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Letter to the Editor

Anticonvulsant Activity of Some *N*-Phenylphthalimide Derivatives in Rats and Mice

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In this letter we describe the anticonvulsant activity of a series of *N*-phenylphthalimide derivatives substituted in position 4 mainly by an amino group. These compounds show activity in the maximal electroshock seizure test (MES). Clark et al (1984, 1985, 1986), Clark & Davenport (1987) and Robertson et al (1987) have reported, in an important series of papers, the anticonvulsant activity of a series of 4-aminobenzanilides, the most potent term in the MES test (subsequently called ameltolide (Clark 1988; Leander et al 1988, 1992; Potts et al 1989; Stark & Albertson 1990; Robertson et al 1991; Leander 1992)) was the derivative with an *o*, *o'*-dimethyl substitution in the *N*-phenyl moiety (**1**). In view of the interesting anticonvulsant and hypnotic properties of thalidomide (**2**) (Mautner & Clemson 1970), we have undertaken the synthesis and the pharmacological evaluation of hybrids of ameltolide and thalidomide (Fig. 1). Molecular modelling studies indicated that the 4-amino substitution gave the best fit with the above two lead structures. Preliminary work established that 3-nitro and 3-amino derivatives were devoid of any significant anticonvulsant activity in mice.

The target compounds were synthesized by reacting a phthalic anhydride derivative with the appropriate aniline in acetic acid at reflux temperature; in the case of 4-nitro-*N*-phenylphthalimide derivatives, the nitro group was reduced by hydrogenation using palladium on charcoal as catalyst. All compounds were pure in TLC and HPLC and gave spectroscopic (^{1}H and ^{13}C NMR, IR) and analytical data consistent with their structure. Compounds **3**–**15** (Table 1) were evaluated by the Anticonvulsant Screening Project (Dr James P. Stables, Preclinical Pharmacology Section, Epilepsy Branch, Division of Convulsive, Developmental and Neuromuscular Disorders, NIH, Bethesda, MD, USA).

In mice (Table 2), compounds **4**, **5** and **10** had an ED50 (MES) in the same range as phenytoin and carbamazepine, but were more toxic in the rotorod test. Compound **9** and **13**, on the other hand, while slightly less effective than phenytoin and carbamazepine in the MES test, had a superior protection index. However, none of the *N*-phenylphthalimides explored were found more active than **1** in the MES test.

In rat (Table 3), compounds **4**, **5** and **14** were found in the MES test to be more active than phenytoin and in the same range of activity as carbamazepine and phenobarbitone. Compounds **4** and **5** also possess a good protection index. It is noteworthy that these compounds show activity in the

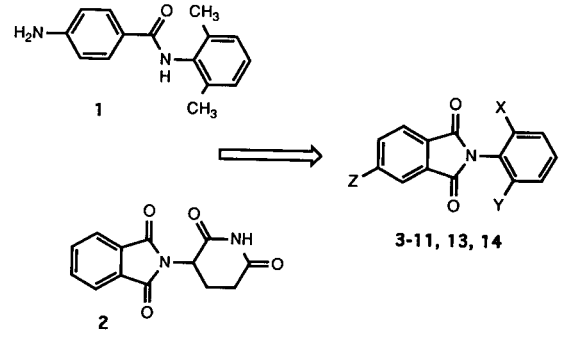
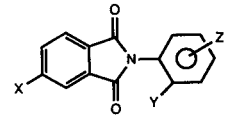


FIG. 1. Design of 4-amino-*N*-phenylphthalimides.

Table 1. *N*-Phenylderivatives.



3–11, 13, 14

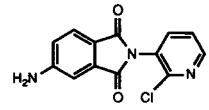
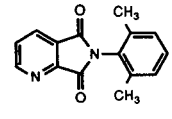
Compound	X	Y	Z	mp (°C)
3	NO_2	CH_3	6-CH_3	176–179
4	NH_2	CH_3	H	189–190
5	NH_2	CH_3	6-CH_3	195–198
6	NH_2	C_2H_5	H	152–154
7	NH_2	$CH(CH_3)_2$	H	172–174
8	NH_2	CH_3	6-C_2H_5	177–180
9	NH_2	CH_3	3-NH_2	282–285
10	NH_2	C_2H_5	6-C_2H_2	173–175
11	NH_2	Cl	6-CH_3	187–189
13	Cl	CH_3	4-NH_2	208–210
14	H	CH_3	3-NH_2	245–248
12				254–256
15				159–161

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Table 2. Minimal neurotoxicity and anticonvulsant potency of intraperitoneally administered compounds and some prototype antiepileptic drugs in mice.

