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Synthesis and pharmacological evaluation of 3-aryl-3-azolylpropan-1-amines as selective triple serotonin/norepinephrine/dopamine reuptake inhibitors

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ABSTRACT

A series of 3-aryl-3-azolylpropan-1-amines was prepared and screened for its capability of inhibiting monoamine reuptake. Analogs with nanomolar potency, good human in vitro microsomal stability, and low drug–drug interaction potential were described. In vivo models were used to evaluate the compound **19r** for antidepressive, anxiolytic, and analgesic activity.

Currently used antidepressants generally interfere with transporter-mediated reuptake of serotonin (5-HT), norepinephrine (NE), or both.[1,2] Dopaminergic transmission is also important, because a dysfunction of dopaminergic mechanisms of reward is related to anhedonia.[3] Suppression of dopamine (DA) reuptake enhances sexual function and may improve cognitive performance.[1,4,5]

Hence, the concept of 5-HT, NE, and DA triple reuptake inhibition has been explored by combination therapy with several currently available antidepressants (Fig. 1). The available data suggest that the combination of a NDRI (norepinephrine and dopamine reuptake inhibitor) bupropion (Wellbutrin® **1**) and either a SSRI (selective serotonin reuptake inhibitor, such as fluoxetine (Prozac® **2**)) or a SNRI (serotonin and norepinephrine reuptake inhibitor, such as venlafaxine (Effexor® **3**) and duloxetine (Cymbalta® **4**)) can be effective for patients unresponsive to monotherapy, and can reduce SSRI or SNRI-associated sexual side effects.[6,7]

Based on these outcomes, there is currently much interest in triple reuptake inhibitors that express antidepressant actions, without effect on sexual behavior and abuse liability in behavioral models.[8–12] Clinical trials showed that DOV216,303 (**5**) was as effective as the SSRI citalopram in severely depressed patients based on changes in the HAM-D.[13] GSK/NeuroSearch's NS2359 (GSK372475, **6**) also went into Phase II though failed therein in depression.[14]

It can be expected that triple reuptake inhibitors will offer improved efficacy in the management of depression. This Letter describes our efforts to obtain compounds with equivalent functional activity at 5-HT, NE, and DA uptake sites, a triple reuptake inhibitor.

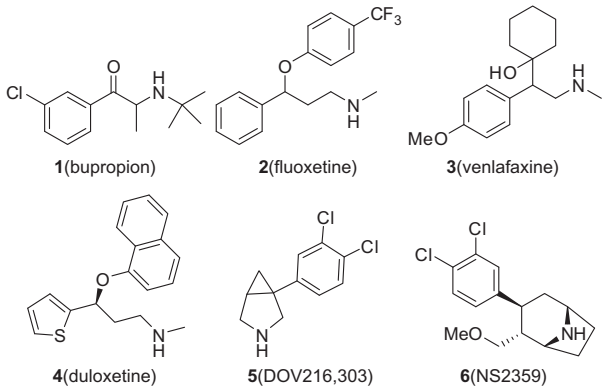

Figure 1. Representative antidepressants.

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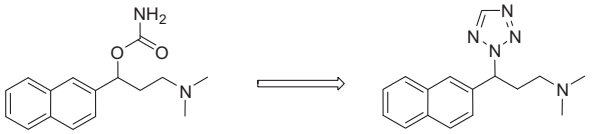
We set out a search for triple reuptake inhibitors from the library of SK compound collection, and identified dimethyl-(3-carbamoyloxy-3-naphthalen-2-yl-propyl)-amine **7** as having micromolar binding affinity for the cerebral rat serotonin transporter.

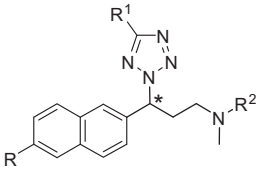
During our exploration of compound **7**, we investigated alternate isostere of carbamoyloxy group. Following a preliminary survey of heterocyclic replacements for the carbamoyloxy group in **7**, we focused our medicinal chemistry efforts on the novel dimethyl-(3-naphthalen-2yl-3-tetrazol-2-yl-propyl)-amine series such as **8**. Compound **8** contains a tetrazole ring as a surrogate for the aryloxy group in the fluoxetine and duloxetine structures. Moreover, this compound was an inhibitor at all three of the monoamine reuptake transporters (Table 3).



