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Tricyclic dihydroquinazolinones as novel 5-HT$_{2C}$ selective and orally efficacious anti-obesity agents

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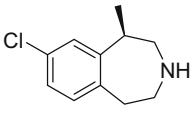
ABSTRACT

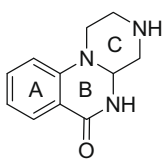
Agonists of the 5-HT$_{2C}$ receptor have been shown to suppress appetite and reduce body weight in animal models as well as in humans. However, agonism of the related 5-HT$_{2B}$ receptor has been associated with valvular heart disease. Synthesis and biological evaluation of a series of novel and highly selective dihydroquinazolinone-derived 5-HT$_{2C}$ agonists with no detectable agonism of the 5-HT$_{2B}$ receptor is described. Among these, compounds (+)-**2a** and (+)-**3c** were identified as potent and highly selective agonists which exhibited weight loss in a rat model upon oral dosing.

The biological effects of the neurotransmitter serotonin (5-HT) are mediated through at least 14 distinctly different receptor subtypes. The serotonin subtype 5-HT$_{2C}$ receptor has been the focus of considerable attention within the pharmaceutical community because of its implication in a variety of conditions including obesity, diabetes and schizophrenia.[1,2] Pre-clinical studies show that 5-HT$_{2C}$ agonists reduce food intake and body weight in rats[3] and the feeding effects can be reversed with selective 5-HT$_{2C}$ antagonists.[4] 5-HT$_{2C}$ receptor knockout mice are obese, hyperphagic, hyperinsulinemic and insensitive to the 5-HT$_{2C}$ agonist fenfluramine.[5,6] Furthermore, clinical studies have shown that 5-HT$_{2C}$ agonism can suppress appetite and reduce body weight in humans.[7] Thus, 5-HT$_{2C}$ is a well validated target for obesity.

While 5-HT$_{2C}$ agonists have the potential to treat obesity, it has been hypothesized that agonism of the closely related 5-HT$_{2B}$ receptor may be associated with heart valvulopathy in humans.[8,9] In addition, agonists of the related 5-HT$_{2A}$ receptor can also have unfavorable characteristics as they can be vasoconstrictive as well as lead to undesirable CNS effects.[10] Thus, the design and identification of a selective 5-HT$_{2C}$ agonist is a necessary requisite for a program targeting this receptor. There have been several reports in the recent literature describing 5-HT$_{2C}$ agonists with significant selectivity over 5-HT$_{2A}$ and 5-HT$_{2B}$ including lorcaserin (**1**), a compound currently in clinical development for the treatment of obesity.[11] In the course of our efforts to identify a potential development candidate, we set a criterion of no-to-minimal activation



Lorcaserin (**1**)
5-HT$_{2C}$ EC$_{50}$ = 9 nM (IA = 1)
5-HT$_{2B}$ EC$_{50}$ = 943 nM (IA = 1)
5-HT$_{2A}$ EC$_{50}$ = 168 nM (IA = 0.75)
(data reported in ref. 11a)



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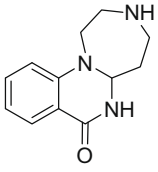

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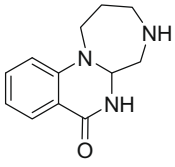

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of the 5-HT$_{2B}$ receptor. This paper outlines the synthesis and biological evaluation of a series of novel and selective 5-HT$_{2C}$ receptor agonists, represented by structures **2**–**4**, based on the known 5-HT$_{2C}$ agonist mCPP.[7] A summary of the SARs leading to the

