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A series of bisaryl imidazolidin-2-ones has shown to be selective and orally active 5-HT$_{2C}$ receptor antagonists

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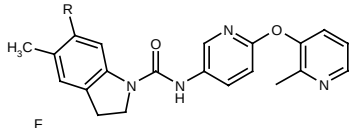
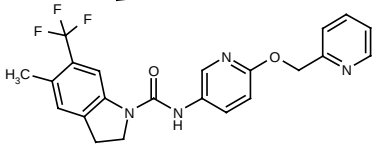
Abstract—Bisaryl cyclic ureas have been identified as high affinity 5-HT$_{2C}$ receptor antagonists with selectivity over 5-HT$_{2A}$ and 5-HT$_{2B}$. Compounds such as **8** and **22** have shown oral activity in a centrally mediated pharmacodynamic model of 5-HT$_{2C}$ function in rodents.

The 5-HT$_2$ superfamily consists of three subtypes, namely, 5HT$_{2A}$, 5HT$_{2B}$ and 5HT$_{2C}$. These have been grouped together because of their close structure homology, pharmacology and secondary messenger systems.[1] The 5-HT$_{2C}$ receptors have long been implicated as potential targets for the treatment of anxiety and depression.[2] Hence, we have been interested in developing selective 5-HT$_{2C}$ ligands for such indications for several years. We have disclosed a number of compounds which are potent 5-HT$_{2C}$ ligands including a series of indolinyl ureas. We developed the first selective 5-HT$_{2C}$ inverse agonist **1** (SB-242084)[3] and subsequently identified **2** (SB-243213)[3] and **3** (SB-247853),[4] which were both progressed to clinical development. Although these compounds had good profiles, they had poor solubility (0.014 mg/mL in 0.1 N HCl for the monohydrochloride salt of **3**).

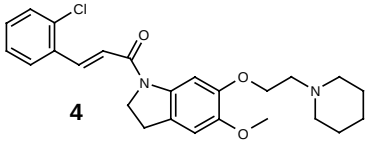


1 R = Cl (SB-242084)
2 R = CF_3 (SB-243213)



3 SB-247853

More recently, we disclosed a series of indolinyl cinnamides[5] such as **4**, developed from a high throughput screening hit. This cinnamide series contained a more strongly basic centre to improve solubility but unfortunately suffered from metabolic issues due to their potential to form glutathione conjugates.



4

We have now derived a third series of highly potent and selective 5-HT$_{2C}$ antagonists such as **8** and **22** by merging SAR from these previous two series. More

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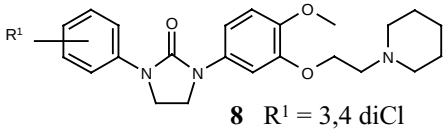
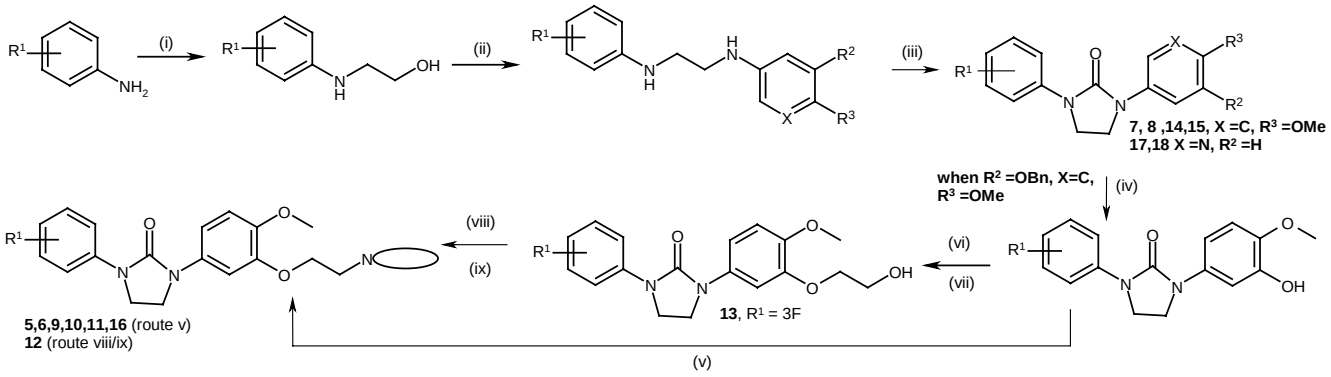
importantly, these cyclic ureas show improved solubility over the indolinyl ureas, greater metabolic stability than the cinnamides and oral activity in a 5-HT_{2C} centrally mediated pharmacodynamic (PD) model.

