Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2549–2552

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Tetrahydrothienopyridylbutyl-tetrahydrobenzindoles: New Selective Ligands of the 5-HT_7 Receptor

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Received 20 May 2002; accepted 24 June 2002

Abstract—The synthesis and the affinity for the 5-HT_7 receptor and other receptors of a novel series of fused-ring tetrahydropyridine derivatives are described. Some of the compounds showed high affinity for the 5-HT_7 receptor. Tetrahydrothienopyridylbutyl-tetrahydrobenzindoles **5d** and **5h** are potent ligands for the 5-HT_7 receptor, with high selectivity over the 5-HT_2 receptor and other receptors. These compounds should be useful tools for clarifying the biological role of the 5-HT_7 receptor.

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) plays important roles in a variety of physiological and pathophysiological processes through the activation of seven types of 5-HT receptors, 5-HT_1–5-HT_7. The 5-HT_7 receptor is the most recent addition to the family of 5-HT receptors.[1–6] Its biological functions are still poorly understood. Early pharmacological data suggested that the 5-HT_7 receptor may be involved in the vasodilation of blood vessels.[7–10] High levels of 5-HT_7 receptor mRNA have also been observed in the brain (hypothalamus, thalamus, brainstem and hippocampus),[1,3,5,11] and the distribution of 5-HT_7 receptor binding sites in rat and guinea pig brain was essentially the same as the mRNA distribution.[11–13] The 5-HT_7 receptor is involved in the control of circadian rhythms of spontaneous electrical activity in the suprachiasmatic nucleus (SCN) of the hypothalamus.[3,14–16] It may be involved in disturbance of circadian rhythms, such as jet lag, delayed sleep phase syndrome (DSPS) and non-24-h sleep–wake disorder (non-24).[17] Strongly, it is suggested that the 5-HT_7 receptor should be a valuable drug target. To examine this possibility, the development of potent and selective ligands for the 5-HT_7 receptor is highly required.

In previous papers, we reported the synthesis and affinities for the 5-HT_7 receptor and other receptors of a series of tetrahydrobenzindoles.[18,19] Compounds **1** (DR4004)[18] and **2** (DR4365)[19] (Chart 1) are highly potent antagonists for the 5-HT_7 receptor, and the tetrahydropyridoindole derivative **2** showed high selectivity for this receptor over the 5-HT_2 receptor. The tetrahydropyridoindoles have the phenyl ring fixed to the tetrahydropyridine ring by C–N bonds, and we considered that this planar structure might be important for high selectivity of these compounds for the 5-HT_7 receptor.

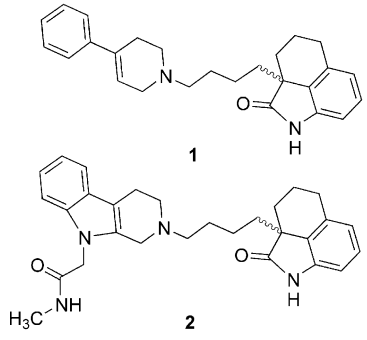

Chart 1. Chemical structures of compound **1** and **2.**

In the present paper, the medicinal chemistry was extended to include other fused-ring tetrahydropyridine derivatives (Scheme 1). We synthesized and tested a range of modified compounds, including the tetrahydroisoquinoline derivatives **5a**–**c**. Other fused heterocycles **5d**–**g** were also investigated. The tetrahydrothienopyridine derivative **5d** was a highly potent and selective

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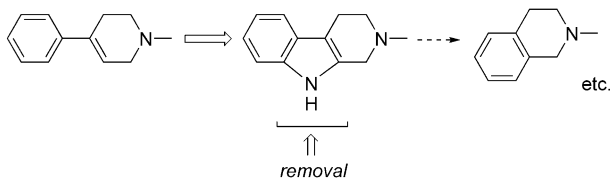
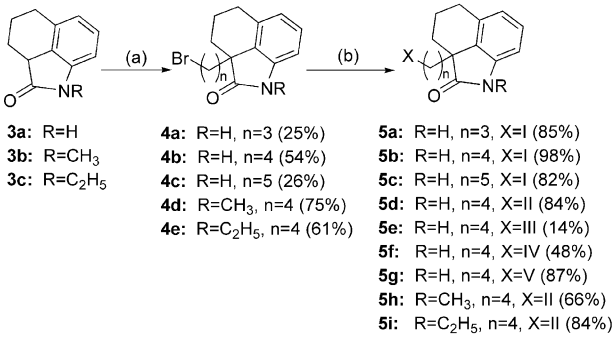
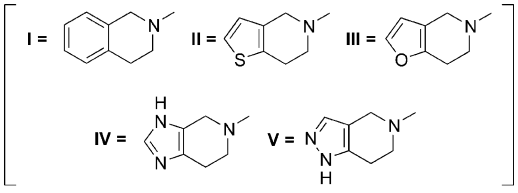
PII: S0960-894X(02)00485-7



