Anticonvulsant and Neurotoxic Activities of Twelve Analogues of Valproic Acid

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Abstract □ Twelve racemic analogues of the antiepileptic drug valproic acid (VPA) were tested and compared with VPA for anticonvulsant activity by the subcutaneous pentylenetetrazol (PTZ) seizure threshold test and for neurotoxicity by the rotorod test. Four compounds produced maximal anticonvulsant activity (100% protection) in equimolar doses (1.5 mmol/kg) to VPA and two compounds showed a similar effect with lower doses (1.0 mmol/kg). Four compounds produced lower activity (38–80% protection), and two compounds showed no anticonvulsant activity at the dose used (1.5 mmol/kg). Two of the 12 compounds, (±)-2-*n*-propyl-4-hexynoic acid (**11**) and (±)-4-methyl-2-*n*-propyl-4-pentenoic acid (**12**), showed no sedation at doses that produced the maximum anticonvulsant effect. For the first time we succeeded to develop two compounds with higher protective index and safety ratios than VPA. Compound **11** had a longer duration of action and higher protective index but a lower safety ratio than **12**. Comparisons of the anticonvulsant and minimal neurotoxic effects of these compounds with their calculated lipophilicity (C log *P*) revealed that compounds with the desired high anticonvulsant activity and minimal neurotoxicity showed C log *P* values between 1.84 and 2.64 and had nine carbon atoms (in contrast to eight carbon atoms for VPA).

To search for new drugs with selective anticonvulsant activity and less toxicity, numerous derivatives and analogues of the widely used valproic acid (VPA; 2-*n*-propylpentanoic acid) have been tested.[1–12] Furthermore, various metabolites of VPA have been investigated and found to exert anticonvulsant activity in rodents.[9,11,13–15] The anticonvulsant and toxic effects of 32 metabolites and analogues of VPA were investigated in mice and it was found that valpromide demonstrated a potent anticonvulsant activity (two to five times that of VPA) but also produced more sedative and toxic effects than either VPA or ethosuximide.[9] Other amides showed higher anticonvulsant and sedative activity than VPA.[6] Valnoctamide, however, produced a better protective index value than VPA and valpromide [in the subcutaneous (sc) pentylenetetrazol (PTZ) test], but its anticonvulsant effect appears to be nonselective.[6] Of the VPA metabolites tested, the unsaturated compounds exhibited promising anticonvulsant activity, particularly the *trans*-isomer of 2-en-VPA (*E*-2-*n*-propyl-2-pentenoic acid). 2-en-VPA showed high anticonvulsant activity in a number of experimental model systems,[16] although its neurotoxicity exceeded that of VPA in some experiments.[16] Up to now, VPA has the optimal chemical structure with regard to selective anticonvulsant activity and minimal neurological toxicity.[7,9]

The use of VPA during pregnancy may be associated with an increased incidence of neural tube defects (spina bifida) along with various other malformations as suggested by retrospective[17,18] and prospective studies,[19–21] as well as a number of case reports.[22] Neural tube defects were also the most apparent lesions in mice given VPA on day 8 of gestation (exencephaly)[23,24] and day 9 of gestation (spina bifida).[25] Of the various metabolites and analogues of VPA evaluated for their embryotoxic and teratogenic potencies, 2-en-VPA (the major VPA metabolite) was found to be nonteratogenic and less embryotoxic than VPA in the mouse.[26] These results, in combination with the favorable anticonvulsant properties discussed above, prompted further development of 2-en-VPA as a possible alternative antiepileptic agent for use in humans.[27,28]

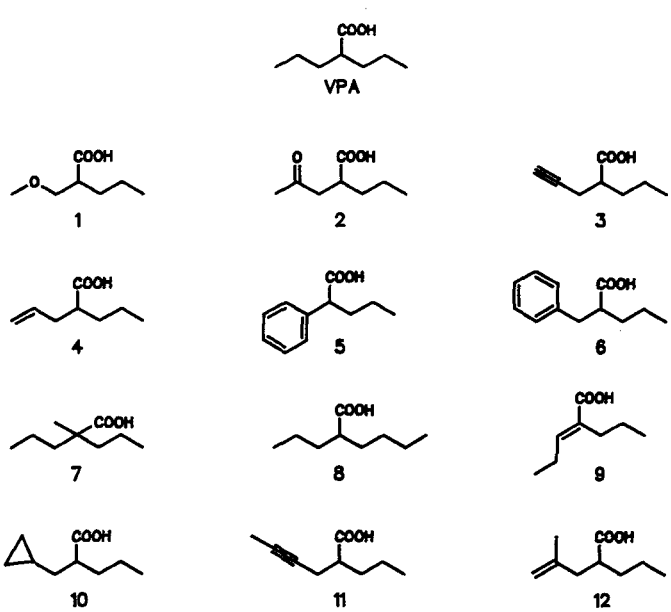
The aim of the present study was to evaluate the anticonvulsant and neurotoxic effects of 12 VPA analogues. These analogues were primarily synthesized for the study of structure–teratogenicity relationships.

