Bioorganic & Medicinal Chemistry Letters 18 (2008) 4355–4359

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Derivatives of (3*S*)-*N*-(biphenyl-2-ylmethyl)pyrrolidin-3-amine as selective noradrenaline reuptake inhibitors: Reducing P-gp mediated efflux by modulation of H-bond acceptor capacity

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ARTICLE INFO

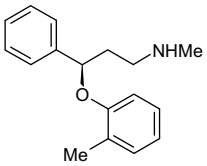
Article history:
Received 13 June 2008
Accepted 23 June 2008
Available online 25 June 2008

Keywords:
Noradrenaline reuptake inhibitor
NRI
Carbamate
H-bond acceptor capacity
CNS penetration

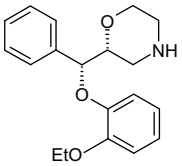
ABSTRACT

Derivatives of (3*S*)-*N*-(biphenyl-2-ylmethyl)pyrrolidin-3-amine are disclosed as a new series of noradrenaline reuptake inhibitors (NRI). Carboxamide **9e**, carbamate **11b** and sulfonamide **13a** were identified as potent NRIs with excellent selectivity over SRI and DRI, good in vitro metabolic stability and weak CYP inhibition. Carbamate **11b** demonstrated superior transit performance in MDCK-mdr1 cell lines with minimal P-gp efflux which was attributed to reduced HBA capacity of the carbamate group. Evaluation in vivo, in rat microdialysis experiments, showed **11b** increased noradrenaline levels by 400% confirming good CNS penetration.

Selective inhibition of noradrenaline reuptake (NRI) has been shown to be an attractive approach for the treatment of a number of diseases.[1,2] For example, atomoxetine (**1**) is a new therapy for the treatment of attention deficit hyperactivity disorder (ADHD)[3] and reboxetine (**2**) is used clinically for the treatment of depression.[4]

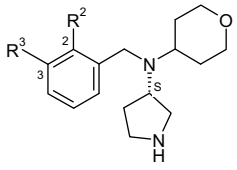


1: atomoxetine



2: (±)-reboxetine

We have reported several new templates that inhibit monoamine reuptake,[5–11] and some of these compounds have now progressed to clinical trials.[12,13] As part of our research efforts to identify potential new NRI drug candidates, we adopted a strategy of exploring multiple chemical templates in order to increase our chances of having compounds survive to become advanced clinical candidates.



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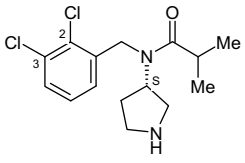
3a: $R^2 = R^3 = Cl$
3b: $R^2 = Ph$; $R^3 = H$



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In this Letter, we disclose derivatives of (3*S*)-*N*-(biphenyl-2-ylmethyl)pyrrolidin-3-amine as potent NRIs with good selectivity over serotonin (5-HT) and dopamine (DA) reuptake inhibition (SRI and DRI, respectively). Furthermore, factors that influence P-glycoprotein (P-gp) transporter mediated recognition and efflux are discussed.

N-(Benzyl)pyrrolidin-3-amines **3** were first disclosed as selective dual serotonin/noradrenaline reuptake inhibitors (SNRI) (e.g., **3a**).[7] As part of this study, during the exploration of the SAR of

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doi:10.1016/j.bmcl.2008.06.071

Table 1
In vitro inhibition of monoamine reuptake,[a,b] human liver microsomal stability and CYP2D6 inhibition for compounds **3a**, **3b** and **4**[c]

	3a	3b	4
NRI, IC_{50} (nM)	5	12	23
SRI, IC_{50} (nM)	10	400	12
DRI, IC_{50} (nM)	89	>4000	1250
HLM, $t_{1/2}$ (min)[d]	100	>120	>120
CYP2D6 inhib., IC_{50} (nM)	4800	100	>3000[e]

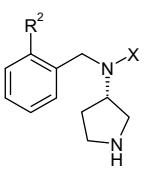
[a] See Ref. 7 for complete details of assay conditions.
[b] Monoamine reuptake IC_{50} values are geometric means of at least three experiments. Differences of <2-fold should not be considered significant.
[c] See Ref. 15 for definitions of terms and assays.
[d] Maximum measured half-life was 120 min.
[e] <10% inhibition at 3 μM.

the aryl ring, biphenyl compound **3b** was identified as a potent NRI with selectivity over SRI and DRI (>30-fold) (Table 1). However, in contrast to **3a**, biphenyl **3b** also possessed an unacceptable level of CYP2D6 inhibition and so could potentially inhibit the metabolism of CYP2D6 substrates.

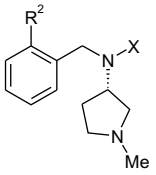
Further modification of this 3-aminopyrrolidine template by acylation of the (3*S*)-amino group gave amides, for example, **4**, with dual SNRI activity and modest inhibition of CYP enzymes (For **4**: CYP1A2/2C9/2D6/3A4, <40% inhibition at 3 μM).[14] Hence, we elected to investigate replacing the 4-THP group of **3b** by amides and other amino derivatives with the aim of retaining NRI activity whilst reducing the activity for CYP2D6 inhibition.