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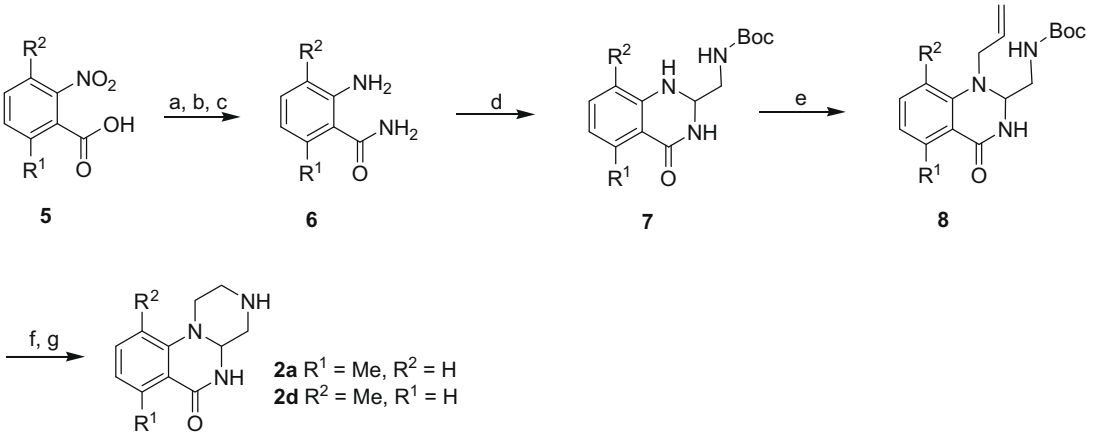
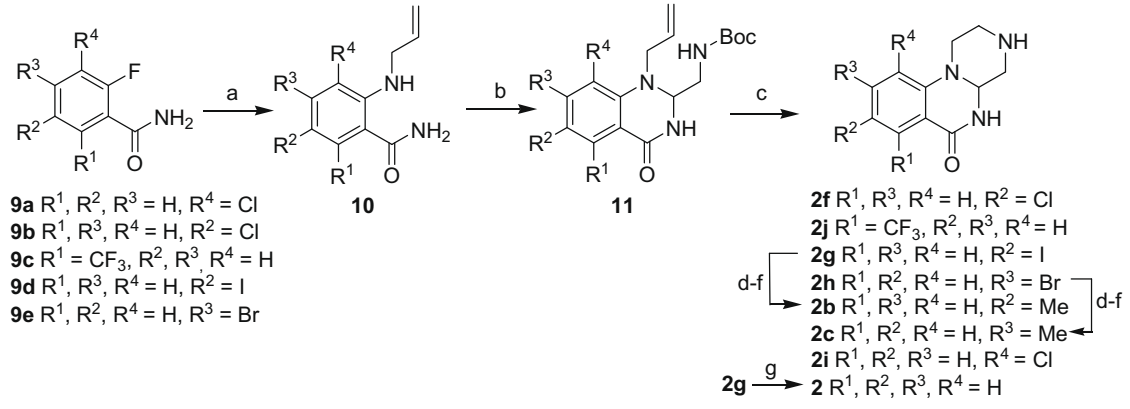
identification of compounds with potent in vitro 5-HT_{2C} agonist activity and no detectable activation of the 5-HT_{2B} and 5-HT_{2A} receptors is described. Finally, the in vivo evaluation of select compounds in rat feeding and weight loss models is described.

Syntheses of the various compounds in the 6,6,6-tricyclic series (**2**) were carried out as outlined in Schemes 1–3. Readily available 2-nitrobenzoic acids **5** were converted to the corresponding 2-aminobenzamides **6** via their respective acid chlorides and 2-nitrobenzamides. Treatment of the aminobenzamides **6** with *N*-boc-aminoacetaldehyde in refluxing toluene (Dean–Stark trap) in the presence of catalytic *p*-toluenesulfonic acid afforded **7**.[12] Allylation of **7** at the 'aniline' nitrogen using allyl bromide and sodium or potassium carbonate in *N,N*-dimethylformamide (DMF) or *N,N*-dimethylacetamide (DMA) followed by treatment of the resulting olefins **8** with sodium periodate in THF–water in the presence of catalytic osmium tetroxide afforded the intermediate aldehydes. Finally, treatment of the aldehydes with excess trifluoroacetic acid and triethylsilane in dichloromethane provided target compounds **2a** and **2d** in 40–60% yield from **8**. In all cases the racemic compounds thus obtained were isolated as free amines and resolved by chiral chromatography affording enantiomerically pure analogs. While both enantiomers were tested for biological activity, Table 1 displays data for the enantiomers with more potent 5-HT_{2c} agonist activity.[13]

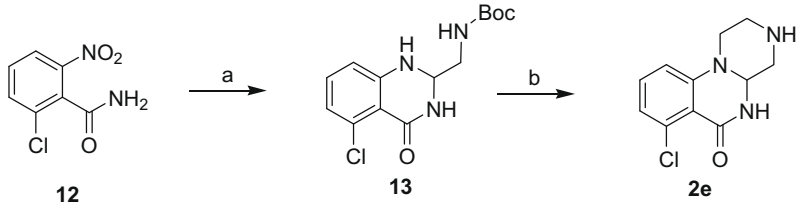
Other analogs related to **2** were prepared from the corresponding *ortho*-fluorobenzamides (Scheme 2) via introduction of the allylamine functionality prior to condensation with *N*-boc-aminoacetaldehyde. Thus, treatment of the readily available benzamides **9a–e** with allylamine in the presence of potassium carbonate in DMA at 130 °C afforded the corresponding allylated benzamides **10** which were converted via **11** to the respective tricyclic amines as described in Scheme 1. The 8- and 9-methyl analogs **2b** and **2c**,



Scheme 1. Reagents and conditions: (a) $(COCl)_2/CH_2Cl_2/100\%$; (b) NH_3/MeOH–THF/90–100%; (c) H_2/10% palladium on carbon/MeOH/95%; (d) *N*-boc-aminoacetaldehyde/pTsOH/toluene/reflux/40–70%; (e) Na_2CO_3 or K_2CO_3/allyl bromide/DMF or DMA/140 °C/50–65%; (f) cat. $OsO_4/NaIO_4$/THF–water/50–65%; (g) TFA/Et_3SiH/CH_2Cl_2/40–60% (2 steps).



