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Synthesis and anticonvulsant activity of *N,N*-phthaloyl derivatives of central nervous system inhibitory amino acids

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In order to study the influence of the length of the amino acid chain of *N,N*-phthaloyl-amino acid amides as analogues of the former anticonvulsant taltrimide on the seizure-antagonizing activity glycine, β-alanine and γ-aminobutyric acid (GABA) derivatives were synthesized. The corresponding taurine derivatives were also included. Generally, the glycine-derived amides showed a higher activity than the β-alanine and GABA derivatives in the maximal electroshock seizure (MES) test in mice upon intraperitoneal administration. The activity was comparable to the respective taurine derivatives. The *N,N*-phthaloyl-glycine amides were also active in the MES test upon oral administration to rats. No significant activity was noted in the seizure threshold test with subcutaneous pentylenetetrazole. The ED_{50} of *N,N*-phthaloyl-glycine ethyl amide (**4b**) in the MES test upon intraperitoneal administration to mice was 19.1 mg/kg. On a molar basis this activity is comparable to the activity of phenytoin with little toxicity in the rotorod test. In conclusion, *N,N*-phthaloyl-glycine amides might represent promising antiepileptic drugs.

Key Words: Anticonvulsants; Glycine; β-Alanine; γ-Aminobutyric acid; *N,N*-Phthaloyl-amino acids

Received: June 22, 2001 [FP595]

Introduction

Worldwide, approximately 40–50 million people (about 0.5–1% of the population) suffer from epilepsy, a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes, in which there is a disturbance of movement, sensation, behavior, perception, and/or consciousness[1]. 20–30% of the patients have seizures that are resistant to the available medical therapies. This fact warrants the search for new anticonvulsant drugs.

Taurine (2-aminoethanesulfonic acid) is present in the central nervous system in high concentrations and associated with numerous physiological actions such as osmoregulation, depression of neuronal firing, and modulation of neuronal action and neurotransmitter release[2]. Early reports on the anticonvulsant activity of taurine in animal models prompted the synthesis and anticonvulsant evaluation of taurine-containing compounds[3–5]. Based on its pharmacological profile in animal experiments 2-phthalimidoethanesulfonic acid *N*-isopropylamide (**9c**) was further developed under the name taltrimide[6]. However, the antiepileptic effect observed in animal experiments could not be confirmed in clinical trials[7,8]. In contrast, seizures increased statistically significantly during taltrimide treatment and further development of the drug was discontinued.

Glycine and γ-aminobutyric acid (GABA) are inhibitory amino acid neurotransmitters in the brain. Their structures have been incorporated into several compounds which showed anticonvulsant properties in several models[9–11] including phthalimido derivatives of glycine and its monoalkyl amides[12] and dialkyl amides[13] as well as phthalimides of GABA[12–15].

The present study was conducted in order to investigate the influence of the length of the amino acid chain. *N,N*-Phthaloyl-amino acid amides of glycine, β-alanine, and GABA were synthesized. β-Alanine is an agonist at the strychnine-sensitive glycine receptor[16] which mediates the inhibitory activity of glycine in the central nervous system. For comparison with the inhibitory amino acid derivatives, the respective *N,N*-phthaloyl-taurine amides were also synthesized and included in the study.

Results and discussion

Chemistry

The synthesis of amides of the phthalimides of glycine, β-alanine, and GABA is depicted in Scheme 1. Reaction of the amino acids with phthalic acid anhydride (**1**) with concomitant removal of water yielded the respective *N,N*-phthaloyl-amino acid (**2a**–**c**) which was converted into the acid chloride (**3a**–**c**) by treatment with thionyl chloride. The target compounds including the amides (**4a**, **5a**, and **6a**), the ethyl amides (**4b**, **5b**, and **6b**), the isopropylamides (**4c**, **5c**, and **6c**), and the benzylamides (**4d**, **5d**, and **6d**) were obtained by reaction of the acid chlorides with the respective amines. When gaseous ammonia or ethylamine were used only the desired products were obtained, independently of whether an excess of the amines or equimolar concentrations were used. However, when *N,N*-phthaloyl-β-alanine chloride or *N,N*-phthaloyl-GABA chloride was

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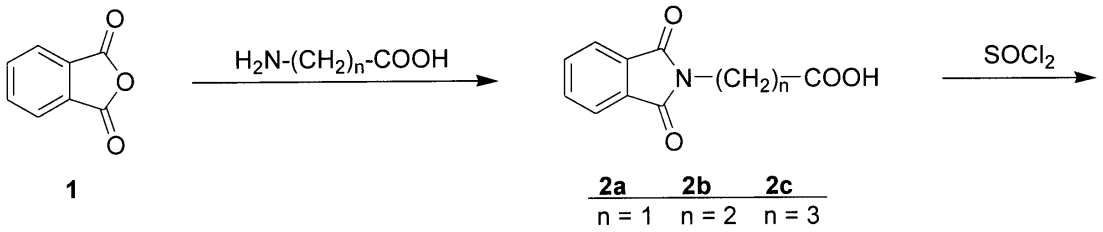
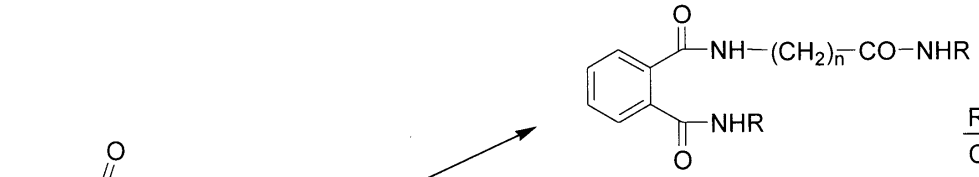
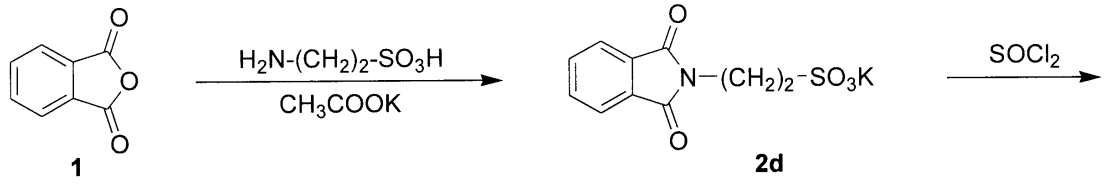
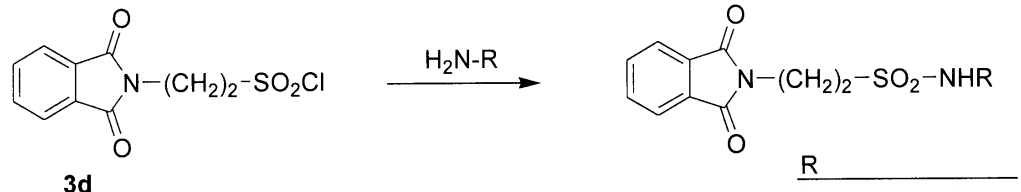




