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4-Phenyl tetrahydroisoquinolines as dual norepinephrine and dopamine reuptake inhibitors

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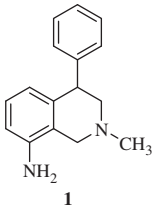
ABSTRACT

Novel 4-phenyl tetrahydroisoquinolines that inhibit both dopamine and norepinephrine transporters were designed and prepared. In this Letter, we describe the synthesis, in vitro activity and associated structure–activity relationships of this series. We also report the ex vivo NET occupancy of a representative compound, **41**.

Monoamine reuptake inhibitors block the uptake of synaptic serotonin, norepinephrine and dopamine by the presynaptic serotonin, norepinephrine and dopamine transporters (SERT, NET and DAT, respectively). For several decades, selective serotonin reuptake inhibitors (SSRIs) and dual serotonin-norepinephrine reuptake inhibitors (SNRIs) have been used to treat a number of CNS disorders, such as depression, anxiety, obsessive compulsive disorder and pain.[1,2]

Nomifensine (**1**) is a monoamine reuptake inhibitor, with a unique dual inhibition activity at the norepinephrine and dopamine transporters and much less activity at the serotonin transporter. It was marketed for use as an antidepressant in the 1970s and was also investigated for the treatment of attention deficit hyperactivity disorder (ADHD).[3,4] Nomifensine was withdrawn from the market in the 1980s mainly due to its association with immune hemolytic anemia.[5,6] Recent studies have explored the potential role of metabolism in these adverse events.[7] In particular, the presence of an aniline group has been implicated as a source of reactive metabolites.[7a,b] We wanted to explore novel dual NET/DAT reuptake inhibitors as such agents could provide benefit in the treatment of depression, and might also have an improved profile for the treatment of ADHD as compared to current therapies. Although stimulants remain the treatment of choice for patients with ADHD due to exceptional response rate, their use is associated with abuse potential.[8] On the other hand, atomoxetine, a NET inhibitor and the only approved non-stimulant for the treatment of ADHD, was generally considered less efficacious compared to the stimulants.[8] A NET/DAT dual inhibitor might overcome these limitations of existing ADHD therapies.



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† These aurhors were employees of DuPont Pharmaceuticals when this work was conducted.

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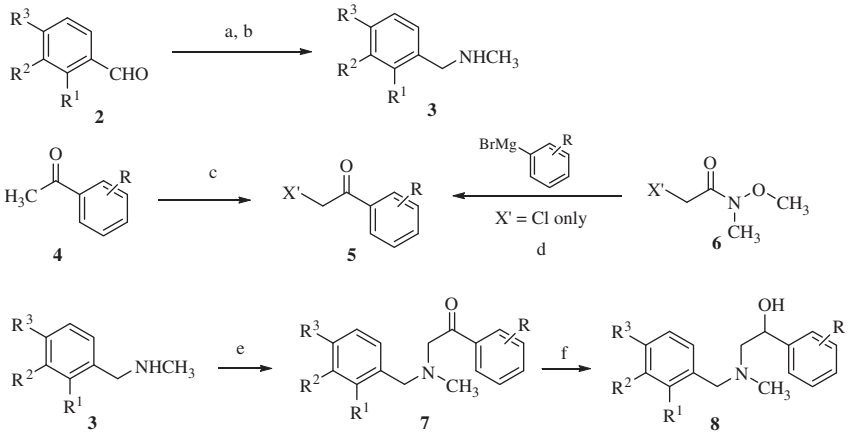
In pursuit of novel NET/DAT inhibitors, our medicinal chemistry efforts explored novel tetrahydroisoquinolines (THIQs) lacking the aniline moiety of **1** with high NET potency (K_i <15 nM), 2- to 10-fold selectivity over DAT and >25-fold selectivity for NET over SERT. Here we describe the preparation of a series of novel 4-phenyl THIQ derivatives, along with the in vitro and in vivo biological evaluation of representative compounds.

Our general synthetic method is shown in Schemes 1 and 2.[9,12] Reductive amination of aldehydes **2** afforded methylamines **3**. Haloacetophenones **5** were prepared by bromination of methyl ketones **4** or by addition of an aryl Grignard reagent to Weinreb amides **6**. Alkylation of amine **3** with **5** afforded ketones **7**. Reduction of **7** provided the hydroxyl intermediates **8**.

