Articles

Structure–Activity Relationships of (Arylalkyl)imidazole Anticonvulsants: Comparison of the (Fluorenylalkyl)imidazoles with Nafimidone and Denzimol[1]

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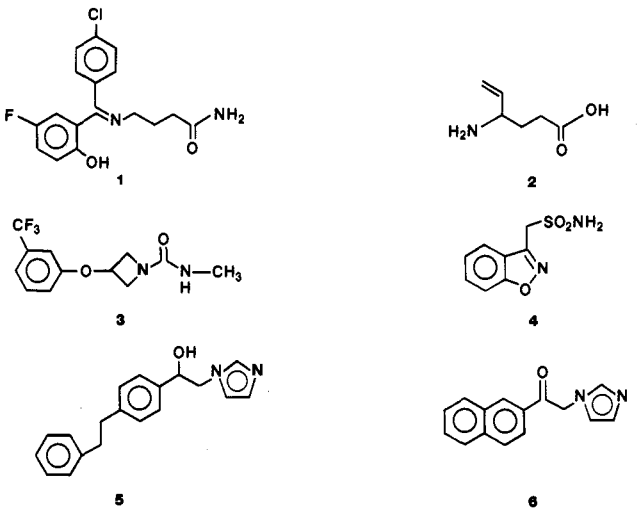
A recently discovered and structurally distinct class of antiepileptic drugs is the (arylalkyl)imidazoles. Two independently discovered representatives of this class, denzimol (α-[4-(2-phenylethyl)phenyl]-1*H*-imidazole-1-ethanol) and nafimidone (2-(1*H*-imidazol-1-yl)-1-(2-naphthalenyl)ethanone), are undergoing clinical evaluation. Our structure–activity relationship (SAR) studies revealed that in addition to the naphthalenyl and phenethylphenyl aryl moieties of nafimidone and denzimol, respectively, fluorenyl, benzo[*b*]thienyl, and benzofuranyl aryl groups provided several highly active (arylalkyl)imidazole anticonvulsants. These structurally diverse aryl moieties, and comparable anticonvulsant activities, lend credence to the hypothesis that the pharmacophore of this class of anticonvulsants is the alkylimidazole portion of the molecule, with the lipophilic aryl portion enabling penetration of the blood–brain barrier. We focused our SAR studies on the (fluorenylalkyl)imidazole series. A representative compound from this series is 1-(9*H*-fluoren-2-yl)-2-(1*H*-imidazol-1-yl)ethanone (**27**). This agent was twice as potent as nafimidone in inhibiting maximal electroshock seizures in mice (po ED_{50}'s = 25 and 56 mg/kg, respectively) and considerably less toxic in the rat (po LD_{50}'s = 4550 and 504 mg/kg, respectively). The tertiary alcohol α-(9*H*-fluoren-2-yl)-α-methyl-1*H*-imidazole-1-ethanol (**46**) was as potent as denzimol in mice (po ED_{50}'s = 10 and 12 mg/kg, respectively). This series of imidazole anticonvulsants was highly selective; while many compounds displayed potent antielectroshock activity, little or no activity was observed against pentylenetetrazole-induced clonic seizures or in the horizontal screen test for ataxia. All active compounds that we tested in this series, as well as denzimol and nafimidone, potentiated hexobarbital-induced sleeping time in mice, probably by imidazole-mediated inhibition of cytochrome P-450. The SAR's for the anticonvulsant activity and the sleeping time potentiation were similar. The propensity of these (arylalkyl)imidazole anticonvulsants to interact strongly with cytochrome P-450 and thereby impair the metabolism of other antiepileptic drugs may severely limit their clinical utility as anticonvulsants.

Epilepsy, with an incidence of 0.5–1% of the population, is second only to stroke as the most common derangement of the central nervous system.[2] The disease, if untreated, can lead to impaired intellectual function or death and is typically accompanied by profound psychopathological consequences such as the loss of self-esteem.[3] Although there are a number of antiepileptic drugs currently available in the United States, improved medications are needed. Whereas some specific seizure disorders, including absence, tonic-clonic, juvenile myoclonic, and rolandic epilepsies, are often well-controlled with existing drugs, therapy is inadequate for many epilepsies including psychomotor and elementary partial seizures.[4] Moreover, the therapeutic effects of these drugs are often accompanied by side effects that include sedation, ataxia, psychoses, suicidal depression, gastrointestinal disturbances, gingival hyperplasia, lymphadenopathies, megaloblastic anemias, hepatotoxicity, nephropathies, hirsutism, and fetal malformations.[5,6] These toxic effects are particularly troublesome since most of the marketed anticonvulsants have fairly low therapeutic ratios. For example, phenytoin, one of the most widely used anticonvulsants, controls seizures in man only when plasma levels exceed 10 μg/mL. Toxic effects such as nystagmus emerge at ca. 20 μg/mL, ataxia is obvious at 30 μg/mL, and lethargy is apparent at about 40 μg/mL.[7] In view of the large percentage of uncontrolled epileptics and the side effects experienced by patients that are controlled with existing medications, there is a definite need for more selective and less toxic anticonvulsant drugs.[8]

Chart I. Some Structurally Novel Anticonvulsants



The prototypical classes of antiepileptic drugs are barbiturates (e.g., phenobarbital) and hydantoins (e.g., phe-

(1) Portions of this work have been presented previously: Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Rathbun, R. C. *Abstracts of Papers*, 189th National Meeting of the American Chemical Society, Miami Beach, FL, April 1985; American Chemical Society; Washington, DC, 1985; MEDI 32.
(2) Hauser, W. A. *Adv. Neurol.* **1978**, *19*, 313.
(3) Rosenbloom, D.; Upton, A. R. M. *Can. Med. Assoc. J.* **1983**, *128*, 261.
(4) Delgado-Escueta, A. V.; Treiman, D. M.; Walsh, G. O. *N. Engl. J. Med.* **1983**, *308*, 1508; **1983**, *308*, 1576.
(5) *Chronic Toxicity of Antiepileptic Drugs*; Oxley, J., Janz, D., Meinardi, H., Eds.; Raven: New York, 1983.
(6) Eadie, M. J. *Drugs* **1979**, *17*, 213. Eadie, M. J. *Drugs* **1984**, *27*, 328.
(7) Rall, T. W.; Schleifer, L. S. In *The Pharmacological Basis of Therapeutics*, 6th ed.; Gilman, A. G., Goodman, L. S., Gilman, A., Eds.; MacMillan: New York, 1980; p 455.
(8) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409.

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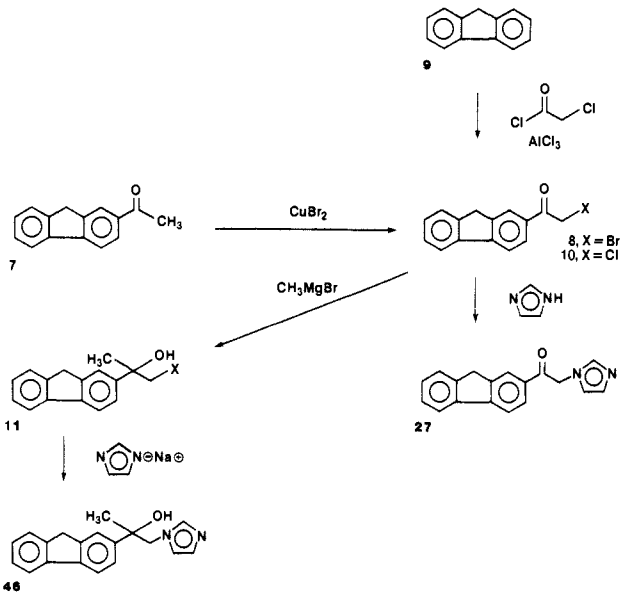
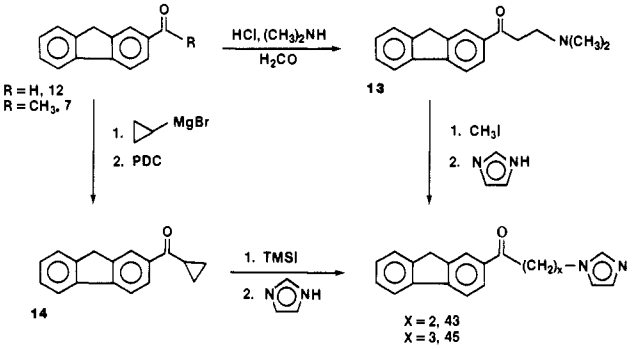
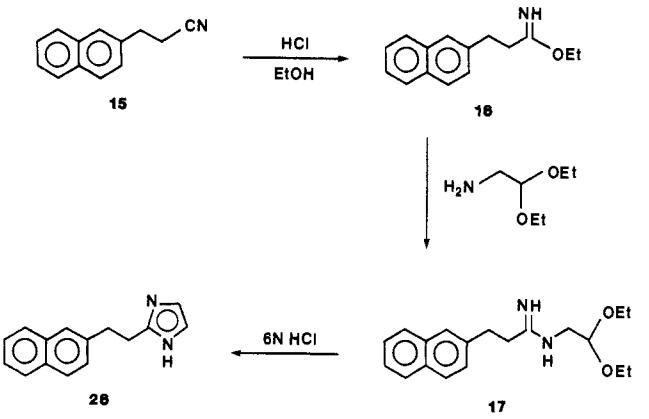
Scheme I



