Bioorganic & Medicinal Chemistry Letters 19 (2009) 1871–1875

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

7-Sulfonamido-3-benzazepines as potent and selective 5-HT$_{2C}$ receptor agonists: Hit-to-lead optimization

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ARTICLE INFO

Article history:
Received 5 February 2009
Revised 18 February 2009
Accepted 18 February 2009
Available online 21 February 2009

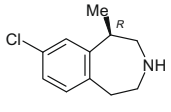
Keywords:
3-Benzazepine
Sulfonamide
5-HT2C receptor
Agonist
Hit-to-lead

ABSTRACT

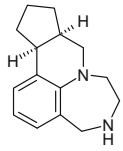
New 7-sulfonamido-3-benzazepines **3** are disclosed as 5-HT$_{2C}$ receptor agonists. Appropriate substitution of the amino group (R^{1}R^{2}N–) gave compounds that were potent 5-HT$_{2C}$ agonists with minimal activation of the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors. Furthermore, representative examples had excellent in vitro ADME properties and good selectivity over ion channel activity.

The neurotransmitter serotonin (5-HT) mediates its effects through at least 14 different receptor subtypes that have been classified into seven major families, 5-HT$_{1-7}$.[1] The 5-HT$_2$ family has three members 2A, 2B and 2C and unlike 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors, the expression of 5-HT$_{2C}$ receptors appears to be restricted to the central nervous system (CNS).[2] 5-HT$_{2C}$ receptor agonists have become attractive drug targets that have potential use in the treatment of a number of conditions including obesity, schizophrenia, sexual dysfunction, and urinary incontinence.[3] For these indications, selectivity over agonism at the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors would be a key objective because 5-HT$_{2A}$ agonists can potentially be hallucinogenic and have cardiovascular (CV) effects,[4] whereas 5-HT$_{2B}$ agonism has been associated with heart valvulopathy and pulmonary hypertension.[5]

The search for potent and selective 5-HT$_{2C}$ agonists has identified lorcaserin (**1**) (APD-356; Arena) which is in advanced clinical trials for the treatment of obesity[6] and vabicaserin (**2**) (SCA-136; Wyeth) as a potential therapy for schizophrenia.[7] Furthermore, several small molecule 5-HT$_{2C}$ agonists have been reported to be in early clinical development.[8]



1: lorcaserin



2: vabicaserin

We have disclosed several new templates as 5-HT$_{2C}$ receptor agonists[9–12] and some of these compounds have now progressed to clinical trials. As part of our research efforts to identify potential new 5-HT$_{2C}$ agonist drug candidates, we adopted a strategy of exploring multiple chemical templates in order to increase our chances of having compounds survive to become advanced clinical candidates. In this Letter, we disclose new 7-sulfonamido-3-benzazepines (**3**) as potent and selective 5-HT$_{2C}$ agonists.

There have been few reports of sulfonamido-3-benzazepines (**3**) as 5-HT$_{2C}$ receptor agonists and these have been restricted to the patent literature with few examples of specific compounds or disclosures of receptor affinity or selectivity.[13] Hence, we initiated a hit-to-lead research program to explore the structure–activity relationships (SAR) of **3** with the objective of seeking potent 5-HT$_{2C}$ agonists with minimal activity at either the 5-HT$_{2A}$ or 5-HT$_{2B}$ receptors. Furthermore, target compounds were designed to have drug-like properties consistent with CNS target space.[14] It was also our intention to evaluate sulfones **4** and reversed sulfonamides **5** as these would explore the effect of the linker group and be available from common intermediates.

Target compounds **3** and **4** were prepared using a short synthesis employing 3-benzazepine-7-sulfonyl chlorides **11**[15] as advanced intermediates (Scheme 1). Sulfonamides **3** were prepared by reaction of **11** with the appropriate amine (R^{1}R^{2}NH) followed by deprotection of the trifluoroacetyl amide under standard conditions. Sulfones **4** were prepared from **11** by activation to the sulfonyl fluoride and then treatment with a Grignard reagent (R^{1}MgX).[16] Where the benzazepines **9** were not readily available, the azepine ring was constructed from the phenylacetic acid **6** by

