Synthesis and insecticidal activity of new amide derivatives of piperine†

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Abstract: The natural lipophilic amides piperine and piperiline were isolated from *Piper nigrum* L (Piperaceae). Piperine was hydrolysed into piperic acid (85% yield) which was converted into 16 amides (28–89% yield). The contact toxicity of all synthetic amides, and also that of piperine and piperiline, at the dose 10 μg per insect, was evaluated for the Brazilian economically important insects *Ascia monuste orseis* Latr, *Acanthoscelides obtectus* Say, *Brevicoryne brassicae* L, *Protopolybia exigua* DeSaus and *Cornitermes cumulans* Kollar. The results demontrated that the insects have different sensivities to the various amides, with mortality ranging from 0 to 97.5% according to the compound and insect species.

Keywords: natural insecticide; piperine; amide

1 INTRODUCTION

The insecticidal properties of black pepper (*Piper nigrum* L, Piperaceae) extracts were first observed in 1924.[1] These extracts were shown to be toxic to several insects, including the housefly *Musca domestica* L, the mosquito *Culex pipiens pallens*, the rice weevil *Sitophilus oryzae* L, the cotton boll weevil *Anthonomus grandis* Boheman, the cowpea weevil *Callosobruchus chinensis* L, the stored bean weevil *Zabrotes subfasciatus* (Boheman); they are also repellent to the adult corn earworms *Heliothis zea* Boddie.[1–4]

The investigation of the chemical constituents of black pepper and other Piperaceae species has led to the identification of approximately 145 lipophilic amides as the major type of metabolites that are responsible for the insecticidal properties of these plants.[5,6] Piperine (Fig 1: **1**) is the major constituent found in *Piper nigrum* and it was found to be more toxic to the domestic fly than piretro.[7,8]

The natural amide piperiline (**2**), also found in *P nigrum*, had no toxic effect for *Toxocara canis*.[9]

The potential of this class of compound as a model for the development of new insecticides has been investigated by several researchers. Although many new amides have been prepared, their insecticidal activity has been evaluated against very few insects.[7–17]

In this paper we describe the preparation of several new amides derivatives of piperine (**1**) and also their activity against five insect species of economic interest from five different Orders, that have not been evaluated before.

2 MATERIALS AND METHODS

2.1 General procedures

Mass spectra were recorded under electron-impact (70 eV) and chemical ionization (NH_3) conditions using a Shimadzu GC/MS QP5000 and a VG Analytical ZAB-E high resolution spectrometer, respectively. Infrared spectra were recorded as potassium bromide disks on a Perkin Elmer FTIR Paragon 1000 Spectrophotometer. NMR spectra were recorded with a Bruker DPX 200 (200 MHz) spectrometer, using tetramethylsilane (TMS) as internal standard. Coupling constants (J) are given in Hertz. Flash chromatography was performed using Crosfield Sorbil C60 (40–60 μm), and the solvents used were purified according to Perrin and Armarego.[18]

2.2 Piperine (1) and piperiline (2) extraction

Dry fruits of black pepper (distributed by Portuense Ltda, Inc) were purchased from the local supermarket,

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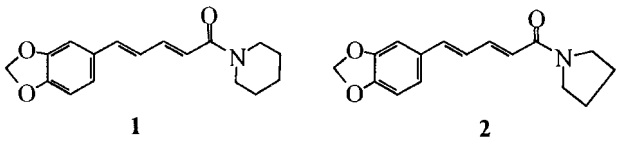


Figure 1. Structures of (**1**) piperine and (**2**) piperiline.

ground (750 g) and extracted with ethanol (2.5 litre), in a Soxhlet apparatus for 72 h. The extract was concentrated under reduced pressure in a rotary evaporator to leave a dark brown oil (8.0 g). This material was fractionated on a silica gel column, eluting with hexane + diethyl ether (1 + 2 by volume). The fractions obtained were combined according to their similarities as analysed by thin layer chromatography (TLC) and this led to the isolation of piperine (**1**) (2.0 g) and piperiline (**2**) (0.3 g). These compounds were recrystallised with a mixture of dichloromethane and hexane and the physical and spectroscopic data obtained were in accordance with those reported in the literature.[9]

