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Discovery of 1-(3,4-dichlorophenyl)-*N*,*N*-dimethyl-1,2,3,4-tetrahydroquinolin-4-amine, a dual serotonin and dopamine reuptake inhibitor

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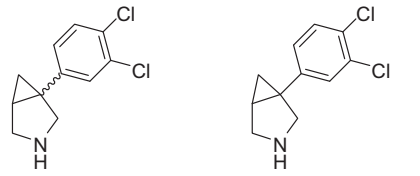
ABSTRACT

The present work describes a series of novel tetrahydroquinoline amines that potently inhibit the in vitro reuptake of serotonin and dopamine (dual reuptake inhibitors). The compounds are structurally related to a series we disclosed previously, but are improved with respect to cytochrome P-450 enzyme (CYP) and potassium ion channel Kv11.1 (hERG) inhibition and synthetic accessibility. The detailed synthesis and in vitro activity and ADME profile of the compounds is described, which represent a previously undisclosed dual reuptake inhibitor chemotype.

The monoamine hypothesis of depression postulates that deficits in serotonin, norepinephrine and dopamine in the central nervous system underlie the disease, and is supported by the clinical efficacy of marketed selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) in alleviating symptoms of depression.[1] Efforts towards the discovery of a single agent that would simultaneously elevate all three monoamines, a triple reuptake inhibitor (TRI), have been driven by a desire to improve the efficacy, onset of the action and adverse effect profile of SSRIs and SNRIs.[2,3] The benefit of adding a dopamine component is supported by the finding of linkages between deficits in mesocorticolimbic dopaminergic function and anhedonia.[4] In addition, dopamine reuptake inhibitors (e.g., buproprion) and dopamine agonists (e.g., pramipexole) are already used clinically as antidepressants[5] and to augment the effects of traditional antidepressants in treatment refractory patients.[6]

The TRI theory was reduced to practice preclinically with DOV-21,947[7] and DOV-216,303.[8] Both compounds potently inhibited the three monamine transporters (IC_{50} for *h*SERT, *h*NET and *h*DAT for DOV-21,947 = 12, 23, 96 nM and for DOV-216,303 = 14, 20, 78 nM, respectively), and exhibited antidepressant-like activity in the rat forced swim and mouse tail suspension tests (Fig. 1).

Although the overall clinical picture for TRIs is still mixed,[9,10] DOV Pharmaceuticals produced a positive Phase II clinical result for a TRI in 2005. DOV-216,303 was shown in a multicenter, active comparator Phase II study of patients with moderate to severe major depressive disorder ($n = 67$) to be safe and as effective as citalopram.[11]



DOV-216,303
racemic

DOV-21,947
(+)-(3,4-dichlorophenyl)-3-azabicyclo[3.3.0]-hexane

Figure 1. Structures of DOV-216,303 and 21,947.

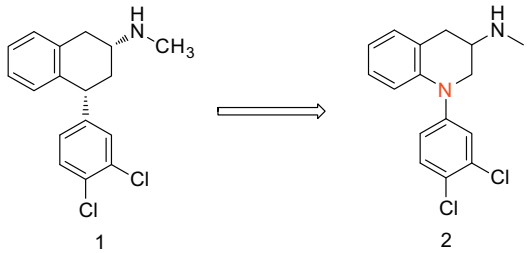


Figure 2. Transformation of tetrahydronaphthalene to tetrahydroquinoline.

