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Analogues of the Dioxolanes Dexoxadrol and Etoxadrol as Potential Phencyclidine-like Agents. Synthesis and Structure–Activity Relationships

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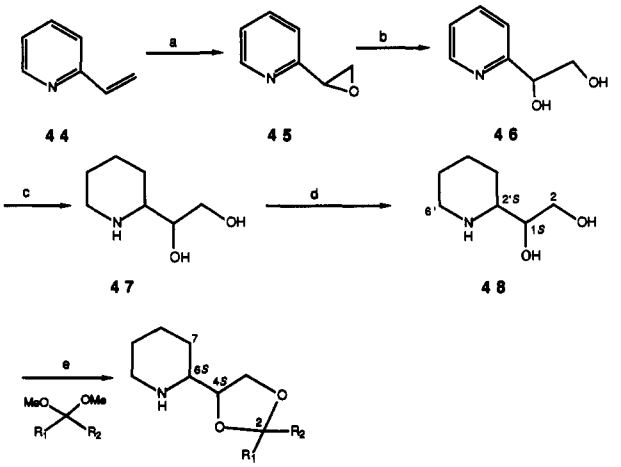
A series of dioxolane analogues based on dexoxadrol ((4*S*,6*S*)-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane) and etoxadrol ((2*S*,4*S*,6*S*)-2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane) were prepared and tested for their ability to displace [^{3}H]TCP (1-[1-(2-thienyl)cyclohexyl]piperidine) from PCP (1-(1-phenylcyclohexyl)piperidine) binding sites in rat brain tissue homogenates. Qualitative structure–activity relationships within this series were explored through modifications of the three major structural units of dexoxadrol, the piperidine, 1,3-dioxolane, and aromatic rings of the molecule. *N*-Alkyl derivatives of dexoxadrol were found to be inactive, as were those analogues where the dioxolane ring was modified. Phenyl-substituted etoxadrol analogues were compared to similarly substituted PCP analogues and distinct differences were found in their structure–activity relationships suggesting that the aromatic rings in these two drug classes interact differently with the PCP binding sites. The replacement of the phenyl ring in etoxadrol by either a 2- or 3-thienyl ring led to compounds with affinity comparable to etoxadrol, and the replacement of the ethyl moiety on etoxadrol's dioxolane ring with propyl (**7**) or isopropyl (**8**) led to compounds which were more potent than etoxadrol or PCP. The most potent compound was (2*S*,4*S*,6*S*)-2-ethyl-2-(1-chlorophenyl)-4-(2-piperidyl)-1,3-dioxolane (**11**), where a chlorine moiety was placed in the ortho position in the aromatic ring of etoxadrol. Its potency was comparable with TCP in vitro.

Dexoxadrol ((4*S*,6*S*)-2,2,-diphenyl-4-(2-piperidyl)-1,3-dioxolane, **1**) was developed in the 1960s as an anesthetic agent. In man, dexoxadrol was found to have analgesic potency equal to that of codeine and to be free of respiratory depression.[1] Anesthetic efficacy was greatly increased by replacing one of the phenyl groups in dexoxadrol with an ethyl group. One of these ethyl isomers, etoxadrol ((2*S*,4*S*,6*S*)-2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane, **2**) showed particular promise as an anesthetic agent.[2] Etoxadrol and dexoxadrol were eventually shown to have limited clinical usefulness after undesirable postanesthetic effects were noted. The psychological state induced by these dioxolane anesthetics resembled that of phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) intoxication. Binding studies later demonstrated that dexoxadrol, but not its enantiomer levoxadrol, had considerable affinity for PCP binding sites in rat brain.[3] The absolute configurations of dexoxadrol[4] and etoxadrol,[5] determined through single-crystal X-ray diffraction studies, were found to be 4*S*,6*S* and 2*S*,4*S*,6*S*, respectively (dexoxadrol numbering is shown in structure **1** of Figure 1). As part of our program to examine the structural requirements for PCP-like activity, we prepared a variety of analogues of these dioxolanes and tested them for their ability to inhibit [^{3}H]1-[1-(2-thienyl)cyclohexyl]piperidine ([^{3}H]TCP) binding at PCP binding sites. The compounds

Scheme I. Preparation of (1*S*,2′*S*)-1-(2-Piperidinyl)-1,2-ethanediol and the Dioxolane Derivatives[a]



[a] Reagents: (a) i, Br_2; ii, $NaHCO_3$. (b) i, TfOH, ii, XAD-400. (c) H_2, PtO_2. (d) Diastereomeric separation and resolution via tartrate salts (ref 8). (e) Dimethyl ketal, IPA, TsOH.

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(1) Allen, R. E.; Thompson, C. R.; Hidalgo, J. Ger. Patent 2001616, 1970; *Chem. Abstr.* 1971, *74*, 13129b.

