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Bioorganic & Medicinal Chemistry Letters 15 (2005) 1467–1470
Bioorganic & Medicinal Chemistry Letters

Discovery and SAR of new benzazepines as potent and selective 5-HT_{2C} receptor agonists for the treatment of obesity

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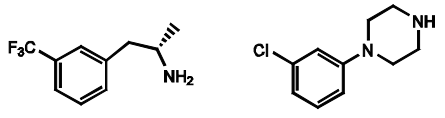
Received 3 November 2004; revised 22 December 2004; accepted 29 December 2004
Available online 23 January 2005

Abstract—We report on the synthesis, biological evaluation and structure–activity relationships for a series of 3-benzazepine derivatives as 5-HT_{2C} receptor agonists. The compounds were evaluated in functional assays measuring [^{3}H] phosphoinositol turnover in HEK-293 cells transiently transfected with h5-HT_{2C}, h5-HT_{2A} or h5-HT_{2B} receptors. Several compounds are shown to be potent and selective 5-HT_{2C} receptor agonists, which decrease food intake in a rat feeding model.

The 5-HT_{2C} receptor is one of more than 14 different 5-HT receptor subtypes, several of which are known to regulate important behavioural responses.[1] Evidence for the involvement of the 5-HT_{2C} receptor in the regulation of feeding and satiety has been the subject of a number of reviews.[2] The nonselective 5-HT_{2C} receptor agonist mCPP has been shown to cause weight loss by reduction of food intake in humans[3] and rodents.[4] Nor-dexfenfluramine, a circulating metabolite of the weight loss drug dexfenfluramine, is a nonselective 5-HT_{2C} receptor agonist, and the anorectic effects of dexfenfluramine and nor-dexfenfluramine are blocked by the selective 5-HT_{2C} receptor antagonist, SB-242084.[5] A number of recent papers describe the anorectic effects in rodents of newer 5-HT_{2C} receptor agonists, such as RO 60-0175,[6] WAY-161503,[7] YM348[8] and VER-5384.[9] Additionally, 5-HT_{2C} receptor knock-out mice have been shown to be hyperphagic and nonresponsive to the anorectic effects of 5-HT_{2C} agonists.[10]

Fenfluramine and dexfenfluramine were withdrawn from the market after reports of valvular heart defects from use among weight loss patients,[11] an effect which may result from the activation of other serotonergic pathways, particularly of 5-HT_{2B} receptors.[12] It has also been proposed that hallucination caused by serotonergic drugs may be an effect of 5-HT_{2A} agonism.[13] With this in mind, the discovery of potent 5-HT_{2C} receptor agonists with appropriate selectivity versus 5-HT_{2A} and 5-HT_{2B} receptors, could lead to a safe and effective treatment for obesity and other diseases or conditions which could benefit from weight loss.



Nor-dexfenfluramine mCPP

We reasoned that by taking features from the nonselective 5-HT_{2C} receptor agonist nor-dexfenfluramine and constraining them into a fused bicyclic structure, we might discover new 5-HT_{2C} receptor agonists with improved selectivity versus 5-HT_{2A} and 5-HT_{2B} receptors. If a different conformation of the nor-dexfenfluramine ethylamino side chain is required to activate the 5-HT_{2C} receptor versus other receptors, and if we could find compounds with this 5-HT_{2C} preferred conformation by sampling a number of possible constrained ring systems, then these compounds might also be selective. What we discovered was that one of these fused bicyclic core structures, the 3-benzazepines, could in fact yield

Keywords: 5-HT_{2C}; Serotonin; Obesity; Benzazepine.
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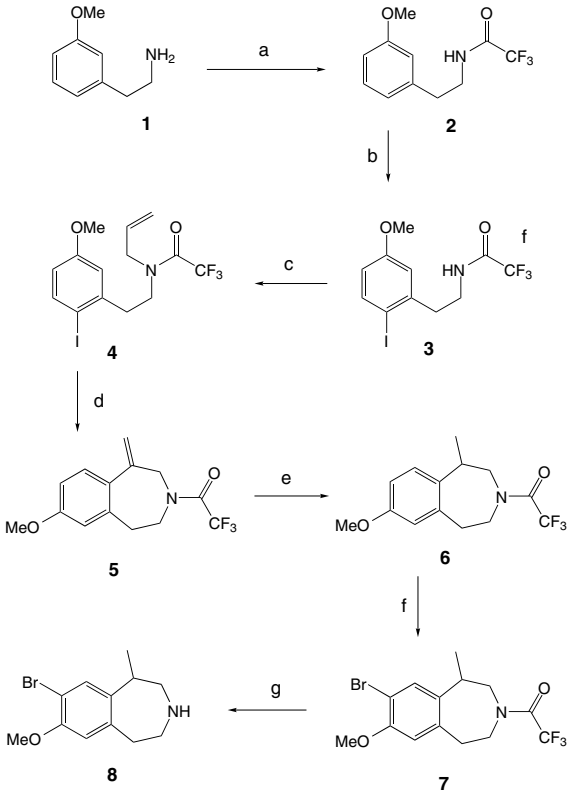
doi:10.1016/j.bmcl.2004.12.080

