Preliminary communication

Synthesis and structure–activity relationships of potential anticonvulsants based on 2-piperidinecarboxylic acid and related pharmacophores

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Abstract – Using N-(2,6-dimethyl)phenyl-2-piperidinecarboxamide (**1**) and N-(α-methylbenzyl)-2-piperidinecarboxamide (**2**) as structural leads, a variety of analogues were synthesised and evaluated for anticonvulsant activity in the MES test in mice. In the N-benzyl series, introduction of 3-Cl, 4-Cl, 3,4-Cl$_2$, or 3-CF$_3$ groups on the aromatic ring led to an increase in MES activity. Replacement of the α-methyl group by either i-Pr or benzyl groups enhanced MES activity with no increase in neurotoxicity. Substitution on the piperidine ring nitrogen led to a decrease in MES activity and neurotoxicity, while reduction of the amide carbonyl led to a complete loss of activity. Movement of the carboxamide group to either the 3- or 4-positions of the piperidine ring decreased MES activity and neurotoxicity. Incorporation of the piperidine ring into a tetrahydroisoquinoline or diazahydrinone nucleus led to increased neurotoxicity. In the N-(2,6-dimethyl)phenyl series, opening of the piperidine ring between the 1- and 6-positions gave the active norleucine derivative **75** (ED$_{50}$ = 5.8 mg kg^{-1}, TD$_{50}$ = 36.4 mg kg^{-1}, PI = 6.3). Replacement of the piperidine ring of **1** by cycloalkane (cyclohexane, cyclopentane, and cyclobutane) resulted in compounds with decreased MES activity and neurotoxicity, whereas replacement of the piperidine ring by a 4-pyridyl group led to a retention of MES activity with a comparable PI. Simplification of the 2-piperidinecarboxamide nucleus of **1** into a glycinecarboxamide nucleus led to about a six-fold decrease in MES activity. The 2,6-dimethylanilides were the most potent compounds in the MES test in each group of compounds evaluated, and compounds **50** and **75** should be useful leads in the development of agents for the treatment of tonic–clonic and partial seizures in man. © 2001 Éditions scientifiques et médicales Elsevier SAS

2,6-dimethylanilides / carboxamides / rotorod test / maximal electroshock seizure test / anticonvulsant

1. Introduction

Epilepsy is a major neurological disorder in the United States and throughout the world [1, 2]. Although 70–80% of epileptics are currently controlled by a variety of drugs, seizure protection is frequently accompanied by numerous adverse effects [3].

Previously, the activity of several 2-piperidinecarboxamides in the maximal electroshock seizure (MES) test in mice was reported. Receptor binding studies indicated that these amides demonstrated weak binding affinity at the phencyclidine (PCP) site on the N-methyl-D-aspartate (NMDA) receptor complex; however, a correlation between binding affinity and seizure protection in the MES test was not observed [4]. As a continuation of this work, a structure–activity relationship (SAR) study of the 2-piperidinecarboxamide nucleus was initiated. The most active compound arising from this study, the 2,6-dimethylanilide (*RS*-**1**, *figure 1*), exhibited an ED$_{50}$ = 5.8 mg kg^{-1} in the MES test and a TD$_{50}$ = 33.2 mg kg^{-1} in the rotorod test to give a PI = 5.7. The (*R*-**1**)-isomer exhibited similar MES activity as the racemate

but was more neurotoxic, whereas the (*S*-**1**)-isomer was less active and less neurotoxic. Additionally, the *N*-(α-methylbenzyl)-2-piperidinecarboxamides **2** (*figure 1*) also exhibited activity in the MES test; however, the stereochemistry at the 2-position of the piperidine ring or at the α-position of the side chain did not significantly affect activity [5].

Although several new drugs such as vigabatrin, lamotrigine, gabapentin, tiagabine, felbamate, topiramate, fosphenytoin, and levetiracetam have appeared on the market, the development of novel agents, particularly compounds effective against complex partial seizures, remains a major focus of antiepileptic drug research [6]. A review on new structural entities having anticonvulsant activity has recently appeared [7]. Since the 2-piperidinecarboxamides represent a novel series of compounds that are active in the MES test in mice, further exploration of the SAR was of interest. Using compounds **1** and **2** as structural leads, the following modifications were explored: (1) substi-

tution on the aromatic ring of compound **2**, (2) replacement of the α-methyl substituent of **2** by other alkyl or aryl groups, (3) introduction of substituents on the piperidine ring nitrogen, (4) reduction of the side chain carbonyl, (5) movement of the carboxamide group to the 3- and 4-positions, (6) incorporation of the piperidine ring into a tetrahydroisoquinoline or diazahydrindanone nucleus, (7) opening of the piperidine ring, (8) replacement of the piperidine ring by cycloalkyl or pyridine, and (9) simplification of the 2-piperidinecarboxamide nucleus into a glycinecarboxamide moiety.

2. Chemistry

The synthesis of the *N*-[(α-alkyl or aryl-substituted)benzyl]-2-piperidine-carboxamides required the preparation of the precursor α-substituted-benzyl-amines which were prepared by the Leuckhart reaction (*figure 2*). The starting ketones were either commercially available or were prepared by Friedel–Crafts acylation of benzene with an appropriate acid chloride. In the case of solid ketones, the reaction of the ketone with a mixture of formic acid and formamide at 140°C usually required a reaction time of about 24 h to afford the *N*-formylamine. Some difficulty was encountered in maintaining the reaction temperature due to the periodic addition of formic acid. When liquid ketones were employed in the reaction, a mixture of the ketone and formic acid was added dropwise to a solution of formamide at 140°C. The intermediate imine was rapidly hydrogenated by formic acid, and the total reaction time to yield the *N*-formylamine was only 6–8 h. Removal of the formyl group was accomplished by refluxing in concentrated hydrochloric acid, and the free amines were generally purified by vacuum distillation followed by formation of the hydrochloride salts (*table I*).

The desired *N*-[(α-alkyl or aryl-substituted)benzyl]-piperidinecarboxamides were prepared by a previously described [5] mixed anhydride coupling procedure. The general method (shown in *figure 4*) involved reaction of a *tert*-butoxycarbonyl (BOC)-protected amino acid with isobutylchloroform (IBCF) and an arylamine or an (α-alkyl or aryl-substituted)benzylamine in the presence of *N*-methylmorpholine (NMM). Deprotection of the resulting BOC-protected carboxamide with hydrogen chloride
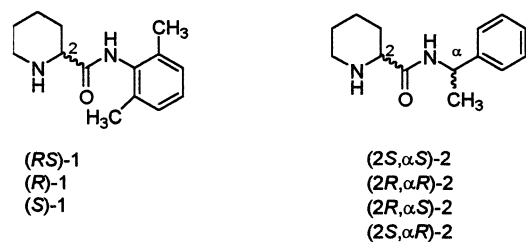

Figure 1. Structures of 2-piperidinecarboxamides with activity against MES in mice.
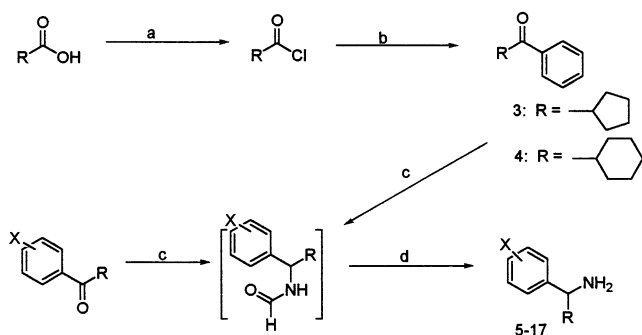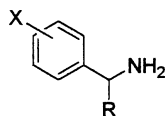

Figure 2. (a) $SOCl_2$–benzene–pyridine; (b) $AlCl_3$–benzene; (c) $HCOOH$–$HCONH_2$; (d) concentrated HCl.

Table I. α-Substituted-benzylamines.

Compound	R	X	Bp (°C), mmHg	Yield (%)	Mp (°C) [a]
5	CH_3	3-OCH_3	129–132 (17)	66	159–161 [b]
6	CH_3	3,4-$(OCH_3)_2$	155–158 (13) [c]	27	221–222 [c]
7	CH_3	3-CF_3	77–81 (18) [d]	67	192–193 [d]
8	CH_3	3-F	99–111 (23)	55	168–169 [e]
9	CH_3	2-Cl	123–126 (25) [d]	60	183–184 [d]
10	CH_3	3-Cl	112–115 (13) [f]	59	176–177 [f]
11	CH_3	4-Cl	112–115 (13) [d]	63	192–193 [d]
12	Et	H	105–108 (27) [d]	77	194–195 [d]
13	*i*-Pr	H	99–104 (14) [d]	85	284–285 [d]
14	Bn	H	165–180 (16) [g]	53	256–257 [h]
15	3-ClC_6H_4	H	140–145 (1) [i]	78	271–273 [i]
16	cC_5H_9	H		44	>300 [j]
17	cC_6H_{11}	H	180–183 (22)	59	>325 [j]

[a] HCl salt. All salts were recrystallised from absolute ethanol–diethyl ether. [b] Ref. [31]. [c] Ref. [32]. [d] Ref. [33]. [e] Ref. [34]. [f] Ref. [35]. [g] Ref. [36]. [h] Ref. [37]. [i] Ref. [38]. [j] Ref. [39].

gas in methylene chloride gave the desired carboxamides. The pyridinecarboxamide **50** was prepared from isonicotinic acid by formation of the acid chloride in pyridine followed by reaction of the crude acid chloride with 2,6-dimethylaniline in tetrahydrofuran (THF).

Reaction of **2**, as a mixture of diastereoisomers, with either benzoyl chloride or benzyl bromide gave the corresponding 1-benzoyl **39** and 1-benzyl derivatives **35**–**38**, respectively. Alkylation of **2** with methyl iodide afforded **34** and some of the undesired disubstituted product. Reduction of **2** with refluxing lithium aluminum hydride (LAH) in THF afforded the diamine **51**. In an effort to incorporate the 2-piperidinecarboxamide moiety into a more rigid framework, **23** was reacted with formaldehyde in ethanol to yield the diazahydrindanone **52**. The physicochemical properties of these compounds are given in *table II*.

Incorporation of the 2-piperidinecarboxamide moiety into a tetrahydroisoquinoline nucleus required the preparation of the key 1,2,3,4-tetrahydroisoquinoline carboxylic acids **55** and **64** as shown in *figure 3*. Using sodium methoxide as the base, cyclisation between α,α-dichloro-*o*-xylene and diethyl-2-(acetylamino)-malonate in refluxing methanol gave the diester **53** in

moderate yield. The reaction occurred with complete transesterification. The diester **53** was converted to the acid **54** via saponification and subsequent decarboxylation during work-up. The isoquinoline-3-carboxylic acid **55** was obtained by refluxing **54** in 6 N hydrochloric acid followed by neutralisation with ammonium hydroxide. The desired carboxamides were prepared by the standard mixed anhydride method to yield **58**–**63**. Catalytic hydrogenation of isoquinoline-1-carboxylic acid using Adams' catalyst gave the tetrahydroisoquinoline-1-carboxylic acid **64**. Reaction of **64** with di-*tert*-butyl dicarbonate followed by amide formation and deprotection gave the carboxamides **66** and **68**. The physicochemical properties of the 1,2,3,4-tetrahydroisoquinolinecarboxamides are given in *table III*.

Ring-opened analogues of the 2-piperidinecarboxamide nucleus were prepared as shown in *figure 4*. The carboxamides **75** and **77** represent analogues in which the piperidine ring has been opened between positions 1 and 6, whereas compounds **82** and **84** represent ring-opened analogues in which the piperidine ring has been cleaved between positions 2 and 3. The physicochemical properties of these derivatives are given in Section 5.

Table II. Piperidinecarboxamides and related derivatives.
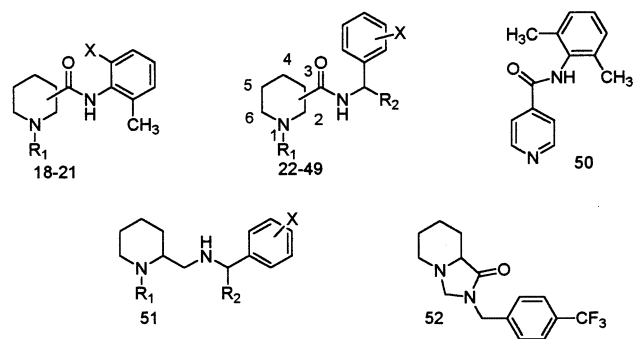
Compound	R_1	R_2	X	Ring position	Mp (°C)	Yield (%)	Formula [a] (recrystallisation solvent) [b]
18	BOC		$CH(CH_3)_2$	2	139–141	30	$C_{21}H_{32}N_2O_3$ (A)
19	H		$CH(CH_3)_2$	2	246–248	67	$C_{16}H_{25}ClN_2O$ [c] (B)
20	H		CH_3	3	196–210	55	$C_{14}H_{21}ClN_2O$ [c] (B)
21	H		CH_3	4	263–265 [d]	41	$C_{14}H_{21}ClN_2O$ [c] (B)
22 [e]	H	H	3-CF_3	2			
23 [e]	H	H	4-CF_3	2			
24	H	H	3-CF_3	3	99–101	43	$C_{14}H_{17}F_3N_2O$ (C)
25	H	CH_3	3-OCH_3	2	63–64	31	$C_{15}H_{22}N_2O_2$ (D)
26	BOC	CH_3	3-F	2	103–105	70	$C_{19}H_{27}FN_2O_3$ (A)
27	H	CH_3	3-F	2	195–210	83	$C_{14}H_{20}ClFN_2O$ [c] (B)
28	H	CH_3	2-Cl	2	238–248	80	$C_{14}H_{20}Cl_2N_2O$ [c] (E)
29	H	CH_3	3-Cl	2	179–183	52	$C_{14}H_{20}Cl_2N_2O$ [c] (B)
30	H	CH_3	4-Cl	2	80–88	37	$C_{14}H_{19}ClN_2O$ (F)
31	H	CH_3	3-CF_3	2	217–225	58	$C_{15}H_{20}ClF_3N_2O$ [c] (B)
32	H	CH_3	3,4-Cl_2	2	288–289	46	$C_{14}H_{19}Cl_3N_2O$ [c] (B)
33	H	CH_3	3,4-$(OCH_3)_2$	2	74–85	38	$C_{16}H_{24}N_2O_3$ (D)
34	CH_3	CH_3	H	2	76–78	54	$C_{15}H_{22}N_2O$ (F)
35	Bn	CH_3	H	2	243–245	39	$C_{21}H_{27}ClN_2O$ [c] (B)
36	4-FC_6H_4	CH_3	H	2	225–228	53	$C_{21}H_{26}ClFN_2O$ [c] (B)
37	4-BrC_6H_4	CH_3	H	2	88–91	53	$C_{21}H_{25}BrN_2O$ (F)
38	3,4-$Cl_2C_6H_3$	CH_3	H	2	159–161	86	$C_{21}H_{25}Cl_3N_2O$ [c] (B)
39	COC_6H_5	CH_3	H	2	144–146	53	$C_{21}H_{24}N_2O_2$ (D)
40	H	CH_3	H	3	107–115	63	$C_{14}H_{20}N_2O$ [f] (F)
41	H	C_2H_5	H	2	185–187	50	$C_{15}H_{23}ClN_2O$ [c] (B)
42	H	i-Pr	H	2	79–83	46	$C_{16}H_{24}N_2O$ (F)
43	H	C_6H_5	H	2	96–98	47	$C_{19}H_{22}N_2O$ (G)
(S,RS)-**44**	H	C_6H_5	3-Cl	2	281–286	43	$C_{19}H_{21}Cl_2N_2O$ [c] (E)
(S,RS)-**45**	H	Bn	H	2	140–143	40	$C_{20}H_{24}N_2O$ (H)
46	BOC	cC_5H_9	H	2	119–122	65	$C_{23}H_{34}N_2O_3$ (A)
47	H	cC_5H_9	H	2	269–271	75	$C_{18}H_{27}ClN_2O$ [c] (B)
48	BOC	cC_6H_{11}	H	2	125–127	63	$C_{24}H_{36}N_2O_3$ (B)
49	H	cC_6H_{11}	H	2	304–305	58	$C_{19}H_{29}ClN_2O$ [c] (B)
50					157–159 [g]	30	
51	H	CH_3	H	–	214–216	44	$C_{14}H_{24}Cl_2N_2$ [h] (I)
52					67–70	86	$C_{15}H_{17}F_3N_2O$ (F)

[a] All compounds gave acceptable C, H, and N analyses, $\pm$ 0.4% of the calculated values, except where indicated.
[b] Recrystallisation solvents, A, EtOH–H_2O; B, absolute EtOH–Et_2O; C, petroleum ether–EtOAc; D, petroleum ether–Et_2O; E, absolute EtOH; F, petroleum ether; G, MeOH–H_2O; H, EtOAc–hexane; I, i-PrOH–Et_2O.
[c] Hydrochloride.
[d] [40] no reported m.p.
[e] Previously reported [5].
[f] Calc. 72.37; found, 71.42.
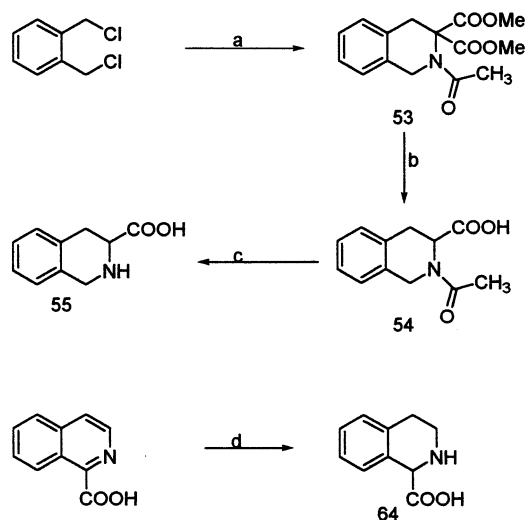[g] [40] m.p. 154–155°C.
[h] Dihydrochloride.

