The solids were filtered and washed with cold water, 2-propanol, and ether to give 15.44 g (82% overall from **9**) of **13h**: mp 226–228 °C; IR 3108, 1729, 1622 cm^{-1}. Anal. Calcd for $C_{13}H_7F_3NO_3$: C, 55.12; H, 2.83; N, 4.95. Found: C, 55.08; H, 2.96; N, 5.06.

1-Ethenyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (13c). To 5.89 g (21.7 mmol) of **15**[15] were added 7.5 g (2.5 equiv) of K_2CO_3 and 300 mL of dry DMF. After the mixture was stirred for 30 min at 50 °C, 45 g (11.0 equiv) of 1,2-dibromoethane was added. The temperature was raised to 80 °C, and the mixture stirred vigorously for 48h. It was concentrated to dryness and the residue was partitioned between H_2O and H_2CCl_2. The organic layer was extracted twice more with water. It was dried and concentrated to a dark oil, which was purified by column chromatography ($HCCl_3$/hexane/2-propanol, 4:5:1) to give 2.58 g (40%) of the ethyl ester **12c**, mp 135–136 °C. To 2.2 g (7.4 mmol) of this material were added 40 mL of AcOH and 20 mL of 3 N HCl, and the mixture was heated for 4 h. Dilution with water and filtration gave 1.35 g (68%) of **13c**: mp 185–186 °C; IR 1728, 1648 cm^{-1}. Anal. Calcd for $C_{12}H_{16}F_3NO_3 \cdot 0.2H_2O$: C, 52.94; H, 2.35; N, 5.14; H_2O, 1.32. Found: C, 52.77; H, 2.41; N, 5.24; H_2O, 0.96.

1-Cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid 14h. General Coupling Procedure. To 5.00 g (17.65 mmol) of **13h** in 50 mL of CH_3CN was added a solution of 2.7 g (1.0 equiv) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2.4 g (1.05 equiv) of *N*-ethyl-3-pyrrolidinemethanamine in 25 mL of CH_3CN. The mixture was refluxed for 2.5 h and was stirred at room temperature overnight. The solids were filtered and washed with 50 mL of CH_3CN, 20 mL of 80% aqueous CH_3CN, 50 mL of ethanol, and 200 mL of ether to give 6.01 g (87%) of **14h** as a white solid: mp 257–258 °C; IR 1730, 1623, 1584 cm^{-1}; NMR (TFA) δ 9.15 (s, 1 H, C_2H), 8.0 (d, J = 12 Hz, 1 H, C_5H), 7.1 (br s, 1 H, NH), 4.1 (m, 5 H, $CH_2NHCH_2CH_3$ and cyclopropyl CH), 3.4 (m, 4 H, pyrrolidine CH_2N), 2.8 (m, 1 H, pyrrolidine C_3H), 2.4 (m, 1 H, pyrrolidine C_4H), 1.9 (m, 1 H, pyrrolidine C_4H), 1.45 (m, 7 H, CH_3 and CH_2CH_2). Anal. Calcd for $C_{20}H_{23}F_2N_3O_3$: C, 61.38; H, 5.88; N, 10.74. Found: C, 61.08; H, 5.94; N, 10.93.

Data Processing. QSAR analyses were run on an IBM 3081 using the SAS[35] program package. In eq 1–14, the figures in parentheses are the standard errors of the regression coefficients. For each equation, n is the number of compounds, r is the correlation coefficient, F is a significance test, and s is the standard error of the estimate. Molecular modeling used the SYBYL program package[25] operating on a VAX 11/780.

Acknowledgment. We thank J. Topliss for helpful discussions on the QSAR analysis and particularly the concept for the UNSAT parameter. We also thank our chemotherapy group for the test results, especially J. Sesnie, M. Shapiro, and T. Leopold.

Registry No. **8**, 1201-31-6; 8 (acid chloride), 94695-48-4; **9**, 94695-50-8; **11a**, 113220-15-8; **11d**, 113220-16-9; **11e**, 113220-17-0; **11f**, 113220-18-1; **11g**, 113220-19-2; **11h**, 94695-51-9; **11i**, 113220-20-5; **11j**, 113220-21-6; **11k**, 113220-22-7; **11l**, 113220-23-8; **11m**, 113220-24-9; **11n**, 113220-25-0; **11o**, 113220-26-1; **11p**, 106809-20-5; **11q**, 105859-07-2; **11r**, 113220-27-2; **12a**, 113220-28-3; **12c**, 91188-95-3; **12d**, 93969-13-2; **12e**, 113220-29-4; **12f**, 100276-66-2; **12g**, 113249-33-5; **12h**, 94242-51-0; **12i**, 113220-30-7; **12j**, 113220-31-8; **12k**, 113220-32-9; **12l**, 113220-33-0; **12m**, 113220-34-1; **12n**, 113220-35-2; **12o**, 113220-36-3; **12p**, 104599-93-1; **12q**, 105859-09-4; **12r**, 106464-85-1; **13a**, 79660-45-0; **13b**, 75338-42-0; **13c**, 91187-99-4; **13d**, 79660-52-9; **13e**, 113220-10-3; **13f**, 100276-67-3; **13g**, 113220-11-4; **13h**, 94695-52-0; **13i**, 98079-84-6; **13j**, 113220-12-5; **13k**, 99724-24-0; **13l**, 113220-13-6; **13m**, 99724-27-3; **13n**, 99724-28-4; **13o**, 99724-30-8; **13p**, 104599-99-7; **13q**, 103994-87-2; **13r**, 106464-84-0; **14a**, 91188-03-3; **14b**, 91188-00-0; **14c**, 91188-02-2; **14d**, 91188-01-1; **14e**, 99735-14-5; **14f**, 103490-74-0; **14g**, 113220-14-7; **14h**, 99734-97-1; **14i**, 99735-25-8; **14j**, 99735-16-7; **14k**, 99735-15-6; **14l**, 99735-19-0; **14m**, 99735-20-3; **14n**, 99735-21-4; **14o**, 99735-24-7; **14p**, 106464-87-3; **14q**, 106486-83-3; **14r**, 106464-86-2; **15**, 79660-46-1; H_3CNH_2, 74-89-5; $F(CH_2)_2NH_2 \cdot HCl$, 460-08-2; $F_3CCH_2NH_2 \cdot HCl$, 373-88-6; $H_3CN(NH_2)CO_2Bu$-*t*, 21075-83-2; $H_3CONH_2 \cdot HCl$, 593-56-6; $(H_3C)_2CHNH_2$, 75-31-0; $C_6H_5NH_2$, 62-53-3; $4\text{-}FC_6H_4NH_2$, 371-40-4; cyclopropylamine, 765-30-0; 2-methylcyclopropanamine hydrochloride, 89123-14-8; 1-methylcyclopropanamine hydrochloride, 88887-87-0; cyclopropanemethanamine, 2516-47-4; cyclobutanamine, 2516-34-9; cyclopentanamine, 1003-03-8; cyclohexanamine, 108-91-8; 2-thiazolylamine, 96-50-4; *N*-ethyl-3-pyrrolidinemethanamine, 91187-83-6; propanedioic acid monoethyl ester, 1071-46-1.

