albumin were measured by the A/G-B test (Wako, Japan) and albumin B-tests (Wako, Japan), respectively.

Acknowledgment. We wish to thank Dr. N. Shimamoto for the assay of lipid peroxidation inhibition, Dr. Y. Yoshimura for measuring log P of compound **24**, and Dr. M. Nishikawa, Dr. A. Imada, Dr. G. Goto, and Dr. Y. Inada for their encouragement and helpful discussions throughout this work. Thanks are also due to Dr. M. Motsenbocker for reviewing the manuscript.

Registry No. **1**, 80809-81-0; **2**, 89667-40-3; 4, 98829-12-0; **5**, 117574-29-5; **6**, 117574-41-1; **7**, 117574-35-3; **8**, 117574-42-2; **9**, 117574-73-9; **10**, 117574-72-8; 11, 117585-81-6; **12**, 117574-37-5; **13**, 117585-82-7; **14**, 117574-38-6; **15**, 117574-34-2; **16**, 117574-36-4; **17**, 117574-39-7; **18**, 117574-49-9; **19**, 117574-52-4; **20**, 117574-30-8; **21**, 117574-33-1; **22**, 117574-45-5; **23**, 117574-32-0; **24**, 117574-40-0; **25**, 117574-44-4; **26**, 129813-29-2; **27**, 129813-30-5; **28**, 129813-31-6; **29**, 129813-32-7; **30**, 129833-16-5; **31**, 700-13-0; **32a**, 4754-27-2; **32b**, 6270-47-9; **32c**, 129813-33-8; **32d**, 100181-52-0; **33c**, 129813-34-9; **33d**, 117574-31-9; **34**, 626-55-1; **36a**, 1570-48-5; **36b**, 1701-72-0; **36c**, 6294-61-7; **37**, 69821-05-2; **38a**, 129813-35-0; **38b**, 129813-36-1; **38c**, 129813-37-2; **39a**, 129813-38-3; **39b**, 129813-39-4; **39c**, 117585-86-1; **40a**, 129813-40-7; **40b**, 129813-41-8; **40c**, 117574-51-3; **41a**, 96-48-0; **41b**, 542-28-9; **41c**, 502-44-3; **42a**, 59578-62-0; **42b**, 117574-57-9; **42c**, 117574-58-0; **43a**, 129813-42-9; **43b**, 129813-43-0; **43c**, 129813-44-1; **44a**, 129813-45-2; **44b**, 129813-46-3; **44c**, 129833-17-6; **45a**, 117574-62-6; **45b**, 129813-47-4; **45c**, 129813-48-5; **46a**, 117574-63-7; **46b**, 117574-66-0; **46c**, 117574-65-9; **47a**, 117574-64-8; **47b**, 117574-67-1; **47c**, 117574-68-2; **47d**, 117574-69-3; **48a**, 117574-70-6; **48b**, 117574-71-7; **48c**, 117574-77-3; **48d**, 117574-78-4; **49a**, 117574-50-2; **49b**, 129813-49-6; **49c**, 117574-55-7; **49d**, 117574-56-8; **50a**, 117574-34-2; **50b**, 117574-36-4; **50c**, 117574-39-7; **50d**, 117574-49-9; **51**, 35896-58-3; **52**, 89048-25-9; **53a**, 4537-09-1; **53b**, 53772-19-3; **54a**, 54757-17-4; **54b**, 34824-73-2; **54c**, 89048-14-6; **55a**, 117574-76-2; **55b**, 129813-50-9; **55c**, 129813-51-0; **56a**, 117574-40-0; **56b**, 117574-44-4; **57**, 137-18-8; **58**, 129813-52-1; **59**, 129813-53-2; **60**, 867-13-0; **61**, 129813-54-3; **62**, 129813-55-4; ethyl 3-[4-(hydroxy-(3-pyridyl)methyl)phenyl)-2-methyl acrylate, 100181-52-0; trimethylchlorosilane, 75-77-4; propionitrile, 107-12-0; valeronitrile, 110-59-8; hetanenitrile, 629-08-3; 5-lipoxygenase, 80619-02-9; thromboxane A_2 synthase, 60832-04-4; thromboxane A_2, 57576-52-0; leucotriene B_4, 71160-24-2.

2,3-Dihydrobenzofuran Analogues of Hallucinogenic Phenethylamines

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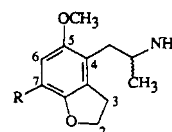
Two 2,3-dihydrobenzofuran analogues of hallucinogenic amphetamines were prepared and evaluated for activity in the two-lever drug-discrimination paradigm in rats trained to discriminate saline from LSD tartrate (0.08 mg/kg) and for the ability to displace $[^{125}I]$-(*R*)-DOI ($[^{125}I]$-(*R*)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) from rat cortical homogenate 5-HT_2 receptors. The compounds, 1-(5-methoxy-2,3-dihydrobenzofuran-4-yl)-2-aminopropane (**6a**) and its 7-brominated analogue **6b**, possessed activity comparable to their conformationally flexible counterparts 1-(2,5-dimethoxyphenyl)-2-aminopropane (**3**) and its 4-bromo derivative DOB (**5**), respectively. The results suggest that the dihydrofuran ring in **6a** and **6b** models the active conformation of the 5-methoxy groups in **3** and **5**. Free energy of binding, derived from radioligand displacement K_A values, indicated that addition of the bromine in either series contributes 2.4–3.2 kcal/mol of binding energy. On the basis of surface area of the bromine atom, this value is 2–3 times higher than would be expected on the basis of hydrophobic binding. Thus, hydrophobicity of the para substituent alone cannot account for the dramatic enhancement of hallucinogenic activity. Although this substituent may play a minor role in orienting the conformation of the 5-methoxy group in derivatives such as **4** and **5**, there appears to be some other, as yet unknown, critical receptor interaction.

