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Studies on the structure–activity relationship of bicifadine analogs as monoamine transporter inhibitors

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ABSTRACT

Compounds with various activities and selectivities were discovered through structure–activity relationship studies of bicifadine analogs as monoamine transporter inhibitors. The norepinephrine-selective 2-thienyl compound *S*-**6j** was efficacious in a rodent pain model.

Bicifadine [**1**, (±)-1-(4-methylphenyl)-3-azabiocyclo[3.1.0]hexane hydrochloride, DOV 220,075, Fig. 1],[1] an inhibitor of norepinephrine and serotonin reuptake transporters (NET and SERT), is being developed for the treatment of acute and chronic pain. Bicifadine is active in models of neuropathic pain with no evidence of abuse liability potential.[2] Clinically, it has been shown to be effective in the treatment of acute dental pain[3] and bunionectomy pain.[4,5] Bicifadine has also been reported to be as effective as the standard of care in reducing chronic lower back pain.[6]

Bicifadine inhibits monoamine neurotransmitter uptake by recombinant human transporters in vitro with a relative potency of NET (IC_{50} = 55 nM) > SERT (IC_{50} = 120 nM) > DAT (IC_{50} = 910 nM).[7] This in vitro profile is supported by microdialysis studies in freely moving rats, where bicifadine (20 mg/kg i.p.) increased extrasynaptic norepinephrine (NE) and serotonin (SER) levels in the prefrontal cortex, NE levels in the locus coeruleus, and dopamine (DA) levels in the striatum.[2] In comparison, DOV 216,303 (**6b**), a close analog of bicifadine, is known as a triple inhibitor (NET IC_{50} = 20.3 nM, SERT IC_{50} = 13.8 nM, DAT IC_{50} = 78 nM)[8,9] and is being studied for the treatment of major depression.[10] Both of its individual enantiomers, DOV 21,947 (*S*-**6b**)[11–13] and DOV 102,677 (*R*-**6b**)[14] (Fig. 1), are profiled as monoamine transporter inhibitors. DOV 21,947 (*S*-**6b**) is also undergoing clinical evaluation for the treatment of pain and other diseases related to these neurotransporters.[15]

Recently, a dual NET/SERT inhibitor duloxetine (**3**) was approved by the FDA for the treatment of diabetic neuropathy.[16] In addition, experience with reboxetine (**5**) suggests that this noradrenergic antidepressant may have efficacy in the treatment of chronic pain in patients with depression.[17] Like reboxetine, atomoxetine (**4**) is also a NET-selective inhibitor and is used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD),[18] demonstrating the therapeutic potential of NET inhibitors.[19]

Bicifadine is a very small molecule (MW = 173) with moderate lipophilicity (*c*Log*P* = 2.0). This feature is distinctly different from the highly lipophilic atomoxetine (*c*Log*P* = 3.3) and duloxetine (*c*Log*P* = 3.7) which have two lipophilic aromatic groups (Fig. 1). However, the metabolic and pharmacokinetic properties of bicifadine[20,21] and DOV 216,303[22] are also significantly different from the structurally related milnacipran (**2**),[23] which is less lipophilic (*c*Log*P* = 1.2). Although bicifadine and DOV 216,303 were initially discovered in the early 1980s,[1] the structure–activity relationship of its analogs at the transporter levels has not been reported. Here, we describe the synthesis and SAR studies of a series of bicifadine analogs as monoamine transporter inhibitors in our efforts to search for NET active compounds.