Figure 3. (a) $NaOCH_3$–MeOH–$CH_3CONHCH(CO_2Et)_2$; (b) KOH; (c) 6 N HCl; (d) H_2–PtO_2–CH_3COOH.

The cycloalkylcarboxamides (**85–93**) were prepared starting from the appropriate carboxylic acid. The intermediate acid chlorides were obtained by treating the cycloalkanecarboxylic acids with thionyl chloride in dichloromethane. Using triethylamine as the base, the acid chlorides gave moderate to high yields of the amides upon treatment with the appropriate amine in THF. The physicochemical properties of these compounds are given in *table IV*.

The 1-aminocyclopentanecarboxamide **97** (*figure 5*) was synthesised via the hydantoin **94**. Using the typical coupling procedure, the 1-aminocyclohexanecarboxamide **99** was prepared from 1-aminocyclohexane carboxylic acid. Hydrogenation of 4-aminobenzoic acid with Adams' catalyst in 30% ethanol yielded a mixture of *cis*-and *trans*-4-aminocyclohexanecarboxylic acids **100** and **101**, respectively. Fractional crystallisation of the reaction mixture from aqueous ethanol yielded *cis*-**100**. Concentration of the mother liquor and recrystallisation of the resulting residue from an aqueous ethanol–diethyl ether mixture gave *trans*-**101**. The desired 2,6-dimethylanilides **104** and **105** (*figure 5*) were prepared from the corresponding BOC-protected acids **102** and **103** in the normal manner. The physicochemical properties of these compounds are given in Section 5. The NMR spectra of all final compounds were consistent with the assigned structures.

3. Pharmacology

3.1. 2,6-Dimethylanilide series

The anticonvulsant activity and the neurotoxicity (*table V*) of the target compounds of this investigation were evaluated by the National Institutes of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) using established procedures [5]. The ED_{50} in MES test and the TD_{50} in the rotorod test were calculated at the time of peak effect for the most active compounds according to a previously described method [4]. In the previous study, the 2,6-dimethylanilide (*RS*-**1**) was shown to exhibit potent activity in the MES test in mice [5]. Replacement of one of the *ortho*-methyl groups in *RS*-**1** by an isopropyl substituent (compound **19**) resulted in similar MES activity ($ED_{50} = 8.3$ mg kg^{-1}). Although the nipecotamide **20** and the isonipecotamide **21** were weakly active in the MES test, N-[(2,6-dimethyl)phenyl]-4-pyridinecarboxamide (**50**, $ED_{50} = 9.7$ mg kg^{-1}; $TD_{50} = 53.3$ mg kg^{-1}; PI = 5.5) approached the MES activity of *RS*-**1** with a similar PI.

Incorporation of the 2-piperidinecarboxamide moiety into a tetrahydroisoquinoline nucleus increased neurotoxicity while maintaining similar MES activity. The isoquinolinecarboxamides (**58** and **68**) exhibited MES activity at 10 mg kg^{-1} in mice, but with neurotoxicity in the rotorod test at 30 mg kg^{-1}. Apparently, the increase in lipophilicity by the fusion of a phenyl ring either at the 3,4- or 4,5-positions in these compounds contributes to the increase in neurotoxicity.

Several open ring analogues exhibited potent activity in the MES test. The norleucine derivative **75** ($ED_{50} = 5.8$ mg kg^{-1}, $TD_{50} = 36.4$ mg kg^{-1}, PI = 6.3) was among the most potent compounds evaluated in the MES test in this study. In these derivatives introduction of a lipophilic *n*-butyl group at the α-position of the amino acid portion increased MES activity by about five-fold (compare compounds **75** and **76**). Positioning the *n*-butyl group on the amine nitrogen (compound **84**) led to a decrease in MES activity. The conformationally constrained 1-amino-1-cyclohexanecarboxamide **99** did not exhibit MES activity at 300 mg kg^{-1}. Possibly, the cyclohexane ring exerts an unfavourable steric effect in this compound.

The cyclobutanecarboxamide **89** exhibited the greatest MES activity among the cycloalkanecarboxamides ($ED_{50} = 35$ mg kg^{-1}, $TD_{50} = 203$ mg kg^{-1}, PI = 5.8). Compared with the cyclobutyl derivative, the cy-

clopentyl **90** (ED$_{50}$ = 55 mg kg^{-1}) and the cyclohexyl **91** (ED$_{50}$ = 62 mg kg^{-1}) derivatives were less active in the MES test. However, the cyclohexyl derivatives **91** and **92** exhibited considerably less neurotoxicity with PIs of >12.1 and >8.8, respectively. The cyclopropane **88** and the cycloheptane **93** derivatives were the least potent of the cycloalkanecarboxamides in the MES test. The presence of an *ortho*-chloro group in compound **92** in place of a methyl substituent led to a decrease in MES activity (ED$_{50}$ = 85 mg kg^{-1}). Introduction of a 4-amino group into the cyclohexane ring (compound **104**) did not eliminate MES activity (active at 100 mg kg^{-1}), but greatly increased the neurotoxicity (neurotoxic at 100 mg kg^{-1}). Compound **104** may be viewed as a saturated analogue of the potent anticonvulsant ameltolide (ED$_{50}$ = 2.6 mg kg^{-1}) [8, 9]. Apparently, modification of the planar

aromatic ring in ameltolide greatly decreases the MES activity.

3.2. (N-Benzyl)carboxamide series

The stereochemistry at the 2-position or at the α-position of the *N*-(α-methylbenzyl) group (see the four stereoisomers of **2** in *table V*) did not significantly affect the MES activity. Introduction of a 3-Cl (**29**, ED$_{50}$ = 20 mg kg^{-1}) or a 3,4-Cl$_2$ (**32**, ED$_{50}$ = 28 mg kg^{-1}) into the aromatic ring led to a slight increase in MES activity; however, the compounds were slightly more neurotoxic. Substitution of an isopropyl group (**42**, ED$_{50}$ = 22 mg kg^{-1}) or a benzyl substituent (*S,RS*-**45**, ED$_{50}$ = 22 mg kg^{-1}) for the α-methyl group resulted in an increase in MES activity, although an increase in neurotoxicity

Table III. 1,2,3,4-Tetrahydroisoquinolinecarboxamides.
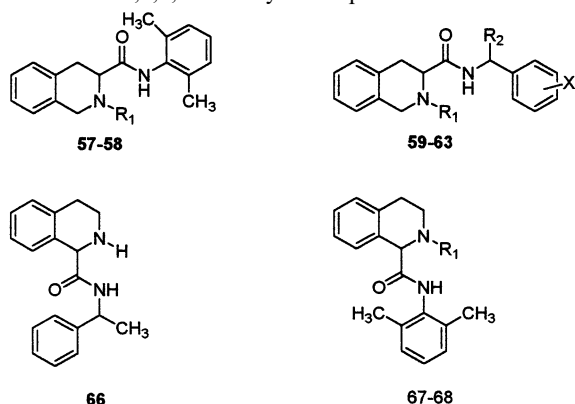
Compound	R$_1$	R$_2$	X	Mp (°C)	Yield (%)	Formula [a] (recrystallisation solvent) [b]
57	BOC			140–141	40	C$_{23}$H$_{28}$N$_2$O$_3$ (A)
58	H			255–258	82	C$_{18}$H$_{21}$ClN$_2$O [c, d] (B)
59	H	H	3-F	221–223	62	C$_{17}$H$_{18}$ClFN$_2$O [c] (B)
60	H	H	3-CF$_3$	141–143	66	C$_{18}$H$_{18}$ClFN$_2$O [c] (C)
61	H	CH$_3$	3-CF$_3$	88–98	46	C$_{19}$H$_{19}$F$_3$N$_2$O [e] (D)
62	H	CH$_3$	4-Cl	100–103	51	C$_{18}$H$_{19}$ClN$_2$O (D)
63	H	Bn	H	124–126	23	C$_{24}$H$_{24}$N$_2$O (E)
66				164–166	37	C$_{18}$H$_{21}$ClN$_2$O [c, f] (B)
67	BOC			198–200	29	C$_{23}$H$_{28}$N$_2$O$_3$ (A)
68	H			283–285	71	C$_{18}$H$_{21}$ClN$_2$O (B)

[a] All compounds gave acceptable C, H, and N analyses, ± 0.4% of the calculated values, except where indicated.
[b] Recrystallisation solvents, A, EtOH–water; B, absolute EtOH–Et$_2$O; C, 95% EtOH–Et$_2$O; D, Et$_2$O–petroleum ether; E, EtOAc–hexane.
[c] Hydrochloride.
[d] Calc. C, 68.24; found, 67.71.
[e] Calc. C, 65.50; found, 65.09.
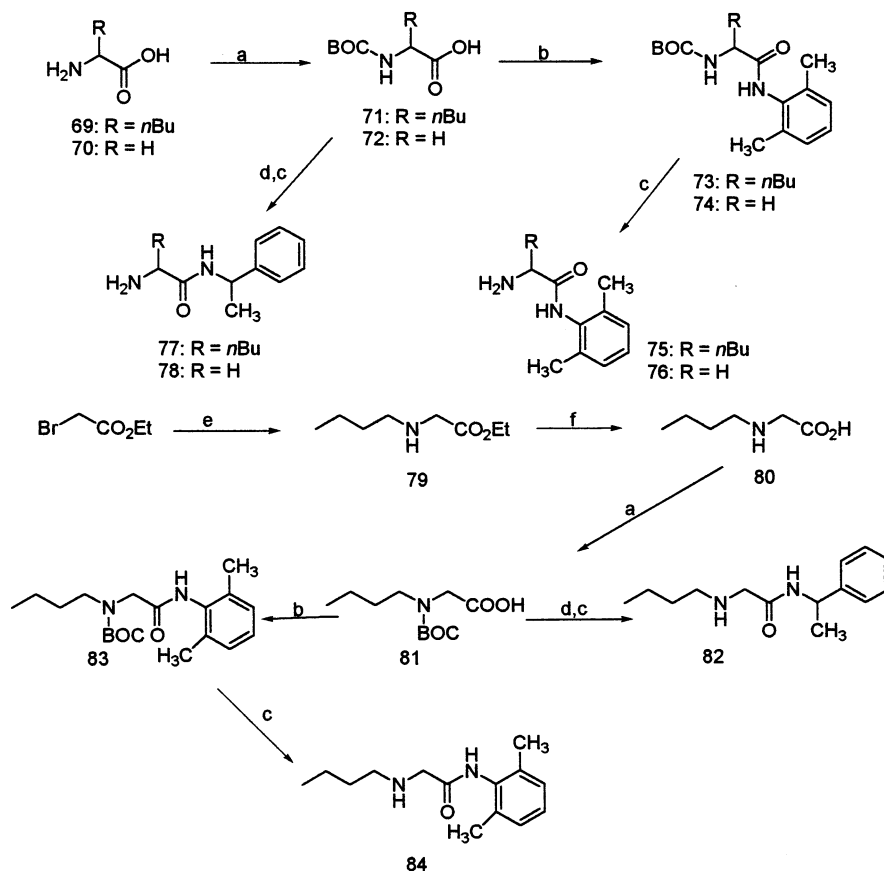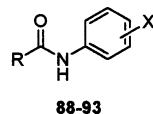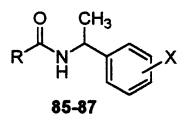[f] Calc. C, 68.23; found, 67.30.

Figure 4. (a) (BOC)$_2$O–NaOH or BOC-ON–Et$_3$N; (b) NMM–IBCF–2,6-dimethylaniline; (c) HCl (g)–CH$_2$Cl$_2$; (d) NMM–IBCF–α-metylbenzylamine; (e) n-butylamine–benzene; (f) 25% NaOH.

Table IV. Cycloalkanecarboxamides.

Compound	R	X	Mp (°C)	Yield (%)	Formula [a] (recrystallisation solvent) [b]
85	cC$_5$H$_9$	3-Cl	82–84	89	C$_{14}$H$_{18}$ClNO (A)
86	cC$_6$H$_{11}$	3-Cl	122–124	49	C$_{15}$H$_{20}$ClNO (A)
87	cC$_6$H$_{11}$	H	112–113	47	C$_{15}$H$_{21}$NO$_2$ (A)
88	cC$_3$H$_5$	2,6–Me$_2$	158–160	31	C$_{12}$H$_{15}$NO (B)
89	cC$_4$H$_7$	2,6-Me$_2$	152–154	53	C$_{13}$H$_{17}$NO (B)
90	cC$_5$H$_9$	2,6-Me$_2$	177–179	75	C$_{14}$H$_{19}$NO (B)
91	cC$_6$H$_{11}$	2,6-Me$_2$	201–202	44	C$_{15}$H$_{21}$NO (B)
92	cC$_6$H$_{11}$	2-Cl,6–Me	190–191	56	C$_{14}$H$_{18}$ClNO (A)
93	cC$_7$H$_{13}$	2,6-Me$_2$	200–204	38	C$_{16}$H$_{23}$NO (B)

[a] All compounds gave acceptable C, H, and N analyses, ± 0.4% of the calculated values.
[b] Recrystallisation solvents, A, EtOAc–hexane; B, EtOAc.

was noted. Introduction of an α-cyclopentyl or α-cyclohexyl substituent (compounds **47** and **49**) afforded carboxamides with MES activity at 100 and 30 mg kg^{-1}, respectively. However, both of these derivatives exhibited neurotoxicity at 100 mg kg^{-1}. Alkylation or acylation of the 1-position of the piperidine ring in the N-(α-methylbenzyl)-2-piperidinecarboxamides (compounds **34–39**) essentially led to a loss of anticonvulsant activity. Reduction of the carbonyl group of N-(α-methylbenzyl)-2-piperidinecarboxamide (**2**) gave the diamine **51** which exhibited no MES activity.