0022-2623/92/1835-1323$03.00/0

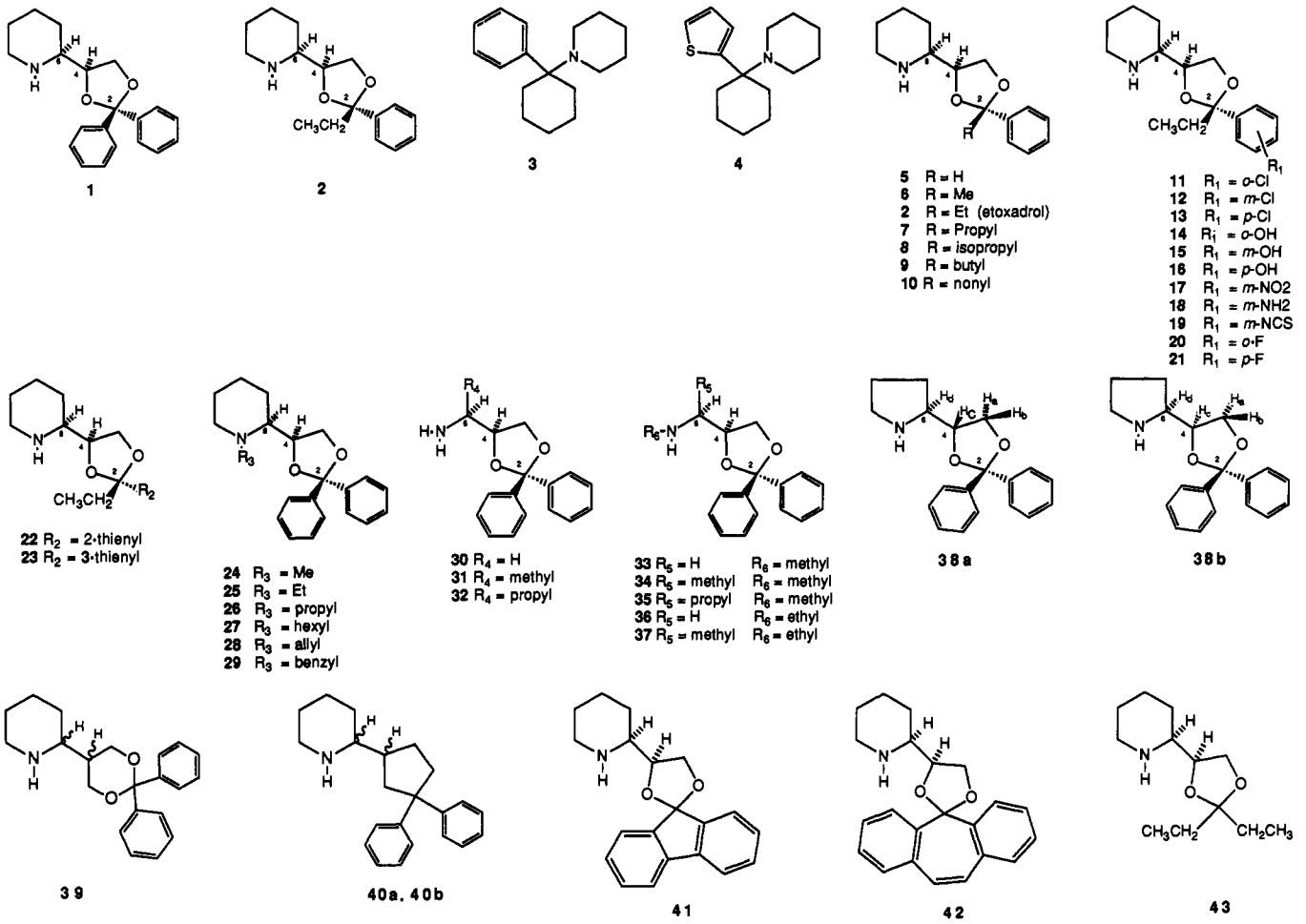


Figure 1. Structures of dexoxadrol, etoxadrol, PCP, TCP, and dioxolane analogues.

which were prepared as structural variants of dexoxadrol and etoxadrol are shown in Figure 1.

Since the 4*S*,6*S* stereochemistry is crucial to the activity of this series, we tried to include this feature into our analogues whenever possible. Thus, we used the intermediate 1*S*,2′*S*-1-(2-piperidinyl)-1,2-ethanediol (**48**, Scheme I) to prepare a variety of different 2-alkyl-2-aryldioxolanes. This strategy allowed us to examine the effects of making individual changes in the nature of the alkyl chain or the aryl moiety on the dioxolane ring of etoxadrol. The importance of the ethyl group on the dioxolane ring of etoxadrol was examined by varying the chain from hydrogen (**5**) through methyl (**6**), ethyl (etoxadrol, **2**), propyl (**7**), isopropyl (**8**), butyl (**9**), and finally nonyl (**10**).

The examination of the nature of the aryl substituent at the 2*S* position of etoxadrol was carried out systematically, with the idea of comparing the aromatic SAR of the dioxolanes to that of the previously established[6] aromatic SAR of PCP (**3**) and its more potent derivative TCP (**4**). Toward this end, an electron-withdrawing group, chlorine (compounds **11**–**13**), or an electron-donating group, hydroxyl (compounds **14**–**16**), was placed at the ortho, meta, and para positions of the phenyl group to determine their effects. Additionally, the 3-nitro (**17**), 3-amino (**18**), 3-isothiocyanato (**19**), 2-fluoro (**20**), and 4-fluoro (**21**) were also examined. The phenyl group of etoxadrol was also replaced by a 2-thienyl (**22**) and 3-thienyl (**23**) in order to further compare the dioxolane system to TCP.

The necessity of the secondary amine in the piperidine ring was challenged through the preparation of tertiary and primary analogues. Tertiary derivatives of deoxadrol were prepared by the substitution of methyl (**24**), ethyl (**25**), propyl (**26**), hexyl (**27**), allyl (**28**), and benzyl (**29**) moieties for the amine hydrogen of **1**. Primary amine derivatives included the 4-(aminomethyl)dioxolane **30** as well as the 4-(2-aminoalkyl)dioxolanes **31** and **32**. A variety of secondary amines (compounds **33**–**37**) were also prepared. Compounds **30** and **33** were prepared with 4*S* absolute stereochemistry. Compounds **31**, **32**, and **34**–**37** were ra-

(2) Wilson, R. D.; Traber, D. L.; Barratt, E.; Creson, D. L.; Schmitt, R. C.; Allen, C. R. Evaluation of CL-1848C: A New Dissociative Anesthetic in Normal Human Volunteers. *Anesthesia Analgesia* **1970**, *49*, 236–241.

(3) Hampton, R. Y.; Medzihdradsky, F.; Woods, J. H.; Dahlstrom, P. J. Stereospecific Binding of ^{3}H-Phencyclidine in Brain Membranes. *Life Sci.* **1982**, *30*, 2147–2154.

(4) Jacobson, A. E.; Harrison, E. A.; Mattson, M. V.; Rafferty, M. F.; Rice, K. C.; Woods, J. H.; Winger, G.; Solomon, R. E.; Lessor, R. A.; Silverton, J. V. Enantiomeric and Diastereomeric Dioxadrols: Behavior, Biochemical and Chemical Determination of the Configuration Necessary for Phencyclidine-like Properties. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 110.

(5) Thurkauf, A.; Zenk, P. C.; Balster, R. L.; May, E. L.; George, C.; Carroll, F. I.; Mascarella, S. W.; Rice, K. C.; Jacobson, A. E.; Mattson, M. V. Synthesis, Absolute Configuration, and Molecular Modeling Study of Etoxadrol, a Potent Phencyclidine-like Agonist. *J. Med. Chem.* **1988**, *31*, 2257–2263.

(6) Kalir, A. Structure Activity Relationships of Phencyclidine Derivatives. In *PCP (Phencyclidine): Current and Historical Perspectives*; Domino, E. F., Ed.; NPP Books: Ann Arbor, MI, 1981; pp 31–46.

cemic and possess C4–C6 relative stereochemistry which corresponds to that found in dexoxadrol.

The importance of ring size within the 4-(2-piperidyl)-dioxolane system was examined by the preparation of the corresponding pyrrolidine derivatives **38a** and **38b** and 1,3-dioxocyclohexane derivative **39**, and the need for oxygen functionality within the five-membered ring was determined through the preparation of **40a** and **40b** as a mixture of diasteromers.