7 8

(3-Naphthyl-3-azolyl-propyl)-methyl-amines (Table 1) were conveniently prepared in a three- or four-step sequence as described in Scheme 1. With variously substituted acetonaphthones **9** as starting materials, a Mannich reaction using *para*-formaldehyde and dimethylamine hydrochloride gave the 3-dimethylaminoketones **10**, which were easily converted to alcohols **11** using sodium borohydride. The alcohols **11** were substituted with various azoles under Mitsunobu conditions to form the desired compounds **12**. Some of these compounds were easily N-demethylated with ethyl chloroformate to afford the corresponding monomethylamines **13**. The enantiomers of **13c** were separated into isomers **13d** and **13e** by using chiral HPLC.[15]

Table 1
Inhibitory activity of (3-naphthyl-3-azolyl-propyl)-methyl-amine series at the rat serotonin transporter



	R	R^1	R^2	Stereochemistry	rSERT (% inhibition)
8	H	H	Me	rac	85.1 ± 6.4% (at 1 μM)[a]
13a	H	H	H	rac	90.4 ± 8.5% (at 1 μM)[a]
13b	Naphthyl-1-yl			rac	51.6 ± 0.7% (at 1 μM)[a]
12c	H	Me	Me	rac	85.0 ± 6.6% (at 1 μM)[a]
13c	H	Me	H	rac	93.6 ± 9.1% (at 1 μM)[a]
13d	H	Me	H	S	60.2 ± 0.7% (100 nM)[b]
13e	H	Me	H	R	34.5 ± 1.8% (100 nM)[b]
12f	H	Ph	Me	rac	92.6 ± 3.2% (at 1 μM)[a]
13f	H	Ph	H	rac	98.4 ± 10.9% (at 1 μM)[a]
12g	Cl	H	Me	rac	54.3 ± 2.8% (at 1 μM)[a]
13g	Cl	H	H	rac	52.1 ± 10.4% (at 1 μM)[a]
12h	Me	H	Me	rac	87.7 ± 2.4% (at 1 μM)[a]
13h	Me	H	H	rac	93.3 ± 6.6% (at 1 μM)[a]
12i	F	H	Me	rac	74.1 ± 3.6% (100 nM)[b]
13i	F	H	H	rac	80.1 ± 2.9% (100 nM)[b]
12j	F	Me	Me	rac	67.5 ± 0.6% (100 nM)[b]
13j	F	Me	H	rac	81.3 ± 1.3% (100 nM)[b]
12k	OMe	H	Me	rac	33.6 ± 3.7% (100 nM)[b]
13k	OMe	H	H	rac	81.2 ± 0.7% (100 nM)[b]
13l	OMe	Me	H	rac	80.2 ± 1.5% (100 nM)[b]
13m	[c]	Me	H	rac	89.9 ± 3.9% (100 nM)[b]

[a] Inhibition of [^{3}H]-paroxetine binding to rat cerebral cortical membranes. Fluoxetine (IC_{50} = 12.6 nM) was used as a standard. Percent inhibition measured at a concentration of 1 μM. Carried out in triplicate.
[b] Percent inhibition measured at the concentration of 100 nM.
[c] 3-Methoxynaphthyl.

Target compounds (Table 2) that contain the phenyl ring instead of the naphthyl group were prepared via a somewhat different synthetic route starting from the substituted benzoic acids **14** (Scheme 2).

This route had an advantage over the Mannich route as the Mannich reaction route showed inconsistency in the construction of a focused library. Starting with appropriately substituted benzoic acids **14**, desired dimethylaminoketones **16** were synthesized via Weinreb amides **15** through vinyl Grignard addition followed by amine addition.[16] Ketones **16** were readily reduced to alcohols **17** and substituted with the azole groups to afford the desired compounds **18**. Next, these products were N-demethylated with chloroethyl chloroformate to form the equivalent monomethyl amines **19**.

The racemic compounds **19** could be separated into enantiomers by using chiral HPLC.[17] Although the absolute stereochemistry of the chiral compounds described in the Tables 1 and 2 have not yet been confirmed individually, scale-up preparation of chiral isomer **19r** (98% ee) using a lipase-mediated transesterification reaction not only provided a quantity of **19r** for in vivo study but also provided information on the absolute stereochemistry of the chiral compounds (Scheme 3).[18]

We set out a strategy that initially selects compounds which show binding affinities for one of the transporters and then determines binding affinities of selected compounds for all three transporters to facilitate identifying optimal triple reuptake inhibitors.