Scheme 2. Reagents and conditions: (a) allylamine/K_2CO_3/DMA/130 °C/61–100%; (b) *N*-boc-aminoacetaldehyde/catalytic pTsOH/dioxane or toluene/reflux/47–59%; (c) as in Scheme 1/40–60%; (d) boc anhydride/Et_3N/THF/100%; (e) $Me_4Sn/Pd(Ph_3P)_4$/LiCl/DMF/95 °C/45–85%; (f) TFA/CH_2Cl_2/100%; (g) H_2/10% palladium on carbon/MeOH/91%.



Scheme 3. Reagents and conditions: (a) Fe°/AcOH/*N*-boc-aminoacetaldehyde/50–55 °C/22% yield; (b) as in Scheme 1 (ca. 10% overall yield).

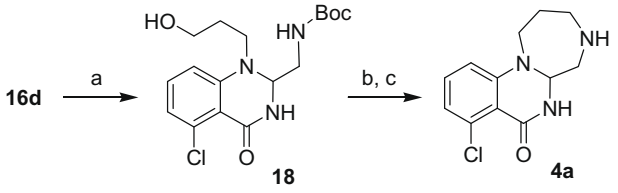
Table 1
Serotonin (5-HT) binding and functional activity of the various tricyclic dihydroquinazolinones[a]

Compound[b]		5-HT_{2C} (nM)		5-HT_{2B} (nM)		5-HT_{2A} (nM)	
#	Chiral column used/peak elution[c]	Binding K_i	Function EC_{50} (IA)	Binding K_i	Function EC_{50} (IA)	Binding K_i	Function EC_{50} (IA)
2	OD/2nd	1936	137 (0.96)	137	ND	1980	ND
(+)-2a	OJ/1st	89 ± 34	45 ± 19 (1.0)	8.6 ± 2	>10,000 (0)	229 ± 109	>10,000 (0)
(−)-2a	OJ/2nd	2076	989 (0.9)	206	ND	4482	ND
2b	OD/2nd	998	133 (1.0)	61	>10,000 (0)	1220	>705 (0.34)
2c	AS/1st	479	34 (1.0)	280	>10,000 (0)	600	>10,00 (0.26)
2d	OD/1st	6145	4197 (0.40)	2395	ND	>10,000	>10,000 (0)
2e	OJ/1st	223	43 (0.80)	18	>10,000 (0)	334	>10,000 (0)
2f	AS/1st	757	110 (0.97)	72	ND	397	ND
2j	OD/1st	153	92 (0.93)	13	>10,000	184	ND
2i	OD/1st	>10,000	>10,000 (0)	>10,000	ND	>10,000	ND
3	OD/1st	49	16 (0.80)	67	101 (0.6)	269	248 (1.0)
3a	OD/1st	2.9	2.0 (1.0)	10	61 (0.44)	141	70 (1.0)
3b	OD/1st	9.0	1.8 (1.0)	23	46 (0.50)	168	130 (0.80)
(+)-3c	AD/1st	6.5 ± 2.8	6.6 ± 1.5 (1.1)	41 ± 12	>10,000 (0)	364 ± 30	952 ± 179 (0.28)
(−)-3c	AD/2nd	60	92 (0.66)	51	ND	454	>10,000 (0.11)
4a	Racemic	1547	ND	734	ND	13560	ND
mCPP[d]	—	17 ± 2	15 ± 4 (1.0)	24 ± 1	287 ± 94 (0.4)	48 ± 4	290 ± 110 (0.3)

[a] K_i and EC_{50} values[14,15] are reported as means of ⩾2 independent 12-point dose response curves ($n \geqslant 4$ for data reported with standard deviations). mCPP was used as a positive control. The reported intrinsic activity (IA) is relative to receptor activation by serotonin at 3 μM (defined as 1.0). ND = value not determined.
[b] All compounds were enantiomerically pure (except **4a** which was a racemate). With the exception of **2a** and **3c**, K_i and EC_{50} values are reported only for enantiomers with higher affinity for 5-HT_{2C}.
[c] Chiral columns (Chiral Technologies) used for separation: AD = CHIRALPAK® AD, OD = CHIRALCEL® OD, AS = CHIRALPAK® AS, OJ = CHIRALCEL® OJ. Eluent used: hexanes–ethanol–methanol–triethylamine, 80:10:10:0.3 to 60:20:20:0.3.
[d] *m*-Chlorophenylpiperazine.

