35428 and 28.7-fold more potent in inhibition of [^{3}H]DA uptake. It was also only slightly less potent than a similar phenyltropane analogue of the WIN series (cf. **43g**, Figure 11, IC_{50} 0.94 for inhibition of [^{3}H]mazindol, Table 10). It is also interesting to note that the *cis*-disubstituted piperidine (−)-**166a** was only 2-fold more potent than its *trans* isomer (+)-**166b**. This result was in sharp contrast to the data reported for the phenyltropane series. In general, epimerization of the substituent at C2 from β to α in phenyltropanes has been found to lower the activity by 30−200-fold.[72] Thus, smaller spread in binding affinities for the piperidines may be due to the smaller size of these

Scheme 41



molecules relative to tropanes, which allow both the *cis* and *trans* isomers to adjust themselves to the binding site on the DAT.

Another interesting feature of this series of compounds was the reduction in potency for the deschloro compound (−)-**170a** relative to (−)-**166a** by 31-fold. A similar effect of a halogen atom has been found in the tropane series, where introduction of a chloro substituent increased potency by 20-fold (WIN 35065-2 (**11a**), IC_{50}, 23 nM; its *p*-chloro analogue (**11c**) 1.12 nM), Figure 3, Table 2).[126] This suggested that the piperidine analogues bind to a similar site as that of phenyltropanes at the DAT.

III. Cocaine Analogues

Cocaine is the flagship compound of a family of tropane alkaloids isolated from the leaves of *Erythroxylon coca*. The chemistry of tropane alkaloids has been exhaustively reviewed by Lounasmaa.[110] Cocaine contains an 8-methyl-8-azabicyclo[3.2.1]octane framework and is one of the eight possible stereoisomers of 8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic methyl ester. Cocaine analogues retain 3β-benzoyloxy or similar functionality unlike phenyltropanes. This series consists of the following compounds: a) stereoisomers of cocaine, (b) 3β-phenyl ring substituted analogues, (c) 2β-substituted analogues, (d) *N*-modified analogues of cocaine, (e) 3β-carbamoyl analogues, (f) 3β-alkylphenyltropanes, (g) 6/7-substituted cocaines, (h) 6-alkyl-3-benzyl tropanes, and (i) piperidine homologues of cocaine.

The rationale to synthesize cocaine analogues was embedded in two facts: (1) *N*-ethylmaleimide was capable of inhibiting about 95% of the specific binding of [^{3}H]mazindol and that the effect of 10 mM *N*-ethylmaleimide was completely prevented by 10 μM cocaine, while neither 300 μM DA nor D-amphetamine afforded significant protection,[33] and (2) aspartate and serine residues lying within the first and seventh hydrophobic putative membrane spanning regions were critical for DA uptake but less so for [^{3}H]WIN 35428 binding.[26] These data have supported the hypothesis that a significant portion of the cocaine binding domain on the DAT is distinct from that of either DA or amphetamine. This distinction has raised hopes to design drugs which could prevent cocaine binding without inhibiting DA uptake.

Synthesis of natural (−)-cocaine has been interesting to chemists. In addition to construction of the 8-methyl-8-azabicyclo[3.2.1]octane ring system, the major hurdle to its synthesis has been the control of stereochemistry, both of enantiomeric integrity and of the thermodynamically unstable *axial* carbomethoxy function. The original and classical Mannich-type construction of the tropane skeleton, developed over one-half of a century ago by Willstatter, Robinson, and Schoepf as the first biomimetic synthesis,[253] is still employed to obtain cocaine analogues.[120,254] These methods involve resolution or separation of racemic or diastereomeric mixtures. Other methods have employed cycloaddition reactions, including the reaction of Rh(II)-stabilized vinylcarbenoids with pyrroles,[255] [3 + 4]cycloaddition of iron oxallyl cations of pyrrole,[256] nitrone cycloaddition,[257] nitroso cycloaddition,[258] and pyridinium betaine-based dipolar cycloaddition.[227,259] Recently, Lin et al.[260] utilized Dieckmann condensation of the *cis*-5-substituted D- and L-proline esters to construct 8-azabicyclo[3.2.1]octane framework.

A. Stereoisomers of Cocaine

Carroll et al. synthesized all eight isomers of cocaine. The goal this study was 2-fold: (1) to define the stereospecific requirements of the cocaine binding site, and (2) to identify the most active isomer, which would serve as the lead stereoisomer for the design of cocaine anatagonist.[5] Figure 29 shows the structure of the stereoisomers of cocaine.

For the most part, *R*-cocaine has been obtained from natural sources and four of its isomers containing the *R*-configuration have been prepared from it. The key features in the synthesis of isomers of cocaine were (1) epimerization of the 2β-carbomethoxy group of *R*-cocaine to the *equatorial* position (2α) upon saponification to give pseudoecgonine methyl ester (*R*-**180**)[261] and (2) epimerization of the 2α-carbomethoxy group to the less stable *axial* position (2β) upon refluxing in water. The isomers *R*-**181** and *R*-**182** were obtained from 2-carbomethoxy-3-tropinone, which in turn was synthesized from commercially available 3-tropinone and dimethyl carbonate in the presence of sodium hydride.[120] Following resolution using (+) and (−)-tartaric acid, *R*-2-carbomethoxy-3-tropinone (*R*-**4**) and (*S*)-2-carbomethoxy-3-tropinone (*S*-**4**) were obtained.[117] Sodium borohydride reduction at −20 °C selectively gave allopseudoecgonine methyl ester (*R*-**181**), which upon refluxing in water followed by esterification afforded *R*-alloecgonine methyl ester *R*-**182**.[118] Scheme 42 shows the synthesis of key intermediates. The isomers were characterized by ^{1}H NMR.[118] Benzoylation of the appropriate tropanols then gave the required isomer of cocaine.[5]

The potencies of *R*-cocaine and its seven isomers to inhibit [^{3}H]WIN 35428 demonstrated that cocaine binding was indeed stereoselective (Table 27). Inversion of the overall configuration (cf. **175**; *S*-cocaine) reduced the binding affinity by 155-fold. Another important finding was that the smaller effects were associated with epimerization at C3 while potency was substantially reduced upon change in configuration at the C2 position.[5]

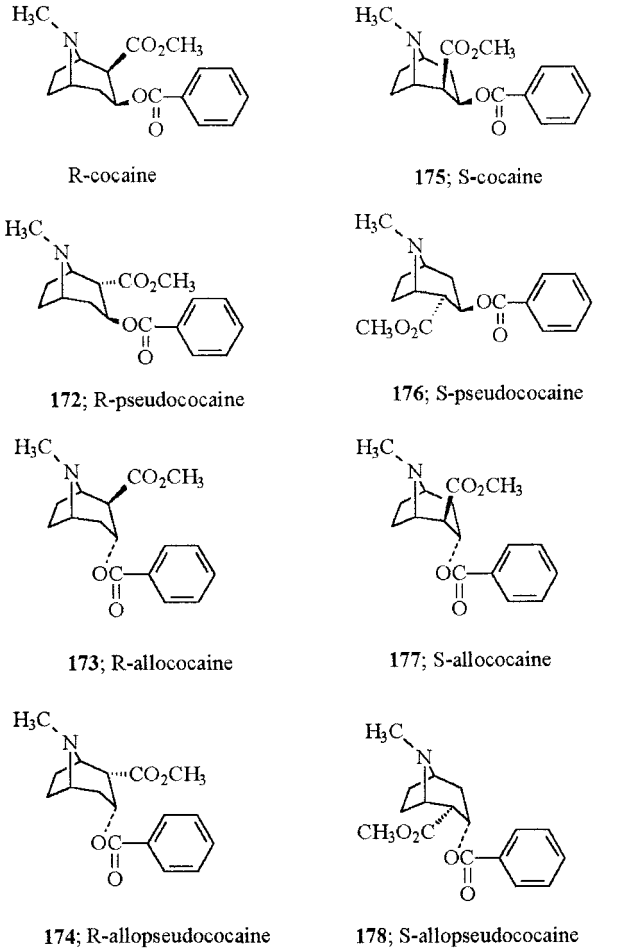


Figure 29. Structures of the stereoisomers of cocaine.

Table 27. Potencies of Stereoisomers of Cocaine for Inhibition of [^{3}H]WIN 35428 Binding to Rat Striatal Membranes

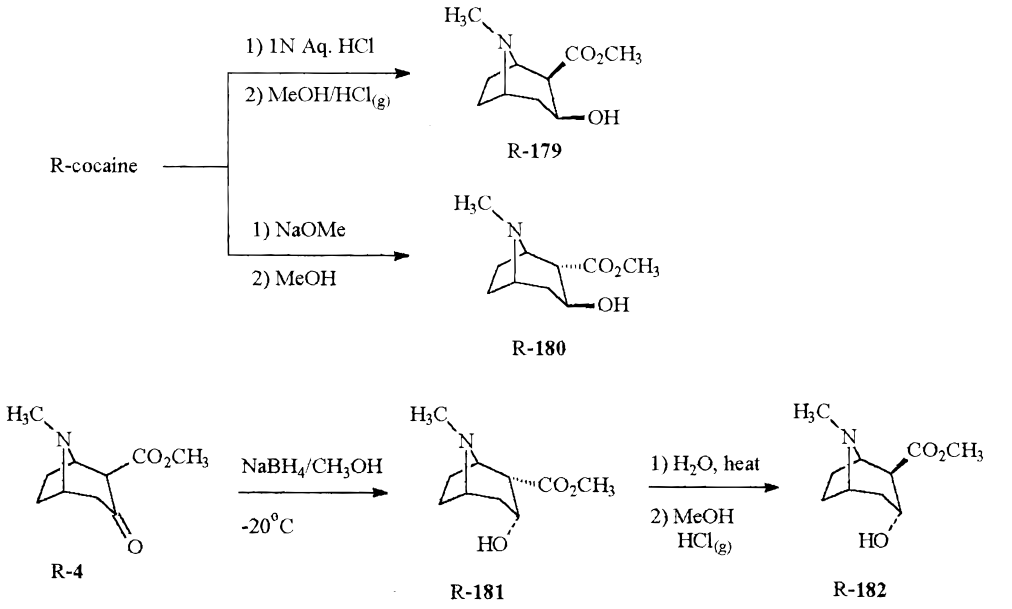
compound no.	IC_{50} (nM)[a]
R-cocaine	102
172; *R*-pseudococaine	15800
173; *R*-allococaine	6160
174; *R*-allopseudococaine	28500
175; *S*-cocaine	15800
176; *S*-pseudococaine	22500
177; *S*-allococaine	9820
178; *S*-allopseudococaine	67700

[a] Standard error of mean in all cases is ≤5%.

B. Phenyl Ring Substituted Cocaines

Many phenyltropanes have been synthesized and evaluated at different transporters. These compounds were, nevertheless, relatively stable and long-lasting ligands for the DAT. The rationale for their high potency at the DAT, in general, resulted from their favorable interaction of the phenyl ring at this site. This perhaps was due to a shorter distance between the bridge nitrogen atom of the tropane ring system and the centroid of the aromatic ring compared to cocaine (cf. 5.6 vs 7.7 Å for phenyltropanes and cocaine, respectively).[126] While phenyltropanes were high-binding compounds, they also possessed en-

Scheme 42



hanced biological activity and, particularly, increased behavioral stimulation.[262,263] The increased behavioral profile of phenyltropanes has led to the general assumption that somehow phenyltropanes fit into the cocaine binding site in such a way that it leads to increased biological activity. This has encouraged the design and synthesis of other classes of compounds with the hope that such drugs might interact at the DAT differently and may be useful as cocaine antagonists.

As shown in Figure 30, the phenyl ring of cocaine has been substituted at the 4′-(**183**), 3′-(**184**), or 2′-position (**185**). The phenyl ring has also been disubstituted (**186**) and even replaced with a naphthyl ring (**187, 188**).

Synthesis of monosubstituted cocaine analogues is shown in Scheme 43. Ecgonine methyl ester (*R*-**179**) was reacted with an appropriately substituted benzoyl chloride (**190**). The acid chloride (**190**) was prepared from a substituted benzoic acid (**189**) or naphthoic acid by reacting with either thionyl chloride or oxalyl chloride.[135,252,264,265] Synthesis of hydroxycocaine (**183d, 184b,** or **185d**) utilized two methodologies. (4′- or 2′)-Hydroxycocaine (**183d** or **185d**) was conveniently prepared via transesterification of 4′- or 2′-acetoxy cocaine (**183c** or **185c**) in anhydrous MeOH/$HCl_{(g)}$. Under these conditions, the benzoyloxy function was found to be stable,[266] Scheme 43. 3′-Hydroxy cocaine (**184b**) was also obtained from 3′-benzyloxy cocaine (**191**) via hydrogenolysis, Scheme 43.[267]

Compound **186** was synthesized as shown in Scheme 44.[252] The commercially available 4-aminosalicyclic acid (**192**) was subjected to diazotization followed by aromatic nucleophilic substitution with iodide ion (I^- or I_3^-) generated from potassium iodide and concentrated sulfuric acid to give 4-iodo salicyclic acid (**193**) in 25% yield. Efforts to alkylate the OH group of **193** with dimethyl sulfate/NaOH were not successful, perhaps due to the reduced reactivity of the hydroxyl group as a nucleophile due to the

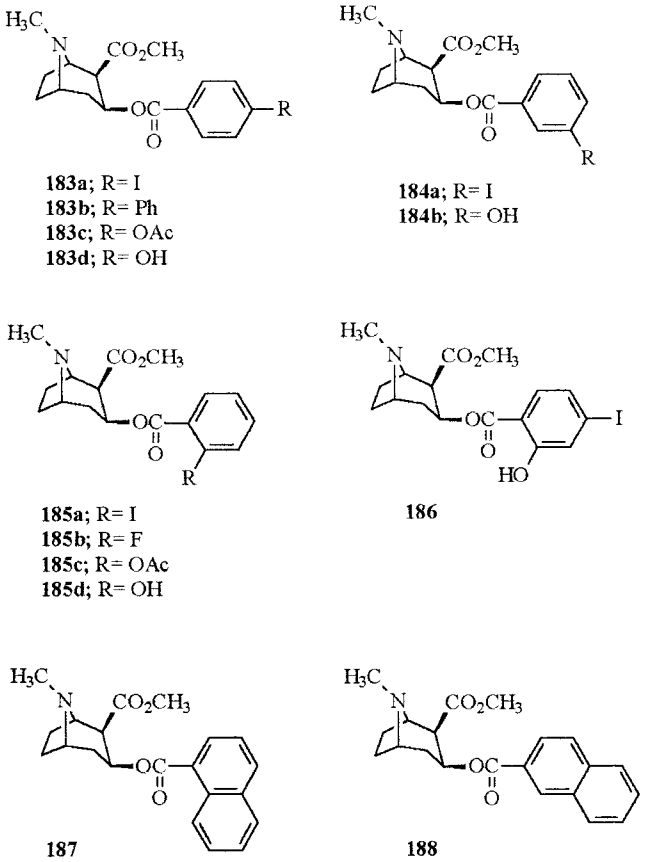
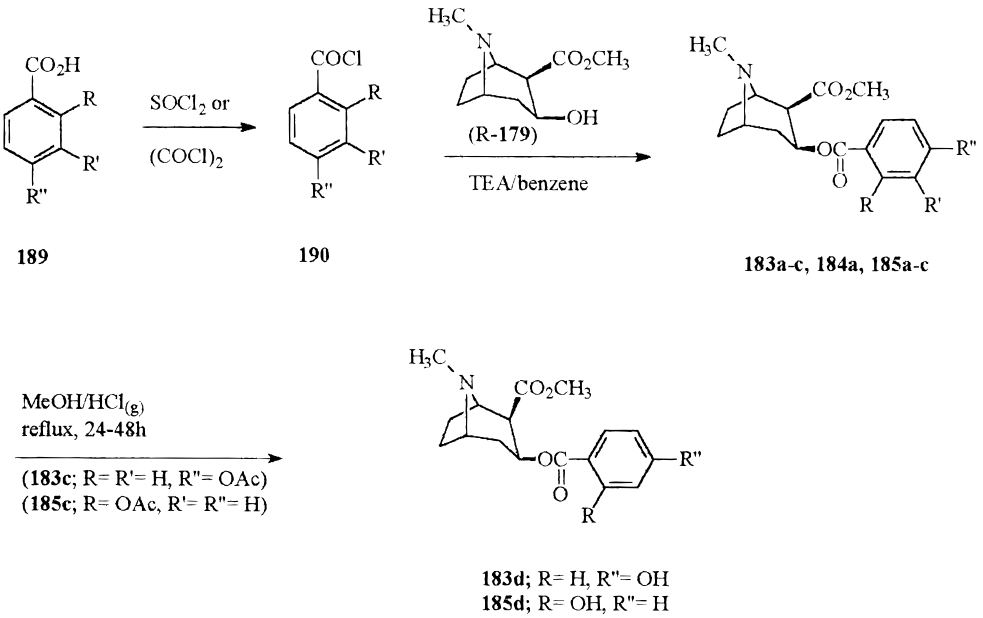


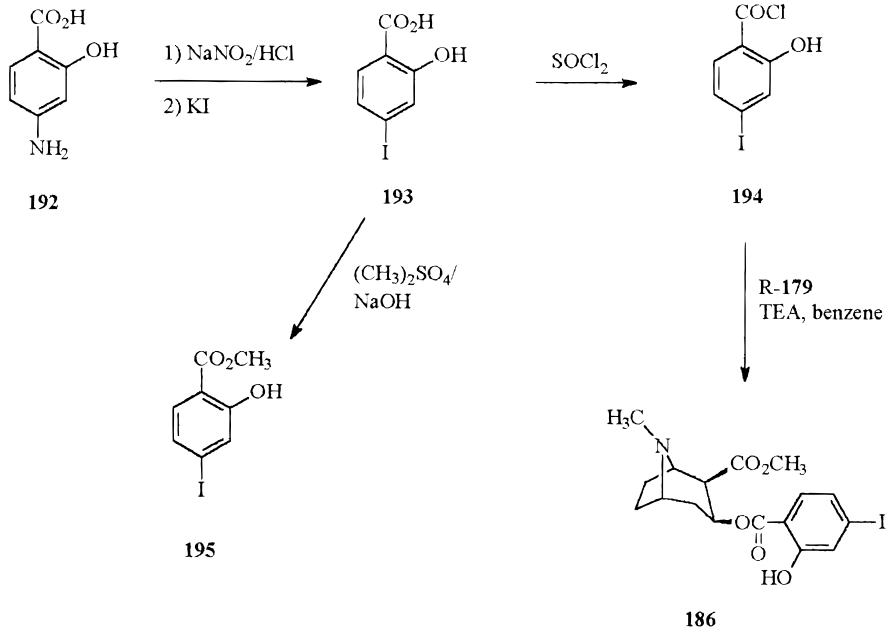
Figure 30. Phenyl ring substituted cocaines.

presence of an electron-withdrawing group (COOH) in the ortho position and intramolecular hydrogen bonding. The reaction of dimethyl sulfate with **193**, however, gave **195**, in which only the carboxylic acid group was methylated. Therefore, **193** was reacted with thionyl chloride to give acid chloride **194**, which upon reaction with *R*-**179** afforded **186** in 22% overall yield. The ^1H NMR of **186** and **193** indicated that the OH group in these compounds was indeed hydrogen-bonded as it appeared at δ 10.75 and 10.39 ppm,

Scheme 43



Scheme 44



respectively (cf. 4.0−7.5 ppm chemical shift for the free phenolic OH group).

As shown in Table 28, substitution in the phenyl ring of cocaine significantly affected the binding potency of the ligand at the monoamine transporter. A bulky group at 4′-, 3′-, or 2′-positions (**183a,b, 184a, 185a**) significantly reduced the potency of cocaine analogues. The most significant finding from Table 28 was the effect of hydroxylation. The relative potency of hydroxylated analogues was in the order 2′-OH > 4′-OH > 3′-OH. 2′-OH cocaine (**185d**) exhibited 10-fold greater potency for the DAT compared to that of cocaine (IC_{50} comparable to that of WIN 35428). 3′-OH and 4′-OH cocaines were much less potent than WIN 35428. Molecular modeling studies using Alchemy 2000 (Tripos) and Insight II

Table 28. Binding Affinities of Phenyl Ring Substituted Analogues of Cocaine

	IC_{50} (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
cocaine	249 ± 37	615 ± 120	2500 ± 70	2.5	10.0
WIN 35428	24 ± 4	690 ± 14	258 ± 40	28.7	10.7
nisoxetine	775 ± 20	762 ± 90	135 ± 21	1.0	0.2
fluoxetine	5200 ± 1270	15 ± 3	963 ± 158	0.003	0.2
183a	2522 ± 4	1052 ± 23	18458 ± 1073	0.4	7.3
183b	486 ± 63				
183c	144 ± 2				
183d	158 ± 8	3104 ± 148	601 ± 11	19.6	3.8
184a	325[a]				
184b	1183 ± 115	793 ± 33	3760 ± 589	0.7	3.2
185a	350[a]				
185b	604 ± 67	1770 ± 309	1392 ± 173	2.9	2.3
185c	70 ± 1	219 ± 20	72 ± 9	3.1	1.0
185d	25 ± 4	143 ± 21	48 ± 2	5.7	1.9
186	215 ± 19	195 ± 10	1021 ± 75	0.9	4.7
187	742 ± 48[a]				
188	327 ± 63[a]				

[a] IC_{50} value for displacement of [^{3}H]cocaine.

(Biosym Technologies) indicated that in addition to intramolecular hydrogen bonding between 2′-OH and the adjacent 3β-carbonyl function in **185d** and **186**, intermolecular hydrogen bonding between the 2′-OH group and the DAT was also possible. The intermolecular hydrogen bonding in **185d** and **186** was rationalized after measuring the interatomic distances. The distance between bridgehead nitrogen N8 and the oxygen of the 2′-OH group in **185d** and **186** was 7.96 Å, which was very close to the distance between the nitrogen atom and the oxygen of the *p*-OH in DA (7.83 Å). The interatomic distance between the nitrogen atom and the oxygen atom of the meta OH group in DA was 6.38 Å. Since, OH groups of the DA molecule are known to engage in hydrogen bonding with serine residues 356 and 359, with possibly serine 356 interacting with the *m*-OH group and serine 359 with the *p*-OH group of the catecholic part of DA, the OH groups in **185d** and **186** could similarly interact with serine 359 of the DAT.[252] It is important to note that 2′-hydroxycocaine (**185d**) behaved similar to phenyltropanes in locomoter stimulation.[268]

C. 2β-Substituted Cocaines

This class of compounds is studied in significant detail. The main purpose of synthesizing these compounds was to probe the structural/pharmacophore requirements of the cocaine binding site and to possibly identify a cocaine antagonist. A large number of compounds have been synthesized which can be further divided into two categories: (1) 2β-substituted cocaines, and (2) 2β- and phenyl ring-substituted cocaines.

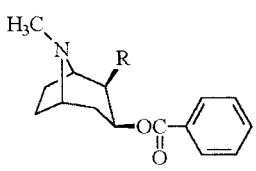
1. 2β-Substituted Cocaines

The following compounds have been identified and evaluated (Figure 31). The 2β-substituted analogues **196a**−**o** and **197a**−**e** were synthesized from cocaine. The 2β-carbomethoxy ester was selectively hydrolyzed by refluxing cocaine free base in water. The 3β-benzoyloxy group was relatively stable under these conditions. The benzoylecgonine (**197e**) thus obtained was converted into acid chloride (**220a**) by treatment with thionyl chloride or imidazolide (**220b**) by reacting with *N*,*N*-formyldiimidazole (CDI). The ester analogues **196a**−**j** were then prepared by treating **202a** or **202b** with an appropriate alcohol.[269] The carboxamides were also prepared in a similar fashion by the reaction of **202a** with ammonium hydroxide or the appropriate amine, Scheme 45.[148] The nitro analogue **196i** was used to prepare analogues **196k**−**o**. The catalytic reduction of the nitro analogue **196i** over platinum oxide catalyst gave the *p*-amino analogue **196k**. Diazotization of **196k** followed by treatment with sodium azide yielded **196m**. Reaction of **196k** with thiophosgene, bromoacetyl bromide, or ethylsuccinoyl chloride afforded the *p*-isothiocyanate **196l** and the amides **196n** and **196o**, respectively.[269]

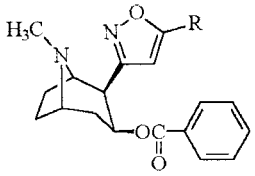
Cocaethylene (**196a**) was also synthesized via a lipophilic ion pair **203**. Thus, benzoylecgonine (**197e**) was stirred with 4-fold excess of tetramethylethylenediamine (TEMED) and 20-fold excess of iodoethane in DCM as the solvent. After 3 days at room temperature there was 85% of **196a**.[270] An important aspect of this synthesis was that intermediate **203** reacted with iodoethane as it formed in situ and there was no need to isolate it (Scheme 46).

The 2β-isoxazole and isoxazoline ring containing analogues of cocaine (**198a**−**e, 199a,b**) were synthesized by utilizing nitrile oxide cycloaddition (NOC) chemistry.[80] Ecgonine methyl ester (*R*-**179**) was converted into alcohol **204** using Dibal-H after protection of the 3β-alcohol group with TBDMSCl. Conversion of the primary alcohol **204** into an aldehyde by Swern oxidation followed by reaction with hydroxylamine hydrochloride led to a 1:1 mixture of *E*/*Z* oximes (**205**). The latter compound was then reacted with an appropriately substituted dipolarophile in the presence of sodium hypochlorite to afford the corresponding isoxazole or isoxazoline product (**207**) via intermediate **206**. Removal of the TBDMS group with TBAF followed by benzoylation provided **198a**−**e, 199a,b** as shown in Scheme 47.

The isoxazole **200** was synthesized by cycloaddition of carboethoxyformonitrile oxide (**209**) to olefin **208**,

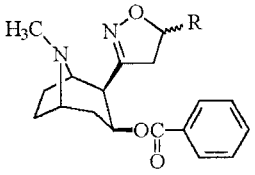


cocaine; R= CO_2CH_3
196a; R= $CO_2CH_2CH_3$ (cocaethylene)
196b; R= $CO_2(CH_2)_2CH_3$
196c; R= $CO_2CH(CH_3)_2$
196d; R= $CO_2C_6H_5$
196e; R= $CO_2CH_2C_6H_5$
196f; R= $CO_2(CH_2)_2C_5H_5$
196g; R= $CO_2(CH_2)_3C_6H_5$
196h; R= $CO_2CH_2CH{=}CHC_6H_5$
196i; R= $CO_2(CH_2)_2C_6H_4$-4-NO_2
196j; R= $CO_2(CH_2)_2C_6H_4$-4-Cl
196k; R= $CO_2(CH_2)_2C_6H_4$-4-NH_2
196l; R= $CO_2(CH_2)_2C_6H_4$-4-NCS
196m; R= $CO_2(CH_2)_2C_6H_4$-4-N_3
196n; R= $CO_2(CH_2)_2C_6H_4$-4-$NHCOCH_2Br$
196o; R= $CO_2(CH_2)_2C_6H_4$-4-$NHCO(CH_2)_2CO_2Et$

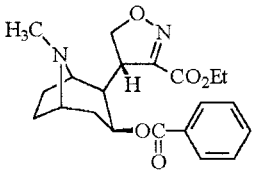


197a; R= $CONH_2$
197b; R= $CON(CH_3)_2$
197c; R= $CON(OCH_3)CH_3$
197d; R= $CONHCH_3$
197e; R= CO_2H
197f; R= CH_2OH
197g; R= H (tropacocaine)

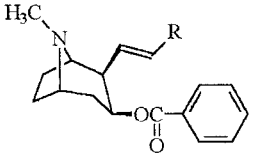
198a; R= H
198b; R= CO_2Et
198c; R= CO_2Bu^t
198d; R= C_6H_5
198e; R= $CH{=}CHCO_2Me$



199a; R= β(or *R*)-CO_2Et
199b; R= α(or *S*)-CO_2Et



200



201a; R= H
201b; R= Cl
201c; R= CO_2Et
201d; R= $CH{=}CHCO_2Et$
201e; R= $PO(OEt)_2$

Figure 31. 2*β*-Substitutes analogues of cocaine.

followed by desilylation and benzoylation. The stereochemistry of **200** was determined based upon mechanistic considerations, Scheme 48.[80] The olefin **208** was obtained from alcohol **204**.

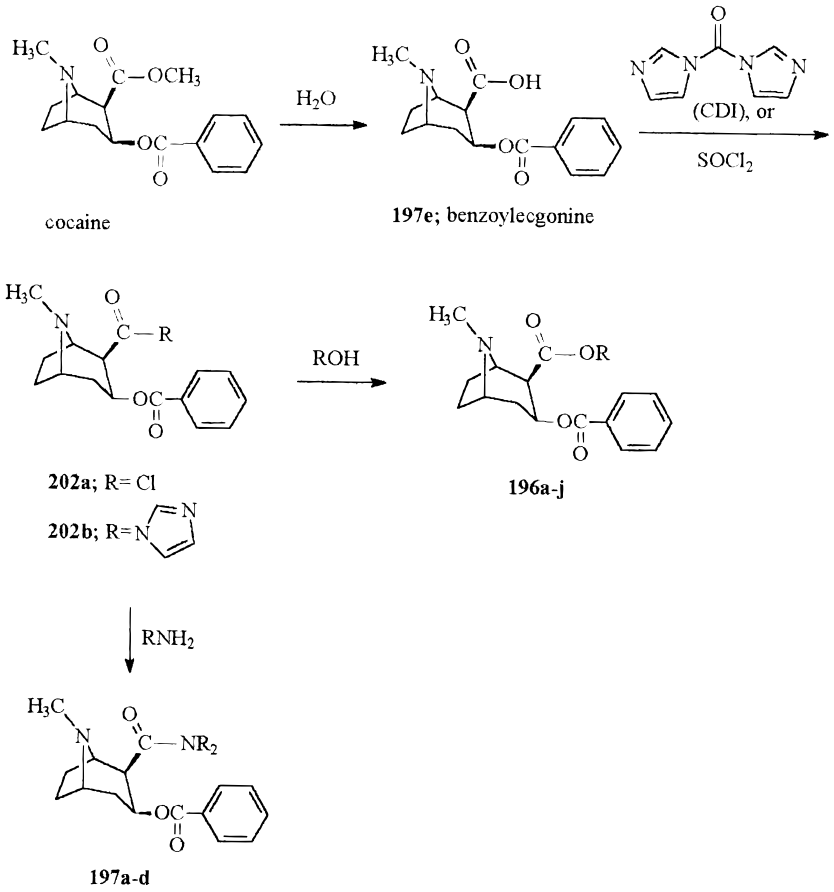
The vinylogous ester analogues of cocaine **201a**−**e** were prepared by a two-step sequence from the aldehyde derived from alcohol **204**. The Wittig reaction with the appropriate (carboalkoxy methylene)-triphenylphosphorane followed by deprotection and subsequent benzoylation afforded **201c,d**. The phosphonate **201e** was prepared by Wadsworth−Emmons protocol using the anion derived from tetraethylmethylene diphosphonate.[80] Compounds **201a** and **201b** were also obtained in a similar manner.

Tables 29 and 30 list the binding potencies of 2*β*-substituted cocaine analogues. The 2*β*-ester and amide analogues (**196, 197**) could still engage in hydrogen bonding like cocaine. Furthermore, a large 2*β*-substituent may distort the tropane skeleton by flattening the piperidine ring, particularly at the 8-aza end, to relieve the steric strain between the 2*β*-substituent and the aza bridge.

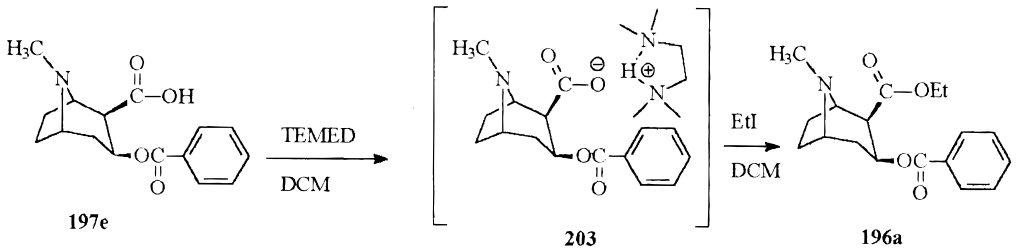
It is important to note that benzoylecgonine (**197e**) has a very low potency (195 000 nM) compared to cocaine. Such a large difference in potency may be due to zwitterion formation or some other factors which interfere with binding.[269] Furthermore, tropacocaine (**197g**) has a low potency compared to cocaine, signifying the importance of a 2*β*-carbomethoxy function in cocaine. As shown in Table 29, replacement of the methyl group of the C2 ester in cocaine with an ethyl (**196a**), propyl (**196b**), isopropyl (**196c**), phenyl (**196d**), benzyl (**196e**), phenethyl (**196f**), phenylpropyl (**196g**), or *trans*-cinnamyl group (**196h**) resulted in small decreases (1.3−4-fold) in potency at the DAT. Determination of the effects on binding at the 5-HTT and NET showed two of the analogues, the isopropyl and phenyl esters, **196c** and **196d** to be reasonably selective for the DAT.[147] Somewhat surprisingly, the benzyl, phenethyl, phenylpropyl, and cinnamyl esters **196e**−**h** showed increased potency (1.7−3.5-fold) at the 5-HTT compared to cocaine. It is also notable that electron-rich aromatic groups in the 2*β*-phenethyl esters (e.g., **196k**) led to higher potency relative to alkyl esters (e.g., **196c**) while electron-deficient aromatic analogues (e.g., **196i**) had reduced potency.[147,269]

To gain additional information, 2*β*-carboxamides (**197a**−**d**) were tested. The tertiary amide **197b** was the most selective compound at the 5-HTT (1131-fold) and only slightly less potent at the DAT and NET compared to cocaine. Compound **197c** was also quite

Scheme 45



Scheme 46

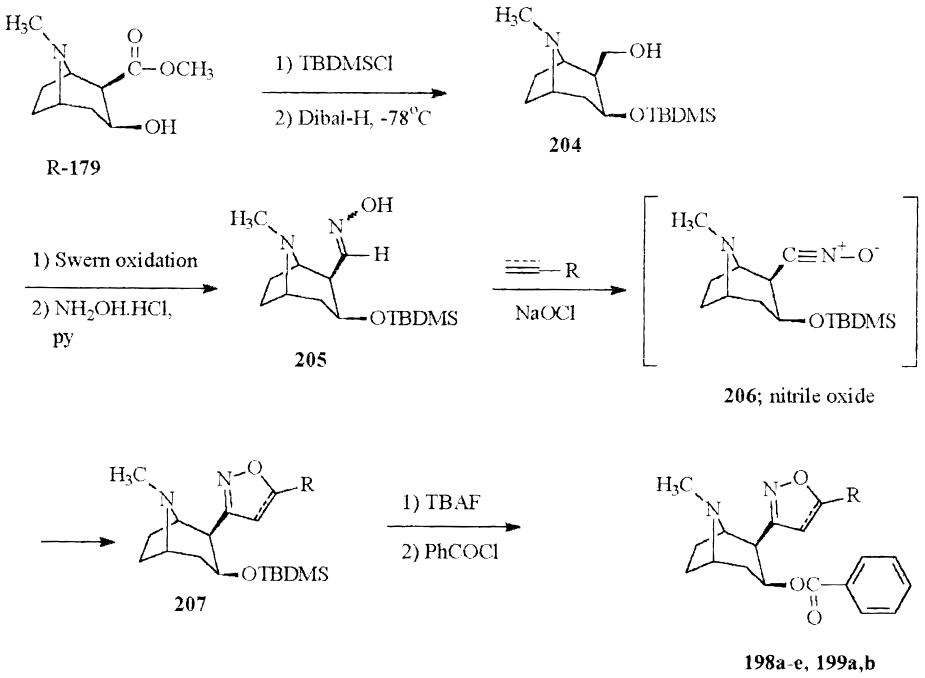


selective at the 5-HTT (469-fold) and was slightly more potent at the DAT and nearly equipotent to cocaine at the NET. These two tertiary amides **197b,c** were 137- and 27-fold less potent at the 5-HTT compared to cocaine. Furthermore, their NET/DAT ratio was better than cocaine.[147] The primary and secondary amide analogues of cocaine (**197a,d**) were much less potent. This reduction in potency of **197a** and **197d** has been rationalized in terms of reduced likelihood of a second hydrogen bonding or at least a weaker second hydrogen bonding.[269]

Taken together, the results summarized in Table 29, showed that in this series of compounds an ester or carboxamide function was important at the 2β-position, because replacement of the 2β-carbomethoxy group with a hydrogen (tropacocaine; **197g**) in cocaine led to reduced potency. Furthermore, it appeared preferable to have a group at the 2β-position which could possibly engage in two hydrogen bonds as an acceptor.[148,269] However, the presence of a 2β-hydrogen bonding group is not an absolute requirement as discussed below.

