Synthesis, Lipophilicity and Structure of 2,5-Disubstituted 1, 3, 5-Dithiazine Derivatives

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A series of 2,5-disubstituted 1,3,5-dithiazine derivatives were synthesized as potential analogues of the potent dopamine uptake inhibitor GBR 12909. The lipophilic character of the 1,3,5-dithiazine derivatives were experimentally (log *P*) and computationally (clog *P*) determined. The *in vitro* binding affinities of the 2,5-disubstituted 1,3,5-dithiazine derivatives at the dopamine transporter were determined to be much less potent than the binding affinity of GBR 12909 due to steric and electronic effects inherent to the 1,3,5-dithiazine ring system. The X-ray crystal structure of 2-(2-[bis(4-fluorophenyl)methoxy]ethyl)-5-(3-phenylpropyl)-1,3,5-dithiazine (**7**) revealed that the 5-(3-phenylpropyl) group is in a pseudo-axial orientation and syn to the 2-ethoxybenzhydryl moiety.

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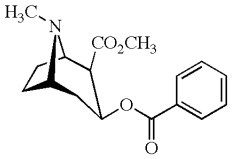
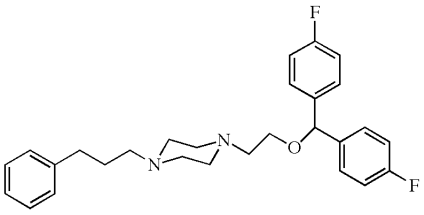
Cocaine (**1**) is a powerful stimulant of the central nervous system. This potentially lethal substance is extremely addictive because it exerts its effects through the reward and pleasure centers of the brain [1]. Despite a significant advancement in understanding the biological mechanisms of action of cocaine, a satisfactory cocaine therapeutic agent has yet to be identified [2]. The search for potential cocaine medications has led to the extensive studies of the structure-activity relationships of a wide variety of dopamine uptake inhibitors at the dopamine transporter [3]. The disubstituted piperazine, GBR 12909 (**2**) is a high affinity selective dopamine transporter ligand [4,5]. GBR 12909 is a potent inhibitor of cocaine binding and exhibits non-stimulant properties in humans [6,7]. Recent studies have focused on GBR 12909 as a template for the design of novel compounds that are selective for the dopamine transporter. These studies have primarily focused on replacement of the piperazine ring of **2** with a variety of mono- and di-nitrogen heterocyclic ring systems [8-12]. To gain a greater understanding of the GBR 12909 pharmacophore it has been of interest in our laboratories to replace the piperazine ring system with novel heterocyclic systems to study the steric and electronic effects on binding affinity at the dopamine transporter. The target 1,3,5-dithiazine derivatives were designed to incorporate novel electronic and conformational features relative to GBR 12909 (**2**) while maintaining the *N*-3-phenylpropyl group and the 2-ethoxybenzhydryl moiety as key structural features believed to be important for potent dopamine transporter selectivity. Herein we wish to describe the synthesis, structure, lipophilic character and dopamine transporter affinity of novel 1,3,5-dithiazine derivatives of GBR 12909.

The syntheses of the 1,3,5-dithiazine derivatives of GBR 12909 were envisaged to proceed *via* alkylation of 5-(3-phenylpropyl)-1,3,5-dithiazine (**3a**) with an appropriately substituted 1-bromo-2-[bis(4-substituted phenyl)-methoxy]ethane. In addition, since structure-activity studies of some GBR analogues have shown that the corresponding benzyl analogues are more selective for dopamine transporters [13,14], corresponding derivatives of the benzyl-1,3,5-dithiazine (**3b**) would also be prepared in similar fashion. As illustrated in Scheme 1, the 5-(3-phenylpropyl)-1,3,5-dithiazine (**3a**) and 5-benzyl-1,3,5-dithiazine (**3b**) were prepared in straightforward fashion using established procedures from 3-phenylpropylamine and benzylamine, respectively [15]. The corresponding amine was condensed with formaldehyde in absolute ethanol. This was followed by addition of a solution of aqueous sodium hydrosulfide at 0 °C and the mixture



cocaine (**1**)



GBR12909 (**2**)

