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5HT1a Receptor Binding Affinities of a Series of Serotonin Transporter (SERT) Inhibitors and Related Thermodynamic Insights^

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JMG, SG and KKP designed the study and wrote the protocol. Authors JMG, CG, CS, MB and KKP collected all data and performed the statistical analysis. Authors SG, KKP and SPS wrote the first draft of the manuscript. Authors GEA, LB, SPS and AS did the literature search and also wrote part of the manuscript. Authors EN, JMG, SG and KKP wrote the final version of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Clinical depression encompasses a complex neurobiology involving multiple interacting systems. This intricate pathophysiology is, in part, correlated with dysfunction in serotonin (5HT) neurochemistry. The 5HT1a receptor (R) and SERT (serotonin transporter) components of this network are highly correlated to mood and anxiety regulation and difficulties in this regard in the realm of depression.

Aims: The current study was designed to develop a series of arylpiperazine derivatives ligands that are antagonists at both H5HT1aR and SERT.

Study Design: Development of new chemotype antagonists at H5HT1aR and SERT.

Place and Duration of Study: University of Catania (Italy) and University of Montana, Missoula, Montana, May 2008 to June 2013.

Methodology: Chinese Hamster Ovary cells transfected with the gene for the Human (H) 5HT1a Receptor were cultured, and membranes containing the receptor were prepared for competition assays between the test compounds and the agonist, [^{3}H]8-OH-DPAT. For thermodynamics, Ki's were determined at a series of temperatures from 0-35 degrees C. Further, membranes from rat brain were utilized for competition assays between the test compounds and the SERT inhibitor, [^{3}H] paroxetine.

Results: Many of these substances show nanomolar affinities at H5HT1aR, and a number of the compounds also have high efficacy in inhibiting SERT. It is of note that some members of this series also substantially discriminate between binding at H5HT1aR and H5HT7R, a receptor studied with these compounds in previous work. Thermodynamic properties for the compound 4-[4-(3-benzo [b] thiophen-3-yl-3-oxopropylamino) piperidin-1-yl] benzonitrile (BTPN; compound15) are also reported.

Conclusions: There are a few of these compounds that excel in all three categories of H5HT1aR affinity, SERT inhibitory activity, and discriminatory binding capacity between the two receptors. Implications in the context of clinical needs in depression and other nervous systems disorders are discussed.

Keywords: Clinical depression; serotonin; 5-HT1A receptor; SERT; thermodynamics studies.

1. INTRODUCTION

The neurobiology of depression [1,2] has been under intense study; multiple neuronal and hormonal systems are involved in the pathophysiology [3,4,5] and complexity [6,7] has been observed in genetic, epigenetic, and environmental events. Evidence suggests an immunologic connection as changes in the immune system influence corticosteroids, perhaps via cytokines IL1 and 6; other signaling pathways including the serotonergic (5HT) are altered. 5HT [8,9] plays a critical role overall [10]. Dys-regulation of 5HT may present vulnerability to a variety of mental disorders including mood regulation [11,12].

The inter-relationships between 5HT, stress [3,13] and increased secretion of cortisol have been noted. These events are due to the link between anxiety and depression [14,15,16].

Coupling of depression to anxiety is but one of many connections being identified between depression and heretofore separate phenomena [17,18,4,19,3]. For example, the metabolic regulator, leptin, has been implicated in regulation of mood. When stressors are extended by intensity and duration, anxiety and depression may ensue. 5HT drugs have a role in returning to homeostasis.

Serotonin (5-hydroxytryptamine; 5HT) receptors (5HTR) are major components of this analysis [20,21,22]. Many of the 5HTR are G Protein-Coupled Receptors (GPCR) [23]. The first crystal structures for 5HTR have opened a new era for 5HT pharmacology [24]. One of the 5HTR sub-types, the 5HT1aR [25] is involved in depressive disorders [26,27]. A meta-analysis has shown H5HT1aR dys-regulation to be correlated with major depressive disorder [28]. At the biochemical level there is evidence to support involvement of both somatodendritic receptors in the raphe nuclei and/or post-synaptic receptors in various brain regions. Evidence suggests that anti-depressant actions are fortified by antagonism at the raphe autoreceptors and agonism at the post-synaptic sites. In Deaf-1 mutant mice, raphe autoreceptors are up-regulated and hippocampal post-synaptic 5HT1a receptors are down-regulated. This produces

behavior consistent with increased anxiety and decreased responsiveness to 5HT transport (SERT) inhibitors (SSRI) [29], potentially of therapeutic importance [30].