2.3 Synthetic procedures

2.3.1 Preparation of piperic acid (3)

In a 1-litre round-bottom flask was placed piperine **1** (6 g), ethanol (500 ml) and an aqueous solution of $LiOH.H_2O$ (90 g litre^{-1}; 100 ml). The resultant solution was refluxed for 140 h, and the reaction was then quenched by addition of concentrated hydrochloric acid (35 ml). The solid formed was removed by filtration and recrystalized from tetrahydrofuran to produce the required acid (**3**) in 85% yield. Piperic acid (**3**). m p 126–127 °C; IR ν_{max} (KBr disk, cm^{-1}: 3200–2200, 1680, 1628, 1600, 1515 and 1500. [^{1}H]NMR (DMSO-d_6) δ: 12.35 (sbr, OH), 7.30 (m, H3), 7.25 (d, J = 1.5 Hz, H2′), 7.02 (dd, J = 1.5 Hz and 8.2 Hz, H6′), 7.00–6.90 (m, H5′, H4, H5), 6.07 (s) and 5.95 (d, J = 15.0 Hz).

*2.3.2 General procedure for the preparation of amides (**5a-p**) from piperic acid*

To a solution of piperic acid (500 mg, 2.29 mmol) in dry THF (10 ml), kept under nitrogen atmosphere, oxalyl chloride (1 ml, 11.5 mmol) was added dropwise. The resultant solution was stirred at room temperature for 6 h, and the excess oxalyl chloride was then removed under reduced pressure to leave the acid chloride (**4**) as an orange residue. This crude compound was dissolved in dry THF (4 ml), and to the resultant solution was added the appropriate amine (2.3 mmol in 3 ml of THF), followed by triethylamine (0.35 g; 3.5 mmol). The reaction mixture was stirred at 60 °C for 1.5 to 2 h when a TLC analysis revealed the complete consumption of the starting material. The solvent was then removed under reduced pressure and the residue obtained was purified by flash column chromatography on silica gel using diethyl ether and hexane (1 + 2 to 2 + 1 by volume) to afford the required amides **5a–p** as yellow solids.

For the less expensive amines, available in larger amounts, 2 equivalents were used and no triethylamine was added.

The physical and spectroscopic data for the synthetic amides are reported in the Appendix (Tables A1–A2).

2.4 Bioassays

This study was carried out with the following insect species: first-instar larvae of *Ascia monuste orseis* Latr (Lepidoptera, Pieridae), adults of *Acanthoscelides obtectus* (Say) (Coleoptera: Bruchidae), *Brevicoryne brassicae* L (Homoptera: Aphididae) and *Protopolybia exigua* DeSaus (Hymenoptera: Vespidae), and *Cornitermes cumulans* Kollar (Isoptera: Termitidae). Groups of 10 insects of each species were transferred to glass Petri dishes. The average weight of each insect species was obtained by measuring, on a analytical balance, the mass of ten groups containing 10 insects each.

To each individual insect was applied topically, via a microsyringe, a solution of the test compound in acetone (10 μg μl^{-1}; 1 μl).

In the case of *A monuste orseis*, 10 larva were placed in a perforated plastic pot containing a small piece of cabbage. In all cases the Petri dishes or the plastic pots were placed in an incubator at 25 (±0.5) °C, 75 (±5)% RH, with a photoperiod of 12 h. The mortality counts were made as following: *Ascia monuste orseis* (after 48 h), *A obtectus* (48 h), *C cumulans* (12 h), *B brassicae* (6 h) and *P exigua* (6 h). The first four are insects species of economic importance and the last

