Richards, and Dr. James M. Riordan.

Registry No. **1a**, 302-79-4; **1b**, 53839-60-4; **1c**, 33631-41-3; **1d**, 33631-47-9; **1e**, 65646-68-6; **2a**, 4759-48-2; **2b**, 73174-99-9; **2c**, 75686-04-3; **2d**, 75686-05-4; **2e**, 75686-07-6; **3**, 71407-30-2; L-**4**, 110683-00-6; DL-**5**, 110683-01-7; DL-**6**, 110683-02-8; L-**6**, 110769-97-6; L-**7**, 110683-03-9; L-**8**, 97885-88-6; DL-**8**, 110769-98-7; L-**9**, 110683-04-0; L-**10**, 110683-05-1; DL-**10**, 110769-99-8; DL-**11**, 110683-06-2; DL-**12**, 110683-07-3; DL-**13**, 110683-08-4; DL-**14**, 110683-09-5; L-**15**, 110769-91-0; L-**16**, 110769-92-1; L-**17**, 110769-93-2; DL-**17**, 110770-00-8; L-**18**, 110769-94-3; DL-**18**, 110770-01-9; L-**19**, 110769-95-4; L-**20**, 110769-96-5; DL-**20**, 110770-02-0; **21**, 110848-61-8; **22**, 110848-62-9; H-DL-Leu-OMe·HCl, 6322-53-8; H-L-Phe-OMe·HCl, 7524-50-7; H-L-Ala-OEt·HCl, 1115-59-9; H-L-Leu-OEt·HCl, 2743-40-0; H-Gly-OEt, 459-73-4.

Supplementary Material Available: Infrared spectral data and MS data for compounds **4**, **6**, **8**, **10–12**, **14**, **16**, **18**, and **20–22** (5 pages). Ordering information is given on any current masthead page.

Triazolines. 14.[1] 1,2,3-Triazolines and Triazoles, a New Class of Anticonvulsants. Drug Design and Structure-Activity Relationships

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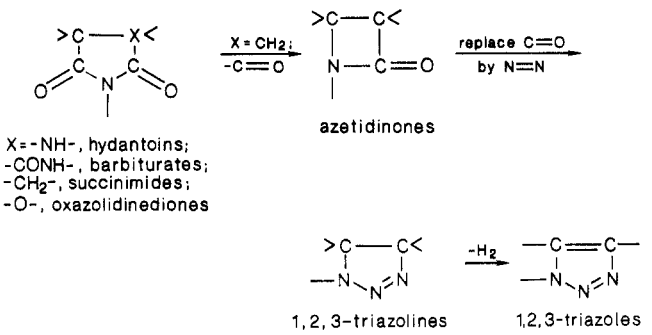
Pioneering studies in our laboratories have led to the emergence of the Δ^2-1,2,3-triazolines (4,5-dihydro-1*H*-1,2,3-triazoles) and the closely related 1*H*-1,2,3-triazoles as a unique family of anticonvulsant agents hitherto unknown. Unlike the traditional anticonvulsants, the dicarboximide moiety is absent from the triazoline ring system. This paper examines the results of evaluation of several groups of 1-aryl-5-pyridyl-substituted triazolines and triazoles with particular reference to structure–activity relationships in each compound group as well as between compounds in the different groups and the 1,5-diaryl compounds. The Topliss manual approach for application of the Hansch method is employed for the rational design of triazoline/triazole anticonvulsants. Anticonvulsant activity was determined, after intraperitoneal administration, in two standard seizure models in the mouse, the MES and scMet tests. Central nervous system toxicity was evaluated in the rotorod ataxia test. Analysis of structure–activity relationships using the Topliss scheme indicated a clear $\pi + \sigma$ dependency in the 1-aryl-5-(4-pyridyl)triazolines while an adverse steric effect (E_s) from 4-substitution appeared to be present in the 1-aryl-5-(3-pyridyl) compounds. A similar but strong steric effect dominated the structure–activity pattern of the 1-aryl-5-(4-pyridyl)triazoles, although a σ dependency was more evident in the 1-aryl-5-(3-pyridyl)- and the 1,5-diaryltriazole series. No significant activity was observed among the 1-aryl-5-(2-pyridyl)triazolines, and although the respective triazoles were active, the parameter dependency was not clearly defined. Similarly, the 1,5-diaryltriazolines, as a group, showed no pronounced anticonvulsant activity. However, replacement of the 5-aryl with a pyridyl group, particularly a 4-pyridyl, led to highly enhanced anticonvulsant activity. In addition, oxidation of triazolines with no anticonvulsant activity yielded, as a rule, triazoles that were active, which could be linked to their chemistry or structural conformation. The triazolines and triazoles evince anticonvulsant activity as a class and compare very well with the prototype antiepileptic drugs—ethosuximide, phenytoin, phenobarbital, valproate—in their anticonvulsant potency and minimal neurotoxicity. They have emerged as a new generation of anticonvulsant agents that show great promise as potentially useful antiepileptic drugs.

Pioneering studies in our laboratories have led to the emergence of the Δ^2-1,2,3-triazolines[2] (4,5-dihydro-1*H*-1,2,3-triazoles) and the closely related 1*H*-1,2,3-triazoles[3] as a unique family of anticonvulsant agents hitherto unknown.[4-6] In an earlier paper, screening results for a series of 1,5-diaryl-1,2,3-triazolines were reported.[7] This paper examines the results of evaluation of several groups of 1-aryl-5-pyridyl-substituted triazolines and triazoles with particular reference to structure–activity relationships in each compound group as well as between compounds in the different groups and the 1,5-diaryl compounds. The Topliss manual approach[8-10] for application of the Hansch method[11] is employed for the rational design of triazoline/triazole anticonvulsants.