Involvement of 5HT1aR not only influences 5HT transmissional homeostasis [25] but other systems such as the corticosteroid [31] and glutaminergic [16]; in turn, chronic cortisol secretion desensitizes 5HT1aR. More evidence comes from post-mortem studies [27] and positron emission tomography (PET) studies in humans using high affinity antagonists show 5HT1aR involvement in anxiety and depression as well as the action of anti-depressant drugs, like transport inhibitors [32]. One specific instance is that involving the 5HT1aR and cannabinoids (CBD: cannabidiol) [33,34] in treating an anxiety disorder, panic [35].

Our laboratories have addressed differential activities of a series of arylpiperazine derivatives at SERT and 5HT1aR [36,37,38,39]. Structurally, the benzo[b]thiophene group is related to SERT inhibition with the arylpiperazine group related to activity at 5HT1aR. These observations were expanded to differential binding to SERT [40,41] vs. 5HT7R [22,42], which is also an anti-depressant target [43], and which has been receiving attention as a neurobiological target [44]. Arylpiperazinlybutyloxindoles have 5HT1a /5HT7/alpha 1 adrenergic actions [45,46]. Our laboratories have focused on the 5HT1aR binding site [47,48,49] and at the receptor/G protein interface [50,51]. The present study focuses on differential benzo [b] thiophene-arylpiperazine activity at SERT versus H5HT1aR with reference to H5HT7R.

There is a small literature on the thermodynamics of binding site ligands at 5HT1aR [51,52,53,54]. Results from the present investigation are the first reported thermodynamics for a new series of ligands [43] interacting with the human 5HT1aR. These preliminary results should be useful, in combination with receptor-based biochemistry and pharmacology using different techniques, to develop better models of the H5HT1aR/G protein system, ultimately producing advances in applied drug development.

2. MATERIALS AND METHODS

2.1 Compound Synthesis and Preparation

The compounds involved in this paper were prepared as previously reported and their structures are presented in Table 1. and Table 2. [43,36,37,38,39].

2.2 Cell Culture

Chinese Hamster Ovary (CHO) cells expressing the human (H) 5HT1aR [55,56] were cultured in Ham's F-12 medium plus 10% fetal calf serum and 200 µg/ml geneticin. Cultures were maintained at 37ºC in a humidified atmosphere of 5% CO_2. Cells were sub-cultured (trypsin) or assayed upon confluency (5-8 days). Cloned H5-HT1aR was kindly provided by Dr. John Raymond, the Medical University of South Carolina [57].

2.3 Receptor Preparation

Cells were trypsinized and centrifuged; the pellet was re-suspended in Earle's Balanced Salt Solution followed by centrifugation. Cells were re-suspended in 10 ml of binding buffer (50 mMTris, 4 mM $CaCl_2$, 10 µM pargyline, pH 7.4), homogenized with Teflon-glass, and centrifuged for 450000 g-min. at 4ºC (10000 g for 45 min. at 4ºC). The pellet was re-suspended in 30 ml of ice-cold binding buffer, and homogenized, with Teflon-glass and then with a Polytron (setting 4) for 5 sec. The preparation was stored on ice and used within 1.5 hrs [51].

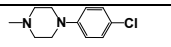
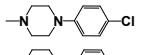
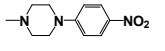
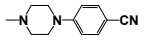
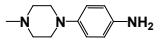
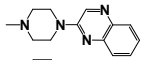
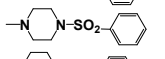
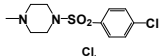
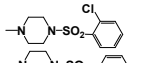
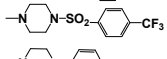
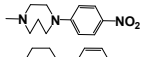
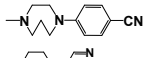
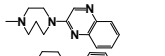
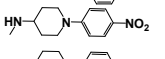
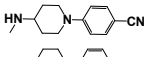
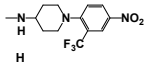
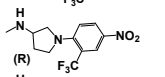
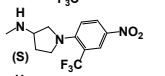
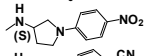
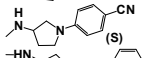
2.4 Assay of Receptor Activity

