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A new class of 5-HT$_{2B}$ antagonists possesses favorable potency, selectivity, and rat pharmacokinetic properties

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ABSTRACT

We have been exploring the potential of 5-HT$_{2B}$ antagonists as a therapy for chronic heart failure. To assess the potential of this therapeutic approach, we sought compounds possessing the following attributes: (a) potent and selective antagonism of the 5-HT$_{2B}$ receptor, (b) low impact of serum proteins on potency, and (c) desirable pharmacokinetic properties. This Letter describes our investigation of a biphenyl benzimidazole class of compounds that resulted in 5-HT$_{2B}$ antagonists possessing the above attributes. Improving potency in a human serum albumin shift assay proved to be the most significant SAR discovery.

Several groups have explored antagonism of the 5-HT$_{2B}$ receptor as a potential therapeutic for various indications.[1] While originally functionally characterized in the rat stomach fundus,[2] subsequent studies implicated 5-HT$_{2B}$ in vascular and gastrointestinal contraction and relaxation. Consequently, 5-HT$_{2B}$ antagonism has attracted attention for indications such as migraine,[3] irritable bowel syndrome,[4] and pulmonary hypertension.[5] Our interest in 5-HT$_{2B}$ antagonism stemmed from the growing body of data supporting the potential of 5-HT$_{2B}$ antagonism for chronic heart failure, a disease typified by maladaptive remodeling of the heart (hypertrophy).

The phenotype of 5-HT$_{2B}$ receptor knock-out mice demonstrates the importance of this receptor for heart development. Surviving mice possess underdeveloped hearts resulting from impaired myocyte proliferation.[6] Conversely, 5-HT$_{2B}$ over expression in mice leads to cardiac hypertrophy.[7] Antagonists of 5-HT$_{2B}$ have been reported to exhibit efficacy in models of cardiac hypertrophy.[8–10] Genomics data from a model of tachypacing-induced decompensatory heart failure in dogs showed an upregulation of 5-HT$_{2B}$ mRNA.[11] An upregulation of 5-HT$_{2B}$ mRNA has also been reported in humans with cardiomyopathies.[12] However, while all of this data supports the hypotheses of 5-HT$_{2B}$ antagonism being beneficial for heart failure, to date no reports of 5-HT$_{2B}$ antagonist showing efficacy in animal models of heart failure have appeared.

To explore the potential of 5-HT$_{2B}$ antagonism for the treatment of chronic heart failure, we desired a class of compounds that at a minimum would demonstrate potent and selective antagonism of the 5-HT$_{2B}$ receptor and possess good pharmacokinetic properties. In addition, we wanted to increase the likelihood of success by favoring antagonists that could maintain potency in the presence of physiological concentrations of serum proteins.[13]

We conducted a high throughput screening campaign to identify new classes of 5-HT$_{2B}$ antagonists. Compound **1**, Table 1, represents one of the compound classes resulting from this effort. To help gauge the attributes of compound **1**, we compared it to selected literature 5-HT$_{2B}$ compounds that had been reported to be efficacious in pharmacological models. These benchmark compounds included the SmithKline antagonist **SB215505**,[14] the Roche antagonist **RS-127445**,[15] and a compound detailed in a patent from Epix Pharmaceuticals referred to as compound **A**.[16]

Compound **1** possessed several attractive features as a lead. It demonstrated potent antagonism of serotonin-induced intracellular Ca^{2+} flux in 5-HT$_{2B}$ receptor-transfected CHO-K1 cells measured by aequorin luminescence. In this assay it compared essentially equally with the benchmark compounds. Compound **1** proved selective for the 5-HT$_{2B}$ receptor, showing no antagonism up to 10 μM of 5HT$_{2A}$ or 5HT$_{2C}$ in analogous FLIPR based cell assays.[17] It compared equally to the most selective of the three benchmark

