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Laboratory note

Design and synthesis of a series of indole glycoprotein IIb/IIIa inhibitors

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Abstract

Synthesis of 1,3-disubstituted indoles derivatives as potential glycoprotein (GP) IIb/IIIa antagonists was reported. Substitution of the indolic nitrogen atom by piperidino or benzamidino moieties was used as mimics of an arginine residue. The acid carboxylic group was linked to the indole scaffold in position-3 via a methylene unit (compounds **4**, **9**, **10**). Introduction of a β-alanine chain was carried out on the acids (**17**–**22**) which after deprotection and basic hydrolysis afforded the final compounds **39**–**46**. The distance between the indole scaffold and the amide bond was modulated from no methylene unit (compound **39**) to 1 (compounds **40**, **41**) or 2 methylene units (compounds **42**–**46**). The presence of a tosylamino group on the β-alanine chain (compound **56**) slightly increased the inhibiting action on platelet aggregation initiated by collagen. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: Indole derivatives; Amino acids; Glycoprotein IIb/IIIa; Platelet aggregation

1. Introduction

The aggregation of platelets is a critical step in hemostasis and arterial thrombosis. Platelets are activated by a variety of agonists including adenosine diphosphate (ADP), collagen, thrombin, adrenaline, thromboxane A_2, vasopressin, platelet activating factor (PAF) and the final common stage resulting in platelet aggregation is the binding of fibrinogen to glycoprotein (GP) IIb/IIIa receptors located on the surface of activated platelets [1–3] (fibrinogen bridging of membrane platelet receptors GPIIb/GPIIIa). In this binding process it is known that: (i) the RGD sequence in fibrinogen is responsible for the recognition [4,5] of GPIIb/IIIa; and (ii) the guanidino group of the Arg residue and the β-carboxylic acid of the Asp residue in the RGD sequence are the essential functionalities in this recognition [6,7]. Subsequent studies have shown that incorporating the RGD motif into constrained cyclic peptides was a successful approach to the discovery of fibrinogen receptor antagonists [8]. Conformational studies of such peptides gave information about the conformation for biological activity depending on the RGD framework. Those informations were used to design potent non-peptide RGD mimetics with improved bioavailability [9–11].

Numerous scaffolds have been used such as 3-oxo-1,4-benzodiazepine [12–19], benzimidazole [20], benzoxazole [20], pyrrolidone [21], benzopyran [22], 2-amino-4-phenylthiazole [23] for designing new GPIIb/IIIa antagonists (Fig. 1).

Recently isoindolinone [24,25] has been used as template for the synthesis of new GPIIb/IIIa antagonists. At the beginning of this program a few years ago we decided to use the indole as bicyclic scaffold and to add a basic moiety and an aspartic acid surrogate in order to fullfill the requirements for a biological activity. The

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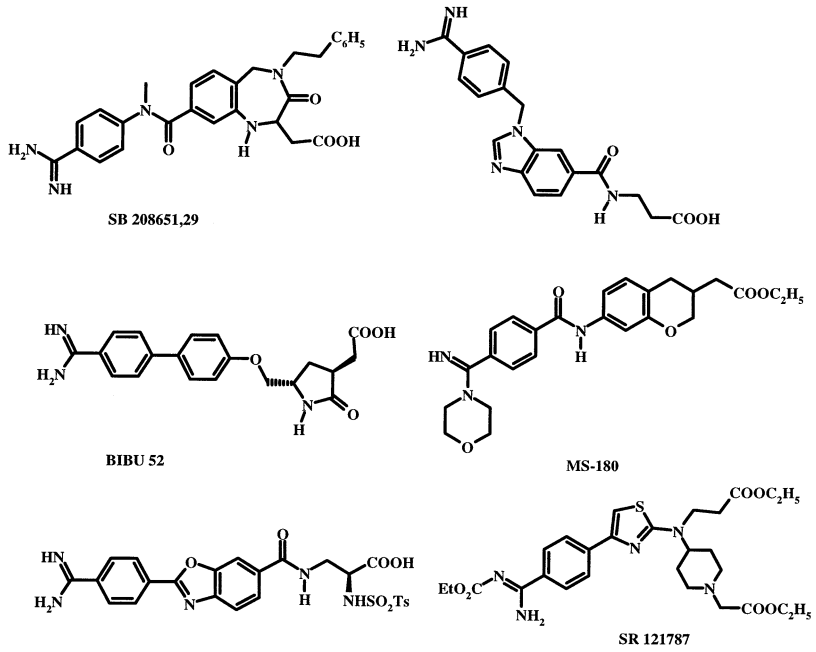


Fig. 1. Chemical structures of GPIIb/IIIa antagonists.

best compounds known in the literature when you build mimics of RGD sequence are 'linear model' and the modelisation of these compounds confirm the obtained biological data [1–3]. Also, biological results in this paper were attempted with the 'curved type' derivatives.

During the course of this work, indole derivatives with antagonistic activity towards GPIIb/GPIIIa appeared in the literature essentially by the Merck's group which published [26] and patented [27] 3,5-, 2,5- and 3,6-disubstituted indole derivatives. Taking into account this new situation it was decided to refocus the research work on the preparation and biological evaluation of 'curved type' derivatives namely the 1,3- (structures A and B, Fig. 2) disubstituted indole derivatives.

The chemical work and the biological activity studies reported here will deal with the preparation and optimisation of compounds in the 1,3 indole family.

2. Chemistry

2.1. Preparation of 'curved type' derivatives: synthesis of 1,3-derivatives

Indole 3-acetic acid was esterified with methyl alcohol at reflux (85% yield) to give the methyl ester **1** [28]. Alkylation on the nitrogen atom with *tert*-butyl bromoacetate afforded **2** (81% yield). The use of NaH as a base, in DMF [29] at room temperature, allowed the exclusive *N*-alkylation without *C*-alkylation in α-position of the methyl ester. Trifluoroacetic acid (TFA) deprotection generated the acid, in quantitative yield, which was further condensed with 4-[*N*(benzyloxycarbonyl)aminoiminomethyl]aniline [30] using EDCI/DMAP in dichloromethane at room temperature to afford compound **3** in 58% yield. Hydrogenolysis of the CbZ group under 2 atm of hydrogen in presence of palladium (80% yield), followed by saponification of the ester group with lithium hydroxide at room temperature and formation of the hydrochloride salt gave **4** (55% for the two steps) (Fig. 3).

The piperidine derivatives **8**–**10** were prepared in a similar way by reacting the sodium salt of methyl indole-3-acetate (**1**) or methyl indole-3-carboxylate (**5**) with the benzyl-4-(2-iodoethyl)-1-piperidinecarboxylate (**6**) or benzyl-4-(2-iodopropyl)-1-piperidinecarboxylate (**7**) in DMF to afford the corresponding *N*-alkylated derivatives **8**–**10**. Yields being ranged from 54 to 87% and best yields were obtained with the more reactive ester **5** (Fig. 4).

In order to increase the distance between the acidic and basic functions we planned first to alkylate the nitrogen atom of methyl 3-(1*H*-3-indolyl)propanoate with the iodoalkylpiperidine **6** or **7** but without success.

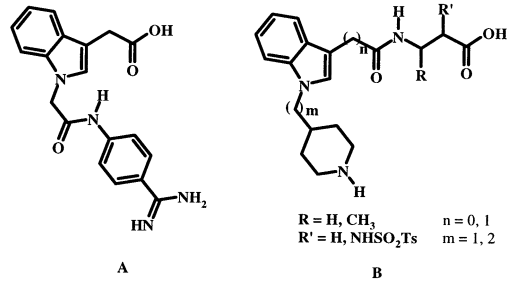


Fig. 2. Structures A and B.

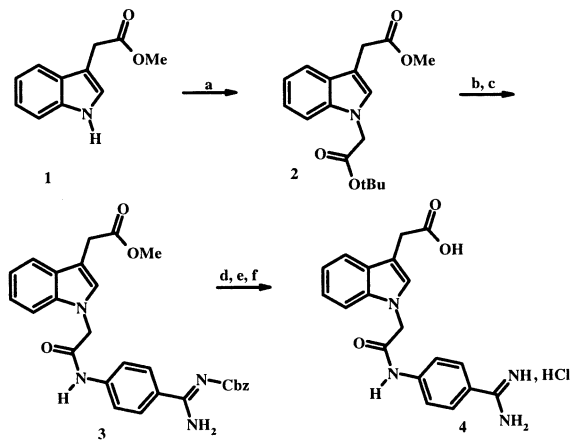


Fig. 3. (a) NaH, DMF, *tert*-butyl bromoacetate, r.t. (81%); (b) TFA, CH_2Cl_2, r.t. (99%); (c) EDCI, DMAP, 4-aminobenzamidineCbz, r.t. (58%); (d) H_2, Pd/C, MeOH, HCl, r.t. (80%); (e) LiOH, r.t.; (f) 3 N HCl (two steps, 55%).

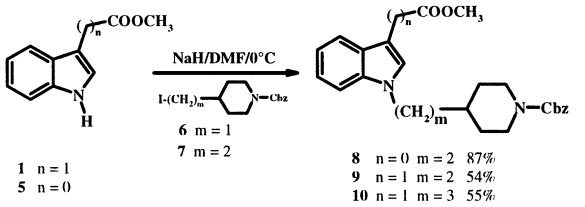


Fig. 4. Synthesis of piperidinyl derivatives **8**–**10**.

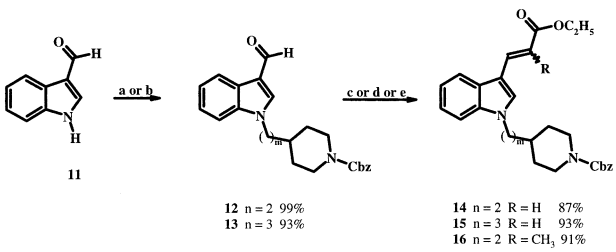


Fig. 5. (a) Potassium carbonate, **6**, acetonitrile, reflux, (**12**); (b) potassium carbonate, **7**, acetonitrile, reflux, (**13**); (c) $(Ph)_3P{=}CH{-}COOC_2H_5$, **12**, toluene, reflux, (**14**); (d) $(Ph)_3P{=}CH{-}COOC_2H_5$, **13**, toluene, reflux, (**15**); (e) $(EtO)_2P(O){-}CH(CH_3)COOC_2H_5$, NaH, **12**, THF, r.t., (**16**).

We decided then to use a more reactive indolic derivative, the 3-formylindole **11** ($pK_a = 12$) [31], commercially available. Compounds **12** and **13** were obtained in good yields, respectively 99 and 93%, by reacting **11** with the iododerivative **6** or **7** in presence of sodium hydride. They were further reacted with the Wittig reagent $(Ph)_3P{=}CH{-}COOC_2H_5$ to afford **14** and **15**, respectively in 87 and 97% yields. The aldehydic derivative **12** was also submitted to a Horner–Emmons reaction with triethyl-2-phosphonopropanoate to give **16** (91% yield) (Fig. 5).

The piperidino compounds **8**–**10**, **14**–**16** obtained were hydrolysed to the corresponding saturated **17**–**19** or unsaturated acids **20**–**22** with lithium hydroxide in ethanol or methanol at room temperature or under reflux (Table 1).

Condensation of acids **17**–**22** with ethyl ester of β-alanine or methyl 3-aminobutanoate in presence of EDCI and DMAP at room temperature afforded the corresponding amido-esters **23**–**30** (Table 1).

The piperidino nitrogen atom of **23**–**25** was deprotected by hydrogenolysis over palladium, at atmospheric pressure, in ethanol to afford **31**–**33**. The double bond of **26**–**30** was also reduced during the deprotection step to give the saturated aminoesters **34**–**38**. Finally acidic hydrolysis (3 N HCl) afforded the corresponding aminoacids **39**–**46**, as hydrochloride salt (Table 1).

2.2. Optimisation of 1,3-derivatives: α-sulfonamides

It has been reported [26,34] that the introduction of a $NHSO_2C_6H_5$ group in position α of a terminal carboxylic function considerably enhances the GPIIb/GPIIIa antagonist activity. Therefore, we have first prepared the methyl 2-(*S*)-tosylamino-3-aminopropanoate (**47**) according to the procedure of Moore [32] and Kato [33] and further reacted that compound with **19** to obtain **48**.

Reaction of substituted piperidino compound **19** with the methyl 2(*S*)-methylphenylsulfonyl-3-aminopropanoate (**47**) afforded derivative **48** (70% yield). The piperidino nitrogen atom was deprotected by hydrogenolysis (**49**, 71% yield) and reacted with Boc_2O to give **50** (90% yield). Saponification of ester **50** afforded acid **51** (92% yield) which upon treatment with HCl 4 N led to the hydrochloride salt (**52**) (76% yield) (Fig. 6).

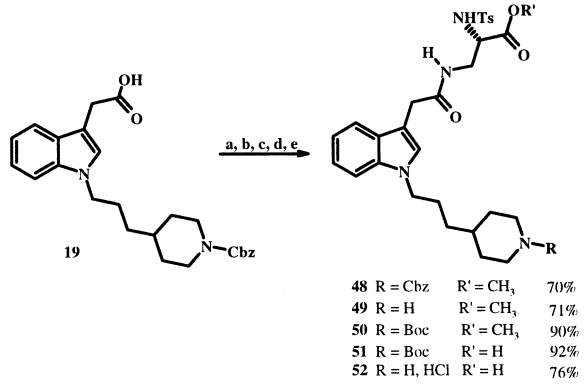
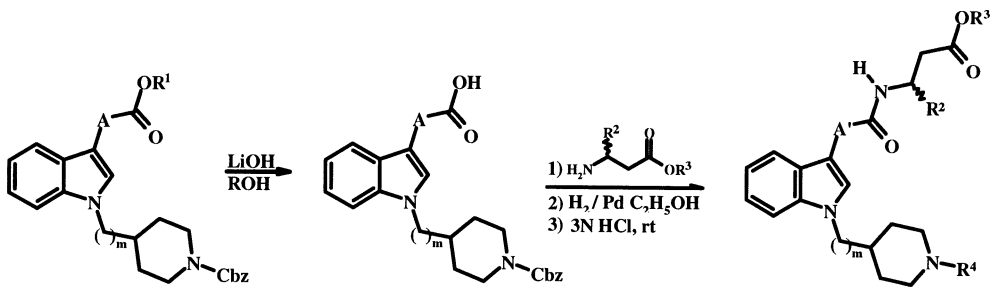


Fig. 6. (a) $H_2N{-}CH_2{-}CH(NHTos){-}COOCH_3$ (**47**), EDCI, DMAP, HOBt, CH_2Cl_2, r.t.; (b) H_2, Pd/C 10%, MeOH, r.t.; (c) Boc_2O, Et_3N, dioxane, r.t.; (d) LiOH, MeOH, r.t.; (e) 4 N HCl, dioxane, 0 °C.