Binding of agonist [^{3}H] 8-OH-DPAT ([^{3}H] 8-hydroxy-2-(di-n-propylamino)tetralin) to H5-HT1aR followed well-characterized protocols [50]. Radioligands were from New England Nuclear, Boston, MA. 1 ml reaction mixtures, in triplicate, were incubated for 30 min. in a 30ºC shaker bath. Composition of the 1 ml reaction mixture: 700 µl of receptor preparation; 100 µl of either binding buffer (for total binding) or 10 µM 5-HT (final concentration for non-specific binding), 100 µl of the tritiated agent (0.5 nM) and 100 µl of test ligand or binding buffer for controls.

Reactions were stopped in 4 ml of ice-cold 50 mMTris buffer, pH 7.4, and vacuum filtration on glass fiber filters (Whatman GF/B). Filters were rinsed twice in 5 ml of ice-cold Tris buffer, dried, and counted in 5 ml of Ecoscint (National Diagnostics) in a Beckman LS 6500 instrument. Homogenates were assayed for protein to maintain a nominal value of 50 µg protein per filter [58]. For the thermodynamics, receptor binding assays were conducted as outlined earlier in this section. As described in greater

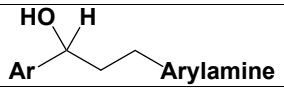
detail in an earlier publication [51] the following parameters were utilized: concentration of compound 15, 10 nM (its apparent Kd); [^{3}H]8-OH-DPAT ranging from 0.2 to 2.0 nM (apparent Kd of about 0.6 nM); and Centigrade temperatures of: 0, 15, 25, 30 and 35 degrees.

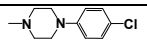
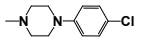
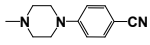
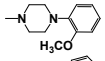
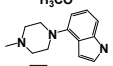
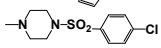
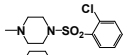
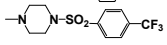
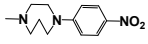
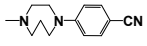
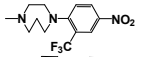
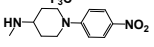
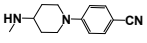
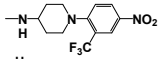
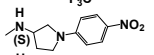
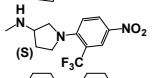
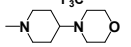
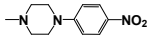
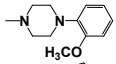
Table 1. Ki's for the ketone set of compounds at the H5HT1aR and binding at the rat SERT

Code (#)	Comp.	Ar	Arylamine	Ki H5HT1aR	SERT (1/10 μM) % Activity remaining
E0005 (3)	1[d]			0.8 +/- 0.06 μM	87 +/-10/33+/-1
E0009 (4)	2[d]			0.52 +/- 0.03 μM	90+/-12/36+/-3
E11 III 27 (36)	3[a]			est. > 2 μM	98+/-17/67+/-11
E11 III 212(10)	4[a]			0.38 +/- 0.024 μM	95+/-1/62+/-5
E11 III 29(48)	5[a]			0.58 +/- 0.03 μM	ND
E11 III 214(11)	6[e]			est. > 2 μM	95+/-8/113+/-36
E11 III 01(39)	7[a]			1.9 +/- 0.13 μM	94+/-1/77+/-21
E11 III 02(40)	8[a]			1.2 +/- 0.07 μM	99+/-2/77+/-8
E11 III 03(9)	9[a]			1.04 +/- 0.05 μM	100+/-10/45/+/-7
E11 III 04(41)	10[a]			1.8 +/- 0.05 μM	ND
E11 IV 27 (12)	11[e]			0.42 +/- 0.013 μM	77+/-11/32+/-9
E11 IV 212(14)	12[a]			0.45 +/- 0.02 μM	99+/-6/37+/-7
E11 IV 214(15)	13[a]			0.52 +/- 0.03 μM	76+/-0/42+/-12
E11 VIII 27(22)	14[e]			31 +/- 2 nM	ND
E11 VIII 212 (24)	15[a]			10.4 +/- 0.7 nM	ND
E11 VIII 28 (23)	16[a]			7 +/- 1 nM	73+/-5/37+/-1
E11 VI 28 (R) (21)	17[a]			7.8 +/- 0.5 nM	84/69
E11 VI 28 (S)(18)	18[a]			16 +/- 0.6 nM	72+/-10/2+/-14
E11 VI 27(S) (17)	19[a]			0.73 +/- 0.04 μM	106+/-6/63+/-3
E11 VI 212(S) (19)	20[a]			2.1 +/- 0.08 μM	102+/-19/54+/-14
E11 VI 06(46)	21[a]			93 +/- 4 nM	ND
E11 VII 27(R) (20)	22[a]			0.64 +/- 0.04 μM	91+/-14/55+/-2
E11 V 27(16)	23 [a]			0.23 +/- 0.01 μM	82+/-1/24+/-5
E11 V 28 (58)	24[e]			0.36 +/- 0.01 μM	132+/-1/136+/-4
E11 IX 216 (25)	25[a]			3.0 +/- 0.2 μM	89+/-10/70+/-17
E21 III 27 (34)	26[a]			0.28 +/- 0.01 μM	106+/-14/84+/-7
E21 III 05 (33)	27[a]			1.1 +/1 0.08 μM	107+/-3/45+/-4
E21 III 27 (38)	28[a]			49 +/- 3 nM	106+/-14/84+/-7