Scheme II



Scheme III



nytoin), and most of the available antiepileptics are derived from these or structurally similar heterocycles. In fact, all antiepileptic drugs marketed until 1968 can be classified as phenobarbital or phenytoin congeners.[9] During the past decade there has been a resurgence of interest in the development of structurally and mechanistically unique antiepileptic drugs. This has resulted in the discovery and clinical evaluation of several novel agents, including the GABAergic agent progabide (1),[10] the GABA-transaminase inhibitor γ-vinylGABA (2),[11] fluzinamide (3),[12] and zonisamide (4)[13] (Chart I). Another recently discovered and structurally distinct class of antiepileptic drugs is the (arylalkyl)imidazoles. Two independently discovered representatives of this class, α-[4-(2-phenylethyl)-phenyl]-1*H*-imidazole-1-ethanol (denzimol, **5**),[14-17] and 2-(1*H*-imidazol-1-yl)-1-(2-naphthalenyl)ethanone (nafimidone, **6**)[18-20] (Chart I), are undergoing clinical evaluation.

Both compounds protect mice and rats against maximal electroshock- or pentylenetetrazole-induced tonic seizures but do not antagonize clonic seizures induced by pentylenetetrazole, strychnine, bicuculline, or picrotoxin. These and other studies indicated that denzimol and nafimidone possess a profile of activity similar to that of phenytoin or carbamazepine but distinct from those of barbiturates or valproic acid. Moreover, both agents display acceptable therapeutic ratios and protective indices.[15,18-20] Although formal accounts of carefully controlled clinical trials have not been reported, preliminary communications indicate these drugs are effective in epileptic patients.[21]

We now disclose a third group of (arylalkyl)imidazole anticonvulsants—the (fluorenylalkyl)imidazoles. In this report we detail the anticonvulsant structure–activity relationships (SAR) of the (fluorenylalkyl)imidazoles and describe some preliminary aspects of their pharmacology.

Results

Chemistry. The majority of these anticonvulsants were prepared by α-bromination of the appropriate arylethanone, followed by reaction with an excess of imidazole as described by Walker[18] (Scheme I, **7**, **8**, **27**). The overall yields for these two steps were usually on the order of 50% (see Experimental Section). However, employing 1-acetylimidazole in the latter reaction would obviate the need for a large excess of imidazole and preclude formation of 1,3-disubstituted imidazolium salts.[14,22] Alternatively,

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(16) Graziani, G.; Cazzulani, P.; Luca, C.; Nava, G.; Testa, R. *Arzneim.-Forsch./Drug Res.* **1983**, *33*, 1161.

(17) Graziani, G.; Barbadoro, E.; Testa, R. *Arzneim.-Forsch./Drug Res.* **1983**, *33*, 1168.

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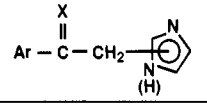
Table I. Structure and Properties of (Arylalkyl)imidazoles



no.	Ar	X	imidazole position	recryst solvent	mp, °C	formula	anal.
6 (nafimidone)	naphthalen-2-yl	O	1	$EtOH/Et_2O$	218–220[a]	$C_{15}H_{12}N_2O\cdot HCl$	C, H, N
5 (denzimol)	4-(2-phenethyl)phenyl	H, OH	1	$EtOH/H_2O$	159–161[b]	$C_{19}H_{20}N_2O$	C, H, N
18	benzo[*b*]thien-2-yl	O	1	Me_2CO/Et_2O	241–243	$C_{13}H_{10}N_2OS\cdot HCl$	C, H, N, Cl
19	benzo[*b*]thien-3-yl	O	1	Me_2CO/Et_2O	217–219	$C_{13}H_{10}N_2OS\cdot HCl$	C, H, N, Cl
20	benzofuran-2-yl	O	1	$EtOH/Et_2O$	212–215	$C_{13}H_{10}N_2O_2\cdot HCl$	C, H, N, Cl
21	phenanthren-2-yl	O	1	$EtOH/H_2O$	300 dec	$C_{19}H_{14}N_2O\cdot HCl$	C, H, N, Cl
22	phenanthren-3-yl	O	1	$EtOH/H_2O$	267–269	$C_{19}H_{14}N_2O\cdot HCl$	C, H, N, Cl
23	9,10-dihydrophenanthren-2-yl	O	1	Me_2CO/Et_2O	229–231	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N, Cl
24	9,10-dihydrophenanthren-3-yl	O	1	Me_2CO/Et_2O	204–206	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N, Cl
25	naphthalen-2-yl	H, H	1	THF/hexane	97–98	$C_{15}H_{14}N_2$	*c*
26	naphthalen-2-yl	H, H	2	THF/hexane	160–161	$C_{15}H_{14}N_2$	C, H, N

[a] Lit.[18] mp 226–228.5 °C. [b] Lit.[14] mp 165–166 °C. [c] Calcd: C, 81.05; H, 6.35; N, 12.60. Found: C, 79.96; H, 6.17; N, 11.97.

the haloacetyl moiety could be directly incorporated into the molecule by Friedel–Crafts acylation with chloroacetyl chloride and aluminum chloride (e.g., **9** to **10**). After introduction of the imidazole moiety, the ketone (e.g., **27**, LY175644) could be modified by standard functional group manipulation to prepare ketals (e.g., **47**), alcohols (e.g., **41**), and α-alkyl ketones (e.g., **53**). However, we were unable to perform Grignard chemistry on the ketones due to their insolubility in ethereal solvents. Consequently, the tertiary alcohol **46** (LY177165) was prepared by treating 2-chloro-1-(9*H*-fluoren-2-yl)ethanone (**10**) with methylmagnesium chloride, followed by reaction of the resulting β-hydroxyalkyl chloride **11** with the sodium salt of imidazole (Scheme I).

Homologues of **27** were examined, and the synthesis of these compounds is depicted in Scheme II. The homologue **43** was prepared by formation of the Mannich base **13** from 1-(9*H*-fluoren-2-yl)ethanone (64%), quaternarization with iodomethane, and then reaction with an excess of imidazole (88%, two steps). Compound **45** was obtained by the following four-step sequence: 2-Fluorenecarboxaldehyde (**12**) was treated with cyclopropylmagnesium bromide (67%). The resulting carbinol was oxidized with pyridinium dichromate (50%) to the corresponding cyclopropyl ketone **14**. Sequential reaction with iodotrimethylsilane and imidazole provided **45**.[23]

Finally, **26**, a 2-(arylalkyl)imidazole analogue of nafimidone, was prepared, and the synthesis is outlined in Scheme III. Reaction of 3-(2-naphthalenyl)propanenitrile (**15**) with hydrogen chloride and ethanol provided imidate ester **16**, which was then treated with 2-aminoacetaldehyde diethyl acetal to form amidine **17**. The imidazole ring was then formed by reaction with 6 N hydrochloric acid.[24] The overall yield of **26** from nitrile **17** was 54%.

Structure–Activity Relationships. Aryl Moiety Variations. From denzimol[14] and nafimidone[18] SAR studies, we hypothesized that the anticonvulsant pharmacophore was the alkylimidazole moiety, with the lipophilic aryl portion of the molecule enabling penetration of the blood–brain barrier. To test this hypothesis, we prepared several planar, lipophilic analogues of nafimidone and tested their ability to antagonize maximal electroshock (MES) seizures in mice. For comparative purposes we also examined nafimidone and denzimol. The fluorenyl ketone **27** (Table II) proved to be twice as potent as nafimidone; after oral administration the ED_{50}'s were 25 and 56 mg/kg, respectively (Table III). The literature MES ED_{50} for nafimidone is 48 mg/kg.[18] Compound **27** displayed no activity against pentylenetetrazole (scPTZ)-induced clonic seizures up to an oral dose of 200 mg/kg. Furthermore, oral administration of up to 800 mg/kg did not impair motor function of mice in the horizontal screen test. Also prepared were benzo[*b*]thienyl analogues **18** and **19** and the benzofuran **20** (Table I); the benzofuran was the most potent of the three and had an oral ED_{50} of 30 mg/kg (Table III).

Because of the highly selective anticonvulsant activity of the tricyclic compound **27**, we determined the effects on anticonvulsant activity of altering the five-membered central ring (Table I). Expansion of the central ring to six members proved to be deleterious; both of the planar phenanthrenes **21** and **22** were less active (ED_{50}'s = 150 and 52 mg/kg, respectively) than the fluorene **27**. Moreover, hydrogenation to the 9,10-dihydrophenanthrene analogues **23** and **24** failed to achieve activity comparable to that of **27**.