Table 1
Synthesis of acids **39–46**



8-16 **17-22**

23-30 R^2 = H, CH_3 R^3 = C_2H_5 A= A' R^4 = Cbz
31-38 R^2 = H, CH_3 R^3 = C_2H_5 A= A' or CH_2CH_2 R^4 =H
39-46 R^2 = H, CH_3 R^3 = H A= A'or CH_2CH_2 R^4 = H

Ester	*m*	A	R^1	Acid	Yield (%)	R^2	R^3	R^4	Ester	Yield (%)	A′	R^4	Ester	Yield (%)	R^3	Acid	Yield (%)
8	2	–	CH_3	**17**	90	H	C_2H_5	Cbz	**23**	89	–	H	**31**	85	H	**39**	82
9	2	CH_2	CH_3	**18**	92	H	C_2H_5	Cbz	**24**	88	CH_2	H	**32**	90	H	**40**	42
10	3	CH_2	CH_3	**19**	80	H	C_2H_5	Cbz	**25**	92	CH_2	H	**33**	91	H	**41**	35
14	2	CH=CH	C_2H_5	**20**	80	H	C_2H_5	Cbz	**26**	86	CH_2CH_2	H	**34**	65	H	**42**	70
15	3	CH=CH	C_2H_5	**21**	90	H	C_2H_5	Cbz	**27**	79	CH_2CH_2	H	**35**	88	H	**43**	80
				20		CH_3	CH_3	Cbz	**28**	77	CH_2CH_2	H	**36**	80	H	**44**	88
				21		CH_3	CH_3	Cbz	**29**	73	CH_2CH_2	H	**37**	87	H	**45**	76
16	2	$CH=C(CH_3)$	C_2H_5	**22**	86	H	C_2H_5	Cbz	**30**	78	$CH_2CH(CH_3)$	H	**38**	84	H	**46**	60

Table 2
In vitro antiplatelet activity of indole derivatives under study on guinea-pig PRP aggregation induced by collagen

Compound	IC_{50} (μM)
4	>1000
31	>1000
32	140
33	25
34	120
35	520
36	230
37	170
38	350
39	>1000
40	210
41	34
42	160
43	520
44	320
45	540
46	340
49	6.2
52	4.5
L756-568	0.0058

3. Pharmacology

The in vitro inhibiting action on platelet aggregation initiated by collagen in guinea-pig platelet-rich-plasma (PRP) was investigated. IC_{50} values were reported on Table 2.

3.1. 1,3-Disubstituted indoles

Benzamidino derivative **4** was totally inactive and we rapidly focused on the piperidino group as substitute for the amidino group.

Among the 18 piperidino derivatives prepared in this series 16 of them are unsubstituted on the α-position of the terminal carboxylic moiety and most of them have IC_{50} only in the submillimolar range in our in vitro test, which is quite unsatisfactory for that type of compound. We can see from data presented in Table 1, that in our assay system, acid or ester derivatives have similar IC_{50} values.

Ester **33**, and the corresponding acid **41** have the lowest IC_{50} of the series, respectively 25 and 34 μM. This pattern prompted us to keep the backbone of those compounds and to try to improve the potency by adding a tosylsulfonamido group on the α-position of the terminal carboxylic moiety as it is generally reported for that type of compound. However, only an improvement by a factor of less than 10 was observed: IC_{50} of 4.5 μM for acid **52** compared to 34 μM for parent compound **41** and 6.2 μM for ester **49** compared to 25 μM for parent compound **33**. This potency enhancement is unfortunately not as spectacular as the one reported by the Merck's group for the corresponding 2,5-disubstituted indole derivatives [26] and remains insufficient for translating into an in vivo antithrombotic activity consistent with any expectation of therapeutic effect.

4. Conclusions

New indole derivatives bearing different structural features on the indole moiety have been prepared as potential inhibitors of platelet GPIIb/IIIa. Among the 18 derivatives tested on their ability to inhibit platelet aggregation induced by collagen, some 1,3-disubstituted indoles derivatives show low micromolar activity. However, compared to the results reported in the literature for 3,5- and 2,5-disubstituted indole analogues, inhibitory potency of our compounds appears to be relatively weaker.

5. Experimental

5.1. Chemistry

M.p.s were determined on a Köfler melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in the indicated solvent on a Bruker Advance DPX250 (250 MHz for proton and 62.9 MHz for carbon). Chemical shifts for ^{1}H are given relative to internal TMS, while the ^{13}C chemical shifts were obtained with the solvent signal set to $\delta(CHCl_3) = 77.0$. The J values were expressed in Hertz. IR spectra were recorded in the range of 4000–600 cm^{-1} on a Perkin–Elmer spectrometer FT PARAGON 1000 PC. MS spectra were recorded under ionspray or heat nebuliser conditions on a Perkin–Elmer mass spectrometer SCIEX API 300 or Nermag R 1010 (70 eV): ($CI–NH_3$). Column chromatographic separation were performed on Merck silica gel 60 (0.040–0.063 mm) using the indicated solvents (Table 3).

5.1.1. Methyl 2-{1-[2-(tert-butoxy)-2-oxoethyl]-1H-3-indolyl}acetate (2)

To a suspension of NaH (38 mg, 1.59 mmol) in DMF (0.5 mL) cooled in an ice-bath indole ester **1** (200 mg, 1.06 mmol) in DMF (1 mL) was dropwise added. The mixture was stirred for 45 min at 0 °C and transferred via a needle to a solution of *tert*-butyl bromoacetate (309 mg, 1.59 mmol) in DMF (1 mL) at 0 °C. The mixture was stirred for 2 h at room temperature (r.t.). After evaporation of the DMF under reduced pressure water–EtOAc was added. Decantation and extraction with EtOAc followed by drying of the organic layers over $MgSO_4$ and evaporation leave an oil which was purified by column chromatography on silica gel using

EtOAc–PE 1:9 as eluent; a yellow oil was obtained; $m = 260$ mg (81%). Analysed for $C_{17}H_{21}NO_4$ (C, H, N).

5.1.2. Methyl 2-(1-{2-[4-amino{(benzyloxy)carbonyl]-imino}methyl)anilino]-2-oxoethyl}-1H-3-indolyl)acetate ***(3)***

5.1.2.1. 2-[3-(2-Methoxy-2-oxoethyl)-1H-1-indolyl]-acetic acid. A solution of **2** (2 g, 6.59 mmol) and trifluoroacetic acid (3 mL) in CH_2Cl_2 (10 mL) was stirred at r.t. for 24 h. Water was added and the organic layer was extracted with a saturated aq. solution of sodium hydrogencarbonate. After acidification of the aq. layer, extraction with CH_2Cl_2 and drying over $MgSO_4$, an oil was obtained after evaporation; $m =$ 1.63 g (quantitative yield). IR (film) ν (cm^{-1}): 1731 (C=O); 2600–3700 (OH). ^{1}H-NMR ($CDCl_3$): δ 3.77 (s, 3H, OCH_3); 3.85 (s, 2H, CH_2); 4.82 (s, 2H, NCH_2); 7.10 (s, 1H, H_2); 7.20–7.32 (m, 3H, H_5, H_6, H_7); 7.68 (d, 1H, H_4, $J = 7.5$ Hz); 10.0 (br s, 1H, COOH). ^{13}C-NMR ($CDCl_3$): δ 31.0 (CH_2); 47.2 (NCH_2); 52.1 (CH_3); 108.5 (C); 109.0 (CH); 119.3 (CH); 120.0 (CH); 122.5 (CH); 127.2 (CH); 127.9 (C); 136.6 (C); 172.6 (CO); 173.6 (CO). MS (IS): m/z 248 [MH^+].

5.1.2.2. Methyl 2-(1-{2-[4-amino{(benzyloxy)carbonyl]-imino}methyl)anilino]-2-oxoethyl}-1H-3-indolyl)acetate ***(3)***. A mixture of 4-aminobenzamidineCbz (240 mg, 0.89 mmol), DMAP (118 mg, 0.97 mmol), 2-[3-(2-methoxy-2-oxoethyl)-1*H*-1-indolyl]acetic acid (200 mg, 0.81 mmol), EDCI (170 mg, 0.89 mmol) in CH_2Cl_2 (20 mL) was stirred for 24 h at r.t. Water was added and the mixture was extracted with CH_2Cl_2. After drying of the organic extracts over $MgSO_4$ and evaporation, the residue was purified by column chromatography on silica gel using EtOAc–PE 1:1 as eluent; a white solid was obtained; $m = 230$ mg (58%); m.p. 174–175 °C. Analysed for $C_{28}H_{26}N_4O_5$ (C, H, N).

5.1.3. 2-[1-(2-{4-Amino(imino)methyl]anilino}-2-oxoethyl)-1H-3-indolyl]acetic acid, hydrochloride ***(4)***

5.1.3.1. Methyl 2-[1-(2-{4-amino(imino)methyl]anilino}-2-oxoethyl)-1H-3-indolyl]acetate. To a solution of compound **3** (1 g, 2 mmol) in MeOH (100 mL) and 4 N HCl (2.5 mL in Et_2O), Pd/C 10% (750 mg) was added. The suspension was stirred for 1 h under 2 atm of hydrogen at r.t. Filtration and evaporation leave a solid as HCl salt which was crystallised in MeOH; $m = 650$ mg (80%); m.p. 238–240 °C (dec.). IR (KBr) ν (cm^{-1}): 1673 (C=O), 1728 (C=O); 3334, 3384 (NH_2, NH). ^{1}H-NMR (DMSO-d_6): δ 3.64 (s, 3H, OCH_3); 3.78 (s, 2H, CH_2); 5.13 (s, 2H, NCH_2CO); 7.06 (t, 1H, H_5 or H_6, $J = 7.3$ Hz); 7.15 (2t, 1H, H_5 or H_6, $J = 7.3$ Hz); 7.34 (s, 1H, H_2); 7.43 (d, 1H, H_7, $J = 7.3$ Hz); 7.53 (d, 1H, H_4, $J = 7.0$ Hz); 7.75 (m, 4H, $H_{arom.}$); 8.89 (br s, 2H, NH_2); 9.22 (br s, 2H, NH_2); 11.02 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ 33.2 (CH_2); 51.8 (NCH_2); 54.4 (OCH_3); 109.6 (C); 112.6 (CH); 121.4 (2CH); 121.5 (CH); 121.7 (CH); 124.2 (CH); 124.7 (CH); 130.3 (C); 131.4 (C); 132.1 (2CH); 139.4 (C); 146.6 (C); 167.5 (N=CN); 170.2 (CO); 174.7 (CO). MS (IS): m/z 365 [MH^+].

5.1.3.2. 2-[1-(2-{4-Amino(imino)methyl]anilino}-2-oxoethyl)-1H-3-indolyl]acetic acid, hydrochloride ***(4)***. A suspension of methyl 2-[1-(2-{4-amino(imino)methyl]-anilino}-2-oxoethyl)-1*H*-3-indolyl]acetate (290 mg, 0.80 mmol) in water (3 mL) was adjusted to pH 12 with a solution of 1 M LiOH and stirred for 24 h at r.t.; pH was adjusted to 7 by addition of diluted aq. HCl. After filtration the solid obtained was stirred, as a suspension, in water (1 mL) and 3 N HCl (350 μL) for 2 h at 0 °C. Filtration gave a solid, HCl salt, which was dried over P_2O_5; $m = 170$ mg (55%); m.p. 240–242 °C (dec.). Analysed for $C_{19}H_{18}N_4O_3$, HCl (C, H, N).

5.1.4. Benzyl 4-(2-iodoethyl)-1-piperidinecarboxylate ***(6)***

To a solution of benzyl 4-(2-hydroxyethyl)-1-piperidinecarboxylate [35] (1.2 g, 4.56 mmol) in $C_6H_5CH_3$–MeCN (18/9 mL) cooled at 0 °C was added triphenylphosphine (1.79 g, 6.84 mmol), imidazole (930 mg, 13.7 mmol) and iodine (1.73 g, 6.84 mmol). The mixture was stirred for 3 h at r.t. After evaporation of the solvent, water was added to the residue which was extracted with CH_2Cl_2. Drying over $MgSO_4$ and evaporation leave a residue which was purified by column chromatography on silica gel using EtOAc–PE 1:4 as eluent to give an oil; $m = 1.59$ g (93%). Analysed for $C_{15}H_{20}INO_3$ (C, H, N).

5.1.5. Benzyl 4-(2-iodopropyl)-1-piperidinecarboxylate ***(7)***

Same procedure as for **6** starting from benzyl 4-(2-hydroxypropyl)-1-piperidinecarboxylate [36]; chromatography (eluent: EtOAc–EP, 3:7); oil; $m = 8.7$ g (89%). Analysed for $C_{17}H_{22}INO_3$ (C, H, N).

5.1.6. General procedure for alkylation: compounds ***8–13***

5.1.6.1. Method A: synthesis of compounds ***8–10***. A solution of indole **1** or **5** (1 equiv.) in DMF (1 mL for 1 mmol) was dropwise added to a suspension of NaH (1.5 equiv.) in DMF (1 mL for 1 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C and transferred slowly to a solution of halogeno derivatives **6** or **7** in DMF (1 mL for 1 mmol). The mixture was stirred at r.t. until disappearance of the indole **1** or **5** and evaporated under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc. Drying over $MgSO_4$ and evaporation leave a residue, which was chromatographed on a silica gel column.

8: Eluent: CH_2Cl_2–MeOH, 95:5; oil; $m = 4.2$ g (87%). Analysed for $C_{25}H_{28}N_2O_4$ (C, H, N).

9: Eluent: CH_2Cl_2; oil; $m = 2.12$ g (54%). Analysed for $C_{26}H_{30}N_2O_4$ (C, H, N).

10: Eluent: EtOAc–EP, 3:7; oil; $m = 330$ mg (55%). Analysed for $C_{27}H_{32}N_2O_4$ (C, H, N).

*5.1.6.2. Method B: synthesis of derivatives **12**, **13**.* A suspension of indole-3-carboxaldehyde (**11**) (1 equiv.), of halogeno derivative **6** or **7** and K_2CO_3 (1.5 equiv.) in MeCN (1 mL for 3 mmol of **11**) was refluxed. After disappearance of **11** the solvent was evaporated and water was added to the residue. Extraction with EtOAc, drying over $MgSO_4$ and evaporation leave a solid, which was chromatographed on a silica gel column.

12: Time reaction 24 h; eluent: EtOAc–PE 1:1; oil; $m = 5.32$ g (99%). Analysed for $C_{24}H_{26}N_2O_3$ (C, H, N).

13: Time reaction 46 h; eluent: AcOEt–PE, 1:1; oil; $m = 4.88$ g (93%). Analysed for $C_{25}H_{28}N_2O_3$ (C, H, N).

*5.1.7. Benzyl 4-(2-{3-[(E)-3-ethoxy-3-oxo-1-propenyl]-1H-1-indolyl}-ethyl)-1-piperidinecarboxylate **(14)***

A solution of aldehyde **12** (2.0 g, 5.1 mmol) and (carbethoxymethylene)triphenylphosphorane (3.93 g, 11.3 mmol) in $C_6H_5CH_3$ (50 mL) was refluxed 17 h. Evaporation of the solvent was followed by column chromatography (eluent: AcOEt–PE, 4:6); oil; $m = 2.04$ g (87%). Analysed for $C_{28}H_{32}N_2O_4$ (C, H, N).