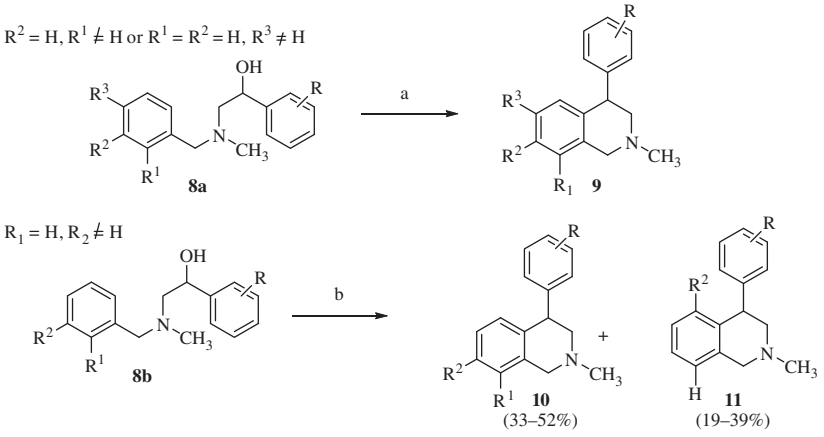
Scheme 2 shows the acid catalyzed cyclization of **8** which provides the THIQ core. When $R^2 = R^3 = H$ and $R^1 \neq H$ (**8a**), **9** was obtained as the sole product. Similarly, for the synthesis of compounds **21** and **22** (**8a,** $R^1 = R^2 = H$, $R^3 = CH_3$ and OCH_3, respectively) the cyclization gave a single regioisomer due to the symmetry of the cyclization precursor. When $R^1 = H$ and $R^2 \neq H$ (**8b**), there are two open positions for the cyclization to occur, thus a mixture of regioisomers **10** and **11** was obtained with **10** as the predominant regioisomer in most cases. Compounds **10** and **11** were readily separated by column chromatography. Single enantiomers of compounds **9–11** typically were obtained by chiral HPLC**.** The final products **9**–**11** were generally converted to the corresponding salt (maleate, fumarate or hydrochloride) for biological testing.

We initially explored substitution on the THIQ core (R^1 through R^4 in Table 1). To simplify the comparison of binding data, these initial analogues did not have substitution on the 4-phenyl ring. As seen in Table 1, **1** has dual activity at NET and DAT and is essentially inactive at SERT. Removal of the anilino group decreased potency at NET and DAT by 2- to 3-fold (Compound **12** vs **1**). Substitution at R_1 with methyl, methoxy and hydroxy groups (compounds **13**–**15**) had no benefit. We were pleased to find out that methyl or methoxy substitution at R^2 (compounds **16** and **18**) increased potency at NET with K_i below 100 nM along with 2.5- to5-fold selectivity for NET over DAT and weaker SERT activity as desired. The R^1–R^2-dimethyl analogue **20** did not have a favorable potency at either NET or DAT. Potency and NET/DAT selectivity suffered when R_3 was methyl or methoxy (**21**–**22**). Substitution at R^4 attenuated activity at both NET and DAT (Compound **23**). From this data, we concluded that substitution at the 7-position (R^2) of the THIQ is preferred for the dual DAT/NET activities.

We next elaborated the pendant aryl ring (Table 2). We focused on analogues with substitutions on the 6- and 7-positions of the THIQ core (R^1 and R^2, respectively), since these compounds seemed to have substantial activity for NET and DAT and demonstrated the desired selectivity over SERT. These compounds were typically separated into enantiomers by chiral HPLC prior to testing. It was determined that the more active enantiomer was (+) in all cases, as seen in Table 2 [comparison of compounds **24-(+)** and **24-(**−**)** and **25**-(+) and **25**-(−)]. It was later determined using X-ray crys-

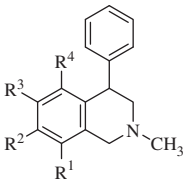


Scheme 1. Reagents and conditions: (a) CH_3NH_2, MeOH; (b) $NaBH_4$, H_2O, MeOH, 0 °C to rt, 2.5 h; (c) HBr, HOAc, rt, 2 h or Bu_4NBr_3, THF, rt, 18 h; (d) THF, −10 °C to rt, 20 min; (e) 5, Et_3 N, CH_2Cl_2, rt, 18 h; (f) $NaBH_4$, EtOH, 0 °C to rt, 1.5 h.