The goal of synthesizing isoxazole and isoxazoline analogues of cocaine was to study the steric requirements of the 2β-carbomethoxy portion of the cocaine pharmacophore. In addition to steric bulk, these compounds could also engage in hydrogen bonding.[80] As shown in Table 30, the isoxazole ring was well tolerated at the 2β-position of cocaine (compound **198a**). Molecular modeling studies also showed close resemblance in the two structures, i.e., **198a** and cocaine. Increasing the bulk at the 5′-position of the isoxazole ring led to a decrease in potency. It was, however, not so in the case of the 5′-carboethoxy-isoxazole analogue (**198b**) which showed nearly 5-times greater potency in binding and 2-times in inhibition of dopamine uptake.[80] The nonplanar isoxazolines (**199a,b**) were less potent, and these compounds were found to exhibit differences in activity stemming from the stereocenter present in the isoxazoline ring. Compound **200** was synthesized to examine the activity upon reversal of the N and O atoms of the isoxazoline ring. It was found to be more

Scheme 47



Scheme 48

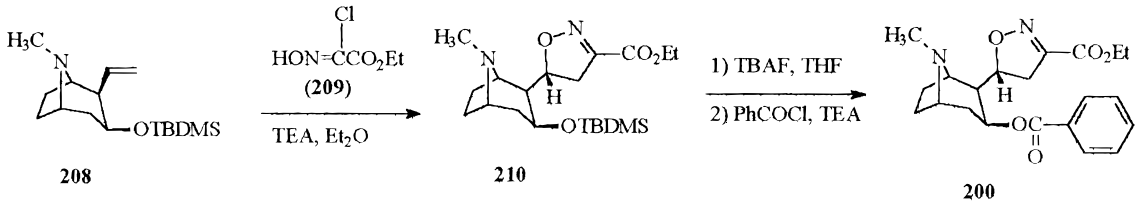


Table 29. Receptor Binding Data for 2β-Substituted Cocaine Analogues

	IC_{50} (nM)			selectivity	
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine	5-HTT/DAT	NET/DAT
cocaine	89 ± 4.8	1045 ± 89	3298 ± 293	11.7	37.0
196a	195 ± 45	5801 ± 493	10000 ± 751	29.7	51.3
196b	196 ± 46	4517 ± 430	6124 ± 262	23.3	31.2
193c	219 ± 48	25224 ± 1498	30384 ± 1685	115	139
196d	112 ± 31	33666 ± 3330	31024 ± 1909	300	277
196e	257 ± 14	302 ± 23	20794 ± 950	1.2	80.9
196f	181 ± 10	615 ± 52	19944 ± 1026	3.4	110
196g	147 ± 19	374 ± 15	4893 ± 344	2.5	33.3
196h	371 ± 15	368 ± 6.3	68931 ± 3476	1.0	186
196i	601 ± 28				
196j	271 ± 12				
196k	72 ± 7				
196l	196 ± 14				
196m	227 ± 19				
196n	61 ± 6				
196o	86 ± 4				
197a	753 ± 41.3	13725 ± 1256	3981 ± 229	18.2	5.3
197b	127 ± 6.36	143713 ± 8854	7329 ± 158	1131	57.7
197c	60 ± 6.4	28162 ± 2565	3935 ± 266	469	65.6
197d	2424 ± 118	44798 ± 2105	4213 ± 206	18.5	1.7
197e	195000				
197f	561 ± 149				
197g	5180 ± 1160				

or less as potent as cocaine but significantly more potent than the related isoxazoline esters **199a** and **199b**.

The vinylogous analogues **201b** and **201c** were significantly more potent as well as somewhat selective at the DAT than cocaine, while other analogues **201a, 201d,** and **201e** were considerably less potent. Thus, it could be inferred that a hydrogen-bond acceptor at the 2β-position was not exclusively necessary for high binding of cocaine analogues.

Table 30. Mazindol Binding and DA Uptake of the 2β-Substituted Cocaine Analogues

	IC_{50} (nM)		selectivity
compound no.	[^{3}H]mazindol	[^{3}H]DA	uptake/binding
cocaine	580 ± 70	570 ± 180	1.0
198a	520 ± 40	260 ± 70	0.5
198b	120 ± 10	290 ± 40	2.4
198c	2230 ± 220	1820 ± 810	0.8
198d	2000 ± 640	2920 ± 1620	1.5
198e	3600 ± 400	3590 ± 1180	1.0
199a	710 ± 150	1060 ± 340	1.5
199b	5830 ± 630	8460 ± 620	1.4
200	880 ± 350	400 ± 140	0.4
201a	1730 ± 550	1120 ± 390	0.6
201b	222 ± 49	368 ± 190	1.6
201c	50 ± 10	130 ± 10	2.6
201d	1220 ± 100	870 ± 50	0.7
201e	4850 ± 470	5500 ± 70	1.1

2. 2β-Substituted 4′-Iodococaines

4′-Iodococaine (**183a**) was 10-fold less potent at the DAT and also less selective at the 5-HTT and NET compared to cocaine (Table 28).[268] However, it was found to possess reduced locomotor activity in mice and reduced cocaine-induced locomotor stimulation in a dose-dependent manner when co-administered with cocaine.[271] Therefore, the main purpose of synthesizing 2β-substituted 4′-iodococaine analogues was to improve upon the binding potency of such compounds at the DAT. It was expected that these compounds might retain the nonstimulant property of **183a**. The choice of different substituents at the 2β-position was based on the modification made in the phenyltropanes series of compounds. Synthesis of the 2′-hydroxylated 4′-iodococaine analogue (**212**) was based upon the observation that 2′-hydroxylation increased the binding affinity of cocaine and **183a** to the DAT by approximately 10-fold.[252]

A diverse group of substituents were introduced at the C2β-position as shown in Figure 32.[272] The synthesis of compounds **211a**−**h** is summarized in Scheme 49. Hydrolysis of 4′-iodococaine (**183a**) free base in refluxing water gave 4′-iodobenzoylecgonine (**213**), which upon reduction with diborane afforded 2β-methanol (**211a**). The alcohol **211a** was treated with Ac_2O to give acetate **211b**. Treatment of **213** with CDI or oxalyl chloride gave the imidazolide **214a** or chloride **214b**, respectively. The *N*-methylamide **211c** was prepared by treating **214a** with a mixture of methylamine hydrochloride and sodium carbonate. Reaction of an appropriate alcohol with either **214a** or **214b** afforded esters **211d**−**g**. The 3-aryl-1,2,4-oxadiazole **211h** was obtained by treating **214b** with benzamidoxime.[272]

2β-Alkyl derivatives of 4′-iodococaine were synthesized from ecgonine methyl ester (*R*-**179**). Thus, *R*-**179** was reduced with Dibal-H after protection with TBDMSCl to give 2β-methanol **215**. The alcohol **215** was subjected to Swern oxidation using DMSO and oxalyl chloride in CH_2Cl_2 at −78 °C to give intermediate aldehyde, which was unstable and directly converted into alkene by a Wittig reaction using methyl triphenylphosphorane generated in situ from methyl triphenylphosphonium bromide and *n*-BuLi in THF. Removal of the TBDMS protecting

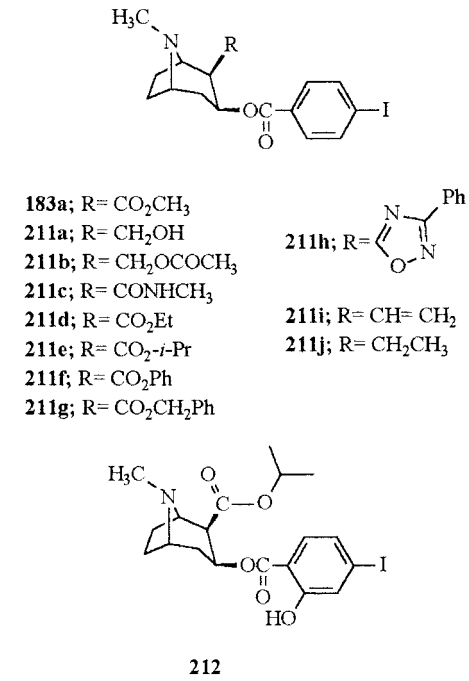


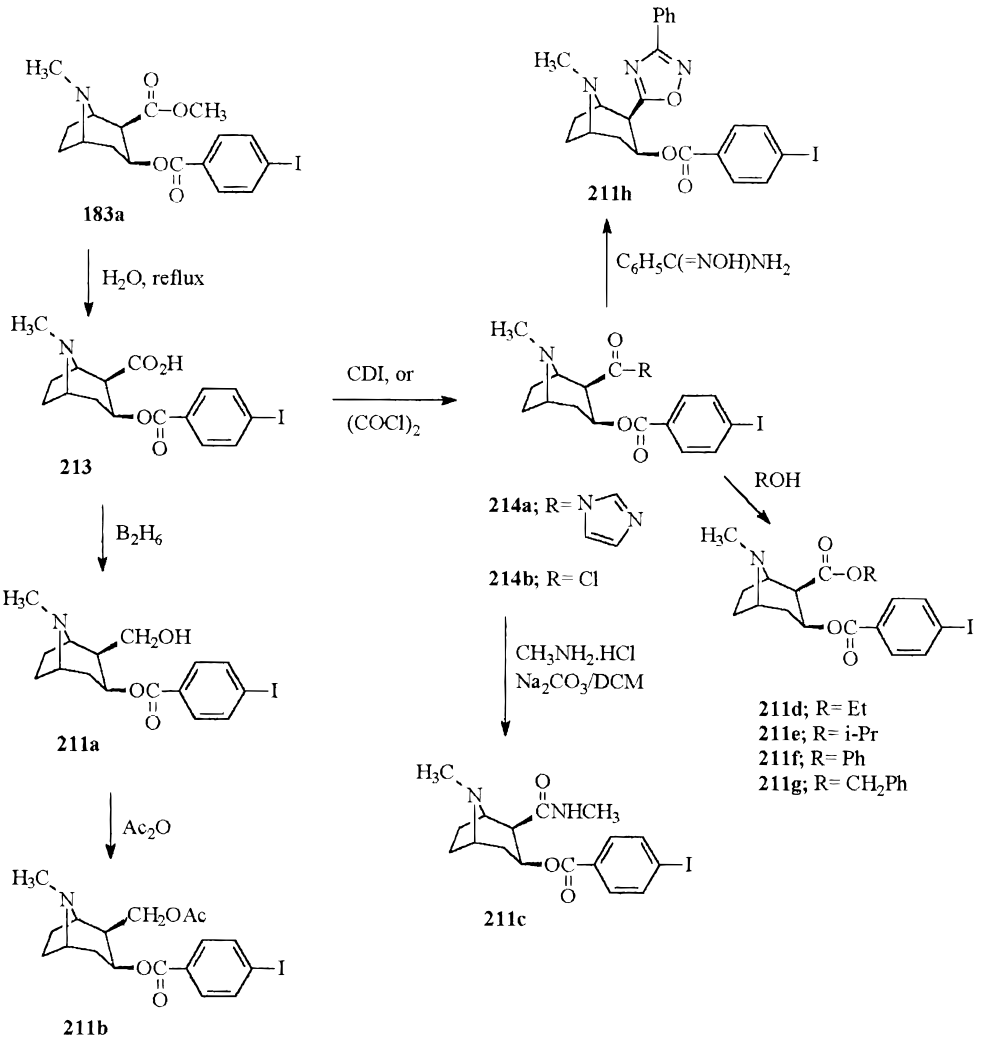
Figure 32. 2β-Substituted analogues of 4′-iodococaine.

group in 75% AcOH gave alkene **216**. The alkene **216** was then benzoylated to give **211i**. It should be noted that **211j** could not be obtained from **211i**. The catalytic hydrogenation led to hydrodehalogenated product in addition to hydrogenation of the 2β-alkenyl group. Therefore, **216** was first hydrogenated and then benzoylated to give **211j,** Scheme 50.[272]

Compound **212** was synthesized in a similar fashion as depicted above in Scheme 44. Ecgonine (*R*-**2**; Scheme 1) was reacted with 2-propanol in an acid-catalyzed esterification and then benzoylated with 4-iodosalicyloyl chloride to give the 2′-hydroxylated 2β-isopropyl ester, **212**.

As seen in Table 31, the IC_{50} values of the 2β-substituted 4′-iodococaine analogues did not follow the same pattern as observed with the 4′-iodophenyltropane analogues (Tables 6−8 and 10). In contrast to phenyltropanes, 2β-substituted 4′-iodococaine analogues were generally less potent. However, upon comparison with **183a**, 2β-isoproyl ester (**211e**) was approximately 2-fold more potent. The least active compound was 2β-amide (**211c**) (IC_{50} > 100 000 nM). Such a reduction in potency could not be explained in terms of weaker hydrogen bonding, rather it may be due to some unknown factors, whereby 2β-amide function could either orient in such a way that no hydrogen bonding was possible or could even interfere with the binding. The role of hydrogen bonding seemed to be important in this series of compounds. For example, 2β-hydroxymethyl derivative (**211a**) was 2.5-fold less potent, which contained only one hydrogen-bonding site. The binding potency was restored upon acetylation (**211b**). In contrast to hydrogen-bonding interaction of the 2β-substituents in these compounds, 2β-vinyl and 2β-ethyl analogues (**211i** and **211j**) had very similar potencies as that of **183a**. Consistent with the previous observation, 2′-hydroxylation of the most potent compound **211e** (i.e.,

Scheme 49



compound **212**) further increased the potency by 2-fold.

D. *N*-Modified Cocaines

To explore the significance of the basic nitrogen atom (N8) of the tropane ring, *N*-modified analogues of cocaine were synthesized. Three kinds of *N*-modified cocaine analogues have been synthesized as shown in Figure 33.

(1) The *N*-alkyl analogues of cocaine (**217, 219a**−**e**) were designed to determine the basicity of nitrogen of tropane.[74,211] (2) The *N*-sulfonyl analogues (**220a**−**f**) were designed to render the bridge nitrogen neutral and incapable of protonation under physiological conditions.[73] (3) The *N*-nitrogen bond analogues (**221a**−**d, 222**) represented directly linked electron-withdrawing substituents to the bridgehead nitrogen of the tropane ring.[74]

Cocaine methiodide (**217**) was obtained by heating cocaine with an excess of methyliodide in acetone.[273] The remaining compounds were obtained from *N*-norcocaine (**218**), which in turn was obtained by *N*-demethylation of cocaine via reaction with excess of Troc-Cl to afford carbamate, followed by reductive removal of the carbamate with zinc/acetic acid.[274] Alkylation of the secondary amino group of norcocaine with an appropriately substituted alkyl bromide afforded *N*-alkyl derivatives **219a**−**e** (Scheme 51). *N*-Acetyl derivative was obtained by treating norcocaine with acetyl chloride. To obtain **219c**, *O*-ethoxyethyl protected 2-bromoethanol was used. The protecting group EE was removed with MeOH/HCl. Similarly benzyl bromoacetate was used to prepare **219e**.

The *N*-sulfonyl analogues of cocaine **220a,c**−**f** were prepared by treating norcocaine with the corresponding sulfonyl chloride in TEA as solvent at −20 °C. Excess TEA was used to trap the acid released during the reaction. Compound **220b** was prepared by treating norcocaine with trifluoromethane sulfonic anhydride (Tf_2O) at −78 °C. These compounds did not form HCl salts due to the relatively neutral character of their nitrogen atom. This was further confirmed by ^{1}H NMR as the protons on the adjacent carbons (H1 and H5) appeared downfield by 0.37 and 0.48 ppm, respectively, compared to cocaine, Scheme 51.[73]

Synthesis of *N*-norcocaine compounds with a nitrogen−nitrogen bond is shown in Scheme 52.[73] Treatment of norcocaine (**218**) with nitrous acid yielded *N*-nitroso-*N*-norcocaine (**221a**), which was easily oxidized to the *N*-nitro compound **221b** by the action of hydrogen peroxide in TFA.[275] Attempts to

Scheme 50

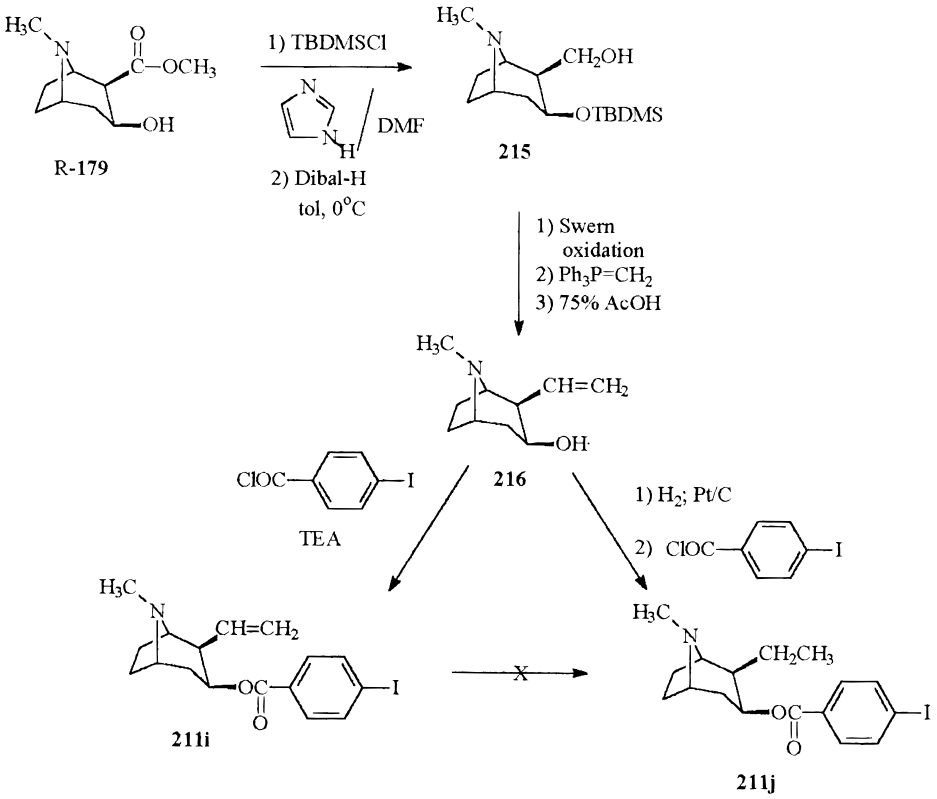


Table 31. DAT Binding Affinities of 4′-Iododocaine-2β-substituted Cocaine Analogues for Displacement of [^{3}H]WIN 35428

compound no.	IC_{50} (nM)
cocaine	249 ± 37
WIN 35428	24 ± 4
183a	2522 ± 4
211a	6214 ± 1269
211b	2995 ± 223
211c	>100000
211d	2031 ± 190
211e	1377 ± 10
211f	2019 ± 253
211g	4602 ± 325
211h	3459 ± 60
211i	2165 ± 253
211j	2692 ± 486
212[a]	663 ± 70

[a] IC_{50} values at 5-HTT and NET were 4507 ± 13 and 34838 ± 796 for displacement of [^{3}H]paroxetine and [^{3}H]nisoxetine, respectively.

reduce the nitroso group of **221a** with Zn/AcOH did not succeed; instead *N*-acetylaminonorcocaine **221c** was obtained.[276] Direct introduction of the amino group in norcocaine with hydroxylamine-*O*-sulfonic acid (HOSA) resulted in the formation of a tricyclic lactam **222**, most likely via an initial formation of hydrazine (**221d**), followed by intramolecular attack on the carbomethoxy group, Scheme 52.[277]

The binding potencies of *N*-modified cocaine analogues are shown in Table 32. The data indicate that substitution at nitrogen can have a large effect on the activity, in particular when changes in electron density at N8 are involved. For example, cocaine methiodide salt (**217**) bearing a formal positive charge on nitrogen was 100-fold less potent than cocaine. Replacement of the *N*-methyl group of cocaine with an electron-withdrawing acetyl group (**219b**) resulted in a 30-fold reduction in binding affinity. The replacement of the *N*-methyl group with hydrogen (i.e., norcocaine; **218**) or an electronically similar but sterically larger group such as benzyl (**219a**) resulted in only 3−7-fold lower potency. The latter data led Stoelwinder et al.[74] to synthesize functionalized *N*-alkyl analogues (**219c**−**e**) in which the electron-withdrawing groups were insulated from the nitrogen atom by a one- or two-carbon-atom spacer. These compounds (**219c**−**e**) also displayed slightly lower (1.3−2.5-fold) binding affinities than cocaine.

The *N*-sulfonamide analogues of cocaine **220a**−**f** showed binding affinities over a wide range. However, these could be viewed in two groups according to their affinities. The first set of compounds included **220a**−**c,** which displayed micromolar to submicromolar K_i values in inhibiting [^{3}H]mazindol binding and [^{3}H]DA uptake. The interesting compounds in this set were **220b** and **220c,** which contained the electron-withdrawing groups on the sulfonyl moiety. These compounds exhibited either nearly similar or enhanced potencies compared to cocaine. The other set of compounds was much less active than cocaine. Perhaps the steric reasons were responsible for the decreased activity of compounds **220d**−**f**, Table 32.

Exchange of the *N*-methyl group with a functional group containing a nitrogen−nitrogen bond led to a much more pronounced change in the binding potency. In these compounds the functional groups were directly connected to the nitrogen atom; therefore, such groups should have a significant effect on the binding affinity. Since the functional groups in the

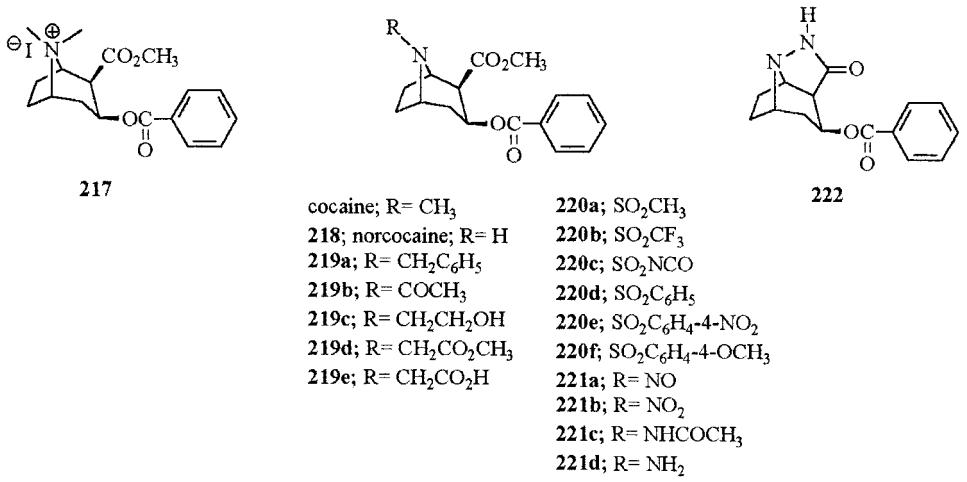
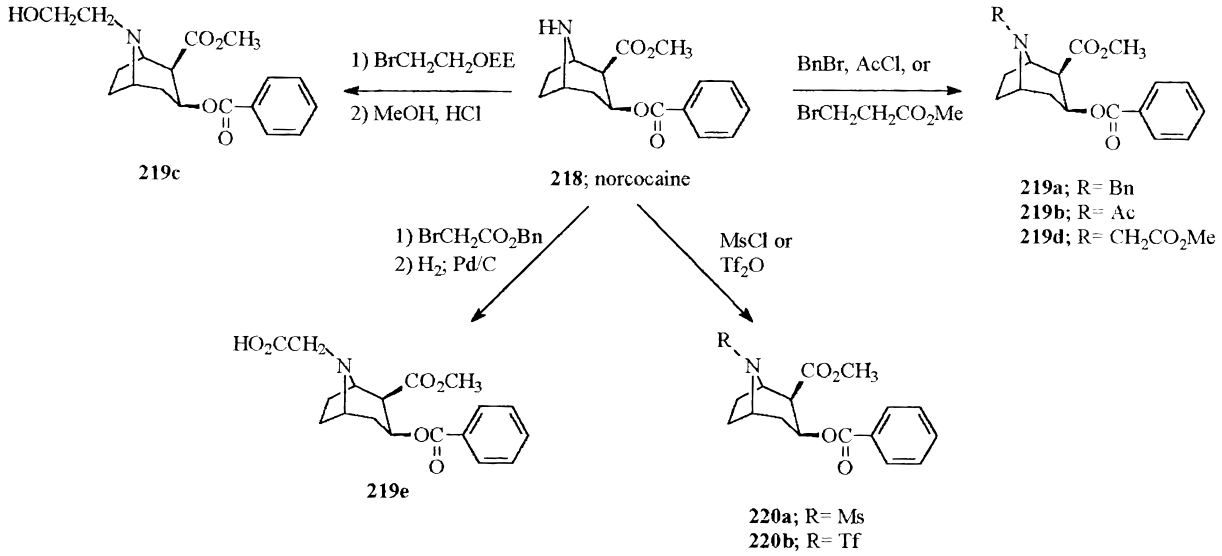
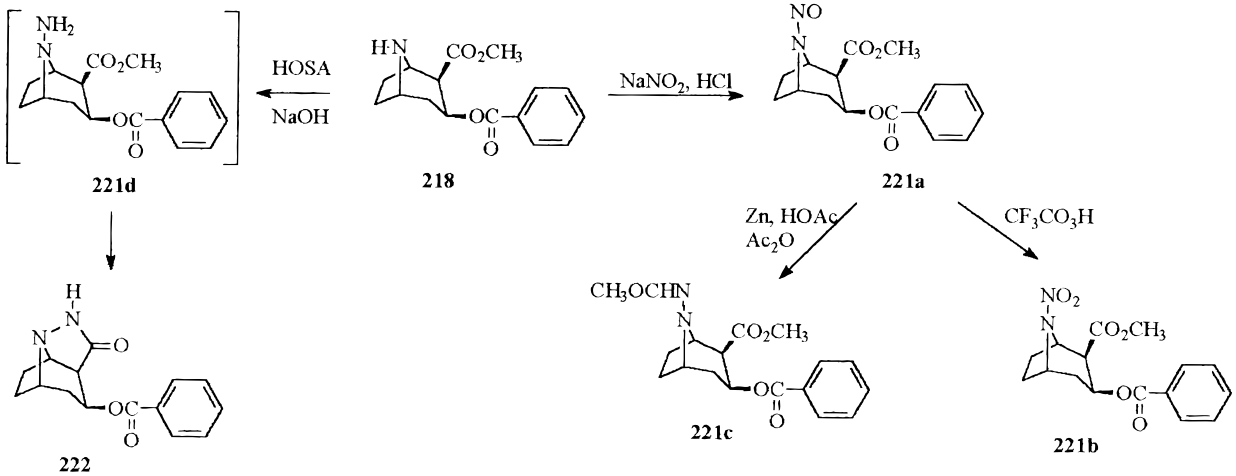


Figure 33. *N*-Modified analogues of cocaine.

Scheme 51



Scheme 52



N−N series were electron-withdrawing, the decrease in binding affinity was expected, as was the case (Table 32, **221a−c, 222**). However, an interesting observation was that the *N*-nitro compound (**221b**) was more potent than *N*-nitroso compound (**221a**) even though a nitro group is more electron-withdrawing.

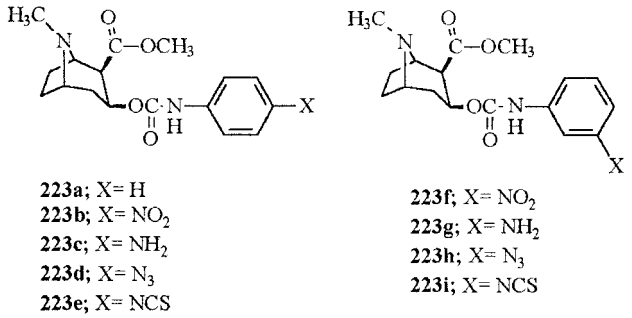
It is important to note that in the *N*-modified cocaine analogues series, all of the compounds were more selective at the DAT binding compared to cocaine, Table 32. Furthermore, the binding affinity data on **220a−f** (Table 32) suggested that these compounds bind to the transporter through hydrogen bonding or weak polar interactions. This explanation

Table 32. [^{3}H]Win 35428/[^{3}H]Mazindol Binding and [^{3}H]DA Uptake of *N*-Modified Cocaine Analogues

	IC_{50} (nM)		selectivity
compound no.	[^{3}H]WIN 35428 binding	[^{3}H]DA uptake	uptake/ binding
cocaine	102		
217	10700 ± 1530		
218; norcocaine	303 ± 59		
219a	668 ± 67		
219b	3370 ± 1080		

	K_i (nM)		selectivity uptake/ binding
	[^{3}H]mazindol	[^{3}H]DA	
cocaine	280 ± 60	320 ± 10	1.1
219c	700 ± 100	1600 ± 200	2.3
219d	480 ± 40	1600 ± 100	3.3
219e	380 ± 20	2100 ± 400	5.5
220a	1290 ± 80	1970 ± 70	1.5
220b	330 ± 30	760 ± 20	2.3
220c	120 ± 10	160 ± 10	1.3
220d	20800 ± 3500	61000	2.9
220e	5720 ± 1140	18800 ± 90	3.3
220f	6820 ± 580	16400 ± 1400	2.4
221a	99500 ± 12300	231700 ± 39500	2.3
221b	7500 ± 900	21200 ± 600	2.8
221c	>1000000	>1000000	
222	44900 ± 6200	115000 ± 15700	2.6

was substantiated by the fact that the compounds presenting the possibility of additional hydrogen bonding (i.e., in addition to the $-SO_2$ group itself) or polar interactions (e.g., **220b** or **220c** as opposed to **220a**) exhibited higher affinity for the DAT. Replacement of the trifluoromethyl group or isocyanate group by a phenyl group led to a sharp reduction in potency (**220d**), whereas some restoration of activity was observed when a methoxy or nitro group was appended to the 4-position of the benzene sulfonyl group (**220e**). A similar explanation could be given for the *N*-nitro derivative (**221b**), which was 13 times more potent than the *N*-nitroso derivative (**221a**), because the former compound has one additional hydrogen-bond acceptor site compared to **221a**. Therefore, it was proposed that the residue of the transporter which is responsible for the recognition of the cocaine nitrogen may be one that can act either as a hydrogen-bond donor or acceptor.



223a; X= H
223b; X= NO_2
223c; X= NH_2
223d; X= N_3
223e; X= NCS

223f; X= NO_2
223g; X= NH_2
223h; X= N_3
223i; X= NCS

Figure 34. 3β-Carbamoyl analogues of cocaine.

E. 3β-Carbamoyl Analogues of Cocaine

3β-Carbamoyl analogues of cocaine were prepared by Kline et al.[278,279] as inhibitors of cocaine binding and DA uptake. These were also evaluated as irreversible and photoaffinity ligands for the DAT. The design of carbamates was inspired by mainly three reasons. First, these compounds retained close structural resemblance to cocaine and were expected to be better probes for labeling the cocaine binding site than cocaine ligands. Second, the carbamoyl functionality was more resistant to hydrolysis than the benzoyl substituent present in cocaine. Third, the synthesis was rather convenient. The following 4′- or 3′-phenyl ring substituted compounds (**223a**−**i**) were prepared as shown in Figure 34.

The synthesis of carbamates was straightforward. Ecgonine methyl ester (*R*-**179**) was refluxed in toluene with either phenyl isocyanate or 4- or 3-nitrophenyl isocyanate to give **223a**, **223b,** or **223f**. Reduction of the nitro group over platinum catalyst afforded amino derivatives **223c** or **223g**. Isothiocyanato derivatives **223e** or **223i** were obtained from amino derivatives by reacting with thiophosgene. Azido analogues **223d** or **223h** were also prepared from the amino derivatives via a diazotization reaction, as described in Scheme 53.

