The design, synthesis and evaluation of tetra-substituted pyridines as potent 5-HT$_{2C}$ receptor agonists

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ABSTRACT: A series of pyrido[3,4-*d*]azepines that are potent and selective 5-HT$_{2C}$ receptor agonists is disclosed. Compound **7** (PF-04781340) is identified as a suitable lead owing to good 5-HT$_{2C}$ potency, selectivity over 5-HT2$_B$ 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$_{1-7}$. The 5-HT$_2$ class of GPCR receptors comprises three members 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$. Agonism of 5-HT$_{2C}$ in the CNS has been recognised to have potential for the treatment of obesity, urinary incontinence, psychiatric disorders and sexual dysfunction.[1] However, it has been established that selectivity over agonism of structurally related receptors 5-HT$_{2A}$ and 5-HT$_{2B}$ is required. Poorly selective agonists have been linked to clinical adverse events in humans. These include hallucinations and cardiovascular effects due to 5-HT$_{2A}$ agonism[2-3] and chronic cardiac valvulopathy and pulmonary hypertension caused by 5-HT$_{2B}$ agonism.[4] Notably the anti-obesity treatment Fen-Phen was withdrawn in 1997 for causing irreversible valvulopathy which has been attributed to chronic 5-HT$_{2B}$ agonism.

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

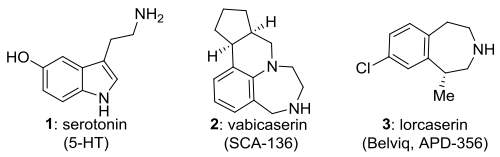


Figure 1. Selected 5-HT$_{2C}$ agonists.

Previously Pfizer disclosed several 5-HT$_{2C}$ agonist series,[9-14] including a pyrimidine-fused azepine template that led to the discovery of PF-03246799 (**4**) which offered good levels of *in vitro* and *in vivo* potency.[14-15] However compound **4**, despite offering excellent selectivity over both 5-HT$_{2A}$ still showed weak but measurable agonism of 5-HT$_{2B}$ at 10 μM in both recombinant cell systems and native human tissue.[14] It was later discovered that 4-methylamino substitution **5** could offer an enhancement to 5-HT$_{2C}$ agonist potency and simultaneously offer superior selectivity over 5-HT$_{2B}$.[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 *in vitro* transfected MDCK cell line (Figure 2).[16] A previous correlation analysis of all compounds tested in this MDCK-MDR1 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.[16] In line with this result, preclinical *in vivo* efficacy studies of compound **5** showed prohibitive levels of CNS restriction limiting therapeutic efficacy even at high plasma concentrations.[16]

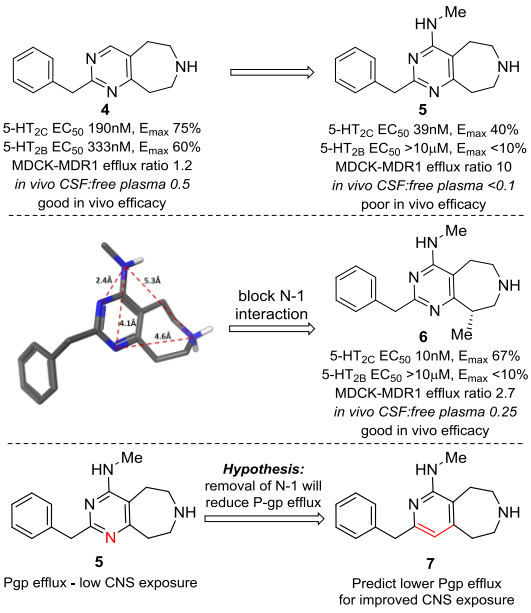


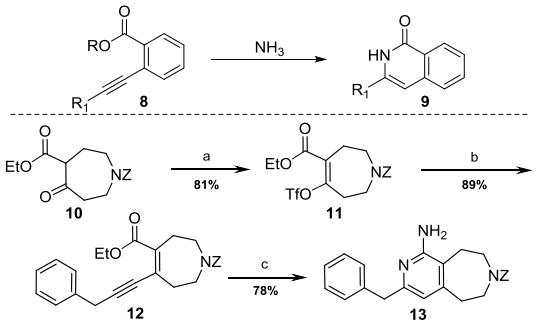
Figure 2. P-gp efflux and CNS exposure.