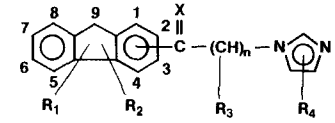
Fluorenyl Modifications. On the basis of these SAR findings and the encouraging preliminary pharmacology of **27**, this fluorenyl compound was selected for further structural modification (Table II). Shifting the alkylimidazole pharmacophore to the 1-position of the fluorene maintained or slightly improved activity (**28**), whereas the 4-fluorenyl analogue **29** was less active (Table III; ED_{50}'s = 19 and 44 mg/kg, respectively). Addition of one or two methyl substituents at the 9-position of the fluorene decreased activity. These data indicate that the inferiority of etheno or ethano bridges between the two conjugated benzene rings (vide supra, phenanthrene or dihydrophenanthrene, respectively) relative to the methano bridge (fluorene) may stem from their greater steric bulk. A series of analogues of **27** substituted in the synthetically accessible 7-position of the fluorene nucleus was studied (compounds **32–36**, Table III). Inclusion of a methoxy, alkyl, or bromo substituent at this position was detrimental.

Imidazole and Alkyl Modifications. The imidazole was necessary for highest levels of anticonvulsant activity; the ED_{50} of tertiary amine **13** (Scheme II) was 100 mg/kg. An alkyl substituent at the 2-position of the imidazole (**37** and **38**) or alkyl (**39**) or phenyl (**40**) substituents at the 4-position invariably diminished activity (Table III). For example, **37**, the 2-methyl analogue (ED_{50} = 210 mg/kg), was only one-tenth as active as **27**. It is of interest that substituents at the 2- or 4-positions were found to decrease

(23) For the ring-opening reaction of electrophilic cyclopropanes with iodotrimethylsilane, see: Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412.

(24) For a discussion, see: Grimmett, M. R. In *Comprehensive Organic Chemistry*; Sammes, P. G.; Ed.; Pergamon: Oxford, 1979; Vol. 4, pp 397–398.

Table II. Structure and Properties of (Fluorenylalkyl)imidazoles



no.	X	fluorenyl	R_1	R_2	R_3	R_4	n	recryst solvent	mp, °C	formula	anal.
27	O	2	H	H	H	H	1	EtOH	212–213	$C_{18}H_{14}N_2O$	C, H, N
28	O	1	H	H	H	H	1	Me_2CO/Et_2O	274–275	$C_{18}H_{14}N_2O\cdot HCl$	C, H, N, Cl
29	O	4	H	H	H	H	1	Me_2CO/Et_2O	267.5–268.5	$C_{18}H_{14}N_2O\cdot HCl$	*a*
30	O	2	9-CH_3	H	H	H	1	Me_2CO	265–266.5	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N, Cl
31	O	2	9-CH_3	9-CH_3	H	H	1	Me_2CO/Et_2O	252–253 dec	$C_{20}H_{18}N_2O\cdot HCl$	C, H, N, Cl
32	O	2	7-OCH_3	H	H	H	1	Me_2CO/MeOH	242.5–245 dec	$C_{19}H_{16}N_2O_2\cdot HCl$	*b*
33	O	2	7-CH_3	H	H	H	1	Me_2CO	263–264.5	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N
34	O	2	7-C_2H_5	H	H	H	1	Me_2CO/MeOH	260–261	$C_{20}H_{18}N_2O\cdot HCl$	C, H, N, Cl
35	O	2	7-$(CH_3)_2CH$	H	H	H	1	Me_2CO/MeOH	237–239 dec	$C_{21}H_{20}N_2O\cdot HCl$	C, H, N, Cl
36	O	2	7-Br	H	H	H	1	MeOH	282–286 dec	$C_{18}H_{13}BrN_2O\cdot HCl$	C, H, N, Cl
37	O	2	H	H	H	2-CH_3	1	Me_2CO/Et_2O	275–276 dec	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N
38	O	2	H	H	H	2-C_2H_5	1	EtOAc/hexane	148–150	$C_{20}H_{18}N_2O$	C, H, N
39	O	2	H	H	H	4-CH_3[c]	1	Me_2CO/MeOH	265 dec	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N
40	O	2	H	H	H	4-C_6H_5[c]	1	$CHCl_3$	214–217	$C_{24}H_{18}N_2O$	C, H, N
41	OH, H	2	H	H	H	H	1	THF/hexane	196–199	$C_{18}H_{16}N_2O$	C, H, N
42	H, $OCOC_6H_5$	2	H	H	H	H	1	Me_2CO/ether	221–222	$C_{25}H_{20}N_2O_2\cdot HCl$	C, H, N, Cl
43	O	2	H	H	H	H	2	Me_2CO/MeOH	200–202 dec	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N
44	OH, H	2	H	H	H	H	2	toluene/EtOH	143–145	$C_{19}H_{18}N_2O$	C, H, N
45	O	2	H	H	H	H	3	Me_2CO	236–237	$C_{20}H_{18}N_2O\cdot HCl$	C, H, N, Cl
46	CH_3, OH	2	H	H	H	H	1	THF/hexane	183–184	$C_{19}H_{18}N_2O$	C, H, N
47	$-SCH_2CH_2S-$	2	H	H	H	H	1	Me_2CO	248	$C_{20}H_{18}N_2S_2\cdot HCl$	C, H, N
48	$-OCH_2CH_2O-$	2	H	H	H	H	1	Me_2CO	163–166	$C_{20}H_{18}N_2O_2$	C, H, N
49	$-OCH_2CH_2CH_2O-$	2	H	H	H	H	1	Me_2CO/MeOH	259 dec	$C_{21}H_{20}N_2O_2\cdot HCl$	C, H, N, Cl
50	$-OCH(CH_3)CH_2O-$	2	H	H	H	H	1	Me_2CO	139–144	$C_{21}H_{20}N_2O_2$	*d*
51	$-OCH_2C(CH_3)_2CH_2O-$	2	H	H	H	H	1	Me_2CO	187–189	$C_{23}H_{24}N_2O_2$	C, H, N
52	$-OCH_2CH_2O-$	2	H	H	H	H	2	EtOAc/MeOH	180–185 dec	$C_{21}H_{20}N_2O_2$	C, H, N
53	O	2	H	H	α-CH_3	H	1	Me_2CO/Et_2O	237–238.5	$C_{19}H_{16}N_2O\cdot HCl$	C, H, N, Cl
54	O	2	H	H	α-C_2H_5	H	1	Me_2CO/Et_2O	209–211	$C_{20}H_{18}N_2O\cdot HCl$	C, H, N, Cl
55	H, H	2	H	H	H	H	1	THF/hexane	130–131	$C_{18}H_{16}N_2$	C, H, N

[a] Calcd: C, 69.79; H, 4.56; N, 9.04; Cl, 11.44. **Found**: C, 68.52; H, 5.07; N, 8.81; Cl, 13.47. [b] Calcd: C, 66.96; H, 5.03; N, 8.22; Cl, 10.40. **Found**: C, 66.19; H, 4.97; N, 7.61; Cl, 9.39. [c] Complete isomeric purity of isolated material was confirmed by the method of Rapoport (ref 52). [d] Calcd: C, 75.88; H, 6.06; N, 8.43. Found: C, 73.70; H, 6.35, N, 7.64.

Table III. Biological Activities of (Arylalkyl)imidazoles following Oral Administration to Mice

