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NOREPINEPHRINE REUPTAKE INHIBITORS FOR DEPRESSION, ADHD AND OTHER NEUROPSYCHIATRIC DISORDERS†

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†*Dedicated to late Dr. Ronald G. Micetich, Naeja Pharmaceutical Inc. (formerly Synphar Laboratories)*

Abstract – Neuropsychiatric disorders have been actively studied for several decades. Many of these disorders were treated by pharmacotherapy, certain forms of psychotherapy, and electroconvulsive therapy. Several classes of drugs with a range of binding selectivities have been discovered and used in the treatment of various central nervous system (CNS) disorders. The earlier drugs had undesired side effects because of their binding to a broad range of neurotransmitters. However, with the advancement of science, there is an increasing understanding of the role of monoamine neurotransmitters in various CNS disorders, which had resulted in the rational design of potent drugs with very selective binding properties. Yet, there are many unanswered questions, and the CNS research is being more actively pursued than ever with newer additional tools such as magnetic resonance imaging (MRI), molecular imaging by positron emission tomography (PET), single-photon emission tomography (SPECT), etc. The goal of this review is to bring together the recent discoveries on selective norepinephrine reuptake inhibitors, developments, and their uses in depression and ADHD. Some of the dual inhibitors of norepinephrine and serotonin transporters have also been included in this review, as these have very similar applications.

This paper is dedicated to Prof. Satoshi Omura on occasion of his 70th birthday.

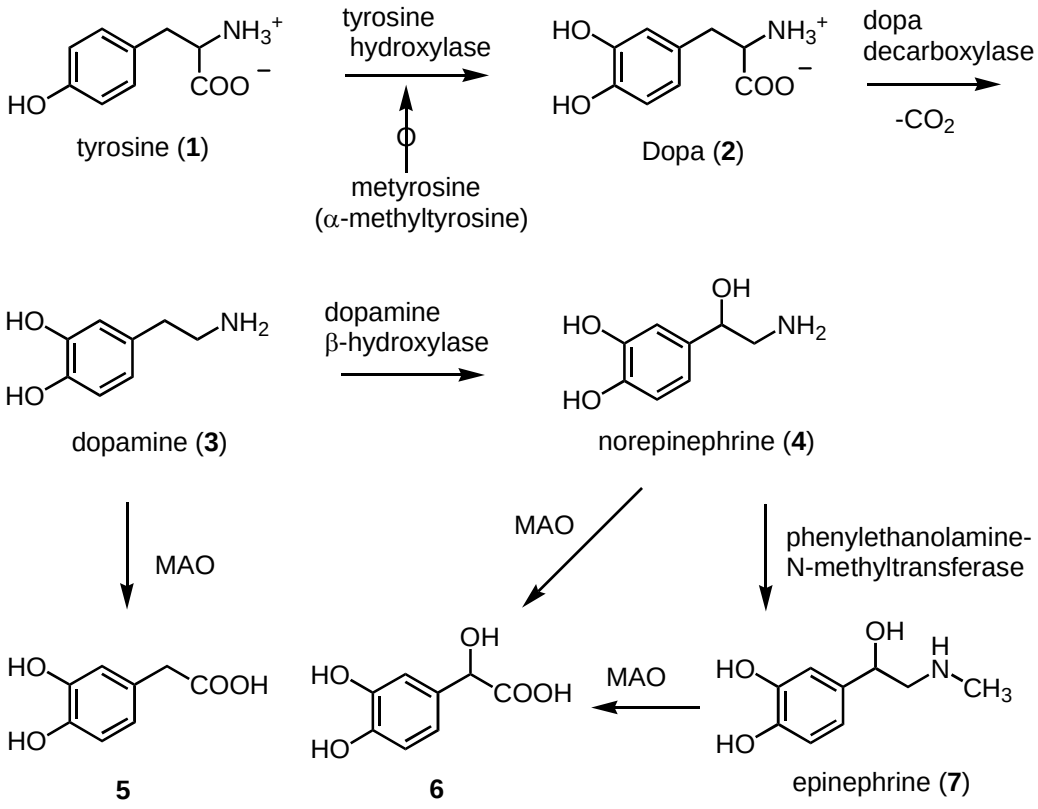
INTRODUCTION

Currently, the research and development in drug discovery is actively pursued in ten main therapeutic areas, and central nervous system (CNS) is the second most-researched area next to cancer. According to a recent report in R & D directions, about 242 drugs are in development for CNS disorders in the year 2005. Depression was the largest specific segment of the CNS market with $15.9 billion in U.S. drug sales in 2004. The heightened importance for CNS drug discovery is obviously because of the identification of increasing number of individuals with some form or other of CNS disorders. This is more prevalent with elderly group of people whose population is increasing worldwide as a result of increase in life expectancy, and elevated fertility during the two decades after World War II (i.e., the "Baby Boom" effect). Neuropsychiatric or CNS disorders include major depression, anxiety, schizophrenia, bipolar disorder, sleep disorders, obsessive-compulsive disorder, alcohol abuse, attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease, Parkinson's disease and stroke, and account for a major portion of the disability in less developed and developing countries.[1-15] CNS drug discovery is more complex and challenging because of several factors, such as complexity of brain, the passage of drug through the blood-brain barrier (BBB) to reach the site of action in brain, and side effects caused by CNS drug candidates because of binding to unwanted sites.[16] A half a century of research aimed at elucidating the etiologies and pathophysiological mechanisms of these devastating CNS disorders, parallel to the rapid development of new chemical entities, have provided several guidelines for CNS drug discoveries and treatment. In particular, the development of modern diagnostic tools such as magnetic resonance imaging (MRI),[17] molecular imaging by positron emission tomography (PET), [18, 19] and single-photon emission tomography (SPECT)[20] have made a stronger impact toward a better understanding of CNS disorders.

Biogenic monoamine neurotransmitters, dopamine (DA), norepinephrine (NE), and serotonin (5-HT), play key role in various CNS activities, and therefore optimum levels of their availability in brain circuits is vital to maintain good emotional or mental health, and physical well-being. These monoamine neurotransmitters are produced in the cell body of the neuron by complex chemical routes as shown in Scheme 1 and Scheme 2.[1,2] Dopamine and norepinephrine transmitters, being in family of catecholamines are inter related to each other, while serotonin has a different synthetic pathway. All these neurotransmitters are metabolized by monoamine oxidase (MAO). Neurotransmitters travel from the terminal of a neuron (presynaptic) across a small gap (i.e., the synaptic cleft) and bind to receptor proteins on the surface of a second neuron. This binding generates intracellular changes that initiate or activate a response in the postsynaptic neuron. Besides metabolism by MAO, inactivation occurs primarily by reuptake of the neurotransmitter back into the presynaptic neuron through neuronal plasma membrane, which are called as monoamine transporters (dopamine transporter - DAT for DA,

norepinephrine transporter – NET for NE, and serotonin transporter – SERT for 5-HT). Thus, the basis for the treatment of neuropsychiatric disorders and drug addiction is to moderate the levels of neurotransmitters. This could be accomplished by two different strategies, which are (i) blocking the respective transporters by chemical entities (antagonists), or (ii) inhibiting the metabolism by monoamine oxidase.

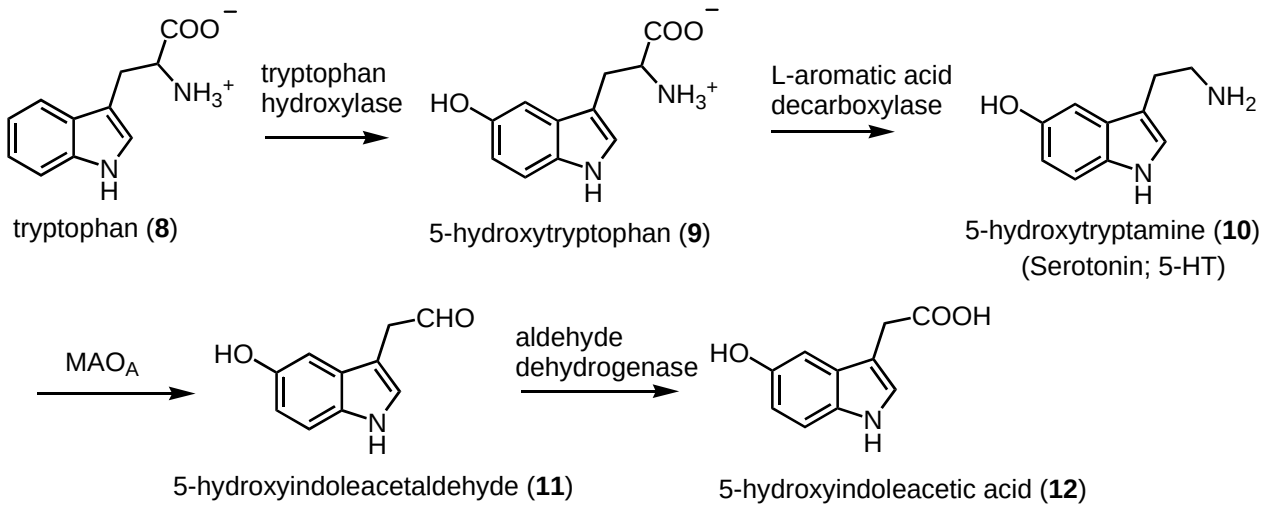
Scheme 1: Biosynthesis and Metabolism of Catecholamines



Monoamine neurotransmitters have been extensively studied, and several articles have appeared in the literature highlighting their importance in various neuropsychiatric disorders.[3-5] The goal of this review is to discuss some of the recent research and developments of norepinephrine reuptake inhibitors (NRI), in particular emphasizing the recent discoveries on anti-depressant and ADHD drugs. Some of the potent dual inhibitors of NET and SERT are also included in this review as these inhibitors have very similar treatment applications. In fact, it has been elucidated that drugs possessing simultaneously NET and SERT inhibition properties have improvement in efficacy for the treatment of depression, and they are also associated with low side-effect potential.[3]

The NET is located in the plasma membrane of noradrenergic neurons, where it functions to take up synaptically released norepinephrine. Accumulating evidence indicates that the norepinephrinergic

Scheme 2: Biosynthesis and metabolism of Serotonin



tryptophan (**8**)

5-hydroxytryptophan (**9**)

5-hydroxytryptamine (**10**) (Serotonin; 5-HT)

5-hydroxyindoleacetaldehyde (**11**)

5-hydroxyindoleacetic acid (**12**)

system modulates drive and energy, whereas the serotonergic system modulates mood. Drugs of abuse such as cocaine, and antidepressants (e.g., desipramine, imipramine, venlafaxine, mirtazapine, reboxetine, bupropion) block NET and result in an elevation of the synaptic concentrations of norepinephrine.[21-30] Drugs that exert their main action on the norepinephrinergic system have been available for sometime, however their lack of selectivity made it difficult to determine specific clinical effects produced by a selective action on norepinephrine reuptake. At present, there are only very few NET-selective drugs available, and it is a great challenge for several researchers both in pharmaceutical and academia, to discover novel candidates with high NET binding potency and selectivity.