Recently, we reported the synthesis and LSD-like biological activity in rats of compounds **1** and **2**, which were considered to be analogues of the hallucinogenic phenethylamine derivative 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**4**, DOM, STP).[1] Evaluation of **1** and **2** in the two-lever drug-discrimination paradigm, in rats trained to discriminate saline from LSD tartrate (0.08 mg/kg), revealed marked attenuation of potency in substituting for LSD when compared with the prototype **4**.

1: R = H
2: R = CH_3

3: R = H
4: R = CH_3
5: R = Br



6a: R = H
6b: R = Br

One explanation offered for this loss of activity was the possibility that the 5-methoxy group of **4** (and hence the unshared electron pairs of the methoxy oxygen) must adopt a particular conformation at the receptor, where the *O*-methyl is directed away from the 4-substituent. That is, the 4-methyl group of **4**, through a nonbonded interaction, forces the 5-methoxy to lie in an anti conformation. We have earlier reported the results of molecular mechanics calculations that illustrate this effect.[2] This was an attractive hypothesis, since it was known that in 2,5-dimethoxy-substituted phenethylamine derivatives such as **4**, virtually any substituent in the 4-position confers high activity on the molecule.[3] Substituents spanning a range of electronic and hydrophobic properties are effective, from

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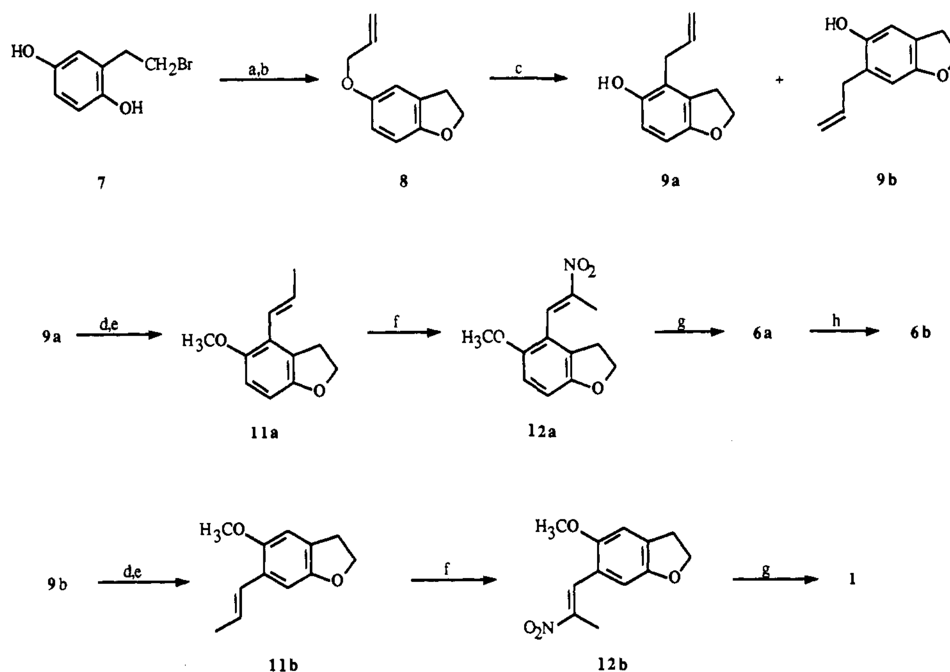
Scheme I[a]



[a] (a) K_2CO_3, acetone, reflux; (b) $CH_2{=}CHCH_2BR$, K_2CO_3, acetone, reflux; (c) heat; (d) CH_3I, K_2CO_3, acetone, reflux; (e) KOH, EtOH, reflux; (f) $AgNO_2$, I_2, Et_3N, pyridine; (g) $LiAlH_4$, THF; (h) Br_2, AcOH.

methoxy, alkylthio, alkyl, and halogen to a nitro group.

On the other hand, this cannot be the complete explanation for the importance of the para substituent. For example, Titeler et al.[4] have shown that affinity for the [^{3}H]DOB-labeled 5-HT_2 site increases if the 4-methyl of 4 is extended to ethyl or propyl or replaced with bromine. However, a methyl would be of sufficient size to direct the orientation of the 5-methoxy.

Lipophilicity is an important determinant of hallucinogenic potency, as noted in an early QSAR study by Barfknecht et al.[5] Shulgin and Dyer have also illustrated this for a limited series of 4-alkyl substituted compounds.[6] Subsequently, using a smooth-muscle assay with a contractile response that was highly correlated with human hallucinogenic potency, we developed a quantitative equation for an extensive series of 2,5-dimethoxy-4-substituted-phenethylamines that clearly identified a role for hydrophobicity of the 4-substituent.[7] However, that study also indicated that the receptor had a limited tolerance for the size of this substituent.

Domelsmith et al.[8] and more recently Clare[9] have carried out extensive QSAR analyses which point to the importance of hydrophobicity of the 4-substituent as a determinant of activity. The apparent correlation between affinity for the 5-HT_2 receptor and hallucinogenic activity has also led Seggel et al.[10] to study the relationship between hydrophobicity of the 4-substituent and affinity for the [^{3}H]ketanserin-labeled 5-HT_2 receptor. For the study of hallucinogens, conclusions from this latter report are somewhat confounded by the inclusion of compounds that are inactive and which appear to be 5-HT_2 antagonists. Nevertheless, hydrophobicity also emerged as an important determinant of binding at that site.