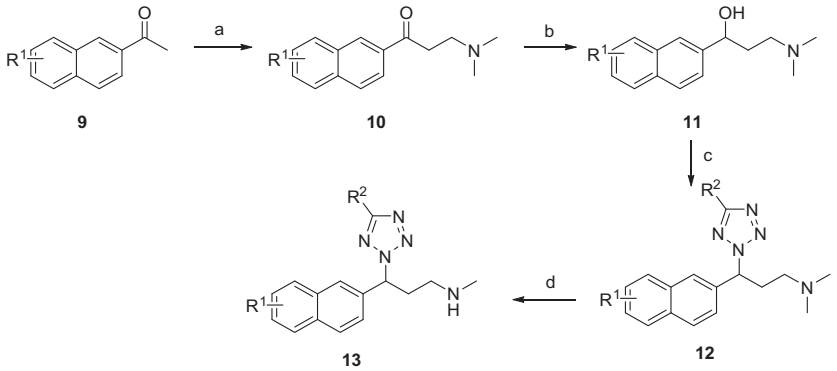
First, we determined binding affinities of compounds for cerebral rat serotonin transporter (rSERT) as a prescreening tool and then evaluated uptake of 5-HT, NE, and DA into cloned human serotonin transporter (hSERT), norepinephrine transporter (hNET), and dopamine transporter (hDAT) for selected compounds.[19]

Compound **8** possessed a high affinity for cerebral rSERT and had IC_{50} values of 138, 264 and 616 nM to the human SERT, NET, and DAT, respectively.

Microsomal metabolism studies of the tertiary amino derivative **8** indicated N-demethylation as one of the primary routes of metabolism. Based on these results, in vitro potencies of a series of (3-naphthyl-3-azolyl-propyl)-methyl-amines for cerebral rat serotonin transporter (rSERT) were measured and summarized in Table 1.

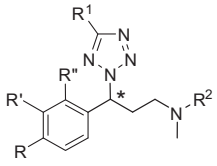
Demethylated analog, **13a** showed a similar activity to **8**, and the corresponding 1-naphthyl derivative **13b** was much less active. Contrary to our expectation, microsomal stability of desmethyl analog **13a** did not improve (Table 3). The smaller methyl and larger phenyl substituents at the tetrazole ring resulted in compounds (**12c** and **12f**) with similar rSERT potency. There was a difference in reuptake potency between the two enantiomers of compound **13c**. Isomer **13d** showed higher potency than its enantiomer **13e** and this activity difference was consistent in all the analogs. As another route of metabolism of **8** was found to be hydroxylation at the naphthyl group, substitution at the 2-naphthyl moiety was studied to suppress the metabolism as well as to improve the activity. While chlorine substitution at the 6-position (**12g** and **13g**) lowered the activity, fluorine substitution was well tolerated (**12i**, **12j**, **13i**, and **13j**). Methyl or methoxy substitution did not seem to change the activity much (**12h**, **12k**, **13h**, **13k**, and **13l**). Substitution at the 3-position (**13m**) showed the similar activity to substitution at the 6-position.

When these compounds were screened for human serotonin, norepinephrine, and dopamine transporters, none of them showed a balance activity for all three transporters except **8** (Table 3). In general, the inhibition potency of DAT uptake was much lower than those of SERT and NET uptakes throughout this series. This result was also reflected in the animal model as well. When tested in the mouse forced swimming test (FST),[21] assay used to evaluate the antidepressant agents, compound **13f** did not show any activities (5.5% reduction of immobility time) at the dose of 30 mg/kg, IP. Comparative data for compound **8** showed antidepressant-like



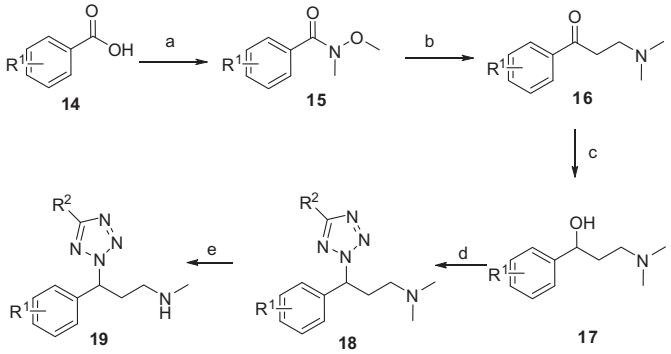
Scheme 1. Reagents: (a) paraformaldehyde, dimethylamine·HCl, EtOH, reflux; (b) $NaBH_4$, MeOH; (c) PPh_3, DIAD, azoles, THF; (d) ethyl chloroformate, $NaHCO_3$, and KOH.