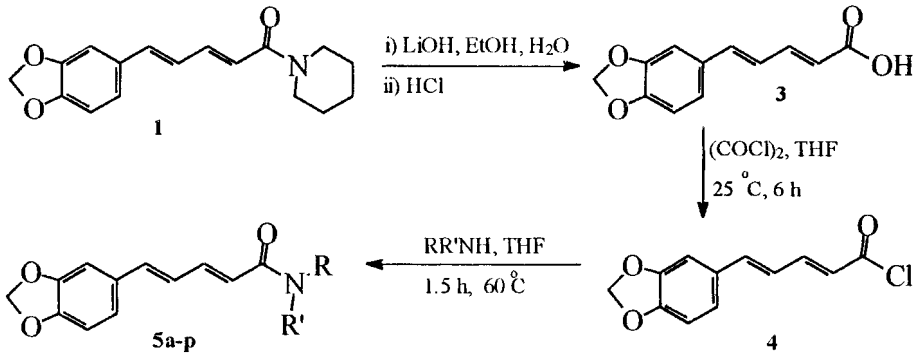
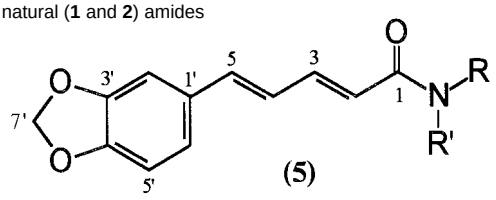
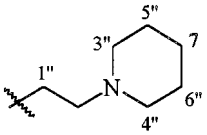
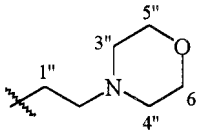
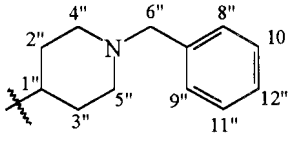
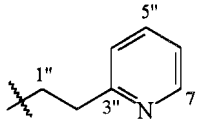


Figure 2. Synthetic scheme for preparation of amides derivatives from piperine (**1**).

Table 1. Contact toxicity of synthetic (**5a–p**) and natural (**1** and **2**) amides



(5)

			Mortality (%)				
Compound	*R*	*R'*	*A monuste orseis*[a] (40 μg mg^{-1} larvae)	*A obtectus*[a] (2.61 μg mg^{-1} insect)	*B brassicae*[b] (31.25 μg mg^{-1} insect)	*C cumulans*[b] (1.19 μg mg^{-1} insect)	*P exigua*[c] (2.63 μg mg^{-1} insect)
1			95.0 A[d]	25.0 A	30.0 C	7.5 C	8.6 C
5a	H	Et	45.0 B	12.5 B	75.0 A	5.0 C	2.5 C
5b	Et	Et	97.5 A	10.0 B	35.0 C	27.5 B	7.7 C
5c	H	*i*-Pr	15.0 C	5.0 C	70.0 B	10.0 C	15.4 C
5d	*i*-Pr	*i*-Pr	95.0 A	25.0 A	52.5 B	42.5 A	45.0 A
5e	H	Bu	40.0 B	10.0 B	7.5 D	15.0 C	27.1 B
5f	H	*i*-Bu	20.0 C	12.5 B	67.5 B	12.5 C	5.9 C
5g	H	Pentyl	7.5 C	12.5 B	82.5 A	10.0 C	25.5 B
5h	H	*i*-Pentyl	20.0 C	5.0 C	65.0 B	5.0 C	9.5 C
5i	H	Hexyl	15.0 C	0.0 C	82.5 A	12.5 C	3.9 C
5j[e]	H	Decyl	–	–	–	–	–
5k[e]	H	Cyclohexyl	–	–	–	–	–
5l	H	Adamantyl	15.0 C	30.0 A	55.0 B	12.5 C	33.2 B
5m	H		15.0 C	25.0 A	62.5 B	25.0 B	17.8 C
5n	H		5.0 C	7.5 B	70.0 B	12.5 C	11.0 C
5o	H		7.5 C	25.0 A	92.5 A	17.5 C	31.6 B
5p	H		7.5 C	12.5 B	62.5 B	12.5 C	10.7 C
2			40.0 B	10.0 B	82.5 A	22.5 B	13.2 C
control	—	—	14.3 C	9.0 B	24.0 C	14.0 C	4.0 C

Mortality count after [a] 48 h, [b]6 h and [c] 12 h.