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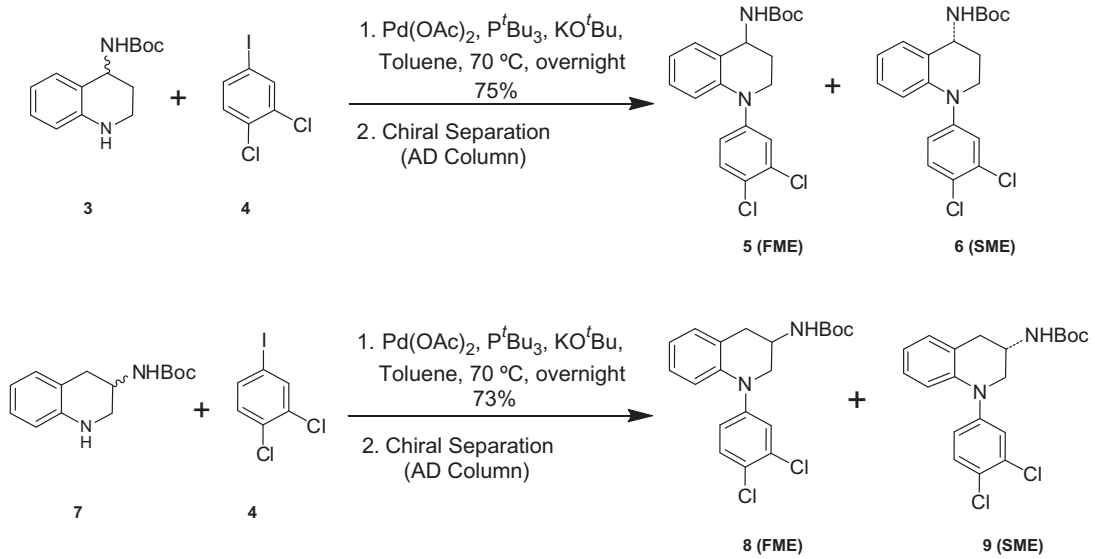
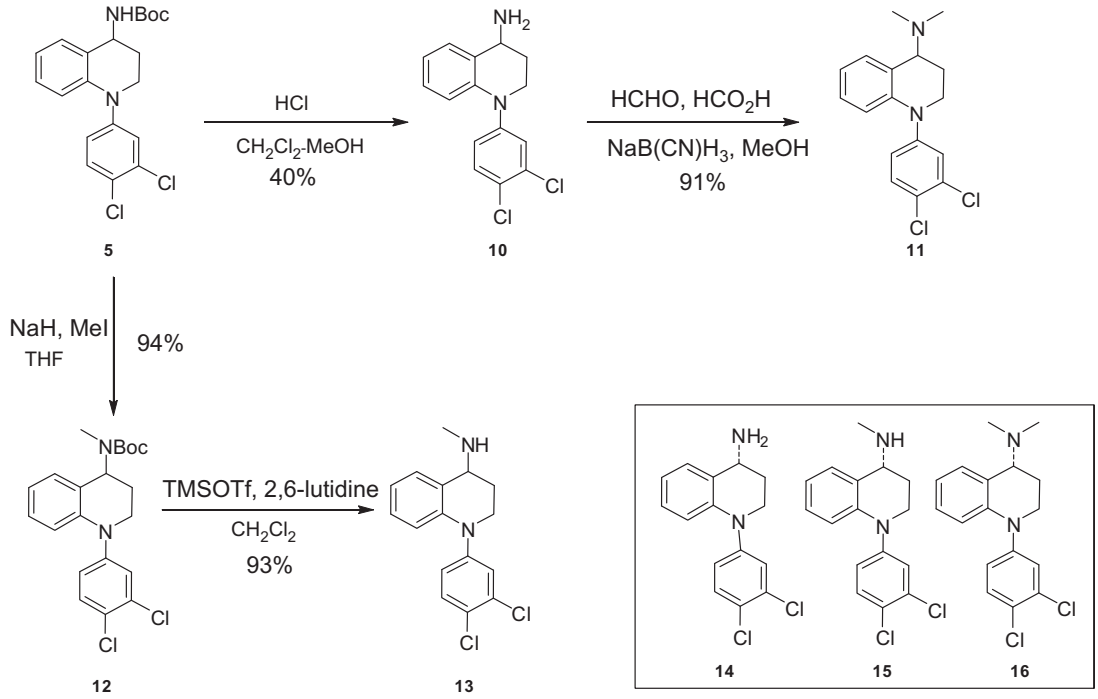
In a previous communication[12] we detailed the synthesis and the in vitro and in vivo profile of compounds such as **1**, which were potent triple reuptake inhibitors against the serotonin, norepinephrine and dopamine transporters (Fig. 2). The compounds were also active in the mouse tail suspension test[13] (10 mg/kg p.o.), an in vivo model widely used to assess antidepressant-like activity. On the negative side, the compound series also showed some inhibition of CYP2D6 and the hERG potassium channel, and we sought to minimize those undesired activities in a subsequent compound series. Our present work focused on an additional modification to the scaffold to create tetrahydroquinolines **2** (Fig. 2). Structure **2** retained the basic amine and lipophilic aromatic features present in **1**, but was simplified by removing the second stereogenic center. Our goal was to determine the in vitro profile of compounds such as **2** to determine if the desired potent reuptake inhibitory activities could be retained while minimizing the detrimental CYP2D6 and hERG inhibitory activities.