R	n = 2	n = 3
C_2H_5	**7a**	**8a**
$CH(CH_3)_2$	**7b**	**8b**

R	n = 1	n = 2	n = 3
H	**4a**	**5a**	**6a**
C_2H_5	**4b**	**5b**	**6b**
$CH(CH_3)_2$	**4c**	**5c**	**6c**
CH_2-C_6H_5	**4d**	**5d**	**6d**





R	
H	**9a**
C_2H_5	**9b**
$CH(CH_3)_2$	**9c**
CH_2-C_6H_5	**9d**

Scheme 1

Table 1. Lipophilicity values (log k_0 and *C* log *P*), anticonvulsant activity in the MES-test, and acute neurological toxicity in the rotorod test after intraperitonal administration to mice. The data are expressed as animals protected / animals tested.

Compd	log k_0	*C* log *P*	Dose [mg/kg]	MES 30 min	MES 4 h	Rotorod 30 min	Rotorod 4 h
4a	0.99	0.15	30	0/1	0/1	0/4	0/2
			100	0/3[a]	0/3	0/8	0/4
			300	1/1	1/1	1/4	0/2
4b	2.01	0.95	30	0/1	0/1	0/4	0/2
			100	3/3	0/3	0/8	0/4
			300	1/1	1/1	0/4	0/2
4c	2.44	1.25	30	0/1	0/1	0/4	0/2
			100	2/3	0/3	1/8	0/4
			300	1/1	1/1	3/4	0/2
4d	3.58	2.30	30	0/1	0/1	0/4	0/2
			100	0/3	0/3	0/8	0/4
			300	0/1	0/1	0/4	0/2
5a	1.43	0.41	30	0/1	0/1	0/4	0/2
			100	0/3	0/3	0/8	0/4
			300	1/1	0/1	1/4	0/2
5b	1.95	1.14	30	0/1	0/1	0/4	0/2
			100	0/3	0/3	0/8	0/4
			300	0/1	0/1	0/4	0/2
5c	2.60	1.45	30	0/1	0/1	1/4	1/2
			100	0/3	0/3	1/8	0/4
			300	0/1	0/1	3/4	0/2
5d	3.67	2.53	30	0/1	0/1	0/4	0/2
			100	0/3	0/3	0/8	0/4
			300	0/1	0/1	0/4	0/2
6a	1.47	0.69	30	0/1	0/1	0/4	0/2
			100	1/3	0/3	1/8	0/4
			300	1/1	0/1	3/4	2/2
6b	2.19	1.36	30	0/1	0/1	0/4	0/2
			100	0/3	0/3	0/8	0/4
			300	0/1	0/1	0/4	0/2
6c	2.3	1.67	30	0/1	0/1	0/4	0/2
			100	0/3[b]	0/3	0/8	0/4
			300	1/1	0/1	4/4	0/2
6d	3.53	2.79	30	0/1	0/1	0/4	0/2
			100	0/3	0/3	1/8	1/4
			300	0/1	0/1	1/4	0/2
9a	1.23	0.11	30	0/1	1/1	0/4	0/2
			100	2/3	2/3	0/8	0/4
			300	1/1	1/1	1/4	0/2
9b	2.30	1.30	30	0/1	0/1	0/4	0/2
			100	3/3	1/3	1/8	0/4
			300	1/1	1/1	4/4	0/2
9c	2.59	1.61	30	0/1	0/1	0/4	0/2
			100	3/3	2/3	0/8	0/4
			300	1/1	1/1	4/4	0/2
9d	3.72	2.42	30	0/1	0/1	0/4	0/2
			100	0/3	0/3	0/8	0/4
			300	0/1	1/1	1/4	0/2

[a] at 1 h: 2/3

[b] at 15 min: 1/3

reacted in the presence of a large excess of either benzylamine or isopropylamine, the respective phthalimides were obtained only in low yields while the ring-open asymmetric phthalic acid diamides **7a**–**b** and **8a**–**b** were the primary products. In these mixtures the *N*,*N*-phthaloyl-amino acid amides were obtained in 20–30% yields while the ring-open phthalic acid diamides were obtained in the range of 60–70%. However, when equimolar amounts of benzylamine or isopropylamine were added to the acid chlorides in the presence of triethylamine as proton scavenger the respective *N*,*N*-phthaloyl-amino acid amides were obtained in excellent yields. No such reactions were observed with the glycine derivatives. Ring opening has been observed during the preparation of amides of *N*,*N*-phthaloyl-α-amino acids bearing a substituent in the α-position[17].

The *N*,*N*-phthaloyl-taurine derivatives **9a**–**d** were prepared by an analogous sequence (Scheme 1). No ring opening of the phthalimide moiety was observed during these syntheses. The assignment of all structures was established on the basis of ^{1}H- and ^{13}C-NMR, mass spectrometry, and microanalysis.

The lipophilicity of the target compounds (Table 1) was estimated by calculation using the ClogP program[18] and

Table 2. Anticonvulsant activity of *N,N*-phthaloyl-glycine ethylamide (**4b**), taltrimide (**9c**) and standard antiepileptic drugs upon i.p. administration to mice measured at the time of peak effect. The data are expressed in μmol/kg. 95% confidence intervals are given in parenthesis, the time of test is listed in square brackets.

