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Letter

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Design and Synthesis of 4-Heteroaryl 1,2,3,4-Tetrahydroisoquinolines as Triple Reuptake Inhibitors

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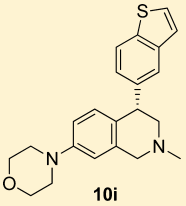
Supporting Information

ABSTRACT: A series of 4-bicyclic heteroaryl 1,2,3,4-tetrahydroisoquinoline inhibitors of the serotonin transporter (SERT), norepinephrine transporter (NET), and dopamine transporter (DAT) was discovered. The synthesis and structure−activity relationship (SAR) of these triple reuptake inhibitors (TRIs) will be discussed. Compound **10i** (AMR-2), a very potent inhibitor of SERT, NET, and DAT, showed efficacy in the rat forced-swim and mouse tail suspension models with minimum effective doses of 0.3 and 1 mg/kg (*po*), respectively. At efficacious doses in these assays, **10i** exhibited substantial occupancy levels at the three transporters in both rat and mouse brain. The study of the metabolism of **10i** revealed the formation of a significant active metabolite, compound **13**.



10i

$SERT\ IC_{50}$ = 3.0 nM
$DAT\ IC_{50}$ = 3.1 nM
$NET\ IC_{50}$ = 8.3 nM

KEYWORDS: *Triple reuptake inhibitor, TRI, serotonin reuptake inhibitor, dopamine reuptake inhibitor, norepinephrine reuptake inhibitor, depression, antidepressant*

Major depressive disorder (MDD) is the leading cause of disability in the U.S. among those aged 15−44.[1] It affects approximately 14.8 million American adults, or about 6.7% of the U.S. population age 18 and older in a given year.[2] Aside from the mental and physical suffering of patients, the economic burden of depression was 83.1 billion dollars in the US alone in 2000.[3]

Currently, nearly all antidepressants prescribed are serotonin or dual serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs respectively), which inhibit central serotonin reuptake transporters (SERT) or both SERT and norepinephrine transporters (NET). Despite the therapeutic benefits of SSRIs and SNRIs, a significant proportion of patients show a suboptimal response.[4,5]

Dopamine is involved in centrally mediated reward responses.[6] The inhibition of dopamine reuptake transporter (DAT) elevates synaptic dopamine levels.[7] It has been suggested that the addition of an appropriate degree of DAT inhibition to SSRI or SNRI therapy might help depressed patients overcome anhedonia, a symptom of depressive disorders inadequately addressed by SSRI and SNRIs alone.[6] Bupropion and methylphenidate are inhibitors of dopamine and norepinephrine transporters (DAT/NET), and they are used in the treatment of various psychiatric disorders.[8,9] Several small clinical studies in MDD using combinations of bupropion or methylphenidate with an SNRI or SSRI have shown improved efficacy in patients refractory to SSRI, SNRI, or bupropion therapy alone.[10−13] These clinical results suggest that a triple reuptake inhibitor (TRI), which blocks SERT, NET, and DAT simultaneously, might benefit patients experiencing an inadequate response to current antidepressant therapies.

A number of TRIs have been reported in the past decade.[14−19] Structurally, the design of novel TRIs originated from our series of dual NET/DAT inhibitors,[20] represented by compound **1**. Following the pharmacological strategy outlined above, we sought structural modifications that would build in SERT activity and retain the NET/DAT reuptake profile of **1**. We now report that the placement of bicyclic heterocycles on the 4-position of the tetrahydroisoquinoline (THIQ) core (Figure 1) accomplished this objective and provided compounds with potent TRI profiles. The structure−activity relationship (SAR) of the 4-phenyl THIQ series suggested

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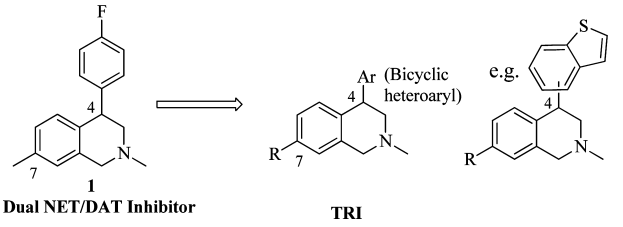
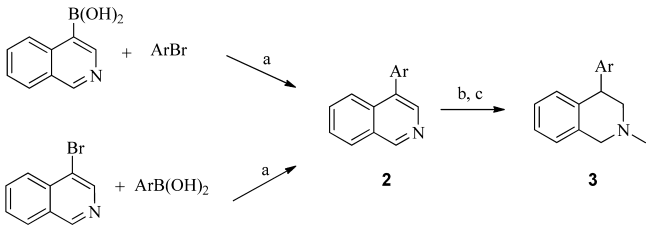


Figure 1. Design of THIQ TRIs.

that substitution on the 7-position of the THIQ often provided potency enhancements. Therefore, we also explored 7-substitution in the current series. In this letter, we report the synthesis and biological evaluation of this novel series of 4-bicyclic heteroaryl 1,2,3,4-THIQ derivatives.