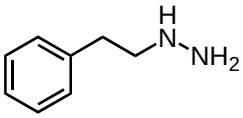
One of the most actively studied neuropsychiatric disorders is the depression disorder. There are several ways to treat depression disorder, which are pharmacotherapy, certain forms of psychotherapy, and electroconvulsive therapy (ECT). However, a significant number of patients do not respond fully to the available treatments or very slowly respond, and some unable to tolerate currently available treatments because of severe side-effects. Since the discovery of first antidepressant imipramine by Ciba-Geigy in the late 1950's, several new classes of drugs have been identified. Mainly, these drugs attempt to elevate the levels of one or more of monoamine neurotransmitters to achieve the desired effect.

These are grouped either based on their inhibitor properties or chemical structure (Figure 1):

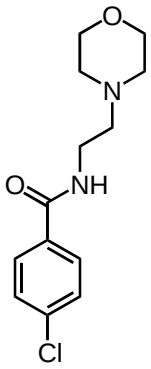
I. The monoamine oxidase inhibitors (MAOI; e.g., moclobemide, and phenelzine)
II. Tricyclic antidepressants (TCA; e.g., imipramine and amitriptyline)
III. Atypical drugs (e.g., Trazodone and Bupropion)
IV. Selective serotonin re-uptake inhibitors (e.g., SSRI; e.g., fluoxetine, paroxetine, escitalopram, and sertraline)

Figure 1: Some examples of antidepressants

I. MAO inhibitors (MAOI)

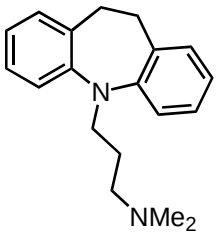


Phenelzine (**13**)

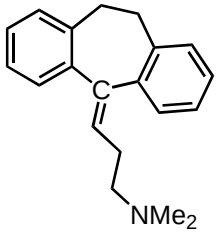


Moclobemide (**14**)

II. Tricyclic antidepressants (TCA)

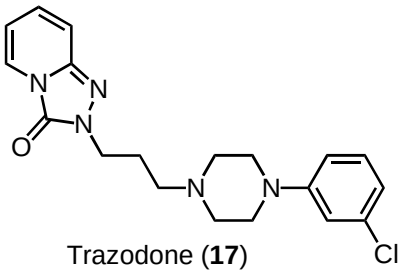


Imipramine (**15**)

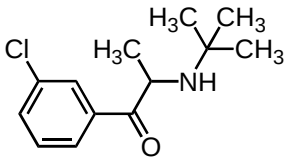


Amitriptyline (**16**)

III. Atypical antidepressants

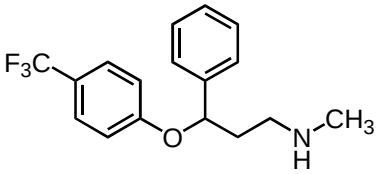


Trazodone (**17**)

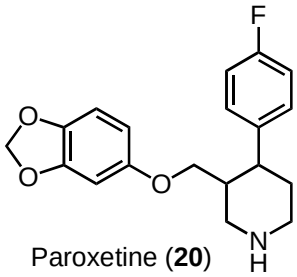


Bupropion (**18**)

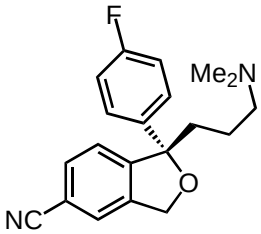
IV. Selective Sertonin reuptake inhibitors (SSRI)



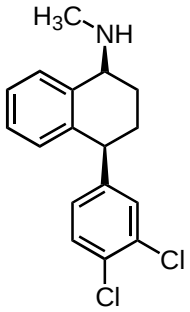
Fluoxetine (**19**)



Paroxetine (**20**)

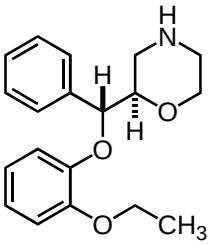


Escitalopram (**21**)



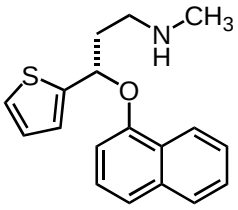
Sertraline (**22**)

V. Selective Norepinephrine reuptake inhibitors (NRI)

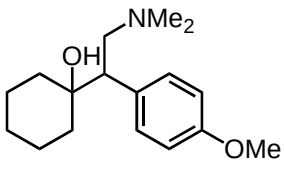


Reboxetine (**23**)

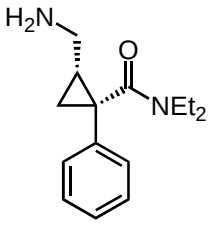
VI. Sertonin and Norepinephrine reuptake inhibitors (SNRI)



Duloxetine (**24**)



Venlafaxine (**25**)



Milnacipran (**26**)

V. Selective norepinephrine re-uptake inhibitors (NRI; e.g., reboxetine)

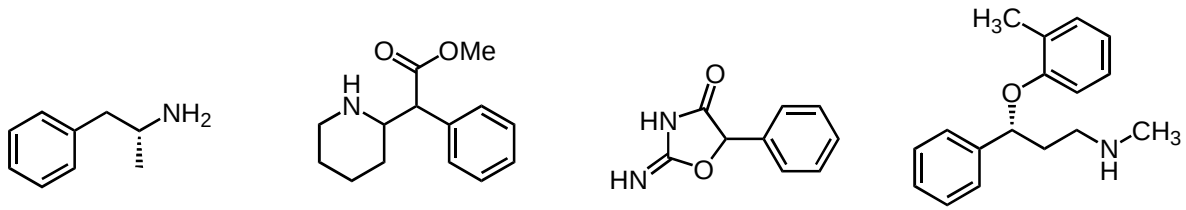
VI. Serotonin and norepinephrine re-uptake inhibitors (SNRI; e.g., duloxetine, venlafaxine, and milnacipran).

WHAT IS ADHD?

Attention-deficit hyperactivity disorder (ADHD) is defined as a persistent and frequent pattern of

developmentally inappropriate inattention and impulsivity, with or without hyperactivity. Persons with the most common type of ADHD have a combination of an attention deficit together with hyperactivity and impulsivity symptoms. The disorder affects approximately 5 % of children between the ages of 5 and 14, with boys being 2-3 times more likely to be affected than girls.

Figure 2: Some examples of ADHD Drugs



D-amphetamine (**27**) Methylphenidate (**28**) Pemoline (**29**) Atomoxetine (**30**)

Studies of the molecular basis of ADHD have focused largely on the mesocorticolimbic dopamine system, but evidence is inconclusive at present as to whether dopaminergic hypo- or hyperfunction is the basis of this disorder. Stimulants have historically been the drugs of choice for treating ADHD.[31-34] The prototypic stimulant, D-amphetamine was first used in 1936, but has been largely supplanted over the years by methylphenidate and pemoline (Figure 2). The central and peripheral effects of these agents derive from their ability to release biogenic amines (dopamine, norepinephrine and serotonin) from nerve terminals, and to block their reuptake by their respective membrane transporters. Approximately 60 – 80 % of children with ADHD respond favorably to one of these psycho stimulants, with a significant increase in attention span and decrease in motor activity and restlessness. Despite this success rate, however, treatment with psycho stimulants is usually discontinued at puberty because of reports of stunted growth in children who continuously take these medications. Newer medications without the abuse liability and side-effects associated with stimulants are therefore badly needed. A new drug, a selective norepinephrine reuptake inhibitor, atomoxetine (Strattera^{TM}) (Figure 2), was recently introduced by Lilly for the treatment of ADHD.[29]

Currently, NET inhibitors are also being studied for their use in stress urinary incontinence, pain associated with depression, treatment of obesity, drug abuse, or narcolepsy.[35-37]

2. DISCUSSION

In this section, the recent discoveries on selective NET inhibitors are discussed along with their current and possible treatment applications. Compounds are grouped based on the structural classification for the ease of convenience.

2.1. Tropane derivatives

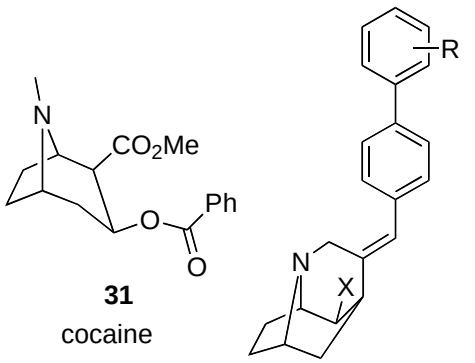
It is well known that the plant alkaloid cocaine (**31**) (Figure 3) can be psychologically addictive, and its possession, cultivation, and distribution are illegal for non-medicinal purposes in almost all parts of the world. Cocaine is a stimulant of the central nervous system and an appetite suppressant.[38] This compound has been a subject of extensive studies for the last two decades for understanding the mechanism of its action on CNS, and hence to discover possible medications. Kozikowski's group has synthesized a number of conformationally constrained tricyclic tropane derivatives containing biaryl or heteroaromatic moiety, and their transporter inhibitory activities were explored.[39-41] Many of these compounds exhibit moderate to high inhibitory activity at the NET but lower activities at the DAT and SERT. Initially, SAR of the lead compound **A** {**32** (R = H), Figure 3} was explored, upon modification of the aryl group. Considering electron-donating substituents, the potency at NET decreases in the sequence *4*-Me (K_i = 22.7 nM) > *4*-MeO (K_i = 39 nM) > *4*-NMe_2 (K_i = 57.9 nM). All these three derivatives and **32,** show good selectivity at NET as their potencies at SERT and DAT are in the order of magnitudes greater than 20-fold. Among the electron-withdrawing substituents, the activity at NET decreases in the sequence *3*-Cl (K_i = 17.5 nM) > *4*-CN (K_i = 32.4 nM) > *4*-I (K_i = 114 nM) > *4*-Cl (K_i = 739 nM) > *4*-CF_3 (K_i = 1146 nM). The DAT potency of *3*-Cl (K_i = 89 nM) and *4*-CN (K_i = 47 nM) are considerably good relative to other derivatives in this group. The *3,4*-dichloro analogue **34d**, has a high potency at NET (K_i = 9.7 nM) and about 25 fold potencies at SERT (K_i = 239 nM) and DAT (K_i = 236 nM).