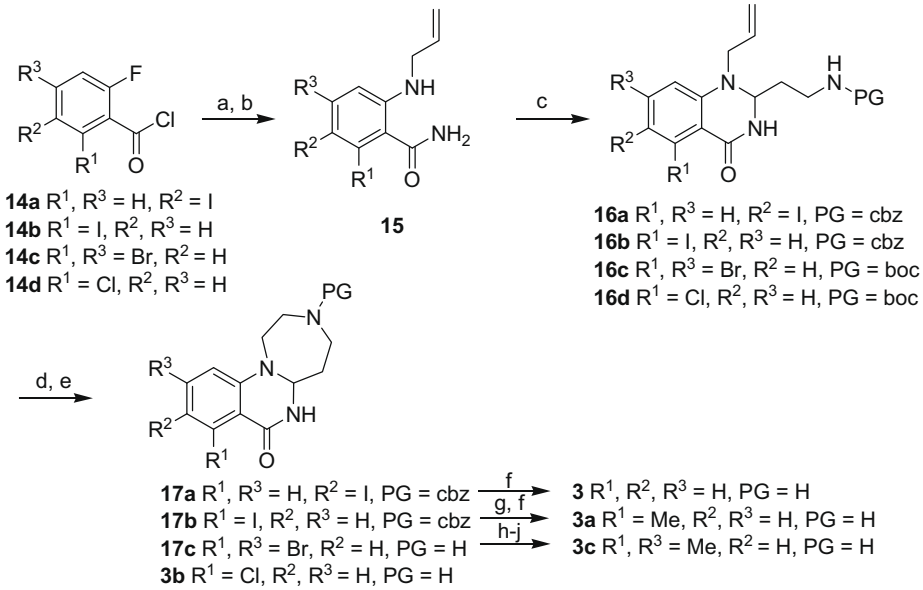
respectively were prepared from the iodo and bromo tricyclics **2g** and **2h** by conducting a Stille coupling reaction on the respective boc-protected amines. The unsubstituted analog **2** was readily prepared from iodo compound **2g** by palladium catalyzed hydrogenolysis. Compound **13**, the intermediate for **2e**, was generated by a one pot reduction/condensation reaction of 2-chloro-6-nitrobenzamide and *N*-boc-aminoacetaldehyde in the presence of iron powder in warm acetic acid (Scheme 3).

Compounds in the related 6,6,7-series were prepared as outlined in Schemes 4 and 5. Treatment of 2-fluorobenzoyl chlorides **14a–d** in THF with a solution of ammonia in methanol afforded the corresponding benzamides which were readily converted to



Scheme 5. Reagents and conditions: (a) BH_3–Me_2S/Et_2O then H_2O_2/NaOH/31%; (b) Dess–Martin periodinane/CH_2Cl_2; (c) TFA/Et_3SiH/CH_2Cl_2 (7% yield from **18**).

16a–d via **15** in a manner analogous to that described in Scheme 2. Oxidative cleavage of the allylic double bond and reductive cycliza-



Scheme 4. Reagents and conditions: (a) NH_3/MeOH–THF/100%; (b) allylamine/K_2CO_3/DMA/140 °C/61–100%; (c) *N*-cbz-3-amino-1-propanal or *N*-boc-3-amino-1-propanal/pTsOH/dioxane/reflux/70–80%; (d) cat. OsO_4/$NaIO_4$/THF–water; (e) Et_3SiH/TFA/CH_2Cl_2/50–60% (2 steps); (f) H_2/10% palladium on carbon/MeOH/100%; (g) $Pd(Ph_3P)_4$/trimethylboroxine/K_2CO_3/water–dioxane (1:9)/100 °C/20%; (h) boc anhydride/Et_3N/THF–CH_2Cl_2/100%; (i) $PdCl_2(dppf)_2$/Me_2Zn/dioxane/100 °C/44%; (j) TFA/CH_2Cl_2/100%.

tion of the resulting aldehyde (with concomitant removal of the protecting group when PG = boc) afforded **17a–c** and **3b**. Removal of the cbz protecting group accompanied by reduction of the iodo group of **17a** via palladium catalyzed hydrogenolysis afforded **3**. Compound **3a** was prepared from **17b** via Suzuki coupling using trimethylboroxine in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate prior to removal of the cbz protecting group. Compound **3c** was similarly prepared from the dibromo compound **17c** using a Negishi coupling reaction. The isomeric 6,6,7-tricyclic analog of **3b**, compound **4a,** could be prepared from **16d** in low overall yield via a sequence that involved hydroboration followed by Dess–Martin periodinane oxidation of the resulting primary alcohol to the corresponding aldehyde and subsequent intramolecular reductive amination (Scheme 5).