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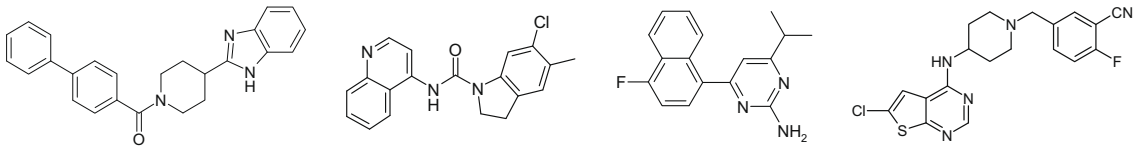
Table 1
Comparison of compound **1** with literature benchmarks



	1	**SB215505**	**RS-127445**	Epix Comp **A**
5-HT_{2B} IC_{50} (nM)[a]	2.4	1.3	0.7	3.5
5-HT_{2B} 4% HSA IC_{50} (nM)[a]	1200	64	19	270
5-HT_{2A} Selectivity (fold)	>10,000	7	2000	>3000
5-HT_{2C} Selectivity (fold)	>10,000	0.5	92	>3000
Rat PK %F	130[b]	—	10[c]	17[d]
1 mg/kg iv CL (%Q)	13	—	29	82
10 mg/kg po oral AUC (ng-h/mL)	25,000		810	500
oral C_{max} (ng/mL)	5000		470	240

[a] Values are means of 2–21 experiments, standard deviations for $n > 2$ experiments ±50% of reported value.
[b] Male Sprague Dawley rats dosed 70/30 PEG400/water.
[c] Male Wistar rats dosed 30/70 Cremophor/aq citric acid.
[d] Male Wistar rats dosed 70/30 PEG400/water.

compounds, the Epix compound **A**. One of the more distinguishing positive attributes of compound **1** is its favorable rat pharmacokinetic profile. Compound **1** demonstrated superior bioavailability, clearance, and oral exposure over both the Epix and RS compounds.

To assess the impact of protein binding on potency, we ran the 5-HT_{2B} aequorin assay in the presence 4% human serum albumin (HSA) and discovered the potency of compound **1** dropped 500-fold.[18] This was clearly the most prominent negative attribute of compound **1** compared to the three benchmark compounds.[19] Consequently, in exploring the SAR and potential of this new class of 5-HT_{2B} antagonists, we desired compounds that maintained the positive potency, selectivity, and pharmacokinetic properties of compound **1** but possessed greater potency in the presence of HSA.

Our SAR investigation commenced with the goal of initially establishing the key pharmacophores for potency. We hoped this investigation would also identify areas in which modifications could be introduced to address the high serum protein shift. As increases in lipophilicity of compounds can correlate with increases in protein binding,[20] attention was placed on identifying modifications that could reduce lipophilicity.

The compounds listed in Tables 1 and 2 provide a general picture of the pharmacophore component of the biphenyl unit of compound **1** and highlight some opportunities for introducing polar functionality.[21] The majority of compounds in these and subsequent tables were prepared in a straightforward manner according the general reaction sequences depicted in Scheme 1.[22]

The lack of potency of compounds **2** and **3** in Table 2 demonstrate the importance of the terminal phenyl group for activity. Introduction of a nitrogen atom into the terminal phenyl reduces potency. This reduction becomes more prominent as the nitrogen moves from the *ortho* to the *meta* and *para* positions (cf. compounds **4**–**6** to compound **1**). Although compound **6** has somewhat weaker potency than compound **1**, the high throughput aqueous solubility of compound **6** at pH 7.4 improves to 63 μg/mL from 3 μg/mL for compound **1**. Unfortunately the introduction of two *ortho* nitrogens (compound **7**) resulted in a further loss of potency.