Scheme 53

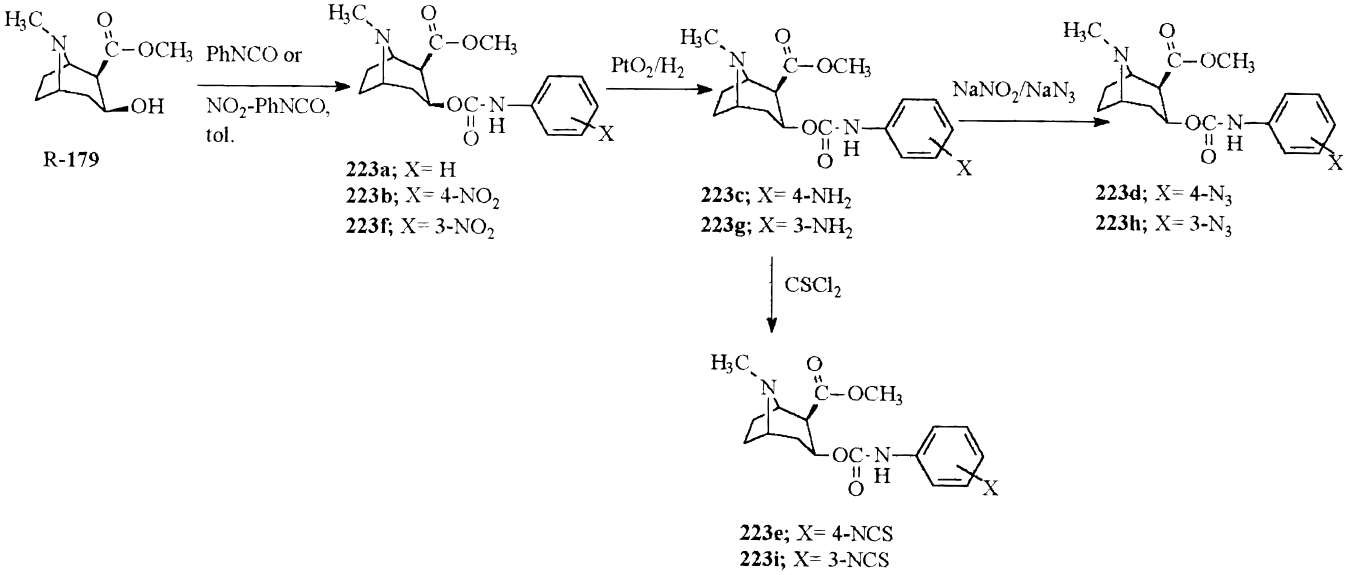


Table 33. Competitive Inhibition of [^{3}H]Cocaine Binding and [^{3}H]DA Uptake by 3β-Carbamoyl Analogues of Cocaine in Rat Striatal Tissue

	IC_{50} (nM)		selectivity
compound no.	[^{3}H]cocaine binding	[^{3}H]DA uptake	uptake/ binding
cocaine	70 ± 10	210 ± 70	3.0
223a	5600 ± 700	52600 ± 3000	9.4
223b	1090 ± 250	5700 ± 1200	5.2
223c	63300 ± 12200	>100000	
223d	1000 ± 240	1180 ± 360	1.2
223e	260 ± 60	490 ± 80	1.9
223f	37 ± 10	178 ± 23	4.8
223g	2070 ± 340	23100 ± 900	11.1
223h	630 ± 150	3900 ± 1590	6.2
223i	960 ± 210	4900 ± 420	5.1

The binding affinity data for carbamates is given in Table 33. It is apparent that the electron-withdrawing groups enhanced potency while electron-donating groups decreased potency. Furthermore, it is interesting to note that by reducing the electron-donating effect of the amino substituent via conversion to either azido or isocyanato group, the affinity for the cocaine binding site was greatly increased. It is also interesting to note that a 3′-substituted analogue was more potent than a 4′-substituted derivative except in the case of isocyanato derivative (**223e** vs **223i**). It was speculated that enhanced potency of 3′-substituted analogue was due to restricted conformational mobility of the carbamate side chain because of its proximity to the methyl ester in the C2-position of the tropane. Thus, conformation of the whole molecule could fit more closely in the active site of the receptor.

F. 3β-Alkylphenyltropanes

These compounds were modeled after the idea that a 3β-substituent in cocaine has the most significant effect on binding to the cocaine receptor as compared to the 2β and tropane nitrogen substituents.[192] An increase in the hydrophobicity at the 3β-phenyl ring has also been known to increase potency (see 3β-phenyltropanes). Furthermore, by increasing the distance of the phenyl ring from the tropane ring via a carbamoyl linkage, Kline et al.[278,279] were able to get compounds with affinities close to cocaine. Combining these two ideas, i.e., increasing the lipophilicity of the 3β-substituent and the distance between the 3β-phenyl ring and the bridgehead nitrogen of the tropane ring, Lieske et al.[135] synthesized 3β-alkylphenyltropanes. In these compounds, the carbonyloxy function at the 3β-position was replaced with an alkyl or alkenyl group. The structures of these compounds (**224a**−**e**) are shown in Figure 35.

The 3β-alkylphenyl analogues of cocaine **224a**−**e** were obtained by a Grignard reaction on anhydroecgonine methyl ester (*R*-**1**) as described in earlier section (see 3β-phenyltropanes).

As seen from the Table 34, 3β-styrene analogue (**224e**) was the most potent compound in this series. It also inhibited DA uptake (cf. uptake/binding ratio of **224e** vs cocaine 2.8 vs 2.1). The two most selective compounds in the series were **224b** and **224c**. Compound **224b** was 10-fold more potent than cocaine at

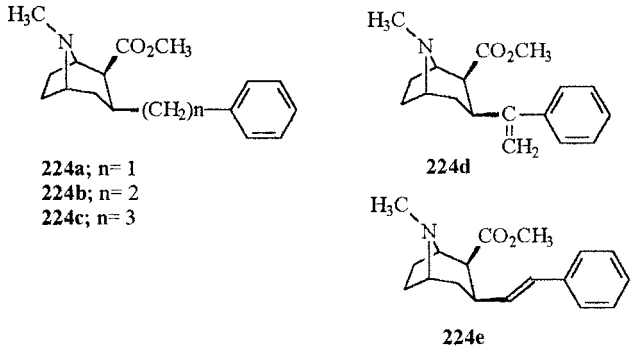


Figure 35. 3β-Alkylphenyl analogues of phenyltropanes.

Table 34. Binding Affinities and Uptake Inhibition by 3β-Alkylphenyltropanes

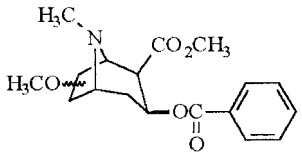
	IC_{50} (nM)		selectivity
compound no.	[^{3}H]cocaine binding	[^{3}H]DA uptake	uptake/ binding
cocaine	101 ± 26	209 ± 20	2.1
224a	885 ± 18	1020 ± 52	1.1
224b	9.9 ± 0.33	70.5 ± 1.0	7.1
224c	344 ± 12	2680 ± 190	7.8
224d	71.6 ± 0.7	138 ± 9	1.9
224e	2.10 ± 0.04	5.88 ± 0.09	2.8

the DAT. CoMFA analysis was used to obtain a rigorous structure−function relationship for these compounds. The results showed that the potencies of these 3β-substituted ecgonine methyl esters were dominated by steric effects and were actually sensitive to the distance between the phenyl ring and the tropane skeleton as well as to the orientation of the phenyl ring relative to the tropane skeleton. Specifically, the binding pocket was extending in a linear fashion away from the tropane ring into which the 3β-substituent must fit during binding. This binding pocket was indicated to be slightly greater in diameter than a phenyl ring and was approximately 9 Å in length. It is such that the barrel was even with or shifted slightly above the CC vector on the bridging nitrogen side of the tropane ring and parallel to or slightly to the side of the CC vector opposite to the 2β-substituent. The CC vector was defined by the bond between the 3β-carbon of the tropane ring and the first carbon of the substituent. It was found that in hydrophilic compounds more favorable aqueous solubility contributed to a decrease in experimental binding values due to additional energy required to desolvate the analogues as they interacted with the cocaine binding site.

G. 6/7-Substituted Cocaine and Pseudococaine

Simoni et al.[222] synthesized 6/7-substituted analogues of cocaine. The main goal of this study was to explore the effect of oxygenation of cocaine's ethylene bridge (i.e., C6−C7) on binding and functional activity. Figure 36 shows the structures of these compounds.

The synthesis of 6/7-substituted analogues of cocaine was performed from 6/7-substituted 2-carbomethoxy-3-tropinone (**114**). The latter compound (**114**) was obtained by a Mannich reaction between acetone dicarboxylic acid (**107**), methylamine, and



225a; 2β, 6β-OCH_3
225b; 2α, 6β-OCH_3
225c; 2β, 7β-OCH_3
225d; 2α, 7β-OCH_3
225e; 2α, 7α-OCH_3

Figure 36. 6/7-Methoxy cocaine analogues.

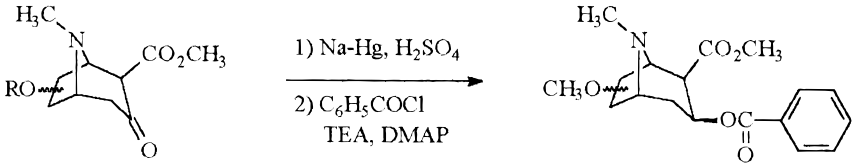
2-methoxysuccindialdehyde as described in Scheme 30.[117,119] The major isomer was a 1:1 mixture of 6*β*/7*β*-methoxytropinone. Only a small amount (6%) of (±)-7α-methoxy isomer was obtained, and only a trace amount of 6α-methoxy isomer was detected. Reduction of the tropinone intermediate (**114**) with sodium amalgam[120] in sulfuric acid solution at pH 3−4 produced a mixture of (±)-methoxy ecgonine methyl ester and (±)-methoxy pseudoecgonine methyl ester derivatives, which were separated and reacted with benzoyl chloride to afford compounds **225a**−**e** in 53−71% yield (Scheme 54). The assignment of the configuration was based upon ^{1}H NMR data. In the 6/7-*β*-OCH_3 configuration, there was lack of coupling between 6/7-H and 5/1-H, respectively. However, a coupling constant of 6.0 Hz was observed between the C1 and C7 protons of compound **225e**. The configuration of the substituents at the C2 and C3 carbon atoms was determined by the size of the coupling constant between C2 and C3 protons (~6.0 Hz for 2*β*-CO_2Me and 10.5 Hz for 2α-CO_2Me).

Kozikowski et al.[280] recently utilized porcine liver esterase (PLE) to resolve racemic mixtures of **225a, 225d,** and **225e** analogues. PLE is known to hydrolyze *S*-cocaine (**175**; Figure 29) at a faster rate than *R*-cocaine.[6] Furthermore, in the case of six-membered ring substrates, an *equatorial* or *pseudoequatorial* ester function is preferred, and in the case of (±) pseudococaine, the (−)-isomer is hydrolyzed preferentially by PLE. Thus, (−)-isomers of pseudococaine derivatives **225d** and **225e** and (+)-isomer of cocaine-like derivative **225a** were reacted with PLE to give methoxyecgonine methyl ester derivatives, which were benzoylated to afford (+)-**225a,** (−)-**225d**, and (−)-**225e**. Compounds (−)-**225a,** (+)-**225d**, and (+)-**225e** were not hydrolyzed by PLE.

Recently, Simoni et al.[281] have developed a concise enantioselective synthesis of 6- and 7-methoxycocaines starting from the known chiral 6-methoxy tropinones (−)-**226** and (+)-**226**. Carbomethoxylation of (−)-**226** with methyl cyanoformate afforded regioisomers (+)-**227** and (+)-**228** in 65% yield (Scheme 55). The following steps were reduction of the keto function with sodium amalgam and benzoylation as shown above in Scheme 54.

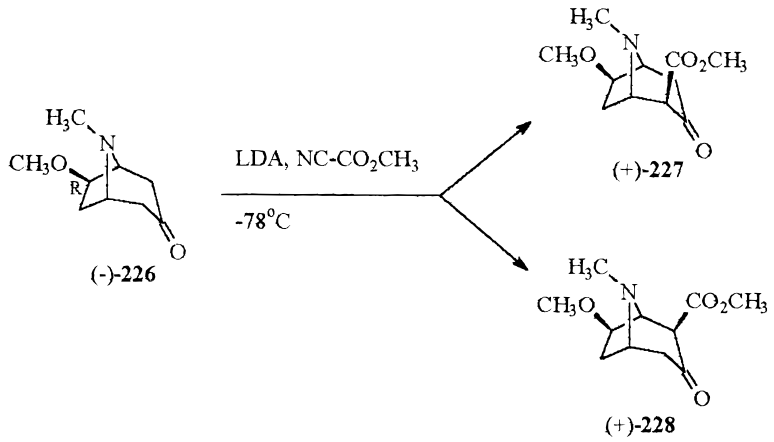
The binding affinities of 6- and 7-methoxy analogues of cocaine are shown in Table 35. It is apparent from the table that methoxylation caused 15−350-fold reduction in potency for the inhibition of [^{3}H]mazindol at the DAT. The data suggested that the cocaine binding site might encompass the region circumscribed by the two-carbon bridge (i.e., C6−C7). The most interesting feature of this series of compounds was the difference in binding with respect to DA uptake. For example, compound **225b** was 2.7-fold less potent in inhibiting DA uptake than inhibiting [^{3}H]mazindol. However, this difference was 3.7 times for compound **225e**. Therefore, **225e** has been viewed as a weak antagonist. Further studies have indicated that compound **225e** may bind to a site(s) that results in inhibition of [^{3}H]DA uptake and at the same time allosterically diminish cocaine binding.

Scheme 54



114; R= Me **225a-e**

Scheme 55



(-)-**226** (+)-**227** (+)-**228**

Table 35. Binding and DA Uptake Data for 6/7-Methoxycocaine Analogues

compound no.	K_i (nM) [^{3}H]mazindol binding	K_i (nM) [^{3}H]DA uptake	selectivity uptake/binding
cocaine	280 ± 60	320 ± 10	1.1
pseudococaine	10400 ± 300	13800 ± 1,500	1.3
225a	98000 ± 12,000	68000 ± 5000	0.7
225b	190000 ± 11,000	510000 ± 110000	2.7
225c	4200 ± 100	6100 ± 200	1.4
225d	45000 ± 5,000	110000 ± 4000	2.4
225e	54000 ± 3,000	200000 ± 70000	3.7

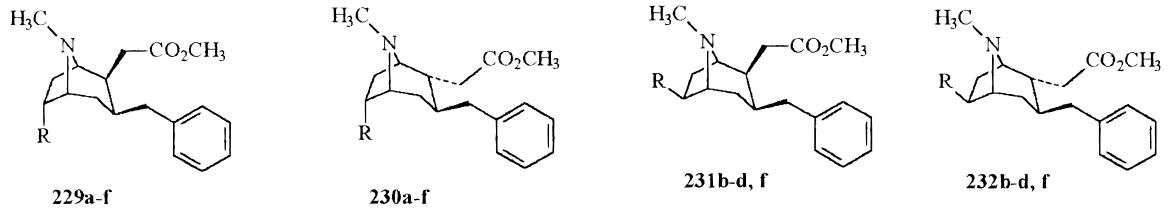
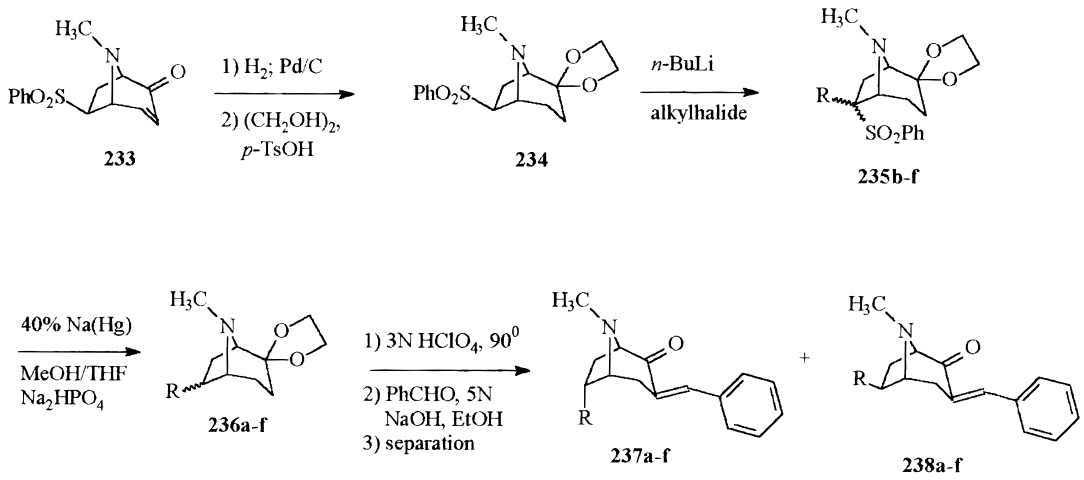


Figure 37. 6-Alkyl-3-benzyl-2-carbomethoxymethyl analogues of cocaine.

Scheme 56



Having developed the procedures for procuring 6- and 7-methoxycocaine analogues in optically pure form by the application of a PLE-catalyzed hydrolysis reaction to racemic mixtures, demethylation of optically active methoxycocaines was attempted. The idea was that such 6- and 7-hydroxylated cocaines would be more useful in gaining access to a diverse library of 6- and 7-functionalized cocaine analogues. However, simple demethylation of already prepared methoxycocaines **225a**−**d** was unsuccessful, because the C2 ester function underwent cleavage more readily than the 6-/7-methyl group, thus producing inseparable mixtures. Consequently, a similar strategy was adopted as shown in Scheme 54.[254]

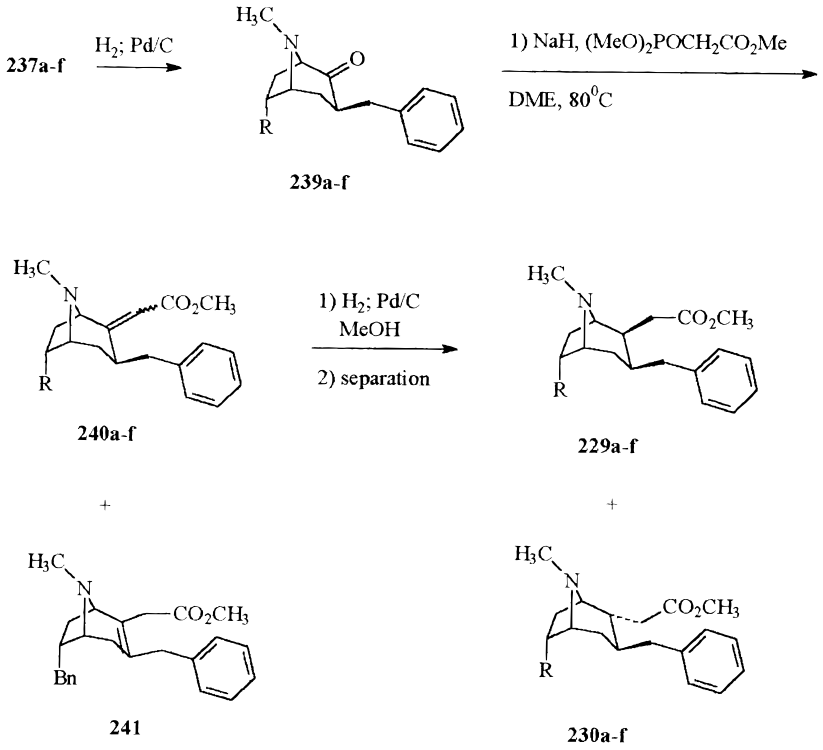
H. 6-Alkyl-3-benzyltropanes

These compounds were designed after the report by Simoni et al.[222] that 6- and 7-methoxycocaine and pseudococaine analogues (Table 35) acted as weak cocaine antagonists. The 3β-benzyl group was envisaged as an isostere of the 3β-benzoyloxy group of 6- and 7-methoxycocaine analogues. The 2β-(methoxycarbonyl)methyl group was incorporated for the ease of synthesis. The following isomers of 6-alkyl-3β-benzyl tropanes were synthesized as shown in Figure 37.[84]

Synthesis of the 6-alkyl-3β-benzyltropane analogues of cocaine was carried out from 6β-(phenylsulfonyl)-8-methyl-8-azabicyclo[3.2.1]octan-2-one (**233**) via alkylation/desulfonylation.[282] The keto function of **233** was protected as ketal after hydrogenation of the C3−C4 double bond to afford **234**, which upon treatment with *n*-BuLi and concomitant addition of an alkyl halide gave the alkylated sulfone derivatives **235b**−**f** as a mixture of isomers in high yield.[283] The desulfonylation of **235b**−**f** was achieved in 40% sodium amalgam in 80−91% yield. It is important to note that 6α (*endo*) isomers, **236b**−**f** were found to be the major products. Deprotection of the ketal followed by condensation with benzaldehyde gave the benzylidene derivatives **237a**−**f** and **238a**−**f** in 70−82% yield as shown in Scheme 56.[283] The 6α-isomers **237b**−**f** and 6β-isomers (*exo*) **238b**−**f** were separated by column chromatography.

The benzylidene derivatives **237a**−**f** were hydrogenated to 3β-benzyl derivatives **239a**−**f** stereose-

Scheme 57



lectively. The ketones **239a**−**f** were subjected to Horner−Wadsworth−Emmons olefination to furnish intermediate alkylidene esters **240a**−**f**. In the case of **239f**, an unsaturated analogue **241** was also formed as a result of base-catalyzed isomerization of the double bond in situ, Scheme 57. Subsequent hydrogenation of the alkylidene esters **240a**−**f** over Pd/C afforded a mixture of the 2β- and 2α-isomers **229a**−**f** and **230a**−**f** in 32−78% yield. It should be noted that in all cases 2α-isomer was the major product. The stereochemistry of the 2α- and 2β-isomers was determined by homonuclear COSY NMR experiments. In addition, the stereochemistry at C2 was also established by quaternization with ethyl iodide. The 2α-isomer only formed quaternary ammonium iodide, while 2β-isomer did not react with ethyl iodide due to steric constraints imposed by the 2β-(methoxycarbonyl)methyl group. The minor benzylidene isomers **238a**−**f** were also converted into the 6β-alkyl analogues **231b**−**d,f** and **232b**−**d,f** in a similar fashion as shown in Scheme 57. The enantiopure parent compounds (−)-**229a** and (+)-**230a** were prepared from (+)-2-tropinone in a fashion similar to that of **229a** and **230a** (Schemes 56 and 57).[284]

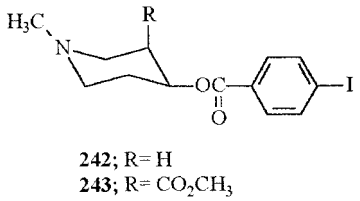
The binding affinities of this new class of compounds are shown in Table 36. The enantiopure (−)-**229a** was equipotent with a high-affinity binding component of cocaine and WIN 35065-2. This demonstrated that the one-carbon homologation at the 2β- and 3β-positions of WIN 35065-2 did not adversely affect the binding or inhibition of DA uptake.

It is also noteworthy that 2α-isomer (+)-**230a** was only 2-fold less potent than its 2β-isomer (−)-**229a**. However, among other cocaine and 3β-aryl tropane analogues, the 2α-isomers typically have been reported to be at least 30−100-fold less potent than the corresponding 2β-isomers.[72]

Table 36. Inhibition of [^{3}H]WIN 35428 Binding and Inhibition of [^{3}H]DA Uptake by 6-Alkyl-3-benzyl-2[(methoxycarbonyl)methyl]tropane Analogues

compound no.	K_i (nM) [^{3}H]WIN 35428	IC_{50} (nM) [^{3}H]DA	selectivity uptake/ binding
cocaine	32 ± 5	405 ± 91	12.6
	338 ± 221	405 ± 91	1.2
11a (WIN 35065-2)	33 ± 17	373 ± 10	11.3
	314 ± 222		
(−)-**229a**	33 ± 5	161 ± 100	4.9
229a	91 ± 10	94 ± 26	1.0
229b	211 ± 23		
229c	307 ± 28		
229d	4180 ± 418		
229e	8580 ± 249		
229f	3080 ± 277		
(+)-**230a**	60 ± 6	208 ± 63	3.5
230a	108 ± 14	457 ± 104	4.2
230b	561 ± 64		
230c	1150 ± 135		
230d	7240 ± 376		
230e	19700 ± 350		
230f	7590 ± 53		
231b	57 ± 5	107 ± 36	1.9
231c	3110 ± 187		
231d	5850 ± 702		
231f	1560 ± 63		
232b	294 ± 29	532 ± 136	1.8
232c	6210 ± 435		
232d	57300 ± 3440		
232f	3080 ± 277		
241	4830 ± 434		

From the SAR data in Table 36, it is apparent that substitution at the C6 position led to reduction in the binding at the DAT. It appeared that the binding site was sensitive to the steric bulk at C6. With the



242; R = H
243; R = CO_2CH_3

Figure 38. Piperidine analogues of 4′-iodococaine.

increase in the bulk of the 6-alkyl group, the ligand was unable to align itself properly in the binding site and as a consequence the affinity was diminished.

The 6-benzyl analogues **229f**, **230f**, **231f**, and **232f** exhibited anomalous binding affinities. They exhibited a higher binding affinity than was expected based on simple steric and lipophilic trends. This suggested that there may be a significant electrostatic interaction between the binding site and the aromatic π-system of the benzyl group at the C6-position. Alternatively, it was possible that the C6 benzyl group facilitated binding of the analogues to a different domain on the DAT than the 6-alkyl analogues and thus led to the observed differences in binding affinity. It is important to note that 6-alkyl compounds also maintained relatively potent DA uptake inhibition.

I. Piperidine Homologues of Cocaine

The piperidine analogues of cocaine were modeled after 4′-iodococaine (**183a**).[252] The interatomic distances in these analogues were similar to **183a**. Figure 38 shows the structures of the piperidine homologues of cocaine.

Compound **242** was obtained in two steps from 1-methyl-4-piperidone (**244**) via reduction with sodium borohydride in IPA at −4 °C followed by acylation with 4-iodobenzoyl chloride. The interesting aspect of sodium borohydride reduction at lower temperature was that only *equatorial* alcohol **(245)** was produced due to relatively unhindered access of the nucleophile, Scheme 58.

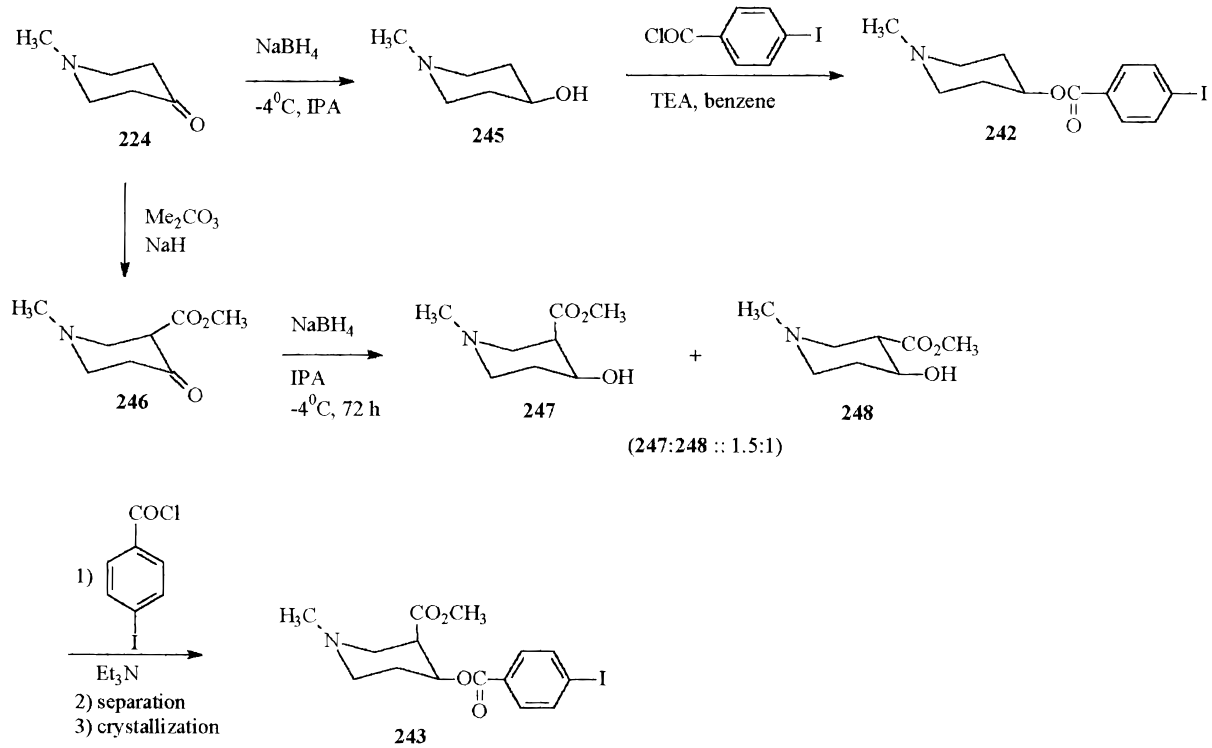
Compound **243** was also synthesized from *N*-methyl-4-piperidone (**244**) as shown in Scheme 58. Carbomethoxylation of **244** followed by sodium borohydride reduction gave a *cis* and *trans* mixture of 3-carbomethoxy alcohols in the ratio of 1.5:1, respectively (**247, 248**). Again, only *equatorial* alcohols were obtained from sodium borohydride reduction at −4 °C. A slight excess of the *cis* isomer possibly resulted from two factors: (1) dipole−dipole repulsion and (2) reduced *synaxial* 1,3-interactions. The separation of the alcohols (**247, 248**) was unsuccessful. Acylation followed by separation and crystallization afforded **243** in 23% overall yield.

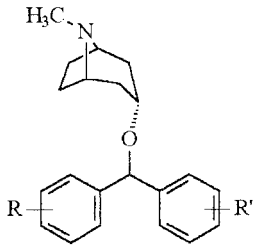
The piperidine analogues of 4′-iodococaine **242** and **243** exhibited much weaker binding affinities for the DAT relative to cocaine and **183a**. It was concluded that although the interatomic distances between the nitrogen atom of the piperidine ring and the iodine atom of the phenyl ring in compounds **242** and **243** were the same as that found in **183a**, the lack of conformational rigidity or the adoption of the other chair conformations perhaps led to poor binding affinities (Table 37).

Table 37. Binding Potency of Piperidine Analogues for [^{3}H]WIN 35428 Displacement

compound no.	IC_{50} (nM)
cocaine	249 ± 37
183a	2522 ± 4
242	11589 ± 4
243	8064 ± 4

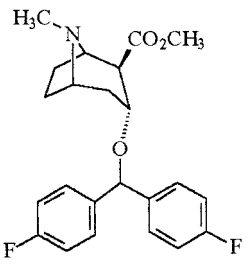
Scheme 58



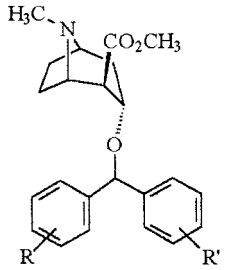


benztropine; R= R'= H
249a; R= 4'-F, R'= H
249b; R= R'= 4'-F
249c; R= 3',4'-di-F, R'= H
249d; R= 4'-Cl, R'= H
249e; R= R'= 4'-Cl
249f; R= 3",4'-di-Cl, R'= H
249g; R= 3',4'-di-Cl, R'= F
249h; R= 4'-Br. R'= H
249i; R= R'= 4'-Br
249j; R= 4'-NO_2, R'= H
249k; R= 4'-CN. R'= H
249l; R= 4'-CF_3, R'= H
249m; R= 4'-OH, R'= H
249n; R= 4'-OMe, R'= H
249o; R= R'= 4'-OMe
249p; R= 4'-Me, R'= H
249q; R= R'= 4'-Me
249r; R= 4'-Et, R'= H
249s; R= 4'-*t*-Bu, R'= H
250a; R= 3'-F, R'= H
250b; R= R'= 3'-F
250c; R= 3'-Cl, R'= H
250d; R= 3'-CF_3, R'= H
251a; R= 2'-F, R'= H
251b; R= 2'-Cl, R'= H
251c; R= 2'-Me, R'= H
251d; R= 2'-NH_2, R'= H

Figure 39. 3α-Diphenylmethoxy tropanes.

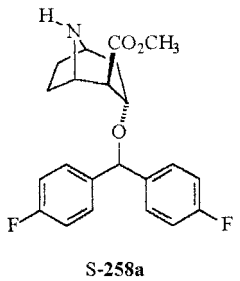


R-256

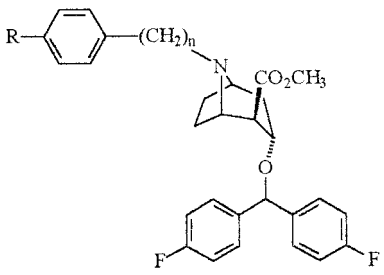


S-257a; R= R'= H
S-257b; R= H; R'= F
S-257c; R= R'= F (difluoropine)
S-257d; R= H; R'= Cl
S-257e; R= R'= Cl
S-257f; R= H; R'= Br
S-257g; R= R'= Br
S-257h; R= H; R'= I
S-257i; R= Br; R'= I
S-257j; R= R'= I
S-257k; R= H; R'= Me
S-257l; R= R'= Me

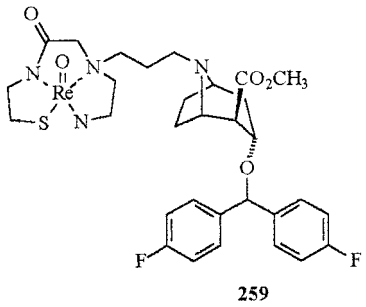
Figure 40. 3α-Diphenylmethoxy-2β-carbomethoxy tropanes.



S-258a



258b; R= H, n= 1
258c; R= H, n= 3
258d; R= Br, n= 3
258e; R= I, n= 3
258f; R= H, n= 5



259

Figure 41. *N*-Modified 2-carbomethoxy benztropines.

IV. 3α-Diphenylmethoxy Tropanes (Benztropine Analogues)

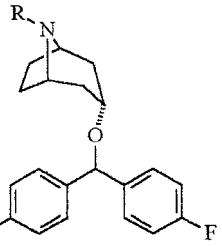
These compounds contain the diphenylmethoxy group attached to the tropane ring at the C3 position in the α-orientation. Such compounds partly mimic GBR compounds (Figure 45) and retain the tropane ring, which is present in cocaine and WIN-type of compounds. The parent idea to synthesize such compounds, including GBR compounds, however, originated from benztropine (3α-(diphenylmethoxy)-1α*H*,5α*H*-tropane, Figure 39), which was synthesized in 1952 and subsequently demonstrated to be useful as an anticholinergic drug in the treatment of Parkinsoniasm.[285] Benztropine is a central nervous system stimulant, and its mechanism of action has been ascribed to the inhibition of DA uptake.[286,287]

The structural features and central stimulant actions of benztropine have made this molecule an interesting template for designing novel DA uptake inhibitors. It was expected that such molecules might possess improved affinity and selectivity for the DAT over that of other monoamine transporters as well as over muscarinic receptors. Four kinds of 3α-diphenylmethoxy tropane analogues have been synthesized: (1) phenyl ring substituted 3α-diphenylmethoxy tropanes (Figure 39), (2) 2-carbomethoxy phenyl ring substituted 3α-diphenylmethoxy tropanes (Figure 40), (3) *N*-modified benztropine analogues (Figures 41−43), and (4) 3α-modified benztropines (Figure 44).

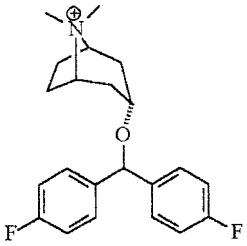
A. Phenyl Ring Substituted 3α-Diphenylmethoxy Tropanes

This series of compounds lack the 2β-carbomethoxy function present in cocaine and WIN analogues. Essentially these are benztropine derivatives. The following compounds have been synthesized, Figure 39.

