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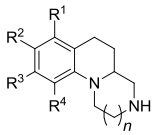

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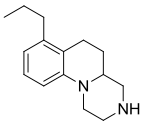

5-HT_{2C}R EC_{50} = 0.2 nM
active *in vivo* (1 mg/kg, PO)

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Tetrahydroquinoline-based tricyclic amines as potent and selective agonists of the 5-HT$_{2C}$ receptor

Thomas O. Schrader [a,*], Michelle Kasem [a], Albert Ren [a], Konrad Feichtinger [a], Bilal Al Doori [a], Jing Wei [b], Chunrui Wu [b], Huong Dang [a], Minh Le [a], Joel Gatlin [a], Kelli Chase [a], Jenny Dong [a], Kevin T. Whelan [a], Carleton Sage [a], Andrew J. Grottick [a], and Graeme Semple [a]

[a]*Department of Medicinal Chemistry, Arena Pharmaceuticals, 6154 Nancy Ridge Drive, San Diego, CA, 92121, USA*
[b]*WuXi AppTec (Wuhan) Co Ltd., 666 Gaoxin Road, East Lake High-tech Development Zone, Wuhan 430075, China*

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ABSTRACT

The syntheses, structure-activity relationships (SARs), and biological activities of tetrahydroquinoline-based tricyclic amines as 5-HT$_{2C}$ receptor agonists are reported. An early lead containing a highly unique 6,6,7-ring system was optimized for both *in vitro* potency and selectivity at the related 5-HT$_{2B}$ receptor. Orally bioactive, potent, and selective 6,6,6-tricyclic 5-HT$_{2C}$ agonists were identified.

By the late 1990s, significant evidence had emerged concerning the role of the 5-HT$_{2C}$ receptor (5-HT$_{2C}$R) in mediating satiety and food intake.[1] The advent of 5-HT receptor subtype-selective ligands was crucial to this understanding.[2] In particular, rodent studies using selective 5-HT$_{2C}$R antagonists revealed the anorectic effects of the previously FDA-approved weight loss agents fenfluramine (Pondimin, figure 1) and its *S*-isomer dexfenfluramine (Redux) were mediated, in part, by potent agonism of the 5-HT$_{2C}$R by the drugs' primary metabolites norfenfluramine and nordexfenfluramine respectively.[3] These data were consistent with a previous human clinical study which demonstrated that the anorectic effect of dexfenfluramine was attenuated with the nonselective 5-HT$_{2C}$R antagonist ritanserin.[4] Other antagonist experiments performed in rodents with the nonselective 5-HT$_{2C}$ agonist *meta*-chlorophenylpiperazine (mCPP), another clinically validated anorectic, confirmed these results.[5] Additional studies involving variably selective 5-HT$_{2C}$ ligands,[5] as well as data obtained from 5-HT$_{2C}$ receptor knockout mice,[6] suggested that agonism of the 5-HT$_{2C}$ receptor was a viable mechanism for the treatment of obesity.

Complicating matters was the 1997 withdrawal[7] of both fenfluramine and dexfenfluramine due to drug related cardiac fibroses and related valvulopathies,[8] side-effects later associated with agonism of the related 5-HT$_{2B}$ receptor (5-HT$_{2B}$R) in cardiac tissue.[9] Other adverse events including hallucinations[10] and cardiovascular effects,[11] are associated with agonism of another closely related target, the 5-HT$_{2A}$ receptor (5-HT$_{2A}$R). These findings led to an industry-wide effort to discover and develop selective 5-HT$_{2C}$R agonists which did not affect 5-HT$_{2B}$R and 5-HT$_{2A}$R function.[12] The result was the 2012 FDA approval of the 5-HT$_{2C}$R selective agonist lorcaserin (**1**, Belviq®)[13] for weight management in obese (BMI >30) or overweight (BMI 27-30) patients with a weight-related medical condition.[14] In addition to obesity, selective 5-HT$_{2C}$R agonists have therapeutic potential for a wide variety of neuropsychiatric disorders.[15] To this end, we report the identification of a series of tetrahydroquinoline-based tricyclic amines as potent and selective agonists of the 5-HT$_{2C}$ receptor. Details of the syntheses and biological activities of these compounds are provided herein.

