Identification of a Potent and Selective 5-HT$_6$ Antagonist: One-Step Synthesis of (*E*)-3-(Benzenesulfonyl)-2-(methylsulfanyl)pyrido[1,2-*a*]pyrimidin-4-ylidenamine from 2-(Benzenesulfonyl)-3,3-bis(methylsulfanyl)acrylonitrile

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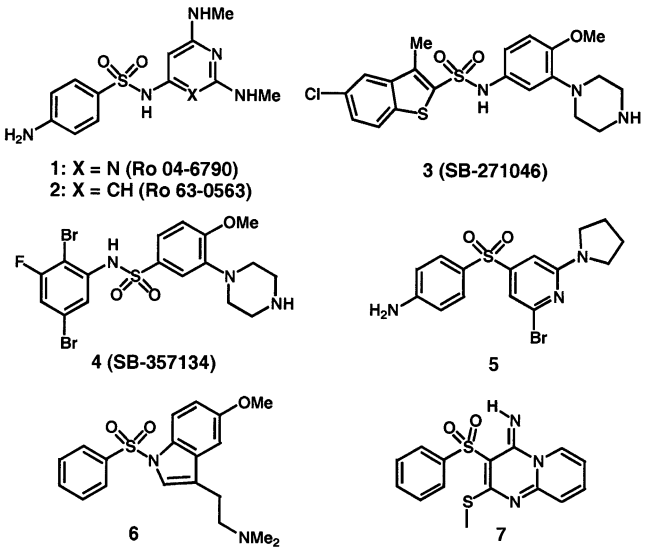
Abstract: (*E*)-3-(Benzenesulfonyl)-2-(methylsulfanyl)pyrido-[1,2-*a*]pyrimidin-4-ylidenamine (**7**) was found to be a potent and selective 5-HT$_6$ antagonist. A one-step synthesis of this compound is described.

Introduction. The 5-HT$_6$ receptor is a member of the family of receptors that mediate the physiological effects of the neurotransmitter serotonin (5-HT).[1−3] This receptor belongs to the G-protein-coupled receptor superfamily and is positively coupled to adenylate cyclase.[1−3] Evaluation of the expression pattern of 5-HT$_6$ receptor mRNA and protein revealed that it is selectively expressed in the central nervous system, exhibiting widespread distribution throughout the brain.[1−6] In addition, the 5-HT$_6$ receptor possesses high affinity for atypical antipsychotics (e.g., clozapine) and tricyclic antidepressants (e.g., amitriptyline and clomipramine).[1,7] Thus, 5-HT$_6$ receptor pharmacology and tissue expression suggest that this receptor may have therapeutic utility in CNS diseases.

Initial studies of 5-HT$_6$ receptor function in vivo utilized antisense oligonucleotides (AOs) to disrupt 5-HT$_6$ receptor expression and evaluate the effects on animal behavior. For example, rats administered 5-HT$_6$ receptor AOs, but not control oligonucleotides, elicited a yawning, stretching, and chewing behavioral syndrome that was blocked by the muscarinic antagonist atropine.[8,9] In this study a 30% decrease in [^{3}H]lysergic acid diethylamide (LSD) binding was observed, suggesting that the antisense treatment decreased expression of 5-HT$_6$ receptors. These results indicate that the 5-HT$_6$ receptor functions as a negative regulator of cholinergic signaling. A role for the 5-HT$_6$ receptor in processes of memory formation is supported by studies demonstrating that administration of 5-HT$_6$ receptor AOs enhanced retention, but not acquisition, in the Morris water maze.[10] However, not all studies with AOs have yielded similar behavioral phenotypes. For example, in two additional studies, central administration of 5-HT$_6$ receptor AOs did not reproduce the cholinergic phenotype of yawning/stretching/chewing, but did produce anxiogenic behavior in social interaction and elevated plus maze tests.[4,11] In these studies, a partial decrease (25%) in 5-HT$_6$ receptor expression was observed as determined by immunohistochemical staining. As none of the AO studies documented a complete inhibition of 5-HT$_6$ receptor expression, differences between studies could be explained by differences in the levels of inhibition of 5-HT$_6$ receptor expression. Thus, while the AO studies suggest that the 5-HT$_6$ receptor plays a role in CNS function, further understanding of the specific role of the receptor required development of 5-HT$_6$ receptor ligands.