Table 1

Crystal Data and Structure Refinement for 1, 3, 5-Dithiazine Analogue **7**

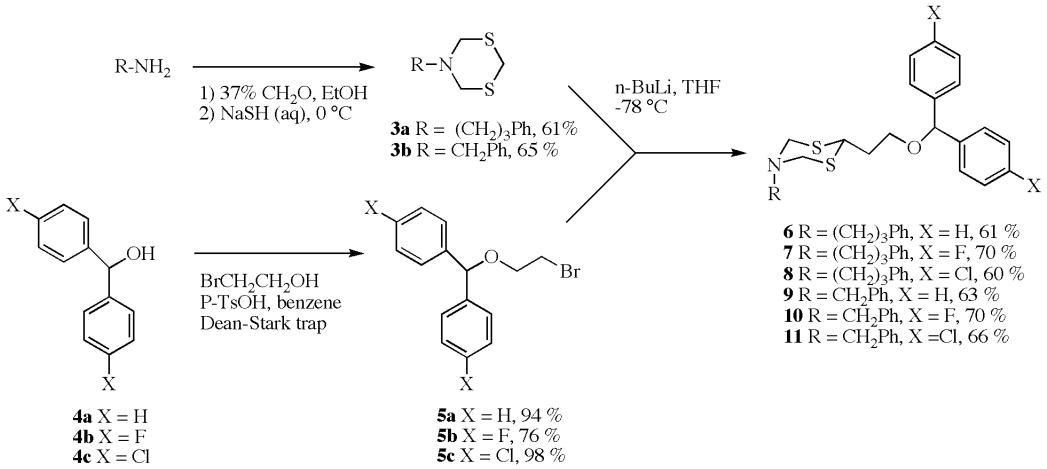
Empirical formula	$C_{27}H_{29}F_2NOS_2$
Formula weight	485.63
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 9.4721(6) Å, α = 90°. b = 33.008(2) Å, β = 02.9190(10)°. c = 7.7860(5) Å, γ = 90°.
Volume	2372.7(3) $Å^3$
Z	4
Density (calculated)	1.359 Mg/m^3
Absorption coefficient	0.261 mm-1
F(000)	1024
Crystal size	0.18 x 0.40 x 0.55 mm^3
Theta range for data collection	1.23 to 26.42°.
Index ranges	-11 £ h £ 11, -41 £ k £ 41, -9 £ l £ 9
Reflections collected	25554
Independent reflections	4856 [R(int) = 0.0445]
Completeness to theta = 26.42°	99.6 %
Absorption correction	Empirical
Max. and min. transmission	1.000000 and 0.700741
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4856 / 0 / 414
Goodness-of-fit on F^2	0.924
Final R indices [I>2sigma(I)]	R1 = 0.0490, wR2 = 0.1158
R indices (all data)	R1 = 0.0835, wR2 = 0.1223
Largest diff. peak and hole	0.752 and -0.399 $e.Å^{-3}$

stirred overnight. This afforded the 5-(3-phenylpropyl)-1,3,5-dithiazine (**3a**, 61%) and 5-benzyl-1,3,5-dithiazine (**3b**, 66%) in good yields. The ease at which these compounds were prepared was somewhat surprising since it had been previously reported that the 5-benzyl-1,3,5-dithiazine was not obtainable [16]. The alkylating agents, 1-bromo-2-[bis(4-substituted phenyl)methoxy]ethanes (**5a-c**) were prepared from 2-bromoethanol and the corresponding substituted benzhydrol (**4a-c**). Acid catalyzed ether formation with azeotropic removal of water *via* a Dean-Stark trap furnished the desired bromides in good yields [17].

The 1, 3, 5-dithiazine ring system was initially developed as synthetic equivalent of a formyl anion. As such the alkylation chemistry of the 1,3,5-dithiazines was already well established [18]. The 2-(2-[bis(4-substituted phenyl)methoxy]ethyl)-5-alkylaryl-1,3,5-dithiazines (**6-11**) were prepared by alkylation of 5-alkylaryl-1,3,5-dithiazine ring system (**3a, b**) with the corresponding bromides (**5a-c**). Treatment of 5-alkylaryl-1,3,5-dithiazine ring system (**3a, b**) with *n*-butyllithium in tetrahydrofuran at –78 °C, followed by addition of solution of the corresponding bromide (**5a-c**) in tetrahydrofuran afforded the 1,3,5-dithiazine derivatives (**6** - **11**) of GBR 12909 in good yields (Scheme 1).