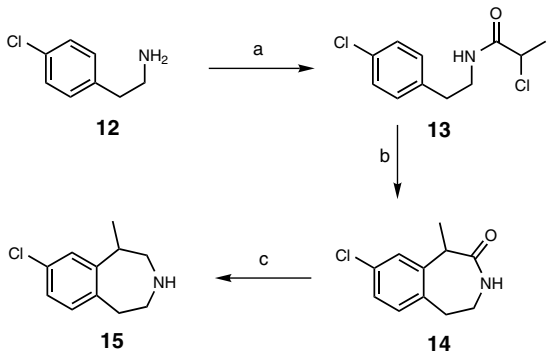
potent and selective 5-HT_{2C} receptor agonists when properly substituted. Herein we describe some of the more interesting SAR for this series.

Entry into the benzazepine series was first accomplished with the synthesis of 8-bromo-7-methoxy-1-methylbenzazepine, **8** (Scheme 1). Important features of this route include the use of a methoxy substituent to activate and direct halogenation on two occasions, and the intramolecular Heck reaction to close the 7-membered ring.[14] A further advantage of this synthesis was the ease at which substitution could be introduced into this series by appropriate manipulation of the late-stage intermediates **6** and **7**. Compounds **9a**–**d** were prepared by eliminating the bromination step (**9a**), substituting NCS (**9b**) or NIS (**9c**) for NBS, or by treating the protected bromide with sodium trifluoroacetate and copper (I) iodide (**9d**). Compounds **10a**–**d** were prepared by removal of the methyl group from intermediate **7** with BBr_3, followed by alkylation of the resulting phenol with the appropriate alkyl halide, and then deprotection. Substitution was also introduced at the 1-position by choosing appropriate allyl bromides for the preparation of intermediates similar to **4**, leading to compounds **11b** and **c**. Oxidation of the olefin **5** to the ketone, followed by reduction with Pd–H_2, resulted in the 1-unsubstituted **11a**. To further explore the SAR of this series, it was desired to make compounds without the 7-methoxy substituent. Benzazepines **15**–**18** were in some cases prepared similarly, starting with mono- or disubstituted halophenethylamines. In this case, the deactivated aromatics were iodinated with bispyridine iodoniumtetrafluoroborate. Alternatively, benzazepines **15**–**19** were also prepared using a Friedel–Crafts cyclization as the key step as shown in Scheme 2 for 8-chlorobenzazepine **15**. Phenethylamine **12** was acylated to form chloroacetamide **13**, which underwent Friedel–Crafts alkylation to benzazepinone **14**. Reduction with BH_3 or LAH, led to the final benzazepine **15**. In this manner, the regioisomeric 7- and 9-chlorobenzazepines **16b** and **c** were made from 3-chlorophenethylamine, separating the regioisomers at the benzazepinone stage. Variations on the Friedel–Crafts acylation were explored, and in some cases, found to have advantages. Racemic compounds of interest were separated by chiral HPLC and the absolute stereochemistry determined by crystallography or comparison of synthetic derivatives. In the case of (*R*)- and (*S*)-**18c**, these compounds were prepared via NCS chlorination of the N-trifluoroacetyl protected (*R*)- or (*S*)-**15**, separation of the regioisomers and then deprotection.



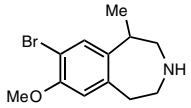
Scheme 1. Reagents and conditions: (a) $(CF_3CO)_2O$, pyridine, CH_2Cl_2; (b) ICl, MeOH; (c) allylbromide, NaOH, K_2CO_3, *n*-Bu_4NBr, toluene; (d) $Pd(OAc)_2$, various conditions; (e) 10% Pd–C, H_2, MeOH; (f) NBS, CH_3CN; (g) NaOH, MeOH–H_2O.