The synthesis of benztropine analogues was carried out using a Williamson ether synthesis and is shown

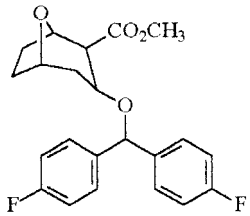


260; R= H
261a; R= 3-phenylpropyl
261b; R= indole-3-ethyl
261c; R= 4-phenylbutyl
261d; R= 4-(4'-nitrophenyl)butyl
261e; R= 3-(4'-fluorophenyl)propyl
262a; R= *n*-butyl
262b; R= cyclopropylmethyl
262c; R= allyl
262d; R= benzyl
262e; R= 4-fluorobenzyl
262f; R= cinnanyl
262g; R= [bis(4-fluorophenyl)methoxy]ethyl
262h; R= [(4-nitrophenyl)phenylmethoxy]ethyl
263; R= Acetyl
264: R= formyl
265a; R= Ts
265b; R= Ms



266

Figure 42. *N*-Modified benztropine analogues.



268: 2β,3β
269; 2α,3β
270; 2α,3α
271; 2β,3α

Figure 43. 8-Oxa-2-carbomethoxy norbenztropines.

in Scheme 59. Tropine (**255**) was reacted with 2′, 3′, or 4′ mono/disubstituted benzhydryl chloride (**254**) at 160 °C. The substituted benzhydryl chloride (**254**) was either commercially available[288] or synthesized from a substituted benzhydrol (**253**) by refluxing in thionyl chloride.[289] Some of the benzhydrols were prepared from substituted benzophenones (**252**) by sodium borohydride reduction. The yield of analogues containing electron-withdrawing groups was generally lower, perhaps due to destabilization of the intermediate carbocation. The yield of 2′-substituted analogues was also lower due to steric hindrance.[290]

The binding affinities of benztropine analogues are shown in Table 38. These compounds showed affinities to the DAT in the range of 11.8−2000 nM.

Table 38. Affinities of Benztropine Analogues for Binding to the DAT and Blockade of DA Uptake

compound no.	K_i (nM) [^{3}H]WIN 35428 binding	IC_{50} (nM) [^{3}H]DA uptake	selectivity uptake/binding
cocaine	388 ± 47		
GBR 12909	11.6 ± 31		
benztropine	118 ± 9	403 ± 115	3.4
249a	32.2 ± 10	48	1.5
249b	11.8 ± 1	71	6.0
249c	27.9 ± 11	181 ± 45.7	6.5
249d	30.0 ± 12	115	3.8
249e	20.0 ± 14	75	3.8
249f	21.1 ± 19	47	2.2
249g	18.9 ± 14	24	1.3
249h	37.9 ± 7	29	0.8
249i	91.6	34	0.4
249j	197 ± 8	219	1.1
249k	196 ± 9	222	1.1
249l	635 ± 10	2155	3.4
249m	297 ± 13	677	2.3
249n	78.4 ± 8	468	6.0
249o	2000 ± 7	2876	1.4
249p	187 ± 5	512	2.7
249q	420 ± 7	2536	6.0
249r	520 + 8	984	1.9
249s	1918	4456	2.3
250a	68.5 ± 12	250 ± 64.7	3.6
250b	47.4 ± 1	407 ± 63.9	8.6
250c	21.6 ± 7	228 ± 77.1	10.5
250d	187 ± 5	457 ± 72.0	2.4
251a	50.0 ± 12	140 ± 17.2	2.8
251b	228 ± 9	997 ± 109	4.4
251c	309 ± 6	1200 ± 1.64	3.9
251d	840 ± 8	373 ± 117	0.4

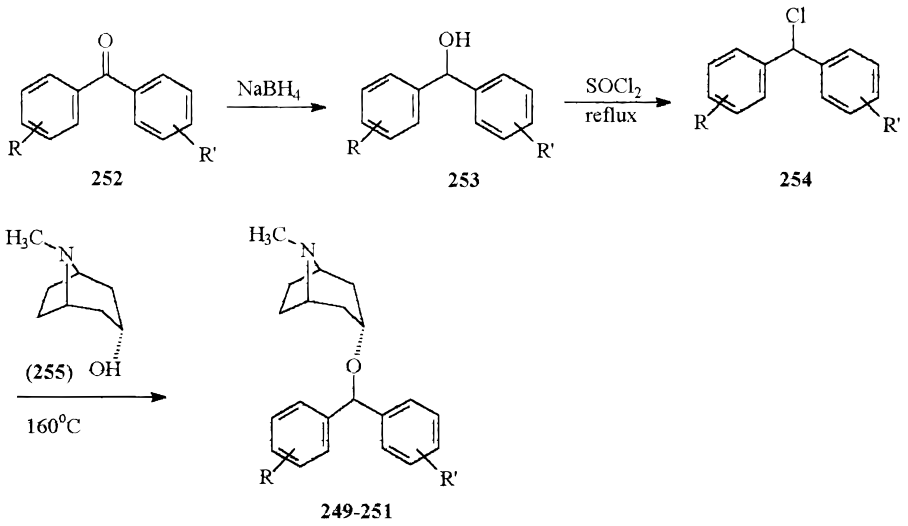
Generally meta-substituted compounds (**250**) were more potent than benztropine and equipotent or slightly less potent than para-substituted homologues (**249**) in inhibiting [^{3}H]WIN 35428 binding. However, these meta-substituted analogues were typically less potent than 4′-substituted analogues in inhibiting [^{3}H]DA uptake. The 2′-substituted analogues (**251**) were generally less potent in both binding and inhibition of uptake at the DAT than either benztropine- or aryl-substituted homologues.[288,289,291]

These compounds were also tested for binding at the 5-HTT and NET as well as muscarinic receptors. While these analogues did not bind potently at the 5-HTT and NET, they bound to muscarinic receptors with high affinity.[289,290] Furthermore, among 4′-substituted analogues 4′-di-F (**249b**), 3′,4′-di-F (**249c**), 4′-OMe (**249n**), and 4′-di-Me (**249q**) and among 3′-substituted analogues 3′-di-F (**250b**) and 3′-Cl (**250c**) were selective in inhibiting [^{3}H]WIN 35428 rather than [^{3}H]DA reuptake (Table 38). It is important to note that the 3β-diarylmethoxy analogues of benztropine showed much reduced affinities to the DAT. This suggested that tropine analogues interacted differently at the DAT domain.

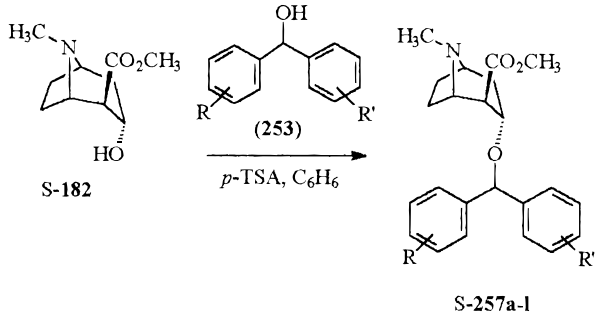
B. 2-Carbomethoxy Phenyl Ring Substituted 3α-Diphenylmethoxytropanes

These compounds were developed by Meltzer et al.[83,292] and contained a 2β-carbomethoxy function present in cocaine and its analogues (Figure 40). The main reason to synthesize these compounds was to enhance the binding potency and selectivity of benztropine and its analogues. It has been noted earlier

Scheme 59



Scheme 60



that 2β-carbomethoxy functionality increases the binding potency of cocaine and phenyltropanes. The tropanes lacking a 2β-carbomethoxy group were substantially poor at the DAT.

All eight stereoisomers were synthesized and evaluated for potency at the DAT and 5-HTT. It was discovered that the *S*-enantiomer (*S*)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane (difluoropine; *S*-**257c**) was considerably more potent than its *R*-enantiomer (*R*-**256**) (Figure 40).[83] Other stereoisomers including 2β,3β, 2α,3β, and 2α,3α were significantly less potent. Therefore, other phenyl ring substituted analogues of the *S*-isomer were prepared (Figure 40).[292] It is, however, interesting to note that in cocaine and phenyltropanes, the *R*-isomers are significantly more potent than the unnatural *S*-isomers. For example, *R*-cocaine is about 200-fold more potent than *S*-cocaine at the DAT.[17] Similarly, the *R*-isomer of β-CIT (RTI-55; **11e**) is about 14 000 times more potent than its *S*-isomer.[82]

The formation of an ether linkage was effected between two alcohols using an acid as catalyst (Scheme 60). The *R*- and *S*-precursor alcohols (**182**) were prepared from 3-tropinone via base-catalyzed α-carbomethoxylation with dimethyl carbonate followed by resolution of (±)-2-carbomethoxy-3-tropinone (*R*/*S*-**4**) with tartaric acid.[5] Reduction with sodium borohydride and epimerization gave *R*-**182** and *S*-**182** as described in Scheme 42.

The 4′-iodo compounds **257h**−**j** were obtained following a standard procedure. The corresponding bromo compounds were converted into tributyl stannyl derivatives with bis(tributyltin) in the presence of tetrakis(triphenyl phosphine)palladium followed by treatment with NIS.

Table 39. Inhibition of [^{3}H]WIN 35428 Binding to the DAT and [^{3}H]Citalopram Binding to the 5-HTT by 2β-Carbomethoxybenztropine Analogues in Cynomologous Monkey Caudate-Putamen

	IC_{50} (nM)		selectivity
compound no.	DAT	5-HTT	5-HTT/DAT
benztropine	312 ± 1.1	24100 ± 14800	77.2
WIN 35428	12.9 ± 1.1	160 ± 20	12.4
R-**256**	2040 ± 283	1460 ± 255	0.7
S-**257a**	33.5 ± 4.5	10100 ± 1740	301
S-**257b**	13.2 ± 1.9	4930 ± 1200	373
S-**257c**	10.9 ± 1.2	3530 ± 1480	324
S-**257d**	15.8 ± 0.95	5960 ± 467	377
S-**257e**	91.4 ± 0.85	3360 ± 1480	36.8
S-**257f**	24.0 ± 4.6	5770 ± 493	240
S-**257g**	72.0 ± 3.65	2430 ± 339	33.7
S-**257h**	55.9 ± 10.3	9280 ± 1640	166
S-**257i**	389 ± 29.4	4930 ± 82	12.7
S-**257j**	909 ± 79	8550 ± 442	9.4
S-**257k**	49.5 ± 6.0	13200	266
S-**257l**	240 ± 18.4	9800 ± 2680	40.8

As shown in Table 39, the rank order for monosubstituted compounds was F > Cl > Br > H > Me > I. The potencies of the disubstituted compounds depended upon the size of the group. For example, 4,4′-difluoro compound (**257c**) was potent and selective for the DAT. Introduction of the larger groups such as 4,4′-dichloro (*S*-**257e**), 4,4′-dibromo (*S*-**257g**), 4,4′-diiodo (*S*-**257j**), or 4,4′-dimethyl (*S*-**257l**) in the diphenylmethoxy moiety reduced potency as well as selectivity. It is also of interest that monosubstituted analogues were relatively more selective than disubstituted analogues at the DAT. Furthermore, the monosubstituted 2-carbomethoxy benztropines were significantly more potent than the corresponding disubstituted compounds at the DAT.

C. *N*-Modified 3α-Diphenylmethoxytropanes

1. N-Modified 2-Carbomethoxybenztropines

As shown in Table 39, *S*-2β-carbomethoxy-3α-(4′,4′-difluorodiphenylmethoxy)tropane (**257c**, Figure 40)

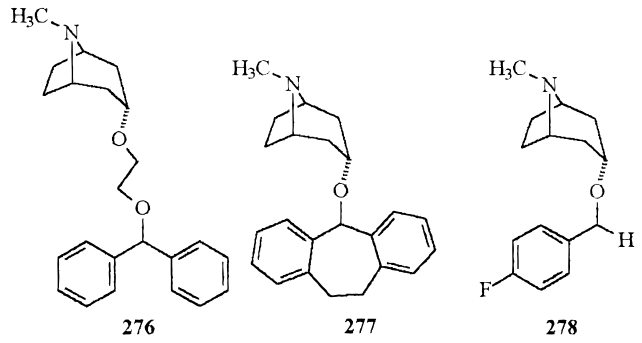


Figure 44. 3α-Modified benztropine analogues.

was the most potent compound in the series.[292] Upon comparison of the chemical structure of **257c** with GBR compounds (Figure 45), it can be deduced that 3α-diphenylmethoxytropanes are more GBR compounds rather than cocaine despite the presence of a tropane moiety.[292] The bridgehead nitrogen in 3α-diphenylmethoxy tropanes is structurally similar to the distal nitrogen of piperidine in GBR compounds. Having established this similarity, it was rationalized to synthesize *N*-substituted 3α-diphenylmethoxy tropanes because GBR compounds, in addition to a diphenylmethoxy and a piperazine, contain a phenylpropyl substituent at the distal nitrogen. Besides, it has been shown by Dutta et al. that the nitrogen distal to the diphenylmethoxy substituent confers greater binding potency than the proximal nitrogen in GBR compounds.[293] The choice of the substituents on the nitrogen of these 3α-diphenylmethoxy tropanes was guided by the SAR data on cocaine, phenyltropanes, and GBR compounds. The following analogues of (+)-2β-carbomethoxy-3α-(4,4′-difluorophenylmethoxy)tropane (**257c**) were synthesized and evaluated (Figure 41).[292]

The synthesis of the analogues (**258a**−**f**) involved *N*-demethylation of **257c** with ACE-Cl followed by refluxing in methanol to afford **258a** in 58% yield. The *N*-nor analogue (**258a**) was then reacted with an appropriate alkyl bromide in the presence of KF/Celite in acetonitrile to give analogues **258b**−**f** in 80−90% yield. The chelated ligand (**259**) was prepared as described above.[209]

The substituents on the nitrogen of the GBR analogues and the 2-carbomethoxy benztropines showed some similarity. Among one, three, and five methylene groups in the spacer chain, the one-carbon linker was the least potent while the three-carbon linker was optimum (**258c**, IC_{50} = 22.0 nM; Table 40). The five-carbon linker was 4.5-fold weaker than the three-carbon spacer. Substitution on the aryl group attached to the nitrogen linker again influenced binding potency markedly. The latter observation was in contrast to GBR series of compounds. It is also noteworthy that *N*-modified 2β-carbomethoxy benztropine analogues were significantly less selective than **257c** (Table 39). The chelated analogue (**259**) was much less potent. However, it was more selective at the DAT compared to other analogues in this series.[209] The above data suggested that a substantial steric bulk could be tolerated at the nitrogen site.

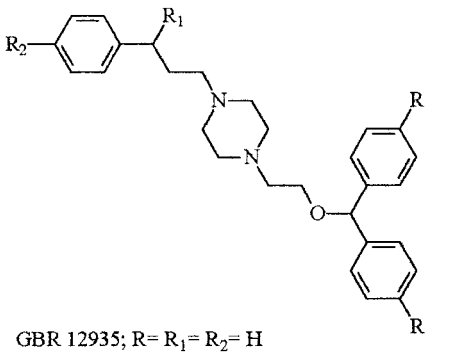
Table 40. Inhibition of [^{3}H]WIN-35428 Binding to the DAT and [^{3}H]Citalopram Binding to the 5-HTT by *N*-Substituted 2β-Carbomethoxybenztropine Analogues in Cynomolgous Monkey Caudate-Putamen

	IC_{50} (nM)		selectivity
compound no.	DAT	5-HTT	5-HTT/DAT
258a	20.3 ± 3.5		
258b	223 ± 53	4970 ± 700	22.3
258c	22.0 ± 11.9	19.7 ± 3	0.9
258d	80.2 ± 8.8	234 ± 0.5	2.9
258e	119 ± 11	2200 ± 1250	18.5
258f	99.0 ± 28	550 ± 63	5.5
259	616 ± 88	55200 + 20000	89.3

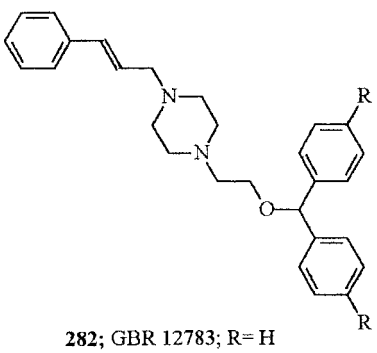
2. N-Modified Benztropines

Following above reports that GBR compounds contain a 3-phenylpropyl group and that bulky groups could be tolerated at the nitrogen of the 2β-carbomethoxybenztropines, Agoston et al. synthesized *N*-modified benztropines.[294] Furthermore, an important aim of synthesizing *N*-alkyl and arylalkyl derivatives of benztropines was to decrease muscarinic receptor binding affinity while retaining high affinity for the DAT. The structures of these compounds are shown in Figure 42.

Synthesis of *N*-modified benztropines is shown in Scheme 61. Nor-3α-[bis(4′-fluorophenyl)methoxy]tropane (**260**) was obtained via urethane intermediate by reaction of **249b** (Figure 39) with ACE-Cl followed



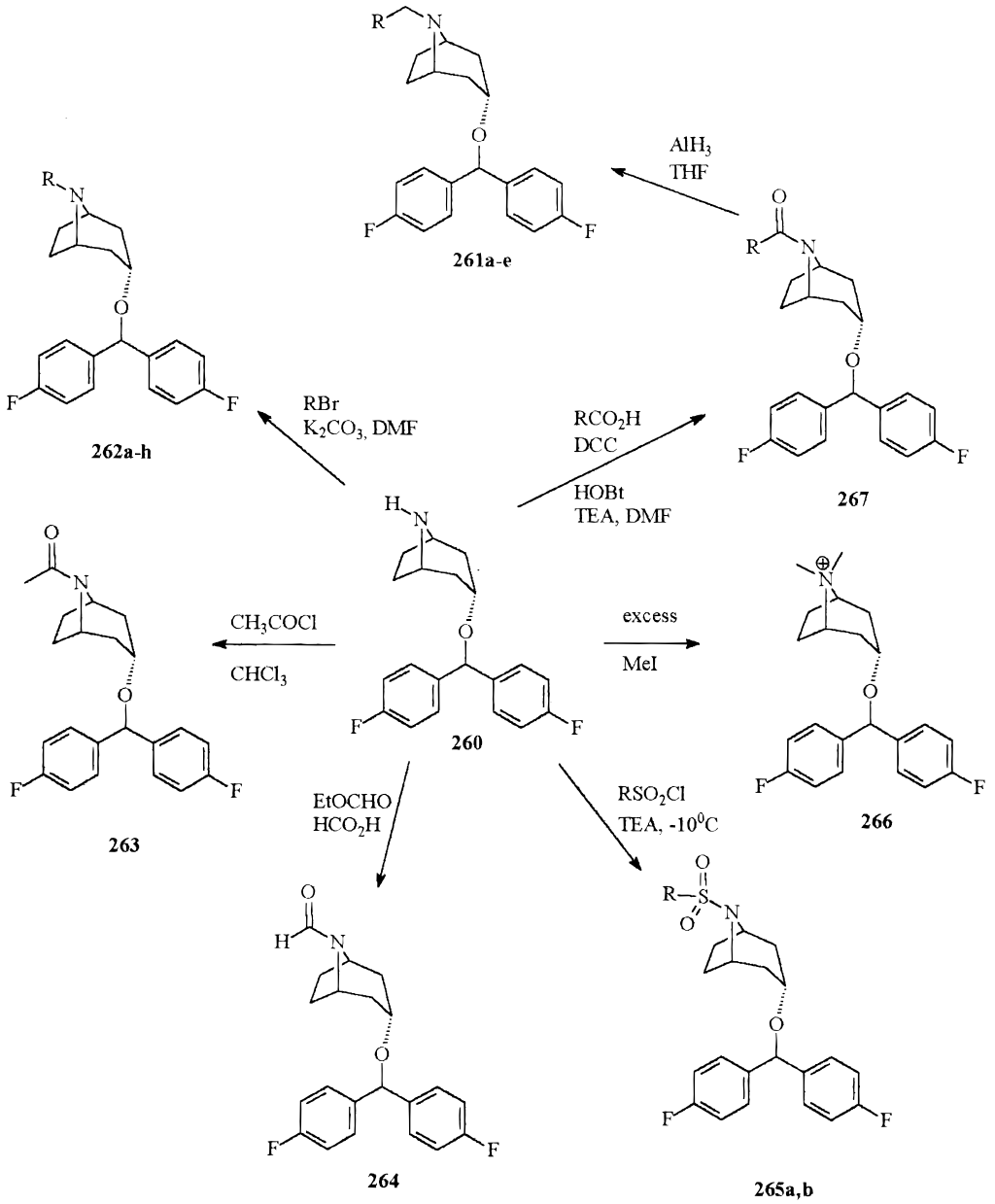
GBR 12935; R= R_1= R_2= H
279; GBR 12909; R= F, R_1= R_2= H
280;GBR 13098; R= F, R_1= H, R_2= F
281; Decanoate 5; R= F, R_1= $OCOC_9H_{19}$, R_2= H



282; GBR 12783; R= H
283; GBR 13069; R= F

Figure 45. Structures of some of the GBR compounds.

Scheme 61



by decomposition with methanol at ambient temperature rather than refluxing.[199] Refluxing of the intermediate in methanol led to elimination product, nortropine. Nor-3α-[bis(4′-fluorophenyl)methoxy]tropane **260** was then reacted with the following reagents: (1) an appropriate acid in the presence of DCC and 1-hydroxybenzotriazole (HOBt) to give an amide **267**, which upon reduction with allane gave amine **261**, (2) alkyl bromide in DMF and potassium carbonate to give *N*-alkyl derivatives directly (**262**), (3) acetyl chloride in chloroform and aqueous bicarbonate under Schotten−Bauman conditions (**263**), (4) ethyl formate in formic acid (**264**), (5) sulfonyl chloride in TEA (**265**), and (6) excess methyl iodide to give the quaternary iodide (**266**) analogue.[294]

As shown in Table 41, all compounds containing a basic tropane nitrogen displaced [^{3}H]WIN 35428 at the DAT (K_i = 8.5−634 nM) and blocked DA uptake (IC_{50} range = 10−1200 nM) in rat caudate putamen. However, ligands with a nonbasic nitrogen were virtually inactive. The latter observation was in contrast to *N*-sulfonyl cocaines, where such compounds retained significant affinities for the DAT. Furthermore, quaternary analogue, **266**, was only 10-fold less potent compared to *N*-methyl analogue, **249b** (Table 38), which again was different than cocaine analogues. The modest decrease in binding affinity could be due to the steric bulk of the additional methyl group. It is also interesting to note that **261c** was the most potent compound and **261d** was the most selective in this series.

Molecular modeling using the SYBYL software package of **262d**, **261a**, and **261c** revealed that the distance between the phenyl ring (centroid) and tropane nitrogen increased from 2.48 (**262d**) to 4.97 Å (**261a**) to 6.26 Å (**261c**). The binding affinity also increased by 10-fold to the DAT (K_i = 82.2 nM to K_i = 8.51 nM for **262d** and **261c**, respectively). It is also of interest to note that the substitution in the phenyl ring attached to the tropane nitrogen did not

Table 41. Binding of *N*-Substituted 3α[Bis(4′-fluorophenyl)methoxy]tropanes to the DAT and Inhibition of DA Uptake

compound no.	K_i (nM) [^{3}H]WIN 35428 DAT	IC_{50} (nM) [^{3}H]DA (uptake)	selectivity uptake/binding
260	11.2 ± 11	9.7	0.9
261a	41.9 ± 11	230	5.5
261b	44.6 ± 11	1200	26.9
261c	8.51 ± 14	39	4.6
261d	20.2 ± 11	650	32.2
261e	60.7 ± 12		
262a	24.6 ± 8	370	15.0
262b	32.4 ± 9	180	5.5
262c	29.9 ± 10	14	0.5
262d	82.2 ± 15	290	3.5
262e	95.6 ± 10	200	2.1
262f	86.4 ± 12	180	2.1
262g	634 ± 23		
262h	57.0 ± 17		
263	2340	4600	2.0
264	2020 ± 13	5400	2.7
265a	0%[a]		
265b	18%[a]		
266	108 ± 12	130	1.2

[a] % Inhibition at 10 μM.

appear to have a large effect on the DAT binding as evidenced by comparison of ligands **261c** and **261d**, **261a**, and **261e**. Bulky *N*-substituted aromatic substituents (**261b**, **262h**) retained high binding affinity to the DAT as well. It is also important to state here that this series of compounds behaved differently from cocaine and phenyltropanes, suggesting a different binding domain at the DAT.

3. 8-Oxa-2-carbomethoxynorbenztropines

These compounds were synthesized by Meltzer et al.[76] The main purpose to synthesize these compounds was to further evaluate the importance of N8 heteroatom in the 3α-diphenylmethoxy tropanes series of compounds. The main feature of these compounds was the substitution of the N8 nitrogen with an oxygen atom, Figure 43.

Table 42. Inhibition of [^{3}H]WIN 35428 Binding to the DAT and [^{3}H]Citalopram Binding to the 5-HTT by 8-Oxanortropane Analogues

compound no.	IC_{50} (nM) DAT	IC_{50} (nM) 5-HTT
R/*S*-**268**	>10000	>1660
R/*S*-**269**	20300	>1660
R/*S*-**270**	22300	>1660
R/*S*-**271**	520	>1660

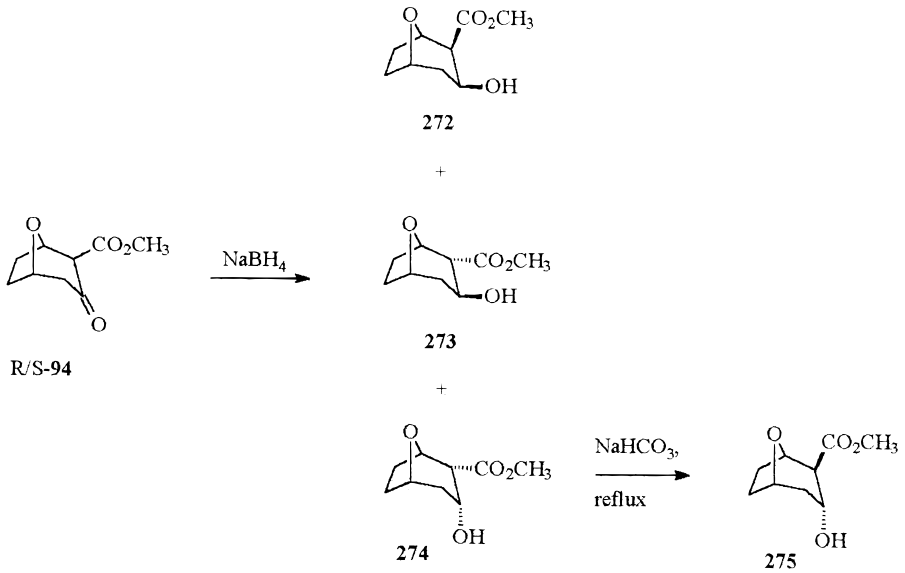
Scheme 62 shows the synthesis of 8-oxa norbenztropine isomers. The synthesis of *R*/*S*-**94** has been previously discussed (Scheme 27). The ketone (*R*/*S*-**94**) was reduced with sodium borohydride at −60 °C to give a mixture of alcohols **272**−**274**, which was separated by column chromatography. The dominant product of low-temperature reduction was 2α-carbomethoxy-3α-hydroxy compound, **274**. The 2β,3α-alcohol (**275**) was formed only in trace amounts. However, inversion of the 2α-carbomethoxy group to the 2β-position was readily achieved by refluxing in mildly basic aqueous solution.[289] The following step was the acid-catalyzed ether formation, as discussed above in Scheme 60.

The binding affinities of the 8-oxanorbenztropine analogues are shown in Table 42. These compounds were extremely weak at the DAT, compared to their 8-aza counterparts. One of the reasons for the low potencies of these compounds might be due to the differences in stereochemistry at C2 and C3. However, the structurally similar, i.e., 2β,3α-isomer (**271**) was also weak.

D. 3α-Modified Benztropines

The structures of these compounds are shown in Figure 44. In these compounds (**276**−**278**) modifications were made in the 3α-diphenylmethoxy function. For example, an ethylene spacer was introduced to mimic GBR compounds (**276**) or a phenyl ring of the diphenylmethoxy group was replaced with a hydrogen (**278**). The synthesis utilized standard conditions as described above for benztropine analogues. The

Scheme 62



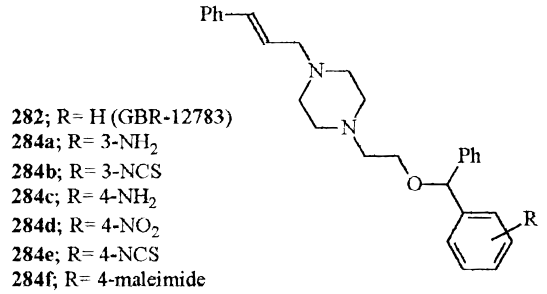


Figure 46. Structures of phenyl ring substituted analogues of GBR 12783.

biological evaluation of these compounds also revealed a significant reduction in potency compared to the parent compound, **249b** (Table 38).[295]

V. GBR Compounds

GBR compounds (aryl 1,4-dialkyl piperazines) were first reported by van der Zee et al. in 1980 as antidepressants and were conceived after benztropine (Figure 39).[286] However, the main structural difference between benztropine and GBR compounds is that the GBR compounds contain a piperazine ring instead of a tropane nucleus present in benztropine (Figure 45).

One of the most promising compounds is GBR 12909 (**279**; Figure 45). It binds tightly to the DAT and attenuates the increase in extracellular DA level induced by cocaine as measured in the microdialysis experiments.[296,297] In addition, it possesses nonstimulant properties in human volunteers[298] and is also shown to selectively block cocaine self-administration in rhesus monkey.[299] Recently, a derivative of GBR 12909, decanoate 5 (**281**; Figure 45), has been found to substantially reduce cocaine self-administration in monkeys for nearly a month with only one injection.[300]

The mechanism of action of GBR 12909 is considered to be the same as cocaine. It has been suggested that both bind to the same site[301] and inhibit the action of DA uptake at the DAT.[302] The only difference in the mechanism of action of GBR 12909 and cocaine is that GBR 12909 produces a relatively modest and long-lasting increase in DA, which does not cause the same degree of euphoria compared to cocaine's burst of pleasure.[296,297] Furthermore, the ability of GBR 12909 to block the action of cocaine is derived from its high potency to the DAT (~500 times greater).

A large number of GBR analogues have been synthesized. These are discussed in several subsections.

A. Phenyl Ring Substituted GBR 12783 Analogues

The rationale behind phenyl ring substituted GBR 12783 analogues (Figure 46) was to obtain irreversible affinity labels containing electrophilic groups which could react covalently with nucleophilic functions present at the DAT.

Synthesis of the GBR 12783 analogues was started from appropriately substituted benzophenone as originally proposed by van der Zee.[287] Both, meta- as well as para-substituted analogues were synthesized. The nitro group was selectively reduced with sodium borohydride sulfur complex in the presence of olefinic bond.[303] The amino group was then converted into isothiocyanate with $CSCl_2$[304] or maleimide with maleic anhydride.[305] A general synthetic pathway is shown in Scheme 63.

Table 43. Inhibition of DAT Binding and DA Uptake by GBR 12783 Analogues

compound no.	K_i (nM) [^{3}H]WIN 35425	IC_{50} (nM) [^{3}H]DA	selectivity uptake/ binding
cocaine	224 ± 3.4	208 ± 7.4	0.93
WIN 35428	24 ± 3.1	14 ± 1.8	0.58
DA	10000 ± 2400	44 ± 5.3	0.004
279; GBR 12909	27 ± 4.1	0.21 ± 0.06	0.007
282; GBR 12783	12 ± 1.2[a]		
284a	12 ± 1.0	7 ± 3.5	0.58
284b	160 ± 17	106 ± 37	0.67
284c	11 ± 0.7	1.6 ± 0.2	0.14
284d	26 ± 9.3	2.7 ± 0.1	0.10
284e	159 ± 12	26 ± 1.8	0.16
284f	2327 ± 1000	476 ± 61	0.20

[a] IC_{50} value for inhibition of [^{3}H]methylphenidate.

As shown in the Table 43, 3-substituted analogues (**284a,b**) had an approximately equal binding-to-inhibition ratio (IC_{50} for uptake/K_i for binding, 0.58−0.67). The 4-substituted GBR 12783 analogues (**284c−f**) were proportionally more potent in inhibiting DA uptake than in inhibiting [^{3}H]WIN 35428 binding. Their ratios of uptake to binding ranged from 0.10 to 0.20 and were lower than group 3-substituted analogues (**284a,b**). GBR 12909 and DA appeared to be potent inhibitors of DA transport but relatively weak inhibitors of [^{3}H]WIN 35428 binding. Uptake-to-binding ratios ranged from 0.007 to 0.004.[99,306]

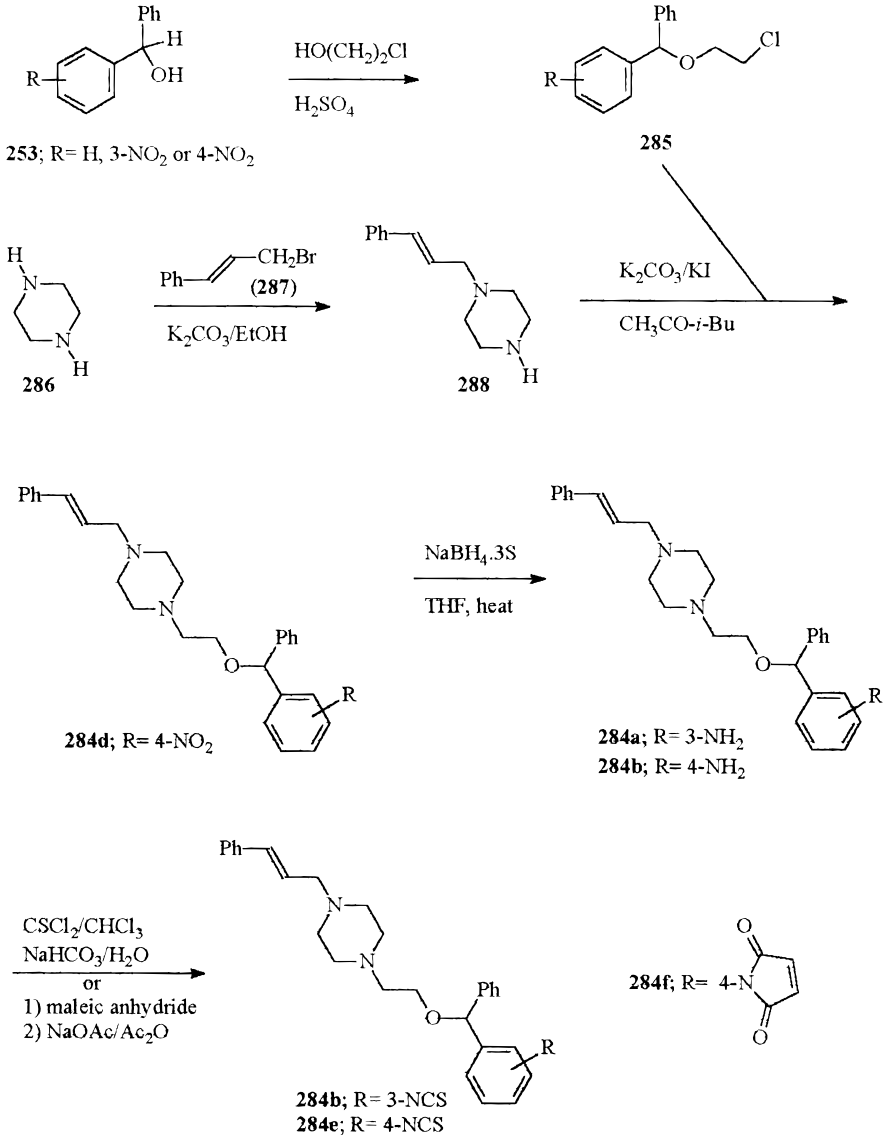
Finally, the above results demonstrated that slight modifications (moving groups from the 3- to the 4-position on one phenyl ring) could produce compounds with an altered relationship between binding and uptake.