However, hydrophobicity of the 4-substituent alone cannot completely account for the variations noted in biological activity for the various substituents studied (e.g. see ref 8). In spite of all these studies, the situation remains complex, and a complete understanding of the role of the 4-substituent has not been gained. It appeared therefore, that studies of compounds **6a** and **6b** might prove useful. In these compounds, the "5-methoxy" function is tethered to the aromatic ring in a sense anti to that present in **1**. Furthermore, if the role of the 4-substituent were solely one of orienting the 5-methoxy, the addition of an atom at the corresponding 7-position of **6a** might be expected to have a minimal effect on biological activity. At the outset however, uncertainty clouded such predictions because of the unknown effect on activity of additional substitution, by virtue of the dihydrofuran ring fusion into the aromatic ring 6-position (position 3a of the fused heterocycle).

This report describes a divergent synthesis that affords both **1** and **6a**. Compounds **6a** and **6b** were tested for substitution in the two-lever drug-discrimination paradigm, in rats trained to discriminate saline from LSD tartrate (0.08 mg/kg, i.p.). Compound 4 was retested with **3**, **6a**, and **6b** to provide side-by-side comparisons of potency, and allow extrapolations to our earlier study.[1] Compounds **1** and **3**–**6b** were also studied for their ability to displace [^{125}I]-(*R*)-(–)-DOI ([^{125}I]-(*R*)-2-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) from binding sites in rat cortical homogenate, as a measure of affinity for the agonist-labeled 5-HT_2 receptor. Affinity for this site has previously been shown to be highly correlated with human hallucinogenic activity.[11,12] All compounds tested were racemic, although

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one would anticipate that their *R* enantiomers would be somewhat more potent.[3]

Chemistry

It was initially envisioned that 2,5-dimethoxybenzaldehyde could be converted to an imine, acetal, or oxazoline and then selectively lithiated at the 6-position, followed by trapping with ethylene oxide to afford the corresponding 6-(2-hydroxyethyl) derivative.[13] This could then have been elaborated to the desired **6a**. However, after extensive efforts, reaction conditions could not be identified that led to significant yields of ethylene oxide adducts of the metalated protected aldehydes. Likewise, use of higher order lithium diaryl cuprates was not successful.

Accordingly, an alternate approach (Scheme I) was devised, which led to the desired target compounds. Following procedures developed by Selander in Nilsson,[14] 2,5-dimethoxyphenylacetic acid was converted to O-demethylated bromide **7**. Treatment of this with K_2CO_3 in acetone at reflux led to intramolecular cyclization. After TLC indicated disappearance of **7**, allyl bromide was added to the reaction and reflux was continued. Thus, in one pot, **7** was converted to allyl ether **8**. Thermal Claisen rearrangement gave a mixture of **9a** and **9b** in a ratio of 1:2.3, determined by NMR analysis, and similar to results reported by Hammond et al.[15] The regioisomers were separated by flash chromatography, and were converted to their *O*-methyl ethers **10a** and **10b** by treatment with methyl iodide and K_2CO_3 in acetone at reflux.

Both allyl derivatives were isomerized to the propenyl derivatives **11a** and **11b** by treatment with KOH in ethanol.[16] Reaction of these with nitryl iodide, followed by base, afforded modest yields of nitrostyrenes **12a** and **12b**.[17] Reduction with $LiAlH_4$ then yielded **6a** and **1**, which were converted to their methane sulfonate salts. Treatment of the free base of **6a** with elemental bromine in glacial acetic acid gave **6b**.

Pharmacology

Compounds **3**, **4**, **6a**, and **6b** were evaluated in the two-lever drug-discrimination assay, in groups of rats trained to discriminate saline from injections of LSD tartrate (0.08 mg/kg, ip) by using methods described previously.[18] For compounds that gave complete substitution, potencies were measured using ED_{50} values.

Ability of compounds to displace 0.25 nM [^{125}I]-(*R*)-DOI from binding sites in rat frontal cortex was measured following procedures outlined earlier.[11] Free energies of binding were estimated by the equation $\Delta G^0 = -RT \ln K_A$,[19] where K_A values were obtained from the radioligand binding studies.

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Table I. Drug-Discrimination Data in LSD-Trained Rats

compd	dose, μmol/kg	n[a]	D[b]	% SDL[c]	ED_{50} (95% CI)
saline		8	0	0	
1					6.99 (4.12–18.5)[d]
3	4.07	8	0	38	
	8.14	9	1	38	
	16.28	9	1	50	
	32.56	9	1	63	
	40.70	12	4	63	
4	0.51	8	0	13	0.89 (0.57–1.39)
	1.02	8	0	75	0.60 (0.38–0.95)[d]
	2.03	9	1	88	
6a	2.03	8	0	25	5.23 (2.71–10.1)
	8.16	8	0	50	
	10.19	8	0	63	
	12.16	9	1	88	
6b	0.25	8	0	25	0.57 (0.29–1.09)
	0.51	8	0	38	
	1.01	8	0	75	
	2.03	10	2	88	

[a] Number of animals tested. [b] Number of animals disrupted. [c] Percentage of animals selecting drug lever. [d] Data from ref 1.

