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Novel 7-phenylsulfanyl-1,2,3,4,10,10a-hexahydro-pyrazino[1,2-*a*]indoles as dual serotonin 5-HT$_{2C}$ and 5-HT$_6$ receptor ligands

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ABSTRACT

Novel 7-phenylsulfanyl-1,2,3,4,10,10a-hexahydro-pyrazino[1,2-*a*]indoles are synthesized using a six-step protocol. Notably, the synthesis route make use of a new and improved ring-closing methodology for the assembly of the hexahydro-pyrazino[1,2-*a*]indole scaffold, which is based on intramolecular C–H insertion of a carbene. The compounds act as dual serotonin 5-HT$_{2C}$- and 5-HT$_6$-ligands.

The serotonin 5-HT$_{2C}$ and 5-HT$_6$ receptors are two of the 14 distinct serotonin receptor subtypes.[1] The 5-HT receptors have been classified into seven distinct subfamilies based on sequence similarity, signal transduction, coupling and pharmacological characteristics. All but one of these receptors are G-protein-coupled, the exception being the 5-HT$_3$ subtype, which is a ligand-gated ion channel. Unlike the majority of 5-HT receptors, the 5-HT$_{2C}$ and 5-HT$_6$ receptors are exclusively localized in the CNS, especially in many areas of the cortex, basal ganglia, hippocampus and thalamus.[2–4] The 5-HT$_{2C}$ and 5-HT$_6$ receptors are also among the five key receptors (D$_3$, D$_2$, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_6$), which has been identified in an analysis of the receptor interaction profiles of various marketed antipsychotics.[5,6] Selective ligands for the 5-HT$_{2C}$ receptor are being pursued clinically for the treatment of obesity and schizophrenia,[7] and selective ligands for the 5-HT$_6$ receptor have been shown to improve cognitive performances in a wide variety of learning and memory paradigms.[8] Dual acting compounds might therefore act as CNS agents with an interesting pharmacological profile, and in this Letter we describe our initial hit-finding approach towards ligands with affinity for both receptors.

The 7-chloro-1,2,3,4,10,10a-hexahydro-pyrazino[1,2-*a*]indole **1** (Fig. 1) is a potent 5-HT$_{2C}$ agonist,[9] and we found it to be an attractive starting point for our ligand design, since it makes up a rigified template, which is ideally placed within the CNS druggability space due to its molecular weight (209), *c* Log *D* (0.9), and TPSA (15 Å^2), which are key molecular properties used to define the desirable CNS drug space.[10] The 5-HT$_{2C}$ SAR for a series of analogs of compound **1**, identified the 7-position as a position where a lipophilic substituent resulted in the highest potency at the 5-HT$_{2C}$-receptor.[9a] Recently it was reported that it was possible to improve the selectivity of compound **1** towards the 5-HT$_{2A}$- and 5-HT$_{2B}$-receptors by making 6,7-disubstited analogs of compound **1**, which is important since 5-HT$_{2A}$-agonist have psychotomimetic properties and 5-HT$_{2B}$-agonism is linked to cardiac toxicity.[9b] Numerous 5-HT$_6$ ligands have been reported during the last decade,[6,11] and a 5-HT$_6$ antagonist pharmacophoric model **2** has been suggested,

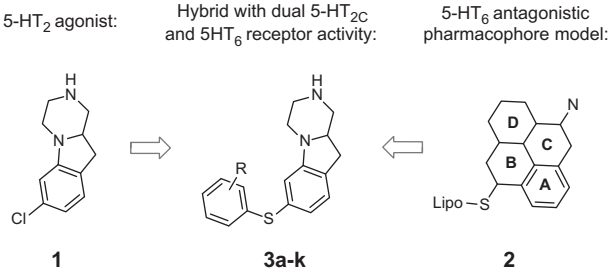

Figure 1. Design strategy for the novel 7-phenylsulfanyl-1,2,3,4,10,10a-hexahydro-pyrazino[1,2-*a*]indoles, seen as a hybrid structure of the 5-HT$_{2C}$ ligand **1** and the general 5-HT$_6$ pharmacophore **2**.