Table 1 displays in vitro data for select analogs in the 6,6,6- and two isomeric 6,6,7-tricyclic amine derived series. All compounds were initially screened in binding assays for the target 5-HT_{2C} receptor as well as for 5-HT_{2B} and 5-HT_{2A} selectivity.[14,15] Compounds with significant binding affinities were also evaluated for activity in corresponding functional assays. The baseline compound **2** in the 6,6,6-tricyclic series displayed a modest binding affinity for the 5-HT_{2C} receptor (1.9 μM). However, it displayed full functional agonism (IA = 0.96) with an EC_{50} value of 137 nM. Introduction of small hydrophobic substituents such as chloro, methyl and trifluoromethyl at the 'A' ring resulted in the generation of a variety of compounds that displayed, with a few exceptions, significantly improved 5-HT_{2C} binding and functional activities (e.g., compounds (+)-**2a** and **2e**). Most compounds in the 6,6,6-tricyclic series displayed relatively higher binding affinity for the 5-HT_{2B} over the 5-HT_{2C} receptor. However, compounds in this series were completely devoid of functional activity at the 5-HT_{2B} receptor. Thus, while (+)-**2a** (5-HT_{2C} EC_{50} = 45 nM, IA = 1) is a potent binder at the 5-HT_{2B} receptor (K_i = 8.6 nM), the lack of functional agonism of the 5-HT_{2B} receptor at concentrations up to 10 μM (IA = 0) represented a more desirable profile. Furthermore, compound (**+**)**-2a**, as well as most compounds in the 6,6,6-series, displayed no significant functional agonism at the 5-HT_{2A} receptor (EC_{50} >10 μM).

Expansion of the 'C' ring afforded two isomeric series of 6,6,7-tricyclic amines with significantly different biological profiles. Chloro compound **4a** showed a significantly diminished binding affinity for the 5-HT_{2C} receptor (K_i = 1547 nM) as compared to **2e**. In contrast, compounds in the isomeric series (represented by compound **3**) were dramatically more potent at the 5-HT_{2C} receptor. As an example, compound **3a** with a K_i value of 2.9 nM showed a 30-fold increased affinity for the 5-HT_{2C} receptor over the corresponding analog in the 6,6,6-series ((+)-**2a**, K_i = 89 nM). Similarly, the chloro analog **3b** (5-HT_{2C} K_i = 9 nM) displayed 25-fold improvement in the binding affinity for 5-HT_{2C} over the corresponding analog in the 6,6,6-series (**2e**, K_i = 223 nM). In addition, compounds in this series showed a marked improvement in 5-HT_{2C} functional activity as demonstrated by a 22-fold increase in potency for compound **3a** (EC_{50} = 2.0 nM, IA = 1.0) over compound (+)-**2a**. However, in contrast to most compounds in the 6,6,6-series, compounds **3a** and the chloro analog **3b** (as well as the baseline compound **3**) are partial agonists (IA = 0.4–0.6) of the 5-HT_{2B} as well as full agonists (IA = 0.8–1.0) at the 5-HT_{2A} receptors. Extensive SAR studies were carried out in this series in order to increase functional selectivity for the 5-HT_{2C} receptor over 5-HT_{2A} and 5-HT_{2B} receptors. These efforts resulted in the generation of the dimethyl analog (+)-**3c** with single digit nM 5-HT_{2C} binding and function (K_i = 6.5 nM, EC_{50} = 6.6 nM, IA = 1.0), no measurable activation of the 5-HT_{2B} receptor (IA = 0 at 10 μM) and only weak activation (EC_{50} = 952 nM, IA = 0.28) of the 5-HT_{2A} receptor. Consistent with the cell based 5-HT_{2B} functional data, compound (+)-**3c** did not show any significant activity in a tissue based (rat fundus) assay at concentrations up to 10 μM. In contrast, the 5-HT_{2B} partial agonist **3a** (5-HT_{2B} EC_{50} = 61 nM, IA = 0.44) produced a weak (IA = 0.2) response in the rat fundus at 10 μM.

Based on these data, two compounds were selected for detailed in vivo testing and characterization. Compound (+)-**2a** displayed favorable PK properties in rat with 49% oral bioavailability when dosed at 1 mpk (Table 2). In addition, when orally dosed at 10 mpk (Table 3), compound (+)-**2a** exhibited plasma and total brain exposures of 2122 nM and 3010 nmol/kg, respectively, 4 h post administration. Demonstrating reasonable exposure, the agonist was advanced into rat efficacy models. In an acute (20 h) feeding assay (Fig. 1), compound (+)-**2a** produced a dose dependent reduction in food intake with a robust 22% reduction in feeding at 10 mpk. Further evaluation of (+)-**2a** was carried out in a subchronic 4 day weight loss model in the rat (Fig. 2). After 30 mpk daily oral dosing, compound (+)-**2a** produced a statistically significant 4.1% reduction in body weight (as well as a 16% reduction in cumulative caloric intake) as compared to vehicle-treated animals.

Dimethyl analog (+)-**3c** was similarly evaluated in vivo. In a rat pharmacokinetic study (10 mpk, po only), (+)-**3c** displayed an AUC (0–8 h) of 9.2 μM h in addition to plasma and total brain exposures of 714 nM and 108 nmol/kg, respectively, at 8 h post dose (Table 3). In the 20 h feeding model in rat (Fig. 1), compound (+)-**3c** produced statistically significant 18% and 25% reductions in food intake at 10 and 30 mpk doses, respectively. As observed with (+)-**2a**, there were minimal effects on locomotor activity and no signs of overt clinical toxicity or malaise with dosing of these compounds. In a separate acute feeding study, the effect on feeding by (+)-**3c** was

Table 2
Pharmacokinetic data for compound (+)-**2a** in male Sprague–Dawley rats[a]

Route	Dose (mpk)	$T_{1/2}$ (h)	Cl (mL/min/kg)	V_{dss} (L/kg)	T_{max} (h)	C_{max} (nM)	$AUC_{0-\infty}$ (nM h)	%F
Intravenous	1	0.9 ± 0.1	27 ± 7.4	1.3 ± 0.1	ND	ND	2344 ± 690	—
Oral	1	2.5 ± 1.6	ND	ND	1.3 ± 0.6	293 ± 95	1154 ± 161	49

[a] Values are reported as means of 3 animals each iv and po. ND = value not determined.