Compound	Toxicity, TD50[a,b]	ED50, MES[a,b]	Protection index[c]	ED50, Pentetrazol[a,b]
1	62 (55–70), 0·50, 10·70	11 (9–13), 0·50, 5·30	6	ne
4	201 (122–332), 0·25, 2·53	48 (37–62), 0·25, 6·12	4	> 198, 0·25
5	131 (112–153), 0·25, 7·20	50 (42–59), 0·50, 8·60	3	> 188, 0·50
7	780 (605–978), 2·00, 7·58	221 (206–246), 0·50, 15·91	4	> 4, 0·50
9	942 (640–1292), 2·00, 3·61	68 (61–81), 0·50, 10·03	14	> 935, 0·50
10	206 (162–255), 0·25, 7·26	51 (43–63), 0·25, 6·83	4	> 340, 0·25
11	320 (216–457), 0·50, 4·45	61 (41–90), 0·25, 4·10	5	162 (129–226), 0·25, 4·87
12	> 1462, 0·50	319 (257–391), 0·50, 6·34	> 5	> 731, 0·50
13	700 (498–929), 2·00, 4·76	70 (47–97), 0·25, 3·65	10	541 (318–1033), 0·25, 2·71
15	310 (247–369), 0·25, 7·44	161 (128–187), 0·25, 13·04	2	> 317, 0·25
Phenytoin	259 (208–286)	38 (32–41), 2·00	7	ne
Carbamazepine	303 (194–570)	37 (23–60), 0·25	8	ne
Phenobarbitone	297 (271–314)	94 (65–110), 1·00	3	57 (25–69), 1·00
Sodium valproate	2565 (2222–2713)	1637 (1488–2036), 0·25	2	895 (739–1066), 0·25
Ethosuximide	3126 (2717–3442)	> 7092, 0·50	nd	925 (787–1067), 0·50

[a] TD50 and ED50 values are in μmol kg^{-1} of drugs delivered intraperitoneally. [b] The values are TD or ED50, in parentheses 95% confidence intervals, time of measurement and slope, respectively. [c] Protection index = TD50/ED50. ne = not effective. nd = not determined.

Table 3. Minimal neurotoxicity and anticonvulsant potency of orally administered compounds and some prototype antiepileptic drugs in rats.

Compound	Toxicity, TD50[a,b]	ED50, MES[a,b]	Protection index[c]	ED50, Pentetrazol[a,b]
1	1912 (1547–2284), 2.0, 6.5	135 (122–150), 1·0, 11·80	14	ne
3	> 1688, 0·25, —	88 (55–122), 1·00, 2·98	> 19	> 844, 1·00, —
4	> 350, 0·25, —	35 (22–52), 0·50, 3·57	> 10	> 174, 0·50, —
5	> 1878, 0·25, —	25 (17–38), 0·25, 2·85	> 75	> 940, 0·25, —
6	> 1390, 2·00, —	73 (41–109), 0·25, 2·64	> 19	> 940, 0·25, —
8	> 1784, 0·25, —	85 (61–105), 0·50, 6·97	> 21	> 892, 0·50, —
10	> 1000, 0·25, —	133 (68–246), 2·00, 1·68	> 8	> 500, 2·00, —
14	> 1570, 0·25, —	32 (25–42), 1·00, 6·40	> 49	> 785, 1·00, —
15	> 1483, 0·25, —	54 (37–69), 0·25, 5·29	> 27	> 741, 0·25,—
Phenytoin	> 11900	118 (87–154), 0·50	> 100	ne
Carbamazepine	3441 (2069–5222)	36 (14–45)	96	ne
Phenobarbitone	263 (188–413)	39 (33–51)	7	50 (33–65)
Sodium valproate	1688 (1153–2125)	2949 (2115–4388)	1	1082 (884–1267)
Ethosuximide	7180 (6395–7867)	> 8510	nd	383 (323–432)

[a] TD50 and ED50 values are in μmol kg^{-1} of drugs delivered orally. [b] The values are TD or ED50, in parentheses 95% confidence intervals, time of measurement and slope, respectively. [c] Protection index = TD50/ED50. ne = not effective. nd = not determined.