The structure of 2-(2-[bis(4-fluorophenyl)methoxy]-ethyl)-5-phenylpropyl-1,3,5-dithiazine (**7**) was unequivocally confirmed by X-ray crystallography [19]. Similar to the piperazine ring system of GBR 12909 derivatives [20], the 1,3,5-dithiazine ring of **7** (Figure 1) was found to exist in a chair conformation with the 2-[bis(4-fluorophenyl)methoxy]ethyl moiety occupying a pseudo-equatorial position. However, the 3-phenylpropyl group on the nitrogen atom of **7** occupied a pseudo-axial position rather than the pseudo-equatorial position observed in derivatives of GBR 12909. In this conformation of the 1,3,5-dithiazine derivative the 2,5-alkyl groups were in syn-orientation to each other rather than exist in an anti orientation found in piperazine derivatives. The pseudo-axial-5-phenylpropyl group is consistent with conformational studies of 5-alkyl-1,3,5-dithiazines that demonstrated that the 5-axial-alkyl-1,3,5-dithiazine is the predominant conformation in solution [15,21]. In addition, based on the longer carbon-sulfur bond lengths (1.81 Å and 1.84 Å, Table 2) and the broad N(1)-C(11)-S(1) and N(1)-C(10)-

Scheme 1



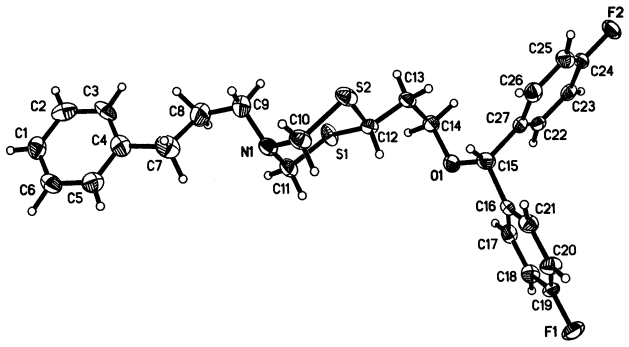


Figure 1

Table 2

Bond Lengths [Å] for 1, 3, 5-Dithiazine Analogue **7**

S(1)-C(12)	1.808(2)	C(7)-C(8)	1.492(4)
S(1)-C(11)	1.841(3)	C(8)-C(9)	1.515(4)
F(1)-C(19)	1.364(3)	C(12)-C(13)	1.522(4)
O(1)-C(15)	1.410(3)	C(13)-C(14)	1.508(4)
O(1)-C(14)	1.430(3)	C(15)-C(16)	1.525(4)
N(1)-C(11)	1.430(3)	C(15)-C(27)	1.529(4)
N(1)-C(10)	1.448(3)	C(16)-C(17)	1.369(4)
N(1)-C(9)	1.471(4)	C(16)-C(21)	1.381(3)
C(1)-C(6)	1.378(4)	C(17)-C(18)	1.388(4)
C(1)-C(2)	1.385(4)	C(18)-C(19)	1.377(3)
F(2)-C(24)	1.359(3)	C(19)-C(20)	1.360(4)
S(2)-C(12)	1.806(3)	C(20)-C(21)	1.379(4)
S(2)-C(10)	1.843(3)	C(22)-C(27)	1.387(4)
C(2)-C(3)	1.395(4)	C(22)-C(23)	1.393(4)
C(3)-C(4)	1.374(4)	C(23)-C(24)	1.374(4)
C(4)-C(5)	1.370(4)	C(24)-C(25)	1.366(4)
C(4)-C(7)	1.555(4)	C(25)-C(26)	1.392(4)
C(5)-C(6)	1.372(4)	C(26)-C(27)	1.367(4)

Symmetry transformations used to generate equivalent atoms.

S(2) bond angles (116°, Table 3), the 1,3,5-dithiazine ring is significantly larger than the piperazine ring of GBR 12909 derivatives.

Since the lipophilic character of GBR 12909 is thought to be important relative to its slow onset of activity and low abuse potential [22], the lipophilic character of the 1,3,5-dithiazine GBR 12909 derivatives **6** - **11** were determined. The experimental log *P* values were determined by a non-traditional shake-flask method as described by Lodge [22] from the average of four HPLC analyses of the octanol phase of a given shake-flask experiment. From the concentration of the analogue in the octanol layer and the known total concentration, the concentration of the analogue in the water layer was determined. The log *P* values were then calculated from the average of three shake-flash experiments (Table 4). The clog *P* values (Table 4) were calculated for comparison using the Leo and Hansch fragmentation method [24]. Both sets of lipophilic values exhibited similar trends in lipophilic character although the experimental log *P* values were generally slightly lower than clog

