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Quantitative structure–activity relationship of phenoxyphenyl-methanamine compounds with $5HT_{2A}$, SERT, and hERG activities

Scot Mente *, Randall Gallaschun, Anne Schmidt, Lorrie Lebel, Michelle Vanase-Frawley, Anton Fliri

Pfizer Global Research and Development, Groton Laboratories, 1 Eastern Point Road, Groton, CT 06355, USA

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ABSTRACT

QSAR models have been used to evaluate activities for compounds in the phenoxyphenyl-methanamine (PPMA) class of compounds. These models utilize Hammett-type donating–withdrawing substituent values as well as simple parameters to describe substituent size and elucidate the SAR of the 'A' and 'B' rings. Using this methodology, intuitive QSAR relationships were found for the three biological activities with R^2 values of 0.73, 0.45, and 0.58 for $5HT_{2A}$, SerT, and hERG activities.

Depression is a mood disorder that is estimated to affect over 100 million people worldwide.[1] Therapies using monoamine reuptake inhibitors (MRIs) represent a primary strategy for the treatment of depression and other mood-related disorders.[2] Although popular, MRIs are troubled with delayed onset of action,[3,4] as well as side effects such as weight gain[2,5–8] and sexual dysfunction.[2,9–11] A strategy designed to alleviate these deleterious features while retaining anti-depressant efficacy is to mix serotonin reuptake inhibition (SRI) with another monamine activity (DRI or NRI) or 5HT receptor pharmacology.[12–20] This work is based upon the latter strategy and demonstrates the dependence of conformation on the pharmacology patterns for the phenoxyphenyl-methanamine PPMA class of molecules.

The PPMA class of compounds has been studied largely due to their structural similarity to Sertraline, a potent serotonin reuptake inhibitor, and their increased conformational flexibility, which enables the possibility of adding secondary pharmacologies. In this regard, these compounds may be thought of as a flexible version of Sertraline: when the di-phenyl-ether bond torsion is ~120°, both aryl rings of the PPMA overlay exactly with the aryl rings of Sertraline, while typical methyl-amine dihedral angles are capable of overlaying with the rigid benzylic-amine of Sertraline. An ideal compound would be able to access geometric patterns than fit both the serotonin transporter as well as other monoamine binding sites. For the compounds studied here, geometries optimal for $5HT_{2A}$ activity have been sought.

Activities and substitution patterns for the 66 compounds used in this analysis are given in Table 1. Three pharmacology values are reported: $5HT_{2A}$ binding, serotonin transporter activity (SERT), and hERG binding. The $5HT_{2A}$ assay measures potency of compounds versus [3H]-Ketanserin binding. Serotonin transporter activity was measured using a standard serotonin uptake inhibition (SRI) assay.[21,22]

hERG data represents the affinity of compounds for the hERG ion channel using a [3H]-dofetilide radioligand binding assay. Preparation of PPMA compounds have been detailed previously.[23–25]

Structure-activity relationships. A simple method has been employed to represent the structural and electronic characteristics of the different PPMA analogues. Using the convention defined in figure 1 as a guide, Hammett values,[26] number of hydrogen bond acceptors, and molecular weights were calculated for the A and B–ring substituents. In addition, a simple count of the number of attached carbons is also included for the positions labeled as R^1 and R^2. These values were manually loaded into a spreadsheet and multiple linear regression models were built using the JMP software[27] for three activities.

Table 2 lists the coefficients found using a multiple linear regression method for the values three activities studied. All correlations represent fits to the –log(IC50). The SAR resulting from this analysis can be summarized as follows:

For the observed $5HT_{2A}$ pharmacology, electron donating functionalities on the B-ring, steric bulk on the para position of the A-

* Corresponding author. Tel.: +1 860 245 0179.
E-mail address: scot.mente@pfizer.com (S. Mente).