Results and Discussion

The results of the substitution tests in LSD-trained rats are presented in Table I. As previously reported,[1] compound **1** has reduced LSD-like activity in this assay, as compared with **4**. In the present work, compound **6a** had relatively low potency but still had greater activity than **1**. In view of the fact that para substitution in the 2,5-dimethoxy series generally increases potency dramatically, **1** seems much less active than would be expected. Interestingly, while **6a** did produce full substitution, compound **3** only produced partial substitution at the highest dose tested, 40.7 μmol/kg (9.4 mg/kg). Although higher doses of **3** might have produced full substitution, **6a** is clearly more potent.

The bromine substitution in **6b** leads to greatly enhanced potency, a result that parallels the structure–activity relationships of 2,5-dimethoxy-4-substituted derivatives. That is, **6b** has a potency comparable to that of **5**. Therefore, this seems to provide evidence that the dihydrofuran moiety in **6a** and **6b** models the active orientation of the 5-methoxy function in **3** and **5**. However, the fact that **6a** has relatively modest potency seems also to suggest that any conformational orienting effect of the 4-substituent may have minor importance. Rather, there must be some specific receptor interaction with this group.

The radioligand binding data provide even more interesting insights into the possible importance of the para substituent. A number of studies have pointed to the importance of hydrophobicity of the 4-substituent as a determinant of activity.[5–9] Nevertheless, the most significant role for the para substituent cannot simply be a hydrophobic interaction with the receptor. As seen in Table II, addition of the methyl or bromine to **3** increases free energy of binding by 1.9 and 3.2 kcal/mol, respectively. On the basis of their van der Waals radii, one could estimate that this represents a binding energy on the order of 50–60 cal/Å^2 for the surface area of the methyl and bromo groups. This is far above the value calculated by Chothia for hydrophobic binding of 20–24 cal/Å^2.[20,21]

It is also clear that the para-substituent has relatively little importance in orienting the *m*-methoxy, since addition of the bromine to **6a** still increased binding energy by 2.4 kcal/mol. This must represent the contribution to

(20) Chothia, C. *Nature* **1974**, *248*, 338.
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Table II. Data from Binding Studies of Analogues 1–6[a]

compd	K_I, nM	Hill coeff	$\Delta G°$,[b] kcal/mol
1	388 ± 47	0.91 ± 0.03	-9.1
3	465 ± 11	0.92 ± 0.06	-9.0
4	18.6 ± 2.0	0.89 ± 0.10	-10.9
5	2.6 ± 0.2	1.09 ± 0.10	-12.2
6a	146 ± 19	0.93 ± 0.05	-9.7
6b	3.1 ± 0.3	1.06 ± 0.03	-12.1

[a] For the radioligand [^{125}I]-(*R*)-DOI the binding data were K_D = 1.34 ± 0.12 nM, n = 4. [b] Approximated by $\Delta G^0 = -RT \ln K_A$ at 37 °C.

binding of a bromine, independent of any component that might arise from an orienting effect on the 5-methoxy. Depending on the method of calculating surface area (van der Waals radius-based or solvent-accessible), this still represents a binding contribution for the bromine of 40–50 cal/Å^2, well above that obtainable from a simple hydrophobic interaction.

If the contribution of the bromine to free energy of binding in **6b** (2.4 kcal/mol) is subtracted from the difference in free energy of binding between **3** and **5**, a 0.8 kcal/mol component remains. Interestingly, the difference in binding energy between **3** and **6a** is 0.7 kcal, a nearly identical value. It is possible that this could represent the energy expended by the receptor to orient the 5-methoxy group of **3**, which in the case of **4**, **5**, **6a**, or **6b** is no longer required. One must note, however, that such an approximation does not take into account possible effects on binding of the methylene of the dihydrofuran ring and the altered electronic properties of the aromatic ring.

However, the high potency of **6b** makes it clear that these rigid analogues do model the active binding conformation for the 5-methoxy of compounds such as **4** and **5**. The nearly identical affinities/binding energies of **1** and **3** indicate that the para substitution in **1** does not play the same role that it serves in **4**. The most logical explanation for this is that the *m*-oxygen unshared electrons in **1** are fixed into an orientation that is not optimally complementary to the receptor. This would seem to point to the necessity for a particular orientation of the oxygen unshared electrons.

Finally, these studies lend some experimental weight to the recent QSAR calculations of Clare,[9] who identified a significant meta–para interaction term in the substituted hallucinogenic amphetamines. That study pointed to a requirement for meta substituents of large volume but low hydrophobicity and a moderate volume and hydrophobicity for the para substituent. Clearly this is an important region of the molecule for productive receptor interaction.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra (500 MHz) were obtained with a Varian VXR-500S NMR instrument in $CDCl_3$, unless otherwise noted. Chemical shifts are reported in δ values (parts per million) relative to an internal reference of $CHCl_3$ (δ 7.24). Abbreviations used in NMR analysis are as follows: br s = broad singlet, d = doublet, dd = doublet of doublets, dq = doublet of quartets, m = multiplet, q = quartet, s = singlet, t = triplet. Chemical ionization mass spectra were obtained with a Finnegan 4000 spectrometer. Fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS 25 spectrometer. Elemental analyses were performed by the Purdue Microanalysis Laboratory or Galbraith Laboratories, Knoxville, TN, and were within ±0.4% of the calculated values unless otherwise noted.