Supplementary Material Available: Correlation matrix for the biological potencies, a tabulation showing the development of eq 5–14, and comparisons of calculated and found potencies for all organisms (5 pages). Ordering information is given on any current masthead page.

Potential Anticonvulsants. 11. Synthesis and Anticonvulsant Activity of Spiro[1,3-dioxolane-2,3′-indolin]-2′-ones and Structural Analogues

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A number of spiro[1,3-dioxolane-2,3′-indolin]-2′-ones were synthesized and tested for anticonvulsant activity in the maximal electroshock seizure (MES) and pentylenetetrazole seizure threshold (sc-Met) tests. 5′-Chlorospiro[1,3-dioxolane-2,3′-indolin]-2′-one was the most active compound in the MES test and had ED_{50} = 27.97 mg/kg. Structural analogues spiro[1,3-dioxane-2,3′-indolin]-2′-one, spiro[1,3-dithiolane-2,3′-indolin]-2′-one, spiro[indoline-3,2′-[1,3]-oxathiolan]-2-one, and 3,3-dimethoxyindolin-2-one were also evaluated for anticonvulsant activity. Almost all compounds submitted for screening exhibited the ability to protect mice against electrically and chemically induced seizures. The ED_{50} and TD_{50} values for some of the title compounds are reported. Anticonvulsant screenings were carried out through NINCDS, NIH.

The search for potent antiepileptic drugs has resulted in the synthesis and evaluation of compounds having diverse chemical structures.[1,2] Many of these compounds have structural features quite different from the more popular antiepileptic drugs viz. carbamazepine, phenytoin, phenobarbital, and primidone.[3] A closer look reveals the presence of an amide moiety (cyclic or otherwise) and a tetrahedral carbon in most anticonvulsants. Unique structural features, such as an amide linkage and a β carbonyl (a site for structural modification), make isatin

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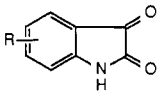
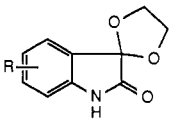
(1)[4] an attractive source for the design of such compounds. Our search for potential antiepileptic drugs has revealed that some isatin derivatives exhibit anticonvulsant activity.[5] Recent reports[6] on anticonvulsant methyl dioxolanylsulfamates prompts us to present our results in the development of such drugs. In a selective preliminary screen of various compounds prepared in our laboratory, we found that spiro[1,3-dioxolane-2,3′-indolin]-2′-one (**11**) posesses the ability to protect mice against chemically and electrically induced seizures.[7] The rationale behind having the title compounds screened lies in the fact that these molecules contain two units: an oxindole and a dioxolane moiety. Since both these substructures have independently been seen in other anticonvulsants,[5,8] we felt a judicious combination of the two units would eventually lead to a novel drug for the treatment of epilepsy. Also, these compounds contain a cyclic amide moiety and a tetrahedral carbon, structural features that have been seen in several anticonvulsants.



	R =
1	H
2	5-Br
3	5-Cl
4	6-Cl
5	4-Cl
6	5-NO_2
7	1-CH_3
8	7-CF_3
9	5-CH_3
10	5-I



	R =
11	H
12	5′-Br
13	1′-CH_2N (O)
14	1′-CH_2N
15	5′-Cl
16	6′-Cl
17	1′-$CH_2C_6H_5$
18	1′-CH_2N
19	5′-NO_2
20	1′-CH_3
21	4′-Cl
22	5′-I
23	5′-CH_3
24	7′-CF_3

Compound **11** served as the lead compound for our structure–activity investigation Structural modification of **11** include incorporation of substituents on the oxindole, substitution of the oxygens in the dioxolane portion of the molecule, and introduction of a different moiety at the spiro center.