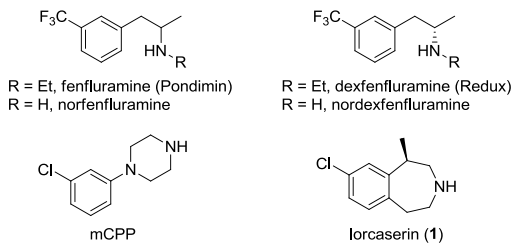
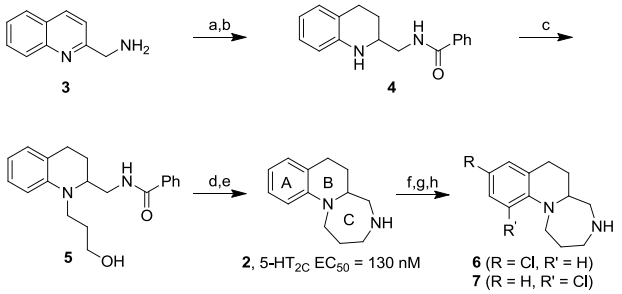


Figure 1. Known anorectic agents.

* Corresponding author. Tel.: +1-858-453-7200; fax: +1-858-453-7210; e-mail: tschrader619@gmail.com

Early in our investigations the racemic 6,6,7-tricyclic amine, 1,2,3,4,5,5a,6,7-octahydro-[1,4]diazepino[1,2-*a*]quinoline (**2**, scheme 1) was identified as a moderately potent agonist of the 5-HT_{2C}R (EC_{50} = 130 nM in IP_3 accumulation assay). The synthesis of this novel compound starts from commercially available 2-quinolinemethanamine (**3**). Benzamide formation via amide coupling was followed by hydrogenation to give the racemic tetrahydroquinoline intermediate (**4**) in 53% yield (two steps). Selective alkylation of the aniline nitrogen was accomplished by heating a mixture of **4** and 3-bromopropan-1-ol in the absence of solvent at 120 °C for 1 h to yield compound **5**. Conversion of the alcohol (of **5**) to the bromide is accomplished by treatment of **5** with aqueous HBr which gives concomitant deprotection of the benzamide group. Finally, base promoted cyclization forms the C-ring to produce **2**. To provide some initial analogs to probe aromatic ring substitution SARs, the racemic mono-chlorinated compounds **6** and **7** were prepared by protecting the free nitrogen of **2** by trifluoracetylation, reaction with NCS, and deprotection with methanolic ammonia.

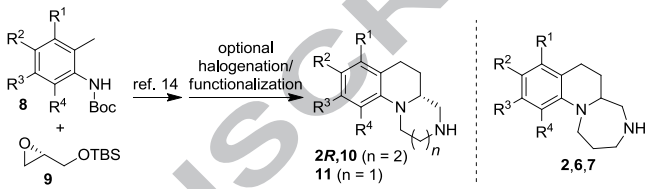


Scheme 1. Reagents and conditions: (a) PhCOOH, EDC·HCl, DMAP, DCM, 40 °C; (b) H_2, PtO_2, MeOH, rt; (c) 3-bromopropan-1-ol, 120 °C; (d) 48 wt.% aq. HBr, rt; (e) Cs_2CO_3, ACN, rt 15 h, 81%, (f) $(CF_3CO)_2O$, Et_3N, DCM, rt; (g) NCS, ACN, 65 °C; (h) NH_3, MeOH, rt.

We previously reported a general asymmetric route to this class of fused tricyclic (*R*)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines and (*R*)-1,2,3,4,5,5a,6,7-octahydro-[1,4]diazepino[1,2-*a*]quinolines.[16] Starting from various *N*-Boc-*o*-toluidines (**8**, Table 1) and (*S*)-*tert*-butyldimethyl(oxiran-2-ylmethoxy)silane (**9**), the enantiopure analogs **2*R***, **10a-c**,**e**,**i-j**, as well as 6,6,6-tricylic compound **11** were prepared. The synthesis of **2*R*** by this method served as a stereochemical structure proof for the individual enantiomers of **2**, which had been originally separated via chiral HPLC. Additional SAR analogs **10d,f-g** were prepared by chlorination of **10c** and **10e**. The benzylated analog **10h** was prepared from **10e** by a four step sequence involving bromination with NBS, Boc-protection, Negishi coupling, and Boc-deprotection (see Supplementary Material).