Compound	ED_{50} MES [μmol/kg]	ED_{50} ScMet [μmol/kg]	TD_{50} [μmol/kg]	PI (TD_{50}/ED_{50})
N,N-Phthaloyl-glycine ethylamide (**4b**)	282 (230–337) [0.25]	755 (627–874) [0.25]	1280 (1105–1520) [0.5]	4.5 / 1.7
Taltrimide (**9c**)	251 (215–276) [0.25]	415 (323–528) [0.25]	628 (4278–1010) [0.5]	2.5 / 1.5
Phenytoin [a]	25.7 (22.4–28.7) [0.5]	– –	170 (144–188) [2]	6.6 / –
Carbamazepine [a]	41.7 (37.1–45.3) [0.25]	– –	202 (166–251) [0.25]	4.9 / –
Valproic acid [a]	1990 (1643–2489) [0.25]	1449 (1220–1727) [0.25]	3350 (2857–3960) [0.25]	1.7 / 2.3

[a] Data from reference [20] converted to μmol/kg.

Table 3. Time course of the anticonvulsant activity in the MES test after oral administration of a dose of 30 mg/kg to rats. The values are expressed as animals protected / animals tested.

Compd	15 min	30 min	1 h	2 h	4 h
2a	2/4	3/4	1/4	0/4	0/4
4a	1/4	2/4	2/4	2/4	3/4
4b[a]	1/4	3/4	2/4	2/4	1/4
4c	1/4	2/4	2/4	2/4	2/4
9a	1/4	1/4	2/4	2/4	2/4
9b	2/4	2/4	2/4	1/4	1/4
9c[b]	3/4	3/4	0/4	2/4	4/4

[a] Dose of phthalimido-glycine ethylamide (**4b**) 20 mg/kg.

[b] Dose of phthalimido-taurine isopropylamide (**9c**) 60 mg/kg.

measured by the determination of isocratic capacity factors, log k_0, by RP-HPLC[19]. The HPLC method generally gave higher values than the computational method. Between the calculated values and the log k_0 values, a correlation of $r^2 = 0.9543$ was obtained ($\log k_0 = 0.94 + 1.05 \times C\log P$). Except for the primary amides **4a**, **5a**, **6a** and the primary sulfonamide **9a** all compounds have $C\log P$ values and log k_0 values greater than 2, a value compatible with access to the CNS by crossing the blood brain barrier via passive diffusion.

Pharmacology

The compounds were tested for anticonvulsant activity according to standard procedures[20] which included the maximal electroshock seizure test (MES test) and the seizure threshold test with subcutaneous pentylenetetrazole (ScMet test). The acute neurological toxicity was determined in the rotorod test. The ring-open asymmetric phthalic acid diamides **7a**,**b** and **8a**,**b** were also included in the study. However, no activity in either test was noted for these compounds when intraperitoneally administered to mice at doses up to 300 mg/kg. The activity of the *N,N*-phthaloyl-amino acid amides in the MES test and rotorod test upon i.p. administration to mice is summarized in Table 1. Generally, the glycine derivatives were more active in the MES test than the *N,N*-phthaloyl-GABA amides while the β-alanine-containing derivatives were essentially inactive. Thus, increasing the chain length between the phthalimido moiety and the amide group results in a decrease in the anticonvulsant activity. A low electroshock seizure-antagonizing activity of the amylamide, *n*-hexylamide, and phenylamide of *N,N*-phthaloyl-GABA has been reported[15]. Each series of the respective inhibitory amino acid exhibited comparable lipophilicity (Table 1) indicating that lipophilicity alone cannot account for the differences in anticonvulsant activity but rather a better fit into a putative molecular target (receptor, enzyme) due to favorable steric interactions.

Phthalimides containing the free acid function, i.e. *N,N*-phthaloyl-glycine (**2a**) and *N,N*-phthaloyl-GABA (**2c**), were inactive in the MES test while displaying low acute neurological toxicity on the rotorod test (data not shown). Our results are in agreement with a study by Bialer and co-workers[13] who found no anticonvulsant activity for *N,N*-phthaloyl-GABA (**2c**). In contrast, the group of Pal reported seizure-antagonizing effect of **2c** in several models including the MES test[14]. No acute neurotoxicity in the rotorod test was noted for the ethyl amides **4b**, **5b**, and **6b** while all other derivatives showed moderate toxicity (Table 1). No significant activity was found for any compound in the ScMet test (data not shown).

Table 4. Anticonvulsant activity of *N*,*N*-phthaloyl-glycine ethylamide (**4b**), taltrimide (**9c**) and standard antiepileptic drugs upon oral administration to rats measured at the time of peak effect. The data are expressed in μmol/kg. 95% confidence intervals are listed in brackets, the time of test is listed in square brackets.

Compound	ED_{50} MES [μmol/kg]	ED_{50} ScMet [μmol/kg]	TD_{50} [μmol/kg]	PI (TD_{50}/ED_{50} MES)
N,*N*-Phthaloyl-glycine ethylamide (**4b**)	82.5 (50.3–122) [0.5 h]	> 1080	> 2150	> 26
Taltrimide (**9c**)	142 (89.9–217) [4 h]	> 422	> 845	> 6
Phenytoin [a]	92.0 (84.8–101) [2 h]	> 990	> 1980	> 22
Carbamazepine [a]	15.1 (10.2–20.0) [1 h]	> 1060	1528 (1350–1700) [1 h]	101
Valproic acid [a]	2740 (2300–3060) [0.5 h]	4300 (3250–6830) [0.5 h]	5960 (4990–7960) [0.5 h]	2.2

[a] Data from reference [20] converted to μmol/kg.