Transformation of the ester (**32**) to **36** having a primary alcohol functional group resulted in loss in NET potency by a factor of about 15-fold. While converting alcohol (CH_2OH) group in **36** to acetate {CH_2OAc (**37**)} improved on NET (K_i = 57 nM), SERT (K_i = 46 nM), and DAT (K_i = 165 nM), whose behavior is much closer to cocaine (**31**), but relatively a more potent compound.

Some of the heteroaromatic tropane derivatives prepared by Kozikowski's group are shown in Figure 4.[40-42] In general, the heteroaromatic derivatives possess higher NET potency than the biaryl derivatives, suggesting that the shape and size of the lipophilic recognition pocket that encompasses the aryl ring(s) of these tropanes are major determinants of a ligand's transporter activity at either the NET or the SERT. Among the heteroaromatic tropanes, compounds having thienyl group show higher potency at NET. Small variation in thienyl group of **42** to iodothienyl group (**43**), altered SERT potency dramatically, and with a 5-fold change in affinity at NET. The NET potency of the furyl derivative (**39)** is similar to that of thienyl derivatives, in contrast, the pyrrolyl derivative (**41)** show less potency at NET.

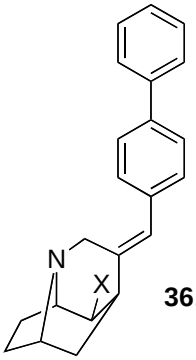
This selectivity profile differs from that of the monoaryl series, as most members of that series display excellent potency and selectivity at SERT.[43] This result further substantiates that the shape and size of the lipophilic recognition pocket are critical factors of a ligand's transporter activity.[40]

Figure 3: Biaryl tropane-based inhibitors {transport values are K_i ± SEM (nM)}



31
cocaine

X = COOMe
A (**32** - **35**)



36, **37**

X = CH_2OH (**36**)[2]
NET = 183 ± 8
DAT = 1298 ± 6
SERT = 1544 ± 242

X = CH_2OAc (**37**)[2]
NET = 57 ± 4
DAT = 165 ± 2
SERT = 46 ± 10

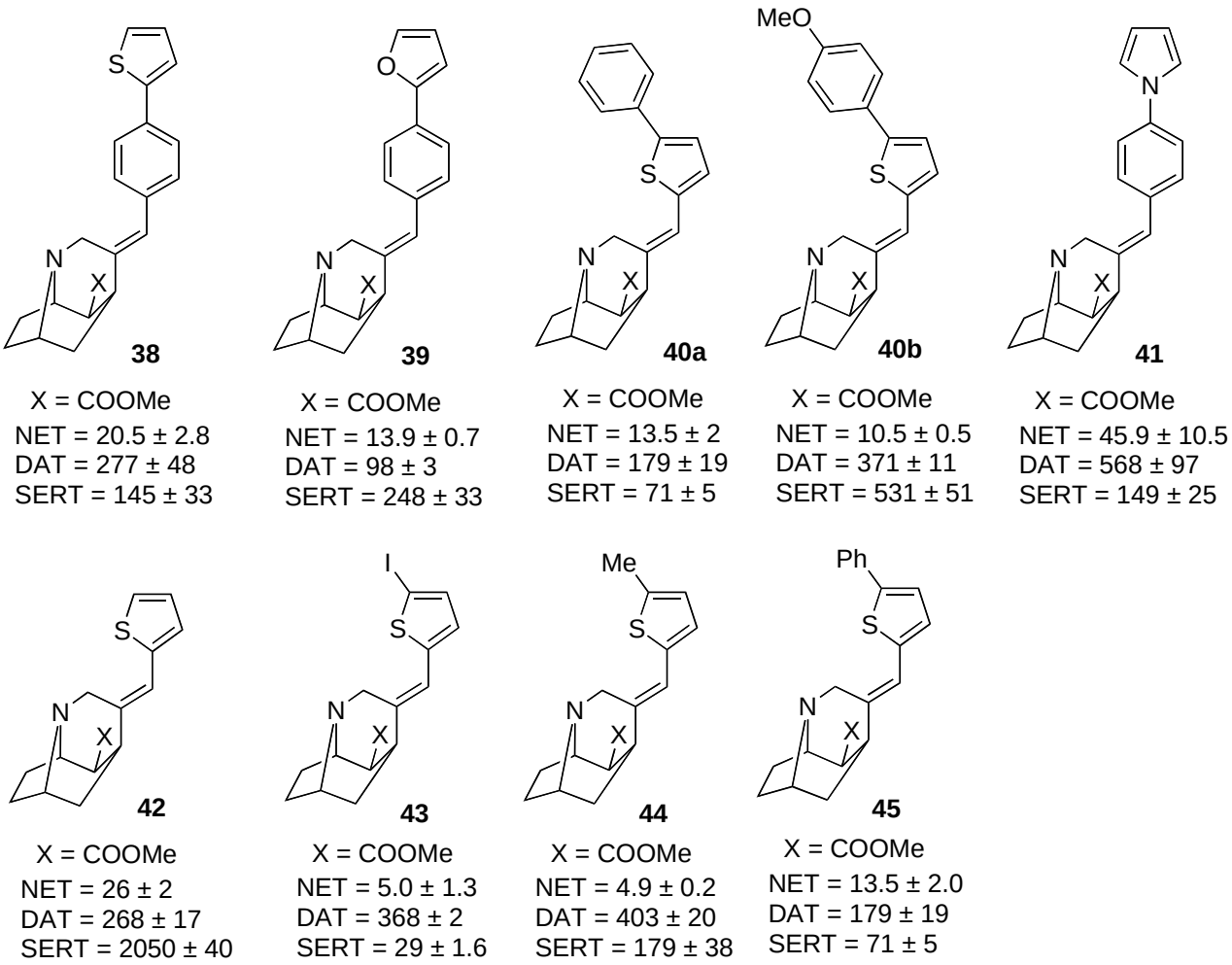
Compound	R	NET	SERT	DAT
Cocaine (**31**)[1]		108 ± 3	155 ± 1	423 ± 147
32[1]	H	12 ± 1	614 ± 105	477 ± 81
33a[2]	*4*-MeO	39 ± 7	3394 ± 598	841 ± 85
33b[2]	*4*-Me	22.7 ± 2.1	1489 ± 142	214 ± 5
34a[2]	*4*-I	114 ± 31	660 ± 87	377 ± 53
34b[2]	*4*-Cl	739 ± 148	1260 ± 99	417 ± 25
34c[2]	*3*-Cl	17.5 ± 2.2	213 ± 51	89 ± 12
34d[2]	*3*,*4*-Cl_2	9.7 ± 2.7	239 ± 37	236 ± 76
34e[2]	*3*,*5*-Cl_2	61 ± 6	384 ± 59	106 ± 14
34f[2]	*2*,*4*-Cl_2	466 ± 103	393 ± 18	1595 ± 201
35a[2]	*4*-NMe_2	57.9 ± 0.65	1002 ± 60.4	1053 ± 107
35b[2]	*4*-CF_3	1146 ± 185	2215 ± 52	3125 ± 0.01
35c[2]	*4*-CN	32.4 ± 1.2	909 ± 85	47 ± 6.6

[1]Data from Ref.39; [2]Data from Ref.40

2.2. QUINOLINONE DERIVATIVES

A novel series of quinolinone derivatives have been discovered as potent and selective norepinephrine reuptake inhibitors by Lilly.[44] Initial high-throughput screen for NET inhibitors resulted in the general scaffold **A** (Table 1), which consist of a basic amine linked by a flexible chain to a quinolinone ring. The SAR studies of **A** revealed a number of potent NET inhibitors with this core (Table 1). The initial potent NET compound (**46-rac**) had a log *D* of -0.48, and suggested poor brain penetration. As could be noticed from Table 1, mono-substitution of Y in the *3*-position with fluoro group (**47a**) was tolerated, whilst a *3*-chloro (**47b**) caused a reduction in NET affinity, implying size constraints. However, the trend is reverse for *4*-fluoro (**48a**) and *4*-Cl (**48b**) derivatives supporting the importance of minor positional and size variations for the overall molecule.

Figure 4: Heterocyclic tropane-based inhibitors {transport values are K_i ± SEM (nM)}[40-42]

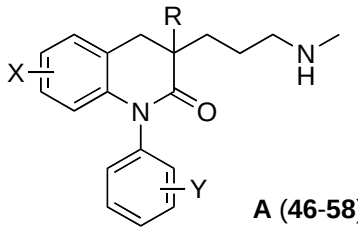


Increasing the size of the alkyl group and hence lipophilicity within this series, e.g., variation of Y-group with *4*-Me (**49a**), *4*-Et (**49b**), or *4*-CF_3 (**49c**), resulted in a reduction of NET activity. However, rational variation of substituents on the scaffold provided compounds both with reasonable lipophilic nature and also potent NET inhibiting property, some of them are listed in Table 1. Log D increased from -0.48 for **46-rac** to 1.8 for quinolinone derivative (**58**).[44]

2.3. PHENYLPROPANAMINES

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (**19**) (Prozac^{TM}),[45] are widely used in the treatment of depression. Only two selective norepinephrine reuptake inhibitors (NRIs) are currently in clinical use. Lilly recently introduced atomoxetine (**30**) (Strattera^{TM})[46] for the treatment of ADHD, and duloxetine (**24**) (Cymbalta^{TM})[47,48] for the treatment of major depression. Duloxetine has shown to improve potency and accelerate onset of action of antidepressant activity.[49] Duloxetine has also been studied for the treatment of stress incontinence after radical prostatectomy or cystectomy.[50]

Table 1: *1*-Aryl-*3*,*4*-dihydro-*1H*-quinolin-*2*-one inhibitors {transport values are K_i ± SEM (nM)}



A (**46**-**58**)