Scheme I



The triazoline ring system is unique; it is different from those of the conventional anticonvulsant drugs, the majority of which have a dicarboximide (CONHCO) or a ureide (NHCONH) function, as in barbiturates, hydantoins, succinimides, and oxazolidinediones or the closely related primidones. The absence of the dicarboximide

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0022-2623/88/1831-0196$01.50/0

function, which contributes to the inherent hypnotic and sedative activity of the barbiturates and related compounds, may be expected to reduce the toxic side effects in potential triazoline anticonvulsants. Unlike the more traditional anticonvulsants where the primary heterocyclic ring is the same except for the X component,[12a] the triazolines may be considered to be derived from the succinimide ring by removal of one C=O moiety and replacement of the other by an N=N group (Scheme I). Such a modification of the succinimide ring system leads to dramatic alterations in its anticonvulsant activity. While several azetidinones[12b] and azetidinethiones[12c] have been reported to have varying degrees of anticonvulsant activity, the triazolines and triazoles described in this paper evince outstanding anticonvulsant activity in both electrically and chemically induced seizure models.

Methodologies. Anticonvulsant activity is determined[12a] after intraperitoneal administration, in two seizure models in the mouse, the maximal electroshock seizure (MES) test and the subcutaneous pentylenetetrazol seizure threshold (scMet) test. These two methods of seizure provocation are known to reliably elicit well-characterized seizure phenomena[13] and are the standard screens of choice for identification of anticonvulsant activity in a compound.[14] Central nervous system (CNS) toxicity is evaluated in the rotorod ataxia test.[15] This test has a clear end point, is quantifiable, and correlates well with the clinical assessment of minimal toxicity. Testing is done in the dose range of 30–600 mg/kg (with a few exceptions) at both 30-min and 4-h intervals. This provides a profile of the anticonvulsant activity, toxicity, potency, and pharmacokinetics of each compound and minimizes the likelihood of failing to identify slowly absorbed compounds or those with possible anticonvulsant activity in a metabolite.

Compounds that demonstrate anticonvulsant activity in the scMet and/or the MES test at a dose of 100 or 30 mg/kg without signs of neurological deficit (and thus have an estimated protective index >1) are assigned an Anticonvulsant Screening Project (ASP)[12a] group classification of I and are deemed the most promising as anticonvulsants. Group II compounds show anticonvulsant activity at doses greater than 100 mg/kg or show activity at 100 mg/kg which is not reinforced by similar activity at 300 mg/kg. Those failing to demonstrate anticonvulsant activity at doses up to 300 mg/kg are considered inactive and are placed in group III.

The ED_{50} values (the dose that elicits an anticonvulsant response in 50% of the animals) in the MES and scMet tests are determined for class I compounds at the time of peak effect (TPE) in the MES test, except when preliminary testing indicates that scMet activity occurs at another time. The rotorod ED_{50} or the TD_{50} (the dose that produces neurological deficit in 50% of animals) is determined at the time of peak neurological deficit.[16] The ratio TD_{50}/ED_{50} defines the protective index (PI) value,[17] which is a measure of the margin of safety, and the greater the PI value, the lesser the toxic side effects of the drug.

Drug Design. Drug design and structure–activity relationships are studied in three groups of 1-aryl-5-pyridyl-1,2,3-triazolines substituted with the 4-, 3-, and 2-pyridyl substituents each and the corresponding three groups of 1,2,3-triazoles as well as a group of 1,5-diaryltriazoles. For each one of the pyridyl substituents in the 5-position, the optimum substitution on the 1-phenyl ring is pursued by the Topliss manual approach to Hansch analysis.[8-10] The superior batchwise analysis of small groups of compounds[9] is used instead of the single compound stepwise approach,[8] because of the relative ease of triazoline and triazole synthesis using methods previously developed in our laboratories.[3,18-21]

The Topliss procedure involves the initial selection of a small group of compounds, usually substituted with a 3,4-Cl_2, Cl, CH_3, and OCH_3 in the 4-position of a phenyl ring in the parent compound. These are then tested and ordered according to potency. The potency order in the initial group is then compared to the projected potency order calculated for various parameter dependencies[22] relating to hydrophobic (π), electronic (σ), and steric (E_s) effects. From this activity-pattern analysis, the probable operative parameters can be deduced and, based on this, a new substituent selection made for the synthesis of potentially more potent analogues. Members of the second group have a high probability of enhanced potency over compounds of the initial group.

The expected potency order for some parameter dependencies is quite similar, and because only a small number of compounds are considered, it is not possible to obtain a precise identification of the operative parameters, but they could be narrowed down to a related group of possibilities. The parameter dependencies in the Topliss scheme encompass those most commonly found in Hansch type correlations,[11] such as, linear and parabolic π, σ, $\pi \pm \sigma$, as well as steric effects, E_s. Based on results from only four or five readily available analogues, the correct synthetic direction for increased potency can often be determined without knowing the precise activity–parameter relationship.

Results and Discussion

Structure–Activity Relationships. Results obtained for the structure–activity relationships of the various groups of triazoline/triazole compounds are presented in Tables I–VII.