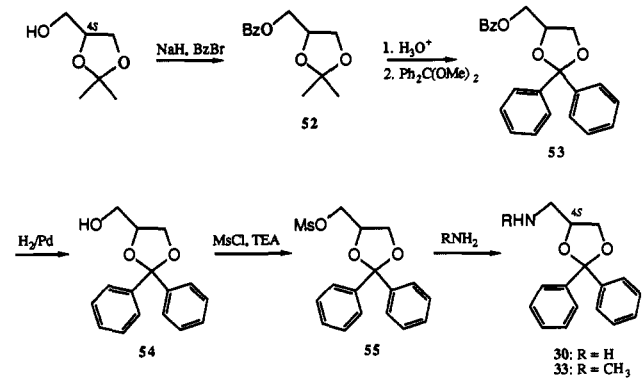
The effects of conformational restriction of the aromatic ring of dexoxadrol were briefly examined by the preparation of the fluorenyl and suberenyl derivatives **41** and **42**, respectively. The requirement for an aromatic ring to be present was examined with the diethyl derivative **43**.

Chemistry

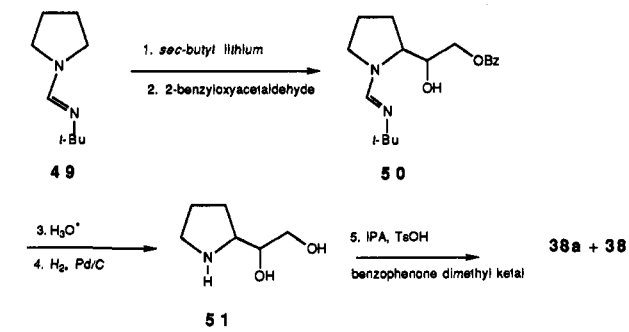
1-(2-Piperidinyl)-1,2-ethanediol (**47**) was prepared from 2-vinylpyridine (**44**) by a variation of the method of Hanzlik et al.[7] (Scheme I). In this variation, which we found to give improved yields, the intermediate 1-(2-pyridyl)oxirane (**45**) was hydrolyzed through the use of aqueous triflic acid to provide the triflate salts of the 1-(2-pyridyl)-1,2-ethanediol enantiomers. The triflate salt was converted to the hydrochloride by use of the ion exchange resin XAD-400. The pyridinediol hydrochloride **46** was then hydrogenated over platinum oxide to provide the diastereomeric piperidine ethanediol hydrochlorides **47**. The *S,S* enantiomer[4] of 1-(2-piperidinyl)-1,2,-ethanediol (**48**) was isolated by the method of Hardie.[8] Compounds **1**, **2**, **5–17**, **20–23**, and **41–43** were prepared by the condensation of **48** with the dimethyl acetals of the corresponding ketones (Scheme I). Ketalizations were carried out in either nitromethane or 2-propanol solvents, the former solvent giving slightly better yields. The required dimethyl acetals were prepared from the corresponding carbonyl precursors by the method of Thurkauf et al.[9] For compounds **5–17**, **20–23**, and **41–43**, the *S* absolute stereochemistry at C-2 was assigned through comparison with the known physical characteristics of etoxadrol (**2**) whose C-2 *S* configuration had previously been confirmed via X-ray crystallographic analysis.[5] As with etoxadrol, each ketalization reaction produced a mixture of two C-2 epimers, usually in a ratio of greater than 8 to 1. In each case the major epimer was characterized by having a higher TLC R_f value (5% MeOH/CH_2Cl_2) and a longer GC retention time (25-m SE-30 column, 165 °C). The epimers were separated by either crystallization or chromatography and, in each case tested, significant receptor binding was observed only in the major epimer.

The preparation of the compounds **17–19**,[10] **24–29**,[11] **31**,[12] **32**,[12] **34–37**,[12] **40a** and **40b**[13] have been previously described.

Scheme II. Preparation of Dioxolanes **30** and **33**



Scheme III. Preparation of Pyrrolidine Derivatives **38a** and **38b**



The diastereomeric mixture **39** was prepared by the condensation of commercially available diol with the dimethyl acetal of benzophenone.

Compound **30** was prepared by conversion of 4(*S*)-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane to the *O*-benzyl derivative **52**, followed by hydrolysis to the diol, which without isolation was converted to the benzophenone ketal **53**, hydrogenation to the alcohol **54**, preparation of the mesylate **55**, and aminolysis with ammonia gas in methanol (Scheme II). Compound **33** was prepared similarly to **30** by substitution of methylamine for ammonia in the final step.

The pyrrolidine derivatives (**38a,b**) were prepared as shown in Scheme III. The *tert*-butylformamidine derivative of pyrrolidine (**49**) was lithiated with *sec*-butyllithium[14] and alkylated with 2-(benzyloxy)acetaldehyde[15]

(7) Hanzlik, R. P.; Edelmann, M.; Michealy, W. J.; Scott, G. Enzymatic Hydration of [^{18}O]epoxides. Role of Nucleophilic Mechanisms. *J. Am. Chem. Soc.* **1976**, *98*, 1952–1955.

(8) Hardie, W. R.; Hildago, J.; Halberstadt, I. F.; Allen, R. E. 4-(2-Piperidyl)-1,3-dioxolanes with Local Anesthetic, Spasmolytic, and Central Nervous System Activity. *J. Med. Chem.* **1966**, *9*, 127–136.

(9) Thurkauf, A.; Jacobson, A. E.; Rice, K. C. An Improved Procedure for Preparation of Ketals from Diaryl Ketones. *Synthesis* **1988**, 234–235.

(10) Thurkauf, A.; Mattson, M. V.; Huguenin, P. N.; Rice, K. C.; Jacobson, A. E. Etoxadro-*meta*-isothiocyanate: a Potent, Enantioselective, Electrophilic Affinity Ligand for the Phencyclidine Binding Site. *FEBS Lett.* **1988**, *238*, 369–374.

(11) Jacobson, A. E.; Thurkauf, A.; Mattson, M. V.; Rice, K. C.; Koek, W.; Williams, A.; Woods, J. H. Analogues of 2-Methyl-3,3,-diphenyl-3-propanolamine (2-MDP) and Dexoxadrol: Synthesis, PCP Receptor Binding and Behavior. In *Sigma Opioid Phencyclidine-like Compounds as Molecular Probes in Biology*; Domino, E., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 35–45.

(12) Ornstein, P. L.; Zimmerman, D. M.; Leander, J. D.; Mendelsohn, L.; Reel, J. K.; Evrard, D. A. The Search for a Phencyclidine (PCP) Antagonist: PCP-like Effects of a Series of Substituted Dioxolanes Related to Dexoxadrol. In *Sigma Opioid and Phencyclidine-like Compounds as Molecular Probes in Biology*, Domino, E. F., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 19–25.