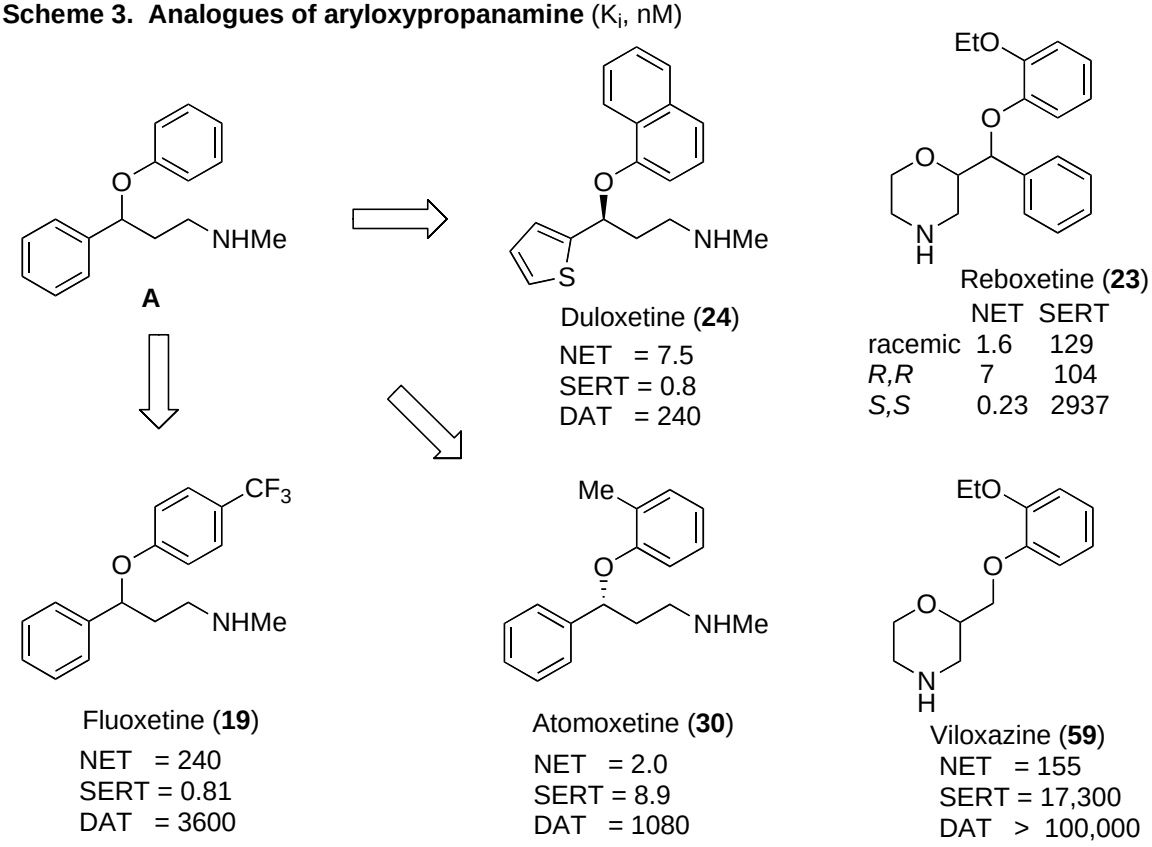
Compound	X	Y	R	NET	SERT	DAT
46-rac	H	H	H	10 ± 4	>100 (0 ± 6%)[a]	>200 (24 ± 7%)[b]
47a-rac	H	3-F	H	18 ± 1	>100 (9 ± 1%)[a]	>200 (10 ± 0.2%)[b]
47b-rac	H	3-Cl	H	79 ± 11	>100 (7 ± 2%)[a]	>200 (64 ± 2%)[b]
48a-rac	H	4-F	H	92 ± 3	>100 (7 ± 2%)[a]	>200 (5 ± 5%)[b]
48b-rac	H	4-Cl	H	21 ± 2	>100 (8 ± 1%)[a]	>200 (50 ± 3%)[b]
49a-rac	H	4-Me	H	3 ± 1	>100 (15 ± 6%)[a]	>200 (19 ± 3%)[b]
49b-rac	H	4-Et	H	150 ± 41	>100 (3 ± 2%)[a]	>200 (9 ± 6%)[b]
49c-rac	H	4-CF_3	H	1430 ± 285	>100 (1 ± 1%)[a]	>200 (12 ± 1%)[b]
50-rac	H	4-Me	Me	9 ± 2	>100 (12 ± 2%)[a]	>200 (3 ± 8%)[b]
51-rac	H	H	Et	10 ± 1	>100 (12 ± 3%)[a]	>200 (6 ± 0.2%)[b]
52-rac	H	H	Pr^n	7 ± 1	>100 (51 ± 2%)[a]	>200 (3 ± 3%)[b]
53-rac	H	4-Me	Et	17± 1	>100 (11 ± 2%)[a]	>200 (11 ± 0.1%)[b]
54-rac	H	4-Me	Pr^n	11 ± 1	160 ± 5	>200 (9 ± 1%)[b]
55-rac	H	4-Me	Bu^n	8 ± 2	N.D.[c]	>200 (18 ± 3%)[b]
56-rac	F	4-Me	H	5 ± 1	>100 (45 ± 3%)[a]	>200 (5 ± 3%)[b]
57-rac	Cl	4-Me	H	6 ± 2	>100 (15 ± 2%)[a]	>200 (7 ± 5%)[b]
58-rac	Cl	4-Me	Et	47 ± 5	128 ± 10	>200 (3 ± 3%)[b]

[a]Percentage displacement of radioligand at 100 nM
[b]Percentage displacement of radioligand at 1000 nM
[c]N.D. (not determined)

This drug enhances the central nervous system's natural continence control mechanisms.[51] Both atomoxetine and duloxetine have advantage of having potent selectivity at both NET and SERT, which is highly preferred in psychopharmacology.[3] These potent and highly selective ligands (**19**, **24** and **30**), have resulted from the SAR of *3*-aryloxypropanamine scaffold **A** (Scheme 3).[33,52] This scaffold in particular has the potential for high affinity binding to biogenic amine transporters. Further SAR on this scaffold has generated several *2*-substituted derivatives of these *3*-aryloxypropanamine compounds.[52c-e] Some of these compounds are potent NET and SERT inhibitors.

Reboxetine (**23**) (Edronax^{TM}), another selective NRI was introduced by Pharmacia (Pfizer), and marketed in Europe and several other countries except US for the treatment of depression.[33,34] Reboxetine has also a motif similar to that of these selective ligands (**19**, **24** and **30**), except it is constrained in a morpholine ring system (Scheme 3).

Scheme 3. Analogues of aryloxypropanamine (K_i, nM)

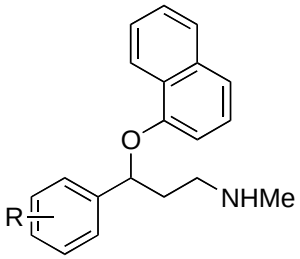


Reboxetine has two chiral centers, but exists only as a mixture of (-)-*R,R* and (+)-*S,S* enantiomers. Reboxetine could be used for the treatment of addictive disorders, psychoactive substance use disorders, nicotine addition or tobacco addiction, and ADHD.[53,54] The *S,S*- enantiomer is more potent and selective than the *R,R*- antipode, it is claimed for a variety of conditions that would benefit from a selective NET, including ADHD.[53] Viloxazine (**59**) is another selective norepinephrine reuptake inhibitor used in the treatment of clinical depression.[6] It is a racemic compound, the (*S*)-isomer being five times as pharmacologically active as the (*R*)-isomer. Viloxazine has also been found successful to some extent for the treatment of alcohol abuse, a disorder frequently associated with depressive disorder.[55] Some of the potent NET inhibitors within this series of 3-aryloxypropanamines could also be used for the treatment of tic disorders,[56] cognitive failure,[57] nausea, emesis and related conditions,[58] learning,[59] motor skills,[59] and stuttering disorders,[60] and hot flashes.[61]

2.4. PHENYL NAPHTHYL ETHERS

Substitution of the phenyl ring on scaffold **A** (Table 2) generated several derivatives (**60**-**73**), which are listed along with their NET and SERT inhibition values in Table 2.[49] No significant improvement of NET potency and selectivity was observed by varying substituents with different electronic nature, and as well as position of substitution. But the *4*-fluoro derivative (**61**) has shown considerable improvement in SERT inhibition, and many other compounds retained SERT inhibition behavior as observed for **60**.

Table 2: Phenyl naphthyl ethers: dual NET and SERT inhibitors {transport values are K_i (nM)}



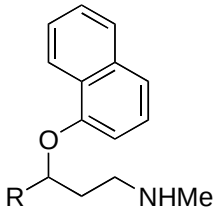
A (**60**-**73**)

Compound	R	SERT	NET
60	H	2.4	20
61	4-F	0.95	42
62	3-Br	7.6	67
63	4-Br	4.1	160
64	2-CF_3	10	38%[a]
65	3-CF_3	19	70
66	4-CF_3	14.5	55%[a]
67	4-Cl	3.8	78
68	2-Me	2.0	110
69	3-Me	4.0	40
70	4-Me	2.1	36
71	2-OMe	2.3	56%[a]
72	3-OMe	2.2	81
73	4-OMe	3.5	74

[a]Percentage inhibition at 1 μM

Isosteric replacement of the phenyl ring generated heterocyclic alternatives of scaffold (**60**), whose SERT and NET inhibition values are listed in Table 3.[49] Some of these compounds (**24**, **75**, and **76**)

Table 3: Heterocyclic naphthyl ethers: dual NET and SERT inhibitors {transport values are K_i (nM)}[49]



A

Compound	R	SERT	NET	DAT
60	Ph	2.4	20	
24	thien-2-yl	1.4	20	
***S*-24**		0.8	7.5	240
***S*-24**		4.6[a]	16[a]	370[a]
***R*-24**		8.8[a]	16[a]	660[a]
75	thien-3-yl	1.1	21	
76	furan-2-yl	0.7	20	
77	thiazol-2-yl	6.4	55	
Fluoxetine (**19**)		48[a]	2000[a]	6000[a]
Atomoxetine (**30**)		1500[a]	4[a]	2000[a]

[a]Inhibition studies on rat synaptosomes

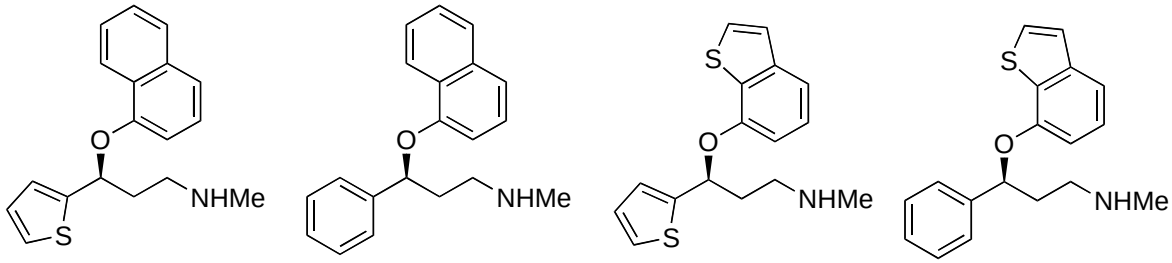
demonstrated improved SERT inhibition, with the furan analog (**76**) having a K_i value of 0.7 nM. Pure enantiomers (***S*-24** and ***R*-24**) were separated from racemic mixture of **24**, which were assessed for their ability to inhibit synaptosomal uptake into rat synaptosomes,[62] in addition to the study at the respective

human transporters. Enantiomer (***S*-24**) was shown to be more active at the SERT and increases serotonin and norepinephrine in rat pre-frontal cortex. This compound has been progressed to the clinic (as duloxetine hydrochloride, Cymbalta^{TM}) and has been shown to be effective in the treatment of depression.

