The design, synthesis and evaluation of tetra-substituted pyridines as potent 5-HT\textsubscript{2c} receptor agonists

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KEYWORDS: Tetra-substituted pyridines, Pyrido[3,4-d]azepine, 5-HT\textsubscript{2c} receptor agonist, CNS penetration.

ABSTRACT: A series of pyrido[3,4-d]azepines that are potent and selective 5-HT\textsubscript{2c} receptor agonists is disclosed. Compound 7 (PF-04781340) is identified as a suitable lead owing to good 5-HT\textsubscript{2c} potency, selectivity over 5-HT\textsubscript{2b} agonism and in vitro ADME properties commensurate with an orally available and CNS penetrant profile. The synthesis of a novel bicyclic tetra-substituted pyridine core template is outlined, including rationale to account for the unexpected formation of aminopyridine 13 resulting from an ammonia cascade cyclisation.

Serotonin (5-hydroxytryptamine, 5-HT 1) acts as a neurotransmitter agonist of at least 14 different receptors classified into seven major families, 5-HT\textsubscript{1-7}. The 5-HT\textsubscript{2} class of GPCR receptors comprises three members 5-HT\textsubscript{2A}, 5-HT\textsubscript{2B} and 5-HT\textsubscript{2C}. Agonism of 5-HT\textsubscript{2C} in the CNS has been recognised to have potential for the treatment of obesity, urinary incontinence, psychiatric disorders and sexual dysfunction.\textsuperscript{1} However, it has been established that selectivity over agonism of structurally related receptors 5-HT\textsubscript{2A} and 5-HT\textsubscript{2B} is required. Poorly selective agonists have been linked to clinical adverse events in humans. These include hallucinations and cardiovascular effects due to 5-HT\textsubscript{2A} agonism\textsuperscript{2,3} and chronic cardiac valvulopathy and pulmonary hypertension caused by 5-HT\textsubscript{2B} agonism.\textsuperscript{4} Notably the anti-obesity treatment Fen-Phen was withdrawn in 1997 for causing irreversible valvulopathy which has been attributed to chronic 5-HT\textsubscript{2B} agonism.

The resulting search for selective 5-HT\textsubscript{2C} agonists identified vabicaserin (2) (SCA-136) as a potential therapy for schizophrenia and lorcanerin (3) (APD-356) which was approved in 2012 as Belviq\textsuperscript{5} for treatment of obesity (Figure 1).\textsuperscript{5} Numerous other preclinical 5-HT\textsubscript{2C} agonists have also been reported.\textsuperscript{6-8}

![Figure 1: Selected 5-HT\textsubscript{2C} agonists.](image)

Previously Pfizer disclosed several 5-HT\textsubscript{2C} agonist series,\textsuperscript{9-14} including a pyrimidine-fused azepine template that led to the discovery of PF-03246799 (4) which offered good levels of \textit{in vitro} and \textit{in vivo} potency.\textsuperscript{14,15} However compound 4, despite offering excellent selectivity over both 5-HT\textsubscript{2A} still showed weak but measurable agonism of 5-HT\textsubscript{2B} at 10 μM in both recombinant cell systems and native human tissue.\textsuperscript{14} It was later discovered that 4-methylamino substitution 5 could offer an enhancement to 5-HT\textsubscript{2C} agonist potency and simultaneously offer superior selectivity over 5-HT\textsubscript{2B}.\textsuperscript{13} However, these structural changes rendered amino-substituted pyrimidine compound 5 a substrate for multidrug resistance P-glycoprotein (P-gp), identified by a large efflux ratio (ER=10) as measured using an \textit{in vitro} transfected MDCK cell line (Figure 2).\textsuperscript{16} A previous correlation analysis of all compounds tested in this MDCK-MDR\textsubscript{1} assay concluded that compounds with efflux ratios of <2.5 are unlikely to be significantly effluxed from the CNS by P-gp whereas compounds with ratios >3.0 are at significant risk of exhibiting appreciable CNS impairment.\textsuperscript{16} In line with this result, preclinical \textit{in vivo} efficacy studies of compound 5 showed prohibitive levels of CNS restriction limiting therapeutic efficacy even at high plasma concentrations.\textsuperscript{15}
To retain the high 5-HT$_{3}$C potency and selectivity of compound 5 but with improved CNS penetration, compounds were sought to provide reduced P-gp efflux. Literature pharmacophore models for P-gp have highlighted the role of aromatic hydrophobic interactions and intramolecular hydrogen bond Acc-Acc distances of ~2.5 Å and ~4.6 Å as P-gp recognition features. As illustrated in Figure 3, compound 5 has Acc-Acc distances of 2.4 Å, 4.1 Å, and 4.6 Å suggesting close similarity to this P-gp pharmacophore pattern of hydrogen bonds. This pointed to N-1 in compound 5 being potentially instrumental to P-gp recognition when combined with a 4-amino substituent. Furthermore SAR from related templates suggested that the N-1 interaction would not be required for 5-HT$_{3}$C activity. To test this hypothesis, several compounds were designed to reduce the propensity for N-1 to interact with P-gp. This led to compounds such as chiral methyl azepine compound 6 that retained good 5-HT$_{3}$C potency, selectivity and reduced P-gp efflux (ER=2.7) that translated to improved in vivo efficacy. It was further proposed that removing N-1 altogether, to give fused aminopyridine azepine 7, would offer good 5-HT$_{3}$C agonist potency without significant P-gp efflux liability.