To assess 5-HT_{2C}R agonism, as well as potential valvulopathogenic activities related to 5-HT_{2B}R activation, functional activities (pEC_{50} and E_{max} values) for prepared compounds were determined in IP_3 accumulation assays.[17] As shown in Table 1, the agonist activity of racemic compound **2** at both 5-HT_{2C}R and 5-HT_{2B}R was entirely attributed to the *R*-enantiomer enantiomer (**2*R***). Other SAR analyses revealed most single substitutions of fluoro (**10a**), chloro (**6**, **7**) and methoxy (**10e,j**) are well tolerated and did not result in significant changes in 5-HT_{2C}R activity as compared with the parent compound **2*R***. Exceptions are the methoxy analogs **10b** (pEC_{50} = 6.2) and **10i** (pEC_{50} = 6.0) which exhibited decreased potency. However, in the case of **10b**, 5-HT_{2C}R activity is returned by adding one (**10c**, pEC_{50} = 7.4) or two (**10d**, pEC_{50} = 8.0) additional chloro substituents. A similar potency increase at the 5-HT_{2C}R is observed when the methoxy analog **10e** (pEC_{50} = 7.1) is chlorinated at the position *para* to the aniline nitrogen (**10g**, pEC_{50} = 8.4). Further elaboration at the *para* position with a larger benzyl substituent decreased activity significantly (**10h**, pEC_{50} = <6) at both receptors. Of particular note is the increase in 5-HT_{2C}R potency observed with the 6,6,6-tricyclic analog **11** (pEC_{50} = 8.6). While none of the compounds displayed meaningful improvements in 5-HT_{2C}R versus 5-HT_{2B}R selectivity as compared with **2*R***, analogs which contained a chloro substituent at the *ortho* position relative to the aniline nitrogen (**7**, **10d**,**f**) led to significant decreases in receptor intrinsic activity (E_{max}≤ 20%) at the 5-HT_{2B}R. The high binding potency of partial agonist **10d** (E_{max}< 5%) was confirmed in [^{125}I]-DOI competition binding assays (5-HT_{2B}R pK_i = 8.3).

Table 1. 5-HT_{2C}R and 5-HT_{2B}R functional activities in intracellular IP_3 accumulation assay for mCPP and tetrahydroquinoline-based tricyclic compounds **2**, **6**,**7**, **10**, and **11**.