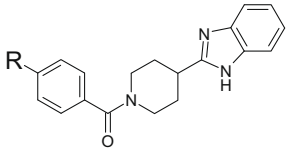
The terminal phenyl in compound **1** can be saturated to cyclohexyl (compound **8**) with a modest 13-fold reduction of potency. A comparison of the structurally related piperidine analog **9** to the morpholine derivative **10** further emphasized the undesirability of a heteroatom in the terminal ring. However, the presence of an oxygen atom at the para position in the form of a methoxy group had minimal effect on potency (compound **11**). Modifications at the para position (compounds **12** and **13**) additionally defined limitations and sensitivity at this region of the molecule. Though the data is not shown in Table 2, it is noteworthy that the terminal phenyl ring tolerate the presence of a 2, 3, or 4 fluoro (IC_{50} 1.5, 2.7; 2.5 nM), chloro (IC_{50} 5.5, 4.2; 4.4 nM), or methoxy (IC_{50} 15, 15; 3.4 nM) substituent.

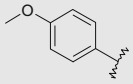
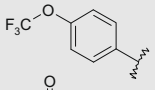
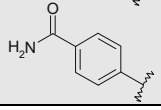
While the presence of heteroatoms in the terminal ring of compound **1** lowered potency, the central ring appeared to better tolerate the presence of nitrogen atoms (Table 3). Compounds **15**–**19** demonstrate some modest diversity in polar functionality. While the decreased lipophilicity of these compounds resulted in improved aqueous solubility over compound **1**, it did not provide a significant improvement in potency in the presence of HSA. The limited examples in Table 3 do not provide a lot more information on the likely role of the central phenyl ring in binding to the 5-HT_{2B} receptor. The substantial decrease in potency observed on saturating this ring (compound **14**) at least highlights the importance of the central phenyl for binding to the receptor and/or appropriately positioning the other pharmacophores.

A comparison of compound **1** to compounds **20** and **21** (Table 4) suggests that the carbonyl group may not be a critical element for potency. While the reduced amide derivative **21** is less potent, removal of the carbonyl introduces substantial conformational flexibility plus introduces a basic amine functionality. The decrease in potency observed for the piperazine derivative **22** and the azetidine derivative **23** suggested the need to appropriately position the benzimidazole functionality relative to the rest of the molecule.

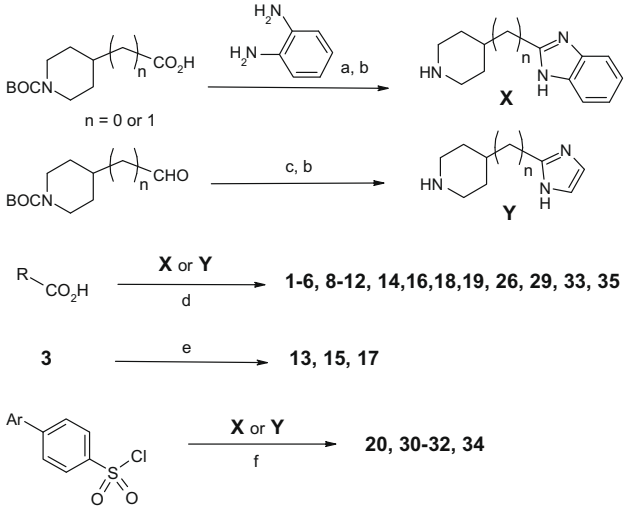
At the initiation of our SAR studies, we hypothesized that the benzimidazole would turn out to be a key pharmacophore for binding to the 5-HT_{2B} receptor. The substantial decrease in potency observed upon methylating the benzimidazole N–H (compound **24**) or even more so upon replacing it with oxygen (compound **25**) supported this belief. We subsequently initiated synthesis of derivatives containing modifications to the phenyl portion of the benzimidazole. However, additions such as a 5-methoxy or 5-CON-HCH_3 (IC_{50} 51 and 4200 nM, respectively) or replacement with a 4 or 5 aza-benzimidazole (IC_{50} 210 and 300 nM, respectively) did not look encouraging. Eventually we tested the essentiality of the phenyl portion of the benzimidazole by preparing the corresponding imidazole analog **26**. To our surprise not only did **26** retain potency for 5-HT_{2B}, it improved potency approximately 15-fold in the HSA

Table 2
Terminal phenyl SAR



Compd	R	5-HT$_{2B}$ IC$_{50}$ (nM)[a]	5-HT$_{2B}$ 4% HSA IC$_{50}$ (nM)[a]
1		2.4	1200
2		>10,000	>10,000
3		>13,000	>26,000
4		>1300	>13,000
5		340	>14,000
6		15	1700
7		120	>2700
8		31	1100
9		48	12,000
10		2300	>26,000
11		3.4	3200
12		95	16,000
13		>2400	>24,000

Effect of R group on potency
[a] Values are means of typically three experiments, standard deviations for $n > 2$ experiments typically ±50% of reported value.