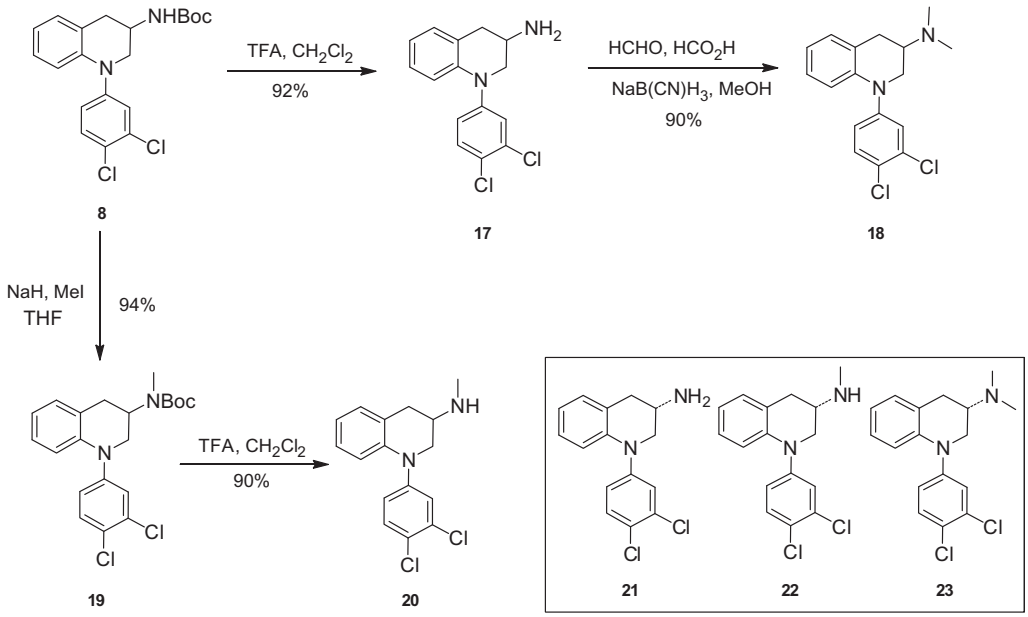
The first step in the synthesis of our potential triple reuptake inhibitors was palladium catalyzed coupling of 1-iodo-3,4-dichlorophenyl benzene to *N*-Boc protected tetrahydroquinoline **3**, which proceeded in good yield to give the desired racemic phenyl tetrahydroquinolines (Scheme 1). Chiral separation on a Chiral Technologies AD column provided pure fast moving enantiomer **5** (FME) and slow moving enantiomer **6** (SME). A similar reaction scheme with the β-amino tetrahydroquinoline **7** provided compounds **8** (FME) and **9** (SME) as pure enantiomers.



Scheme 1. Synthesis of tetrahydroquinolines **5**, **6**, **8**, and **9**.



Scheme 2. Synthesis of compounds **10**, **11**, **13**, and **14**–**16**.



Scheme 3. Synthesis of compounds **17**, **18**, **20**, and **21**–**23**.