Application of the Topliss procedure and rank ordering according to potency in the initial group of 1-phenyl-5-(4-pyridyl)-1,2,3-triazolines indicated a structure–activity pattern that could be related to the lipophilic (π) and electronic (σ) character of the substituent groups on the 1-phenyl ring (Table I). This indicated that, for synthesis of the second set of analogues with a good probability of increased potency, the substituent selection would be 3,4-Cl_2; 3-CF_3, 4-Cl; 4-CF_3; etc.[22] However, the failure of

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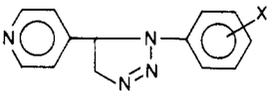
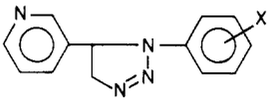
Table I. 1-Phenyl-5-(4-pyridyl)-1,2,3-triazolines



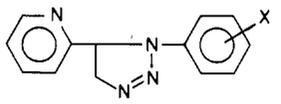
no.	X	anticonvulsant act. (I > II > III) ASP group classification (scMet)	rank order obsd	rank order calcd π	rank order calcd σ	rank order calcd $\pi + \sigma$
		Initial Compound Group				
1	4-Cl	I	1	1	1	1
2	4-CH_3	II	2–3	2	3	2
3	4-OCH_3	III	4	3–4	4	4
4	H	II	2–3	3–4	2	3
		Second Compound Group				
5	3,4-Cl_2	III				
6	4-Br	III				
7	4-F	I				
8	4-CF_3	I				
9	3-Cl	II				
10	3-CF_3	I				
11	4-c-C_6H_{11}	III				

Table II. 1-Phenyl-5-(3-pyridyl)-1,2,3-triazolines



no.	X	anticonvulsant activity (I > II > III) ASP group classification (scMet)	rank order obsd	rank order calcd E_s	rank order calcd σ	rank order calcd π	rank order calcd $\pi + \sigma$
		Initial Compound Group					
12	4-Cl	III (ED, >600 mg/kg)	2–4	2–4	1	1	1
13	4-CH_3	III (ED, >600 mg/kg)	2–4	2–4	3	2	2
14	4-OCH_3	III (ED, >600 mg/kg)	2–4	2–4	4	3–4	4
15	H	III (ED, 600 mg/kg)	1	1	2	3–4	3
		Second Compound Group					
16	4-Br	III					
17	3,4-Cl_2	III					
18	3-Cl, 4-F	II (ED, 300 mg/kg)					
19	3-Cl	I (ED, 100 mg/kg)					

Table III. 1-Phenyl-5-(2-pyridyl)-1,2,3-triazolines



no.	X	anticonvulsant act. (I > II > III) ASP group classification (scMet)	rank order obsd	rank order calcd σ	rank order calcd π	rank order calcd $\pi + \sigma$
		Initial Compound Group				
20	4-Cl	II (ED, 300 mg/kg)	1	1	1	1
21	4-OCH_3	III	3	3	2–3	3
22	H	II (ED, 600 mg/kg)	2	2	2–3	2
		Second Compound Group				
23	3-Cl	III				
24	3,4-Cl_2	III				
25	3,4-F_2	III				
26	4-NO_2	III				

the 3,4-Cl_2 and the 4-Br analogues **5** and **6**, respectively, to exceed the activity of the 4-Cl analogue **1**, which in turn was more active than the 4-F compound **7**, may be ascribed to their high lipophilic values exceeding the optimum for maximum activity. Such parabolic relationship between potency and hydrophobicity[23,24] may result when the drug, due to its high lipid solubility, becomes sequestered within the lipid matrix of the membrane with a reduction in the probability that it will ever find a receptor.[25]

The σ dependency was more operative in the 4-CF_3 analogue **8** in the second compound group, and as expected it was much more selective and much less toxic than the

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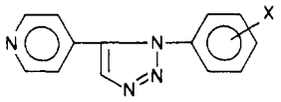
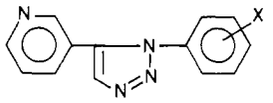
Table IV. 1-Phenyl-5-(4-pyridyl)-1*H*-1,2,3-triazoles



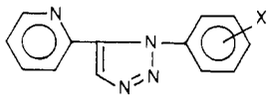
no.	X	anticonvulsant act. (I > II > III) ASP group classification (ScMet)	rank order obsd	rank order calcd E_s	rank order calcd σ	rank order calcd π	rank order calcd $\pi + \sigma$
		Initial Compound Group					
27	3,4-Cl_2	II	2–4	2–5	1	1	1
28	4-Cl	III	5	2–5	2	2	2
29	4-CH_3	II	2–4	2–5	4	3	3
30	4-OCH_3	II	2–4	2–5	5	4–5	5
31	H	I (ED_{50}, 73.73 mg/kg)	1	1	3	4–5	4
		Second Compound Group					
32	4-F	II					
33	3,5-Cl_2	I					
34	3-Cl	I (ED_{50}, 29.21 mg/kg)					
35	3-CF_3	I					
36	3-F	I					
37	3-Br	I					
38	3-CH_3	II					

Table V. 1-Phenyl-5-(3-pyridyl)-1*H*-1,2,3-triazoles



no.	X	anticonvulsant act. (I > II > III) ASP group classification (scMet)	rank order obsd	rank order calcd π	rank order calcd σ	rank order calcd $\pi + \sigma$
		Initial Compound Group				
39	4-Cl	I (ED_{50}, 26.95 mg/kg)	1	1	1	1
40	4-CH_3	III	3–4	2	3	2
41	4-OCH_3	III	3–4	3–4	4	4
42	H	I (ED_{50}, 39.69 mg/kg)	2	3–4	2	3
		Second Compound Group				
43	3,4-Cl_2	II				
44	4-I	III				
45	4-CF_3	II				
46	4-F	I				
47	4-Br	I				

Table VI. 1-Phenyl-5-(2-pyridyl)-1*H*-1,2,3-triazoles



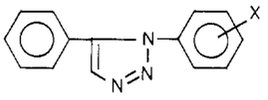
no.	X	anticonvulsant act. (I > II > III) ASP group classification (scMet)	rank order obsd	rank order calcd π	rank order calcd σ	rank order calcd $\pi + \sigma$
		Initial Compound Group				
48	4-Cl	I (ED_{50}, 50.35 mg/kg	-	1	1	1
49	4-CH_3	III	-	2	3	2
50	H	IV[a] (ED_{50}, 25.64 mg/kg	-	3	2	3
		Second Compound Group				
51	4-Br	I				
52	3,4-F_2	I				

[a] A group classification of IV indicates anticonvulsant activity and toxicity at 30 mg/kg.