Scheme 1. Reagents and conditions: (a) P(OPh)$_3$, pyridine, 125 °C, 18 h, 40–50%; or 4 M HCl, water, 130 °C, 2 days, 38%; (b) 2 M HCl, ether, 100%; (c) 40% glyoxal, water, NH$_3$(g), MeOH, 47–50%; (d) EDC, DMAP, CH_2Cl_2 or $ClCH_2CH_2Cl$; or EDC, HOBt, Et$_3$ N, CH_2Cl_2, 2–96%; (e) ArB(OH)$_2$, Pd(dppf)Cl$_2$, 2 M aq NaHCO$_3$, MeOH–dioxane, 7–80%; (f) *i*Pr$_2$EtN or Et$_3$N, CH_2Cl_2.

shift assay. The imidazole appears to contain the critical pharmacophore for binding as judged by the drop in potency of the corresponding amide analog **27**.

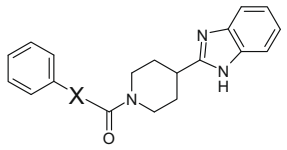
The SAR in Table 4 suggested that potency was sensitive to positioning of the imidazole portion of the antagonist. Thus we were further surprised when we discovered that inserting a methylene group between the imidazole and the piperidine ring increased potency (cf. compound **26** and **28**, Table 5). This increase in potency also translated to the HSA shift assay. The effect of the extra methylene group appeared to be less pronounced for the corresponding benzimidazole analog (cf. compounds **1** and **29**) although the serum shift potency did improve.

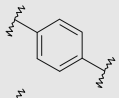
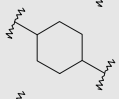
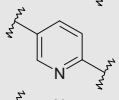
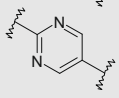
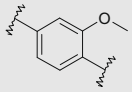
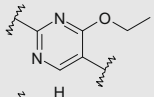
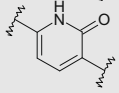
Given the similar potency of the carbonyl and sulfonamide analogs **1** and **20**, we examined the effect of the new imidazole modifications on antagonists possessing a sulfonamide group (Table 6). We saw an equivalent effect between the carbonyl and sulfonamide series for replacing a directly attached benzimidazole with an imidazole (cf. compounds **1** to **26** with compounds **20** to **30**). In contrast, the sulfonamide series lost potency relative to the carbonyl series when the imidazole/benzimidazole group was attached via a methylene (cf. compounds **26** to **28** with compounds **30** to **31**; compounds **1** to **29** with compounds **20** to **32**). These latter results reemphasized the subtleties influencing optimal imidazole orientation.

The imidazole compounds highlighted in Tables 5 and 6 show improved potency in the presence of HSA into the range of the best literature benchmark. Table 7 completes the initial profiling of this new series of 5-HT$_{2B}$ antagonists. All three antagonists possess favorable rat pharmacokinetic properties. The imidazole analog **33** provides a combination of oral bioavailability, iv clearance and oral exposure comparable to the original lead compound. Interestingly, the sulfonamide analog **34** possesses a weaker pharmacokinetic profile compared to the corresponding amide analog. Overall, compound **35** appears to have the best combination of potency and rat pharmacokinetic properties.