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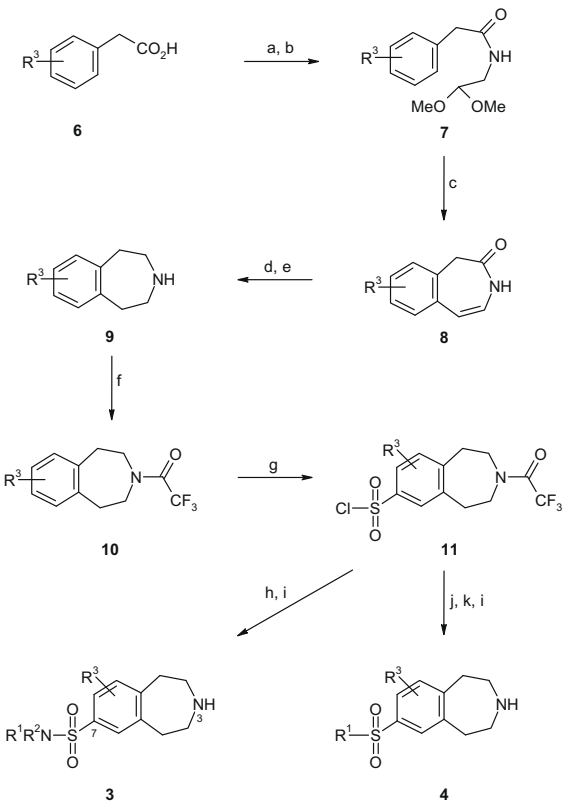
doi:10.1016/j.bmcl.2009.02.071

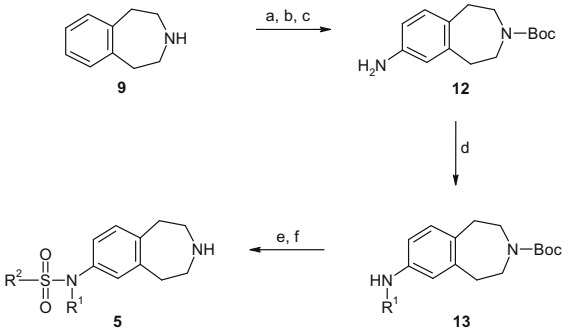


Scheme 1. Synthesis of sulfonamides **3** and sulfones **4**. Reagents: (a) $SOCl_2$; (b) $H_2NCH_2CH(OMe)_2$; (c) concd HCl; (d) H_2, Pd/C, AcOH; (e) BH_3·THF; (f) $(CF_3CO)_2O$; (g) $ClSO_3H$; (h) R^1R^2NH; (i) K_2CO_3, MeOH; (j) KF, 18-crown-6 (cat), MeCN; (k) R^1MgX, THF.

acid-catalyzed cyclization of **7** to give **8** followed by sequential reduction of the alkene and then amide.[17] Protection of the azepine N-atom followed by chlorosulfonylation furnished **11**.

Reversed sulfonamides **5** were also prepared from benzazepine **9** (Scheme 2). Nitration of **9** with fuming HNO_3 selectively introduced a 7-NO_2 group in good yield.[18] Boc protection of the azepine and hydrogenolysis of the 7-NO_2 group afforded aniline **12**.[19] Reductive amination of **12** with aldehydes under standard conditions gave *sec*-amines **13** and then reaction with sulfonyl chlorides followed by deprotection of the azepine *N*-Boc group gave **5**.

The 5-HT_{2C} agonist activity of target compounds (Table 1) was initially evaluated by measuring the ability to induce a fluorescent based calcium mobilization signal in a FLIPR assay employing recombinant CHO K1 cells expressing the human 5-HT_{2C} receptor.[12]



Scheme 2. Synthesis of reversed sulfonamides **5**. Reagents: (a) fuming HNO_3; (b) $(Boc)_2O$; (c) H_2, Pd/C; (d) aldehyde, MeOH then $NaBH_4$; (e) R^2SO_2Cl; (f) CF_3CO_2H.

Target compounds were also tested for their ability to inhibit binding of [^{3}H]-meselurgine at the human 5-HT_{2C} receptor utilizing SPA technology and cellular membrane preparations generated from recombinant Swiss 3T3 cells.[12] Agonist activity at the 5-HT_{2B} receptor was measured in recombinant cell-based systems expressing the human receptor.