Chart 1



Recently, several selective 5-HT$_6$ receptor antagonists have been developed including Ro 04-6790 (**1**, Chart 1),[12] Ro 63-0563 (**2**),[12] SB-271046 (**3**),[13] SB-357134 (**4**),[14] 4-(2-bromo-6-pyrrolidin-1-ylpyridine-4-sulfonyl)phenylamine (**5**),[15] and N_1-(benzenesulfonyl)tryptamine **6**.[16] Several of these agents have been used to investigate 5-HT$_6$ receptor function in vivo. Consistent with the previous studies using AOs, Ro 04-6790 produced a stretching behavior that was selectively blocked by muscarinic antagonists, suggesting that the 5-HT$_6$ receptor is involved in regulation of cholinergic signaling.[17] A role for the 5-HT$_6$ receptor in processes of learning and memory was also supported as SB-271046 and SB-357134 were efficacious in a spatial memory task in rats[18] and Ro 04-6790 improved learning consolidation in an autoshaping task.[19] In addition, systemic administration of SB-271046 selectively enhanced the levels of excitatory amino acids within the frontal cortex.[20,21] While several studies suggest that 5-HT$_6$ receptor antagonists may have utility as cognition enhancers, not all studies have replicated these results.[22] Therefore, the development of additional potent and selective 5-HT$_6$ receptor antagonists will provide additional tools for delineating the role of the 5-HT$_6$

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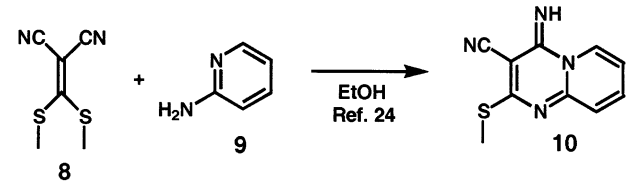
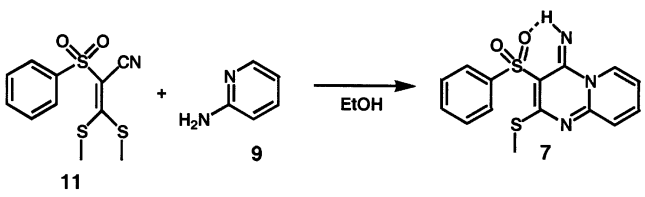
Scheme 1



Scheme 2



receptor in vivo. In this report, we describe the discovery of (*E*)-3-(benzenesulfonyl)-2-(methylsulfanyl)pyrido[1,2-*a*]pyrimidin-4-ylidenamine (**7**, Chart 1) as a potent and selective 5-HT_6 antagonist and a one-step synthesis of this compound.

Lead Identification and Chemistry. A four-point pharmacophore model[23] based on the known 5-HT_6 receptor antagonists, Ro 04-6790 (**1**), Ro 63-0563 (**2**), and SB-271046 (**3**), was used in a virtual screen to select a set of compounds from the Bristol-Myers Squibb (BMS) compound collection for evaluation in 5-HT_6 radioligand binding assays. In these assays, HEK293 membranes containing recombinant human 5-HT_6 receptors were evaluated for displacement of [^{3}H]lysergic acid diethylamide (LSD) binding using known and novel 5-HT_6 receptor ligands. Further analysis of compounds from this screen identified compound **7** as a potent (IC_{50} 4 nM) inhibitor of [^{3}H] LSD binding. In the same assay, Ro 04−6790 showed an IC_{50} of 26.3 nM.