2.5. BENZOTHIENYLOXY PHENYLPROPANAMINES

With an objective to synthesize a more acid stable dual reuptake inhibitors, duloxetine SAR was explored, which gave rise to a series of heterocyclic phenylpropylamines. Some of these are emerging clinical targets with dual SERT and NET inhibitors activity. Three molecules were targeted in order to gauge, which fragments were responsible for the observed acid instability. The binding affinities of these compounds (**60**, **78**, **79)** are listed in Table 4,[63] which are comparable to duloxetine (**24**). The acid stability of these compounds in 0.1 M HCl solution at 37 ^{0}C for 2 h and the percentage of parent remaining were also listed in Table 4. As it is evident, when the electron rich thiophene substituent was present the acid stability was reduced.

Table 4: Acid stability and binding affinities at monoamine transporters for benzothienyloxy phenyl propanamines {transport values are K_i (nM)}



Duloxetine (**24**) **60** **78** **79**

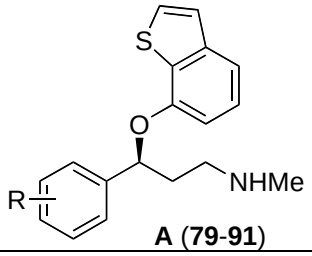
Compound	SERT	NET	DAT	Acid[a] Stability
Duloxetine (**24**)	0.8 ± 0.04	7.5 ± 0.3	240 ± 23	18 %
60	1.0 ± 0.1	6.1 ± 0.25	190 ± 3	99 %
78	1.5 ± 0.1	1.4 ± 0.3	120 ± 10	40 %
79	8.2 ± 1.3	2.2 ± 0.1	220 ± 5	99 %

[a]% parent remaining at 2h and 37 ^{0}C

Later, the SAR focused on maintaining the phenyl ring of **60** and **79** and in finding alternatives to *1*-naphthalene and *7*-benzothiophene. Another group of compounds were synthesized by varying the linking position of benzothiophene in **79**, and it was concluded that *4*- and *7*-linked benzothiophene derivatives are more appropriate for further investigation.

Table 5 shows the SAR of the *7*-linked benzothiophene scaffold **A**, giving rise to derivatives (**79 - 91**) with variation of substituents on phenyl group.[63] There is no significant improvement on binding profile

Table 5: Binding affinities at monoamine transporters for benzothienyloxy phenyl propanamines {transport values are K_i (nM)}



A (**79**-**91**)

Compound	R	Isomer	SERT	NET	DAT
79	H	1	8.2 ± 1.3	2.2 ± 0.1	220 ± 5
80	3-Me	1	2.2 ± 0.4	2.2 ± 0.5	114 ± 4
81	3-Me	2	2.4 ± 0.1	0.6 ± 0.1	147 ± 2
82	2-F	1	0.4 ± 0.05	1± 0.1	-61.4 ± 1%[a]
83	2-F	2	1.5 ± 0.1	1.1 ± 0.1	-55.0 ± 1%[a]
84	3-F	1	1.4 ± 0.1	0.7 ± 0.1	100 ± 3
85	3-F	2	1.1 ± 0.1	0.4 ± 0.05	134 ± 2
86	4-F	1	1.1 ± 0.05	2.0 ± 0.1	164 ± 7
87	4-F	2	0.5 ± 0.1	0.6 ± 0.1	176 ± 9
88	3-OMe	1	2.2 ± 0.3	4.6 ± 0.2	196 ± 4
89	3-OMe	2	2.4 ± 0.3	0.9 ± 0.1	177 ± 11
90	3-CF_3	1	13 ± 1	23 ± 2	-54.2 ± 0.1%[a]
91	3-CF_3	2	3.2 ± 0.1	0.5 ± 0.05	280 ± 3

[a]% Inhibition at 1μM.

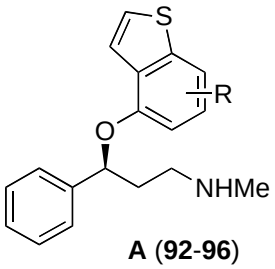
with respect to the introduction of new substituents, but notable exception being compound (**90**), the *3*-trifluoromethyl substituent phenyl analogue (isomer 1), which had reduced affinity for both SERT and NET.

Table 6 displays the SAR of another series of compounds resulting from the substitutions at phenyl in *4*-benzothiophene scaffold **A**.[63] Fluorination of benzothiophene phenyl group has minimal changes on serotonin transporter affinity, whereas inhibition of norepinephrine uptake is more variable, in particular *2*-fluorination is detrimental to norepinephrine reuptake. Introduction of nitrile group at *2*-position, a functional group very different in terms of electronic and steric nature to that of H or F, markedly reduces norepinephrine transporter inhibition. Considering the ease of synthesis and potent activity, compound (*S*)-**92** was advanced for in vivo studies. In vivo microdialysis experiments with (*S*)-**92**, increases above basal levels of synaptic serotonin and norepinephrine levels of 222 ± 14 % and 215 ± 9 % at 3 mg/kg p.o.

2.6. ARYLTHIOMETHYL MORPHOLINES

Analogues of reboxetine, arylthiomethyl morpholine compounds are potent selective norepinephrine reuptake inhibitors and dual serotonin/norepinephrine reuptake inhibitors.[64-66]

Table 6: Binding affinities at monoamine transporters for benzothienyloxy phenyl propanamines {transport values are K_i (nM); Ref 46}



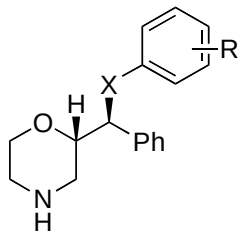
A (**92**-**96**)

Compound	R	Stereo	SERT	NET	DAT
92	H	*R*	5.4 ± 1.5	10 ± 1	930 ± 15
92	H	*S*	0.5 ± 0.1	4.4 ± 0.25	440 ± 10
93	2-F	*R*	1.9 ± 0.5	32 ± 4	-57 ± 2%[a]
93	2-F	*S*	4.1 ± 1.1	18 ± 1.3	-47 ± 2%[a]
94	5-F	*R*	0.4 ± 0.1	1.4 ± 0.1	-57 ± 1%[a]
94	5-F	*S*	0.4 ± 0.1	0.6 ± 0.05	-57 ± 1%[a]
95	7-F	*R*	0.7 ± 0.05	11 ± 2	540 ± 20
95	7-F	*S*	0.9 ± 0.1	12 ± 1	1400 ± 100
96	2-CN	*R*	13 ± 2	-41 ± 1%[a]	-58 ± 1%[a]
96	2-CN	*S*	0.25 ± 0.05	-47 ± 1.5%[a]	-22 ± 1%[a]

[a]% Inhibition at 1μM.

All target compounds were tested as *S,S*/*R,R* racemates for reuptake inhibition at the NET, SERT and DAT. Table 7 shows the inhibitory activity of a limited set of *2*-substituted-thioaryl morpholines

Table 7: Arylthiomethyl morpholine inhibitors {transport values are K_i ± SEM (nM)}



(*S*,*S*/*R*,*R*)

97-**101**

Compound	X	R	NET	SERT	DAT
97	S	H	17.6 ± 2.4	36 ± 0.3	522.1 ± 48.7
98 (SS/RR)	S	2-OMe	10.7 ± 2.2	1.2 ± 1.1	>200 (9.7 ± 3.0 %)[b]
98 Isomer 1	S	2-OMe	1.7 ± 0.4	66.2 ± 3.0	>200 (2.8 ± 1.8 %)[b]
98 Isomer 2	S	2-OMe	24.6 ± 2.3	1.5 ± 0.2	>200 (19.0 ± 3.4 %)[b]
99	S	2-Me	8.3 ± 1.0	0.2 ± 0.1	226.9 ± 34.9
100	S	3-Me	108.6 ± 7.4	3.2 ± 1.2	>200 (51 ± 0.2 %)[b]
101	S	4-Me	364.3 ± 19.3	>100 (19.3 ± 2.3)[a]	>200 (8 ± 1.1 %)[b]
Reboxetine (**23**)	O	2-OEt	1.9 ± 0.2	>100 (25 ± 18%)[a]	>200 (2 ± 1.7 %)[b]

[a]Percentage displacement of radioligand at 100 nM
[b]Percentage displacement of radioligand at 1000 nM

compared with (*R,R*/*S,S*) reboxetine. Methoxy analogue of reboxetine (**23**) had been reported to give poor SERT.[67] The thioaryl analogues (**97** - **100**) maintained potent levels of NET and SERT activities

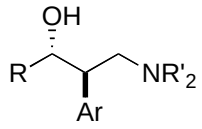
but poor activity against DAT. NET and SERT inhibition of methyl substituted morpholines (**99** - **101**) appeared to decrease in the order *ortho* > *meta* > *para*.

The enantiomers of **98** (isomer 1 and isomer 2) were separated from *rac*-**98** using chiral HPLC. Interestingly, isomer 1 was found to be a potent selective NET inhibitor whereas the slower eluting isomer 2 showed potent inhibition at both NET and SERT. This demonstrates that NET and SERT selectivity could reside in different enantiomers of a member of this series.