Chemistry

Acid catalyzed cyclocondensation reaction of isatin (**1**) with ethylene glycol, 2-mercaptoethanol, 1,2-ethanedithiol, 1,3-propanediol, and 3-chloro-1,2-propanediol gave compounds **11**, **25**, **27**,[9] **32**, and **33**, respectively. Spiro[1,3-dioxolane-2,3′-indolin]-2′-ones (**12**, **15**, **16**, **19–24**) and sulfur analogues **26** and **28** were similarly prepared from commercially available isatins **2–10**. Via a procedure similar to that described by us earlier,[5b] reaction of **11** with aqueous formaldehyde and secondary amines such as morpholine, piperidine, and pyrrolidine gave Mannich products **13**, **14**, and **18**, respectively. Compounds **29** and **30** were similarly synthesized from **27**. Treatment of the anion of **11** (prepared by using NaH/DMF) with benzyl bromide furnished **17**. Transacetalation of isatin (**1**) by reaction with trimethyl orthoformate in methanol gave **31**.[10]

Table I. Phase I Anticonvulsant Identification Test Results of Spiro[1,3-dioxolane-2,3′-indolin]-2′-ones **11–24**[a]

		MES[b]		sc-Met[c]		TOX[d]	
no.	hour	100	300[e,f]	100	300[e,f]	100	300[e,g]
11	0.5	1/3	1/1	0/1	1/1	1/8	4/4[h]
12	0.5	2/3	1/1	0/1	1/1	4/8	4/4[h]
	0.25			1/2		2/2	
13	0.5	0/3	1/1[i]	0/1	1/1	0/8	2/4
	0.25	1/2		0/2		1/4	
14	0.5	0/3	1/1	0/1	1/1	0/8	4/4
	0.25	0/2		1/2		0/4	
15	0.5	3/3	1/1	0/1	1/1	8/8	4/4[j]
	0.25			1/2		2/2	
	1			0/2		2/2	
	4	0/3	1/1	0/1		0/4	2/2[k]
16	0.5	3/3	1/1[l]	0/1	1/1	7/8	4/4[h]
	4	0/3	1/1	0/1	1/1[m]	0/4	1/2
17	0.5	0/3	0/1	0/1	0/1	0/8	0/4
18	0.5	0/3	1/1	0/1	1/1[n]	0/8	4/4
	0.25	0/2		0/2		1/4	
19	0.5	1/3	1/1	0/1	0/1[o]	1/8	4/4
20	0.5	3/3	1/1	0/1	1/1	8/8	4/4[h,p]
	4	0/3	1/1	0/1	0/1	0/4	2/2[q]
21	0.5	3/3	1/1	0/1	1/1	7/8	4/4[h]
	4	0/3	0/1	0/1	0/1[m]	0/4	1/2
22	0.5	3/3	1/1	0/1	1/1	6/8	4/4[r]
23	0.5	2/3	1/1	0/1	1/1	0/8	4/4[p]
24	0.5	0/3	1/1	0/1	1/1[s]	0/8	4/4

[a] Anticonvulsant screenings were carried out through the ADD program, NINCDS, NIH. The standard screening protocol of that group was followed. [b] MES = maximal electroshock seizure test. [c] sc-Met = subcutaneous pentylenetetrazole (Metrazol) seizure threshold test. [d] TOX = neurotoxicity (rotorod test). [e] Dose levels are in milligrams/kilogram. [f] Results are expressed as number of animals protected/number of animals tested. [g] Results are expressed as number of animals exhibiting toxicity/number of animals protected. [h] Unable to hold on to rotorod. [i] Toxic at 0.5 h. [j] 2/4 loss of righting reflex, 2/4 anesthetized. [k] 1/2 died before 4-h test. [l] MES at 0.5 h = 1/1 at 30 mg/kg. [m] Toxic at 4 h. [n] Repeat results: 0/4 protected, 4/4 toxic. [o] Clonic seizure followed by continuous seizure action and death. [p] Anesthetized. [q] 1/2 unable to hold onto rotorod. [r] Loss of righting reflex. [s] Repeat results: 3/4 protected, 3/4 toxic.

Results and Discussion

The phase I anticonvulsant identification test results for compounds **11–24** are shown in Table I. In this set of compounds substituents have been incorporated in the oxindole moiety of the parent compound (**11**). Except for the 1′-benzyl analogue (**17**), all compounds exhibited the ability to protect mice against electrically induced seizures (MES test) at 300 mg/kg. Introduction of a halogen in the oxindole portion of **11** led to more active compounds in phase I. Position of the chlorine (4′, 5′, or 6′) does not seem to affect the activity of these compounds in the identification test. Compound **22** (5′-iodo) was equally active in the MES test, whereas the bromo analogue **12** was less active.