With compound **7** identified as a potent 5-HT_6 antagonist, we required a sizable amount of this compound for further biological evaluations. As this compound was acquired from another company more than three decades ago, the synthesis protocol was unavailable within BMS. To our knowledge, this compound is unknown in the literature. Thus, a synthetic methodology was developed. Gommper et al. had previously reported that treatment of 2-(bis(methylsulfanyl)methylene)malononitrile (**8**) with pyridin-2-ylamine (**9**) in ethanol under reflux resulted in the tandem Michael addition−methylsufanyl elimination−nucleophilic addition reactions to provide 4-imino-2-methylsulfanyl-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carbonitrile (**10**) in 50% yield (Scheme 1).[24] The amidine configuration was not disclosed. Thus, we sought to determine if **7** could be prepared from 2-(benzenesulfonyl)-3,3-bis(methylsulfanyl)acrylonitrile (**11**)[25] in an analogous fashion. Indeed, when a solution of **9** and **11** in ethanol was heated under reflux, we obtained the desired product **7** as a single isomer in 24% yield (not optimized) after recrystallization from ethanol (Scheme 2). The solid-state conformation of **7** was determined by X-ray single-crystal analysis.[26] As shown in Figure 1, the hydrogen of the amidine group points toward one of the sulfonyl oxygen atoms to form an intramolecular hydrogen bond in a six-membered ring.

We also attempted to prepare the desmethylsulfanyl analogue of **7** (i.e., **14**, Scheme 3) from 2-(benzenesulfonyl)-3-methoxyacrylonitrile (**12**).[27] However, when

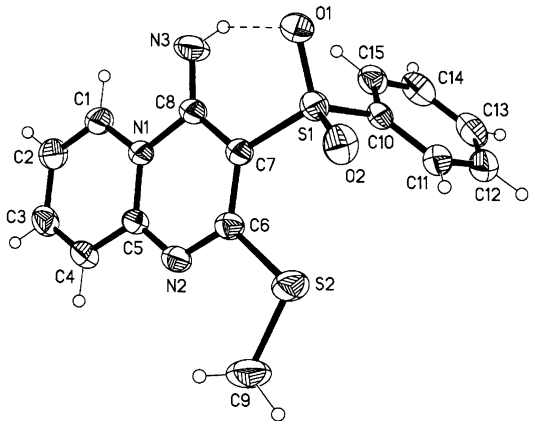
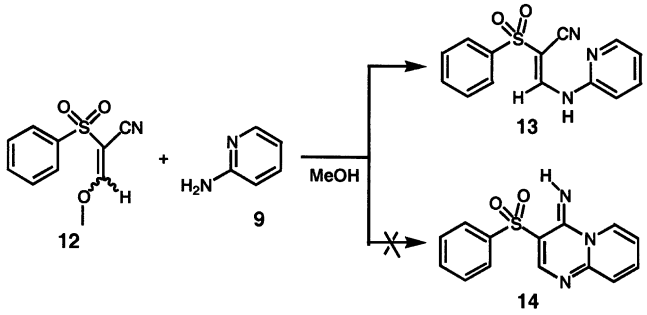


Figure 1. Thermal ellipsoid plot (35% ellipsoids) of **7**. Crystallographic atom numbering.

Scheme 3



12 was treated with **9** in refluxing methanol, the uncyclized product **13** was obtained exclusively as a single isomer in 74% yield. X-ray diffraction analysis of crystalline **13** showed the *E* configuration.[26] Our efforts to convert **13** into **14** under various conditions (e.g., K_2CO_3 in DMF, Hünig base in ethanol) met without success.

Results and Discussion. Compound **7** was evaluated in 5-HT_6 receptor functional assays using the human receptor expressed in HeLa and HEK293 cells. In these assays, we evaluated 5-HT_6 receptor-mediated activation of adenylate cyclase (data not shown) and activation of Ca^{2+} mobilization via coexpression of the G-protein subunit Gα15 (Figure 2). Compound **7** antagonized 5-HT stimulation of the 5-HT_6 receptor in a dose-dependent manner (Figure 2). To evaluate further the antagonist properties of **7** at the 5-HT_6 receptor, 5-HT dose−response curves were obtained in the presence of increasing concentrations of **7** and a Schild analysis was performed (Figure 3). These studies demonstrated the interaction of **7** with the 5-HT_6 receptor was consistent with properties of a competitive antagonist (slope −0.95; K_D 4.7 nM). This compound also exhibited no evidence of intrinsic activity at the receptor as demonstrated by lack of effect by compound alone (data not shown). Thus, the functional data demonstrated that **7** is a 5-HT_6 receptor antagonist.