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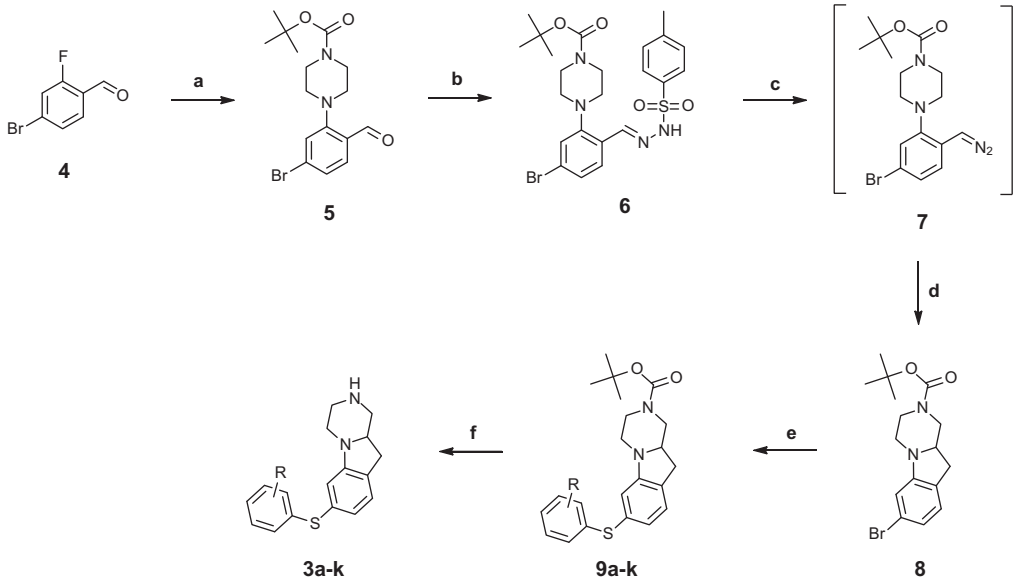


Scheme 1. Reagents and conditions: (a) Boc-piperazine, K_2CO_3, DMSO, 95 °C, four days; (b) tosylhydrazide, toluene, microwave irradiation, 12 min; (c) NaH (60%), toluene, microwave irradiation, 135 °C; (d) microwave irradiation, 135 °C, 12 min; (e) $Pd_2(dba)_3$, (oxydi-2,1-phenylene)bis(diphenylphosphine), KO-*t*-Bu, substituted thiophenol, toluene, 100 °C, 18 h; (f) 2 M HCl in Et_2O, Et_2O, MeOH, rt (18 h).

which contains four interactions points: A basic nitrogen, two lipophilic moieties, one represented by aromatic ring **A** and the other lipophilic group (Lipo) bound via sulphur or sulphone (Fig. 1).[11,12]

Based on the 5-HT_6 antagonist pharmacophoric model and the 5-HT_{2C} SAR from **1**, we proposed a 1,2,3,4,10,10a-hexahydro-pyrazino[1,2-*a*]indole with a arylthioether in the 7-position to be a candidate for a compound with a dual activity at these receptors. In this paper we describe the synthesis of a series of 7-phenylsulfanyl-1,2,3,4,10,10a-hexahydro-pyrazino[1,2-*a*]indoles and their in vitro binding pharmacology at human 5-HT_{2C} and 5-HT_6 receptors.

The compounds were synthesized using the six-step protocol outlined in Scheme 1. Notably, the synthetic route make use of a new and improved ring-closing methodology for the assembly of the hexahydro-pyrazino[1,2-*a*]indole scaffold, which is based on intramolecular C–H insertion of a carbene (Scheme 1, step d). The synthesis starts by a nucleophilic aromatic substitution reaction (S_NAr) from the commercially available 2-fluoro-benzaldehyde **4** using Boc-protected piperazine to give the Boc-protected 4-bromo-2-piperazino benzaldehyde **5** using reaction conditions analogous to those previously described.[13] The Boc-protected 4-bromo-2-piperazino benzaldehyde **5** was then converted in high yield into the tosylhydrazone intermediate **6** by sonication in toluene of a mixture of aldehyde **5** and tosylhydrazide.[14] After drying ($MgSO_4$) and filtration, the tosylhydrazone **6** was converted into the diazo intermediate **7** in situ by deprotonation using sodium hydride followed by thermal elimination of sulfinate using microwave irradiation to 135 °C.[15]