*5.1.8. Benzyl 4-(2-{3-[(E)-3-ethoxy-3-oxo-1-propenyl]-1H-1-indolyl}-propyl)-1-piperidinecarboxylate **(15)***

Obtained from **13** using similar conditions as for **14**. Chromatography (eluent: EtOAc–PE, 4:6); oil; $m =$ 3.18 g (97%). Analysed for $C_{29}H_{34}N_2O_4$ (C, H, N).

*5.1.9. Benzyl 4-(2-{3-[(E)-3-ethoxy-2-methyl-3-oxo-1-propenyl]-1H-1-indolyl}-ethyl)-1-piperidinecarboxylate **(16)***

A solution of triethyl-2-phosphonopropanoate (1.9 g, 9.2 mmol) in THF (10 mL) was dropwise added to a suspension of NaH (202 mg, 8.45 mmol) in THF (30 mL) at 0 °C. After 30 min, a solution of aldehyde **12** (3 g, 7.7 mmol) in THF (20 mL) was dropwise added to the mixture which was stirred at r.t. for 2 h. Evaporation of the solvent, addition of water and extraction with EtOAc leave after drying over $MgSO_4$ and evaporation of a residue which was chromatographed on silica gel column (eluent: EtOAc–PE, 3:7); oil; $m = 3.32$ g (91%). Analysed for $C_{29}H_{34}N_2O_4$ (C, H, N).

*5.1.10. General procedure of esters hydrolysis: compounds **17**–**22***

5.1.10.1. Method A. A solution of indolic esters **8**–**10** or **14**–**16** (1 mmol) and aq. 1 M LiOH (2.5 mL for 1 mmol) in MeOH or EtOH (2 mL for 1 mmol) was stirred at r.t. until disappearance of the starting indolic ester. After evaporation under reduced pressure, water was added and the mixture was made acidic with 1 M HCl. The precipitated acid was collected.

5.1.10.2. Method B. Similar to Method A except refluxing of the solvent.

17: Method A; $m = 3.50$ g (90%); solid, m.p. 168–170 °C. Analysed for $C_{24}H_{26}N_2O_4$ (C, H, N).

18: Method A; $m = 1.84$ g (92%); solid, m.p. 134–135 °C. Analysed for $C_{25}H_{28}N_2O_4$ (C, H, N).

19: Method A; $m = 2.20$ g (80%); solid, m.p. 115–116 °C. Analysed for $C_{26}H_{30}N_2O_4$ (C, H, N).

20: Method B; $m = 1.1$ g (80%); m.p. 65 °C (dec.). Analysed for $C_{26}H_{28}N_2O_4$ (C, H, N).

21: Method B; $m = 2.68$ g (90%); m.p. 85 °C (dec.). Analysed for $C_{27}H_{30}N_2O_4$ (C, H, N).

22: Method B; $m = 2.50$ g, (86%); m.p. 70 °C (dec.). Analysed for $C_{27}H_{30}N_2O_4$ (C, H, N).

*5.1.11. General procedure for amidification: compounds **23**–**30***

A solution of β-alanine ethyl ester hydrochloride (1.1 equiv.) in CH_2Cl_2 (20 mL for 1 mmol) was cooled at 0 °C. DMAP (1.65 equiv.), acids **17**–**22** (1 equiv.), EDCI (1.1 equiv.) were added to the mixture and stirred at r.t. until disappearance of the acid. Water was added and the organic layer dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel.

23: Eluent: CH_2Cl_2–MeOH, 98:2; oil; $m = 2.0$ g (89%). Analysed for $C_{29}H_{35}N_3O_5$ (C, H, N).

24: Eluent: CH_2Cl_2–MeOH, 97:3, v/v; oil; $m = 750$ mg (88%). Analysed for $C_{30}H_{37}N_3O_5$ (C, H, N).

25: Eluent: EtOAc–PE, 7:3; oil; $m = 2.65$ g (92%). Analysed for $C_{31}H_{39}N_3O_5$ (C, H, N).

26: Eluent: EtOAc–PE, 8:2; oil; $m = 800$ mg (86%). Analysed for $C_{31}H_{37}N_3O_5$ (C, H, N).

27: Eluent: EtOAc–PE, 7:3; oil; $m = 960$ mg (79%). Analysed for $C_{32}H_{39}N_3O_5$ (C, H, N).

28: Eluent: EtOAc–PE, 8:2; oil; $m = 1.65$ g (77%). Analysed for $C_{31}H_{37}N_3O_5$ (C, H, N).

29: Eluent: EtOAc–PE, 7:3; oil; $m = 470$ mg (73%). Analysed for $C_{32}H_{39}N_3O_5$ (C, H, N).

30: Eluent: EtOAc–PE, 7:3 ; oil; $m = 1.90$ g (78%). Analysed for $C_{32}H_{39}N_3O_5$ (C, H, N).

*5.1.12. General procedure for debenzylation: compounds **31**–**38***

Compounds **23**–**30** were dissolved in EtOH or MeOH (5 mL for 1 mmol) and a catalytic amount of

Pd/C 10% (10% in weight) was added. The suspension was stirred under 1 atm of hydrogen at r.t. until the disappearance of the starting material (2–12 h). After filtration the solvent was evaporated and the crude residue chromatographed on silica gel column.

31: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:30:3; oil; $m = 1.0$ g (85%); m.p. 219–221 °C (oxalate). Analysed for $C_{21}H_{29}N_3O_3$ (C, H, N).

32: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:10:1 then 100:20:2; oil; $m = 610$ mg (90%); m.p. 213–215 °C (oxalate). Analysed for $C_{22}H_{31}N_3O_3$ (C, H, N).

33: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:20:2; oil; $m = 1.73$ g (91%); m.p. 208–210 °C (oxalate). Analysed for $C_{23}H_{33}N_3O_3$ (C, H, N).

34: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:20:2; oil; $m = 430$ mg (65%); m.p. 210–212 °C (oxalate). Analysed for $C_{23}H_{33}N_3O_5$ (C, H, N).

35: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:20:2; oil; $m = 570$ mg (88%); m.p. 205–206 °C (oxalate). Analysed for $C_{24}H_{35}N_3O_5$ (C, H, N).

36: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:20:2; oil; $m = 695$ mg (80%); m.p. 210–212 °C (oxalate). Analysed for $C_{23}H_{33}N_3O_3$ (C, H, N).

37: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:20:2; oil; $m = 265$ mg (87%); m.p. 204–206 °C (oxalate). Analysed for $C_{24}H_{35}N_3O_3$ (C, H, N).

38: Eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:20:2; oil; $m = 1.22$ g (84%); m.p. 212–213 °C (oxalate). Analysed for $C_{24}H_{35}N_3O_3$ (C, H, N).

*5.1.13. Hydrolysis of esters: compounds **31**–**38***

A solution of esters **31**–**38** (1.50 mmol) in 3 N HCl (3 mL) was stirred for 7 days at r.t. After addition of Et_2O to the reaction mixture a solid was obtained to afford acids **39**–**46** as hydrochloride.

*5.1.14. 3-[({1-[2-(4-Piperidyl)ethyl]-1H-3-indolyl}-methanoyl)amino]propanoic acid, hydrochloride (**39**)*

White solid; $m = 435$ mg (82%); m.p. 132 °C (dec.) (chlorhydrate). Analysed for $C_{19}H_{25}N_3O_3$, HCl (C, H, N).

*5.1.15. 3-[({1-[2-(4-Piperidyl)ethyl]-1H-3-indolyl}-ethanoyl)amino]propanoic acid, hydrochloride (**40**)*

Yellow solid; $m = 250$ mg (42%); m.p. 120–122 °C (dec.) (chlorhydrate). Analysed for $C_{20}H_{27}N_3O_3$, HCl (C, H, N).

*5.1.16. 3-[({1-[2-(4-Piperidyl)propyl]-1H-3-indolyl}-ethanoyl)amino]propanoic acid, hydrochloride (**41**)*

Yellow solid; $m = 250$ mg (35%); m.p. 80 °C (dec.) (chlorhydrate). Analysed for $C_{21}H_{29}N_3O_3$, HCl (C, H, N).

*5.1.17. 3-[({1-[2-(4-Piperidyl)ethyl]-1H-3-indolyl}-propanoyl)amino]propanoic acid, hydrochloride (**42**)*

White solid; $m = 335$ mg (70%); m.p. 96–98 °C (chlorhydrate). Analysed for $C_{21}H_{29}N_3O_3$, HCl (C, H, N).

*5.1.18. 3-[({1-[2-(4-Piperidyl)propyl]-1H-3-indolyl}-propanoyl)amino]propanoic acid, hydrochloride (**43**)*

White solid; $m = 327$ mg (80%); m.p. 120–122 °C (chlorhydrate). Analysed for $C_{22}H_{31}N_3O_3$, HCl (C, H, N).

*5.1.19. 3-[(3-{1-[2-(4-Piperidyl)ethyl]-1H-3-indolyl}-propanoyl)amino]butanoic acid, hydrochloride (**44**)*

White solid; $m = 374$ mg (88%); m.p. 96 °C (dec.) (chlorhydrate). Analysed for $C_{22}H_{31}N_3O_3$; HCl (C, H, N).

*5.1.20. 3-[(3-{1-[2-(4-Piperidyl)propyl]-1H-3-indolyl}-propanoyl)amino]butanoic acid, hydrochloride (**45**)*

White solid; $m = 335$ mg (76%); m.p. 106 °C (dec.) (hydrochloride). Analysed for $C_{23}H_{33}N_3O_3$, HCl (C, H, N).

*5.1.21. 3-[(2-Methyl-3-{1-[2-(4-piperidyl)ethyl]-1H-3-indolyl}propanoyl)amino]propanoic acid, hydrochloride (**46**)*

White solid; $m = 300$ mg (60%); m.p. 119 °C (dec.) (chlorhydrate). Analysed for $C_{22}H_{31}N_3O_3$, HCl (C, H, N).

*5.1.22. Benzyl 4-[3-(3-{2-[(3-methoxy-2-{[(4-methylphenyl)-sulphonyl]amino}-3-oxopropyl)amino]-2-oxoethyl}-1H-1-indolyl)propyl]-1-piperidinecarboxylate (**48**)*

Compound **19** (2 g, 4.6 mmol), EDCI (971 mg, 5.06 mmol), HOBt (775 mg, 5.06 mmol), DMAP (928 mg, 3.3 mmol) were added to the aminoacid **47** as hydrochloride salt (1.56 g, 5.06 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After stirring for 24 h at r.t. water was added and the organic layer was dried over $MgSO_4$. Evaporation leaves a residue which was chromatographed on a silica gel column (eluent: EtOAc–PE, 7:3); white solid; $m = 2.2$ g (70%); m.p. 74–76 °C. $[\alpha]_D$: +20.8° (c 0.5, $CHCl_3$). Analysed for $C_{37}H_{44}N_4O_7S$ (C, H, N).

*5.1.23. Methyl 2-{[(4-methylphenyl)sulfonyl]amino}-3-[(2-{1-[3-(4-piperidinyl)propyl]-1H-3-indolyl}acetyl)-amino]propanoate (**49**)*

Obtained by hydrogenolysis of **48** according to the general procedure. Chromatography (eluent: CH_2Cl_2–MeOH–NH_4OH 30%, 100:20:2); white solid; $m = 800$ mg (71%); m.p. 118–120 °C. $[\alpha]_D$: +16.3° (c 0.3, MeOH). Analysed for $C_{29}H_{38}N_4O_5S$ (C, H, N).

Table 3
IR, ^{1}H- and ^{13}C-NMR data for compounds **2–4**, **6–46** and **48-52**.

