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Design and synthesis of piperazinylpyrimidinones as novel selective 5-HT_{2C} agonists

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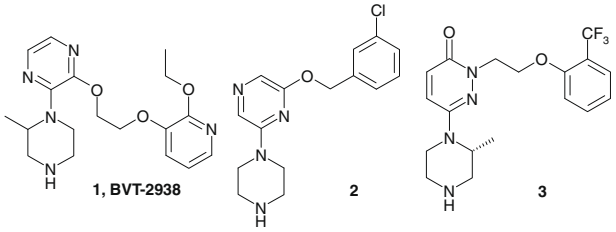
ABSTRACT

This Letter reports the design and synthesis of several novel series of piperazinyl pyrimidinones as 5-HT_{2C} agonists. Several of the compounds presented exhibit good in vitro potency and selectivity over the closely related 5-HT_{2A} and 5-HT_{2B} receptors. Compound **11** was active in in vivo models of stress urinary incontinence.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter involved in a diverse range of physiological functions, mediated by at least 14 distinct 5-HT receptors distributed widely in the central and peripheral nervous systems. The 5-HT_2 receptor subfamily comprises three subtypes, namely 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. These receptors exhibit 46–50% sequence homology and belong to the large family of seven-transmembrane domain G protein-coupled receptors.[1] The 5-HT_{2C} receptor is reported to have a number of potential therapeutic uses including treatment of urinary incontinence, obesity, sexual dysfunction, schizophrenia and depression[2] and while a number of agents are reported to be in clinical development,[3] no selective 5-HT_{2C} agonist is currently approved for any of the proposed indications. Our goal was to identify potent and selective 5-HT_{2C} agonists for potential use in the treatment of urinary incontinence (improving both bladder and urethral function) and sexual dysfunction.

A key challenge was to identify agonists of the 5-HT_{2C} receptor with selectivity over the closely related receptors 5-HT_{2A} and 5-HT_{2B}, as agonism of these receptors is associated with undesirable physiological outcomes. Activation of the 5-HT_{2A} receptor is thought to cause hallucinogenic effects, platelet aggregation and an increase in peripheral vasoconstriction.[4] 5-HT_{2B} agonism is associated with pulmonary hypertension and valvulopathy.[5] Additionally, the 5-HT_{2C} receptor is expressed primarily in the brain, and compounds would therefore have to be able to cross the blood–brain barrier in order to achieve in vivo efficacy.

A number of series of 5-HT_{2C} agonists have been reported in the literature, which have a heterocyclic core substituted by a piperazine and a pendant aromatic ring, for example, the agonists **1**[6] and **2**.[7] Our strategy was to retain the overall architecture of these agonists whilst incorporating polarity into the core, as it was anticipated that this might provide agonists with improved overall profiles.[8]



Earlier work had identified the pyridazinone template, exemplified by compound **3**, which was potent, metabolically stable and free of the mutagenic liability seen with compound **2**.[9] This series did however show efflux in an MDCK-mdr1 cell line, a model which indicates affinity for P-gp efflux transporters and a potential for reduced CNS penetration.[10]

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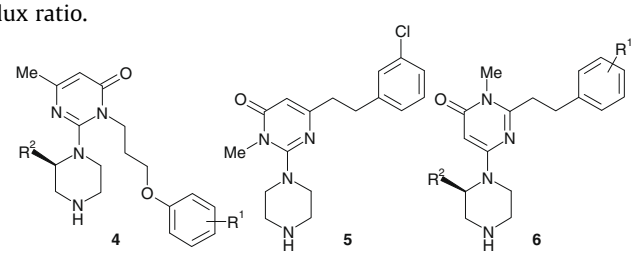
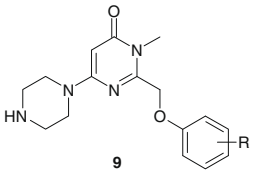
In this Letter we disclose novel pyrimidinone templates **4**–**6**, their activity at the 5-HT_{2C} receptor and their potential to provide improved CNS penetration, as measured by their MDCK-mdr1 efflux ratio.