The functional activity of the compounds for the h5-HT_{2C} (INI isoform), h5-HT_{2A} and h5-HT_{2B} receptors was determined by measurement of [^{3}H]phosphoinositol turnover in transiently transfected HEK-293 cells, and the results are summarized in Tables 1–4. Compound **8**, our first designed compound in this series, demonstrated excellent 5-HT_{2C} receptor potency and moderate selectivities versus the 5-HT_{2A} and 5-HT_{2B} receptors (Table 1). With this result in hand, a small set of compounds based on **8** was designed to explore the effects of substitution at the 8-, 7- and 1-positions. At the 8-position, substitution of chlorine (**9b**), iodine (**9c**) or trifluoromethyl (**9d**) resulted in compounds of similar 5-HT_{2C} receptor potencies and selectivities towards 5-HT_{2A} and 5-HT_{2B} receptors. The 8-unsubstituted compound (**9a**) was of much lower potency at all receptors. At the 7-position, replacing the methyl with hydrogen (**10a**), ethyl (**10b**) or isopropyl (**10c**) showed a trend towards decreasing potency at the 5-HT_{2C} receptor with increasing size of the substituent, but little change in potencies at the 5-HT_{2A} and 5-HT_{2B} receptors was observed. The anomaly was the 7-benzyl ether (**10d**), which was of similar potency to the isopropyl ether (**10c**) at the 5-HT_{2C} recep-



Scheme 2. Reagents and conditions: (a) $CH_3CHClCOCl$, pyridine, CH_2Cl_2; (b) $AlCl_3$, 150–200 °C; (c) BH_3, ether.

Table 1. 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} functional activity for compounds **8**–**11**



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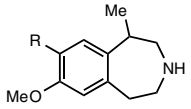

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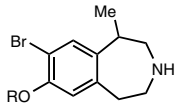

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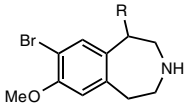
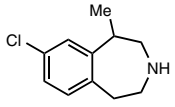


11

Compd	R	EC_{50} (nM)		
		5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
8		5	80	100
9a	H	2000	>10,000	Not active
9b	Cl	11	80	140
9c	I	2	61	64
9d	CF_3	4	42	130
10a	H	3	63	190
10b	Et	28	110	180
10c	*i*-Pr	68	97	230
10d	Bn	56	22	>10,000
11a	H	8	100	400
11b	Et	11	100	40
11c	*i*-Pr	160	Not active	1000
11d	(*R*)-Me	3	80	220
11e	(*S*)-Me	5	30	30

Table 2. 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} functional activity for compounds **15**–**17**



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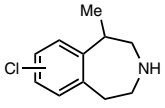

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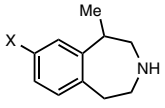
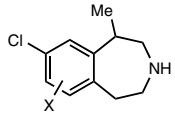


17

Compd	X	EC_{50} (nM)		
		5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
15	8-Cl	11	260	1100
16a	6-Cl	860	>5000	>5000
16b	7-Cl	35	150	530
16c	9-Cl	930	>5000	>5000
17a	8-F	410	1600	>10,000
17b	8-Br	12	510	1500
17c	8-CF_3	7	100	380
17d	8-OMe	420	940	780
17e	8-H	340	1600	>5000

tor, but with increased potency at the 5-HT_{2A} receptor and greatly reduced potency at the 5-HT_{2B} receptor. At the 1-position, the difference in 5-HT_{2C} receptor potency observed between hydrogen (**11a**), ethyl (**11b**), *R*-methyl (**11d**) or *S*-methyl (**11e**) is small, when compared to the greater than 10-fold reduction in potency observed for the isopropyl substitution (**11c**). There appears to be a trend towards increasing potency at the 5-HT_{2B} receptor for *S*-methyl > ethyl > *R*-methyl > hydrogen. Comparison of the enantiomers **11d** and **e** shows the *R*-methyl enantiomer **11d** to be somewhat more potent at the 5-HT_{2C} receptor and significantly more selective versus the 5-HT_{2A} and 5-HT_{2B} receptors. Data for some mono substituted analogues is shown in Table 2. The first compound from this group to be prepared, the 8-chloro derivative **15**, showed improved receptor selectivity over the previous set of compounds, **8**–**11**. Moving the chloro substituent around the ring shows the 6-chloro (**16a**) and 9-chloro (**16c**) to be nearly 100-fold less potent at the 5-HT_{2C} receptor, with reduced potencies also observed at the 5-HT_{2A} and 5-HT_{2B} receptors. Moving the chlorine to the 7-position (**16b**), results in a 3-fold drop in potency at the 5-HT_{2C} receptor, but slightly increased potency at the 5-HT_{2A} and 5-HT_{2B} receptors.