(13) Harrison, E. A.; Rafferty, M. F.; Rice, K. C.; Creveling, C. R.; Winger, G. D.; Woods, J. H.; Jacobson, A. E. Evidence for Separation of Anesthetic Activity from Prototypic Phencyclidine Action in Drug Discrimination by Molecular Modification of Dioxadrol. In *Problems of Drug Depenedence*, 1984; Harris, L. S., Ed.; NIDA Research Monograph 55, U.S. Govt. Print. Off: Washington, DC, 1985; pp 90–96.

to give **50**. The compound **50** in turn was first hydrolyzed and then hydrogenated to give a mixture of the diastereomers **51** without isolation of the intermediates from **49**. The mixture was then condensed with benzophenone dimethyl ketal to give a mixture of diastereomeric 2,2-diphenyl-4-(2-pyrrolidinyl)-1,3-dioxolanes **38a** and **38b** which were separated chromatographically. The relative stereochemistry of **38a** and **38b** was assigned through NMR analysis. We have assigned the relative stereochemistry portrayed in compound **38a** to that diastereomer having the larger coupling constant (6.1 vs 5.1 Hz) between protons H_c and H_d. This assignment is supported through molecular modeling studies[16] designed to determine the H_c–H_d coupling constants for two diastereomers. This compound (**38a**) is further characterized by having lower R_f value on TLC (5% $CH_3OH/CHCl_3$) and a shorter GC retention time (11.3 vs 11.5 min for **38b**, 25-m SE-30 column, 165 °C). We emphasize that this assignment is tentative. Both compounds were subsequently tested for their ability to displace [^{3}H]TCP from PCP binding sites.

Results and Discussion

The results of [^{3}H]TCP displacement experiments for compounds **1–43** are presented in Table I.

The inactivity of **5** indicates that an alkyl group is required at this position of the dioxolane ring for activity. Potency was found to reach a maximum at a chain length of three (**7**, R = propyl) and diminish with longer or shorter alkyl groups. It is also interesting to note that branching at the C-1 position of this alkyl chain (**8**, R = isopropyl) was also beneficial. Both **7** and **8** were more potent than etoxadrol or PCP.

Examination of the aryl-substituted derivatives of etoxadrol (compounds **11–21**) revealed consistent SAR patterns for the series. Ortho substituents produced greater potency than the corresponding meta or para derivatives (**11** vs **12** and **13**; **14** vs **15** and **16**; and **20** versus **21**). The binding affinity of (2*S*,4*S*,6*S*)-2-ethyl-2-(1-chlorophenyl)-4-(2-piperidyl)-1,3-dioxolane (**11**), with a chlorine moiety in an ortho position in the aromatic ring of etoxadrol, was comparable to TCP in vitro. Derivatives containing electron-withdrawing halogens (F, Cl) showed increased activity over electron-donating groups (OH, NH_2) at all ring positions. These patterns of activity contrast strongly with those within the phenylcyclohexylamine class where electron-donating groups at the meta position contribute positively to binding affinity while serving to decrease binding affinity when situated at the ortho or para positions.[19] Some steric effects may also be significant. Analogue **21**, with the smaller, more electronegative para fluorine atom, has greater affinity for PCP binding sites than **13**, which has the larger chlorine atom in the para position. The activities were reversed when these atoms were present in the ortho position, the *o*-chloro analogue **11** having higher affinity than the corresponding *o*-fluoro analogue **20**.

The thienyl derivative of PCP (TCP, **4**) has a 7-fold greater affinity than PCP. In contrast, one possible corresponding 2-thienyldioxolane, **22**, showed diminished

Table I. Binding Affinities of Dioxolane Analogues

	cmpd	K_i,[a] μM
	dexoxadrol	0.112
	etoxadrol	0.107
	PCP[b]	0.080
	TCP[c]	0.012
C-2 alkyl analogues	**5**	25[d]
	6	0.847 ± 0.028
	7	0.069 ± 0.014
	8	0.045 ± 0.002
	9	0.200 ± 0.018
	10	43 ± 4
phenyl-substituted etoxadrols	**11**	0.0143 ± 0.0024
	12	0.059 ± 0.002
	13	2.8 ± 0.1
	14	0.293 ± 0.075
	15	0.489 ± 0.050
	16	19.9 ± 1.3
	17	1.32 ± 0.12
	18	1.23 ± 0.13
	19	0.590[e]
	20	0.036 ± 0.002
	21	0.649 ± 0.099
thienyl derivatives	**22**	0.205 ± 0.037
	23	0.124 ± 0.037
N-alkyldexoxadrols	**24**	4.4 ± 0.5
	25	6.9 ± 0.9
	26	6.8 ± 0.6
	27	21.2 ± 0.8
	28	15.2 ± 0.2
	29	10.1 ± 1.7
(aminomethyl)dioxolanes	**30**	1.4 ± 0.1
	31	0.607[d,f]
	32	3.45 ± 0.05[f]
	33	7.3 ± 0.2
	34	0.703[d,f]
	35	7.0 ± 1.2[f]
	36	8.4 ± 0.5[f]
	37	9.0 ± 0.6[f]
pyrrolidine analogues	**38a**	3.3[d,f]
	38b	>10[d,f]
miscellaneous analogues	**39**	>100[d,g]
	40a	52[f,h]
	40b	8.3[f,h]
	41	15.5 ± 0.2
	42	0.325 ± 0.012
	43	87 ± 12

[a] Determined by displacement of [^{3}H]TCP from tissue homogenate preparation of whole rat brain minus cerebellum. The K_i values (mean ± standard deviation) were calculated using the Chang–Prusoff equation from displacement data run in triplicate except as indicated. Data analyzed using GRAPHPAD software (ref 18). [b] 1-(1-Phenylcyclohexyl)piperidine. [c] 1-[1-(2-Thienyl)cyclohexyl]piperidine. [d] Single experiment, run in triplicate. [e] "Apparent IC_{50}" estimated from competitive displacement curves (see ref 10). [f] Racemic. [g] Mixture of diastereomers. [h] Reference 13.

(14) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. α-Amino Carbanions via Formamidines. Alkylation of Pyrrolidines, Piperidines and Related Heterocycles. *J. Am. Chem. Soc.* **1984**, *106*, 3270–3276.

(15) Prepared by the ozonolysis of allyl benzyl ether (a) ozonolysis conditions, see: Muller, N.; Hoffman, W. Oyclocitrale Aus Jononen. *Synthesis* **1975**, 781. (b) 2-(Benzyloxy)-acetaldehyde, see: Rigby, W. Oxidations with Sodium Bismuthate. *J. Chem. Soc.* **1950**, 1907. Danishefsky, S. J.; DeNinno, M. P. The Total Synthesis of (+)-N-acetylneuraminic acid. *J. Org. Chem.* **1986**, *51*, 2615–2617. Garner, P.; Park, J. M. A Convenient Synthesis of 2-Benzyloxyacetaldehyde. *Synth. Commun.* **1987**, *17*, 189–194.

(16) Evans and Sutherland PS390 Graphics system linked to a Digital Equipment Corp. microVax work station, software employed was the MacroModel program (version 2.5) from Columbia University, New York, NY.

(17) Cheng, Y. C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_i) and the Concentration of Inhibitor which Causes Fifty Percent Inhibition (IC_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3103.

(18) Motulsky, H. J. *GraphPAD InPlot, Vers. 3.04*; GraphPAD Software: San Diego, CA.