Chemistry. A convenient synthetic route to 4-bicyclic heteroaryl THIQ derivatives without substitution on the 7-position is illustrated in Scheme 1.[21] Commercially available

Scheme 1[a]



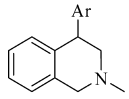
[a]Reagents and conditions: (a) PPh_3, $Pd(OAc)_2$, 1,2-dimethoxyethane, aq. Na_2CO_3; (b) CH_3I, $CHCl_3$ or MeOTf, CH_2Cl_2; (c) $NaCNBH_3$, MeOH, HCl.

isoquinolin-4-ylboronic acid or 4-bromoisoquinoline underwent Suzuki coupling with ArBr or $ArB(OH)_3$ (or the corresponding boronate ester), respectively, to give the 4-aryl isoquinoline **2**. A one-pot methylation followed by reduction yielded the desired 4-bicyclic heteroaryl 1,2,3,4-THIQs **3** (Table 1).

Alternatively, the 4-quinolinyl analogues **3v** and **3w** (Table 1) were prepared by α-arylation of dihydroisoquinolinone (**4a**) with aryl bromide followed by reduction of the lactam **4** (Scheme 2).[22]

The general synthetic route for the majority of the 4-bicyclic heteroaryl 1,2,3,4-THIQs with substitution on the 7-position is illustrated in Scheme 3.[20] Alkylation of benzylamines **5** with bromoacetophenones **4** yielded the desired ketones **6**. Reduction of **6** with $NaBH_4$ followed by a Friedel–Crafts cyclization using methanesulfonic acid gave 4-aryl THIQs **7** as the major regioisomer. For the Friedel–Crafts cyclization step, we found that both the desired regioselectivity and the yield were greater for the methoxy compounds (**6b**) versus the bromides (**6a**). The cyclization typically gave a 2:1 ratio of the desired 7-methoxy isomer **7** over the undesired 5-methoxy isomer in ~60% isolated yield of **7b**. The *O*-demethylation of **7b** followed by the treatment with triflic anhydride provided the triflates **9**. Further functionalization of **9** or bromides **7a**, usually via palladium mediated coupling reactions, provided the final products **10**. For compound **10a**, **10b**, or **10d**, benzylamine **5** with the appropriate R_1 as Y (i.e., $-CH_3$, $-OCH_3$, and $-F$, respectively) was used for the alkylation step (Scheme 3).[21] Compounds **10f–10h** were derived from **10e** using straightforward transformations.[21] The reduction of **10e**

Table 1. Potency at SERT, DAT, and NET Expressed as IC_{50}s or % Inhibition at 100 nM



3

Entry	Ar	Chirality	SERT (IC_{50}, nM)	DAT (IC_{50}, nM)	NET (IC_{50}, nM)
MPH[a]		(+/-)	>10000	34	340
1[b]		(+)	230	36	7.6
3a		(+)	24	5.7	2.6
3b		(+/-)	250	7.5	5.2
3c		(+/-)	110	16	< 1.0
3d		(+/-)	67	51	15
3e		(+/-)	29	43	22
3f		(+/-)	31	>300	69
3g*		(+)	1.7	5.1	3.4
3h		(-)	69	190	350
3i		(+/-)	40	4.5	10
3j		(+/-)	35	38	130
3k		(+/-)	16%	70%	58%
3l		(+/-)	130	200	52
3m*		(+)	68	110	7.8
3n		(+/-)	170	4.5	6.0
3o*		(+)	6.4	12	8.8
3p		(+/-)	24%	40%	48%
3q*		(+)	260	23	11
3r*		(+)	31	270	13
3s*		(+)	32	53	6.8
3t*		(+)	96	78	19
3u*		(+/-)	130	44	22
3v*		(+/-)	6.9	890	1000
3w		(+/-)	78%	6%	15%
3x		(+/-)	82%	28%	32%

[a,b]Inhibition values are K_is.[23,20] Inhibition data (**3a–3x**) were obtained using assay protocol 2 except for data for compounds with "*", which were measured using assay protocol 1 (see Supporting Information). % Inhibition at 100 nM measured using assay protocol 2. The two protocols gave similar results based on the examination of a small set of data generated using both protocols. All data were measured with at least $n = 2$.