MES test for over a wide range of time (more than 50% of the animals were protected at 50 mg kg^{-1} from 0·25 until 6 h).

With the exception of compound **11**, all compounds were devoid of significant activity in the pentetrazol test in both animal models.

In conclusion, these pharmacological data indicate that *N*-phenylphthalimide derivatives show interesting anticonvulsant properties very similar to those of phenytoin and carbamazepine and may constitute an interesting lead for the future development of clinically useful antiepileptic drugs.

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J. Pharm. Pharmacol. 1995, 47: 91

Book Review

The Shape of Powder-Particle Outlines
(Materials Science and Technology Series/1)
Arthur E. Hawkins
Published 1993 Research Studies Press Ltd, Taunton, Somerset
150 pages
ISBN 0 86380 142 0 (Research Studies Press Ltd) £39.95
ISBN 0 471 93878 5 (John Wiley & Sons Inc.)

As the title clearly indicates, this book concentrates mainly on the numerical description of the two-dimensional outline of small particles, when investigated by microscopy. It also gives a brief introduction into the qualitative description of the projection of particles, and compares techniques of particle shape separation.

Widely used descriptors such as particle shape or roundness, which were often confused in earlier literature, are clearly defined as independent variables, and the chapter 'Single-number classification' also tries to tidy up the variety of shape descriptors, which are often similar in their numerical composition but presented with different nomenclature. Especially detailed and informative are chapters 5 and 6, which compare different ideas of multivariate shape representation by a series and the problems of fractal geometry to analyse the nature of a particle outline. It is extremely pleasing to see that the author clearly identifies the originator of ideas and uses original source material.

Comparatively short and less comprehensive are the comments on image analysis. The technique of appropriate image acquisition is too important to be buried in the chapter 'Single-number classification'. It also seems necessary to give some more details about available image analysis equipment, including comments on advantages, disadvantages and difficulties involved. This aspect reflects the absence of more recent references with only a few post 1990.

The intention of Dr Hawkins has been to write a book which should be read from cover to cover to obtain most benefit. In this he succeeds. It can be recommended for anybody who initially needs a deeper basic understanding of the subject. They can then use the large list of references for studying particular problems.

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J. Pharm. Pharmacol. 1995, 47: 91

Book Review

Glycopeptide Antibiotics
(Drugs and the Pharmaceutical Sciences Series/63)
Edited by Ramakrishnan Nagarajan
Published 1994 Marcel Dekker, Inc., New York
432 pages
ISBN 0 8247 9193 2 $165.00

This is a well written and produced book which succeeds in its aim of producing an authorative one volume coverage of the current knowledge on the glycopeptide antibiotics. It consists of a generously referenced nine chapters written by experts, mainly from the sectors of the pharmaceutical industry which have been responsible for the production of vancomycin and teicoplanin. This is particularly relevant for the chapters on the discovery; separation; structure-activity relationships; and the analytical quantitation of these drugs. It is less appropriate on chapters giving or containing clinical overviews and possibly for the chapter on resistance and mode of action. For these chapters it might have been more appropriate to have authors not directly associated with the industry. An academic input was used for the chapters discussing the relevant chemistry of the carbohydrate components and for the chapter describing the advances made towards the synthesis of vancomycin, vancomycin aglycones and other similar chemical structures. Insights are given on attempts to obtain more potent and hopefully less toxic semisynthetic glycopeptides.

The authorative nature and wide literature coverage of this book ensures that it will be of great interest to researchers and provide an important reference source for all involved with aspects of the use and development of glycopeptide antibiotics. Academic libraries should certainly be encouraged to stock a copy of this book.

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