Target compounds **8**, **9**, and **11**–**16** (Table 2) were prepared using a short synthesis employing *N*-(benzyl)pyrrolidin-3-amines **7** as advanced intermediates (Scheme 1). This route allowed for the selective functionalisation of the exocyclic *sec*-amine group to afford a number of different amino derivatives viz. carboxamides **9**, carbamates **11**, ureas **12**, sulfonamides **13** and sulfonyl ureas **14**.

Table 2
In vitro inhibition of monoamine reuptake,[a,b] human liver microsomal stability and CYP2D6 inhibition for compounds **8**, **9**, **11**–**16**[c,d]



8, **9**, **11-14**



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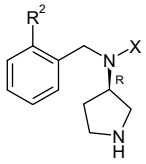

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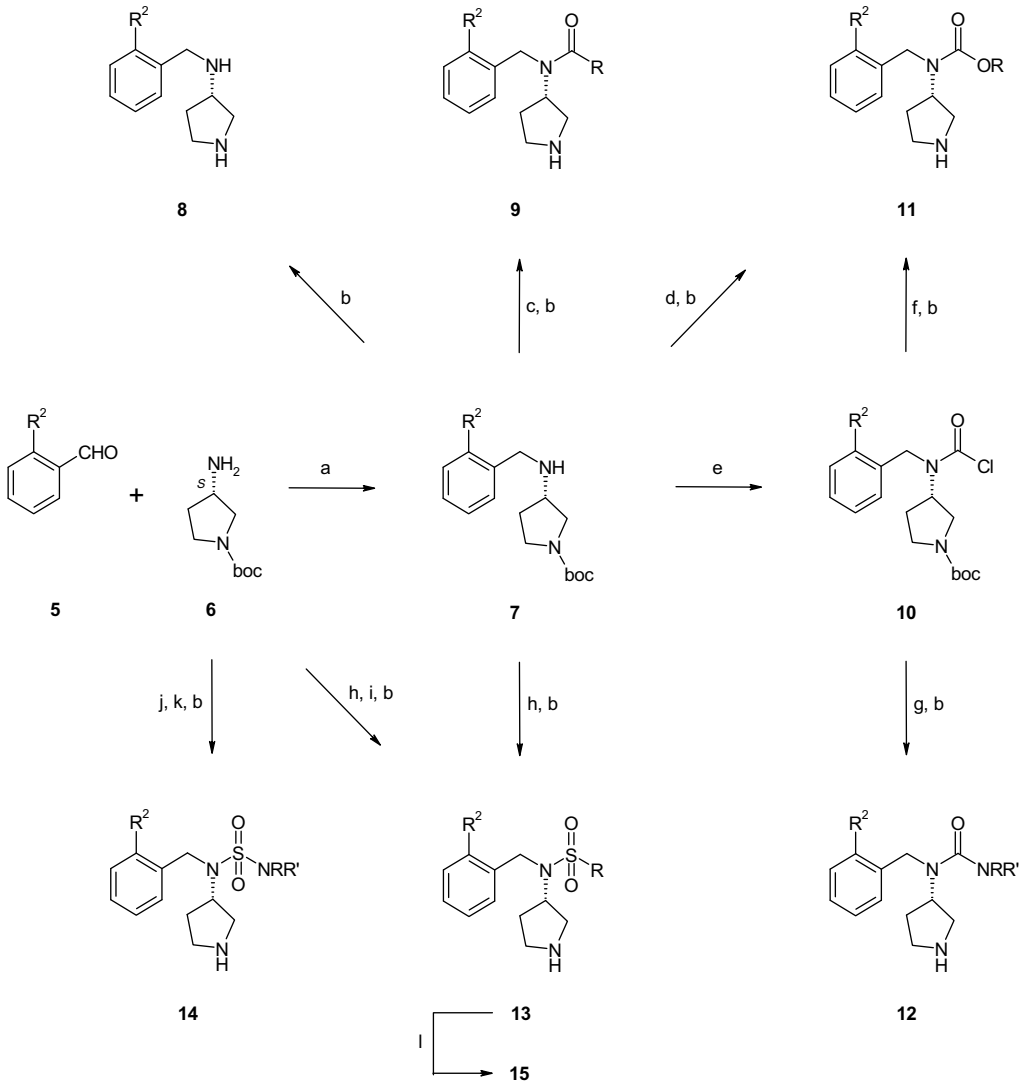
Compound	X	R^2	NA K_i (nM)	5-HT K_i (nM)	DA K_i (nM)	HLM Cl_i (μL/min/mg)	CYP2D6-i IC_{50} (nM)	clog*P*
8	H	Ph	271	1070	2470			3.0
9a	–COH	Ph	118	869	2130			2.5
9b	–COMe	Ph	124	5810	NT	<7		2.7
9c	–COEt	Ph	30	2680	NT	<7		3.2
9d	–CO*n*-Pr	Ph	25	730	2610	<7		3.8
9e	–CO*i*-Pr	Ph	6	960	3740	<7	1860	3.5
9f	–CO*i*-Bu	Ph	30	415	NT	9		4.2
9g	–CO*i*-Pr	*i*-Pr	70	544	3410	<7		3.3
9h	–CO*i*-Pr	*c*-Pr	74	124	2920			2.9
9i	–CO*i*-Pr	CF_3	63	133	NT	<7		2.8
9j	–CO*i*-Pr	SMe	65	50	1380			2.5
9k	–CO*i*-Pr	OPh	34	229	3500	10		4.1
11a	–COOMe	Ph	18	4440	3190	<7	10,600	3.7
11b	–COOEt	Ph	8	1110	3030	<7	1210	4.2
11c	–COO*i*-Pr	Ph	14	787	2010			4.5
11d	–COOEt	*i*-Pr	49	764	3340			4.0
11e	–COOEt	CF_3	46	427	3210			3.5
11f	–COOEt	SMe	89	353	NT			
11g	–COOEt	OPh	23	444	1900	21	420	4.7
12a	$–CONMe_2$	Ph	53	5010	2970			3.3
12b	$–CON(CH_2)_4$	Ph	27	NT	4190			4.1
13a	$–SO_2Me$	Ph	5	4120	2670	7	3100	2.6
13b	$–SO_2Et$	Ph	5	5620	2760	<7	1890	3.2
13c	$–SO_2$*n*-Pr	Ph	7	5680	2070	12	185	3.7
13d	$–SO_2$*i*-Pr	Ph	10	4690	2700	20	350	3.5
13e	$–SO_2CF_3$	Ph	30	5280	2080			3.7
13f	$–SO_2Me$	CF_3	86	2890	2890			1.9
13g	$–SO_2Me$	SMe	86	1250	2950	<7		1.6
13h	$–SO_2Me$	OPh	96	2700	2550			3.1
14	$–SO_2NMe_2$	Ph	8	3330	2690	16	840	2.8
15a	$–SO_2Me$	Ph	748	>10,000	NT			3.2
15b	$–SO_2Et$	Ph	466	>10,000	NT			3.6
16a	–COOEt	Ph	16	410	2910	<7	350	4.2
16b	$–SO_2Me$	Ph	29	5350	2390	<7	5360	2.6