Only in the cycloalkanecarboxamides did the N-(α-methyl)benzyl-carboxamides approach the MES activity of the 2,6-dimethylanilides (compare compounds **85** and **90**). However, the neurotoxicities of these derivatives were greater than the corresponding 2,6-dimethylanilides.

4. Conclusions

In agreement with previous findings on the N-(benzyl)piperidinecarboxamides, introduction of 3-Cl, 4-Cl, 3,4-Cl$_2$, or 3-CF$_3$ groups on the aromatic ring of N-(α-methylbenzyl)-piperidinecarboxamides led to an increase in MES activity. Replacement of the α-methyl group of α-methylbenzylamides with either *i*-Pr (**42**, ED$_{50}$ = 22 mg kg^{-1}) or benzyl (S,RS-**45**, ED$_{50}$ = 22 mg kg^{-1}) increased MES activity with no increase in neurotoxicity. In the piperidine series, movement of the carboxamide moiety to either the 3- or 4-positions of the piperidine ring led to a decrease in anticonvulsant activity and neurotoxicity. Interestingly, the 4-pyridinecarboxamide (**50**, ED$_{50}$ = 9.7 mg kg^{-1}, TD$_{50}$ = 53.3 mg kg^{-1}, PI = 5.5) was highly active in the MES test. Any substitution on the piperidine ring nitrogen resulted in a decrease in MES activity and neurotoxicity. Also, reduction of the amide functional group (compound **51**) led to a loss of anticonvulsant activity.

The incorporation of the piperidine ring into a tetrahydroisoquinoline nucleus increased neurotoxicity, while incorporation of the piperidine ring into a diazahydrindanone moiety (compound **52**) led to a loss of anticonvulsant activity. Several open ring analogues exhibited potent activity in the MES test. The norleucine derivative **75** was among the most potent compounds in the MES test, which were evaluated in this study. In these derivatives the lipophilicity of the compound and the substitution at the α-position of the amino acid derivative played key roles in the quantitative anticonvulsant activity.

Compared with the piperidinecarboxamides, the cyclohexanecarboxamides showed decreased neurotoxicity. In fact, the cyclohexanecarboxamides (**91** and **92**) had high PI values (>8.9) when evaluated in mice. In general, these derivatives were, however, less potent than derivatives containing a basic nitrogen. Among the cyclohexanecarboxamides, the cyclobutane, cyclopentane, and cyclohexane analogues were active in the MES test, while the cyclopropane and cycloheptane derivatives were much less active.

The 2,6-dimethylanilides were the most potent compounds in the MES test in each group of compounds evaluated. The anticonvulsant activity of carbamazepine and phenytoin has, in part, been attributed to inhibition of voltage-dependent Na$^+$ channels [10, 11]. Since the 2,6-dimethylanilides exhibit a similar anticonvulsant profile as phenytoin and carbamazepine, a similar mode of action is possible. Further studies are needed to fully characterise the mode of action of these novel anticonvulsants. The pyridinecarboxamide **50** and the norleucinecarboxamide **75** should serve as useful leads in the development of compounds with therapeutic potential in the treatment of tonic–clonic and partial seizures in man.

5. Experimental protocols

5.1. Chemistry

All chemicals were of reagent grade and were used without further purification. Melting points were determined on a Thomas Hoover melting point apparatus and were not corrected. The IR spectra were recorded as potassium bromide pellets or as liquid films on a Nicolet Impact 400D spectrometer. The NMR spectra were
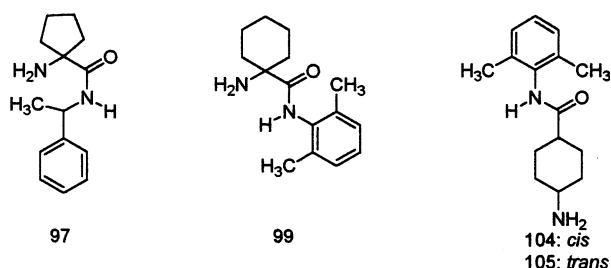

Figure 5. Structures of compounds **97**, **99**, **104**, and **105**.

Table V. Anticonvulsant activity of 2-piperidinecarboxamides and related derivatives in mice (all compounds were administered by ip injection, $++++$, $+++$, $++$, and $+$ denote antiseizure activity or toxicity at 10, 30, 100, and 300 mg kg^{-1}, respectively; $-$ denotes no activity up to 300 mg kg^{-1}). ED$_{50}$ and TD$_{50}$ values were determined at the time of peak effect of the experimental compound and are reported as mg kg^{-1} with the 95% confidence limits in parentheses [4]).

Compound	MES		Toxicity [a]		PI
	0.5 h	4.0 h	0.5 h	4.0 h	
(RS)-**1**	5.8 (4.7–7.5) [b]		33.2 (28.6–37.1) [b]		5.7
(2S,αS)-**2**	46 (40–53) [b]		[b, c]		
(2R,αR)-**2**	39 (34–44) [b]		>150 [d]		>3.9
(2R,αS)-**2**	35 (29–43) [b]		159 (145–175) [b]		>4.5
(2S,αR)-**2**	47 (39–55) [b]		162 (143–185) [b]		3.5
19	8.3 (6.4–10.6) [e]		$+++$ [f]	$++$	
20	$+$	$-$	$+$	$-$	
21	$++$	$++$	$+$	$+$	
22	24 (21–26) [b]		82 (78–87) [b]		3.4
23	42 (38–46) [b]		132 (121–144) [b]		3.1
24	$++$	$++$	$++$	$++$	
25	49 (43–55) [e]		135 (115–151) [e]		2.8
27	$++$	$-$	$++$	$+$	
28	$++$	$-$	$++$	$+$	
29	20 (17–25) [e]		78 (71–84) [e]		3.9
30	$+++$	$++$	$++$	$-$	
31	$+++$	$++$	$++$	$+$	
32	28 (23–33) [e]		79 (69–84) [e]		2.8
33	$-$	$-$	$+$	$-$	
34	$++$	$-$	$-$	$-$	
36	$++$	$-$	$-$	$-$	
37	$-$	$++$	$-$	$-$	
38	$-$	$-$	$-$	$-$	
39	$-$	$-$	$-$	$-$	
40	$-$	$-$	$++$	$+$	
41	$+++$	$++$	$++$	$+$	
42	22 (17–25) [e]		66 (55–77) [e]		3.0
43	$+++$	$++$	$++$	$+$	
(S,RS)-**44**	$+++$	$++$	$++$	$-$	
(S,RS)-**45**	22 (19–28) [e]		64 (56–75) [e]		2.9
47	$++$	$-$	$++$	$++$	
49	$+++$	$++$	$++$	$++$	
50	9.7 (7.9–11.3) [e]		53.3 (45.9–67.5) [e]		5.5
51	$-$	$-$	$-$	$-$	
52	$-$	$-$	ND [g]		
58	$++++$	$-$	$+++$	$++$	
59	$++$	$-$	$++$	$+$	
60	$++$	$-$	$++$	$++$	
68	$++++$	$-$	$+++$	$++$	
75	5.8 (4.5–6.9) [e]		36.4 (31.6–40.2) [e]		6.3
76	30 (22–36) [e]	$-$	82 (70–98) [e]		2.7
77	$++$		$-$	$-$	
78	$++$		$-$	$-$	
84	$+++$	$-$	$++$	$-$	
85	59 (44–82) [e]		104 (83–118) [e]		1.8
86	180 (156–216) [h]		>500 [i]		2.8
87	76 (66–86) [e]		230 (185–266) [e]		3.0
88	$++$	$-$	$++$	$-$	
89	35 (28–43) [e]		203 (185–266) [e]		5.8
90	55 (47–62) [e]		209 (184–243) [e]		3.8
91	62 (49–74) [i]		>750 [i]		>12.1

Table V. (*Continued*)

Compound	MES		Toxicity [a]		PI
	0.5 h	4.0 h	0.5 h	4.0 h	
92	85 (68–107) [i]		>750 [i]		>8.8
93	++	−	−	−	
97	43 (42–46) [e]		126 (106–155) [e]		2.9
99	−	−	−	−	
104	−	++	++	+	
CBZ	9.85 (8.77–10.7) [b]		47.8 (39.2–59.2) [b]		4.85 [b]
PTN	6.48 (5.65–7.24) [b]		42.8 (36.4–47.5) [b]		6.60 [b]

[a] Neurotoxicity as measured by the rotorod test.
[b] Previously reported [5].
[c] Death at 80 mg kg^{-1}.
[d] Death at 170 mg kg^{-1}.
[e] Determined at 0.25 h.
[f] Unable to determine TD_{50}.
[g] Not determined.
[h] Determined at 1 h.
[i] Determined at 2 h.

recorded on a JEOL FX 90Q spectrometer. Chemical shifts were recorded in parts per million (δ) relative to tetramethylsilane (1%). Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. Ion exchange chromatography was performed on an Econo-Column (5 cm×10 cm) purchased from Bio-Rad using Amberlite IR-120 (H$^+$ form, 16–45 mesh) ion exchange resin which was purchased from Fluka. Ninhydrin spray reagent (0.1%) was purchased from Brinkmann Instruments Inc. Analytical data were obtained from Oneida Research Services Inc., Whitesboro, NY, Micro-Analysis Inc., Wilmington, DE, and Desert Analytics, Tucson, AZ.

5.1.1. Cyclopentyl phenyl ketone (**3**)

The synthesis of this compound was accomplished using the method described by Padwa and Eastman [12]. A solution of cyclopentanecarboxylic acid (11.4 g, 100 mmol) in dry benzene (60 mL) was treated in a dropwise manner with a solution of thionyl chloride (22.8 g, 190 mmol) in dry benzene (20 mL) at room temperature under nitrogen. The reaction mixture was heated to 50°C and treated with several drops of pyridine. After stirring for 2 h, the mixture was evaporated under reduced pressure. The resulting acid chloride was dissolved in dry benzene (100 mL) and added to a well-stirred suspension of powered anhydrous aluminum chloride (20.0 g, 150 mmol) in dry benzene (100 mL).

The reaction mixture was refluxed for 1 h, cooled, and poured into a mixture of concentrated hydrochloric acid (200 mL) and ice. The aqueous solution was extracted with diethyl ether (3×75 mL), and the combined extracts were washed with a saturated solution of NaHCO$_3$ followed by water, dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give an oil. Vacuum distillation afforded 9.8 g (56%) of **3** as a clear, colourless oil: b.p. 155–159°C; (27 mm) [12], b.p. 136–140°C; (16 mm); IR (neat) 3061, 1680 (C=O), 1600, 1450, 991, 700 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.82 (br m, 8H), 3.65 (m, 1H, CHCO), 7.52 (m, 3H, ArH), 8.02 (m, 2H, ArH); ^{13}C-NMR (CDCl$_3$) δ 26.3, 30.0, 46.4, 128.5, 132.7, 137.0, 202.8 (C=O).

5.1.2. Cyclohexyl phenyl ketone (**4**)

Following the procedure used for the preparation of **3**, cyclohexanecarboxylic acid (25.6 g, 200 mmol), thionyl chloride (45.7 g, 380 mmol), and anhydrous aluminum chloride (40.0 g, 300 mmol) gave an oil. Following vacuum distillation [b.p. 180–185°C (27 mm)], recrystallisation of the resulting solid from petroleum ether gave 17.2 g (46%) of **4**: m.p. 55–57°C ([13] m.p. 54°C); IR (KBr) 1682 (C=O) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.64 (br m, 10H), 3.25 (m, 1H, CHCO), 7.45 (m, 3H, ArH); ^{13}C-NMR (CDCl$_3$) δ 25.9, 26.0, 29.4, 45.6, 128.3, 128.6, 132.7, 136.4, 203.9 (C=O).

5.1.3. General procedure for the synthesis of (α-substituted)benzylamines by the Leuckhart reaction: (±)-1-(3-methoxyphenyl)ethylamine (5)

According to the method described by Moore [14], a three-necked flask was equipped with a thermometer, an addition funnel, and a reflux condenser. The top of the condenser was connected to a short-path distillation apparatus. The flask was charged with 3″-methoxyacetophenone (15.0 g, 100 mmol), formamide(18.5 g, 400 mmol), and formic acid (2.1 g, 46.6 mmol), and the mixture was refluxed for 8 h at a temperature of approximately 180°C. To prevent the deposition of ammonium carbonate in the condenser and to maintain a slightly acidic reaction mixture, formic acid (2.6 g) was added portionwise on a hourly basis. The solution was cooled and extracted with toluene (3×50 mL), and the toluene extracts were combined and evaporated under reduced pressure to yield an oil. The oil was suspended in concentrated hydrochloric acid (20 mL) and refluxed for 1 h. The warm mixture was treated with toluene (40 mL), and the aqueous portion was separated, basified to pH 11 with 30% NaOH solution, and extracted with ethyl acetate (3×75 mL). The ethyl acetate extracts were combined, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield an oil. Vacuum distillation gave 10.0 g of **5** as a colourless oil: ^{1}H-NMR (CDCl$_3$) δ 1.38 (d, 3H, $J = 6.6$ Hz, CHCH_3), 1.58 (s, 2H, CHNH_2), 3.81 (s, 3H, OCH_3), 4.09 (q, 1H, CHCH$_3$), 6.86 (br m, 3H, ArH), 7.26 (m, 1H, ArH); ^{13}C-NMR (CDCl$_3$) δ 25.6, 51.3, 55.2, 111.3, 112.0, 118.0, 129.4, 149.6, 159.7. Using this method, the α-substituted-benzylamines **6–17** were prepared. The physicochemical properties of these derivatives are given in *table I*.

5.1.4. Synthesis of (±)-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (56): general procedure for the preparation of BOC-amino acids using BOC-ON

Following a previously reported procedure [15], the acid **55** (7.1 g, 40.0, mmol) was dissolved in a mixture of water (50 mL) and acetone (50 mL) and treated with triethylamine (6.2 g, 60.0 mmol) followed by the addition of BOC-ON (10.9 g, 44.0 mmol). After stirring overnight, a mixture of water (100 mL) and ethyl acetate (150 mL) was added. The ethyl acetate layer was separated and washed with water (100 mL). The combined aqueous phase was washed with ethyl acetate (50 mL), acidified with cold 1 N HCl, and extracted with ethyl acetate (3×100 mL). The combined ethyl acetate extracts were dried (sodium sulphate), filtered, and evaporated to give a white solid upon trituration with hexane. Recrystallisation from ethyl acetate–hexane yielded 7.8 g (70%) of **56**: m.p. 150–151°C; IR (KBr) 1716 (C=O, acid), 1697 (C=O, carbamate); ^{1}H-NMR (CDCl$_3$) δ 1.45 (s, 9H, C(CH$_3$)$_3$), 3.18 (d, 2H, CH_2CHCOOH), 4.57 (m, 3H, CHNCH_2), 7.14 (s, 4H, ArH), 9.82 (s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 28.4, 31.2, 44.4, 53.5, 81.1, 126.3, 126.9, 128.2, 132.0, 134.0, 155.0, 176.6. Anal. (C$_{15}$H$_{19}$NO$_4$) C, H, N.

5.1.5. N-(tert-Butoxycarbonyl)glycine (72)

Following the method for the preparation of **56**, glycine (5.0 g, 66.6 mmol) in a mixture of water (50 mL) and acetone (50 mL), triethylamine (10.2 g, 99.9 mmol), and BOC-ON (18.1 g, 73.0 mmol) gave a white solid upon cooling. Recrystallisation from ethyl acetate–petroleum ether yielded 8.9 g (76%) of **72**: m.p. 87–89°C ([16] m.p. 85–89°C); IR (KBr) 1749 (C=O, acid), 1670 (C=O, carbamate); ^{1}H-NMR (CDCl$_3$) δ 1.46 (s, 9H, C(CH$_3$)$_3$), 3.93 (br d, 2H, NHCH_2COOH), 6.82 (br s, 1H, OCONH), 11.20 (s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 28.3, 42.3, 43.4, 80.5 (C(CH$_3$)$_3$), 156.2 (CONH), 174.7 (COOH).