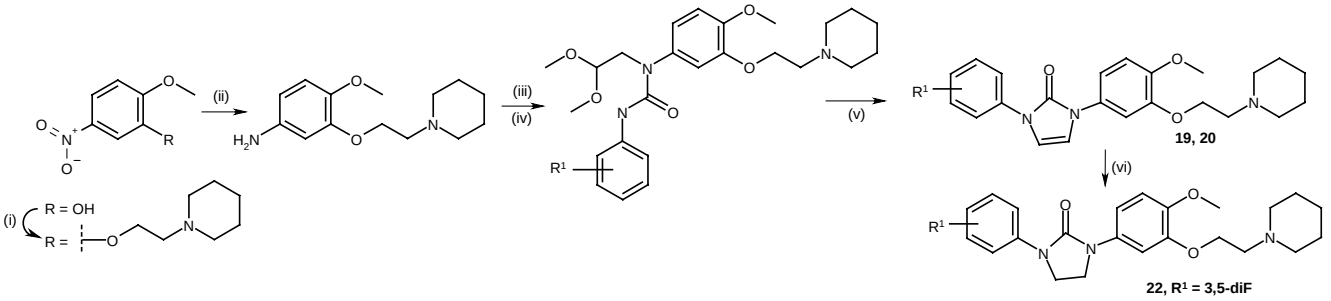


8 R^1 = 3,4 diCl
10 R^1 = 3-F

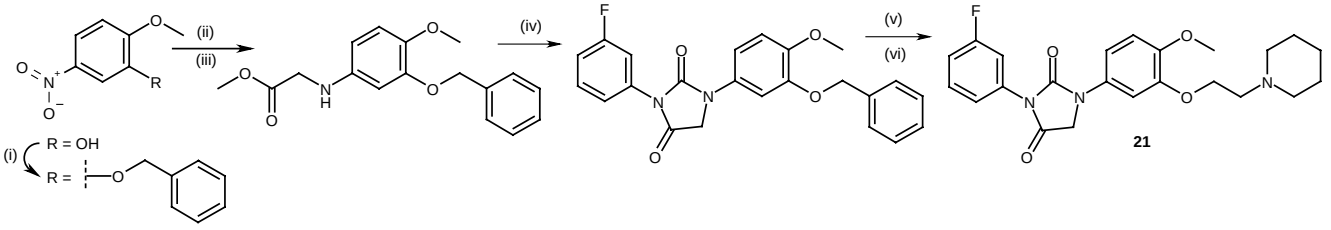
The final compounds were prepared according to Schemes 1–3.[6] Compounds **5**–**18** were obtained by reacting the appropriately substituted aniline with 2-chloroethyl chloroformate followed by treatment with potassium hydroxide to afford the aminoethanol.[7] Mesylation of the alcohol and displacement with the desired aniline gave the diamine. Subsequent cyclisation with phosgene gave the desired imidazolidin-2-one core. When R^2 was *O*-benzyl, unmasking the phenol allowed alkylation to incorporate the amine moiety as the last step (Scheme 1). Compounds **19** and **20** (Scheme 2) were prepared by alkylation of the phenol with 1-(2-chloroethyl)piperdine and subsequent nitro reduction to the aniline. Reductive amination with glyoxal 1,1-dimethyl acetal followed by reaction with the suitably substituted isocyanate afforded the dimethoxy-ethyl urea, which when cyclised gave the 1,3-