Table 3
Oral pharmacokinetic data for compounds (+)-**2a** and (+)-**3c** in male Sprague–Dawley rats[a]

Compound	Dose (mpk)	T_{max} (h)	C_{max} (nM)	AUC (nM h)[b]	Plasma level (nM)[c]	Brain level (nmol/kg)[c]
(+)-**2a**	1	1	398	1040	219	326
(+)-**2a**	10	0.5	5376	12637	2122	3010
(+)-**3c**	10	1.5	1749	9242	714	108

[a] Compounds were dosed only po; values are reported as means of 2 animals.
[b] The reported data was collected over 4 h for compound (+)-**2a** and 8 h for compound (+)-**3c**.
[c] Exposure levels for (+)-**2a** and (+)-**3c** at 4 and 8 h, respectively.

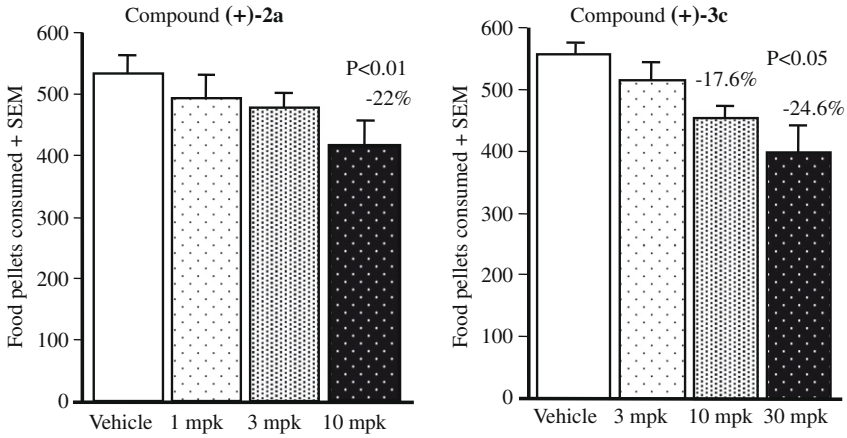


Figure 1. Effects on feeding in an acute (20 h) rat operant model upon treatment with compounds (+)-**2a** and (+)-**3c**. Male Sprague–Dawley rats (n = 6) were dosed orally with test compound or vehicle (14% propylene glycol, 1% tween, 85% water, v/v/v) 60 min prior to the onset of the dark cycle (the most active period of feeding). Food pellets consumption data for compound treated animals was compared to that for vehicle treated animals in order to determine percent reduction of food intake over a 20 h period. Water intake and locomotor activity were also measured simultaneously to assess potential adverse effects (see Ref. 15 for detail design of all in vivo studies).

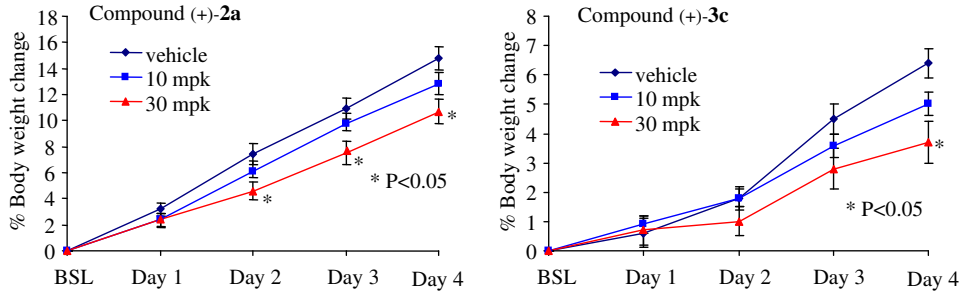


Figure 2. Effect of 4 days chronic treatment with compounds (+)-**2a** and (+)-**3c** on body weight in rats. Male Sprague–Dawley rats weighing approximately 240 g (n = 8) were dosed orally once a day with test compound or vehicle (14% propylene glycol, 1% tween, 85% water, v/v/v) for 4 days. Body weight and consumption of food and water were measured daily. See Ref. 15 for detail design of all in vivo studies. BSL = Baseline.

completely reversed by co-administration of the selective 5-HT_{2C} antagonist SB243213,[16] supporting a mechanism-based (5-HT_{2c}) reduction in food intake.[17] Compound (+)-**3c** was also evaluated in the 4-day rat model (Fig. 2), affording statistically significant 19% and 2.7% reductions in total caloric consumption and body weight, respectively, at a daily oral dose of 30 mpk.