[d] Means in the same column with the same letter are not significantly different by the Scott–Knott test at $P < 0.05$.

[e] Due to the lower solubility in acetone these amides were tested in lower dose (**5j**, 9 mg ml^{-1}; **5k**, 5 mg ml^{-1}) and were not toxic (0% mortality).

one is a natural enemy of *A monuste orseis* and other insects.

In a control experiment, carried out under the same conditions, 1 μl of acetone was applied on each insect.

All experiments and the respective controls, were carried out in four replicates and the data were analysed by Scott–Knott[19] test at 0.05 probability level.

3 RESULTS AND DISCUSSION

3.1 Synthesis

Piperine (**1**), obtained from extraction of dried seeds of *Piper nigrum*, was converted into the acid (**3**) with 85% yield by means of hydrolysis using LiOH/EtOH. An initial attempt to convert the acid (**3**) into the amide (**5**) was carried out using thionyl chloride followed by the appropriate amine,[20] but the yields of the products were very low, and partial decomposition of the starting material was observed. The use of Ph_3P/CCl_4[21] to convert the amide (**1**) into the acid chloride (**4**), followed by addition of an amine, resulted in the amides with low yield (<20%). Another drawback with this methodology was the formation of large amount of $Ph_3P=O$ that caused some difficulties in the isolation of the required amides.

A methodology involving the use of oxalyl chloride[22] was successfully applied for the preparation of the chloride (**4**). This chloride was then converted into 16 amides as shown in Fig. 2. For the preparation of amides **5a–k**, 2 equivalents of the amines were used. In all other cases, as the amines were very expensive and available in small amounts, only 1 equivalent was used, along with 2 equivalents of triethylamine to neutralize the HCl formed.

All amides prepared were characterized from their spectroscopic and physical data (IR, [^{1}H]NMR, MS and C,H,N analysis).

To the best of our knowledge and according to the literature investigated, only the amides **5a**, **5b**, **5d–f**, 5h and **5k** have been prepared previously.[7] Even in these cases no spectroscopic data were given, so we present full data for all compounds.

3.2 Biological activity

The effects of the natural amides piperine (**1**) and piperiline (**2**) and also several amides (**5**) prepared from piperine (**1**) were evaluated against *A monuste orseis, A obtectus, B brassicae, C cumulans* and *P exigua*. The first four are insect species of economic importance and the last one is a natural enemy of *A monuste orseis* and other insects. Although amides **5a**, **5b**, **5d–f**, **5h** and **5k** have been prepared previously,[7] their effects were evaluated only against the housefly (*Musca domestica* L). In this work, the aim was to evaluate the contact toxicity of each compound, and find out if the structural modification carried out on piperine would result in a synthetic product more active than the natural product. In order to avoid possible oral intoxication, the insects were not supplied with food. Preliminary experiments were set up to evaluate the adequate exposure time.

The results of the contact bioassays are shown on Table 1. The dose applied and the period of incubation varied according to the species.

Of the 16 synthetic amides tested, only six were active against *A monuste orseis*. The most toxic were **5b** (97.5%) and **5d** (95.0%), which were comparable to the reference piperine (**1**) (95% mortality). The mortality caused by the other three (**5a**, **5e** and **2**) varied from 40.0 to 45.0%.

Extracts of *P nigrum* have been shown to be active, by ingestion, against several stored grain insects, including *A obtectus* [1–4,8] In the present study only five compounds (**1**, **5d**, **5l**, **5m** and **5o**) were active against this insect, and the mortality varied from 25.0 to 30.0%. This low activity could, in part, be due to the lower dose applied (2.6 $\mu g\,mg^{-1}$ insect).

B brassicae was sensitive to 13 amides, with mortalities ranging from 52.5 to 92.5%. The most active amides in this case were **5a**, **5g**, **5i**, **5o** and **2** that caused mortality ranging from 75.0 to 92.5%. The natural amide piperine (**1**) was not active against this insect.