Scheme 1. Reagents and conditions: (i)—(a) $ClCO_2CH_2CH_2Cl$, DCM, pyridine, RT, 16 h, (b) KOH, EtOH, 90 °C, 4 h; (ii)—(a) methanesulphonyl chloride, DCM, NEt_3, 0 °C to RT, 0.5 h, (b) aniline, DMF, K_2CO_3, 70 °C, 16 h; (iii) phosgene, THF, NEt_3, RT, 16 h; (iv) methanol, ammonium formate, 10% Pd/C, reflux, 1 h; (v) 2-chloroethylamine–HCl, DME, water, K_2CO_3, NaI, 90 °C, 16 h; (vi) benzyl 2-bromoethyl ether, DMF, K_2CO_3, NaI, 60 °C, 16 h; (vii) ethanol, 10% Pd/C, H_2, atmospheric pressure; (viii) methanesulphonyl chloride, DCM, NEt_3, 0 °C to RT, 1 h, (ix) amine, DMF, K_2CO_3, NaI, 80 °C, 16 h.

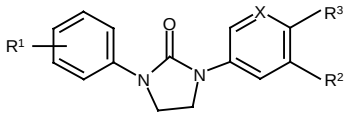


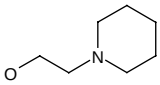
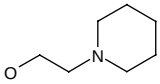
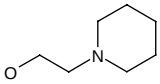
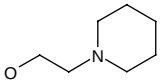
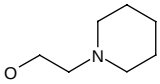
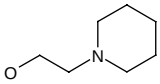
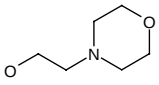
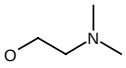
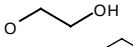
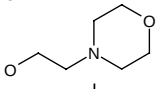
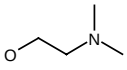
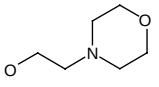
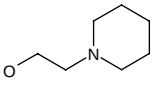
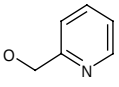
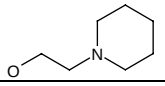
Scheme 2. Reagents and conditions: (i) 1-(2-chloroethyl)piperidine monohydrochloride, DME, aq potassium carbonate solution, RT, 24 h; (ii) 10% Pd/C, ethanol, H_2, atmospheric pressure, 16 h; (iii) dimethoxyacetal aldehyde, ethanol, 10% Pd/C, H_2, atmospheric pressure, 31 h; (iv) aryl isocyanate, DCM, RT, 18 h; (v) toluene, concd HCl, reflux, 3 h; (vi) 10% Pd/C, ethanol, H_2, atmospheric pressure, 16 h.



Scheme 3. Reagents and conditions: (i) benzyl bromide, DME, aq potassium carbonate solution, sodium iodide, 65 °C, 23 h; (ii) iron powder, methanol, satd aq ammonium chloride solution, reflux, 2 h; (iii) ethyl bromoacetate, potassium carbonate, sodium iodide, DMF, 80 °C, 17 h; (iv) 3-fluorophenylisocyanate, toluene, 85 °C, 10 h; (v) 10% Pd/C, H_2, ethanol, DMF, atmospheric pressure, 18 h; (vi) *N*-(2-hydroxyethyl)piperidine, triphenylphosphine, DEAD, THF, RT, 24 h.