To retain the high 5-HT_{2C} 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.[17] 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.[18-19]

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_{2C} 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_{2C} potency, selectivity and reduced P-gp efflux (ER=2.7) that translated to improved *in vivo* efficacy.[13, 15] It was further proposed that removing N-1 altogether, to give fused aminopyridine azepine **7**, would offer good 5-HT_{2C} 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.[20] 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).[21-22]

Scheme 1



[a]Reagents and conditions: (a) Tf_2O, NaO*t*Bu, CH_2Cl_2, 23 °C, 0.5 h, then Tf_2O, 23 °C, 2 h; (b) BnCCH, DIPEA, CuI, $Pd(PPh_3)_2Cl_2$, DMF, 23 °C, 2 h; (c) NH_3, MeOH, 80 °C, 15 h.

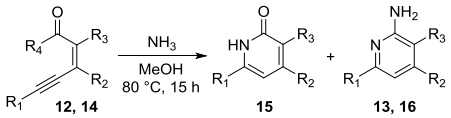
Carboxybenzyl protected azepine β-ketoester **10** was converted to corresponding vinyl triflate **11** in 81% yield by treatment with triflic anhydride under basic conditions (Scheme 1). Sonogashira coupling with benzylacetylene then provided the desired yne-ene-ester **12** in preparation for the key 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 aminopyridine **13**.

This unexpected result was repeated to provide gram quantities of aminopyridine **13** and a sample was crystallized from CD_3OD, enabling an X-ray structure to be obtained to further confirm structure assignment (CCDC 1024393 and supporting information).

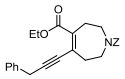
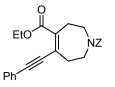
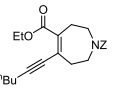
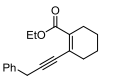
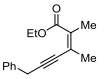
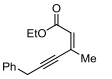
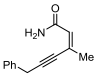
In order to discount a metal-mediated reaction,[23] the ammonia cyclisation was also carried out using yne-ene-ester **12** that had been pre-treated overnight with various metal scavenger resins (QPTU, QMTU, QSMP; 1g resin per 0.25mmol of **12**). However, these pre-treatments did not alter yield or 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



Cmpd	Reactant	Crude product ratio[a]	Isolated yield (16)

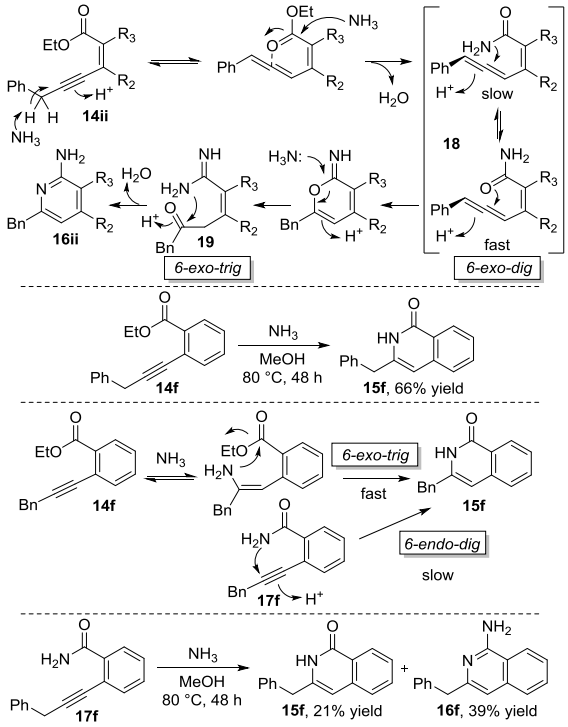
		(15)	(16)	
12		0	100	78%
14a		trace <5%	0	86% Rec. SM
14b		0	trace <5%	90% Rec. SM
14c		0	100	91%
14d		0	100	40%
14e		0	100	64%
17e		0	100	71%

[a]Product ratio determined by crude ^{1}H NMR integration. Rec. SM dentoes yield of recovered starting material

Interestingly if R_1=Bn was replaced by R_1=Ph **14a** or R_1=^{n}Bu **14b** then the reaction did not proceed, instead returning mostly unreacted starting material. However, when the cyclisation reactant contained a benzylic R_1, and aliphatic R_2 and R_3 (**12, 14c-e**), then cyclisation proceeded to consistently give the corresponding aminopyridines **13**, **16c-e** in good yields. To rationalize these results it is proposed that systems where R_1=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).