Experimental Section

Chemicals—VPA and PTZ were obtained from Sigma (Deisenhofen, Germany). Methoxymethylbromide, propargylbromide, allylbromide, 2-butyn-1-ol, phosphorotribromide, cyclopropylmethylchloride, 3-chloro-2-methyl-1-propen, *n*-butylbromide, *n*-propylbromide, and benzylbromide were purchased from Aldrich (Steinheim, Germany).

Synthesis—The racemic mixtures of the compounds (**1**, **2**, **4**, **6**, **7**, **8**, **10**, and **12**; see structures) were synthesized by alkylation of diethyl-*n*-propylmalonate with the according alkyl-halides, subsequent alkaline hydrolysis, and decarboxylation according to known malonic ester synthetic procedures. Compound **2** was synthesized by hydratization of the C≡C triple bond of **3** (4-yn-VPA) with an acidified aqueous solution of mercury(II)-sulfate.[29] Compound **7** was synthesized by a α-methylation of VPA after treatment with *n*-butyllithium.[30] Compound **5** was synthesized according to malonic ester synthetic procedures starting with the alkylation of diethylphenylmalonate with *n*-propylbromide.

Chemical purities of >99% were determined by gas chromatographic analysis of the TMS derivatives of the acids. Compound **9** was kindly provided by the Desitin Company (Germany).



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Animals—Male Swiss albino mice of an inbred strain, weighing 25–31 g, were maintained under controlled conditions of temperature (25 °C) and relative humidity (~50%) at the Islamic Centre for Medical Sciences in Kuwait.

Animal Experiments—A preliminary experiment was designed to compare the anticonvulsant and neurotoxic effects of all compounds with VPA. Anticonvulsant activity was measured by the sc PTZ seizure threshold test, and minimal neurotoxicity was evaluated by the rotorod toxicity test. A dose of the sodium salt of the acid of 1.5 mmol/kg of body weight was applied initially (a similar dose of VPA produced 100% protection). Compounds that produced the same 100% effect were retested with lower doses. Neurotoxicity of the compounds was evaluated with the sodium salt of the acid at doses of 1.5 mmol or the lowest dose that produced a 100% anticonvulsant effect. In a follow-up experiment, compounds that showed a greater degree of anticonvulsant activity than of sedative activity were tested at various dose levels to calculate the median (ED_{50}) and maximal (ED_{97}) effective anticonvulsant doses and the relative potency as compared with VPA. In addition, compounds that showed maximum anticonvulsant protection with minimal neurotoxicity in the preliminary screening study were tested further at various dose levels on the rotorod to calculate minimal (TD_3) and median (TD_{50}) sedative doses.

Subcutaneous PTZ Seizure Threshold Test—Compounds were injected intraperitoneally (ip) as the sodium salt (10 mL/kg) in groups of 5–8 animals. After 15 min, PTZ at 65 mg/kg (0.65% solution in saline) was applied sc in a loose fold of skin on the back of the neck. The animals were then observed for 30 min. The number of animals protected (those showing an absence of a single 5-s episode of clonic spasms; threshold seizure[31]) was recorded and compared both with the control (dosed only with PTZ) and VPA-treated mice.

Rotorod Toxicity Test—Compounds were injected ip (10 mL/kg of sodium salt) in groups of five mice, and 15 min later the mice were placed for 1 min on a rod rotating at 15 rpm (Rotorod, Ugo Basile, Italy). The animals showing neurological deficits (ataxia and sedation), as indicated by the inability to maintain equilibrium on the rod for at least 1 min in each of three trials, were recorded.[32] The animals were retested at 30 and 45 min and compared with those animals given VPA (1.5 mmol/kg). None of the animals used in the rotorod test showed neurological deficits when tested 1 day earlier.

