Bioorganic & Medicinal Chemistry Letters 20 (2010) 2809–2812

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Heterocyclic cycloalkanol ethylamines as norepinephrine reuptake inhibitors

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ARTICLE INFO

Article history:
Received 16 February 2010
Revised 10 March 2010
Accepted 11 March 2010
Available online 15 March 2010

Keywords:
Monoamine reuptake inhibitors
Selective norepinephrine reuptake inhibitor
Cycloalkano ethylamines

ABSTRACT

A series of heterocyclic cycloalkanol ethylamines have been prepared to expand our norepinephrine reuptake inhibitor (NRI) program. Synthesis of a variety of heterocycles identified (+)-*S*-**21**, a potent NRI efficacious in an animal model for thermoregulatory dysfunction.

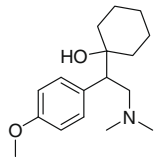
The cycloalkanol ethylamine scaffold was successfully utilized in the discovery and development of dual serotonin (5-HT)/norepinephrine (NE) reuptake inhibitors (SNRIs).[1] Drugs such as venlafaxine (**1**) and duloxetine (**2**) possessing norepinephrine reuptake inhibition, either selectively or in combination with serotonin reuptake inhibition were approved for major depressive disorder (MDD). Recently, SNRIs have been evaluated clinically for the treatment of stress urinary incontinence (SUI),[2] and fibromyalgia.[3] Further studies show that estrogen may stimulate the activity of both the norepinephrine and/or serotonin neurotransmitter pathways.[4,5]

Compounds containing an aryl propanamine pharmacophore are known to have monoamine reuptake properties.[6] Efforts to discover novel selective NRIs using the cycloalkanol ethylamine scaffold as exemplified by venlafaxine (**1**) (Table 1) resulted in the identification of piperazine analogue **3**.[7] A program to further expand the cycloalkanol ethylamine SAR by designing selective NRIs was initiated. Consequently, we have structurally extended the SAR of this template in a variety of ways to maintain potency and achieve better norepinephrine transporter (NET) selectivity over serotonin (SERT) and dopamine transporters (DAT).

Compound **3** while having potent NRI activity with excellent selectivity over SERT.[7] also had affinity for DAT, which was outside the therapeutic goals of the program. In addition, **3** had poor microsomal stability in rats ($t_{1/2}$ <1 min).

Consequently, structural modifications to eliminate DAT binding while improving oral bioavailability were explored.

Table 1
Inhibitory effect at human norepinephrine, serotonin, and dopamine transporters



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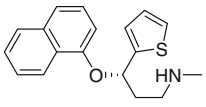

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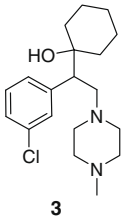

3

Compd	hNET IC_{50}[a] (nM)	hSERT IC_{50}[b] (nM)	hDAT IC_{50}[c] (nM)
1	535	27	>10,000
2	4	3	>1000
3	56	>2000	247

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET. Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard.
[b] Inhibition of serotonin uptake in JAR cells, natively expressing human SERT. Fluoxetine (IC_{50} = 9.4 ± 3.1 nM) was used as a standard.
[c] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant hDAT. Mazindol (22.1 ± 6.5 nM) was used as a standard.

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doi:10.1016/j.bmcl.2010.03.059