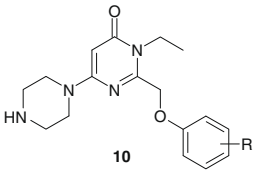


The 5-HT_{2C} agonist activity of target compounds (Tables 1 and 2) was evaluated by measuring the ability to induce a fluorescent based calcium mobilisation signal in a FLIPR assay employing recombinant CHO K1 cells expressing the human 5-HT_{2C} receptor.[11] Agonist activity at the 5-HT_{2A} and 5-HT_{2B} receptors was measured in similar recombinant cell-based systems expressing the human receptors.[11]

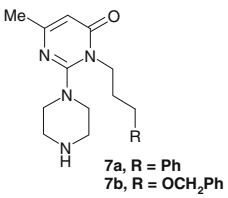
The pyrimidinones **4** were designed as more polar analogues of pyrazines such as **1** and, encouragingly, the simple phenyl analogue **4a** was found to be a 5-HT_{2C} agonist, albeit relatively weak (EC_{50} = 1020 nM) (Table 1). Even more encouraging was the fact that **4a** showed a reduced efflux ratio in the MDCK-mdr1 assay relative to compound **3** (1.6 vs 3.4), indicating lower P-gp affinity. Changing the length of the spacer between the pendant phenyl ring and the pyrimidinone core (**7a**,**b**) abolished the 5-HT_{2C} agonist activity, as did, surprisingly, *meta* or *para* substitution of the phenyl ring with a fluorine (**4c**,**d**). *para*-Chloro substitution was tolerated, while a *meta*-chloro group gave a fourfold increase in potency (**4f**,**g**). A significant increase in potency was given by *ortho*-substitution with either a fluorine (**4b**) or a chlorine (**4e**), giving agonists with sub 100 nM potency. Potency could also be increased sixfold by (2*R*)-methyl substitution of the piperazine ring (**4h**). Disappointingly however, compounds from this series that were tested for 5-HT_{2B} activity showed significant agonism. Given the risks associated with this, despite the encouraging potency and MDCK-mdr1 flux, work on series **4** was discontinued in order to focus on pyrimidinones **5** and **6** as analogues of compound **2**.

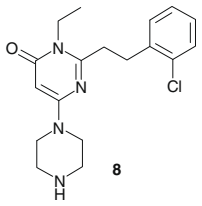
Table 2
SAR of ether linked series





Compound	R	5-HT_{2C}		Log $D_{7.4}$	HLM Cl_i (μL/min/mg)
		EC_{50} (nM)	Emax (%)		
9a	2-CF_3	30	72	1.4	14
9b	2-Cl	73	61	0.8	11
9c	2-Me	228	60	0.8	<7
9d	3-CF_3	487	49	1.3	
9e	3-Cl	493	66	1.0	<7
9f	3-CN	319	63	0.3	<7
9g	4-CF_3	>10,000	—	1.1	8
9h	4-Cl	>10,000	—	0.8	<7
9i	2-Me, 5-F	46	84	1.0	<7
9j	2-Me, 5-Cl	160	84	1.5	<7
9k	2-Cl, 5-F	361	48	1.0	<7
10a	3-CN	112	77	0.4	<7
10b	2-Cl, 5-F	103	46	1.4	<7





The 2-piperazinyl pyrimidinone **5** showed no 5-HT_{2C} agonism at all, in contrast to the corresponding 4-piperazinyl isomer **6b**,