4-Cl compound **1**. However, this was evidenced only upon oral administration of **8** [po mouse, ED_{50}, mg/kg, 4-Cl compound **1**, scMet, 152.56; MES, 290.72; TD_{50}, 704.92; 4-CF_3 compound **8**, scMet, 164.47; MES ~700; TD_{50}, >1000]. When administered intraperitoneally, the 4-CF_3 analogue **8** was much less potent than the 4-Cl compound **1** (Table VIII); the reduced potency by the ip route may be due to its insufficient solubility in water, which prevents it from being absorbed into the blood stream from the peritoneal cavity.

In the 5-(3-pyridyl)- and 5-(2-pyridyl)-substituted triazolines (Tables II and III), there was no significant anticonvulsant activity or sufficient spread for a meaningful analysis.[9] However, in the 5-(3-pyridyl) series, the lower effective dose of 300 mg/kg for the 3-Cl, 4-F compound **18** compared to that of the initial compound group **12–15**

Table VII. 1-5-Diphenyl-1*H*-1,2,3-triazoles



no.	X	anticonvulsant activity (I > II > III) ASP group classification (scMet)	rank order obsd	rank order calcd π	rank order calcd σ	rank order calcd $\pi + \sigma$
		Initial Compound Group				
53	4-Cl	I (100% protection)	1	1	1	1
54	4-CH_3	III	3	2	3	2
55	H	I (65% protection)	2	3	2	3
		Second Compound Group				
56	3,4-Cl_2	III				
57	4-Br	I				
58	4-I	III				
59	4-CF_3	III				
60	4-F	III				

(600 mg/kg) indicated the possible operation of an adverse steric effect arising from 4-substitution, and indeed, the 3-chloro analogue **19** showed a significant increase in activity with a group classification of I. The data from the initial compound set did in fact weakly suggest an adverse steric effect of 4-substitution, and the inactivity of the 4-Br and 3,4-Cl_2 analogues **16** and **17**, respectively, further supported this observation. The failure to show a complete lack of activity by compound **18**, despite a 4-F group, was logically ascribed to the small size of the fluorine atom.[9] On the other hand, a σ or $\pi + \sigma$ effect appeared to operate in the 5-(2-pyridyl) series, but it was not pronounced enough to impart improved activity to any of the analogues in the second compound group including the 4-NO_2 compound **26**.

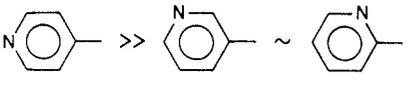
The Topliss approach for congener synthesis in the 1-phenyl-5-(4-pyridyl)-1,2,3-triazole series (Table IV) revealed the parent compound to be the most potent. The inference was drawn that there was probably an adverse steric effect dominant at the 4-position and therefore the second compound group should have substituents in the 3- and 3,5-positions. And indeed the 3,5-Cl_2, **33**; 3-Cl, **34**; 3-CF_3, **35**; 3-F, **36**; and 3-Br, **37** all had an ASP group classification of I.

A σ dependency was more evident in the 5-(3-pyridyl)-substituted 1-aryltriazoles (Table V) as well as the 1,5-diaryltriazoles (Table VII). In the 5-(3-pyridyl) series, the 4-Cl, 4-F, and 4-Br analogues **39**, **46**, and **47**, respectively, were all active, but not the 4-I compound **44**, which appeared to exceed a critical σ value or possibly a steric requirement for optimum activity. Similarly, the reduction in activity of the 3,4-Cl_2 analogue **43** was ascribed either to an unfavorable steric effect of meta substitution or, as in the case of the 4-CF_3 compound **45**, to exceeding the optimum σ value of the substituent groups. Similar arguments also explained the lack of activity in the 3,4-Cl_2, 4-I, and 4-CF_3 analogues **56**, **58**, and **59**, respectively, among the 1,5-diaryltriazoles, although the 4-F compound **60** appeared to be an exception. Alternately, the inactivity of the 4-F compound may be directed to too low a σ value, although the greater activity of the parent **55** relative to 4-F would then be an anomaly.

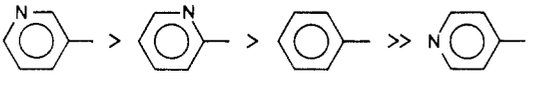
In the 5-(2-pyridyl)-substituted triazoles (Table VI), there was no clear parameter dependency; although the parent compound **50** was twice as effective as the 4-Cl analogue **48** in the scMet test, it was also more toxic.

Several structure–activity relationships have become evident among compounds in a given class as well as between related compounds in the different classes. No pronounced activity was observed among the 1,5-diaryltriazolines in general.[7] However, replacement of the 5-aryl with a 4-pyridyl group imparted significant anticonvulsant activity (Table I). 1,5-Diaryltriazoles, on the other hand, possessed considerable activity (Table VII) and replacement of the 5-aryl with a pyridyl group led to a much lesser enhancement in activity (Tables IV–VI).

In the triazoline series (Tables I–III), a 5-(4-pyridyl) substituent contributed most to activity:



[when the various 1-(4-chlorophenyl)-5-pyridyl compounds **1**, **12**, and **20** were compared], while among the triazoles (Tables IV–VIII, the order was reversed:



[when the 1-(4-chlorophenyl)triazoles **28**, **39**, **48**, and **53** were compared].