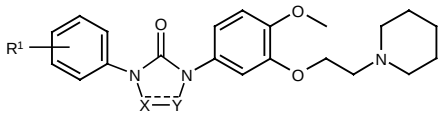
Table 1. The 5-$HT_{2A/2B/2C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B} and in vivo activity[e] of compounds **1**–**4**, 1-[3-(2-substituted)-4-methoxy-phenyl]-3-aryl-imidazolidin-2-ones **5**–**16**, **22** and of 1-(3,4-dichloro-phenyl)-3-(6-substituted-pyridin-3-yl)-imidazolidin-2-ones **17** and **18**



Compound	R^1	R^2	R^3	X	pK_i 5-HT_{2C}[b]	pK_i (selectivity)		% reversal at 2 h[e]
						5-HT_{2A}[c]	$5HT_{2B}$[d]	
1	—	—	—	—	9.0	6.8 (160)	7.0 (100)	ID_{50} 2.0[f]
2	—	—	—	—	9.0	6.8 (160)	7.0 (100)	ID_{50} 0.7
3	—	—	—	—	9.3	6.2 (1300)	7.5 (60)	ID_{50} 1.0
4	—	—	—	—	9.2	6.4 (630)	6.9 (200)	71
5	$3CF_3$, 4Me		OMe	C	8.7	6.4 (200)	7.1 (200)	IA[g]
6	2Cl		OMe	C	7.5	5.4 (130)	<5.1 (>250)	—
7	2,3-diCl		OMe	C	8.0	5.8 (160)	5.9 (130)	IA
8	3,4-diCl		OMe	C	9.1	6.2 (790)	6.5 (400)	75%
9	H		OMe	C	8.9	5.6 (2000)	5.9 (1000)	IA
10	3F		OMe	C	8.8	5.7 (1300)	6.3 (320)	7%
11	3F		OMe	C	7.9	<5.2 (>500)	6.1 (60)	10%
12	3F		OMe	C	8.4	5.6 (630)	5.8 (400)	40%
13	3F		OMe	C	5.9	<5.0 (>8)	5.9	—
14	3,4-diCl		OMe	C	8.5	<5.3 (>1600)	6.5 (100)	7%
15	3,4-diCl		OMe	C	8.9	6.3 (400)	6.3 (400)	IA
16	$3CF_3$, 4Me		OMe	C	8.1	5.5 (400)	6.9 (16)	IA
17	3,4-diCl	H		N	7.6	6.0 (40)	6.8 (6)	—
18	3,4-diCl	H		N	6.4	<5.0 (>25)	<5.2 (>16)	—
22	3,5-diF		OMe	C	9.0	<5.0 (>10,000)	<5.3 (>5000)	40%

[a] All values represent the mean of at least three determinations, with each determination lying within 0.3 log unit of the mean.
[b] Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]mesulergine).[3]
[c] Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]ketanserin).[3]
[d] Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]5-HT).[3]
[e] Percentage reversal at 10 mg/kg po of mCPP (7 mg/kg ip administered 20 min pretest) induced hypolocomotion.
[f] Dose of compound required to reverse mCPP (7 mg/kg ip administered 30 min pretest) induced hypolocomotion by 50%.[3]
[g] IA, inactive.

Table 2. The 5-$HT_{2A/2B/2C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B}, and in vivo activity[e] of [4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-3-aryl-1,3-dihydro-imidazol-2-ones **19** and **20** and 3-(3-fluoro-phenyl)-1-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenyl]-imidazolidine-2,4-dione **21**



Compound	R^1	X⁄⁄⁄⁄Y	pK_i 5-HT_{2C}[b]	pK_i (selectivity)		% reversal at 2 h[e]
				5-HT_{2A}[c]	5-HT_{2B}[d]	
19	3F	CH=CH	8.2	<6.0 (>160)	5.7 (320)	IA
20	3,5-diF	CH=CH	8.1	<5.0 (>1250)	<5.1 (>1000)	—
21	3F	CO–CH_2	7.3	<5.0 (>200)	<5.2(130)	—

[a–e]See corresponding footnotes in Table 1.

dihydro-imidazol-2-ones (**19**, **20**). Hydrogenation of **20** allowed the preparation of **22**. Compound **21** (Scheme 3) was prepared by protection of the phenol, nitro reduction and subsequent aniline alkylation with ethyl bromoacetate. Treatment with 3-fluorophenyl isocyanate and heating yielded the imidazol-2,4-dione core. Removal of the benzyl protecting group and alkylation with 1-(2-chloroethyl)piperidine afforded the final compound.