Scheme 1.





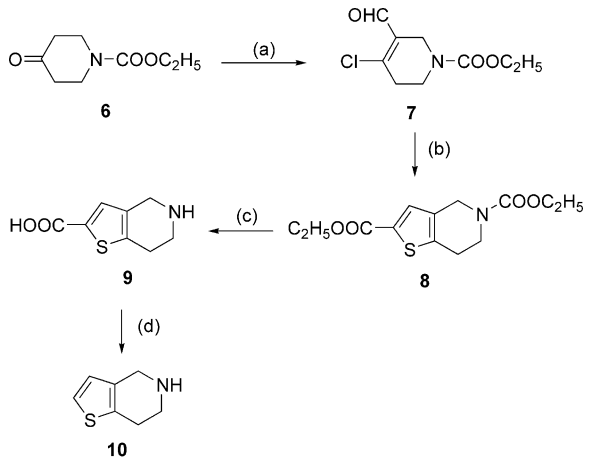
Scheme 2. (a) Corresponding dibromide, 55% NaH, DMF, −40 to 0 °C; (b) corresponding amine, K_2CO_3, DMF, 60 °C.

5-HT_7 receptor ligand. The *N*-methyltetrahydrobenzindole analogue **5h** and the *N*-ethyltetrahydrobenzindole analogue **5i**, corresponding to **5d**, were also synthesized.

The synthetic procedures to the target compounds are shown in Scheme 2. Compound **4b** was prepared by reacting the tetrahydrobenzindole **3a** with sodium hydride and 1,4-dibromobutane. Compounds **4a**,**c**–**e** were synthesized in a similar manner to compound **4b**. Compounds **5a**–**i**[20] were obtained by allowing compounds **4a**–**e** to react with the corresponding amines in the presence of K_2CO_3.[18,19]

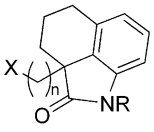
1,2,3,4-Tetrahydroisoquinoline is commercially available. 4,5,6,7-Tetrahydro-furo[3,2-*c*]pyridine,[21] 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine,[22] and 4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine[23] were prepared by literature methods. 4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine **10** was synthesized starting from compound **6**, and compounds **7**–**9** were prepared by the method of Matsumura et al.[24] Reaction of compound **6** with Vilsmeier reagent, which was prepared from DMF and $POCl_3$, gave compound **7**. Compound **8** was obtained by treatment of **7** with ethyl mercaptoacetate followed by cyclization in the presence of KOH. The 5-position ethoxycarbonyl group in compound **8** was removed by alkaline hydrolysis to provide compound **9**. Compound **10** was obtained by the decarboxylation of compound **9** in 95% yield (Scheme 3).

Compounds **5a**–**i** were evaluated for affinity for the 5-HT_7 and 5-HT_2 receptors. The affinity for the 5-HT_7 receptor was assayed in terms of the ability to displace the radioligand [^{3}H]5-carboxyamidotryptamine ([^{3}H]5-CT) from cloned human 5-HT_7 receptor expressed in COS-7 cells. The results, expressed as pK_i, are summarized in Table 1.



Scheme 3. (a) $POCl_3$, DMF (77%); (b) (i) $HSCH_2COOC_2H_5$, Et_3N, pyridine; (ii) 50% KOH aq (27%); (c) 3.5 N KOH aq, reflux (83%); (d) 47% HBr aq, reflux (95%).