Compound **7** was tested in a commercial screening package (Cerep) and did not exhibit significant (i.e. <20% inhibition at 10 μM concentration) interactions at over 70 other receptors including all seven 5-HT receptors assayed (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_{5A}, 5-HT_7).

The cytochrome P450 inhibitory potential of **7** was determined using recombinant human CYP1A2, CYP2C9,

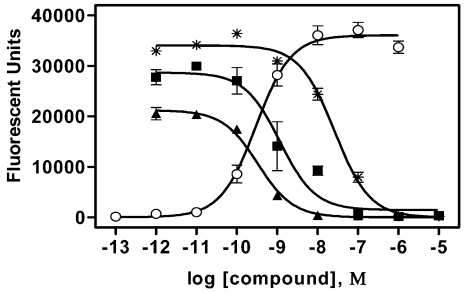


Figure 2. Effect of **7** on 5-HT-stimulated calcium mobilization in HEK293 cells transfected with the human 5-HT$_6$ receptor. Cells were treated with the indicated concentrations of 5-HT (○), or compound **7** in the presence of 1 nM 5-HT (▲), 3 nM 5-HT (■), or 10 nM 5-HT (*). Data points represent the mean of duplicate determinations from a typical experiment that was repeated at least twice.

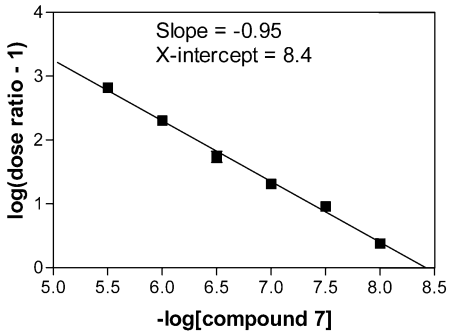


Figure 3. Schild analysis of **7**. 5-HT EC_{50} values were determined in the absence or presence of increasing concentrations of **7** and dose ratios were calculated by dividing the EC_{50} values determined in the presence of **7** with the EC_{50} determined for 5-HT alone. The linear transformation of the data plotting the log (dose ratio − 1) vs −log[compound **7**] yielded a slope of −0.95 with an *X* intercept of 8.4. Data points represent the mean of triplicate determinations from a typical experiment that was repeated at least twice.

Table 1. Human Cytochrome P450 Inhibitory Data of **7**

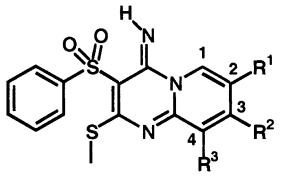
CYP isoform	IC_{50} (μM)[a]
1A2	>40
2C9	24.2 ± 8.35
2C19	0.86 ± 0.27
2D6	>40
3A4-BFC[b]	>40
3A4-BzRes[c]	>40

[a] IC_{50} values were determined for inhibition of deethylation of 3-cyano-7-ethoxycoumarin (CYP1A2 and CYP2C19), for dealkylation of 7-methoxy-4-trifluoromethylcoumarin (CYP2C9), and for inhibition of demethylation of 3-[2-(*N*,*N*-diethyl-*N*-methylamino-)ethyl]-7-methoxy-4-methylcoumarin (CYP2D6). Two different substrates were used to determine the IC_{50} values for CYP3A4; the inhibition of dealkylation of BzRes (benzoylresorufin) and of BFC (7-benzyloxy-4-trifluoromethylcoumarin). These values are the mean ± SEM (n = 7). [b] BFC was used as the substrate. [c] BzRes was used as the substrate.

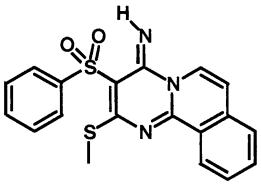
CYP2C19, CYP2D6, and CYP3A4 (Table 1) in order to assess the potential likelihood of drug interactions. Low to moderate levels of inhibition were observed at several major human P450 enzymes with the highest level of inhibition against CYP2C19 (IC_{50} 0.86 μM).