B. Piperazine Ring Altered GBR 12909, 12935, and 12783 Analogues

The main focus of these studies was to obtain compounds with greater selectivity for the DAT compared to 5-HTT. In these compounds the piperazine moiety was altered as shown in Figure 47. The following modifications were made: (1) alteration of the steric bulk of the piperazine moiety, i.e., *trans*-2,5-dimethylpiperazine (**289a−d**) or seven- and eight-membered analogues (**290a−d** and **292**) and dimethylhomopiperazine (**291**), (2) opening of the piperazine ring (**293−295**), (3) changes in the dihedral angle between C−N bonds (e.g., homopiperazines, **296** and **297**), and (4) replacement of a piperazine ring with a pyrrolidine ring (**298a−c**).

Chemical synthesis of the piperazine ring modified analogues followed the standard methods as shown in Scheme 63.[307] The only difference in the synthesis was that phenylalkyl or phenylalkenyl group in the

Scheme 63



piperazine moiety was introduced via an amide by reaction with an appropriate acid chloride as shown in Scheme 64.[307] The reduction of the amide group was carried out using two metal hydrides: sodium borohydride and aluminum hydride. The advantage of aluminum hydride was that it did not reduce the C=C double bond in conjunction with the carbonyl group (C=O).[308]

Compound **289b** was also obtained in the optically active form. The intermediate monoalkyl *trans*-2,5-dimethylpiperazine ether **299** (R = F) was resolved using (−)- and (+)-dibenzoyl tartaric acid before subjecting to acylation and reduction.[309]

Synthesis of the dimethyl- substituted homopiperazine analogue (**291**) or 1,4-diazaoctane (**292**) was achieved by refluxing open-ring precursors **294** or **295**, respectively, with an excess of 1,2-dibromoethane in xylene (Scheme 64).[307] The homopiperidine analogues were synthesized from α-amino-ϵ-caprolactam using a standard sequence of reactions.

Synthesis of the optically active pyrrolidine analogues utilized commercially available L-(−)-prolinamide (**300**) and *N*-Boc-D-(+)-proline (**302**) as shown in Scheme 65. The coupling of the intermediate diphenylmethoxy pyrrolidine amine with the acid chloride was effected with DCC in order to obtain (−)-**298c**. However, to obtain the amide (**303**), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) was used as the activating agent. Deprotection of the *N*-Boc group with TFA gave **303**.

The binding affinities and the inhibition of DA and 5-HT uptake of the piperazine ring modified GBR analogues (Figure 47) are shown in Table 44. It is noteworthy that expansion of the piperazine ring of GBR 12935 to the seven-membered ring in the structure of **290a** did not significantly change the potency for inhibition of [^{3}H]DA but greatly improved selectivity at this site (>4700-fold).[310] However, further increase in the bulk of piperazine moiety or addition of two methyl groups to this ring (**292, 291**) attenuated both the affinity and selectivity of these ligands at the DAT site in comparison to GBR 12935 and **290a**.

The ring-opened analogues also had reduced potencies but slightly improved selectivity for the DA uptake compared to 5-HT uptake. This indicated that

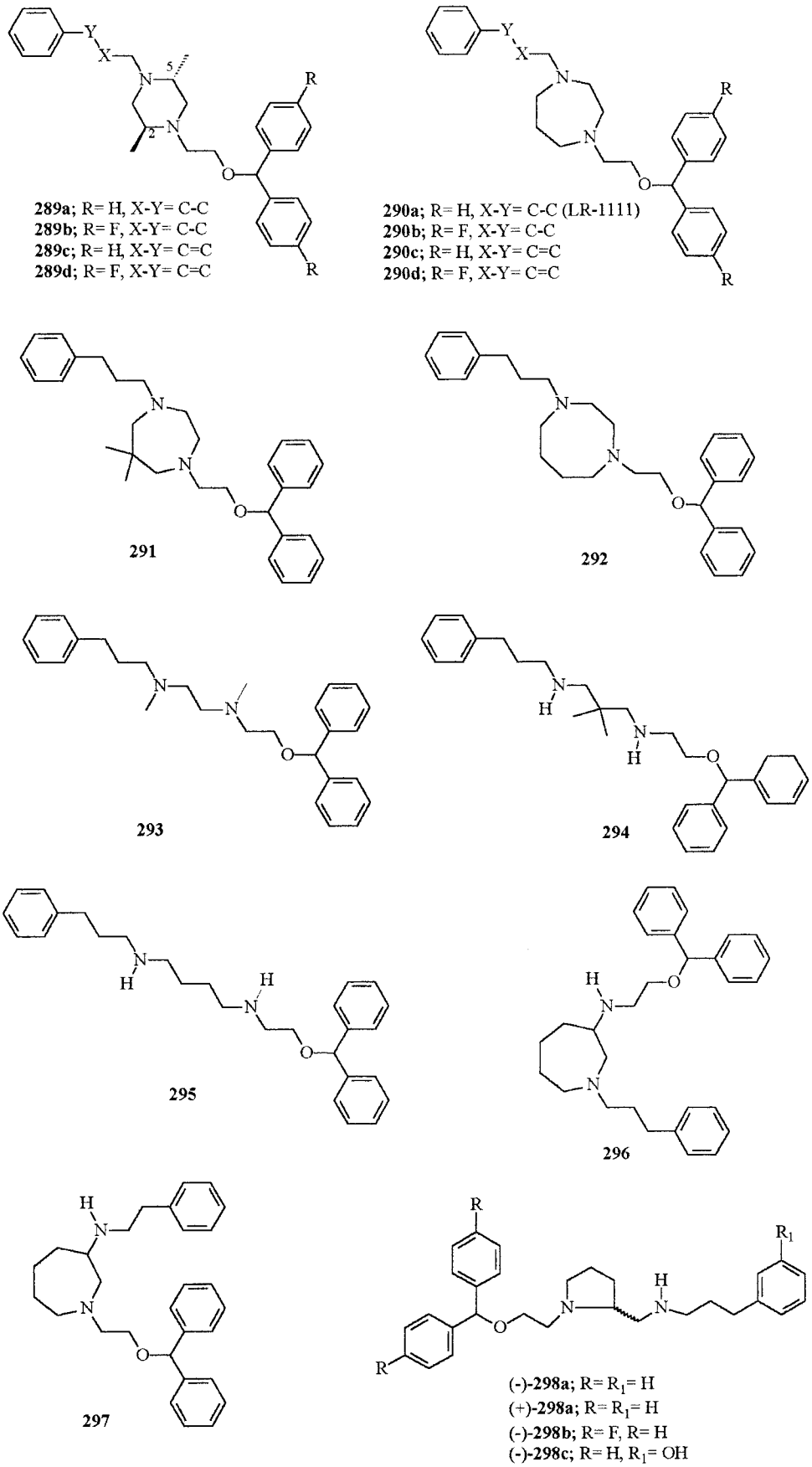
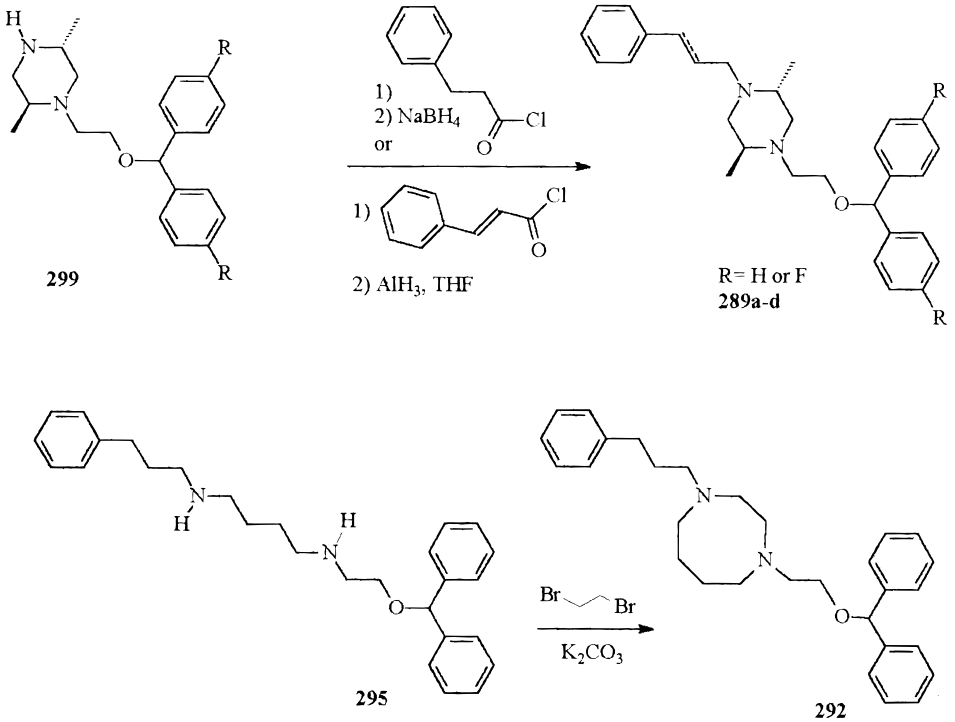


Figure 47. Piperazine ring altered analogues of GBR 12909, GBR 12935, and GBR 12783 compounds.

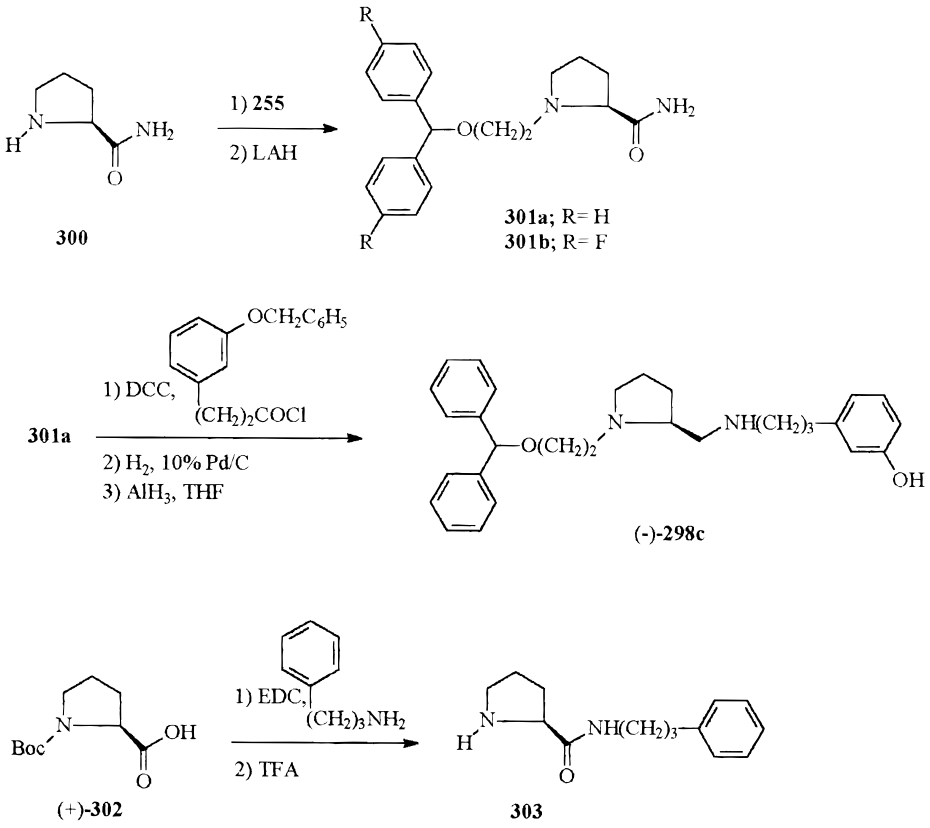
a conformationally rigid piperazine ring was not essential for binding at the DAT. Some degree of structural flexibility was allowed at this site.

The semirigid homopiperidine analogues, the regioisomers **296** and **297**, exhibited a 6-fold difference in affinity for the inhibition of [^{3}H]DA reuptake as

Scheme 64



Scheme 65



well as a 3-fold difference in selectivity at this site in favor of **297**.

It should be noted from the Table 44 that in the homopiperazines and *trans*-2,5-dimethylpiperazine series of GBR derivatives, bis-(4-fluoro)-substituted congeners were slightly more potent than their desfluoro counterparts for binding to the DAT, except for **289a** and **289b**. However, the desfluoro analogues were more selective in inhibiting [^{3}H]DA reuptake vs [^{3}H]5-HT reuptake, mainly due to their significantly lower affinity at the 5-HT sites (cf. **289a**−**d**, **290a**−**d**). Addition of a double bond increased affinity

Table 44. Binding Affinities and DA and 5-HT Uptake Inhibition by Piperazine Ring-Altered Analogues of GBR Compounds

	IC_{50} (nM)			selectivity	
compound no.	[^{3}H]GBR 12935 binding	[^{3}H]DA uptake	[^{3}H]5-HT uptake	[^{3}H]DA uptake/ DAT binding	[^{3}H]5-HT/ [^{3}H]DA uptake
cocaine	660 ± 30[a]	478 ± 25	304 ± 10	0.72	0.64
GBR12935	4.1 ± 0.6	3.7 ± 0.4	289 ± 29	0.90	78.1
279; GBR12909	5.5 ± 0.4	4.3 ± 0.3	73 ± 1.5	0.78	17.0
289a	21 ± 1.0	9.6 ± 1.5	1720 ± 70	0.46	179
289b	40 ± 1	15 ± 2	459 ± 26	0.37	30.6
(−)**289b** (2*S*,5*R*)	3.6 ± 0.14	8.1 ± 0.3		2.25	
(+)**289b** (2*R*,5*S*)	125 ± 7.0	87 ± 4.1		0.70	
289c	103 ± 13	20 ± 4	2680 ± 122	0.19	134
289d	23 ± 3	28 ± 5	1180 ± 404	1.22	42.1
290a (LR1111)	7.9 ± 1.7	7.2 ± 0.5	34100 ± 359	0.91	4736
290b	4.4 ± 0.4	3.4 ± 0.4	112 + 24	0.77	32.9
290c	8.6 ± 1.1	0.6 ± 0.1	503 ± 103	0.07	838
290d	2.6 ± 0.4	3.4 ± 0.4	234 ± 10	1.31	68.8
291	286 ± 8	87 ± 5	3150 ± 491	0.30	36.2
292	864 ± 91	93 ± 6	1590 ± 60	0.11	17.1
293	27 ± 4	18 ± 1	2450 ± 57	0.67	136
294	169 ± 5	83 ± 7	1890 ± 268	0.49	22.8
295	80 ± 6	35 ± 2	376 ± 19	0.44	10.7
296	74 ± 5	57 ± 10	2860 ± 45	0.77	50.2
297	20 ± 0.7	9.3 ± 1.8	1480 ± 69	0.46	159
(−)**298a**	5.1 ± 0.4	0.7 ± 0.05	986 ± 34	0.14	1409
(+)**298a**	747 ± 163	127 ± 10	3210 ± 450	0.17	25.3
(−)**298b**	104 ± 8	29 ± 2	20100 ± 2400	0.28	693
(−)**298c**	222 ± 13	31 ± 0.1	857 ± 17	0.14	27.6

[a] K_i value.

for inhibition of [^{3}H]DA reuptake 12 times (cf. **290a**, **290c**). However, this trend was not consistent with other analogues.

The effect of chirality was also studied by separating[309] or synthesizing enantiomerically pure[307] GBR analogues. The (−)-isomer (2*S*,5*R*) of **289b** was more selective at both the DAT binding and DA uptake by 35- and 11-fold, respectively, than its (+)-isomer (2*R*,5*S*), which suggested some degree of structural homology at this site. Two pyrrolidine analogues (−)- and (+)-**298a** displayed 181- and 146-fold enantioselectivity for the inhibition of [^{3}H]DA uptake and binding to the DAT, respectively (Table 44). There was also a striking difference in the ratio of IC_{50} for the inhibition of [^{3}H]5-HT vs [^{3}H]DA reuptake inhibition for these two isomers (1409- vs 25-fold). Hydroxylation of the aromatic ring (**298c**) proved to be dramatically less selective at the DA vs the 5-HT reuptake site than its precursor (−)-**298a** (27.6- vs 1409-fold, respectively). However, compared to (+)-**298a**, it was slightly more selective at the DA vs 5-HT reuptake site (27.6- vs 25.3-fold).

In summary, the above results indicated that in the GBR series of compounds, significant structural variations were admissible and that the conformationally restricted piperazine ring could be substituted with other, more flexible or more bulky, diamine moieties and still retain the high affinity for both binding to the DAT and inhibition of [^{3}H]DA uptake.

C. Heteroaromatic Analogues of GBR 12935, 12909, 12783, and 13069

It has been shown above that the modification of the central piperazine ring in GBR 12935 and 12909 improved upon the selectivity at the DAT site. To further explore the SAR and to obtain compounds with higher potency as well as selectivity, the phenylpropyl portion of the GBR compounds was modified. Two kinds of compounds were synthesized: (1) in which the phenyl ring in the phenylpropyl chain was replaced with either thiophene, furan, or pyridine and (2) in which the phenylpropyl chain of the GBR molecule was replaced with aromatic, heteroaromatic, five- and six-membered fused-ring systems. The structures of these compounds are shown in Figure 48.[311]

The rationale to synthesize five-membered fused-ring compounds (**308a,b**−**311a,b**) was to make GBR 12935 and 12909 more rigid and to retain the favorable three-atom linkage between the nitrogen atom of piperazine and the phenyl ring in the phenylpropyl side chain of the typical GBR structure. The six-membered fused ring analogues were designed to evaluate the effect of one or more atom(s) between the nitrogen atom of piperazine and the phenyl ring.

Synthesis of the GBR analogues **304**−**318** proceeded from monosubstituted piperazine, 1-[2-(diphenylmethoxy)ethyl]piperazine or 1-[2-[bis(4-fluorophenyl)-methoxy]ethyl]piperazine (**319a** or **319b**), which in turn was synthesized in a two-step sequence: reaction of appropriately substituted benzhydrol (**253a** or **253b**) with 2-chloroethanol in the presence of sulfuric acid and subsequent reaction of the resulting alkyl chloride with excess of piperazine. The coupling of these monosubstituted amines was carried out under three different reaction conditions: (1) DCC-catalyzed coupling with heteroaromatic acid, (2) aqueous sodium bicarbonate catalyzed coupling with acid chloride in chloroform under Schotten−Baumann conditions, and (3) potassium

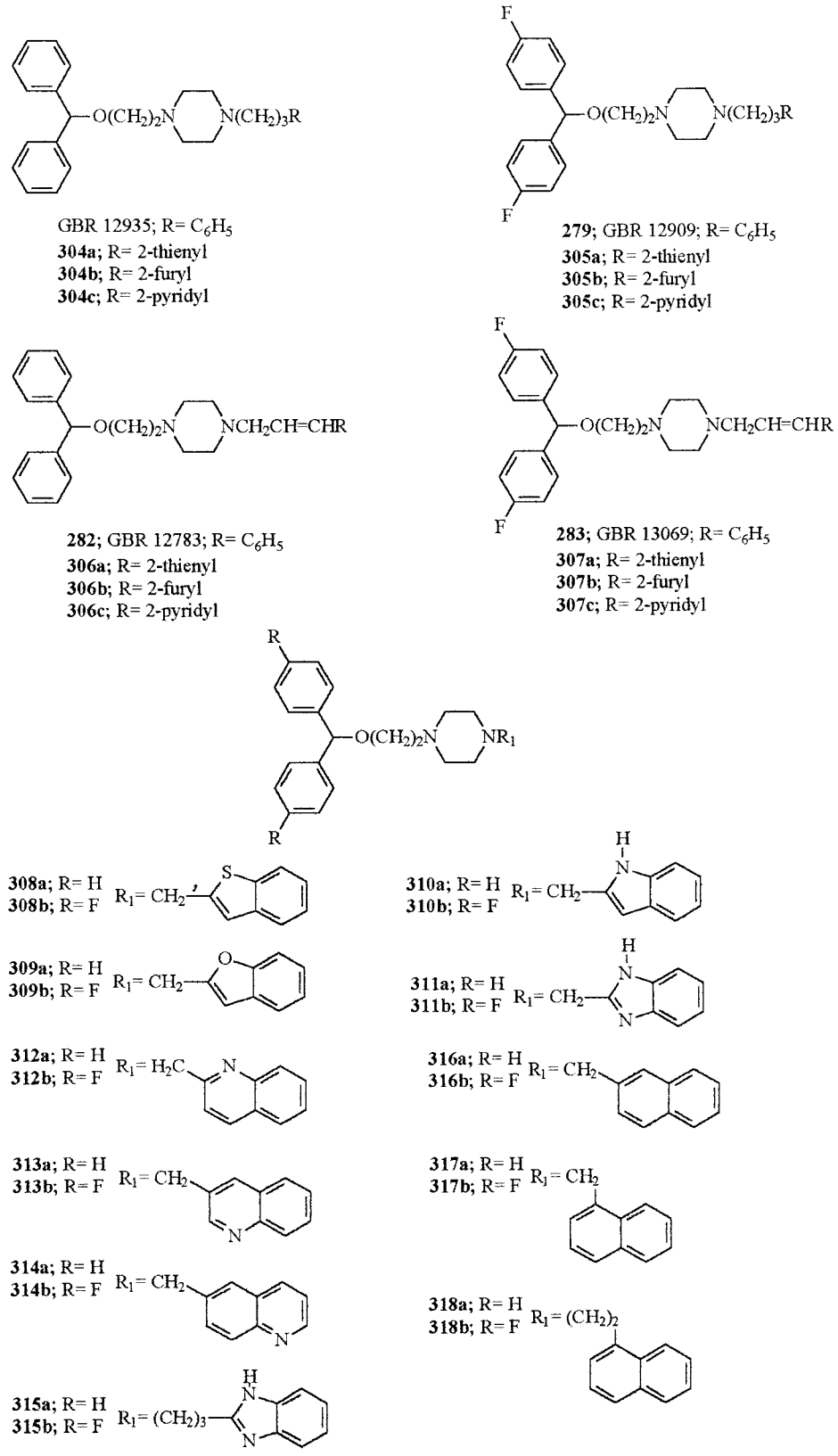
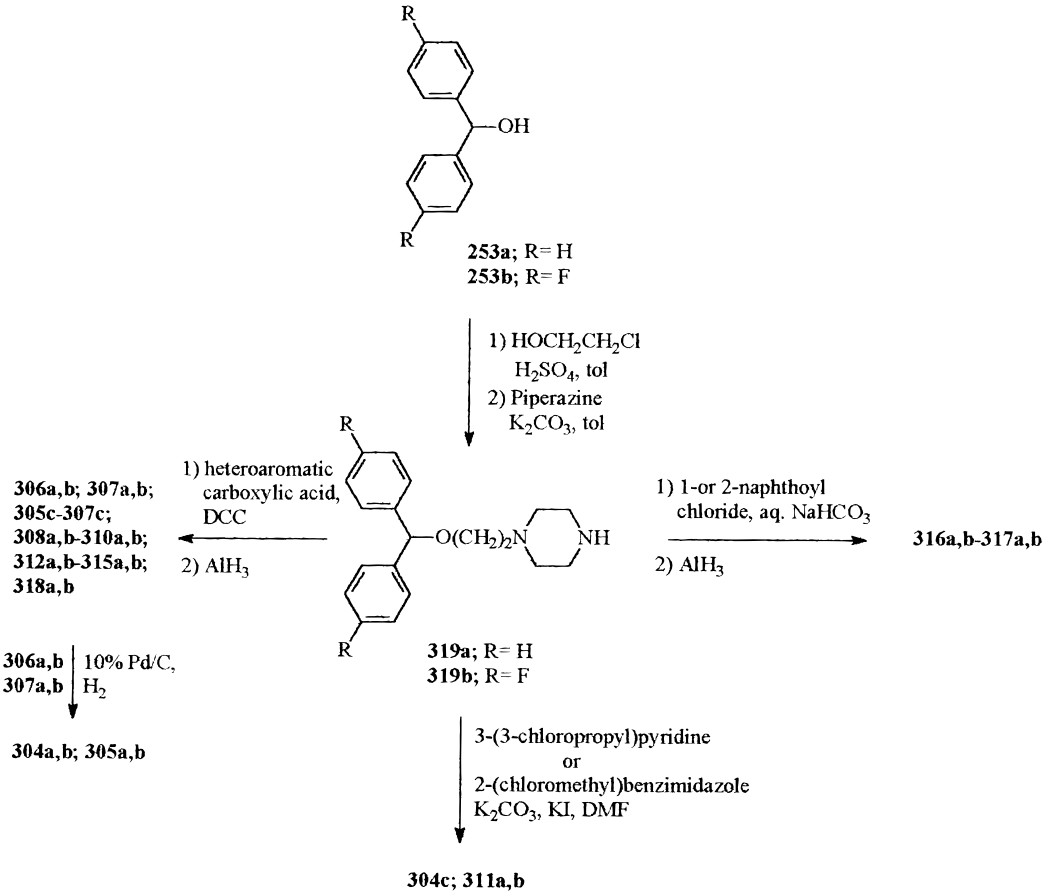


Figure 48. Heteroaromatic analogues of GBR 12935, 12909, 12783, and 13069.

carbonate catalyzed coupling with chloroalkyl heteroaromatic ring in DMF in the presence of potassium iodide. The amides were reduced using aluminum hydride.[312] The carbon−carbon double bond was hydrogenated using 10% Pd/C in MeOH. A general reaction sequence in shown in Scheme 66.

The potencies of these compounds for the transporter and reuptake are shown in Table 45. Among the biosteric analogues **304a**−**c**−**307a**−**c**, the furan-containing derivative of GBR 13069 (i.e., **307b**) was the most potent at DAT (IC_{50} = 1.8 nM) while the furan-containing analogue of GBR 12783 (i.e., **306b**)

Scheme 66



was the most selective ligand (368- and 281-fold more potent for the binding to the DAT vs 5-HT and inhibition of DA vs 5-HT reuptake, respectively). Pyridine-containing derivatives **304c, 305c, 306c,** and **307c** were less potent compared to furan and thiophene analogues. An interesting observation was that the bis(4-fluoro)-substituted compounds containing an unsaturated side chain (i.e., compounds **307a**−**c**, respectively) exhibited slightly higher affinity at the DAT than their desfluoro (**306a**−**c**) and saturated analogues (**305a**−**c**), Figure 48. However, in the fused-ring ligands **308a,b**−**318a,b**, the ratio was always higher for the bis(4-fluoro)-substituted compounds than for their desfluoro analogues.

Among fused-ring analogues, in general, most of the five-membered aromatic ring-containing compounds (**308a,b, 309a,b, 310a,b, 311a,b**; Figure 48) exhibited the highest selectivity for both DAT (vs 5-HT) binding and DA (vs 5-HT) reuptake inhibition. The indole derivative **310b**, an analogue of GBR 12909, was the most potent ligand for binding to the DAT (IC_{50} = 0.7 nM), whereas **310a**, the indole derivative of GBR 12935, displayed highest DAT/SERT binding selectivity (over 600-fold) at this site. Furthermore, the fused-ring derivative with only one heteroatom placed in the 2-position appeared to be more favorable in terms of selectivity of the new ligands at the DAT site (cf. **308a,b, 309a,b, 310a,b**). Incorporation of an additional nitrogen atom in the five-membered ring (benzimidazole derivatives, **311a,-b**) resulted in reduction of both affinity and selectivity at the DAT site.

An increase in the number of atoms between the piperazine nitrogen and heteroaromatic ring (**315a,b** vs **311a,b**, respectively) further decreased the selectivity of these ligands at the DA uptake site, mainly because of improved affinity at the 5-HT uptake site.

Compounds containing a quinoline ring (**312a,b**−**314a,b**) displayed a broad range of affinities for binding to the DAT. It is intriguing that whereas 2-indole congener (**310b**) was one of the most selective ligands, its quinoline analogue (**312b**) exhibited a comparably high affinity at both DA and 5-HT sites. Such a difference may be due to either the different electronic character of their nitrogen atoms or the presence of a hydrogen-bonding donor in **310b**.

In the series of naphthalene analogues (**316a,b, 317a,b, 318a,b,** Figure 48), the 2-naphthalene methyl derivatives (**316a,b**) were the most selective compounds for both binding to the DAT and inhibition of DA reuptake. In contrast to their isomers, **317a,b**, with naphthalene substituted in the 1-position lost selectivity at these sites. Addition of another carbon (compounds **318a,b**) between the piperazine nitrogen atom and the phenyl ring of the 1-nephthalene moiety resulted in at least 10-fold improvement in the affinity for inhibition of DA reuptake compared to **317a,b**. It is also important to note that in this series of compounds, 1-naphthalene derivative, **317b** (Figure 48), was more than 10-fold potent at the DAT compared to DA uptake. The latter compound can serve as a lead compound for developing cocaine antagonists.

Table 45. Binding Affinities at the DAT and 5-HTT Labeled with [^{125}I]RTI-55 and Affinities for DA and 5-HT Reuptake Inhibition of Heteroaromatic and Fused Ring GBR Analogues

	IC_{50} (nM)				selectivity	
	binding [^{125}I]RTI-55		reuptake		binding	uptake
compound no.	DAT	5-HTT	[^{3}H]DA	[^{3}H]5-HT	5-HTT/DAT	[^{3}H]5-HT/[^{3}H]DA
GBR12935	3.7 ± 0.3	623 ± 13	3.7 ± 0.4	298 ± 29	168	80.5
GBR12909	3.7 ± 0.4	126 ± 5	7.3 ± 0.2	73 ± 2	34.0	10.0
GBR13069	0.9 ± 0.1	135 ± 7	11 ± 0.6	576 ± 32	150	52.4
304a	5.2 ± 0.3	842 ± 30	9.7 ± 0.2	1990 ± 58	162	205
304b	6.5 ± 0.2	1520 ± 47	8.5 ± 0.5	2550 ± 87	34	300
304c	78 ± 4	2420 ± 65	70 ± 6	3700 ± 148	31.0	52.8
305a	3.3 ± 0.1	105 ± 2	6.1 ± 0.7	335 ± 17	31.8	54.9
305b	5.9 ± 0.3	204 ± 7	7.9 ± 0.5	412 ± 9	34.6	52.1
305c	16 ± 0.2	2800 ± 139	20 ± 0.8	6520 ± 293	175	326
306a	6.4 ± 0.3	1170 ± 31	10 ± 0.7	2020 ± 141	183	202
306b	5.0 ± 0.3	1840 ± 59	9.6 ± 0.3	2700 ± 136	368	281
306c	44 ± 3	2670 ± 66	64 ± 2	3620 ± 179	60.7	56.6
307a	2.2 ± 0.1	88 ± 2	13 ± 1.4	374 ± 17	40.0	28.8
307b	1.8 ± 0.3	109 ± 4	7.2 ± 0.4	442 ± 23	60.5	61.4
307c	13.6 ± 0.2	334 ± 12	14.5 ± 1.9	666 ± 21	24.5	45.9
308a	18.1 ± 1	2420 ± 109	19 ± 1	3520 ± 289	134	185
308b	4.1 ± 1.1	495 ± 18	34 ± 2	1230 ± 40	121	36.2
309a	17 ± 0.5	1890 ± 48	22 ± 0.7	3040 ± 213	111	138
309b	6.4 ± 0.2	286 ± 10	18.6 ± 0.6	767 ± 27	44.7	41.2
310a	1.1 ± 0.1	668 ± 39	8.8 ± 0.7	2120 ± 166	607	241
310b	0.7 ± 0.1	119 ± 5	13 ± 0.2	506 ± 23	170	38.9
311a	46 ± 1	1884 ± 72	37 + 2	4076 ± 221	41.0	110
311b	15 ± 0.2	256 ± 7	20 ± 0.8	797 ± 43	17.1	39.8
312a	199 ± 5	1990 ± 5	192 ± 8	4120 ± 212	10.0	21.5
312b	56 ± 1	51 ± 16	106 ± 12	339 ± 31	0.9	3.2
313a	72 ± 2	1160 ± 27	111 ± 3	3040 ± 252	16.1	27.4
313b	16 ± 3	485 ± 16	74 ± 3	851 ± 36	30.3	11.5
314a	190 ± 6	845 ± 15	140 ± 4	1640 ± 58	4.4	11.7
314b	62 ± 2	551 ± 21	73 ± 3	1040 ± 46	8.9	14.2
315a	23 ± 0.5	309 ± 9	17 ± 0.7	627 ± 12	13.4	36.9
315b	2.5 ± 0.1	28 ± 2	8.1 ± 0.3	74 ± 4	11.2	9.1
316a	43 ± 2	903 ± 47	32 ± 0.6	926 ± 33	21.0	28.9
316b	8.0 ± 0.3	312 ± 15	30 ± 1	588 ± 39	39.0	19.6
317a	114 ± 5	336 ± 22	406 ± 11	83 ± 5	2.9	0.2
317b	31 ± 1	243 ± 6	312 ± 19	257 ± 12	7.8	0.8
318a	92 ± 13	462 ± 17	42 ± 0.9	578 ± 17	5.0	13.8
318b	7.8 ± 0.2	46 ± 1	25 ± 0.8	119 ± 4	5.9	4.8

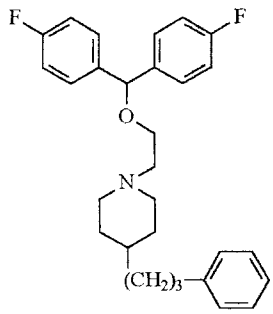
D. Piperidine Analogues of GBR Compounds

It has been shown above that substitution of the piperazine ring of GBR 12935 with a homopiperazine ring (**290a**; Table 44) resulted in retention of high affinity for the DAT binding sites.[307,310,314] Madras et al. focused their effort upon the examination of the role of each of the nitrogen atom in the piperazine ring itself.[315] The piperazine moiety of GBR 12909 was replaced with a piperidine ring. Once piperidine was in place, it was important to determine whether the nitrogen atom in the piperidine should be proximal to the diphenyl methyl ether or distal to this moiety. Initially two compounds were synthesized,[293] O-526 (**321**) and O-549 (**320**) (Figure 49).[315] Having determined the positional requirement of the nitrogen atom of the piperidine ring, a large number of compounds were designed after the compound O-526 (Figure 49).