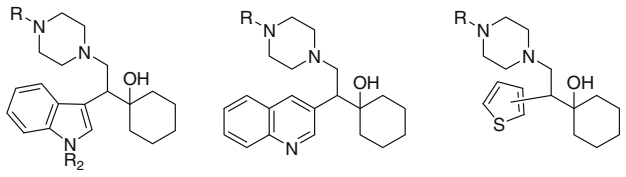


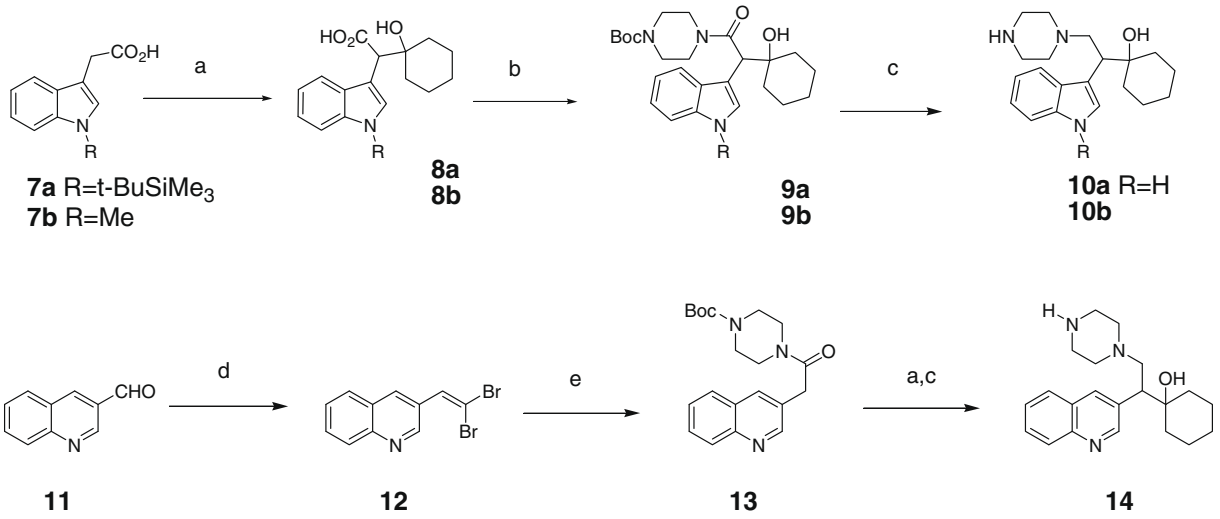
Figure 1. Selected heterocyclic targets for NRI.

Previous SAR in this series established the piperazine moiety to impart hNET selectivity over hSERT.[8,9] Moreover, DAT could be manipulated by aromatic substitution, particularly in the 3-position. We therefore concentrated our efforts on targets replacing the 3-chloro phenyl group with indole (**4**), quinoline (**5**), and thiophene (**6**) cores that would further explore this topology (Fig. 1).

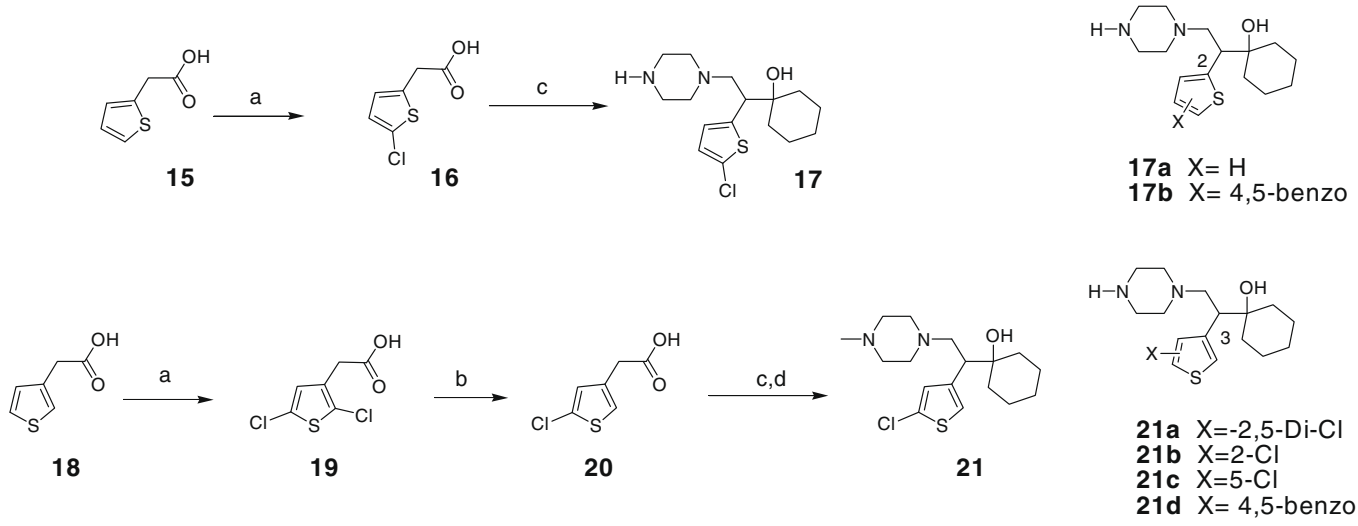
Scheme 1 illustrates the standard synthesis of the nitrogen based analogues from commercially available or synthesized aryl acetic acids. Treatment of the aryl acetic acids **7a**,**b** with LDA at −78 °C in THF followed by addition of cyclohexanone provided the alkanols **8a**,**b**. The piperidine amides **9a**,**b** were formed by standard peptide coupling with BOP reagent. The target products **10a**,**b** were generated by reduction of the amide with borane in THF. Addition of HCl in ether removed the BOC group and in the case of **10a**, the protecting groups were removed by treatment with HCl in ether.