(19) Kamenka, J.-M.; Geneste, P. The Biologically Active Conformation of PCP and its Consequences: A Hypothesis. In *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*; Kamenka, J.-M., Domino, E. F., Geneste, P., Eds.; NPP Books: Ann Arbor, MI, 1983; pp 1–12.

activity relative to the phenyl derivative etoxadrol (2), and another, 23, was essentially equipotent with etoxadrol.

The lack of correlation between either phenyl substituents (compounds 11–21) or thienyl derivatives 22 and 23 suggests that the aromatic ring of the dioxolanes and the aromatic ring of the arylcyclohexylamines may serve different functions in the mechanism of binding of these two classes of compounds to PCP binding sites.

Additional substitution at the nitrogen atom of dexoxadrol (compounds 24–29)[11] gave inactive compounds. This is in contrast to the substantial activity of the tertiary arylcyclohexylamines. The inactivity of the tertiary derivatives of dexoxadrol is possibly less a result of their tertiary nature and more a consequence of steric considerations which limit their ability to fit within our defined PCP pharmacophore.[5]

When considering the necessity for a piperidine ring for the activity of dexoxadrol, a number of structural considerations must be addressed. For instance, the ring size might be modified or the ring opened to form an acyclic amine portion having alkyl residues on nitrogen and/or on the C-4 position of the dioxolane. Compounds 30–37 represent the latter possibility and are formally partial structures of dexoxadrol. Compounds 30 and 33 have 4*S* absolute configuration and are therefore true partial structures of dexoxadrol. The remaining compounds were tested as racemates, and this should be taken into account when comparing the binding affinities of these compounds (Table I) to that of dexoxadrol. The fact that compounds 30, 31, and 34, despite their minimal structural resemblance to dexoxadrol, maintain appreciable activity in the binding assay indicates that a complete piperidine ring is not essential for activity in this series. Although none of the compounds within this series show activity comparable to that of dexoxadrol, when judged against each other it is evident that an alkyl substituent at the C-6 position is beneficial to activity of the dioxolanes (compared 30 to 31 and 33 to 34). The racemic compounds 31 and 34, which represent the removal of carbon atoms 8–10 and 8 and 9 of the piperidine ring, show submicromolar binding affinity. An alkyl group at the C-6 position may well serve to restrict the rotational options of the amine nitrogen and thereby force it, on an average, into a conformer acceptable for binding.

The pyrrolidine analogues 38a and 38b showed low affinity for the PCP binding site, as did the diastereomeric 1,3-dioxocyclohexane derivatives 39.

An interesting contrast is seen between the two conformationally restricted analogues 41 and 42. Whereas the suberenyl derivative 42 has appreciable binding activity, the fluorenyl derivative 41 is inactive. The large increase in binding affinity that occurs from increasing the distance between the centers of the aromatic rings may reflect upon the location of the aromatic binding site for this class of compounds.

The 2,2-diethyldioxolane 43 was essentially inactive in the binding assay. This result indicates the importance of an aromatic residue within this series of compounds. To date, only the nonaromatic compounds from the (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (MK-801) series have been shown to display appreciable in vitro activity at the PCP site.[20]

Conclusion

Our original idea behind the preparation and testing of the compounds described here was to identify a common structural determinant between two structurally dissimilar classes of PCP agonists, those being the arylcyclohexylamines (PCP and TCP) and the dioxolanes (dexoxadrol and etoxadrol). That such a comparison had merit was indicated by the facts that representative compounds in each class have similar in vivo activity[21] and are competitive inhibitors of one another at their in vitro binding sites.[22,23]

Comparison of the results of the binding studies on the series of dexoxadrol analogues described here with the known structure–activity relationships for PCP analogues served only to widen the disparity in SAR between these two classes of compounds. This is most evident when considering the role of the aromatic moiety of PCP with that of the monophenyl dioxolane etoxadrol. In the case of PCP, an electron-donating group at the meta position has been shown to greatly improve affinity relative to the parent compound. In contrast, except for the *m*-nitro analogue 17, electron-donating groups at any position on the phenyl ring of etoxadrol serve to diminish the affinity and electron withdrawing substituents at the ortho and meta positions produce higher affinity ligands. Another contrasting situation between these molecules can be found in the replacement of the phenyl group by a thienyl group. Replacement of the phenyl group in PCP by a 2-thienyl group greatly increases affinity. Replacement of the phenyl group of etoxadrol with a 2-thienyl provided an analogue having markedly less affinity while the corresponding 3-thienyl derivative was equipotent with etoxadrol.

Concerning the amine segment within each class, again dissimilarities can be observed. PCP exhibits activity as either the tertiary amine or after transformation into a secondary amine, e.g., *N*-ethyl-1-phenylcyclohexylamine. The latter, in fact, leads to improved affinity.[25] However, changing the secondary amine character of dexoxadrol by conversion to a variety of tertiary amines leads to virtually inactive compounds (compounds 24–29).

Our results indicate that, although the arylcyclohexylamines and the dioxolanes show very similar in vivo and in vitro profiles of activity, they show some distinct differences in the structure–activity relationships of their common structural units.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra of

(20) Lyle, T. A.; Magill, C. A.; Britcher, S. F.; Denny, G. H.; Thompson, W. J.; Murphy, J. S.; Knight, A. R.; Kemp, J. A.; Marshall, G. R.; Middlemiss, D. N.; Wong, E. H. F.; Anderson, P. S. Structure and Activity of Hydrogenated Derivatives of (+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (MK-801). *J. Med. Chem.* **1990**, *33*, 1047–1052.

(21) Brady, K. T.; Woolverton, W. L.; Balster, R. L. Discriminative Stimulus Properties of Etoxadrol and Dexoxadrol in Monkeys. *J. Pharmacol. Exp. Ther.* **1982**, *220*, 56–62.

(22) Mendelsohn, L. G.; Kerchner, G. A.; Kalra, V.; Zimmerman, D. M.; Leander, J. D. Phencyclidine Receptors in Rat Brain Cortex. *Biochem. Pharmacol.* **1984**, *33*, 3529–3535.

(23) Sethy, V. H.; McCall, J. M. High Affinity (^{3}H)-Dexoxadrol Binding to Rat Brain Membranes. *Drug Devl. Res.* **1984**, *4*, 635–645.

(24) Carroll, F. I.; Brine, G. A.; Boldt, K. G.; Mascarella, S. W.; Moreland, C. G.; Sumner, S. J.; Burgess, J. P.; Stejskal, E. O. Solid State Conformation of Phencyclidine and Phencyclidine Analogues. In *Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology*; Domino, E. F., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 91–106.