2.7. COMPOUNDS WITH GAMMA-AMINO ALCOHOL FUNCTIONAL GROUP

As discussed before in section 2.3, a number of aryloxypropanamine derivatives are potent NET or SERT or dual NET and SERT inhibitors. All of these structures have gamma-amino ether group in common.

Table 8: Equilibrium dissociation constants for SERT, NET, and DAT of gamma-amino alcohol compounds {transport values are K_D ± SEM (nM)}[a]



A (**102**-**113**)

Compound	R	R'	Ar	SERT	NET	DAT
(rac)-**102**	Ph	H	Ph	3,050 ± 280	12,500 ± 260	24,000 ± 900
(rac)-**103**	*c*-C_6H_{11}	H	*4*-MeO-C_6H_4	76 ± 3	1,540 ± 90	4,310 ± 60
(rac)-**104**	Mes	H	Ph	118 ± 3	22,500 ± 1,200	340 ± 30
(rac)-**105**	Bu^t	H	Ph	1,100 ± 40	47,900 ± 2,700	7,260 ± 40
(rac)-**106**	Bu^t	H	*2*-Naphth	6.1 ± 0.3	55 ± 1	27,000 ± 2,000
(rac)-**107**	Ph	H	*2*-Naphth	6.2 ± 0.3	21 ± 1	140 ± 20
(rac)-**108**	Ph	Me	Ph	48 ± 5	2,250 ± 110	12,000 ± 1,800
(rac)-**109**	*c*-C_6H_{11}	Me	*4*-MeO-C_6H_4	30 ± 0.9	1,800 ± 100	3,500 ± 200
(rac)-**110**	Mes	Me	Ph	8.5 ± 0.2	35,800 ± 2,900	42,000 ± 4,000
(rac)-**111**	Bu^t	Me	Ph	40 ± 2	3,430 ± 90	21,400 ± 2,000
(rac)-**112**	Bu^t	Me	*2*-Naphth	1.2 ± 0.9	29.9 ± 0.4	340 ± 10
(rac)-**113**	Ph	Me	*2*-Naphth	5.59 ± 0.02	44 ± 2	70 ± 8
(*rac*)-fluoxetine (**19**)				0.81 ± 0.02	240 ± 10	3,600 ± 100
(*rac*)-atomoxetine (**30**)				8.9 ± 0.3	2.03 ± 0.06	1,080 ± 50
(*rac*)-viloxazine (**59**)				17,300 ± 500	155 ± 8	>100,000

[a]tested as hydrochloride salts

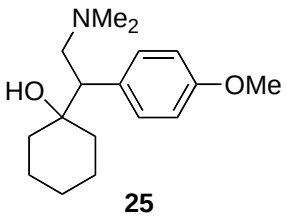
Venlafaxine, another dual SERT and NET inhibitor, has a gamma-amino alcohol functional group, which is discussed in the following section along with its silyl analogue. In this connection, a series of gamma-amino alcohols were synthesized by Carlier and coworkers,[68] and screened for monoamine reuptake inhibition according to the procedure of Richelson using human transporters.[69] Their inhibition profile for monoamine reuptake is displayed in Table 8 along with the data generated for known

antidepressants for comparison. With the exception of **102** and **105**, all compounds displayed potent binding to SERT. Compounds having *2*-naphthyl group are particularly interesting, **106** and **112** showed potent binding to both SERT and DAT, while **107** and **113** are particularly remarkable in having affinities for all three transporters (SERT, NET and DAT). This data has further been substantiated by rat synaptosomal studies according to the procedure of Bolden-Watson and Richelson.[70]

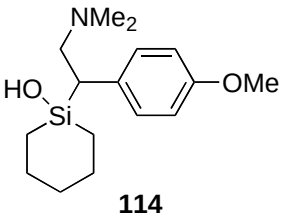
2.8. VENLAFAXINE AND SILA-VENLAFAXINE

Another interesting gamma amino alcohol compound is Venlafaxine (**25**, Effexor™, Efexor™ and Trevilor™) used in the treatment of depression, which is a potent inhibitor of SERT and NET.[71,72] Sila-substitution (the carbon/silicon switch) has been used successfully for the development of new chemical entities, and sila-substitution of **25** gave Sila-Venlafaxine (**114**).[73,74] The monoamine reuptake transporter inhibition profile is shown in Table 9. It is interesting to note that the inhibition values of

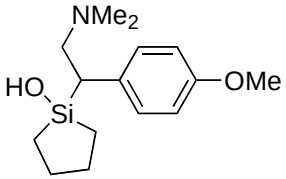
Table 9: Analogs of venlafaxine - monoamine reuptake transporter inhibition profiles[a]



25
Venlafaxine



114
Sila-Venlafaxine



115

Compound	SERT	NET	DAT
rac-**25**	0.020	0.149	4.430
(*R*)-**25**	0.030	0.061	19.600
(*S*)-**25**	0.006	0.754	6.670
rac-**114**	1.063	0.109	2.630
(*R*)-**114**	3.168	0.251	5.270
(*S*)-**114**	0.791	4.715	36.350
rac-**115**	0.904	0.275	0.707

[a]Data expressed as IC_{50} values (μM); compounds were tested as hydrochloride salts.

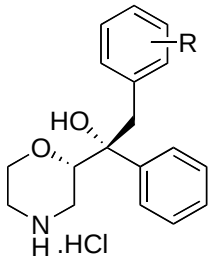
rac-**25** and *rac*-**114** at norepinephrine and dopamine transporters are essentially unaffected by sila-substitution (within experimental biological variation). However, the potency at serotonin transporter is reduced by two orders of magnitude. The single sila enantiomer (*R*)-**114** shows a selective NE reuptake inhibitor profile that is not observed with the enantiomers of (*R*)-**25**. A comparable profile is observed by varying the six-membered ring in **114** to five-membered ring in **115**. It has also been demonstrated that a selective NET inhibitor, (*R*)-**114** hydrochloride, effectively inhibits emetic episodes (nausea and vomiting) caused by an emetogen, such as morphine, in a well-characterized animal model

(ferret model of morphine-induced emesis study).[75] Compounds with this mechanism of action may have clinical utility in the prevention and treatment of post-operative nausea and vomiting (PONV), particularly in settings where morphine is used for post-operative pain relief.

2.9. TERTIARY ALCOHOL CONTAINING BENZYL MORPHOLINES

Synthesis and biological activity of a series of tertiary alcohol containing 2-substituted benzyl morpholines have been reported by Cases-Thomas recently.[76,77] All compounds were tested as single enantiomers for their binding affinity to the NET, SERT and DAT transporters. Some of the potent and selective inhibitors of the NE transporter of this series are shown in Table 10. The key synthetic step is the highly diastereoselective nucleophilic addition of benzyl Grignard reagents to enantiopure (*4*-benzylmorpholin-*2*-yl)phenylmethanone, which provided access to the targets in enantiomerically pure form. X-Ray crystallographic analysis of the *2*-bromo-analogue (**122**) allowed determination of absolute stereochemistry (2*S*,2'*R*), on this basis the stereochemistry of other products have been assigned. The

Table 10: Tertiary alcohol containing benzyl morpholine inhibitors {transport values are K_i ± SEM (nM)}



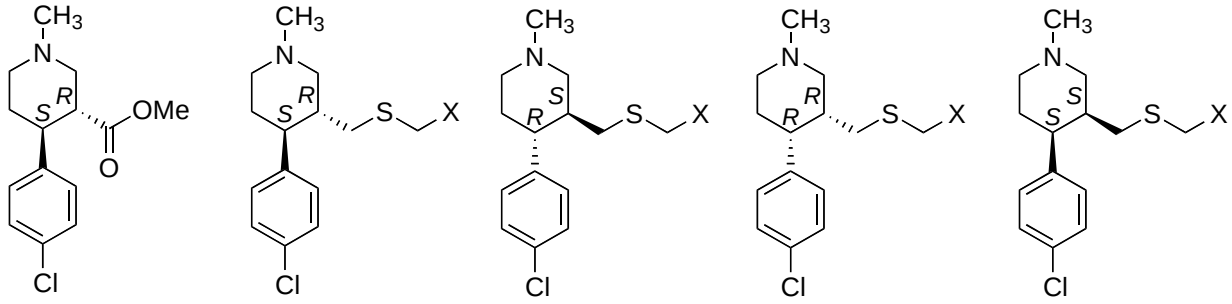
A

Compound	R	NET	SERT[a]	DAT[b]
116 (Isomer 4)	2-OMe	3.2 ± 0.4	5.5 ± 0.7%	3.8 ± 3.1%
117	3-OMe	19.8 ± 0.8%[a]	2.8 ± 1.4%	4.3 ± 2.2%
118	4-OMe	25.2 ± 9.5%[a]	4.3 ± 4.7%	6.2 ± 0.1%
119	2-OEt	5.2 ± 1	2.4 ± 2.2%	3.8 ± 3.2%
120	2-OPr^i	7.7 ± 3.7	2.7 ± 4%	5.1 ± 3.5%
121	2-Cl	30 ± 9.7	4.6 ± 0.7%	20.8 ± 4.8%
122	2-Br	11.9 ± 2.4	13 ± 3.6%	24.1 ± 1.1%
123	2-Ph	3.7 ± 1	3 ± 0.6%	2.9 ± 4%

[a]Percentage displacement of radioligand at 100 nM
[b]Percentage displacement of radioligand at 1000 nM

NET binding affinity for **116** (K_i = 3.2 nM) was comparable to those of atomoxetine (**30**; K_i = 2.0 nM) and reboxetine (**23**; K_i = 1.6 nM). Larger alkoxy substitution (**119** and **120**) also retained high binding affinity to the NET. Relative to *o*-derivative (**116**), the *m*-derivative (**117**) and *p*-derivative (**118**) displayed reduced binding affinity to the transporters, which suggest a preference for substitution in the *2*-position for the NET. A similar preference for ortho substitution has previously been reported for a series of arylthiomethyl morpholine-based inhibitors of the NET.[64] The tertiary alcohol functionality was found to be both chemically and configurationally stable under aqueous acidic conditions.