Table 3

Bond Angles [°] for 1,3,5-Dithiazine Analogue **7**

C(12)-S(1)-C(11)	98.41(13)	O(1)-C(15)-C(16)	106.2(2)
C(15)-O(1)-C(14)	115.9(2)	O(1)-C(15)-C(27)	113.2(2)
C(11)-N(1)-C(10)	111.9(2)	C(16)-C(15)-C(27)	111.1(2)
C(11)-N(1)-C(9)	115.0(3)	C(17)-C(16)-C(21)	118.3(2)
C(10)-N(1)-C(9)	112.9(2)	C(17)-C(16)-C(15)	123.7(2)
C(6)-C(1)-C(2)	118.4(3)	C(21)-C(16)-C(15)	118.0(2)
C(12)-S(2)-C(10)	98.02(14)	C(16)-C(17)-C(18)	122.1(2)
C(1)-C(2)-C(3)	120.2(3)	C(19)-C(18)-C(17)	117.3(3)
C(4)-C(3)-C(2)	121.0(3)	C(20)-C(19)-F(1)	119.0(2)
C(5)-C(4)-C(3)	117.9(3)	C(20)-C(19)-C(18)	122.3(2)
C(5)-C(4)-C(7)	118.6(3)	F(1)-C(19)-C(18)	118.7(2)
C(3)-C(4)-C(7)	123.6(3)	C(19)-C(20)-C(21)	118.9(2)
C(4)-C(5)-C(6)	122.1(3)	C(20)-C(21)-C(16)	121.0(3)
C(5)-C(6)-C(1)	120.4(3)	C(27)-C(22)-C(23)	121.2(3)
C(8)-C(7)-C(4)	115.8(3)	C(24)-C(23)-C(22)	117.7(3)
C(7)-C(8)-C(9)	113.2(3)	F(2)-C(24)-C(25)	118.9(2)
N(1)-C(9)-C(8)	116.3(3)	F(2)-C(24)-C(23)	118.5(2)
N(1)-C(10)-S(2)	116.13(19)	C(25)-C(24)-C(23)	122.6(2)
N(1)-C(11)-S(1)	116.86(18)	C(24)-C(25)-C(26)	118.5(3)
C(13)-C(12)-S(2)	109.93(18)	C(27)-C(26)-C(25)	121.1(3)
C(13)-C(12)-S(1)	108.97(18)	C(26)-C(27)-C(22)	118.9(2)
S(2)-C(12)-S(1)	112.57(14)	C(26)-C(27)-C(15)	119.4(3)
C(14)-C(13)-C(12)	114.5(2)	C(22)-C(27)-C(15)	121.7(2)
O(1)-C(14)-C(13)	115.3(2)		

Symmetry transformations used to generate equivalent atoms.

Table 4

Theoretical and Experimental Octanol/Water Partition Coefficients for 1,3,5-Dithiazine Analogues

Compound	log *P* [a]	clog *P* [b]
2		4.76 [c]
6	3.41 ± 0.62	3.8
7	4.32 ± 0.10	4.6
8	4.67 ± 0.627	5.7
9	2.37 ± 0.35	2.8
10	3.50 ± 0.03	3.5
11	4.37 ± 0.37	4.6

[a] log *P* ± SD values calculated by *Shake-Flask* method, Reference [23]; [b] clog *P* values were calculated by Leo and Hansch Fragmentation Method, reference [24]; [c] Literature value, reference[25].

P values. The log *P* and clog *P* values of **7** (4.32 and 4.6) were only slightly less than the clog *P* value of **2** (4.7) [25]. From this it can be inferred that the replacement of the piperazine ring of GBR 12909 with the 1,3,5-dithiazine ring had a minimal effect on the lipophilic character of the molecule. Therefore lipophilic effects were not expected to influence the binding affinity of the dithiazine analogue **7** relative to GBR 12909. As expected, the unsubstituted benzhydryl derivative **6** and benzyl analogues **9** and **10** exhibited considerably decreased lipophilicity, while the dichlorobenzhydryl derivatives **8** and **11** exhibited increased lipophilic character.

The dopamine transporter binding affinity was determined for the dithiazine derivatives **7** - **11** based on their

Table 5
Dopamine Transporter Affinities of 1, 3, 5-Dithiazine Analogues

Compound	K_i (± SEM, μM)
2	0.012 ± 0.031[a]
6	NT
7	31 ± 2.3
8	18 % [b]
9	40% [b]
10	5.2 ± 2.1
11	3 % [b]

[a] K_i value was obtained from reference [28] and obtained under identical conditions; [b] Percent inhibition at highest dose tested.

ability to displace bound [^{3}H]WIN 35,428 from rat caudate-putamen tissue using previously established protocol [26,27]. The K_i values that are reported in Table 5 are inhibition constants derived for the unlabeled ligands and are the mean of three experiments performed in triplicate. All compounds were tested either as the hydrochloride salt or the maleate salt and were dissolved in 50% methanol/water solution or dimethyl sulfoxide for testing. The dithiazine derivative **6** was not tested since attempts to convert it into a salt resulted in cleavage of the benzhydryl moiety.