The most active compound against *C cumulans* was **5d** (42.5% mortality), and three other compounds (**5b**, **5m** and **2**) were also toxic, causing 22.5 to 27.5% mortality. In this case also, the low toxicity could be due to the lower dose (1.1 $\mu g\,mg^{-1}$ insect) used.

For the Vespidae *P exigua*, the compounds **5e**, **5j**, **5l** and **5o** presented low toxicity, with mortalities ranging from 25.6% to 33.2%. The most toxic compound was **5d** (45.0% mortality). It was also observed that amides **5b** and **5d** had some selectivity for *P exigua*, a predator for the Lepidoptera *A monuste orseis*. These compounds were respectively 12.7 and 2.1 times more toxic to *A monuste orseis* than *P exigua*.

Although several reports have shown that the most active piperamides are those *N*-isobutyl substituted,[12,16,23] in the present study this was not observed. Compound **5f** (*N*-isobutylpiperamide) was active only against *B brassicae*, a species sensitive to most amides tested.

From the results obtained (Table 1), no clear correlation between structure and activity was observed, but in the case of *A monuste orseis* the most active amides were those *N*,*N*-disubstituted.

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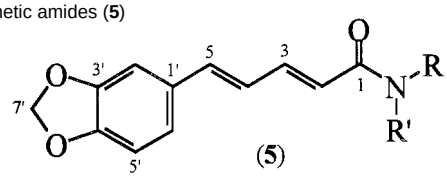
APPENDIX: PHYSICAL, ANALYTICAL AND SPECTROSCOPIC DATA

Table 1A. Physical and analytical data for the synthetic amides (**5**)



(**5**)

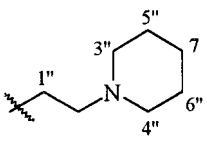
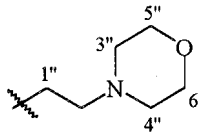
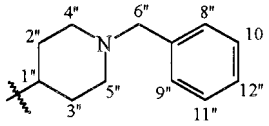
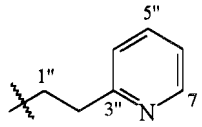
						Calculated (%)[a]			Found (%)[a]		
Compound	*R*	*R'*	*Molecular formula*	*Yield (%)*	*mp (°C)*	*C*	*H*	*N*	*C*	*H*	*N*
5a	H	Et	$C_{14}H_{15}NO_3$	60	162–164	68.56	6.16	5.71	68.44	6.16	5.72
5b	Et	Et	$C_{16}H_{19}NO_3$	87	85–87	70.31	7.01	5.12	69.69	6.86	5.16
5c	H	*i*-Pr	$C_{15}H_{17}NO_3$	40	171–173	69.48	6.61	5.40	69.36	6.61	5.54
5d	*i*-Pr	*i*-Pr	$C_{18}H_{23}NO_3$	85	81–83	71.73	7.69	4.65	71.29	7.66	4.58
5e	H	Bu	$C_{16}H_{20}NO_3$	69	144–145						
5f	H	*i*-Bu	$C_{16}H_{19}NO_3$	83	160–161	70.31	7.01	5.12	70.63	7.00	5.21
5g	H	Pentyl	$C_{17}H_{22}NO_3$	45	139–141						
5h	H	*i*-Pentyl	$C_{17}H_{22}NO_3$	78	136–138						
5i	H	Hexyl	$C_{18}H_{23}NO_3$	80	132–133	71.73	7.69	4.65	71.81	7.30	4.70
5j	H	Decyl	$C_{22}H_{31}NO_3$	56	136–138	73.92	8.74	3.92	74.31	8.65	4.01
5k	H	Ciclohexyl	$C_{18}H_{21}NO_3$	89	199–200	72.22	7.07	4.68	72.16	6.96	4.78
5l	H	Adamantyl	$C_{22}H_{25}NO_3$	68	150–151	75.19	7.17	3.99	74.72	7.08	4.12
5m	H		$C_{19}H_{24}N_2O_3$	28	128–129	69.49	7.37	8.53	67.18	7.40	8.19