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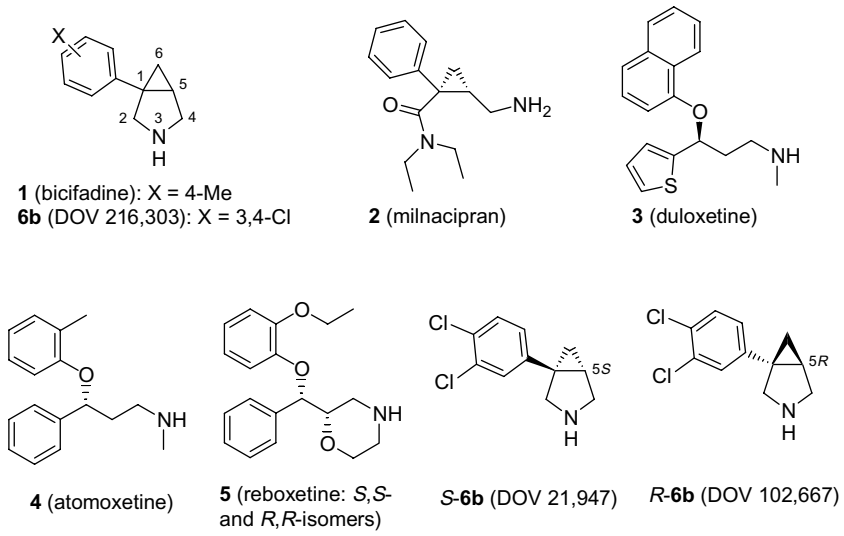


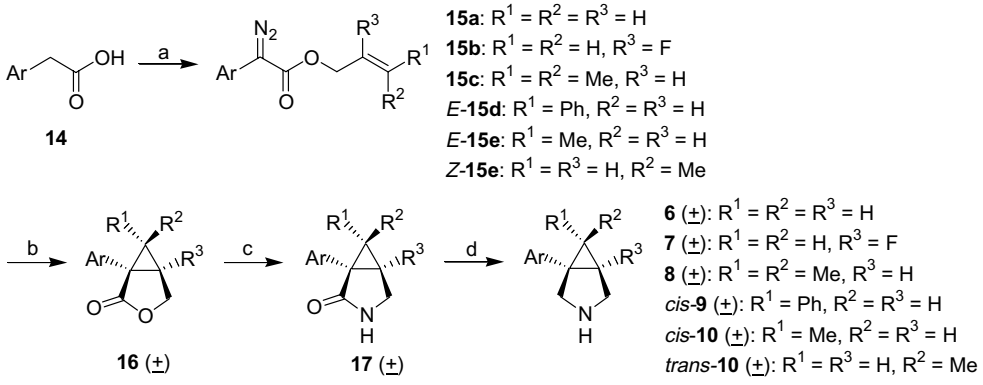
Figure 1. Chemical structures of bicifadine (**1**) and some other monoamine transporter inhibitors.

The target compounds **6**–**10** as pairs of enantiomers were synthesized from arylacetic acids **14** as shown in Scheme 1. Alkylations of **14** with allyl bromides provided the ester intermediates which were converted to the corresponding diazo compounds **15** using a sulfonylazide. Rhodium-catalyzed cyclizations of **15** gave the lactones **16**.[24] Elaboration of **16** by ring opening with potassium phthalimide, followed by activation of the carboxylic acid and deprotection of the amine resulted in the lactams **17**. Finally, the reduction of **17** with lithium aluminumhydride provided the bicifadine analogs **6**–**10**.

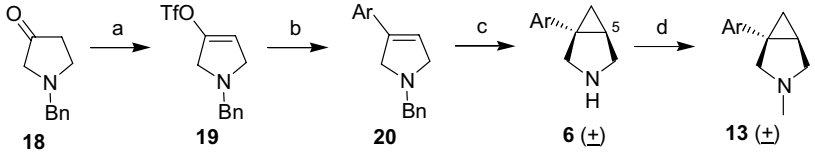
Alternately, compounds **6** were prepared from 1-benzyl-3-oxopyrrolidine **18** as shown in Scheme 2. Conversion of **18** to the triflate **19** was achieved under basic conditions.[25] Coupling reactions of **19** with various arylboronic acids using a palladium catalyst provided the corresponding arylolefins **20**, which were subjected to cyclopropanations[26] to give the bicycles **6** as a mixture of 5*S*- and 5*R*-isomers after debenzylation. *N*-Methylation of **6j** (Ar = 2-thienyl) by a reductive alkylation with formaldehyde gave the tertiary amine **13**.

