Eur. J. Med. Chem. 33 (1998) 23–31

Preliminary communication

Synthesis of 2-piperidinecarboxylic acid derivatives as potential anticonvulsants

Bin Ho[a,b], Prabha M. Venkatarangan[a,c], Sharon F. Cruse[d], Christine N. Hinko[e], Peter H. Andersen[f], Albert M. Crider[a]*, Ahmad A. Adloo[a], David S. Roane[a], James P. Stables[g]

[a]*School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209-0470, USA*
[b]*College of Pharmacy, Oregon State University, Corvallis, OR 97331, USA*
[c]*College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612, USA*
[d]*Department of Chemistry, Northeast Louisiana University, Monroe, LA 71209-0470, USA*
[e]*College of Pharmacy, The University of Toledo, Toledo, OH 43606, USA*
[f]*Novo Nordisk A/S, Bagsvaerd, Denmark*
[g]*Epilepsy Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD 20892-9020, USA*

(Received 30 April 1997; accepted 25 September 1997)

Abstract – A variety of 2-piperidinecarboxamides were synthesized and evaluated for anticonvulsant activity using the MES and sc PTZ tests in mice and rats. Neurotoxicity was determined by the rotorod test. Several *N*-(benzyl)-2-piperidinecarboxamides exhibited potent MES activity in mice [2-CF_3 **14**, ED_{50} = 29 mg/kg; 3-F **16**, ED_{50} = 31 mg/kg; and 3-CF_3 **17**, ED_{50} = 24 mg/kg]. The most active compounds in the MES test in mice were the 2,6-dimethylanilides [*(R,S)*-**34**, ED_{50} = 5.8 mg/kg; *(R)*-**35**, ED_{50} = 5.7 mg/kg; and *(S)*-**36**, ED_{50} = 14.8 mg/kg]. The enantiomer *(S)*-**36** was about two-fold less potent in the MES test than *(R)*-**35** and also was less neurotoxic. Acylation of the piperidine ring nitrogen of **12** and **34** led to a decrease in the MES activity. In the *N*-(α-methylbenzyl)-2-piperidinecarboxamides, the stereochemistry at either the 2-position of the piperidine ring or at the α-position of the *N*-(α-methylbenzyl) group does not significantly affect MES activity. © Elsevier, Paris

2-piperidinecarboxamide / MES test / phenytoin / epilepsy / anticonvulsant

1. Introduction

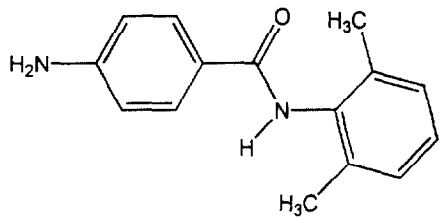
Approximately 2.5 million people in the United States [1] and 50 million individuals worldwide [2] are afflicted with epilepsy. Although 70–80% of all epileptics are adequately treated by currently available drugs, seizure protection is often accompanied by numerous side effects including drowsiness, ataxia, gastrointestinal disturbances, gingival hyperplasia, hirsutism, and megaloblastic anemia [3].

Previously, we reported the activity of derivatives of 3-piperidinecarboxylic acid (nipecotic acid) against chemically-induced seizures [4–7]. As a continuation of this work, a recent study evaluated the activity of several amide derivatives of 2-piperidinecarboxylic acid (pipecolic acid) in the maximal electroshock seizure (MES) test in mice. Receptor binding studies indicated that these amides exhibited weak affinity at the phencyclidine (PCP) site on the *N*-methyl-D-aspartate (NMDA) receptor complex in displacement studies utilizing [^{3}H]*N*-[1-(2-thienyl)cyclohexyl]-piperidine ([^{3}H]TCP); however, a direct correlation between binding affinity and anti-MES activity was not observed [8]. Other studies by Kohn et al. [9–14] showed that benzylamide derivatives of amino acids afforded protection against MES-induced seizures; however, the mechanism of action of these com-

*Correspondence and reprints

Abbreviations: SAR (structure–activity relationship), BOC (*tert*-butoxycarbonyl), NMM (*N*-methylmorpholine), IBCF (isobutyl chloroformate), BOC-ON [(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile], MES (maximal electroshock seizure), sc PTZ (subcutaneous pentylenetetrazole), CBZ (carbamazepine), PTN (phenytoin), po (oral), ip (intraperitoneal), PI (protective index, TD_{50}/ED_{50})

pounds has not been elucidated. Clark et al. [15, 16] synthesized a number of benzamides of aminobenzoic acids having potent activity against MES seizures in mice. The 2,6-dimethylanilide, ameltolide **1**,



1: Ameltolide

proved to be the most potent compound arising from these studies with an ED_{50} of 2.6 mg/kg when administered by an ip route in mice.

Since the 2-piperidinecarboxamides represent a series of novel compounds which exhibit anticonvulsant activity in the MES test in mice, further structural modification of this basic nucleus was of interest. The development of new anticonvulsants which act by different mechanisms of action than currently available drugs is a major goal of antiepileptic research [17], particularly the discovery of compounds for the treatment of refractory complex partial seizures [2].

Based on the preliminary anticonvulsant activity of *(R,S)-N*-(benzyl)-2-piperidinecarboxamide hydrochloride (**12**, table III), an examination of the SAR of the 2-piperidinecarboxamide nucleus was initated. In this regard, the importance of the stereochemistry at the 2-position of the piperidine ring and at the α-position of *N*-(benzyl)-substituted amides was evaluated. A second objective was to examine the effect of aromatic substitution on the anti-MES activity of *N*-(benzyl)-substituted amides. Additionally, the distance between the amide functional group and the phenyl ring was varied. A final objective of this research was to determine whether the basic piperidine ring nitrogen was necessary for activity against MES-induced seizures. Although our earlier paper [8] described the anticonvulsant activity of some of the 2-piperidinecarboxamides reported in this investigation, the synthesis of these compounds has not been reported.

2. Chemistry

The 2-piperidinecarboxamides which were evaluated for anticonvulsant activity were synthesized using general methods I–IV as described in the *Experimental protocols* and shown in *figure 1*. The intermediate 1-BOC-2-piperidine-carboxamides (Method I) were generally not isolated, but were directly deprotected with hydrogen chloride gas in methylene chloride at 0–5 °C (Method II) to afford the desired 2-piperidinecarboxamide hydrochlorides in good yields. In Method III, reaction of *(R,S)*-1-carbethoxy-2-piperidinecarboxylic acid **5** or its *S*-enantiomer **6** with thionyl chloride possibly leads to the formation of a *N*-carboxyanhydride **7** as a reactive intermediate [18]. Ring opening of **7** with an amine to produce the desired carboxamide eliminated a separate deprotection step at the piperidine ring nitrogen. Although some of the target compounds were synthesized by mixed anhydride formation followed by deprotection (Methods I–II), improved yields were generally realized with the acid chloride coupling procedure (Method IV).