The controlled syntheses of tri- and tetra-substituted pyridines, despite their favourable characteristics and popularity within medicinal chemistry, present formidable challenges. Preferred synthetic methods typically comprise the selective functionalization of a pre-existing pyridine ring or de novo ring synthesis. However, in this instance, the need for a fused bicyclic tetra-substituted pyridine meant that most known methods were not compatible owing to either not supporting fused ring construction or providing the wrong substitution pattern. As a result, it was necessary to develop suitable chemistry to access amino-pyridine fused azepine template 7. A route was proposed based on limited precedent for biaryl ring synthesis via ammonia cyclisation of an alkyne 8 to give isoquinolone 9 (Scheme 1).

**Scheme 1**

Reagents and conditions: (a) TfO, NaOrBu, CH$_2$Cl$_2$, 23 °C, 0.5 h, then Tf$_2$O, 23 °C, 2 h; (b) BnCCH, DIPEA, CuI, Pd(PPh$_3$)$_2$Cl$_2$, DMF, 23 °C, 2 h; (c) NH$_3$, MeOH, 80 °C, 15 h.

Carboxybenzyl protected azepine β-ketoester 10 was converted to corresponding vinyl triflate 11 in 81% yield by treatment with triflic anhydride under basic conditions (Scheme 1). Sonogashira coupling with benzylacetylene then provided the desired yne-ene-ester 12 in preparation for the key cascade cyclisation to the corresponding pyridinone. Treatment of 12 with excess ammonia in methanol at 80 °C led to conversion of starting material to a single product. Rather than being the anticipated pyridinone, the product was instead determined to be amino-pyridine 13.

This unexpected result was repeated to provide gram quantities of aminopyridine 13 and a sample was crystallized from CD$_2$OD, enabling an X-ray structure to be obtained to further confirm structure assignment (CCDC 1024393 and supporting information).

In order to discount a metal-mediated reaction, the ammonia cyclisation was also carried out using yne-ene-ester 12 that had been pre-treated overnight with various metal scavenger resins (QPTU, QMTU, QSMP; 1g resin per 0.25mmol of 12). However, these pre-treatments did not alter yield or product distribution of the cyclisation. To investigate the mechanism of the cyclisation cascade and further establish the general applicability of this reaction, several related alkyne systems were tested under the same reaction conditions (Table 1).

**Table 1. Ammonia-mediated cyclisations**

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Reactant</th>
<th>Crude product ratio$^a$</th>
<th>Isolated yield (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12, 14</td>
<td>R$_1$</td>
<td>80°C, 15 h</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>NH$_3$</td>
<td>13, 16</td>
<td>81%</td>
</tr>
</tbody>
</table>