5.1.6. Synthesis of 1-[(N-tert-butoxycarbonyl)amino]-1-cyclopentanecarboxylic acid (96): general procedure for the preparation of BOC-amino acids using di-tert-butyl dicarbonate

According to the method of Shuman et al. [17], 1-amino-1-cyclopentane-carboxylic acid (**95**, 4.6 g, 35.9 mmol) was dissolved in a mixture of 2 N NaOH (40 mL) and *tert*-butanol (40 mL) and di-*tert*-butyl dicarbonate (9.4 g, 43.0 mmol) were added in one portion. After stirring overnight, the *tert*-butanol was evaporated under reduced pressure, and the remaining water layer was extracted with diethyl ether (2×50 mL). The diethyl ether was discarded, and the water layer was acidified with cold 1 N HCl and extracted with ethyl acetate (3×100 mL). The combined ethyl acetate extracts were dried (sodium sulphate), filtered, and evaporated to yield after recrystallisation from ethyl acetate–hexane 3.2 g (39%) of **96**: m.p. 131–133°C ([18] m.p. 131–133°C); IR (KBr) 1734 (C=O, acid), 1697 (C=O, carbamate) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.44 (s, 9H, C(CH$_3$)$_3$), 1.91 (br m, 8H), 7.21 (br s, 1H, CONH), 9.45 (s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 24.5, 25.1, 28.3 (C(CH$_3$)$_3$), 37.7, 66.0, 80.2 (C(CH$_3$)$_3$), 158.1 (OCONH), 179.5 (COOH).

5.1.7. (±)-N-(tert-Butoxycarbonyl)-1,2,3,4-tetrahydro-1-isoquinolinecarboxylic acid (65)

Following the method for the preparation of **96**, the acid **64** (4.7 g, 26.6 mmol) and di-tert-butyl dicarbonate (7.0 g, 31.9 mmol) gave 6.2 g (84%) of **65** as an oil: ^{1}H-NMR (CDCl$_3$) δ 1.44 (s, 9H, C(CH$_3$)$_3$), 2.87 (m, 2H, CH$_2$CH$_2$N), 3.45 (m, 2H, CH$_2$CH$_2$N), 5.53 (d, 1H, CHCOOH), 7.35 (m, 4H, ArH), 9.45 (s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 28.3, 28.7, 39.9, 41.0, 57.6, 58.7, 80.9, 81.3, 126.6, 128.0, 128.6, 129.7, 135.4, 135.8, 155.0, 155.5, 176.2, 176.8.

The BOC-acid was dissolved in diethyl ether (100 mL), and dicyclohexylamine (1.8 g, 10 mmol) was added to the solution. After standing in the freezer overnight, the precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford 4.4 g (96%) of the dicyclohexylamine salt as colourless crystals: m.p. 175–177°C ([17] no reported m.p.); IR (KBr) 1697 (C=O, carbamate) and 1633 (C=O, COO$^-$) cm^{-1}.

5.1.8. (±)-N-(tert-Butoxycarbonyl)norleucine (71)

According to the method used for the preparation of **96**, norleucine (5.0 g, 38.1 mmol) and di-tert-butyl dicarbonate (10.0 g, 45.7 mmol) gave 7.6 g (87%) of **71** after recrystallisation from petroleum ether: m.p. 75–76°C ([19] no reported m.p.); IR (KBr) 1720 (C=O, acid), 1669 (C=O, carbamate); ^{1}H-NMR (CDCl$_3$) δ 1.35 (br m, 9H), 1.45 (s, 9H, C(CH$_3$)$_3$), 4.30 (br m, 1H, CHCOOH), 5.16 (br s, 1H, OCONHCH), 10.8 (s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 13.9, 22.3, 27.4, 28.3 (C(CH$_3$)$_3$), 32.2, 53.4, 54.7, 80.3 (C(CH$_3$)$_3$), 155.8 (CONH), 177.7 (COOH).

5.1.9. N-(tert-Butoxycarbonyl)-2-(n-butyl)aminoacetic acid (81)

The ethyl ester **79** (9.1 g, 57.2 mmol) was refluxed with 25% NaOH solution (50 mL) for 2 h. The reaction mixture was cooled, neutralised with 2 N HCl, and evaporated to dryness under reduced pressure to yield a solid which was used directly in the next step. Using the general method described for **96**, the crude amino acid and di-tert-butyl dicarbonate (13.1 g, 61.9 mmol) gave 9.4 g (71%) of **81** as an oil: IR (neat) 1732 (C=O, acid), 1699 (C=O, carbamate) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.92 (t, 3H, CH$_3$CH$_2$), 1.35 (br m, 4H, CH$_3$(CH$_2$)$_2$CH$_2$), 1.45 (s, 9H, C(CH$_3$)$_3$), 3.28 (t, 2H, CH$_3$(CH$_2$)$_2$CH$_2$), 3.98 (br s, 2H, NCH$_2$COOH), 9.88 (br s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 13.8, 20.0, 28.4, 30.4, 48.4, 49.1, 80.6, 156.0, 174.8. Anal. Found: C, 55.87. Calc. for (C$_{11}$H$_{21}$NO$_4$): C, 57.12%; H; N.

5.1.10. 1-[N-(tert-Butoxycarbonyl)amino]-cyclohexanecarboxylic acid (98)

In a similar manner as described for the synthesis of **96**, 1-amino-1-cyclohexanecarboxylic acid (5.0 g, 35.0 mmol) and di-tert-butyl dicarbonate (9.1 g, 42.0 mmol) gave 5.1 g (60%) of **98** after recrystallisation from ethyl acetate–hexane: m.p. 177–178°C ([20] m.p. 175–176°C); IR (KBr) 1682 (C=O, acid and carbamate); ^{1}H-NMR (CDCl$_3$) δ 1.44 (s, 9H, C(CH$_3$)$_3$), 1.78 (br m, 10H), 6.90 (br s, 1H, NHCOO), 9.14 (br s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 21.2, 25.2, 28.3 (C(CH$_3$)$_3$), 32.6, 58.8, 80.8 (C(CH$_3$)$_3$), 155.7 (NHCOO), 179.7 (COOH).

5.1.11. cis-4-[N-(tert-Butoxycarbonyl)amino]-cyclohexanecarboxylic acid (101)

The cis-acid **100** (3.2 g, 22.4 mmol) and di-tert-butyl dicarbonate (5.9 g, 26.9 mmol) gave 4.2 g (76%) of cis-**102** after recrystallisation from ethyl acetate: m.p. 169–172°C ([21] m.p. 164–168°C); IR (KBr) 1701 (C=O, acid), 1639 (C=O, carbamate) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.37 (s, 9H, C(CH$_3$)$_3$), 1.55 (br m, 8H), 2.42 (m, 1H, CHCOOH), 3.43 (m, 1H, NHCH), 6.67 (br s, 1H, NHCOO), 12.1 (br s, 1H, COOH); ^{13}C-NMR (DMSO-d_6) δ 24.8, 28.3 (C(CH$_3$)$_3$), 29.3, 39.2, 47.4, 77.3 (C(CH$_3$)$_3$), 154.9 (CON), 176.0 (COOH).

5.1.12. trans-4-[N-(tert-Butoxycarbonyl)amino]-cyclohexanecarboxylic acid (103)

The trans-acid **101** (0.4 g, 2.8 mmol) and di-tert-butyl dicarbonate (0.73 g, 3.4 mmol) gave 0.5 g (66%) of trans-**103** after recrystallisation from ethyl acetate–hexane: m.p. 183–185°C ([22] no reported m.p.); IR (KBr) 1682 (C=O, acid and carbamate) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.40 (s, 9H, C(CH$_3$)$_3$), 1.65 (br m, 8H), 1.95 (m, 1H, CHCOOH), 3.55 (br m, 1H, NHCH), 6.75 (br s, 1H, NHCOO), 9.45 (s, 1H, COOH); ^{13}C-NMR (CDCl$_3$) δ 27.7, 28.3 (C(CH$_3$)$_3$), 31.7, 41.7, 48.7, 77.4 (C(CH$_3$)$_3$), 154.8 (CON), 176.5 (COOH).

5.1.13. Synthesis of (±)-1-(tert-butoxycarbonyl)-N-[3-fluoro-α-(methyl)benzyl]-2-piperidinecarboxamide (26): general procedure for the mixed anhydride method

Using the previously reported method [5], a solution of (R,S)-1-(tert-butoxycarbonyl)-2-piperidinecarboxylic acid (4.6 g, 20.0 mmol) in dry THF (100 mL) was cooled to 0–5°C, and NMM (2.0 g, 20.0 mmol) was added under nitrogen. After stirring for 5 min, IBCF (2.7 g, 20.0 mmol) was added in one portion and immediately a white precipitate formed. The reaction was allowed to proceed for an additional 5 min, and a solution of

(±) - 3 - fluoro - α - (methyl)benzylamine (**14**, 2.8 g, 20.0 mmol) in THF (20 mL) was added over 10 min at 0–5°C. The reaction mixture was stirred at room temperature for 1 h, and the precipitated NMM hydrochloride was suction filtered. Removal of the solvent under reduced pressure gave a white solid upon trituration with ethyl acetate. Recrystallisation from ethanol–water yielded 4.9 g (70%) of **26**: m.p. 102–105°C; IR (KBr) 1697 (C=O, carbamate), 1655 (C=O, amide) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.46 (d, 3H, $J = 6.6$ Hz, CHCH_3), 1.47 (s, 9H, C(CH$_3$)$_3$), 2.10 (br m, 9H), 5.15 (m, 1H, CHCH$_3$), 6.45 (br s, 1H, CONH), 7.02 (m, 4H, ArH); ^{13}C-NMR (CDCl$_3$) δ 20.4, 22.0, 24.8, 25.4, 28.3 (C(CH$_3$)$_3$), 42.0, 48.3 (CONHCH), 54.5 (NCCO), 80.8 (C(CH$_3$)$_3$), 112.4, 113.4, 113.7, 114.6, 121.6, 121.7, 130.0, 130.3, 146.1, 157.5 (NHCOO), 168.4, 170.3 (CONH), 170.5 (CONH). Anal. (C$_{19}$H$_{27}$FN$_2$O$_3$) C, H, N. Using this procedure, the carboxamides **18**, **46**, **48**, **57**, and **67** were prepared. The physicochemical properties of these compounds are given in *tables II and III*.

5.1.14. (±)-2-(tert-Butoxycarbonyl)-amino-N-[(2,6-dimethyl)phenyl]hexaneamide (73)

(±)-N-(*tert*-Butoxycarbonyl)norleucine(**71**, 3.5 g, 15.0 mmol), NMM (1.5 g, 15.0 mmol), IBCF (2.0 g, 15.0 mmol), and 2,6-dimethylaniline (3.0 g, 25.0 mmol) gave 2.9 g (59%) of **73** after recrystallisation from ethanol–water: m.p. 152–155°C; IR (KBr) 1710 (C=O, carbamate), 1622 (C=O, amide) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.90 (t, 3H, CH_3(CH$_2$)$_3$), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.51 (br m, 6H, CH$_3$(CH_2)$_3$), 2.15 (s, 6H, 2,6-diCH$_3$), 4.26 (m, 1H, CH$_3$(CH$_2$)$_3$CH), 5.55 (br s, 1H, OCONH), 7.02 (s, 3H, ArH), 7.93 (br s, 1H, CONHAr); ^{13}C-NMR (CDCl$_3$) δ 13.9, 18.3, 22.4, 28.0, 28.3 (C(CH$_3$)$_3$, 32.0, 54.9, 80.1 (C(CH$_3$)$_3$), 127.2, 128.3, 133.6, 135.4, 156.0 (NCOO), 171.0 (CONH). Anal. (C$_{19}$H$_{30}$N$_2$O$_3$) C, H, N.

5.1.15. 2-{[N-(tert-Butoxycarbonyl)-N-(n-butyl)]amino}-N-[(2,6-dimethyl)-phenyl]acetamide (83)

The BOC-acid **81** (3.0 g, 13.0 mmol), NMM (1.3 g, 13.0 mmol), IBCF (1.8 g, 13.0 mmol), and 2,6-dimethylaniline (3.0 g, 25.0 mmol) yielded 2.3 g (53%) of **83** after recrystallisation from methanol–water: m.p. 85–87°C; IR (KBr) 1780 (C=O, carbamate) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.94 (t, 3H, CH_3(CH$_2$)$_3$), 1.35 (br m, 4H, CH$_3$(CH_2)$_2$CH$_2$), 1.50 (s, 9H, C(CH$_3$)$_3$), 2.22 (s, 6H, 2,6-diCH$_3$), 3.35 (t, 2H, CH$_3$(CH$_2$)$_2$CH_2), 4.02 (s, 2H, NCH_2CO), 7.08 (s, 3H, ArH); ^{13}C-NMR (CDCl$_3$) δ 13.8, 18.5, 19.9, 28.4 (C(CH$_3$)$_3$), 30.4, 48.8, 52.1, 81.0

(C(CH$_3$)$_3$), 127.4, 128.2, 135.3, 168.5 (CONH). Anal. (C$_{19}$H$_{30}$N$_2$O$_3$) C, H, N.

5.1.16. Synthesis of (±)-n-[3-fluoro-α-(methyl)benzyl-2-piperidinecarboxamide hydrochloride (27): general procedure for the removal of the BOC-protecting group

A solution of **26** (3.7 g, 10.6 mmol) in dichloromethane (50 mL) was cooled to 0–5°C and was saturated with hydrogen chloride gas. The mixture was stirred for another 2 h, and the solvent was removed under reduced pressure to yield an oil which solidified upon trituration with diethyl ether. Recrystallisation from absolute ethanol–diethyl ether yielded 2.52 g (83%) of **27**: m.p. 195–210°C; IR (KBr) 1682 (amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.39 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.78 (br m, 6H), 2.94 (br m, 2H, CH_2NH$_2^+$ CH), 3.80 (m, 1H, NH$_2^+$CHCO), 4.96 (m, 1H, CHCH$_3$), 7.24 (m, 4H, ArH), 9.15 (br s, 2H, NH$_2^+$), 9.35 (br d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 21.2, 21.6, 22.4, 26.9, 27.1, 43.2, 48.1, 56.7, 56.9, 112.1, 112.5, 113.1, 113.4, 114.0, 121.8, 122.0, 122.3, 122.4, 130.1, 130.5, 147.3, 147.6, 158.8, 167.6 (CONH); MS (CI, methane) m/z 251 (M$^+$+1). Anal. (C$_{14}$H$_{20}$ClFN$_2$O) C, H, N.

5.1.17. (±)-2-Amino-N-[(2,6-dimethyl)phenyl]-hexaneamide hydrochloride (75)

The BOC-amide **73** (2.3 g, 6.9 mmol) gave 1.0 g (52%) of **75** after recrystallisation from methanol–diethyl ether: m.p. 215–217°C; IR (KBr) 1662 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.93 (t, 3H, CH_3(CH$_2$)$_3$), 1.62 (br m, 6H, CH$_3$(CH_2)$_3$), 2.19 (s, 6H, 2,6-diCH$_3$), 4.15 (t, 1H, NH$_3^+$CHCO), 7.07 (s, 3H, ArH), 8.53 (br s, 3H, NH$_3^+$), 10.28 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 13.7, 18.3, 21.9, 26.4, 31.0, 52.4, 126.7, 127.8, 134.1, 135.1, 167.2.; MS (CI, methane) m/z 235 (M$^+$+1). Anal. Found: C, 59.16; N, 9.85. Calc. for (C$_{14}$H$_{23}$ClN$_2$O): C, 62.10; H; N, 10.34%.