Scheme 2. Reagents and conditions (a) H_2SO_4, CH_2Cl_2, 0 °C to rt, 20 min, 58–73%; (b) H_2SO_4, CH_2Cl_2, 0 °C to rt, 20 min.

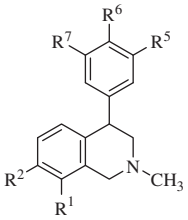
Table 1
In vitro inhibition of NET, DAT and SERT[a]



Compd.	Substitution				K_i (nm)		
	R^1	R^2	R^3	R^4	NET	DAT	SERT
1	NHH_2	H	H	H	47	84	2057
12	CH_3	H	H	H	100	276	1430
13	OCH_3	H	H	H	136	157	4224
14	OH	H	H	H	137	129	2050
15	H	H	H	H	238	371	1510
16	H	CH_3	H	H	35	112	1220
17	H	Et	H	H	54	233	767
18	H	OCH_3	H	H	31.8	82	1450
19	H	OEt_3	H	H	115	210	352
20	CH_3	CH_3	H	H	135	227	1750
21	H	H	CH_3	H	116	107	2850
22	H	H	OCH_3	H	1020	173	1570
23	H	H	H	CH_3	806	1840	N.D.

[a] Data are for racemates. N.D. not determined.

Table 2
In vitro inhibition NET, DAT and SERT[a]



Compd.	Substitution					K_i (nm)		
	R^1	R^2	R^5	R^6	R^7	NET	DAT	SERT
1	NH_2	H	H	H	H	47	84	2057
24-(+)	NH_2	H	H	H	H	21.5	43	935
24-(−)	NH_2	H	H	H	H	6450	13400	1550
25-(+)	H	H	H	Cl	H	28	38	25
25-(−)	H	H	H	Cl	H	630	356	1776
26	H	H	F	F	H	12.3	98.8	266
27	H	H	F	Cl	H	7.2	44.7	81.7
28	H	H	F	CH_3	H	4.4	30.1	102
29	H	H	CH_3	F	H	13.5	61	118
30	CH_3	H	F	F	H	37	58	ND
31	CH_3	H	H	CH_3	H	19	10.6	822
32	H	F	H	H	H	29	687	1470
33	H	OCH_3	F	F	H	9	77	530
34	H	OCH_3	CH_3	H	H	7.3	25	479
35	H	OCH_3	F	CH_3	H	16.5	21.5	111
36	H	OH	F	F	H	13	64	287
37	H	CH_3	H	CH_3	H	15	27	121
38	H	CH_3	F	F	H	14	106	594
39	H	CH_3	Cl	H	H	5	36	338
40	H	CH_3	F	H	F	5.8	78	2149
41	H	CH_3	H	F	H	7.1	36.2	231
42	H	CH_3	H	Cl	H	47	40.5	116
43	H	CH_3	F	H	H	35	291	2310

[a] Except where noted, compound is the (+)-enantiomer N.D.: not determined.

tallography that the (+)-enantiomer of a representative compound **41** has the (*S*) configuration (data not shown). Halogenated or methylated phenyl analogues (such as compounds **26**–**29**) afforded high potency at NET, and varied selectivities versus DAT and SERT.

Table 3
NET Ki and occupancy data (10 mg/kg)

Compd.	NET K_i (nM)		Occupancy (%)
	Human	Rat	
1	23	20	67
Duloxetine	5.97	3.9	70
Compound **41**	7.1	6.3	49

Two of these compounds (**27** and **28**) provided the first compounds with single-digit nM NET activity. Introduction of a methyl group at R^1 (compounds **30** and **31**) resulted in loss of selectivity over DAT.

Compounds **32**–**43** are all 7-substituted THIQ analogues. The 7-F THIQ **32** had relatively low activity at NET and DAT. Compounds **33**–**36** (all 7-methoxy or phenolic analogues) displayed good potency for NET and DAT and generally good selectivity over SERT. Compounds substituted with methyl at the 7-position were generally very potent at NET (**37**–**43**). Selectivity over SERT was also generally good, with the exception of the *p*-methyl phenyl analogue **37**, which was not sufficiently selective with respect to DAT or SERT. A number of compounds such as **26**, **40**, and **41** in Table 2 met our initial binding criteria for the three transporters. We selected compound **41** as a representative example for further biological testing.