Compounds *S*-**6** and *R*-**6** were synthesized from arylacetonitriles **21** using a stereo-selective procedure[12] as shown in Scheme 3. Cyclizations of **21** with *S*-(+)- or *R*-(−)-epichlorohydrin promoted by NaHMDS provided the stereoisomers *S*-**16** or *R*-**16**, respectively. Elaboration of these intermediates using a procedure described in Scheme 1 afforded the single isomers *S*-**6** and *R*-**6**.

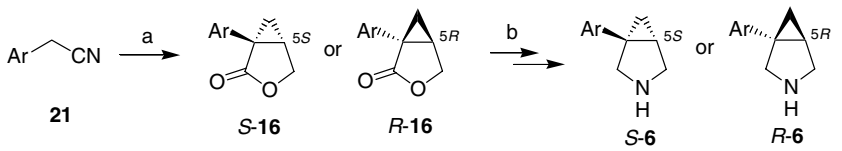
The *cis*- and *trans*-4-methyl analogs of **6b** were synthesized from the lactone **16** (Scheme 4). Ring opening of **16** with diethylamine gave an alcohol which was oxidized with TPAP to give the aldehyde **22**. The Grignard reaction of **22** with methylmagnesium bromide was stereo-selective, and the secondary alcohol **23**-I



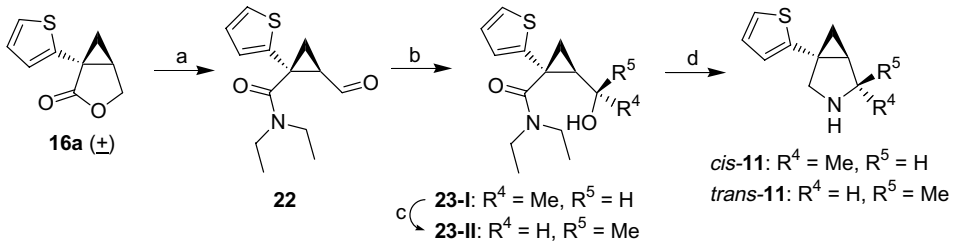
Scheme 1. Reagents and conditions: (a) i—$BrCH_2C(R^3)=CR^1R^2/CsCO_3$/acetone/rt, 10 h; ii—4-$AcNHC_6H_4SO_2N_3$/DBU/ACN/0 °C to rt, 3 h; (b) $Rh(OAc)_2$/DCM/reflux, 3 h; (c) i—potassium phthalimide/DMF/140 °C, 16 h; ii—$(COCl)_2$/DMF (cat.)/DCM/0 °C to rt, 2 h; iii—MeONHMe · HCl/Et_3N/DCM/0 °C to rt, 2 h; iv—$MeNHNH_2$/EtOH/rt, 20 h; (d) $LiAlH_4$/THF/reflux, 2 h.



Scheme 2. Reagents and conditions: (a) i—KHMDS/THF/−78 °C, 1 h; ii—$PhN(Tf)_2$/THF/0 °C, 3 h; (b) $ArB(OH)_2$/$Pd(PPh_3)_4$/CsF/THF/reflux, 8 h; (c) i—CH_2I_2/Et_2Zn/DCM/0 °C, 0.5 h, then rt, 18 h; ii—$CH_3CH(Cl)OCOCl$/DIEA/DCM/rt, 16 h; (d) For **6j**: $CH_2O/B_{10}H_{14}$/MeOH/H_2O/rt, 1 h.



Scheme 3. Reagents and conditions: (a) i—NaHMDS/THF/0 °C; ii—(*S*)-(+)- or (*R*)-(−)-epichlorohydrin/0 °C to rt, 16 h; iii—KOH/EtOH/reflux, 8 h; iv—12 NHCl/0 °C to rt, 2.5 h; (b) see Scheme 1.