Table 1
IC_{50} values at inhibition of human recombinant SERT, NET and DAT transporters for tetrahydroquinolines

Compound	IC_{50} (nM)		
	5-HT	NE	DA
1	107	73	72
10	650	926	246
11	3	7141	5033
13	20	934	39
14	116	138	12
15	132	601	8
16	7	1184	16
17	2550	2597	605
18	436	1857	122
20	985	1005	177
21	2400	1849	465
22	128	1246	100
23	5558	3091	309

Elaboration of the amines in **5** and **6** was straightforward and is shown in Scheme 2. Removal of the Boc protecting group using HCl gave primary amine **10**, which was dimethylated under reductive amination conditions using formic acid and sodium cyanoborohydride to give dimethyl amine **11**. Alternatively, alkylation of the *N*-Boc starting material **5** gave methyl amine **12**, which was deprotected using TMSOTf in CH_2Cl_2 to give monomethyl amine **13**. A similar reaction scheme using chiral amine **6** as starting material provided compounds **14**–**16**.

Starting from the β-amino tetrahydroquinoline **8**, deprotection using TFA in CH_2Cl_2 provided primary amine **17**, which was dimethylated (formic acid, sodium cyanoborohydride) to give dimethyl amine **18** (Scheme 3). Alternatively, methylation of the *N*-Boc starting material **8** provided compound **19**, which was deprotected to give monomethyl amine **20**. A similar reaction sequence using the enantiomeric starting material **9** provided compounds **21**–**23**.

Table 1 details the in vitro data for the novel tetrahydroquinolines for inhibition of human recombinant serotonin,[14] norepinephrine,[15] and dopamine[16] transporters using published methods.

For the first series of compounds, inhibition at SERT was best for the dimethyl amines (compounds **11** and **16**), and most of the compounds showed modest inhibition at NET. Compound **14** was an exception, showing an IC_{50} of 138 nM at NET. For inhibition at DAT, the compounds were generally potent inhibitors, with the exception of compound **11**, which selectively inhibited SERT. The standouts in the α-amino-tetrahydroquinolines series from a triple reuptake perspective were primary amine **14**, which was below 200 nM at SERT and NET and below 20 nM on DAT, and dimethyl amine **16**, which was a potent dual dopamine serotonin reuptake inhibitor (DSRI).

In general, SERT inhibition was weak in the β-amino-tetrahydroquinoline series, with only compound **22** showing an IC_{50} <200 nM. Inhibition at DAT was significant for the mono and dimethyl amines in the second series, while none of the β-amino-tetrahydroquinolines showed inhibition at NET below 1 μM.

Table 2
In vitro microsomal stability, CYP and hERG inhibition for selected compounds

Compound	Microsomal stability $t_{1/2}$ (min)		CYP450 inhibition IC_{50} (μM)					hERG IC_{50} (μM)
	Human	Mouse	1A	2C9	2C19	2D6	3A4	
14	>300	201	>25	>25	>25	4.87	>25	3.5
13	199	22	>25	>25	14.1	3	>25	7.8
15	>300	>300	>25	>25	19	1.5	>25	3.25
16	>300	.300	>25	.25	>25	6.02	>25	8.6
22	237	20	n.t.*	n.t.	n.t.	0.10	n.t.	n.t.

* n.t., not tested.

The in vitro microsomal stability, CYP and hERG inhibition profiles of series one compounds **13**–**16** and series two compound **22** are shown in Table 2. All of the compounds showed excellent stability in the human microsomal stability assay, with half-lives greater than 200 min in most cases. The CYP inhibition profile of the series one compounds was similar or slightly improved compared to initial lead **1** (CYP2D6 IC_{50} = 2.78 μM), with primary amine **13** showing an IC_{50} at CYP2D6 of almost 5 μM, and dimethyl amine **16** showing an IC_{50} of 6.02 μM. Inhibition at the hERG potassium channel was also reduced for the series one compounds, with compound **13** and **16** showing IC_{50}'s of 7.8 and 8.6 μM, respectively. The only compound tested from series 2, monomethyl amine **22**, showed good stability in the human microsomal stability assay, but also showed potent inhibition against CYP2D6 (IC_{50} = 100 nM). No other isoforms were tested for compound **22** due to the significant CYP2D6 inhibition.