5.1.18. 2-Amino-N-[(2,6-dimethyl)phenyl]acetamide hydrochloride (76)

N-(*tert*-Butoxycarbonyl)glycine (**72**, 1.5 g, 8.3 mmol), NMM (0.8 g, 8.3 mmol), IBCF (1.1 g, 8.3 mmol), and 2,6-dimethylaniline (2.4 g, 20.0 mmol) gave 1.4 g (59%) of the BOC-amide after recrystallisation from ethanol–water: m.p. 120–122°C; IR (KBr) 1696 (C=O, carbamate), 1655 (C=O, amide); ^{1}H-NMR (CDCl$_3$) δ 1.45 (s, 9H, C(CH$_3$)$_3$), 2.18 (s, 6H, 2,6-diCH$_3$), 3.94 (d, 2H, $J = 5.9$ Hz, COCH_2NH), 5.55 (br s, 1H, OCONH), 7.05 (s, 3H, ArH), 7.81 (br s, 1H, CONH). In the usual manner, the BOC-amide (1.2 g, 4.3 mmol) gave 0.8 g

(81%) of **76** after recrystallisation from absolute etha-
nol–diethyl ether: m.p. 292–294°C; IR (KBr) 1674
(C=O, amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.16 (s, 6H,
2,6-diCH_3), 3.84 (s, 2H, CH_2CONH), 7.08 (s, 3H, ArH),
8.34 (br s, 3H, NH$_3^+$), 10.11 (s, 1H, CONH); ^{13}C-NMR
(DMSO-d_6) δ 18.2, 40.3, 126.7, 127.8, 134.2, 135.1,
164.6 (CONH); MS (CI, methane) m/z 179 (M$^+$+1).
Anal. (C$_{10}$H$_{15}$ClN$_2$O) C, H, N.

5.1.19. Reaction of (±)-**71** with (±)-(α-methyl)benzylamine: formation of the diastereoisomeric mixture (**77**)

(±)-**71** (2.3 g, 10.0 mmol), NMM (1.0 g, 10.0 mmol),
IBCF (1.4 g, 10.0 mmol), and (±)-α-methylbenzylamine
(1.2 g, 10.0 mmol) afforded a diastereoisomeric mixture
as an oil. After deprotection in the normal manner, the
mixture was chromatographed on a silica gel column
using ethyl acetate–ammonium hydroxide (99:1) as the
mobile phase. Fractions homogeneous by TLC were
combined and concentrated under vacuum to yield 0.5 g
(21%) of a light yellow oil of the less-polar diastereoiso-
mer as a racemic mixture: IR (neat) 1655 (C=O, amide)
cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.88 (t, 3H, CH_3(CH$_2$)$_3$CH),
1.37 (br m, 6H), 1.49(d, 3H, J = 6.8 Hz, CHCH_3), 1.51
(s, 2H, NH$_2$), 3.41 (m, 1H, NH$_2$CHCO), 5.08 (m, 1H,
NHCHCH$_3$), 7.31 (m, 5H, ArH), 7.53 (m, 1H, CONH);
^{13}C-NMR (CDCl$_3$) δ 14.0, 22.1, 22.5, 28.0, 34.8, 48.1,
55.3, 126.1, 127.1, 128.6, 143.9, 174.2. Anal. Found: C,
69.99; N, 11.54. Calc. for (C$_{14}$H$_{22}$N$_2$O): C, 71.75; H; N,
11.96%.

The more polar diastereoisomer was obtained as a
light yellow oil as a racemic mixture. The hydrochloride
was prepared and recrystallised from isopropanol–di-
ethyl ether to afford 0.7 g (26%): m.p. 198–200°C; IR
(KBr) 1678 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.78 (t,
3H, J = 5.4 Hz, CH_3(CH$_2$)$_3$CH), 3.76 (m, 1H, NH$_3^+$
CHCO), 4.96 (m, 1H, CONHCHCH$_3$), 7.31 (m, 5H,
ArH), 9.07 (d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ
13.7, 21.7, 22.3, 26.1, 30.9, 48.3, 52.2, 125.9, 126.8,
128.2, 144.2, 167.9. Anal. (C$_{14}$H$_{23}$ClN$_2$O) C, H, N.

5.1.20. 2-Amino-N-(α-methylbenzyl)acetamide hydrochloride (**78**)

BOC-glycine (**72**, 1.8 g, 10.0 mmol), NMM (1.0 g,
10.0 mmol), IBCF (1.4 g, 10.0 mmol), and (±)-α-methyl-
benzylamine (1.2 g, 10.0 mmol) yielded an oil. After
deprotection, the hydrochloride was recrystallised from
absolute ethanol–diethyl ether to give 1.6 g (73%) of **78**:
m.p. 124–127°C; IR (KBr) 1660 (C=O, amide) cm^{-1};
^{1}H-NMR (DMSO-d_6) δ 1.38 (d, 3H, J = 7.1 Hz,

CHCH_3), 3.59 (s, 2H, CH_2CONH), 4.96 (m, 1H,
NHCHCH$_3$), 7.33 (m, 5H, ArH), 8.27 (br s, 3H, NH$_3^+$),
9.15 (d, 1H, J = 8.0 Hz, CONH); ^{13}C-NMR (DMSO-d_6)
δ 22.4, 40.0, 48.3, 126.0, 126.7, 128.2, 143.9, 164.8
(CONH). Anal. (C$_{10}$H$_{15}$ClN$_2$O) C, H, N.

5.1.21. (±)-2-(n-Butylamino)-N-(α-methylbenzyl)-acetamide hydrochloride (**82**)

The BOC-acid **81** (4.6 g, 20.0 mmol), NMM (2.0 g,
20.0 mmol), IBCF (2.7 g, 20.0 mmol), and (±)-α-methyl-
benzylamine (2.4 g, 20.0 mmol) gave an oil. After depro-
tection, the hydrochloride was recrystallised from
absolute ethanol–diethyl ether to yield 2.2 g (41%) of
82: m.p. 129–131°C; IR (KBr) 1666 (C=O) cm^{-1}; ^{1}H-
NMR (CDCl$_3$) δ 0.86 (t, 3H, J = 6.6 Hz, CH_3CH$_2$), 1.48
(d, 3H, J = 6.8 Hz, CHCH_3), 1.50 (br m, 4H,
CH$_3$(CH_2)$_2$), 2.82 (m, 2H, CH$_3$(CH$_2$)$_2$CH_2), 3.85 (s, 2H,
NH$_2^+$CH_2CO), 4.99 (m, 1H, CHCH$_3$), 7.27 (m, 5H,
ArH), 9.00 (br m, 3H, NH$_2^+$ and CONH); ^{13}C-NMR
(CDCl$_3$) δ 13.5, 19.8, 22.5, 27.9, 48.0, 48.7, 50.1, 126.2,
127.2, 128.6, 143.4, 164.2. Anal. Found: C, 60.93. Calc.
for (C$_{14}$H$_{23}$ClN$_2$O): C, 62.09%; H; N.

5.1.22. 2-(n-Butylamino)-N-[(2,6-dimethyl)phenyl]-acetamide hydrochloride (**84**)

The BOC-amide **83** (2.0 g, 6.0 mmol) gave 1.2 g (71%)
of **84** after deprotection and recrystallisation from abso-
lute ethanol: m.p. 139–141°C; IR (KBr) 1676 (C=O,
amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.89 (t, 3H,
CH_3(CH$_2$)$_3$), 1.45 (br m, 4H, CH$_3$(CH_2)$_2$CH$_2$), 2.17 (s,
6H, 2,6-diCH_3), 2.95 (br t, 2H, CH$_3$(CH$_2$)$_2$CH_2NH),
4.00 (s, 2H, NHCH_2CO), 7.08 (s, 3H, ArH), 9.33 (br s,
2H, NH$_2^+$), 10.27 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6)
δ 13.4, 18.1, 19.2, 27.2, 46.5, 47.5, 126.7, 127.6, 134.0,
135.0, 163.6 (CONH); MS (CI, methane) m/z 235 (M$^+$+
1). Anal. (C$_{14}$H$_{23}$ClN$_2$O) C, H, N.

5.1.23. (±)-1-Amino-N-[(α-methyl)benzyl]-cyclopentanecarboxamide (**97**)

The BOC-acid **96** (2.3 g, 10.0 mmol), NMM (1.0 g,
10.0 mmol), IBCF (1.4 g, 10.0 mmol), and (±)-α-methyl-
benzylamine afforded 1.1.g (48%) of **97** after deprotec-
tion and recrystallisation from diethyl ether–petroleum
ether: m.p. 77–78°C; IR (KBr) 1642 (C=O, amide)
cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.48 (d, 3H, J = 7.1 Hz,
CH_3CH), 1.81 (br m, 10H), 5.08 (m, 1H, CONHCH),
7.31 (s, 5H, ArH), 8.12 (br s, 1H, CONH); ^{13}C-NMR
(CDCl$_3$) δ 22.3, 24.5, 40.6, 48.5, 65.1, 126.1, 127.1,
128.6, 143.9, 176.3 (CONH). Anal. (C$_{14}$H$_{20}$N$_2$O) C, H,
N.

5.1.24. N-[(2,6-Dimethyl)phenyl]-1-aminocyclohexanecarboxamide (99)

The BOC-acid **98** (2.4 g, 10.0 mmol), NMM (1.0 g, 10.0 mmol), IBCF (1.4 g, 10.0 mmol), and 2,6-dimethylaniline (2.4 g, 20.0 mmol) gave, after deprotection and recrystallisation from petroleum ether, 0.4 g (16%) of **99** as the free base: m.p. 133–135°C; IR (KBr) 1666 (C=O, amide) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.61 (m, 12H), 2.20 (s, 6H, 2,6-diCH$_3$), 7.06 (s, 3H, ArH), 9.38 (br s, 1H, CONH). Anal. (C$_{15}$H$_{22}$N$_2$O) C, H, N.

5.1.25. cis-N-[(2,6-Dimethyl)phenyl]-4-aminocyclohexanecarboxamide hydrochloride (104)

The *cis*-BOC-acid **102** (3.7 g, 15.0 mmol), NMM (1.5 g, 15.0 mmol), IBCF (2.0 g, 15.0 mmol), and 2,6-dimethylaniline (2.4 g, 20.0 mmol) afforded, after deprotection and recrystallisation from absolute ethanol–diethyl ether, 2.1 g (49%) of **104**: m.p. 275°C; IR (KBr) 1651 (C=O, amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.75 (br m, 8H), 2.13 (s, 6H, 2,6-diCH$_3$), 3.27 (br m, 2H, C*H*NH$_2$ and C*H*CONH), 7.05 (s, 3H, ArH), 8.21 (br s, 3H, NH$_3^+$), 9.32 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.2, 24.3, 27.1, 40.4, 47.4, 126.3, 127.6, 135.3, 172.9 (CONH); MS (CI, methane) m/z 247 (M$^+$+1). Anal. Found: C, 62.96. Calc. for (C$_{15}$H$_{23}$ClN$_2$O): C, 63.70%; H; N.

5.1.26. trans-N-[(2,6-Dimethyl)phenyl]-4-aminocyclohexanecarboxamide hydrochloride (105)

The *trans*-acid **103** (0.4 g, 1.4 mmol), NMM (0.1 g, 1.4 mmol), IBCF (0.2 g, 1.4 mmol), and 2,6-dimethylaniline (1.0 g, 8.3 mmol) gave, after deprotection and recrystallisation from absolute ethanol–diethyl ether, 0.15 g (38%) of *trans*-**105**: m.p. >325°C; IR (KBr) 1637 (C=O, amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.75 (br m, 8H), 2.11 (s, 6H, 2,6-diCH$_3$), 3.07 (br m, 2H, NH$_3^+$ and C*H*CONH), 7.05 (s, 3H, ArH), 8.25 (br s, 3H, NH$_3^+$), 9.29 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.0, 27.4, 29.5, 42.6, 48.8, 126.3, 127.6, 135.2, 173.0 (CONH). Anal. (C$_{15}$H$_{23}$ClN$_3$O) C, H, N.

5.1.27. General procedure for the synthesis of cycloalkanecarboxamides: synthesis of (±)-N-(α-methylbenzyl)cyclohexanecarboxamide (87)

A solution of cyclohexanecarboxylic acid (2.6 g, 20.0 mmol) in methylene chloride (50 mL) was cooled to 0–5°C under a nitrogen atmosphere, and the mixture was treated in a dropwise manner with a solution of SOCl$_2$ (7.1 g, 59.7 mmol) in methylene chloride (20 mL). The reaction mixture was allowed to warm to room

temperature and was stirred overnight. The solvent was evaporated under reduced pressure, and additional methylene chloride was added and again evaporated. The resulting residue was dissolved in dry THF (80 mL), cooled to 0–5°C, and triethylamine (2.0 g, 20.0 mmol) was added under nitrogen. The cooled solution was treated dropwise with (±)-α-methylbenzylamine (2.4 g, 20.0 mmol) in dry THF (20 mL). After warming to room temperature, the reaction mixture was stirred for 2 h and filtered to remove the precipitated triethylamine hydrochloride. Evaporation of the filtrate under reduced pressure gave an oil which was partitioned between ethyl acetate (100 mL) and 1 N HCl (50 mL). The ethyl acetate layer was separated, washed with water (100 mL), dried (Na$_2$SO$_4$), filtered, and evaporated under reduced pressure to afford a solid. Recrystallisation from ethyl acetate–hexane yielded 2.2 g (47%) of **87**: m.p. 112–113°C; IR (KBr) 3321 (NH, amide), 1644 (C=O, amide) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.44 (d, 3H, $J = 6.8$ Hz, CHC*H*$_3$), 1.51 (br m, 11H), 5.19 (m, 1H, CONHC*H*CH$_3$), 6.05 (br s, 1H, CONH), 7.28 (s, 5H, ArH); ^{13}C-NMR (CDCl$_3$) δ 21.8, 25.7, 29.6, 45.5, 48.2, 126.1, 127.1, 128.5, 143.6, 175.2 (CONH). Anal. (C$_{15}$H$_{21}$NO$_2$) C, H, N. Following this method, the cycloalkanecarboxamides **85**, **86**, and **88**–**93** were prepared. The physicochemical properties of these compounds are given in *table IV*.

5.1.28. (±)-1-Benzyl-N-[(α-methylbenzyl)-2-piperidinecarboxamide hydrochloride (35)

To a suspension of the carboxamide **2** (2.0 g, 8.6 mmol) and potassium carbonate (1.4 g, 10.3 mmol) in DMF (40 mL), a solution of benzyl bromide (1.8 g, 10.3 mmol) in DMF (10 mL) was added dropwise under nitrogen. The reaction mixture was heated at 50°C for 5 h, and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and water (50 mL), and the ethyl acetate phase was separated, dried (Na$_2$SO$_4$), filtered, and evaporated under vacuum to afford an oil. A hydrochloride was prepared and recrystallised from absolute ethanol–diethyl ether to yield 1.2 g (39%) of **35**: m.p. 243–245°C; ^{1}H-NMR (DMSO-d_6) δ 1.46 (d, 3H, CHC*H*$_3$), 1.64 (br m, 6H), 3.68 (br m, 5H, C*H*$_2$(C*H*$_2$)NH$^+$C*H*), 5.05 (m, 1H, CONHC*H*CH$_3$), 7.41 (m, 10H, ArH), 9.48 (br s, 1H, NH$^+$), 9.91 (m, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 21.1, 21.7, 22.3, 28.2, 48.6, 50.8, 58.0, 64.7, 125.8, 126.9, 128.3, 128.7, 129.5, 131.5, 143.9, 166.9. Anal. (C$_{21}$H$_{27}$ClN$_2$O) C, H, N.