It is remarkable that, in several cases, oxidation of the triazoline to the corresponding triazole converted the inactive triazoline to a potent anticonvulsant triazole compound; this was readily apparent in the conversion of the diaryl and the 5-(3- and 2-pyridyl)-substituted triazolines to the respective triazoles, although in the case of the 5-(4-pyridyl) compounds, the reverse was true. These differences in the anticonvulsant activity of similarly substituted triazolines and triazoles may be associated with differences in their chemistry and/or their structural conformations. While the triazole ring is aromatic and planar,[26] the triazoline ring is nonaromatic and has an envelope conformation.[2,27]

General Significance. The present work illustrates the utility of the Topliss manual method toward the rational design and structure–activity evaluations of triazoline/triazole anticonvulsants, in a logically unified and systematic manner, without resorting to computers and statistical methodology as in the standard Hansch analysis. In every case, except Tables III and VII, the proportion of class I compounds is higher in the second set which is proposed from the results of the initial set; thus application of the Topliss method leads to an increase in the efficiency

(26) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33.
(27) Olsen, C. E. *Acta Chem. Scand.* **1974**, *28*, 425.

Table VIII. Effective Dose (ED_{50}), Toxic Dose (TD_{50}), and Protective Index (PI) Values for the Most Active (Class I) Triazolines and Triazoles (Mouse, Ip)

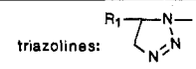
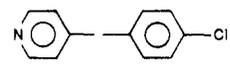
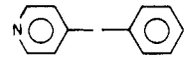
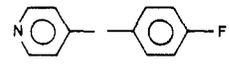
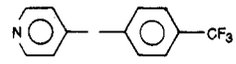
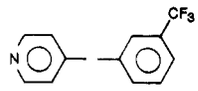
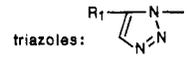
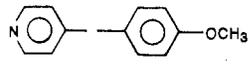
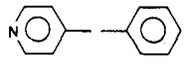
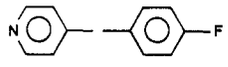
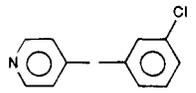
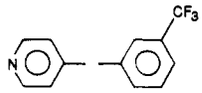
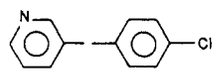
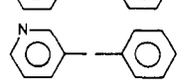
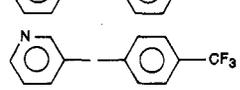
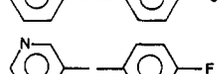
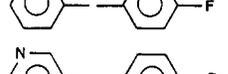
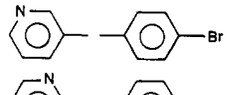
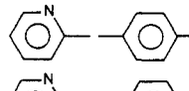
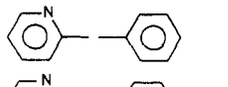
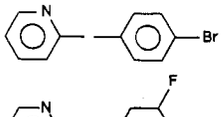
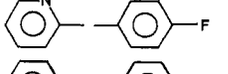
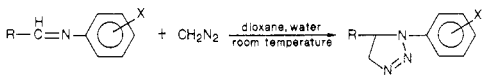
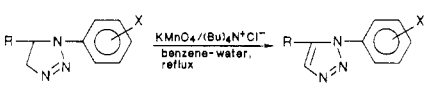
no.	R_1	R_2	ED_{50}, mg/kg (95% confidence interval; slope of regression line) MES	ED_{50}, mg/kg (95% confidence interval; slope of regression line) scMet	TD_{50}, mg/kg (95% confidence interval; slope of regression line)	PI: TD_{50}/ED_{50} MES	PI: TD_{50}/ED_{50} scMet
			triazolines: 				
1			257.42 (235.75–297.53; 12.88)	43.53 (39.00–49.96; 8.75)	1132.85 (970.45–1333.28; 7.92)	4.4	26.0
4			165.02 (128.07–223.89; 4.62)	106.09 (68.17–150.22; 3.88)	589.91 (530.46–639.95; 17.91)	3.6	5.6
7			239.17 (192.12–296.85; 4.61)	202.69 (110.65–296.86; 2.40)	585.97 (546.37–626.29; 19.06)	2.5	2.9
8			689.25 (461.83–1020.52; 3.19)	420.65 (332.24–491.17; 6.97)	>2000	>2.9	>4.8
10			52.07 (45.22–59.50; 11.58)	51.05 (37.94–68.87; 3.70)	137.15 (122.00–158.30; 13.20)	2.63	2.69
			triazoles: 				
30			311.24 (191.66–449.94; 3.22)	no protection afforded up to 600 mg/kg	545.12 (465.72–659.20; 7.60)	1.75	-
31			78.83 (65.98–92.08; 9.16)	73.73 (43.33–108.41; 3.15)	157.31 (143.97–170.27; 13.17)	2.0	2.1
32			91.56 (85.38–99.26; 18.86)	119.34 (84.95–155.96; 2.85)	181.13 (158.17–214.82; 10.09)	2.0	1.5
34			37.96 (30.43–46.44; 6.57)	29.21 (20.86–44.17; 4.04)	68.71 (52.61–87.83; 3.56)	1.8	2.4
35			68.19 (58.33–76.50; 9.67)	44.70 (35.54–53.67; 4.85)	68.03 (58.79–77.18; 9.52)	0.99	1.52
39			65.76 (51.82–83.19; 5.43)	26.95 (9.89–55.08; 1.21)	244.51 (221.82–275.17; 13.86)	3.7	9.1
42			76.37 (72.25–80.08; 30.75)	39.69 (26.30–53.86; 3.74)	132.57 (98.44–177.47; 5.37)	1.7	3.3
45			92.27 (80.55–107.01; 11.27)	90.47 (37.12–163.01; 1.58)	379.12 (324.23–456.97; 9.85)	4.1	4.2
46			74.61 (69.48–80.48; 19.25)	47.88 (40.31–56.67; 9.27)	167.65 (101.89–238.92; 4.39)	2.5	3.5
47			87.15 (61.83–106.90; 5.02)	40.65 (16.70–69.83; 1.87)	496.03 (413.41–594.95; 5.61)	5.7	12.2
48			95.25 (69.37–124.72; 4.44)	50.35 (20.71–106.70; 1.35)	233.94 (193.62–292.49; 7.41)	2.5	4.6
50			41.10 (32.01–51.40; 5.48)	25.64 (20.25–31.81; 6.51)	87.87 (71.72–99.63; 11.75)	2.1	3.4
51			67.95 (48.54–83.43; 6.97)	88.57 (63.81–117.78; 5.24)	265.30 (141.80–392.01; 2.76)	3.9	3.0
52			62.55 (59.24–65.15; 25.93)	123.21 (91.63–157.47; 5.46)	192.41 (167.86–231.29; 9.70)	3.1	1.6
53			232.65 (184.52–279.26; 6.10)	95.18 (41.72–157.63; 2.35)	465.66 (369.95–587.01; 4.83)	2.0	4.9
ethosuximide			no protection up to 1000	130.35 (110.99–150.45; 10.06)	440.83 (383.09–485.34; 18.37)	<0.44	3.38
phenytoin			9.50 (8.13–10.44; 13.66)	no protection up to 300	65.46 (52.49–72.11; 15.23)	6.89	<0.22
phenobarbital			21.78 (14.99–25.52; 14.98)	13.17 (5.87–15.93; 5.93)	69.01 (62.84–72.89; 24.67)	3.17	5.24
valproate			271.66 (246.97–337.89; 12.83)	148.59 (122.64–177.02; 11.85)	425.84 (368.91–450.40; 20.84)	1.57	2.87