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Table 1
Substituent patterns and activity values of PPMA analogues

Compound	Amine		A-ring		B-ring		Pharmacology [IC_{50}, nM]		
	R^1	R^2	R^3	R^4	R^5	R^6	SerT	$5HT_{2A}$	hERG
1	H	H	F	H	H	H	381	670	
2	C	H	H	H	Cl	Cl	0.35	144	2120
3	C	H	H	H	H	Cl	1.68	1980	
4	H	H	F	H	Cl	Cl	3.28	206	5570
5	C	H	N	H	Cl	Cl	4.99	724	
6	H	H	H	H	Cl	Cl	4.02	721	3880
7	C	H	CC(=O)N	H	Cl	Cl	2.43	2240	
8	C	H	H	H	H	SC	1	458	3020
9	C	C	H	H	Cl	Cl	3.27	87.8	900
10	C	H	H	H	H	C	3.46	74.2	
11	C	H	H	CF3	Cl	Cl	17.1	41.5	1120
12	C	H	H	H	F	F	34.4	1000	
13	H	H	F	H	C	C	7.55	52.4	20000
14	H	H	H	H	C	C	12.8	66.4	
15	H	H	H	H	H	Cl	13.9	1050	
16	H	C	H	H	H	C	94.1	55.1	
17	H	H	H	CF3	Cl	Cl	29.6	362	1190
18	H	H	H	Cl	Cl	Cl	6.22	89.5	1240
19	H	C	F	H	Cl	Cl	8.09	301	6830
20	H	H	H	F	Cl	Cl	36	651	3010
21	H	C	H	H	Cl	Cl	23	379	3850
22	H	C	H	H	H	Cl	56.8	179	
23	H	H	OC	H	Cl	Cl	3.77	1450	
24	H	H	F	H	H	Cl	9.47	495	7390
25	H	C	F	H	H	Cl	34.8	206	5230
26	C	H	C	H	Cl	Cl	2.36	376	3390
27	H	H	H	Br	Cl	Cl	5.1	66.8	974
28	H	H	Br	H	Cl	Cl	4.8	787	1620
29	H	H	OC	OC	Cl	Cl	14.1	249	10100
30	C	H	H	OC	Cl	Cl	3.61	36.8	234
31	H	H	C#N	H	Cl	Cl	2.5	3180	4560
32	H	H	CNSO2	H	Cl	Cl	9.35	5570	4800
33	H	H	C	C	Cl	Cl	8.9	79.4	1480
34	H	H	H	C#N	Cl	Cl		315	1310
35	H	H	NC(=O)	H	Cl	Cl	3.78	1550	5440
36	H	C	F	H	Cl	Cl	92.2	109	6120
37	H	C	F	H	Cl	Cl	7.36	603	4910
38	H	H	CF3	H	Cl	Cl	21.8	1800	1310
39	H	H	F	Cl	Cl	Cl	4.37	230	3210
40	H	H	H	OC	Cl	Cl	8.72	105	692
41	H	H	F	H	F	Cl	19.3	2010	4670
42	H	H	F	H	Cl	F	37.5	575	8290
43	H	C	CF3	H	Cl	Cl	61.2	291	3030
44	H	C	C	H	Cl	Cl	39.6	172	2690
45	H	H	F	H	H	Ph	28.9	378	
46	H	C	H	OC	Cl	Cl	41.2	88	785
47	H	H	F	OC	Cl	Cl	4.51	74.6	2150
48	H	H	CF3	H	H	Cl	31.1	324	5110
49	H	H	CF3	H	H	C	74.7	34.7	10400
50	H	H	H	Cl	C	C	4.67	3.42	1740
51	H	H	H	Cl	H	C	17	1.18	1640
52	H	H	F	H	CC	Cl	5.53	274	4560
53	H	H	H	Cl	CC	Cl	20.7	47.1	1150
54	H	H	H	Cl	H	Cl	9.2	6.59	645
55	H	C	H	Cl	H	C	187	3.54	3690
56	H	C	H	Cl	C	C	115	6.82	2470
57	H	H	Cl	H	C	C	9.81	51	5230
58	H	H	Cl	H	Cl	Cl	5.73	429	3120
59	H	H	Cl	H	H	Cl	7.49	90.2	4790
60	H	H	H	Cl	Cl	C	4.19	9.11	1060
61	H	H	H	Cl	C	Cl	4.27	9.04	1780
62	H	H	H	Cl	Cl	H	77.5	48.6	2110
63	H	H	H	Cl	C	F	31.2	32.9	3040
64	H	H	H	Cl	Cl	F	25.4	60.9	2110
65	H	H	H	Cl	CF3	F	9.71	48.9	873
66	H	H	H	Cl	F	Cl	88	58.1	1230

ring and a hydrogen-bond accepting group on the meta position of the A-ring are generally found to be favorable for activity. No significant effect is seen when going from the mono-methylamine to the di-methylamine, however adding a carbon to the R^2 position does favor $5HT_{2A}$ activity.