Table 1
SAR of pyrimidinones **4**–**8**

Compound	R^1	R^2	Log $D_{7.4}$	HLM Cl_i (μL/min/mg)	MDCK-mdr1 efflux ratio	5-HT_{2C}		5-HT_{2A} % agonism @ 10 μM	5-HT_{2B} % agonism @ 10 μM
						EC_{50} (nM)	E_{max} (%)		
3	—	—	1.4	15	3.4	47	45	50	<10
4a	H	H	0.7	26	1.6	1020	77	44	57
4b	*o*-F	H	0.45	—	—	77	92	39	35
4c	*m*-F	H	0.8	—	—	>10,000	—	—	—
4d	*p*-F	H	0.7	—	—	>10,000	—	—	—
4e	*o*-Cl	H	1.0	27	—	56	83	58	46
4f	*m*-Cl	H	1.2	—	—	262	86	—	—
4g	*p*-Cl	H	—	—	—	899	91	—	—
4h	H	Me	0.9	16	—	163	84	—	—
5	—	—	1.3	<7	—	>10,000	—	—	—
6a	H	H	0.6	<7	3.4	275	43	13	<5
6b	*m*-Cl	H	1.2	<7	4.0	96	59	57	<5
6c	H	Me	1.0	<7	—	262	50	58	<5
6d	*m*-Cl	Me	1.6	<10	3.7	26	59	76	13
6e	*o*-Cl	Me	1.6	24	3.1	21	46	27	<5
6f	*o*-Me	Me	1.4	18	3.5	26	59	50	<5
6g	*o*-CF_3	Me	1.8	29	—	64	59	45	6
7a	—	—	—	—	—	>10,000	—	—	—
7b	—	—	—	—	—	>10,000	—	—	—
8	—	—	1.9	30	4.3	21	50	16	<5

See Ref. 11 for complete details of assay conditions. Values (EC_{50}, E_{max}) are geometric or arithmetic means of two or more experiments. Differences of <2-fold should not be considered significant.

which had significant agonist activity with an EC_{50} of 96 nM. One potential reason for this marked difference is the inability of the piperazine ring in **5** to sit in the same plane as the pyrimidinone ring due to a steric clash with the N3 methyl group. This is consistent with behaviour we have observed in other related series (unpublished results) where the piperazine and pendant aromatic group have a *meta* relationship on the heterocyclic core. In contrast, with the piperazine and pendant aromatic group having an *ortho* relationship (**4**) the piperazine ring clearly does not need to sit in the same plane as the core as these compounds still have good 5-HT_{2C} activity.

Encouragingly, **6b** had excellent metabolic stability in human liver microsomes (HLM) and was completely devoid of 5-HT_{2B} agonism up to 10 μM. Slightly disappointingly, **6b** had an MDCK-mdr1 efflux ratio of 4.0 indicating some affinity for P-gp. While incorporating a methyl group on the piperazine ring of the simple phenyl analogue caused no increase in potency (**6c** vs **6a**), in the case of **6b** the corresponding methyl piperazine **6d** was approximately fourfold more potent. However this also increased the activity at 5-HT_{2A} (76% at 10 μM) and introduced a low level of 5-HT_{2B} agonism. Moving the chloro group from the *meta* to the *ortho* position (**6e**) eliminated the 5-HT_{2B} activity and reduced the 5-HT_{2A} activity whilst retaining potency at 5-HT_{2C}. Metabolic stability was reduced however, with HLM turnover increasing to 24 μL/min/mg. *ortho*-Substitution with methyl or trifluoromethyl (**6f**,**g**) gave compounds with very similar profiles.

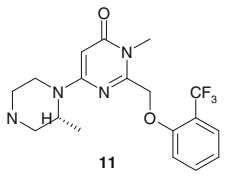
Varying the pyrimidinone N3-substituent from methyl to ethyl was also investigated (**8**). While this gave an excellent pharmacology profile (potent 5-HT_{2C} agonism and excellent selectivity over 5-$HT_{2A/2B}$) it also resulted in increased HLM turnover and MDCK-mdr1 efflux.