2-(2-Bromoethyl)-1,4-dihydroquinone (7). Following exactly methods developed for a similar compound by Selander and Nilsson,[14] 25.45 g (130 mmol) of 2,5-dimethoxyphenylacetic acid was reduced quantitatively to the corresponding alcohol with diborane in THF. Treatment with PBr_3 afforded the phenethyl bromide and reaction of this with BBr_3 in CH_2Cl_2 at -78 °C gave the desired hydroquinone **7**. The overall yield of the sequence was 35%. An analytical sample was purified by recrystallization from methylene chloride to give off-white crystals: mp 116–117 °C; ^{1}H NMR (CD_3OD) δ 6.49 (m, 3, ArH), 3.47 (t, 2, CH_2, J = 7.8 Hz), 2.98 (t, 2, CH_2, J = 7.8 Hz); CIMS 217 (MH$^+$). Anal. ($C_8H_9BrO_2$) C, H.

5-(Allyloxy)-2,3-dihydrobenzofuran (8).[14,15] A mixture of **7** (9.69 g, 44.7 mmol) and K_2CO_3 (30 g, 219 mmol) in 100 mL of acetone was heated at reflux under N_2 until TLC showed no **7** remaining (56 h). Allyl bromide (4.6 mL, 53.1 mmol) was then added, along with 10 g of fresh K_2CO_3, and reflux was continued another 18 h until TLC indicated complete reaction. The mixture was filtered to remove potassium salts, dried ($MgSO_4$), swirled with silica gel, and refiltered, and the solvent was removed to afford an amber oil. Purification by flash chromatography using methylene chloride as eluent afforded 7.11 g (90%) of **8** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.79 (m, 1, ArH), 6.65 (m, 2, ArH), 6.02 (m, 1, CH), 5.37 (d, 1, H-CH, J = 17.3 Hz), 5.24 (d, 1, H-CH, J = 10.5 Hz), 4.52 (t, 2, CH_2OAr, J = 8.7 Hz), 4.45 (d, 2, CH_2O, J = 5.3 Hz), 3.16 (t, 2, $ArCH_2$, J = 8.7 Hz); FABMS 176 (M$^+$).

4-Allyl-2,3-dihydrobenzofuran-5-ol (9a) and 6-Allyl-2,3-dihydrobenzofuran-5-ol (9b).[15] Upon heating in an oil bath at 200 °C for 3 h, the neat oil **8** (7.42 g, 42.2 mmol) underwent thermal Claisen rearrangement to form a 1:2.3 mixture of **9a** and **9b** as determined by NMR analysis of the crude product. Separation and purification by flash chromatography yielded, in order of elution with 1,2-dichloroethane, **9b** (4.02 g, 54%) and **9a** (1.37 g, 18.5%).

9a: ^{1}H NMR ($CDCl_3$) δ 6.58 (d, 1, ArH, J = 8.4 Hz), 6.54 (d, 1, ArH, J = 8.4 Hz), 5.96 (m, 1, CH), 5.09 (m, 2, CH_2), 4.55 (t, 2, CH_2O, J = 8.6 Hz), 4.48 (s, 1, OH), 3.35 (d, 2, benzylic allyl CH_2, J = 6.0 Hz), 3.13 (t, 2, benzylic CH_2, J = 8.6 Hz); CIMS 177 (MH$^+$).

9b: ^{1}H NMR ($CDCl_3$) δ 6.70 (s, 1, ArH), 6.55 (s, 1, ArH), 5.98 (m, 1, CH), 5.16 (d, 1, H-CH, J = 7.2 Hz), 5.13 (s, 1, H-CH), 4.55 (s, 1, OH), 4.51 (t, 2, CH_2O, J = 8.6 Hz), 3.34 (d, 2, benzylic allyl CH_2, J = 6.3 Hz), 3.14 (t, 2, benzylic CH_2, J = 8.6 Hz); CIMS 177 (MH$^+$).

4-Allyl-5-methoxy-2,3-dihydrobenzofuran (10a). A mixture of **9a** (1.27 g, 7.22 mmol), K_2CO_3 (5 g, 36 mmol), and methyl iodide (0.60 mL, 9.63 mmol) in 100 mL of acetone was heated at reflux for 34 h. The mixture was then filtered, evaporated to dryness, redissolved in methylene chloride and refiltered to remove any residual inorganic salts. Solvent removal afforded a quantitative yield of **10a** as the crude oil which was carried on to the next step without purification. An analytical sample was purified by centrifugal radial chromatography (Chromatotron) using methylene chloride as eluent: ^{1}H NMR ($CDCl_3$) δ 6.62 (d, 1, ArH, J = 8.6 Hz), 6.57 (d, 1, ArH, J = 8.6 Hz), 5.89 (m, 1, CH), 4.95 (m, 2, CH_2), 4.52 (t, 2, CH_2O, J = 8.6 Hz), 3.74 (s, 3, OCH_3), 3.32 (d, 2, benzylic allyl CH_2, J = 6.2 Hz), 3.10 (t, 2, benzylic CH_2, J = 8.6 Hz); CIMS 191 (MH$^+$). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42. Found: C, 74.56; H, 7.27.

6-Allyl-5-methoxy-2,3-dihydrobenzofuran (10b). Following a procedure similar to that of **10a**, 3.5 g (19.9 mmol) of **9b** gave a quantitative yield of **10b**: ^{1}H NMR ($CDCl_3$) δ 6.77 (s, 1, ArH), 6.61 (s, 1, ArH), 5.95 (m, 1, CH), 5.03 (m, 2, CH_2), 4.52 (t, 2, CH_2O, J = 8.6 Hz), 3.77 (s, 3, OCH_3), 3.32 (d, 2, benzylic allyl CH_2, J = 6.7 Hz), 3.17 (t, 2, benzylic CH_2, J = 8.6 Hz); CIMS 19 (MH$^+$). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42. Found: C, 74.13; H, 7.27.