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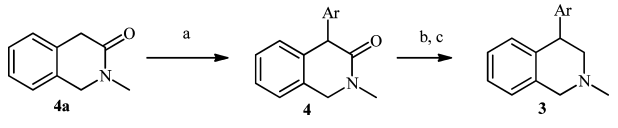
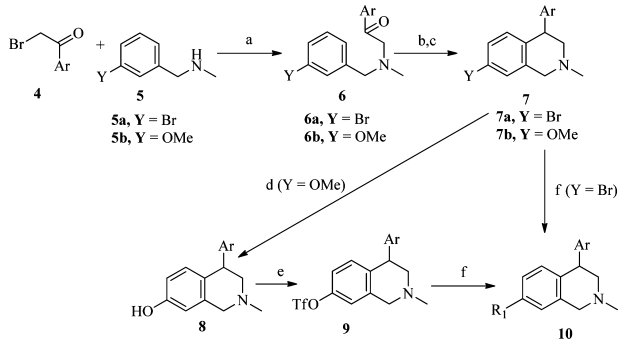
Scheme 2[a]



[a]Reagents and conditions: (a) ArBr, $Pd(OAc)_2$, (0.1 equiv), BINAP (0.1 equiv), NaO^tBu (3.0 equiv) dioxane, reflux; (b) BH_3-Me_2S, THF, 50 °C; (c) MeOH then aq 6 N HCl, dioxane, reflux.

Scheme 3[a]



[a]Reagents and conditions: (a) DIPEA, CH_2C1_2, 0 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) CH_2Cl_2, MsOH, 0 °C; (d) HBr (48%) reflux or E_tSNa, DMF, 140 °C; (e) Tf_2O, Py, CH_2Cl_2; (f) Pd, L, base, R_1X.

with lithium aluminum hydride gave **10f**. A reductive amination reaction of **10f** with formalin and sodium cyanoborohydride afforded **10g**. Compound **10h** was obtained by the bis-alkylation of **10f** with oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) in the presence of sodium carbonate in refluxing acetonitrile. Compounds **3d**, **3i**, and **3l** were also prepared using the route outlined in Scheme 3 since the corresponding aryl bromides or aryl boronic acids were not commercially available.[21] Single enantiomers of compounds **3** and **10** typically were obtained by chiral high-performance liquid chromatography (HPLC) using ChiralpakAD or ChiralcelOD columns.

Results and Discussion. We first examined a variety of bicyclic heterocycles on the 4-position of the THIQ core. The inhibition activities for SERT, DAT, and NET are listed in Table 1. The inhibition data for known dual DAT/NET inhibitors methylphenidate (MPH)[23] and our reported compound **1**[20] are also included in Table 1. In general, a racemic compound was separated into single enantiomers if it showed potent triple inhibition or if a new structural moiety was introduced. To our surprise, while the 4-phenyl THIQs such as **1** possessed a dual NET/DAT inhibition profile, many of the 4-bicyclic heterocycle THIQs inhibited all three transporters with similar potency. In general, benzofuran, benzothiophene, and indole substituted THIQs (**3a**−**3p**) possessed the greatest activity across the three transporters. The point of connection on the pendant heteroaryls had a significant impact on the TRI profile: attachment to the 5- or 6-position on these three heterocycles was optimal for transporter potency. Benzothiophene **3g** was particularly potent and demonstrated low nanomolar inhibition of all three transporters. Compound **3g** was found to be a modestly potent CYP2D6 inhibitor (IC_{50} = 0.8 μM), which represents a potential drug−drug interaction liability. Consistent with our previous observation,[20] there is a stereogenic preference in transporter binding activity. The (+)-enantiomers were found to be more potent than the (−)-enantiomers (exemplified by **3g** and **3h**) in all enantiomeric pairs examined. It is also interesting to note that both the indole and indazole compounds (**3n** and **3q**) with the connecting point at the 5-position had dual DAT/NET activity and that compounds **3f** and **3r** had SERT/NET profiles. The indole and indazole compounds in general had weaker transporter and CYP2D6 inhibition activities compared to the benzofuran and benzothiophene analogues (data not shown). The [6.6]-fused heterocycles (**3v**−**3x**), however, demonstrated a more SERT-selective profile. From the SAR in Table 1, it was clear to us that both the choice of bicyclic heterocycle and the point of connection can have profound impact on the transporter inhibition profile.