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
2	1737 (C=O)	1.50 (s, 9H, *t*-Bu); 3.75 (s, 3H, OCH_3); 3.84 (s, 2H, CH_2); 4.77 (s, 2H, NCH_2); 7.16 (s, 1H, H_2); 7.19–7.29 (m, 3H, H_5, H_6, H_7); 7.66 (d, 1H, H_4, $J = 7.7$ Hz)	28.0 ($(CH_3)_3$); 31.1 (CH_2CO); 48.5 (NCH_2); 51.9 (CH_3); 82.6 (Me_3C); 108.0 (C); 109.1 (CH); 119.2 (CH); 119.7 (CH); 122.2 (CH); 127.4 (CH); 127.9 (C); 136.7 (C); 167.7 (CO); 172.4 (CO)	326 [MNa^+] 304 [MH^+]
3	1692 (C=O), 1722 (C=O), 3328, 3390 (NH_2, NH)	3.63 (s, 3H, OCH_3); 3.79 (s, 2H, C_3–CH_2); 5.07 (s, 2H, CH_2); 5.11 (s, 2H, NCH_2); 7.05 (t, 1H, H_5 or H_6, $J = 7.0$ Hz); 7.15 (t, 1H, H_5 or H_6, $J = 7.0$ Hz); 7.33–7.43 (m, 7H, C_6H_5, H_2, H_7); 7.53 (d, 1H, H_4, $J = 7.0$ Hz); 7.69 (d, 2H, $H_{3'}$, $H_{5'}$, $J = 8.8$ Hz); 7.99 (d, 2H, $H_{2'}$, $H_{6'}$, $J = 8.8$ Hz); 9.13 (br s, 2H, NH_2); 10.67 (s, 1H, NH)	31.1 (CH_2); 49.5 (NCH_2); 52.0 (OCH_3); 66.4 (CH_2); 107.3 (C); 110.2 (CH); 118.8 (CH); 119.2 (2CH); 119.4 (CH); 121.9 (CH); 128.0 (C); 128.2 (CH); 128.3 (2CH); 128.8 (2CH); 129.1 (C and CH); 129.2 (2CH); 137.1 (C); 137.6 (C); 142.6 (C); 164.2 and 166.5 (N=C–N and C=O); 167.4 (CO); 172.3 (CO)	499.5 [MH^+]
4	1673 (C=O), 1728 (C=O), 3335, 3385 (NH_2, NH)	δ 3.64 (s, 3H, OCH_3); 3.78 (s, 2H, CH_2); 5.13 (s, 2H, NCH_2CO); 7.06 (t, 1H, H_5 or H_6, $J = 7.3$ Hz); 7.15 (2t, 1H, H_5 or H_6, $J = 7.3$ Hz); 7.34 (s, 1H, H_2); 7.43 (d, 1H, H_7, $J = 7.3$ Hz); 7.53 (d, 1H, H_4, $J = 7.0$ Hz); 7.75 (m, 4H, $H_{arom.}$); 8.89 (br s, 2H, NH_2); 9.22 (br s, 2H, NH_2); 11.02 (s, 1H, NH)	33.2 (CH_2); 51.8 (NCH_2); 54.4 (OCH_3); 109.6 (C); 112.6 (CH); 121.4 (2CH); 121.5 (CH); 121.7 (CH); 124.2 (CH); 124.7 (CH); 130.3 (C); 131.4 (C); 132.1 (2CH); 139.4 (C); 146.6 (C); 167.5 (N=CN); 170.2 (CO); 174.7 (CO)	365 [MH^+]
6	1697 (C=O)	1.12–1.23 (m, 2H, H_{3a-5a}); 1.59–1.73 (m, 3H, H_{3b-5b}, H_4); 1.80 (q, 2H, CH_2CH_2I, $J = 7.3$ Hz); 2.76–2.86 (m, 2H, H_{2a-6a}); 3.24 (t, 2H, CH_2–I, $J = 7.3$ Hz); 4.18–4.24 (m, 2H, H_{2b-6b}); 5.15 (s, 2H, CH_2Ph); 7.32–7.39 (m, 5H, Ph)	4.1 (CH_2–I); 31.6 (C_4H); 32.4 (C_3H_2 and C_5H_2); 41.8 (CH_2); 44.4 (C_2H_2 and C_6H_2); 67.1 (OCH_2), 127.8, 127.9, 128.5 ($5CH_{arom.}$); 136.9 ($C_{arom.}$); 157.0 (CO)	374 [MH^+]
7	1697 (C=O)	1.12–1.21 (m, 2H, H_{3a-5a}); 1.33–1.41 (m, 2H, CH_2); 1.41–1.46 (m, 1H, H_4); 1.67–1.72 (m, 2H, H_{3b-5b}); 1.87 (m, 2H, CH_2); 2.73–2.83 (m, 2H, H_{2a-6a}); 3.2 (t, 2H, CH_2–I, $J = 7.0$ Hz); 4.13–4.18 (m, 2H, H_{2b-6b}); 5.15 (s, 2H, CH_2); 7.33–7.39 (m, 5H, Ph)	δ 6.6 (CH_2I); 30.8 (CH_2); 32.2 (C_4H); 32.8 (C_3H_2 and C_5H_2); 34.0 (CH_2); 45.3 (C_2H_2 and C_6H_2); 67.1 (CH_2Ph); 128.7, 128.8, 129.3 ($5CH_{arom.}$); 136.8 ($C_{arom.}$); 157.2 (CO)	388 [MH^+]
8	1700 (C=O), 1720 (C=O)	1.16–1.25 (m, 2H, $H_{3'a-5'a}$); 1.40–1.44 (m, 1H, $H_{4'}$); 1.54–1.64 (m, 2H, $H_{3'b-5'b}$); 1.81 (q, 2H, CH_2 $J = 7.0$ Hz); 2.67–2.77 (m, 2H, $H_{2'a-6'a}$); 3.89 (s, 3H, OCH_3); 4.14–4.19 (m, 4H, CH_2N and $H_{2'b-6'b}$); 5.10 (s, 2H, CH_2Ph); 7.24–7.33 (m, 8H, H_5, H_6, H_7, Ph); 7.79 (s, 1H, H_2); 8.14–8.18 (m, 1H, H_4)	33.8 ($2CH_2$); 35.3 (CH); 38.2 (CH_2); 45.8 ($2CH_2$); 46.2 (CH_2); 53.0 (OCH_3); 69.0 (CH_2Ph); 109.1 (C); 111.8 (CH); 123.8 (CH); 123.9 (CH); 124.8 (CH); 128.6 (C); 129.8, 129.9, 130.3 (5CH), 135.9 (CH); 138.3 (C); 138.8 (C); 157.2 (NC=O); 167.4 (CO)	421 [MH^+]
9	1698 (C=O), 1737 (C=O)	1.23–1.37 (m, 2H, $H_{3'a-5'a}$); 1.47–1.55 (m, 1H, $H_{4'}$); 1.64–1.68 (m, 2H, $H_{3'b-5'b}$); 1.85 (q, 2H, CH_2 $J = 7.2$ Hz); 2.76–2.86 (m, 2H, $H_{2'a-6'a}$); 3.76 (s, 3H, OCH_3); 3.84 (s, 2H, C_3–CH_2); 4.19 (t, 2H, CH_2N, $J = 7.2$ Hz); 4.18–4.24 (m, 2H, $H_{2'b-6'b}$); 5.19 (s, 2H, CH_2Ph); 7.14 (s, 1H, H_2); 7.18 (td, 1H, H_5, $J = 7.5$, 1.0 Hz); 7.28 (td, 1H, H_6, $J = 7.5$, 1.0 Hz); 7.35 (d, 1H, H_7, $J = 7.5$ Hz); 7.41 (s, 5H, Ph); 7.67 (d, 1H, H_4, $J = 7.5$ Hz)	34.1 (CH_2); 34.9 ($2CH_2$); 36.4 (CH); 39.6 (CH_2); 44.8 (CH_2); 47.0 ($2CH_2$); 54.9 (OCH_3); 70.0 (CH_2Ph); 110.1 (C); 112.2 (CH); 122.1 (CH); 122.2 (CH); 124.8 (CH); 129.4 (CH); 130.8, 130.9, 131.5 (5CH and C); 136.2 (C); 139.9 (C); 158.2 (NCO); 172.5 (CO)	435 [MH^+]

Table 3 (*Continued*)

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
10	1694 (C=O), 1736 (C=O)	1.09–1.18 (m, 2H, $H_{3'a-5'a}$); 1.26–1.35 (m, 2H, C_4–CH_2); 1.39–1.43 (m, 1H, $H_{4'}$); 1.64–1.70 (m, 2H, $H_{3'b-5'b}$); 1.88 (qt, 2H, CH_2, $J = 7.3$ Hz); 2.70–2.80 (m, 2H, $H_{2'a-6'a}$); 3.73 (s, 3H, OCH_3); 3.81 (s, 2H, C_3–CH_2); 4.10 (t, 2H, CH_2N, $J = 7.3$ Hz); 4.13–4.20 (m, 2H, $H_{2'b-6'b}$); 5.15 (s, 2H, CH_2); 7.11 (s, 1H, H_2); 7.16 (td, 1H, H_5, $J = 7.9$, 1.2 Hz); 7.25 (td, 1H, H_6, $J = 7.9$, 1.2 Hz); 7.33–7.40 (m, 6H, H_7, Ph); 7.64 (d, 1H, H_4, $J = 7.9$ Hz)	29.6 (CH_2); 33.3 (CH_2); 34.2 ($2CH_2$); 35.9 (CH_2); 37.9 (CH); 46.3 ($2CH_2$); 48.6 (CH_2); 54.2 (OCH_3); 69.1 (CH_2Ph); 109.0 (C); 111.6 (CH); 121.2 (CH); 121.3 (CH); 124.0 (CH); 128.8 (CH); 129.9; 130.0; 130.1, 130.6 (5CH, C); 138.3 (C); 139.1 (C); 157.4 (N–C=O); 174.8 (CO)	449 [MH^+]
12	1659 (C=O), 1694 (C=O), 2857 (CH)	1.19–1.31 (m, 2H, $H_{3'a-5'a}$); 1.48–1.55 (m, 1H, $H_{4'}$); 1.73–1.78 (m, 2H, $H_{3'b-5'b}$); 1.90 (q, 2H, CH_2, $J = 7.5$ Hz); 2.74–2.84 (m, 2H, $H_{2'a-6'a}$); 4.13–4.22 (m, 2H, $H_{2'b-6'b}$); 4.25 (t, 2H, CH_2N, $J = 7.5$ Hz); 5.15 (s, 2H, CH_2Ph); 7.31–7.39 (m, 8H, H_5, H_6, H_7, Ph); 7.74 (s, 1H, H_2); 8.32–8.36 (m, 1H, H_4); 10.04 (s, 1H, CHO)	31.6 ($2CH_2$); 33.2 (CH); 36.0 (CH_2); 43.7 ($2CH_2$); 44.4 (CH_2); 66.9 (CH_2Ph); 109.8 (CH); 118.0 (C); 122.0 (CH); 122.8 (CH); 123.9 (CH); 125.3 (C); 127.7, 127.8, 128.3 (5CH); 136.6 (C); 136.9 (C); 137.9 (CH); 155.0 (N–C=O); 184.3 (CHO)	391 [MH^+]
13	1660 (C=O), 1691 (C=O), 2853 (CH)	1.08–1.19 (m, 2H, $H_{3'a-5'a}$); 1.24–1.35 (m, 2H, CH_2); 1.40–1.50 (m, 1H, $H_{4'}$); 1.63–1.68 (m, 2H, $H_{3'b-5'b}$); 1.94 (qt, 2H, CH_2, $J = 7.5$ Hz); 2.69–2.79 (m, 2H, $H_{2'a-6'a}$); 4.10–4.21 (m, 4H, $H_{2'b-6'b}$, CH_2N); 5.14 (s, 2H, CH_2Ph); 7.29–7.39 (m, 8H, H_5, H_6, H_7, Ph); 7.72 (s, 1H, H_2); 8.31–8.35 (m, 1H, H_4); 10.02 (s, 1H, CHO)	27.0 (CH_2); 31.9 ($2CH_2$); 33.6 (CH_2); 35.7 (CH); 44.1 ($2CH_2$); 47.4 (CH_2); 67.0 (CH_2Ph); 110.0 (CH); 118.1 (C); 122.2 (CH); 122.9 (CH); 124.0 (CH); 125.5 (C); 127.8; 127.9, 128.5 (5CH); 136.9 (C); 137.1 (C); 138.0 (CH); 155.2 (N–C=O); 184.5 (CHO)	405 [MH^+]
14	1623 (C=O), 1705 (C=O)	1.21–1.32 (m, 2H, $H_{3'a-5'a}$); 1.39 (t, 3H, CH_3, $J = 7.1$ Hz); 1.43–1.49 (m, 1H, $H_{4'}$); 1.70–1.77 (m, 2H, $H_{3'b-5'b}$); 1.82 (q, 2H, CH_2, $J = 7.2$ Hz); 2.72–2.81 (m, 2H, $H_{2'a-6'a}$); 4.13–4.22 (m, 4H, $H_{2'b-6'b}$, CH_2N); 4.31 (q, 2H, CH_2O, $J = 7.1$ Hz); 5.16 (s, 2H, CH_2–Ph); 6.46 (d, 1H, =CHCO, $J = 15.9$ Hz); 7.25–7.40 (m, 9H, H_2, H_5, H_6, H_7, Ph); 7.93 (d, 1H, CH=, $J = 15.9$ Hz); 7.94–7.95 (m, 1H, H_4)	14.4 (CH_3); 31.8 ($2CH_2$); 33.3 (CH); 36.3 (CH_2); 43.9 ($3CH_2$); 60.0 (OCH_2); 67.0 (CH_2Ph); 109.9 (CH); 112.3 (C); 112.7 (CH); 120.8 (CH); 121.3 (CH); 122.9 (CH); 126.2 (C); 127.8, 128.0, 128.5 (5CH); 131.8 (CH); 136.8 (C); 137.2 (C); 137.9 (CH); 155.2 (CO); 168.3 (CO)	461 [MH^+]
15	1623 (C=O), 1697 (C=O)	1.07–1.13 (m, 2H, $H_{3'a-5'a}$); 1.25–1.40 (m, 6H, CH_2, CH_3 and $H_{4'}$); 1.63–1.67 (m, 2H, $H_{3'b-5'b}$); 1.90 (q, 2H, CH_2N, $J = 7.4$ Hz); 2.68–2.75 (m, 2H, $H_{2'a-6'a}$); 4.11–4.20 (m, 4H, $H_{2'b-6'b}$, CH_2N); 4.30 (q, 2H, CH_2O, $J = 7.1$ Hz); 5.14 (s, 2H, CH_2Ph); 6.45 (d, 1H, =CHCO, $J = 15.9$ Hz); 7.27–7.40 (m, 9H, H_2, H_5, H_6, H_7, Ph); 7.92 (d, 1H, CH=, $J = 15.9$ Hz); 7.94–7.97 (m, 1H, H_4)	14.9 (CH_3); 27.5 (CH_2); 32.4 ($2CH_2$); 34.0 (CH_2); 36.1 (CH); 44.5 ($2CH_2$); 47.3 (CH_2); 60.4 (OCH_2); 67.4 (CH_2Ph); 110.4 (CH); 112.6 (C); 113.1 (CH); 121.2 (CH); 121.6 (CH); 123.3 (CH); 126.6 (C); 128.2, 128.3, 128.9 (5CH); 132.5 (CH); 137.3 (C); 137.7 (C); 138.4 (CH); 155.6 (N–C=O); 168.7 (CO)	475.5 [MH^+]
16	1619 (C=O), 1695 (C=O)	1.23–1.33 (m, 2H, $H_{3'a-5'a}$); 1.42 (t, 3H, CH_3, $J = 7.1$ Hz); 1.45–1.52 (m, 1H, $H_{4'}$); 1.68–1.74 (m, 2H, $H_{3'b-5'b}$); 1.84 (q, 2H, CH_2, $J = 7.5$ Hz); 2.22 (d, 3H, =C–CH_3, $J = 1.1$ Hz); 2.73–2.82 (m, 2H, $H_{2'a-6'a}$); 4.17–4.27 (m, 4H, $H_{2'b-6'b}$, CH_2N); 4.33 (q, 2H, CH_2O, $J = 7.1$ Hz); 5.17 (s, 2H, CH_2); 7.25–7.40 (m, 9H, H_2, H_5, H_6, H_7, Ph); 7.87 (d, 1H, H_4, $J = 7.3$ Hz); 8.08 (s, 1H, CH=)	14.9 (CH_3); 15.6 (CH_3); 32.3 ($2CH_2$); 34.0 (CH); 36.9 (CH_2); 44.4 ($2CH_2$); 44.6 (CH_2); 61.0 (OCH_2); 67.5 (CH_2Ph); 109.9 (CH); 112.5 (C); 119.6 (CH); 120.9 (CH); 122.7 (C); 123.2 (CH); 128.3, 128.4, 128.9 (5CH), 129.0 (C); 129.3 (CH); 130.2 (CH); 136.0 (C); 137.3 (C); 155.6 (N–C=O); 169.4 (CO)	475.5 [MH^+]

Table 3 (*Continued*)

