Pergamon

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Bioorganic & Medicinal Chemistry Letters 13 (2003) 2369–2372

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

2,3,4,5-Tetrahydro- and 2,3,4,5,11,11a-Hexahydro-1H-[1,4]diazepino[1,7-*a*]indoles: New Templates for 5-HT$_{2C}$ Agonists

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Received 17 March 2003; revised 11 April 2003; accepted 15 April 2003

Abstract—The design and synthesis of the novel 2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,7-*a*]indole **5** is described. This azepinoindole has excellent affinity for 5-HT$_{2C}$ (K_i 4.8 nM) and modest selectivity over 5-HT$_{2A}$ (~4-fold). Several N- and C$_{11}$-substituted analogues of **5** were prepared, as were a number of biaryl indoline derivatives. The anxiolytic potential for the azepinoindole template **5** is demonstrated by activity in a mouse shock–aggression assay.

The treatment of psychiatric disorders by modulation of receptors for central nervous system neurotransmitters has become standard therapy. Many the most commonly prescribed CNS medications worldwide are those that affect the function of serotonin (5-HT). Among the 14 identified sub-types of the 5-HT receptor, the 5-HT$_{2C}$ sub-type has received considerable attention as a potential therapeutic target for several indications, including anxiety, epilepsy, schizophrenia, and obesity.[1] The search for agents with high selectivity for this site has proven difficult in light of the close sequence homology among the sub-family of 5-HT$_2$ receptors (i.e., 5-HT$_{2A}$ and 5-HT$_{2B}$), and few reports of highly selective agonists have emerged.[2] Many of the reported agonists are indole-based derivatives possessing 5-HT$_{2C}$ selectivity of 5–10-fold relative to 5-HT$_{2A}$. Herein we describe the synthesis and preliminary pharmacological evaluation of a new class of selective 5-HT$_{2C}$ azepinoindole-based agonists with potential for the treatment of anxiety.

The azepino[4,5-*b*]indole **1**[3] was identified as a potent 5-HT$_{2C}$ partial agonist from high-throughput screening of Pharmacia's compound collection (Fig. 1). Interestingly, the *N*-methyl derivative **2** was evaluated in human clinical trials in the mid 1960s and found to cause weight loss.[4a] Like **1**, **2** is a potent 5-HT$_{2C}$ agonist but is non-selective with regard to affinity at the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors.[4b] Recently, the anxiolytic activity of a related azepino[4,5-*b*]indole **3** has been described.[5] In 1997, the *iso*tryptamine (*S*)-**4** was reported as a potent 5-HT$_{2C}$ ligand (K_i 4 nM) with excellent selectivity over 5-HT$_{2A}$ (63-fold), superior to the 10-fold selectivity of the corresponding racemic tryptamine analogue.[6a] However, it has been shown that receptor affinities are highly dependent upon assay protocols, and a re-examination of

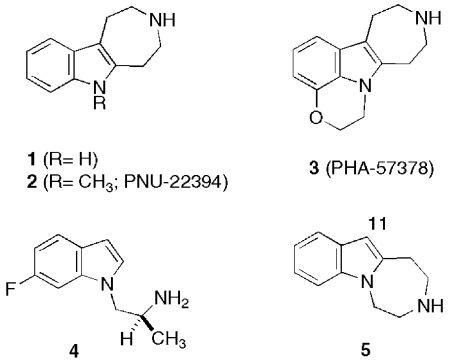

Figure 1. Azepinoindoles **1**, **2**, **3**, and **5** and isotryptamine **4**.

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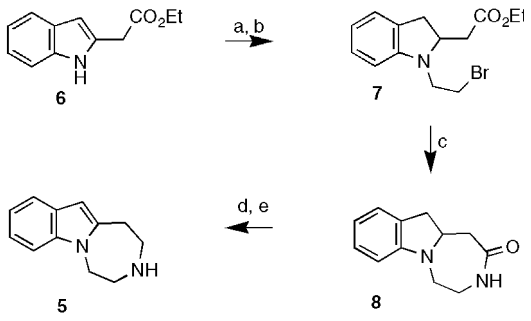
doi:10.1016/S0960-894X(03)00403-7



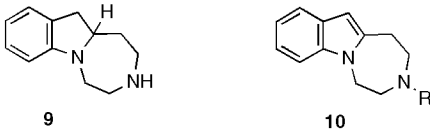
Scheme 1. (a) $NaCNBH_3$, HOAc (82%); (b) 1,2-dibromoethane, K_2CO_3, CH_3CN (81%); (c) NH_3, MeOH (72%); (d) BH_3–SMe_2, THF (89%); (e) DDQ, dioxane (52%).

the binding profiles for isotryptamines such as **4** has demonstrated greatly reduced selectivity ($\leq 10\times$) using human receptors and agonist radioligands.[6b] Based on these observations, we envisioned that the azepino[1,7-*a*]indole **5** would be a useful template upon which an analogue program targeting selective 5-HT_{2C} agonists could be based.