Scheme 4. Reagents and conditions: (a) i—Et_2NH/Me_3Al/toluene/reflux, 16 h; ii—TPAP/NMO/molecular sieves/DCM/0 °C to rt, 16 h; (b) MeMgBr/THF/−78 °C, 1 h, then rt, 16 h; (c) i—PDC/CH_2Cl_2/rt, 16 h; ii—Dibal-H/THF/−78 °C, 2 h; (d) i—$NaN_3/PPh_3/CBr_4$/DMF/rt, 16 h; ii—H_2/Pd-d/MeOH/rt, 16 h; iii—Et_3N/toluene/reflux, 20 h; iv—$LiAlH_4$/THF/reflux, 2 h.

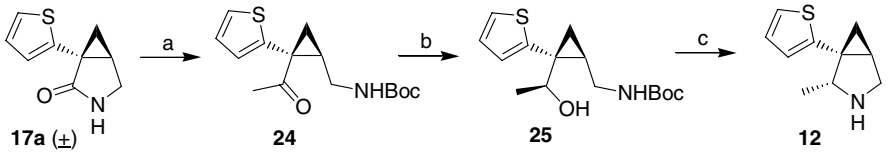
was purified to give a pair of diastereoisomers.[27] **23**-I was converted to the corresponding azide with the retention of configuration.[28] Hydrogenation of this azide intermediate gave an amine which was cyclized to the corresponding lactam, followed by a $LiAlH_4$ reduction to give the methyl derivative *cis*-**11**. Alternatively, oxidation of **23**-I with PDC gave a ketone which was reduced with Dibal-H to give **23**-II, which was converted to the corresponding *trans*-**11**.

The 2-methyl analog **12** was prepared from the lactam **17a** as shown in Scheme 5. Reaction of **17a** with $(Boc)_2O$, followed by a MeLi addition afforded the ketone **24**,[29] which was reduced with KBH_4 to give the alcohol **25** as a pair of stereoisomers. Treatment of **25** with methanesulfonyl chloride, followed by trifluoroacetic acid, gave **12** as a pair of *cis*-isomers.

The activity of bicifadine **1** at the cloned human monoamine transporters was recently reported.[2,7] Inhibition of rat brain synaptosomal uptake of norepinephrine and serotonin was reported by Beer et al. in a patent application and the IC_{50} values of **1** were 215 and 96 nM at NET and SERT, respectively.[30] In comparison, the unsubstituted phenyl compound **6a** displayed IC_{50} values of 401 and 470 nM, respectively, indicating the additional methyl group of **1** improves SERT activity by 5-fold but only 2-fold at NET. In our assays using cloned human transporters,[31] **6a** was somewhat NET-selective (NET = 350 nM, SERT = 5200 nM, DAT = 2700 nM, Table 1) at the cloned human monoamine transporters. The lipophilic 3,4-dichloro analog **6b** (DOV 216,303) was much more potent at all three transporters compared to **6a**, particularly at SERT (IC_{50} = 27 nM). Between the individual stereoisomers, the 1*R*,5*S*-compound *S*-**6b** (DOV 21,947) was about 8-fold more potent than the 1*S*,5*R*-isomer *R*-**6b** (DOV 102,667) at both NET and SERT. Although these compounds are known as triple inhibitors,[22] *S*-**6b** was somewhat more potent at SERT (IC_{50} = 8.6 nM) than at the other two transporters (NET IC_{50} = 51 nM, DAT IC_{50} = 260 nM) in our assays.