The α- and β-amino tetrahydroquinolines described in the present work are a significant synthetic improvement over the β-amino tetrahydronaphthalenes described in our initial work. With only one chiral center, the synthesis was comparably easier, eliminating the need to separate the mixtures of diastereomers present in any work using tetralone precursors. The series one tetrahydroquinoline-4-amines showed better CYP2D6 and hERG inhibition profiles, which should reduce the potential for cardiac toxicity (hERG) and drug–drug interactions (CYP2D6), while maintaining potent reuptake inhibition against the serotonin and dopamine transporters. The loss of norepinephrine reuptake inhibition may improve the safety profile of this class of compounds; the NE transporter is expressed in heart tissue and the clinical effects of NE reuptake inhibitors on heart function is an area of active research.[17] Future communications will detail the in vivo efficacy profile of this novel class of dual reuptake inhibitors.

References and notes

1. Hirschfeld, R. M. *J. Clin. Psychiatry* **2000**, *61*, 4.
2. British Association for Psychopharmacology. Evidence based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines [online]. available from URL: http://www.bap.org.uk.
3. Paul, I. A. *Pharma. News* **2001**, *8*, 33.
4. D'Aquila, P. S.; Collu, M.; Gessa, G. L.; Serra, G. *Eur. J. Pharmacol.* **2000**, *405*, 365.
5. Corrigan, M. H.; Denahan, A. Q.; Wright, C. E.; Ragual, R. J.; Evans, D. L. *Depress. Anxiety* **2000**, *11*, 58.
6. Sporn, J.; Ghaemi, S. N.; Sambur, M. R.; Rankin, M. A.; Recht, J.; Sachs, G. S.; Rosenbaum, J. F.; Fava, M. *Ann. Clin. Psychiatry* **2000**, *12*, 137.
7. Skolnick, P.; Popik, P.; Janowsky, A.; Beer, B.; Lippa, A. S. *Eur. J. Pharmacol.* **2003**, *461*, 99.
8. (a) Beer, B.; Stark, J.; Krieter, P.; Czobor, P.; Beer, G.; Lippa, A.; Skolnick, P. *J. Clin. Pharmacol.* **2004**, *44*, 1360; (b) Skolnick, P.; Popik, P.; Janowsky, A.; Beer, B.; Lippa, A. S. *Life Sci.* **2003**, *73*, 3175.
9. Graff, O.; Learned, S.; Roychowdhury, S. M.; Moate, R.; Morrison, D.; Lavergne, A; Krishnan, K. R.; Archer, G.; Modell, J.; Alexander, R.; Ratti, E. ACNP Poster 2009.
10. Sepracor Inc. Press Release, July 1, 2009.
11. DOV Pharmaceutical Press Release, September 27, 2005.
12. Shao, L.; Wang, F.; Malcolm, S. C.; Ma, J.; Hewitt, M. C.; Campbell, U.; Varney, M. *Bioorg. Med. Chem.* **2010**, doi:10.1016/j.bmc.2010.10.034.
13. Steru, L.; Chermat, R.; Thierry, B.; Simon, P. *Psychopharmacology* **1985**, *85*, 367.
14. Gu, H.; Wall, S.; Rudnick, G. *J. Biol. Chem.* **1994**, *269*, 7124.
15. Galli, A.; DeFelice, L. J.; Duke, B. J.; Moore, K. R.; Blakely, R. D. *J. Exp. Biol.* **1995**, *198*, 2197.
16. Pristupa, Z. B.; Wilson, J. M.; Hoffman, B. J.; Kish, S. J.; Niznik, H. B. *Mol. Pharmacol.* **1994**, *45*, 125.
17. Vincent, S.; Bieck, P. R.; Garland, E. M.; Loghin, C.; Bymaster, F. P.; Black, B. K.; Gonzales, C.; Potter, W. Z.; Robertson, D. *Circulation* **2004**, *109*, 3202.