Our synthesis of azepino[1,7-*a*]indole **5** centered on the elaboration of the known indol-2-yl acetate **6** (Scheme 1).[7] Reduction of **6** to the corresponding indoline and subsequent alkylation with 1,2 dibromoethane gave **7** in 66% overall yield. Treatment of **7** with ammonia-saturated methanol at 50 °C generated the tricyclic lactam **8** in 72% yield. Reduction of **8** with borane-dimethylsulfide and subsequent oxidation of the resulting indoline (**9**) with DDQ at room temperature generated the targeted azepino[1,7-*a*]indole **5** in 46% overall yield. Alkylation of the azepine nitrogen in **5** provided *N*-alkyl analogues **10** (see Table 1). Protection of **5** as the trifluoroacetamide allowed for preparation of the C-11 analogues **11** (see Table 2) following mild acetamide hydrolysis (MeOH, K_2CO_3).

Given below in Table 1 are the 5-HT_{2C} and 5-HT_{2A} binding affinities and 5-HT_{2C} efficacies for **1**, **2**, **3**, **5**, **9**, and the *N*-alkylated analogues **10a**–**c**.[8] Although both **1** and **5** had comparable 5-HT_{2C} affinities, azepino[1,7-*a*]-

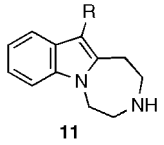
Table 1. 5-HT_{2C} and 5-HT_{2A} binding affinities and 5-HT_{2C} efficacies for **1**, **2**, **3**, **5**, **9**, and *N*-alkyl analogues **10a**–**c**



Compd	R	K_i (nM)		5-HT_{2C}
		5-HT_{2C}	5-HT_{2A}	Intrinsic efficacy
1		6.1	10	66%
2		19	19	83%
3		4.3	4.1	105%
5		4.8	18	80%
9[a]		721	805	ND
10a	Me	13	28	49%
10b	Et	38	30	66%
10c	Pr	64	56	ND

[a]Tested as a racemic mixture. ND = not determined.

Table 2. 5-HT affinity and selectivity for C-11 substituted analogues **11**



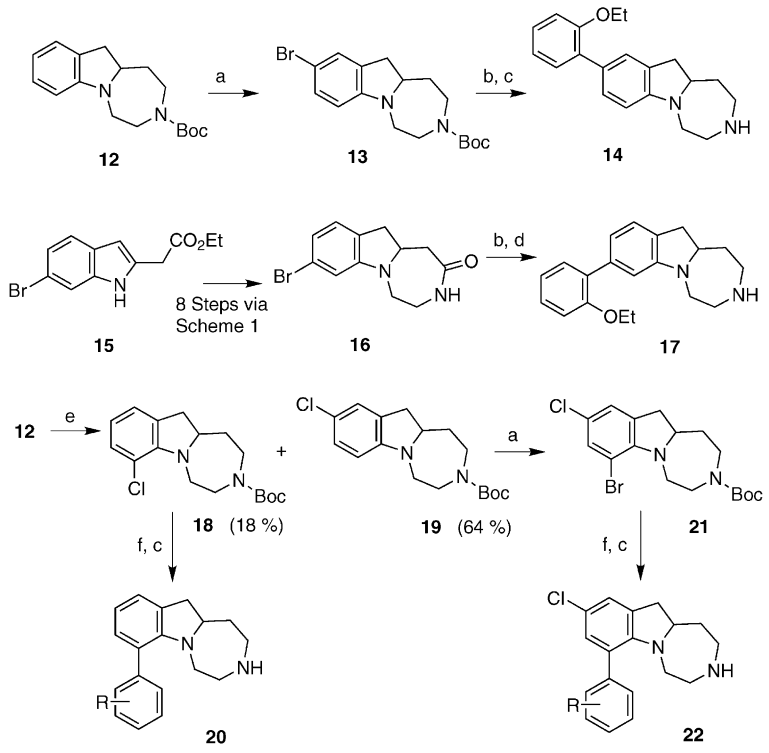
Compd	R	K_i (nM)		2A/2C
		5-HT_{2C}	5-HT_{2A}	Selectivity
5	H	4.8	18	3.8
11a	Cl	4.7	6.5	1.4
11b	CHO	12	29	2.4
11c	CH_3	6.8	12	1.8
11d	CN	85	83	1.0
11e	$CONH_2$	74	46	0.6
11f	$COCF_3$	54	40	0.7
11g	$C(O)CONH_2$	136	316	2.3

indole **5** displayed slightly enhanced 2A/2C selectivity. In addition, azepino[1,7-*a*]indole **5** possessed greater intrinsic activity than **1**. The racemic indoline **9** showed severely attenuated affinity at both 5-HT_{2C} and 5-HT_{2A} relative to **5**. Substitution of the azepine nitrogen of **5** with a methyl group attenuated 5-HT_{2C} affinity and dramatically reduced 5-HT_{2C} efficacy. Substitution with larger groups also resulted in decreasing 5-HT_{2C} affinity.