In cases where the aryl acetic acid was unavailable or was difficult to handle, an alternative synthesis was employed. The quinoline system **14** was made from the aryl aldehyde **11** by conversion to the dibromo olefin **12**.[10] This intermediate was then converted to the aryl acetyl amide **13** by treatment with Boc-piperazine and water. This route avoids handling of amino acid intermediates which may provide low if any yield while attempting to alkylate with cyclohexanone. The desired cyclohexanol ring was then added via alkylation with LDA. The target compound **14** was then made via BH_3·THF reduction as before.

Scheme 2 depicts the synthesis of key thiophene analogues. The 2-position of a 3-substituted thiophene is the more reactive position therefore chlorination with 1 equiv of NCS gave exclusively

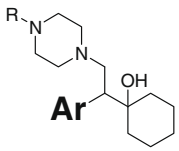


Scheme 1. Synthesis of indole and isoquinoline analogues. Reagents and conditions: (a) LDA, THF, cyclohexanone, −78 °C (62–76%); (b) BOP reagent, Boc-piperazine, DMF (68%); (c) (1) BH_3, THF; (2) 2 N HCl, ether, methanol (65%); (d) CBr_4, Ph_3P, THF (69%); (e) KOH, H_2O, Boc-piperazine (30%).



Scheme 2. Synthesis of thiophene analogues. Reagents and conditions: (a) NCS, AcOH (72%); (b) Na (Hg), methanol (45%); (c) (1) LDA, THF, cyclohexanone, −78 °C (79%); (2) BOP reagent, Boc-piperazine, DMF (69%); (3) BH_3·THF, (62%); (4) HCl; (d) (1) HCO_2H, H_2CO; (2) HCl(55%).

Table 2
Inhibitory activity of heterocyclic cycloalkanol ethylamines at hNET, hSERT, and hDAT



Compd	Ar	R	hNET %I @1[a] (μM)	hNET IC_{50}[a] (nM)	hSERT %I @1[b] (μM)	hDAT IC_{50}[c] (nM)
10a	Indol-3-yl	H	21	ND	90	ND
10b	*N*-Methyl indol-3-yl	H	32	ND	ND	ND
14	Quinolin-3-yl	H	19	ND	ND	ND
21a	2,5-Cl-thien-3-yl	H	94	225 ± 65	12.2	ND
21b	2-Cl-thien-3-yl	H	55	720 ± 190	34	ND
21c	2-Cl-thien-4-yl	H	86	100 ± 35	−1	(43)[d]
21d	Benzothiophen-3-yl	H	82	255 ± 85	48	(51)[d]
17b	Benzothiophen-2-yl	H	73	550 ± 97	89	(61)[d]
17a	Thien-2-yl	H	54	ND	ND	ND
17	5-Cl-thien-2-yl	H	50.8	ND	ND	ND
21	2-Cl-thien-4-yl	Me	88	95 ± 22	−3	389 ± 46
(+)-*S*-**21**	2-Cl-thien-4-yl	Me	91	57 ± 10	−1	212 ± 46
(−)-*R*-**21**	2-Cl-thien-4-yl	Me	0	18,000	−1	>6000
(+)-*S*-**3**	3-Cl-phenyl	Me	92	30 ± 3.2	−3	175 ± 45
(−)-*R*-**3**	3-Cl-phenyl	Me	ND	576 ± 46	32	30 ± 3.2

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET. Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard.
[b] Inhibition of serotonin uptake in JAR cells, natively expressing human SERT. Fluoxetine (IC_{50} = 9.4 ± 3.1 nM) was used as a standard.
[c] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant hDAT. Mazindol (22.1 ± 6.5 nM) was used as a standard.
[d] %Inhibition measured at a concentration of 1000 nM. ND = not determined.

the 2-chlorothiophen-3-acetic acid. Treatment with 2 equiv of NCS ultimately gave chlorination at the 2- and 5-positions (**19**). The higher reactivity of the 2-position was then exploited by treatment with sodium amalgam to reduce the chlorine at position 2 as the major product **20**. The 3-benzothiophene target **21d** was made from 3-benzothiophene acetic acid in an analogous manner to **10b**. The 2-benzothiophene target **17b** was made from 2-benzothiophene carboxaldehyde analogous to **14**. Enantiomers of the most interesting compounds were separated by chiral HPLC.