To investigate whether the SAR from the original urea and cinnamide series could be transferred to the new cyclic urea series, compounds **5** and **6** were prepared. Although **5** maintained good 5-HT_{2C} affinity with very similar selectivity over 5-HT_{2B} compared to **2** and showed good solubility (0.82 mg/mL in 0.1 N HCl for the oxalate salt), it was inactive in the rat hypolocomotion model. In this centrally mediated PD model of 5-HT_{2C} function, the ability of compounds to block the hypolocomotion in rats produced by a standard dose of the moderatively selective 5-HT_{2C} agonist meta chlorophenylpiperazine (mCPP) was measured.[2] In contrast, the 2-Cl analogue **6** showed a significant reduction in 5-HT_{2C} affinity and proved 25-fold less potent than the unsubstituted analogue **9**. This prompted a further investigation of alternative aromatic substitution. Incorporation of an additional chlorine substituent at the 3 position to give **7** gave some improvement in 5-HT_{2C} affinity. However, transposing the unfavourable 2-Cl substituent to the 4 position gave a highly potent and selective compound **8**, which showed significant activity in the rat hypolocomotion model. In addition, the solubility of compound **8** (190 μg/mL in 0.1 N HCl for the hydrochloride salt) was improved over the original urea **3**. With the aim of improving this further, the less lipophilic analogue **10** was targeted. Compound **10** also showed an excellent binding profile, improved solubility (480 μg/mL in 0.1 N HCl for the hydrochloride salt) although much reduced activity in the PD model. Our attention then moved to optimization of the basic amino group. In comparison with the morpholine and dimethyl amino compounds, the piperidine analogues showed the best combination of 5-HT_{2C} affinity with good selectivity over 5-HT_{2A} and 5-HT_{2B}. The morpholine analogues consistently showed reduced 5-HT_{2B} selectivity particularly in compound **16**. No direct correlation between 5-HT_{2C} affinity and in vivo activity in the hypolocomotion model was observed. However, pharmacokinetic profiling in the rat revealed that weakly active compounds **10** and **11** showed high in vivo clearance (>120 mL/min/kg). In contrast, much lower clearance (45 mL/min/kg) was observed for compound **8**. Confirmation that a basic amine substituent was essential for 5-HT_{2C} affinity in this series was seen with compound **13**. Compounds **17** and **18** incorporated additional aspects from the indolinyl ureas series whilst maintaining the 3,4-diCl aromatic substitution pattern. Changing the central aryl core to a pyridine gave disappointing 5-HT_{2C} binding affinities so were not progressed to the hypolocomotion model.

The effects of introducing unsaturation (**19**, **20**) or an additional carbonyl group (**21**) were also studied. Both modifications resulted in lower 5-HT_{2C} affinity though selectivity over 5-HT_{2A} and 5-HT_{2B} was still achievable (Table 2). Interestingly, compound **22** (Table 1) obtained from the double bond reduction of **20** and containing a 3,5 disubstituted phenyl combined high 5-HT_{2C} affinity, exceptional selectivity and activity in the hypolocomotion model. Further modifications will be reported in future publications.

In summary, a series of cyclic urea analogues has been prepared with excellent 5-HT_{2C} affinity and selectivity over 5-HT_{2A} and 5-HT_{2B}. This series has been shown to be selective against a range of other 5-HT and dopaminergic receptor subtypes and antagonist activity at 5-HT_{2C} has been confirmed in a functional assay. Improved solubility over the indolinyl urea **3** has also been achieved along with improved metabolic stability over the indolinyl cinnamide **4**. Compounds **8**, **12** and **22** have also shown significant oral activity in the rat hypolocomotion model.

References and notes

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