Table IX. Newly Synthesized 1,2,3-Triazolines and 1,2,3-Triazoles

no.	substituent R	substituent X	mp,[a] °C	yield,[b] %	formula	analysis[c]
						
5	4-pyridyl	3,4-Cl_2	171–172	82	$C_{13}H_{10}N_4Cl_2$	C, H, N
6	4-pyridyl	4-Br	158–160	51	$C_{13}H_{11}N_4Br$	C, H, N
7	4-pyridyl	4-F	139–140	91	$C_{13}H_{11}N_4F$	C, H, N
8	4-pyridyl	4-CF_3	149–150	58	$C_{14}H_{11}N_4F_3$	C, H, N
9	4-pyridyl	3-Cl	109–111	80	$C_{13}H_{11}N_4Cl$	C, H, N
10	4-pyridyl	3-CF_3	68–71	42	$C_{14}H_{11}N_4F_3$	C, H, N
11	4-pyridyl	4-c-C_6H_{11}	161	76	$C_{19}H_{22}N_4$	C, H, N
12	3-pyridyl	4-Cl	164–165	80	$C_{13}H_{11}N_4Cl$	C, H, N
13	3-pyridyl	4-CH_3	125–126	71	$C_{14}H_{14}N_4$	C, H, N
14	3-pyridyl	4-OCH_3	99–101	50	$C_{14}H_{14}N_4O$	C, H, N
15	3-pyridyl	H	113–114	27	$C_{13}H_{12}N_4$	C, H, N
16	3-pyridyl	4-Br	170–172	73	$C_{13}H_{11}N4_{Br}$	C, H, N
17	3-pyridyl	3,4-Cl_2	116–117	73	$C_{13}H_{10}N_4Cl_2$	C, H, N
18	3-pyridyl	3-Cl, 4-F	88–91	51	$C_{13}H_{10}N_4ClF$	C, H, N
19	3-pyridyl	3-Cl	75–77	75	$C_{13}H_{11}N_4Cl$	C, H, N
21	2-pyridyl	4-OCH_3	84–86	36	$C_{14}H_{14}N_4O$	C, H, N
22	2-pyridyl	H	83–85	53	$C_{13}H_{12}N_4$	C, H, N
23	2-pyridyl	3-Cl	82–84	22	$C_{13}H_{11}N_4Cl$	C, H, N
24	2-pyridyl	3,4-Cl_2	108–109	75	$C_{13}H_{10}N_4Cl_2$	C, H, N
25	2-pyridyl	3,4-F_2	101.5–103.5	69	$C_{13}H_{10}N_4F_2$	C, H, N
26	2-pyridyl	4-NO_2	168–169	25	$C_{13}H_{11}N_5O_2$	C, H, N
						
27	4-pyridyl	3,4-Cl_2	138–140	40	$C_{13}H_8N_4Cl_2$	C, H, N
32	4-pyridyl	4-F	155–156	75	$C_{13}H_9N_4F$	C, H, N
33	4-pyridyl	3,5-Cl_2	130–131	40	$C_{13}H_8N_4Cl_2$	C, H, N
34	4-pyridyl	3-Cl	109–110	51	$C_{13}H_9N_4Cl$	C, H, N
35	4-pyridyl	3-CF_3	114–116	47	$C_{14}H_9N_4F_3$	C, H, N
36	4-pyridyl	3-F	87–89	33	$C_{13}H_9N_4F$	C, H, N
37	4-pyridyl	3-Br	125–126.5	50	$C_{13}H_9N_4Br$	C, H, N
38	4-pyridyl	3-CH_3	76–79	47	$C_{14}H_{12}N_4$	C, H, N
39	3-pyridyl	4-Cl	121–122	85	$C_{13}H_9N_4Cl$	C, H, N
40	3-pyridyl	4-CH_3	121–122	63	$C_{14}H_{12}N_4$	C, H, N
41	3-pyridyl	4-OCH_3	94–96	55	$C_{14}H_{12}N_4O$	C, H, N
42	3-pyridyl	H	155–157.5	67	$C_{13}H_{10}N_4$	C, H, N
43	3-pyridyl	3,4-Cl_2	160–162	74	$C_{13}H_8N_4Cl_2$	C, H, N
44	3-pyridyl	4-I	147–149	61	$C_{13}H_9N_4I$	C, H, N
45	3-pyridyl	4-CF_3	122–124	66	$C_{14}H_9N_4F_3$	C, H, N
46	3-pyridyl	4-F	155–156.5	80	$C_{13}H_9N_4F$	C, H, N
47	3-pyridyl	4-Br	139–141	79	$C_{13}H_9N_4Br$	C, H, N
49	2-pyridyl	4-CH_3	90–92	52	$C_{14}H_{12}N_4$	C, H, N
50	2-pyridyl	H	76–78	66	$C_{13}H_{10}N_4$	C, H, N
51	2-pyridyl	4-Br	103–105	45	$C_{13}H_9N_4Br$	C, H, N
52	2-pyridyl	3,4-F_2	101–102.5	46	$C_{13}H_8N_4F_2$	C, H, N
56	phenyl	3,4-Cl_2	100–102	60	$C_{14}H_9N_3Cl_2$	C, H, N
57	phenyl	4-Br	100–102	63	$C_{14}H_{10}N_3Br$	C, H, N
58	phenyl	4-I	112–114	33	$C_{14}H_{10}N_3I$	C, H, N
59	phenyl	4-CF_3	128–130	45	$C_{15}H_{10}N_3F_3$	C, H, N
60	phenyl	4-F	158–161	63	$C_{14}H_{10}N_3F$	C, H, N