no.	TPE,[a] h	MES[b] ED_{50}, mg/kg	HS[c] ED_{50}, mg/kg	sc PTZ[d] ED_{50}, mg/kg	hexobarb ST,[e] min
nafimidone	1.0	56 (45–71)[f]	NE[g] (400)	>400	59.1 ± 4.3
denzimol	1.0	12 (9.3–15)	NE (100)	50 (max)[h]	157.4 ± 7.7[j]
18	1.0	86 (71–103)	>400	>400	
19	1.0	59 (48–72)	NE (400)	>400	
20	1.5	30 (27–34)	NE (300)	>400	110.5 ± 12.0[j]
21	1.0	150 (120–180)	>400	NE (400)	
22	1.0	52 (45–60)	>400	NE (400)	
23	2.0	60 (47–77)	ca. 550	NE (400)	
24	1.0	71 (58–87)	NE (400)	>400	
25	1.0	51 (35–75)	NE (200)	NE (200)	
26	1.0	NE (300)	NT[i]	NE (100)	
27	3.0	25 (19–32)	>1000	>200	73.7 ± 3.4[j]
28	2.0	19 (15–25)	>100	>200	
29	1.0	44 (32–60)	>400	ca. 400	
30	2.0	33 (28–39)	NE (200)	NE (200)	69.7 ± 4.1[j]
31	1.0	48 (33–70)	>400	>400	
32	2.0	360 (250–510)	NE (400)	NE (800)	56.9 ± 2.8
33	2.0	68 (50–93)	NE (400)	NE (400)	
34	1.0	240 (180–320)	NE (400)	>400	
35	2.0	190 (120–130)	NE (400)	NE (400)	
36	2.0	79 (60–100)	NE (400)	NE (400)	
37	1.0	210 (160–280)	>400	NT	
38	2.0	190 (130–280)	>400	>400	
39	1.0	90 (74–110)	>400	NE (400)	
40	2.0	NE (800)	NE (800)	NE (800)	
41	1.0	22 (17–28)	NE (200)	ca. 400	118.3 ± 12.6[j]
42	1.0	32 (21–49)	NE (400)	>400	
43	1.0	19 (16–22)	>200	>100	
44	1.0	33 (27–39)	>400	NE (400)	75.0 ± 5.5[j]
45	0.5	27 (19–39)	NE (200)	NE (200)	
46	2.0	10 (8.4–12)	NE (400)	NE (400)	146.9 ± 12.4[j]
47	2.0	41 (31–54)	>400	NE (400)	
48	4.0	23 (17–31)	>100	NE (100)	88.7 ± 5.8[j]
49	1.0	32 (20–50)	>400	NE (400)	
50	2.0	21 (16–27)	>400	>200	
51	2.0	65 (56–77)	NE (200)	NE (200)	
52	1.0	26 (18–39)	NE (400)	>400	
53	1.5	35 (27–45)	>400	260	103.0 ± 7.14[j]
54	1.0	50 (34–74)	NE (400)	>400	
55	2.0	17.8 (15–22)	NE (100)	>200	

[a] TPE = time to peak anticonvulsant effect. [b] MES = maximal electroshock assay. [c] HS = horizontal screen test. [d] sc PTZ = subcutaneous pentylenetetrazole assay. [e] Hexobarb ST = hexobarbital-induced sleeping time assay. A hypnotic dose of hexobarbital (100 mg/kg, ip) was administered at the time of peak effect of the test compound. Test compounds were administered at 10 mg/kg, po, and reported values are the mean ±SEM for 10 animals. In this experiment, control animals slept 48.6 ± 5.2 min. [f] Values in parentheses represent 95% confidence limits. [g] NE = no effect at the highest dose tested as indicated in parentheses. [h] Bell-shaped dose–response curve. Maximum protection achieved at indicated dose. [i] NT = not tested. [j] $p < 0.05$.

the inhibition of cytochrome P-450 by 1-substituted imidazoles.[25] The ketone could be modified considerably while still maintaining anticonvulsant activity. Secondary alcohol **41** (ED_{50} = 22 mg/kg) had activity comparable to ketone **27**, as did homologated compounds **43** and **45** (ED_{50}'s = 19 and 27 mg/kg, respectively). Addition of a methyl substituent to form tertiary alcohol **46** led to a significant increase in activity (ED_{50} = 10 mg/kg). Ketalization also furnished active compounds (**47–52**), but sterically demanding and/or lipophilic ketals displayed decreased activity (e.g., **51**, ED_{50} = 65 mg/kg). Alkylation α to the ketone (e.g., **53** and **54**) led to diminished anticonvulsant activity. Compound **55** demonstrated that absence of an oxygen substituent in the alkyl bridge did not lower intrinsic activity (ED_{50} = 17.8 mg/kg).

Finally, 1-substituted imidazoles were essential for activity. To probe this aspect of the SAR and to determine if anticonvulsant and sleeping time (vide infra) activities could be dissociated, we examined the 1- and 2-substituted imidazoles **25** and **26** (Table I). The 1-substituted (naphthalenylethyl)imidazole **25** had an ED_{50} of 51 mg/kg, which is comparable to the reported value.[18] In dramatic contrast, the isomeric 2-substituted (naphthalenylethyl)imidazole **26** was completely inactive at 300 mg/kg.

Potentiation of Hexobarbital-Induced Sleeping Time. 1-Alkyl- or 1-aryl-substituted imidazoles are often potent inhibitors of cytochrome P-450;[25–27] consequently we examined the effects of some of these imidazole anticonvulsants on hexobarbital-induced sleeping time in mice. All active imidazole anticonvulsants that we tested potentiated hexobarbital-induced sleeping time. Eleven compounds were tested orally at 10 mg/kg (Table III), and the most potent anticonvulsants produced the greatest increases in hexobarbital-induced sleeping time. The dose-dependent nature of this phenomenon was demonstrated with several compounds, and results obtained with **46** are illustrative (Figure 1). A hypnotic dose of hexobarbital (100 mg/kg, ip) was administered 1 h following oral administration of 0–10 mg/kg of **46**, and the imidazole anticonvulsant was found to profoundly increase hexobarbital-induced sleeping time. Whereas control animals slept 50 ± 6 min, animals that received 10 mg/kg (the

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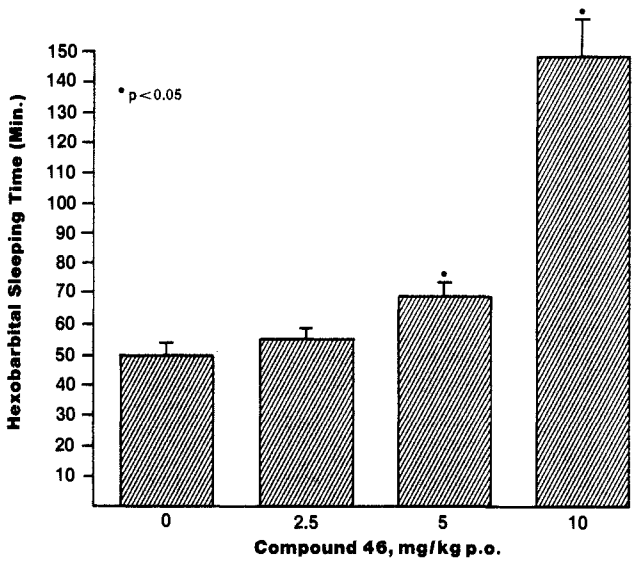

Figure 1. Dose-dependent effects of **46** on hexobarbital-induced sleeping time in mice. A hypnotic dose of hexobarbital (100 mg/kg, ip) was administered 1 h following administration of the indicated doses of **46**. The duration of loss of righting reflex was monitored. Values are the mean ± SEM for 10 animals. In this experiment control animals slept 50.0 ± 6.0 min.

Table IV. Effects on [^{3}H]Flunitrazepam Labeling in Vitro and in Vivo[a]

compd	% of control	
	in vitro	in vivo
nafimidone	102.0 ± 1.2	116 ± 4
20	99.1 ± 1.0	142 ± 3[b]
21	128.0 ± 1.0[b]	128 ± 6[c]
22	123.2 ± 1.2[b]	121 ± 5[b]

[a] Compounds were tested in triplicate samples at 5×10^{-5} M in vitro and at a dose of 20 mg/kg, ip, in groups of five rats in vivo as described in the text. Means ±SEM in percent of control are presented with statistical significance as indicated (b, $p < 0.001$; c, $p < 0.005$).

approximate anticonvulsant ED_{50}) of **46** slept 147 ± 12 min. The 18-min increase in sleeping time after administration of 5 mg/kg of **46** was also significant ($p < 0.05$). Denizmol (10 mg/kg) produced a 109-min increase in sleeping time (Table III), and the well-studied metabolic inhibitor cimetidine,[28,29] at a dose of 50 mg/kg, produced a 21-min increase in sleeping time (data not shown).

Effects on [^{3}H]Flunitrazepam Binding. We have conducted preliminary experiments to determine if these imidazole anticonvulsants have an impact on the binding of [^{3}H]flunitrazepam in vitro or in vivo, and the results are summarized in Table IV. Nafimidone (20 mg/kg, ip) increased labeling of the particulate fraction of rat cortical homogenate in vivo, but the enhancement was not statistically significant. Compounds **21** and **22**, at 50 μM, significantly enhanced [^{3}H]flunitrazepam binding to cortical membranes in vitro by 28% and 23%, respectively; **20** had no effect. Following ip administration of 20 mg/kg, all three compounds enhanced benzodiazepine binding in vivo, and **20**, the most potent anticonvulsant examined, was particularly efficacious (42% increase relative to control).

Toxicity. We compared the acute toxicity in rats of **27**, a representative compound from the fluorenyl series, and nafimidone (refer to Experimental Section for protocol). The oral LD_{50} of **27** was estimated to be 4550 mg/kg, whereas that of nafimidone was 504 mg/kg.

Discussion

These SAR studies revealed that in addition to the naphthalenyl and phenethylphenyl aryl moieties of nafimidone and denzimol, respectively, fluorenyl, benzo[*b*]-thienyl, and benzofuranyl aryl groups provided several highly active (arylalkyl)imidazole anticonvulsants. These structurally diverse aryl moieties and comparable anticonvulsant activities lend credence to the hypothesis that the pharmacophore in this class of anticonvulsants is the alkylimidazole portion of the molecule, with the lipophilic aryl portion enabling penetration of the blood–brain barrier.