Our SAR studies of the 4-phenyl series[20] revealed that substitution on the 7-position of the THIQ scaffold often provided significant activity at all three transporters. Encouraged by the high potency of the benzothiophene compound **3g**, we decided to explore the substitution of the 7-position with the objective of identifying compounds with TRI profiles and reduced CYP2D6 activity.

We prepared a number of analogues of **3g** with various substitutions at the 7-position of the THIQ core (Table 2). As expected, these compounds frequently demonstrated good inhibition at the three transporters. A simple methyl substitution (**10a**) at the THIQ 7-position did not change the TRI profile compared to **3g**. Methoxy or hydroxy substitution also had little impact on the potency at the three transporters (**10b** and **10c**). However, **10a**−**c** were still CYP2D6 inhibitors (IC_{50} <1 μM). Fluoro and cyano (**10d** and **10e**) weakened the inhibition significantly, suggesting that electron withdrawing groups were not favored. Aminomethyl analogues **10f**−**10h** showed very potent triple profiles. The morpholino analogue **10i** had very potent inhibition at all three transporters with a much reduced CYP2D6 inhibition (IC_{50} = 11 μM). As observed in the 7-unsubstituted series (**3**), the (+)-enantiomers of **10** that were examined were more potent TRIs, but also more potent as CYP2D6 inhibitors when compared to the (−)-enantiomers. It is worth noting that the (−)-enantiomer of **10i**, i.e., **10j**, showed weaker, but significant activity at the three transporters. The absolute stereochemistry of **10i** was determined to be (*S*) by X-ray crystallography as shown in Figure 2.

The benzothiophen-6-yl analogue **10k** showed weaker activity at DAT compared to the benzothiophen-5-yl **10i**. The benzothiophen-2-yl analogue **10l**, however, had a transporter inhibition profile very similar to that of **10i**. Replacing the morpholine with piperidine (**10m**) and pyrrolidine (**10n**) resulted in an overall reduction of transporter inhibition potency.

On the basis of its most potent and balanced triple inhibition profile and weak CYP2D6 inhibition profile, compound **10i**[24] was advanced for profiling in a number of *in vitro* and *in vivo* assays. An *ex vivo* binding assay was used to measure the transporter occupancy levels in rodent brain.[25] Clinically effective doses of SSRIs and SNRIs are associated with significant SERT occupancy, as measured by positron emission tomography (PET).[26,27] Following oral administration of **10i** in the rat at 0.3, 1, and 3 mg/kg, *ex vivo* binding was significant and dose-dependent at SERT, NET, and DAT at 1 h postdosing (Table 3),[28] with SERT and NET occupancies

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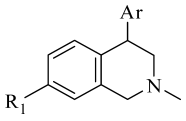
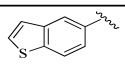
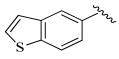
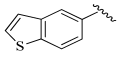
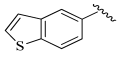
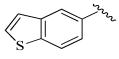
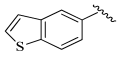
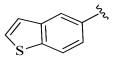
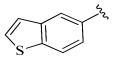
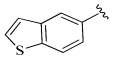
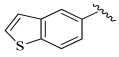
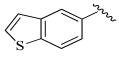
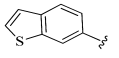
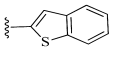
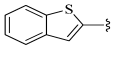
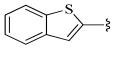
Table 2. Potency at SERT, DAT, and NET for 10[a]



Entry	Ar	R_1	Chirality	SERT (IC_{50}, nM)	DAT (IC_{50}, nM)	NET (IC_{50}, nM)
3g*		H	(+)	1.7	5.1	3.4
10a		CH_3	(+/-)	4.9	12	1.3
10b		OCH_3	(+)	5.3	9.0	5.0
10c		OH	(+)	10	6.9	5.5
10d*		F	(+)	8.4	66	41
10e*		CN	(+)	18	110	180
10f			(+)	28	11	2.9
10g			(+)	4.4	5.3	<3.0
10h			(+/-)	88%	68%	99%
10i*			(+)	3.0	3.1	8.3
10j*			(-)	4.9	140	93
10k			(+)	4.5	88	23
10l*			(+)	4.4	5.8	16
10m			(+)	38	570	110
10n			(+/-)	79%	5%	35%

[a]Inhibition data were obtained using assay protocol 2 except for compounds with "*", which were measured using assay protocol 1 (see Supporting Information). Data for compounds **10h** and **10n** are inhibition at 100 nM. The two protocols gave similar results based on the examination of a small set of data generated using both protocols. All data were measured with at least $n = 2$.

approaching full occupancy of the transporters at the highest dose.