An attractive feature of the azepino[1,7-*a*]indole template **5** is the potential for analogue generation by derivatization of the indole C-11 position. Using well-known transformations, compounds **11a**–**g** were prepared and their binding affinities are given in Table 2. Unfortunately, none of the analogues prepared displayed 5-HT_{2C} affinity or selectivity superior to that of the parent template **5**.

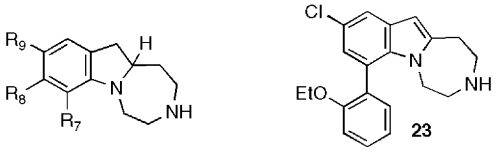
In addition to the N- and C_{11}-substituted analogues described above, we have examined a series of biaryl indoles and indolines derived from **5**. Encouraging this effort are recent reports of selective 5-HT_{2C} agonists containing a related biaryl carboline motif.[9] The preparation of these analogues is illustrated in Scheme 2.

Bromination of the protected indoline **12** occurred regioselectively to give the C-9 bromo derivative **13** exclusively. Palladium-mediated coupling of **13** with 2-ethoxy phenylboronic acid and subsequent deprotection provided the 9-aryl substituted azepinoindoline **14**. Access to the 8-aryl substituted azepinoindoline **17** was achieved by carrying the bromo indole **15**[10] through the sequence of reactions illustrated in Scheme 1 to the bromo-lactam **16**. Suzuki coupling of **16** provided the targeted 8-aryl analogue after lactam reduction with borane-dimethylsulfide. The 7-aryl analogues **20** could be prepared from the chloride **18**. In contrast to the selective bromination described above, chlorination of **12** afforded a separable mixture of **18** and **19** in 18 and 64% isolated yields, respectively. We obtained yields between 73 and 83% for Suzuki couplings of **18** with a variety of phenylboronic acids when employing tris(dibenzylideneacetone) dipalladium (0) and tri-cyclohexyl



Scheme 2. (a) *N*-bromosuccinimide, DMF; (b) 2-ethoxyphenylboronic acid, $(PPh_3)_2PdCl_2$, 2M Na_2CO_3, benzene (yield range); (c) TFA, CH_2Cl_2; (d) BH_3-SMe_2; (e) *N*-chlorosuccinimide, DMF; (f) $ArB(OH)_2$, Pd_2dba_3, $P(cy)_3$, Cs_2CO_3, dioxane.

Table 3. Effect of regiochemistry on binding affinity for biaryl indolines



Compd[a]	R_9	R_8	R_7	K_i (nM)	
				5-HT_{2C}	5-HT_{2A}
14	2-EtOPh	H	H	4815	>10,000
17	H	2-EtOPh	H	932	1581
20a	H	H	2-EtOPh	110	440
22a	Cl	H	2-EtOPh	54	218
23a	(indole of **22a**)			112	32

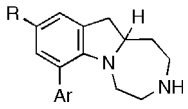
[a]All compounds except **23** were tested as racemic mixtures.

phosphine as the ligand.[11] Finally, deprotection of the coupled products gave the targeted 7-aryl analogues **20**. In addition, bromination of **19** provided the 7-bromo-9-chloro derivative **21**. Suzuki coupling of **21** occurred exclusively at the C-7 bromo position to ultimately afford the 9-chloro-7-biaryl derivatives **22**.

The binding profiles for the initial set of regioisomeric 2-ethoxyphenyl biaryl indolines is given in Table 3. It is clear that the analogue bearing the aromatic ring at the 9-position (**20a**) is superior to the 7- and 8-position isomers in terms of both affinity and selectivity for 5-HT_{2C}. Interestingly, introduction of a 9-chloro substituent enhances affinity at both 5-HT_{2C} and 5-HT_{2A} (**22a**). For comparison, the corresponding 9-chloro-7-(2-ethoxyphenyl)azepino[1,7-*a*]indole **23** displayed reduced 5-HT_{2C} affinity (112 nM) and significant 5-HT_{2A} affinity (32 nM). Based upon these results, we embarked on a more thorough exploration of 7-arylazepinoindolines, including an examination of the effect of absolute stereochemistry on receptor affinity. The analogues prepared for this study and their corresponding binding profiles are given in Table 4.[12]

