Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 4449–4454

BIOORGANIC & MEDICINAL CHEMISTRY

Arylguanidine and Arylbiguanide Binding at 5-HT_3 Serotonin Receptors: A QSAR Study

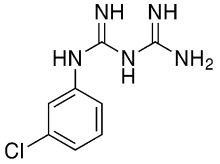
Richard A. Glennon,[a,*] Maha Khalifa Daoud,[a] Małgorzata Dukat,[a] Milt Teitler,[b] Katharine Herrick-Davis,[b] Anil Purohit[b] and Hasan Syed[b]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond VA 23298, USA*
[b]*Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY 12208, USA*

Received 2 October 2002; accepted 26 June 2003

Abstract—For a series of monosubstituted arylguanidines, 5-HT_3 receptor affinity was found generally related to the electron withdrawing nature of the substituent at the aryl 3-position and the lipophilicity of the 4-position substituent. A broader examination of 35 arylguanidines and arylbiguanides revealed that affinity could be described by molecular polarizability, a Chi index term ($^8\chi_P$), and the sum of all (–Cl) E-State values (SsCl) in the molecule.

5-HT_3 receptors are unique among the diverse populations of serotonin (5-hydroxytryptamine; 5-HT) receptors in being the only ones that are ion channel receptors.[1,2] 5-HT_3 receptors are thought to be involved in migraine, memory, and anxiety, but from a therapeutic perspective, 5-HT_3 antagonists have found application primarily as antiemetic agents.[1–3] Much less has been published about 5-HT_3 agonists because relatively few such agents are known. Phenylbiguanide and its 3-chloro derivative *meta*-chlorophenylbiguanide (*m*CPBG; **1**)[4] are fairly standard 5-HT_3 agonists. More recently, other types of agonists have been described. NMQ (Chart 1) was shown early on to be a high-affinity 5-HT_3 ligand.[5] Manipulation of this molecule, particularly by fusing aryl or heteroaryl rings at various positions, has resulted in compounds with a full range of efficacies, including agonists and partial agonists.[6–10] Representative structures of some of these agents are shown in Chart 1. Pharmacophore models have been described for agents with 5-HT_3 agonist or partial agonist action[9–12] and, although arylbiguanides were not the basis for any of these studies, at least one model seemingly accounts for the binding of *m*CPBG (**1**).[11]



1

In a structure–affinity study, we showed that the entire biguanide moiety of phenylbiguanides is not required for 5-HT_3 receptor binding. That is, arylbiguanides can be abbreviated to their corresponding arylguanidines (e.g., **3**) with retention of affinity,[13] and where investigated, the arylguanidines retained agonist activity.[13,14] None of the pharmacophore models mentioned above seems to account for the binding of arylguanidines due to their shorter centroid-to-amine distance relative to the arylbiguanides or other structures that were examined. Structure–affinity studies of the binding of arylbiguanides and arylguanidines further suggest that the two types of agents likely bind at 5-HT_3 receptors in a similar manner.[13,15] A QSAR (i.e., CoMFA) study indicated that the binding of these agents, as a group, is sensitive to the electronic and possibly lipophilic nature of substituents at the aryl 3- and 4-positions.[15] Unfortunately, only a limited number of mono-substituted compounds were available for the initial QSAR study and it was not possible to directly test these hypotheses at that time. The goal of the present investigation was to examine a small number of 3- and 4-monosubstituted

*Corresponding author. Tel.: +1-804-828-8487; fax: +1-804-828-7404; e-mail: glennon@hsc.vcu.edu

0968-0896/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0968-0896(03)00488-7