The electroshock seizure-antagonizing activity of the *N*,*N*-phthaloyl-glycine amides was comparable to the respective *N*,*N*-phthaloyl-taurine analogues (Table 1). No activity was noted for the benzylamides. It has been reported previously[4] that aromatic amides of *N*,*N*-phthaloyl-taurine were inactive in the MES test while aliphatic amides generally showed good activity. The same appears to be true for *N*,*N*-phthaloyl-glycine amides although the number of derivatives is limited so far. In contrast, *N*-(benzyloxycarbonyl)-glycine *N*-benzylamide showed good anticonvulsant properties in several test models[11]. Quantitative data of **4b** in comparison to taltrimide (**9c**) and prototype anticonvulsant drugs upon i.p. administration to mice are summarized in Table 2. Both **4b** and **9c** exhibited comparable activity which was lower than the activity of phenytoin and carbamazepine but higher than valproic acid. **4b** and **9c** were more active in the ScMet test than valproic acid.

Both *N*,*N*-phthaloyl-glycine and *N*,*N*-phthaloyl-taurine amides effectively antagonized electrically-induced seizures upon oral administration to rats (Table 3). The benzylamides which were inactive when administered intraperitoneally were not included. Interestingly, *N*,*N*-phthaloyl-glycine (**2a**) with the free carboxyl group which was inactive upon i.p. injection showed activity after oral administration. Quantitative data of *N*,*N*-phthaloyl-glycine *N*-ethylamide (**4b**) in comparison with taltrimide (**9c**) and standard anticonvulsant drugs upon oral administration to rats are summarized in Table 4. On a molar basis the glycine derivative **4b** is about as active as phenytoin with little toxicity, resulting in a high protective index (PI = TD_{50}/ED_{50}). Good oral MES activity with low toxicity has also been reported for the *N*,*N*-diethylamide and *N*,*N*-diisopropylamide of *N*,*N*-phthaloyl-glycine[13].

N-Phenylphthalimides represent another group of anticonvulsant compounds containing the phthalimide moiety[29–31]. As the present phthalimides of amino acid amides, these compounds displayed a similar seizure-antagonizing profile in the MES and ScMet tests as phenytoin. In addition, a *N*-phenylphthalimide derivative was shown to interact with ion channels such as blockade of the voltage-gated sodium channels[29] explaining the observed anticonvulsant effects. Whether such interactions with ion channels are also the basis of the pharmacological activity of the present amino acid amides remains to be elucidated.

In conclusion, *N*,*N*-phthaloyl-glycine *N*-monoalkylamides were more effective than the corresponding derivatives containing β-alanine or GABA demonstrating the influence of the chain length of the incorporated amino acid. In agreement with earlier studies phthalimido-glycine amides might represent a new class of antiepileptic drugs.

Acknowledgement

C.O. Usifoh was supported by a stipend from the Deutscher Akademischer Austauschdienst (DAAD). The anticonvulsant and toxicity testing by Dr. J. P. Stables at the NINDS Epilepsy Branch, National Institutes of Health, Rockville, MD, USA, and the financial support by the Fonds der Chemischen Industrie are gratefully acknowledged.

Experimental

General: Melting points were determined with a Kofler melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Gemini 200. Chemical shifts are reported in ppm relative to tetramethylsilane. EI mass spectra were obtained on a Finnigan MAT 44S, with an ionization voltage of 70 eV. Elemental analyses were performed at the Elemental Analytical Laboratory, Department of Chemistry, University of Jena, and were within ±0.4% of the theoretical values. TLC was performed on silica gel 60 F_{254} plates from Merck (Darmstadt, Germany). The starting materials were obtained from commercial sources and used without purification.

Synthesis of N,N-phthaloyl-amino acids **2a–d**

74 g (0.5 mol) of phthalic acid anhydride and 0.5 mol of the respective amino acid were refluxed in 300 ml toluene in the presence of 6.5 ml triethylamine for 2 h in a Dean-Stark apparatus. The organic solvents were removed *in vacuo*, 700 ml of water and 10 ml of concentrated HCl were added and the mixture stirred for 30 minutes, filtered, and dried. Recrystallization from ethanol yielded 2-phthalimidoacetic acid (**2a**), 95.4 g, 93%, mp 197–198 °C (lit.[21] 199–202 °C), 3-phthalimidopropionic acid (**2b**), 99.9 g, 91%, mp 151–152 °C (lit.[21] 150–152 °C), and 4-phthalimidobutyric acid (**2c**), 95.5 g, 82%, mp 116–118 °C (lit.[21] 116–117 °C). 2-Phthalimidoethanesulfonic acid potassium salt (**2d**) was prepared from 45 g (0.3 mol) of phthalic acid anhydride, 38 g (0.3 mol) taurine and 34 g (0.35) mol potassium acetate according to[22], yield 77 g, 88% of **2d**, mp 339 °C.

Synthesis of N,N-phthaloyl amino acid chlorides **3a–d**

0.2 mol of the respective *N,N*-phthaloyl-amino acid was refluxed in 20 ml of thionyl chloride for 1 h. Excess thionyl chloride was removed *in vacuo*. The resulting solid was used without further purification. Analytical samples were recrystallized from light petrol ether (60–80 °C) and CH_2Cl_2 to yield (1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)acetyl chloride (**3a**), mp 83–85 °C (lit.[23] 84–85 °C), 3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)propionyl chloride (**3b**), mp 107–108 °C (lit.[24] 107–108 °C), and 4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)butyryl chloride (**3c**), mp 105–106 °C (lit.[25] 106–107 °C). 2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)sulfonyl chloride (**3d**) was synthesized by refluxing 59 g (0.2 mol) **2d** and 73 g PCl_5 (0.35 mol) in 400 ml toluene. Work-up according to lit.[22], mp 160–161 °C (lit.[22] 159–162 °C).

Synthesis of amides

10 mmol of the *N,N*-phthaloyl-amino acid chlorides were dissolved in 30 ml CH_2Cl_2 and treated with ammonia gas at 0–4 °C for 30 min. The mixture was stirred at room temperature overnight. The resulting precipitate was filtered and recrystallized.

