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2,5-Disubstituted pyridines: The discovery of a novel series of 5-HT$_{2A}$ ligands

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Abstract—This report describes the effect of replacing the central basic amine present in many known 5-HT$_{2A}$ ligands with an aromatic residue. We targeted the isomeric phenethylpyridines **2** and **3** and these compounds proved to be excellent leads, possessing good 5-HT$_{2A}$ receptor binding affinity and selectivity over the 5-HT$_{2C}$ subtype. Optimization of one isomer led to the identification of **25**, a compound with sub-nanomolar 5-HT$_{2A}$ affinity and selectivity over 5-HT$_{2C}$ of greater than 4600-fold.

A recent meta-analysis of epidemiological studies on insomnia indicated that between 30% and 48% of the global population find difficulty in initiating or maintaining sleep.[1] Moreover, a significant proportion of people (9–15%) exhibit insomnia symptoms that are accompanied by daytime consequences. These effects range from sleepiness, irritability, and memory impairment to clinically significant anxiety and depression.[2] There is also a higher incidence of serious accidents among insomniacs, along with increased job absenteeism and health care costs.[3] All currently approved prescription remedies for the condition are sedative hypnotic agents that act by allosterically modulating the GABA-A ion channel. Benzodiazepines are one such class of compounds that have been in use since the 1960s. Although they significantly increase sleep bout duration they are also associated with numerous side effects.[4] These include withdrawal reactions, daytime drowsiness, and cognitive impairment—effects not unlike the symptoms of insomnia. Newer, non-benzodiazepine hypnotic agents, including Ambien® and Lunesta®, have addressed some of these issues. However, they are listed by the DEA under Schedule IV as they retain potential for abuse.[5] Hence an unmet medical need persists for novel, non-sedating therapies that lack abuse potential.

Selective antagonism of the 5-HT$_{2A}$ receptor has emerged as a promising new mechanism for the treatment of insomnia. In fact, the non-selective 5-HT$_2$ antagonist Ritanserin was first shown to enhance slow-wave sleep (SWS), a component of deep sleep, in humans 20 years ago.[6] Much more recently, the benchmark selective 5-HT$_{2A}$ antagonist M100907 (Fig. 1) has been shown to increase SWS and total sleep time, and reduce the time spent awake after sleep onset (WASO) in elderly patients.[7] In-house preclinical studies with rats fitted with telemetry devices showed that our proprietary selective antagonist **1** (Fig. 1) significantly enhanced SWS and reduced the number of awakenings without effecting REM bout duration.[8] No effect was observed

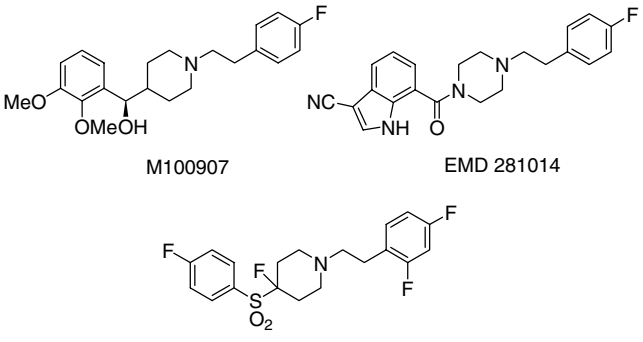

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Figure 1. Selected 5-HT$_{2A}$ antagonists.

Keywords: 5-HT$_{2A}$ ligand; Pyridine; Styrene.
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on sleep onset latency, strongly suggesting that sleep architecture can be beneficially modified without inducing somnolence. In addition, selective 5-HT_{2A} antagonists should lack the adverse effects associated with GABA-receptor pharmacology, such as memory loss and residual sedation.