The secondary sulfonamides **3a–f** were found to be weak 5-HT_{2C} agonists with 5-HT_{2B} activity, and several examples were more active at the 5-HT_{2B} receptor (**3b**) (Table 1). In contrast, tertiary sulfonamides **3g–m**, whether alkyl, benzyl or cyclic amines, had improved 5-HT_{2C} activity and some examples demonstrated minimal 5-HT_{2B} activity. Dihydrobenzofuran **3n** was one of the most potent 5-HT_{2C} agonists from this set and had no significant 5-HT_{2B} activity (<10% @ 10 μM). As part of our next iteration of analogue synthesis, we elected to explore further this motif by scaffold hopping from the dihydrobenzofuran to aryloxy amines **II**-**X** (Fig. 1). These targets were designed to be more chemically enabled and promote a rapid exploration of the SAR of the amine ring size and aryl ring substitution.

Azetidines **3o–q**, pyrrolidines **3r,s** and piperidines **3t–w** all furnished examples of potent 5-HT_{2C} agonists with minimal 5-HT_{2B} activity. The aryloxy group was clearly making an important contribution to both these SARs (e.g. **3r** vs **3k** and **3v** vs **3l**).

Introduction of a second or third substituent on the aryl ring of the benzazepine **3x-aa** proved detrimental within this very limited set of R^3 groups (e.g. **3v** vs **3y** vs **3aa**). Further investigation of this SAR, where R^3 was from a broader set of substituents, would represent a suitable position for potential optimization of **3**.

An analysis of 5-HT_{2C} activity of **3** aligned by R^1R^2N- clusters for all the compounds ($n = 169$) was performed with scatter plots which assisted in the identification of SAR trends and preferred compounds (Fig. 2). For example, it proved difficult to divorce 5-HT_{2C} and 5-HT_{2B} activity with aniline derivatives (**3**: R^1 = Ar) whereas compounds containing azetidines and pyrrolidines furnished many potent 5-HT_{2C} agonists with minimal activity at 5-HT_{2B}.

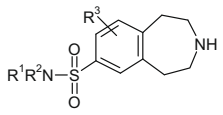
Aryl sulfones **4** were potent 5-HT_{2C} agonists which also demonstrated significant 5-HT_{2B} agonist activity and were not pursued. Reversed sulfonamides **5** failed to show any significant 5-HT_{2C} activity which highlighted the importance of the sulfonamide of **3** in picking up specific favourable interactions and/or presenting the amino substituents in a favourable trajectory.

Selected compounds were then screened in high throughput in vitro ADME and safety screens as a wider assessment of their properties: metabolic stability in human liver microsomes (HLM), transit performance across MDCK-mdr1 cells to assess membrane permeability,[20] and binding to the potassium hERG channel as a measure of ion channel activity (Table 2). In general, sulfonamides **3** had good metabolic stability consistent with low predicted clearance, good membrane permeability with low affinity for P-gp efflux transporters, and moderate affinity for the potassium hERG channel.

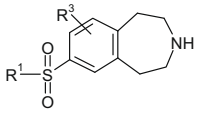
Pharmacological evaluation for activity at the 5-HT_{2A} receptor was measured in a FLIPR assay employing Swiss 3T3 cells expressing the recombinant human 5-HT_{2A} receptor, and in vitro tissue preparations with femoral artery.[21] Screening of **3v** in the recombinant assay gave a significant response with an EC_{50} 32 nM and E_{max} 70%. However, our experience has taught us that this was a highly expressed/coupled cell-line which over estimates 5-HT_{2A} activity and that the tissue preparation assay was a better predictor of in vivo outcomes.[22,23] Evaluation of **3v** in the canine femoral artery gave a minimal response of <10% at 0.54 μM, and we concluded that **3v** has no significant 5-HT_{2A} activity.

Compound **3v** was then evaluated in additional ADME and pharmacology screens as a representative example from this series. Sulfonamide **3v** had weak inhibition of CYP450 enzymes 1A2,

Table 1
5-HT_{2C} and 5-HT_{2B} activity for compounds **3**–**5**[a,b,c]



3



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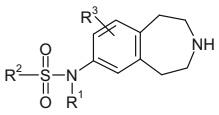
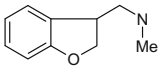
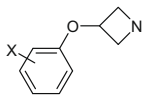