Investigation of the importance of the stereochemistry at the 2-position of the piperidine ring and at the α-position of the *N*-(benzyl)amide group on anticonvulsant activity required the resolution of pipecolic acid into its individual enantiomers. Formation of the tartrate salts of (±)-pipecolic acid with either D- or L-tartaric acid followed by fractional recrystallization and chromatography using Amberlite IR-120 cation exchange columns afforded the optically active *(R)*- and *(S)*-pipecolic acids [19]. Subsequently, the BOC-protected pipecolic acids [*(R,S)*-**2**, *(R)*-**3**, and *(S)*-**4**] were prepared by reported methods [5, 20, 21]. The optical purity of the resulting amides **48–51** prepared by either Method II or III was analyzed by HPLC. Only compound **48**, which was synthesized by the acid chloride coupling procedure, showed any detectable epimerization. The physicochemical data for all novel compounds are given in *tables I* and *II*, and the NMR spectra for all intermediates and final products were consistent with the assigned structures.

3. Pharmacology

The anticonvulsant activity and the neurotoxicity of the 2-piperidinecarboxamides are given in *tables III* and *IV*. Compounds **12**, **14–17**, **19–25**, **28–29**, **32**, **38**, and **45–51** were evaluated for anticonvulsant activity and neurotoxicity at The University of Toledo and were the subject of an earlier report [8]. The remaining compounds were evaluated by the Epilepsy Branch, Anticonvulsant Screening Project (ASP) of the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) using established procedures [22]. With the mono-substituted *N*-(benzyl)amides, the most active compounds in the MES test were [**14** (2-CF_3), ED_{50} = 29 mg/kg; **16** (3-F), ED_{50} = 31 mg/kg; and **17** (3-CF_3), ED_{50} = 24 mg/kg]. Replacement of the phenyl ring of **12** by a 2-thienyl group (**28**) or a 2-furo group (**29**) resulted in a dramatic increase in neurotoxicity.

Compared with **12**, the α-methylbenzylamides **46–51** exhibited increased activity in the MES test

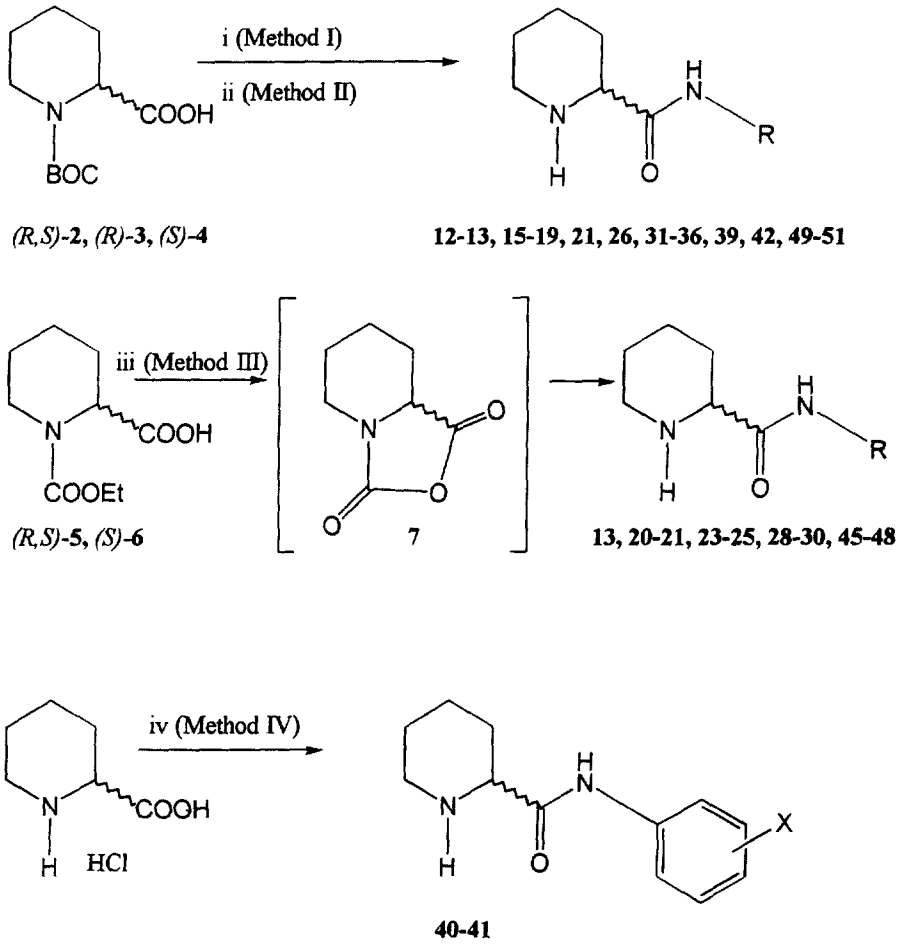
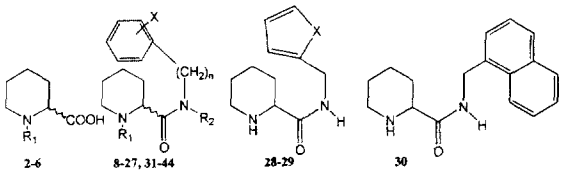


Figure 1. (i) NMM/IBCF/RNH_2; (ii) HCl (g)/CH_2Cl_2; (iii) $SOCl_2/CH_2Cl_2/RNH_2$; (iv) $PCl_5/CH_3COCl/ArNH_2$.

and decreased neurotoxicity in the rotorod test, resulting in PI values of 3.5–4.5 (*table III*). The stereochemistry at either the 2-position of the piperidine ring or at the α-position of the *N*-(α-methylbenzyl) group does not significantly affect the MES activity. Our previous work showed that several of the 2-piperidinecarboxamides displaced [^{3}H]TCP in rat brain homogenates with IC_{50} values in the micromolar range. Although a clear correlation between inhibition of [^{3}H]TCP binding and MES activity was not apparent, a possible relationship exists between inhibition of [^{3}H]TCP binding and neurotoxicity. Evaluation of the four α-methylbenzylamides **48–51** showed that the (2*S*, α*S*) isomer **48** exhibited an IC_{50} value of 18 μM in displacement of [^{3}H]TCP in rat brain homogenates. The other stereoisomers **49–51** exhibited IC_{50} values greater than 300 μM and showed less neurotoxicity [8].