We focused our SAR studies on the (fluorenylalkyl)-imidazole series. A representative compound from this series was 1-(9*H*-fluoren-2-yl)-2-(1*H*-imidazol-1-yl)ethanone (**27**). This agent was twice as potent as nafimidone in inhibiting maximal electroshock seizures in mice (po ED_{50}'s = 25 and 56 mg/kg, respectively) and considerably less toxic in the rat (po LD_{50}'s = ca. 4550 and 504 mg/kg, respectively). The tertiary alcohol α-(9*H*-fluoren-2-yl)-α-methyl-1*H*-imidazole-1-ethanol (**46**) was as potent as denizmol in mice (po ED_{50}'s = 10 and 12 mg/kg, respectively). Other modifications of **27**, including homologation, α-alkylation, formation of ketals, reduction to the secondary alcohol, or complete removal of the oxygen, furnished active anticonvulsants, but no compound was more potent than the teritary alcohol **46**. Substitutions at the synthetically accessible 7- or 9-positions of the fluorene were not well-tolerated.

One of the impressive features of the imidazole anticonvulsants is their high degree of selectivity. While many displayed potent antielectroshock activity, little or no activity was observed against pentylenetetrazole-induced clonic seizures or in the horizontal screen test for ataxia. Moreover, other investigators have reported little activity of this class of anticonvulsants against a variety of chemically induced seizures.[15]

All active compounds that we tested in this series, as well as denzimol and nafimidone, were potent potentiators of hexobarbital-induced sleeping time in mice, probably by the well-known imidazole-mediated inhibition of cytochrome P-450.[25-27] Nafimidone and its reduced metabolite, nafimidone alcohol, were recently shown to inhibit cytochrome P-450 mediated metabolism of phenytoin and carbamazepine in vitro.[30,31] In our studies, significant effects on sleeping time occurred at doses below the anticonvulsant ED_{50}'s. The most potent anticonvulsant of the series, **46**, was 10-fold more potent than cimetidine as a potentiator of hexobarbital sleeping time. Anticonvulsant and sleeping time potentiation SAR's were parallel with the most potent anticonvulsants being the most potent potentiators of hexobarbital-induced sleeping time. The correlation between MES log ED_{50}'s and percent increases in hexobarbital-induced sleeping times was highly significant ($p < 0.005$). Moreover, alkyl substituents at the 2- and 4-positions of the imidazole ring or transferring the arylalkyl moiety from the 1- to the 2-position of the imidazole produced significant decreases in the potency of the compounds as anticonvulsants; similar SAR results have been reported for the imidazole-mediated inhibition

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of cytochrome P-450.[25] Our studies indicate, therefore, that the anticonvulsant and hexobarbital sleeping time effects, if separable, will be dissociated only with difficulty.

The molecular mechanism of action of most anticonvulsants is still enigmatic. However, some specific receptor interactions are being discovered. For example, phenytoin increases the number of benzodiazepine binding sites in the CNS, and this phenomenon may be responsible for the ability of phenytoin to potentiate the anticonvulsant activities of diazepam.[32] Moreover, the anticonvulsant 1-[5,6-bis(4-tolyl)-*as*-triazin-3-yl]-4-piperidinol (LY81067) increases the labeling of benzodiazepine receptors in vitro.[33] In the present study we have demonstrated that several imidazole anticonvulsants promote the binding of [^{3}H]-flunitrazepam both in vitro and in vivo. After our studies were completed, Mennini and co-workers[34] reported that administration of denzimol to rats increased the number of [^{3}H]flunitrazepam binding sites in cortex and hippocampus but not in cerebellum. Further studies are needed to define the relationship, if any, between enhancement of benzodiazepine binding and anticonvulsant activity for the (arylalkyl)imidazole anticonvulsants.

Regardless of their mechanism of action, the pharmacological profiles of these highly selective anticonvulsants portend utility in the clinical management of generalized tonic-clonic, complex partial, and simple partial seizures.[21] However, the propensity of these (arylalkyl)imidazole anticonvulsants to interact strongly with P-450 and thereby profoundly impair the metabolism of other antiepileptic drugs may severely limit their clinical utility; concomitant administration of these imidazoles with phenytoin, phenobarbital, or carbamazepine may lead to intoxication with the latter compounds.[30,35] The imidazole cimetidine, which is considerably less potent as a metabolic inhibitor than denzimol or **46**, has a definite impact on clinical pharmacokinetics of phenytoin, carbamazepine, and sodium valproate.[36-40] Moreover, preliminary reports indicate that nafimidone and denzimol markedly inhibit the metabolism of carbamazepine and phenytoin in man.[41-44] If it were possible to separate the CNS and cytochrome P-450 effects of these highly selective and potent anticonvulsants, it could represent a significant advance in pharmacological management of epilepsy.

Experimental Section

Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H NMR) spectra were taken on a Bruker WM-270 spectrometer. Chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). The ^{1}H NMR data are presented in the form: (solvent in which spectra were taken), δ value of signal (peak multiplicity, integrated number of protons and assignment). Mass spectra were recorded from a Varian MAT CH-5 spectrometer, at the ionization voltage expressed in parentheses. Only the peaks of high relative intensity or of diagnostic importance are presented in the form: m/e (intensity relative to base peak). Microanalytical data were provided by the Physical Chemistry Department of the Lilly Research Laboratories; only symbols of elements analyzed are given and they were within 0.4% of theoretical values unless indicated otherwise.

Except where noted, a standard procedure was used for product isolation. This involved quenching by addition to water, filtration or exhaustive extraction with a solvent (washing of extract with aqueous solutions, on occasion), drying over an anhydrous salt, the evaporation of solvent under reduced pressure. Particular solvents, aqueous washes (if needed), and drying agents are mentioned in parentheses after the phrase "product isolation".

Most of the starting materials are commercially available or are well-known in the literature. The method of Gray[45] was used to prepare 2-methoxy-9*H*-fluorene from 2-hydroxy-9*H*-fluorene.[46]

Syntheses of (Fluorenylalkyl)imidazoles. The following procedures illustrate the synthetic methods used in this study.

1-(9*H*-Fluoren-1-yl)ethanone. Methyllithium (2 mol of a 6 M solution in ether) was added slowly to a solution of 9*H*-fluorene-1-carboxylic acid (108 g, 514 mmol) in 2 L of THF at −78 °C. The reaction was stirred at room temperature for 3 h and then poured into 3 L of water. Product isolation (ethyl acetate, Na_2SO_4) and chromatography over silica gel afforded 41 g (38%) of homogeneous product. The analytical sample was recrystallized from ethyl acetate/hexane: mp 84–87 °C. Anal. ($C_{15}H_{12}O$) C, H.

9-Methyl-9*H*-fluorene. A solution of *n*-butyllithium (120.5 mL of a 1.6 M solution in hexane, 199 mmol) was added in a dropwise fashion to a solution of fluorene (30 g, 180 mmol) in 500 mL of THF at −78 °C. After stirring for 30 minutes, the reaction mixture was added to a solution of methyl iodide (56.2 mL, 902 mmol) in 60 mL of THF at −78 °C. The reaction was stirred for 30 min at −78 °C and then overnight at room temperature. Product isolation (ethyl acetate, water, brine, $MgSO_4$) and recrystallization from methanol provided 26.5 g (81.4%) of 9-methyl-9*H*-fluorene, mp 44–45 °C (lit.[47] mp 46–47 °C). Anal. ($C_{14}H_{12}$) C, H.

2-Methyl-9*H*-fluorene. A mixture of 9*H*-fluorene-2-carboxaldehyde (20 g, 100 mmol), 2 g of 5% palladium on carbon, and 1 mL of concentrated hydrochloric acid in 127 mL of acetic acid was hydrogenated in a Parr apparatus at room temperature overnight. The reaction mixture was filtered through Celite and the filtrate was poured into water. The resulting solid was recovered by filtration and dissolved in ethyl acetate. Product isolation (water, brine, $MgSO_4$) afforded 17.98 g (97%) of homogeneous product with the following: mp 90–93 °C (lit.[48] mp 104–105 °C); ^{1}H NMR (Me_2SO-d_6) δ 2.38 (s, 3, CH_3), 3.86 (s, 2, fluorenyl CH_2), 7.18–7.86 (m, 7, Ar H); mass spectrum (70 eV), m/e (relative intensity) 180 (98, M^+), 165 (100).

2-Ethyl-9*H*-fluorene. This intermediate was prepared from 1-(9*H*-fluoren-2-yl)ethanone following the procedure for the preparation of 2-methyl-9*H*-fluorene. Recrystallization from ethyl acetate/hexane afforded product (74.2%) with mp 96–98 °C. Anal. ($C_{15}H_{14}$) C, H.