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
17	1665 (C=O), 1693 (C=O), 2500–3500 (OH)	1.17–1.30 (m, 2H, $H_{3'a-5'a}$); 1.45–1.51 (m, 1H, $H_{4'}$); 1.65–1.75 (m, 2H, $H_{3'b-5'b}$); 1.83 (q, 2H, CH_2, $J = 7.0$ Hz); 2.68–2.78 (m, 2H, $H_{2'a-6'a}$); 4.10–4.22 (m, 4H, CH_2N, $H_{2'b-6'b}$); 5.10 (s, 2H, CH_2); 7.24–7.36 (m, 8H, H_5, H_6, H_7, Ph); 7.88 (s, 1H, H_2); 8.19–8.23 (m, 1H, H_4)	33.2 ($2CH_2$); 34.8 (CH); 37.8 (CH_2); 45.4 ($2CH_2$); 45.9 (CH_2); 68.5 (CH_2Ph); 108.0 (C); 111.4 (CH); 123.5 (CH); 123.7 (CH); 124.5 (CH); 128.4 (C), 129.3, 129.5, 130.0 (5CH); 136.6 (CH); 138.0 (C); 138.3 (C); 156.7 (NC=O); 171.8 (CO)	407 [MH^+]
18	1682 (C=O), 1715 (C=O)	1.22–1.33 (m, 2H, $H_{3'a-5'a}$); 1.45–1.55 (m, 1H, $H_{4'}$); 1.75–1.79 (m, 2H, $H_{3'b-5'b}$); 1.81 (q, 2H, CH_2, $J = 7.2$ Hz); 2.74–2.84 (m, 2H, $H_{2'a-6'a}$); 3.85 (s, 2H, C_3–CH_2); 4.18 (t, 2H, CH_2N, $J = 7.2$ Hz); 4.20–4.30 (m, 2H, $H_{2'b-6'b}$); 5.18 (s, 2H, CH_2); 7.13 (s, 1H, H_2); 7.18 (td, 1H, H_5, $J = 7.7$, 1.0 Hz); 7.28 (td, 1H, H_6, $J = 7.7$, 1.0 Hz); 7.35 (d, 1H, H_7, $J = 7.7$ Hz); 7.41 (s, 5H, Ph); 7.66 (d, 1H, H_4, $J = 7.7$ Hz)	33.9 (CH_2); 34.8 ($2CH_2$); 35.4 (CH); 39.6 (CH_2); 46.6 (CH_2); 47.0 ($2CH_2$); 70.1 (CH_2Ph); 109.5 (C); 112.3 (CH); 122.1 (CH); 122.3 (CH); 124.9 (CH); 129.6 (CH); 130.7 (C), 130.9, 131.0, 131.5 (5CH); 139.1 (C); 139.8 (C); 158.3 (NC=O); 179.9 (CO)	421 [MH^+]
19	1682 (C=O), 1701 (C=O), 2500–3500 (OH)	1.08–1.17 (m, 2H, $H_{3'a-5'a}$); 1.25–1.38 (m, 3H, $C_{4'}$–CH_2, $H_{4'}$); 1.63–1.68 (m, 2H, $H_{3'b-5'b}$); 1.87 (qt, 2H, CH_2, $J = 7.2$ Hz); 2.70–2.79 (m, 2H, $H_{2'a-6'a}$); 3.83 (s, 2H, C_3–CH_2); 4.10 (t, 2H, CH_2N, $J = 7.2$ Hz); 4.12–4.21 (m, 2H, $H_{2'b-6'b}$); 5.15 (s, 2H, CH_2); 7.10 (s, 1H, H_2); 7.17 (td, 1H, H_5, $J = 7.8$, 1.2 Hz); 7.24 (td, 1H, H_6, $J = 7.8$, 1.2 Hz); 7.30–7.38 (m, 6H, H_7, Ph); 7.63 (d, 1H, H_4, $J = 7.8$ Hz)	29.8 (CH_2); 33.4 (CH_2); 34.4 ($2CH_2$); 36.1 (CH_2); 38.1 (CH); 46.6 ($2CH_2$); 48.9 (CH_2); 69.4 (OCH_2Ph); 108.6 (C); 111.8 (CH); 121.5 (CH); 121.7 (CH); 124.2 (CH); 129.2 (CH); 130.1, 130.2, 130.3, 130.9 (5CH and C); 138.5 (C); 139.2 (C); 157.7 (CO); 180.1 (CO)	435 [MH^+]
20	1621 (C=O), 1696 (C=O), 2600–3600 (OH)	1.21–1.28 (m, 2H, $H_{3'a-5'a}$); 1.31–1.37 (m, 1H, $H_{4'}$); 1.73–1.78 (m, 2H, $H_{3'b-5'b}$); 1.86 (q, 2H, CH_2, $J = 7.4$ Hz); 2.73–2.83 (m, 2H, $H_{2'a-6'a}$); 4.18–4.24 (m, 4H, $H_{2'b-6'b}$, CH_2N); 5.15 (s, 2H, CH_2Ph); 6.45 (d, 1H, =CHCO, $J = 15.9$ Hz); 7.30–7.43 (m, 8H, H_5, H_6, H_7, Ph); 7.71 (s, 1H, H_2); 7.94–7.95 (m, 1H, H_4); 8.00 (d, 1H, CH=, $J = 15.9$ Hz)	33.3 ($2CH_2$); 34.9 (CH); 37.9 (CH_2); 45.4 and 45.6 ($3CH_2$); 68.6 (OCH_2Ph); 111.5 (CH); 113.1 (C); 113.7 (CH); 122.3 (CH); 123.1 (CH); 124.6 (CH); 127.7 (C); 129.4, 129.5, 130.0 (5CH); 131.2 (CH); 138.3 (C); 138.8 (C); 141.7 (CH); 156.7 (N–C=O); 174.7 (CO)	433 [MH^+]
21	1621 (C=O), 1697 (C=O), 2600–3600 (OH)	1.08–1.15 (m, 2H, $H_{3'a-5'a}$); 1.27–1.38 (m, 3H, CH_2, $H_{4'}$); 1.62–1.67 (m, 2H, $H_{3'b-5'b}$); 1.83–1.93 (m, 2H, CH_2); 2.69–2.79 (m, 2H, $H_{2'a-6'a}$); 4.13–4.19 (m, 4H, $H_{2'b-6'b}$, CH_2–N); 5.14 (s, 2H, CH_2); 6.45 (d, 1H, =CHCO, $J = 15.9$ Hz); 7.28–7.37 (m, 8H, H_5, H_6, H_7, Ph); 7.44 (s, 1H, H_2); 7.95–7.98 (m, 1H, H_4); 8.02 (d, 1H, CH=, $J = 15.9$ Hz)	27.8 (CH_2); 32.7 ($2CH_2$); 34.3 (CH_2); 36.4 (CH); 44.8 ($2CH_2$); 47.6 (CH_2); 67.7 (CH_2Ph); 110.8 (CH); 112.5 (C); 112.8 (CH); 121.5 (CH); 122.2 (CH); 123.7 (CH); 126.9 (C); 128.5; 128.6; 129.2 (5CH); 133.4 (CH); 137.6 (C); 138.1 (C); 140.8 (CH); 156.0 (NC=O); 174.2 (CO)	447.5 [MH^+]
22	1619 (C=O), 1694 (C=O), 2600–3600 (OH)	1.23–1.30 (m, 2H, $H_{3'a-5'a}$); 1.48–1.53 (m, 1H, $H_{4'}$); 1.75–1.80 (m, 2H, $H_{3'b-5'b}$); 1.89 (q, 2H, CH_2, $J = 7.1$ Hz); 2.23 (s, 3H, =C–CH_3); 2.74–2.84 (m, 2H, $H_{2'a-6'a}$); 4.23–4.29 (m, 4H, $H_{2'b-6'b}$, CH_2N); 5.16 (s, 2H, CH_2); 7.28–7.40 (m, 8H, H_5, H_6, H_7, Ph); 7.46 (s, 1H, H_2); 7.88 (d, 1H, H4, $J = 7.4$ Hz); 8.24 (s, 1H, CH=)	14.9 (CH_3); 31.9 ($2CH_2$); 33.6 (CH); 36.6 (CH_2); 44.0 ($2CH_2$); 44.4 (CH_2); 67.1 (CH_2Ph); 109.5 (CH); 112.2 (C); 119.3 (CH); 120.8 (C); 121.0 (CH); 123.0 (CH); 127.9, 128.0, 128.5 (5CH); 128.6 (C); 129.4 (CH); 132.2 (CH); 135.7 (C); 136.8 (C); 155.3 (NC=O); 174.2 (CO)	447.5 [MH^+]
23	1668 (C=O), 1734 (C=O), 3338 (NH)	1.12–1.28 (m, 2H, $H_{3'a-5'a}$); 1.30 (t, 3H, CH_3, $J = 7.1$ Hz); 1.40–1.50 (m, 1H, $H_{4'}$); 1.70–1.79 (m, 2H, $H_{3'b-5'b}$); 1.83 (q, 2H, CH_2, $J = 7.1$ Hz); 2.70 (t, 2H, $CH_{2\alpha}$, $J = 6.0$ Hz); 2.73–2.80 (m, 2H, $H_{2'a-6'a}$); 3.80 (q, 2H, $CH_{2\beta}$, $J = 6.0$ Hz); 4.16–4.25 (m, 6H, CH_2N, $H_{2'b-6'b}$, OCH_2); 5.14 (s, 2H, CH_2); 6.69–6.74 (m, 1H, NHCO); 7.27–7.40 (m, 8H, H_5, H_6, H_7, Ph); 7.73 (s, 1H, H_2); 7.96–8.00 (m, 1H, H_4)	15.8 (CH_3); 33.4 ($2CH_2$); 34.9 (CH); 35.9 (CH_2); 36.3 (CH_2); 38.0 (CH_2); 45.5 ($2CH_2$); 45.7 (CH_2); 62.4 (O–CH_2); 68.7 (CH_2–Ph); 111.7 (C); 112.7 (CH); 121.8 (CH); 123.2 (CH); 124.1 (CH); 126.9 (C); 129.5, 129.6, 130.1 (5CH); 133.0 (CH); 138.1 (C); 138.4 (C); 156.8 (N–C=O); 166.5 (CO); 174.8 (CO)	506.5 [MH^+]

Table 3 (*Continued*)

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
24	1694 (C=O), 1731 (C=O), 3326 (NH)	1.10 (t, 3H, CH_3, $J = 7.1$ Hz); 1.18–1.29 (m, 2H, $H_{3'a-5'a}$); 1.44–1.56 (m, 1H, $H_{4'}$); 1.70–1.76 (m, 2H, $H_{3'b-5'b}$); 1.80 (q, 2H, CH_2, $J = 7.1$ Hz); 2.44 (t, 2H, $CH_{2\alpha}$, $J = 6.1$ Hz); 2.71–2.81 (m, 2H, $H_{2'a-6'a}$), 3.43 (q, 2H, $CH_{2\beta}$, $J = 6.1$ Hz), 3.69 (s, 2H, C_3–CH_2), 3.93 (q, 2H, OCH_2, $J = 7.1$ Hz); 4.14 (t, 2H, CH_2N, $J = 7.1$ Hz); 4.14–4.24 (m, 2H, $H_{2'b-6'b}$); 5.12 (s, 2H, CH_2); 7.02 (s, 1H, H_2); 7.12 (td, 1H, H_5, $J = 7.2$, 1.1 Hz); 7.20 (td, 1H, H_6, $J = 7.2$, 1.1 Hz); 7.29–7.37 (m, 6H, H_7, Ph); 7.51 (d, 1H, H_4, $J = 7.2$ Hz)	13.9 (CH_3); 32.4 ($2CH_2$); 33.8 (CH_2 and CH); 34.5 (CH_2); 35.3 (CH_2); 37.1 (CH_2); 44.1 (CH_2); 44.4 ($2CH_2$); 60.9 (OCH_2); 67.5 (CH_2Ph); 107.5 (C); 109.3 (CH); 118.8 (CH); 119.4 (CH); 122.0 (CH); 126.7 (CH); 127.4 (C); 127.7, 127.8, 128.3 (5CH); 136.2 (C); 136.7 (C); 155.1 (N–C=O); 171.3 (CO); 171.9 (CO)	520.5 [MH^+]
25	1694 (C=O), 1731 (C=O), 3328 (NH)	1.14 (t, 3H, CH_3, $J = 7.2$ Hz); 1.26–1.35 (m, 4H, $C_{4'}$–CH_2, $H_{3'a-5'a}$); 1.44–1.56 (m, 1H, $H_{4'}$); 1.64–1.69 (m, 2H, $H_{3'b-5'b}$); 1.85–1.91 (m, 2H, –CH_2); 2.47 (t, 2H, $CH_{2\alpha}$, $J = 6.1$ Hz); 2.70–2.80 (m, 2H, $H_{2'a-6'a}$); 3.46 (q, 2H, $CH_{2\beta}$, $J = 6.1$ Hz); 3.72 (s, 2H, C_3–CH_2); 3.96 (q, 2H, OCH_2, $J = 7.2$ Hz); 4.09–4.19 (m, 4H, CH_2N, $H_{2'b-6'b}$); 5.14 (s, 2H, CH_2Ph); 6.19–6.23 (m, 1H, NHCO); 7.05 (s, 1H, H_2); 7.14 (td, 1H, H_5, $J = 7.8$, 1.1 Hz); 7.26 (td, 1H, H_6, $J = 7.8$, 1.1 Hz); 7.29–7.37 (m, 6H, H_7, Ph); 7.53 (d, 1H, H_4, $J = 7.8$ Hz)	14.1 (CH_3); 27.4 (CH_2); 31.9 ($2CH_2$); 33.5 (CH_2); 33.7 (CH_2); 34.1 (CH_2); 34.9 (CH); 35.7 (CH_2); 44.1 ($2CH_2$); 46.5 (CH_2); 60.5 (OCH_2); 67.0 (OCH_2Ph); 107.4 (C); 109.6 (CH); 118.9 (CH); 119.5 (CH); 122.0 (CH); 127.1 (CH); 127.5 (C); 127.8, 127.9 and 128.5 (5CH); 136.4 (C); 136.9 (C); 155.3 (NC=O); 171.6 (CO); 172.0 (CO)	534.5 [MH^+]
26	1654 (C=O), 1699 (C=O), 1735 (C=O), 3285 (NH)	1.19–1.28 (m, 2H, $H_{3'a-5'a}$); 1.31 (t, 3H, CH_3, $J = 7.1$ Hz); 1.40–1.50 (m, 1H, $H_{4'}$); 1.70–1.83 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.65 (t, 2H, $CH_{2\alpha}$, $J = 5.9$ Hz); 2.70–2.80 (m, 2H, $H_{2'a-6'a}$); 3.70 (q, 2H, $CH_{2\beta}$, $J = 5.9$ Hz); 4.13–4.25 (m, 6H, $H_{2'b-6'b}$, CH_2N, CH_2O); 5.15 (s, 2H, CH_2); 6.24–6.26 (m, 1H, NHCO); 6.40 (d, 1H, =CHCO, $J = 15.6$ Hz); 7.24–7.39 (m, 8H, H_2, H_5, H_6, H_7, Ph); 7.85 (d, 1H, CH=, $J = 15.6$ Hz); 7.91 (dd, 1H, H_4, $J = 7.0$, 1.5 Hz)	15.1 (CH_3); 32.8 ($2CH_2$); 34.3 (CH); 35.2 (CH_2); 35.9 (CH_2); 37.3 (CH_2); 44.9 ($3CH_2$); 61.7 (O–CH_2); 68.0 (CH_2–Ph); 110.8 (CH); 113.2 (C); 116.4 (CH); 121.6 (CH); 121.9 (CH); 123.7 (CH); 127.1 (C); 128.8, 128.9, 129.4 (5CH); 132.1 (CH); 135.3 (CH); 137.8 (C); 138.1 (C); 156.2 (NC=O); 168.0 (CO); 173.9 (CO)	532.5 [MH^+]
27	1688 (C=O), 1728 (C=O), 3340 (NH)	1.08–1.18 (m, 2H, $H_{3'a-5'a}$); 1.24–1.34 (m, 6H, CH_2, CH_3, $H_{4'}$); 1.62–1.67 (m, 2H, $H_{3'b-5'b}$); 1.88 (m, 2H, CH_2); 2.65 (t, 2H, $CH_{2\alpha}$COOEt, $J = 6.0$ Hz); 2.67–2.77 (m, 2H, $H_{2'a-6'a}$); 3.70 (q, 2H, $CH_{2\beta}$, $J = 6.0$ Hz); 4.09–4.25 (m, 6H, $H_{2'b-6'b}$, CH_2N, CH_2O); 5.14 (s, 2H, CH_2Ph); 6.22–6.24 (m, 1H, NHCO); 6.39 (d, 1H, =CHCO, $J = 15.6$ Hz); 7.24–7.38 (m, 8H, H_2, H_5, H_6, H_7, Ph); 7.85 (d, 1H, CH=, $J = 15.6$ Hz); 7.90 (dd, 1H, H_4, $J = 7.0$, 2.0 Hz)	14.4 (CH_3); 27.3 (CH_2); 32.1 ($2CH_2$); 33.8 (CH_2); 34.5 (CH_2); 35.3 (CH_2); 35.8 (CH); 44.3 ($2CH_2$); 47.0 (CH_2); 60.9 (OCH_2); 67.2 (CH_2Ph); 110.2 (CH); 112.3 (C); 115.6 (CH); 120.8 (CH); 121.1 (CH); 122.9 (CH); 126.4 (C); 128.0, 128.1, 128.7 (5CH); 131.7 (CH); 134.6 (CH); 137.1 (C); 137.4 (C); 155.5 (NC=O); 167.4 (CO); 173.1 (CO)	546.5 [MH^+]
28	1653 (C=O), 1731 (C=O), 3307 (NH)	1.20–1.35 (m, 5H, $H_{3'a-5'a}$, CH_3); 1.40–1.50 (m, 1H, $H_{4'}$); 1.68–1.87 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.65 (d, 2H, $CH_{2\alpha}$COOEt, $J = 5.5$ Hz); 2.72–2.81 (m, 2H, $H_{2'a-6'a}$); 3.74 (s, 3H, CH_3); 4.11–4.20 (m, 4H, $H_{2'b-6'b}$, CH_2N); 4.51–4.59 (m, 1H, CH_β); 5.15 (s, 2H, CH_2); 6.19–6.22 (m, 1H, NHCO); 6.39 (d, 1H, =CHCO, $J = 15.6$ Hz); 7.22–7.39 (m, 8H, H_2, H_5, H_6, H_7, Ph); 7.84 (d, 1H, CH=, $J = 15.6$ Hz); 7.92 (dd, 1H, H_4, $J = 7.0$, 1.8 Hz)	20.2 (CH_3); 31.8 ($2CH_2$); 33.3 (CH); 36.3 (CH_2); 39.9 (CH_2); 42.0 (CH); 43.9 ($3CH_2$); 51.7 (OCH_3); 67.0 (CH_2Ph); 109.8 (CH); 112.3 (C); 115.7 (CH); 120.7 (CH); 120.9 (CH); 122.7 (CH); 126.2 (C), 127.8, 128.0, 128.4 (5CH); 131.1 (CH); 134.2 (CH); 136.8 (C); 137.1 (C); 155.2 (N–C=O); 166.4 (CO), 172.4 (CO)	532.5 [MH^+]