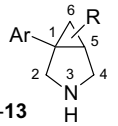
To explore the influence of a small substituent at the core structure, compounds **7**–**10** were prepared, and their activities were compared with **6a** and **6b**. In human subjects, bicifadine is oxidized to the corresponding 4-oxo metabolite, and both had similar plasma concentrations.[21] Compound **7** with a fluorine at the 5-position was designed to potentially reduce the rate of this oxidation. However, **7** was substantially less potent than **6a**, despite the fact that the fluorine atom is only about 40% larger in size than hydrogen. Incorporation of two methyl groups at the 6-position of **6a** almost abolished its activity at NET (**8**, IC_{50} = 7200 nM). However, a 6-phenyl group at the same side of the 1-phenyl of **6a** improved its potency, especially at SERT (*cis*-**9a**, IC_{50} = 240 nM). These results indicate that a 6-methyl group at the opposite side of the 1-phenyl of **6a** is detrimental to its inhibitory activity at NET. This hypothesis is supported by a pair of 6-methyl analogs of **6b**. Thus, *cis*-**10** was almost 20-fold more potent than *trans*-**10** at NET, although these two stereoisomers showed similar potencies at SERT and DAT. The *cis*-phenyl analog *cis*-**9b** displayed a slightly higher activity at NET than **6b** but was less potent at SERT. It is worth noting that bicifadine has polymorphism in crystalline forms, which is mainly caused by the different orientation of its aryl group.[32] The fact that *trans*-**10** is much less potent than *cis*-**10** suggests that a small steric effect of the *trans*-methyl of **10** reduces its interaction with both NET and SERT, while the *cis*-methyl group might affect the orientation of the phenyl ring that is required by SERT.

SAR of different phenyl substitutions showed that the ethylenedioxyphenyl derivative **6c** was much less potent than **6a** at NET. This aryl group displays a 6-fold improvement at milnacipran **2**,[33] indicating different pharmacophores between these two templates despite some similarity in chemical structure. Compared to the biphenyl compound **6d**, the naphthyl analog **6e** was much more potent at all three transporters. Among the bicyclic heterocycles **6f**–**6i**, the hydrophilic 6-quinolinyl **6f** showed a weak potency, while the lipophilic 2-benzothienyl **6h** had IC_{50} values around



Scheme 5. Reagents and conditions: (a) i—$(Boc)_2O$/DMAP/CAN/rt, 16 h; ii—MeLi/THF/−78 °C to rt, 1 h; (b) KBH_4/MeOH, rt, 1 h; (c) i—MsCl/Et_3N/DCM/rt, 1 h; ii—TFA/DCM/rt, 2 h.

Table 1
SAR of bicifadine analogs at monoamine transporters[a]



6-13

Compound	Ar	R	NET IC_{50} (nM)	SERT IC_{50} (nM)	DAT IC_{50} (nM)	*c*Log*P*
6a[b]	Phenyl	H	350	5200	2700	1.5
7	Phenyl	5-F	1800	2900	>10,000	1.3
8	Phenyl	6,6-Me	7200	1800	>10,000	2.5
cis-**9a**	Phenyl	6-Ph	120	240	8,700	3.1
6b[b,c]	Phenyl, 3,4-dichloro	H	88	27	380	2.6
R-**6b**[d]	Phenyl, 3,4-dichloro	H	430	66	330	2.6
S-**6b**[d]	Phenyl, 3,4-dichloro	H	51	8.6	260	2.6
trans-**10**	Phenyl, 3,4-dichloro	6-Me	500	200	500	3.1
cis-**10**	Phenyl, 3,4-dichloro	6-Me	29	190	400	3.1
cis-**9b**	Phenyl, 3,4-dichloro	6-Ph	34	350	360	4.2
6c	Phenyl, 3,4-ethylenedioxy	H	3500	1500	>10,000	1.2
6d	Phenyl, 4-phenyl	H	360	160	2300	3.3
6e	2-Naphthyl	H	36	50	190	2.7
6f	6-Quinolinyl	H	1400	640	3900	1.4
6g	2-Benzofuranyl	H	48	140	330	2.0
6h	2-Benzothienyl	H	53	71	180	3.7
6i	3-Benzothienyl	H	220	73	780	3.7
6j	2-Thienyl	H	130	4500	7500	1.2
R-**6j**	2-Thienyl	H	150	4900	6200	1.2
S-**6j**	2-Thienyl	H	92	1900	2400	1.2
trans-**11**	2-Thienyl	4-Me	320	7600	3400	1.7
cis-**11**	2-Thienyl	4-Me	560	6000	9500	1.7
cis-**12**	2-Thienyl	2-Me	150	5800	8900	1.7
13	2-Thienyl	3-Me	1600	6300	>10,000	1.6
17a	2-Thienyl	2-Oxo	>10,000	>10,000	>10,000	−0.3
6k	2-Thienyl, 5-chloro	H	130	190	3300	1.8
R-**6k**	2-Thienyl, 5-chloro	H	590	1300	2500	2.6
S-**6k**	2-Thienyl, 5-chloro	H	77	81	1500	1.8
6l	2-Thienyl, 5-bromo	H	190	140	2400	2
6m	2-Thienyl, 3,5-dichloro	H	5300	4200	>10,000	2.4
6n	2-Thienyl, 4-methyl	H	6800	>10,000	>10,000	1.6
6o	2-Thienyl, 5-trifluoromethyl	H	3100	190	>10,000	2.2
R-**6l**	2-Thienyl, 5-bromo	H	340	380	1700	2
R-**6p**	3-Thienyl	H	300	6800	8200	1.2
R-**6q**	5-Benzofuranyl, 2,3-dihydro	H	4800	610	9100	1.4
R-**6r**	5-Indenyl, 1,2-dihydro	H	2000	97	>10,000	2.6
S-**6s**	2-Thienyl, 5-fluoro	H	470	8100	>10,000	1.5
S-**6t**	2-Benzothienyl, 5-fluoro	H	67	33	420	3.7
S,S-**5**			3.1	5200	>10,000	2.8