Results are mean +/- standard error of the mean. Drugs are from the following previously published investigations: (a) Berrade et al., [43]; (d) Orus et al., [38]; and (e) Perez-Silanes et al. [39]. ND: Experiment Not Performed

Table 2. Ki's for the hydroxy set of compounds at the H5HT1aR and activity at the rat SERT



Code #	Comp.	Ar	Arylamine	Ki H5HT1aR	SERT (1/10μM) %Activity remaining
E0014 (7)	29[d]			0.31 +/- 0.02 μM	109+/-1/61+/-4
E0015 (8)	30[d]			0.64 +/- 0.05 μM	88+/-6/41+/-15
E12 III 212 (51)	31[a]			1.0 +/- 0.03 μM	83+/-9/62+/-1
E0012 (6)	32[d]			2 +/- 0.2 nM	109+/-7/53+/-3
E0004 (2)	33[b]			1.6 +/- 0.13 nM	66+/-1/30+/-4
E12 III 02 (26)	34[a]			est. > 2 μM	85+/-11/52+/-2
E12 III 03 (43)	35[a]			1.4 +/- 0.1 μM	105+/-12/73+/-10
E12 III 04 (44)	36[a]			0.85 +/- 0.08 μM	109+/-1/71+/-1
E12 IV 27 (27)	37[e]			0.47 +/- 0.03 μM	70+/-6/52+/-18
E12 IV 212 (53)	38[a]			1.2 +/- 0.06 μM	80+/-9/63+/-14
E12 IV 28 (28)	39[a]			0.44 +/- 0.03 μM	115+/-23/64+/-11
E12 VIII 27 (31)	40[e]			100 +/- 6 nM	60/7
E12 VIII 212 (54)	41[a]			50 +/- 3.2 nM	64/7
E12 VIII 28 (57)	42[e]			22 +/- 2 nM	169+/-20/114+/-1
E12 VI 27 (S) (29)	43 [a]			0.55 +/- 0.02 μM	72+/-11/51+/-4
E12 VI 28 (30)	44[e]			76 +/- 3 nM	78+/-7/62+/-21
E12 IX 216 (32)	45[a]			est. > 2 μM	98+/-9/36+/-11
E22 III 27 (50)	46[e]			1.2 +/- 0.09 μM	81+/-12/74+/-12
E0011 (5)	47[c]			0.16 +/- 0.01 μM	90+/-8/47+/-6
E0002 (1)	48[b]			0.64 +/- 0.05 nM	80+/-8/43+/-4
E22 III 04 (35)	49[a]			est. > 2 μM	121+/-12/82+/-7

Results are mean +/- standard error of the mean. Compounds are from the following previously published investigations: (a) Berrade et al., [43]; (b) Martinez et al., [36]; (c) Martinez-Esparza et al., [37]; (d) Orus et al., [38]; and (e) Perez-Silanes et al [39].