Table 1. 5-HT_7 and 5-HT_2 receptor affinities of compounds **5a**–**i**



Compd	*n*	X[b]	R	pK_i[a]	
				5HT_7[c]	5HT_2[d]
5a	3	I	H	8.08±0.18	6.31±0.07
5b	4	I	H	8.35±0.05	6.21±0.16
5c	5	I	H	7.90±0.14	6.16±0.05
5d	4	II	H	8.19±0.15	6.08±0.04
5e	4	III	H	7.80±0.21	<6
5f	4	IV	H	6.25±0.23	<6
5g	4	V	H	6.09±0.10	<6
5h	4	II	CH_3	8.01±0.09	6.02±0.05
5i	4	II	C_2H_5	6.76±0.16	6.31±0.10

[a]The pK_i values are means ±SE of 8–12 values.
[b]See Scheme 2.
[c]Binding affinity (human recombinant receptors in mammalian cells; [^{3}H]5-CT).
[d]Binding affinity (rat cerebral cortex membranes; [^{3}H]ketanserin).[29]

Compound **5b** was a potent ligand for the 5-HT_7 receptor, being at least 2-fold more selective than compounds **5a** and **5c**. This result is consistent with findings in our previous series of phenylpiperazine derivatives, whose optimum carbon chain length was also $n=4$.[18] These results suggests that the distance between the basic nitrogen atom and the tetrahydrobenzindole ring is important in determining the selectivity for the 5-HT_7 receptor.

Next, we fixed the carbon chain length at the optimum value ($n=4$) and synthesized other fused heterocycles. The thienopyridine **5d**, as well as the isoquinoline **5b**,

showed both high affinity and high selectivity for the 5-HT_7 receptor, and the furopyridine **5e** had moderate affinity for this receptor. This may be due to the difference of their aromaticity,[25] because affinity for the 5-HT_7 receptor appeared to depend on aromaticity in our previous study.[26] The imidazopyridine **5f** and the pyrazolopyridine **5g** showed very low affinity for the 5-HT_7 receptor, and were not further evaluated.

Compound **5h**, which is the *N*-methyl-tetrahydrobenzindole analogue of compound **5d**, was a potent 5-HT_7 ligand with high selectivity for this receptor over the 5-HT_2 receptor,[27] while the *N*-ethyl-tetrahydrobenzindole **5i** showed very low affinity and selectivity for the 5-HT_7 receptor. These results suggested that the size of R group influences the binding to the 5-HT_7 receptor. The small R groups may be preferred for the 5-HT_7 receptor binding. The *N*-methylbenzindole **5h** (DR4446) should be suitable for positron emission tomography (PET) studies,[28] because the *N*-methyl group is available for introduction of a ^{11}C isotope label.

On the basis of its potential utility for investigation of the 5-HT_7 receptor, the thienopyridine derivatives **5d** and **5h** were selected for further evaluation. As can be seen from Table 2, compound **5d** was found to be highly selective for the 5-HT_7 receptor over the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_3, 5-HT_4 and 5-HT_6 receptors, and *N*-methyl derivative **5h** was as selective as compound **5d**. Thus, compounds **5d** and **5h** were confirmed to be high-affinity ligands for the 5-HT_7 receptor with high selectivity.

Compound **5d** was evaluated for influence on 5-HT-induced stimulation of cAMP accumulation in HEK293 cells expressing the human 5-HT_7 receptor. Intracellular cAMP formation was measured by enzyme-immunoassay. Compound **5d** on its own did not stimulate basal activity, that is it lacked agonist activity, but it inhibited 5-HT-induced stimulation of cAMP accumulation (Fig. 1). Compound **5d** is thus a 5-HT_7 receptor antagonist.

Table 2. Receptor binding profile of **5d** and **5h**[a]

Receptor	Affinity (pK_i)[b]	
	5d	**5h**
5-HT_{1A}	6.29±0.12	6.11±0.07
5-HT_{1B}	<6	<6
5-HT_{2C}	<6	<6
5-HT_2	6.08±0.04	6.02±0.05
5-HT_3	<6	<6
5-HT_4	<6	<6
5-HT_6	<6	<6
5-HT_7	8.19±0.15	8.01±0.09

[a]Binding experiments were conducted as follows. Receptors and radioligands used in binding assay: 5-HT_{1A} (human recombinant (mammalian);[30] [^{3}H]8-OH-DPAT); 5-HT_{1B} (rat striatal; [^{125}I](−)-iodocyanopindolol);[31] 5-HT_{2C} (pig choroid plexus; [^{3}H]mesulergine);[31] 5-HT_2 (rat cerebral cortex; [^{3}H]ketanserin);[29] 5-HT_3 (N1E-115 cells; [^{3}H]GR65630);[32] 5-HT_4 (guinea-pig striatum; [^{3}H]GR-113808);[33] 5-HT_6 (human recombinant (mammalian); [^{3}H]LSD);[34] 5-HT_7 (human recombinant (mammalian); [^{3}H]5-CT).
[b]The pK_i values are means ±SE of 8–12 values.