Statistical Calculations—The values of ED_{50}, ED_{97}, TD_3, TD_{50}, slope of the regression line, potency, and slope ratios compared with VPA were calculated according to Litchfield and Wilcoxon.[33] Lipophilicity was calculated according to Rekker and Mannhold.[34]

Results

In the present study, PTZ at 65 mg/kg (sc) was the minimal dose to produce threshold (clonic) seizures in ~100% of the control animals. Higher doses (85 and 100 mg/kg), however, induced tonic extension of the hind limbs with some mortality.

Preliminary screening of the anticonvulsant activity of the tested compounds is shown in Table I. VPA (1.5 mmol/kg) produced 100% protection against PTZ-induced threshold seizures in mice. Similar anticonvulsant activity (100% protection) was shared by six other compounds (**7**–**12**) that produced the maximal anticonvulsant activity in equimolar doses (i.e., 1.5 mmol/kg). Two of these compounds (**7** and **11**) showed a similar effect (100% protection) when tried at a lower dose (1.0 mmol/kg). Four compounds (**3**–**6**) also produced significant anticonvulsant activity: doses of 1.5 mmol/kg produced protection in 38–80% of the animals. Two compounds (**1** and **2**) showed no anticonvulsant activity at the dose used (1.5 mmol/kg).

The sedative activity of the compounds was assessed on the rotorod in the doses used for evaluation of anticonvulsant activity. The test was conducted at 15, 30, and 45 min after administration. The peak sedative effect was at 15 min. Compounds **1**, **2**, **11**, and **12** caused no sedation at a dose of 1.5 mmol/kg. Compounds **3**, **4**, and **10** produced sedation in 20–29% of the animals; this was slightly less than the sedation produced by VPA (33%). Compounds **5**–**9**, however, produced higher sedation (60–80%) than did VPA (Table I).

The compounds that showed a greater degree of anticonvulsant activity than neurotoxic activity in the preliminary screening test were tested further to evaluate their median effective dose (ED_{50}) and the relative potency compared with VPA (Table II). The slopes of the anticonvulsant regression lines of the eight racemic acids tested was parallel, within experimental errors, to that of VPA. Compound **11** produced significantly higher potency than VPA (relative potency = 2.5 times greater). Compounds **3** and **4**, however, showed lower potency. The other five compounds showed relative potencies of 0.73–1.75, which were not significantly different when compared with VPA.

Compounds **11** and **12** (which showed no sedation at doses that produced maximum anticonvulsant protection) were found to have significantly less neurotoxicity than VPA when evaluated at various dose levels on the rotorod (Table III). Both **11** and **12** had higher protective indices and safety ratios than VPA. Compared with each other, **11** had higher protective index but with lower safety ratio than **12** (Table III). In addition, **11** had a longer duration of action when retested on the rotorod at 30 and 45 min after administration (data not shown).

Structure–Activity Relationships—One of the two 2-*n*-propyl groups of VPA was altered in all compounds (**1**–**12**), except **7** and **9** (see structure). The α-hydrogen atom was substituted by a methyl group in **7**. In **9**, the α-carbon atom is connected to only three groups because of the double bond, resulting in a planar structure (sp^2) instead of a tetrahedral one (sp^3).

Comparison of *C* log *P* (calculated lipophilicity[34]) and anticonvulsant and neurotoxic activity (at a dose of 1.5

Table I—Preliminary Screening of the Anticonvulsant and Neurotoxic Activities of All Compounds[a]