Increasing the distance between the amide group and the phenyl ring of **12** (compounds **43** and **44**) did not significantly alter the pharmacological profile; however, decreasing the distance between the amide group and the phenyl ring (anilides) resulted in several compounds with potent MES activity. The substitution pattern on the phenyl ring was very important. Although the 3-CF_3-anilide **32** (ED_{50} = 77 mg/kg) was less active than the 3-CF_3-(*N*-benzyl)amide **17** (ED_{50} = 24 mg/kg) in the MES test, the 2,6-dimethylanilides **34–36** demonstrated potent activity in this test. The racemate **34**, a known metabolite of the local anesthetics bupivacaine and mepivacaine [23], had an ED_{50} = 5.8 mg/kg in the MES test and a TD_{50} = 33.2 mg/kg in the rotorod test to give a PI of 5.7. Compared with the racemate **34**, the *(R)*-isomer *(R)*-**35** exhibited similar MES activity but about twice the neurotoxicity. The enantiomer *(S)*-**36** was about two-

Table I. 2-Piperidinecarboxamides and related precursors.

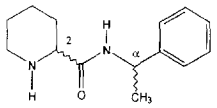


2-6 8-27, 31-44 28-29 30

Compound	R_1	R_2	n	X	Mp (°C)	Yield (%) (method)	Formula[a] (recrystallization solvent)[b]	
(RS)-**2**	BOC				128–130[c]	74	$C_{11}H_{19}NO_4$	(A)
(R)-**3**	BOC				119–123[d]	88	$C_{11}H_{19}NO_4$	(A)
(S)-**4**	BOC				122–125[e]	88	$C_{11}H_{19}NO_4$	(A)
(RS)-**5**	CO_2Et				87–89[f]	83	$C_9H_{15}NO_4$	(B)
(S)-**6**	CO_2Et				83–86	60	$C_9H_{15}NO_4$	(C)
8	BOC	H	1	H	120–122	63 (I)	$C_{18}H_{26}N_2O_3$	(D)
9	BOC	H	1	3-F	125–126	52 (I)	$C_{18}H_{25}N_2O_3$	(D)
10	BOC	H	1	3-CF_3	92–94	60 (I)	$C_{19}H_{25}F_3N_2O_3$	(D)
11	BOC	H	1	3-CH_3	93–95	58 (I)	$C_{19}H_{28}N_2O_3$	(D)
12	H	H	1	H	212–214	77 (II)	$C_{13}H_{19}ClN_2O$[g]	(E)
(S)-**13**	H	H	1	H	198–200	59 (II)	$C_{13}H_{19}ClN_2O$[g,h]	(E)
14	H	H	1	2-CF_3	152–154	89 (III)	$C_{14}H_{18}ClF_3N_2O$[g]	(E)
15	H	H	1	2-CH_3	78–80	65 (I,II)	$C_{14}H_{20}N_2O$[i]	(F)
16	H	H	1	3-F	223–225	90 (II)	$C_{13}H_{18}ClFN_2O$[g]	(E)
17	H	H	1	3-CF_3	218–220	75 (II)	$C_{14}H_{18}ClF_3N_2O$[g]	(G)
(S)-**18**	H	H	1	3-CF_3	198–200	71 (II)	$C_{14}H_{18}ClF_3N_2O$[g,j]	(H)
19	H	H	1	3-CH_3	179–180	93 (II)	$C_{14}H_{21}ClN_2O$[g]	(E)
20	H	H	1	3-NO_2	103–104	70 (III)	$C_{13}H_{17}N_3O_3$[i,k]	(B)
21	H	H	1	3-Cl	80–82	67 (I,II)	$C_{13}H_{17}ClN_2O$	(H)
22	H	H	1	4-CF_3	207–208	93 (III)	$C_{14}H_{18}ClF_3N_2O$[g]	(A)
23	H	H	1	4-CH_3	216–218	60 (III)	$C_{14}H_{21}ClN_2O$[g]	(G)
24	H	H	1	4-NO_2	260–261	60 (III)	$C_{13}H_{18}ClN_3O_3$[g]	(F)
25	H	H	1	3,4-Cl_2	227–228	36 (III)	$C_{13}H_{17}Cl_3N_2O$[g,l]	(F)
26	H	CH_3	1	H	197–205	35 (I,II)	$C_{14}H_{21}ClN_2O$[g]	(E)
27	CH_3CO	H	1	H	108–110	30	$C_{15}H_{20}N_2O_2$	(I)
28	H			S	227–229	56 (III)	$C_{11}H_{13}ClN_2OS$[g]	(G)
29				O	183–184	52 (III)	$C_{11}H_{13}ClN_2O_2$[g]	(G)
30					78–80	50 (III)	$C_{13}H_{20}N_2O$[i]	(H)
31	H	H	0	2-Et	225–235	45 (I,II)	$C_{14}H_{21}ClN_2O$[g]	(J)
32	H	H	0	3-CF_3	270–271	14 (I,II)	$C_{13}H_{16}ClF_3N_2O$[g]	(G)
33	CH_3CO	H	0	2,6-Me_2	169–171	74	$C_{16}H_{22}N_2O_2$	(A)
(RS)-**34**	H	H	0	2,6-Me_2	114–115	28 (I,II)	$C_{14}H_{20}N_2O$[i,m]	(H)
(R)-**35**	H	H	0	2,6-Me_2	128–130[n]	32 (I,II)	$C_{14}H_{20}N_2O$	(H)
(S)-**36**	H	H	0	2,6-Me_2	130–132[o]	26 (I,II)	$C_{14}H_{20}N_2O$	(H)
37	BOC	H	0	2*i*Pr, 6Me	139–141	30 (I)	$C_{21}H_{32}N_2O_3$	(D)
38	H	H	0	2*i*Pr, 6Me	246–248	67 (I,II)	$C_{16}H_{25}ClN_2O$[g]	(B)
39	H	H	0	2,3-Me_2	282–284	51 (I,)	$C_{14}H_{21}ClN_2O$[g]	(J)
40	H	H	0	2,4-Me_2	96–98	72 (IV)	$C_{14}H_{20}N_2O$[i]	(H)
41	H	H	0	2,5-Me_2	98–100	54 (IV)	$C_{14}H_{20}N_2O$[i]	(H)
42	H	H	0	3,5-Me_2	276–278	46 (I,II)	$C_{14}H_{21}ClN_2O$[g]	(J)
43	H	H	2	H	179–181	88 (I,II)	$C_{14}H_{21}ClN_2O$[g]	(E)
44	H	H	3	H	167–169	89 (I,II)	$C_{15}H_{23}ClN_2O$[g]	(E)