5.1.29. (±)-1-Benzoyl-N-(α-methylbenzyl)-2-piperidinecarboxamide (39)

A solution of benzoyl chloride (0.6 g, 4.0 mmol) and triethylamine (0.4 g, 4.0 mmol) in THF (50 mL) was cooled to 0–5°C under nitrogen and treated dropwise with a solution of the amide **2** (mixture of diastereoisomers) (0.9 g, 4.0 mmol) in THF (20 mL). The mixture was stirred at room temperature for 2 h, the precipitated triethylamine hydrochloride was suction filtered, and the filtrate was removed under reduced pressure to give a yellow solid. The resulting solid was partitioned between ethyl acetate (100 mL) and water (50 mL), and the organic layer was washed with 1 N HCl, dried (Na$_2$SO$_4$), filtered, and evaporated under vacuum to afford 0.7 g (53%) of **39** after recrystallisation from petroleum ether–diethyl ether: m.p. 144–146°C; ^{1}H-NMR (CDCl$_3$) δ 1.64 (d, 3H, CHCH_3), 2.04 (br m, 6H), 3.35 (br m, 3H, CH_2NHCH), 5.21 (m, 1H, CONHCHCH$_3$), 6.90 (br s, 1H, CONH), 7.35 (m, 10H, ArH); ^{13}C-NMR (CDCl$_3$) δ 10.5, 22.2, 25.6, 46.1, 48.7, 52.8, 126.1, 127.2, 127.4, 129.1, 130.2, 135.4, 143.5, 169.9, 172.3. Anal. (C$_{21}$H$_{24}$N$_2$O$_2$) C, H, N.

5.1.30. N-[(2,6-Dimethyl)phenyl]-4-pyridinecarboxamide (50)

A suspension of isonicotinic acid (2.5 g, 20.0 mmol) in pyridine (100 mL) was cooled to 0-5°C under a nitrogen atmosphere and treated in a dropwise manner with a solution of thionyl chloride (7.1 g, 60.0 mmol) in pyridine (20 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed under vacuum, and the resulting residue was dissolved in THF (50 mL) and treated with triethylamine (2.0 g, 20.0 mmol) followed by the dropwise addition of 2,6-dimethylaniline (2.4 g, 20.0 mmol) in THF (20 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h, the triethylamine hydrochloride was suction filtered, and the filtrate was evaporated under vacuum to give a solid upon trituration with hexane. Recrystallisation from ethyl acetate–hexane gave 1.4 g (30%) of **50**: m.p. 157–159°C; ^{1}H-NMR (CDCl$_3$) δ 2.19 (s, 6H, 2,6-diCH$_3$), 7.11 (s, 3H, ArH), 7.64 (dd, 2H, J = 1.7, 4.5 Hz, H-3, H-5), 8.18 (br s, 1H, CONH), 8.66 (dd, 2H, J = 1.7, 4.5 Hz, H-2, H-6); ^{13}C-NMR (CDCl$_3$) δ 18.3, 121.1, 127.8, 128.3, 133.3, 135.5, 141.4, 150.5, 164.1. Anal. (C$_{14}$H$_{14}$N$_2$O) C, H, N.

5.1.31. [1-(Phenylethyl)piperidin-2-yl]methylamine (51)

A solution of the carboxamide **2** (2.0 g, 8.6 mmol) in dry THF (40 mL) was added dropwise to a stirred suspension of LAH (1.0 g, 25.8 mmol) in dry THF (60 mL) under a nitrogen atmosphere. The mixture was refluxed for 12 h, cooled, treated carefully with water to decompose the excess LAH, and basified with 1 N NaOH to pH 10. The precipitate was filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was partitioned between ethyl acetate (100 mL) and water (100 mL), and the ethyl acetate phase was separated, dried (Na$_2$SO$_4$), filtered, and evaporated to yield an oil. The crude product was subjected to flash chromatography on a silica gel column using ethyl acetate–methanol–ammonium hydroxide (80:20:1) as the mobile phase. Fractions homogeneous by TLC were combined and concentrated under reduced pressure to afford an oil. A dihydrochloride was prepared and recrystallised from 2-propanol–diethyl ether to yield 1.1 g (44%) of **51**: m.p. 214–216°C; ^{1}H-NMR (D$_2$O) δ 1.74 (d, 3H, J = 7 Hz, CHCH_3), 1.78 (br m, 6H), 3.25 (br m, 5H, CH_2NH$_2^+$CHCH$_2$NH$_2^+$), 4.53 (q, 1H, J = 7 Hz, CHCH$_3$), 7.55 (s, 5H, ArH); ^{13}C-NMR (D$_2$O) δ 17.6, 20.6, 20.8, 21.7, 23.5, 23.9, 28.9, 47.7, 49.6, 49.8, 55.7, 55.9, 57.0, 62.3, 62.5, 130.4, 132.2, 132.7, 137.4. Anal. (C$_{14}$H$_{24}$Cl$_2$N$_2$) C, H, N.

5.1.32. (±)-2-[(4-Trifluoromethyl)benzyl]-2,3,5,6,7,8-hexahydroimidazo[1,5-a]-pyridin-1-one (52)

Using the described method [23], a mixture of **23** (6.0 g, 21.0 mmol), formaldehyde (60 mL), and ethanol (5 mL) was refluxed under a nitrogen atmosphere for 2 h. The reaction mixture was concentrated to half volume under reduced pressure, diluted with water (60 mL), and extracted with diethyl ether (3×30 mL). The combined diethyl ether extracts were washed with water (50 mL), dried (Na$_2$SO$_4$), filtered, and evaporated under reduced pressure to give a solid upon cooling. Recrystallisation from petroleum ether afforded 5.4 g (86%) of **52**: m.p. 67–70°C; IR (KBr) 1696 (C=O, lactam) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 2.05 (br m, 9H), 3.81 (dd, 1H, J = 2 Hz, 5.1 Hz, H-3$_{ax}$), 4.04 (d, 1H, J = 5.1 Hz, H-3$_{eq}$), 4.52 (q, 2H, NCH$_2$Ar), 7.48 (m, 4H, ArH); ^{13}C-NMR (CDCl$_3$) δ 23.2, 24.4, 24.9, 45.0, 49.6, 63.2, 67.7, 118.3, 125.8, 126.0, 126.1, 128.3, 140.6, 173.0. Anal. (C$_{15}$H$_{17}$F$_3$N$_2$O) C, H, N.

5.1.33. Dimethyl 2-acetyl-1,2,3,4-tetrahydro-3,3-isoquinolinedicarboxylate (53)

Using the method of Kammermeier et al. [24], a stirred suspension of α,α'-dichloro-o-xylene (17.5 g, 100

mmol) and diethyl acetamidomalonate (21.7 g, 100 mmol) in methanol (175 mL) was treated dropwise with 30% sodium methoxide in methanol (20 mL, 111 mmol) over 10 min at room temperature under nitrogen. The reaction mixture was heated to reflux, treated with additional 30% sodium methoxide in methanol (22 mL, 122 mmol) in a dropwise fashion over 2 h, and stirred for another 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting solid residue was partitioned between water (100 mL) and ethyl acetate (150 mL). The aqueous phase was extracted with ethyl acetate (2×75 mL), and the combined ethyl acetate extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a solid. Recrystallisation from 2-propanol–$tert$-butyl methyl ether gave 12.3 g (43%) of **53**: m.p. 141–143°C; ([24] m.p. 141–143°C); IR (KBr) 1745 (C=O, ester), 1649 (C=O, amide) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 2.29 (s, 3H, NHCOCH_3), 3.43 (s, 2H, ArCH_2CHN), 3.68 (s, 6H, CH(COOCH_3)$_2$), 4.68 (s, 2H, ArCH$_2$N), 7.20 (br m, 4H, ArH); ^{13}C-NMR (CDCl$_3$) δ 22.3, 37.6, 47.9, 52.9, 68.2, 126.1, 127.5, 127.8, 127.9, 132.3, 132.7, 168.5, 171.0.

5.1.34. (±)-2-Acetyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (54)

Following the method of Kammermeier et al. [24], a well-stirred suspension of **53** (10.7 g, 37.0 mmol) in a mixture of methanol (100 mL) and water (20 mL) was treated portionwise with KOH (4.6 g, 81 mmol) over 30 min. The mixture was refluxed for 5 h, cooled, and evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and 2 N HCl (pH 1), and the aqueous phase was separated and extracted with ethyl acetate (3×50 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated under vacuum to yield 7.2 g (89%) of **54** after trituration with $tert$-butyl methyl ether: m.p. 161–165°C ([24] m.p. 171–173°C); IR (KBr) 1738 (C=O, acid), 1649 (C=O, amide) cm^{-1}.

5.1.35. (±)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (55)

Compound **54** (6.5 g, 30.0 mmol) was refluxed in 6 N HCl (50 mL) for 5 h, cooled to 0–5°C in an ice-water bath, and treated with aqueous NH_3 (25%) to pH 7. The mixture was stirred for an additional 1 h in an ice-water bath. The resulting precipitate was filtered, washed with water, and dried to yield 4.4 g (83%) of **55**: m.p.

327–330°C ([24] m.p. 321–325°C); IR (KBr) 1600 (C=O), 1497, 1460 cm^{-1}.

5.1.36. (±)-1,2,3,4-Tetrahydro-1-isoquinolinecarboxylic acid (64)

Using the method of Shuman et al. [17], a mixture of 1-isoquinoline-carboxylic acid (12.5 g, 72.2 mmol) and platinum(IV) oxide (1.0 g) in glacial acetic acid (100 mL) was shaken on a Parr hydrogenator at an initial pressure of 60 psi for 24 h. The catalyst was filtered through a Celite pad, and the solvent was removed under reduced pressure to afford a solid. The solid was triturated with water, filtered, and dried to give 7.51 g (59%) of **64**: m.p. 269–271°C ([17] no reported m.p.); IR 1614 (C=O).

5.1.37. Ethyl 2-(n-butyl)aminoacetate (79)

According to the method described by Speziale and Jaworski [25], a solution of n-butylamine (16.8 g, 230 mmol) in benzene (100 mL) was treated dropwise with a solution of ethyl bromoacetate (16.7 g, 10 mmol) in benzene(15 mL) at room temperature. The reaction mixture was heated at reflux for 2 h, cooled, and basified with 2 N NaOH to pH 10. The organic layer was separated, washed with water (2×50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give an oil. Vacuum distillation yielded 9.1 g (57%) of **79** as a colourless oil: b.p. 57–60°C (1.1 mm, [25] b.p. 52°C (1.1 mm); IR (neat) 1739 (C=O) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.04 (t, 6H, CH_3(CH$_2$)$_2$ and OCH$_2$CH_3), 1.42 (br m, 5H, CH$_3$(CH_2)$_2$CH$_2$NH), 2.60 (t, 2H, $J = 6.6$ Hz, CH$_3$(CH$_2$)$_2$CH_2), 3.41 (s, 2H, NCH_2CO), 4.00 (q, 2H, OCH_2CH$_3$).

5.1.38. (5,5-Tetramethylene)hydantoin (94)

Using the method of Henze and Speer [26], a mixture of ammonium carbonate (45.5 g, 470 mmol) and cyclopentanone (8.4 g, 100 mmol) in 50% ethanol (250 mL) was treated with NaCN (9.8 g, 200 mmol). After heating at 58–60°C for 2 h, the reaction mixture was cooled to room temperature, concentrated to a volume of about 150 mL under reduced pressure, and chilled in an ice-bath. The resulting precipitate was filtered to give 9.8 g (64%) of **94**: m.p. 202–203°C ([26] m.p. 204–205°C).

5.1.39. 1-Amino-1-cyclopentanecarboxylic acid (95)

Using the method of Conners and Ross [27], a mixture of **94** (7.83 g, 50.8 mmol) and barium hydroxide

octahydrate (28.0 g, 88.8 mmol) in water (170 mL) was heated to reflux for 3 h. The mixture was cooled to room temperature, and the precipitated barium carbonate was filtered. The filtrate was treated with ammonium carbonate (6.3 g, 65.7 mmol) to remove the excess barium. Evaporation of the filtrate under reduced pressure gave 4.6 g (71%) of **95** after recrystallisation from ethanol–water: m.p. >317°C ([27] m.p. 328°C).

*5.1.40. cis-4-Aminocyclohexanecarboxylic acid (**100**) and trans-4-aminocyclohexanecarboxylic acid (**101**)*

Using the method of Skaric et al. [28], a mixture of 4-aminobenzoic acid (1.6 g, 11.6 mmol) and platinum-(IV) oxide (0.4 g) in 30% ethanol was shaken on a Parr hydrogenator at an initial pressure of 52 psi for 24 h at room temperature. This process was repeated six times, and the solutions were combined. After removal of the catalyst by filtration, the filtrate was removed under reduced pressure to give 8.0 g (81%) of a mixture of *cis*-and *trans*-diastereoisomers after recrystallisation from aqueous ethanol–diethyl ether: m.p. >300°C ([28] m.p. >300°C).

Using the method of Ferber and Bruker [29], the diastereoisomeric mixture (8.0 g, 55.9 mmol) was dissolved in water, and ethanol was added to induce crystallisation of the *cis*-isomer. The crystals were collected, and the filtrate was treated in a similar manner to obtain two additional crops of the *cis*-acid. Recrystallisation of the combined crops from ethanol–water gave 3.9 g (49%) of *cis*-**100**: m.p. 295–298°C ([30] m.p. 258–264°C); ¹H-NMR (D₂O) δ 1.77 (br m, 8H), 2.41 (m, 1H, C*H*COOH), 3.27 (m, 1H, C*H*NH₂); ¹³C-NMR (D₂O) δ 27.6, 30.1, 44.3, 51.8, 186.4. The filtrates were combined and concentrated under reduced pressure, and the resulting solid was crystallised from aqueous ethanol–diethyl ether to give the *trans*-acid. The filtrate yielded two additional crops of the *trans*-acid. Recrystallisation of the combined crops from aqueous ethanol–diethyl ether yielded 1.3 g (16%) of *trans*-**101**: m.p. 297–302°C ([30] m.p. 262–267°C); ¹H-NMR (D₂O) δ 1.71 (br m, 4H), 2.13 (br m, 5H), 3.15 (m, 1H, C*H*NH₂); ¹³C-NMR (D₂O) δ 30.3, 32.3, 47.9, 52.5, 187.4.

6. NMR data

Compound **6**. ¹H-NMR (CDCl₃) δ 1.37 (d, 3H, $J = 6.4$ Hz, CHC*H₃*), 1.58 (s, 2H, CHN*H₂*), 3.86 (s, 3H, OC*H₃*), 3.89 (s, 3H, OC*H₃*), 4.09 (q, 1H, $J = 6.4$ Hz, C*H*CH₃), 6.87 (m, 3H, ArH); ¹³NMR (CDCl₃) δ 25.8 (CH*C*H₃), 51.1 (*C*HCH₃), 56.2 (O*C*H₃), 109.8, 111.9, 117.8, 140.9, 148.3, 149.5.

Compound **7**. ¹H-NMR (CDCl₃) δ 1.49 (s, 2H, CHN*H₂*), 2.90 (m, 2H, CHC*H₂*), 4.18 (m, 1H, C*H*CH₂), 7.26 (m, 10H, ArH); ¹³C-NMR (CDCl₃) δ 46.7 (CH*C*H₂), 57.7 (*C*HCH₂), 126.4, 126.5, 127.1, 128.5, 129.4, 139.3, 145.9.

Compound **8**. ¹H-NMR (CDCl₃) δ 1.71 (s, 2H, CHN*H₂*), 5.13 (s, 1H, C*H*NH₂), 7.28 (m, 9H, ArH); ¹³C-NMR (CDCl₃) δ 59.5 (*C*HNH₂), 125.2, 126.9, 127.3, 128.7, 129.7, 134.5, 145.1, 147.9.