(25) Jasinski, D. R.; Shannon, H. E.; Cone, E. J.; Vaupel, D. B.; Rismar, M. R.; McQuinn, R. L.; Su, T. P.; Pickworth, W. B. Interdisciplinary Studies on Phencyclidine. In *PCP (Phencyclidine): Current and Historical Perspectives*; Domino, E. F., Ed.; NPP Books: Ann Arbor, MI, 1981; pp 331–400.

the free bases were obtained on a Varian XL-300 instrument. Mass spectra (CI) were obtained on a Finnigan 1015D instrument. Gas chromatographic analysis was performed on a Hewlett-Packard 5880 instrument equipped with a 25-m SE-30 capillary column and a flame-ionization detector. Optical rotations were obtained on the free bases with a Perkin-Elmer Model 241 polarimeter. Where elemental analysis are indicated only by symbols of these elements, analytical results obtained are within 0.4% of the theoretical values. These combustion analyses were obtained at Galbraith Laboratories, Inc., Knoxville, TN, or at Atlantic Microlaboratories, Inc., Atlanta, GA. Molecular models were constructed with a molecular modeling system (an Evans and Sutherland ES 390 graphics system linked to a micro VAX work station). Software employed was the MACROMODEL program (Version 2.5) from Columbia University, New York, NY.

1-(2-Pyridyl)oxirane (45). To a mixture of 500 mL of dioxane and 1800 mL of water was added 148.1 g (1.4 mol) of 2-vinylpyridine and 84 g of acetic acid. The reaction mixture was stirred and 274 g (1.1 equiv) of *N*-bromosuccinimide was added in portions over 30 min. After stirring for 1 h, sodium carbonate (300 g, 2 equiv) was added in portions and the reaction stirred for 30 min. The reaction mixture was then extracted three times using 500-mL portions of ethyl acetate. The organic layer were dried ($NaSO_4$) and concentrated to a volume of 300 mL. After the organic layer was cooled in an ice–water bath, precipitated succinamide was removed by filtration. The filtrate was then concentrated and distilled (bp 58 °C, 0.2 Torr) to provide 112 g (66%) of the oxirane as a viscous yellow oil.

1-(2-Pyridyl)-1,2-ethanediol (46). Trifluoromethanesulfonic acid (104 g, 0.69 mol) was added dropwise to a mixture of **45** (80 g, 0.66 mol) in distilled water (150 mL) which had been cooled to 5 °C. After the addition was complete the solution was refluxed for 3 h. After the solution was cooled to room temperature, 500 g of chloride ion exchange resin (previously rinsed using 2 L of distilled water) was added to the solution and the resulting homogeneous mixture allowed to stand overnight. Filtration and concentration of the solution provided a residue which was dried through repeated addition of 200-mL portions of absolute ethanol followed by reconcentration. The final residue was further dried in a vacuum oven at 80 °C to provide essentially pure 1-(2-pyridyl)ethane-1,2-diol hydrochloride (**46**, 93 g, 81%), mp 120–121 °C.

(1*S*,2′*S*)-1-(2-Piperidyl)ethanediol Hydrochloride (48). Compound **48** was prepared and purified using the method of Hardie et al.[8]

Representative Procedures for the Preparation of the Dioxolanes. (2*S*,4*S*,6*S*)-2-Phenyl-2-methyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride (6). To a refluxing solution of (4*S*,6*S*)-1-(2-piperidyl)-1,2-ethanediol hydrochloride (0.5 g 2.75 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) in 10 mL of dry nitromethane was added a solution of acetophenone dimethyl acetal (0.57 g, 3.4 mmol, 1.25 equiv) in 3 mL of dry nitromethane. After 10 min the reaction was cooled in an ice bath and poured into a separatory funnel containing 10 mL of 1.0 N NaOH solution and 30 mL of ether. The organic layer was removed, dried ($MgSO_4$), and concentrated to give 0.53 g (78%) of a mixture of **6** and its C-2 epimer. GC analysis (SE-30 column, 170 °C) showed a 95:3 ratio of acetal isomers. The retention times for the isomers were 2.41 and 2.21 min, respectively. The major isomer (**6**) was isolated (in >99.5% purity as determined by GC) from the mixture by crystallization of the hydrochloride salt from ethyl acetate: mp 223–224 °C; mass spectrum (CI, NH_3), *m/e* 248 (M + 1); ^1H NMR ($CDCl_3$) 7.35 (d, *J* = 7 Hz, 2 H), 7.2 (m, 3 H), 4.25 (dd, *J* = 4, 9 Hz, 1 H), 4.10 (dd, *J* = 4.5, 9 Hz, 1 H), 3.71 (dd, *J* = 7, 7 Hz, 1 H), 3.48 (bd, *J* = 7 Hz, 1 H), 2.98 (ddd, *J* = 3, 7, 12 Hz, 1 H), 2.75 (ddd, *J* = 3, 3, 12 Hz, 1 H), 1.61 (s, 3 H, Me), 1.4–1.9 (m, 6 H). Anal. ($C_{15}H_{21}NO_2$·HCl) C, H, N.

(2*S*,4*S*,6*S*)-2-(3-Hydroxyphenyl)-2-ethyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride (15). To a refluxing solution of (4*S*,6*S*)-1-(2-piperidyl)-1,2-ethanediol hydrochloride (0.4 g, 2.2 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) in 10 mL of 2-propanol was added a solution of 3-hydroxypropiophenone dimethyl ketal (650 mg, 1.5 equiv) in 2-propanol (2 mL). After 20 min the solution was allowed to cool to room temperature. The solution was then poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was discarded. The aqueous layer was neutralized with NH_4OH and extracted with chloroform. The chloroform was dried (Na_2SO_4) and concentrated to give an oil. The dioxolane **15** was isolated as the hydrochloride salt from EtOAc (420 mg, 61%): mp 191–193 °C; mass spectrum (CI, NH_3), *m/e* 278 (M + 1); ^1H NMR ($CDCl_3$) 7.05 (dd, *J* = 7, 7 Hz, 1 H), 6.86 (s, 1 H), 6.81 (d, *J* = 7, 7 Hz, 1 H), 6.73 (dd, *J* = 7 Hz, 1 H), 4.3 (m, 1 H), 3.95 (dd, *J* = 9.8, 4.6 Hz, 1 H), 3.73 (dd, *J* = 8.2, 8.2 Hz, 1 H), 3.32 (m, 1 H), 2.92 (m, 1 H), 2.80 (m, 1 H), 1.9–1.35 (m, 8 H), 0.79 (t, *J* = 7 Hz, 3 H). Anal. ($C_{16}H_{23}O_3N$·HCl) C, H, N.

(4*S*,6*S*)-4-(2-Piperidyl)spiro[1,3-dioxolane-2,9′-[9*H*]-fluorene] (41). A solution of **48** (410 mg, 2.3 mmol) and *p*-toluenesulfonic acid (20 mg) in 5 mL of 2-propanol was added to a refluxing solution of fluorenone dimethyl acetal (2 g) in 30 mL of 2-propanol. After 20 min the solution was allowed to cool to room temperature. The solution was then poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was discarded. The aqueous layer was neutralized with NH_4OH and extracted with chloroform. The chloroform was dried (Na_2SO_4) and concentrated to give an oil. The hydrochloride salt was prepared in EtOAc (0.57 g, 71%), mp 249–250 °C dec.