[a]All compounds gave acceptable C, H, N analyses, ±0.4% of the calculated values, except where indicated. [b]Recrystallization solvents, A = EtOAc/hexane, B = Et_2O/hexane, C = hexane, D = EtOH/H_2O, E = absolute EtOH/Et_2O, F = 95% EtOH/Et_2O, G = *i*PrOH/Et_2O, H = petroleum ether/Et_2O, I = EtOAc/petroleum ether, J = absolute EtOH. [c]Mp 128–129 °C, [20]. [d]$[\alpha]_D^{24°}$ = +47.6 (*c*1, MeOH); [21] mp 113–123 °C, $[\alpha]_D^{24°}$ = +47.1 (*c*1, MeOH). [e]$[\alpha]_D^{23°}$ = –44.5 (*c*1, MeOH); [21] mp 128–132 °C, $[\alpha]_D^{24°}$ = –45.8 (*c*1, MeOH). [f]No reported mp, [18]. [g]Hydrochloride. [h]$[\alpha]_D^{24°}$ = +3.0 (*c*1.5, EtOH). [i]Analyzed as the free base. [j]$[\alpha]_D^{24°}$ = +3.5 (*c*1.5, EtOH). [k]Calc. for N, 15.96; found 15.53. [l]Calc. for H, 5.23; found 4.73. [m][23] no reported mp. [n]$[\alpha]_D^{24°}$ = –4 (*c*1, EtOH); [23] mp 130–132 °C, $[\alpha]_D^{25°}$ = –11.05 (*c*5, MeOH). [o]$[\alpha]_D^{24°}$ = +5 (*c*1, EtOH); [23] mp 130–132 °C, $[\alpha]_D^{25°}$ = +46.1 (*c*2.3, 1 N HCl).

Table II. *N*-(α-Methylbenzyl)-2-piperidinecarboxamides.



Compound	Mp (°C)	$[\alpha]_D^{24°}$ (degrees)	Yield (%) (Method)[a]	Formula
(2*RS*,α*RS*)-**45**	72–74		48 (III)	$C_{14}H_{20}N_2O$
(2*RS*,α*R*)-**46**	86–88	+91 (*c*1, EtOH)	32 (III)	$C_{14}H_{20}N_2O$
(2*RS*,α*S*)-**47**	83–85	–89 (*c*1, EtOH)	35 (III)	$C_{14}H_{20}N_2O$
(2*S*,α*S*)-**48**	102–104	–99 (*c*1, EtOH)	28 (III)	$C_{14}H_{20}N_2O$
(2*R*,α*R*)-**49**	104–105	+100 (*c*1, EtOH)	63 (I,II)	$C_{14}H_{20}N_2O$
(2*R*,α*S*)-**50**	91–92	–79 (*c*1, EtOH)	60 (I,II)	$C_{14}H_{20}N_2O$
(2*S*,α*R*)-**51**	94–95	+79 (*c*1, EtOH)	60 (I,II)	$C_{14}H_{20}N_2O$

[a]All compounds were recrystallized from petroleum ether/Et_2O and gave acceptable C, H, and N analyses, ±0.4% of the calculated values.

fold less potent in the MES test and also was less neurotoxic. The PI values for the two enantiomers were equivalent, but less than the PI for the racemate. As a result of the low ED_{50} values in the MES test, *(R)*-**35** and *(S)*-**36** were evaluated for anticonvulsant activity and neurotoxicity in rats by the oral route. In contrast to the MES test in mice, *(S)*-**36** was more active than *(R)*-**35** in rats (ED_{50} values = 43.2 mg/kg and 64.2 mg/kg, respectively). Also, *(S)*-**36** exhibited a two-fold greater PI value than *(R)*-**35** (*table IV*). The positional isomers of **34**, compounds **39–42** (*table III*), were less active in the MES test. In fact, the 2,4-dimethylanilide **40** was inactive.

In summary, the 2-piperidinecarboxamides *(R,S)*-**34**, *(R)*-**35**, and *(S)*-**36** exhibited potent activity in the MES test and, like phenytoin, were devoid of activity in the scPTZ test at doses up to 300 mg/kg. Since no apparent correlation exists between displacement of [^{3}H]TCP from the PCP site of the NMDA receptor complex in rat whole brain homogenates and MES activity, other mechanisms of action appear to be responsible for the anticonvulsant activity of these compounds. However, the affinity for the PCP site correlates well with the neurotoxicity of several of the 2-piperidinecarboxamides [8]. Acetylation of the piperidine ring nitrogen leads to a decrease in MES activity (compare compounds **33** and **34** and **12** and **27**); thus, the presence of a basic nitrogen seems to be important for imparting potent anticonvulsant activity in this series. Decreasing the distance between the amide group and the phenyl ring (anilides) increased MES activity in compounds having 2,6-dimethyl-substitution. The racemate **34** and its 1-acetyl derivative **33** exhibited the greatest PI values (5.7 and 7.4, respectively) of any of the 2-piperidinecarboxamides which were evaluated for seizure protection in the MES test. Based on the results of this study, these novel 2-piperidinecarboxamides may have therapeutic potential in the treatment of tonic–clonic and partial seizures in man. Additional studies are in progress to further explore the SAR of the 2-piperidinecarboxamide nucleus.

4. Experimental protocols

4.1. Chemistry

Unless otherwise specified, 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 recorded on a JEOL FX 90Q spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (1%). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. HPLC analyses were performed on an IBM LC/9560 ternary gradient liquid chromatograph using a Supelcosil C18 column and a LS/9563 variable wavelength detector. Ion exchange chromatography was performed on an Econo-Column (5 x 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. UV spectra were recorded on a Gilford 'Response' UV-Vis spectrophotometer. Analytical data were obtained from Oneida Research Services, Inc., Whitesboro, NY, Micro-Analysis, Inc., Wilmington, DE, and Desert Analytics, Tucson, AZ.

4.1.1. (R)-(+)-Pipecolic acid

Using the method of Hardtmann et al., *(R,S)*-pipecolic acid (5.0 g, 38.7 mmol) was suspended in hot MeOH (19 mL) and

Table III. Anticonvulsant activity and neurotoxicity of the 2-piperidinecarboxamides in mice[a].