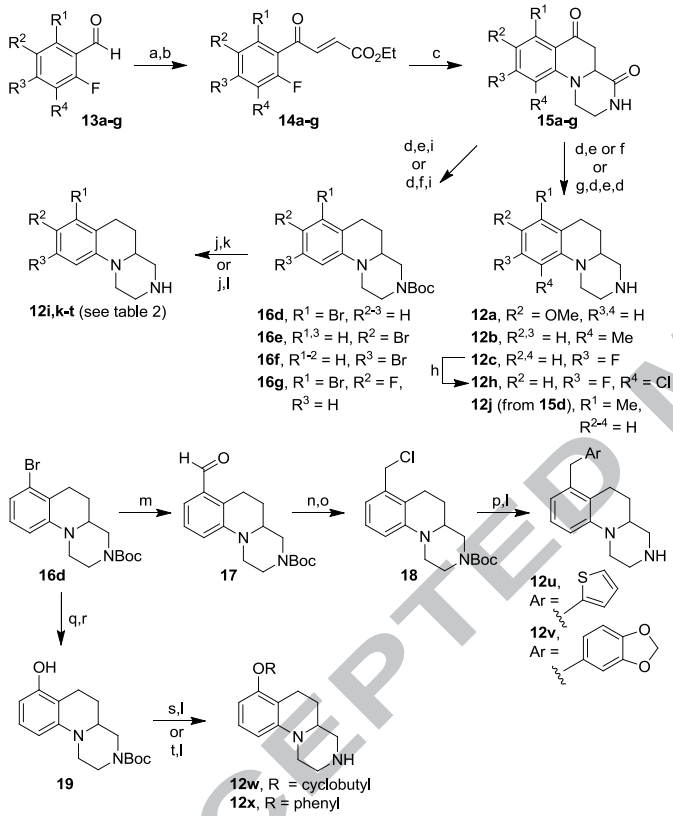


					5-HT_{2C}R		5-HT_{2B}R	
Cmpd	R^1	R^2	R^3	R^4	pEC_{50}[a]	E_{max}[b]	pEC_{50}[a]	E_{max}[b]
mCPP					7.9 [0.1]	90	7.4 [0.6]	22
2	H	H	H	H	6.9 [0.1]	99	6.0 [0.1]	60
2*R*	H	H	H	H	7.2 [0.2]	86	6.3 [0.1]	53
2*S*	H	H	H	H	<5		<5	
6	H	Cl	H	H	6.7 [0.7]	83	6.2 [0.2]	71
7	H	H	H	Cl	7.6 [0.3]	85	7.0 [0.1]	20
10a	H	F	H	H	7.6 [0.2]	94	6.2 [0.2]	59
10b	H	OMe	H	H	6.2 [0.4]	80	5.9 [0.5]	76
10c	H	OMe	Cl	H	7.4 [0.2]	91	6.8 [0.2]	23
10d	H	OMe	Cl	Cl	8.0 [0.3]	80	N.D.[c]	<5
10e	H	H	OMe	H	7.1 [0.3]	95	6.2 [0.1]	37
10f	H	H	OMe	Cl	6.8 [0.9]	72	8.1 [1.3]	7
10g	H	Cl	OMe	H	8.4 [0.3]	85	7.2 [0.3]	84
10h	H	Bn	OMe	H	<6		<6	
10i	OMe	H	H	H	6.0 [1.5]	92	6.4 [1.5]	74
10j	H	H	H	OMe	7.5 [0.2]	17	7.0 [0.8]	55
11	H	H	H	H	8.6 [0.6]	97	7.2 [0.2]	28

[a]pEC_{50} values are geometric means of at least two experiments. Numbers in brackets are 95% confidence intervals. [b]E_{max} % based on maximum asymptote at 10 μM relative to serotonin (5-HT). [c]Due to low intrinsic activity (E_{max} < 5%), pEC_{50} was not determined (N.D).

The finding that 6,6,6-tricyclic compound **11** displayed the most potent agonist activity at the 5-HT_{2C}R without negatively impacting selectivity versus the 5-HT_{2B}R prompted further investigations of this scaffold. In order to efficiently prepare SAR analogs (**12a-c,h-x**, Scheme 2) with varied aromatic ring substituents, we opted to prepare the compounds as racemates using chemistry developed by Bernotas.[18] In this method, the lithium anion of ethyl propiolate is reacted with *ortho*-fluorobenzyaldehydes (**13a-g**), and the resultant alcohols are rearranged to enones **14a-g** by treatment with Et_3N in dioxane at 60 °C. A key one-step double cyclization is accomplished by reaction of enones **14a-g** with 1,2-diaminoethane in DMF at 60 °C to provide tricyclic ketones **15a-g**. Compounds **12a-c** were prepared from **15a-c** by ketone removal with TFA and Et_3SiH followed by amide reduction with either $LiAlH_4$ or BH_3·THF. Chlorination of **12c** with NCS gave the bis-halogenated compound **12h**. Methyl analog **12j** was prepared from **15d** (R^1 =