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2-(9*H*-Fluoren-2-yl)-2-propanol. Methylmagnesium chloride (125.2 mL of a 2.9 M solution in THF, 363 mmol) was added to a solution of 1-(9*H*-fluorene-2-yl)ethanone (25.2 g, 121 mmol) in 375 mL THF at 0 °C. After the mixture was stirred for 1 h, the reaction was quenched by the dropwise addition of saturated ammonium chloride. Product isolation and recrystallization from ethyl acetate/hexane provided 22.37 g (83%) of product with mp 122–123 °C. Anal. ($C_{16}H_{16}O$) C, H.

2-Isopropyl-9*H*-fluorene. This intermediate was prepared from 2-(9*H*-fluoren-2-yl)-2-propanol following the procedure for the preparation of 2-methyl-9*H*-fluorene. Recrystallization from ethyl acetate/hexane afforded product (92%) with mp 78–79.5 °C. Anal. ($C_{16}H_{16}$) C, H.

2-Chloro-1-(7-methyl-9*H*-fluoren-2-yl)ethanone. A solution of 2-methyl-9*H*-fluorene (8.74 g, 48 mmol) in 100 mL of methylene chloride was cooled to 0 °C. Anhydrous aluminum chloride (9.05 g, 70 mmol) was added, and after 15 min of stirring, 5.4 mL (70 mmol) of chloroacetyl chloride was added in a dropwise fashion. After stirring 15 min at 0 °C and 45 min at room temperature, the mixture was poured into a mixture of 1 L of ice and 200 mL of hydrochloric acid. Product isolation (methylene chloride, water, brine, $MgSO_4$) afforded chromatographically homogeneous product.

2-Bromo-1-(9*H*-fluoren-2-yl)ethanone (8). A slurry of cupric bromide (107.25 g, 480 mmol) in 1 L of ethyl acetate was heated to reflux. A solution of 1-(9*H*-fluoren-2-yl)ethanone (50 g, 240 mmol) in 500 mL of chloroform was added over 15 min. The reaction was heated at reflux for 3.5 h and then filtered while still hot through a Celite pad. The filter cake was washed with ethyl acetate and the combined filtrate was evaporated in vacuo to provide 68.4 g of 8, which was used without further purification in the following reaction.

1-(9*H*-Fluoren-2-yl)-2-(2-methyl-1*H*-imidazol-1-yl)-ethanone Hydrochloride (37). A solution of 8 (12.0 g, 41.8 mmol) in 150 mL of DMF was rapidly added to a solution of 2-methylimidazole (24 g, 290 mmol) in 150 mL of DMF at 0 °C. The homogeneous reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was poured into water containing 1 equiv of sodium hydroxide. The resulting precipitate was filtered and the filtrate was extracted with ethyl acetate. The ethyl acetate solution was washed first with water and then with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was combined with the filtered precipitate and dissolved in hot acetone. Three equivalents of hydrochloric acid was added, and upon addition of diethyl ether, 6.65 g (49%) of product was obtained with mp 275–276 °C. Anal. ($C_{19}H_{16}N_2O$·HCl) C, H, N.

α-(9*H*-Fluoren-2-yl)-1*H*-imidazole-1-ethanol (41). Sodium borohydride (2 g, 52.85 mmol) was added in portions to a stirred suspension of 2-(1*H*-imidazol-1-yl)-1-(9*H*-fluoren-2-yl)ethanone (10 g, 36.5 mmol) in 100 mL of ethanol at room temperature. After 1 h, the reaction mixture was poured into 700 mL of water and the resulting precipitate was recovered by filtration. Crystallization of the solid from THF/hexane provided 9.7 g (96%) of product: mp 196–199 °C. Anal. ($C_{18}H_{16}N_2O$) C, H, N.

α-(9*H*-Fluoren-2-yl)-1*H*-imidazole-1-ethanol Benzoate Ester Hydrochloride (42). A mixture of α-(9*H*-fluoren-2-yl)-1*H*-imidazole-1-ethanol (9.0 g, 32.61 mmol) and benzoic anhydride (9.59 g, 42.4 mmol) in 200 mL of pyridine was heated at 55 °C for 5 h and then poured into water. Product isolation (ethyl acetate, brine, Na_2SO_4) and recrystallization from acetone/diethyl ether/hydrochloric acid provided 9.2 g (68%) of product: mp 221–222 °C. Anal. ($C_{25}H_{20}N_2O_2$·HCl) C, H, N, Cl.

3-(Dimethylamino)-1-(9*H*-fluoren-2-yl)-1-propanone Hydrochloride (13). A mixture of 1-(9*H*-fluoren-2-yl)ethanone (2.0 g, 9 mmol), paraformaldehyde (2.15 g), dimethylamine hydrochloride (3.07 g, 29 mmol), and concentrated hydrochloric acid (1 mL) in 100 mL of absolute ethanol was heated to reflux for 48 h. Upon cooling, the product was filtered and dried to yield 1.85 g (64%) of product with mp 192–193 °C. Anal. ($C_{18}H_{19}NO$·HCl) C, H, N.

1-(9*H*-Fluoren-2-yl)-3-(1*H*-imidazol-1-yl)-1-propanone Hydrochloride (43). To a solution of 3-(dimethylamino)-1-(9*H*-fluoren-2-yl)-1-propanone (8.8 g, 33 mmol) in diethyl ether was added methyl iodide (10 mL, 160 mmol). After the mixture was stirred for 3 h, the resulting precipitate (10.5 g) was filtered and added to a solution of imidazole (12.3 g, 180 mmol) in 100 mL of DMF. The solution was heated to 65 °C overnight and then poured into 1 L of water. Filtration of the resulting precipitate and recrystallization from acetone/methanol/hydrochloric acid provided 7.4 g (88.4%) of product: mp 200–202 °C. Anal. ($C_{19}H_{16}N_2O$·HCl), C, H, N.

α-Cyclopropyl-9*H*-fluorene-2-methanol. A solution of 9*H*-fluorene-2-carboxaldehyde (25 g, 128.8 mmol) in 150 mL of THF was added in a dropwise fashion to a solution of cyclopropylmagnesium bromide (prepared from Mg (3.71 g, 154.6 mg-atom) and cyclopropyl bromide (18.6 g, 154.6 mmol)) in 125 mL of THF at 0 °C. After 1 h, saturated ammonium chloride was added carefully. Product isolation (ether, brine, Na_2SO_4) and chromatography over silica gel afforded 20.5 g (67%) of product as a homogeneous, light yellow solid: ^{1}H NMR (Me_2SO-d_6) δ 0.43 (m, 4, cyclopropyl CH_2's), 1.09 (m, 1, cyclopropyl CH), 3.88 (s, 2, fluorenyl CH_2), 4.05 (d, 1 CHO), 7.25–7.90 (m, 7, Ar H); mass spectrum (70 eV), *m/e* (relative intensity) 236 (59, M^+), 208 (100).

Cyclopropyl-9*H*-fluoren-2-ylmethanone (14). A solution of α-cyclopropyl-9*H*-fluorene-2-methanol (17 g, 72 mmol), pyridinium dichromate (40.6 g, 108 mmol), and pyridinium trifluoroacetate (5.6 g, 28.8 mmol) in 500 mL of methylene chloride was stirred at room temperature for 18 h. The reaction was diluted with 2 L of ether and filtered through a pad of $MgSO_4$. Removal of solvent in vacuo and chromatography over silica gel afforded 8.4 g (50%) of product: ^{1}H NMR ($CDCl_3$) δ 1.05 and 1.28 (m, 4, cyclopropyl CH_2's), 2.75 (m, 1, cyclopropyl CH), 3.97 (s, 2, fluorenyl CH_2), 7.36–8.20 (m, 7, Ar H); mass spectrum (70 eV), m/e (relative intensity) 234 (100, M^+).

1-(9*H*-Fluoren-2-yl)-4-iodobutanone. Iodotrimethylsilane (6.15 g, 30.8 mmol) was added in a dropwise fashion to cyclopropyl-9*H*-fluoren-2-ylmethanone (6 g, 25.6 mmol) in 500 mL of carbon tetrachloride at −10 °C. After 1 h, the reaction was warmed to room temperature and stirred for an additional 1.5 h. Product isolation (2 L of ether, 1 M sodium sulfite, brine, $MgSO_4$) afforded 9.3 g (100%) of product: ^{1}H NMR ($CDCl_3$) δ 2.29 (m, 2, CH_2CH_2I), 3.0–3.51 (m, 4 CH_2I and $COCH_2$), 3.99 (s, 2, fluorenyl CH_2), 7.25–8.17 (m, 7, Ar H).

