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## Design and synthesis of pyridazinone-based 5-HT<sub>2C</sub> agonists

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### ABSTRACT

The SAR of a series of pyridazinone derived 5-HT<sub>2C</sub> agonists has been explored and resulted in identification of a compound with excellent levels of 5-HT<sub>2C</sub> functional agonism and selectivity over 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub>. This compound displayed good in vivo efficacy in pre-clinical models of stress urinary incontinence, despite having physiochemical properties commensurate with impaired CNS penetration.

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Serotonin (5-HT) is a neurotransmitter which plays an important role in mood, sleep, emesis, sexuality and appetite.<sup>1</sup> 5-HT receptors mediate the effects of serotonin. There are many sub-types of 5-HT receptors and the processes they mediate are quite diverse. The 5-HT<sub>2C</sub> receptor is found primarily in the brain, and 5-HT<sub>2C</sub> agonists have the potential for treating a number of conditions including obesity, schizophrenia, sexual dysfunction and urinary incontinence.<sup>2</sup> Our aim was to identify potent 5-HT<sub>2C</sub> agonists, with selectivity over 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub>, and good CNS penetration, for potential use in the treatment of urinary incontinence and sexual dysfunction. The selective serotonin and noradrenaline reuptake inhibitor Duloxetine has shown efficacy in reducing episodes of stress urinary incontinence (SUI) in controlled clinical trials.<sup>3</sup> This effect has been hypothesized to be at least partly due to increases in serotonergic and noradrenergic stimulation of neurons within Onuf's nucleus, a key site within the sacral spinal cord which is known to be involved in contraction of the external urethral sphincter.<sup>4</sup> Interestingly pre-clinical studies have indicated a role for 5-HT<sub>2C</sub> receptors in these pathways. In particular 5-HT<sub>2C</sub> receptor agonism appears to increase urethral tone in multiple species, suggesting potential utility in the treatment of SUI.<sup>5</sup>

Similarly pre-clinical studies have highlighted a role for 5-HT<sub>2C</sub> agonism in the control of bladder function<sup>6</sup> and in sexual function in both males and females.<sup>7</sup> Achieving functional selectivity over the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptor sub-types was a key challenge for the project, and particularly important since 5-HT<sub>2A</sub> agonism

is associated with hallucinogenic and cardiovascular effects, while 5-HT<sub>2B</sub> agonism has been linked to potentially fatal heart valvulopathy in man.<sup>8</sup>

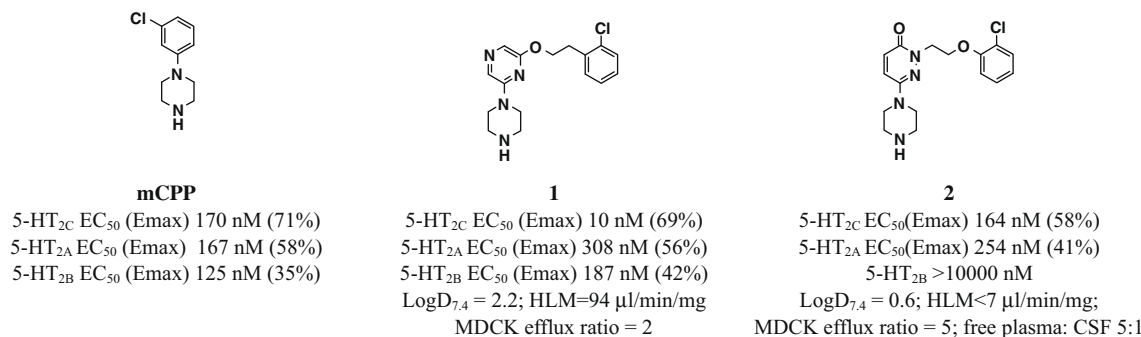
Our SAR studies commenced with the pyrazine lead compound **1**, which originated from in-house work optimizing the known non-selective 5-HT<sub>2C</sub> agonist *meta*-chlorophenyl piperidine (*m*-CPP) (Fig. 1).<sup>9</sup> Compound **1** is a potent and CNS penetrant 5-HT<sub>2C</sub> agonist with moderate selectivity over the 5-HT<sub>2A</sub> sub-type but poor selectivity over 5-HT<sub>2B</sub>. In addition, compound **1** was mutagenic in the in vitro AMES assay.<sup>10</sup>

SAR studies were commenced to look at a range of alternative templates with the aim of identifying a series with an improved in vitro functional selectivity profile over compound **1** and no mutagenic activity. The pyridazinone template as exemplified by compound **2** was identified as meeting the above requirements. Compound **2** is a partial 5-HT<sub>2C</sub> agonist with excellent functional selectivity over the 5-HT<sub>2B</sub> receptor sub-type, and displayed no mutagenic activity in the AMES assay. In addition the compound showed improved metabolic stability due to the reduced lipophilicity, but this also resulted in impaired CNS penetration (free plasma concentration:CSF 5:1). Hence SAR work commenced with the aim of maintaining the selectivity seen with compound **2**, while minimizing the potential dose required to achieve efficacy in man, by enhancing potency and preferably also improving CNS penetration. In addition the SAR studies were focused on determining the optimal lipophilicity range to enable good CNS penetration, while maintaining metabolic stability.