(4) For a review of the chemistry of isatin, see: Popp, F. D. *Adv. Heterocycl. Chem.* **1975**, *18*, 1.
(5) (a) Popp, F. D. *J. Heterocycl. Chem.* **1984**, *21*, 1641. (b) Rajopadhye, M.; Popp, F. D. *J. Heterocycl. Chem.* **1984**, *21*, 289. (c) Pajouhesh, H.; Parson, R.; Popp, F. D. *J. Pharm. Sci.* **1983**, *72*, 318. (d) Popp, F. D. *J. Heterocycl. Chem.* **1982**, *19*, 589. (e) Popp, F. D.; Pajouhesh, H. *J. Pharm. Sci.* **1982**, *71*, 1052. (f) Popp, F. D.; Parson, R.; Donigan, B. E. *J. Pharm. Sci.* **1980**, *69*, 1235. (g) Popp, F. D.; Donigan, B. E. *J. Pharm. Sci.* **1979**, *68*, 519.
(6) (a) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. *J. Med. Chem.* **1987**, *30*, 880. (b) Maryanoff, B. E.; Nortey, S. O. U.S. Pat. 4 591 601, 1986; *Chem. Abstr.* **1986**, *105*, 78920*f*.
(7) Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, NINCDS, NIH. The standard screening protocol of that group was followed.
(8) For examples of anticonvulsant dioxolanes, see: (a) Reference 3. (b) Hardie, W. R.; Hidalgo, J.; Halverstadt, I. F.; Allen, R. E. *J. Med. Chem.* **1966**, *9*, 127.
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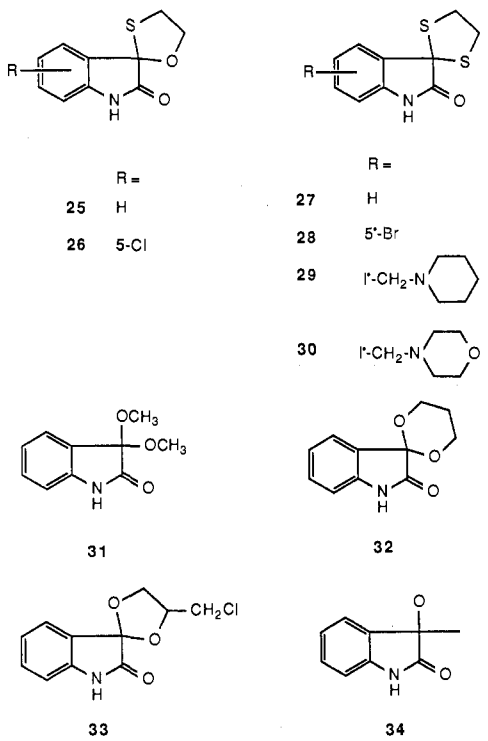

In general a bulky substituent at the 1′-position (oxindole N) tends to decrease the activity of **11** in the MES test, as seen for compounds **13**, **14**, and **18**. The 1′-benzyl group was introduced to make compound **11** more hydrophobic,[11] but this led to an inactive compound (**17**). Compound **20** having a CH_3 at the 1′-position was more active in phase I than **11** and as active as the chlorinated analogues in the MES test. Interestingly, it has been reported[12] that replacement of a small *N*-alkyl group by a (dialkylamino)alkyl (e.g. piperidinomethyl) group reduces MES and sc-Met activity in succinimides. Isomer **23** (5′-CH_3) was somewhat less active than **20**.

Except for compounds **17** and **19**, all substituted analogues of **11** prevented pentylenetetrazole (Metrazol) induced convulsions at 300 mg/kg (sc-Met test).

Table II shows the phase I results for compounds **25–33**. The lead compound (**11**) has also been included for comparison. This set of compounds represents analogues in which the dioxolane moiety has been modified. Spiro[1,3-oxathiolane-2,3′-indolin]-2′-one (**25**) was as active as **11**, whereas the dithio analogue **27** was less active. Introduction of halogens in either **25** or **27** did not enhance anticonvulsant activity, which is contrary to that observed with **11**. The homologue **32**, having a dioxane moiety,[13] and compound **31**, envisaged as a less rigid analogue of **11**, were less potent. The removal of the spiro center[14] does not seem to adversely affect the activity of isatin ketals. Isatin (**I**) itself displays 100% protection in the MES test at 400 mg/kg.[3] Compound **33**, the 4-chloromethyl analogue of **11**, was active in the sc-Met test at 300 mg/kg but was inactive in the MES test. The 4-chloromethyl group in **33** is a potential site for further structural modifications, perhaps via nucleophilic substitution of the halogen.

As seen in Tables I and II most compounds exhibited considerable neurologic toxicity (rotorod test). Methyl analogues **20** and **23** also exhibited anesthetic properties during the rotorod test.

Table II. Phase I Anticonvulsant Identification Test Results of Spiro[1,3-dioxolane-2,3′-indolin]-2′-one Analogues **25–33**[a]

		MES		sc-Met		TOX	
no.	hour	100	300	100	300	100	300
11	0.5	1/3	1/1	0/1	1/1	1/8	4/4[b]
25	0.5	1/3	1/1	0/1	1/1	5/8	4/4[b]
26	0.5	0/3	1/1	0/1	0/1[c]	0/8	3/4
	4	0/3	1/1[c]	0/1	0/1[c]	0/4	2/2
27	0.5	0/3	1/1[c]	0/1	0/1	0/8	2/4
	0.25	2/2				0/2	
	1	1/2				0/2	
28	0.5	0/3	0/1	0/1	0/1	0/8	0/4
29	0.5	0/3	0/1	0/1	0/1[c]	0/8	1/4
30	0.5	0/3	1/1	1/1	0/1	0/8	0/4[d]
31	0.5	0/3	1/1	0/1	1/1[e]	0/8	4/4[b]
32	0.5	1/3	1/1	0/1	1/1	1/8	4/4[b]
	0.25			0/2		1/2	
33	0.5	0/3	0/1	0/1	1/1[f]	0/8	0/4

[a] See Table I for explanation of headings. [b] Unable to hold on to rotorod. [c] Toxic at 0.5 h. [d] Repeat results: 0/4 protected, 0/4 toxic. [e] Repeat results: 4/4 protected, 4/4 toxic.[b] [f] Repeat results: 3/4 protected, 0/4 toxic.