Table 2
Inhibitory activity of (3-phenyl-3-azolyl-propyl)-methyl-amine series at the rat serotonin transporter

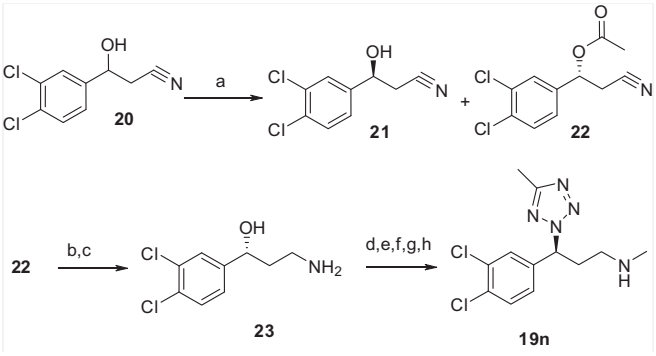


	R	R′	R″	R^1	R^2	*	rSERT (% inhibition)
19a	H	H	Cl	Me	H	rac	5.9 ± 0.2% (100 nM)[b]
18b	H	Cl	H	H	Me	rac	−5.6 ± 3.2% (100 nM)[b]
18c	Cl	H	H	H	Me	rac	32.4 ± 0.7% (at 1 μM)[a]
19c	Cl	H	H	H	H	rac	41.1 ± 1.3% (at 1 μM)[a]
19d	Br	H	H	H	H	rac	10.7 ± 3.7% (100 nM)[b]
19e	CF_3	H	H	H	H	rac	15.3 ± 4.3% (100 nM)[b]
19f	CF_3O	H	H	H	H	rac	3.1 ± 0.9% (100 nM)[b]
18g	*t*Bu	H	H	Me	Me	rac	−3.0 ± 0.1% (100 nM)[b]
19h	PhO	H	H	H	H	rac	−1.7 ± 0.0% (100 nM)[b]
18i	BnO	H	H	H	Me	rac	9.5 ± 6.3% (100 nM)[b]
18j	Cl	H	Cl	H	Me	rac	−0.2 ± 1.7% (100 nM)[b]
19k	Cl	Cl	Cl	H	H	rac	39.1 ± 4.3% (100 nM)[b]
18l	Me	Me	H	H	Me	rac	49.2 ± 1.6% (at 1 μM)[a]
18m	F	F	H	H	Me	rac	25.3 ± 0.7% (at 1 μM)[a]
18n	OMe	OMe	H	H	Me	rac	12.9 ± 0.0% (100 nM)[b]
18o	OMe	Cl	H	H	Me	rac	39.9 ± 2.3% (at 1 μM)[a]
18p	Cl	Cl	H	H	Me	rac	72.0 ± 2.5% (at 1 μM)[a]
19p	Cl	Cl	H	H	H	rac	86.0 ± 2.0% (at 1 μM)[a]
18q	Cl	Cl	H	Me	Me	rac	69.4 ± 1.9% (at 1 μM)[a]
19q	Cl	Cl	H	Me	H	rac	86.0 ± 3.8% (at 1 μM)[a]
19r	Cl	Cl	H	Me	H	S	61.2 ± 2.6% (100 nM)[b]
19s	Cl	Cl	H	Me	H	R	20.0 ± 0.4% (100 nM)[b]
18t	Cl	Cl	H	[c]	Me	rac	69.9 ± 3.1% (at 1 μM)[a]
19t	Cl	Cl	H	[c]	H	rac	81.0 ± 2.2% (at 1 μM)[a]
19u	Cl	Cl	H	[c]	H	S	30.5 ± 0.8% (100 nM)[b]
19v	Cl	Cl	H	[c]	H	R	8.5 ± 0.2% (100 nM)[b]

[a] Inhibition of [^{3}H]-paroxetine binding to rat cerebral cortical membranes. Fluoxetine (IC_{50} = 12.6 nM) was used as a standard. Percent inhibition measured at a concentration of 1 μM. Carried out in triplicate.
[b] Percent inhibition measured at a concentration of 100 nM.
[c] [1,2,3]Triazol-2-yl.