The identification of potent and selective leads from the 4-piperazinyl series **6** was encouraging, but some of the more potent compounds from this series were relatively lipophilic and were predicted to have poor metabolic stability. With these issues in mind, we set out to identify a more polar expression of this series, with the aim of identifying compounds with improved metabolic stability. Replacement of the benzylic methylene with oxygen reduces the lipophilicity of the template, and analogues from this ether series were synthetically accessible in a one-pot sequence from a readily available intermediate **23** (Scheme 4).[12]

A small set of analogues was synthesised with a view to probing the effect of substitution of the phenyl ring (Table 2). *ortho*-Substitution with lipophilic groups was found to give good levels of potency. For example, **9a** (*o*-CF_3) met our objectives in terms of potency, although metabolic stability was compromised. *meta* Substitution was tolerated, but *para* substitution with various groups resulted in complete loss of 5-HT_{2C} activity. In an attempt to fine tune the properties, a number of *ortho* and *meta* disubstituted compounds were made. SAR seemed not to be additive and was therefore unpredictable, but a number of 2,5-disubstituted analogues, for example, **9i** and **9j**, retained good potency and stability. All compounds from this series were selective over 5-HT_{2B}, with no agonism seen at 10 μM.

It was subsequently found that substitution of the pyrimidinone nitrogen with ethyl (**10a** and **10b**) resulted in a threefold increase in 5-HT_{2C} potency and, in spite of the increase in lipophilicity compared with the *N*-methyl analogue, there was no apparent reduction in stability in human liver microsomes (HLM).

In an attempt to identify more potent compounds from the series some methylpiperazinyl analogues were prepared and profiled. In the case of compound **11**, this led to a threefold increase in potency, in comparison with the *des*-methyl analogue. This increase in lipophilicity resulted in a reduction in metabolic stability, however, **11** represented the best balance of potency and metabolic stability from the series and was more fully profiled.



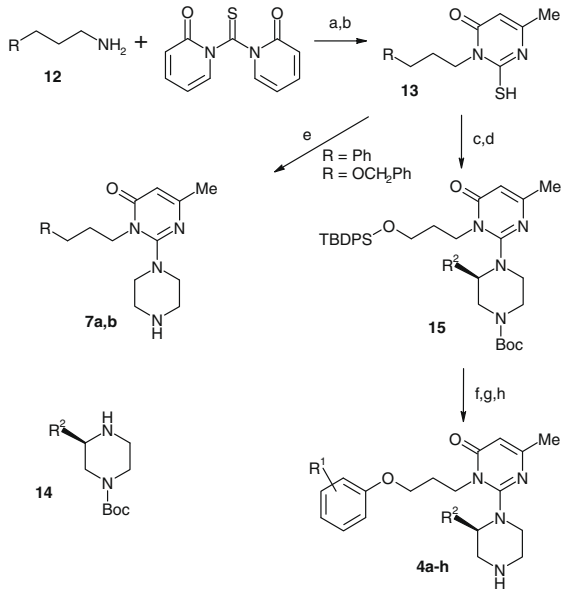
11

5-HT_{2C} EC_{50} (E_{max}) 9 nM (41%)
5-HT_{2A} EC_{50} > 1.5 μM
5-HT_{2B} EC_{50} >10 μM
HLM 27 μL/min/mg
hERG Ki > 13 μM
MDCK-mdr1 AB/BA 13/41 x10^{-6} cms^{-1}

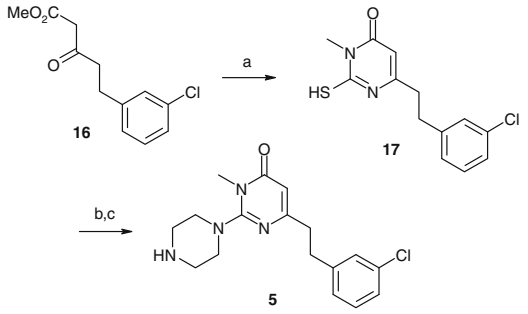
Compound **11** was selective over 5-HT_{2A} and 5-HT_{2B}, was moderately stable in human liver microsomes and had no measurable affinity for the potassium hERG channel. In order to assess membrane permeability, the transit performance across MDCK-mdr1 cells was measured. An efflux ratio of 3.2 suggested some affinity for P-gp transporters and therefore that some impairment of CNS penetration might be expected for this compound. In addition, **11** was screened for off-target pharmacology against a panel of receptors, enzymes and ion channels (CEREP, Bioprint™) and was shown to have a very clean profile, with moderate binding affinities for only the 5-HT_{1B} (210 nM) and dopamine D3 receptors (480 nM). **11** was also found to have weak binding affinity (1–5 μM) for the 5-HT_{4E}, β2 and M3 receptors and the Ca^{2+} (L-Verapamil site) ion channel.