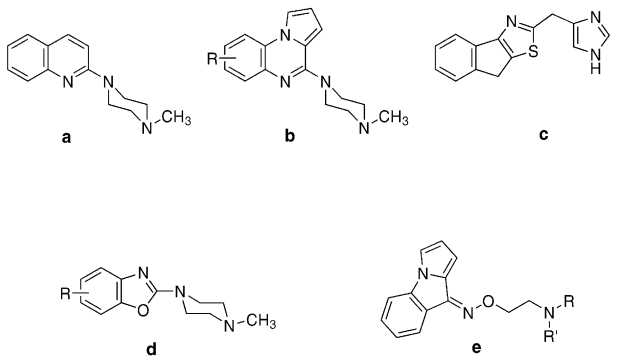


Chart 1. Structures of *N*-methylquipazine (NMQ; **a**),[5] pyrroloquinoxaline agonists (**b**),[6] the fused thiazole agonist YM-31636 (**c**),[7] and benzisoxazole-type[8] and aminoalkyloximinopyrrolizine-type[9] partial agonists **d** and **e**, respectively.

arylguanidines to determine whether the electronic or lipophilic contribution of the substituents was more important for binding. Inclusion of several multi-substituted derivatives was planned for a follow-up study to see if the identified relationships could be extended to arylguanidines bearing more than a single substituent. Because of evidence implicating an electronic contribution, a QSAR study was also conducted on a series of arylguanidines and arylbiguanides by examining properties of the molecules as a whole.

Substituent Analysis

To determine whether electronic or lipophilic character at the 3-position is more important for the binding of arylguanidines at 5-HT_3 receptors, a Hansch analysis was conducted with eight arylguanidines (i.e., the unsubstituted parent **2**, and the 3-monosubstituted compounds **3**–**9**). No correlation was found between 5-HT_3 affinity (pK_i) and π ($r = 0.132$), but a better relationship exists with σ_m ($r = 0.760$) (eq 1). Interestingly, if compound **4** is excluded, $r = 0.870$; however, there was no reason to exclude this data point.

$$pK_i = 2.30(\pm 0.81)\sigma_m + 5.53$$
$$n = 8, r = 0.760, \quad F = 8.17 \qquad (1)$$

A similar analysis was conducted with the unsubstituted compound **2** and six 4-monosubstituted compounds (**10**–**15**). In this case, there was little relationship between pK_i and σ_p ($r = 0.207$) but a better correlation between affinity and π_4 ($r = 0.906$) (eq 2).

$$pK_i = 1.80(\pm 0.23)\pi_4 + 5.69$$
$$n = 7, r = 0.906, \quad F = 23.0 \qquad (2)$$

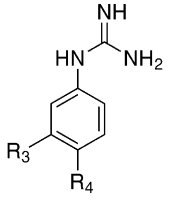
On the basis of the above results, a multiple linear regression analysis was conducted using both σ_m and π_4 in the same equation. The results were encouraging with the 14 compounds ($r = 0.820$; results not shown); subsequently, this regression analysis was repeated with the inclusion of four additional di-substituted compounds (i.e., **16**–**19**). This resulted in eq 3 (which includes **2**–**19**).

$$pK_i = 2.59(\pm 0.59)\sigma_m + 1.38(\pm .24)\pi_4 + 5.52$$
$$n = 18, r = 0.852, \quad F = 19.9 \qquad (3)$$

Up to this point, for the 18 compounds examined, it seems that the electron withdrawing nature of substituents at the 3-position contributes somewhat to affinity, as does the lipophilic nature of the substituents at the 4-position (eq 3). As a partial test of this hypothesis, a hydrophilic 4-hydroxy group was added to **2** to provide **20**; as expected, **20** did not bind at 5-HT_3 receptors ($K_i > 10{,}000$ nM; Table 1).

To further test the hypothesis, several new compounds with lipophilic 4-position substituents were prepared and evaluated (i.e., the 4-*t*Bu analogue **21**, the 4-cyclohexyl derivative **22**, and the 4-benzyl derivative **23**). Interestingly, these compounds did not bind with the expected high affinity (Table 1). Evidently, eq 3. fails to account for these three added compounds. However, it was noticed that the 4-position substituents in these last three compounds are wider than any of those in the other compounds examined. The regression analysis was repeated and an indicator variable (I_4) was added; I_4 was set at 0 for 4-position substituents with a Verloop B_2 value[16] of <2.5, and $I_4 = 1$ for substituents where $B_2 > 2.5$. This resulted in eq 4 (which includes all compounds in Table 1, excluding **20** for which the K_i value was indeterminate).