Part of our SAR strategy involved identifying ways to reduce lipophilicity with the hope of improving potency in the HSA shift assay. The greatest impact came from replacing the benzimidazole with an imidazole. The difference in protein shift between compounds **1** and **26** is approximately 15-fold. The magnitude of this shift is lower when comparing compounds **28** to **29** and compounds **20** to **30** (both approximately fourfold). However, we obtained data on eight additional benzimidazole imidazole pairs containing modifications to the biphenyl ring beyond those introduced in Tables 1 and 2 (compounds and data not shown). The 11 pairs in total returned an average shift of 7.4 ± 3.9-fold. It is noteworthy that the reduction in lipophilicity as calculated by *c*log*P*, *A*log*P*, or *x*log*P* in going from a benzimidazole to an imidazole ($\Delta\log P = 1.45–1.63$ depending on method) is slightly less than going from a benzene to a pyrimidine ($\Delta\log P = 1.68–2.21$, i.e.,

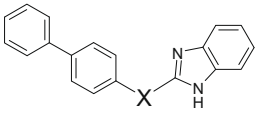
Table 3
Central Phenyl SAR

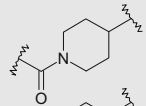
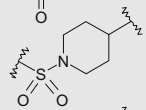
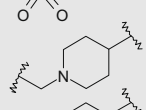
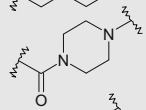
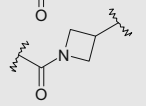


Compd	X	5-HT$_{2B}$ IC$_{50}$ (nM)[a]	5-HT$_{2B}$ 4% HSA IC$_{50}$ (nM)[a]
1		2.4	1200
14		610	>20,000
15		12	>2400
16		2.5	710
17		4	1200
18		6	910
19		22	>3000

Effect of X group on potency.
[a] See footnote for Table 2.

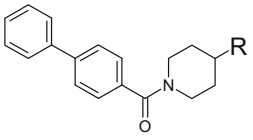
Table 4
Piperidyl carbonyl SAR

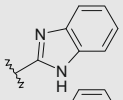
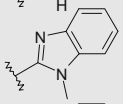
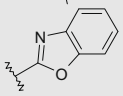
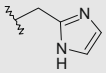
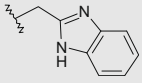


Compd	X	5-HT$_{2B}$ IC$_{50}$ (nM)[a]	5-HT$_{2B}$ 4% HSA IC$_{50}$ (nM)[a]
1		2.4	1200
20		1.9	840
21		65	7300
22		6900	>25,000
23		150	>2800

Effect of X group on potency.
[a] See footnote for Table 2.

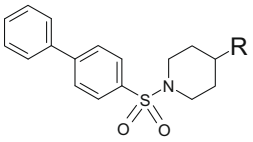
Table 5
Benzimidazole SAR

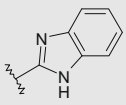
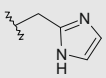
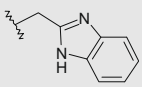


Compd	R	5-HT$_{2B}$ IC$_{50}$ (nM)[a]	5-HT$_{2B}$ 4% HSA IC$_{50}$ (nM)[a]
1		2.4	1200
24		80	10,000
25		1,500	>20,000
26		2.4	76
27		>6500	—
28		0.4	14
29		2.3	300

Effect of R group on potency.
[a] See footnote for Table 2.

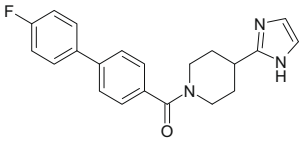
Table 6
Sulfonamide antagonists

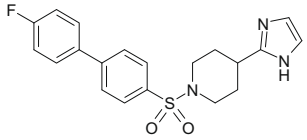


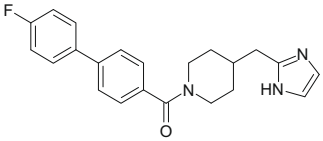
Compd	R	5-HT$_{2B}$ IC$_{50}$ (nM)[a]	5-HT$_{2B}$ 4% HSA IC$_{50}$ (nM)[a]
20		1.9	840
30		0.3	32
31		6.5	990
32		1100	>23,000

Effect of R group on potency.
[a] See footnote for Table 2.