[a] Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. [b] The yields shown are for the pure recrystallized products. [c] The elemental analyses (C, H, and N) for all new compounds were well within ±0.4% of the calculated values. The microanalyses were conducted by Galbraith Laboratories, Inc., Knoxville, TN.

of identification of the active compounds as early as possible in the analogue scheme.

The present studies have led to the emergence of the triazoline/triazole heterocycles as a new generation of anticonvulsant agents; their anticonvulsant potency and minimal neurotoxicity compare very well with four prototype antiepileptic drugs in clinical use, ethosuximide, phenytoin, phenobarbital, and valproate (Table VIII). The PI values of compounds **1**, **4**, **8**, **39**, **47**, and **53** by the scMet test are equal to or greater than that of phenobarbital with the highest PI of all four prototypes. By the MES test, although only one compound (**47**) approaches the high PI value of phenytoin, compounds **1**, **4**, **39**, **45**, **47**, **51**, and **52** all have PI values equal to or bettern than that of phenobarbital, which ranks second to phenytoin. The PI value of compound **1** by the scMet test is 5 times greater than that of phenobarbital while, at the same time, it exceeds the latter in its PI by the MES test.[28] The structural modifications effected in the succinimide ring system, in order to derive the triazoline/triazole heterocycles, lead to significant alterations in the anticonvulsant activity of the succinimides. Unlike ethosuximide, which fails to antagonize electrically induced convulsions in the

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MES test, the triazolines and triazoles exhibit significant anticonvulsant activity in both the MES and the scMet tests. They not only increase seizure threshold but also prevent seizure spread and hold promising potential as therapeutically useful antiepileptic drugs.

Experimental Section

Chemistry. The 1,5-substituted 1,2,3-triazolines and triazoles were synthesized according to methods previously developed in our laboratories.[3,18-21] Data on newly synthesized compounds are presented in Table IX.

The Topliss Procedure for Analogue Synthesis. The Topliss approach for compound groups[9] was followed. Initially, a selected group of four analogues representing different types of substitution on the 1-phenyl ring was synthesized. This included the parent compound and the 4-Cl, 4-CH_3, and 4-OCH_3 analogues. The projected potency order of these four compounds, as calculated for the π, σ, and E_s parameter dependencies,[22] was then compared with the experimentally determined anticonvulsant potency order in the scMet test. This allowed a deduction to be made of the probable operative parameters, and this, in turn, provided the basis for a new substituent selection and synthesis of a second group of compounds with a high probability of enhanced potency over compounds of the initial group (Tables I–VII).

Pharmacology. The triazolines and triazoles were screened by the Anticonvulsant Screening Project (ASP) under the Antiepileptic Drug Development (ADD) program of the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).[12a]

The compounds were solubilized in 30% polyethylene glycol 400. The solvent was tested for anticonvulsant and toxic effects and was found to introduce no significant bias into the testing of anticonvulsant activity. The compounds were administered intraperitoneally (ip) in a volume of 0.01 mL/g body weight to male Carworth Farms No. 1 mice weighing ~20 g.[29] Testing was done at dose levels of 30, 100, 300, and 600 mg/kg, and a total of 16 animals were used, four for each dose. After 30 min, each animal was examined for toxicity in the rotorod test.[15] Immediately thereafter, anticonvulsant activity was evaluated by subjecting one mouse to the MES test and another to the scMet test. The same tests were repeated 4 h later on the two remaining mice at each dose level. When compounds were found to afford protection, the test was repeated at that dose level and time with four animals, and the results were expressed as number of animals protected/number of animals tested.

The MES test was performed according to the method of Swinyard et al.,[30] and abolition of the hind limb tonic extensor component of maximal seizures was defined as protection. In the scMet test, 85 mg/kg of pentylenetetrazol was administered as a 0.5% solution subcutaneously in the posterior midline, and failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5-s duration) was defined as protection.[30]

To evaluate neurotoxicity,[15] the animal was placed on a wooden 2.8-cm-diameter rod rotating at 6 rpm. Normal mice remained on a rod rotating at this speed indefinitely. Neurological toxicity was defined as the failure of the animal to remain on the rod for 1 min and was expressed as number of animals exhibiting toxicity/number of animals tested.

To determine ED_{50} or TD_{50} values, five logarithmically spaced doses of the test compound were administered to animals in groups of 10, to cover 0–100% protection or toxicity. The dose required to produce the desired end point in 50% of the animals in each test, (ED_{50}, TD_{50}), together with the 95% confidence limits and the slopes of the regression lines, were then obtained graphically by using the method of Litchfield and Wilcoxon.[31] The MES and scMet ED_{50} values along with the TD_{50} values are presented in Table VIII.