The dithiazine analogues displayed severely diminished binding affinity with respect to GBR 12909 (**2**) at the dopamine transporter. The difluoro-substituted analogues **7** (K_i = 31 μM) and **10** (K_i = 5 μM) had the greatest affinity for the dopamine transporter albeit >500-fold less potent than **2**. The dichloro analogues **8** and **11** as well as the unsubstituted benzyl analogue **9** did not fully displaced the bound radiolabeled ligand at the highest concentration tested (100 μM). From these results it is apparent that the 1,3,5-dithiazne ring system cannot replace the piperazine ring of GBR 12909 for potent molecular recognition at the dopamine transporter. The low affinity of these compounds could be due to steric effects either imposed by the larger dithiazine ring system or the pseudo-axial nitrogen substituent. Alternatively, electronic effects may be the source of the poor binding affinity of the dithiazine analogues. The electronegative sulfur atoms that flank either side of the diarylmethoxylethyl moiety may interact unfavorably with the dopamine transporter or induce a molecular dipole that is unfavorable for molecular recognition at the transporter binding site. A similar effect on binding affinity at the dopamine transporter was observed for a series of 2,6-dioxopiperazine derivatives of GBR 12909 which possess electronegative carbonyl oxygen atoms at the 2, 6-positions of **2** [9].

In summary, the 1,3,5-dithiazine analogue **7** was found to possess comparable lipophilic character to GBR 12909. However, 1,3,5-dithiazine ring was significantly larger than the piperazine ring of **2** and the *N*- phenylpropyl group existed in an axial and syn orientation to the equatorial 2-[bis(4-fluorophenyl)methoxy]ethyl moiety. The low binding affinity for the dopamine transporter suggests that the novel conformational and electronic characteristics of the 1,3,5-dithiazine ring are not compatible for molecular recognition at the GBR binding site of the dopamine transporter.

EXPERIMENTAL

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Anhydrous tetrahydrofuran (THF), dichloromethane and methanol were purchased from Baker Chemical Company and stored under argon. Chromatography refers to chromatography on silica gel (Silica Gel 60, 230-400 mesh, E. M. Science). Petroleum ether refers to pentanes with a boiling point range of 30-60 °C. Reported melting points are uncorrected. NMR spectra were recorded on the Varian-Gemini 300 MHz and the Varian Gemini 400 MHz multiprobe spectrometers as indicated. Chemical shifts are reported as δ values from tetramethylsilane in deuteriochloroform. Mass spectra were recorded on a Micromass Autospec Mass Spectrometer fitted with a Fisson GC 8060. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA. Existence of fractional moles of water in some analytical samples persisted despite vigorous drying (110 °C, 24 h) under vacuum (0.01 mm Hg). All compounds were homogeneous by thin layer chromatography.

General Method for the Synthesis 5-Alkylaryl-1,3,5-dithiazine (**3a-b**).

To a cooled solution (0 °C) of alkylarylamine (50 mmol) and absolute ethanol (80 ml) was added formaldehyde (33 g, 1.1 mol, 37 wt % in water). The solution was stirred at 0 °C for 10 minutes. Sodium hydrosulfide (20 g, 357 mmol) was dissolved in water (30 ml) and the resulting solution was added to the reaction mixture. The mixture was stirred at 0 °C for an additional 20 minutes, then the ice bath was removed and the mixture stirred overnight at room temperature. Ethanol was removed under reduced pressure and water (50 ml) was added. The resulting precipitate was filtered by vacuum filtration. The semi-solid residue was washed with water (3 × 50 ml) and dissolved in dichloromethane. A white precipitate formed which was filtered using gravity filtration. The filtrate was dried over anhydrous sodium sulfate. Dichloromethane was remove under reduced pressure and the residue was purified by column chromatography with ethyl acetate:hexane(15:85) as an eluent.

5-(3-Phenylpropyl)-1,3,5-dithiazine (**3a**).

This compound was obtained as a colorless oil in 61% yield. ^{1}H nmr (deuteriochloroform): δ 1.73 (quintet, 2H, J = 7.4 Hz), 2.63 (t, 2H, J = 7.7 Hz), 3.02 (t, 2H, J = 7.4 Hz), 4.02 (s, 2H), 4.43 (s, 4H), 7.16 (m, 5H). ^{13}C nmr (deuteriochloroform): δ 29.3, 33.9, 34.7, 48.7, 58.9, 126.5, 129.96, 129.0, 142.4. ms: (chemical ionization) *m/z* 240 (molecular ion).

Anal. Calcd. for $C_{12}H_{17}NS_2$: C, 60.21; H, 7.16; N, 5.85. Found: C, 60.43; H, 7.17; N, 5.86.

5-Benzyl-1, 3, 5-dithiazine (**3b**).