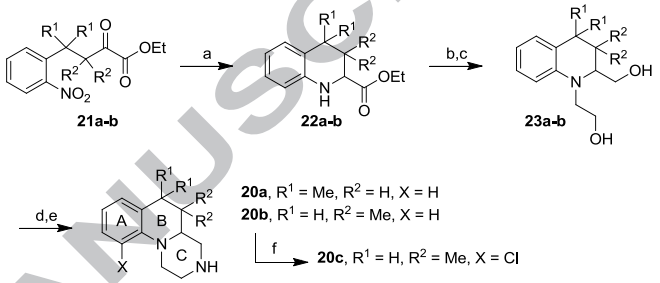
Br) by palladium-catalyzed coupling with trimethlboroxine followed by reductions of the carbonyl groups. The brominated Boc-protected intermediates **16d-g**, were also prepared from **15d-g** respectively by the ketone removal/amide reduction sequence, with an added Boc-protection. The bromine atoms served as handles to perform palladium-catalyzed coupling reactions, which delivered analogs **12i,k-t** after acid-mediated Boc-deprotections. Aldehyde **17** was prepared from **16d** via lithium-bromine exchange and formylation with DMF. Reduction of the aldehyde (**17**) with $NaBH_4$ and conversion to the benzyl chloride (**18**) allowed the synthesis of benzyl analogs **12u-v** by Suzuki couplings. Lastly, conversion of the bromine atom of **16d** to phenol **19** was accomplished by palladium-catalyzed pinacolboration followed by oxidative deboronation. Alkylation of **19** with cyclobutyl bromide or copper-mediated coupling with phenylboronic acid gave **12w** and **12x** after Boc-group removal with 4N HCl in dioxane.



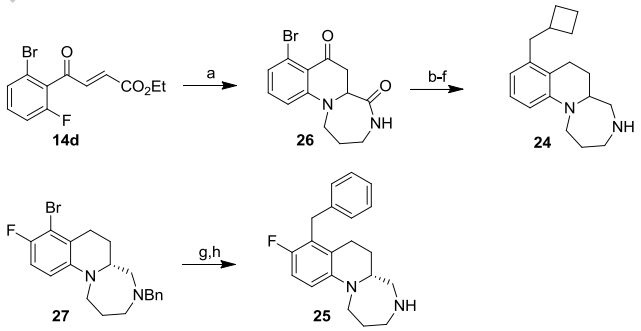
Scheme 2. Reagents and conditions: (a) ethyl propiolate, LDA, THF, 0 °C, 0.5 h then **13a-g**, THF, -78 °C to rt; (b) Et_3N, dioxane, 60 °C; (c) 1,2-diaminoethane, DMF, 60 °C; (d) TFA, Et_3SiH, rt; (e) $LiAlH_4$, THF, rt; (f) BH_3·THF, reflux; (g) Trimethylboroxine, cat. $Pd(PPh_3)_4$, K_2CO_3, dioxane, 100 °C; (h) NCS, DCM, rt; (i) Boc_2O, DCM, rt; (j) Pd-catalyzed coupling reactions, see Supplementary Material; (k) TFA, DCM, rt; (l) 4N HCl, dioxane, rt; (m) *n*-BuLi, THF, -78 °C, 0.75 h then DMF; (n) $NaBH_4$, EtOH, 0 °C to rt; (o) MsCl, Et_3N, DCM, rt; (p) $ArB(OH)_2$, cat. $Pd(dppf)Cl_2$·DCM, Na_2CO_3, dioxane, H_2O, 90 °C; (q) bis(pinacolato)diboron, cat. $Pd(dppf)Cl_2$·DCM, KOAc, THF, 100 °C; (r) 30% aq. H_2O_2, THF, rt; (s) cyclobutyl bromide, K_2CO_3, DMF, 65 °C; (t) $PhB(OH)_2$, Et_3N, $Cu(OAc)_2$, DCM, rt.

Analogs **20a-c**, which contained gem-dimethyl substituents on the saturated B-ring of the tricycle, were prepared as shown in scheme 3. In this sequence, intramolecular reductive aminations of nitrophenyl ketones **21a-b** produced the tetrahydroquinoline esters **22a-b**. Alkylation of the nitrogen atom with ethyl bromoacetate followed by $LiAlH_4$ reduction gave diols **23a-b**. The C-rings are formed via reaction of **23a-b** with MsCl and DIEA, followed by amination with aqueous ammonia to deliver tricycles **20a-b**. An additional molecule (**20c**) containing a chloro-substituent adjacent the aniline nitrogen was prepared from **20b** by chlorination with NCS.