Scheme 2. Reagents: (a) *N*,*O*-dimethylhydroxylamine·HCl, CDI, TEA, THF; (b) vinylmagnesium bromide, dimethylamine, THF; (c) $NaBH_4$, MeOH; (d) PPh_3, DIAD, Azoles, THF; (e) chloroethyl chloroformate, DiPEA,CH_2Cl_2, and MeOH, reflux.



Scheme 3. Reagents and conditions: (a) lipase PS-C, vinyl propionate, diisopropyl ether, 40 °C, 12 h (**21** 20% and **22** 46%); (b) K_2CO_3/H_2O/MeOH, rt, 70%; (c) BH_3-DMS, THF, rt to reflux, 12 h; (d) $(Boc)_2O$, TEA, CH_2Cl_2, rt, 77%; (e) PPh_3, DIAD, 5-methyltetrazole, THF 0 °C to rt, 2 h 54%; (f) 6% HCl in MeOH, rt, 4 h; (g) excess ethyl formate, 80 °C, 12 h 83%; (h) LAH in THF.

activity (43.2% reduction of immobility time, p <0.05) at the same dose.

The limited success of analogs of the naphthyl moiety was presumed due to presence of multiple aromatic groups in the compounds. Therefore, a series of substituted phenyl analogs that possess only one benzene ring in the molecules was prepared and screened for the activity for rSERT (Table 2).

Examining the inhibition activities of the analogs with different phenyl substituents indicated that the position, size, and nature of the aryl substituent had significant impact on rSERT potency. Compounds **18c**, **18j**, **18o**, and **18p** demonstrated that 3,4-dichloro substitution on phenyl ring was optimal to surrogate the naphthyl ring of **8** for the high rSERT binding. In the same trend as the naphthyl series, (*S*)-isomers showed the higher activity than the opposite stereoisomers (**19r** vs **19s**, **19u** vs **19v**). Substitution at the tetrazole ring did not affect the activity (**18q** and **19q**). Replacing tetrazole ring with triazole ring was well tolerated (**18t**, **19t**, **19u**, and **19v**).

Selected compounds from Table 2 along with the compounds from Table 1 were screened for human serotonin, norepinephrine, and dopamine transporters and summarized in Table 3. Some of

Table 3
Inhibitory activity of (3-aryl-3-azolyl-propyl)-methyl-amine series at the human serotonin, norepinephrine, and dopamine transporters

	hSERT % inhibition[a,d]/ IC_{50} (nM)	hNET % inhibition[b,d]/ IC_{50} (nM)	hDAT % inhibition[c,d]/ IC_{50} (nM)	RLM[e] ($t_{1/2}$, min)	HLM[f] ($t_{1/2}$, min)
8	41%	30%	20%	3	50
	138 nM	264 nM	616 nM		
13a	78%	84%	10%	12	49
	32 nM	13.3 nM	1240 nM		
13d	82%	79%	7%		
13e	23%	37%	3%		
12g	46%	32%	18%		
13g	−4%	20%	−21%		
13h	93%	55%	3%		
12i	61%	12%	7%	3	>60
13i	59%	25%	6%	29	>60
12j	61%	10%	6%		
13j	58%	39%	10%	27	>60
12k	44%	39%	36%		
13k	88%	70%	4%		
13l	82%	84%	3%		
18p	27%	37%	58%	3	55
	279 nM	234 nM	78 nM		
19p	35%	56%	48%	>60	>60
	181 nM	69 nM	116 nM		
19r	43%	84%	62%	56	>60
	143 nM	19.8 nM	58 nM		
19u	10%	76%	44%		
	660 nM	14.7 nM	91.7 nM		
2	3.1 nM	NT[g]	NT[g]		
3	35 nM	581 nM	7340 nM		
5	215 nM	72.4 nM	93.8 nM		