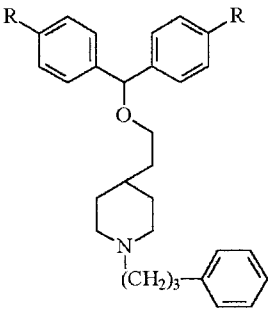
The synthetic strategy to obtain O-549 utilized a commercially available ketal **333**. The key steps were *N*-protection, Wittig reaction, and *N*-alkylation. Thus, ketal was benzylated under basic conditions followed by acid-catalyzed deketalization and Wittig reaction with (3-phenylpropyl)triphenylphosphonium bromide in the presence of phenyllithium. Hydrogenation over 10% Pd/C reduced the carbon−carbon double bond as well as *N*-debenzylated. Further alkylation of the amine with an appropriate alkyl chloride (**285**) gave O-549 in overall good yield, Scheme 67. [293]

Synthesis of O-526 and other related compounds utilized a modified strategy as shown in Scheme 68. The alkylation reagent was carefully selected so that it could serve both purposes: (1) protection of the amine function and (2) easily modified into the required pharmacophore. The *N*-alkylation was accomplished by using mainly three methods depending upon the final compound, e.g., (1) using a substituted alkyl halide in the presence of base,[316,317] (2) using a substituted acid chloride followed by reduction with LAH,[317,318] and (3) using a substituted aldehyde followed by reduction with sodium cyanoborohydride (reductive amination).[317] Another modification was in the synthesis of substituted diphenylmethyl ether attached to piperidine through a spacer. Most of these analogues were prepared via the intermolecular dehydration method. However, in some cases the Williamson reaction was exploited (e.g., **322d**, Scheme 68).[317]

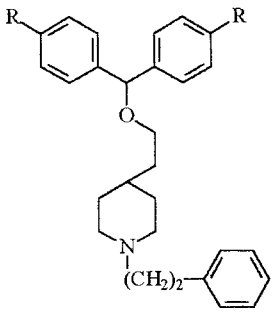
Synthesis of compounds **325**−**327** (Figure 49) utilized a similar strategy as shown in Scheme 68. Since



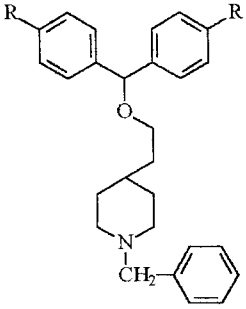
320; O-549



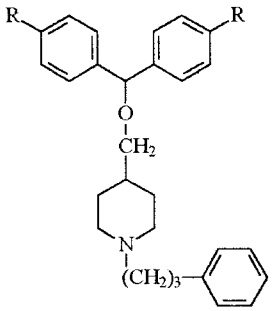
321; O-526; R= F
322a; R= H
322b; R= Cl
322c; R=Br
322d; R= OCH_3



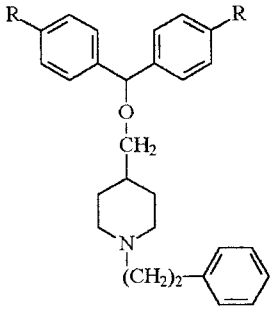
323a; R= H
323b; R= F
323c; R= Cl
323d; R=Br
323e; R= CH_3



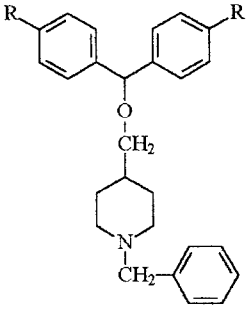
324a; R= H
324b; R= F



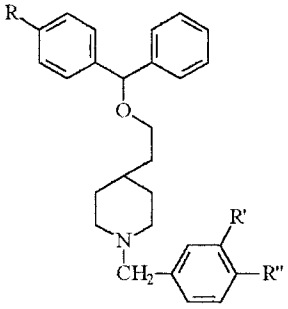
325a; R= H
325b; R= F



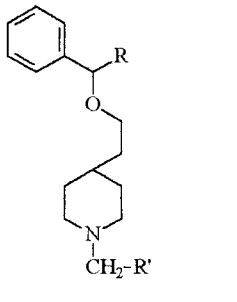
326a; R= H
326b; R= F



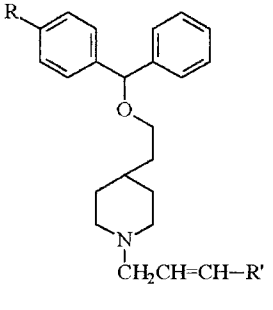
327a; R= H
327b; R= F



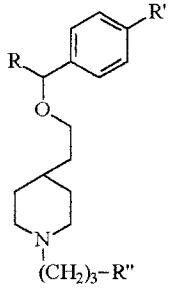
328a; R= R'= H, R"= F
328b; R= R'= H, R"= Cl
328c; R= R'= H, R"= Br
328d; R= H, R'= R"= Cl
328e; R= R'= H, R"= OCH_3
328f; R= Cl, R'= H, R"= F
328g; R= F, R'= H, R"= F
328h; R= R'= H, R"= CH_3
328i; R= H, R'= Cl, R"= F
328j; R= R'= H, R"= NO_2
328k; R= R'= H, R"= NH_2



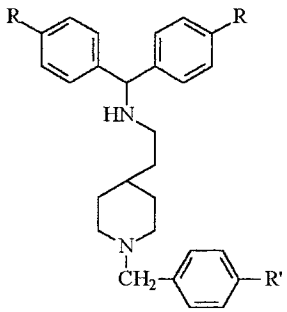
329a; R= Ph, R'= 3-pyridyl
329b; R= Ph, R'= 2-benzo[*b*]thiophenyl
329c; R= Ph, R'= 2-thienyl
329d; R= 2-thienyl, R'= Ph
329e; R= 2-thienyl, R'= 4-F-Ph
329f; R= 2-thienyl, R'= 3-pyridyl



330a; R= F, R'= 4-F-Ph
330b; R= F, R'= Ph
330c; R= H, R'= Ph
330d; R= H, R'= 4-F-Ph
330e; R= H, R'= 2-thienyl



331a; R= Ph, R'= H, R"= 4-F-Ph
331b; R= Ph, R'= H, R"= 3-pyridyl
331c; R= 2-thienyl, R'= H, R"= Ph
331d; R= 2-thienyl, R'= F, R"= Ph

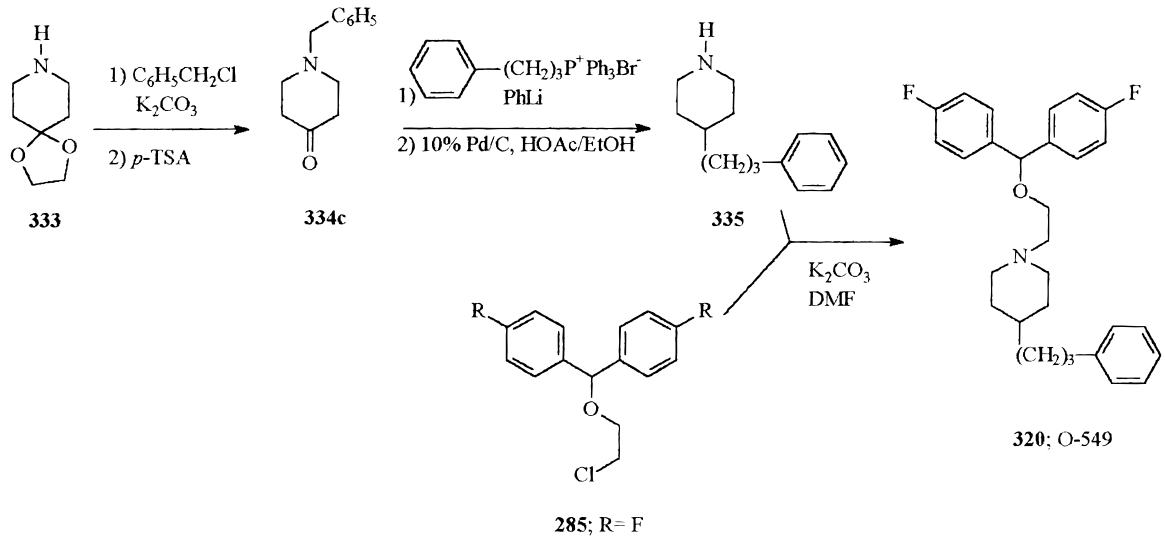


332a; R= H, R'= F
332b; R= F, R'= H

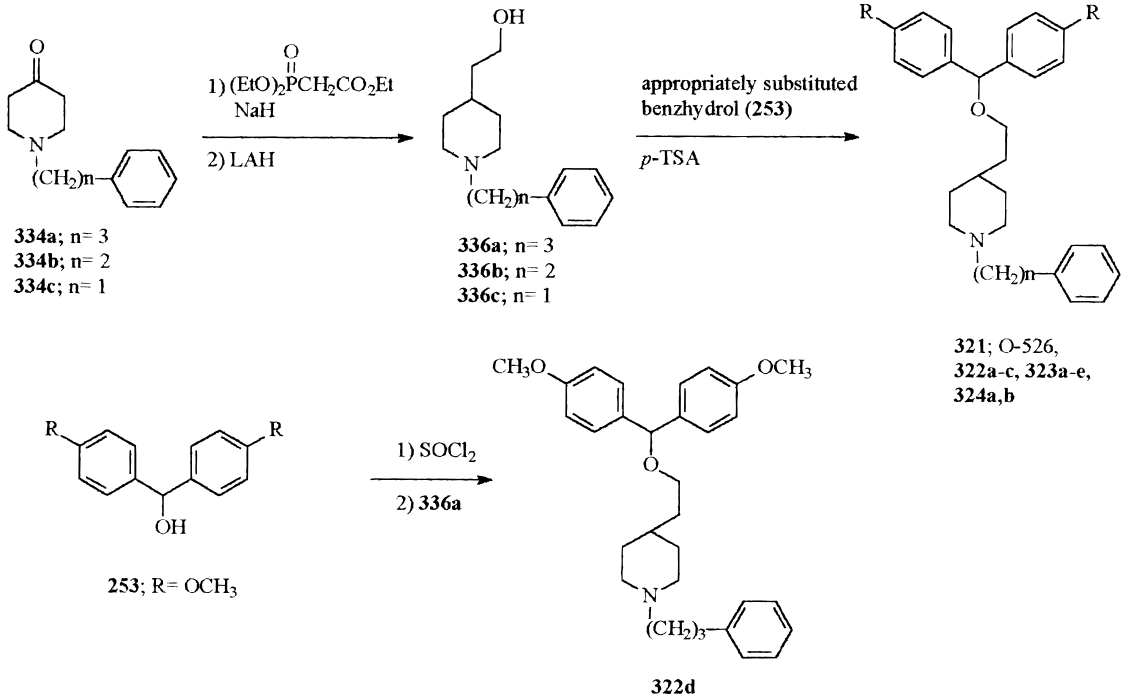
Figure 49. Structures of the piperidine analogues of GBR type of compounds.

these compounds contained a one-carbon atom spacer between the piperidine ring and the diphenylmethoxy pharmacophore, commercially available ethyl isonipecotate was used as the starting material, which was

Scheme 67



Scheme 68



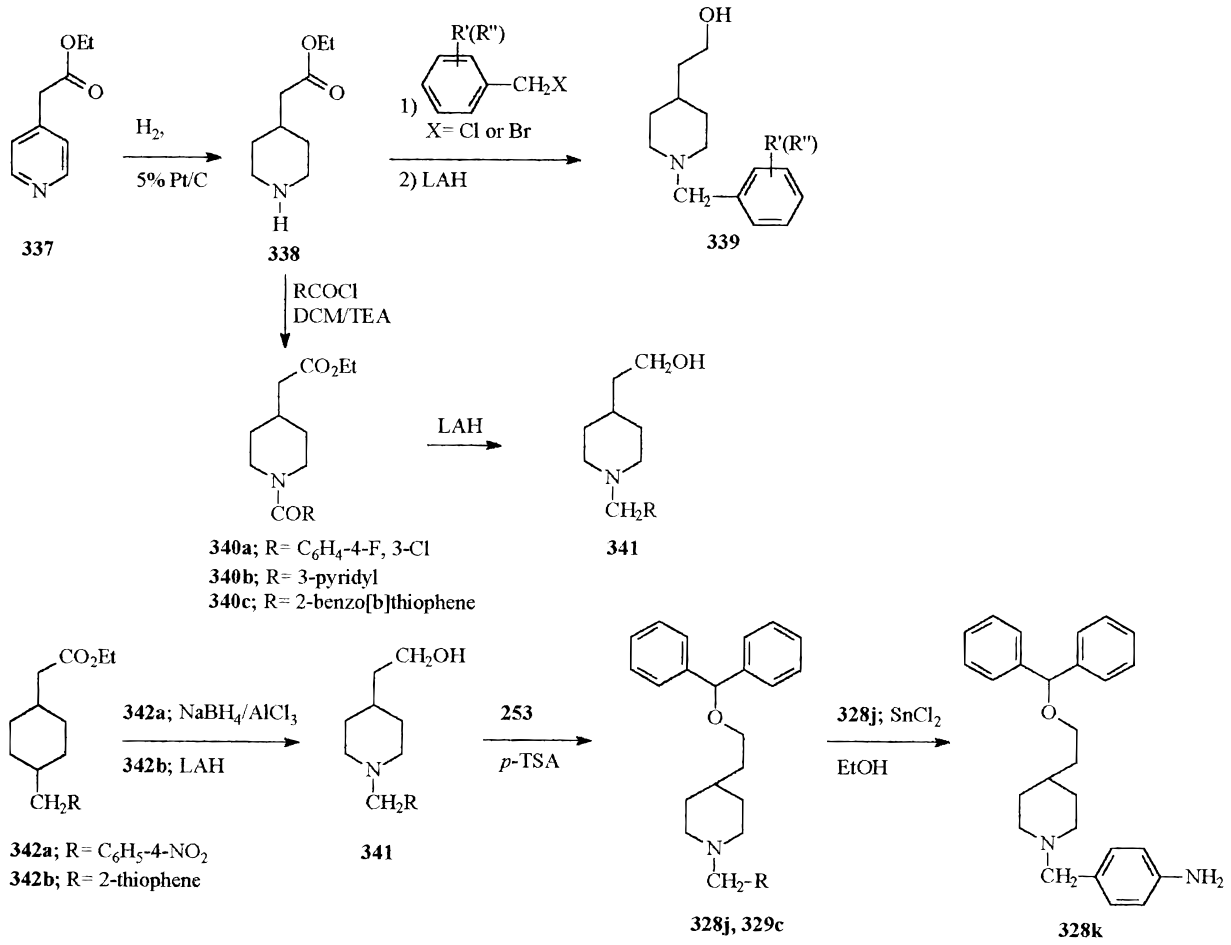
first *N*-alkylated and then reduced with LAH to give *N*-alkylated alcohol. Ether linkage was formed by dehydration under acidic conditions.[319]

Synthesis of compounds **328**−**329** (Figure 49) is shown in Scheme 69. The commercially available ethyl 4-pyridyl acetate (**337**) was hydrogenated over 5% Pt/C catalyst to give amino ester **338**, which served as the common intermediate for the synthesis of **328**−**329** analogues. The alkylation of amine **338** was performed by either reductive amidation or reductive amination.[320] The compound **342a** was reduced with a mild reducing agent, $NaBH_4/AlCl_3$, to ensure selective reduction of the ester functionality.[321] The nitro group was reduced with $SnCl_2$ in ethanol. Compounds **329d**−**f** (Figure 49) were synthesized in a similar fashion as shown in Scheme 68.

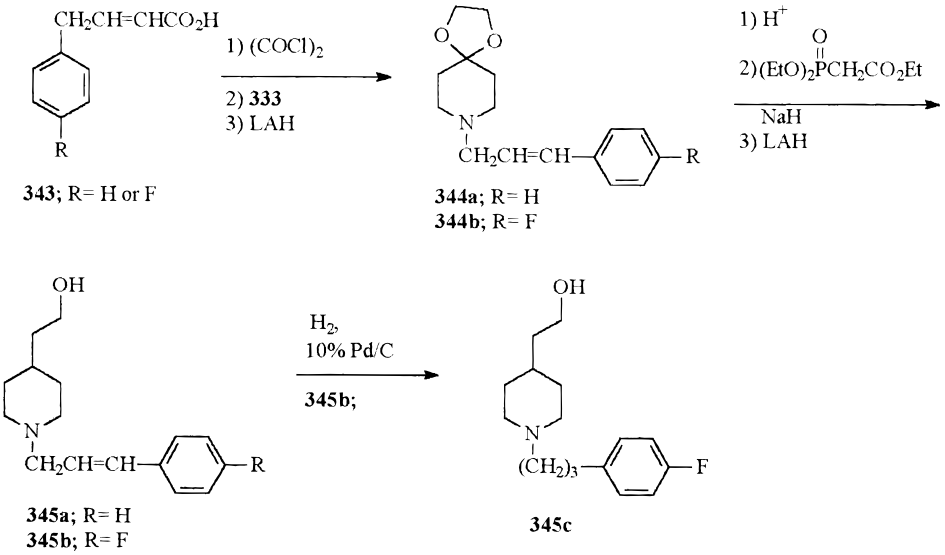
Synthesis of **330a**−**d** and **331a** (Figure 49) was performed as shown in Scheme 70.[316] Thus, *N*-alkylation of ketal amine **333** with *trans*-cinnamyl bromide (**343**) furnished **344a**, and similarly *N*-acylation with *trans*-cinnamoyl chloride followed by reduction with LAH produced **344b**. Deketalization of **344a,b** under acidic conditions, followed by Wittig reaction and reduction with LAH, provided alcohols **345a,b**. Hydrogenation of **345b** gave saturated alcohol **345c**. Final compounds were obtained by reacting alcohols with appropriate benzhydrols under azeotropic distillation conditions.[319]

Syntheses of **330e** and **331b**−**d** are shown in Scheme 71 and followed an essentially similar strategy as described above. Thus, reductive amination of aldehyde **349** with amine **338** in the presence of sodium cyanoborohydride produced ester,[320] which upon reduction with LAH gave alcohol **347** (Scheme 71). Reaction with benzhydrol gave **331b**. Similarly, acylation of amine **338** with acid chloride of *trans*-

Scheme 69



Scheme 70

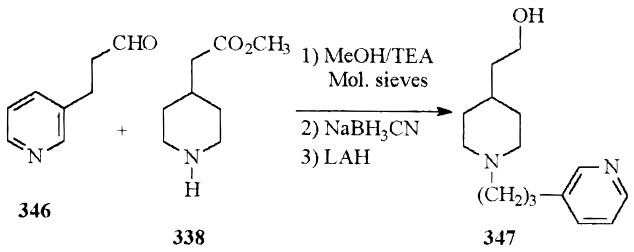


thieny acrylic acid provided ester, which upon reduction gave alcohol. Reaction with benzhydrol then gave **330e**. Compounds **331c,d**, were also synthesized following a common route.

The *N*-atom-containing compounds **332a,b** were synthesized from *N*-benzyl piperidine acetate (**348**) as shown in Scheme 72.[322] Hydrolysis of the ester **348** was accomplished using a mixture of TFA/HCl/H_2O (1:1:1) under refluxing conditions. The acid **349** thus obtained was activated using water-soluble coupling agent, EDC, and HOBt and reacted with appropriately substituted aminodiphenylmethane to afford an amide (**350**).[323] Reduction of the amide with diborane/THF complex provided the final compounds **332a,b**.

The rationale to synthesize piperidine analogues, O-526 (**321**) and O-549 (**320**), was to improve upon the selectivity of GBR compounds. GBR compounds are potent ligands for the DAT in brain, but they also

Scheme 71



bind to a widely distributed piperazine acceptor site.[324] As shown in Table 46, O-526 retained selectivity for the DAT over 5-HTT but O-549 was relatively nonselective as well as several fold less potent.[315] These results indicated that (1) only one of the two nitrogens on the basic GBR structure was needed for high-affinity binding to the DAT and (2) the position of the nitrogen was crucial for determining selectivity to the DA over 5-HT transporter. It should also be mentioned that O-526 displayed a lower affinity for the "piperazine acceptor site" (IC_{50} = 404 ± 74 nM) than did GBR 12909 (IC_{50} = 37 ± 3 nM). These results were encouraging and led to the design of a large number of O-526 type of compounds (Figure 49).

Initially, alkyl chains of varying lengths and different substitutions in the phenyl ring(s) of the diphenyl methyl ether part of the molecule were introduced in order to optimize activity and selectivity for the DAT (compounds **322**−**327**; Figure 49). As shown in Table 46, unsubstituted and fluoro-substituted analogues were the most active and selective for the DAT. These results also indicated that shortening of ethylene linkage connected to the oxygen atom of the diphenyl methoxy moiety into a methylene unit did not change the potency of compounds **325a,b, 326b** at the DAT. On the other hand, **327a,b** turned out to be much less potent, which reflected the low tolerance of the DAT for *N*-benzyl substitution. It is also noteworthy that the activities in this series of molecules with a connection of one methylene unit (**325**−**327**) were more dependent on the variation of the *N*-alkyl chain length, showing the weakest activity for compounds with the shortest chain length (**327a,b**). One of the compounds, 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperidine (**324a**) was highly potent and was also the most selective for the DAT (5-HTT/DAT = 49) in this series of compounds. Compound **324b**, on the other hand, was the most potent for DAT. To explain the dissimilarities in potency and selectivity of **324a,b** as compared to GBR 12909, the differences in the pK_a were invoked. It has been suggested that the reduced selectivity of GBR 12909 was due to its lower pK_a, which affected binding at the 5-HT transporter.[316]

Using **324a** as the lead compound, several substituents were introduced in the aromatic rings to evaluate the influences of electronic and steric interactions upon their binding to the DAT (compounds **328a**−**k**). Additionally, in some compounds, one of the aromatic rings was replaced with a bioisosteric equivalent thienyl or pyridyl ring (compounds **329a**−**f**). The rationale behind introducing polar biosteric moieties was 2-fold: (1) to examine the effect on activity, i.e., SAR, and (2) to decrease the lipophilic character of these molecules since high lipophilicity of GBR molecules required great caution in carrying out biological assays due to the tendency of adsorption to the walls of the tubes used for incubation.[318]

Among **328**−**329** (Table 46) compounds, **328a,j** and **329e** were equipotent to GBR 12909 but had the highest selectivity for the DAT (5-HTT/DAT = 112, 108, and 101, respectively). It appeared that compounds with electron-withdrawing substituents (F, NO_2, **328a,j**) had maximal preferential interaction at the DAT. The possibility of existence of complimen-

Scheme 72

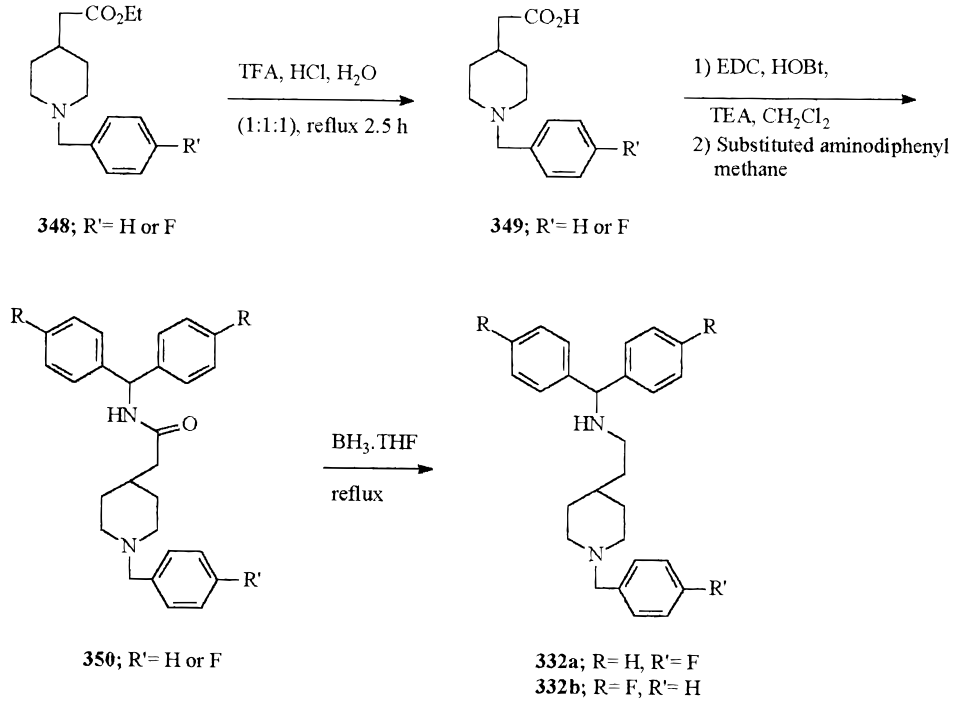


Table 46. Binding Affinities of Piperidine Analogues of GBR Compounds for the DAT and 5-HTT

	IC_{50} (nM)		selectivity
compound no.	DAT [^{3}H]WIN 35428	5-HTT [^{3}H]citalopram	5-HTT/DAT
GBR12909	14.0 ± 0.6	82 ± 4	5.8
320; O-549	595 ± 148	38 ± 127	0.6
321; O-526	24.9 ± 3.23	248 ± 72	9.9
322a	12.0 ± 0.4	232 ± 28	19.3
322b	65.0 ± 12	224 ± 10	3.4
322c	159 ± 56	835 ± 142	5.2
322d	255 ± 32	340 ± 24	1.3
323a	10.6 ± 0.85	102 ± 5	9.6
323b	19.9 ± 9.5	31.9 ± 7.1	1.6
323c	115 ± 22	414 ± 32	3.6
323d	382 ± 167	638 ± 71	1.7
323e	311 ± 71	888 ± 58	2.8
324a	15.2 ± 2.8	743 ± 6	48.9
324b	9.7 ± 0.4	198 ± 7	20.4
325a	14.5 ± 1.9	58 ± 7	3.7
325b	13.0 ± 2.5	112 ± 4	8.6
326a	108 ± 14	456 ± 90	4.2
326b	13.5 ± 2.6	237 ± 53	17.5
327a	702 ± 34	544 ± 91	0.8
327b	126 ± 13	761 ± 101	6.0
328a	17.2 ± 4.7	1920 ± 233	111.6
328b	24.7 ± 5.5	1610 ± 119	65.2
328c	31.1 ± 2.9	1490 ± 319	47.9
328d	85.7 ± 4.7	2880 ± 281	33.6
328e	27.8 ± 6.8	1240 ± 342	44.6
328f	52.4 ± 7.8	1810 ± 107	34.5
328g	14.0 ± 3.3	1260 ± 72	90.0
328h	23.0 ± 3.7	1390 ± 240	60.4
328i	28.2 ± 3.1	2530 ± 50	89.7
328j	16.4 ± 3.0	1770 ± 305	107.9
328k	101 ± 13	1570 ± 201	15.5
329a	48.6 ± 8.4	680 ± 12.0	14.0
329b	172 ± 16.4	1540 ± 251	8.9
329c	59.3 ± 5.8	1250 ± 87	21.1
329d	27.2 ± 0.1	741 ± 108	27.2
329e	13.8 ± 3.4	1390 ± 243	101
329f	58.3 ± 5.7	927 ± 34	15.9
330a	15.1 ± 2.0	75.8 ± 22.1	5.0
330b	41.4 ± 8.0	271 ± 18.4	6.5
330c	10.1 ± 1.6	231 ± 4.5	22.9
330d	10.8 ± 3.2	205 ± 13.3	19.0
330e	9.8 ± 2.4	290 ± 63	29.6
331a	6.6 ± 1.4	223 ± 32.3	33.8
331b	29.9 ± 0.3	194 ± 20.1	6.5
331c	6.0 ± 0.5	180 ± 21.6	30.0
331d	11.7 ± 1.0	85.7 ± 2.6	7.3
332a	9.4 ± 2.6	585 ± 101	62.2

tary electropositive/electron-accepting sites on the DAT to favor the observed interaction and vice versa on 5-HTT have been suggested. Replacement of the phenyl ring of *N*-benzyl group with a bioisosteric moiety was not tolerated very well, which indicated unfavorable electronic interactions. However, higher activity was observed when one of the phenyl rings of the benzhydryl part of the molecule was substituted with a bioisosteric thiophene ring (**329e**, IC_{50} = 13.8 nM), suggesting a positive interaction with the transporter.[317]

To understand the mode of binding of piperidine analogues of GBR 12935 and to make a comparison with conventional GBR analogues, further structural variations in compound 4-[2-(diphenyl methoxy)-ethyl]-1-(3-phenylpropyl)piperidine (**322a**) were undertaken by introducing a double bond in the *N*-propyl side chain (**330a**−**e**) and also by replacing the phenyl moiety with biosteric thiophene and pyridine rings (**331a**−**d,** Figure 49).

As apparent from Table 46, introduction of a double bond in the *N*-propyl side chain did not have a major effect on the biological activity. Nevertheless, greater conformational flexibility in the saturated *N*-propyl chain analogues (e.g., **331a,c,d**, Figure 49) resulted in a more favorable interaction with the DAT. Furthermore, replacement of the aromatic ring with a thiophene ring produced the most active compound (**331c**), indicating more tolerance for the thiophene ring by the DAT compared to the pyridine moiety.[318]

Recently, Dutta et al.[322] have designed compounds **332a,b** (Figure 49) by replacing the benzhydric oxygen atom in 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperidine derivative with a nitrogen atom. The main aim of this study was to discover new molecular determinants and also to obtain further insight into the molecular characterization of binding to the DAT. As shown in Table 46, the *N*-containing compound **332a** was more potent than GBR 12909 as well as more selective at the DAT. These compounds (**332a,b**) were also tested in cloned human DAT and human 5-HTT proteins and were found to be quite potent, but more importantly these were more selective compared to previously synthesized piperidine analogues of GBR compounds. The reason for this enhancement in selectivity of **332a,b** could be due to reduction in lipophilicity (4-fold less lipophilic solubility for **332a** compared to GBR 12909). Nevertheless, these compounds are very interesting and deserve further SAR studies.

From the above SAR studies, it has been demonstrated that some of the key structural features, which were needed for good potency and selectivity in these molecules for the DAT, were as follows: (1) the unsubstituted or fluoro-substituted aromatic rings in the diphenyl methoxy moiety were best tolerated, (2) different *N*-benzyl substitutions at the piperidine ring of the molecule produced some of the most potent and selective molecules for the DAT, and (3) different alkyl chain lengths connected to the 1- and 4-positions of the piperidine ring played important roles in the activities.

VI. Methylphenidate Analogues

Ritalin, (±)-*threo*-methylphenidate, was first synthesized in 1944[325] and was identified as a stimulant in 1954.[326] It is used to treat the hyperkinetic syndrome (or attention deficit disorder, ADD) in children.[327,328] Originally it was marketed as a mixture of two racemates, 80% (±)-*erythro* and 20% (±)-*threo* (Figure 50). Subsequent studies of the racemates showed that the central stimulant activity was associated with the *threo* racemate and were focused on the separation and interconversion of the *erythro* isomer into biologically more active *threo* isomer.[329−331] Further investigation with the enantiomers of *threo* methylphenidate revealed that it was the (+)-*threo* isomer which was active in the racemic mixture.[332] Besides, it has been suggested that the anti-conformer of the (+)-*threo* isomer, which is stabilized by the hydrogen bonding between the protonated amine (pK_a 8.5) and the ester carbonyl and has reduced

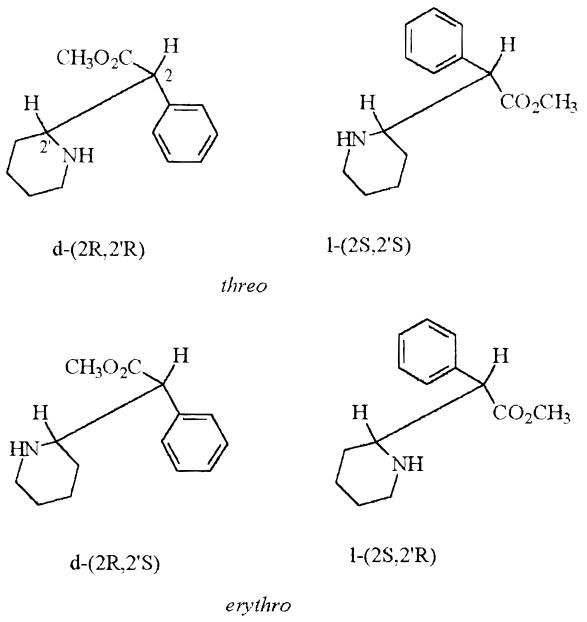


Figure 50. Stereochemical assignments of methylphenidate isomers.

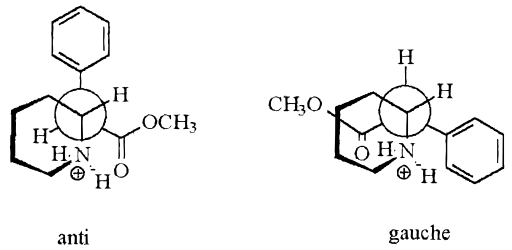


Figure 51. Anti and gauche conformations of D-*threo*-methylphenidate.

gauche−gauche interactions, may be responsible for the pharmacological activity of the *threo*-methylphenidate enantiomer (Figure 51).[332]

The conformational analysis of *threo*-methylphenidate also indicated that the carbonyl oxygen was oriented toward and made a good intramolecular hydrogen bond with the protonated amines.[333] The superimposition of the global minimum of *threo*-methylphenidate over WIN 35428 indicated that the sequence of atoms from the nitrogen atom through the ester group was identical in the two compounds. However, the position of the phenyl ring varied in (−)- and (+)-*threo*-methylphenidate isomers and between WIN 35428 and cocaine.