Table 1A. Continued

Compound	*R*	*R′*	*Molecular formula*	*Yield (%)*	*mp (°C)*	*Calculated (%)*[a]			*Found (%)*[a]		
						C	*H*	*N*	*C*	*H*	*N*
5n	H		$C_{18}H_{22}N_2O_4$	73	165–167	65.44	6.71	8.48	56.26	7.22	9.04
5o	H		$C_{24}H_{26}N_2O_3$	35	166–168						
5p	H		$C_{19}H_{18}N_2O_3$	80	138–139	70.79	5.63	8.69	71.04	5.68	8.70

[a] For compounds **5e, 5g, 5h, 5i** and **5o** the exact masses were obtained and were in agreement with the calculated values.

Table 2A. Spectroscopic data for the synthetic amides (**5**)

Compound	*IR ν_{max} (cm^{-1})*	*[^{1}H]NMR ($CDCl_3$) δ*	*[^{13}C]NMR ($CDCl_3$) δ*
5a	3288, 3080, 1641, 1607, 1544, 1503	5.58 (m, NH), 3.40 (m, H1″), 1.19 (t, 7.2, H2″)	34.49 (C1″), 14.90 (C2″)
5b	2975, 1640, 1602, 1520, 1505	3.47–3.40 (m, 2×H1″), 1.28–1.14 (t, 7.2, 2×2″)	42.61 (C1″), 41.36 (C2″), 15.41 (C3″), 13.64 (C4″)
5c	3247, 3059, 1643, 1605, 1545, 1504	5.54 (dbr, 7.5, NH), 4.19 (m, H1″), 1.20 (d, 4,5, H2″), 1.20 (d, 4.5, H3″)	41.47 (C1″), 22.86 (C2″), 22.86 (C3″)
5d	3070, 1637, 1617, 1589, 1503	4.10 (m, 2×H1″), 1.33 (sbr, 2×H2″), 1.33 (sbr, 2×H3″)	47.25 (C1″), 21.25 (C2″), 21.25 (C3″)
5e	3291, 3071, 1642, 1604, 1540, 1500	5.64 (sbr, NH), 3.35 (q, 6.7, H1″), 1.74–1.28 (m, H2″) 1.74–1.28 (m, H3″), 0.93 (t, 7.1, H4″)	39.43 (C1″), 31.80 (C2″), 20.13 (C3″), 13.78 (C4″)
5f	3300, 2962, 1643, 1620, 1560, 1552, 1506	5.71 (tbr, NH), 3.22 (dd, 6.7 and 6.3, H1″), 1.82 (m, H2″), 0.94 (d, 6.7, H3″ and H4″)	47.03 (C1″), 28.66 (C2″), 20.16 (C3″), 20.16 (C4″)
5g	3288, 3072, 1642, 1605, 1541, 1500	5.67 (tbr, NH), 3.35 (td, H1″), 1.55 (tt, 7.1 and 6.8, H2″), 1.40–1.20 (m, H3″), 1.40–120 (m, H4″), 90 (t, 6.7, H5″)	39.70 (C1″), 29.41 (C2″), 29.13 (C3″), 22.39 (C4″), 13.99 (C5″)
5h	3300, 3070, 1645, 1610, 1550, 1503	5.62 (tbr, NH), 3.37 (td, 7.4 and 5.8, H1″), 1.63 (m, H3″), 1.49–1.38 (m, H2″), 0.93 (d, 6.5, H4″), 0.93 (d, 6.5, H5″)	39.00 (C1″), 38.40 (C2″), 26.31 (C3″), 22.88 (C4″), 22.88 (C5″)
5i	3310, 3070, 1638, 1610, 1540, 1500	5.60 (tbr, NH), 3.35 (td, H1″), 1.54 (m, H2″), 1.37–1.25 (m, H3″, H4″ and H5″), 0.89 (t, 6.5, H6″)	39.74 (C1″), 31.52 (C2″), 29.69 (C3″), 26.65 (C4″), 22.57 (C5″), 14.02 (C6″)
5j	3298, 2960, 1640, 1615, 1530, 1502	5.59 (tbr, NH), 3.34 (td, H1″), 1.52 (m, H2″), 1.26 (m, H3″, H4″, H5″, H6″, H7″, H8″, H9″), 0,88 (t, H10″)	39.75 (C1″), 31.89 (C2″), 29.73 (C3″), 29.56 (C4″), 29.56 (C5″), 29.31 (C6″), 29.31 (C7″), 26.90 (C8″), 22.68 (C9″), 14.11 (C10″)
5k	3320, 3073, 1642, 1615, 1585, 1504	5.45 (dbr, 7.3, NH), 3.88 (m, H1″), 1.96 (m, H2″), 1.75 (m, H3″), 1.50–1.05 (m, H4″, H5″ and H6″)	48.28 (C1″), 33.28 (C2″), 33.28 (C3″), 25.59 (C6″), 24.90 (C4″), 24.90 (C5″)