Table 1. Arylguanidines used in deriving eqs 1–4



	R_3	R_4	K_i	(SEM)[a]
2	–H	–H	2340	
3	–Cl	–H	32	
4	$-CF_3$	–H	2440	
5	$-NO_2$	–H	85	(4)
6	–OH	–H	2020	(180)
7	–CN	–H	123	(6)
8	$-CH_3$	–H	6520	
9	$-OCH_3$	–H	1600	
10	–H	$-CH_3$	442	
11	–H	–Cl	325	(40)
12	–H	$-CF_3$	230	
13	–H	$-OCH_3$	990	
14	–H	$-C_2H_5$	785	(110)
15	–H	$-C_6H_5$	7.0	(2)
16	–Cl	–Cl	3.1	
17	$-CF_3$	–Cl	36	
18	$-OCH_3$	$-OCH_3$	2710	
19	–CH=CH–CH= CH–		18	
20	–H	–OH	>10,000	
21	–H	$-C(CH_3)_3$	2070	(200)
22	–H	$-C_6H_{11}$	2500	(180)
23	–H	$-CH_2-C_6H_5$	250	(4)

[a] K_i values were previously reported[13,15] except where SEM are provided (SEM not obtained where $K_i > 10{,}000$ nM).

$$pK_i = 2.48(\pm 0.90)\sigma_m + 1.27(\pm 0.25)\pi_4 - 2.40(\pm .55)I_4 + 5.60$$
$$n = 21, r = 0.824, \quad F = 11.9 \qquad (4)$$

Eq 4 indicates that affinity is related to the electron withdrawing nature of the 3-position substituent and the lipophilicity of the 4-position substituent; however, it appears that the latter is dependent upon the size of the substituent and that wide substituents are not well tolerated at this position. Interestingly, the original QSAR study had already provided some indication that bulky substituents might not be particularly well tolerated at the 4-position.[15] In addition, as with eq 1, deletion of the 3-trifluoromethyl analogue **4** from eqs 3 and 4 resulted in an improved correlation coefficient.

Molecular Analysis

The substituent constant σ is related to electronic effects of an atom or group of atoms. Polarizability is another electronic term that is more related to the molecule as a whole[17] and reflects the ease of distortion of the electron cloud of a molecule due to the proximity of a charged species. Using a whole-molecule approach, several additional multi-substituted derivatives, possessing substituents at positions other than the 3- and 4-position, could now be added (i.e., compounds **24–26**; Table 2). Eqs 2–4 indicate that binding involves more than simply the electronic character of the substituents. Thus, a random search was conducted for a relating equation that contained a polarizability term together with any additional 2-dimensional or 3-dimensional descriptor using the program MDL QSARIS. This search resulted in eq 5a. In the equation, P is the polarizability of the molecule, $^8\chi_P$ is the simple 8th order chi index,[18] SsCl is the sum of all (–Cl) E-State values in the molecule,[18] and Vol = the molecular volume.

$$pK_i = -0.68(\pm 0.15)P + 2.04(\pm 0.84)^8\chi_P + 0.39(\pm 0.05)\mathrm{SsCl} + 0.012(\pm 0.008)\mathrm{Vol} + 8.53$$
$$n = 24, \quad r = 0.908, \quad F = 22.3 \qquad (5a)$$

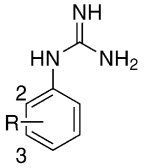
The $^8\chi_P$ descriptor is a count of paths of eight bonds; substitution at one of the aryl *meta* positions by a monoatomic substituent would be expected to add an additional path. Substitution at both meta positions would add even further. Thus, compounds bearing substituents at the 3- and the 3,5-positions would be favored. Chloro groups at these positions (as indicated by the SsCl descriptor) are specifically favored.

Eq 5a is statistically significant but contains four independent variables. Furthermore it contains both a polarizability term and a volume term. Because specific polarizability (SpcPol) = P/Vol, the process was repeated using specific polarizability rather than polarizability, leading to eq 5b.