Table III. Phase II Quantification Test Results[a]

no.	MES, ED_{50} [95% CI][b]	TOX, TD_{50} [95% CI][b]	PI[c]
11	69.85 [62.09–80.07]	130.49 [97.24–151.53]	1.87
12	46.15 [32.78–67.36]	86.49 [53.59–137.10]	1.87
13	90.03 [76.80–108.10]	170.01 [151.73–185.95]	1.89
14	134.89 [114.30–166.71]	187.22 [159.36–230.35]	1.39
15	27.97 [19.40–39.27][d]	63.67 [54.63–72.55]	2.28
16	71.97 [51.85–86.96]	120.56 [97.71–150.58]	1.68
20	90.86 [69.89–108.44]	118.36 [107.20–127.34]	1.30
21	95.58 [87.59–110.97]	122.43 [109.25–132.51]	1.24
25	60.35 [51.33–68.28][d]	99.84 [73.09–136.97]	1.65
27	173.85 [140.63–213.33]		
31	82.03 [77.00–86.82][d]	202.51 [187.37–227.66]	2.47
32	110.48 [84.16–124.57]	184.73 [190.93–197.14]	1.67

[a] Time of test = 0.25 h. [b] ED_{50} and TD_{50} are in milligrams/kilogram. 95% CI = 95% confidence intervals. [c] PI (protective index) = TD_{50}/ED_{50}. PI values are for MES tests. [d] sc-Met ED_{50} [95% CI]: **15**, 104.48 [66.32–151.64]; **25**, 76.16 [50.31–115.84]; **31**, 80.61 [60.20–108.06].

Table IV. Phase II Evaluation at Time of Peak Effect (TPE)[a]

no.	MES/TEST, dose[b]	TOX/TEST, dose[c]
11	3/4, 100	8/8, 200
12	4/4, 100	6/8, 150
13	3/4, 100	8/8, 200
14	4/4, 150	5/8, 200
15	4/4, 100	8/8, 100
16	4/4, 125	6/8, 150[d]
20	2/4, 125	2/4, 125
21	4/4, 150[d]	2/8, 110
25	3/4, 60	5/8, 120
27	3/4, 400	3/8, 500
31	4/4, 100	8/8, 300
32	4/4, 200[e]	7/8, 200

[a] TPE for all compounds in the MES and TOX tests is 0.25 h unless otherwise noted. [b] MES/TEST, dose = number of animals protected in the MES test/number of animals tested at the dose level (milligrams/kilogram) indicated. [c] TOX/TEST, dose = number of animals exhibiting neurologic toxicity/number of animals tested at the dose level (milligrams/kilogram) indicated. [d] TPE = 0.5 h. [e] TPE = 0.25 h and 0.5 h.

(11) Camerman, A.; Camerman, N. In *Antiepileptic Drugs: Mechanism of Action*; Glaser, G. H., Penry, J. K., Woodbury, D. M., Eds.; Raven: New York, 1980; p 223.
(12) Vida, J. A.; Gerry, E. H. In ref 2, pp 191.
(13) (a) Anticonvulsant activity of the related spiro[indoline-3,2′-tetrahydro-1,3-thiazin]-2-one has been investigated: Wolf, M. U.S. Pat. 3 458 525, 1969; *Chem. Abstr.* **1970**, *72*, 21715*p*. (b) A number of oxindoles with a spiro carbon at the 3-position have been synthesized owing to the diverse biological activity associated with such systems. For a review on this aspect, see: Joshi, K. C.; Jain, R.; Chand, P. *Heterocycles* **1985**, *23*, 957.
(14) For recent examples of spiro compounds exhibiting anticonvulsant activity, see: Borenstein, M. R.; Doukas, P. H. *J. Pharm. Sci.* **1987**, *76*, 300.

The spiro compounds were also submitted[7] for phase II quantification testing. The median effective dose (ED_{50}) and the median toxic dose (TD_{50}) for compounds **11–16**, **25**, **27**, **31**, and **32** were determined at the time of peak effect and are shown in Table III. The time of peak effect (TPE), for anticonvulsant action (MES) and neurologic toxicity, for these compounds was determined to be 0.25 h. The protection results and the dose levels at the time of peak effect are shown in Table IV. Compound **15** (5′-chloro) was found to be most potent in the MES test showing ED_{50} = 27.97 mg/kg and PI = 2.28. In comparison, phenobarbital has PI = 3.16 and ED_{50} = 21.8 mg/kg in the MES test.[15] Compound **12** (5′-bromo) is less potent with an ED_{50} = 46.15 mg/kg. Although **15** and **25** are more potent than the parent compound **11**, analogue **26** was found to have poor activity in the MES test and was inactive in the sc-Met test. The high TD_{50} value for **31** resulted in a PI of about 2.5 in the MES and sc-Met tests, which compares well with mephenytoin (PI = 2.54, MES ED_{50} = 60.5 mg/kg) and methsuximide (PI = 2.46, MES ED_{50} = 76.3 mg/kg) tested under similar conditions.[15] The PI for compounds **11–14**, **16**, **25**, and **32** is comparable to that of valproic acid (PI = 1.57 in the MES test).

Conclusions

Anticonvulsant screening results indicate spiro[1,3-dioxolane-2,3′-indolin]-2′-ones to be a novel class of anticonvulsants having high potential. X-ray analyses would, perhaps, indicate a suitable model that accommodates the spatial characteristics of the anti-MES active spiro[1,3-dioxolane-2,3′-indolin]-2′-ones and the anticonvulsant non spiro phenacyloxindoles.[5f,16] The structural pattern of **34** seems important for the anticonvulsant activity of substituted oxindoles.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B spectrophotometer. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-24B instrument. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. Elemental analyses were carried out by Spang Microanalytical Laboratory.