(*E*)-5-Methoxy-4-(1-propenyl)-2,3-dihydrobenzofuran (11a). A solution of **10a** (1.37 g, 7.22 mmol) and 3 g of KOH in 10 mL of ethanol was heated at reflux in a 100 °C oil bath for 12 h.[16] After cooling and dilution with 250 mL of H_2O, the mixture was extracted repeatedly with diethyl ether. The combined ethereal extract was washed with brine (20 mL), dried ($MgSO_4$), and filtered. Solvent removal yielded an orange oil which was partially purified by centrifugal radial chromatography (Chromatotron) (CH_2Cl_2) to afford 1.16 g (85%) of **11a** as a pale yellow oil which solidified on standing. An analytical sample was purified by sublimation: mp 43–44 °C; ^{1}H NMR ($CDCl_3$) δ 6.64 (d, 1, ArH, J = 8.6 Hz), 6.59 (d, 1, ArH, J = 8.6 Hz), 6.58 (d, 1, ArCH=, J = 16.1 Hz), 6.22 (dq, 1, CH, J = 6.6, 16.1 Hz), 4.54 (t, 2, CH_2O, J = 8.5 Hz), 3.79 (s, 3, OCH_3), 3.25 (t, 2, CH_2, J = 8.5 Hz), 1.92

(d, 3, CH_3, J = 6.6 Hz); CIMS 191 (MH^+). Anal. ($C_{12}H_{14}O_2$) C, H.

(*E*)-5-Methoxy-6-(1-propenyl)-2,3-dihydrobenzofuran (11b). Following a procedure similar to that of **11a**, 3.78 g (19.9 mmol) of **10b**, gave 3.74 g (99%) of **11b** as a tan solid. An analytical sample was purified by sublimation to afford white crystals: mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 1, ArH), 6.74 (s, 1, ArH), 6.66 (d, 1, ArCH=, J = 15.8 Hz), 6.12 (dq, 1, CH, J = 6.6, 15.8 Hz), 4.51 (t, 2, CH_2O, J = 8.6 Hz), 3.76 (s, 3, OCH_3), 3.16 (t, 2, CH_2, J = 8.6 Hz), 1.86 (d, 3, CH_3, J = 6.6 Hz); CIMS 191 (MH^+). Anal. ($C_{12}H_{14}O_2$) C, H.

5-Methoxy-4-(2-nitro-1-propenyl)-2,3-dihydrobenzofuran (12a). A solution of $AgNO_2$ (308 mg, 2.0 mmol) and I_2 (508 mg, 2.0 mmol) in 20 mL of dry THF was stirred under N_2 at room temperature for 45 min. To this stirred solution were added **11a** (190 mg, 1.0 mmol) and pyridine (0.32 mL, 4.0 mmol) in 10 mL of THF, and stirring was continued for 5.5 h. At this time, 1.5 mL of triethylamine was added via syringe, and stirring was continued for 1 h. The solvent was removed on a rotary evaporator and the residue was redissolved in ethyl ether. The ethereal mixture was washed with saturated $NaHSO_3$ (2 × 20 mL), 5% HCl (20 mL), saturated $NaHCO_3$ (2 × 20 mL), and H_2O (20 mL), dried (Na_2SO_4), and filtered. Solvent removal and recrystallization from methanol yielded 174 mg (74%) of **12a** as yellow-orange needles of two isomorphs: mp 68–69 °C with resolidification, then mp 77–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1, CH), 6.78 (d, 1, ArH, J = 8.7 Hz), 6.69 (d, 1, ArH, J = 8.7 Hz), 4.58 (t, 2, CH_2O, J = 8.6 Hz), 3.78 (s, 3, OCH_3), 3.06 (t, 2, $ArCH_2$, J = 8.6 Hz), 2.15 (s, 3, CH_3); CIMS 236 (MH^+). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

5-Methoxy-6-(2-nitro-1-propenyl)-2,3-benzofuran (12b). Following a procedure simlar to that of **12a**, 380 mg (2.0 mmol) of **11b** gave, after recrystallization from methanol, 290 mg (62%) of **12b** as orange needles: mp 95–96 °C (lit.[1] mp 89–91 °C).

1-(5-Methoxy-2,3-dihydrobenzofuran-4-yl)-2-aminopropane Methanesulfonate (6a). Nitro compound **12a** (300 mg, 1.28 mmol) was reduced with $LiAlH_4$ (306 mg, 7.66 mmol) in dry THF. The usual workup[1] afforded 233 mg (88%) of the free base **6a** as a nearly colorless oil. Preparation of the methanesulfonate salt and recrystallization from ethanol/ethyl ether gave white needles: mp 167–168 °C; ^{1}H NMR ($CDCl_3$, free base) δ 6.61 (d, 1, ArH, J = 8.5 Hz), 6.59 (d, 1, ArH, J = 8.5 Hz), 4.53 (t, 2, CH_2O, J = 8.6 Hz), 3.75 (s, 3, OCH_3), 3.20 (m, 3, CHN and $ArCH_2$), 2.59 (m, 2, $ArCH_2$ side chain), 1.46 (br s, NH_2), 1.10 (d, 3, CH_3, J = 6.4 Hz); CIMS 208 (free base) (MH^+). Anal. ($C_{13}H_{21}NO_5S$) C, H, N.