The mechanism for the stimulant properties of methylphenidate is considered to be the same as cocaine.[334] Studies with [^{3}H]methylphenidate showed that its binding sites were localized primarily on dopaminergic nerve terminals[335] and were associated with DA uptake.[94] Furthermore, it was found that the stimulant properties of (±)-*threo*-methylphenidate and a series of alkylesters were directly correlated to their ability to bind to the uptake sites.[335] Methylphenidate is self-administered by animals. However, it does not seem to have as great an abuse potential in humans as cocaine despite its widespread availability.[336] It has been suggested that it may actually reduce craving for cocaine because of the differences in the exact manner or the exact site where methylphenidate and cocaine interact. For example, the entropy of binding ($\Delta s°$, measured using [^{3}H]GBR 12783 at 25 °C) for methylphenidate was −25.5 kcal/mol whereas for cocaine it was −5.6 kcal/mol.[34]

A diverse group of methylphenidate analogues have been synthesized. The rationale to synthesize them is mainly 2-fold: (1) methylphenidate binds potently and somewhat selectively to the DAT[12,335,337] and (2) it has been used to study the stimulant binding sites.[306] Since both the phenyl ring and the piperidine ring of methylphenidate are important for the binding at the DAT, the design of the methylphenidate analogues has mainly focused on modifying these two pharmacophores. The analogues of methylphenidate are divided into four classes: (1) phenyl ring substituted, (2) *N*-methylphenyl ring substituted, (3) phenyl ring modified, and (4) piperidine ring modified. The structures of these analogues are shown in Figures 52−55.

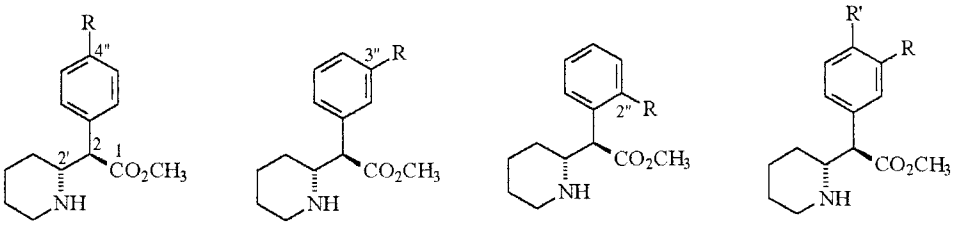
A. Phenyl Ring Substituted Analogues of Methylphenidate

This series of compounds comprises substitutions in the phenyl ring of methylphenidate at the 4″-, 3″-, and 2″-positions, (**351**−**354**; Figure 52).

Some of the phenyl ring-substituted analogues of methylphenidate (e.g., **351c, 352c, 353c**) were synthesized[338] by employing the original strategy developed in 1944.[325] The following steps were involved: acid hydrolysis of the nitrile group into an amide group, hydrogenation of the pyridine ring using a transition metal catalyst, sodium hydroxide catalyzed epimerization, acid hydrolysis of the amide group into a carboxylic acid group, and esterification with methanol/HCl. The 4″-hydroxy analogue (**351g**) was obtained from 4″-methoxy analogue (**351h**) by hydrolysis in refluxing 48% HBr.[339] 4″-Iodo analogue (**351f**) was prepared directly from methylphenidate via nitration and diazotization. The 3″-iodo-4″-hydroxy derivative **354b** was synthesized from **351g** by electrophilic iodination.[340]

Deutsch et al. improved upon the existing synthetic pathway of (±)-*threo*-methylphenidate.[341] The improved synthesis utilized potassium-*tert*-butoxide as a base to effect coupling between 2-bromopyridine (**355**) and appropriately substituted phenyl acetonitrile **356**. Concentrated HCl was used to hydrolyze the nitrile group into an amide (**358**) instead of sulfuric acid, which in some cases (e.g., methoxy-substituted nitriles) caused aromatic sulfonation. Another modification was the hydrolysis of the amides **358** into the acids **361** prior to epimerization. The remaining steps were straightforward. A general synthetic strategy of (±)-methylphenidate is shown in Scheme 73.[341]

Recently, an asymmetric synthesis of 4″-bromo **351d** and 4″-methoxy **351h** analogues of methylphenidate has been reported as shown in Scheme 74.[342] It utilized enantiopure amino acid D-pipecolic acid (**366**) as the starting material, which in turn was prepared by resolution of (±)-pipecolic acid using tartaric acid. The amino group of **366** was protected as *N*-Boc (compound **367**) and subsequently con-



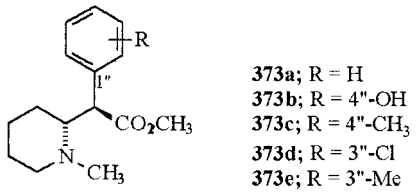
methylphenidate; R = H
351a; R = F
351b; R = Cl
351c; R = Br
351d; (d) R= Br
351e; (l) R= Br
351f; R = I
351g; R = OH
351h; R = OCH_3
351i; (d) R= OCH_3
351j; (l) R= OCH_3
351k; R = CH_3
351l; R = *t*-Bu
351m; R = NH_2.HCl
351n; R = NO_2

352a; R = F
352b; R = Cl
352c; R = Br
352d; R = OH
352e; R = OMe
352f; R = Me
352g; R = NH_2.HCl

353a; R = F
353b; R = Cl
353c; R = Br
353d; R = OH
353e; R = OCH_3

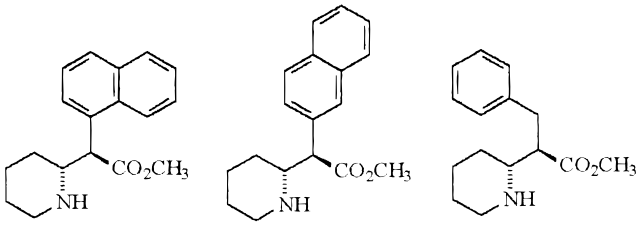
354a; R = R' = Cl
354b; R = I, R' = OH
354c; R = R' = OMe

Figure 52. Phenyl ring substituted methylphenidate analogues.



373a; R = H
373b; R = 4"-OH
373c; R = 4"-CH_3
373d; R = 3"-Cl
373e; R = 3"-Me

Figure 53. *N*-Methyl phenyl ring substituted methylphenidate analogues.

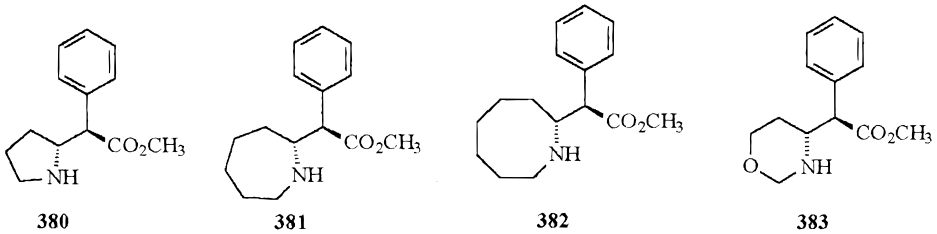


374 **375** **376**

Figure 54. Phenyl ring modified methylphenidate analogues.

verted into *N*,*O*-dimethylamide **368** using BOP as coupling agent.[343] The latter compound was treated with 100 mol % of phenyllithium in ether at −23 °C to afford 73% of ketone **369**. Use of excess of organolithium reagent (110 mol %) caused approximately 10% racemization. Once ketone was obtained, it was converted into the chiral aromatic alkene **370** using a Wittig reaction. Next, hydroboration of the terminal alkene was performed. Several reagents were tried, including (+)-Ipc-BH_2, $(cyclohexyl)_2$-BH, BH_3·Me_2S, and BH_3·THF. (+)-Ipc-BH_2 gave 100% *threo* isomer but the conversion was only 23%. Dicyclohexyl borane gave only 18% yield, and the ratio of *threo* to *erythro* was 57:43. Therefore, BH_3·THF was used which gave 89% yield of *threo*/*erythro* alcohols (**371:372** = 72:28).[344] The alcohol **371** was then oxidized and esterified with diazomethane. Removal of the *N*-Boc protecting group gave the final products. By using a similar strategy, L-*threo*-methylphenidate and its analogues (**351e, 351j**) were prepared.

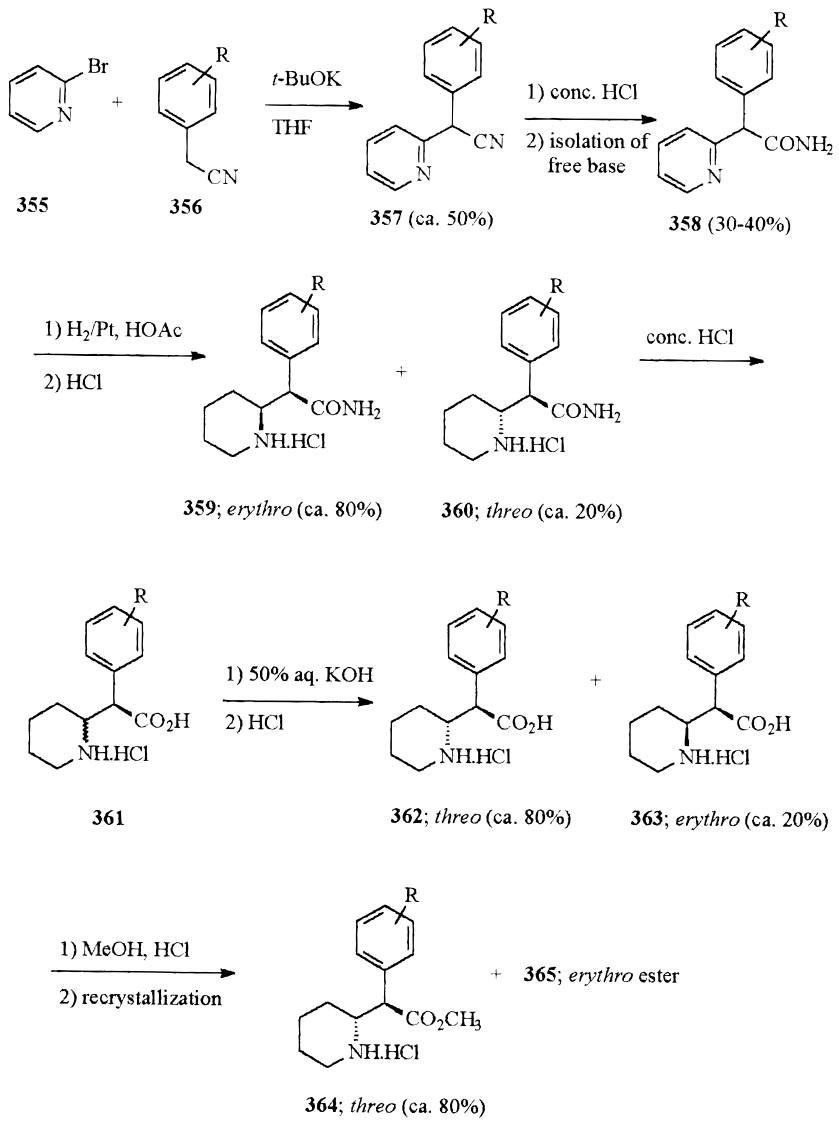
In general, *erythro* isomers of methylphenidate analogues were less active than their *threo* counterparts. Table 47 lists the IC_{50} values of the *threo*-methylphenidate analogues. D-*threo*-Methylphenidate was more potent than its L-enantiomer. Their eudismic ratio for the displacement of [^{3}H]WIN 35428 was 16.4 and that of DA uptake was 20.9. However, an eudismic ratio of 8.6 for [^{3}H]DA uptake for D- and L-*threo*-methylphenidate has been reported by Thai et al.[342] The eudismic ratio is a measure of the degree of stereoselectivity, i.e., the ratio of activities of a pair of enantiomers. The eudismic term is derived from eutomer (the more active enantiomer) and distomer (the less active enantiomer).[345] Among phenyl ring substituted (±)-*threo*-methylphenidate analogues, the derivatives with substituents in the 2″-position were much less potent than those with the same substituents in the 3″- or 4″-position. This loss of activity



380 **381** **382** **383**

Figure 55. Piperidine ring modified methylphenidate analogues.

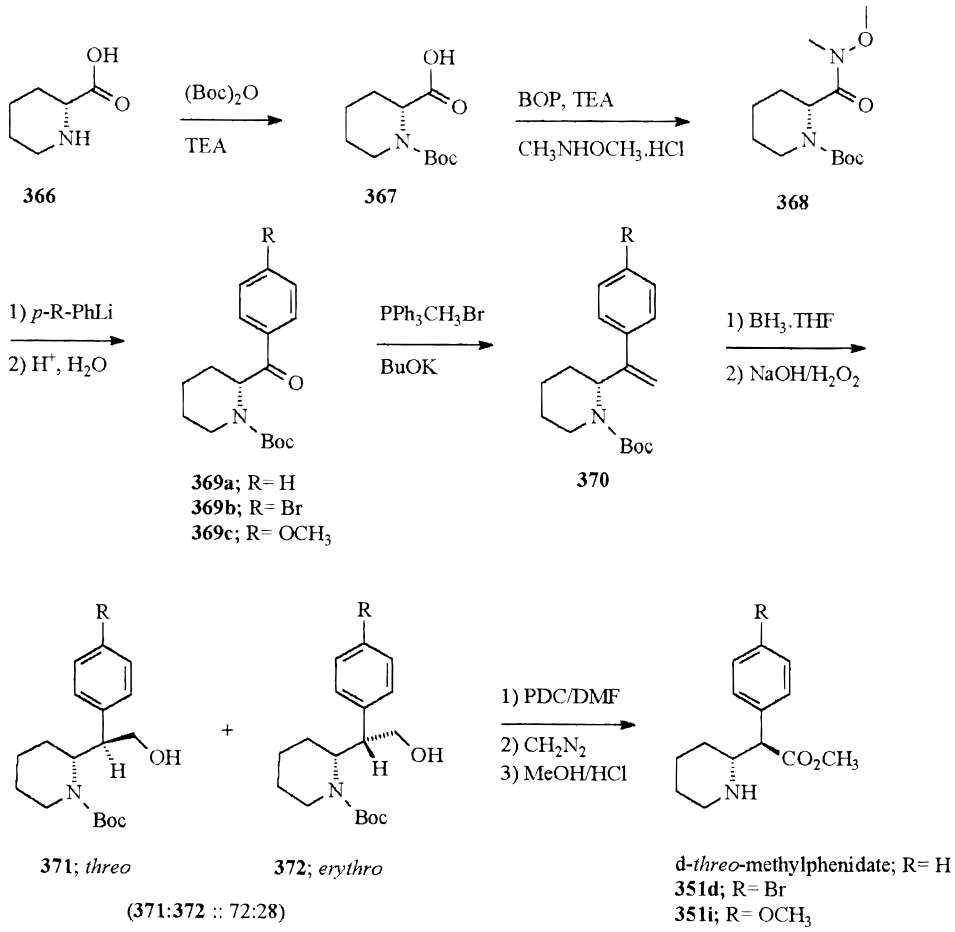
Scheme 73



was largest for methoxy analogue **353e**, followed by hydroxy **353d**, chloro **353b**, bromo **353c**, and fluoro **353a** analogues, respectively. The effect was roughly correlated with the size of the substituent and appeared to be steric rather than electronic in nature. It was supported by the solid-state conformations of (±)-*threo*-4″-chloro (**351b**) and 2″-methoxymethylphenidate (**353e**), which appeared to be quite similar, suggesting that a substitution at the 2″-position did not induce a large conformational change around the C1″- to C2-bond. For example, the torsion angles C2″−C1″−C2−H(C)-2 for **351b** and **353e** were −1° and 2°, respectively.[341] In addition, ^{1}H NMR data suggested that there were not large differences between the solution conformations of these and other 2″- and 4″-substituted compounds. The average proton coupling constant between HC-2 and HC-2′ was 9.3 Hz for 4″-substituted and 8.8 Hz for 2″-substituted compounds. These *J* values were quite consistent with the solid-state conformations, which showed that the torsion angles HC-2−C2−C2′−HC-2′ for the above compounds were 164° and 162°, respectively.[341]

Among 3″,4″-disubstituted compounds of (±)-*threo*-methylphenidate, the analogues with electron-withdrawing substituents generally possessed increased binding potency whereas those with electron-donating groups were little affected or less potent than the parent compound. However, substantial differences existed between the effects of substituents at the 3″- and 4″-positions. For example, compounds containing F, Cl, Br, or methyl group in the 3″-position were either equipotent or more potent than their respective 4″-substituted compounds. However, for amino, methoxy, and hydroxy groups, substitution in the 4″-position did not change potency greatly whereas 3″-substituted corresponding compounds were less active than methylphenidate. Larger groups, such as nitro and *tert*-butyl groups, in the 4″-position produced less active compounds. As is apparent from Table 47 that the most active compounds were 3″-chloro **352b** and 3″-bromo **352c** derivatives of methylphenidate (IC_{50}= 5.1 and 4.2 nM, respectively). The 3″,4″-dichloro analogue **354a** was equipotent to **352b,** while 3″-iodo-4″-hydroxy **354b** and 3″,4″-dimethoxy **354c** analogues were less potent.[340,341]

Scheme 74



The enantiomeric pairs **351d,e** and **351i,j** followed the same pattern as that of D- and L-*threo*-methylphenidate (eudismic ratio = 18.1 and 17.5, respectively). These enantiomeric pairs were also evaluated for [^{3}H]NE uptake. The pattern was very similar to that of [^{3}H]DA uptake.[342] These compounds were, however, not active at the 5-HTT (IC_{50} > 5μM).[342]

B. *N*-Methyl Phenyl Ring Substituted Analogues of Methylphenidate

These compounds were obtained by reductive formylation of their respective phenyl ring substituted methylphenidate analogues. The structures are depicted in Figure 53.[346]

The *N*-methyl derivatives (Figure 53) were consistently lower in potency by a factor of 4−30 as compared to the corresponding secondary amine analogues of methylphenidate (Table 48).[346] The rationale for this reduced potency was explored using NMR and conformational analysis. The NMR studies showed that the *N*-methyl group in *N*-methyl-substituted methylphenidate analogues preferably remained in the *equatorial* position. Furthermore, conformational analysis revealed that the *N*-methyl group occupied the same region as that required for the ammonium hydrogen of WIN 35428. Thus, it has been suggested that the steric interference by the *N*-methyl group might be responsible for impairing the binding of the *N*-methylphenidate analogues **373a**−**e** to the DAT.[346]

C. Phenyl Ring Modified Analogues of DL-*Threo*-Methylphenidate

This series of compounds was synthesized to evaluate the significance of the aryl pharmacophore in methylphenidate analogues. The phenyl group of methylphenidate was replaced with a naphthyl or a benzyl group (**374**−**376**; Figure 54).[347] A general synthetic strategy is shown in Scheme 75. The key step in the synthesis was stereoselective formation of a β-lactam. Thus, phenyl glyoxylate **377** upon reaction with piperidine afforded α-ketoamide, which was condensed with tosyl hydrazine to give tosyl hydrazone **378**. The latter compound was cyclized to a mixture of 6:1 *exo*/*endo* β-lactam **379** using potassium-*tert*-butoxide in refluxing toluene and subsequently hydrolyzed in acidic methanol to afford hydrochloride salt of DL-*threo*-methylphenidate as the single diastereoisomer, in which the relative stereochemistry of the β-lactam was completely preserved.

The same synthetic methodology was amenable to modification of both the piperidine and the aryl moieties of methylphenidate. For example, replacement of ethylphenylglyoxylate (**377**) with other arylketoacid esters led to the incorporation of other aryl groups into the methylphenidate framework. The requisite ketoesters were prepared by addition of an aryllithium derived from 1- or 2-bromonaphthalene. The homologated methylphenidate **376** (Figure 54) was prepared by stereoselective alkylation of 1-azabicyclo[4.2.0]octan-8-one with benzyl bromide, followed

Table 47. Inhibition of [^{3}H]WIN 35428 Binding and [^{3}H]DA Uptake by Phenyl Ring Substituted Methylphenidate Analogues

compound no.	IC_{50} (nM) [^{3}H]WIN 35428	IC_{50} (nM) [^{3}H]DA	selectivity uptake/binding
cocaine	173 ± 13	404 ± 26	2.3
D-*threo*-methylphenidate	33	244 ± 142 (171 ± 10)[a]	7.4
L-*threo*-methylphenidate	540	5100 (1468 ± 112)[a]	9.4
D/L-*threo*-eudismic ratio	16.4	20.9 (8.6)[a]	
DL-*threo*-methylphenidate	83.0 ± 7.9	224 ± 19	2.7
351a	35.0 ± 3.0	142 ± 2.0	4.1
351b	20.6 ± 3.4	73.8 ± 8.1	3.6
351c	6.9 ± 0.1	26.3 ± 5.8	3.8
351d		22.5 ± 2.1[a]	
351e		408 ± 17[a]	
351e/d eudismic ratio		18.1	
351f	14.0 ± 0.1	64.5 ± 3.5	4.6
351g	98.0 ± 10	340 ± 70	3.5
351h	83 ± 11	293 ± 48	3.5
351i		205 ± 10[a]	
351j		3588 ± 310[a]	
351j/i eudismic ratio		17.5	
351k	33.0 ± 1.2	126 ± 1	3.8
351l	13500 ± 450	9350 ± 950	0.7
351m	34.6 ± 4.0	115 ± 10	3.3
351n	494 ± 33	1610 ± 210	3.3
352a	40.5 ± 4.5	160 ± 0.00	4.0
352b	5.1 ± 1.6	23.0 ± 3.0	4.5
352c	4.2 ± 0.2	12.8 ± 0.20	3.1
352d	321 ± 1.0	790 ± 30	2.5
352e	288 ± 53	635 ± 35	.2
352f	21.4 ± 1.1	100 ± 18	4.7
352g	265 ± 5	578 ± 160	2.2
353a	1420 ± 120	2900 ± 300	2.1
353b	1950 ± 230	2660 ± 140	1.4
353c	1870 ± 135	3410 ± 290	1.8
353d	23100 ± 50	35,800 ± 800	1.6
353e	101,000 ± 10,000	81,000 ± 2000	0.8
354a	5.3 ± 0.7	7.0 ± 0.6	1.3
354b	42 ± 21	195 ± 197	4.6
354c	810 ± 10	1760 ± 160	2.2

[a] Values from ref 342.

Table 48. Inhibition of Binding at the DAT by *N*-Methyl Analogues of Methylphenidate

compound no.	IC_{50} (nM)
373a	500 ± 25
373b	1220 ± 140
373c	139 ± 13
373d	161 ± 18
373e	108 ± 16

by hydrolysis of the resulting substituted β-lactam in acidic methanol. Very recently an enantioselective synthesis of D-*threo*-methylphenidate has been reported starting from (*R*)-4-phenyl-*N*-phenylacetyl-2-oxazolidinone and 5-chlorovaleraldehyde. The key steps in the synthesis were Evan's asymmetric aldol reaction, selective reductive removal of the 2-oxazolidine chiral auxiliary, an extension of Masamune's method to piperidine ring formation, and Sharpless's oxidation of a primary alcohol to the carboxylic acid.[348]

Compounds containing a bulky naphthyl ring instead of the phenyl ring in methylphenidate **374, 375** (Table 49) were more potent than the parent compound at the DAT. Furthermore, 2-naphthyl analogue **375** was approximately 2.5-fold more potent than its 1-naphthyl isomer. The benzyl group containing analogue **376** was significantly less potent than methylphenidate. It is interesting to note that the 2-naphthyl analogue **375**, which was more potent at the DAT, was equally potent in inhibiting [^{3}H]DA uptake. The 1-naphthyl analogue, **374**, on the other hand, was relatively less potent at the DAT but significantly less potent in inhibiting [^{3}H]DA uptake.

Table 49. Inhibition of Binding and Transport by Phenyl Ring Modified Methylphenidate Analogues

compound no.	K_i (nM) [^{125}I]IPT binding	K_i (nM) [^{3}H]DA uptake	selectivity uptake/binding
D-*threo*-methylphenidate	324		
DL-*threo*-methylphenidate	582 ± 77	429 ± 88	0.7
374	194 ± 15	1981 ± 443	10.2
375	79.5	85.2 ± 25	1.0
376	>5000		

Scheme 75

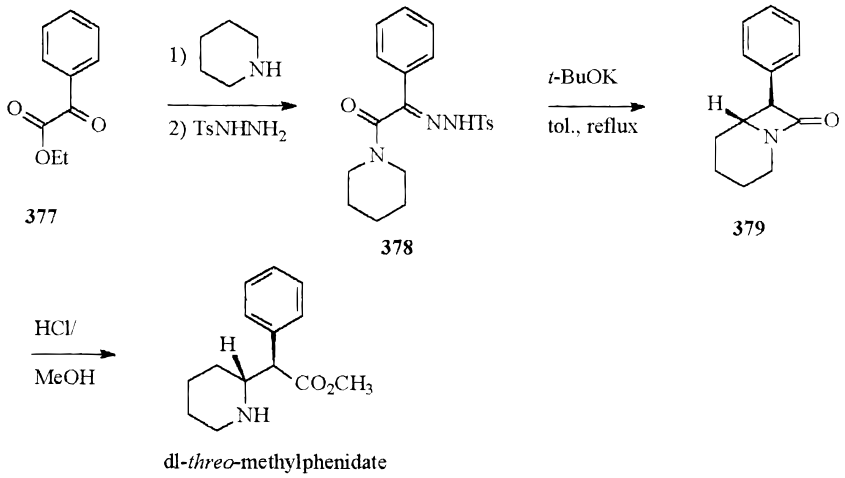


Table 50. Inhibition of Binding by Piperidine Ring Modified Analogues of Methylphenidate

compound no.	K_i (nM)
380	1336 ± 108
381	1765 ± 113
382	3321 ± 551
383	6689 ± 1348

The analogue **374** was approximately 10-fold less potent in inhibiting DA uptake compared to methylphenidate.[347]

D. Piperidine Ring Modified Analogues of Methylphenidate

These compounds (**380**−**383**, Figure 55) were synthesized using the same synthetic strategy, as shown in Scheme 75.[347] In the first step of synthesis, instead of piperidine, other secondary amines were reacted with phenylglyoxylate **377** to afford **380**−**383**.

The piperidine ring modified analogues **380**−**383** were less potent by a factor of 5−10 (Table 50). This meant that the DAT receptor was sensitive to subtle changes in the piperidine pharmacophore.[347]

In summary, methylphenidate analogues followed a different pattern as compared to phenyltropanes. Among the phenyl ring substituted analogues of methylphenidate, the compounds containing Br, I, or Cl in the 4″-position, Br, Cl, or Me in the 3″-position, and Cl in the 3″- and 4″-position were more potent than the parent compound. *N*-Methylation of the piperidine caused reduction in potency. In addition, modifications in the piperidine ring led to reduction in the potency similar to tropanes, where alterations in the tropane framework led to diminished activity. The most interesting compound in the methylphenidate series of compounds was 1-naphthyl derivative **374** (Figure 54), which was more than 10-fold less potent in inhibiting [^{3}H]DA uptake compared to inhibition of [^{125}I]IPT at the DAT.

VII. Mazindol Analogues

Mazindol is considered to be a Type 2 inhibitor because of its low abuse liability and demonstrated dopamine reuptake inhibitor activity.[30] However, the therapeutic utility of mazindol for cocaine addiction has been investigated with rather mixed results. For example, in healthy volunteers, mazindol had no reinforcing property but was an effective reinforcer in rhesus monkeys and beagle dogs;[349] in squirrel monkeys, mazindol maintained self-administration in only one-half of the monkeys studied.[350] Clinical studies with cocaine abuse have led to inconclusive results about the efficacy of mazindol in decreasing the use of cocaine.[351]

Currently, mazindol, 5-(4-chlorophenyl)-2,3-dihydro-5-hydroxy-5*H*-imidazo[2,1-*a*]isoindole (SaH 42548; AN-448, Figure 56), is marketed in the United States as an anorexic agent (exogenous obesity) and as an orphan drug for the treatment of Duchenne muscular dystrophy.[352] It is a potent inhibitor of uptake and binding at the transporter sites of DA,[12,45] NE,[45] and 5-HT.[353] It inhibits the uptake of DA and also inhibits [^{3}H]cocaine and [^{3}H]WIN 35428.[25,45,354]

Mazindol inhibits cocaine at the DAT,[354] but it differs from cocaine in the mouse locomotor assay. This suggests that cocaine and mazindol may bind

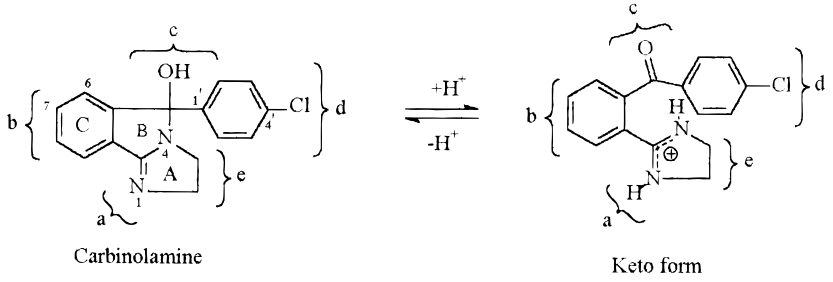


Figure 56. Tautomeric forms of mazindol in neutral and acidic media and putative interactions at the DAT. a and c = ionic or H-bond. b and d = lipophilic aromatic (π) type. e = lipophilic aliphatic (σ) type.

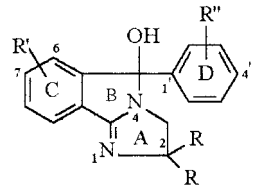
in a different manner.[355] Furthermore, mazindol differs from cocaine in its effects on DA. For example, in cultured fetal mesencephalic DA neurons, mazindol increased DA uptake while cocaine did not alter dopaminergic function;[356] in CO*S*-7 cells transfected with a cloned human DAT cDNA, mazindol inhibited both uptake and spontaneous release of DA whereas cocaine had no effect on DA release.[357]

Mazindol is known to exist in the keto−enol tautomeric forms. The tricyclic (ol) form is favored in neutral media (95% EtOH), and the protonated benzophenone (keto) tautomer exists in acidic media (95% EtOH/HCl, Figure 56).[358] Since the DA binding and the DA uptake assays for WIN 35428 are carried out at pH 7.40 and 7.35, respectively, the ol form of a mazindol analogue is expected to be the predominant tautomer in solution. However, comparison of the tautomeric forms of mazindol with those of a number of potent DA and NE uptake inhibitors suggests that the keto form might be the active structure at these sites.[42] The putative pharmacophore model for mazindol has been proposed and is depicted in Figure 56. Imidazole nitrogen atom (N1) and carbinol 5-ol/keto act as ionic or hydrogen-bonding sites. The aromatic rings and aliphatic part of the imidazole ring bind by lipophilic interactions.[359]

Since mazindol inhibits binding of [^{3}H]cocaine and [^{3}H]WIN 35428 in the nanomolar range[45] but differs from either cocaine or WIN 35428 in stimulation of locomotor activity,[355] the main goal of synthesizing mazindol analogues was to obtain compounds that were more selective for the DAT and had an improved uptake/binding inhibition ratio. In this section only those analogues of mazindol are discussed which were designed to interact at the DAT and not those which were evaluated for anorectic activity, although some analogues of mazindol which were originally designed for anorectic activity but recently have been evaluated for inhibition of [^{3}H]WIN 35428 binding and [^{3}H]DA uptake are included. The analogues of mazindol are divided into two main types: (1) substituted in either ring C or the pendant aryl ring with one (**384a**−**h,n**−**p**), two (**384i**−**l**), or three (**384m**) H, F, Cl, Br, or I atoms (Figure 57) and (2) six-membered ring A homologues with one H, F, or Cl atom (**388a**−**g**) and seven-membered ring A homologues containing one (**389a,b**) H or Cl atoms or two (**389c**) Cl atoms (Figure 58).

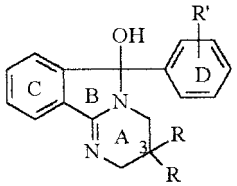
A. Phenyl Ring Substituted Analogues of Mazindol

Synthesis of these mazindol analogues (Figure 57) involved the reaction of an N, *o*-dilithio derivative of **387a**−**e** with a methyl or ethyl halogenobenzoate/benzoate.[359−361] Following workup, the 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (**384a**−**p**) and the 6-aryl-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ols (**388a**−**g**) were obtained in good to excellent yields. The 2-aryl-4,5-dihydro-1*H*-imidazolines (**387a**−**d**) and 5,5-dimethyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (**387e**) were obtained by treating a benzonitrile (**386**) with 1,2-ethanediamine or a 1,2- or 1,3-diaminopropane (**385**) in refluxing ethylene glycol in the presence of *p*-TSA, Scheme 76.[359]

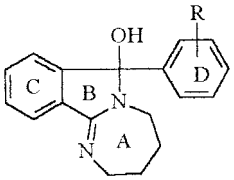


mazindol; R= R'= H, R"= 4'-Cl
384a; R= R'= R"= H
384b; R= R'= H, R"= 4'-F
384c; R= R"= H, R'= 7-F
384d; R= R'= H, R"= 2'=Cl
384e; R= R'= H, R"= 3'-Cl
384f; R= CH_3, R'= H, R"= 4'-Cl
384g; R= R"= H, R'= 6-Cl
384h; R= R"= H, R'= 7-Cl
384i; R= H, R'= 7-F, R"= 4'-Cl
384j; R= H, R'= 7-Cl, R"= 4'-F
384k; R= R'= H, R"= 2',4'-Cl_2
384l; R= R'= H, R"= 3',4'-Cl_2
384m; R= H, R'= 7,8-Cl_2, R"= 4'-Cl
384n; R= R'= H, R"= 2'-Br
384o; R= R'= H, R"= 4'-Br
384p; R= R'= H, R"= 4'-I

Figure 57. Phenyl ring substituted analogues of mazindol.



388a; R= R'= H
388b; R= H, R'= 2'-F
388c; R= H, R'= 3'-F
388d; R= H, R'= 4'-F
388e; R= H, R'= 3'-Cl
388f; R= H, R'= 4'-Cl
388g; R= CH_3, R'= 4'-Cl



389a; R= H
389b; R= 4'-Cl
389c; R= 3',4'-Cl_2

Figure 58. Ring A homologues of mazindol.