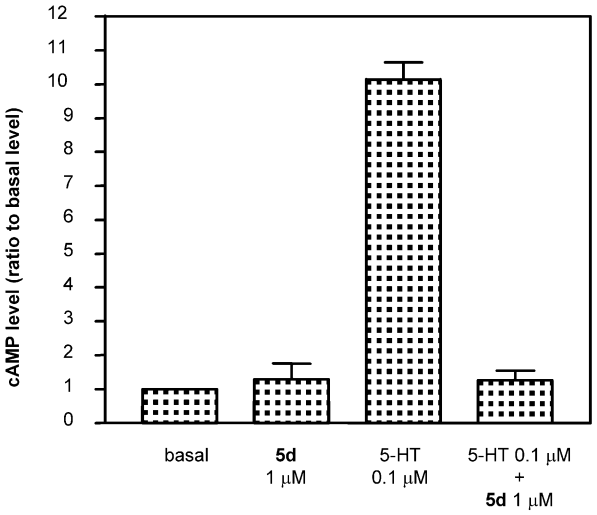


Figure 1. 5-HT-induced stimulation of cAMP accumulation in HEK273 cells expressing the 5-HT_7 receptor and its inhibition by compound **5d**. Data represent the mean±SE of at least three determinations.

In summary, we have described the synthesis and the affinity for the 5-HT_7 receptor and other receptors of a novel series of fused-ring tetrahydropyridine derivatives. A limited structure–activity relationship study for these derivatives indicated that the distance between the basic nitrogen atom and the tetrahydrobenzindole ring was important in determining the selectivity for the 5-HT_7 receptor. Some of the compounds showed high affinity and high selectivity for the 5-HT_7 receptor. In particular, the thienopyridine derivatives **5d** and **5h** were potent and highly selective ligands for the 5-HT_7 receptor, and should be useful tools for clarifying the biological role of the 5-HT_7 receptor.

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20. New compounds were characterized by ^{1}H NMR and MS. 2a-[4-(4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-5-yl)butyl]-2a,3,4,5-tetra-hydrobenz[*cd*]indol-2(1*H*)-one (**5d**): ^{1}H NMR ($CDCl_3$) δ 1.03–1.16 (1H, m), 1.29–1.41 (2H, m), 1.41–1.56 (2H, m), 1.77–1.93 (3H, m), 2.06–2.20 (2H, m), 2.38–2.50 (2H, m), 2.59–2.73 (3H, m), 2.79–2.89 (3H, m), 3.48 (2H, s), 6.66–6.69 (2H, m), 6.79 (1H, d, $J=7.8$ Hz), 7.04 (1H, d, $J=5.1$ Hz), 7.11 (1H, dd, $J=7.6$ Hz), 8.00 (1H, br s); EIMS *m*/*z* 366 (M^+). 1-Methyl-2a-[4-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)butyl]-2a,3,4,5-tetrahydrobenz[*cd*]indol-2(1*H*)-one (**5h**): ^{1}H NMR ($CDCl_3$) δ 0.95–1.07 (1H, m), 1.14–1.33 (2H, m), 1.39–1.53 (2H, m), 1.74–1.94 (3H, m), 2.07–2.19 (2H, m), 2.36–2.47 (2H, m), 2.59–2.72 (3H, m), 2.81–2.91 (3H, m), 3.17 (3H, s), 3.47 (2H, s), 6.63 (1H, d, $J=7.6$ Hz), 6.69 (1H, d, $J=5.1$ Hz), 6.82 (1H, d, $J=7.8$ Hz), 7.05 (1H, d), 7.17 (1H, dd); TSPMS *m*/*z* 381 ($M+H^+$).
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