Spiro[1,3-dioxolane-2,3′-indolin]-2′-ones (11, 12, 15, 19, and 20). A mixture of the appropriate isatin, ethylene glycol, and *p*-toluenesulfonic acid (catalytic amounts) in benzene was heated at reflux, with azeotropic removal of the water formed, to give the title compounds as reported in the literature. Compound **11** (72%) had mp 131–132 °C (benzene) (lit.[17] mp 134 °C); **12** (54%) had mp 189–190 °C (ethanol) (lit.[17] mp 191–192 °C); **15** (63%) had mp 175–176 °C (ethanol) (lit.[17] mp 178–180 °C); **19** (29%) had mp 216–217 °C (ethanol) (lit.[17] mp 218 °C); **20** (60%) had mp 90–91 °C (benzene) (lit.[18] mp 93 °C).

1′-(Morpholinomethyl)spiro[1,3-dioxolane-2,3′-indolin]-2′-one (13). A mixture of **11** (2.25 g, 0.012 mol), morpholine (1.04 g, 0.012 mol), and 37% formaldehyde (1.07 g) in 25 mL of absolute ethanol was heated at reflux for 10 h. The reaction mixture was concentrated in vacuo and kept overnight. The product obtained upon filtration was recrystallized from ethanol to give **13** in 72% yield: mp 133–134 °C; IR (KBr) 3000, 2940, 2880, 2840, 1730, 1610, 1480, 1460, 1390, 1350, 1260, 1200, 1120, 1040, 940, 860 cm^{-1}. Anal. ($C_{15}H_{18}N_2O_4$) C, H.

1′-(Piperidinomethyl)spiro[1,3-dioxolane-2,3′-indolin]-2′-one (14). Following the procedure as described for **13** but with **11** (2.25 g, 0.012 mol), piperidine (1.01 g, 0.012 mol), and 37% formaldehyde (1.07 g) gave, after recrystallization from absolute ethanol, 60% of **14**: mp 122–123 °C; IR (KBr) 2960, 2875, 2840, 1730, 1615, 1490, 1470, 1350, 1300, 1235, 1190, 1140, 1030, 940, 860 cm^{-1}. Anal. ($C_{16}H_{20}N_2O_3$) C, H.

6′-Chlorospiro[1,3-dioxolane-2,3′-indolin]-2′-one (16). A mixture of **4** (1.46 g, 0.008 mol), ethylene glycol (1.84 g, 0.03 mol), and *p*-toluenesulfonic acid (0.04 g) in 100 mL of benzene was heated under reflux for 13 h in a Dean–Stark separator. The reaction mixture was cooled, and the solution was concentrated in vacuo and kept overnight at room temperature. The product thus obtained was recrystallized from benzene to give 61% of **16**, mp 174–175 °C. Anal. ($C_{10}H_8ClNO_3$) C, H.

1′-Benzylspiro[1,3-dioxolane-2,3′-indolin]-2′-one (17). To a well-stirred solution of **11** (2.40 g, 0.0125 mol) and benzyl bromide (1.6 mL, 0.0125 mol) in 15 mL of anhydrous dimethylformamide at room temperature was added 50% sodium hydride in oil (0.91 g, 0.019 mol). After being stirred for 16 h, the mixture was poured onto ice and the product filtered. The crude product was washed with cold water and recrystallized from ethanol to give **17** in 38% yield: mp 114–115 °C; IR (KBr) 2975, 2900, 1720, 1620, 1490, 1470, 1375, 1320, 1180, 1130, 1040, 960 cm^{-1}. Anal. ($C_{17}H_{15}NO_3$) C, H.

1′-(Pyrrolidinomethyl)spiro[1,3-dioxolane-2,3′-indolin]-2′-one (18). Following the procedure as described for **13** but with **11** (1.91 g, 0.01 mol), pyrrolidine (0.71 g, 0.01 mol), and 37% formaldehyde (0.91 g) gave, after recrystallization from absolute ethanol, 64% of **18**, mp 113–114 °C; IR (KBr) 3000, 2950, 2850, 1735, 1620, 1485, 1470, 1370, 1340, 1300, 1220, 1195, 1140, 1035, 960 cm^{-1}. Anal. ($C_{15}H_{18}N_2O_3$) C, H.

4′-Chlorospiro[1,3-dioxolane-2,3′-indolin]-2′-one (21). Following the procedure as described for **16** but with **5** (1.46 g, 0.008 mol) and ethylene glycol (1.84 g, 0.03 mol) gave after recrystallization from benzene 98% of **21**, mp 186–188 °C. Anal. ($C_{10}H_8ClNO_3$) C, H.

5′-Iodospiro[1,3-dioxolane-2,3′-indolin]-2′-one (22). Following the procedure as described for **16** but with **10** (1.37 g, 0.005 mol) and ethylene glycol (1.53 g, 0.025 mol) gave after recrystallization from ethanol 43% of **22**, mp 173–175 °C. Anal. ($C_{10}H_8INO_3$) C, H, N.

5′-Methylspiro[1,3-dioxolane-2,3′-indolin]-2′-one (23). Following the procedure as described for **16** but with **9** (1.61 g, 0.01 mol) and ethylene glycol (1.05 g, 0.017 mol) gave after recrystallization from ethanol 20% of **23**, mp 133–135 °C. Anal. ($C_{11}H_{11}NO_3$) C, H, N.