The data in Table 4 show that incorporation of a chlorine substituent at the indoline C-9 position does not generally lead to analogues with either greater affinity or selectivity for the 5-HT_{2C} receptor relative to analogues without the chlorine. Although such an enhancement was seen in the 7-(2-ethoxyphenyl) series (e.g., **20a** and **22a**, Table 3), the corresponding 7-(2-chlorophenyl) and 7-(2-methylphenyl) series showed the opposite trend (see **20b** and **22e**). It is also observed that monosubstitution at the 2′-position on the 7-aryl substituent is greatly preferred (compare the 2′-ethoxy analogue **22a** with the corresponding 3′- or 4′-ethoxy compounds **22b** and **22c**). Disubstituted analogues **22h–j** also displayed inferior receptor binding profiles. Not unexpectedly, 7-aryl substituted indolines **20** and **22** exhibit an enantiopreference wherein the favored isomer possesses a 5-HT_{2C} K_i about 2–5 times lower than its enantiomer. In general, this series favors the (+)-isomer, although the (−)-isomer in the 2′-trifluoromethyl series (**20d**) is an exception. Typically, that enantiomer showing greater affinity for the 5-HT_2 receptor also displays improved 2A/2C selectivity, often by 2-fold or higher (see (+)-**20c**, for example). The 7-(2′-methylphenyl) analogue (+)-**20c** is the most selective compound to emerge from this series. With an affinity at the 5-HT_{2C} site of 30 nM

Table 4. 5-HT_{2C} affinity and selectivity for 7-aryl azepinoindolines **20** and **22**



Compd	R	Ar	K_i (nM)		2A/2C Selectivity
			5-HT_{2C}	5-HT_{2A}	
(+)-20a	H	2-EtO	103	458	4.45
(−)-20a	H	2-EtO	196	980	5.00
20b	H	2-Cl	23	82	3.57
(+)-20c	H	2-Me	30	191	6.37
(−)-20c	H	2-Me	39	136	3.45
(+)-20d	H	2-CF_3	59	107	1.81
(−)-20d	H	2-CF_3	14	45	3.21
(+)-22a	Cl	2-EtO	32	116	3.63
(−)-22a	Cl	2-EtO	178	354	1.99
22b	Cl	3-EtO	472	233	0.49
22c	Cl	4-EtO	265	182	0.69
22d	Cl	2-Me	43	88	2.05
22e	Cl	2-Cl	57	102	1.79
22f	Cl	2-F	223	141	0.63
22g	Cl	4-F	310	146	0.47
22h	Cl	2,4-di Cl	386	426	1.10
22i	Cl	2,5-di Cl	160	70	0.44
22j	Cl	5-Cl-2-MeO	793	756	0.95

Table 5. Anxiolytic activity in the shock-induced aggression assay and motor impairment (ataxia) for **5** and alprazolam in mice

	Dose[a]	Latency to fight (mean s)	Time on rotating rod (mean s)
Vehicle		5.8±1.0	95.5±6.6
Alprazolam	0.3	11.9±2.1*	74.2±9.2#
Alprazolam	3.0	35.2±3.7†	14.5±2.6†
5	3.0	12.8±2.3††	102.0±0.0
5	30	27.0±4.5†	87.6±9.6

*$p<0.05$; #$p<0.01$; †$p<0.001$; ††$p=0.09$ compared to vehicle.
[a]$N=10$–12/group.

and a 2A/2C selectivity of 6.4, this analogue represents a dramatic improvement in receptor binding profile relative to the unsubstituted parent azepinoindoline **9**.

The anxiolytic properties of the tetracyclic azepinoindole **3** have already been mentioned, as have the anorexic effects of **2**. We hypothesize that both of these activities could be due to the 5-HT_{2C} agonist properties of these compounds. While we were investigating the SAR around the azepino[1,7-*a*]indole template **5**, we examined its anxiolytic properties in a mouse shock-induced aggression assay.[13] Azepino[1,7-*a*]indole **5** caused a dose-dependent increase in the latency-to-fight times comparable to that seen with alprazolam, albeit at 10-fold higher doses (Table 5). Unlike alprazolam, however, **5** failed to induce ataxia at anxiolytic doses as determined by a standard Rotarod assay.

We have described a new azepino[1,7-*a*]indole template **5** with high affinity and intrinsic activity at the 5-HT_{2C} receptor. This template possesses anxiolytic activity in an in vivo behavioral model at doses which do not sedate or impair motor function. In addition, we have also examined a series of aryl-substituted azepinoindolines to identify 5-HT_{2C}-selective analogues. From this effort has emerged the (+)-7-(2′-methylphenyl)-azepinoindoline **(+)-20c**, which has good affinity and improved 2A/2C selectivity.

Acknowledgements

We thank L. Dolak, E. Seest, and M. Hester for chromatographic resolution of the enantiomers in Table 4.

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