The identification of 5-HT_{2C}R agonists in the 6,6,6-tricyclic series which displayed exceptional functional selectivity over the 5-HT_{2B}R encouraged us to reexamine a number of similar analogs in the 6,6,7-series. Therefore compounds **24** and **25** (Scheme 4) were prepared. Expanding the scope of the Berntoas[18] methodology, the synthesis of the racemic 6,6,7-ring compound **24** employed 1,2-diaminopropane in the double-cyclization reaction of **14d** to give ketone **26** in 42% yield. The remaining steps were performed in similar fashion as described previously. The enantiopure compound **25**, was prepared from previously reported tricycle **27**[16] by a Suzuki coupling with benzyltrifluoroborate and benzyl deprotection under transfer hydrogenation conditions.



Scheme 3. Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, rt; (b) ethyl bromoacetate, K_2CO_3, ACN, 80-100 °C: (c) $LiAlH_4$, THF, rt; (d) MsCl, DIEA, DCM; (e) NH_3, H_2O, ACN, 80 °C; (f) NCS, DCM, rt.

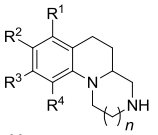


Scheme 4. Reagents and conditions: (a) 1,3-diaminopropane, DMF, 60 °C; (b) TFA, Et_3SiH, rt; (c) BH_3·THF, reflux; (d) Boc_2O, DCM, rt; (e) (cyclobutylmethyl)zinc bromide, cat. $Pd(dppf)Cl_2$·DCM, THF, 90 °C; (f) 4N HCl, dioxane, rt; (g) Potassium benzyltrifluoroborate, cat. $Pd(OAc)_2$, RuPhos, K_2CO_3, PhMe, H_2O, 115 °C; (h) 10% Pd/C, $NH_4^+COO^-$, MeOH, 40 °C.

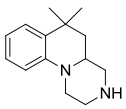
5-HT_{2C}R and 5-HT_{2B}R functional activities for second generation 6,6,6- and 6,6,7-tricyclic compounds are presented in Table 2. 5-HT_{2A}R functional activities and binding affiinities (p*Ki*)[19] for all 5-HT_2 receptors are included for potent 5-HT_{2C}R agonists (pEC_{50} > 8) which exhibited significantly greater potencies versus the 5-HT_{2B}R (ΔpEC_{50}[2C-2B] ≥ 2.7). Similar to trends observed for the compounds in Table 1, the methoxy subsituent *para* (R^2) to the aniline nitrogen (**12a**, pEC_{50} = 6.6) resulted in decreased 5-HT_{2C}R activity versus the enantiopure parent compound (**11**, pEC_{50} = 8.6) while the *para* (R^2) fluoro substituent (**12i**, pEC_{50} = 8.5) had little effect. However, a small increase in activity was observed with the *meta* (R^3) fluoro analog **12c** (pEC_{50} = 9.1). Substitutions of methyl (**12b**) and chloro (**12h**) at the position *ortho* (R^4) to the aniline nitrogen led to a significant decrease in 5-HT_{2B}R signaling (E_{max}) as was also observed in the 6,6,7-series. While smaller substitutions at all aromatic positions did not result in any significant improvement in 5-HT_{2C}R versus 5-HT_{2B}R selectivities, an increase in alkyl chain length from methyl (**12j**, ΔpEC_{50}[2C-2B] = 1.2) to propyl

(**12k**, ΔpEC_{50}[2C-2B] = 3.0) at the R^1 position had a significant impact. In addition, the ΔpK_i[2C-2B] and ΔpK_i[2C-2A] binding selectivities observed for **12k** (1.8 and 1.2 respectively) provide an adequate safety margin for avoiding 5-HT_{2B}R and 5-HT_{2A}R agonism related side effects.[21] Examination of the *n*-propyl substituent at the alternate R^2 (**12s**) and R^3 positions (**12t**) did not yield the same results. This discovery led us to further probe the SARs at the R^1 position. Though R^1 substitutions of cyclobutyl (**12l**) and phenyl (**12n**) did not show increases in 5-HT_{2C}R receptor activities or selectivities over the 5-HT_{2B}R, extension of these substitutions with a methylene linker (**12m,o-p**) did improve the compound profiles. However, the benzyl substituent at R^1 (**12o-p**) led to a decrease in 5-HT_{2C}R versus 5-HT_{2A}R binding (p*Ki*) selectivities (ΔpK_i[2C-2A] < 0.4). The cyclobutylmethyl and benzyl substituents at R^1 were also studied in the 6,6,7-series (**24** and **25**) but the results were not as impactful. Similar to the benzyl substituent in 6,6,6-analogs **12o-p**, the methylene linked 2-thiophene (**12u**) and 1,3-benzodioxole (**12v**) at R^1 showed good 5-HT_{2C}R versus 5-HT_{2B}R receptor selectivities but suffered from decreased selectivities over the 5-HT_{2A}R. Other R^1 variants which incorporated sulfur (**12r**) or oxygen (**12q**,**w-x**) linkers, were not as advantageous as the analogous carbon linked R^1 substitutions.