*2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)acetamide (***4a***)*

Yield 1.5 g, 65%; mp 270 °C (methanol) (lit.[17] 269–270 °C); ^{1}H-NMR (D_6-DMSO) d 4.14 (s, 2 H, CH_2), 7.24 (s, 1 H, NH), 7.68 (s, 1 H, NH), 7.88 (m, 4 H, Ar-H); ^{13}C-NMR (D_6-DMSO) δ 167.9, 167.5, 134.5, 131.7, 123.1, 39.9; MS *m/z* (%) = 204 [M^+] (2), 161 (100), 147 (9), 133 (13), 104(12); $C_{10}H_8N_2O_3$ (204.19) C, H, N.

*3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propionamide (***5a***)*

Yield 1.64g , 75%; mp 208–209 °C (ethanol) (lit.[17] 202–206 °C); ^{1}H-NMR (DMSO-d_6) δ 2.41 (t, *J* = 7.4 Hz, 2 H, 2′-H), 3.75 (t, *J* = 7.0 Hz, 2 H, 1′-H), 6.86 (s, 1 H, $CONH_2$), 7.44 (s, 1 H, $CONH_2$), 7.83 (m, 4 H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ 33.5, 34.2, 122.9, 131.7, 134.3, 167.6, 171.6; MS *m/z* (%) 218 [M^+] (1), 201 (12), 173 (100), 160 (27), 147 (12), 133 (11), 117 (3), 104 (11), 77 (7), 50 (5); $C_{11}H_{10}N_2O_3$ (218.21) C, H, N.

*4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)butyramide (***6a***)*

Yield 1.97 g, 85%; mp 166–168 °C (ethanol) (lit.[17] 168–169 °C); ^{1}H-NMR (DMSO-d_6) δ 1.78 (m, 2 H, 2′-H), 2.06 (t, *J* = 7.0 Hz, 2 H, 3′-H), 2.49 (t, *J* = 7.0 Hz, 2 H, 1′-H), 6.73 (s, 1 H, $CONH_2$), 7.24 (s, 1 H, $CONH_2$), 7.84 (m, 4 H, Ar-H); ^{13}C-NMR (DMSO-d_6) d 23.9, 32.4, 37.2, 122.9, 131.6, 134.3, 167.9, 173.4; MS *m/z* 232 [M^+] (4%), 215 (58), 197 (3), 187 (22), 174 (100), 160 (78), 147 (35), 133 (29), 117 (10), 104 (15), 85 (77), 59 (14); $C_{12}H_{12}N_2O_3$ (232.24) C, H, N.

*2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethanesulfonic acid amide (***9a***)*

Yield 2.1 g, 84%; mp 207–209 °C (ethanol) (lit.[22] 209–212 °C); ^{1}H-NMR (D_6-DMSO) δ 3.35 (t, *J* = 6.5 Hz, 2 H, NCH_2), 3.98 (t, *J* = 6.5 Hz, 2 H, CH_2SO_2), 7. 07 (s, 2 H, NH_2), 7.87 (m, 4 H, Ar-H); ^{13}C-NMR (D_6-DMSO) δ 32.6, 51.7, 123.1, 131.7, 134.4, 167.5; MS (CI, ammonia) *m/z* 272 ([M + NH_4]$^+$, 100%); $C_{10}H_{10}N_2O_4S$ (254.26) C, H, N.

Synthesis of N-ethylamides

10 mmol of the *N,N*-phthaloyl-amino acid chlorides were dissolved in 30 ml CH_2Cl_2 and cooled in an ice bath. Ethylamine was transferred by bubbling nitrogen through an aqueous solution of the ethylamine (70%) that was warmed to 30 °C. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was poured into ice-cold 2 M HCl and extracted with CH_2Cl_2. The organic phases were combined, washed with brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol.

*2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-N-ethyl-acetamide (***4b***)*

Yield 1.35 g, 58%; mp 236–237 °C (lit.[26] 240 °C); ^{1}H-NMR (D_6-DMSO) δ 1.00 (t *J* = 7.2 Hz, 3 H, CH_3), 3.04 (m, 2 H, CH_2CH_3), 4.15 (s, 2 H, CH_2CO), 7.88 (m, 4 H, Ar-H), 8.20 (t, *J* = 4.9 Hz, 1 H, NH); ^{13}C-NMR (D_6-DMSO) δ 22.2, 39.5, 40.7, 123.0, 131.7, 134.4, 164.7, 167.4; MS *m/z* (%) 232 [M^+] (3), 161 (100), 160 (37), 133 (19), 132 (16), 117 (56), 105 (13), 104 (23), 77 (19); $C_{12}H_{12}N_2O_3$ (232.08) C, H, N.

*3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-N-ethyl-propionamide (***5b***)*

Yield 1.73 g, 70%; mp 197–198 °C; ^{1}H-NMR (DMSO-d_6) δ 1.10 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.60 (t, *J* = 7.1 Hz, 2 H, 2′-H), 3.27 (m, 2 H, CH_2CH_3), 4.00 (t, *J* = 7.2 Hz, 2 H, 1-H), 5.75 (s, 1 H, NH), 7.72 (m, 2 H, Ar-H), 7.83 (m, 2 H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ 12.1, 31.8, 32.3, 120.7, 129.4, 131.4, 165.5, 166.7; MS *m/z* (%) 246 [M^+] (12), 203 (20), 173 (39), 161 (100), 147 (13), 133 (13), 70(28); $C_{13}H_{14}N_2O_3$ (246.27) C, H, N.

*4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-N-ethyl-butyramide (***6b***)*

Yield 1.82 g, 70%; mp 131–133 °C (lit.[12] 129–131 °C); ^{1}H-NMR (DMSO-d_6) δ 1.13 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.05 (m, 2 H, 2′-H), 2.19 (t, *J* = 6.4 Hz, 2 H, 3′-H), 3.26 (m, 2 H, CH_2CH_3), 3.74 (t, *J* = 6.2 Hz, 2 H, 1′-H), 6.00 (s, 1 H, NH), 7.73 (m, 2 H, Ar-H), 7.83 (m, 2 H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ 14.9, 25.1, 33.9, 34.5, 37.3, 123.3, 132.1, 134.1, 168.7, 171.8; MS *m/z* 261 [M^+ + 1] (3%), 260 [M^+] (4), 232(8), 216 (25), 188 (26), 160 (100), 148 (10), 130 (24), 117 (13), 100 (17), 87 (59), 77 (14); $C_{14}H_{16}N_2O_3$ (260.29) C, H, N.