This compound was obtained as a colorless oil in 66% yield. ^{1}H nmr (deuteriochloroform): δ 4.13 (br s, 2H), 4.22 (s, 2H), 4.43 (br s, 4H), 7.25 (m, 5H). ^{13}C nmr ($CDCl_3$): δ 34.2, 53.5, 58.1,

127.7, 128.8, 129.4, 137.4. ms: (chemical ionization) *m/z* 212 (molecular ion).

Anal. Calcd. for $C_{10}H_{13}NS_2$: C, 56.83; H, 6.20; N, 6.63. Found: C, 56.96; H, 6.27; N, 6.67.

General Procedure for the Preparation of 1-Bromo-2-[bis(4-substituted phenyl)methoxy]ethane (**5a-c**).

A mixture of the corresponding 4,4'-disubstituted benzhydrol (**4a-c**, 64 mmol), 2-bromoethanol (5.9 g, 47 mmol), *p*-toluenesulfonic acid (1.0 g, 5.3 mmol) in benzene (150 ml) were combined under nitrogen. The mixture was heated to reflux with azeotropic removal of water by a Dean-Stark trap. After 18 h, the reaction mixture was allowed to cool to room temperature. The benzene was then removed under reduced pressure and the resulting residue was combined with saturated aqueous sodium bicarbonate (150 ml). The product was extracted into ether (2 × 150 ml). The organic extracts were combined and dried over anhydrous sodium sulfate and the ether was removed under reduced pressure. The compound was purified by column chromatography with ethyl acetate:hexane (6:94) as an eluent.

1-Bromo-2-(diphenylmethoxy)ethane (**5a**) [17].

This compound was obtained as a colorless oil in 94% yield. ^{1}H nmr (deuteriochloroform): δ 3.48 (t, 2H, J = 6.0 Hz), 3.74 (t, 2H, J = 6.2 Hz), 5.41 (s, 1H), 7.20-7.36 (m, 10H). ^{13}C nmr (deuteriochloroform): δ 32.7, 68.7, 82.2, 126.6, 127.3, 128.3, 124.1.

1-Bromo-2-[bis(4-fluorophenyl)methoxy]ethane (**5b**) [17].

This compound was obtained as a colorless oil in 88% yield. ^{1}H nmr (deuteriochloroform): δ 3.40 (t, 2H, J = 6.2 Hz), 3.73 (t, 2H, J = 6.0 Hz), 5.38 (s, 1H), 6.94 - 7.00 (m, 4H), 7.26 - 7.31 (m, 4H). ^{13}C nmr (deuteriochloroform): δ 30.6, 68.6, 82.3, 115.2, 115.3, 128.5, 128.6, 137.2, 137.3, 160.4, 163.7.

1-Bromo-2-[bis(4-chlorophenyl)methoxy]ethane (**5c**).

This compound was obtained as a yellow oil in 94% yield. ^{1}H nmr (deuteriochloroform): δ 3.48 (t, 2H, J = 6.2), 3.71 (t, 2H, J = 6.2 Hz), 2.19 (s, 1H), 7.20 –7.79 (m, 8H). ^{13}C nmr (deuteriochloroform): δ 33.8, 71.0, 82.0, 128.5, 128.8, 133.6, 142.1.

Anal. Calcd. for $C_{15}H_{13}Cl_2BrO$: C, 50.04; H, 3.64. Found: C, 50.06; H, 3.47.

General Procedure for the Preparation of 2-(2-[Bis(4-substituted phenyl)methoxy]ethyl)-5-alkylaryl-1, 3, 5-dithiazine (**6-11**).

3-Alkylaryl-1,3,5-dithiazine (2.4 mmol) was placed in a 50-ml round-bottom flask and the flask was charged with argon. Dry THF (15 ml) was syringed into the flask and the flask was cooled to 78 °C. Butyllithium (2.5 ml, 3.6 mmol, 1.4 *M* in hexanes) was added *via* syringe and the solution was stirred for 1.5 hours. The corresponding 1-bromo-2-[bis(4-substituted phenyl)methoxy]-ethane (**5a-c**, 2.6 mmol) was dissolved in dry THF in a 25-ml pear-shaped flask. The flask was charged with argon and cooled to –78 °C. The bromide solution was transferred to the flask containing the lithiated 3-alkylaryl-1,3,5-dithiazine *via* cannula under the positive pressure of argon. The resulting mixture was stirred for 6 hours at -78 °C. The acetone and dry ice bath was subsequently replaced with an ice bath. After stirring for 1 hour at 0 °C, the mixture was stirred at room temperature for 6 hours. The mixture was quenched by the addition of water (25 ml). The compound was extracted with dichloromethane (3 × 25 ml). The combined organic layers were washed with brine (50 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the compound was purified by column chromatography with ethyl acetate: petroleum ether (10:90) as the eluent.