The IC_{50} values of the mazindol analogues (**384a**−**p**; Figure 57) are shown in Table 51. All compounds, except the 2′-chloro (**384d**) and 2′-bromo (**384n**) analogues, exhibited affinities greater than cocaine for the WIN 35428 binding site (up to 90-fold) and in blocking the uptake of [^{3}H]DA (up to 800-fold) in rat striatal membranes. Structure−activity studies indicated that one or two halogen atoms, preferably Cl or Br, in the 3′- or 4′-position of the free phenyl group (ring D) gave the best activity in the five-membered ring A (imidazo) series. The rank order of binding potency of the 4′-monohalogen analogues of mazindol was Br > Cl > I > F. A similar trend (Br > Cl > F) was reported for (±)-*threo*-methylphenidate analogues against [^{3}H]WIN 35428 binding.[341] However, Carroll et al.[72] found a different

Scheme 76

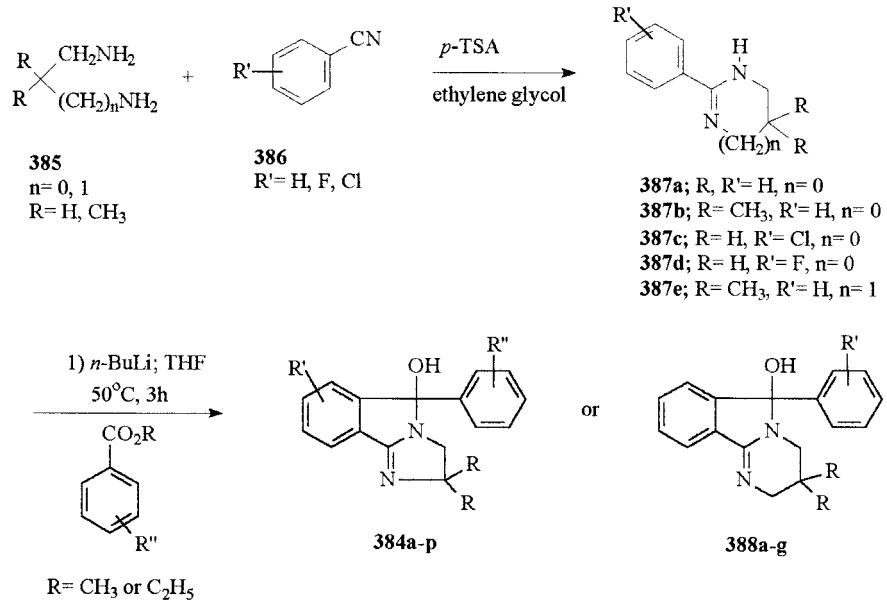


Table 51. Inhibition of Binding and Uptake by Phenyl Ring Substituted Mazindol Analogues

	IC_{50} (nM)		selectivity
compound no.	[^{3}H]WIN 35428	[^{3}H]DA	uptake/binding
cocaine	89.1 ± 8	208 ± 12	2.3
mazindol	8.1 ± 1.2	8.4 ± 1.3	1.0
384a	66.0 ± 8.9	124 ± 37	1.9
384b	13.3 ± 1.8	25.4 ± 2.7	1.9
384c	29.7 ± 7.0	78 ± 46	2.6
384d	294 ± 6	770 ± 159	2.6
384e	4.3 ± 0.4	9.2 ± 5.3	2.1
384f	50.4 ± 5.5	106 ± 5.6	2.1
384g	57.2 ± 8.3	58 ± 6.4	1.0
384h	85.4 ± 14	55.17	0.6
384i	6.5 ± 1.2	15 ± 9	2.3
384j	52.8 ± 8.7	53 ± 18	1.0
384k	76.5 ± 1.11	92 ± 19	1.2
384l	2.5 ± 0.5	1.4 ± 1.6	0.6
384m	13.6 ± 1.5		
384n	1340 ± 179		
384o	2.6 ± 1.5	8.6 ± 3.5	3.3
384p	17.2 ± 0.9	14 ± 6.4	0.8

trend (Cl ~ I > Br > F) in the WIN series of compounds.

Substitution in the 6- or 7-position (**384g,h**) had minimal effect on binding and uptake inhibition relative to **384a**; however, a 7-fluoro substituent (**384c**) resulted in a 2-fold increase. Addition of a second or third halogen (F, Cl) in the monohalogenated analogues either had no effect or led to loss of potency.

B. Six- and Seven-Membered Ring A Homologues of Mazindol

The six-membered homologues of mazindol were synthesized according to Scheme 76. These could also be synthesized using a different strategy as shown in Scheme 77.[362] The condensation of 2-aroylbenzoic acid (**390**) with 1,3-diamino propane in refluxing xylene gave the 10b-aryl-1,3,4,10b-tetrahydro pyrimido[2,1-*a*] isoindol-6-(2*H*)ones (**391**). The ketone **391** upon treatment with LAH in THF afforded labile alcohol **393**, which was treated with a stream of air (O_2) in THF/MeOH to give the 6-aryl-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ols (**388a**−**g**) via oxidation of the alcohol to a ketone, imine formation, and addition of a hydroxyl group.

The seven-membered ring A homologues (**389a**−**c**; Figure 58) were also synthesized as shown in Scheme 77. Replacement of the imidazo ring A by a six-(pyrimido) or seven-(diazepino) membered ring enhanced binding affinity. The most potent inhibitors of [^{3}H]WIN 35428 binding and [^{3}H]DA uptake in this series of compounds were 6-(3′-chlorophenyl)-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ol (**388e**; 8-fold greater than mazindol) and 7-(3′,4′-dichlorophenyl)-2,3,4,5-tetrahydro-7*H*-diazepino[2,1-*a*]isoindol-7-ol (**389c**; 32-fold greater than mazindol), respectively, Table 52. Furthermore, mazindol and the pyrimido and diazepino homologues **388f** and **389b** showed a selectivity for the DA uptake over the 5-HT uptake

Scheme 77

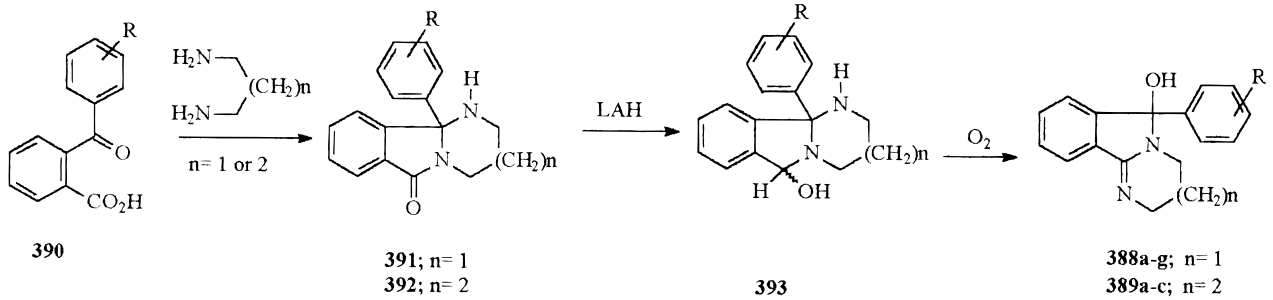


Table 52. Inhibition of Binding and DA Transport by Ring A Homologues of Mazindol

	IC_{50} (nM)		selectivity
compound no.	[^{3}H]WIN 35428	[^{3}H]DA	uptake/binding
388a	5.8 ± 1.6	18 ± 11	3.1
388b	23.2 ± 1.7	89 ± 2.8	3.8
388c	2.0 ± 0.02	3.1 ± 1.8	1.6
388d	3.2 ± 1.7	8.5 ± 4.9	0.4
388e	1.0 ± 0.2	1.3 ± 0.14	1.3
388f	1.7 ± 0.2	1.4 ± 0.35	0.8
388g	6.3 ± 4.5	1.7 ± 1.6	0.3
389a	5.9 ± 0.1	11 ± 3.2	2.0
389b	1.5 ± 0.1	3.4 ± 2.3	2.3
389c	1.7 ± 0.1	0.26 ± 0.16	0.2

sites by 5-, 250-, and 465-fold, respectively, and displayed weak or no affinity for a variety of neurotransmitter receptor sites.

Molecular modeling and further structure−activity relationship studies will be required to fully comprehend the mazindol series of compounds.

VIII. Anti-Cocaine Antibodies

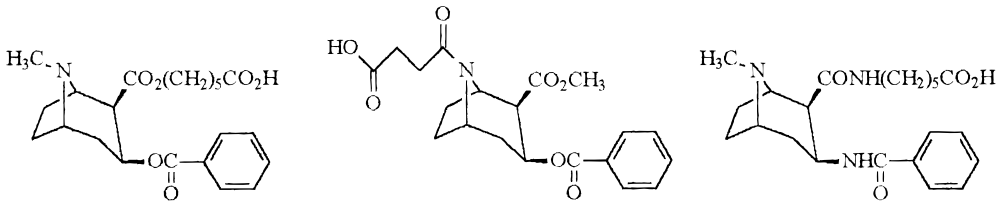
Antibodies (abzymes) are proteins that mediate the humoral immune response in animals. Their main function is to bind and neutralize the foreign substances called antigens. Pauling first pointed out that binding forces utilized by both enzymes and antibodies are fundamentally the same.[363] However, the fundamental difference between enzymes and antibodies is that the former selectively stabilize the transition state of the reaction by lowering the energy of activation for conversion of substrate to product and the latter bind the ground-state structure of substrate.[363] The other major distinction is that the antibody specificity evolves on a time scale of weeks whereas enzyme specificity is evolved over a million years.[364] Thus, it has been proposed that the active site structure of an enzyme has evolved to be precisely complementary to the reactants in their activated transition state geometry rather than their ground state geometry.[363] Thus, the immune system could be manipulated to yield antibodies with catalytic activity. This was indeed demonstrated when Pollack et al.[365] and Tramontano et al.[366] in 1986 showed that antibodies raised to tetrahedral, negatively charged phosphate and phosphonate transition state analogues (TSAs) of compounds (haptens) selectively catalyzed the hydrolysis of carbonates and esters, respectively. As early as 1969, Jencks[367] suggested that antibodies with combining sites that were complementary to stable transition state analogues would be catalytically active in the same way as natural enzymes. Another major advance in the development of catalytic antibodies was the advent of monoclonal antibody technology in 1975.[368]

The use of catalytic antibodies to detoxify cocaine is particularly interesting for two reasons: (1) cocaine is a diester and hydrolysis of either ester produces inactive metabolites,[369] which do not cross blood brain barrier,[370] and (2) the large hydrophobic surface of the benzoyl ester moeity in cocaine makes it suitable to elicit antibodies with strong binding and catalysis. Furthermore, antibody-catalyzed acyl hydrolysis has been extensively studied,[371,372] and in some cases, rates approaching that of enzymes have been achieved.[372,373] The following strategies are being pursued to generate anti-cocaine antibodies.[374]

A. Noncatalytic Anti-Cocaine Antibodies

The anti-cocaine antibodies were raised to cocaine emulsification in complete Freund adjuvant (CFA) or cocaine conjugated to a carrier protein, keyhole limpet hemocyanin (KLH), plus CFA.[375,376] This strategy was later expanded by Carrera et al.[377] Rats actively immunized with a stable cocaine conjugate (**394**; Figure 59) expressed anti-cocaine antibodies, which suppressed locomotor activity and stereotyped behavior induced by cocaine but not by amphetamine. Fox et al.[378] used compound **395** (Figure 59) as an immunogenic hapten. Sakurai et al.[379] recently synthesized a cocaine−diamide **396** (Figure 59) in an effort to obtain a potent, long-lasting anti-cocaine immune response for the treatment of cocaine abuse. The design of **396** was based on two reasons: (1) the amide functionalities of **396** would induce hydrogen-bonding interactions at the antibody combining site, which then can be available for additional favorable binding to cocaine, and (2) enhanced stability of the immunoconjugates of **396** would result in both greater sustained antigen concentration together with the absence of trace competitive antigens during immunization.

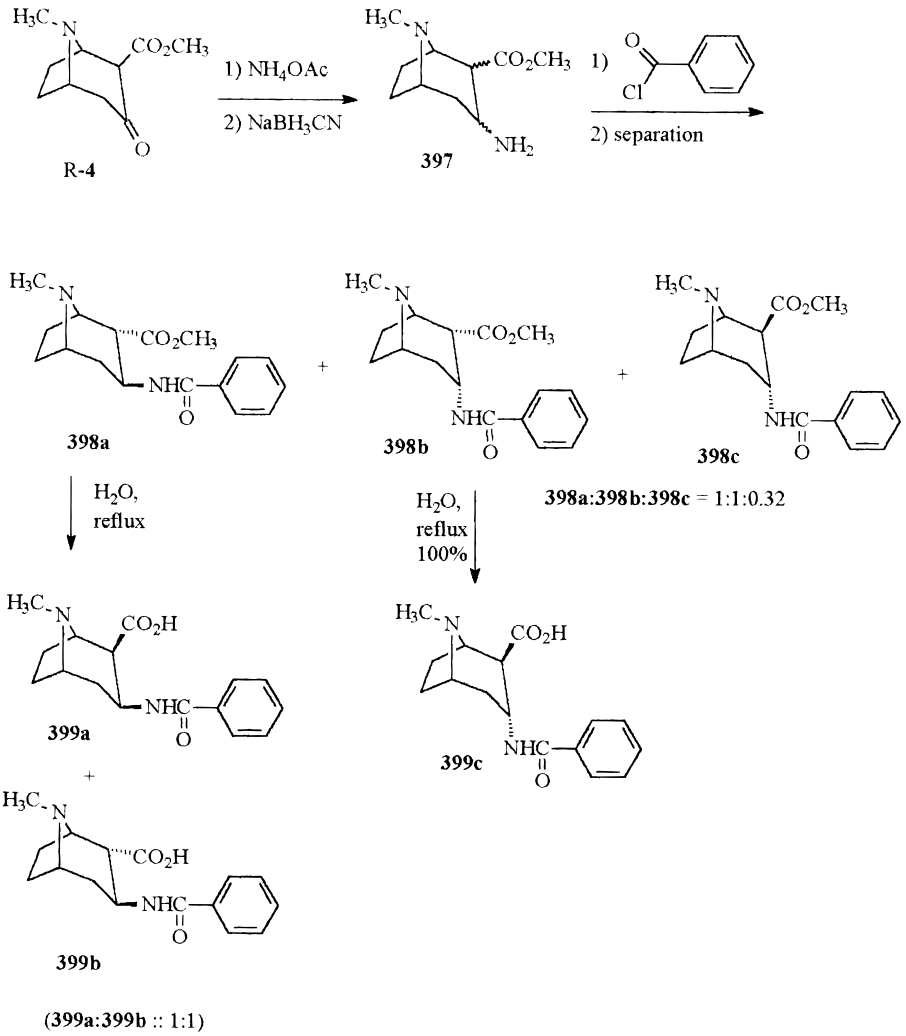
As shown in Scheme 78, the diamide **396** was synthesized from *R*-2-carbomethoxy-3-tropinone (*R*-**4**)[83,119] via enamine[380] followed by reduction with sodium cyanoborohydride at pH 4.0.[320] A mixture of all the possible isomers of amine (**397**) was obtained, which was benzoylated using benzoyl chloride without separating the required isomer. Three isomers of monoamide (**398a:398b:398c** = 1:1:0.32) were separated. It is interesting to note that allopseudo-analogue **398b** was completely converted into acid **399c** similar to allopseudoecgonine methyl ester in cocaine chemistry.[118] However, epimerization of the monoamide pseudoisomer (**398a**) in water gave a 1:1 mixture of the product acid (**399a:399b**), suggesting



394 395 396

Figure 59. Structures of the haptens used to produce noncatalytic antibodies against cocaine.

Scheme 78



that the stable conformer of tropane-2-carboxylic acid was dependent on the C3 configuration rather than C3 substituents.[379] The coupling of the acid **399a,b** with aminocaproate linker followed by separation and hydrogenolysis afforded the diamide **396**.

It is important to note here that a straightforward strategy to introduce an amino group at C3 in alloecgonine methyl ester (*R*-**182**; Scheme 42)[381] via azidation[382,383] followed by reduction did not work, rather elimination product anhydroecgonine (*R*-**1**) was formed.[121] Since azide is a good leaving group, the elimination occurred even under very mild basic conditions, perhaps via epimerization at C2.[261]

B. Catalytic Anti-Cocaine Antibodies

The second strategy is to produce either monoclonal or polyclonal catalytic cocaine antibodies. The catalytic antibodies have advantage over noncatalytic antibodies because the latter merely bind the drug and are depleted stoichiometrically by complex formation but the former bind to the drug, transform (degrade) it, release the product(s), and are available for additional binding.

It is well established that the hydrolysis of the benzoyl ester of cocaine occurs via a tetrahedral transition state (**400**; Figure 60),[384] and can be mimicked by the phosphonate moiety because it can stably impart oxyanionic and tetrahedral features to the transition state.[365] The following kinds of transition state analogues (TSAs) of cocaine have been synthesized (**401**−**403**; Figure 60).[385−390] The reason to synthesize a number of diverse TSAs by varying the site of tether (carrier protein) attachment and also introducing different spacers was to increase the diversity of the immune response. Another reason was that the monoclonal antibodies generated from a single TSA (hapten) tend to have nearly identical complimentarity determining regions (CDRs). Such limited diversity among catalytic antibodies of similar specificity is a problem since the capacity of any single group of homologous catalytic antibodies to yield one catalytic antibody of high activity, whether through repetitive screening of hybridomas or through antibody mutagenesis, is unpredictable. One such monoclonal antibody mAb 15A10, generated against TSA **402e** coupled to bovine serum albumin (BSA) protein, has been found to accelerate the hydrolysis of cocaine at the benzoyl ester by 23 000 times.[388] Consistent with accelerated catalysis, mAb 15A10 has been found to protect rats from cocaine-induced seizures and sudden death in a dose-dependent manner. In addition, it has been shown to completely block the reinforcing effects of cocaine in rats.[389]

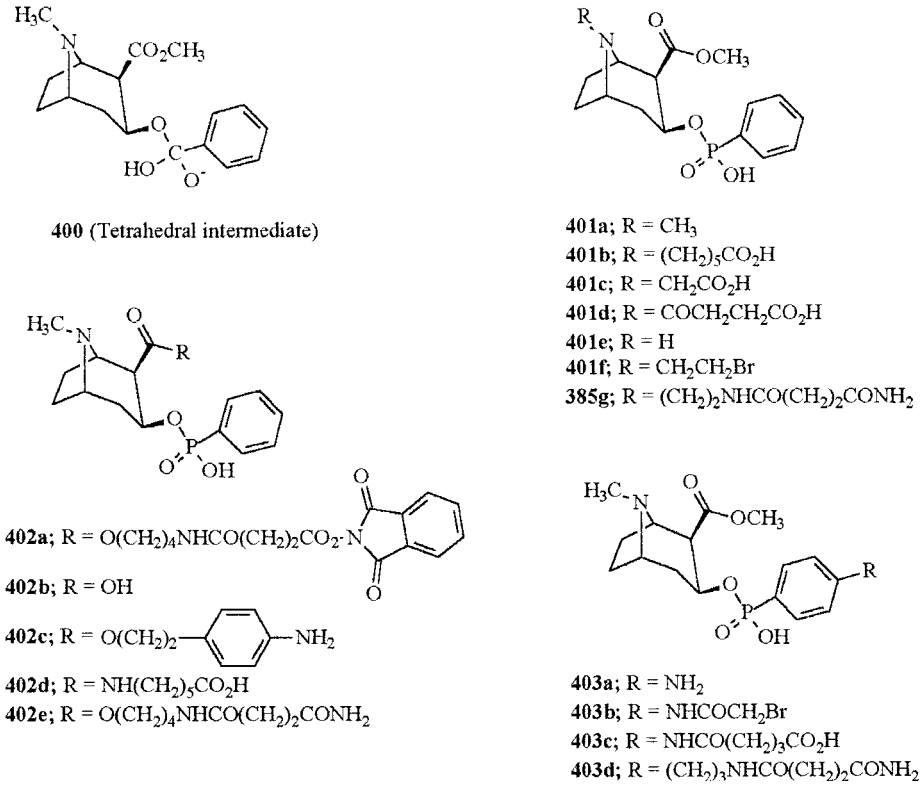
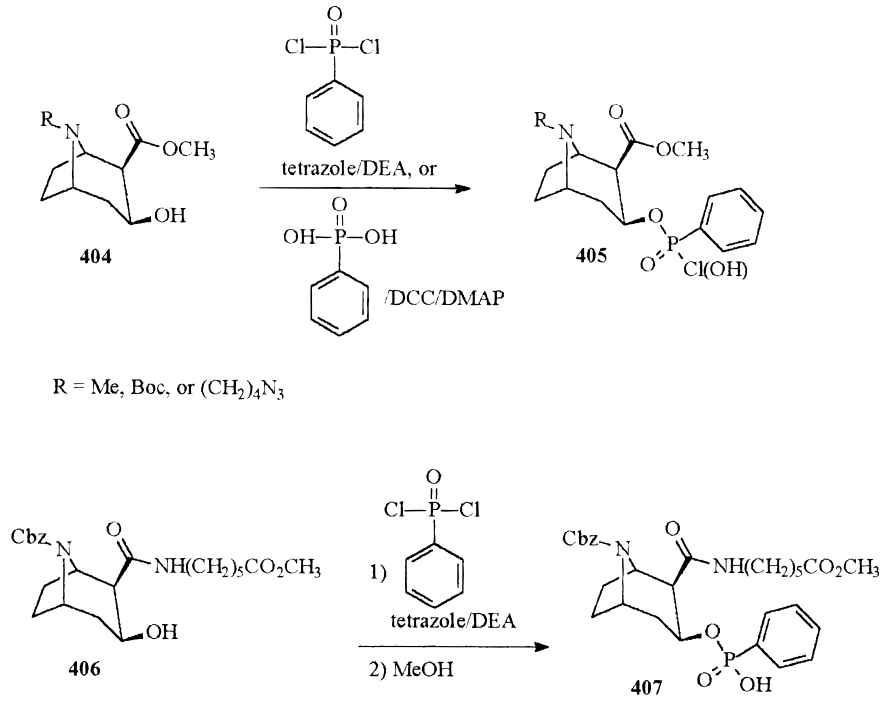


Figure 60. Structures of the transition state analogues (TSAs) of cocaine used to generate catalytic antibodies against cocaine.

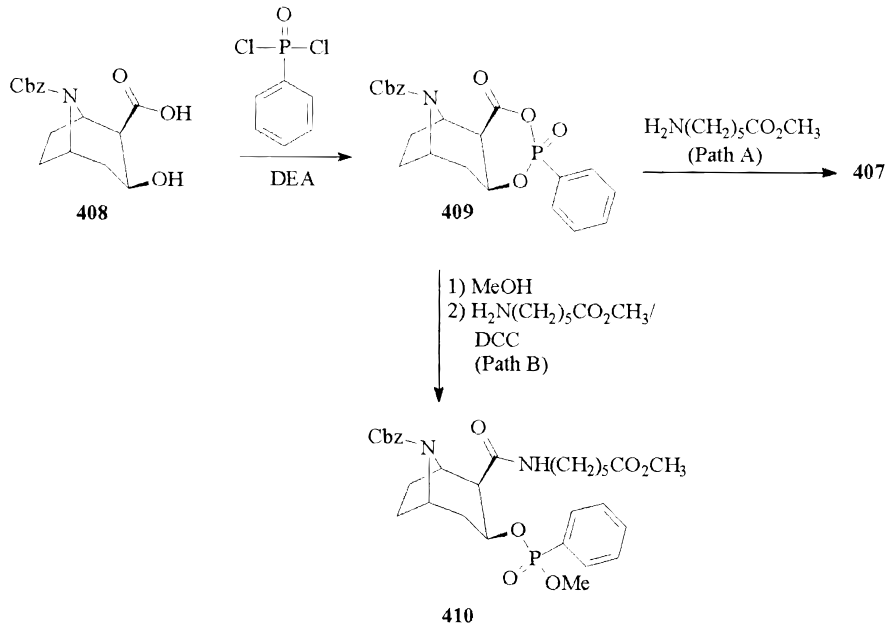
Scheme 79



These results are very promising and might lead to developing a vaccine which could be used to immunize the persons who are either addicted to cocaine or are prone to being addicted.

There are two methods to prepare the phosphonate esters: (1) tetrazole-catalyzed[385,386,390,391] and (2) DCC-catalyzed.[387,388] As shown in Scheme 79, the tertazole- or DCC-catalyzed phenylphosphonylation of ecgonine-2β-carboxylic acid esters (**404**) worked fine as long as the 2β-ester function was a small group (**405**). However, when C2 carboxylic acid ester was an alkylamide, the tetrazole catalysis failed to produce phenylphosphonate ester. It possibly resulted from electronic interactions between bridgehead N8 nitrogen and phosphonylating reagent, in addition to steric hindrance caused by a bulky alkylamide at C2.[390] This was circumvented by protecting the N8 nitrogen with benzyl chloroformate (Cbz-Cl).[392] Thus,

Scheme 80



N-benzyloxy carbonyl (Cbz) ecgonine (**406**) was successfully phosphonylated with phenylphosphonic dichloride using tetrazole as catalyst after introducing an alkylamide at C2 (**407**) (Scheme 79).

In addition, the phenylphosphonylation reaction was successfully conducted in the absence of any catalytic reagent.[390] In this strategy the advantage was taken of the proximity and *cis*-configuration of the C2 carboxylic acid and C3 alcohol (Scheme 80). Thus, the reaction of **408** with phenylphosphonic dichloride gave the mixed anhydride **409**, which was then amidated to **407** either in a single step by reaction with 6-aminocaproate[393] or in two steps to **410** with MeOH followed by DCC-catalyzed amidation with 6-aminocaproate. As expected, opposite regioselectivity was observed when the cyclic intermediate **409** was intercepted with methanol to produce the corresponding methylphosphonate **410**.[390] Further modifications led to the target TSAs (**401**−**403**; Figure 60).

The molecular modeling studies were performed with the anionic intermediate of cocaine hydrolysis (**400**) and one of the transition state analogues[385,388] using PM3 semiemperical molecular orbital methods implemented within the SPARTAN software package.[394] The PM3-calculated phosphonate TSA had an electrostatic potential comparable to the values for the PM3-calculated anionic transition state of cocaine, but the TSA potential was more symmetrical about the central phosphorus atom, while the potential in anionic transition state was asymmetrical about the central carbon atom.[395] It is important to note that although a TSA of cocaine does not have asymmetry in charge distribution around the central phosphorus atom, its absolute fidelity to the transition state of the uncatalyzed reaction is not essential, because a single TSA can elicit a multistep catalytic activity. Perhaps the design of other TSAs that have potential about the central phosphorus atom asymmetrical, such as thio or iminophosphonate transition state analogues, might lead to the generation of more active anti-cocaine catalytic antibodies.

C. Antiidiotypic Anti-Cocaine Antibodies

The third approach is to generate antiidiotypic antibodies. In this approach, the first antibody (Ab1) is raised that recognizes the active site of an enzyme, e.g., cholinesterase. The Ab1 is characterized as an inhibitor of the enzymatic reaction. After screening, production, and purification, the idiotypic antibody (Ab1) is used as an antigen to elicit antiidiotypic antibodies (Ab2).[396] A modification of the above strategy is to raise catalytic anti-cocaine antibodies against enzyme (e.g., esterase) that has been stabilized in its active configuration with a competitive inhibitor of cocaine.[397,398] A variation of this concept has been advanced by Lerner and is coined reactive immunization.[399]

D. Enzyme-Catalyzed Detoxification of Cocaine

Other than using enzyme−inhibitor complex to generate catalytic antibodies, human plasma butylcholinesterase is also being evaluated for cocaine detoxification.[400]

IX. Conclusion

It was originally believed that cocaine was a competitive inhibitor of DA uptake. Subsequent investigations at the molecular level revealed the existence of two distinct binding sites for DA and cocaine at the DAT. This raised the possibility for discovering a true cocaine antagonist which could inhibit cocaine binding without interfering DA transport at the DAT.

In the beginning, cocaine analogues were designed to segregate the addiction and toxicity associated with cocaine while retaining its stimulant and euphorigenic properties. Later on research was focused on identifying high-affinity ligands for the cocaine

binding site and cocaine antagonist(s). A systematic approach was undertaken to delineate the pharmacophores necessary for a ligand to bind to the cocaine binding site. The following strategies were used to design cocaine analogues: (1) alterations in the interatomic distances between two pharmacophores, e.g., phenyltropanes, (2) biosteric replacement, e.g., 2β-substituted analogues and 8-oxanortropane analogues, (3) alterations in the ring size, e.g., [3.3.1]-azanonane, [2.2.1]azaheptane, piperidine analogues, piperazine-ring altered GBR compounds, piperidine ring modified analogues of methylphenidate and homologues of mazindol, (4) changes in the stereochemistry, and (5) homologation of alkyl chains and rigid analogues, e.g., heteroaromatic and piperidine analogues of GBR compounds.

In the phenyltropanes, increased electron density in the phenyl ring was found to significantly improve the potency of the compounds. A C2 substituent was necessary for binding at the DAT. The evaluation of a large number of compounds, however, showed that the pharmacophore at C2 could be an H-bond acceptor, a heterocyclic bioisostere, or even a lipophilic group. The demethylation of the bridgehead nitrogen (N8) in the phenyltropanes was found to improve selectivity for the 5-HTT. The N8 could also be replaced with an oxygen or even a carbon without significant loss of potency for the cocaine binding site at the DAT.

In the cocaines, modifications in the stereochemistry led to a significant loss in potency. This, was however, not the case in 2β-carbomethoxybenztropine analogues. Substitution in the ethylene bridge (C6, C7) with a methoxy group improved the binding vs uptake ratio. Nevertheless, modifications in the topology of the tropane ring system caused reduction in potency except in piperidine analogues of phenyltropanes.

In general, phenyltropanes had improved binding potency for the cocaine binding site but they were also equally potent in inhibiting DA uptake. Among cocaines and 3α-diphenylmethoxytropanes, some of the compounds were quite potent but the data is insufficient to classify them as antagonists.

In the GBR-type of compounds, modifications in the piperazine ring including its replacement with a piperidine ring generally improved the selectivity of the compounds for binding vs uptake at the DAT. Heteroaromatic analogues were also potent and selective.

Among methylphenidate and mazindol analogues, substitutions in the phenyl ring generally followed the same pattern as that of phenyltropanes. However, when the phenyl ring in methylphenidate was replaced with a naphthyl group, the selectivity for binding vs uptake at the DAT improved several fold. Modifications in the piperidine ring of methylphenidate diminished potency. In the mazindol series of compounds, expansion of the heterocyclic ring (A) led to improvements in the binding vs uptake ratio.

The development of antibodies against cocaine is another attractive approach for combating cocaine addiction. There are four approaches being followed currently. Catalytic antibodies have therapeutic potential in the form of a vaccine. One such antibody mAb 15A10 has already been identified and is in preclinical trials.

A large number of compounds have been covered in this review. A select few lead compounds can be picked from each section. These compounds can be further refined toward designing more selective ligands by utilizing the data from other compounds presented in the tables. Perhaps a combinatorial approach can be taken to combine the structural features of the lead compounds. This can expedite the process of discovering a true cocaine antagonist.

X. Selected Abbreviations and Definitions

Ab	antibody
Ac	acetyl
ACE-Cl	α-chloroethyl chloroformate
Agonist	a drug that binds to a receptor and mimics the effect of the endogenous regulatory compound. In other words, any compound that activates or facilitates a receptor on the presynaptic or postsynaptic cell
AIBN	2,2′-azabisisobutyronitrile
Antagonist	a compound which itself is devoid of intrinsic regulatory activity but produces effect by inhibiting the action of an agonist (e.g., by competition for agonist binding sites). In other words, any compound that inhibits receptor on the presynaptic or postsynaptic cell
Ar	aryl
Bn	benzyl
Boc	butoxycarbonyl
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
Cbz-Cl	benzyl chloroformate (benzyloxycarbonyl chloride)
CDI	carbonyldiimidazole
CFA	complete Freund's adjuvant
Cp	cyclopentadienyl
cy-hex	cyclohexane
DA	dopamine
DAT	dopamine transporter
dba	*trans*,*trans*-dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DEA	diethylamine
Dibal-H	diisobutyl aluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropyl ethylamine
DMAP	4-(dimethylamino)pyridine
DME	ethylene glycol dimethyl ether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Domain	a structurally and/or functionally discrete portion of a protein membrane
EDC	1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide
EE	1-ethoxyethyl
Et	ethyl
Eudismic ratio	ratio of the biological activities of a pair of enantiomers; the more active is called eutomer and the less active distomer
GBR compounds	aryl-1,4-dialkylpiperazines designed after benztropine by van der Zee et al. at **G**ist-**Br**ocada, The Netherlands

Hapten	derived from the Greek word "haptein" meaning 'to fasten' and referring to the ability of a simple chemical molecule to bind antibody. A hapten is not able to induce an immune response when administered alone but may do so when attached to a carrier molecule (e.g., KLH)
HMPA	hexamethylformamide
HOBt	1-hydroxybenzotriazole
HOSA	hydroxylamine-O-sulfonic acid
5-HT	5-hydroxytryptamine or serotonin
5-HTT	serotonin transporter
IC_{50}	concentration at which a 50% inhibition (reduction) of specific binding of the radiolabeled ligand is attained. $IC_{50} = K_i(1 + [S]/K_m)$, where [S] is substrate concentration and K_m is the Michaelis constant
IPA	2-propanol
Ipc	isopinocampheyl
IPT	*N*-3-iodoprop-(2*E*)-ene-2β-carbomethoxy-3β-(4′-chlorophenyl)tropane
K_i	state of equilibrium between the free receptor sites or enzyme protein (E), inhibitor (I), and the receptor site or enzyme−inhibitor complex (E·I). $K_i = [E][I]/[E{\cdot}I]$
KLH	keyhole limpet hemocyanin
LAH	lithium aluminium hydride
LDA	lithium diisopropyl amide
mAb	monoclonal antibody
Me	methyl
MOM	methoxymethyl
MoOPH	MoO_5·pyridine·HMPA complex
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NE	norepinephrine
NET	norepinephrine transporter
NIS	*N*-iodosuccinimide
Ph	phenyl
Pht	phthalimido
PLE	porcine liver esterase
p-TSA	*p*-toluenesulfonic acid
py	pyridine
Ra-Ni	Raney nickel
Receptor	the term is used to denote any cellular macromolecule (protein) found in the postsynaptic side of the synapse, which specifically recognizes a binding molecule, ligand, and thereby initiates either a specific biological response (the wide sense of receptor) or the transduction of a signal (the narrow sense of receptor) to carry out secondary effects
RTI-55	common name for β-CIT, 2β-carbomethoxy-3β-4′-iodophenyltropane developed by Carroll et al. at **R**esearch **T**riangle **I**nstitute
Synapse	the synapse is a junction between an axon of one neuron and the cell membrane of another neuron. Neurotransmitters travel across the space, or synaptic cleft, from presynaptic neuron and are received by receptors on the postsynaptic neuron
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMED	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilane
tol	toluene
Transporter	the term is used for those systems that use the energy contained in an ion gradient across the plasma membrane to transport ions or other solutes (e.g., dopamine transporter)
Troc-Cl	2,2,2-trichloroethyl chloroformate
TRODAT	a general term used for the dopamine transporter (DAT) imaging agents
Ts	4-toluenesulfonyl
TSA	transition state analog
WIN 35065-2	2β-carbomethoxy-3β-phenyltropane (β-CPT)
WIN 35428	2β-carbomethoxy-3β-(4′-fluorophenyl)tropane (β-CFT)
WIN-type of compounds	2β-carbomethoxy-3β-phenyltropanes, developed by Clarke et al. at Sterling-**Win**throp Research Institute, NY, as stimulants or cocaine agonists

XI. Acknowledgment

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