Table 3 (*Continued*)

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
29	1654 (C=O), 1698 (C=O), 1737 (C=O), 3288 (NH)	1.05–1.16 (m, 2H, $H_{3'a-5'a}$); 1.21–1.26 (m, 2H, CH_2); 1.31 (d, 3H, CH_3, $J = 6.9$ Hz); 1.33–1.38 (m, 1H, $H_{4'}$); 1.57–1.64 (m, 2H, $H_{3'b-5'b}$); 1.83–1.90 (m, 2H, CH_2); 2.62 (d, 2H, $CH_{2\alpha}$COOEt, $J = 5.1$ Hz); 2.66–2.76 (m, 2H, $H_{2'a-6'a}$); 3.72 (s, 3H, OCH_3); 4.07–4.20 (m, 4H, $H_{2'b-6'b}$, CH_2N); 4.48–4.56 (m, 1H, CH_β); 5.11 (s, 2H, CH_2); 6.12–6.15 (m, 1H, NHCO); 6.35 (d, 1H, =CHCO, $J = 15.5$ Hz); 7.19–7.39 (m, 9H, H_2, H_5, H_6, H_7, Ph); 7.82 (d, 1H, CH=, $J = 15.5$ Hz); 7.89 (d, 1H, H_4, $J = 6.8$ Hz)	20.2 (CH_3); 27.1 (CH_2); 31.9 ($2CH_2$); 33.6 (CH_2); 35.6 (CH); 39.9 (CH_2); 41.9 (CH); 44.1 ($2CH_2$); 46.7 (CH_2); 51.7 (OCH_3); 66.9 (CH_2Ph); 109.9 (CH); 112.1 (C); 115.6 (CH); 120.7 (CH); 120.9 (CH); 122.6 (CH); 126.2 (C); 127.8, 127.9 and 128.5 (5CH), 131.4 (CH); 134.3 (CH); 136.9 (C); 137.2 (C); 155.2 (N–C=O); 166.4 (CO), 172.4 (CO)	546.5 [MH^+]
30	1693 (C=O), 1729 (C=O), 3366 (NH)	1.22–1.34 (m, 5H, $H_{3'a-5'a}$, CH_3); 1.42–1.50 (m, 1H, $H_{4'}$); 1.73–1.90 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.19 (d, 3H, =C–CH_3, $J = 1.0$ Hz); 2.67 (t, 2H, $CH_{2\alpha}$COOEt, $J = 5.9$ Hz); 2.72–2.82 (m, 2H, $H_{2'a-6'a}$); 3.71 (q, 2H, $CH_{2\beta}$, $J = 5.9$ Hz); 4.17–4.26 (m, 6H, $H_{2'b-6'b}$, CH_2N, OCH_2); 5.15 (s, 2H, CH_2); 6.56–6.61 (m, 1H, NHCO); 7.19–7.39 (m, 9H, H_2, H_5, H_6, H_7, Ph); 7.67 (s, 1H, CH=); 7.80 (d, 1H, H_4, $J = 7.5$ Hz)	14.6 (CH_3); 15.8 (CH_3); 32.2 ($2CH_2$); 33.8 (CH); 34.5 (CH_2); 35.9 (CH_2); 36.9 (CH_2); 44.3 ($3CH_2$); 61.0 (OCH_2); 67.4 (CH_2Ph); 109.8 (CH); 112.2 (C); 119.6 (CH); 120.6 (CH); 122.9 (CH); 125.6 (CH); 127.8 (C); 128.2, 128.3, 128.4 (5CH); 128.6 (C); 128.9 (CH); 136.0 (C); 137.2 (C); 155.6 (N–C=O); 170.2 (CO); 173.1 (CO)	546.5 [MH^+]
31	1624 (C=O), 1731 (C=O), 3292 and 3397 (NH)	1.21–1.36 (m, 5H, $H_{3'a-5'a}$, CH_3); 1.41–1.46 (m, 1H, $H_{4'}$); 1.73–1.89 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.25 (br s, 1H, NH); 2.57–2.67 (m, 2H, $H_{2'a-6'a}$); 2.71 (t, 2H, $CH_{2\alpha}$COOEt, $J = 6.0$ Hz); 3.10–3.16 (m, 2H, $H_{2'b-6'b}$); 3.80 (q, 2H, $CH_{2\beta}$, $J = 6.0$ Hz); 4.16–4.26 (m, 4H, CH_2N, OCH_2); 6.69–6.75 (m, 1H, NHCO); 7.26–7.41 (m, 3H, H_5, H_6, H_7); 7.74 (s, 1H, H_2); 7.95–7.99 (m, 1H, H_4)	14.3 (CH_3); 32.1 ($2CH_2$); 33.7 (CH); 34.4 (CH_2); 34.8 (CH_2); 36.3 (CH_2); 43.9 (CH_2); 44.5 ($2CH_2$); 60.9 (OCH_2); 110.2 (C); 111.0 (CH); 120.4 (CH); 121.7 (CH); 122.6 (CH); 125.4 (C); 131.5 (CH); 136.5 (C); 165.1 (CO); 173.2 (CO)	372 [MH^+]
32	1645 (C=O), 1729 (C=O), 3295 and 3411 (NH)	1.15 (t, 3H, CH_3, $J = 7.2$ Hz); 1.26–1.38 (m, 2H, $H_{3'a-5'a}$); 1.42–1.58 (m, 1H, $H_{4'}$); 1.75–1.78 (m, 2H, $H_{3'b-5'b}$); 1.83 (q, 2H, CH_2, $J = 7.3$ Hz); 2.28 (br s, 1H, NH); 2.48 (t, 2H, $CH_{2\alpha}$COOEt, $J = 6.2$ Hz); 2.57–2.66 (m, 2H, $H_{2'a-6'a}$); 3.11–3.13 (m, 2H, $H_{2'b-6'b}$); 3.47 (q, 2H, $CH_{2\beta}$, $J = 6.2$ Hz); 3.73 (s, 2H, C_3–CH_2); 3.97 (q, 2H, OCH_2, $J = 7.2$ Hz), 4.17 (t, 2H, CH_2N, $J = 7.3$ Hz); 6.27 (m, 1H, NHCO); 7.07 (s, 1H, H_2); 7.18 (td, 1H, H_5, $J = 8.0$, 1.0 Hz); 7.27 (td, 1H, H_6, $J = 8.0$, 1.0 Hz); 7.36 (d, 1H, H_7, $J = 8.0$ Hz); 7.54 (d, 1H, H_4, $J = 8.0$ Hz)	14.0 (CH_3); 32.1 ($2CH_2$); 33.1 (CH); 33.4 (CH_2); 34.1 (CH_2); 34.9 (CH_2); 36.9 (CH_2); 43.5 (CH_2); 44.0 ($2CH_2$); 60.5 (OCH_2); 107.7 (C); 109.5 (CH); 118.9 (CH); 119.5 (CH); 122.1 (CH); 126.9 (CH); 127.5 (C); 136.0 (C); 171.5 (CO) 172.1 (CO)	386 [MH^+]
33	1652 (C=O), 1731 (C=O), 3286 and 3405 (NH)	^{1}H-NMR (CDCl3) δ 1.12 (t, 3H, CH_3, $J = 7.1$ Hz); 1.19–1.32 (m, 5H, $H_{3'a-5'a}$, $H_{4'}$, CH_2); 1.64–1.70 (m, 2H, $H_{3'b-5'b}$); 1.85 (m, 2H, CH_2); 2.45 (t, 2H, $CH_{2\alpha}$COOEt, $J = 6.1$ Hz); 2.58–2.63 (m, 2H, $H_{2'a-6'a}$); 3.08–3.13 (m, 2H, $H_{2'b-6'b}$); 3.43 (q, 2H, $CH_{2\beta}$, $J = 6.1$ Hz); 3.69 (s, 2H, C_3–CH_2); 3.94 (q, 2H, OCH_2, $J = 7.1$ Hz); 4.08 (t, 2H, CH_2N, $J = 7.2$ Hz); 6.18–6.28 (m, 1H, NHCO); 7.03 (s, 1H, H_2); 7.11 (td, 1H, H_5, $J = 8.0$, 1.0 Hz); 7.23 (td, 1H, H_6, $J = 8.0$, 1.0 Hz); 7.32 (d, 1H, H_7, $J = 8.0$ Hz); 7.50 (d, 1H, H_4, $J = 8.0$ Hz)	14.0 (CH_3); 27.3 (CH_2); 32.5 ($2CH_2$); 33.4 (CH_2); 34.1 (CH_2 and CH); 34.9 (CH_2); 35.6 (CH_2); 46.1 (CH_2); 46.5 ($2CH_2$); 60.5 (OCH_2); 107.4 (C); 109.6 (CH); 118.8 (CH); 119.4 (CH); 122.0 (CH); 127.2 (CH); 127.5 (C); 136.4 (C); 171.6 (CO); 172.0 (CO)	400 [MH^+]

Table 3 (*Continued*)