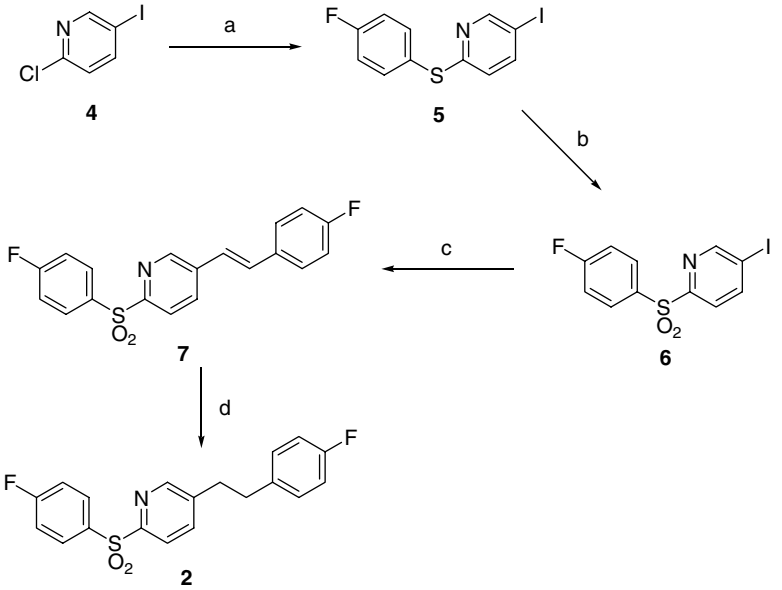
The focus of our ongoing program had centered on the 4-sulfonylpiperidine series, exemplified by **1**, which we have previously disclosed.[8,9] Recent work in our laboratory identified a series of high affinity non-basic piperidines.[10] These ligands are structurally related to "linear" antagonists such as M100907, EMD 281014 (Fig. 1), and our own 4-sulfonylpiperidines but lack the central ammonium ion previously considered to be an essential recognition feature. We hoped to further extend existing pharmacophore models[11] by replacing the central cyclic amine with an aromatic unit. Hence we targeted the isomeric sulfonylpyridines **2** and **3** as potential new leads.[12]

Both isomers were accessed from 2-chloro-5-iodopyridine **4** following analogous synthetic routes differing only in the first step (Schemes 1 and 2). Thus, for **2**, sulfide **5** was generated by nucleophilic displacement of the 2-chloro substituent. The complementary sulfide **8** (R^1 = 4-F) was constructed via a copper-catalyzed Ullman reaction of the 5-iodo group.[13] Oxidation to the halo sulfonylpyridines **6** and **9** (R^1 = 4-F) was carried out using either MCPBA or Oxone®. Subsequent incorporation of the styryl side-chain via a microwave[14] assisted Suzuki protocol provided **7** and **10** (R^1 = 4-F, R^2 = H). Finally, hydrogenation of the olefins gave the target phenethylpyridines **2** and **3**.

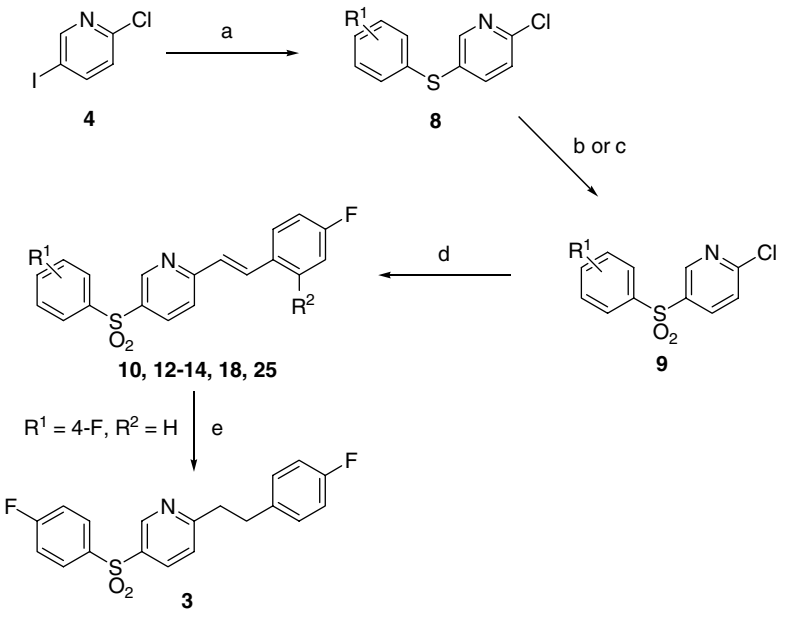
The binding affinities of compounds **2**, **3**, **7**, and **10** were measured for the human 5-HT_{2A} receptor, related GPCRs (h5-HT_{2C} and hD_2), and the hERG potassium ion channel (Table 1). We were gratified to see the high affinity and selectivity for the target receptor of these new pyridine ligands. The 2-sulfonylpyridine isomers (**2** and **7**) showed a small increase in binding affinity for the hERG channel. Blockade of this ion channel in vivo can lead to prolongation of the QT_c interval and ultimately cardiac arrhythmia. Hence the improved off-target profile exhibited by **3** and **10** prompted us to focus on the 5-sulfonylpyridine isomer for further structural modifications.