In light of these encouraging data, **11** was screened in a suitable pre-clinical in vivo model of urethral function in the anaesthetised dog.[13] Compound **11** significantly increased urethral pressure in two animals when infused intravenously, evoking a 20–30% increase in peak urethral pressure (considered clinically meaningful) over measured free plasma concentrations of 19–53 nM. In one animal a cerebro spinal fluid (CSF) sample was obtained and the ratio of CSF/free plasma concentrations was found to be 0.34, suggesting that CNS penetration was only slightly impaired.

Pyrimidinones **4** and **7** were synthesised starting from the primary amines **12** (Scheme 1). Treatment with thiocarbonyldi-2(1*H*)-pyridone followed by quenching with aqueous ammonia generated the corresponding primary thioureas.[14] These were then cyclised to the pyrimidinones **13** by treatment with ethyl acetoacetate and base in ethanol at reflux. The 2-mercapto pyrimidinones



Scheme 1. Synthesis of pyrimidinones **4** and **7**. Reagents and conditions: (a) CH_2Cl_2, 0 °C to room temperature then NH_4OH (79–91%); (b) ethyl acetoacetate, DBU, EtOH, reflux (63–69%); (c) $(COCl)_2$, cat. DMF, CH_2Cl_2, room temperature then reflux (80%); (d) piperazine **14**, K_2CO_3, EtCN, 100 °C (92–97%); (e) $(COCl)_2$, cat. DMF, CH_2Cl_2, room temperature then reflux followed by piperazine (58–75%); (f) NH_4F, MeOH (98%); (g) phenol, polymer supported PPh_3, *t*-butyl azodicarboxylate, toluene, CH_3CN; (h) 4 M HCl in dioxane (30–56% over two steps).

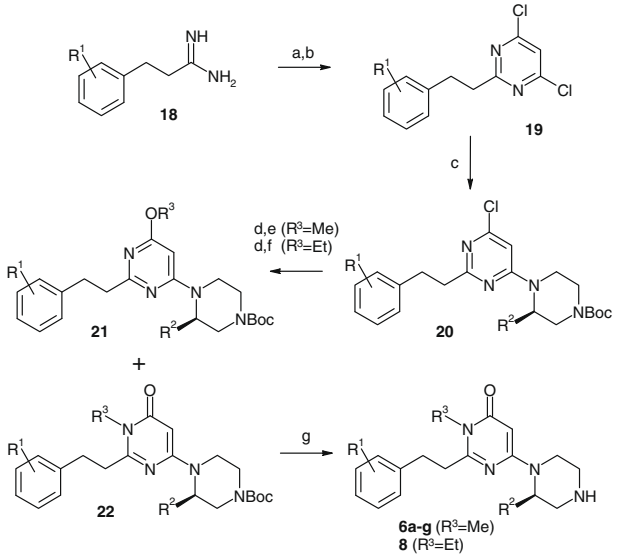


Scheme 2. Synthesis of pyrimidinone **5**. Reagents and conditions: (a) *N*-methylthiourea, DBU, EtOH, reflux; (b) $(COCl)_2$, cat. DMF, CH_2Cl_2, room temperature then reflux; (c) piperazine CH_2Cl_2 (35% over three steps).