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
34	1652 (C=O), 1731 (C=O), 3291 (NH)	1.25 (t, 3H, CH_3, $J = 7.1$ Hz); 1.31–1.40 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.75–1.83 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.21 (br s, 1H, NH); 2.46 (t, 2H, $CH_{2\alpha}COOEt$, $J = 6.0$ Hz); 2.57 (t, 2H, C_3–CH_2, $J = 7.5$ Hz); 2.60–2.68 (m, 2H, $H_{2'a-6'a}$); 3.04–3.19 (m, 4H, CH_2CONH, $H_{2'b-6'b}$); 3.49 (q, 2H, $CH_{2\beta}$, $J = 6.0$ Hz); 4.07–4.15 (m, 4H, CH_2N, CH_2O); 5.98–6.02 (m, 1H, NHCO); 6.92 (s, 1H, H_2); 7.11 (td, 1H, H_5 or H_6, $J = 7.0$, 1.2 Hz); 7.22 (td, 2H, H_5 or H_6, $J = 7.0$, 1.2 Hz); 7.30 (d, 1H, H_7, $J = 7.0$ Hz); 7.60 (d, 1H, H_4, $J = 7.0$ Hz	14.1 (CH_3); 21.2 (CH_2); 33.2 ($2CH_2$); 33.8 (CH); 34.0 (CH_2); 34.7 (CH_2); 37.3 (CH_2); 37.4 (CH_2); 43.4 (CH_2); 46.4 ($2CH_2$); 60.6 (OCH_2); 109.2 (CH); 113.6 (C); 118.7 (CH); 118.9 (CH); 121.4 (CH); 125.2 (CH); 127.6 (C); 136.2 (C); 172.5 (CO); 172.7 (CO)	400 [MH^+]
35	1650 (C=O), 1731 (C=O), 3272 (NH)	1.12–1.32 (m, 8H, CH_3, CH_2, $H_{3'a-5'a}$, $H_{4'}$); 1.65–1.71 (m, 2H, $H_{3'b-5'b}$); 1.83 (m, 2H, CH_2); 2.46 (t, 2H, $CH_{2\alpha}COOEt$, $J = 6.0$ Hz); 2.53–2.63 (m, 4H, C_3–CH_2, $H_{2'a-6'a}$); 3.04–3.14 (m, 4H, CH_2CONH, $H_{2'b-6'b}$); 3.48 (q, 2H, $CH_{2\beta}$, $J = 6.0$ Hz); 4.02–4.14 (m, 4H, CH_2N, CH_2O); 6.01–6.04 (m, 1H, NHCO); 6.92 (s, 1H, H_2); 7.11 (td, 1H, H_5 or H_6, $J = 7.1$, 1.1 Hz); 7.21 (td, 1H, H_5 or H_6, $J = 7.1$, 1.1 Hz); 7.30 (d, 1H, H_7, $J = 7.1$ Hz); 7.60 (d, 1H, H_4, $J = 7.1$ Hz)	14.5 (CH_3); 21.5 (CH_2); 27.5 (CH_2); 29.1 ($2CH_2$); 33.4 (CH_2); 34.2 (CH); 34.3 (CH_2); 35.0 (CH_2); 37.7 (CH_2); 44.3 ($2CH_2$); 46.3 (CH_2); 61.0 (OCH_2); 109.5 (CH); 114.0 (C); 119.1 (CH); 119.3 (CH); 121.9 (CH); 125.5 (CH); 128.0 (C); 136.5 (C); 172.8 (CO); 173.1 (CO)	414 [MH^+]
36	1653 (C=O), 1725 (C=O), 3287 and 3425 (NH)	1.09 (d, 3H, CH–CH_3, $J = 6.8$ Hz); 1.15–1.26 (m, 2H, $H_{3'a-5'a}$); 1.30–143 (m, 1H, $H_{4'}$); 1.68–1.76 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.37–2.43 (m, 2H, $CH_{2\alpha}COOMe$); 2.47–2.60 (m, 4H, C_3–CH_2, $H_{2'a-6'a}$); 3.03–3.10 (m, 2H, CH_2CO, $H_{2'b-6'b}$); 3.61 (s, 3H, OCH_3); 4.05 (t, 2H, CH_2N, $J = 7.4$ Hz); 4.25–4.33 (m, 1H, CH_β); 6.17–6.21 (m, 1H, NHCO); 6.89 (s; 1H; H_2); 7.07 (t, 1H, H_5, $J = 7.8$ Hz); 7.18 (t, 1H, H_6, $J = 7.8$ Hz); 7.26 (d, 1H, H_7, $J = 7.8$ Hz); 7.57 (d, 1H, H_4, $J = 7.8$ Hz)	21.3 (CH_3); 23.2 (CH_2); 34.7 ($2CH_2$); 35.5 (CH); 39.1 (CH_2); 39.5 (CH_2); 41.8 (CH_2); 43.8 (CH); 45.3 (CH_2); 48.0 ($2CH_2$); 53.5 (OCH_2); 111.1 (CH); 115.5 (C); 120.6 (CH); 120.8 (CH); 123.4 (CH); 127.1 (CH); 129.6 (C); 138.1 (C); 173.9 (CO); 174.0 (CO)	400 [MH^+]
37	1643 (C=O), 1731 (C=O), 3283 and 3418 (NH)	1.12 (d, 3H, CH–CH_3, $J = 6.8$ Hz); 1.19–1.39 (m, 5H, $H_{3'a-5'a}$, CH_2, $H_{4'}$); 1.63–1.69 (m, 2H, $H_{3'b-5'b}$); 1.83 (qt, 2H, CH_2, $J = 7.4$ Hz); 2.41–2.45 (m, 2H, $CH_{2\alpha}COOMe$); 2.52–2.62 (m, 4H, C_3–CH_2; $H_{2'a-6'a}$); 3.08–3.14 (m, 4H, CH_2CO, $H_{2'b-6'b}$); 3.64 (s, 3H, OCH_3); 4.04 (t, 2H, CH_2N, $J = 7.4$ Hz); 4.28–4.39 (m, 1H, CH_β); 5.98–6.01 (m, 1H, NHCO); 6.92 (s, 1H, H_2); 7.10 (t, 1H, H_5, $J = 7.1$ Hz); 7.21 (t, 1H, H_6, $J = 7.1$ Hz); 7.30 (d, 1H, H_7, $J = 7.1$ Hz); 7.61 (d, 1H, H_4, $J = 7.1$ Hz)	19.9 (CH_3); 21.2 (CH_2); 27.3 (CH_2); 32.6 ($2CH_2$); 34.1 (CH_2); 35.6 (CH); 37.6 (CH_2); 39.8 (CH_2); 41.8 (CH); 46.1 and 46.3 ($3CH_2$); 51.6 (OCH_2); 109.3 (CH); 113.4 (C); 118.7 (CH); 118.9 (CH); 121.4 (CH); 125.3 (CH); 127.6 (C); 136.3 (C); 171.9 (CO); 172.0 (CO)	414 [MH^+]
38	1652 (C=O), 1731 (C=O), 3290 (NH)	1.18–1.40 (m, 9H, CH–CH_3, CH_3, $H_{3'a-5'a}$, $H_{4'}$); 1.72–1.78 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.20–2.48 (m, 1H, $CH(CH_3)$); 2.54–2.64 (m, 4H, $CH_{2\alpha}COOEt$, $H_{2'a-6'a}$); 2.78–3.14 (m, 4H, C_3–CH_2, $H_{2'b-6'b}$); 3.36–3.41 (m, 2H, $CH_{2\beta}$); 3.83 (br s, 1H, NH); 4.00–4.12 (m, 4H, CH_2N, OCH_2); 5.91–5.95 (m, 1H, NHCO); 6.90 (s, 1H, H_2); 7.09 (t, 1H, H_5, $J = 7.8$ Hz); 7.19 (t, 1H, H_6, $J = 7.8$ Hz); 7.27 (d, 1H, H_7, $J = 7.8$ Hz); 7.58 (d, 1H, H_4, $J = 7.8$ Hz)	14.3 (CH_3); 20.0 (CH_3); 20.7 (CH); 32.0 ($2CH_2$); 34.8 (CH); 36.2 (CH_2); 36.8 (CH_2); 38.7 (CH_2); 44.8 ($2CH_2$); 45.4 (CH_2); 47.0 (CH_2); 60.3 (OCH_2); 111.3 (CH); 114.9 (C); 121.1 (CH); 121.3 (CH); 123.7 (CH); 128.0 (CH); 130.2 (C); 138.2 (C); 174.6 (CO); 178.3 (CO)	414 [MH^+]
39	1625 (C=O), 1726 (C=O), 2500–3600 (NH_2^+, OH)	1.32–1.56 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.72–1.81 (m, 2H, CH_2); 1.84–1.90 (m, 2H, $H_{3'b-5'b}$); 2.50–2.56 (m, 2H, $CH_{2\alpha}COOH$); 2.79–2.87 (m, 2H, $H_{2'a-6'a}$); 3.21–3.26 (m, 2H, $H_{2'b-6'b}$); 3.44–3.48 (m, 2H, $CH_{2\beta}$); 4.24 (t, 2H, CH_2N, $J = 7.0$ Hz); 7.14 (t, 1H, H_5, $J = 7.1$ Hz); 7.21 (t, 1H, H_6, $J = 7.1$ Hz); 7.53 (d, 1H, H_7, $J = 7.1$ Hz); 7.94–7.96 (m, 1H, NHCO), 8.09 (s, 1H, H_2); 8.13 (d, 1H, H_4, $J = 7.1$ Hz); 8.58 and 8.79 (2 br s, 2H, NH, HCl)	31.0 ($2CH_2$); 33.6 (CH); 37.3 (CH_2); 37.8 (CH_2); 38.5 (CH_2); 45.8 ($2CH_2$); 46.2 (CH_2); 112.7 (C); 113.2 (CH); 123.6 (CH); 124.2 (CH); 124.9 (CH); 129.5 (C); 133.8 (CH); 138.8 (C); 167.3 (CO); 176.1 (CO)	344 [MH^+]

Table 3 (*Continued*)

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
40	1652 (C=O), 1731 (C=O), 2500–3600 (NH_2^+, OH)	1.33–1.43 (m, 2H, $H_{3'a-5'a}$); 1.43–1.53 (m, 1H, $H_{4'}$); 1.70 (q, 2H, CH_2, $J = 7.2$ Hz); 1.83–1.88 (m, 2H, $H_{3'b-5'b}$); 2.38 (t, 2H, $CH_{2\alpha}COOH$, $J = 6.8$ Hz); 2.75–2.84 (m, 2H, $H_{2'a-6'a}$); 3.17 (s, 2H, C_3–CH_2); 3.18–3.24 (m, 2H, $H_{2'b-6'b}$); 3.27 (q, 2H, $CH_{2\beta}$, $J = 6.8$ Hz); 4.16 (t, 2H, CH_2N, $J = 7.2$ Hz); 7.00 (t, 1H, H_5, $J = 7.5$ Hz); 7.13 (t, 1H, H_6, $J = 7.5$ Hz); 7.24 (s, 1H, H_2); 7.42 (d, 1H, H_7, $J = 7.5$ Hz); 7.54 (d, 1H, H_4, $J = 7.5$ Hz); 8.04 (m, 1H, NHCO); 8.54 and 8.78 (2 br s, 2H, NH, HCl)	32.3 ($2CH_2$); 33.4 (CH); 33.6 (CH_2); 34.3 (CH_2); 35.1 (CH_2); 37.2 (CH_2); 43.6 (CH_2); 43.9 ($2CH_2$); 107.9 (C); 109.6 (CH); 118.9 (CH); 119.7 (CH); 122.3 (CH); 126.8 (CH); 127.7 (C); 136.2 (C); 170.9 (CO); 180.1 (CO)	358 [MH^+]
41	1653 (C=O), 1729 (C=O), 2500–3600 (NH_2^+, OH)	0.85–0.99 (m, 5H, $H_{3'a-5'a}$, $H_{4'}$, CH_2–$C_{4'}$); 1.42–1.47 (m, 4H, CH_2, $H_{3'b-5'b}$); 2.16 (t, 2H, $CH_{2\alpha}COOH$, $J = 6.5$ Hz); 2.48–2.57 (m, 2H, $H_{2'a-6'a}$); 3.03–3.08 (m, 2H, $H_{2'b-6'b}$); 3.17 (t, 2H, $CH_{2\beta}$, $J = 6.5$ Hz); 3.44 (s, 2H, C_3–CH_2); 3.76 (br s, 2H, CH_2N); 4.63 (s, HOD), 6.86–6.96 (m, 2H, H_2, H_5); 7.04 (t, 1H, H_6, $J = 7.9$ Hz); 7.12 (d, 1H, H_7, $J = 7.9$ Hz); 7.37 (d, 1H, H_4, $J = 7.9$ Hz)	25.9 (CH_2); 27.8 ($2CH_2$); 31.9 (CH_2); 32.1 (CH); 35.9 ($2CH_2$); 36.2 (CH_2); 43.5 ($2CH_2$); 45.2 (CH_2); 106.4 (C); 109.8 (CH); 118.3 (CH); 119.0 (CH); 121.4 (CH); 125.5 (C); 127.8 (CH); 135.7 (C); 174.3 (CO); 179.3 (CO)	372 [MH^+]
42	1636 (C=O), 1730 (C=O), 2500–3500 (NH_2^+, OH)	1.35–1.50 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.66–1.69 (m, 2H, CH_2); 1.81–1.86 (m, 2H, $H_{3'b-5'b}$); 2.34–2.44 (m, 4H, C_3–CH_2, $CH_{2\alpha}COOH$); 2.71–2.80 (m, 2H, $H_{2'a-6'a}$); 2.86–2.92 (m, 2H, CH_2CONH); 3.18–3.28 (m, 4H, $CH_{2\beta}$, $H_{2'b-6'b}$); 4.13 (t, 2H, CH_2–N, $J = 7.0$ Hz); 7.00 (t, 1H, H_5, $J = 7.8$ Hz); 7.09–7.18 (m, 2H, H_2, H_6); 7.40 (d, 1H, H_7, $J = 7.8$ Hz); 7.53 (d, 1H, H_4, $J = 7.8$ Hz); 7.98–8.02 (m, 1H, NHCO); 8.83 and 9.00 (2 br s, 2H, NH, HCl)	22.8 (CH_2); 30.0 ($2CH_2$); 32.7 (CH); 35.8 (CH_2); 36.6 (CH_2); 37.7 (CH_2); 38.0 (CH_2); 44.5 (CH_2); 44.7 ($2CH_2$); 111.4 (CH); 115.3 (C); 120.1 (CH); 120.6 (CH); 122.9 (CH); 127.4 (CH); 129.3 (C); 137.7 (C); 173.5 (CO); 174.8 (CO)	372 [MH^+]
43	1634 (C=O), 1727 (C=O), 2500–3500 (NH_2^+, OH)	1.10–1.22 (m, 4H, $H_{3'a-5'a}$, CH_2); 1.40–1.50 (m, 1H, $H_{4'}$); 1.69–1.75 (m, 4H, CH_2, $H_{3'b-5'b}$); 2.34–2.44 (m, 4H, C_3–CH_2, $CH_{2\alpha}COOH$); 2.73–2.81 (m, 2H, $H_{2'a-6'a}$); 2.87 (t, 2H, CH_2CONH, $J = 7.4$ Hz); 3.15–3.28 (m, 4H, $CH_{2\beta}$, $H_{2'b-6'b}$); 4.19 (t, 2H, CH_2–N, $J = 6.9$ Hz); 6.99 (t, 1H, H_5, $J = 7.7$ Hz); 7.08–7.16 (m, 2H, H_2, H_6); 7.40 (d, 1H, H_7, $J = 7.7$ Hz); 7.53 (d, 1H, H_4, $J = 7.7$ Hz); 7.97–8.00 (m, 1H, NHCO); 8.73 and 8.99 (2 br s, 2H, NH, HCl)	22.1 (CH_2); 28.0 (CH_2); 29.4 ($2CH_2$); 33.8 (CH_2); 35.0 (CH and CH_2); 37.3 (CH_2); 37.7 (CH_2); 44.2 ($2CH_2$); 46.4 (CH_2); 110.8 (C); 114.5 (CH); 119.4 (CH); 119.9 (CH); 122.2 (CH); 126.6 (C); 128.6 (CH); 137.1 (C); 172.1 (CO); 174.1 (CO)	386 [MH^+]
44	1635 (C=O), 1724 (C=O), 2500–3600 (NH_2^+, OH)	1.06 (d, 3H, CH_3, $J = 6.8$ Hz); 1.40–1.46 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.65–1.70 (m, 2H, CH_2); 1.81–1.86 (m, 2H, $H_{3'b-5'b}$); 2.39–2.47 (m, 4H, $CH_{2\alpha}COOH$, C_3–CH_2); 2.73–2.82 (m, 2H, $H_{2'a-6'a}$); 2.90 (t, 2H, CH_2–CO–NH, $J = 7.5$ Hz); 3.18–3.24 (m, 2H, $H_{2'b-6'b}$); 4.03–4.16 (m, 3H, CH_2–N, CH_β); 7.00 (t, 1H, H_5, $J = 7.9$ Hz); 7.12 (t, 1H, H_6, $J = 7.9$ Hz); 7.15 (s, 1H, H_2); 7.40 (d, 1H, H_7, $J = 7.8$ Hz); 7.54 (d, 1H, H_4, $J = 7.8$ Hz); 7.85–7.88 (m, 1H, NH–CO); 8.87 and 9.06 (2 br s, 2H, NH, HCl)	22.1 (CH_3); 22.9 (CH_2); 30.0 ($2CH_2$); 32.8 (CH); 37.8 (CH_2); 38.3 (CH_2); 42.7 (CH_2); 43.6 (CH); 44.6 (CH_2); 44.8 ($2CH_2$); 111.4 (CH); 115.4 (C); 120.2 (CH); 120.7 (CH); 123.0 (CH); 127.4 (CH); 129.4 (C); 137.8 (C); 173.0 (CO); 174.4 (CO)	386 [MH^+]
46	1637 (C=O), 1719 (C=O), 2500–3600 (NH_2^+, OH)	0.99 (d, 3H, CH_3, $J = 6.2$ Hz); 1.33–1.42 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.65–1.71 (m, 2H, CH_2); 1.81–1.86 (m, 2H, $H_{3'b-5'b}$); 2.32 (t, 2H, $CH_{2\alpha}COOH$, $J = 6.5$ Hz); 2.57–2.63 (m, 1H, CHCO); 2.73–2.82 (m, 2H, $H_{2'a-6'a}$); 2.90–2.95 (m, 2H, C_3–CH_2); 3.20–3.25 (m, 4H, $H_{2'b-6'b}$, $CH_{2\beta}$); 4.14 (t, 2H, CH_2N, $J = 7.1$ Hz); 7.00 (t, 1H, H_5, $J = 7.7$ Hz); 7.18–7.14 (m, 1H, H_6, H_2); 7.40 (d, 1H, H_7, $J = 7.7$ Hz); 7.55 (d, 1H, H_4, $J = 7.7$ Hz); 7.89–7.93 (m, 1H, NHCO); 8.69 and 8.87 (2 br s, 2H, NH, HCl)	17.0 (CH_3); 27.4 ($2CH_2$); 28.4 (CH); 30.1 (CH_2); 33.2 (CH_2); 34.0 (CH_2); 35.1 (CH_2); 39.8 (CH); 41.9 (CH_2); 42.2 ($2CH_2$); 108.7 (CH); 111.3 (C); 117.5 (CH); 118.2 (CH); 120.2 (CH); 125.6 (C); 127.0 (CH); 135.0 (C); 172.2 (CO); 174.9 (CO)	386 [MH^+]