Compound	MES		scPTZ		Toxicity[b]		PI
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h	
12	53 (46-61)		ND[c]		88 (79-98)		1.7
(S)-**13**	+++	–	–	–	++	++	
14	29 (25-34)	–	–	–	++	++	
15	38 (31-45)		ND[c]		86 (83-88)		2.9
16	31 (27-37)		ND[c]		121 (115-127)		3.9
17	24 (21-26)		ND[c]		82 (78-87)		3.4
(S)-**18**	+++	–	–	++	++		
19	99 (81-121)		ND[c]		124 (109-141)		1.3
20	70 (59-83)		ND[c]		[d]		
21	38 (33-44)		ND[c]		118 (111-125)		3.1
22	42 (38-46)		ND[c]		132 (121-144)		3.1
23	>120		ND[c]		120[e]		
24	99 (90-110)		ND[c]		ND[d,f]		
25	37 (32-43)		ND[c]		99 (89-111)		2.7
26	++	–	–	–	++	+	
27	>90		ND[c]		ND[c]		
28	[d]		[d]		[d]		
29	+++	–	–	–	++	++	
30	++	–	–	–	+++	+	
31	++	–	–	–	++	+	
32	77 (68-88)		ND[c]		~ 160		~ 2
33	55.2 (43.3-61.8)		+	–	388 (292-646)		7.4
(RS)-**34**	5.8 (4.7-7.5)		–	–	33.2 (28.6-37.1)		5.7
(R)-**35**	5.7 (4.9-6.0)		–	–	16.9 (14.2-19.3)		3.0
(S)-**36**	14.8 (12.9-16.6)		–	+++	50.1 (39.9-58.9)		3.4
38	+++	–	–		++	++	
39	++	–	–	–	+	+	
40	–	–	–	–	+++	++	
41	++	–	–	–	+++	+	
42	+++	–	–	–	++	+	
43	+++	–	–	–	++	+	
44	++	–	–	++	+	+	
46	38 (33-43)		ND[c]		143 (125-163)		3.8
47	29 (25-34)		ND[c]		111 (104-119)		3.8
48	46 (40-53)		ND[c]		[g]		
49	39 (34-44)		ND[c]		> 150[h]		> 3.9
50	35 (29-43)		ND[c]		159 (145-175)		4.5
51	47 (39-55)		ND[c]		162 (143-185)		3.5
CBZ	9.85 (8.77-10.7)[i,j]		> 50[i,j]		47.8 (39.2-59.2)[i,j]		4.85
PTN	6.48 (5.65-7.24)[i,k]		> 50[i,l]		42.8 (36.4-47.5)[i,m]		6.60

[a]All compounds were administered by ip injection. +++, ++, and + denote antiseizure activity or toxicity at 30, 100 and 300 mg/kg, respectively; – denotes no activity up to 300 mg/kg. ED_{50} and TD_{50} values reported as mg/kg with the 95% confidence limits in parentheses. Compounds **12–25**, **27–29**, and **46–51** were tested at The University of Toledo and were previously reported [8]. All other compounds were tested by the ASP of NINDS (NIH). [b]Neurotoxicity as measured by the rotorod test. [c]Not determined. [d]3/4 died at 100 mg/kg. [e]2/4 died at 175 mg/kg. [f]Unable to determine due to toxicity. [g]Death at 80 mg/kg. [h]Death at 170 mg/kg. [i][22]. [j]Determined at 0.25 h. [k]Determined at 1 h. [l]Determined at 1 h. [m]Determined at 0.5 h.

treated with L-tartaric acid (5.8 g, 38.7 mmol) in one portion with thorough stirring. The resulting clear, light yellow solution was placed in the refrigerator to induce crystallization. After standing for several h, the light gray crystals were filtered, washed with MeOH, and dried to yield 4.7 g of the tartrate salt: m.p. 182–184 °C ([19]: m.p. 189–190 °C). The crude tartrate was dissolved in a mixture of water (5.1 mL) and acetone (2.1 mL), and additional acetone was added until the point of cloudiness. The resulting crystals were filtered and thoroughly washed with acetone/water (4:1). A second crop of crystals was obtained in a similar manner to afford a combined yield of 3.2 g (59%) of the (+)-tartrate salt of pipecolic acid: m.p. 194–195 °C (m.p. 195–196 °C; $[\alpha]_D^{23°}$ = + 20° (*c*2, H_2O) ([19]: $[\alpha]_D^{23°}$ = + 21° (*c*2, H_2O)). A solution of the (+)-tartrate

Table IV. MES activity and neurotoxicity of *(R)*-**35** and *(S)*-**36** in rats[a].

Compound	MES	Toxicity	PI
(R)-**35**	64.2 (41.9–114.9)	> 186	> 2.9
(S)-**36**	43.2 (28.6–56.3)	< 250	< 5.7
CBZ	3.57 (2.41–4.72)[b]	361 (319–402)[b]	101.1
PTN	23.2 (21.4–25.4)[c]	> 500[d]	> 21.6

[a]All compounds were administered po. ED_{50} and TD_{50} values reported as mg/kg. This data was obtained from the ASP of NINDS (NIH) using described methods [22]. [b]Determined at 1 h. [c]Determined at 2 h. [d]Determined at 0.25–24 h.

salt of pipecolic acid (3.2 g, 11.5 mmol) in water (7.0 mL) was subjected to ion-exchange chromatography on an Amberlite IR-120 (30 mL) column eluting with water followed by aqueous NH_3 (10%). Fractions homogeneous by TLC using ninhydrin spray reagent (0.1%) as the detecting agent were combined and concentrated under reduced pressure to give a white solid. Recrystallization from MeOH/Et_2O gave 1.2 g (81%) of *(R)*-(+)-pipecolic acid: m.p. 274–276 °C ([19]: m.p. 277–279 °C); $[\alpha]_D^{23°}$ = + 26.7° (*c*1.5, H_2O) ([19]: $[\alpha]_D^{23°}$ = + 25° (*c*1.5, H_2O)); IR (KBr) 1639 (C=O, acid) cm^{-1}; ^1H NMR (D_2O) δ 1.90 (br m, 6 H), 3.25 (br m, 3 H, CH_2NHCH).