5

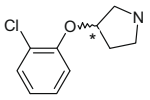
Where -NR^1R^2 =



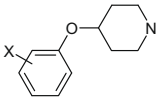
I



II: X = 2-Cl
III: X = 3-Cl
IV: X = 4-Cl



V: * = *R*
VI: * = *S*



VII: X = H
VIII: X = 2-F
IX: X = 2-Cl
X: X = 3-Cl

Compound	R^1	R^2	R^3	5-HT_{2C}		5-HT_{2C}	5-HT_{2B}	
				EC_{50} (nM)	E_{max} (%)	K_i (nM)	EC_{50} (nM)	E_{max} (%)
Secondary								
3a	nPr	H	H	959	59	531	197	30
3b	Ph	H	H	697	38	382	69	50
3c	2-F–Ph	H	H	197	47	133	75	41
3d	2-Cl–Ph	H	H	857	38	156	478	16
3e	CH_2(2-Cl–Ph)	H	H	46	48	30	802	19
3f	CH_2cPr	H	H	631	47	235	103	47
Tertiary								
3g	Me	Me	H	47	74	87	125	57
3h	Ph	Me	H	—	23%[d]	1200	478	46
3i	CH_2Ph	Me	H	94	40	10	>9940	—
3j	CH_2cPr	Me	H	71	88	7	17	50
3k	Pyrrolidine		H	50	86	51	357	68
3l	Piperidine		H	84	66	9	34	89
3m	Morpholine		H	186	55	196	NT	—
3n	**I**		H	41	74	58	>9940	—
Azetidines								
3o	**II**		H	31	76	NT	>9940	—
3p	**III**		H	12	82	NT	>9940	—
3q	**IV**		H	28	66	NT	>9940	—
Pyrrolidines								
3r	**V**		H	14	73	NT	>9940	—
3s	**VI**		H	31	47	NT	>9940	—
Piperidines								
3t	**VII**		H	508	59	NT	>9940	—
3u	**VIII**		H	115	52	15	>9940	—
3v	**IX**		H	31	66	13	>9940	—
3w	**X**		H	273	71	NT	>9940	—
Aryl substitution								
3x	CH_2Ph	Me	6-OMe	—	<10%[d]	NT	NT	—
3y	**IX**		6-OMe	—	<10%[d]	NT	NT	—
3z	CH_2Ph	Me	6,9-$(OMe)_2$	170	50	NT	>9940	—
3aa	**IX**		6,9-$(OMe)_2$	365	57	NT	NT	—
Sulfones								
4a	Ph	—	H	9	71	6	18	61
4b	2-F–Ph	—	H	7	70	NT	18	66
4c	3-F–Ph	—	H	9	81	NT	33	67
4d	4-F–Ph	—	H	80	47	NT	15	60
Reversed sulfonamides								
5a	H	2-F–Ph	H	—	18%[d]	NT	NT	—
5b	Me	2-F–Ph	H	—	10%[d]	NT	NT	—
5c	H	CH_2(4-F–Ph)	H	—	10%[d]	NT	NT	—
5d	Me	CH_2(4-F–Ph)	H	—	20%[d]	NT	NT	—

[a] See Ref. 12 for complete details of assay conditions.
[b] Values (EC_{50}, E_{max}, K_i) are geometric means of 2–4 experiments. Differences of <2-fold should not be considered significant.
[c] NT denotes not tested.
[d] % activation at 10 μM.

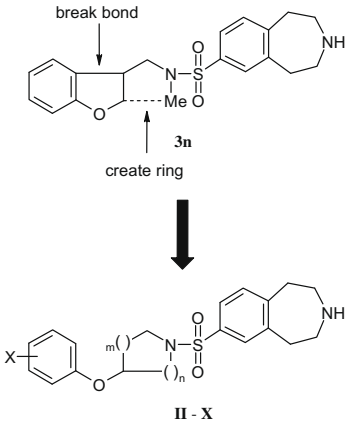


Figure 1. Design of aryloxy cyclic sulfonamides **II-X** derived from dihydrobenzofuran **3n**.

2C9, 3A4 (<50% @ 3 μM) although **3v** did show moderate inhibition of CYP2D6 (69% @ 3 μM). Sulfonamide **3v** had modest ion channel activity as measured by binding to representative sodium (site 2: K_i 2400 nM) and calcium (L-type, diltiazem: K_i 1200 nM) channels. Compound **3v** was also screened for off-target pharmacology against a panel of 110 receptors, enzymes and ion channels (CEREP, Bioprint™) and was found to have binding affinity for the human 5-HT_{1B}, 5-HT_6 and dopamine D3 receptors. Hence, further optimisation of sulfonamides such as **3v** would need to reduce these activities.