The decision was made to concentrate on the styryl side-chain since **10** had improved selectivity over **3** and was significantly more stable when incubated with rat (turnover: 29% and 83%, respectively) and human (0% and 18%, respectively) liver microsomes. We were able to efficiently explore the SAR of the distal aromatic units by constructing a small series of 2-chloro-5-sulfonylpyridines **9** (Scheme 2, steps a and b). The 4-fluoro and 2,4-difluorostyrene[15] side-chains were accessible via the Suzuki chemistry described above (Scheme 2, step d). All attempts to react **9** directly with substituted styrenes according to various Heck protocols proved unsuccessful. Alternatively, a vinyl group was installed via a microwave assisted Stille coupling with tributyl(vinyl)stannane, yielding **11**. A "reverse" Heck coupling was then employed to vary the side-chain aromatic, again using microwave acceleration (Scheme 3).

Binding affinities of a range of compounds are shown in Table 1. Moving the fluorine atom from the 4-position of the phenylsulfone to the 3- and 2-positions or removing it altogether resulted in a 2- to 3-fold increase in 5-HT_{2A} receptor binding relative to **10** (compounds **12**, **13**, and **14**). The very low binding affinities for the 5-HT_{2C} subtype and hERG ion channel were retained. The 2-fluorostyrene side-chain imparted further



Scheme 1. Reagents and conditions: (a) ArSH, K_2CO_3, MeCN, reflux; (b) oxone, MeOH, rt; (c) [(*E*)-2-(4-fluorophenyl)vinyl]boronic acid, $Pd(PPh_3)_4$, THF, 2 N Na_2CO_3, 150 °C, 10 min, microwave reactor; (d) H_2 (50 psi), EtOAc, AcOH, Pd/C.



Scheme 2. Reagents and conditions: (a) ArSH, K_2CO_3, CuI, ethylene glycol, IPA, reflux; (b) MCPBA, DCM, rt; (c) oxone, MeOH, rt; (d) [(*E*)-2-(4-fluorophenyl)vinyl]boronic acid or [(*E*)-2-(2,4-difluorophenyl)vinyl]boronic acid, $Pd(PPh_3)_4$, THF, 2 N Na_2CO_3, 150 °C, 10 min, microwave reactor; (e) H_2 (1 atm), AcOH, PtO_2.

improvements in 5-HT_{2A} affinity (compound **15**), giving rise to a compound with selectivity in excess of 1500-fold and lacking hERG binding. The 3-fluorostyrene analog **16** and heterocycles such as pyridine **17** gave a significant reduction in potency.

Contrary to the lack of 5-HT_{2C} binding observed for 4- and 2-fluorostyrenes **13** and **15**, an order of magnitude increase in potency was observed for **18** bearing both fluorine atoms. Further losses in selectivity were found with 2-chloro-4-fluorostyrene **19** (36-fold), 2-methyl-4-fluorostyrene **20** (27-fold), and 2-cyano-4-fluorostyrene **21** (2-fold). In contrast, the 2-hydroxy-4-fluoro analog **22** was found to be especially selective for the 5-HT_{2A} receptor (3000-fold) by virtue of its sub-nanomolar binding to this subtype. Removal of the 4-fluoro substituent to give 2-hydroxystyrene **23** resulted in an order of magnitude drop in 5-HT_{2A} affinity and selectivity. Capping the hydroxy with a methyl group was poorly tolerated, illustrated by the much reduced affinity of **24**. All oxygenated styrene analogs had prohibitive hERG binding.