Table 11: Piperidine based inhibitors {transport values are K_i ± SEM (nM)}



(+)-trans-**124** Nocaine | *(+)-trans* | *(-)-trans* | *(+)-cis* | *(-)-cis*

(**125** - **132**)

Compound	X	ClogP	DAT	SERT	NET
cocaine (**31**)			423 ± 147	155 ± 1	108 ± 4
nocaine (**124**)		3.22	233 ± 62	8490 ± 1430	252 ± 43
(+)-*trans*-**125**	COOMe	3.15	80 ± 23	208 ± 47	25 ± 6
(-)-*trans*-**125**	COOMe	3.15	2620 ± 390	69 ± 15	57 ± 1
(+)-*cis*-**125**	COOMe	3.15	598 ± 32	403 ± 9	98 ± 6
(-)-*cis*-**125**	COOMe	3.15	38 ± 4	182 ± 24	22 ± 1
(+)-*trans*-**126**	$CONH_2$	2.19	159 ± 19	557 ± 150	39 ± 5
(-)-*trans*-**126**	$CONH_2$	2.19	1100 ± 27	545 ± 167	53 ± 1
(-)-*cis*-**126**	$CONH_2$	2.19	54 ± 1.9	21 ± 4	69 ± 14
(+)-*trans*-**127**	CONHMe	2.29	13 ± 3	110 ± 45	25 ± 2
(-)-*trans*-**127**	CONHMe	2.29	164 ± 6	116 ± 26	44 ± 2
(+)-cis-**127**	CONHMe	2.29	215 ± 15	1770 ± 140	5.5 ± 1.6
(-)-cis-**127**	CONHMe	2.29	311 ± 4	347 ± 52	18 ± 1
(+)-*trans*-**128**	$CONHPr^i$	3.13	1.0 ± 0.2	1.1 ± 0.4	0.8 ± 0.1
(-)-*trans*-**128**	$CONHPr^i$	3.13	663 ± 42	138 ± 19	67 ± 2
(+)-*cis*-**128**	$CONHPr^i$	3.13	142 ± 5	36 ± 4	11 ± 1
(-)-*cis*-**128**	$CONHPr^i$	3.13	13 ± 5	154 ± 14	16 ± 2
(+)-*trans*-**129**	$CON\text{-}(CH_2)_5$-	3.80	83 ± 1	4.5 ± 0.7	0.7 ± 0.3
(-)-*trans*-**129**	$CON\text{-}(CH_2)_5$-	3.80	>3000	190 ± 29	82 ± 1
(+)-*cis*-**129**	$CON\text{-}(CH_2)_5$-	3.80	>3000	572 ± 46	134 ± 14
(-)-*cis*-**129**	$CON\text{-}(CH_2)_5$-	3.80	34 ± 5	42 ± 2	13 ± 1
(+)-*trans*-**130**	CH_2OH	2.81	16 ± 5	158 ± 5	0.9 ± 0.3
(-)-*trans*-**130**	CH_2OH	2.81	185 ± 62	129 ± 2	123 ± 29
(+)-*cis*-**130**	CH_2OH	2.81	160 ± 5	305 ± 30	>3000
(-)-*cis*-**130**	CH_2OH	2.81	37 ± 5	185 ± 16	26 ± 4
(+)-*trans*-**131**	CH_2OCOPh	5.45	68 ± 22	6.7 ± 1.5	4.5 ± 1.2
(-)-*trans*-**131**	CH_2OCOPh	5.45	378 ± 7	71 ± 6	56 ± 14
(+)-*cis*-**131**	CH_2OCOPh	5.45	1470 ± 430	270 ± 5	143 ± 6
(-)-*trans*-**132**	CONHBz	4.34	1570 ± 110	753 ± 81	32 ± 1
(-)-*cis*-**132**	CONHBz	4.34	3.9 ± 0.8	23 ± 5	85 ± 4

2.10. Piperidine and Pyrrolidine derivatives

With an aim to identifying molecules for use in the treatment of cocaine addiction, and as well as ADHD and depression, a new series of compounds having piperidine based structure analogous to nocaine {(+)-methyl-*4*β-(*4*-chlorophenyl)-*1*-methylpiperidine-*3*α-carboxylate (**124**)} have been studied.[78-80]

Four stereoisomeric forms of these piperidine derivatives comprising a sulfur-bearing side chain containing an ester, amide, or alcohol group are shown in Table 11. These compounds were tested for the abilities to inhibit uptake of [^{3}H]DA, [^{3}H]5-HT, and [^{3}H]NE through the corresponding transporters using rat synaptosomal nerve endings. The ClogP, uptake data, and selectivity profiles (based on the Ki values) of these compounds are listed in Table 11. Some of these compounds exhibited good selectivity at the NET or mixed NET/DAT or NET/SERT selectivity. Most of these compounds have suitable ClogP value ($1 < \text{ClogP} < 5$) and molecular weight (MW < 500), as expected for good penetration through the blood-brain barrier.

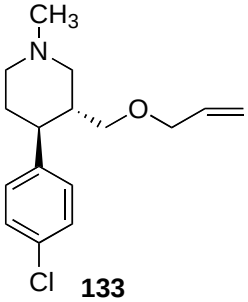
Compound (+)-*cis*-(**127**) (NET 5.5 nM) was the most potent and selective compound available within this series, having 39 fold DAT potency, and about 320 fold SERT potency. This compound will be valuable for exploration in animal models to gain a better understanding of NET-associated behavioral characteristics. Compounds, (-)-*trans*-(**132**), (-)-*trans*-(**126**), and (-)-*cis*-(**127**) were also NET selective ligands, although the potency is relatively lesser than (+)-*cis*-**127**. Compounds (+)-*trans*-(**129**), and (+)-*trans*-(**131**), were NET potent ligands and as well as potent at SERT. Compound (+)-*trans*-(**130**) is both NET and DAT potent. Interestingly, compound (+)-*trans*-(**128**) is potent at all three reuptake proteins.

The ester group in nocaine (**124**) has been replaced with a variety of substituents by Kozikowski's group (Figure 5). While replacement of ester group with its bioisosteric equivalent, an oxadiazole group, did not result in a significant change of reuptake values for monoamines relative to nocaine.[81] Whereas, replacement of ester group with a propyl moiety as represented by structure (**136)**, offered a superior NET active compound.[79] Moderate NET activities were observed with compounds (**133 – 135)** in which the ester group is replaced with an alkyl ether link (**133**), alkyl amide link (**134**) or an alkyl ester link (**136**). Compound **137**, a naphthyl piperidine derivative has a moderate NET activity among several other substituted naphthyl piperidine derivatives synthesized.[82]

Some of the *3,4*-disubstituted pyrrolidine derivatives (**138**-**140**) with good NET selectivity are shown in Figure 5.[83] Couple of these compounds (**139** and **140**) were found to function as weak cocaine antagonists, which were evaluated based on the IC_{50} values of cocaine in the presence of these compounds versus IC_{50} values of pure cocaine.

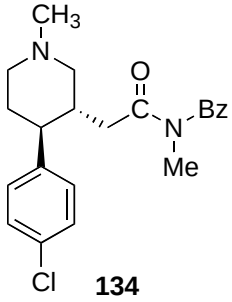
Another interesting and potent NET piperidine derivative is methylphenidate (MPH). This was patented in 1954 by the Ciba Pharmaceutical company (a precursor to Novartis). This drug is an amphetamine-like prescription stimulant, was initially used for the treatment for depression, chronic and fatigue. Since 1960's, and now this drug is commonly being used to treat ADHD in children and adults around the world. The therapeutic efficacy of methylphenidate is believed to be due to its ability to block the reuptake of DA and NE in the central nervous system.

Figure 5: Piperidine and Pyrrolidine based inhibitors {transport values are K_i ± SEM (nM)}



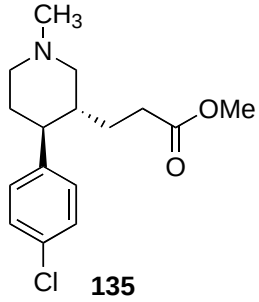
133

NET = 20±3
DAT = 60±4.5
SERT = 231±36



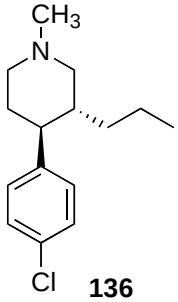
134

NET = 32±2
DAT = 165±2
SERT = 66±6



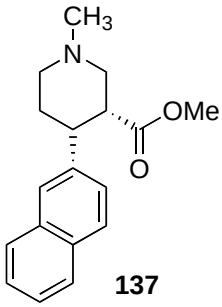
135

NET = 31±3
DAT = 68±12
SERT = 255±27



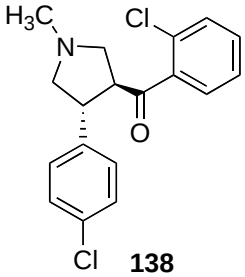
136

NET = 6.5±1
DAT = 20±2
SERT = 228±22



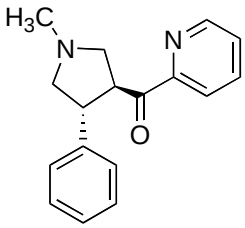
137

NET = 27±2
DAT = 87±9
SERT = 192±16



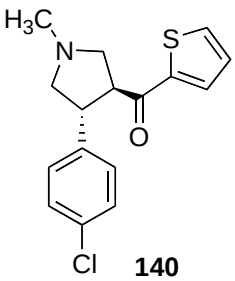
138

NET = 69 ± 1
DAT = 610 ± 30
SERT = 540 ± 30



139

NET = 44 ± 1
DAT = 630 ± 20
SERT = 830 ± 50



140

NET = 31 ± 4
DAT = 200 ± 10
SERT = 230 ± 10

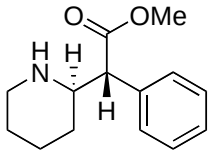
However, as the half life of methylphenidate is short because of the presence of easily metabolized ester group, an alternate stable group is necessary which should possess similar binding potential as methylphenidate. The synthesis of these analogs has proven to be more difficult due to the highly acidic proton that is alpha to both the phenyl ring and the carbonyl group of the ester. Many efforts have failed but recently vinylogous amides of methylphenidate have been reported,[84] which have rigid three dimensional structures that are quite similar to the global minimum of threo-(*R*,*R*)-methylphenidate.[85] The structures of these analogs along with their IC_{50} values are shown in Table 12.