Serotonin transporter activity appears sensitive to the methyl substitution pattern: switching from the mono-methylamine to the di-methylamine favors activity, while adding a carbon to the R^2 position disfavors SERT activity. Electron withdrawing at the para position of the B-ring favors activity. In the traditional medic-

inal chemistry terms outlined by Topliss[28] this SAR appears counter to that observed for $5HT_{2A}$ activity. In general, any substitution on the A-ring has a marginal effect on SERT activity.

Finally, potency increase for hERG is observed primarily through increase of the molecular weight on either ring and addition of a methyl group to the amine. Further potency increase for hERG is also observed via addition of hydrogen-bond accepting groups to the para position of the A-ring, while this same substitution weakens activity when made at the meta position. hERG potency tracks with SERT activity at the methyl-amine site, while no correlation is found at the R^2 site. The hydrogen-bond accepting group SAR of the A-ring is interesting since it appears consistent with SAR found in other hERG blockers. We envisage that this series partially matches published pharmacophore models for hERG activity,[29–41] with the A-ring nestled into the pore region of the channel, which is lined by a tetrameric arrangement of putative hydrogen-bond donors (SER and THR), and the B-ring placed into a more 'non-specific' binding pocket based upon the correlation with molecular weight at this site.

This SAR highlights the difficulties of optimizing multiple potencies at one time. For instance, $5HT_{2A}$ and SERT display disparate SAR at the A-ring para site and the methyl-amine. $5HT_{2A}$ activity may be gained at the B-ring para position, however this substitution pattern (addition of CH3, OH and O-alkyl groups) also has the effect of increasing cytochrome P450 2D6 metabolism. Addition of halogen substituents to this ring to block 2D6 and other CYP subtype metabolism has the effect of weakening $5HT_{2A}$ activity making it necessary to achieve potency gains for this receptor at the A-ring sites. Adding to this difficult balancing act is the fact that hERG activity, which is a deleterious effect responsible for QT prolongation,[39,40] tracks with $5HT_{2A}$ at the A-ring (HBA) and with SERT activity at the methyl-amine site. In fact, addition of larger alkyl or aryl functionalities at the R^1 position generally brings in additional hERG potency.

Correlation coefficients of 0.73, 0.45, and 0.58 are achieved for $5HT_{2A}$, SERT, and hERG activities, respectively. Comparable correlation coefficients are achieved using a leave-group-out cross validation based on 5 random sets of 12 compounds (20%). Of the three activities, the $5HT_{2A}$ activity appears to be the most sensitive to this set of descriptors. Only five parameters are required to achieve a reasonable fit, whereas six parameters are needed for the hERG prediction. From the exemplified SAR, it appears that the SERT and hERG activities are more responsive to steric and electrostatic interactions, represented here by the somewhat crude substituent parameters molecular weight (MW) and hydrogen-bond accepting counts (HBA).

Conversely, the $5HT_{2A}$ activity appears more responsive to the B-ring electronic effects. The dynamic range of the $5HT_{2A}$ potencies is larger than the dynamic range of the other two activities, which likely increases model performance statistics. From a drug design perspective, the $5HT_{2A}$ model is more useful, since most compounds with this scaffold have reasonable activity for SERT, and relatively poor activity for hERG. This can be seen semi-quantitatively in the intercept values, which translate to ~14 nM for SERT, 115 nM for $5HT_{2A}$ and 5000 nM for hERG.