4.1.2. (S)-(–)-Pipecolic acid

Following the procedure described above, *(R,S)*-pipecolic acid (5.0 g, 38.7 mmol) in hot MeOH (30 mL) was treated with D-(–)-tartaric acid to yield 4.8 g of the (–)-tartrate salt of pipecolic acid as light gray crystals: m.p. 183–184 °C ([19]: no reported m.p.). The resulting crystals were dissolved in a mixture of water (8.1 mL) and acetone (4.4 mL), and additional acetone was added to the point of cloudiness. The resulting crystals were filtered and dried to give 4.1 g (75%) of the (–)-tartrate salt of pipecolic acid: m.p. 194–196 °C ([19]: no reported m.p.); $[\alpha]_D^{23°}$ = – 19.5° (*c*2, H_2O) ([19]: no reported optical rotation). Using an Amberlite IR-120 ion-exchange column, the (+)-tartrate of pipecolic acid (4.1 g, 11.5 mmol) gave 1.1 g (59%) of *(S)*-(–)-pipecolic acid as a white solid after recrystallization from MeOH/Et_2O: m.p. 278–279 °C ([19]: no reported m.p.); $[\alpha]_D^{23°}$ = – 24° (*c*1.5, H_2O) ([19]: $[\alpha]_D^{23°}$ = – 27.5° (*c*2.0, H_2O)); IR (KBr) (D_2O) δ 1.90 (br m, 6 H), 3.25 (br m, 3 H, CH_2NHCH).

4.1.3. Determination of the optical purity of (R)-(–)- and (S)-(–)-pipecolic acid

The optical purity was determined by formation of the diastereoisomeric *N*-(α-methylbenzyl)amides with either *(R)*-(+)-α-methylbenzylamine or *(S)*-(–)-α-methylbenzylamine using Methods I–II.

(2*S*,α*S*)-**48**: ^1H NMR ($CDCl_3$) δ 1.48 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.68 (s, 1 H, CH_2NHCH), 1.87 (br m, 6 H), 2.91 (br m, 3 H, CH_2NHCH), 5.13 (m, 1 H, $CHCH_3$), 7.05 (br s, 1 H, CONH), 7.30 (s, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.9, 24.2, 26.2, 30.2, 45.9, 48.2, 60.4, 126.2, 127.3, 128.7, 143.6, 173.1.

(2*R*,α*R*)-**49**: ^1H NMR ($CDCl_3$) δ 1.48 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.66 (s, 1 H, CH_2NHCH), 1.92 (br m, 6 H), 2.85 (br m, 3 H, CH_2NHCH), 5.13 (m, 1 H, $CHCH_3$), 7.05 (br s, 1 H, CONH), 7.30 (s, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.9, 24.2, 26.2, 30.2, 45.9, 48.2, 60.4, 126.2, 127.3, 128.7, 143.6, 173.1.

(2*R*,α*S*)-**50**: ^1H NMR ($CDCl_3$) δ 1.48 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.61 (s, 1 H, CH_2NHCH), 1.78 (br m, 6 H), 2.95 (br m, 3 H, CH_2NHCH), 5.12 (m, 1 H, $CHCH_3$), 7.05 (br s, 1 H, CONH), 7.30 (s, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 22.0, 24.2, 26.2, 30.1, 46.0, 48.2, 60.5, 126.1, 127.2, 128.7, 143.7, 173.0.

(2*S*,α*R*)-**51**: ^1H NMR ($CDCl_3$) δ 1.48 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.68 (s, 1 H, CH_2NHCH), 1.85 (br m, 6 H), 2.93 (br m, 3 H, CH_2NHCH), 5.13 (m, 1 H, $CHCH_3$), 7.05 (br s, 1 H, CONH), 7.30 (s, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 22.0, 24.2, 26.2, 30.1, 46.0, 48.2, 60.5, 126.1, 127.2, 128.7, 143.7, 173.0.

The *N*-(α-methylbenzyl)amides were analyzed by HPLC using the following conditions: column-Supercosil LC-18, 5 μm, 25 cm x 4.6 mm ID; mobile phase-CH_3CN: 66 mM KH_2PO_4: Et_3N (17.5: 82.5: 0.1); flow rate 1 mL/min; detection-uv, 220 nm; and injection 10 ppm in MeOH, 10 μL. Retention times: (2*S*,α*S*)-**48**, 13.2 min; (2*R*,α*R*)-**49**, 13.2 min; (2*R*,α*S*)-**50**, 10.9 min; (2*S*,α*R*)-**51**, 10.9 min. The results of the HPLC analyses showed that the *(R)*-(+)- and *(S)*-(–)-pipecolic acids were optically pure, e.e. 100%. NMR analyses of the diastereoisomeric amides **49**–**51** confirmed the above with no detectable amounts of the corresponding diastereoisomer present.

4.1.4. (R,S)-1-(tert-Butoxycarbonyl)-2-piperidinecarboxylic acid ***2***

Using the method described by Crider et al. [5], *(R,S)*-pipecolic acid (10.0 g, 77.4 mmol) was dissolved in a mixture of water (50 mL) and acetone (50 mL) and treated with triethylamine (12.3 g, 121 mmol) followed by the addition of BOC-ON (20.1 g, 81.6 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 x 100 mL). The combined ethyl acetate extracts were dried (Na_2SO_4), filtered, and evaporated to give a white solid. Recrystallization from EtOAc/hexane afforded 13.2 g of *(R,S)*-**2**: IR (KBr) 3100 (OH), 1759 (C=O, acid), 1631 (C=O, carbamate) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H, $C(CH_3)_3$), 1.93 (br m, 6 H), 2.96 (m, 1 H, H-6), 3.93 (m, 1 H, H-6), 4.91 (m, 1 H, H-2), 8.93 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 20.7, 24.7, 26.7, 28.3, 41.2, 42.1, 53.7, 54.7, 80.4, 156.1 (NCOO), 177.5 (COOH).

*4.1.5. (S)-(–)-1-Carbethoxy-2-piperidinecarboxylic acid (S)-****6***

Following the procedure described by Vecchietti et al. [18], a solution of *(S)*-pipecolic acid [19] (1.5 g, 11.6 mmol) in 2 N NaOH (6 mL) was cooled to 0–5 °C in a three-necked flask equipped with two addition funnels. The solution was treated in a dropwise manner with ethyl chloroformate (1.3 g, 12.0 mmol) and 4 N NaOH (3 mL) simultaneously over a period of 20 min. The mixture was stirred for an additional 10 min, treated with concentrated HCl (10 mL), and extracted with dichloromethane (2 x 50 mL). The dichloromethane extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield an oil. The solid obtained upon trituration with hexane was filtered and recrystallized from hexane to yield 1.4 g of *(S)*-**6**: $[\alpha]_D^{23°}$ = – 5° (*c*1, EtOH); IR (KBr) 1752 (C=O, acid), 1645 (C=O, carbamate) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.92 (br m, 6 H), 3.01 (m, 1 H, H-6), 3.96 (m, 1 H, H-6), 4.17 (q, 2 H, *J* = 7.0 Hz, CH_2CH_3), 4.91

(m, 1 H, H-2), 9.60 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 14.6, 20.8, 24.8, 26.8, 41.9, 54.4 (NCHCO), 61.9, 156.8 (NCOO), 176.6 (COOH).