[a] Data are average of two or more independent measurements.
[b] The following IC_{50} values at rat synaptosomal preparations were reported by Beer and Epstein.[30] For **6a**: NET = 401 nM, SERT = 470 nM; for **1**: NET = 215 nM, SERT = 96 nM; for **6b**: NET = 145 nM, SERT = 26 nM; DAT = 232 nM.
[c] The following data for **6b** at the cloned human monoamine transporters were reported by Skolnick et al.[9] NET = 20.3 nM, SERT = 13.8 nM, DAT = 78 nM.
[d] The following data at the cloned human monoamine transporters were reported by Skolnick et al., for *S*-**6b**:[11] NET = 22.8 nM, SERT = 12.3 nM, DAT = 96 nM; for *R*-**6b**:[14] NET = 103 nM, SERT = 133 nM, DAT = 129 nM.

100 nM for all three transporters. These results suggest that a lipophilic aromatic group generally increases potency but not selectivity.

The 2-thienyl compound **6j** displayed an IC_{50} of 130 nM at NET and was over 30-fold selective over SERT and DAT. The two individual enantiomers *R*-**6j** and *S*-**6j** were separated using chiral HPLC and were found to possess NET selectivity. Thus 1*S*,5*S*-isomer *S*-**6j**, its stereochemistry was confirmed by a chiral synthesis using the procedure described in Scheme 3, was slightly more potent than the 1*R*,5*R*-isomer *R*-**6j**. Since **6j** possessed the NET-selectivity and a good physicochemical property (*c*Log*P* = 1.2), we further explored the effect of a methyl substitution on its transporter activity. A conformational analysis of **6j** showed that the aromatic thienyl group was freely rotatable despite its compact structure, and a small methyl group might slow down the rotation. Both *cis*-**11** and *trans*-**11** had reduced potencies compared to **6j**, while *cis*-**12** had a comparable potency. *N*-Methylation of **6j** also reduced its potency at NET (**13**, NET IC_{50} = 1600 nM), while the 2-oxo analog of **6j** was inactive (**17a**), confirming the importance of the basic amine. Chlorine substitution at the 5-position of the 2-thienyl ring of **6j** resulted in an about 20-fold improvement in SERT activity (**6k**, IC_{50} = 190 nM), further demonstrating that a lipophilic aromatic ring is preferred for SERT activity. For the two individual stereoisomers, the 1*S*,5*S*-compound *S*-**6k** was more potent than the 1*R*,5*R*-isomer *R*-**6k** at all three transporters. Compound *S*-**6k** had an equal potency at NET and SERT and was about 20-fold selective over DAT. The bromo compound **6l** displayed a similar profile to its chloro analog **6k**. Unexpectedly, the 3,5-dichloro-2-thienyl compound **6m** had very low activities at all three transporters, suggesting that a steric effect of the 3-chlorine limits its rotation to a favored orientation. The 4-methyl **6n** and the 5-trifluoromethyl-2-thienyl compound **6o** were also weakly active at NET.