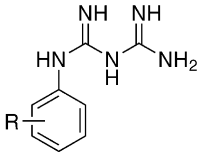
$$pK_i = -125.9(\pm 27.9)\mathrm{SpcPol} + 1.69(\pm 0.44)^8\chi_P + 0.39(\pm 0.05)\mathrm{SsCl} + 8.53$$
$$n = 24, r = 0.902 \quad F = 29.2 \qquad (5b)$$

As expected, a polarizability descriptor had now been implicated as being involved in binding, and the calculated versus observed K_i values for the 24 arylguanidines are plotted as Figure 1. As already mentioned in the Introduction, we have previously shown that arylbiguanides bind at 5-HT_3 receptors in a manner that mimics the arylguanidines. Hence, it was felt justified to combine the arylguanidines with a series of similarly substituted arylbiguanides (i.e., **1**, **27–33**; Table 3) for purpose of examination. The best 3-term equation identified was eq 6a, which included a total of 32 compounds. The descriptors appearing in eq 6a were similar to those found in eq 5a.

Table 2. Additional arylguanidines (**24–26**) and arylbiguanides (**1**, **27–33**) used in the present study[a]



24-26



1, 27-33

	R	K_i (nM)
24	3,4,5-Cl_3	0.7
25	3,5-Cl_2	5
26	3-Cl, 5-OCH_3	18
1	3-Cl	18
27	3,5-Cl_2	1.8
28	3,4-Cl_2	12
29	3,4,5-Cl_3	2.7
30	2-Cl	62
31	4-Cl	210
32	4-CH_3	890
33	–H	1200

[a] K_i values previosuly reported[13,15] except for compound **26** ($K_i = 18 \pm 1$ nM).

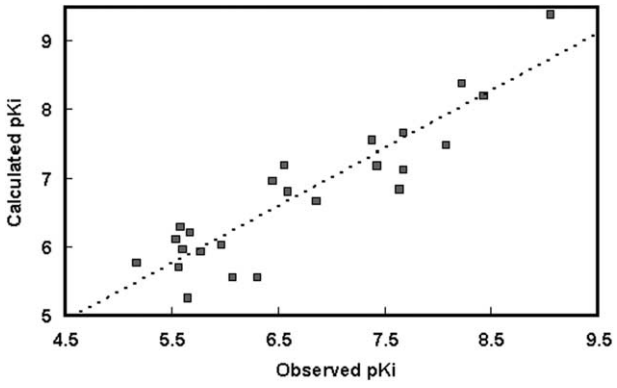


Figure 1. Observed versus calculated 5-HT_3 receptor affinities (pK_i values) for 24 arylguanidines using eq 5b.

$$pK_i = -0.64(\pm 0.14)P + 2.74(\pm 0.53)^8\chi_P + 0.37(\pm 0.05)\mathrm{SsCl} + 8.03 \quad (6a)$$
$$n = 32, \quad r = 0.903, \quad F = 41.2$$

Three arylbiguanides (**34–36**) were purposely excluded from this investigation so as to be able to test any relating equation that might be identified. These compounds were not chosen for exclusion because they possessed any particular substitution pattern, but rather because it was desired to exclude three compounds that represented a range of affinities. The only selection criteria for their exclusion was that the excluded compounds should have approximate K_i values of 10, 100, and 1,000 nM. The three compounds selected are shown in Table 3. The three 'test' compounds were predicted quite well and their calculated and observed affinities varied by less than 2-fold (Table 3).

Eq 6a was recalculated by including the three additional compounds (**34–36**; Table 3) leading to eq 6b. A plot of calculated versus observed affinities using eq 6b. is shown as Figure 2. It might be noted that Figure 2, which includes both arylbiguanide and arylguanidine derivatives, is generally similar to Figure 1 that includes only the arylguanidines.

$$pK_i = -0.63(\pm 0.13)P + 2.75(\pm 0.43)^8\chi_P + 0.37(\pm 0.04)\mathrm{SsCl} + 8.03 \quad (6b)$$
$$n = 35, \quad r = 0.907, \quad F = 47.7$$

Several years ago, Morain and co-workers[19] reported the 5-HT_3 receptor affinities of a series of halogen-containing arylbiguanides; among these compounds were several that we had not prepared or examined. As a final test of eq 6b, the affinities of these eight arylbiguanides (i.e., **37–44**; Table 3) were calculated. Table 3 shows the reported[19] and calculated (from eq 6b) K_i values and these are closely correlated ($r = 0.941$; $n = 8$); these are plotted in Figure 3. It might be noted that the higher affinity compounds **37–39** are particularly well predicted.