1-[[2-(9*H*-Fluoren-2-yl)-1,3-dioxolan-2-yl]methyl]-1*H*-imidazole (48). To a mixture of 2-(1*H*-imidazol-1-yl)-1-(9*H*-fluoren-2-yl)ethanone (10 g, 36.5 mmol) in 100 mL of toluene were added ethylene glycol (4.53 g, 73 mmol), and *p*-toluenesulfonic acid (13.9 g, 73 mmol). The mixture was heated overnight at reflux with azeotropic removal of water. The reaction was poured into water and taken to basicity with 1 N sodium hydroxide. Product isolation (ethyl acetate, water, brine, Na_2SO_4) and recrystallization from acetone provided 8.64 g (75%) of product: mp 163–166 °C. Anal. ($C_{20}H_{18}N_2O_2$) C, H, N.

1-[[2-(9*H*-Fluoren-2-yl)-1,3-dithiolan-2-yl]methyl]-1*H*-imidazole Hydrochloride (47). To a solution of 2-(1*H*-imidazol-1-yl)-1-(9*H*-fluoren-2-yl)ethanone (10 g, 36.5 mmol) in 25 mL of methanesulfonic acid was added 1,2-ethanedithiol (12.2 mL, 146 mmol). After stirring overnight at room temperature, the reaction mixture was poured into water and the solution was made basic with sodium hydroxide. The resulting solid was recovered by filtration and recrystallized from acetone/hydrochloric acid to provide 10.16 g (72%) of product: mp 248 °C. Anal. ($C_{20}H_{18}N_2S_2$·HCl) C, H, N.

1-Chloro-2-(9*H*-fluoren-2-yl)-2-propanol (11). Methylmagnesium chloride (65.0 mL of a 2.9 N solution in THF, 188.5 mmol) was added in a dropwise fashion to a solution of 2-chloro-1-(9*H*-fluoren-2-yl)ethanone (15.0 g, 62.9 mmol) in 300 mL of THF at 0 °C. The reaction was stirred at room temperature for 2 h and then cooled to 0 °C. Ammonium chloride (200 mL of a 50% solution) was then added in a dropwise fashion. Product isolation (ethyl acetate, brine, Na_2SO_4) and silica gel chromatography provided 3.3 g (20.5%) of product: mp 65–68 °C.

1-(1*H*-Imidazol-1-yl)-2-(9*H*-fluoren-2-yl)-2-propanol (46). Imidazole (2.53 g, 37.1 mmol) was added to a mixture of sodium hydride (743 mg of a 60% dispersion in oil, 18.6 mmol) in 50 mL of dry DMF. After hydrogen evolution ceased, a solution of 1-chloro-2-(9*H*-fluoren-2-yl)-2-propanol (3.2 g, 12.4 mmol) in 50 mL of dry DMF was added. The mixture was heated to 60 °C for 1 h and then stirred overnight at room temperature. After heating an additional 2.5 h at 85 °C, the reaction mixture was poured into 700 mL of water. Product isolation (ethyl acetate,

water, brine, Na_2SO_4), chromatography over silica gel, and crystallization from THF/hexane provided 1.27 g (35%) of product: mp 183–184 °C. Anal. ($C_{19}H_{18}N_2O$) C, H, N.

2-(1*H*-Imidazol-1-yl)-1-(9*H*-fluoren-2-yl)-1-propanone Hydrochloride (53). A solution of 2-(1*H*-imidazol-1-yl)-1-(9*H*-fluoren-2-yl)ethanone (15.0 g, 54.7 mmol) in 250 mL of DMF was slowly added to a mixture of sodium hydride (1.34 g, 55.8 mmol) in 20 mL of DMF at 0 °C. After the mixture was stirred for 30 min at 0 °C, methyl iodide (7.9 g, 55.8 mmol) was added in one portion. The reaction was stirred at room temperature for 1 h and poured into water. Product isolation (ethyl acetate, brine, Na_2SO_4) and recrystallization from acetone/ether/hydrochloric acid provided 7 g (44%) of product: mp 237–238.5 °C. Anal. ($C_{19}H_{16}N_2O$·HCl) C, H, N, Cl.

3-(2-Naphthalenyl)propanenitrile (15). Methanesulfonyl chloride (9.45 mL, 122 mmol) was added in a dropwise fashion to a solution of triethylamine (17.0 mL, 122.1 mmol) and 2-(2-naphthalenyl)ethanol (20.0 g, 116 mmol) in 200 mL of THF at 0 °C. The reaction was stirred 3 h at room temperature, whereupon product isolation (water, ethyl acetate, water, brine, Na_2SO_4) provided 27.69 g (95.2%) of homogeneous product that was used directly in the next reaction: ^{1}H NMR (Me_2SO-d_6) δ 3.12 (s, 3, SO_2CH_3), 3.17 (t, 2, CH_2 Ar), 4.52 (t, 2, CH_2O), 7.50–7.94 (m, 7, Ar H); mass spectrum (70 eV), m/e (relative intensity) 250 (45, M^+) 154 (100).

Potassium cyanide (18.3 g, 280 mmol) was added in one portion to a solution of 2-[2-(methylsulfonyl)ethyl]naphthalene (vide supra; 17.53 g, 70.1 mmol) in 100 mL of DMF. The reaction was heated to 70 °C overnight and then poured into 500 mL of water. Product isolation (filtration, ethyl acetate, Na_2SO_4) followed by flash chromatography (silica gel, 0–20% ethyl acetate in hexane gradient) provided the homogeneous nitrile (10 g, 79%) as a white solid: mp 77–78 °C. Anal. ($C_{13}H_{11}N$) C, H, N.

2-[2-(2-Naphthalenyl)ethyl]-1*H*-imidazole (26). A solution of 3-(2-naphthalenyl)propanenitrile (5.0 g, 27.6 mmol) in 100 mL of absolute ethanol was cooled to −78 °C whereupon the starting material precipitated. Sufficient methylene chloride was added to achieve homogeneity. Finely dispersed hydrogen chloride was passed through the solution for 20 min, at such a rate to maintain the reaction temperature below −10 °C. The reaction was stirred for 2 h at −10 °C, and then volatile solvents were removed in vacuo. Ether was added and removed in vacuo to afford the imidate ester **16** (7.25 g) as a solid that was used without purification in the subsequent reaction.

2-Aminoacetaldehyde diethyl acetal (3.68 g, 27.6 mmol) was added via syringe to a solution of the imidate ester **16** (7.25 g) in 200 mL of absolute ethanol. The reaction was stirred at room temperature for 72 h and then solvent was removed in vacuo. The resulting amidine **17** (9.65 g) was used without purification in the subsequent reaction.

A solution of the amidine **17** (9.65 g) in 80 mL of 6 N hydrochloric acid was heated to 90 °C for 1 h. The reaction was poured into water and the pH was adjusted to 8 with 5 N sodium hydroxide. The product was filtered and flash chromatographed (silica gel, 0–10% methylene chloride in methanol gradient) to afford 3.31 g (54% for three steps) of homogeneous product (**26**). Recrystallization from THF/hexane provided 2.6 g (43%) of product as white crystals: mp 160–161 °C. Anal. ($C_{15}H_{14}N_2$) C, H, N.

Pharmacological Methods. Effects on Horizontal Screen (HS).[49] Three groups of four previously trained, fasted male mice (Crl: CF1^{R}BR; Charles River; 20–25 g) were administered a range of oral doses of each compound as a suspension in 5% acacia/water. Treated animals were placed individually on top of a square (13 cm × 13 cm) wire screen (no. 4 mesh) that was mounted on a metal rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen within 1 min was determined. This measurement was performed 0.5, 1, 2, 3, and 4 h posttreatment to determine the approximate time of peak effect. Each compound was then retested at the estimated time of peak effect with use of at least 4 doses, including 12 mice per dose.

Inhibition of MES-Induced Seizures. Three groups of mice were administered a range of oral doses of each compound as a suspension in 5% acacia/water. The time to peak effect was determined by challenging the mice with MES 0.5, 1, 2, 3, and 4 h posttreatment. Electroshock (40 mA, 0.1 s, ac) was administered through corneal electrodes, and the mice were observed for clonic, tonic-flexor, and tonic-extensor convulsions. Each compound was then retested at the estimated time of peak effect with use of at least four doses with 12 mice at each dose. The MES ED_{50} for the prevention of tonic-extensor convulsions was calculated according to the method of Litchfield and Wilcoxon.[50]

Inhibition of Subcutaneous PTZ-Induced Seizures. The ability of the test compounds to protect against threshold seizures induced by the subcutaneous injection of pentylenetetrazole (sc PTZ) was measured. Pentylenetetrazole (110 mg/kg) was dissolved in water and administered into a loose fold of skin on the back of the neck in a volume of 10 mL/kg of body weight. The convulsant was administered at the previously determined time of peak effect of test compound. Mice were observed for 15 min for the presence or absence of a clonic seizure.