2.5 SERT Assay

The in vitro inhibitory capability of ligands was determined using a rat cortical SERT competition assay [59] with [^{3}H] paroxetine. The assays were performed with aliquots of partially purified rat cortex membrane (Pel-Freeze Biologicals, Inc.). Suspensions were incubated with 0.25 nM [^{3}H] paroxetine (DuPont-NEN, sp. act. 2.5 Ci mmol^{-1}) and 1 or 10 μM of test ligands. Incubations were stopped by dilution in ice-cold buffer, filtered and rinsed on a Brandell cell harvester, dried and counted with a Packard scintillation counter. Specific binding was defined as the binding difference in the presence and absence of unlabeled paroxetine. Non-specific binding was defined by adding 1 μM paroxetine. Assay data were run in triplicate and repeated three times.

2.6 Data Analysis

All statistics (means, standard errors of the mean (SEM), t tests and ANOVA, Pearson correlation coefficients(r), and graphical procedures were conducted with PSI-Plot (Version 8) software (Poly Software International), Prism (version 4.0c), or using a H-P Graphing Calculator, HP48. Experiments were with a minimum of n = 3, in triplicate. Most experiments were n = 3-5.

3. RESULTS AND DISCUSSION

The compounds examined in this study (Tables 1 and 2) were designed to maximize high affinity binding at H5HT1aR and to achieve maximal inhibition at SERT. IC 50's were determined at H5HT1aR in a cell culture system as outlined in Methods; these values were then converted to Ki's (Table 1 and Table 2) as determined by the Cheng-Prusoff relationship [60]. Regarding H5HT1aR, binding values ranged in activity from nearly inactive to sub-nanomolar affinities.

Those compounds giving at least low micro molar affinity generated full, hyperbolic concentration-dependent displacement relationships to the agonist, [^{3}H] 8-OH-DPAT. An example from compound 18 is given in graphical format in (Fig. 1). This substance has the seventh rated Ki at 16 nM and the highest SERT binding (98% inhibition at 10 μM).

An interesting comparison comes from the relative affinities of these compounds for displacement at H5HT1aR versus H5HT7R; these ratios are shown in (Fig. 2). Note that Ki values for H5HT7R are from Berrade et al. [43].

Binding at SERT was determined in an *in vitro* setting as described in Methods. These SERT results are presented in (Tables 1) and (Table 2). Activity at the serotonin transporter (SERT), assayed at 1 and 10 μM test compound, also ranged from inactive to substantial inhibition.

There are some potentially useful analyses that can be made by bringing all of these parameters together: Ki's at H5HT1aR; activities at SERT; and the ratio of affinities between H5HT1aR and H5HT7R. In looking at the top five compounds in each of these categories, compound 48 tops the list of Ki's (H5HT1aR) at 0.64 nM, followed in order by #33 (1.6 nM); #32 (2 nM); #16 (7 nM); and #17 (7.8 nM). For SERT inhibition at 10 μM, the top compound is #18 (see Fig. 1 and Table 1) followed by compounds 40, 41, 23 and 33. In the H5HT1aR vs. H5HT7R comparison (Fig. 2), the top five are #'s 33, 48, 32, 18, and 42 (in this figure a high value indicates that affinity is greater at H5HT1aR than at H5HT7R). Of particular note is the observation that three of these compounds: #'s 18, 32, and 48 make two of these three lists, while compound 33 can be found on all three.