4.1.6. (R,S)-N-(Benzyl)-1-(tert-butoxycarbonyl)-2-piperidinecarboxamide ***8***

Method I: A solution of *(R,S)*-**2** (3.0 g, 13.1 mmol) in dry THF (100 mL) was cooled at 0–5 °C and NMM (1.3 g, 13.1 mmol) was added under nitrogen. After stirring for 5 min, IBCF (1.8 g, 13.1 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 benzylamine (1.4 g, 13.1 mmol) in THF (15 mL) was added over 10 min at 0–5 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h, and the NMM hydrochloride was filtered. Removal of the solvent under reduced pressure gave a white solid upon trituration with ethyl acetate. Recrystallization from EtOH/H_2O afforded 2.6 g of **8**: IR (KBr) 1730 (C=O, carbamate), 1680 (C=O, amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H, $C(CH_3)_3$), 2.17 (br m, 9 H), 4.46 (d, 2 H, J = 5.8 Hz, $CONHCH_2$), 6.55 (br s, 1 H, CONH), 7.20 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.2, 25.4, 26.1, 28.5 ($C(CH_3)_3$), 42.8, 43.4 ($CONHCH_2$), 56.1 (NHCHCO), 80.7 ($C(CH_3)_3$), 122.4, 124.6, 129.8, 132.1, 141.1, 159.7 (NCOO), 172.3 (CONH).

4.1.7. (R,S)-N-(Benzyl)-2-piperidinecarboxamide hydrochloride ***12***

Method II: A solution of **8** (1.3 g, 4.1 mmol) in dichloromethane (50 mL), cooled to 0–5 °C, was saturated with hydrogen chloride gas, and the mixture was stirred for 2 h. The solvent was evaporated under reduced pressure to yield an oil which solidified upon trituration with diethyl ether. Recrystallization from absolute EtOH/Et_2O yielded 0.8 g of **12**: IR (KBr) 1682 (C=O, amide), cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.75 (br m, 9 H), 4.34 (d, 2 H, J = 5.9 Hz, $CONHCH_2$), 7.30 (m, 5 H, ArH), 9.22 (br s, 2 H, NH_2^+); ^{13}C NMR (D_2O) δ 23.9, 24.0, 29.7, 45.8, 46.8 ($CONHCH_2$), 60.6 (NHCHCO), 130.0, 130.3, 131.6, 140.4, 172.3 (CONH).

4.1.8. (R,S)-N-[(3-Trifluoromethyl)benzyl]-2-piperidinecarboxamide hydrochloride ***17***

Method III: A solution of *(R,S)*-1-carbethoxy-2-piperidinecarboxylic acid (**5**, 4.0 g, 19.9 mmol) [18] in dichloromethane (20 mL) was cooled to 0–5 °C and treated in a dropwise manner with a solution of thionyl chloride (6.7 g, 56.3 mmol) in dichloromethane (20 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 20 h, and the solvent was evaporated under reduced pressure. Additional dichloromethane was added and evaporated. The resulting residue was dissolved in dichloromethane (80 mL), cooled to 0–5 °C under nitrogen, and treated dropwise with (3-trifluoromethyl)benzylamine (7.6 g, 43.4 mmol) in dichloromethane (40 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 20 h. The mixture was washed with 5% $NaHCO_3$ (2 x 50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give an oil. The oil was dissolved in ethanolic hydrogen chloride (40 mL), and the solvent was evaporated under reduced pressure to yield a white solid. Recrystallization from isopropanol/diethyl ether gave 5.7 g of **17**: IR (KBr) 3285 (NH, amide), 1689 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.55 (br m, 9 H), 4.50 (d, 2 H, J = 5.9 Hz, $CONHCH_2$), 6.55 (br s, 1 H, CONH), 7.44 (br m, 4 H, ArH), 9.45 (br s, 2 H, NH_2^+); ^{13}C NMR (DMSO-d_6) δ 21.3, 21.7, 27.0, 41.7, 43.3 ($CONHCH_2$), 56.8 (NHCHCO), 123.5, 123.8, 129.5, 131.8, 140.5, 168.9 (CONH).

4.1.9. (R,S)-N-[(2,5-Dimethyl)phenyl]-2-piperidinecarboxamide ***41***

Method IV: The synthesis of this compound was accomplished by the method of Ekenstam et al. [24]. A stirred suspension of the hydrochloride of pipecolic acid (2.0 g, 12.1 mmol) in acetyl chloride (20 mL) was treated with phosphorous pentachloride (2.0 g, 9.6 mmol) in one portion under a nitrogen atmosphere. The reaction mixture was warmed to 35 °C, and additional phosphorous pentachloride (1.0 g, 4.8 mmol) was added after 4 h. After stirring for an additional 3 h, the reaction mixture was cooled in an ice bath. The resulting precipitate was filtered, washed with toluene followed by acetone, and suspended in acetone (40 mL). The stirred suspension was treated in one portion with 2,5-dimethylaniline (3.6 g, 29.7 mmol) and was heated to reflux for 2 h. After cooling to room temperature, the precipitate was filtered, washed with acetone, treated with 1 N NaOH, and extracted with ethyl acetate (2 x 75 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give 1.5 g of **41** after recrystallization from diethyl ether/petroleum ether: IR (KBr) 1691 (C=O, amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 6 H), 1.74 (s, 1 H, CH_2NHCH), 2.21 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 3.01 (br m, 3 H, CH_2NHCH), 6.94 (m, 2 H, ArH), 7.87 (s, 1 H, ArH), 8.84 (br s, 1 H, CONH); ^{13}C NMR ($CDCl_3$) δ 17.3, 21.2, 23.8, 26.1, 29.9, 45.6, 60.6, 122.2, 124.8, 125.1, 130.1, 135.7, 136.5, 172.1 (CONH); MS (CI, methane) m/z 233 (M^+ + 1).