Reexamination of Arylguanidines

Having found that the affinity of arylguanidines seems to be influenced both by the electronic and lipophilic character of the aryl substituents (eq 4) but that, by themselves, the electronic character of 3-position substituents do not satisfactorily account for binding, and that the electronic nature of the molecules as a whole needs to be considered (eq 6b), a final investigation was undertaken. Excluding compounds **4**, **8**, and **15**, there is a modest correlation between pK_i and π_3 ($r = 0.691$; $n = 20$). For this same set of compounds, there is also a correlation between $\Sigma\sigma$ (the sum of the σ values for all

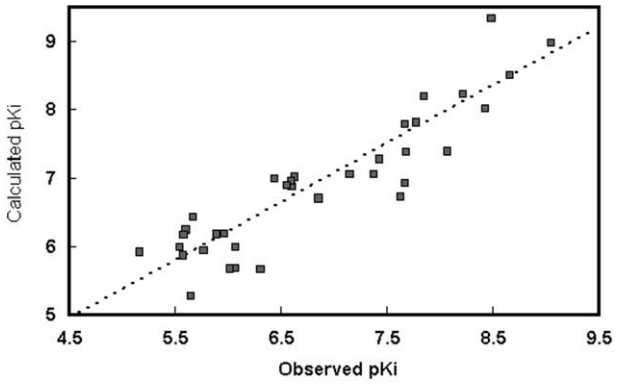
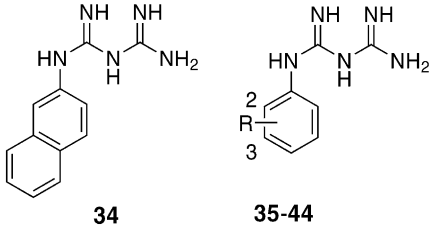


Figure 2. Observed versus calculated 5-HT_3 receptor affinities (pK_i values) for 35 arylguanidines and arylbiguanides using eq 6b.

Table 3. Observed and calculated 5-HT_3 receptor affinity for compounds **34–36** using eq 6a, and the parameters[a] employed to obtain the calculated values



34 **35-44**

	R	P	χ_{P8}	SsCl	K_i (Calc)[b]	K_i (Obs)[c]
34	—	5.03	1.092	0	16	14
35	3-Cl, 4-CH_3	6.96	0.424	5.91	120	225
36	3-CH_3	5.03	0.440	0	965	780
37	2,3,5-Tri Cl	10.04	0.495	17.45	0.4	0.4
38	2,5-Di Cl	8.11	0.415	11.60	5.9	2.9
39	2,3-Di Cl	8.11	0.418	11.64	5.0	4.7
40	2,4-Di F	4.08	0.310	0	535	260
41	2-Cl,5-CF_3	6.69	0.460	5.69	80	300
42	4-F	4.17	0.322	0	570	620
43	3-CF_3	4.76	0.490	0	470	700
44	3,5-Di CF_3	5.26	0.836	0	110	1200

[a]Parameters are from MDL QSARIS.
[b]K_i values calculated using eq 6a (compounds **34–36**), and eq 6b (compounds **37–44**).
[c]K_i values previously reported for compounds **34–36**[15] and **37–44**.[19]