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Registry No. **1**, 55643-87-3; **2**, 55643-89-5; **3**, 55643-90-8; **4**, 55643-88-4; **5**, 106878-43-7; **6**, 110684-09-8; **7**, 97230-32-5; **8**, 97230-35-8; **9**, 97230-33-6; **10**, 106878-52-8; **11**, 110684-10-1; **12**, 106878-45-9; **13**, 110684-11-2; **14**, 110684-12-3; **15**, 110684-13-4; **16**, 106878-46-0; **17**, 106878-48-2; **18**, 110684-14-5; **19**, 110684-15-6; **20**, 55643-92-0; **21**, 110684-16-7; **22**, 97230-34-7; **23**, 110684-17-8; **24**, 110684-18-9; **25**, 110684-19-0; **26**, 110684-20-3; **27**, 110684-21-4; **28**, 68090-20-0; **29**, 68090-19-7; **30**, 68090-21-1; **31**, 68090-18-6; **32**, 110684-22-5; **33**, 110684-23-6; **34**, 110684-24-7; **35**, 110684-25-8; **36**, 110684-26-9; **37**, 110684-27-0; **38**, 110684-28-1; **39**, 110684-29-2; **40**, 110684-30-5; **41**, 110684-31-6; **42**, 110684-32-7; **43**, 110684-33-8; **44**, 110684-34-9; **45**, 110684-35-0; **46**, 110684-36-1; **47**, 110684-37-2; **48**, 68090-22-2; **49**, 110684-38-3; **50**, 110684-39-4; **51**, 110684-40-7; **52**, 110684-41-8; **53**, 49750-41-6; **54**, 84817-37-8; **55**, 4874-85-5; **56**, 110684-42-9; **57**, 18250-08-3; **58**, 110684-43-0; **59**, 64214-86-4; **60**, 110684-44-1; CH_2N_2, 334-88-3; 4-[(3,4-dichlorophenyl)iminomethyl]pyridine, 35507-57-4; 4-[(4-bromophenyl)iminomethyl]-pyridine, 110684-45-2; 4-[(4-fluorophenyl)iminomethyl]pyridine, 110684-46-3; 4-[(4-trifluoromethylphenyl)iminomethyl]pyridine, 110684-47-4; 4-[(3-chlorophenyl)iminomethyl]pyridine, 35507-55-2; 4-[(3-trifluoromethylphenyl)iminomethyl]pyridine, 70318-57-9; 4-[(4-cyclohexylphenyl)iminomethyl]pyridine, 110698-39-0; 3-[(4-chlorophenyl)iminomethyl]pyridine, 41855-64-5; 3-[(4-methylphenyl)iminomethyl]pyridine, 110684-48-5; 3-[(4-methoxyphenyl)iminomethyl]pyridine, 41855-73-6; 3-(phenyliminomethyl)pyridine, 29722-97-2; 3-[(4-bromophenyl)iminomethyl]-pyridine, 110684-49-6; 3-[(3,4-dichlorophenyl)iminomethyl]-pyridine, 110684-50-9; 3-[(3-chloro-4-fluorophenyl)iminomethyl]pyridine, 110684-51-0; 3-[(3-chlorophenyl)iminomethyl]pyridine, 41855-62-3; 2-[(4-methoxyphenyl)iminomethyl]pyridine, 26930-67-6; 2-(phenyliminomethyl)pyridine, 7032-25-9; 2-[(3-chlorophenyl)iminomethyl]pyridine, 29202-16-2; 2-[(3,4-dichlorophenyl)iminomethyl]pyridine, 110684-52-1; 2-[(3,4-difluorophenyl)iminomethyl]pyridine, 110684-53-2; 2-[(4-nitrophenyl)iminomethyl]pyridine, 67912-40-7; 1-(3,5-dichlorophenyl)-4,5-dihydro-5-(4-pyridyl)-1*H*-1,2,3-triazole, 106878-44-8; 1-(3-fluorophenyl)-4,5-dihydro-5-(4-pyridyl)-1*H*-1,2,3-triazole, 106878-49-3; 1-(3-bromophenyl)-4,5-dihydro-5-(4-pyridyl)-1*H*-1,2,3-triazole, 106878-50-6; 1-(3-methylphenyl)-4,5-dihydro-5-(4-pyridyl)-1*H*-1,2,3-triazole, 106878-51-7; 1-(4-iodophenyl)-4,5-dihydro-5-(3-pyridyl)-1*H*-1,2,3-triazole, 110684-54-3; 1-(4-trifluoromethylphenyl)-4,5-dihydro-5-(3-pyridyl)-1*H*-1,2,3-triazole, 106878-53-9; 1-(4-fluorophenyl)-4,5-dihydro-5-(3-pyridyl)-1*H*-1,2,3-triazole, 106878-47-1; 1-(4-methylphenyl)-4,5-dihydro-5-(2-pyridyl)-1*H*-1,2,3-triazole, 110684-55-4; 1-(4-bromophenyl)-4,5-dihydro-5-(2-pyridyl)-1*H*-1,2,3-triazole, 17843-17-3; 1-(3,4-dichlorophenyl)-4,5-dihydro-5-phenyl-1*H*-1,2,3-triazole, 110684-56-5; 1-(4-bromophenyl)-4,5-dihydro-5-phenyl-1*H*-1,2,3-triazole, 10480-35-0; 1-(4-iodophenyl)-4,5-dihydro-5-phenyl-1*H*-1,2,3-triazole, 110684-57-6; 1-(4-trifluoromethylphenyl)-4,5-dihydro-5-phenyl-1*H*-1,2,3-triazole, 110684-58-7; 1-(4-fluorophenyl)-4,5-dihydro-5-phenyl-1*H*-1,2,3-triazole, 110684-59-8.

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