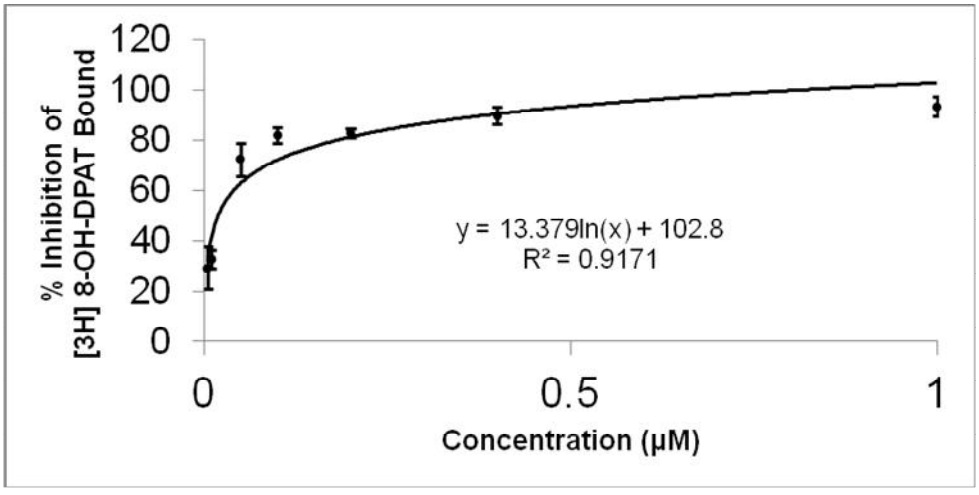


Fig. 1. Concentration-Dependency of a Prototypical Compound (18). Procedures for the binding assays are described in Materials and Methods

Briefly, membranes expressing H5HT1aR were exposed to 0.5 nM [^{3}H] 8-OH-DPAT for 30 min. at 4°C in the presence of varying concentrations of compound 18. Reactions were stopped in cold binding buffer, and bound receptor was isolated by filtration, and quantified by liquid scintillation.

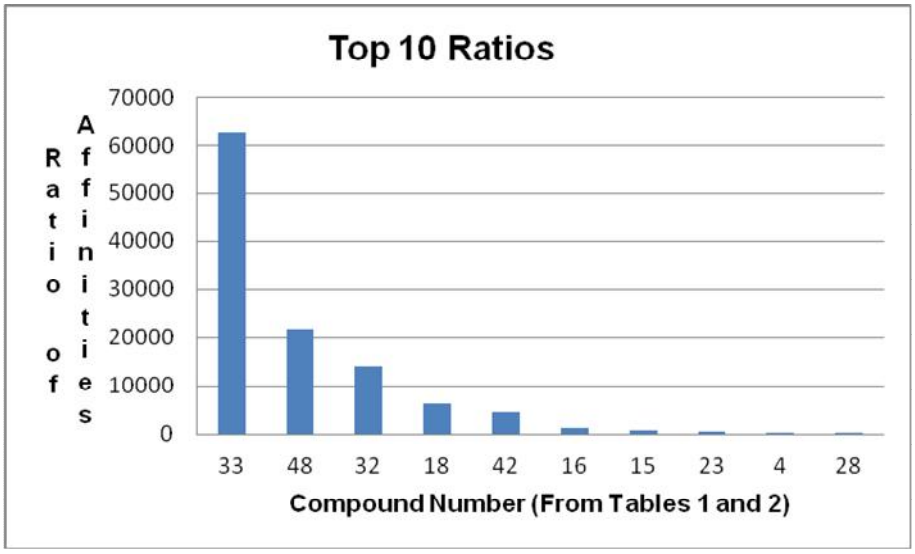


Fig. 2. Graphical Comparison of H5HT1aR vs. H5HT7R Binding Activities. Ratios were derived from H5HT1aR affinities presented in this communication and H5HT7R affinities previously published by Berrade et al. [43]

Binding affinities for H5HT1aR under investigation in this communication were determined as detailed in Materials and Methods. Briefly, membranes expressing H5HT1aR were exposed to 0.5 nM [^{3}H] 8-OH-DPAT for 30 min. at 4°C in the presence of varying concentrations of the compounds under investigation. Reactions were stopped in cold binding buffer, and bound receptor was isolated by filtration, and quantified by liquid scintillation. The larger a value in this calculation, the greater the affinity at H5HT1aR compared to H5HT7R.

Top rated compounds are found in both series (Table 1 [ketones] and Table 2 [hydroxyls]) in all categories. While the very best compounds for H5HT1aR affinity and ratio of H5HT1aR vs. H5HT7R affinities are found in (Table 2), the top-rated SERT inhibitor is in (Table 1). Of the compounds that are in the top five for two or more of the parameters, one is from (Table 1) with three from (Table 2).

The ketone versus hydroxyl designation does not seem to be discriminatory for SERT inhibitory activity. On the other hand, 6 of the top 10 ligands differentiating between H5HT1aR and H5HT7R binding are ketones (Fig. 2). Four of the top five (32,33,48,42) however, including the top three (33,48,32) are alcohols. Compound 33, in the top five for all three parameters, is an alcohol.