1-(7-Bromo-5-methoxy-2,3-dihydrobenzofuran-4-yl)-2-aminopropane Methanesulfonate (6b). The free base **6a** (38 mg, 0.184 mmol) was treated with elemental bromine (29.3 mg, 0.184 mmol as a 0.37 M solution in AcOH) in 5 mL of acetic acid at room temperature for 1 h. The acetic acid and bromine were removed via rotary evaporation, and the residue was redissolved in H_2O, basified with Na_2CO_3, and extracted with ethyl ether (3 × 15 mL), and the combined ethereal extract was dried (Na_2SO_4) and filtered. Solvent removal yielded 42.6 mg (81%) of the free base **6b** as a colorless oil. Preparation of the methanesulfonate salt and recrystallization from ethanol/ethyl ether gave white needles: mp 191–193 °C; ^{1}H NMR ($CDCl_3$, free base) δ 6.72 (s, 1, ArH), 4.60 (t, 2, CH_2O, J = 8.7 Hz), 3.72 (s, 3, OCH_3), 3.22 (m, 3, CH_2CH), 2.51 (m, 2, $ArCH_2$), 1.44 (br s, NH_2), 1.06 (d, 3, CH_3, J = 6.3 Hz); CIMS 286, 288 (free base) (MH^+). Anal. ($C_{13}H_{20}BrNO_5S$) C, H, N.

1-(5-Methoxy-2,3-dihydrobenzofuran-6-yl)-2-aminopropane Methanesulfonate (1). Similarly to **6a**, reduction of 596 mg (2.54 mmol) of **12b** with 608 mg (16.8 mmol) of $LiAlH_4$ in dry THF afforded, after workup, 525 mg (81%) of the free base **1**. Preparation of the methanesulfonate and recrystallization from ethanol/ethyl ether gave tan crystals: mp 148–151 °C (lit.[1] mp 141–144 °C).

Pharmacology Methods. Drug-Discrimination Studies. Male Sprague–Dawley rats, weighing approximately 200 g at the beginning of the study, were obtained from Harlan Laboratories, Indianapolis, IN. Except for the first week, all rats were housed individually in a temperature-controlled room (25 °C) with an 0600–2000 lights on, 2000–0600 lights off schedule. Twenty-four rats were used for the LSD studies.

Immediately following scheduled discrimination sessions the animals were returned to their home cages. Food was provided to maintain each rat at about 80% of the free-feeding weight. On Sundays, no sessions were run and animals were allowed to feed at their regularly scheduled time. Water was available ad lib, except during the training and testing periods.

Apparatus. Six identical standard operant chambers (Coulbourn Instruments) equipped with two response levers separated by a food-pellet delivery system were employed. Food pellets (Bioserve, 45 mg dustless) were used as reinforcement. Chambers contained a white house light and masking white noise and were enclosed in ventilated, sound-attenuated cubicles. The operant chambers were controlled by solid-state logic interfaced through a Coulbourn Instruments Dynaport to an IBM-PC located in an adjacent control room. Data acquisition and control were handled by the PC using locally developed software.

Drug Administration. The training dose of *d*-LSD tartrate (NIDA, 185.5 nM/kg; 0.08 mg/kg) or appropriate test drugs were administered in saline in a volume of 1 mL/kg of body weight. All injections were administered intraperitoneally 30 min prior to the start of discrimination sessions.

Discrimination Training. To avoid positional preference, half of the animals were trained to press TRAINING DRUG-L and SALINE-R, while the other half were trained vice versa. Rats were trained on an FR-50 schedule with 15-min maintenance sessions. No significant difference in responding rate was seen between the training dose of LSD and saline ($p > 0.05$, Student's *t* test). The complete training procedure has been published elsewhere.[18]

Stimulus Generalization. Testing sessions were run once or twice per week, with training sessions held the rest of the week and Sundays off. At least one drug session and one saline session preceded each test session. On test days, the animal was placed into the operant chamber 30 min after injection. Test sessions lasted until the rat emitted 50 responses on either lever or until 5 min had passed, whichever came first. If the rat did not emit 50 responses on either lever within 5 min, he was scored as disrupted and was not included in the calculations. In either case, no reinforcement was given. In order to receive a test drug, the animals were required to satisfy the 85% correct lever response criterion on each of the two preceding training sessions. Also, following the procedure of Colpaert et al.,[22] test data were discarded and the test condition later retested if the test session was followed by failure to meet the 85% criterion in either of the two subsequent training sessions. This procedure was employed to increase the reliability of the individual test data. If the animal was not included in the test procedure on a given day, the session was used for training.

Several preliminary experiments to determine appropriate dosages for new compounds were carried out; these data were discarded. All drug treatments were randomized. At least eight animals were tested at each dose, except in cases where very high doses produced an excessive number of disruptions.

Data Analysis. Animals were scored as drug positive if they selected the LSD-appropriate lever (i.e. if they emitted 50 responses on the drug lever). If generalization occurred (greater than 80% of the rats selected the LSD-appropriate level at some dose), these quantal data were analyzed by the method of Litchfield and Wilcoxon[23] to determine an ED_{50}.