Compound **10i** was also tested in two rodent models used to predict clinical antidepressant activities. In the rat forced swim model, **10i** significantly reduced immobility (a measure of despair) with a lowest effective dose of 1 mg/kg (Figure 3).

When compound **10i** was tested in the mouse tail suspension model,[28] it was found to significantly reduce the duration of immobility in a dose-dependent manner with a minimum effective dose of 1 mg/kg (Figure 4). In a mouse occupancy study, **10i** showed 84% SERT, 82% NET, and 60% DAT

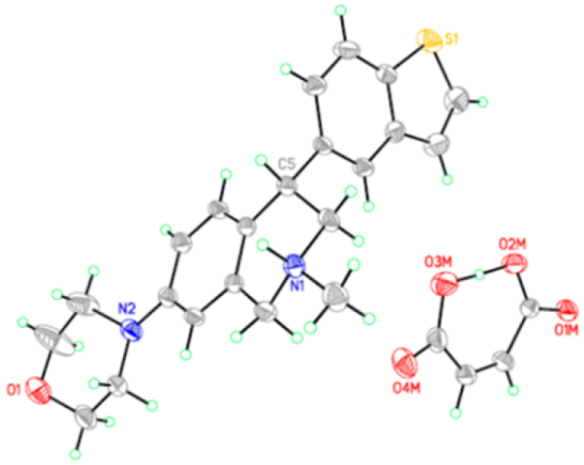


Figure 2. Single crystal structure of **10i** (maleate salt).

Table 3. SERT, DAT, and NET Occupancies for 10i at Different Doses

compd **10i** PO dose (mpk)	SERT occupancy	DAT occupancy	NET occupancy
0.3	84 ± 6%	23 ± 7%	88 ± 3%
1	90 ± 4%	52 ± 5%	94 ± 2%
3	95 ± 8%	77 ± 5%	98 ± 1%

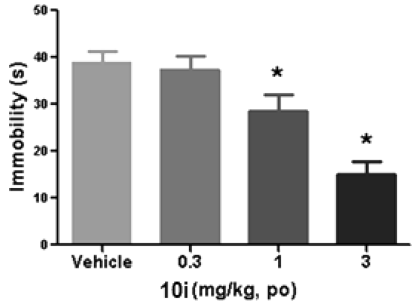


Figure 3. Rat forced-swim test results. Asterisk-marked bars denote significance at $p < 0.05$ versus vehicle for duration of immobilities (n = 12−13). Immobility was measured at 1 h postdosing.

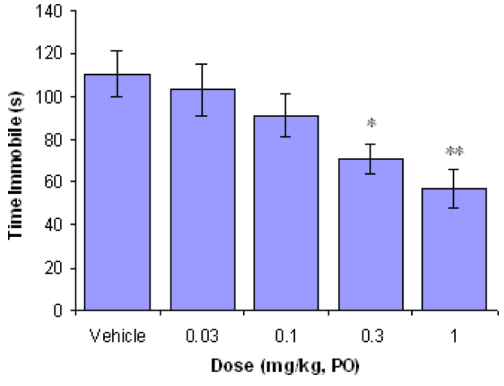


Figure 4. Mouse tail suspension test results for **10i**. *$p < 0.05$ and **$p < 0.01$ versus vehicle for duration of immobilities (n = 10−12). Immobility was measured at 1 h postdosing.

occupancy 1 h after a dose of 1 mg/kg p.o., consistent with the rat transporter occupancy results.

Compound **10i** was screened against a broad panel of receptors and enzymes and showed no significant activity at 1

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μM. Compound **10i** was also negative in the Ames test, which evaluates mutagenic potential. In an *in vitro* assay for evaluating the formation of reactive metabolites, no dansyl−glutathione adducts were detected. In the hERG patch-clamp assay, compound **10i** exhibited an IC_{50} of approximately 1 μM.

The key pharmacokinetic parameters in rats and monkeys for compound **10i** are summarized in Table 4. Compound **10i** exhibited moderate clearance, extensive distribution (high Vd), and was readily absorbed with good oral bioavailability. A brain/plasma ratio of 3 was determined in rat 1 h after oral dosing indicating good CNS penetrance.