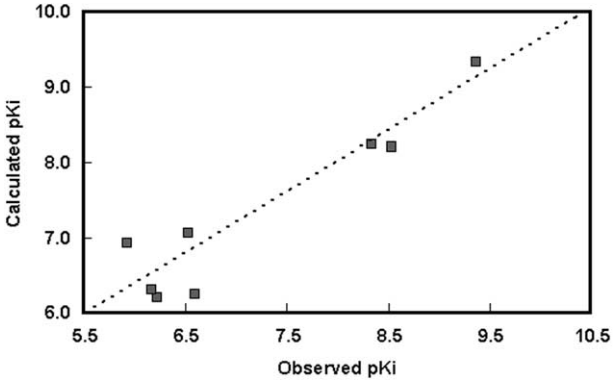


Figure 3. Observed versus calculated 5-HT_3 receptor affinities (pK_i values) for compounds **37**–**44** using eq 6b ($r = 0.941$; $n = 8$).

aryl substituents in the molecule) and pK_i ($r = 0.812$; $n = 20$). If both variables are included in the same study, eq 7 is obtained:

$$pK_i = 1.81(\pm 0.28)\Sigma\sigma + 1.02(\pm 0.22)\pi_3 + 6.19$$
$$n = 20, r = 0.924, \quad F = 49.3 \qquad (7)$$

Thus, in addition to the electronic character of the molecule, the lipophilicity of the 3-position substituents might be playing a small role in binding.

Summary

The present investigation examined the QSAR of arylguanidine binding at 5-HT_3 receptors. One of the results of the study is that the binding of arylguanidines is favored by the presence of electron withdrawing substituents at the 3-position and lipophilic substituents at the 4-position. We, like Morain et al.,[19] find it difficult to explain the lower than expected affinity of the 3-trifluoromethyl derivatives. Deletion of trifluoromethyl derivative **4** from eqs 1, 3 and 4 resulted in an improved correlation. One possible explanation for the low affinity of 3-trifluoromethyl compounds relates to substituent size. The $-CF_3$ group, like –Cl and $-NO_2$, is electron withdrawing; however, the size (van der Waal's radius) of –F is comparable to that of oxygen.[20] Consequently, the $-CF_3$ group is sterically much larger than $-CH_3$ and, in fact, is closer in size to that of an isopropyl group.[20] Hence, the receptor might be simply unable to accommodate the larger size of a trifluoromethyl substituent at the 3-position, and such derivatives bind with reduced affinity despite the electron withdrawing nature of the substituent.

By themselves, σ_m and π_4 only account for about 73% of the variation in affinity (eq 5a). Consideration of the width of 4-position substituents enhanced the correlation; that is, wide lipophilic substituents are not well tolerated (eq 5b) at 5-HT_3 receptors. As a cautionary note, the consequences of rotameric binding cannot be overlooked. Whereas the electron withdrawing nature of *meta* substituents seems to play a role in binding, there are two positions (i.e., the 3- and 5-positions) *meta* to the aryl amine function. At this time there is insufficient information to allow a determination of whether all *meta*-substituted derivatives are binding in a common manner. A whole molecule approach best accounted for the affinities of the arylguanidines and arylbiguanides as a group, and eq 6b was capable of predicting the affinities of agents not included in the original investigations. 5-HT_3 receptor affinities, for a series of arylguanidines and arylbiguanides whose K_i values spanned a > 15,000-fold range, were found to be associated with the polarizability of the molecule (which can be remotely viewed as being related to the electron withdrawing influence of substituents on the aryl ring), a particular path length (where substituents at the *meta* positions importantly contribute to binding), and the presence of chloro groups.

Experimental

Synthesis

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini 300 MHz spectrometer and tetramethylsilane was used as an internal standard. Infrared spectra were obtained on a Nicolet 5ZDX FT-IR spectrometer. Elemental analysis was performed by Atlantic Microlab Inc. (Norcross, GA, USA), and determined values are within 0.4% of theory.

Several of the compounds were previously reported by us;[13,15] others that have been described in the literature include **5** nitrate,[21] **6** HCl,[22] **14** nitrate,[21] **15** sulfate,[22] and **20** HCl.[22] The remaining compounds are novel and were typically prepared by the method of Hughes et al.;[22] a representative example is provided below. All new compounds analyzed within 0.4% of theory for C, H, and N.