Pharmacology Methods. Radioligand Binding Studies. $[^{125}I]$-(*R*)-DOI was synthesized by the porcedure of Mathis et al.[24] at a specific activity of 2000 Ci/mmol. The radioligand binding procedure of Johnson et al.[11] was employed with only minor modifications. Briefly, triplicate determinations including varying concentrations of displacing drugs, rat prefrontal cortex homogenate, and 0.25 nM $[^{125}I]$-(*R*)-DOI were allowed to equilibrate at 37 °C for 15 min. Specific binding was defined as that displaceable with 1 μM cinanserin. Under these conditions $[^{125}I]$-(*R*)-DOI was found to bind to a single site (Hill coefficient

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= 0.99 ± 0.03) with a K_D of 1.34 ± 0.12 nM and a B_{max} of 45.8 ± 3.0 fmol/mg of protein. Data were analyzed by using the computer programs EBDA and LIGAND, described elsewhere.[25] Protein concentrations were determined according to the method of Bradford.[26] Values for free energy of binding at 37 °C (310 K) were calculated from $\Delta G^0 = -RT \ln K_A$.[19]

Acknowledgment. Support for this work was provided by USPHS Grant DA-02189 from the National Institute on Drug Abuse. We also thank Jim Schirger for assistance with the early synthetic work.

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Synthesis and Benzodiazepine Binding Activity of a Series of Novel [1,2,4]Triazolo[1,5-*c*]quinazolin-5(6*H*)-ones

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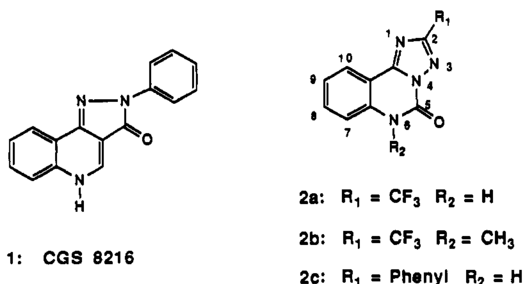
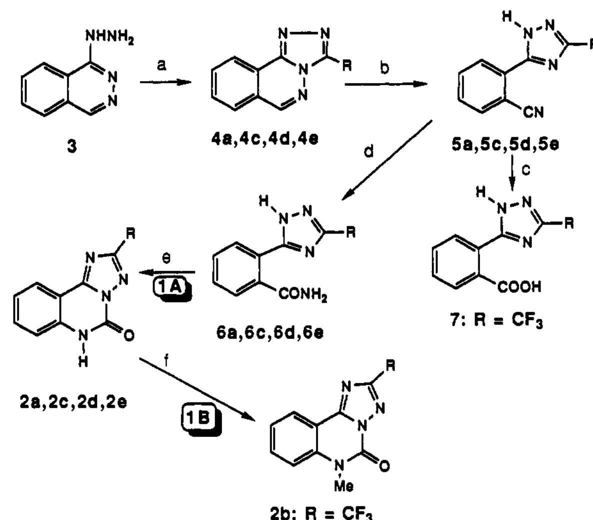
Received February 12, 1990

Investigation of tricyclic heterocycles related to the 2-arylpyrazolo[4,3-*c*]quinolin-3(5*H*)-ones, structures with high affinity for the benzodiazepine (BZ) receptor, led to the synthesis of 2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one, a compound with 4 nM binding affinity to the BZ receptor. Analogues were prepared to assess the importance of the 2-substituent and ring substitution in modifying activity. Several novel synthetic routes were designed to prepare the target compounds, including a two-step synthesis beginning with an anthranilonitrile and a hydrazide. Of the 34 compounds screened in this series, three compounds were found to be potent BZ antagonists in rat models. The leading compound, 9-chloro-2-(2-fluorophenyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (CGS 16228), showed activity comparable to that of CGS 8216 from the pyrazolo[4,3-*c*]quinoline series.

The discovery of CGS 8216 (**1**) at CIBA-GEIGY as a potent benzodiazepine (BZ) receptor antagonist[1] pioneered our efforts in the investigation of other tricyclic heterocycles of similar molecular size and shape. In 1972, CGS 1761 (**2a**)[2] and CGS 1792 (**2b**) were screened for overt effects in the rat and were thought to have weak anxiolytic profiles.[3] Although these compounds were found later to have poor binding to the BZ receptor (i.e., with an IC_{50} value greater than 1 μM), replacement of the trifluoromethyl group of **2a** by the phenyl moiety produced a structure that mimicked the size and shape of **1** very closely, except for the position of the carbonyl group. This compound, CGS 13767 (**2c**), showed a BZ binding affinity IC_{50} value of 4 nM, a substantial improvement over the values for **2a** and **2b**, though not quite as impressive as that for **1**.[1] Modifications of **2c** were designed to assess the importance of the 2-substituent, the oxo group, and selected substitution in the benzene ring.



Scheme I. Methods 1A and 1B[a]



a: R = CF_3 c: R = phenyl d: R = 4-chlorophenyl e: R = 3-pyridyl

[a] Reagents: (a) RCOOH, RCOOCOR, or RCOCl, NaOH, THF or (i) RCHO, MeOH, (ii) Br_2, HOAc, Ac_2O; (b) NaOH, EtOH, or NaOMe, EtOH; (c) (i) 10 N NaOH, (ii) HCl; (d) 85% H_2SO_4; (e) NaBrO, H_2O or $Pb(OAc)_4$, DMF with Et_3N or HOAc; (f) NaH or NaOMe, DMSO, MeI.

Chemistry

A Sandoz patent[4] described the synthesis of 8,9-dimethoxy[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one by hydrolysis and Dimroth rearrangement[5] of 5-chloro-8,9-di-

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