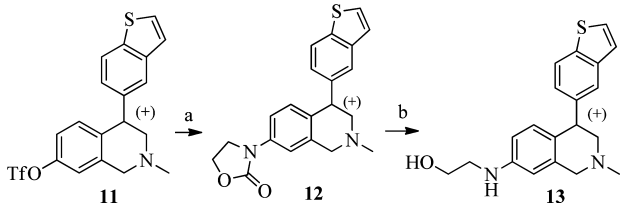
Table 4. Pharmacokinetic Parameters for 10i in Rat and Monkey

species	CL (mL/min/kg)	Vdss (L/kg)	F (%)
rat[a]	47	14	81
monkey[b]	27	16	39

[a]Average of 3 male Sprague−Dawley rats; p.o. 10 mg/kg; i.v. 1 mg/kg. [b]Average of 3 male cynomolgus monkeys; p.o. 2 mg/kg; i.v. 0.5 mg/kg.

Metabolite profiling studies of compound **10i** in human and rat liver microsomes and subsequent structural analysis of metabolites revealed a significant morpholine N,O-dealkylated metabolite **13** (prepared in Scheme 4). To confirm the proposed structure, compound **13** was synthesized starting with triflate **11**[21] via a Buchwald coupling with oxazolidin-2-one to give **12**, followed by hydrolysis (Scheme 4). A pharmacokinetic study of compound **10i** in monkey revealed that **13** was formed in significant amounts (>50% based on AUCs) relative to the parent **10i**. Compound **13** was found to be almost equally potent to parent compound **10i** with IC_{50}s for SERT, DAT, and NET of 2.5, 1.4, and 9.1 nM, respectively. In contrast to the observation of **13** in monkey, the formation of metabolite **13** in rat was not significant. To quickly assess the brain penetrance of this metabolite, **13** was administered intravenously to rat at 2 mg/kg. Significant concentrations (~3−5 μM) of **13** were detected in rat brain tissue 15 min and 1 h after dosing, with brain to plasma ratios of 2.2 (15 min) and 3.6 (1 h). These findings suggested that **13** might contribute significantly to the *in vivo* pharmacology of **10i**. Compound **13** was also a CYP2D6 inhibitor (IC_{50} = 1 μM) and therefore carries a potential drug−drug interactions liability. The formation of a significant amount of an active metabolite could potentially complicate the development of compound **10i**.[29] We have continued to explore compounds with more desirable metabolism profiles and will report our findings in due course.

Scheme 4[a]



[a]Reagents and conditions: (a) oxazolidin-2-one, $Pd_2(dba)_3$, CS_2CO_3, Xantphos, dioxane, reflux, 2 h, 81%; (b) LiOH, H_2O, EtOH, 80 °C, 1 h, 62%.

In conclusion, we have discovered a novel series of potent 4-bicyclic heteroaryl THIQ triple monoamine reuptake inhibitors (TRIs). Varying the pendant 4-aryl group and the substituent at the 7-position on the THIQ scaffold resulted in potent TRIs with a range of triple inhibition profiles. A representative compound **10i** demonstrated significant occupancy at SERT, NET, and DAT after oral dosing in an *ex vivo* binding assay and showed excellent efficacy in two animal models used to predict clinical antidepressant efficacy.

■ ASSOCIATED CONTENT

Supporting Information

Binding, *ex vivo* occupancy, and rat forced-swim and tail suspension study protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) The World Health Organization. The World Health Report 2004: Changing History, Annex Table 3: Burden of Disease in DALYs by Cause, Sex, and Mortality Stratum in WHO Regions, Estimates for 2002. WHO: Geneva, Switzerland, 2004.

(2) Kessler, R. C.; Chiu, W. T.; Demler, O.; Walters, E. E. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Arch. Gen. Psychiatry* **2005**, *62* (6), 617−627.

(3) Greenberg, P. E.; Kessler, R. C.; Birnbaum, H. G.; Leong, S. A.; Lowe, S. W.; Berglund, P. A.; Corey-Lisle, P. K. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J. Clin. Psychiatry* **2003**, *64* (12), 1465−1475.

(4) Walter, M. W. Monoamine reuptake inhibitors: highlights of recent research developments. *Drug Dev. Res.* **2005**, *65*, 97−118.

(5) Liu, S.; Molino, B. F. Recent developments in monoamine reuptake inhibitors. *Annu. Rep. Med. Chem.* **2007**, *42*, 13−26.

(6) D'Aquila, P. S.; Collu, M.; Gessa, G. L.; Serra, G. The role of dopamine in the mechanism of action of antidepressant drugs. *Eur. J. Pharmacol.* **2000**, *405*, 365−373.