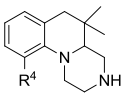
Table 2. 5-HT_2R functional activities in intracellular IP_3 accumulation assays and [^{125}I]-DOI competition binding (pK_i) data for mCPP and tetrahydroquinoline-based tricyclic compounds **11**, **12**, **20, 24-25**.



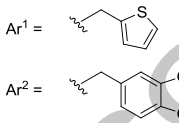
11, (n = 1, *R*-isomer)
12, (n = 1)
24, (n = 2)
25, (n = 2, *R*-isomer)



20a



20b-c



					5-HT_{2C}R			5-HT_{2B}R			5-HT_{2A}R		
Cmpd	R^1	R^2	R^3	R^4	pEC_{50}[a]	E_{max}[b]	pK_i[a]	pEC_{50}[a]	E_{max}[b]	pK_i[a]	pEC_{50}[a]	E_{max}[b]	pK_i[a]
mCPP					7.9 [0.1]	90	8.1 [<0.1]	7.4 [0.6]	22	8.0 [0.1]	6.6 [0.2]	12	7.6 [<0.1]
11	H	H	H	H	8.6 [0.6]	97		7.2 [0.2]	28				
12a	H	OMe	H	H	6.6 [0.7]	101		6.1 [<0.1]	57				
12b	H	H	H	Me	7.2 [0.7]	86		7.3 [1.8]	10				
12c	H	H	F	H	9.1 [0.2]	100		7.5 [0.2]	38				
12h	H	H	F	Cl	8.2 [0.2]	94		8.7 [2.3]	12				
12i	H	F	H	H	8.5 [0.4]	96		6.9 [0.3]	44				
12j	Me	H	H	H	8.7 [0.5]	108		7.5 [0.2]	65				
12k	*n*-Pr	H	H	H	9.7 [0.2]	101	9.4 [0.1]	6.7 [0.1]	80	7.6 [0.2]	6.3 [0.3]	104	8.2 [0.1]
12l	*c*Bu	H	H	H	8.5 [0.3]	110		7.4 [0.3]	112				
12m	CH_2*c*Bu	H	H	H	8.5 [0.2]	106	9.2 [0.1]	5.7 [0.4]	31	7.2 [0.2]	5.7 [0.2]	135	8.1 [0.1]
12n	Ph	H	H	H	6.9 [0.1]	97		5.6 [0.4]	72				
12o	CH_2Ph	H	H	H	8.8 [0.2]	104	9.2 [0.1]	5.6 [0.5]	20	7.4 [0.2]	6.9 [0.2]	85	8.8 [0.1]
12p	CH_2Ph	F	H	H	9.0 [0.5]	102	9.4 [0.3]	6.2 [0.4]	32	7.9 [0.2]	7.0 [0.8]	114	9.2 [0.3]
12q	CH_2OMe	H	H	H	7.7 [0.6]	113		5.9 [0.3]	77				
12r	SEt	H	H	H	9.5 [0.2]	101		7.1 [0.2]	46				
12s	H	*n*-Pr	H	H	7.7 [0.3]	100		6.2 [0.9]	9				
12t	H	H	*n*-Pr	H	7.2 [0.9]	87		6.7 [0.2]	19				
12u	Ar^1	H	H	H	9.1 [0.7]	106	9.5 [0.4]	6.4 [0.3]	24	7.6 [0.6]	7.1 [0.6]	94	7.6 [0.6]
12v	Ar^2	H	H	H	8.2 [0.4]	100	9.1 [0.1]	5.4 [0.5]	26	6.9 [0.6]	6.7 [0.2]	64	8.8 [0.2]
12w	O-*c*Bu	H	H	H	7.7 [0.1]	98		6.1 [0.1]	9				
12x	OPh	H	H	H	7.0 [3.3]	112		5.2 [<0.1]	94				
20a					5.9 [0.4]	84		<5					
20b				H	<6			<6					
20c				Cl	<5		6.1 [0.2]	7.0 [1.0]	84	8.2 [0.6]	<5		5.7 [0.3]
24	CH_2*c*Bu	H	H	H	6.9 [0.2]	116		<6					
25	CH_2Ph	F	H	H	7.7 [0.1]	108		5.1 [0.6]	71				