Compound 48 which has the highest affinity for H5HT1aR equals or betters the ability of 8-OH-DPAT for binding to H5HT1aR (about 1 nM) (Table 2). Since there are many ligands that have high affinity for the H5HT1aR, this characteristic of compound 48 may not be especially noteworthy. However, 8-OH-DPAT does not readily discriminate in binding to H5HT1aR versus H5HT7R whereas compound 48 does. This property of a number of new ligands studied here will be discussed later in this section. Compound 48 also nearly reduces SERT binding to less than half at 10 μM. Further, compound 18 (which is number four in the receptor discrimination category) reduces SERT binding to near zero at 10 μM, making it an attractive pharmacological and therapeutic candidate. There are two additional compounds (33 and 32) with Ki's for H5HT1aR at or below 2 nM, putting them in the range of 8-OH-DPAT.

Compound 18, (Table 1) and (Fig. 1), deserves special attention due to its leading SERT inhibitory activity in combination with solid affinity for H5HT1aR. At 10 μM this compound produces near complete inhibition of SERT. With a Ki of 16 nM at H5HT1aR compound 18 has 25 times lower affinity for the receptor than does compound 48; nevertheless, 16 nM is a very respectable affinity. Since the primary goal of this research was to produce drugs with dual SERT/H5HT1aR activity, compound 18 may be one of the best products depending on how the two activities are prioritized in ranking the candidates. These two characteristics are vital to the thesis that these compounds bring important properties to bear as potential anti-depressant therapeutic agents.

Compound 33 leads the way in differentiating between the two serotonin receptors 1a and 7, with 48 in second position, (Table 2) and (Fig. 2). Compounds 32 and 18 are next in line followed by six additional substances with affinities for H5HT1aR at least 100 times greater than at H5HT7R. This is a very robust feature of this series of chemicals, and this receptor delineation may have implications beyond the affective disorders. In addition to their therapeutic potential, the most active of these agents and the most discriminating may be useful as tools for better understanding serotonergic systems. In considering all three of the parameters discussed here: affinity for H5HT1aR; ability to discriminate by binding to H5HT1aR compared to H5HT7R; and ability to inhibit SERT, one of the compounds, number 33, can be found in the top 5 of each of these considerations. Considering this versatility, compound 33 may be the lead candidate for a substantial experimental and therapeutic tool. Compound 18 may not be far behind as a lead candidate.

To begin the process of better understanding the receptor binding properties of these compounds, we measured the thermodynamics [61,62] for one of the compounds, compound 15. This compound has a moderately high affinity for H5HT1aR of 10 nM, and a standard free energy for binding of negative 50 kJoules per mole. The standard enthalpy is 28 kJoules per mole, while the standard entropy is 261 Joules per mole. These values compare to negative 52 kJoules per mole, 13 kJoules per mole, and 220 Joules per mole, respectively, for the agonist [^{3}H] 8-OH-DPAT [51].

4. CONCLUSION

There are structure-activity themes of note impacting all three of the comparisons mentioned earlier. In the current larger library of test compounds, the structure-activity relationships postulated by Berrade et al. [43] are upheld: affinity for H5HT1aR is conferred by the arylpiperazine function while SERT inhibitory activity is related to the presence of the benzothiophene group. In the present study, two subgroups, one with a ketone moiety conjugating the two main groups, and the other with an alcohol, three of the top five high affinity H5HT1aR agents are from the hydroxyl subset (48,33,32) while the next two, 16 and 17, are ketones.

Based on the thermodynamic data, binding of BTPN (compound 15) to H5HT1aR seems to be entropy driven. While difficult to generalize about efficacy from the thermodynamics of binding, conclusions can sometimes be suggested within a drug group [50,51]. Within H5HT1a receptor agents, we hypothesize that agonists like DPAT have the least unfavorable enthalpies and least favorable entropies, while partial agonists (such as DPT; dipropyltryptamine), inverse agonists (perhaps BTPN; compound 15), and antagonists have more unfavorable enthalpies and more favorable entropies.

Future work with these two series of compounds will focus on further maximizing the parameters discussed here. Additional characteristics of individual priority compounds, such as their thermodynamics of receptor interactions will also be considered. Further, establishing efficacy (or lack) of priority compounds in the signal transduction system will be important in consideration of the potential for this series of drugs. Potential application of these drugs to related disorders such as PTSD (Post Traumatic Stress Disorder) [63,64], and schizophrenia [65] will be considered.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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