Substance	Chemical Formula	*C* log *P*	sc PTZ Seizure Threshold Test, %[b]	Rotorod Toxicity Test, %[c]
VPA (2-*n*-Propylpentanoic acid	$C_8H_{16}O_2$	2.720	100	33
1 [(±)-2-(Methoxymethyl)pentanoic acid]	$C_7H_{14}O_3$	1.013	0	0
2 [(±)-2-*n*-Propyl-4-oxo-pentanoic acid]	$C_8H_{14}O_3$	0.954	0	0
3 [(±)-2-*n*-Propyl-4-pentynoic acid]	$C_8H_{12}O_2$	1.312	38	20
4 [(±)-2-*n*-Propyl-4-pentenoic acid]	$C_8H_{14}O_2$	2.176	63	29
5 [(±)-2-Phenylpentanoic acid]	$C_{11}H_{14}O_2$	2.781	80	80
6 [(±)-2-Benzylpentanoic acid]	$C_{12}H_{16}O_2$	3.080	80	80
7 (2-Methyl-2-*n*-propylpentanoic acid)	$C_9H_{18}O_2$	3.119	100	80
8 [(±)-2-*n*-Propylhexanoic acid]	$C_9H_{18}O_2$	3.249	100	80
9 [*E*-2-*n*-Propyl-2-pentenoic acid]	$C_8H_{14}O_2$	2.586	100	60
10 [(±)-2-(Cyclopropylmethyl)pentanoic acid]	$C_9H_{16}O_2$	2.635	100	20
11 [(±)-2-*n*-Propyl-4-hexynoic acid]	$C_9H_{14}O_2$	1.841	100	0
12 [(±)-4-Methyl-2-*n*-propyl-4-pentenoic acid]	$C_9H_{16}O_2$	2.575	100	0

[a] Tested 15 min after ip administration of 1.5 mmol sodium salt/kg. [b] Percentage of mice protected from sc PTZ-induced threshold seizures in groups of 5–8 mice. [c] Percentage of mice showing minimal neurological deficits on a rotating rod in groups of 5–7 animals.

Table II—Median Anticonvulsant Dose (ED_{50}), Relative Potency, and Slope of the Anticonvulsant Regression Line of the Compounds in Comparison with VPA.[a]

Substance	ED_{50}, mmol/kg	Relative Potency	Slope of Regression Line
VPA	0.71 (0.48–1.08)[b]	1.00	1.65 (0.96–2.74)[b]
3	1.78 (1.19–2.67)	0.39[c]	1.91 (1.02–3.59)
4	1.29 (1.00–1.67)	0.54[c]	1.48 (1.00–2.21)
7	0.40 (0.24–0.67)	1.75	2.10 (1.18–3.74)
8	0.78 (0.52–1.16)	0.91	1.38 (0.84–2.26)
9	0.68 (0.43–1.07)	1.03	1.80 (1.28–1.94)
10	0.96 (0.64–1.44)	0.74	1.61 (1.02–2.54)
11	0.28 (0.16–0.50)	2.54[c]	2.58 (1.01–6.58)
12	0.84 (0.56–1.28)	0.85	1.45 (0.98–2.15)

[a] Results are calculated and compared with those of VPA according to Litchfield and Wilcoxon.[29] [b] 95% confidence interval. [c] $p < 0.05$.

Table III—Anticonvulsant and Neurotoxic Profiles of 11 and 12 Compared with VPA

Parameter	VPA	11	12
TD_3[a]	1.20	2.0	2.15
TD_{50}[a]	1.65 (1.44–1.89)[c]	2.3[b] (2.12–2.49)	2.7[b] (2.41–3.02)
ED_{50}[d]	0.71 (0.48–1.08)	0.28[b] (0.16–0.50)	0.84 (0.56–1.28)
ED_{97}[d]	1.80	1.70	1.70
PI[e]	2.36	8.21	3.20
Safety ratio[f]	0.67	1.18	1.27

[a] TD_3 and TD_{50} are the minimal and median neurotoxic doses, respectively (mmol/kg). [b] $p < 0.05$. [c] 95% confidence interval. [d] ED_{50} and ED_{97} are the median and maximal anticonvulsant doses, respectively (mmol/kg). [e] Protective index = TD_{50}/ED_{50}. [f] Safety ratio = TD_3/ED_{97}.