*2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethanesulfonic acid ethylamide (***9b***)*

Yield 0.8 g, 29%; mp 115 °C; ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.20 (m, 2 H, CH_2CH_3), 3.40 (t, *J* = 6.5, 2 H, Hz, NCH_2), 4.14 (t, *J* = 6.5 Hz, 2 H, CH_2SO_2), 4.99 (t, *J* = 5.9 Hz, 1 H, NH), 7.74 (m, 2 H, Ar-H), 7.86 (m, 2 H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 15.8, 32.9, 38.3, 49.3, 123.6, 131.9, 134.3, 168.0; MS (CI, ammonia) *m/z* 300 [M + NH_4]$^+$ (100%); $C_{12}H_{14}N_2O_4S$ (282.32) C, H, N.

Synthesis of N-isopropylamides

Method A: 10 mmol of the *N,N*-phthaloyl-amino acid chlorides were dissolved in 20 ml CH_2Cl_2 and added dropwise to a solution of 0.6 g (10 mmol) isopropylamine and 1.5 g triethylamine in 20 ml CH_2Cl_2 at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was poured into ice-cold 2 M HCl and extracted with CH_2Cl_2. The organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol.

Method B: 10 mmol of the *N,N*-phthaloyl-amino acid chlorides were dissolved in 20 ml CH_2Cl_2 and added dropwise to a solution of 3.5 g (60 mmol) isopropylamine in 20 ml CH_2Cl_2 at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was poured into ice-cold 2 M HCl and extracted with CH_2Cl_2. The organic phases were combined, washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2-methanol, 98:1, *v/v*).

*2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-N-isopropylacetamide (***4c***)*

Method B: Yield 1.3 g, 54%; mp 223–225 °C (lit.[27] 226 °C); ^{1}H-NMR (D_6-DMSO) δ 1.05 (d, *J* = 6.6 Hz, 6 H, 2 × CH_3), 3.83 (m, 1 H, CH), 4.14 (s, 2 H, CH_2CO), 7.88 (m, 4 H, Ar-H), 8.07 (d, *J* = 7.5 Hz, 1 H, NH); ^{13}C-NMR (D_6-DMSO) δ 22.2, 40.1, 40.8, 123.0, 131.7, 134.4, 164.7, 167.4; MS *m/z* (%) 246 [M^+] (1), 161 (100), 160 (50), 133 (18), 132 (12), 117 (45), 105 (11), 104 (19), 77 (17); $C_{13}H_{14}N_2O_3$ (246.27) C, H, N.

*3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-N-isopropylpropionamide (***5c***)*

Method A: Yield 1.77 g, 68%; mp 219–220 °C; ^{1}H-NMR (DMSO-d_6) δ 0.94 (d, *J* = 6.5 Hz, 6 H, 2 × CH_3), 2.35 (t, *J* = 7.3 Hz, 2 H, 2′-H), 3.76 (m, 1 H, $CH(CH_3)_2$), 3.76 (t , *J* = 7.5 Hz, 2 H, 1′-H), 7.83 (m, 5 H, Ar-H, N-H); ^{13}C-NMR (DMSO-d_6) δ 22.2, 34.2, 34.5, 40.1, 122.9, 131.7, 134.3, 167.6, 168.3; MS *m/z* (%) 245 (4), 217 (2), 202 (51), 173 (14), 161 (100), 147 (7), 133 (10), 105 (6), 77(6), 58 (53); $C_{14}H_{16}N_2O_3$ (260.29) C, H, N.

*4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-N-isopropylbutyramide (***6c***)*

Method A: Yield 2.14 g, 78%; mp 149–150 °C. ^{1}H-NMR (DMSO-d_6) δ 1.16 (d, *J* = 6.6 Hz, 6 H, 2 × CH_3), 2.02 (m, 2 H, 2′-H), 2.17 (t, *J* = 7.3Hz, 2 H, 1′-H), 3.74 (t, *J* = 7.2 Hz, 2 H, 3′-H), 4.05 (m, 1 H, $CH(CH_3)_2$), 5.84 (s, 1 H, NH), 7.73 (m, 2 H, Ar-H), 7.84 (m, 2 H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ 22.8, 25.2, 34.1, 37.3, 41.5, 123.4, 132.1, 134.1, 168.7,170.9; MS *m/z* (%) 274 [M^+] (2), 259 (7), 216 (61), 188 (42), 174 (12), 160 (100), 148 (15), 130 (26), 117 (14), 101(53), 86(19), 77(15); $C_{15}H_{18}N_2O_3$ (274.32) C, H, N.

*2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethanesulfonic acid isopropylamide (taltrimide) (***9c***)*

Method B: Yield 1.6 g, 55%; mp 139 °C. ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, *J* = 6.5 Hz, 6 H, 2 × CH_3), 3.38 (t, *J* = 6.5 Hz, 2 H, NCH_2), 3.67 (m, 1 H, CH), 4.15 (t, *J* = 6.5 Hz, 2 H, CH_2SO_2), 4.71 (d, *J* = 7.8 Hz, 1 H, NH), 7.75 (m, 2 H, Ar-H), 7.85 (m, 2 H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 24.3, 33.0, 46.4, 50.3, 123.6, 131.9, 134.3, 168.1; MS (CI, ammonia) *m/z* (%) 314 [M + NH_4]$^+$ (100); $C_{13}H_{16}N_2O_4S$ (296.35) C, H, N.