[a] Inhibition of serotonin uptake in HEK-293 cells at, stably transfected with human SERT. Fluoxetine (IC_{50} = 3.1 nM) was used as a standard. Carried out in duplicate.
[b] Inhibition of norepinephrine uptake in MDCK cells, stably transfected with human NET. Desipramine (IC_{50} = 0.786 nM) was used as a standard. Carried out in duplicate.
[c] Inhibition of dopamine uptake in CHO-K1 cells, stably transfected with human DAT. Nomifensine (IC_{50} = 16.4 nM) was used as a standard. Carried out in duplicate.
[d] Percent inhibition measured at a concentration of 100 nM.
[e] RLM, rat liver microsomes.
[f] HLM, human liver microsomes.
[g] NT denotes not tested.

the compounds were screened for metabolic stability in rat and human liver microsomes (RLM and HLM).[20] The IC_{50} values of reuptake inhibition were determined for representative compounds from the naphthyl series (**8** and **13a**), a compound with triazole (**19u**) for comparison and compounds with similar activities across the transporters from the phenyl series (**18p**, **19p**, and **19r**). When compared to naphthyl analog **8**, the 3,4-dichlorophenyl analog **18p** was over 10-fold more potent at DAT. 3,4-Dichlorophenyl moiety is also found in structure of DOV216,303 and NS2359. So 3,4-dichlorophenyl moiety within this series is important for SERT and DAT dual binding. Compound **18p** showed moderate but balanced potencies at all three hSERT/NET/DATs but also showed poor in vitro stability. Demethylated compound **19p** was more potent at hSERT and hNET than its dimethylamino analog **18p**, which was consistent with the previous SAR trend in the naphthyl series. Triazole analog **19u** showed similar microsomal stability (HLM $t_{1/2}$ >60 min) and rSERT affinity to **19p**. However **19u** displayed lower potency to the hSERT compared to **19p**. Thus maintaining 3,4-dichloro substituents at phenyl ring and substituting with methyl group at tetrazole ring produced a potent chiral inhibitor **19r**, which had an excellent metabolic stability in HLM.

The data (Table 3) suggest that **19u** is a relatively selective inhibitor of NE and DA transporter, whereas **19r** is a more balanced inhibitor across all three transporters. Among the most potent analogs, the reuptake potencies of compounds **19p** and **19r** were similar to that of **5** (DOV216,303).[22] Compound **19r** was selected for further study since **19r** is a single enantiomer while **19s** is a racemate. Compound **19r** had minimal off-target activity against a panel of representative aminergic receptors (α_1, H_1, M_1, M_3 <20% at 10 μM; 5-HT_{2C} 66% at 10 μM). Compound **19r** was further evaluated for the effects of CYP inhibition: **19r** showed no appreciable inhibition against CYP1A2, CYP2C9, CYP2C19, and CYP3A4, with IC_{50} >10 μM, while **19r** was a moderate inhibitor against CYP2D6 (IC_{50} 6.9 μM).

Based on these data, the compound **19r** was then selected for in vivo evaluation (Table 4).

A series of in vivo models were used to evaluate the CNS activity of **19r:** potentiation of 5-hydroxytryptophan (5-HTP, the precursor of serotonin)-induced serotonin syndrome-like behavior (head twitch) in mouse for 5-HT activity,[23–25] FST, and tail suspension test (TST)[26–28] for antidepressant activity, mouse acetic acid-induced writhing test (AA) for anti-pain activity,[29–31] mouse marble burying test (MB) for anxiolytic activity,[32,33] and mouse spontaneous locomotor activity test (LMA) for DA activity.[34,35]

The compound **19r** dose-dependently increased the stereotypy counts induced by 5-HTP with a minimal effective dose (MED) of 30 mg/kg. In agreement with serotonin reuptake data in the Table 2, fluoxetine was the most potent in 5-HTP model (MED 3 mg/kg), whereas a 10-fold higher dose of **19r** was required to significantly enhance the effect of 5-HTP. In a similar way, venlafaxine

Table 4
Pharmacology of **19r** compared with antidepressant agents in animal models