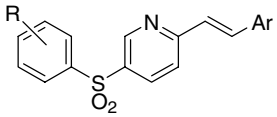
Interestingly, the loss in selectivity observed for 2,4-disubstituted styrenes **18**–**21** was not seen for 2,4-difluorostyrene **25** lacking a substituent on the phenylsulfone. In contrast, a significant enhancement of 5-HT_{2A} binding was achieved while maintaining the lack of affinity for the 5-HT_{2C} subtype. Consequently **25** was found to possess the best in vitro data with an excellent off-target profile (hERG binding: 27% inh at 10 μM) and exceptionally high selectivity over 5-HT_{2C} (>4600-fold). These data are indicative of a lack of additivity between the substituents on the phenylsulfone and styrene units.

During the course of our studies with the sulfones we became interested in profiling the related 5-sulfinylpyridines in the hope that the more polar sulfoxide unit would improve the physical properties of the compounds. The synthetic route is analogous to that of the sulfones except that only one equivalent of MCPBA is used for the oxidation step to provide the complementary racemic chloropyridine intermediates **26** (Scheme 4). No effect on 5-HT_{2A} binding resulted from the change in oxidation state (Table 2). Hence affinities of the 5-sulfinylpyridines **27**–**32** were almost identical to the corresponding analogs from the parent series. However, a dramatic increase in 5-HT_{2C} affinity was consistently observed, resulting in diminished selectivity. For example **30**, the sulfoxide analog of **25**, showed only a 38-fold separation over 5-HT_{2C} equating to a decrease of at least two orders of magnitude. We hoped that resolution of **30** would furnish a more selective compound but, as shown with **31** and **32**, the high affinity for both receptor subtypes resided with the same enantiomer. An additional drawback of the sulfoxides, with the exception of **28**, was a substantial increase in hERG binding.

Having identified **25** as a potent and selective 5-HT_{2A} ligand we now wished to measure the pharmacodynamic response of this analog in vivo. To investigate the effect of the sulfur oxidation state we also assayed **30** despite the shortcomings of this series. The compounds were dosed in rats at 5 mg/kg po. with co-administration of a radiolabeled selective 5-HT_{2A} ligand.[16] Receptor occupancy[17] and drug concentrations in both plasma and brain were determined at 1 h (Table 3). Using this protocol we were able to determine brain permeability and gain some indication of pharmacokinetic parameters and exposure-occupancy relationships.

The sulfone proved to be inferior to the corresponding sulfoxide, with **30** attaining 3-fold higher plasma levels, 6-fold higher brain levels, and 2-fold higher occupancy.