Effects on Hexobarbital-Induced Sleeping Time. Groups of 10 fasted mice were treated orally with various doses of each compound in 5% acacia/water. At the previously determined time of peak effect, hexobarbital (100 mg/kg, ip) was administered to the mice. The hexobarbital was solubilized with stoichiometric quantities of sodium hydroxide, and the volume of administration for all test compounds, acacia, and hexobarbital was 10 mL/kg. Sleeping time or the time of loss of righting reflex was determined to the nearest minute for each mouse.

Effects on Flunitrazepam Binding. Cortical membranes (180 μg of protein) isolated from rat brain were incubated in triplicate samples at 4 °C for 40 min in a medium containing 50 mM Tris·HCl (pH 7.4) and 2 nM [^{3}H]flunitrazepam. Samples were filtered through Whatman GF/B filters and were washed three times with 5 mL of ice-chilled Tris·HCl buffer. Diazepam at 3 μM was used to establish nonspecific binding of [^{3}H]flunitrazepam, which represented less than 10% of total binding. Other conditions were as described previously.[33]

Groups of five male Sprague–Dawley rats (100 g) were treated with either saline or one of the compounds at a dose of 20 mg/kg, ip. Thirty minutes later, [^{3}H]flunitrazepam (31 Ci/mmol, Amersham) was administered intravenously via the tail vein at 100 μCi/kg. Rats were killed by decapitation 20 min later. Cerebral cortex was removed and homogenized by a Polytron in a 40× volume of 50 mM Tris·HCl, pH 7.4. Aliquots of homogenate were filtered and rinsed as above. Other conditions were as described previously.[51]

Acute Oral Toxicity Testing in Rats. Groups of six fasted female Fischer 344 rats, weighing 130–145 g, were administered a single dose of 500, 620, 800, or 1000 mg/kg of nafimidone by oral gavage. The dose was prepared as a 100 mg/mL suspension in 10% aqueous acacia solution. Animals were observed 24 h for mortality and signs of toxicity. Toxicity included leg weakness, ataxia, salivation, tonic convulsions, hyperresponsiveness, exophthalmos, chromorhinorrhea, hindlimb paralysis, unawareness of surroundings, chromodacryorrhea, perianal soiling, clear ocular discharge, poor grooming, and generalized paralysis. The 24-h median lethal dose (LD_{50} with 95% confidence limits) of nafimidone was 504 (422–603) mg/kg.

Groups of four fasted female Fischer 344 rats, weighing 130–150 g, were administered a single dose of 2000, 2750, 3650, or 5000 mg/kg of **27** by oral gavage. The dose was prepared as a 250 mg/mL suspension in 10% aqueous acacia solution. Animals were observed 7 days for mortality and signs of toxicity. Deaths occurred among animals given 5000 mg/kg (3/4). All other animals survived the 7-day observation period after dosing. Signs of toxicity were leg weakness, ataxia, clear ocular discharge, exophthalmos, hyperemia, salivation, curling into a ball on their side with no movement, poor grooming, chromodacryorrhea, chro-

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morhinorrhea, lack of feces production, hypoactivity, ptosis, coma, lethargy, and perianal staining. All survivors except one given 3650 mg/kg appeared normal at 7 days after dosing. This animal continued to have leg weakness and poor grooming. The 7-day median lethal dose (LD_{50}) of **27** was estimated to be 4550 mg/kg.

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Registry No. **8**, 39696-13-4; **10** (7-methyl), 98216-24-1; **11** (X = Cl), 98216-60-5; **12**, 30084-90-3; **12** (R = $(CH_2)_3I$), 102072-40-2; **13**·HCl, 98216-38-7; **13**, 98216-39-8; **14**, 102072-20-8; **14** (alcohol), 102072-39-9; **15**, 95104-51-1; **16**, 102072-21-9; **17**, 102072-22-0; **18**, 102072-42-4; **18**·HCl, 102072-23-1; **19**, 102072-43-5; **19**·HCl, 102072-24-2; **20**, 80170-20-3; **20**·HCl, 102072-25-3; **21**, 102072-44-6; **21**·HCl, 102072-26-4; **22**, 102072-45-7; **22**·HCl, 102072-27-5; **23**, 102072-46-8; **23**·HCl, 102072-28-6; **24**, 102072-47-9; **24**·HCl, 102072-29-7; **25**, 72459-49-5; **26**, 102072-30-0; **27**, 98216-44-5; **28**, 98216-67-2; **28**·HCl, 98216-36-5; **29**, 98216-68-3; **29**·HCl, 98216-37-6; **30**, 98216-64-9; **30**·HCl, 98216-32-1; **31**, 98216-65-0; **31**·HCl, 98216-33-2; **32**, 102072-48-0; **32**·HCl, 102072-31-1; **33**, 98216-34-3; **34**, 102072-49-1; **34**·HCl, 102072-32-2; **35**, 102072-50-4; **35**·HCl, 102072-33-3; **36**, 98216-63-8; **36**·HCl, 98216-31-0; **37**, 98242-50-3; **38**, 98216-29-6; **39**, 98216-30-9; **40**, 102072-34-4; **41**, 98216-47-8; **42**, 98216-50-3; **42**·HCl, 98216-49-0; **43**, 98216-42-3; **43**·HCl, 98216-41-2; **44**, 98216-48-9; **45**, 102072-51-5; **45**·HCl, 102072-35-5; **46**, 98216-61-6; **47**, 98242-51-4; **48**, 98216-54-7; **49**, 102072-52-6; **49**·HCl, 102072-36-6; **50**, 98216-55-8; **51**, 102072-37-7; **52**, 98216-58-1; **53**, 98216-45-6; **53**·HCl, 98216-43-4; **54**, 98216-69-4; **54**·HCl, 98216-46-7; **55**, 102072-38-8; 1-9*H*-fluorenecarboxylic acid, 6276-03-5; 1-(9*H*-fluoren-1-yl)ethanone, 36272-09-0; 9-methyl-9*H*-fluorene, 2523-37-7; fluorene, 86-73-7; 2-methyl-9*H*-fluorene, 1430-97-3; 2-ethyl-9*H*-fluorene, 1207-20-1; 2-(9*H*-fluoren-2-yl)-2-propanol, 54527-61-6; 2-isopropyl-9*H*-fluorene, 1687-92-9; 2-methylimidazole, 693-98-1; imidazole, 288-32-4; cyclopropyl bromide, 4333-56-6; 2-chloro-1-(9*H*-fluoren-2-yl)ethanone, 24040-34-4; 2-(2-naphthalenyl)ethanol, 1485-07-0; 2-[(methylsulfonyl)oxy]-1-(9*H*-fluoren-2-yl)ethane, 102072-41-3.

Synthesis and Renal Vasodilator Activity of 2-Chlorodopamine and N-Substituted Derivatives

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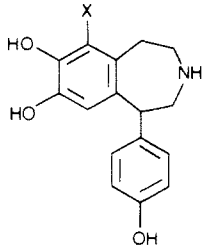
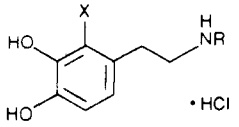
A four-step synthesis of 2-chlorodopamine (**2b**) is presented as well as methods for the syntheses of the *N*-methyl, ethyl, and *n*-propyl analogues (**2c–e**). Compounds **2b** and **2c** were essentially equipotent to dopamine for increasing renal blood flow in anesthetized dogs that had been treated with the α-adrenergic antagonist phenoxybenzamine. The increases in renal blood flow were blocked by the DA_1 antagonist (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine. Compounds **2d** and **2e** were significantly less potent than dopamine in the same model; the increases in renal blood flow were attenuated by propranolol and blocked by a combination of propranolol and (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine. The significance of an *o*-chloro substituent on dopamine analogues for the activation of the DA_1 receptor is briefly discussed.

There has been considerable interest in renal vascular DA_1 receptors[2] following the report that fenoldopam (**1a**) (SKF 82526), a renal vasodilator, is a specific dopamine agonist selective for the DA_1 receptor.[3] The importance of the chlorine on **1a** for its activity was demonstrated by replacement with either fluorine or hydrogen. The fluoro analogue (**1b**) had the pharmacological profile of a partial agonist, while the hydrogen analogue (**1c**) was inactive as a renal vasodilator.[4] 2-Fluorodopamine (**2a**) has been prepared[5-7] and its effects on dopamine receptors studied in detail.[8] In contrast to 2-fluoronorepinephrine, which more closely resembled isoproterenol in its biological effects, **2a** was indistinguishable from dopamine. In light of these results, it was surprising to find no mention of 2-chlorodopamine (**2b**) in the literature.



1a: X = Cl
b: X = F
c: X = H



2a: X = F, R = H
b: X = Cl, R = H
c: X = Cl, R = CH_3
d: X = Cl, R = CH_2CH_3
e: X = Cl, R = $CH_2CH_2CH_3$

Our interest in dopamine receptor activation[9,10] has prompted us to report the synthesis and renal effects of

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