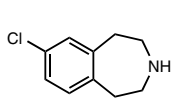
Table 3. 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} functional activity for compounds **18**



18

Compd	X	EC_{50} (nM)		
		5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
18a	6,8-DiCl	20	170	840
18b	7,8-DiCl	4	16	78
18c	8,9-DiCl	6	220	1800
18d	8-Cl, 7-F	7	72	360
18e	8-Cl, 9-F	22	840	>10,000

Table 4. 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} functional activity and percent responses relative to serotonin control for compounds **19**, (*R*)-**15**, (*S*)-**15**, (*R*)-**18c** and (*S*)-**18c**



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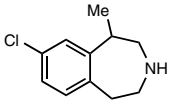

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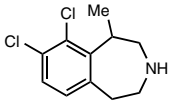

18c

Compd	EC_{50} in nM (% maximal response relative to serotonin)		
	5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
19	12 (85)	90 (100)	1000 (100)
(*R*)-**15**	11 (100)	190 (70)	1000 (100)
(*S*)-**15**	16 (100)	265 (70)	1400 (100)
(*R*)-**18c**	230 (85)	2400 (100)	>10,000
(*S*)-**18c**	3 (90)	135 (35)	(25 @ 10 uM)

Replacement of the 8-chloro substituent with fluorine (**17a**), methoxy (**17d**) or hydrogen (**17e**) results in a 30-fold reduction in potency at the 5-HT_{2C} receptor and a 5-fold reduction in potency at the 5-HT_{2A} receptor. Interestingly, a similar 5-fold reduction in potency is observed at the 5-HT_{2B} receptor for the 8-fluoro (**17a**) and 8-unsubstituted (**17c**) compounds, but no shift in 5-HT_{2B} potency is observed for the 8-methoxy compound (**17d**). For replacement of 8-chloro (**15**) with 8-bromo (**17b**) or 8-trifluoromethyl (**17c**), similar 5-HT_{2C} potencies are observed, with 5-HT_{2A} and 5-HT_{2B} selectivities being somewhat increased for the bromo analogue and decreased for the trifluoromethyl analogue. Functional activity data for some dihalo analogs, **18a**–**e**, is displayed in Table 3. The 6,8-dichlorobenzazepine (**18a**)

has a slightly lower 5-HT_{2C} potency compared to **15** and lower selectivity.

Adding a 7-position substituent to **15** increases 5-HT_{2C} potency as seen with compounds **18b** and **18d** (compare also compound **8**), but an even greater increase in 5-HT_{2A} and 5-HT_{2B} receptor potencies results in reduced selectivities. In contrast, the 8,9-disubstituted benzazepines **18c** and **e**, show significant improvement in receptor selectivity compared to **15**, with 5-HT_{2C} potency slightly increased for **18c**, and decreased for **18e**. Upon comparison of the enantiomers of **15** with the enantiomers of **18c**, unexpected results were obtained. It can be seen that (*R*)-**15**, (*S*)-**15** and **19**[15] are all of similar potency and selectivity. A slight advantage in 5-HT_{2C} potency for (*R*)-**15** and **19** over (*S*)-**15** is observed and a slight advantage in 5-HT_{2A} selectivity is observed for (*R*)-**15** and (*S*)-**15** over **19**. In comparison,(*S*)-**18c** is about 70-fold more potent at the 5-HT_{2C} receptor than (*R*)-**18c**, which represents not only a change in magnitude, but also a switch in preferred stereochemistry. Also of interest is the drop in 5-HT_{2A} maximal response, relative to the serotonin control, observed for (*S*)-**18c**. In all previous cases, compounds have been full, or nearly full agonists at the three receptors. The 5-HT_{2C} and 5-HT_{2B} responses have all been in the 90–100% range. The 5-HT_{2A} responses have occasionally dipped to 70%. For (*S*)-**18c**, the 5-HT_{2A} maximal response is only 35%, and for the 5-HT_{2B} receptor only 25% response is observed at the highest test concentration of 10 uM. In this case, we believe that a steric interaction between the (*S*)-1-methyl and 9-chloro substituents further locks the seven-membered ring into a conformation favorable to 5-HT_{2C} receptor activation and less favourable to either 5-HT_{2A} or 5-HT_{2B} activation. In contrast, the interaction between the (*R*)-1-methyl and 9-chloro substituents of (*R*)-**18c** locks the seven-membered ring into a conformation less favourable to activation of all three receptors.

A number of compounds were screened for the ability to reduce food intake in male Sprague–Dawley rats. Rats were caged separately and spent two weeks on reverse light cycle. On the day of the experiment rats (8 per group) were injected P.O. (oral gavage) with vehicle, 12.5, 25 and 50 mg/kg 1 h before the dark cycle. Food intake was measured 6 h post injection and compared to vehicle control. A number of compounds including **8**, **9b** and **c**, **15**, **17c** and **18b–e**, were shown to decrease food intake with ED_{50} values in the range of 10–40 mg/kg over a 6 h period.

Using structural features from known 5-HT_{2C} agonists and incorporating these into a rigid framework, a series of 3-benzazepines was designed. This series has provided a number of potent and selective 5-HT_{2C} receptor agonists which are orally active in an acute feeding model in Sprague–Dawley rats. Further studies have resulted in the identification and advancement of one compound from this series into human clinical trials.

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