Further heating at 135 °C led to the in situ generation of the highly reactive carbene by thermal decomposition of the diazo compound. The carbene reacted selectively with C–H insertion into the piperazine fragment to give the protected hexahydro-pyrazino[1,2-*a*]indole **8**.[16] Purification of the intermediary hydrazone by recrystallisation did not improve overall yields, hence isolation and purification of this intermediate can be omitted. The introduction of the lipophilic thioaryl ether moiety was performed by a palladium catalyzed coupling of substituted thiophenols with the Boc-protected 7-bromo hexahydro-pyrazino[1,2-*a*]indole **8**[17] and the final compounds **3a–k** were conveniently obtained after removal of the Boc-protection group. The yields of the coupling reaction and the removal of the Boc-group were generally high (Table 1).

Interestingly, the ring-closing step performed by the intramolecular C-H insertion as described in Scheme 1, appear to be a more general methodology for the assembly of the hexahydro-pyrazino[1,2-*a*]indole scaffold, where both many different aromatic substituents are tolerated and the piperazine can be replaced with for example, morpholine or homopiperazine. Especially the homopiperazine raised the interesting aspect of regioselectivity of the C–H insertion, however, we observed a complete lack of regioselectivity in the C–H insertion in homopiperazine, probably due to the high reactivity of the thermally generated carbene. We are currently investigating and expanding the scope of this methodology.[19]

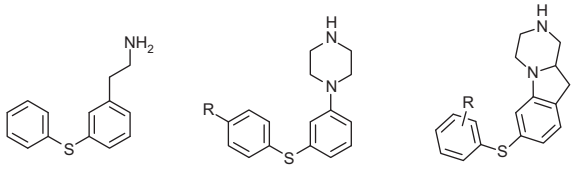
The binding affinities of the compounds at the human 5-HT_{2C} receptor was determined in a [^{3}H]mesulergine binding assay using tsA201 cells expressing the human 5-HT_{2C} receptor and the binding affinities of the compounds at the human 5-HT_6 receptor was determined in a [^{3}H]5-LSD ([*N-methyl*-^{3}H]Lysergic acid, diethylamide) binding assay using HeLa cells stably transfected with the human 5-HT_6 receptor. The IC_{50} values were determined by non-linear curve fitting using XlFit (IDBS), and K_i values were calculated from the Cheng–Prusoff equation and are shown in Table 2.

The binding affinities displayed by the compounds at the two serotonin receptors appear to be affected similarly by the different substitutions. Both receptors appeared relatively insensitive to the size of the substitutions in the thiophenol moiety. The trifluoromethyl group is not detrimental to activity on 5-HT_{2C} and 5-HT_6

Table 1
Yields of cross-coupling products **9a–k** and subsequent deprotection to give final compounds **3a–k**

Compd	R	% Yield of **9**	% Yield of **3**
a	2-Me	88	74
b	3-Me	82	77
c	4-Me	91	60
d	2-OMe	94	65
e	3-OMe	88	78
f	4-OMe	83	66
g	2-F	76	79
h	4-F	87	81
i	2-CF_3	74	91
j	3-CF_3	77	88
k	4-CF_3	81	70

Table 2
The pharmacological data from testing **10**, **11a**, **11b** and **3a–3k** in 5-HT_{2C} and 5-HT_6 binding assays and the corresponding data for representative antipsychotics