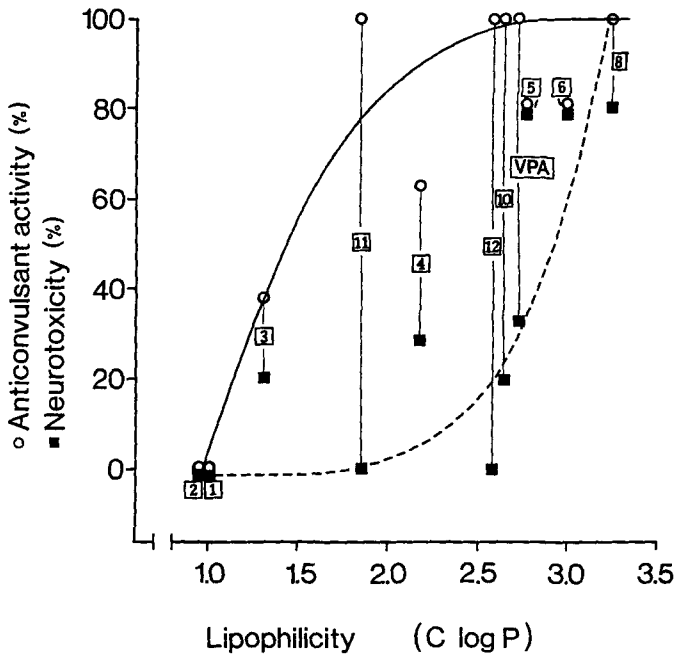

Figure 1—Comparison of *C* log *P* (calculated lipophilicity) and anticonvulsant and neurotoxic activity (at a dose of 1.5 mmol/kg) of VPA and all compounds having only one alteration (**1**–**12**, except **7** and **9**). Compounds with low lipophilicity (**1** and **2**) were not centrally active. Compound **3** showed low activity. In contrast, **11**, with an additional methyl group at the terminal triple bond of **3**, resulted in a carboxylic acid containing nine carbon atoms (C_9) with high anticonvulsant activity and minimal neurotoxicity.

mmol/kg) of VPA and all compounds having only one alteration (**1**–**12**, except **7** and **9**) is shown in Figure 1. Compounds with low lipophilicity (**1** and **2**) were not centrally active. Compound **3** showed low activity. In contrast, **11**, with an additional methyl group at the terminal triple bond of **3**, resulted in a carboxylic acid containing nine carbon atoms (C_9) with high anticonvulsant activity and minimal neurotoxicity.

Discussion

VPA is most widely employed clinically in absence and myoclonic seizures. Experimentally, it is characterized by a marked ability to increase PTZ seizure thresholds with relatively low effects (about half the potency) on seizure spread (anti-maximal electroshock seizure).[31] Therefore in the present experiment, the PTZ-induced seizure threshold method was used to evaluate the anticonvulsant activity of the tested compounds and to calculate their relative potencies in comparison with VPA. The preliminary experiment was designed to identify compounds with anticonvulsant potencies equal to or better than that of VPA and with relatively less sedative effect. The test was carried out 15 min after ip administration of the compounds, a time that was found to show peak anticonvulsant effect.

VPA showed an ED_{50} of 0.71 mmol/kg, which was comparable with that reported earlier using PTZ-induced seizure thresholds.[35–37] Compounds **4** and **9** have been evaluated previously[9] by the maximal electroshock seizure test and PTZ (100 mg/kg)-induced generalized tonic clonic seizures. The authors reported a lower potency for these two compounds and for VPA than found in the present experiment. The anticonvulsant activity of **3** was also investigated earlier.[38] Compound **9** (2-en-VPA), the major active metabolite of VPA, showed anticonvulsant potency similar to that of VPA but a higher sedative action in the present study. Using other models, however, 2-en-VPA showed higher anticonvulsant and sedative potency than VPA.[16] There is a current interest in 2-en-VPA as a valuable alternative drug in antiepileptic therapy because it lacks the teratogenic and possibly also the hepatotoxic adverse effects of VPA.[16,39,40]

Structure–Activity Relationships—The neurotoxic as well as anticonvulsant activity of a compound depends on molecular parameters, such as lipophilicity, which enable the compound to cross the blood–brain barrier and reach the cellular site of action. Recently it was observed that the neurotoxicity and anticonvulsant activity decreased in the order VPA > 4 > 3, which was related to a similar decrease in lipophilicity of these substances.[38] Thus, the influence of lipophilicity on neurotoxicity and anticonvulsant activity of VPA and structurally related carboxylic acids was investigated. Our results show (Figure 1) that all acids with C_9 exhibited 100% anticonvulsant activity, whereas C_8 acids (other than VPA) produced lower anticonvulsant activity. Furthermore, the C_9 acids (**10**–**12**) showed minimal neurotoxicity. In general, with increasing lipophilicity (values >2.6), the neurotoxicity increased to 80%. Therefore, for VPA-related compounds to produce central (anticonvulsant and sedative) actions, they must possess a certain lipophilicity (>1.0). Compounds with the desired high anticonvulsant activity and minimal neurotoxicity showed *C* log *P* values between 1.84 (**11**) and 2.64 (**10**) and had nine carbon atoms. The C_8 acids with comparable lipophilicity (**4**) showed lower anticonvulsant and higher neurotoxicity (Figure 1).