A series of quantum chemical torsional profiles have been carried out on a smaller set of potent ligands, with dual objectives of further explaining the substituent effects upon ligand potency as well as generating a structural model that can differentiate between $5HT_{2A}$ and SERT activities. Looking first at compounds with potent SERT activity, we find a very good overlap with a low-energy conformation of compound **2** with Sertraline, a very rigid, potent and selective serotonin reuptake inhibitor (Fig. 2). Because Sertraline is rigid, it is reasonable to assume that it is this conformation of the PPMA compounds that binds to the Serotonin transporter. However, other low-energy conformations of PPMA ligands exist which adopt a similar conformation where the methylamine and A-ring overlay well with Sertraline, but the B-ring position is altered via a rotation about the di-phenyl-ether bond (Fig. 2, right). It is this aryl-ether bond variation that is examined using by the calculation of the torsional profiles in an attempt to differentiate between PPMA compounds with weak and potent activity for $5HT_{2A}$. These energy profiles have been determined from ab initio calculations at the RHF/6-31G(d,p) level using the Gaussian 03 program.[42] For each molecule, 16 separate geometry optimizations were performed, in which the aryl-ether torsion angle (bonds outlined in Fig. 1) is held fixed while all other geometric angles and bond lengths are allowed to relax. Every angle between 75° and 300° was held fixed at 15° increments. Torsional profiles resulting from a sequence of energy minimizations about this bond are shown in Figure 3 for compounds **51** and **18**. A clear differentiation is observed between compound **18** which is selective for SerT (Sert/$5HT_{2A}$ = 0.07) versus compound **51** which is 14× selective for $5HT_{2A}$. In fact, all compounds possessing the electron-donating functionality on the B-ring also share local minima at or near the di-phenyl-ether bond of 180° suggesting that adding electron density to the ether linker from electron-donating substituents allows this preferred conformation to be achieved without an enthalpic penalty.

Torsional profiles for 12 compounds, which have been selected based upon substituent diversity, reveal a correlation between the energy difference between these two conformations and one in which the di-phenyl-ether bond is ~180°. This energy difference is plotted versus the $5HT_{2A}$ activity in Figure 4. For compounds with electron-donating substituents on the B-ring, this energy difference approaches 0, meaning that there is either no energy penalty for adopting this conformation, or that the energy curve itself

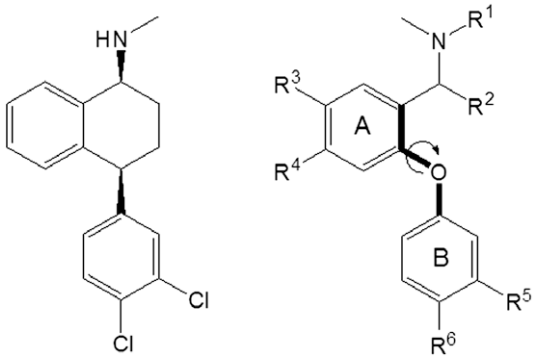

Figure 1. Sertraline (left) and the flexible PPMA scaffold (right).

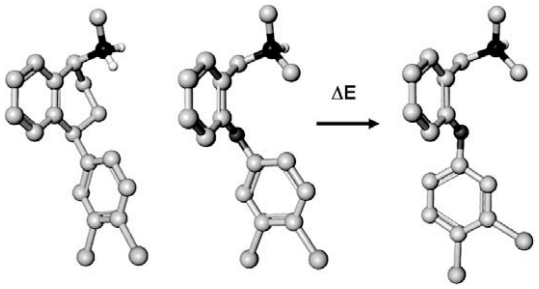

Figure 2. Side-by-side illustration of Sertraline with compound **2**. The minimum energy value of the Car-Car-O-Car dihedral angle of compound **2** is typically 120 or 180, depending on the substitution.

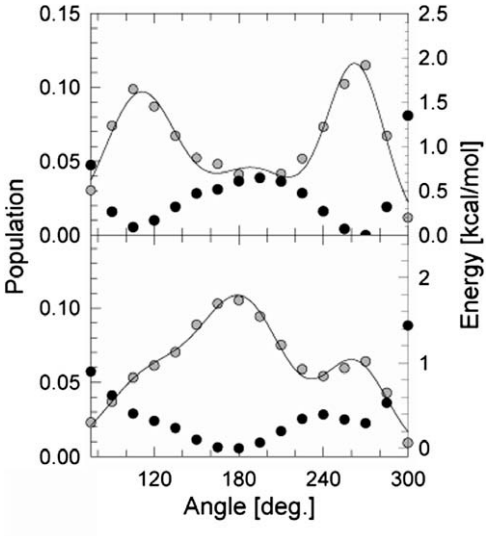

Figure 3. Ab initio energy values (black symbols) and corresponding Boltzmann populations (gray symbols) for compounds **51** (top panel) and **18** (bottom panel).