***N*-(3-Chloro-5-methoxyphenyl)guanidine nitrate (26).** A mixture of 3-chloro-5-methoxyaniline (0.30 g, 1.89 mmol), one equivalent of concentrated HCl, and NH_2CN (0.12 g, 1.90 mmol) in EtOH (10 mL) was heated at reflux for 20 h. The reaction mixture was chilled to 0 °C overnight; the solvent was evaporated under reduced pressure and the residue was triturated with a small amount of H_2O. The mixture was extracted with Et_2O (2×15 mL) and the combined ethereal portion was evaporated to about half its original volume. Excess NH_4NO_3 solution was added and the product was collected by filtration. Following recrystallization from absolute EtOH, 0.03 g (10%) of **26** was obtained as a pale-orange crystalline solid, mp 179–180 °C. Anal. ($C_8H_{10}ClN_3O \cdot HNO_3$) C, H, N.

Compounds **7** (mp 222–225 °C; 10% yield), **21** (mp 183–185 °C; 28% yield), **22** (mp 212–215 °C; 20% yield), and **23** (mp 130–132 °C; 13% yield) were obtained as their nitrate salts in a similar manner and recrystallized from absolute EtOH.

Radioligand binding assay

The assay was performed as previously reported[13] using NG108-15 cells (obtained from Dr. Marshall Nirenberg; National Institutes of Health) which express the 5-HT_3 receptor. The cells were grown in Dulbecco's modified Eagle's medium with fetal bovine serum (10%), penicillin/streptomycin (200 units/mL), L-glutamine (2 nM/mL), hypoxanthine (25 μM), aminopterin (0.5 μM), and thymidine (4 μM), in cell culture flasks, to confluence. The cells were harvested in 50 mM Tris–HCl buffer, 0.5 mM EDTA, and 10 nM $MgSO_4$ and centrifuged at 9000*g* for 25 min. The pellet was resuspended in buffer, incubated at 37 °C for 15 min, and centrifuged again at 9000*g* for 20 min. The pellets were stored at −40 °C until used. Radioligand binding assays were performed in triplicate in a 2.0-mL volume containing 1 nM [^{3}H]GR65630 (New England Nuclear); 1 μM tropisetron (ICS 205-930) was used to define nonspecific binding, with varying concentrations of competing drug and membranes prepared from NG108-15 cells (100 mg protein/mL). A 64% specific binding signal was produced using 1 nM [^{3}H]GR65630 (84.2 Ci/mmol). Assay tubes were incubated for 30 min at room temperature; suspensions were filtered on Schleicher & Schuell #32 glass fiber filters (presoaked in 0.1% polyethyleneimine), and washed with 10 mL ice-cold buffer. The filters were counted by a Beckman 3801 liquid scintillation counter in 5 mL of aqueous counting scintillant (Ecoscint; National Diagnostic). Data from binding assays were plotted as log concentration versus percent inhibition and analyzed by nonlinear least squares techniques in which 100% maximal inhibition was assumed at high test compound concentrations. The IC_{50} values obtained from such data treatment were used to calculate apparent inhibition constants from the following equation: $K_i = IC_{50}/1 + ([c]/K_D)$ where [*c*] is the concentration of radioligand employed in the binding assay, and K_D is its receptor dissociation constant ($K_D = 0.7$ nM) for [^{3}H]GR65630.

QSAR studies

The σ and π values employed in the present investigation are those of Hansch et al.,[23] and the Verloop parameters are those reported by Verloop et al.[16] QSAR analysis was conducted using QsarIS Version 2.1(2002) (MDL Information Systems, Inc., San Leandro, CA 94577, USA). The default parameters were employed.

Acknowledgements

M.K.D. (Al-Azhar University; Cairo, Egypt) was supported by a fellowship from the Egyptian Channel Program coordinated by Prof. M. K. Ibrahim. The re-investigation of the arylguanidines using Σσ was suggested by Dr. Corwin Hansch and we thank him for his insightfulness.