Table 1. Binding affinities of the sulfonylpyridines



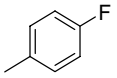
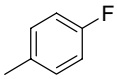
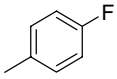
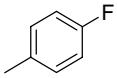
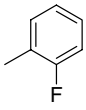
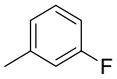
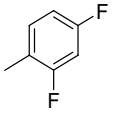
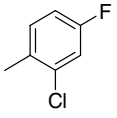
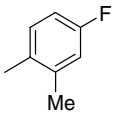
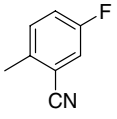
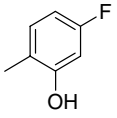
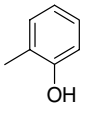
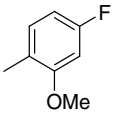
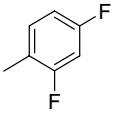
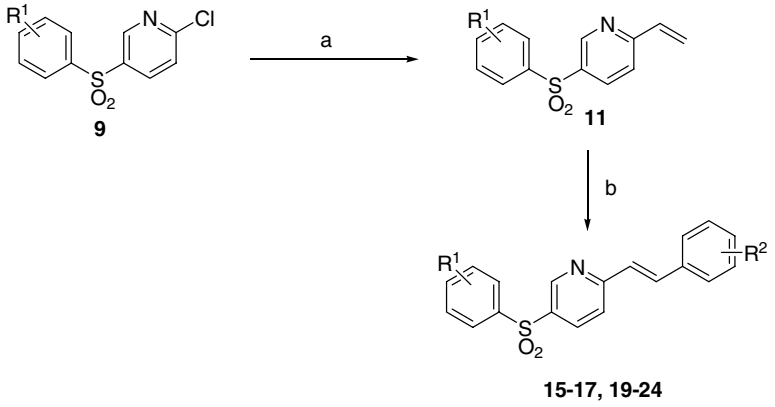
Compound	R	Ar	h5-HT$_{2A}$ K_i (nM)[a]	h5-HT$_{2C}$ K_i (nM)[a]	2C/2A ratio	hD$_2$ K_i (nM)[a]	hERG K_i (nM)[a]
M100907[b]			0.31	13	42	1300	1100
1			0.39	180	460	310	5600
2			19	>4000	>210	>1000	6900
3			23	2700	120	>1000	8200
7			28	>4000	>140	>1000	3300
10	4-F		17	>4000	>230	>1000	9500
12	3-F		9.6	>4000	>420	>1000	>9000
13	2-F		5.4	>4000	>740	>1000	>9000
14	H		7.4	>4000	>540	>1000	>9000
15	2-F		2.6	>4000	>1500	>2000	>9000
16	2-F		150	>4000	>27	>2000	>9000
17	2-F		790	>4000	>5	>2000	4200
18	2-F		2.6	410	160	>1000	>9000
19	2-F		1.8	64	36	>2000	4800
20	2-F		8.2	220	27	>2000	5000
21	2-F		9.9	19	2.1	>2000	1500
22	2-F		0.19	580	3000	>2000	2100
23	2-F		3.6	810	220	>2000	1400

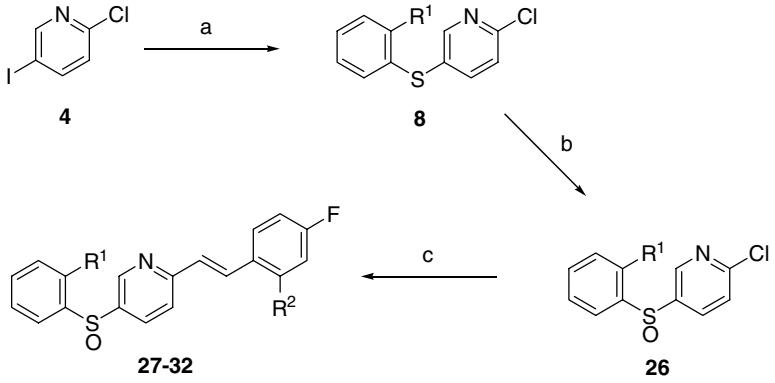
Table 1 (*continued*)

Compound	R	Ar	h5-HT_{2A} K_i (nM)[a]	h5-HT_{2C} K_i (nM)[a]	2C/2A ratio	hD_2 K_i (nM)[a]	hERG K_i (nM)[a]
24	2-F		65	1400	22	>2000	1400
25	H		0.86	>4000	>4600	>2000	>9000

[a] h5-HT_{2A}, h5-HT_{2C}, hD_2, and hERG binding affinities were determined as described in Ref. 9 ($n \geqslant 2$).
[b] Data from Ref. 9.



Scheme 3. Reagents and conditions: (a) tributyl(vinyl)stannane, $Pd(PPh_3)_4$, THF, 150 °C, 10 min, microwave reactor; (b) ArI, $Pd(PPh_3)_2Cl_2$, tri-*o*-tolylphosphine, MeCN, Et_3N, 170 °C, 20 min, microwave reactor.

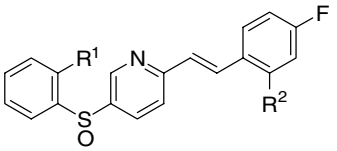


Scheme 4. Reagents and conditions: (a) benzenethiol or 2-fluorobenzenethiol, K_2CO_3, CuI, ethylene glycol, IPA, reflux; (b) MCPBA, DCM, rt; (c) [(*E*)-2-(4-fluorophenyl)vinyl]boronic acid or [(*E*)-2-(2,4-difluorophenyl)vinyl]boronic acid, $Pd(PPh_3)_4$, THF, 2 N Na_2CO_3, 150 °C, 10 min, microwave reactor.