Compound **9**. ¹H-NMR (CDCl₃) δ 0.82 (t, 3H, $J = 7.2$ Hz, CH₂C*H₃*), 1.40 (s, 2H, CHN*H₂*), 1.62 (m, 2H, C*H₂*CH₃), 3.71 (t, 1H, $J = 6.8$ Hz, C*H*CH₃), 7.24 (s, 5H, ArH); ¹³C-NMR (CDCl₃) δ 10.9 (CH₂*C*H₃), 32.5 (*C*HCH₃), 57.8 (*C*HCH₂), 126.4, 126.8, 128.3, 146.5.

Compound **10**. ¹H-NMR (CDCl₃) δ 0.77 (d, 3H, $J = 6.6$ Hz, CHC*H₃*), 0.97 (d, 3H, $J = 6.6$ Hz, CHC*H₃*), 1.54 (s, 2H, CHN*H₂*), 1.75 (m, 1H, CHC*H*(CH₃)₂), 3.58 (d, 1H, $J = 7.3$ Hz, C*H*CH(CH₃)₂), 7.27 (s, 5H, ArH); ¹³C-NMR (CDCl₃) δ 18.9, 19.8, 35.4, 62.5, 126.8, 127.0, 128.1, 145.5.

Compound **11**. ¹H-NMR (DMSO-*d₆*) δ 1.75 (br m, 9H), 3.98 (d, 1H, $J = 9.5$ Hz, C*H*NH₃⁺), 7.48 (m, 5H, ArH), 8.85 (br s, 3H, NH₃⁺); ¹³C (DMSO-*d₆*) δ 24.4, 24.9, 29.6, 30.0, 44.6 (*C*HCHNH₃⁺), 59.2 (*C*HNH₃⁺), 127.8, 128.2, 128.5, 138.6.

Compound **12**. ¹H-NMR (CDCl₃) δ 1.48 (br m, 11H), 1.58 (s, 2H, CHN*H₂*), 3.56 (d, 1H, $J = 7.1$ Hz, C*H*NH₂), 7.25 (s, 5H, ArH); ¹³C-NMR (CDCl₃) δ 26.1, 26.3, 29.4, 30.0, 45.1 (*C*HCHNH₂), 61.6 (*C*HNH₂), 126.6, 126.9, 128.0, 145.4.

Compound **13**. ¹H-NMR (CDCl₃) δ 1.39 (d, 3H, $J = 6.6$ Hz, CHC*H₃*), 1.52 (s, 2H, CHN*H₂*), 4.19 (q, 1H, $J = 6.6$ Hz, C*H*CH₃), 7.55 (m, 4H, ArH); ¹³C-NMR (CDCl₃) δ 25.8 (CH*C*H₃), 51.1 (*C*HCH₃), 118.1 (*C*F₃), 122.7, 122.8, 123.0, 123.5, 123.6, 123.8, 124.0, 128.9, 129.3, 130.5, 148.9, 170.0, 182.0.

Compound **14**. ¹H-NMR (CDCl₃) δ 1.36 (d, 3H, $J = 6.6$ Hz, CHC*H₃*), 1.52 (s, 2H, CHN*H₂*), 4.11 (q, 1H, $J = 6.6$ Hz, C*H*CH₃), 7.14 (m, 4H, ArH); ¹³C-NMR (CDCl₃) δ 25.7 (CH*C*H₃), 51.0 (*C*HCH₃), 112.1, 113.1, 114.0, 121.3, 121.4, 129.7, 130.1, 150.4, 150.7, 157.6, 168.5.

Compound **15**. ¹H-NMR (CDCl₃) δ 1.37 (d, 3H, $J = 6.6$ Hz, CHC*H₃*), 1.53 (s, 2H, CHN*H₂*), 4.53 (q, 1H, $J = 6.6$ Hz, C*H*CH₃), 7.32 (m, 4H, ArH); ¹³C-NMR (CDCl₃) δ 23.6 (CH*C*H₃), 47.5 (*C*HCH₃), 126.2, 127.1, 127.7, 129.5, 132.6, 144.6.

Compound **16**. ^{1}H-NMR (CDCl$_3$) δ 1.36 (d, 3H, $J = 6.6$ Hz, CHCH_3), 1.50 (s, 2H, CHNH_2), 4.11 (q, 1H, $J = 6.6$ Hz, CHCH$_3$), 7.27 (m, 4H, ArH); ^{13}C-NMR (CDCl$_3$) δ 25.7 (CHCH$_3$), 51.0 (CHCH$_3$), 124.0, 126.1, 126.9, 129.7, 134.5, 150.1.

Compound **17**. ^{1}H-NMR (CDCl$_3$) δ 1.35 (d, 3H, $J = 6.6$ Hz, CHCH_3), 1.49 (s, 2H, CHNH_2), 4.10 (q, 1H, $J = 6.6$ Hz, CHCH$_3$), 7.27 (m, 4H, ArH); ^{13}C-NMR (CDCl$_3$) δ 25.8 (CHCH$_3$), 50.8 (CHCH$_3$), 127.2, 128.6, 132.5, 146.4.

Compound **18**. ^{1}H-NMR (CDCl$_3$) δ 1.20 (d, 6H, $J = 6.8$ Hz, CH(CH_3)$_2$), 1.51 (s, 9H, C(CH$_3$)$_3$), 1.85 (br m, 9H), 2.23 (s, 3H, 6-CH$_3$), 3.09 (m, 1H, CH(CH$_3$)$_2$), 7.16 (m, 3H, ArH), 7.46 (br s, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 18.9, 20.7, 23.5, 25.0, 25.6, 28.4 (C(CH$_3$)$_3$), 28.7, 80.9 (C(CH$_3$)$_3$), 123.4, 127.9, 128.1, 135.9, 145.6, 155.1 (NCOO), 170.1 (CONH).

Compound **19**. ^{1}H-NMR (CDCl$_3$) δ 1.11 (d, 6H, CH(CH_3)$_2$), 1.62 (br m, 6H), 2.14 (s, 3H, 6-CH$_3$), 3.15 (br m, 3H, CHNH$_2^+$CH_2 and CH(CH$_3$)$_2$), 4.07 (s, 1H, CHNH$_2^+$CH$_2$), 7.16 (s, 3H, ArH), 9.20 (br s, 2H, NH$_2^+$), 10.21 (s, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 18.4, 21.2, 21.7, 23.4, 27.3, 27.7, 43.2, 56.9, 123.1, 127.4, 127.5, 132.6, 135.7, 145.7, 167.7 (CONH).

Compound **20**. ^{1}H-NMR (DMSO-d_6) δ 1.71 (br m, 4H), 2.09 (s, 6H, 2,6-diCH$_3$), 3.54 (br m, 5H, CH_2NH$_2^+$CH_2CH), 7.04 (s, 3H, ArH), 9.26 (br s, 2H, NH$_2^+$), 9.64 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.0, 21.1, 26.5, 38.6, 42.8, 44.3, 126.5, 127.6, 134.6, 135.1, 170.3 (CONH).

Compound **21**. ^{1}H-NMR (DMSO-d_6) δ 1.81 (br m, 4H), 2.11 (s, 6H, 2,6-diCH$_3$), 2.94 (br m, 5H, CH_2NH$_2^+$CH_2 and CH$_2$CHCH$_2$), 7.05 (s, 3H, ArH), 9.34 (br s, 2H, NH$_2^+$), 9.52 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.1, 24.5, 38.9, 42.3, 126.4, 127.6, 135.0, 135.2, 171.7 (CONH).

Compound **24**. ^{1}H-NMR (CDCl$_3$) δ 1.68 (s, 1H, CH$_2$NHCH), 1.75 (br m, 6H), 2.89 (br m, 3H, CH_2NHCH), 4.47 (d, 2H, $J = 5.9$ Hz, CONHCH_2), 7.25 (br s, 1H, CONH), 7.55 (br m, 4H, ArH); ^{13}C-NMR (CDCl$_3$) δ 23.7, 26.2, 30.1, 42.3, 45.8, 60.1, 117.8 (CF$_3$), 123.4, 123.6, 129.3, 131.2, 139.5, 174.5.

Compound **25**. ^{1}H-NMR (CDCl$_3$) δ 1.46 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.59 (s, 1H, CH$_2$NHCH), 1.65 (br m, 6H), 2.90 (br m, 3H, CH_2NHCH), 3.80 (s, 3H, OCH$_3$), 5.08 (m, 1H, CHCH$_3$), 7.05 (br m, 5H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 21.9, 24.2, 26.3, 30.1, 46.0, 48.2, 55.3 (OCH$_3$), 60.5 (NHCHCO),

112.4, 112.6, 118.5, 129.7, 145.4, 160.1, 173.1 (CONH).

Compound **28**. ^{1}H-NMR (DMSO-d_6) δ 1.37 (d, 3H, $J = 7.1$ Hz, CHCH_3), 2.50 (br m, 6H), 3.01 (m, 2H, CH_2NH$_2^+$), 3.89 (m, 1H, CH$_2$NH$_2^+$CH), 5.32 (m, 1H, CONHCH), 7.36 (m, 4H, ArH), 9.15 (br s, 2H, NH$_2^+$), 9.45 (br d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 20.8, 21.1, 21.5, 26.8, 43.2, 45.7, 56.6, 56.8, 126.7, 127.3, 127.5, 128.5, 129.3, 131.2, 131.4, 141.5, 167.5 (CONH).

Compound **29**. ^{1}H-NMR (DMSO-d_6) δ 1.42 (d, 3H, $J = 6.9$ Hz, CHCH_3), 2.01 (br m, 6H), 3.35 (br m, 3H, CH_2NH$_2^+$CH), 5.03 (m, 1H, CONHCH), 7.61 (m, 4H, ArH), 8.95 (br s, 2H, NH$_2^+$), 9.45 (br d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 21.1, 21.4, 21.9, 26.9, 43.2, 45.9, 48.0, 56.7, 56.8, 124.4, 124.8, 125.7, 125.9, 126.6, 130.0, 132.9, 146.4, 146.7, 167.5 (CONH).

Compound **30**. ^{1}H-NMR (CDCl$_3$) δ 1.45 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.57 (s, 1 H, CH$_2$NHCH), 1.65 (br m, 6H), 2.85 (br m, 3H, CH_2NHCH), 5.07 (m, 1H, CHCH$_3$), 7.25 (br m, 5H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 21.8, 24.1, 26.2, 30.0, 45.9, 47.6, 60.2, 127.6, 128.8, 133.0, 142.3, 173.1 (CONH).

Compound **31**. ^{1}H-NMR (DMSO-d_6) δ 1.42 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.91 (br m, 6H), 3.05 (br m, 3H, CH_2NH$_2^+$CH), 5.07 (m, 1H, CONHCH), 7.62 (m, 4H, ArH), 9.04 (br s, 2H, NH$_2^+$), 9.36 (br d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 21.2, 21.5, 22.3, 26.8, 27.1, 43.2, 48.2, 56.6, 56.8, 118.1 (CF$_3$), 122.4, 123.6, 129.5, 130.0, 145.5, 145.8, 167.7 (CONH).

Compound **32**. ^{1}H-NMR (DMSO-d_6) δ 1.39 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.81 (br m, 6H), 3.25 (br m, 3H, CH_2NH$_2^+$CH), 4.90 (m, 1H, CONHCH), 7.50 (m, 3H, ArH), 9.45 (br d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 21.2, 21.5, 21.9, 26.8, 43.1, 47.5, 56.6, 126.2, 127.9, 130.5, 130.9, 145.4, 167.8 (CONH).

Compound **33**. ^{1}H-NMR (CDCl$_3$) δ 1.47 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.60 (s, 1H, CH$_2$NHCH), 1.65 (br m, 6H), 2.90 (br m, 3H, CH_2NHCH), 3.87 (s, 6H, 3,4-diOCH$_3$), 5.08 (m, 1H, CHCH$_3$), 6.85 (s, 3H, ArH), 6.95 (br s, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 21.8, 24.2, 26.3, 30.1, 46.0, 47.8, 47.9, 56.2, 60.4, 110.7, 110.9, 112.0, 118.2, 118.3, 136.6, 148.7, 149.5, 173.0 (CONH).

Compound **34**. ^{1}H-NMR (CDCl$_3$) δ 1.50 (d, 3H, $J = 7.1$ Hz, CHCH_3), 1.67 (br m, 6H), 2.23 (s, 3H, NCH$_3$), 2.25 (br m, 2H, CH$_2$N), 2.83 (m, 1H, NCHCO), 5.17 (m, 1H, CONHCHCH$_3$), 6.89 (br s, 1H, CONH), 7.31 (s, 5H, ArH); ^{13}C-NMR (CDCl$_3$) δ 21.7, 23.4, 25.4, 30.9, 44.7, 47.6, 55.5, 69.9, 126.1, 127.2, 128.6, 143.4, 173.5 (CONH).

Compound **36**. ^{1}H-NMR (DMSO-d_6) δ 1.64 (d, 3H, $J = 7.1$ Hz, CHC*H*$_3$), 2.02 (br m, 6H), 3.74 (br m, 5H, CH$_2$(C*H*$_2$)NH$^+$C*H*), 5.07 (m, 1H, CONHC*H*CH$_3$), 7.36 (m, 9H, ArH), 8.86 (m, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.0, 21.8, 22.3, 27.0, 27.7, 48.4, 49.7, 50.5, 52.1, 56.7, 57.6, 59.2, 70.0, 115.6, 115.9, 116.5, 116.9, 122.9, 123.0, 124.8, 126.0, 126.7, 127.3, 127.5, 128.7, 133.6, 134.0, 143.5, 158.1, 165.7, 166.6, 169.3.

Compound **37**. ^{1}H-NMR (CDCl$_3$) δ 1.46 (d, 3H, $J = 7.1$ Hz, CHC*H*$_3$), 1.65 (br m, 6H), 3.35 (br m, 5H, C*H*$_2$(C*H*$_2$)N*H*), 5.13 (m, 1H, CONHC*H*CH$_3$), 7.18 (m, 10H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 21.3, 21.7, 23.4, 24.8, 30.4, 30.6, 47.9, 48.1, 51.6, 51.8, 60.0, 67.8, 120.8, 120.9, 126.0, 126.2, 127.3, 127.5, 128.7, 129.9, 130.1, 131.3, 131.5, 136.8, 137.1, 142.8, 143.2, 173.4 (CONH).

Compound **38**. ^{1}H-NMR (DMSO-d_6) δ 1.46 (d, 3H, $J = 6.8$ Hz, CHC*H*$_3$), 1.88 (br m, 6H), 3.71 (br m, 5H, C*H*$_2$(C*H*$_2$)NH$^+$C*H*), 5.00 (m, 1H, CONHC*H*CH$_3$), 7.57 (m, 8H, ArH), 9.82 (br s, 1H, NH$^+$), 10.21 (m, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 21.1, 21.7, 22.4, 28.2, 48.7, 51.0, 56.6, 65.0, 125.6, 125.8, 126.8, 128.3, 130.2, 130.8, 131.2, 131.9, 132.5, 133.5, 144.1, 166.8 (CONH).

Compound **40**. ^{1}H-NMR (CDCl$_3$) δ 1.43 (d, 3H, CHC*H*$_3$), 1.64 (br m, 4H), 1.84 (s, 1H, CH$_2$N*H*CH$_2$), 2.32 (m, 1H, C*H*CONH), 2.88 (br m, 4H, C*H*$_2$NHCH$_2$), 5.15 (m, 1H, C*H*CH$_3$), 7.34 (s, 5H, ArH), 7.88 (br s, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 22.1, 23.7, 27.8, 42.3, 42.5, 46.7, 48.1, 48.3, 126.3, 127.2, 128.8, 144.1, 174.1 (CONH).