Preparation of (4*S*)-4-(Aminomethyl)dioxolanes 30 and 33. (4*S*)-2,2-Dimethyl-4-[(benzyloxy)methyl]-1,3-dioxolane (52). A solution of (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (3 g, 22.7 mmol) in 10 mL of dry THF was added to a stirred suspension of 60% sodium hydride (1.75 g, 73 mmol) in 10 mL of dry THF. After 10 min, a solution of benzyl bromide (3.9 g, 1 equiv) in 5 mL of THF was added. The reaction was refluxed for 30 min, cooled, and carefully poured into a separatory funnel containing 150 mL of chloroform and 100 mL of water. The organic layer was dried (Na_2SO_4) and concentrated. Purification through chromatography on silica (10% EtOAc/hexane) offered 3.58 g (71%) of the desired benzyl ether (**52**) as an oil: ^1H NMR ($CDCl_3$) 7.4 (m, 5 H), 4.38 (s, 2 H), 4.30 (m, 1 H), 4.06 (dd, *J* = 8, 6 Hz, 1 H), 3.74 (dd, *J* = 9, 6 Hz, 1 H), 3.56 (dd, *J* = 10, 6 Hz, 1 H), 3.37 (dd, *J* = 10, 6 Hz, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H).

(4*S*)-2,2-Diphenyl-4-[(benzyloxy)methyl]-1,3-dioxolane (53). Dioxolane **52** (3.5 g) was refluxed for 3 h in a solution of 40 mL of THF and 30 mL of 3 N HCl solution. At the end of this time period, the solution was concentrated. The concentrate was dissolved in 50 mL of absolute ethanol and reconcentrated. The second concentrate was dissolved in 30 mL of 2-propanol, 50 mg of *p*-toluenesulfonic acid monohydrate was added, and the resulting solution was brought to reflux. To this was added a solution of 5.37 g of benzophenone dimethyl acetal in 10 mL of 2-propanol. After 10 min of reflux, the solution was cooled to room temperature and poured into a separatory funnel containing 100 mL of chloroform and 100 mL of water. The organic layer was removed, dried (Na_2SO_4), and concentrated. Purification on silica (5% EtOAc/hexanes) provided 2.6 g (48%) of the desired 2,2-diphenyldioxolane **53**: mass spectra (CI, NH_3), *m/e* 347 (M + 1), $[\alpha]^{23}_D$ +12.3° (*c* = 0.044, MeOH).

(4*S*)-2,2-Diphenyl-4-(hydroxymethyl)-1,3-dioxolane (54). Compound **53** (4 g, 11.6 mmol) was dissolved in 150 mL of methanol and hydrogenated overnight on a Parr hydrogenator using 200 mg of 10% palladium on carbon as the hydrogenation catalyst. The solution was filtered through Celite and concentrated to **54** (2.6 g) as an oil which was carried on the next step without purification: mass spectra (CI, NH_3), *m/e* 257 (M + 1); IR (neat) 3605 cm^{-1}.

(4*S*)-2,2-Diphenyl-4-[[(methylsulfonyl)oxy]methyl]-1,3-dioxolane (55). To a solution of 2.5 g (10 mmol) of **54** in 20 mL of chloroform containing 1.5 g of triethylamine was added 1.22 g of methanesulfonyl chloride. After 10 min the reaction was washed with water (10 mL) and 10% Na_2CO_3 (10 mL), dried, and concentrated to provide the product (**55**) as an oil (2.7 g, 88%): ^1H NMR ($CDCl_3$) 7.5 (m, 4 H), 7.3 (m, 1 H), 4.49 (m, 1 H), 4.29 (dd, *J* = 9, 2 Hz, 2 H), 4.08 (dd, *J* = 9, 7 Hz, 1 H), 4.00 (dd, 9, 8 Hz, 1 H), 2.93 (s, 3 H, OMs).

(4*S*)-2,2-Diphenyl-4-[(methylamino)methyl]-1,3-dioxolane (33). The mesylate **55** (0.5 g) was dissolved in 10 mL of methanol, and an excess of 40% aqueous methylamine was added. After standing 2 h the mixture was concentrated, redissolved in ether, and washed with water. The resulting organic layer was dried and concentrated. The hydrochloride salt was prepared in 2-

propanol and recrystallized from ethyl acetate (yield 315 mg): mp 209–210 °C; mass spectra (CI, NH_3), m/e 270 (M + 1); ^1H NMR 7.60 (d, J = 6 Hz, 2 H), 7.50 (d, J = 6 Hz, 2 H), 7.3 (m, 6 H), 4.82 (m, 1 H), 4.15 (dd, J = 8, 9 Hz, 1 H), 3.83 (dd, J = 9, 7 Hz, 1 H), 3.15 (m, 1 H), 2.9 (m, 1 H), 2.72 (s, 3 H, Me). Anal. ($C_{17}H_{19}NO_2$·HCl) C, H, N.

(4*S*)-2,2-Diphenyl-4-[(dimethylamino)methyl]-1,3-dioxolane (30) was prepared from **55** in a manner similar to **33**, substituting ammonia for methylamine, mp 218–220 °C. Anal. ($C_{16}H_{17}NO_2$·HCl) C, H, N.

Preparation of Pyrrolidine Derivatives 38a and 38b. Preparation of the Diastereomeric 1-(2-Pyrrolidinyl)-1,2-ethanediols (51). A solution of **49**[15] (1.8 g, 11.7 mmol) in anhydrous ether (115 mL) under an atmosphere of nitrogen was treated at room temperature with a 1.0 M solution of *sec*-butyllithium in cyclohexane (12.5 mL). The solution of the anion was allowed to stir at room temperature for 45 min and then was cooled to −78 °C and treated with a solution of 2-(benzyloxy)-acetaldehyde (**15**, 2.1 g, 14 mmol) in ether (5 mL). The reaction mixture was allowed to warm to room temperature. Water (1.5 mL) was added to the reaction, and the resulting mixture was concentrated. The residue was taken up in chloroform (15 mL), filtered through a pad of sodium sulfate, and reconcentrated. The crude material was then heated to reflux in DMF (15 mL) containing 0.5 equiv of concentrated sulfuric acid until TLC analysis indicated complete hydrolysis of the formamidine **50**. At this time the reaction was cooled, made basic with NH_4OH, and concentrated. The residue was taken up in 40% methanol in chloroform (25 mL) to form a slurry which was filtered through a pad of silica gel. The silica gel pad was then washed with a further 25 mL of the methanol/chloroform solution, and the filtrate was concentrated. The resulting oil was triturated with ether and the triturate discarded. The oil was then taken up in absolute ethanol and reconcentrated to remove traces of water. The resulting oil was then taken up in methanol (50 mL), made neutral with MeOH/HCl, and hydrogenated on a Parr apparatus using 10% Pd/C. The hydrogenation mixture was filtered through Celite, the filter pad was washed with water (10 mL), and the resulting filtrate was concentrated. The resulting off-white solid residue was dried by the addition of absolute ethanol (50 mL) and reconcentration. Although ^1H NMR analysis (D_2O) of the resulting solids (0.4 g) indicated impurities, the highly polar nature of the 1-(2-pyrrolidinyl)ethanediols (**51**) precluded purification at this point and the material was carried on to the next synthetic step.