For the chiral compounds synthesized, the 5*R*-compounds *R*-**6l**, and *R*-**6p**–**6r** were not very active at NET, including the 3-thienyl *R*-**6p** (NET IC_{50} = 300 nM). The 5-fluoro-2-thienyl *S*-**6s** (NET

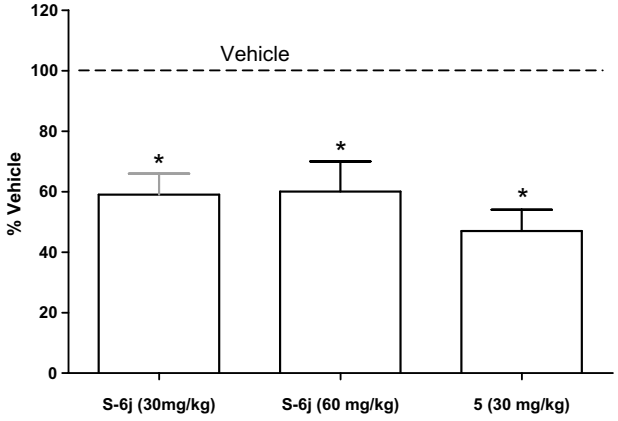


Figure 2. Compound *S*-**6j** in comparison with *S*,*S*-**5** in phase 2 of the formalin test in rats. One hour after administration of *S*-**6j** or *S*,*S*-**5**, mice received a mid-plantar injection of 5% formalin solution. Hindpaw flinching number was recorded between 10 and 40 min after formalin injection.

IC_{50} = 470 nM) were significantly less potent than *S*-**6j**, indicative of an electronic requirement of the aromatic ring. The 5-fluoro-2-benzothienyl *S*-**6t** was quite potent as a dual NET/SERT inhibitor. However, its selectivity over DAT was slightly lower than the 5-chloro-2-thienyl *S*-**6k**. In general, 5*S*-isomers were more active than the 5*R*-counterparts.

The moderately lipophilic *S*-**6j** was further profiled because its NET activity matched with DOV 216,303 (**6b**, NET IC_{50} = 88 nM). In an in vitro human liver microsomal assay, *S*-**6j** displayed moderate metabolic stability with a CL_{sys} of 12.7 mL/min.kg. In a Caco-2 monolayer assay, *S*-**6j** showed high permeability ($P_{app} = 17.6 \times 10^{-6}$ cm/s) and low efflux ratio (0.7).

The antinociceptive efficacy of bicifadine has been examined by Basile et al. in the formalin model of persistent pain processes, and their results show that the antinociceptive actions of bicifadine in formalin-treated mice are more pronounced in Phase 2 than in Phase 1, with all doses of bicifadine (5–60 mg/kg) significantly reducing the time spent licking by as much as 89% at 60 mg/kg.[2] We studied *S*-**6j** in the formalin model to compare its effects with the NET-selective *S*,*S*-reboxetine (*S*,*S*-**5**). Oral administration of *S*-**6j** at 30 mg/kg reduced the number of hindpaw flinches as much as 40% compared to vehicles, which was only slightly less effective than *S*,*S*-reboxetine at the same dose. Increase of *S*-**6j** dose to 60 mg/kg had no significant additional effect (Fig. 2).

In conclusion, a series of bicifadine analogs were synthesized and profiled as monoamine transporter inhibitors. Lipophilic aromatic compounds such as 2-naphthyl and 2-benzothienyl derivatives possessed high activity at NET and SERT and low selectivity over DAT. The 1*S*,5*S*-isomer *S*-**6j** displayed a good potency at NET and selectivity over SERT and DAT. *S*-**6j** also demonstrated efficacy in a rat formalin model with comparable activity to *S*,*S*-reboxetine.

Acknowledgments

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