In conclusion, most compounds based on the 6,6,6-dihydroquinazolinone core displayed complete functional selectivity for 5-HT_{2C} over the 5-HT_{2B} and 5-HT_{2A} receptors.[18] The lead compound (+)-**2a** exhibited good bioavailability in the rat with micromolar plasma and brain exposures when dosed at 10 mpk. In addition, (+)-**2a** was efficacious in both an acute 20 h food intake study and a 4 day rat weight loss model. Evaluation of (+)-**2a** for off-target activities showed no significant inhibition (IC_{50} >40 μM) of cytochrome P450 enzymes (CYP1A2, 2C9, 2C19, 2D6, and 3A4) and no evidence of significant (>50% inhibition at 10 μM) binding or enzyme inhibition in a broad panel of profiling assays, including a variety of monoaminergic receptors. In addition, (+)-**2a** displayed weak hERG ion channel inhibition (37% at 30 μM) in a patch clamp assay.

The 6,6,7-dihydroquinazolinones generally displayed superior 5-HT_{2C} in vitro potency. While functional selectivity for the 5-HT_{2C} receptor (vs 5-HT_{2B} and 5-HT_{2A}) was suboptimal for most compounds in this series, the dimethyl analog (+)-**3c** was completely selective for 5-HT_{2C} (EC_{50} = 6.6 nM, IA = 1.0) vs 5-HT_{2B} (EC_{50} >10 μM, IA = 0). However, in contrast to the 6,6,6-series, (+)-**3c** and most other compounds in this series exhibited relatively lower brain exposures (vs plasma) in the rat (brain:plasma ~ 0.1–0.2). Consequently, compounds in this series were often less efficacious in the rat despite superior in vitro activity. Efforts to uncover the origin of this disparity between the two series supported involvement of the P-glycoprotein (P-gp) transporter as indicated by a differential in the efflux and influx permeability rates in Caco-2 cells for most compounds in the 6,6,7-series ((+)-**3c**: Caco A−B = 30 nm/sec, B−A = 166 nm/sec). Efforts to improve brain exposures of the 6,6,7-series will be discussed in due course.

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References and notes

1. (a) Monck, N. J. T.; Kennett, G. A. *Prog. Med. Chem.* **2008**, *46*, 281; (b) Miller, K. J. *Mol. Interventions* **2005**, *5*, 282; (c) Vickers, S. P.; Benwell, K. R.; Porter, R. H.; Bickerdike, M. J.; Kennett, G. A.; Dourish, C. T. *Br. J. Pharmacol.* **2000**, *130*, 1305; (d) Dunlop, J.; Marquis, K. L.; Lim, H. K.; Leung, L.; Kao, J.; Cheesman, C.; Rosenzweig-Lipson, S. *CNS Drug Rev.* **2006**, *12*, 167; (e) Zhou, L.; Sutton, G. M.; Rochford, J. J.; Semple, R. K.; Lam, D. D.; Oksanen, L. J.; Thornton-Jones, Z. D.; Clifton, P. G.; Yueh, C.-Y.; Evans, M. L.; McCrimmon, R. J.; Elmquist, J. K.; Butler, A. A.; Heisler, L. K. *Cell Metabolism* **2007**, *6*, 398; (f) Wacker, D. A.; Miller, K. J. *Curr. Opin. Drug Discov. Devel.* **2008**, *11*, 438.
2. (a) Allerton, C. M. N.; Andrews, M. D.; Blagg, J.; Ellis, D.; Evrard, E.; Green, M. P.; Liu, K. K.-C.; McMurray, G.; Ralph, M.; Sanderson, V.; Ward, R.; Watson, L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5791; (b) Andrews, M. D.; Green, M. P.; Allerton, C. M. N.; Batchelor, D. V.; Blagg, J.; Brown, A. D.; Gordon, D. W.; McMurray, G.; Millns, D. J.; Nichols, C. L.; Watson, L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5343; (c) Fish, P. V.; Brown, A. D.; Evrard, E.; Roberts, L. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1871.
3. Walsh, A. E. S.; Smith, K. A.; Oldman, A. D.; Williams, C.; Goodall, E. M.; Cowen, P. J. *Psychopharmacology* **1994**, *116*, 120.