Preliminary structure−activity relationship studies on **7** have been carried out. Thus, both fluoro substitution at C2 of pyridinylidene moiety (i.e., **15**, Chart 2) and ethyl substitution at C3 (i.e., **16**) reduced the binding affinity by about 22- and 18-fold, respectively

Chart 2



15: R^1 = F, R^2 = R^3 = H
16: R^1 = R^3 = H, R^2 = Et
17: R^1 = Me, R^2 = H, R^3 = Br



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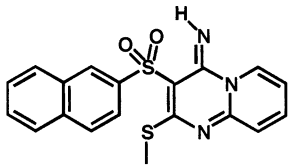

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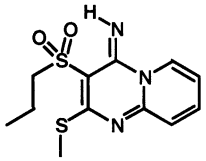

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Table 2. 5-HT$_6$ Receptor Binding Affinity Data

compd	IC_{50} (nM)[a]	compd	IC_{50} (nM)[a]
1	26.3 ± 7.5	**17**	269 ± 89
7	4 ± 0.8	**18**	68.9 ± 11
13	524 ± 47	**19**	79.2 ± 14.5
15	87.6 ± 21.2	**20**	3580 ± 80
16	70.1 ± 11.2		

[a] Concentration required to inhibit 50% [^{3}H]LSD binding. These values are the mean ± SEM (n = 2−6).

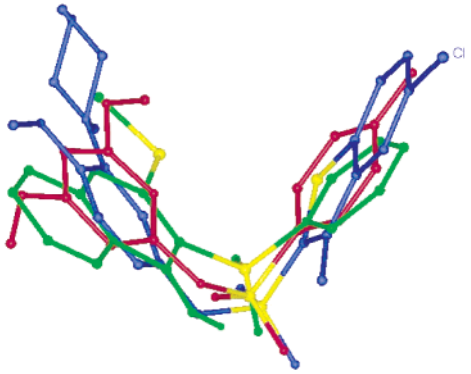

Figure 4. Overlap of Ro 04−6790 (**1**, red) and SB-271046 (**3**, blue) onto crystal structure of **7** (green) with sulfur atoms colored yellow.

(Table 2). Dramatic reduction in binding affinity was observed with 2-methyl-4-bromo disubstitution (i.e., **17**, IC_{50} 269 nM). It is interesting to note that both the isoquinolinyl analogue **18** and 2-naphthyl analogue **19** still maintained moderate binding affinity (IC_{50} 68.9 and 79.2 nM, respectively). Replacement of the phenyl group in **7** with alkyl groups such as *n*-propyl (i.e., **20**) removed binding activity (IC_{50} 3.6 μM). This suggests that the phenyl group of **7** may play a critical role in the interaction with 5-HT$_6$ receptors. Finally, it is worth noting that the uncyclized product **13** (Scheme 3) exhibited weak binding activity (IC_{50} 524 nM) presumably due to the lack of a cyclized amidine functionality as shown in **7**.

Molecular modeling overlays of the X-ray structure of **7** were performed with compounds **1** and **3**, using Sybyl's superimposition algorithm.[28] The sulfur atoms of the arylsulfonyl groups were marked to be coincident but the reminder of the molecule was left to find the

best fit. It was found that the B3LYP/6-31G* optimized geometries of both **1** and **3** overlaid well onto X-ray structure of **7** (Figure 4). This suggests that these compounds may all bind in the same fashion to the 5-HT_6 receptors.

Conclusion. Compound **7** was identified as a potent and selective 5-HT_6 antagonist, and a one-step synthesis has been developed. This compound represents a distinct novel chemotype of 5-HT_6 ligands and is expected to be a useful tool for further pharmacological evaluation of the function of the 5-HT_6 receptors. Future efforts are directed at improving both cytochrome P450 inhibition profiles and metabolic stability of **7**.

Acknowledgment. We thank Dr. Joanne Bronson for helpful discussions and critical reading of the manuscript.

Supporting Information Available: Experimental section containing the synthesis of **7**, **13**, and **15**−**20**, 5-HT_6 receptor Ca^{2+} flux assay, and a brief computational methodology section. This material is available free of charge via the Internet at http:/pubs.acs.org.

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