$^a$Reagents and conditions: (a) TfO, NaOrBu, CH$_2$Cl$_2$, 23 °C, 0.5 h, then Tf$_2$O, 23 °C, 2 h; (b) BnCCH, DIPEA, CuI, Pd(PPh$_3$)$_2$Cl$_2$, DMF, 23 °C, 2 h; (c) NH$_3$, MeOH, 80 °C, 15 h.
Interestingly if R₁=Bn was replaced by R₁=Ph 14a or R₁=°Bu 14b then the reaction did not proceed, instead returning mostly unreacted starting material. However, when the cyclisation reactant contained a benzylic R₁, and aliphatic R₂ and R₃ (12, 14c-e), then cyclisation proceeded to consistently give the corresponding aminopyridines 13, 16c-e in good yields. To rationalise these results it is proposed that systems where R₁=Bn 14ii undergo rapid rearrangement to allenes on treatment with ammonia, driven by extended conjugative stabilization of the allene with the Bn aromatic ring (Scheme 2). The allene system likely reacts with excess ammonia to form primary amide 18, either directly or via transient cyclisation of the ester carbonyl to form an activated electrophilic oxonium. Amide 18 then cyclizes onto the allene via a 6-exo-dig ring closure preferentially through oxygen due to superior orbital overlap versus the nitrogen with the exo-allene π⁺ orbital to form a reactive hemi-aminal. An ammonia mediated ring opening to form keto-amidine 19 is then followed by a 6-exo-trig closure to provide the product aminopyridine 16ii. Further support for this mechanism comes from the reaction of preformed primary amide 17e with ammonia to successfully provide aminopyridine 16e, suggesting amide 17e to be an intermediate on the reaction cascade. In contrast, aromatic alkyne-ester 14f, under identical reaction conditions, provided pyridinone 15f exclusively, with no evidence for formation of the aminopyridine 16f. However, if pre-formed primary amide 17f was exposed to the reaction conditions the anticipated pyridinone product did not form, resulting in a mixture favouring aminopyridine 16f. This suggests that an alternative mechanistic pathway predominates for substrate 14f (Scheme 2).

Scheme 2

It is postulated that in this case the ammonia undergoes nucleophilic conjugate addition to the alkyne, as opposed to facilitating allene formation, followed by 6-exo-trig ring closure to directly give pyridinone 15f. However, if primary amide 17f is pre-formed this would necessitate 6-endo-dig closure to give pyridinone 15f, for which orbital overlap is suboptimal, rationalising the observed mixture of pyridinone 15f and aminopyridine 16f products. Furthermore, when pyridinone 15f was treated with ammonia under the same reaction conditions no reaction occurred, ruling out the formation of 16f via 15f.

Aminopyridine 13 proved to be a versatile intermediate (Scheme 3). Reductive amination with aldehydes yielded mono-alkylated products 21a-f in moderate to good yields. Also, alkylation using iodomethane provided dimethylated compound 21g. Finally, the application of Sandmeyer conditions enabled conversion of aminopyridine 13 to chloropyridine 20h. The chlorine was then reduced to give trisubstituted pyridine 21h (Scheme 3).

Compounds 7 and 21a-h were investigated for their ability to inhibit the binding of a Cy3B™ conjugated analogue of serotonin to human 5-HT₁c receptor utilizing fluorescence polarisation technology and cellular membrane preparations generated from recombinant Swiss 3T3 cells (Table 2, Kᵢ values).
Table 2. 5-HT2C activity, physicochemistry and in vitro PK data for compounds 7 & 21a-h

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>R</th>
<th>logD</th>
<th>5-HT2c EC50 (nM)a</th>
<th>5-HT2c Emax</th>
<th>Kd (nM)a</th>
<th>5-HT1b EC50 (nM)b</th>
<th>5-HT1b Emax</th>
<th>Kd (nM)b</th>
<th>HLM Clint (mL/min mg⁻¹)</th>
<th>RRCK AB Papp (cm/s)</th>
<th>MDR1 ER (BA/AB)</th>
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<tr>
<td>7</td>
<td>NHMe</td>
<td>0.4</td>
<td>9</td>
<td>99%</td>
<td>3</td>
<td>1484</td>
<td>69%</td>
<td>-</td>
<td>19</td>
<td>8</td>
<td>2.5</td>
</tr>
<tr>
<td>21a</td>
<td>NHEt</td>
<td>0.6</td>
<td>11</td>
<td>79%</td>
<td>18</td>
<td>28%</td>
<td>7</td>
<td>1.8</td>
<td>13</td>
<td>7</td>
<td>2.3</td>
</tr>
<tr>
<td>21b</td>
<td>NHCH2Pr</td>
<td>1.7</td>
<td>36</td>
<td>95%</td>
<td>12</td>
<td>nt</td>
<td>nt</td>
<td>nt</td>
<td>nt</td>
<td>nt</td>
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<tr>
<td>21c</td>
<td>NHCH2cPr</td>
<td>1.2</td>
<td>21</td>
<td>100%</td>
<td>0.5</td>
<td>22</td>
<td>53%</td>
<td>-</td>
<td>27</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>21d</td>
<td>NHPr</td>
<td>1.0</td>
<td>nt</td>
<td>nt</td>
<td>4</td>
<td>27</td>
<td>38%</td>
<td>-</td>
<td>11</td>
<td>4</td>
<td>1.5</td>
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<tr>
<td>21e</td>
<td>NHPr</td>
<td>1.0</td>
<td>nt</td>
<td>nt</td>
<td>13</td>
<td>33</td>
<td>32%</td>
<td>-</td>
<td>nt</td>
<td>nt</td>
<td>nt</td>
</tr>
<tr>
<td>21f</td>
<td>NHBn</td>
<td>1.7</td>
<td>158</td>
<td>37%</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>121</td>
<td>35</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>21g</td>
<td>NMe2</td>
<td>0.6</td>
<td>nt</td>
<td>nt</td>
<td>12</td>
<td>30</td>
<td>38%</td>
<td>-</td>
<td>43</td>
<td>8</td>
<td>2.1</td>
</tr>
<tr>
<td>21h</td>
<td>H</td>
<td>0.5</td>
<td>nt</td>
<td>nt</td>
<td>35</td>
<td>27</td>
<td>53%</td>
<td>-</td>
<td>&lt;8</td>
<td>18</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Values are geometric means of up to five experiments. Differences of <2-fold should not be considered significant; % activation by maximum asymptote at 10 μM relative to 5-HT; % activation by maximum asymptote at 30 μM relative to 5-HT; nt denotes not tested.