Compounds **11** and **12** showed higher protective indices (TD_{50}/ED_{50}) and safety ratios (TD_3/ED_{97}) than that of VPA (Table III), indicating that their maximum anticonvulsant protection is achieved in non-neurotoxic doses.[31] Compound **11**, on the other hand, showed longer duration of action than other compounds. This can be due to lower rates of metabolism and elimination.[41] Lower metabolism and elimination

rates were also observed for 3.[42] Both 3 and 11 contain a triple bond that may inhibit liver microsomal metabolizing enzymes.[43–45]

Compared with VPA, both 11 and 12 produced lower teratogenicity and embryolethality in the mouse model.[46] Exencephaly rates of 3 and 1% for 11 and 12, respectively, were induced by doses of 3.0 mmol/kg given ip at day 8 of gestation (compared with 44% exencephaly induced by the same dose of VPA).

Recently it has been shown what the anticonvulsant activities of 4-yn-VPA (3) and 4-en-VPA (4) are independent of the stereochemical configuration of the respective enantiomers.[38] This indicates that the anticonvulsant effect, in contrast to teratogenicity, may not be the consequence of stereoselective interaction with chiral biological structures. This lack of stereoselectivity of the anticonvulsant and neurotoxic action together with the high enantioselectivity of the teratogenic action of VPA-related compounds may encourage further investigations of the anticonvulsant, neurotoxic, and teratogenic action of 11 and 12 enantiomers. One enantiomer of each compound may still have the favorable high anticonvulsant activity and minimal neurotoxicity with even lower teratogenicity than the racemic mixture.