(7) Gerasimov, M. R.; Franceschi, M.; Volkow, N. D.; Gifford, A.; Gatley, S. J.; Marsteller, D.; Molina, P. E.; Dewey, S. L. Comparison between intraperitoneal and oral methylphenidate administration: A microdialysis and locomotor activity study. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 51−57.

(8) Capp, P. K.; Pearl, P. L.; Conlon, C. Methylphenidate HCl: therapy for attention deficit hyperactivity disorder. *Expert Rev. Neurother.* **2005**, *5* (3), 325−31.

(9) Fava, M.; Rush, A. J.; Thase, M. E.; Clayton, A.; Stahl, S. M.; Pradko, J. F.; Johnston, J. A. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim. Care Companion J. Clin. Psychiatry* **2005**, *7* (3), 106−113.

(10) Papakostas, G. I.; Worthington, J. J., III; Iosifescu, D. V.; Kinrys, G.; Burns, A. M.; Fisher, L. B.; Homberger, C. H.; Mischoulon, D.; Fava, M. The combination of duloxetine and bupropion for treatment-resistant major depression disorder. *Depression Anxiety* **2006**, *23*, 178−180.

(11) Trivedi, M. H.; Fava, M.; Wisniewski, S. R.; Thase, M. E.; Quitkin, F.; Warden, D.; Ritz, L.; Nierenberg, A. A.; Lebowitz, B. D.; Biggs, M. M.; Luther, J. F.; Shores-Wilson, K.; Rush, A. J. Medication augmentation after the failure of SSRIs for depression. *New Engl. J. Med.* **2006**, *354*, 1243−1252.

(12) Lavretsky, H.; Park, S.; Siddarth, P.; Kumar, A.; Reynolds, C. F., III. Methylphenidate-enhanced antidepressant response to citalopram