10 **11** **3a-k**

Compd	R	5-HT_{2C}[a] K_i (nM)	5-HT_6[b] K_i (nM)	Molecular weight	Polar surface area (Å^2)	*c* Log *D* (7.4)
Aripiprazole[18]	—	22	574	448	45	4.4
Clozapine[18]	—	15	17	327	31	3.5
Olanzapine[18]	—	14	6	312	31	2.8
Risperidone[18]	—	33	224	410	62	1.8
Sertindole[18]	—	1	5	441	41	4.1
Ziprasidone[18]	—	13	61	413	48	4.0
10[12]	H	150	nt	226	25	1.4
11a	H	91	nt	270	15	2.3
11b	4-OMe	74	nt	300	25	2.3
3a	2-Me	49	81	296	15	2.8
3b	3-Me	77	50	296	15	2.8
3c	4-Me	68	110	296	15	2.8
3d	2-F	41	23	312	25	1.9
3e	4-F	120	110	312	25	2.3
3f	2-OMe	57	78	312	25	2.3
3g	3-OMe	49	150	300	15	2.5
3h	4-OMe	61	160	300	15	2.5
3i	2-CF_3	83	330	350	15	3.3
3j	3-CF_3	180	300	350	15	3.3
3k	4-CF_3	280	760	350	15	3.3

Calculated molecular properties relevant for judging CNS druggability are also presented.
nt = not tested.
[a] K_i-values reported are means of at least four experiments, and a typical standard deviation was ±30%.
[b] K_i-values reported are means of at least four experiments, and a typical standard deviation was ±30%.

(**3i–3k**) but it seems to weaken the affinity for both receptors. The CF_3-group is electron withdrawing, lipophilic and very large (same volume as an isopropyl), but due to the limited number of compounds in the present study it is not possible to determine which of the three factors actually drives the drop in potency seen especially on 5-HT_6. The 2-fluorine derivative **3d** displays an affinity of 23 nM for the 5-HT_6, which is approximately 15 times more potent than the 2-trifluoromethyl derivative **3i**. Generally, substituents in the 3-position seemed marginally favoured compared to substituents in the 2-position. Substitutions in the 4-position were disfavoured with the methyl substituted derivative (**3c**) being the exception. The most potent compound in this series is the 2-fluorine derivative **3d** which displays an affinity of 23 nM for the 5-HT_6 receptor and 41 nM for the 5-HT_{2C} receptor.

In conclusion, a series of novel 7-phenylsulfanyl-1,2,3,4,10,10a-hexahydro-pyrazino[1,2-*a*]indoles have been synthesized. Notably, the synthesis route make use of a new and improved ring-closing methodology for the assembly of the hexahydro-pyrazino[1,2-*a*]indole scaffold, which is based on intramolecular C–H insertion of a carbene. The compounds act as dual serotonin 5-HT_{2C}- and 5-HT_6-ligands.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.07.105.

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16. *Synthesis of compound* **8**: compound **5** (902 mg, 2.44 mmol) was dissolved in 10 mL toluene and tosylhydrazide (485 mg, 2.60 mmol) was added. The mixture was exposed to sonification at room temperature for 4 h. The mixture was semi concentrated in vacuo (azeotrope water-removal), toluene and $MgSO_4$ were added and after 10 min of standing the mixture was filtered into a 20 mL microwave vial. Toluene was added until a total volume of 20 mL, NaH (105 mg, 2.63 mmol) was added and the mixture purged with argon for 15 min. The vial was sealed and heated using microwave irradiation at 135 °C for 10 min. The mixture was added EtOAc and washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, concentrated in vacuo and purified using flash chromatography to yield **8** 387 mg (45%) of yellowish oil.
17. *General method for syntheses of compounds* **9a–k**: toluene was purged with argon for 20 min **8** (300 mg, 0.85 mmol), tris(dibenzylideneacetone)-dipalladium (15.6 mg, 0.02 equiv), (oxydi-2,1-phenylene)bis(di-phenylphosphine) (36.6 mg, 0.08 equiv) and potassium *tert*-butoxide (114 mg, 1.2 equiv) were suspended in toluene (2.5 mL) in a 5 mL vial. The mixture was purged with argon, the thiol (1.1 equiv) was added and the vial was immediately sealed afterwards. The mixture was stirred for 18 h at 100 °C. The mixture was transferred to a test tube containing Et_2O and 2 M NaOH. After thorough mixing, the organic phase was isolated and the aqueous phase was reextracted with Et_2O. The combined organic phases were washed with brine, and after extraction of the brine with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered through a plug of Celite, concentrated in vacuo and purified by flash chromatography using a Flash Master (20 g column).
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