Table 3 (*Continued*)

Compound	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (IS): m/z
48	1162 (SO_2), 1686 (C=O), 1745 (C=O), 3332 (NH)	1.01–1.15 (m, 2H, $H_{3'a-5'a}$); 1.22–1.31 (m, 2H, C_4–CH_2); 1.33–1.43 (m, 1H, $H_{4'}$); 1.60–1.65 (m, 2H, $H_{3'b-5'b}$); 1.80–1.89 (m, 2H, CH_2); 2.38 (s, 3H, CH_3); 2.65–2.75 (m, 2H, $H_{2'a-6'a}$); 3.40–3.47 (m, 2H, $CH_{2\beta}$); 3.47 (s, 3H, OCH_3); 3.68 (s, 2H, C_3–CH_2); 3.90–3.95 (m, 1H, CH_αCOOMe); 4.05–4.15 (m, 4H, CH_2N, $H_{2'b-6'b}$); 5.10 (s, 2H, CH_2Ph); 5.65–5.68 (m, 1H, NH); 6.21–6.26 (m, 1H, NHCO); 7.10 (s, 1H, H_2); 7.13 (t, 1H, H_5, $J = 7.8$ Hz); 7.21–7.34 (m, 9H, H_6, H_7, $2H_{tosyl}$, Ph); 7.53 (d, 1H, H_4, $J = 7.8$ Hz); 7.62 (d, 2H, $2H_{tosyl}$, $J = 8.3$ Hz)	21.5 (CH_3); 27.4 (CH_2); 32.0 ($2CH_2$); 33.0 (CH_2); 33.7 (CH_2); 35.7 (CH); 41.7 (CH_2); 44.1 ($2CH_2$); 46.5 (CH_2); 52.9 (OCH_3); 55.5 (CH); 66.9 (CH_2Ph); 106.9 (C); 109.7 (CH); 118.9 (CH); 119.6 (CH); 122.1 (CH); 127.1 (2CH and C); 127.6 (2CH); 127.8 (2CH); 127.9 (CH); 128.4 (CH); 129.7 (2CH); 136.4 (2C); 136.9 (C); 143.8 (C); 155.2 (N–C = O); 170.0 (CO); 172.6 (CO)	689.5 [MH^+]
49	1161 (SO_2), 1655 (C=O), 1743 (C=O), 3283, 3385 (NH)	1.15–1.32 (m, 5H, $H_{3'a-5'a}$, $C_{4'}$–CH_2, $H_{4'}$); 1.64–1.69 (m, 2H, $H_{3'b-5'b}$); 1.83–1.92 (m, 2H, CH_2); 2.40 (s, 3H, CH_3); 2.54–2.63 (m, 2H, $H_{2'a-6'a}$); 3.08–3.13 (m, 2H, $H_{2'b-6'b}$); 3.35–3.49 (m, 2H, $CH_{2\beta}$); 3.49 (s, 3H, OCH_3); 3.69 (s, 2H, C_3–CH_2); 3.91–3.95 (m, 1H, CH_αCOOMe); 4.10 (t, 2H, CH_2–N, $J = 7.0$ Hz); 4.87 (br s, 2H, 2NH); 6.22–6.27 (m, 1H, NHCO); 7.10 (s, 1H, H_2); 7.14 (d, 1H, H_5, $J = 7.8$ Hz); 7.22–7.35 (m, 4H, H_6, H_7, $2H_{tosyl}$); 7.53 (d, 1H, H_4, $J = 7.8$ Hz); 7.62 (d, 2H, $2H_{tosyl}$, $J = 8.2$ Hz)	21.9 (CH_3); 27.6 (CH_2); 32.5 ($2CH_2$); 33.5 (CH_2); 34.4 (CH_2); 35.7 (CH); 42.1 (CH_2); 46.2 ($2CH_2$); 46.9 (CH_2); 53.2 (OCH_3); 56.0 (NCHCO); 107.4 (C); 110.1 (CH); 119.3 (CH); 119.9 (CH); 124.5 (CH); 127.5 (2CH); 128.0 (CH and C); 130.1 (2CH); 136.8 (C); 137.0 (C); 144.1 (C); 170.6 (CO); 172.9 (CO)	555.5 [MH^+]
50	1161 (SO_2), 1655 (C=O), 1743 (C=O), 3283, 3385 (NH)	1.05–1.16 (m, 2H, $H_{3'a-5'a}$); 1.23–1.38 (m, 3H, C_4–H–CH_2, $H_{4'}$); 1.46 (s, 9H, *t*-Bu); 1.62–1.68 (m, 2H, $H_{3'b-5'b}$); 1.87–1.93 (m, 2H, CH_2); 2.42 (s, 3H, CH_3); 2.60–2.70 (m, 2H, $H_{2'a-6'a}$); 3.43–3.52 (m, 2H, $CH_{2\beta}$); 3.53 (s, 3H, OCH_3); 3.72 (s, 2H, C_3–CH_2); 3.93–3.97 (m, 1H, CH_αCOOMe); 4.05–4.18 (m, 4H, $H_{2'b-6'b}$, CH_2N); 5.52–5.55 (m, 1H, NH); 6.16–6.20 (m, 1H, NHCO); 7.13 (s, 1H, H_2); 7.17 (t, 1H, H_5, $J = 7.8$ Hz); 7.25–7.38 (m, 4H, H_6, H_7, $2H_{tosyl}$); 7.56 (d, 1H, H_4, $J = 7.8$ Hz); 7.64 (d, 2H, $2H_{tosyl}$, $J = 8.3$ Hz)	21.6 (CH_3); 27.5 (CH_2); 28.5 ($C(CH_3)_3$); 32.1 ($2CH_2$); 33.1 (CH_2); 33.8 (CH_2); 35.8 (CH); 41.7 (CH_2); 43.9 ($2CH_2$); 46.6 (CH_2); 52.9 (OCH_3); 55.6 (N–CH–CO); 79.9 (CMe_3); 107.4 (C); 110.1 (CH); 119.3 (CH); 119.9 (CH); 124.5 (CH); 127.5 (2CH); 128.0 (CH and C); 130.1 (2CH); 136.8 (C); 137.0 (C); 144.1 (C); 155.2 (NC=O); 170.6 (CO); 172.9 (CO)	555.5 [M − Boc], 655.5 [MH^+]
51	1162 (SO_2), 1663 (C=O), 1685 (C=O), 1735 (C=O), 3387 (NH), 2800–3500 (OH)	1.02–1.14 (m, 2H, $H_{3'a-5'a}$); 1.29–1.40 (m, 3H, C_4–CH_2, $H_{4'}$); 1.46 (s, 9H, *t*-Bu); 1.62–1.67 (m, 2H, $H_{3'b-5'b}$); 1.88–1.97 (m, 2H, CH_2); 2.33 (s, 3H, CH_3); 2.60–2.70 (m, 2H, $H_{2'a-6'a}$); 3.25–3.35 (m, 2H, $CH_{2\beta}$); 3.53–3.63 (m, 1H, CH_αCOOH); 3.68 (s, 2H, C_3–CH_2); 3.95–4.05 (m, 2H, $H_{2'b-6'b}$); 4.19 (t, 2H, CH_2N, $J = 6.6$ Hz); 7.06 (t, 1H, H_5, $J = 8.2$ Hz); 7.18 (t, 1H, H_6, $J = 8.2$ Hz); 7.23 (s, 1H, H_2); 7.32 (d, 2H, $2H_{tosyl}$, $J = 8.0$ Hz); 7.39 (d, 1H, H_7, $J = 8.2$ Hz); 7.55 (d, 1H, H_4, $J = 8.2$ Hz); 7.71 (d, 2H, $2H_{tosyl}$, $J = 8.0$ Hz)	21.8 (CH_3); 28.8 (CH_2); 29.0 ($C(CH_3)_3$); 33.6 ($2CH_2$); 34.0 (CH_2); 35.1 (CH_2); 37.1 (CH); 43.2 (CH_2); 45.6 ($2CH_2$); 47.5 (CH_2); 57.5 (NCHCO); 81.1 ($C(CH_3)_3$); 108.9 (C); 110.9 (CH); 120.1 (CH); 120.4 (CH); 122.9 (CH); 128.6 (2CH); 128.8 (CH); 129.6 (C); 131.0 (2CH); 138.2 (C); 139.4 (C); 145.0 (C); 156.9 (N–C=O); 173.0 (CO); 175.6 (CO)	541.5 [M − Boc], 641.5 [MH^+], 663.5 [MNa^+]
52	1160 (SO_2); 1658 (C=O); 1734 (C=O); 2500–3500 (NH_2^+, OH)	1.05–1.21 (m, 4H, $H_{3'a-5'a}$, $C_{4'}$–H–CH_2); 1.30–1.35 (m, 1H, $H_{4'}$); 1.66–1.78 (m, 4H, $H_{3'b-5'b}$, CH_2); 2.33 (s, 3H, CH_3); 2.65–2.75 (m, 2H, $H_{2'a-6'a}$); 3.10–3.18 (m, 3H, $H_{2'b-6'b}$, $CH_{\beta b}$); 3.40–3.52 (m, 2H, $CH_{\beta a}$); 3.48 (s, 2H, C_3–CH_2); 3.88–3.93 (m, 1H, CH_αCOOH); 4.01 (t, 2H, CH_2N, $J = 6.9$ Hz); 6.92 (t, 1H, H_5, $J = 7.9$ Hz); 7.03 (t, 1H, H_6, $J = 7.9$ Hz); 7.07 (s, 1H, H_2); 7.16 (d, 2H, $2H_{tosyl}$, $J = 7.9$ Hz); 7.24 (d, 1H, H_7, $J = 7.9$ Hz); 7.40 (d, 1H, H_4, $J = 7.9$ Hz); 7.56 (d, 2H, $2H_{tosyl}$, $J = 7.9$ Hz)	20.5 (CH_3); 27.1 (CH_2); 28.9 ($2CH_2$); 32.5 (CH_2); 33.1 (CH_2); 33.4 (CH); 41.8 (CH_2); 44.2 ($2CH_2$); 45.9 (CH_2); 56.4 (CH); 107.7 (C); 109.6 (CH); 118.8 (CH); 119.1 (CH); 121.6 (CH); 127.2 (2CH); 127.5 (CH); 128.3 (C); 129.6 (2CH); 136.8 (C); 138.0 (C); 143.8 (C); 171.5 (CO), 174.3 (CO)	541 [MH^+]

^{1}H-, ^{13}C-NMR in DMSO-d_6 for compounds **2**, **4**, **39**, **40**, **42**–**46** in D_2O for **41** and CD_3OD for **51**, **52**.

*5.1.24. tert-Butyl 4-[3-(3-{2-[(3-methoxy-2-{[(4-methylphenyl)sulfonyl]amino}-3-oxopropyl)amino]-2-oxo-ethyl}-1H-1-indolyl)propyl]-1-piperidinecarboxylate (**50**)*

To a solution of **49** (430 mg, 0.78 mmol) in a mixture of dioxane–water (8 mL, 1:1) were added Et_3N (120 μL, 0.85 mmol, 86 mg) and di-*tert*-butoxycarbonyle dicarbonate (211 mg, 0.97 mmol). After stirring for 24 h at r.t., the mixture was evaporated, water was added and the residue extracted with EtOAc. Drying over $MgSO_4$ of the organic extracts and evaporation leave a solid which was chromatographied on silica gel column (eluent: EtOAc–PE, 7:3); white solid; $m = 455$ mg (90%); m.p. 92–94 °C. $[\alpha]_D$: +12.5° (*c* 1.1, $CHCl_3$). Analysed for $C_{34}H_{49}N_4O_7S$ (C, H, N).

*5.1.25. 3-{[2-(1-{3-[1-(tert-Butyloxycarbonyl)-4-piperidyl]propyl}-1H-3-indolyl)acetyl]amino}-2-{[(4-methyl-phenyl)sulfonyl]amino}propanoic acid (**51**)*

Acid **51** was obtained from ester **50** according to the general method, by precipitation at pH 1; white solid; $m = 385$ mg (92%); m.p. 150 °C (dec.). $[\alpha]_D$: +26.8° (*c* 0.25, $CHCl_3$). Analysed for $C_{33}H_{44}N_4O_7S$ (C, H, N).

*5.1.26. 2-{[(4-Methylphenyl)sulfonyl]amino}-3-[(2-{1-[3-(4-piperidyl)propyl]-1H-3-indolyl}acetyl)amino]-propanoic acid, hydrochloride (**52**)*

Compound **51** (220 mg, 0.34 mmol) and 4 N HCl in dioxane (5 mL) were stirred for 1 h at 0 °C. After evaporation the residue was crystallised in EtOAc to give **52**, as HCl salt; white solid; $m = 150$ mg (76%); m.p. 112 °C (dec.). $[\alpha]_D$: +15.2° (*c* 0.25, water–MeOH). Analysed for $C_{28}H_{36}N_4O_5S$, HCl (C, H, N).

5.2. Platelet aggregation studies

In vitro platelet aggregation studies were performed in male Dunkin–Hartley guinea-pig PRP. Blood was obtained by cardiac puncture on unanesthetised animals (300–235 g body weight) and was drawn into plastic syringues containing 1/10 volume of trisodium citrate 1.55%. PRP was prepared by centrifugation ($100 \times g$ for 15 min) at r.t. of citrated whole blood. After removal, platelet count in PRP was determined with a Technicon H1 System (Bayer). PRP samples of three animals were pooled in order to obtain enough plasma to perform in vitro experiments. Platelet poor plasma (PPP) was obtained by centrifugation of the remaining whole blood ($1500 \times g$ for 15 min). The optimal platelet concentration for the aggregation response was determined during preliminary studies. Final platelet concentration in PRP was adjusted to $150–300 \times 10^3$ platelet μL^{-1} with autologus PPP.

Aliquots of PRP (450 μL) were placed in a cuvette; the cuvettes were incubated at 37 °C. PRP was stirred at 1000 rpm and aggregation was monitored spectrophotometrically (Chronolog Aggregometer models 490-4D or 560-VS). Aggregation was initiated with collagen (1 μg mL^{-1}) 5 min after infusion of the studied compound (or vehicle) and was measured for 15 min. Percent inhibition was calculated from control aggregation of PRP only containing vehicle. IC_{50} values were obtained from the mean-dose–response curve computed for four pools of PRP in a 1–1000 μM concentration range.

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