in the elderly: a double-blind, placebo-controlled pilot trial. *Am. J. Geriatr. Psychiatry* **2006**, *14* (2), 181−185.
(13) Masand, P. S.; Anand, V. S.; Tanquary, J. F. Psychostimulant augmentation of second generation antidepressants: A case series. *Depression Anxiety* **1998**, *7* (2), 89−91.
(14) Skolnick, P.; Popik, P.; Janowsky, A.; Beer, B.; Lippa, A. S. Antidepressant-like actions of DOV21,947: a "triple" reuptake inhibitor. *Eur. J. Pharmacol.* **2003**, *461*, 99−104.
(15) Liang, Y.; Shaw, A. M.; Boules, M.; Briody, S.; Robinson, J.; Oliveros, A.; Blazar, E.; Williams, K.; Zhang, Y.; Carlier, P. R.; Richelson, E. Antidepressant-like pharmacological profile of a novel triple reuptake inhibitor, (1*S*,2*S*)-3-(methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (PRC200-SS). *J. Pharmacol. Exp. Ther.* **2008**, *327* (2), 573−583.
(16) Micheli, F.; Cavanni, P.; Arban, R.; Benedetti, R.; Bertani, B.; Bettati, M.; Bettelini, L.; Bonanomi, G.; Braggio, S.; Checchia, A.; Davalli, S.; Di Fabio, R.; Fazzolari, E.; Fontana, S.; Marchioro, C.; Minick, D.; Negri, M.; Oliosi, B.; Read, K. D.; Sartori, I.; Tedesco, G.; Tarsi, L.; Terreni, S.; Visentini, F.; Zocchi, A.; Zonzini, L. 1-(Aryl)-6-[alkoxyalkyl]-3-azabicyclo[3.1.0]hexanes and 6-(aryl)-6-[alkoxyalkyl]-3-azabicyclo[3.1.0]hexanes: A new series of potent and selective triple reuptake inhibitors. *J. Med. Chem.* **2010**, *53*, 2534−2551.
(17) Lucas, M. C.; Weikert, R. J.; Carter, D. S.; Cai, H. Y.; Greenhouse, R.; Iyer, P. S.; Lin, C. J.; Lee, E. K.; Madera, A. M.; Moore, A.; Ozboya, K.; Schoenfeld, R. C.; Steiner, S.; Zhai, Y.; Lynch, S. M. Design, synthesis, and biological evaluation of new monoamine reuptake inhibitors with potential therapeutic utility in depression and pain. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5559−5566.
(18) Shao, L.; Hewitt, M. C.; Malcolm, S. C.; Wang, F.; Ma, J.; Campbell, U. C.; Spicer, N. A.; Engel, S. R.; Hardy, L. W.; Jiang, Z. D.; Schreiber, R.; Spear, K. L.; Varney, M. A. Synthesis and pharmacological characterization of bicyclic triple reuptake inhibitor 3-aryl octahydrocyclopenta[c]pyrrole analogues. *J. Med. Chem.* **2011**, *54*, 5283−5295.
(19) Gopishetty, B.; Hazeldine, S.; Santra, S.; Johnson, M.; Modi, G.; Ali, S.; Zhen, J.; Reith, M.; Dutta, A. Further structure−activity relationship studies on 4-((((3*S*,6*S*)-6-benzhydryltetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol: Identification of compounds with triple uptake inhibitory activity as potential antidepressant agents. *J. Med. Chem.* **2011**, *54*, 2924−2932.
(20) Pechulis, A. D.; Beck, J. P.; Curry, M. A.; Wolf, M. A.; Harms, A. E.; Xi, N.; Opalka, C.; Sweet, M. P.; Yang, Z.; Vellekoop, A. S.; Klos, A. M.; Crocker, P. J.; Hassler, C.; Laws, M.; Kitchen, D. B.; Smith, M. A.; Olson, R. E.; Liu, S.; Molino, B. F. 4-Phenyl tetrahydroisoquinolines as dual norepinephrine and dopamine reuptake inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7219−7222.
(21) US patent US 7,541,357 B2. Synthetic procedures and characterizations for all compounds in Tables 1 and 2 except for **3p**, **3u**, **3v**, and **3w** are described in this patent. Compound **3p** was prepared using a Boc-protected 2-bromoindole via Scheme 1. Compound **3u** was prepared using 6-bromopyrazolo[1,5-a]pyridine via Scheme 1.
(22) Hu, M.; Guzzo, P. R.; Zha, C.; Nacro, K.; Yang, Y.-L.; Hassler, C.; Liu, S. A facile synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines. *Tetrahedron Lett.* **2011**, *53*, 846−848.
(23) Bymaster, F. P.; Katner, J. S.; Nelson, D. L.; Hemrick-Luecke, S. K.; Threlkeld, P. G.; Heiligenstein, J. H.; Morin, S. M.; Gehlert, D. R.; Perry, K. W. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* **2002**, *27*, 699−711.
(24) For the process development of **10i**, see: Yang, Q.; Ulysse, L. G.; McLaws, M. D.; Keefe, D. K.; Haney, B. P.; Zha, C.; Guzzo, P. R.; Liu, S. Initial process development and scale-up of the synthesis of a triple Reuptake Inhibitor ALB 109780. *Org. Process Res. Dev.* **2012**, *16*, 499−506.
(25) Lengyel, K.; Pieschl, R.; Strong, T.; Molski, T.; Mattson, G.; Lodge, N. J.; Li, Y.-W. Ex vivo assessment of binding site occupancy of monoamine reuptake inhibitors: Methodology and biological significance. *Neuropharmacology* **2008**, *55*, 63−70.
(26) Myer, J. H.; Wilson, A. A.; Sagrati, S.; Hussey, D.; Carella, A.; Potter, W. Z.; Ginovart, N.; Spencer, E. P.; Cheok, A.; Houle, S. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: An [^{11}C]DASB positron emission tomography study. *Am. J. Psychiatry* **2004**, *161*, 826−835.
(27) Lundberg, J.; Tiger, M.; Landén, M.; Halldin, C.; Farde, L. Serotonin transporter occupancy with TCAs and SSRIs: a PET study in patients with major depressive disorder. *Int. J. Neuropsychopharmacol.* **2012**, *15*, 1167−1172.
(28) Bristow, L. J.; Easton, A.; Seager, M.; Olson, R.; Liu, S.; Jones, K.; La-Paglia, M.; Heman, K.; Li, Y.-W.; Macor, J.; Sargent, B.; Houston, J.; Molino, B. F.; Zaczek, R. *The Triple Monoamine Reuptake Inhibitor, AMR-2, Improves Attentional Set Shifting in a Rat Neurodevelopmental Model of Schizophrenia*. American College of Neuropharmacology (ACNP), Dec. 4−8th, 2011, Hawaii, USA.
(29) Smith, D. A.; Obach, R. S. Metabolites in safety testing (MIST): Considerations of mechanisms of toxicity with dose, abundance, and duration of treatment. *Chem. Res. Toxicol.* **2009**, *22*, 267−279.