In order to assess the in vivo activity and brain penetrance of compound **41**, we selected a rat ex vivo binding assay and measured the occupancy levels at NET in frontal cortex. Animals were dosed orally with vehicle, duloxetine (as a NET positive control), **1** or compound **41**, then sacrificed after one hour.[10,11] The results displayed in Table 3 show the NET occupancy levels after oral administration of duloxetine, **1** and compound **41**(10 mg/kg) after 1 hour. Compound **41** demonstrated significant NET occupancy under these conditions, comparable to that of duloxetine and **1**.

Compound **41** was found to be selective when screened for off-target activity. The compound displayed excellent selectivity against a panel of approximately 50 receptors and enzymes (Novascreen), including MAO-A and MAO-B. Compound **41** was also negative in an Ames assay. However, when tested in a CYP450 inhibition assay, **41** exhibited moderate inhibition of CYP2D6 with an IC_{50} value of 0.48 μM. A number of other analogues in this series also exhibited various amounts of CYP2D6 inhibition (data not shown).

In summary, a series of substituted 4-phenyl tetrahydroisoquinolines was prepared in an effort to find new treatments for CNS disorders. Removal of the aniline group of **1** and optimization provided potent NET/DAT inhibitors. A representative compound in the series, compound **41**, demonstrated potent NET and DAT dual inhibition with desirable selectivity over SERT. These values met our selectivity criteria. Compound **41** was shown to penetrate the CNS and occupy the site of action (NET). However, the possibility of drug–drug interactions predicted by CYP2D6 inhibition hindered progression of this series. Further optimization of this series was pursued and the results will be reported in due course.

Acknowledgment

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12. The synthesis of these THIQ analogues is exemplified by the preparation of **43** as described below:
Step A: *m*-Tolualdehyde (1.66 g, 14.0 mmol) was treated with methylamine (40% aqueous, 1.39 ml, 18.0 mmol) in methanol (20 ml) at room temperature. The reaction was stirred for 20 min and treated with sodium borohydride (0.26 g, 7.0 mmol) portionwise. The reaction was stirred for 1 h and treated with 3′-fluoro-2-bromoacetophenone (3.0 g, 14.0 mmol) followed by stirring for 45 min at room temperature. The reaction was finally treated with sodium borohydride (0.52 g, 14.0 mmol) portionwise, and stirring continued overnight. The reaction was diluted with water (100 ml) and extracted with methylene chloride (3 × 100 ml). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate, followed by filtration and concentration in vacuo. Purification by column chromatography on silica gel eluting with hexanes/ethyl acetate (3/1) provided the amino alcohol (4.3 g) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 7.30 (m, 7H), 4.73 (t, J = 6.0 Hz, 1H), 3.60 (ABq, J_{AB} = 14.0 Hz, 2H), 2.55 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H), 2.31 (s, 3H); CI MS m/z = 274 $[C_{17}H_{20}NFO+H]^+$.
Step B: The product from Step A (1.0 g, 4.0 mmol) was stirred in methylene chloride (100 ml) and treated dropwise with concentrated sulfuric acid (98%, 7.0 ml) over 3 min. After stirring for 1 h, the reaction mixture was diluted with ice chips and made basic with 25% aqueous ammonium hydroxide. The reactions mixture was extracted with methylene chloride (3 × 100 ml) and the organic extracts combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography, eluting with hexanes/ethyl acetate (3/1), afforded the desired tetrahydroisoquinoline as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 7.00 (m, 5H), 6.75 (d, J = 8.0 Hz,1H), 4.21 (t, J = 7.0 Hz, 1H), 3.64 (ABq, J_{AB} = 15.0 Hz, 2H), 3.02 (m, 1H), 2.56 (m, 1H), 2.41 (s, 3H), 2.29 (s, 3H); CI MS m/z = 256 $[C_{17}H_{18}NF+H]^+$.
Step C: The product from Step B was subjected to chiral HPLC separation employing a Chiral Technologies.
Chiracel™ AD column (5 × 50 cm) eluting with hexanes/isopropanol (9/1) to afford the (R), $[\alpha]_D^{25}$ −16.3 (c = 0.498, MEOH) and (S), $[\alpha]_D^{25}$ +16.3 (c = 0.476, MeOH) enantiomers in order of elution. The (S)-(+) enantiomer was treated with maleic acid (1.0 equiv) and the resultant maleate salt filtered and dried to constant weight. (S)-(+)-2,7-dimethyl-4-(3-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline, maleate salt: mp 172–173.5 °C.