The SAR within the pyridazinone series was limited, with the majority of substitutions resulting in a complete loss of 5-HT<sub>2C</sub>

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**Figure 1.** Structures and activity data for lead compounds *m*-CPP, **1** and **2**.

agonism. Substitution off the pyridazinone ring with aliphatic groups, including formation of a bicyclic ring, resulted in a loss of 5-HT<sub>2C</sub> functional agonism (Table 1). *R*-Me substitution was tolerated off the piperidine ring adjacent to the substituted nitrogen (6, Table 2), but homology to an ethyl group resulted in a reduction of activity (8).

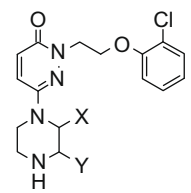
*S*-Me substitution off the ethyloxy side chain adjacent to the pyridazinone nitrogen resulted in good 5-HT<sub>2C</sub> agonism (12, Table 3), while all other substitutions resulted in a loss of in vitro efficacy. *Ortho* substituents on the phenyl ring were found to be preferable for 5-HT<sub>2C</sub> functional agonism over *meta* and *para* substitution, although only a trifluoromethyl group resulted in sub 100 nM potency (compound 21, Table 4). Hence only compounds 6, 12 and 21 displayed 5-HT<sub>2C</sub> functional agonism worthy of further investigation.

The most encouraging compounds (compounds 6, 12 and 21, Table 5), all showed greater potency in the 5-HT<sub>2C</sub> functional assay than the lead compound 2, although they all displayed similar levels of partial intrinsic efficacy. In addition compound 24, which combined the favorable *R*-Me piperazine substituent with the *ortho*-CF<sub>3</sub> phenyl substituent, showed the highest 5-HT<sub>2C</sub> functional potency. The increases in functional potency seen with these compounds was achieved through an increase in binding affinity for the 5-HT<sub>2C</sub> receptor, as demonstrated by the 5-HT<sub>2C</sub> binding data (Table 5).

As stated earlier, achieving selectivity over the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> sub-types was a key goal for the project in order to avoid the associated cardiovascular and hallucinogenic side effects. Compounds 6, 12 and 24 (Table 5) showed low levels of selectivity vs 5-HT<sub>2A</sub>, although benchmarking using an in vitro 5-HT<sub>2A</sub> human platelet aggregation biomarker showed increased selectivity.<sup>14</sup> Compound 12 also displayed some functional agonist efficacy at the 5-HT<sub>2B</sub> receptor which was considered to be a key risk for the compound, while compounds 6, 21 and 24 showed excellent

**Table 2**

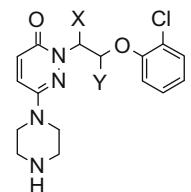
SAR for compounds 6–10, investigating substituents off the piperazine ring



	X	Y	5-HT <sub>2C</sub> EC <sub>50</sub> nM <sup>11</sup> (E <sub>max</sub> %)
<b>6</b>	<i>R</i> -Me	H	25 (51)
<b>7</b>	<i>S</i> -Me	H	>10,000
<b>8</b>	<i>R</i> -Et	H	407 (41)
<b>9</b>	C=O	H	>9980
<b>10</b>	H	<i>S</i> -Me	>10,000

**Table 3**

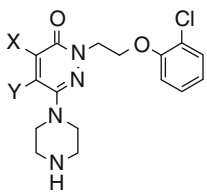
SAR generated via substituents off the alkyl side chain



	X	Y	5-HT <sub>2C</sub> EC <sub>50</sub> nM <sup>11</sup> (E <sub>max</sub> %)
<b>11</b>	<i>R</i> -Me	H	>1920 (55)
<b>12</b>	<i>S</i> -Me	H	25 (77)
<b>13</b>	H	<i>R</i> -Me	858 (53)
<b>14</b>	H	<i>S</i> -Me	360 (87)

**Table 1**

SAR for compounds 3–5, investigating substituents off the pyridazinone ring



	X	Y	5-HT <sub>2C</sub> EC <sub>50</sub> (nM) <sup>11</sup> (E <sub>max</sub> %)
<b>3</b>	Me	H	>10,000
<b>4</b>	–(CH <sub>2</sub> ) <sub>3</sub>	H	>10,000
<b>5</b>	H	Me	510 (31)

selectivity over this sub-type. This selectivity was further confirmed using a human colon in vitro biomarker.<sup>15</sup>

Due to their excellent potency and selectivity, compounds 6 and 24 were progressed. Both compounds displayed similar in vitro ADME data to the lead compound 2 (Table 6) indicating that the compounds should have low hepatic clearance in man, but that impaired CNS penetration would be expected. The project felt that it was unrealistic to look to increase CNS penetration through incorporating further lipophilicity since based on prior SAR this would compromise the excellent selectivity and metabolic stability profile of the compounds. Compound 24 was selected for further profiling since the project felt it had the best balance of potency, selectivity and ADME properties. It was screened for off-target pharmacology against a panel of receptors, enzymes and ion channels (CEREP, Bioprint™) and found to have sub 1 µM binding

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