7′-(Trifluoromethyl)spiro[1,3-dioxolane-2,3′-indolin]-2′-one (24). Following the procedure as described for **16** but with **8** (0.90 g, 0.0042 mol) and ethylene glycol (1.0 g, 0.016 mol) gave after recrystallization from ethanol 73% of **24**, mp 138–142 °C. Anal. ($C_{11}H_8F_3NO_3$) C, H, N.

Spiro[indoline-3,2′-[1,3]oxathiolan]-2-one (25). A mixture of **1** (4.41 g, 0.03 mol), 2-mercaptoethanol (3.12 g, 0.04 mol), and *p*-toluenesulfonic acid (0.04 g) in 100 mL of benzene was heated under reflux for 8 h in a Dean–Stark separator. The reaction mixture was cooled, and the solution was concentrated in vacuo and kept overnight at room temperature. The product thus obtained was recrystallized from benzene to give 3.05 g (49%) of **25**: mp 155–156 °C; IR (KBr) 3200, 3140, 2975, 2925, 2870, 1750, 1620, 1470, 1420, 1325, 1265, 1210, 1110, 1075, 1000, 910 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.37–6.73 (aromatic, 4 H), 4.49 (t, 2 H, CH_2O, J = 6 Hz), 3.45 (t, 2 H, CH_2S, J = 6 Hz). Anal. ($C_{10}H_9NO_2S$) C, H.

5-Chlorospiro[indoline-3,2′-[1,3]oxathiolan]-2-one (26). Following the procedure as described above but with **3** gave after recrystallization from ethanol 53% of **26**, mp 134–136 °C. Anal. ($C_{10}H_8ClNO_2S$) C, H, N.

Spiro[1,3-dithiolane-2,3′-indolin]-2′-one (27) was prepared as reported. Compound **27** had mp 197–198 °C (ethanol) (lit.[9] mp 200–201 °C).

5′-Bromospiro[1,3-dithiolane-2,3′-indolin]-2′-one (28). A mixture of **2** (2.21 g, 0.01 mol), 1,2-ethanedithiol (1.0 g, 0.011 mol), and *p*-toluenesulfonic acid (0.02 g) in 80 mL of benzene was heated

(15) For quantification (data) of anticonvulsant activity and neurotoxicity of most antiepileptic drugs marketed in the United States, see: Gladding, G. D.; Kupferberg, H. J.; Swinyard, E. A. In *Antiepileptic Drugs*; Frey, H. H., Janz, D., Eds.; Springer Verlag: Berlin, 1985; p 341.

(16) Codding, P. W.; Lee, T. A.; Richardson, J. F. *J. Med. Chem.* **1984**, *27*, 649.

(17) Zhungietu, G. I.; Gorgos, V. I.; Rekhter, M. A.; Korpan, A. I. *Ser. Biol. Khim. Nauk.* **1980**, 61.

(18) Zhungietu, G. I.; Chmykhova, N. I.; Gorgos, V. I.; Rekhter, M. A.; Khariton, K. S. *Khim. Geterotsikl. Soedin.* **1977**, 642.

under reflux for 36 h. The water formed was azeotropically removed in a Dean–Stark separator. The reaction mixture was allowed to cool to room temperature. The product thus obtained was filtered and recrystallized from ethanol, and then from benzene to give **28** in 57% yield: mp 195–196 °C; IR (KBr) 3160, 3100, 3040, 2960, 2910, 2880, 1710, 1610, 1470, 1440, 1280, 1230, 1185, 1120, 1040 cm^{-1}. Anal. ($C_{10}H_8BrNOS_2$) C, H.

1′-(Piperidinomethyl)spiro[1,3-dithiolane-2,3′-indolin]-2′-one (29). Following the procedure as described for **13** but with **27** (1.12 g, 0.005 mol), piperidine (0.43 g, 0.005 mol), and 37% formaldehyde (0.45 g) gave, after recrystallization from absolute ethanol, 78% of **29**: mp 145–146 °C; IR (KBr) 2960, 2875, 2810, 1715, 1600, 1480, 1465, 1345, 1300, 1240, 1165, 1120, 1040 cm^{-1}. Anal. ($C_{16}H_{20}N_2OS_2$) C, H.

1′-(Morpholinomethyl)spiro[1,3-dithiolane-2,3′-indolin]-2′-one (30). Following the procedure as described for **13** but with **27** (1.12 g, 0.005 mol), morpholine (0.45 g, 0.005 mol), and 37% formaldehyde (0.45 g) gave, after recrystallization from ethanol, 81% of **30**: mp 143–144 °C; IR (KBr) 3000, 2960, 2880, 2845, 1720, 1605, 1480, 1460, 1420, 1340, 1305, 1290, 1260, 1230, 1155, 1120, 1000, 860 cm^{-1}. Anal. ($C_{15}H_{18}N_2O_2S_2$) C, H.

3,3-Dimethoxyindolin-2-one (31) was prepared as reported. Compound **31** had mp 92–93 °C (lit.[10] mp 94 °C).