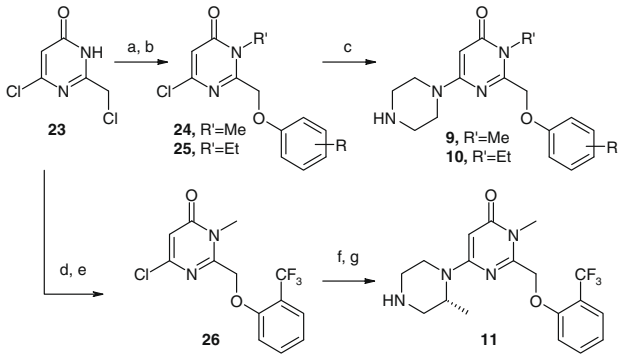
13 were converted to the corresponding chloro compounds by treatment with oxalyl chloride and catalytic DMF; in the case of the pyrimidinones **7** the chloro compounds were not isolated but treated directly with piperazine to generate the desired products, which were isolated by column chromatography. For the pyrimidinones **4**, the intermediate chloro compound was isolated by column chromatography before being reacted with the appropriate Boc-protected piperazine **14** to generate the protected intermediates **15**. Deprotection of the silyl protecting group with ammonium fluoride was followed by a Mitsunobu reaction to introduce the substituted phenyl group. Finally, Boc deprotection with 4 M HCl in dioxane generated the desired products **4**.

Pyrimidinone **5** was synthesised in a three-step sequence starting from the β-dicarbonyl compound **16** (Scheme 2).[15] Cyclisation with *N*-methylthiourea generated the 2-mercapto pyrimidinone **17** which was converted to the corresponding chloro compound with oxalyl chloride and catalytic DMF. Treatment with piperazine then allowed isolation of the pyrimidinone **5** by column chromatography.

The 4-piperazinyl pyrimidinones **6** and **8** were synthesised in a six-step sequence starting from the amidines **18** (Scheme 3).[16] Cyclisation with diethyl malonate under basic conditions gave the corresponding pyrimidine dione in moderate yield, which



Scheme 3. Synthesis of pyrimidinones **6** and **8**. Reagents and conditions: (a) $CH_2(CO_2Et)_2$, NaOEt, EtOH, reflux (27–51%); (b) $POCl_3$, Et_4NCl, EtCN, reflux (97–100%); (c) piperazine **14**, $^iPr_2NEt$, THF, reflux (79–82%); (d) KOTMS, DMSO, 100 °C (27–58%); (e) MeOTs, K_2CO_3, DMF, 80 °C (29–50% of **22** and 11–37% of **21**); (f) EtI, K_2CO_3, acetone, reflux; (g) 4 M HCl in dioxan (80–100%).



Scheme 4. Synthesis of the ether series **9**–**11**. Reagents and conditions: (a) phenol, Cs_2CO_3 (2 equiv), DMF, room temperature; (b) MeI or EtI, then evaporate; (c) piperazine, ethanol, 45 °C (30–50% over three steps); (d) *ortho*-trifluoromethylphenol, Cs_2CO_3 (2 equiv), DMF, room temperature; (e) MeI (45% over two steps); (f) Boc-(*R*)-3-methylpiperazine; NEt_3, DMSO 120 °C (72%); (g) 4 M HCl in dioxane (80%).

was chlorinated with $POCl_3$ to give the dichloropyrimidines **19**. Displacement of one of the chlorines with the appropriate Boc-protected piperazine **14** gave the chloropyrimidines **20**. Hydrolysis to the corresponding pyrimidinone was achieved using K^+TMSO^- in DMSO at 100 °C. Alkylation using methyl tosylate (R=Me) or ethyl iodide (R=Et) gave a roughly 1:2 mixture of the O- and N-alkylation products, **21** and **22**, respectively. Boc deprotection then gave the desired pyrimidinones **6** and **8**.

Compounds from the ether series **9** and **10** could easily be accessed in parallel, using a one-pot, three-step sequence from the known precursor **23** (Scheme 4).[12] Addition of **23** to the appropriate phenol and 2 equiv of caesium carbonate in DMF at room temperature, was followed by addition of iodomethane or iodoethane to give **24** or **25**, respectively. Removal of the solvent by evaporation was followed by addition of piperazine in ethanol and warming to 45 °C. Once the reaction was complete, the solvent was removed and products **9** or **10** were isolated by column chromatography (typical yields 30–50%). Compound **11** was made using a similar route, except that intermediate **26** was isolated and purified before being heated with Boc-protected (*R*)-3-methylpiperazine in DMSO. The Boc-protected intermediate was then deprotected with HCl in dioxane.

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