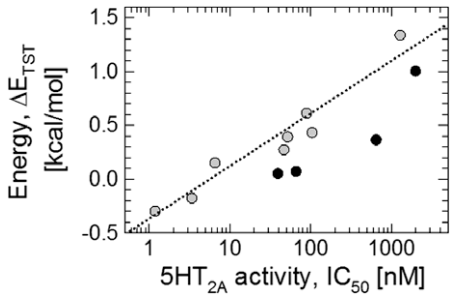

Figure 4. Comparison of the $5HT_{2A}$ activity with the energy of rotation required to achieve a 180° di-phenyl-ether bond angle (ΔE). Four of the 12 compounds are less active than would be expected based on the calculated energy difference (compounds **14**, **6**, **20**, and **66**) and are represented with black symbols. Other compounds included in this analysis are (in order of decreasing $5HT_{2A}$ potency): **51**, **50**, **54**, **13**, **18**, **4**, **53**, and **40**).

changes shape as the electronic characteristics of this system are altered. There is an observed correlation between this energy difference and the potency a compound has for the $5HT_{2A}$ receptor ($R^2 = 0.60$). Despite the good general correlation, four of the twelve compounds are less active than would be predicted (compounds **14**, **6**, 20, and **66**). Three of these compounds (**14**, 6, and **20**) have either no substitution on the A-ring or a small substituent (F) which, consistent with the QSAR relation in Table 2, should decrease the potency of this compound relative to the others. The final compound is a thio-ether which may likely disturb the alkyl-amine torsion. In absence of these four compounds, the correlation coefficient between $5HT_{2A}$ activity and the torsional energy difference for the remaining eight compounds 0.78.

A related study has recently appeared[43] in which a large survey of conformational distributions is used to analyze torsional preferences. These authors bin the di-phenyl-ether torsion into the 'medium' barrier height region in which the barrier itself occurs at a 90° and the preferred conformations appear to occur at either 60° or 150°. Our analysis differs from their study, in having an ortho-substituted alkyl-amine which alters the calculated minima (120°, 180°, and 240°) and shows a strong dependence on the type of substitution. Using their criteria, this ortho-substituted di-phenyl-ether class has 'low' barrier height which may be modified via inductive effects.

Table 2
Coefficients for simple Hammett QSAR analysis

Parameter	$5HT_{2A}$	SERT	hERG
Intercept	6.94	7.85	5.18
Ncarbons R^1		+0.566**	+0.330**
Ncarbons R^2	+0.319*	−0.560**	
σR^3			+0.41*
HBA R^3	−0.449*		−0.369**
MW R^3			
HBA R^4			+0.25*
MW R^4	+0.0210**		+0.0100**
σR^5	−1.19**		
MW R^5			+0.0057*
σR^6	−1.75**	+1.02**	
MW R^6			
R^2 Correlation	0.73	0.45	0.58
Q^2 (LGO-CV)	0.69	0.40	0.56
MSE	0.17	0.18	0.07

* $p < 0.05$.
** $p < 0.005$.

In summary, based upon the QSAR analysis, calculations and thermodynamic model, the following general conclusions may be implied.

(1) $5HT_{2A}$ activity depends upon the σ values of the B-ring for PPMA compounds. Electron donating compounds alter the rotational barrier of the di-phenyl-ether bond in such a way as to increase the fraction of compounds that have the geometry preferred for $5HT_{2A}$ binding. We presume that this 'correct' geometry corresponds to a DPE bond of ~180°.
(2) A corresponding SERT binding model may be constructed by overlaying the calculated low-energy conformations of preferentially SERT active compounds with the rigid structure of Sertraline. The geometric requirements of the DPE bond in the PPMA compounds are ~120°.
(3) Ideal compounds with both SERT and $5HT_{2A}$ activity should have relatively low energy barriers to access these states. This idea should be general and therefore possible to extrapolate to other flexible ligand scaffolds.

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