Table 7
Potency and pharmacokinetic data for top compounds







	33	34	35
5-HT_{2B} IC_{50} (nM)[a]	1.1	0.6	0.2
5-HT_{2B} 4% HSA IC_{50} (nM)[a]	35	30	7
Rat PK[b] %F	100	54	118
1 mg/kg iv CL (%Q)	17	60	29
10 mg/kg po oral AUC (ng h/mL)	14,000	2300	6500
Oral C_{max} (ng/mL)	1700	870	600

[a] See footnote for Table 2.
[b] Male Sprague Dawley rats dosed 70/30 PEG400/water.

compound **1** to **16**). Similarly, HSA binding calculations ($Log K_{HSA}$) predict the phenyl to pyrimidine change would lead to a slightly greater reduction in binding to HSA than the benzimidazole to imidazole change.[23] Despite the predictions from calculated physicochemical properties, introducing polar functionality had less of an impact on potency in our HSA assay than removing a phenyl ring. We measured equilibrium dialysis plasma protein binding for compounds **1**, **16**, and **26** (99.9, 99.1, and 99.9, respectively). Interestingly, despite all being very high, these values do not match the trends from either the HSA shift assay or the predictions from calculated physicochemical properties. There are of course caveats with interpreting each of these three methods for ranking protein binding, not the least of which is the role of plasma components other than HSA. Nonetheless, we hypothesize that the consequences of relative binding to serum protein in a functional cell assay will be more predictive of impact in vivo. The veracity of this hypothesis requires an in-depth analysis of pharmacological efficacy and associated pharmacokinetics which is beyond the scope of this publication. Nevertheless we felt it instructive to highlight some results involving structure–protein binding relationships.

In summary we have discovered a new series of 5-HT_{2B} antagonists that maintain good potency in the presence of HSA and possess favorable pharmacokinetic properties in rats. These compounds provide a better balance of potency, selectivity and PK than currently published literature benchmarks. Consequently these compounds should make superior tools for assessing the potential of 5-HT_{2B} antagonists for chronic heart failure.

References and notes

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17. Compound **1** returned <65% inhibition at 10 μM of a panel of 40 receptors conducted at MDS Pharma Services. Dopamine D4.2 was the one receptor showing significant inhibition (99% at 10 μM).
18. We chose to use a serum shift assay to estimate the impact of protein binding because standard equilibrium dialysis experiments to determine protein binding are not high throughput and are not sensitive enough to distinguish between highly protein bound compounds. Rusnak, D. W.; Lai, Z.; Lansing, T. J.; Rhodes, N.; Gilmer, T. M.; Copeland, R. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2309. Using 4% HSA proved convenient as an estimate for the effect of serum components, since the use of serum in the assay stimulated calcium release presumably due to endogenous serotonin.
19. The plasma protein binding for compound **1**, **RS-127445**, and compound **A** were determined by equilibrium dialysis to be 99.9%, 99.9%, and 99%, respectively.
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21. All compounds in Tables 2–6 did not inhibit either 5-$HT_{2A/C}$ at concentrations up to ~10 μM.
22. Most of the biaryl carboxylic acids are commercially available. So are the amine pieces in compounds **22**, **25** and **27** which were coupled to biphenyl carboxylic acid by the options in Scheme 1. The azetidine fragment in compound **23** was prepared in the same manner as compound **X**.
23. These calculations were based on a QSAR model implemented in the program QIKPROP that was developed from high-performance affinity chromatography determinations of binding affinities of 95 diverse drugs and druglike compounds to HSA. See Colmenarejo, G. *J . Med. Chem.* **2001**, *44*, 4370–4378; also Colmenarejo, G. *Med. Res. Rev.* **2003**, *23*, 275–301. $Log K_{HSA}$ values for the training set range from −2.69 to +1.37 for low HSA to high HSA binding. The values for compounds **1**, **16**, **26** were calculated to be +1.01, +0.62, and +0.66 respectively.