*N-(2-Methylethyl)-3-benzamidopropionamide-2-(2-methylethyl)-carboxamide (***7a***)*

Method B, chromatographic purification gave 0.5 g **5c** (20%) and 2.2 g **7a** (60%); mp 197–199 °C; ^{1}H-NMR (DMSO-d_6) δ 1.02 (d, *J* = 6.7 Hz, 6 H, 2 × CH_3), 1.11 (d, *J* = 6.5 Hz, 6 H, 2 × CH_3), 2.28 (t, *J* = 7.3 Hz, 2 H, 2′-H), 3.35 (m, 2 H, 1′-H), 3.90 (m, 2 H, 2 × CH $(CH_3)_2$), 7.42 (m, 4 H, Ar-H), 7.79 (d, *J* = 7.8 Hz, 1 H, NH), 8.08 (d, *J* = 7.8Hz, 1 H, NH), 8.18 (t, *J* = 5.5 Hz, 1 H, NH); ^{13}C-NMR (DMSO-d_6) δ 22.1, 22.3, 35.2, 36.0, 40.1, 40.8, 127.4, 127.6, 129.0, 129.1, 136.0, 136.2, 167.1, 168.1, 169.3; MS *m/z* (%) 319 [M^+] (5), 318 (6), 276 (5), 260 (74), 234 (12), 218 (13), 202 (100), 190 (34), 174 (27), 161 (63), 148 (64), 130 (36), 105 (8), 77 (5), 58 (26); $C_{17}H_{25}N_3O_3$ (319.40) C, H, N.

*N-(2-Methylethyl)-4-benzamidobutyramide-2-(2-methylethyl)-carboxamide (***8a***)*

Method B, chromatographic purification gave 0.8 g **6c** (30%) and 1.9 g **8a** (58%); mp 171–173 °C; ^{1}H-NMR (DMSO-d_6) δ 1.03 (d, *J* = 6.6 Hz, 6 H, 2 × CH_3), 1.11 (d, *J* = 6.6 Hz, 6 H, 2 × CH_3), 1.70 (m, 2 H, 2′-H), 2.08 (t, *J* = 7.3 Hz, 3 H, 3′-H), 3.16 (m, 2 H, 1′-H), 3.83 (m, 1 H, C*H*$(CH_3)_2$), 3.98 (m, 1 H, C*H*$(CH_3)_2$), 7.44 (s, 4 H, Ar-H), 7.65 (d, *J* = 7.7 Hz, 1 H, NH), 8.10 (d, *J* = 7.6 Hz, 1 H, NH), 8.23 (t, *J* = 5.5 Hz, 1 H, NH); ^{13}C-NMR (DMSO-d_6) δ 22.2, 22.4, 25.5, 33.0, 38.6, 40.1, 40.8, 127.4, 129.1, 136.3, 167.3, 168.2, 170.9; MS *m/z* (%) 333 [M^+] (4), 290 (9), 274 (43), 259 (4), 248 (6), 233 (24), 216 (25), 190 (100), 174 (20), 160 (20), 148 (77) 130 (36), 101 (10), 86 (8); $C_{18}H_{27}N_3O_3$ (333.43) C, H, N.

Synthesis of N-benzylamides

Method A: 10 mmol of the *N,N*-phthaloyl-amino acid chlorides were dissolved in 20 ml CH_2Cl_2 and added dropwise to a solution of 1.1 g (10 mmol) benzylamine and 1.5 g triethylamine in 20 ml CH_2Cl_2 at 0 °C. Further treatment and work-up was performed as described above for the isopropylamides.

Method B: 10 mmol of the *N,N*-phthaloyl-amino acid chlorides were dissolved in 20 ml CH_2Cl_2 and added dropwise to a solution of 6.5 g (60 mmol) benzylamine in 30 ml CH_2Cl_2 at 0 °C. Further treatment and work-up was performed as described above for the isoproyplamides.

*N-Benzyl-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)acetamide (***4d***)*

Method B, yield 1.4 g, 48%; mp 215 °C (lit.[23] 217–219 °C); ^{1}H-NMR (D_6-DMSO) δ 4.26 (s, 2 H, CH_2CO), 4.31 (t, *J* = 5.5 Hz, 2 H, $CH_2C_6H_5$), 7.26 (m, 5 H, Ar-H), 7.87 (m, 4 H, Ar-H), 8.76 (t, *J* = 5.5 Hz, 1 H, NH); ^{13}C-NMR (D_6-DMSO) δ 40.2, 42.2, 123.1, 126.8, 127.1, 128.2, 131.7, 134.4, 138.8, 166.1, 167.5; MS *m/z* (%) 294 [M^+] (3), 161 (15), 160 (29), 133 (14), 117 (16), 106 (100), 104 (13), 91 (19), 77 (16); $C_{17}H_{14}N_2O_3$ (294.14) C, H, N.

*N-Benzyl-3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propionamide (***5d***)*

Method A, yield 2.0 g, 65%; mp 199–200 °C (lit.[28] 198–199.5 °C); ^{1}H-NMR (DMSO-d_6) δ 2.51 (t, *J* = 7.8 Hz, 2 H, 2′-H), 3.81 (t, *J* = 7.5 Hz, 2 H, 1′-H), 4.20 (d , *J* = 6.0 Hz, 2 H, CH_2-Bn), 7.20 (m, 5 H, Ar-H), 7.85 (m, 4 H, Ar-H), 8.47 (t, *J* = 6.0 Hz, 1 H, NH); ^{13}C-NMR (DMSO-d_6) δ 33.8, 34.4, 42.0, 122.9, 126.7, 127.1, 128.1, 131.6, 134.3, 139.2, 167.6, 169.4; MS *m/z* (%) 308 [M^+] (4), 280 (5), 263 (1), 175 (2), 160 (23), 147 (3), 130 (6), 106 (100), 91(5), 79(12), 65(3); $C_{18}H_{16}N_2O_3$ (308.34) C, H, N.