2-(2-[Diphenylmethoxy]ethyl)-5-(3-phenylpropyl)-1,3,5-dithiazine (**6**).

This compound was obtained as a colorless oil in 61% yield. The free base was converted to the hydrochloride salt mp 141-144 °C. ^{1}H nmr (deuteriochloroform): δ 1.71 (quintet, 2H, J = 7.50 Hz), 2.05 (q, 2H, J = 6.4 Hz), 2.62 (t , 2H, J = 7.7 Hz), 2.88 (t, 2H, J = 7.2 Hz), 3.62 (t, 2H, J = 6.2 Hz), 4.15 (d, 2H, J = 13.2 Hz); 4.49 (t, 1H, J = 7.1 Hz); 4.57 (d, 2H, J = 13.2 Hz); 5.36 (s, 1H); 7.15-7.30 (m, 15H). ^{13}C nmr (deuteriochloroform): δ 28.7, 33.2, 37.3, 46.9, 47.9, 58.6, 64.2, 83.8, 125.8, 127.0, 127.4, 128.3, 128.4, 141.9, 142.2.

Anal. Calcd. for $C_{27}H_{31}NOS_2$•HCl: C, 66.71; H, 6.63; N, 2.88. Found: C, 66.88; H, 6.57; N, 2.89.

2-(2-[Bis(4-fluorophenyl)methoxy]ethyl)-5-(3-phenylpropyl)-1,3,5-dithiazine (**7**).

This compound was obtained as a colorless crystal in 70% yield. The free base was converted to the hydrochloride salt affording a white powder, mp 172-176 °C. ^{1}H nmr (deuteriochloroform): δ 1.70 (quintet, 2H, J = 7.5 Hz), 2.04 (q, 2H, J = 6.4 Hz), 2.61 (t, 2H, J = 7.7 Hz), 2.87 (t, 2H, J = 7.2 Hz), 3.58 (t, 2H, J = 6.0 Hz), 4.14 (d, 2H, J = 13.2 Hz), 4.45 (t, 1H, J = 7.1 Hz), 4.55 (d, 2H, J = 13.2 Hz), 5.30 (s, 1H); 6.96 (m, 4H); 6.96-7.14 (m, 9H). ^{13}C nmr (deuteriochloroform): δ 28.4, 32.9, 37.0, 58.3, 64.0, 82.1, 114.8 (J_{C-F} = 21.5 Hz), 125.6, 128.1, 128.2, 128.3, 137.5, 141.6, 160.2 (J_{C-F} = 246.2 Hz). ms: (chemical ionization) *m/z* 486 (molecular ion).

Anal. Calcd. for $C_{27}H_{30}ClF_2NOS_2$•HCl: C, 32.11; H, 5.79; N, 2.68. Found: C, 62.24; H, 5.65; N, 2.70.

2-(2-[Bis(4-chlorophenyl)methoxy]ethyl)-5-(3-phenylpropyl)-1,3,5-dithiazine (**8**).

This compound was obtained as a light green oil in 66% yield. The free base was converted to the hydrochloride salt affording a white powder, mp 150-152 °C. ^{1}H nmr (deuteriochloroform): δ 1.74 (quintet, 2H, J = 7.4), 2.04 (q, 2H, J = 6.3 Hz), 2.67 (t, 2H, J = 7.5 Hz), 2.88 (t, 2H, J = 7.2 Hz), 3.59 (t, 2H, J = 5.40 Hz), 4.16 (d, 2H, J = 13.5 Hz), 4.45 (t, 2H, J = 7.05 Hz), 4.57 (d, 2H, J = 14.0), 5.29 (s, 1H), 7.05-7.16 (m, 13H). ^{13}C nmr (deuteriochloroform): δ 28.9, 33.5, 37.5, 47.2, 48.2, 58.8, 64.7, 82.7, 126.0, 128.4, 128.5, 128.5, 128.8, 133.6, 140.4, 142.0.

Anal. Calcd. for $C_{27}H_{29}Cl_2NOS_2$•HCl: C, 58.43; H, 5.45; N, 2.52. Found: C, 58.68; H, 5.61; N, 2.54.

2-(2-[Diphenylmethoxy]ethyl)-5-benzyl-1,3,5-dithiazine (**9**).

This compound was obtained as a white powder in 63% yield mp 81-83 °C. ^{1}H nmr (deuteriochloroform): δ 2.07 (q, 2H, J = 7.3 Hz), 3.62 (t, 2H, J = 6.2 Hz), 4.05 (s, 2H), 4.08 (d, 2H, J = 13.2), 4.48 (t, 2H, J = 6.9 Hz), 4.53 (d, 2H, J = 12.9 Hz); 5.34 (s, 1H); 7.17-7.35 (m, 15H). ^{13}C nmr (deuteriochloroform): δ 37.9, 47.5, 53.7, 58.8, 64.9, 84.4, 127.5, 128.0, 128.9, 129.1, 129.8, 137.8, 142.7.