A series of *N*-alkyl-*N*-arylmethylpiperidin-*4*-amine compounds was reported by Lilly recently (Table 13).[86] These compounds are dual inhibitors of serotonin and norephinephrine reuptake, thus offering potential for superior anti-depressant activity[3] as demonstrated by clinical experience with duloxetine (Cymbalta^{TM}), a dual serotonin and norepinephrine reuptake inhibitor.[49,87]

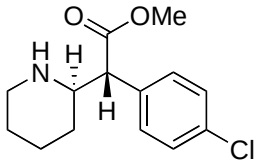
Several compounds with nanomolar affinity at SERT and NET were identified. The initial compounds synthesized in this series for SAR studies were analogs of **A**, where R^1 was varied with groups like alkyl, cycloalkyl and substituted alkyl groups. All of these analogs maintained their dual 5-HT and NE transport inhibition. The SAR trend was as follows: (i) substitution on an alkyl chain alpha to the *4*-amine is detrimental to NE uptake (e.g., **151**), however cycloalkyl substitution (e.g., **152**) does not impact NE uptake; (ii) branching beta to the *4*-amine is better tolerated (e.g., **148**, **150**, and **153**);

(iii) having CF_3 group at the terminus of an alkyl chain instead of methoxy does not affect significantly the potency at NET and SERT (e.g., **154** and **155**).

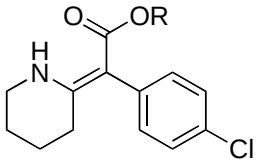
Table 12: Analogs of Methylphenidate[a]



threo-(*R*,*R*)-methylphenidate (**141**)



4-Cl-methylphenidate (**142**)



R = Me (**143**), Et (**144**), Pr^i (**145**)

Compound	DA Reuptake	5HT Reuptake	NE Reuptake
141	190 ± 50	55,000 ± 16, 000	38 ± 4
142	11 ± 2	>9800	11 ± 3
143	6,300 ± 1,100	>10 μM	>9,500
144	1,800 ± 600		
145	1,100 ± 80		

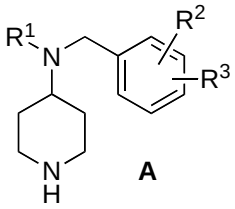
[a]Reuptake inhibition potency (IC_{50}, nM) of compounds with recombinant human DAT, SERT, and NET expressed in human embryonic kidney 293 cells

However, the trifluoromethoxy analogue (**157**) showed reduced activity compared to the methoxy analogue (**156**). It was concluded that isobutyl group containing compound (**148**) had the best activity, later substitutions on phenyl group was studied.

The positional isomers of **148** (*2*-CF_3), for e.g., *3*-CF_3 and *4*-CF_3 derivatives, have dramatic decrease in binding affinity for NE transporters. While the binding affinity of **148** at NET is K_i = 3.1 nM, whereas for *3*-CF_3 and *4*-CF_3 isomers, K_i = 255 nM, and 300 nM respectively. On the other hand, replacement of *2*-CF_3 group with *2*-methyl as represented by **158**, *2*-chloro (**159**), *2*-methylthio (**160**) or *2*-trifluoromethoxy (**161**) group retained the dual NET and SERT inhibition property. In addition, the dopamine transporter affinity was more prevalent with certain substitution patterns, for instance the *2*-Cl derivative (**159**) had inhibition of dopamine transport (Ki = 83 nM) of less than 100 nM.

Disubstitution was more rewarding than monosubstitution. Thus maintaining methyl, trifluoromethyl or chloro substituents in the *2*-position and substituting with fluorine, methyl or chlorine produced potent dual inhibitors (e.g, **163**, and **165**).

Table 13: *N*-Alkyl-*N*-arylmethylpiperidin-*4*-amines: dual NET and SERT inhibitors {transport values are K_i ± SEM (nM)}



A

Compound	R^1	R^2	R^3	SERT	NET	DAT[b]
146	Pr^n	2-CF_3	H	2.2 ± 0.2	6.5 ± 0.4	(-12 ± 1%)
147	Bu^n	2-CF_3	H	1.5 ± 0.4	5.1 ± 0.5	(-31 ± 2%)
148	Me_2CHCH_2	2-CF_3	H	1.4 ± 0.1	3.1 ± 0.3	200 ± 30%)
149	c-$C_3H_5CH_2$	2-CF_3	H	1.5 ± 0.1	6 ± 1	(-27 ± 0.1%)
150	Me_3CCH_2	2-CF_3	H	4.3 ± 0.5	2.7 ± 0.1	160 ± 14%)
151	Et_2CH	2-CF_3	H	6.8 ± 1.2	86 ± 2	(-41 ± 0.4%)
152	c-$C_5H_9CH_2$	2-CF_3	H	3.6 ± 0.1	4.1 ± 0.1	(-45 ± 0.7%)
153	Et_2CHCH_2	2-CF_3	H	6.9 ± 0.6	6.1 ± 1.5	(-39 ± 1%)
154	$MeO(CH_2)_2$	2-CF_3	H	2.5 ± 0.03	8.3 ± 0.2	(4 ± 3%)
155	$F_3C(CH_2)_2$	2-CF_3	H	2.8 ± 0.1	9.8 ± 0.7	(-35 ± 3%)
156[b]	$MeO(CH_2)_3$	2-CF_3	H	2.2 ± 0.2	6.8 ± 0.7	(-8 ± 2%)
157[b]	$F_3CO(CH_2)_2$	2-CF_3	H	17 ± 0.5	51 ± 1	(-8 ± 1%)
158	Me_2CHCH_2	2-Me	H	1.5 ± 0.4	3.3 ± 0.2	240 ± 19
159	Me_2CHCH_2	2-Cl	H	1.6 ± 0.1	1.4 ± 0.1	83 ± 3
160	Me_2CHCH_2	2-MeS	H	1.1 ± 0.2	3.3 ± 0.2	(-17.5 ± 0.1%)
161	Me_2CHCH_2	2-OCF_3	H	2.2 ± 0.2	7.1 ± 0.3	(-16.4 ± 0.3%)
162	Me_2CHCH_2	2-CF_3	5-F	7.9 ± 0.9	3.4 ± 0.1	(-19 ± 2%)
163	Me_2CHCH_2	2-Me	4-Me	0.39 ± 0.12	4.8 ± 0.3	(-16 ± 1%)
164	Me_2CHCH_2	2-CF_3	6-F	4.1 ± 0.40	6.0 ± 0.8	(-18 ± 2%)
165	Me_2CHCH_2	2-CF_3	4-F	0.3 ± 0.1	1.8 ± 0.3	190 ± 20
166	Me_2CHCH_2	2-Cl	4-Cl	0.96 ± 0.1	2.0 ± 0.2	230 ± 20
167	Me_2CHCH_2	2-Cl	5-Cl	2.1 ± 0.2	5.5 ± 0.3	(-22 ± 3%)
168	Me_2CHCH_2	2-F	4-CF_3	5.8 ± 1	2.2 ± 0.1	120 ± 20

[a]Percentage inhibition at 1 μM

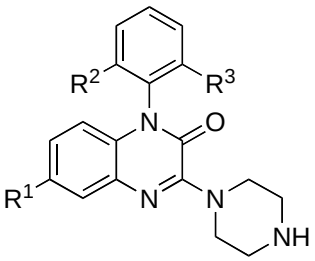
[b]tested as tartrate salt, and the rest as fumarate salt

2.11. Quinoxalin-2-one and quinazoline derivatives

A series of quinoxalin-2-one and quinazoline compounds have been synthesized and their binding

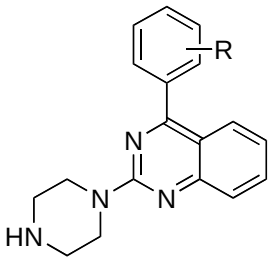
properties with a variety of monoamine neurotransporters have been studied at Pfizer.[88,89] The available data indicate that some of these compounds are strong inhibitors of NET, while some others are inhibitors

Figure 6: Quinoxalin-2-one and quinazoline based inhibitors {transport values are K_i ± SEM (nM)}



quinoxalin-2-ones

R^1, R^2, R^3 = H (**169**); NET = 21
R^1 = F; R^2, R^3 = H (**170**); NET = 12
R^1, R^2 = H; R^3 = F (**171**); NET = 11
R^1, R^2 = H; R^3 = Cl (**172**); NET = 44
R^1, R^2 = H; R^3 = Me (**173**); NET = 69
R^1, R^2, R^3 = F (**174**); NET = 15



quinazolines

R = H (**175**); NET = 4.8
R = *2*-F (**176**); NET = 1.7, SERT = 12.0
R = *2*,*3*-F_2 (**177**); NET = 3.0
R = *2*,*4*-F_2 (**178**); NET = 2.0

of both NET and SERT. Some of the representative compounds having potent NET binding property are shown in Figure 6. SAR studies of compound (**169**) have shown that addition of fluoride or fluorides to aryl ring is beneficial towards better NET binding relative to chloro or alkyl. Further SAR on these scaffolds may lead to better candidates with higher selectivity and potent NET binding property.

3. CONCLUSIONS

Several nanomolar active norepinephrine transport inhibitors are reported in this review. Most of the current literature has been included, although not complete because of the availability of partial data from some patent sources. There is certainly a multifold increase in interest towards the discovery and development of novel CNS candidates with potent inhibitor binding to monoamine neurotransporters SERT, or NET, or both, with an intention to increase the availability of serotonin or norepinephrine, or both, in the synaptic cleft. It is interesting to note that the molecular weight of most of these active compounds fall around 300 daltons, perhaps this might be an assisting factor for easy blood brain penetration. A comparative binding affinity data reported by Wong and Bymaster illustrates that some of the selective and potent inhibitors (e.g., duloxetine, venlafaxine, milnacipran, fluoxetine, paroxetine, reboxetine, tomoxetine) of SERT and NET still have weaker binding to neurotransmitters or neurotransporter proteins, for instance, α_1-adrenergic, α_2-adrenergic, histamine H_1, muscarinic non-selective, muscarinic M_3 and dopamine-D_2. However, the magnitudes of these binding affinities are

relatively much lesser (a factor of about 1000 -10000 fold) than tricyclic antidepressants (TCA). Hence, these novel compounds have low side-effect potential and better tolerability than TCA. Still, there is plenty of opportunity to discover drugs with even more selectivity to limit the interactions with unwanted sites, which is the ultimate goal of CNS researchers. Eventually, this will prevent any undesired side effects that may arise after treatment. As is true with any drug discovery, further SAR on existing potent binding scaffolds and recently developed scaffolds would greatly help to achieve this goal. On the other hand, the discovery of new scaffolds or inhibitors of NET and SERT is also very essential, and is of high interest at this moment. Further, with the availability of more number of novel selective NET inhibitors or dual NET and SERT inhibitors, the treatment applications are expanding at a much higher pace from depression and ADHD to several other CNS areas on demand.

ACKNOWLEDGEMENTS

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