4. Kennett, G. A.; Wood, M. D.; Bright, F.; Trail, B.; Riley, G.; Holland, V.; Avenell, K. Y.; Stean, T.; Upton, N.; Bromidge, S.; Forbes, I. T.; Brown, A. M.; Middlemiss, D. N.; Blackburn, T. P. *Neuropharmacology* **1997**, *36*, 609.
5. Tecott, L. H.; Sun, L. M.; Akana, S. F.; Strack, A. M.; Lowenstein, D. H.; Dallman, M. F.; Julius, D. *Nature* **1995**, *374*, 542.
6. Vickers, S. P.; Clifton, P. G.; Dourish, C. T.; Tecott, L. H. *Psychopharmacology* **1999**, *143*, 309.
7. Sargent, P. A.; Sharpley, A. L.; Williams, C.; Goodall, E. M.; Cowen, P. J. *Psychopharmacology* **1997**, *133*, 309.
8. Fitzgerald, L. W.; Burn, T. C.; Brown, B. S.; Patterson, J. P.; Corjay, M. H.; Valentine, P. A.; Sun, J.-H.; Link, J. R.; Abbaszade, I.; Hollis, J. M.; Largent, B. L.; Hartig, P. R.; Hollis, G. F.; Meunier, P. C.; Robichaud, A. J.; Robertson, D. W. *Mol. Pharmacol.* **2000**, *57*, 75.
9. Rothman, R. B.; Baumann, M. H.; Savage, J. E.; Rauser, L.; McBride, A.; Hufeisen, S. J.; Roth, B. L. *Circulation* **2000**, *102*, 2836.
10. Roth, B. L.; Willins, D. L.; Kristiansen, K.; Kroeze, W. K. *Pharmacol. Ther.* **1998**, *79*, 231.
11. (a) Thomsen, W. J.; Grottick, A. J.; Menzaghi, F.; Reyes-Saldana, H.; Espitia, S.; Yuskin, D.; Whelan, K.; Martin, M.; Morgan, M.; Chen, W.; Al-Shamma, H.; Smith, B.; Chalmers, D.; Behan, D. *J. Pharmacol. Exp. Ther.* **2008**, *325*, 577; (b) Smith, S. R.; Prosser, W. A.; Donahue, D. J.; Morgan, M. E.; Anderson, C. M.; Shanahan, W. R. *Obesity* **2009**, *17*, 494; (c) Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Dosa, P. I.; Covel, J. A.; Ren, A.; Webb, R. R.; Beeley, N. R. A.; Martin, M.; Morgan, M.; Espitia, S.; Saldana, H. R.; Bjenning, C.; Whelan, K. T.; Grottick, A. J.; Menzaghi, F.; Thomsen, W. J. *J. Med. Chem.* **2008**, *51*, 305.
12. The condensation could also be carried out in refluxing dioxane in the presence of catalytic *p*-toluenesulfonic acid.
13. The absolute stereochemistry of compounds reported herein is unknown. Attempts to obtain a suitable crystalline form of the amide derived from coupling the secondary amino group of compound (+)-**2a** with *1R*-(−)-10-camphorsulfonyl chloride for X-ray analysis were unsuccessful. In most cases there was a ca. 10–40-fold difference in 5-HT_{2C} binding activities between the two enantiomers.
14. Radioligand binding studies were conducted to determine the binding affinities (K_i values) of compounds for the human recombinant 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. [^{125}I]DOI was used as a radioligand for the 5-HT_{2C} and 5-HT_{2A} assays. [^{3}H]LSD was used for the 5-HT_{2B} assay. Functional screenings were carried out by measuring calcium mobilization in HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor using FLIPR^{384} (Molecular Devices, Sunnyvale, CA). See Ref. 15 for complete description of all in vitro and in vivo assays.
15. Wacker, D. A.; Varnes, J. G.; Malmstrom, S. E.; Cao, X.; Hung, C.-P.; Ung, T.; Wu, G.; Zhang, G.; Zuvich, E.; Thomas, M. A.; Keim, W. J.; Cullen, M. J.; Rohrbach, K. W.; Qu, Q.; Narayanan, R.; Rossi, K.; Janovitz, E.; Lehman-McKeeman, L.; Malley, M. F.; Devenny, J.; Pelleymounter, M. A.; Miller, K. J.; Robl, J. A. *J. Med. Chem.* **2007**, *50*, 1365.
16. Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Davies, S.; Duckworth, D. M.; Forbes, I. T.; Gaster, L. M.; Ham, P.; Jones, G. E.; King, F. D.; Mulholland, K. R.; Saunders, D. V.; Wyman, P. A.; Blaney, F. E.; Clarke, S. E.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Lightowler, S.; Middlemiss, D. N.; Trail, B.; Riley, G. J.; Wood, M. D. *J. Med. Chem.* **2000**, *43*, 1123.
17. In the reversal study, a 10 mpk dose of compound (+)-**3c** alone produced a significant 19.7% reduction in food intake versus a statistically insignificant 5% increase in food consumption when (+)-**3c** (10 mpk) was co-administered with a 10 mpk dose of the 5-HT_{2C} antagonist SB243213. SB243213 alone produced a significant 26.7% increase in food consumption at the 10 mpk dose.
18. Compounds (+)-**2a** and (+)-**3c** were also tested in an IP3 accumulation assay for 5-HT_{2B} activity and displayed no agonism at concentrations up to 10 μM. The lack of 5-HT_{2B} functional agonism and high binding affinity (K_i = 8.6 nM) displayed by (+)-**2a** supports potent antagonism at the receptor.