Anal. Calcd. for $C_{25}H_{27}NOS_2$•0.25 H_2O: C, 70.40; H, 6.45; N, 3.29. Found: C, 70.44; H, 6.48; N, 3.24.

2-(2-[Bis(4-fluorophenyl)methoxy]ethyl)-5-benzyl-1,3,5-dithiazine (**10**).

This compound was obtained as a white solid in 32% yield. The free base was converted to the maleate salt affording a white powder, mp 96-98 °C. ^{1}H nmr (deuteriochloroform): δ 2.10 (q,

2H, J = 6.4 Hz), 3.61 (t, 2H, J = 6.2 Hz), 4.12 (s, 2H); 4.15 (d, 2H, J = 13.2 Hz), 4.49 (t, 1H, J = 4.1 Hz), 4.64 (d, 2H, J = 13.2 Hz), 5.33 (s, 1H), 6.98 (m, 4H), 7.25 (m, 9H). ^{13}C nmr (deuteriochloroform): δ 37.7, 47.4, 53.7, 58.6, 65.0, 83.2, 115.8 (J_{C-F} = 21.42 Hz), 128.3, 129.1, 129.1, 129.2, 120.0, 138.4, 164.4 (J_{C-F} = 245.6 Hz). ms: (chemical ionization) *m/z* 458 (molecular ion).

Anal. Calcd. for $C_{25}H_{25}F_2NO•C_4H_4O_4•0.5\ H_2O$: C, 59.79; H, 5.19; N, 2.41. Found: C, 59.60; H, 5.36; N, 2.26.

2-(2-[Bis(4-chlorophenyl)methoxy]ethyl)-5-benzyl-1,3,5-dithiazine (**11**).

This compound was obtained as a yellow crystal in 60% yield. The free base was converted to the hydrochloride salt affording a white powder, mp 144-145 °C. ^{1}H nmr (deuteriochloroform): δ 2.04 (q, 2H, J = 8.1 Hz), 3.61 (t, 2H, J = 6.3 Hz), 4.10 (s, 2H), 4.14 (d, 2H, J = 13.2 Hz), 4.49 (t, 1H, J = 4.1 Hz), 4.60 (d, 2H, J = 13.2 Hz), 5.30 (s, 1H),7.24 (m, 13H). ^{13}C nmr (deuteriochloroform): δ 37.1, 46.8, 53.1, 58.1, 64.5, 82.0, 127.6, 128.3, 128.6, 128.7, 129.3, 133.5, 136.9, 140.3.

Anal. Calcd. for $C_{25}H_{25}Cl_2NOS_2•HCl$: C, 56.98; H, 4.97; N, 2.66. Found: C, 57.05; H, 5.05; N, 2.74.

Lipophilicity Measurements.

Shake-flask Method.

A solution was prepared of the free-base analogue (5 mg) and octanol (1 mL, ACS ± 99.5% HPLC grade). The solution was prepared in a 15-ml Pyrex® centrifuge tube (conical with screw cap, Aldrich). To the centrifuge tube was added 10-mL of HPLC grade water. The solution was vortexed for 1 minute followed by 15 minutes of centrifuging. The sequence of vortexing and centrifuging was carried out two additional times. A 14.5-μL aliquot of the octanol layer was carefully removed with the HPLC syringe. The needle was wiped clean with a Kim wipe®. Toluene (0.5 μL) was then added to the syringe for use as the internal calibration standard. The sample was then injected onto the HPLC column.

HPLC Analysis.

The HPLC system consisted of a Waters 501 HPLC Pump and Waters 486 Turnable Absorption Detector (wavelength of 254 nm, sensitivity of 2). The system was fitted with Nova-Pak® C18 column (4 μm, 3.3 × 150 mm). The mobile phase consisted of methanol (ACS ±99.5% HPLC grade) and HPLC grade water, with the percent composition of methanol ranging from 90-75%. For a given analysis the HPLC was operated with no change in the composition of the mobile phase during a run. The flow rate was set at 1 ml/minute. Based on these conditions, the retention times were < 8.5 minutes. All HPLC analyses were carried out in quadruplicate. The standard deviations for a given shake-flask experiment were on average ±0.046 log *P* units for four analytical samples of the octanol layer (average standard deviations obtained by Lodge [23] utilizing similar shake-flask procedure was ±0.030 log *P* units).

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