Scheme 3

Reagents and conditions: (a) aldehyde or ketone, DCE, AcOH, 23 °C, 30 min, then PS-BH-CN, 55 °C, 18-40 h; (b) Pd/C, H2, EtOH, 45 psi, 23 °C, 3-24 h; (c) MeI, K2CO3, DMF, 80 °C, 22 h; (d) NaN3, HCl, H2O, MeCN, 23 °C, 1 h; (e) Pd/C, HCOONa, EtOH, 75 °C, 2 h.

The 5-HT2c and 5-HT1b functional agonist activities of selected compounds were evaluated relative to 5-HT (1) by measuring ability to induce G-protein activation via recruitment of GTPγS and mobilization of intracellular calcium for 5-HT2c and 5-HT1b respectively (Table 2, EC50 and Emax). Previous studies within Pfizer have shown compound K at the 5-HT2c receptor to be the most predictive indicator of free brain exposure required to elicit 5-HT2c related pharmacological effects in vivo (see SI for cell culture and assay protocols).

Compounds 7 and 21a-h exhibited excellent 5-HT2c binding potency and agonist efficacy (Table 2). Varying the 2-amino substituent sampled a range of molecular weight and lipophilicity. However, despite larger and more lipophilic substituents being generally well tolerated they appeared less ligand and lipophilic efficient, providing no appreciable improvements in 5-HT2c potency. Furthermore, although this series generally showed similar levels of 5-HT1b potency (EC50), the compounds were either weak partial agonists at 5-HT1b characterized by low Emax values, or showed antagonism (compound 21f). Overall, compounds also tended to exhibit good metabolic stability in human liver microsomes (HLM) and moderate to good passive permeability in RRCK cells.

Methyamino-substituted pyridine compound 7 looked the most promising on balance of physicochemistry, potency, selectivity and metabolic stability. In accordance with the original design hypothesis, compound 7 also exhibited a low efflux ratio in the MDCK-MDR1 P-gp assay (P-gp ER=2.8), a pronounced improvement over the equivalent pyrimidine compound 5 (P-gp ER=10). This level of P-gp efflux (ER=2.8) correlates well with other examples from the broader azepine series such as pyrimidine compound 6 (ER=2.7) that previously achieved good CNS exposure and efficacy in preclinical in vivo studies.

In summary, the rational design and synthesis of a series of pyridine-fused azepines with potent 5-HT2c agonist activity and low P-gp efflux ratios has been described to deliver lead compound 7 (PF-04781340). Chemistry was developed and rationalized to access this template, including an ammonia-mediated cascade synthesis of amipyrindine 13. These methods have also been extended to the synthesis of poly-substituted and fused bicyclic amipyrindines, illustrating potential for broader application.

ASSOCIATED CONTENT

Supporting Information Available
Experimental procedures and ‘H NMR, 13C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.
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ACKNOWLEDGMENT

We thank the Primary Pharmacology Group for screening
data, Jiamin Sun for spectra, Dr J. E. Davies for X-ray crys-
tallography and Asser Bassyouni for 5-HT_{1A} selectivity data.
We would also like to thank the EPSRC (SVL, grant n°
EP/K009949/1 and n° EP/K039520/1) for financial support.

ABBREVIATIONS

CCDC, Cambridge Crystallographic Data Centre; CNS, cen-
tral nervous system; HLM, human liver microsomes; MDCK,
Madin-Darby canine kidney; MDR1, multidrug resistance
gene; P-gp, P-glycoprotein; RRCK, Ralph Russ canine kidney
cell line; SM, starting material; Z, carboxybenzyl.

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