References and Notes

1. Benoit-Guyot, M.; Benoit-Guyot, J.-L.; Boucherle, A.; Broll, M.; Eymard, P. *Chim. Thér.* **1972a**, *7*, 388–392.
2. Benoit-Guyot, M.; Benoit-Guyot, J.-L.; Boucherle, A.; Broll, M.; Eymard, P. *Chim. Thér.* **1972b**, *7*, 393–399.
3. Benoit-Guyot, M.; Benoit-Guyot, J.-L.; Boucherle, A.; Broll, M.; Eymard, P. *Chim. Thér.* **1973**, *8*, 412–418.
4. Carraz, G.; Bériel, H.; Luu-Duc, H.; Lebreton, S. *Thérapie* **1965**, *20*, 419–426.
5. Chapman, A. G.; Meldrum, B. S.; Mendes, E. *Life Sci.* **1983**, *32*, 2023–2031.
6. Haj-Yehia, A.; Bialer, M. *Pharmaceut. Res.* **1989**, *6*, 683–689.
7. Keane, P. E.; Simiand, J.; Mendes, E.; Santucci, V.; Morre, M. *Neuropharmacology* **1983**, *22*, 875–879.
8. Lespagnol, A.; Mercier, J.; Erb-Debruyne, F.; Dessaigne, S. *Ann. Pharmacol. Franc.* **1972**, *30*, 193–198.
9. Löscher, W.; Nau, H. *Neuropharmacology* **1985**, *24*, 427–435.
10. Maitre, M.; Ciesielski, L.; Mandel, P. *Biochem. Pharmacol.* **1974**, *23*, 2363–2368.
11. Taillandier, G.; Benoit-Guyod, J.-L.; Boucherie, A.; Broll, M.; Eymard, P. *Eur. J. Med. Chem.* **1975**, *10*, 453–462.
12. Whittle, S. R.; Turner, A. J. *Biochem. Pharmacol.* **1981**, *30*, 1191–1196.
13. Löscher, W. *Archs Int. Pharmacodyn. Ther.* **1981**, *249*, 158–163.
14. Schäfer, H.; Lührs, R.; Reith, H. In *Antiepileptic Therapie: Advances in Drug Monitoring*; Johannessen, S. I.; Morselli, P. L.; Pippenger, C. R.; Richens, A.; Schmidt, D.; Meinardi, H., Eds.; Raven: New York, 1980; pp 103–108.
15. Weissman, D.; Ciesielski, S.; Mandel, P. *C. R. Soc. biol.* **1978**, *172*, 707–712.
16. Löscher, W. *Pharm. Weekbl. [Sci.]* **1992**, *14(3A)*, 139–143.
17. Lindhout, D.; Meinardi, H. *Lancet* **1984**, *II*, 396.
18. Robert, E.; Rosa, F. *Lancet* **1983**, *II*, 1142.
19. Jäger-Roman, E.; Deichl, A.; Jakob, S.; Hartmann, A.-M.; Koch, S.; Rating, D.; Steldinger, R.; Nau, H.; Helge, H. *J. Pediatr.* **1986**, *108*, 997–1004.
20. Koch, S.; Jäger-Roman, E.; Rating, D.; Helge, H. *J. Pediatr.* **1983**, *103*, 1007.
21. Nau, H.; Rating, D.; Koch, S.; Häuser, I.; Helge, H. *J. Pharmacol. Exp. Ther.* **1981**, *219*, 768–777.
22. Tein, I.; MacGregor, D.L. *Arch. Neurol.* **1985**, *42*, 291–293.
23. Kao, J.; Brown, N. A.; Schmid, B.; Goulding, E. H.; Fabro, S. *Teratog. Carcinog. Mutagen.* **1981**, *1*, 367–382.
24. Nau, H.; Zierer, R.; Spielmann, H.; Neubert, D.; Gansau, C. *Life Sci.* **1981**, *29*, 2803–2814.
25. Ehlers, K.; Stürje, H.; Merker, H-J.; Nau, H. *Teratology* **1992**, *45*, 145–154.
26. Nau, H.; Löscher, W. *Fund. Appl. Toxicol.* **1986**, *6*, 669–676.
27. Düsing, R. H. *Pharm. Weekbl. [Sci.]* **1992**, *14(3A)*, 152–158.
28. Gram, L. *Pharm. Weekbl. [Sci.]* **1992**, *14(3A)*, 159–160.
29. Miocque, M.; Nguye, Manh Hung; Vo, Quang Yen. *Ann. Chim.* **1963**, *8*, 157–174.
30. Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451–458.
31. Swinyard, E. A.; Woodhead, J. H. In *Antiepileptic Drugs*, 2nd ed.; Woodbury, D. M.; Penry, J. K.; Pippenger, C. E., Eds.; Raven: New York, 1982; pp 111–126.
32. Dunham, N. W.; Miya, T. A. *J. Am. Pharm. Assoc.* **1957**, *46*, 208–209.
33. Litchfield, J. T., Jr.; Wilcoxon, F. *J. Pharm. Exp. Ther.* **1949**, *96*, 99–113.
34. *Calculation of Drug Lipophilicity*; Rekker, R. F.; Mannhold, R., Eds.; VCH: Weinheim, New York, Basel, Cambridge, 1992; pp 14–61.
35. Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409–428.
36. Shuto, N.; Nishigaki, T. *Pharmacometrics* **1970**, *4*, 937–949.
37. Swinyard, E. A. Ph.D. Thesis; University of Utah, Salt Lake City, 1964; pp 1–23.
38. Hauck, R.-S.; Elmazar, M. M. A.; Nau, H. *Naturwissenschaften* **1991**, *78*, 272–274.
39. Nau, H. *Teratology* **1986**, *33*, 21–27.
40. Nau, H.; Siemes, H. *Pharm. Weekbl. [Sci.]* **1992**, *14(3A)*, 101–107.
41. Hauck, R.-S., et al., unpublished results.
42. Hauck, R.-S.; Elmazar, M. M. A.; Plum, C.; Nau, H. *Toxicol. Lett.* **1992**, *60*, 145–153.
43. Oritz de Montellano, P. R.; Kunze, K. L. *Biochemistry* **1981**, *20*, 7266–7271.
44. Testa, B.; Jenner, P. *Drug Metab. Rev.* **1981**, *12*, 1–117.
45. Wilkinson, C. F.; Murray, M. *Drug Metab. Rev.* **1984**, *15*, 897–917.
46. Nau, H.; Hauck, R.-S. Ehlers, K. *Pharmacol. Toxicol.* **1991**, *69*, 310–321.

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