	Value	**19r**	**3**	**5**	**2**
5-HTP[a]	MED[g] PO	30 (158%*)	10 (129%*)	30 (54%*) 60 (156%)	3 (146%*)
FST[b]	MED PO	10 (14.9%*)	30 (35.2%*)	10 (18%)	50 (14.8%*)
	ED_{50} PO	22.2 (95% CL 16.5–29.9)	38.4 (95% CL 28.9–51.0)	30.1 (95% CL 16.2–55.9)	
TST[c]	MED PO	3 (59.6%*)	7 (56.3%*)	5 (33.2%*)	
AA[d]	% inhibition at 30 SC	94.4%*	70.2%*	93.7%*	
MB[e]	% inhibition at 30 IP	94.4%*	82.3%*	99.1%*	60.3%* (10 IP)
LMA[f]	% change	92% (30 PO) 142%* (90 PO) 134% (150 PO)	119%* (30 PO) 139%* (60 PO)	150%*(30 PO) 131% (60 PO) 148% (90 PO)	

[a] 5-HTP potentiation of 5-HTP symptoms in mice. In parentheses, percentage of potentiation (control group: 0%).
[b] FST forced swimming test in mice. In parentheses, percentage of immobility reduction.
[c] TST tail suspension test in mice. In parentheses, percentage of immobility reduction.
[d] AA acetic acid-induced writhing test in mice. Inhibition percentage of number of writhing.
[e] MB marble burying test in mice. Inhibition percentage of number of marbles buried.
[f] LMA locomotor activity test in mice (control group: 100%). In parentheses, doses inducing changes are indicated. *p <0.05.
[g] MED, minimal effective dose. Doses are expressed in mg/kg, PO (oral), SC (subcutaneous) or IP (intraperitoneal).

Table 5
Pharmacokinetic parameters of the compound **19r**[a] after single oral and IV (intravenous) administration to rat

Parameters	PO (10 mg/kg, $n = 4$)	IV (10 mg/kg, $n = 4$)
C_{max} (ng/mL)	334	3834
t_{max} (h)	0.75	
$t_{1/2}$ (h)	5.48	3.12
AUC_{all} (ng h/mL)	1276	3833
AUC_{inf} (ng h/mL)	1793	4150
CL (mL/kg/min)		42
V_{ss} (L/kg)		6.8
% Bioavailability	43.2	

[a] HCl salt was used.

significantly potentiated the syndrome induced by the 5-HT precursor at the dose of 10 mg/kg. DOV216,303 showed a similar efficacy at the dose of 60 mg/kg.

Oral administration of **19r** significantly reduced the immobility time in the FST. Compounds **5** (DOV216,303) and **3** (venlafaxine) were slightly less potent than **19r**. In dose–response assays of the TST, **19r** induced a significant and marked reduction of mice immobility at the dose of 3 mg/kg. Venlafaxine (**3**) mimicked these actions, reaching statistical significance at the dose of 7 mg/kg. Compound **19r** induced the marked antidepressant-like effects and was the most potent drug in both FST and TST models. Compound **19r**, **3**, and **5** significantly reduced the number of writhes and marbles buried at the dose of 30 mg/kg. Significant but slight increases in spontaneous locomotor activity in mice were observed at 1 h after the oral administration of **19r**, **3**, and **5** at the test doses. Antidepressant-like activity of **19r** does not appear to be due to motor stimulation since **19r** was active in the forced swim test at doses that do not increase motor activity. On the other hand, DOV 216,303 has been shown to have modest but statistically significant increases in motor activity at doses that produce meaningful reductions in immobility in the forced swim test.[13] SSRIs and SNRIs were reported to enhance the locomotor activity of mice exposed to a novel environment.[36]

With promising in vitro and in vivo results in hand, pharmacokinetic properties of **19r** were evaluated, which is summarized in Table 5.

After oral administration of a 10 mg/kg dose of **19r** to rats, a C_{max} of 334 ng/mL was observed at 0.75 h. The elimination half-life for **19r** following oral administration was 5.48 h in rats. Compound **19r** showed good oral bioavailability ($F = 43.2\%$) and high blood clearance (42 mL/kg/min) in rats.

In summary, we identified a series of 3-aryl-3-azolylpropan-1-amine derivatives as triple reuptake inhibitors for the treatment of depressive disorders. SAR studies were performed via variation of azole group and modification of substituents on aryl group. Based on the outcomes of in vitro studies and in animal models, **19r** was identified as a lead compound for this antidepressant program. The compound **19r** was also active in animal models predictive of anxiolytic and analgesic activity. Further studies on the development of potent triple reuptake inhibitors will be reported in due course.

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