2,2-Diphenyl-4-(2-pyrrolidinyl)-1,3-dioxolanes (38a and 38b). The crude mixture of 1-(2-pyrrolidinyl)-1,2-ethanediol (**51**) hydrochlorides were taken up in 2-propanol (10 mL). To this was added *p*-toluenesulfonic acid monohydrate (30 mg), and the mixture was brought to reflux. Solid benzophenone dimethyl ketal (1.6 g, 7 mmol) was added in portions. After the addition was complete the reaction was allowed to cool to room temperature. The reaction mixture was the poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was discarded, the aqueous layer was returned to the separatory funnel, chloroform was added (30 mL) and the acidic aqueous layer was neutralized by the addition of 28% aqueous NH_3. The organic layer was then dried and concentrated. The resulting diastereomeric dioxolanes were separated through chromatography on silica gel (10% MeOH/$CHCl_3$) and subsequent preparation of the hydrochloride salts from 2-propanol to provide 221 mg of the racemate **38a** and 65 mg of the racemate **38b**. Overall combined yields of the 2,2-diphenyldioxolane compounds **38a** and **38b** from *N'-tert*-butyl-*N*-pyrrolidinylformamidine was 8.3%. **38a**: mp 204–205 °C; ^1H NMR ($CDCl_3$) 7.2–7.6 (m, 10 H), 4.59 (ddd, J = 6.1, 5.6, 5.6 Hz, 1 H, H_c), 4.10 (dd, J = 10.1, 5.6 Hz, 1 H, H_a), 4.07 (dd, J = 10.1, 5.6 Hz, 1 H, H_b), 3.72 (m, 1 H, H_d), 3.3 (m, 1 H), 3.12 (m, 1 H), 1.9–2.1 (m, 4 H); mass spectrum (CI, NH_3), m/e 296 (M + 1). Anal. ($C_{19}H_{21}NO_2$·HCl) C, H, N. **38b**: mp 276–277 °C; ^1H NMR ($CDCl_3$) 7.2–7.6 (m, 10 H), 4.72 (ddd, J = 5.6, 5.6, 5.1 Hz, 1 H, H_c), 4.12 (dd, J = 10.5, 5.6 Hz, 1 H, H_a), 4.07 (dd, J = 10.5, 5.6 Hz, 1 H, H_b), 3.71 (m, 1 H, H_d), 3.3 (m, 2 H), 1.9–2.15 (m, 4 H); mass spectrum (CI, NH_3), m/e 296 (M + 1). Anal. ($C_{19}H_{21}NO_2$·HCl) C, H, N.

Molecular Modeling Study of 38a and 38b. Computer models of **38a** and **38b** were constructed from phenyl, 1,3-dioxolane, and pyrrolidine subunits found in the MACROMODEL fragment library. These fragments were linked by bonds of average C–C bond length and valence angle as provided by the MACROMODEL parameter set. The conformational analysis was treated in two parts: (1) the effect of pseudorotation of the dioxolane ring and (2) the conformational interaction of the freely rotating phenyl and pyrrolidinyl substituents. The systematic conformational search was performed using the "Multi-C" option of MACROMODEL. Relative populations within each of the determined low-energy conformations were calculated using a Boltzmann distribution, and ^1H NMR coupling constants were determined using a weighted average.

Binding Studies. Performed as previously described by Jacobson et al.[4] using a fresh tissue homogenate preparation of whole rat brain minus cerebellum. Incubation was carried out at 5 °C with [^3H]TCP as the radioligand. Rapid filtration was done through glass fiber filters (Schleicher and Scheull #32) presoaked in 0.03% polylysine for 2 h at 5 °C. The inhibition constant (K_i) for determination of the affinity of the compound for the PCP binding site was calculated using the Cheng–Prusoff[17] equation using our predetermined K_d for TCP (16.5 nM) from Scatchard analysis. TCP (10 μM) was used for the determination of the nonspecific binding. Specific binding was determined to be to be >95%. Data were analyzed using GRAPHPAD software.[18]

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Registry No. **5**, 139238-96-3; **6**, 139132-58-4; **7**, 139132-59-5; **8**, 139132-60-8; **9**, 139132-61-9; **10**, 139132-62-0; **11**, 139132-63-1; **12**, 139132-64-2; **13**, 139132-65-3; **14**, 139132-66-4; **15**, 139132-67-5; **16**, 139132-68-6; **17**, 117994-58-8; **18**, 139132-69-7; **19**, 117994-64-6; **20**, 139132-70-0; **21**, 139132-71-1; **22**, 139132-72-2; **23**, 139132-73-3; **24**, 122440-37-3; **25**, 122269-20-9; **26**, 139238-97-4; **27**, 122269-19-6; **28**, 122269-18-5; **29**, 122440-38-4; **30**, 139132-74-4; (±)-**31**, 139238-98-5; (±)-**32**, 139238-99-6; **33**, 139132-75-5; (±)-**34**, 139239-00-2; (±)-**35**, 139239-01-3; (±)-**36**, 139132-76-6; (±)-**37**, 139239-02-4; (±)-**38a**, 139166-05-5; (±)-**38b**, 139166-06-6; (±)-(*R**,*R**)-**39**, 139132-77-7; (±)-(*R**,*S**)-**39**, 139132-90-4; (±)-**40a**, 139132-87-9; (±)-**40b**, 139132-88-0; **41**, 139132-78-8; **42**, 139132-79-9; **43**, 139132-80-2; **44**, 100-69-6; (±)-**45**, 139239-03-5; (±)-**46**, 139132-81-3; (±)-(*R**,*R**)-**47**, 139239-04-6; (±)-(*R**,*S**)-**47**, 139239-05-7; **48**, 117994-55-5; **49**, 85152-51-8; **50**, 139132-86-8; (±)-(*R**,*R**)-**51**, 139132-82-4; (±)-(*R**,*S**)-**51**, 139132-91-5; **52**, 16495-03-7; **53**, 139132-83-5; **54**, 139132-84-6; **55**, 139132-85-7; $Ph_2C(OMe)_2$, 2235-01-0; (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol, 22323-82-6; acetophenone dimethyl acetal, 4316-35-2; 3-hydroxypropiophenone dimethyl ketal, 139132-89-1.