Both compounds achieved exposure in the brain 250-fold above their K_i for the rat 5-HT_{2A} receptor (0.72 nM for **25**; 4.1 nM for **30**). Receptor occupancy is often poorly correlated with concentration of drug in the brain and is highly dependent on the degree of non-specific protein binding. It is feasible that the enhanced occupancy of **30** over **25** is a reflection of their relative c Log P values (4.2 for **25**; 3.4 for **30**). Due to this decrease in lipophilicity, the non-specific binding of **30** will likely be reduced relative to the sulfone resulting in increased binding to the target receptor. By extrapolation, a logical strategy to improve the pharmacodynamic response of the sulfonylpyridines is to reduce lipophilicity by adding polar groups that are compatible with partitioning across the blood–brain barrier. Work of this nature, including the application of related biarylsulfones to the modification of sleep architecture, is the subject of a forthcoming publication.[12]

In conclusion, we have discovered a novel series of isomeric sulfonylpyridines that show high affinity for the 5-HT_{2A} receptor. Initial optimization of one isomer

Table 2. Binding affinities of the sulfinylpyridines



Compound	R^1	R^2	h5-HT_{2A} K_i (nM)[a]	h5-HT_{2C} K_i (nM)[a]	2C/2A ratio	hD_2 K_i (nM)[a]	hERG K_i (nM)[a]
27	F	H	4.6	160	35	>2000	2900
28	F	F	3.5	43	12	>2000	>9000
29	H	H	7.7	200	26	>2000	3900
30	H	F	0.79	30	38	>2000	2800
31 (*R* or *S*)	H	F	30	2400	80	>2000	4200
32 (*S* or *R*)	H	F	0.70	25	36	>2000	6500

[a] h5-HT_{2A}, h5-HT_{2C}, hD_2 and hERG binding affinities were determined as described in Ref. 9 ($n \geqslant 2$).

Table 3. Occupancy data

Compound	Occupancy (%)	[Plasma] (nM)	[Brain] (nM)
25	45	80	180
30	90	230	1070

demonstrated that selectivity over the 5-HT_{2C} subtype was highly dependent on the nature of the substituents carried by the styrene side-chain. Hence, selectivity ranged from as low as 2-fold to greater than 4600-fold. The corresponding sulfoxide analogs showed consistently reduced selectivity but improved physicochemical properties, reflected in their superior in vivo occupancy. These new compounds illustrate that the central cyclic aliphatic amine present in many 5-HT_{2A} ligands can be replaced by an aromatic residue. The sulfonyl and sulfinyl groups are sufficiently electron-withdrawing to effectively render the pyridines non-basic, with calculated pK_a values for representative compounds **7**, **25**, and **30** of −3.0, 0.1, and 0.8, respectively. This provides further evidence that a basic amine is not a prerequisite for efficient 5-HT_{2A} receptor binding. Thus the compounds presented belong to a new family of ligands that continue to expand the established pharmacophore models.

Acknowledgments

We thank Mark Chambers for the preparation of compound **29**, Steve Thomas for separating the sulfoxide enantiomers **31** and **32**, and David Witter and Jonathan Young for their helpful suggestions in the preparation of this manuscript.

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13. Kwong, F. K.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517.
14. All microwave reactions were performed in a Smith Synthesizer® microwave reactor from Personal Chemistry.
15. [(*E*)-2-(2,4-difluorophenyl)vinyl]boronic was prepared from 1-ethynyl-2,4-difluorobenzene and catechol borane according to the method described in Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249: δ_H (360 MHz, DMSO-d_6) 6.16 (1H, d, J = 18.6 Hz), 7.11 (1H, m), 7.25 (1H, m), 7.34 (1H, d, J = 18.6 Hz), 7.68 (1H, m), 7.87 (2H, s).
16. [^{3}H] radioligand (6 μCi) was administered by tail vein injection. Full assay details are described in Ref. 8.
17. Occupancy at the 5-HT_{2A} receptor was calculated using the following equation: Total binding (TB) = Vehicle counts; Compound binding (CB) = Compound counts; Occupancy (%) = 100—[100 × (CB/TB)].