Table 2A. Continued

Compound	*IR ν_{max} (cm^{-1})*	*[^{1}H]NMR ($CDCl_3$) δ*	*[^{13}C]NMR ($CDCl_3$) δ*
5l	3390, 2907, 1655, 1617, 1521, 1504	5.26 (sbr, NH), 2.06 (m, 9H, H2″, H3″, H4″, H5″, H6″, H7″, H8″, H9″ and H10″), 1.67 (m, 6H, H2″, H4″, H6″, H8″, H9″ and H10″)	52.11 (C1″), 41.75 (C2″), 41.75 (C8″), 41.75 (C9″), 36.40 (C4″), 36.40 (C6″), 36.40 (C10″), 29.49 (C3″), 29.49 (C5″), 29.49 (C7″)
5m	3299, 3078, 1642, 1607, 1550, 1503	6.31 (tbr, NH), 3.44 (td, H1″), 2.48 (t, 6.1, H2″), 2.41 (t, H3″), 2.41 (t, H4″), 1.59 (m, H5″), 1.59 (m, H6″), 1.47 (m, H7″)	57.21 (C1″), 54.30 (C3″), 54.30 (C4″), 36.10 (C2″), 25.91 (C5″), 25.91 (C6″), 24.34 (C7″)
5n	3265, 3082, 1647, 1617, 1560	6.18 (tbr, NH), 3.73 (m, H5″), 3.73 (m, H6″), 3.47 (td, H1″) and 2.60–2.46 (m, H2″, H3″ and H4″).	66.85 (C5″), 66.85 (C6″), 57.06 (C1″), 53.32 (C3″), 53.32 (C4″), 35.66 (C2″)
5o	3304, 3072, 1642, 1607, 1542, 1501	7.33–7.23 (m, H8″–H12″), 5.45 (dbr, 8.1, NH), 3.92 (m, H1″), 3.50 (s, H6″), 2.82 (m, H4″ or H5″), 2.14 (td, 11.5 and 2.1, H4″ or H5″), 1.95 (m, H2″ or H3″), 1.48 (dq, 11.5 and 3.4, H2″ or H3″)	138.43 (C7″), 129.10 (C8″), 129.10 (C9″), 128.22 (C10″), 128.22 (C11″), 127.03 (C12″), 63.10 (C6″), 52.31 (C4″), 52.31 (C5″), 46.67 (C1″), 32.40 (C2″), 32.40 (C3″)
5p	3299, 3088, 1643, 1606, 1553	8.53 (m, H7″), 7.62 (ddd, 7.7 and 1.8, H6″), 7.18 (dd, 7.7 and 1.8, H4″), 7.16 (ddd, 7.7 and 1.8, H5″), 6.63 (tbr, NH), 3.77 (td, 6.5 and 5.8, H1″), 3.04 (t, 6.5, H2″)	159.70 (C3″), 149.13 (C7″), 136.64 (C4″), 123.51 (C6″), 121.56 (C5″), 38.78 (C1″), 36.88 (C2″).