4.1.10. (R,S)-1-Acetyl-N-(benzyl)-2-piperidinecarboxamide ***27***

A solution of **12** (2.0 g, 7.9 mmol) and triethylamine (0.8 g, 7.9 mmol) in dichloromethane (20 mL) was treated dropwise with acetic anhydride (0.8 g, 7.9 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 1 h and refluxed under nitrogen for 8 h. The solvent was evaporated to yield a white solid. Recrystallization from EtOAc/petroleum ether gave 0.6 g of **27**: IR (KBr) 1682, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3 H, CH_3), 2.55 (br m, 9 H), 4.50 (d, 2 H, J = 5.9 Hz, $CONHCH_2$), 6.40 (br s, 1 H, CONH), 7.20 (br m, 5 H, ArH); ^{13}C NMR (DMSO-d_6) δ 20.5, 21.6, 25.5, 43.6, 44.6 ($CONHCH_2$), 52.2 (NHCHCO), 127.5, 127.7, 128.8, 138.7, 170.9 (CONH).

4.1.11. (R,S)-1-Acetyl-N-[(2,6-dimethyl)phenyl]-2-piperidinecarboxamide ***33***

A solution of acetyl chloride (0.4 g, 4.9 mmol) and triethylamine (0.5 g, 4.9 mmol) in THF (50 mL) was cooled to 0–5 °C under nitrogen and treated dropwise with a solution of the amide **34** (1.1 g, 4.9 mmol) in THF (20 mL). The mixture was stirred at room temperature for 2 h, and the precipitated triethylamine hydrochloride was filtered. Removal of the solvent under reduced pressure afforded a yellow solid which was partitioned between ethyl acetate (100 mL) and water (100 mL). The ethyl acetate layer was washed with 1 N HCl, dried (Na_2SO_4), filtered, and evaporated under vacuum to afford 1.0 g of **33** after recrystallization from EtOAc/hexane: IR (KBr) 3342, 3308 (NH, amide), 1647 (C=O, amide), 1502, 1414, 1263, 995, 782 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69 (br m, 6 H), 2.15 (s, 3 H, CH_3CO), 2.17 (s, 6 H, 2,6-diCH_3), 3.50 (br m, 2 H, CH_2NCH), 5.35 (m, 1 H, NCHCO), 7.04 (m, 3 H, ArH), 7.65 (br s, 1 H, CONH); ^{13}C NMR ($CDCl_3$) δ 18.5, 20.3, 21.7, 25.2, 25.4, 39.8, 44.6, 51.8, 58.3, 127.0, 128.1, 128.3, 133.8, 135.0, 169.5 (CON), 171.2 (CONH).

4.2. Anticonvulsant testing

The anticonvulsant testing was carried out at the University of Toledo and at the Epilepsy Branch (NINDS) of the NIH by the ASP, using established methods [8, 22].

Acknowledgements

This research was supported by the School of Pharmacy, Northeast Louisiana University, and completed in collaboration with Novo Nordisk A/S, Bagsvaerd, Denmark, and the University of Toledo. The authors are grateful to the ASP of NINDS for providing some of the pharmacological data.

References

[1] McNamara J.O., in: Hardman J.G., Limbird L.E., Molinoff P.B., Ruddon R.W., Gilman A.G. (Eds.), The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, 1990, 9th ed., pp. 461–486.
[2] Loscher W., Schmidt D., Epilepsy Res. 17 (1994) 95–134.
[3] Davies-Jones G.A.B., Anticonvulsants, in: Dukes M.N.G. (Ed.), Meyler's Side Effects of Drugs, Elsevier Science, New York, 1988, 11th ed., pp. 120–126.
[4] Crider A.M., Wood J.D., Tschappat K.D., Hinko C.N., J. Pharm. Sci. 73 (1984) 1612–1616.
[5] Crider A.M., Tita T.T., Wood J.D., Hinko C.N., J. Pharm. Sci. 71 (1982) 1214–1219.
[6] Hinko C.N., Seibert K., Crider A.M., Neuropharmacology 23 (1984) 1009–1014.
[7] Hinko C.N., Crider A.M., Wood J.D., Neuropharmacology 27 (1988) 475–483.
[8] Hinko C.N., Crider A.M., Kliem M.A., Steinmiller C.L., Seo T.H., Ho B., Venkatarangan P., El-Assadi A.A., Chang H., Burns C.M., Tietz E.I., Andersen P.H., Klitgaard H., Neuropharmacology 35 (1996) 1721–1735.
[9] Conley J.D., Kohn H., J. Med. Chem. 30 (1987) 567–574.
[10] Kohn H., Sawhney K.N., LeGall P., Conley J.D., Robertson D.W., Leander J.D., J. Med. Chem. 33 (1990) 919–926.
[11] Kohn H., Sawhney K.N., LeGall P., Robertson D.W., Leander J.D., J. Med. Chem. 34 (1991) 2444–2452.
[12] Kohn H., Sawhney K.N., Bardel P., Robertson D.W., Leander J.D., J. Med. Chem. 36 (1993) 3350–3360.
[13] Bardel P., Bolanos A., Kohn H., J. Med. Chem. 37 (1994) 4567–4571.
[14] Choi D., Stables J.P., Kohn H., J. Med. Chem. 39 (1996) 1907–1916.
[15] Clark C.R., Sanson R.T., Lin C.-M., Norris G.N., J. Med. Chem. 28 (1985) 1259–1262.
[16] Clark C.R., Lin C.-M., Sanson R.T., J. Med. Chem. 29 (1986) 1534–1537.
[17] Porter R.J., Cereghino J.J., Gladding G.D., Hessie B.J., Kupferberg H.J., Scoville B., White B.G., Cleve Clin. Q 51 (1984) 293–305.
[18] Vecchietti V., Giordani A., Giardina G., Colle R., Clarke G.D., J. Med. Chem. 34 (1991) 397–403.
[19] Hardtmann G.E., Houlihan W.J., Giger R.K.A., US Patent 4,760,065, 1988.
[20] Shuman R.J., Orstein P.L., Paschal J.W., Gesellchen P.D., J. Org. Chem. 55 (1990) 738–741.
[21] Bachem Bioscience, King of Prussia, PA 19406.
[22] White H.S., Woodhead J.H., Franklin M.R., Swinyard E.A., Wolf H.H., in: Levy R.H., Mattson R.H., Meldrum B.S. (Eds.), Antiepileptic Drugs, Raven Press, New York, 1995, 4th ed., 99–109.
[23] Tullar B.F., J. Med. Chem. 14 (1971) 891–892.
[24] Ekenstam B.T., Egner B., Petterson G., Acta Chem. Scand. 11 (1957) 1183–1190.