In vitro data for hNET, hSERT, and hDAT for the heterocyclic propanol amine series is depicted in Table 2. The nitrogen based analogues (**10a**, **10b**, **14**) were weak inhibitors (<35% inh @ 1 μM) and their IC_{50}s not determined. The benzothiophene analogues **21d**, **17b** had moderate NRI potency, however the most potent NRIs were the chloro substituted thiophene based analogues **21**, **21a**, **21c**. As expected, compound **21**, a thiophene core containing similar topology as compound **3**, had comparable activity in hNET and selectivity over hSERT. Disappointingly, there was no increased selectivity over hDAT with compound **21**. The enantiomers of these two compounds were separated by chiral HPLC and the eutomer (**+**)-*S*-**21** determined by X-ray crystallography. In both cases, the *S*-enantiomer was the preferred isomer for NRI potency (compound (**+**)-*S*-**21** (IC_{50} value of 57 nM) and compound (**+**)-*S*-**3** (IC_{50} value of 30 nM)) with both compounds possessing very similar potency. The R-enantiomer was significantly less active in both cases (compound (**+**)-*R*-**21** and compound (**+**)-*R*-**3**). Figure 2 shows the X-ray structure of compound (**+**)-*S*-**21** confirming the *S* configuration.

The release of norepinephrine in the hypothalamus is involved in temperature regulation and sleep.[11] Rodent models of estrogen deficiency associated thermoregulatory dysfunction are based on measuring changes in tail–skin temperature (TST) in ovariectomized (OVX) rats.[12] Intact cycling rats exhibit a diurnal TST pattern with lower TST during the active (dark) phase and higher TST during the inactive (light) phase over a 24 h period. In OVX rats, the TST decrease during the active phase is reduced. Estrogen restores the TST pattern in OVX rats, that is, transition to the active phase coincides with a decrease in TST. An implanted chip was used to

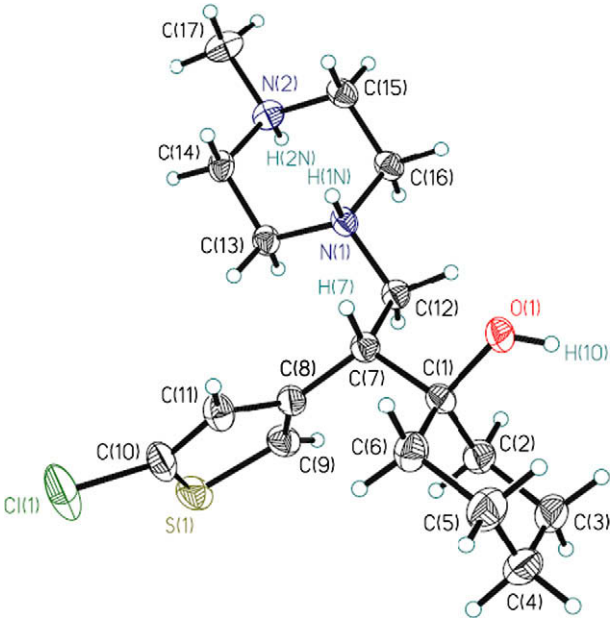


Figure 2. X-ray structure of (+)-*S*-**21**.

Table 3
Summary of selected compounds in Telemetric Rat Model of OVX-Induced Thermoregulatory Dysfunction dosed 30 mg/kg

Compd	Route of administration[a]	Duration of action (h)	Mean reduction in TST from baseline (°C)	Max reduction in TST from baseline (°C)
21	ip	6	−2.75	−4.2
(+)-*S*-**21**	ip	5.5	−3.3	−4.6
3	sc	6.5	−2.6	−3.5
3	po	3	−3.1	−3.8

[a] ip and po dosing in 2% Tween 80/0.5% methylcellulose in water as the vehicle, sc dosing in sterile water as the vehicle.

measure TST and thus the method was defined as the Telemetric Rat Model.

Compounds **21** and (**+**)-*S*-**21** were tested in the Telemetric Model at 30 mg/kg ip and compared to compound **3** according to our previously published procedure.[13] The summarized results (Table 3) depict significant reduction of TST for the compounds regardless of the route of administration dosed at 30 mg/kg. The compound **21** and its active enantiomer (**+**)-*S*-**21** showed significant maximum reduction in TST when dosed ip.

In conclusion, we have expanded our cyclohexanol ethylamine program by synthesizing a variety of heterocyclic core derivatives. As in the case of the phenyl derivatives, ring substitution was critical to maintaining NRI activity and the thiophene cores produced the most active compounds. The novel thiophene core with matching topology to the previous lead compound produced the most active compound of the series. The compounds had excellent activity in vivo as well, however we did not achieve the desired selectivity over DAT with the thiophene core.

Acknowledgments

The authors wish to acknowledge the expertise of the Discovery Analytical Chemistry group at Wyeth, in particular Christopher Petucci, Rebecca Dooley, Scott Brecker, Diane Andraka and Oliver McConnell.

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