*N-Benzyl-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyramide (***6d***)*

Method A, yield 2.29 g, 71%; mp 140–142 °C; ^{1}H-NMR (DMSO-d_6) δ 1.86 (m, 2 H, 2′-H), 2.17 (t, *J* = 7.3 Hz, 2 H, 3′-H), 3.58 (t, *J* = 6.8 Hz, 2 H,1′-H), 4.19 (d, *J* = 6.0 Hz, 2 H, Bn-CH_2), 7.25 (m, 5 H, Ar-H), 7.84 (m, 4 H, Ar-H), 8.27 (t, *J* = 5.6 Hz, 1 H, NH); ^{13}C-NMR (DMSO-d_6) δ 24.1, 32.7, 37.2, 38.3, 41.9, 122.9, 126.6, 127.1, 128.2, 131.7, 134.3, 139.5, 167.9, 171.2; MS *m/z* (%) 322 [M^+ + 1] (3), 294 (4), 277 (2), 238 (1), 216 (1) 188 (3), 160 (22), 149 (5), 130 (7), 106 (100), 91 (13), 79 (10); $C_{19}H_{18}N_2O_3$ (322.36) C, H, N.

*2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethanesulfonic acid benzylamide (***9d***)*

Method B, yield: 3.2 g, 92%; mp 118 °C; ^{1}H-NMR ($CDCl_3$) δ 3.24 (t, *J* = 6.4 Hz, 2 H, NCH_2), 3.98 (t, *J* = 6.4 Hz, 2 H, CH_2SO_2), 4.33 (d, *J* = 6.1 Hz, 2 H, $CH_2C_6H_5$), 5.31 (t, *J* = 6.1 Hz, 1 H, NH), 7.33 (m, 5 H, Ar-H), 7.75 (m, 2 H, Ar-H), 7.83 (m, 2 H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 37.7, 47.3, 50.1, 123.6, 128.2, 129.0, 131.9, 134.3, 136.8, 168.1; MS (CI, ammonia) *m/z* (%) 362 [M + NH_4]$^+$ (100); $C_{17}H_{16}N_2O_4S$ (344.40) C, H, N.

*N-Benzyl-3-benzamidopropionamide-2-benzyl-carboxamide (***7b***)*

Method B, column chromatography yielded 0.8 g **5d** (25%) and 2.7 g **7b** (66%); mp 216–218 °C. ^{1}H-NMR (DMSO-d_6) δ 2.40 (t, *J* = 7.3 Hz, 2 H, 2′-H), 3.39 (m, 2 H, 1′-H), 4.26 (d , *J* = 6.0 Hz, 2 H, Bn-CH_2), 4.40 (d, *J* = 6.0 Hz , 2 H, Bn-CH_2), 7.35 (m, 14 H, Ar-H), 8.30 (t, *J* = 6.0 Hz, 1 H, NH), 8.43 (t, *J* = 6.0 Hz, 1 H, NH), 8.81 (t, *J* = 6.0 Hz, 1 H, NH); ^{13}C-NMR (DMSO-d_6) δ 35.1, 36.0, 42.0, 42.5, 107.1, 126.7, 127.1,127.2, 127.5, 127.6, 128.1, 128.2, 129.2, 129.3, 135.9, 136.4, 139.5, 168.1, 168.2, 170.4; MS *m/z* (%) 415 [M^+] (4%), 309 (30), 281 (2), 237 (50), 219 (30), 202 (27), 178 (22), 160 (25), 130 (14), 106 (100), 91(55), 79 (26), 65 (12); $C_{25}H_{25}N_3O_3$ (415.49) C, H, N.

*N-Benzyl-4-benzamidobutyramide-2-benzyl-carboxamide (***8b***)*

Method B, column chromatography yielded 0.6 g **6d** (19%) and 3.0 g **8b** (70%); mp 152–153 °C; ^{1}H-NMR (DMSO-d_6) δ 1.75 (m , 2 H, 2′-H), 2.21 (t, *J* = 7.2 Hz, 2 H, 3′-H), 3.18 (m, 2 H, 1′-H), 4.25 (d, *J* = 5.9 Hz, 2 H, Ph-CH_2), 4.38 (d, *J* = 5.9 Hz, 2 H, Ph-CH_2), 7.26 (m, 10 H, Ar-H), 7.47 (m, 4 H, Ar-H), 8.29 (t, *J* = 5.6 Hz, 2 H, NH), 8.81 (t, *J* = 6.1 Hz, 1 H, NH); ^{13}C-NMR (DMSO-d_6) δ 25.4, 32.8, 42.0, 42.4, 126.6, 127.1, 127.5, 128.1, 129.1, 129.3, 135.9, 136.6, 139.3, 139.6, 168.2, 171.9; MS *m/z* (%) 429 [M^+] (4), 411 (2) 338 (1), 323 (50), 281 (5), 237 (23), 216 (14) 192 (16), 176 (32), 160 (17), 130 (12), 118 (4), 106 (100), 91(90), 79 (16), 65 (10); $C_{26}H_{27}N_3O_3$ (429.52) C, H, N.

Lipophilicity

log k_0 Determinations

The log k_0 values were measured according to Bechalany[19]. The HPLC system consisted of a Shimadzu LC 6A solvent delivery module, a Shimadzu SPD 6A UV detector operated at 254 nm, and a Shimadzu C-R6A integrator (Shimadzu AG, Duisburg, Germany). The stationary phase was a LiChrospher 100 RP-18 column 125 × 4.6 mm, particle size 5 μm (Merck, Darmstadt, Germany). The mobile phases consisted of 10–50% methanol and 50–90% water (*v/v*), the flow rate was 1 ml/min. The log k_0 values were extrapolated from at least four determinations using different eluent compositions.

log P Calculations

The log *P* calculations were conducted on a Macintosh Power PC using the ClogP 4.0 program[18] (Biobyte Corp., Claremont, CA, USA).

Pharmacology

Anticonvulsant testing was provided by the Antiepileptic Drug Development Program, Epilepsy Branch, Division of Convulsive, Infectious and Immune Disorders, National Institutes of Health, Rockville, MD, USA, according to standard procedures[20] and included the maximal electroshock test and the seizure threshold test with subcutaneous pentylenetetrazole. The acute neurological toxicity was determined in the rotorod test. For all these evaluations the compounds were dissolved or suspended in 0.5% aqueous methyl cellulose.

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