In summary, new 7-sulfonamido-3-benzazepines **3** are disclosed as 5-HT_{2C} receptor agonists. Appropriate substitution of the amino group (R^1R^2N–) gave compounds that were potent 5-HT_{2C} agonists with minimal activation of the 5-HT_{2A} and 5-HT_{2B} receptors. Furthermore, representative examples had excellent in vitro ADME properties and good selectivity over ion channel activity. The next phase of this lead optimization program will be to reduce unwanted off-target pharmacology by further modification of structural features whilst maintaining appropriate physicochemical properties for CNS penetration.

Table 2
Measured distribution coefficients (Log$D_{7.4}$), ADME properties and ion channel affinities for examples of **3** and **4**[a]

Compound	Log $D_{7.4}$	HLM Cl_i (μL/min/mg)	MDCK-mdr1 AB/BA ($P_{app} \times 10^{-6}$ cms^{-1})	hERG K_i (nM)
3i	1.0	NT	29/33	NT
3n	1.0	NT	18/34	2990
3o	1.1	NT	NT	3410
3p	1.7	9	12/20	3690
3q	1.6	<8	NT	2090
3r	1.3	36	15/34	3430
3s	1.3	34	NT	5240
3v	2.0	17	15/26	2900
4a	0.5	<8	21/25	>7200

[a] NT denotes not tested.

Acknowledgements

We thank Gordon McMurray, Nick Edmunds (Discovery Biology) and the Primary Pharmacology Group for screening data, and Peter Bungay (PDM) for additional studies.

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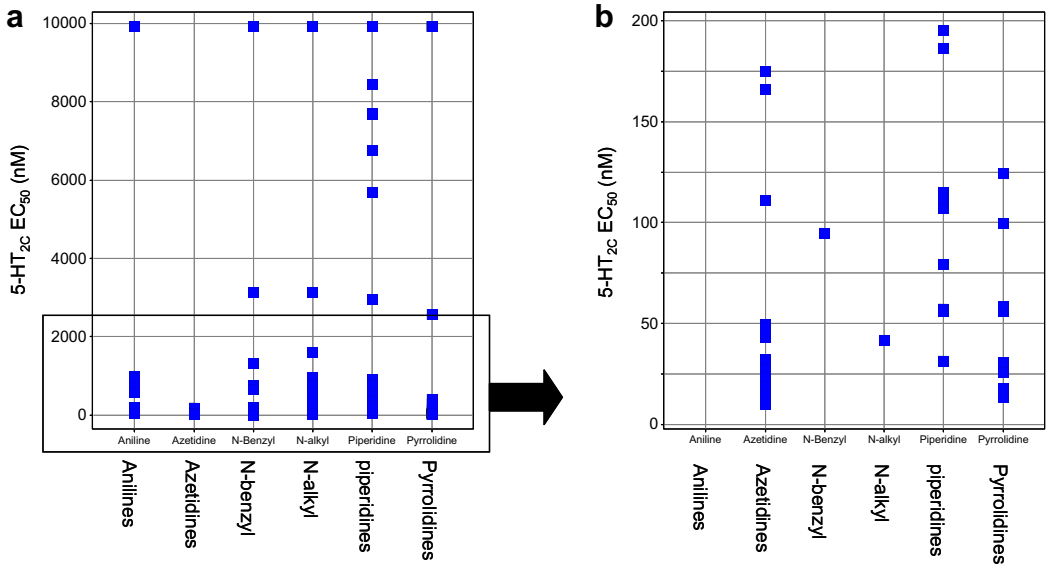

Figure 2. Scatter plots of 5-HT_{2C} activity aligned by amine clusters (R^1R^2N-) for **3**. (a) Data for all compounds prepared. (b) Only 5HT_{2C} agonists ($EC_{50} \leqslant 200$ nM) with no significant 5-HT_{2B} agonist activity (E_{max} < 10% @ 10 μM).

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23. Several compounds from different chemical series have been evaluated to assess the correlation of performance in our cell-based screen with established in vitro and in vivo models of 5-HT_{2A} agonist activity. For example, compound **14** (structure not shown) gave a response in the recombinant assay (EC_{50} 68 nM; E_{max} 82%) but a much weaker response in the canine femoral artery (EC_{50} 3400 nM; E_{max} 51%). Evaluation of **14** in the rat head-twitch model (Ref. 22) at 10 mg/kg (po, $n = 8$) gave no response and **14** had no significant effect on blood pressure or heart rate during a CV assessment in an anaesthetized dog model up to 0.5 mg/kg (iv infusion over 60 min, $n = 4$).