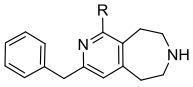
Scheme 2



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-HT_{2C} receptor utilizing fluorescence polarisation technology and cellular membrane preparations generated from recombinant Swiss 3T3 cells (Table 2, K_i values).[24]

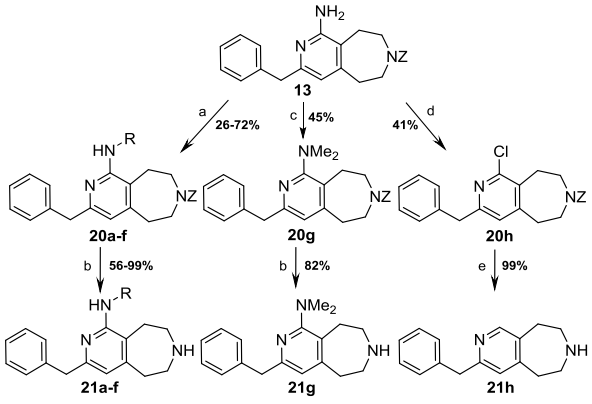
Table 2. 5-HT2C activity, physicochemistry and in vitro PK data for compounds 7 & 21a-h



Cmpd	R	logD	5-HT$_{2C}$			5-HT$_{2B}$			HLM Cl_{int} (mL min^{-1} mg^{-1})	RRCK ($\times10^{-6}$ cm/s)	MDCK-MDR1 AB P_{app} ($\times10^{-6}$ cm/s)	MDCK-MDR1 ER (BA/AB)
			EC_{50} (nM)[a]	E_{max}[a,b]	K_i (nM)[a]	EC_{50} (nM)[a]	E_{max}[a,c]	K_b (nM)[a]				
7	NHMe	0.4	9	99%	3	1484	69%	-	19	8	2.5	2.8
21a	NHEt	0.6	11	79%	3	18	28%	-	13	7	1.8	2.3
21b	NHCH$_2$*i*Pr	1.7	36	95%	12	nt	nt	-	nt	nt	nt	nt
21c	NHCH$_2$cPr	1.2	21	100%	0.5	22	51%	-	27	2	0.8	6.1
21d	NH*n*Pr	1.0	nt	nt	4	27	38%	-	11	4	1.5	3.5
21e	NH*i*Pr	1.0	nt	nt	13	33	32%	-	nt	12	nt	nt
21f	NHBn	1.7	158	37%	22	-	-	121	35	2	0.6	3.6
21g	NMe_2	0.6	nt	nt	12	30	38%	-	43	8	2.1	2.2
21h	H	0.5	nt	nt	35	27	53%	-	<8	18	3.9	1.5

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

Scheme 3[a]



[a]Reagents and conditions: (a) aldehyde or ketone, DCE, AcOH, 23 °C, 30 min, then PS-BH_3CN, 55 °C, 18-40 h; (b) Pd/C, H_2, EtOH, 45 psi, 23 °C, 3-24 h; (c) MeI, K_2CO_3, DMF, 80 °C, 22 h; (d) $NaNO_2$, HCl, H_2O, MeCN, 23 °C, 1 h; (e) Pd/C, $HCOONH_4$, EtOH, 75 °C, 2 h.

The 5-HT$_{2C}$ and 5-HT$_{2B}$ 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-HT2$_C$ and 5-HT2$_B$ respectively (Table 2, EC_{50} and E_{max}).[13, 24] Previous studies within Pfizer have shown compound K_i at the 5-HT$_{2C}$ receptor to be the most predictive indicator of free brain exposure required to elicit 5-HT$_{2C}$ related pharmacological effects *in vivo*[25] (see SI for cell culture and assay protocols).

Compounds **7** and **21a-h** exhibited excellent 5-HT$_{2C}$ 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-HT$_{2C}$ potency. Furthermore, although this series generally showed similar levels of 5-HT$_{2B}$ potency (EC_{50}), the compounds were either weak partial agonists at 5-HT$_{2B}$, characterized by low E_{max} 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.[13]

In summary, the rational design and synthesis of a series of pyridine-fused azepines with potent 5-HT$_{2C}$ 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 aminopyridine **13**. These methods have also been extended to the synthesis of poly-substituted and fused bicyclic aminopyridines, illustrating potential for broader application.

ASSOCIATED CONTENT

Supporting Information Available

Experimental procedures and ^{1}H NMR, ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

CCDC, Cambridge Crystallographic Data Centre; CNS, central 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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