[a] pEC_{50} and pK_i values are geometric means of at least two experiments. Numbers in brackets are 95% confidence intervals. [b] E_{max} % based on maximum asymptote at 10 μM relative to serotonin (5-HT).

Exploration of gem-dimethyl substitutions on the aliphatic B ring revealed that compounds **20a-c** displayed little or weak agonism on the 5-HT_{2C}R. Interestingly, the chlorinated analog **20c** did display appreciable agonism at the 5-HT_{2B}R (pEC_{50} = 7.0, E_{max} = 84%) with no agonism observed at either the 5-HT_{2C}R or the 5-HT_{2A}R. Good binding (p*Ki*) selectivities were also observed for **20c** (ΔpK_i[2B-2C] = 2.1 and ΔpK_i[2B-2A] = 2.5). To our knowledge this represents the first example of a selective 5-HT_{2B}R agonist and further characterization of this molecule (**20c**) both *in vitro* and *in vivo* may be warranted.

To assess both pharmacodynamic and pharmacokinetic properties of identified potent and selective 5-HT_{2C}R agonists **12k** and **12m**, their effects on acute food intake in male Sprague-

Dawley rats were measured (Figure 2). Oral doses of **12k** (3 mg/kg) and **12m** (10 mg/kg) both produced full suppression (99%) of food intake measured at 1 h. At doses of 1 mg/kg compound **12k** produced a 66% decrease in food intake as compared to a 27% decrease observed for **12m**. In a separate study (see Supplementary Material), the effects of compound **12m** (5 mg/kg) were abrogated by preadministration (IP) with the selective 5-HT_{2C}R antagonist SB242084 (1 mg/kg).[22] These studies demonstrated compounds **12k** and **12m** were orally bioavailable, and doses of as low as 1 mg/kg provided adequate brain exposures to elicit 5-HT_{2C}R mediated hypophagia.

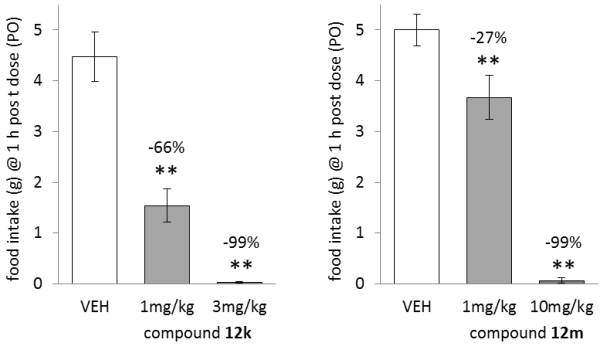


Figure 2. Acute food intake in rat. Data represent mean ± S.E.M. Numbers above bar (treatment groups) represent % inhibition versus vehicle. **Significantly different as compared to vehicle (p <0.001).

In conclusion, the syntheses, SARs, and biological activities of a series of tetrahydroquinoline-based tricyclic amines as 5-HT_{2C}R receptor agonists was reported. An early lead containing a novel 6,6,7-ring system was optimized for *in vitro* potency as well as selectivity versus the related 5-HT_{2B}R and 5-HT_{2A}R. Ultimately, two potent, selective, orally bioactive 6,6,6-tricyclic 5-HT_{2C}R agonists were identified. Further evaluation of these and other structurally related molecules will be disseminated in future publication(s).

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Supplementary Material

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at: .