Spiro[1,3-dioxane-2,3′-indolin]-2′-one (32). A mixture of 1 (2.94 g, 0.02 mol), 1,3-propanediol (3.04 g, 0.04 mol), and *p*-toluenesulfonic acid (0.02 g) in 80 mL of toluene was heated under reflux for 13 h. The water formed was azeotropically removed in a Dean–Stark separator. The reaction mixture was allowed to cool to room temperature, decanted, and evaporated in vacuo. The product thus obtained was recrystallized from ethanol to give **32** in 48% yield: mp 150–151 °C; IR (KBr) 3200, 3120, 3010, 2925, 2875, 1700, 1620, 1460, 1325, 1275, 1245, 1210, 1115, 1080, 900, 845 cm^{-1}. Anal. ($C_{11}H_{11}NO_3$) C, H.

4-(Chloromethyl)spiro[1,3-dioxolane-2,3′-indolin]-2′-one (33). A mixture of 1 (2.94 g, 0.02 mol), 3-chloro-1,2-propanediol (2.61 g, 0.02 mol), and *p*-toluenesulfonic acid (0.02) in 80 mL of toluene was heated at reflux. After 12 h the solvent was removed in vacuo. The product thus obtained was recrystallized from benzene to give 0.77 g (16%) of **33**: mp 158–159 °C; IR (KBr) 3200, 3150, 2960, 2940, 1730, 1620, 1465, 1320, 1225, 1120, 1065, 1000, 930, 850 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.73–7.03 (aromatic, 4 H), 5.05–4.4 (multiplets, 3 H, CH_2O, CH), 4.27 (d, 2 H, CH_2Cl, J = 6 Hz). Anal. ($C_{11}H_{10}ClNO_3$) C, H.

Pharmacological Evaluation.[7,19,20] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), NIH. Each compound submitted was tested for its ability to protect mice (male Carworth Farm No. 1) against electrically and chemically induced seizures. This evaluation (phase I) was performed at three dose levels viz. 30, 100, and 300 mg/kg. The compounds were administered ip, generally in PEG. The maximal electroshock seizure test evaluates the ability of a compound to prevent seizure spread through neural tissue. Maximal electroshock seizures are elicited with 60 cycle alternating current of 50-mA intensity delivered for 0.2 s via corneal electrodes. Protection in the MES test was defined as the abolition of the hind limb tonic extension component of the seizure. Pentylenetetrazole (85 mg/kg) is administered as a 0.5% solution subcutaneously. The subcutaneous pentylenetetrazole test estimates the ability to raise seizure threshold for excitation of neural tissue. Protection in the sc-Met test was defined as the failure to observe even a single episode of clonic spasms of at least 5-s duration (threshold seizure). All compounds were tested for neurotoxicity. The rotorod test was used to evaluate central nervous system toxicity. Neurologic toxicity was defined as the failure of the dosed animal to remain on a 1-in. diameter knurled plastic rod, rotating at 6 rpm, for 1 min. Compounds exhibiting anticonvulsant activity at 100 mg/kg or less are usually advanced to phase II (quantitative) testing. Phase II determines the time of peak anticonvulsant and toxic effect. The TD_{50} and ED_{50} are then determined (the tests being performed at the time of peak effect).

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Registry No. 1, 91-56-5; 2, 87-48-9; 3, 17630-76-1; 4, 6341-92-0; 5, 6344-05-4; 6, 611-09-6; 7, 2058-74-4; 8, 391-12-8; 9, 608-05-9; 10, 20780-76-1; 11, 6714-68-7; 12, 75822-54-7; 13, 113549-01-2; 14, 113549-02-3; 15, 75822-57-0; 16, 113549-03-4; 17, 113549-04-5; 18, 113549-05-6; 19, 75822-55-8; 20, 63707-29-9; 21, 113549-06-7; 22, 34058-27-0; 23, 75822-58-1; 24, 113549-07-8; 25, 113549-08-9; 26, 113549-09-0; 27, 38168-18-2; 28, 113549-10-3; 29, 113549-11-4; 30, 113549-12-5; 31, 66346-69-8; 32, 113549-13-6; 33, 113549-14-7; ethylene glycol, 107-21-1; morpholine, 110-91-8; formaldehyde, 50-00-0; piperidine, 110-89-4; pyrrolidine, 123-75-1; 2-mercaptoethanol, 60-24-2; 1,2-ethanedithiol, 540-63-6; 1,3-propanediol, 504-63-2; 3-chloro-1,2-propanediol, 96-24-2.

(19) For a description of the NINCDS screening protocol, see: (a) Reference 15. (b) Pharmacology section of Conley, J. D.; Kohn, H. *J. Med. Chem.* **1987**, *30*, 567. (c) Clark, C. R.; Davenport, T. W. *J. Med. Chem.* **1987**, *30*, 1214.

(20) Information obtained from ADD Program, NINCDS, NIH.

9-(2-Fluorobenzyl)-6-(alkylamino)-9*H*-purines. A New Class of Anticonvulsant Agents

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Several substituted aryl and 6-alkylamino analogues of the anticonvulsant purine 9-(2-fluorobenzyl)-6-(methylamino)-9*H*-purine (1) were synthesized and tested for anticonvulsant activity against maximal electroshock-induced seizures (MES) in rats. Derivatives with a second fluoro substituent in the 5- or 6-position of the aryl moiety were very active with ip ED_{50}'s that ranged from 2 to 4 mg/kg. Congeners in which the purine 6-substituent was varied among a number of alkylamino groups possessed potent activity against MES that was comparable to or several times better than phenytoin.

Although several drugs are used in the treatment of epilepsy, many patients fail to experience satisfactory seizure control with them, or they do so at the expense of significant side effects.[1,2] Due to the need for new im-

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(1) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia (N.Y.)* **1978**, *19*, 409.

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