Compound **41**. ^{1}H-NMR (DMSO-d_6) δ 0.87 (t, 3H, CH$_2$C*H*$_3$), 2.60 (br m, 8H), 3.45 (br m, 3H, C*H*$_2$NH$_2^+$C*H*), 4.75 (m, 1H, CONHC*H*), 7.25 (br m, 5H, ArH), 9.40 (br m, 3H, NH$_2^+$ and CONH); ^{13}C-NMR (DMSO-d_6) δ 11.1, 21.2, 21.6, 27.0, 27.4, 29.4, 43.3, 54.6, 56.7, 57.0, 126.3, 126.7, 128.2, 143.1, 143.4, 167.8 (CONH).

Compound **42**. ^{1}H-NMR (CDCl$_3$) δ 0.85 (dd, 6H, CH(CH$_3$)$_2$), 1.65 (s, 1H, CH$_2$N*H*CH), 1.70 (br m, 7H), 2.80 (br m, 3H, C*H*$_2$NHC*H*), 4.82 (t, 1H, CONHC*H*), 7.35 (br s, 6H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 18.8, 19.8, 24.1, 26.0, 30.4, 33.7, 45.8, 58.2, 60.6, 127.0, 128.4, 141.8, 173.3 (CONH).

Compound **43**. ^{1}H-NMR (CDCl$_3$) δ 1.34 (br m, 6H), 1.56 (s, 1H, CH$_2$N*H*CH), 2.84 (br m, 3H, C*H*$_2$NHC*H*), 6.02 (d, 1H, $J = 8.8$ Hz, CONHC*H*), 6.82 (br s, 1H, CONH), 7.15 (m, 10H, ArH); ^{13}C-NMR (CDCl$_3$) δ 24.2, 26.2, 30.1, 46.0, 48.2, 56.3, 60.5, 127.4, 127.6, 128.7, 142.1, 173.2 (CONH).

Compound (*S*,*RS*-**44**). ^{1}H-NMR (DMSO-d_6) δ 1.64 (br m, 6H), 3.16 (br m, 2H, C*H*$_2$NHCH), 3.95 (m, 1H, CH$_2$NHC*H*CO), 6.18 (d, 1H, $J = 8.3$ Hz, CON-HC*H*), 7.36 (m, 9H, ArH); ^{13}C-NMR (DMSO-d_6) δ 21.2, 21.6, 27.1, 43.3, 55.7, 56.7, 125.7, 126.2, 126.8, 127.0, 127.4, 128.6, 130.4, 133.1, 141.1, 141.3, 144.3, 144.5, 167.9 (CONH).

Compound (*S*,*RS*-**45**). ^{1}H-NMR (CDCl$_3$) δ 1.55 (br m, 7H), 2.75 (br m, 5H, ArCHC*H*$_2$Ar and C*H*$_2$NHC*H*), 5.18 (m, 1H, ArC*H*CH), 7.23 (m, 11H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 23.9, 24.1, 26.1, 29.8, 30.0, 42.9, 45.6, 45.8, 53.8, 53.8, 60.1, 60.4, 126.5, 127.3, 128.3, 128.5, 129.4, 137.7, 141.9, 173.3.

Compound **46**. ^{1}H-NMR (DMSO-d_6) δ 1.48 (s, 9H, C(CH$_3$)$_3$), 1.51 (br m, 15H), 3.10 (m, 2H, C*H*CO), 3.89 (m, 1H, NCHCO), 4.66 (m, 1H, CONHC*H*), 7.38 (s, 5H, ArH), 8.35 (m, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 19.6, 24.3, 24.7, 24.9, 25.0, 28.0 (C(C*H*$_3$)$_3$), 29.6, 29.7, 29.9, 30.0, 45.0, 57.1, 78.7 (*C*(CH$_3$)$_3$), 126.6, 126.8, 127.0, 128.0, 143.6, 143.8, 155.1 (NCOO), 170.5 (CONH).

Compound **47**. ^{1}H-NMR (DMSO-d_6) δ 1.54 (br m, 15H), 3.07 (br m, 2H, NH$_2^+$C*H*$_2$), 3.80 (m, 1H, NH$_2^+$C*H*CO), 4.57 (m, 1H, CONHC*H*), 7.31 (m, 5H, ArH), 9.01 (br s, 2H, NH$_2^+$), 9.35 (t, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 21.1, 21.5, 24.7, 24.9, 26.8, 27.4, 29.5, 29.7, 43.2, 45.1, 45.3, 56.7, 56.7, 56.9, 57.5, 57.6, 126.8, 127.2, 128.1, 142.8, 143.2, 167.6 (CONH).

Compound **48**. ^{1}H-NMR (CDCl$_3$) δ 1.49 (s, 9H, C(CH$_3$)$_3$), 1.51 (br m, 17H), 2.54 (br m, 2H, C*H*$_2$NCH), 4.03 (m, 1H, NCHCO), 4.75 (m, 1H, CONHC*H*), 7.28 (s, 5H, ArH); ^{13}C-NMR (CDCl$_3$) δ 20.4, 25.0, 25.2, 26.0, 26.2, 28.4 (C(C*H*$_3$)$_3$), 29.2, 30.1, 30.3, 42.0, 43.0, 43.3, 58.3, 80.7 (*C*(CH$_3$)$_3$), 126.9, 128.4, 141.5, 170.4 (CONH).

Compound **49**. ^{1}H-NMR (DMSO-d_6) δ 1.48 (br m, 17H), 3.17 (br m, 2H, C*H*$_2$NH$_2^+$), 3.91 (m, 1H, NH$_2^+$C*H*CO), 4.62 (m, 1H, CONHC*H*), 7.39 (s, 5H, ArH), 9.13 (m, 3H, CONH and NH$_2^+$); ^{13}C-NMR (DMSO-d_6) δ 21.1, 21.5, 25.5, 25.8, 26.9, 29.1, 29.6, 43.2, 56.7, 58.2, 126.7, 127.0, 128.1, 141.9, 167.8 (CONH).

Compound **57**. ^{1}H-NMR (DMSO-d_6) δ 1.55 (s, 9H, C(CH$_3$)$_3$), 1.78 (s, 6H, 2,6-diCH$_3$), 3.35 (br m, 2H, C*H*$_2$CHN), 4.55 (m, 2H, ArCH$_2$N), 4.92 (m, 1H, NCHCO), 6.97 (m, 2H, ArH), 7.23 (m, 6H, ArH and CONH); ^{13}C-NMR (DMSO-d_6) δ 17.8, 28.4 (C(C*H*$_3$)$_3$), 31.9, 32.1, 45.5, 56.0, 56.4, 81.6 (*C*(CH$_3$)$_3$), 126.4, 127.0, 127.3, 127.8, 128.0, 128.4, 133.2, 133.9, 135.3, 155.6 (NCOO), 170.0 (CONH).

Compound **58**. ^{1}H-NMR (DMSO-d_6) δ 2.20 (s, 6H, 2,6-diCH_3), 3.41 (br m, 2H, CH_2CHN), 4.34 (m, 3H, CH_2NH$_2^+$CH), 7.10 (s, 3H, ArH), 7.27 (s, 4H, ArH), 9.95 (br s, 2H, NH$_2^+$), 10.49 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.2, 29.6, 43.6, 54.1, 126.6, 126.9, 127.4, 127.8, 128.6, 128.7, 130.9, 133.9, 135.2, 166.5 (CONH).

Compound **59**. ^{1}H-NMR (DMSO-d_6) δ 3.15 (br m, 2H, CH_2CHNH$_2^+$), 4.32 (m, 5H, CONHCH_2 and CH_2NH$_2^+$CH), 7.26 (m, 8H, ArH), 9.57 (br t, 2H, NH$_2^+$), 9.85 (br s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 29.4, 41.6, 43.8, 54.0, 113.3, 113.5, 114.2, 114.4, 123.2, 123.3, 126.6, 126.9, 127.5, 128.6, 130.2, 130.5, 131.1, 141.5, 141.9, 156.9, 167.7, 168.0.

Compound **60**. ^{1}H-NMR (DMSO-d_6) δ 3.25 (br m, 2H, CH_2CHNH$_2^+$), 4.35 (m, 5H, CONHCH_2 and CH_2NH$_2^+$CH), 7.26 (s, 4H, ArH), 7.65 (s, 4H, ArH), 9.58 (br t, 2H, NH$_2^+$), 11.1 (br s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 29.5, 41.7, 43.7, 53.8, 123.7, 126.4, 126.7, 127.3, 128.5, 129.3, 130.9, 131.3, 140.1, 168.0.

Compound **61**. ^{1}H-NMR (CDCl$_3$) δ 1.49 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.92 (s, 1H, CH$_2$NHCH), 3.25 (br m, 3H, CH_2CHNH), 3.98 (s, 2H, CH_2NH), 5.16 (m, 1H, CHCH$_3$), 7.35 (m, 9H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 22.0, 30.9, 47.5, 48.1, 56.4, 118.1 (CF$_3$), 122.5, 122.7, 122.9, 123.0, 123.9, 124.1, 124.2, 124.4, 125.6, 126.3, 126.7, 129.2, 129.8, 130.2, 134.2, 135.8, 144.5, 172.4.

Compound **62**. ^{1}H-NMR (CDCl$_3$) δ 1.46 (d, 3H, $J = 6.8$ Hz, CHCH_3), 1.69 (s, 1H, CH$_2$NHCH), 3.15 (br m, 3H, CH_2CHNH), 3.98 (s, 2H, CH_2NH), 5.15 (m, 1H, CHCH$_3$), 7.20 (m, 9H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 21.9, 31.1, 47.4, 47.6, 47.7, 47.8, 56.4, 56.6, 125.6, 126.3, 126.8, 127.4, 127.6, 128.8, 129.2, 133.2, 134.5, 135..9, 142.2, 172.3.

Compound **63**. ^{1}H-NMR (CDCl$_3$) δ 1.56 (s, 1H, CH$_2$NHCH), 3.05 (br m, 5H, CH_2CHNH and ArCH_2CH$_2$), 3.88 (d, 2H, $J = 7.8$ Hz, CH_2NH), 5.28 (m, 1H, ArCHCH$_2$), 7.20 (m, 15H, ArH), 7.57 (br d, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 30.7, 31.0, 42.9, 47.3, 53.7, 54.1, 56.3, 125.5, 126.2, 126.6., 127.3, 128.3, 128.5, 129.1, 129.4, 134.5, 135.9, 136.1, 137.5, 141.8, 172.3.

Compound **66**. ^{1}H-NMR (DMSO-d_6) δ 1.48 (d, 3H, $J = 6.6$ Hz, CHCH_3), 3.25 (m, 4H), 4.91 (m, 1H, NHCHCH$_3$), 5.16 (br s, 1H, NH$_2^+$CHCO), 7.33 (m, 9H, ArH), 9.75 (br d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 22.3, 24.4, 39.0, 48.8, 55.2, 126.1, 126.3,

126.6, 127.0, 128.1, 128.4, 129.2, 132.7, 143.7, 165.9 (CONH).

Compound **67**. ^{1}H-NMR (CDCl$_3$) δ 1.52 (d, 9H, C(CH$_3$)$_3$), 2.12 (s, 6H, 2,6-diCH_3), 2.93 (m, 2H, ArCH_2), 3.73 (t, 2H, ArCH$_2$CH_2N), 5.65 (br s, 1H, NCHCO), 7.16 (m, 8H, ArH and CONH); ^{13}C-NMR (CDCl$_3$) δ 18.3, 28.4 (C(CH_3)$_3$), 28.7, 41.0, 58.9, 59.1, 59.2, 81.2 (C(CH$_3$)$_3$), 126.5, 127.1, 127.7, 128.1, 128.3, 131.8, 133.6, 135.1, 135.3, 155.5 (NCOO), 169.2 (CONH).

Compound **68**. ^{1}H-NMR (DMSO-d_6) δ 2.16 (s, 6H, 2,6-diCH_3), 3.16 (br m, 2H, CH_2CH$_2$NH$_2$), 3.65 (m, 2H, CH$_2$CH_2NH$_2^+$), 5.52 (s, 1H, NH$_2^+$CHCO), 7.10 (s, 3H, ArH), 7.33 (m, 4H, ArH), 7.74 (br d, 2H, NH$_2^+$), 10.77 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.3, 24.5, 39.0, 55.3, 126.6, 126.9, 127.9, 128.1, 129.2, 132.8, 133.8, 135.1, 165.6 (CONH).

Compound **85**. ^{1}H-NMR (DMSO-d_6) δ 1.32 (d, 3H, $J = 7.1$ Hz, CHCH_3), 1.56 (br m, 8H), 2.54 (m, 1H, CHCONH), 4.90 (m, 1H, CONHCHCH$_3$), 7.23 (m, 4H, ArH), 8.24 (br d, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 22.4, 25.6, 29.7, 30.0, 44.1, 47.4, 124.6, 125.7, 126.4, 130.1, 132.9, 147.7, 174.4 (CONH).

Compound **86**. ^{1}H-NMR (CDCl$_3$) δ 1.42 (d, 3H, $J = 7.1$ Hz, CHCH_3), 1.61 (br m, 11H), 5.06 (m, 1H, CONHCHCH$_3$), 6.15 (br s, 1H, CONH), 7.23 (m, 4H, ArH); ^{13}C-NMR (CDCl$_3$) δ 21.8, 25.7, 29.6, 45.4, 47.9, 124.4, 126.1, 127.3, 129.9, 134.4, 145.8, 175.3 (CONH).

Compound **88**. ^{1}H-NMR (CDCl$_3$) δ 0.52 (br m, 4H), 1.52 (m, 1H, CHCONH), 1.85 (s, 6H, 2,6-diCH_3), 6.76 (s, 3H, ArH), 9.19 (br s, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 6.7, 13.8, 18.3, 126.6, 127.9, 135.5, 171.8 (CONH).

Compound **89**. ^{1}H-NMR (CDCl$_3$) δ 2.10 (s, 6H, 2,6-diCH_3), 2.11 (br m, 6H), 3.12 (m, 1H, CHCONH), 6.98 (s, 3H, ArH), 7.25 (br s, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 18.3, 25.1, 25.4, 39.7, 126.9, 127.9, 128.4, 134.0, 135.4, 173.5 (CONH).

Compound **90**. ^{1}H-NMR (CDCl$_3$) δ 1.71 (br m, 8H), 2.10 (s, 6H, 2,6-diCH_3), 2.62 (m, 1H, CHCONH), 6.98 (s, 3H, ArH), 7.32 (br s, 1H, CONH); ^{13}C-NMR (CDCl$_3$) δ 18.3, 25.9, 30.6, 45.6, 126.9, 127.9, 135.4, 174.8 (CONH).

Compound **91**. ^{1}H-NMR (DMSO-d_6) δ 1,55 (br m, 11H), 2.09 (s, 6H, 2,6-diCH_3), 7.03 (s, 3H, ArH), 9.05 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.0, 25.3, 25.5, 29.4, 44.2, 126.2, 127.5, 135.2, 173.7 (CONH).

Compound **92**. ^{1}H-NMR (DMSO-d_6) δ 1.56 (br m, 10H), 2.14 (s, 3H, 6-CH$_3$), 2.38 (m, 1H, CHCONH),

7.27 (m, 3H, ArH), 9.35 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6) δ 18.2, 25.3, 25.5, 29.2, 44.0, 126.8, 127.5, 128.8, 132.0, 134.0, 138.3, 173.9 (CONH).

Compound **93**. ^{1}H-NMR (CDCl$_3$) δ 1.66 (br m, 12H), 2.14 (s, 6H, 2,6-diCH$_3$), 2.45 (m, 1H, CHCONH), 7.01 (m, 4H, ArH and CONH); ^{13}C-NMR (DMSO-d_6) δ 18.4, 26.7, 28.1, 32.0, 47.7, 127.0, 128.0, 134.0, 135.6, 175.7 (CONH).

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