References and Notes

1. Glennon, R. A.; Dukat, M.; Westkaemper, R.B. In Watson, S. J., Ed. *Psychopharmacology, A Generation of Progress*; Lippincott-Raven: New York, 1998 (CD ROM version).
2. Gozlan, H. 5-HT_3 receptors. In Olivier B, van Wijngaarden I, Soudin, W. Eds, *Serotonin Receptors and Their Ligands*; Elsevier: Amsterdam, 1997; p 221.
3. King, F. D.; Jones, B. J.; Sanger, G. J., Eds. 5-*Hydroxytryptamine-3 Receptor Antagonists*; CRC: Boca Raton, FL, 1994.
4. Kilpatrick, G. J.; Butler, A.; Burridge, J.; Oxford, W. *Eur. J. Pharmacol.* **1990**, *182*, 193.
5. Glennon, R. A.; Ismaiel, A. M.; McCarthy, B. G.; Peroutka, S. J. *Eur. J. Pharmacol.* **1989**, *168*, 387.
6. Campiani, G.; Cappelli, A.; Nacci, V.; Anzini, M.; Vomero, S.; Hamon, M.; Cagnotto, A.; Fracasso, C.; Uboldi, C.; Caccia, S.; Consolo, S.; Mennini, T. *J. Med. Chem.* **1997**, *40*, 3670.
7. Ito, H.; Kiso, T.; Miyata, K.; Kamato, T.; Yuki, H.; Akuzawa, S.; Nagakura, Y.; Yamano, M.; Susuki, M.; Naitoh, Y.; Sakai, H.; Iwaoka, K.; Yamaguchi, T. *Eur. J. Pharmacol.* **2000**, *409*, 195.
8. Sato, Y.; Yamada, M.; Yoshida, S.; Soneda, T.; Ishikawa, M.; Nizato, T.; Suzuki, K.; Konno, F. *J. Med. Chem.* **1998**, *41*, 3015.
9. Daveu, C.; Bureau, R.; Baglin, I.; Prunier, H.; Lancelot, J.-C.; Rault, S. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 362.
10. Cappelli, A.; Anzini, M.; Vomero, S.; Mennuni, L.; Makovec, F.; Hamon, M.; De Benedetti, P. G.; Menziani, M. C. *Cur. Topics Med. Chem.* **2002**, *2*, 599.
11. Yamada, M.; Sato, Y.; Kobayashi, K.; Konno, F.; Soneda, T.; Watanabe, T. *Chem. Pharm. Bull. (Tokyo)* **1998**, *46*, 445.
12. Bureau, R.; Daveu, C.; Baglin, I.; Sopkova-De Oliviera Santos, J.; Lancelot, J. C.; Rault, S. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 815.
13. Dukat, M.; Abdel-Rahman, A. A.; Ismaiel, A. M.; Ingher, S.; Teitler, M.; Gyermek, L.; Glennon, R. A. *J. Med. Chem.* **1996**, *39*, 4017.
14. Dukat, M.; Young, R.; Darmani, N. N.; Ahmed, B.; Glennon, R. A. *Psychopharmacology (Berlin)* **2000**, *150*, 200.
15. Dukat, M.; Choi, Y.; Teitler, M.; Du Pre, A.; Herrick-Davis, K.; Smith, C.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1599.
16. Verloop, A.; Hoogenstraaten, W.; Tipker, J. In Ariens, E. J., Ed., *Drug Design*; Academic: New York, 1976; Vol. 7, p 165.
17. Taft, R. W.; Topsom, R. D. *Progr. Phys. Org. Chem.* **1987**, *16*, 1.
18. Kier, L. B.; Hall, L. H. *Molecular Connectivity in Chemistry and Drug Research*; Academic: New York, 1976.
19. Morain, P.; Abraham, C.; Portevin, B.; DeNanteuil, G. *Mol. Pharmaol* **1994**, *46*, 732.
20. Smart, B. E. In Banks, R. E., Smart, B. E., Tatlow, J. C., Eds; *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, 1994; Chapter 4, p 57.
21. King, H.; Tonkin, I. M. *J. Chem. Soc.* **1946**, 1063.
22. Hughes, J. L.; Liu, R. C.; Enkoji, T.; Smith, C. M.; Bastian, J. W.; Luna, P. D. *J. Med. Chem.* **1975**, *18*, 1077.
23. Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.