[a] See Ref. 9 for complete details of assay conditions.
[b] Monoamine reuptake K_i values are geometric means of at least three experiments. Differences of <2-fold should not be considered significant.
[c] NT denotes not tested.
[d] See Ref. 15 for definitions of terms and assays.



Scheme 1. Synthesis of target compounds: amine **8**, amides **9**, carbamates **11**, ureas **12**, sulfonamides **13**, sulfonyl urea **14**, and *N*-methyl pyrrolidine derivatives **15**. Reagents and conditions: (a) MeOH, RT, then $NaBH_4$, or $NaBH(OAc)_3$, THF, RT; (b) TFA, CH_2Cl_2, RT; (c) RCOCl, NEt_3, dioxane, RT; (d) ROCOCl, NEt_3, dioxane, RT → 70 °C; (e) triphosgene, DMAP, NEt_3, PhMe, RT; (f) ROH, NEt_3, PhMe, RT → 60 °C; (g) RR′NH, NEt_3, PhMe, RT → 60 °C; (h) RSO_2Cl, NEt_3, CH_2Cl_2, RT; (i) $ArCH_2Cl$, NaOH, nBu_4NHSO_4, CH_2Cl_2–H_2O, RT; (j) $R'RNSO_2Cl$, NEt_3, CH_2Cl_2, RT; (k) $ArCH_2Br$, NaOH, K_2CO_3, MeCN, reflux; (l) 37% aq HCHO, $NaBH(OAc)_3$, CH_2Cl_2, RT.

Reductive amination of *N*-BOC-(3*S*)-aminopyrrolidine (**6**) with benzaldehydes **5** under standard conditions gave benzylamines **7** and deprotection of the pyrrolidine *N*-BOC group afforded *sec*-amines **8**. Acylation of **7** with acyl chlorides and deprotection gave amides **9**. Carbamates **11** were prepared either by reaction of **7** with the alkyl chloroformate or by conversion of **7** to the carbamoyl chloride **10** with triphosgene and then reaction with the alcohol. Treatment of **10** with amines gave ureas **12**. Methyl sulfonamides **13** (R = Me) were prepared by reaction of **7** with $MeSO_2Cl$, whereas all other sulfonamides **13** ($R \neq Me$) were prepared by conversion of **6** to the *sec*-sulfonamide followed by N-benzylation under standard conditions. Sulfonyl ureas **14** were prepared from **6** by a similar two-step sequence of sulfonylation and then benzylation. A few preferred *sec*-amines (**13a**, **13b**) were converted by N-methylation of the pyrrolidine ring to the corresponding *tert*-amines (**15a**, **15b**) by reductive amination employing standard conditions. The (*R*)-enantiomers **16** were prepared by an identical sequence but starting with *N*-BOC-(3*R*)-aminopyrrolidine.

Target compounds (Table 2) were tested for their ability to inhibit specific binding of selective radioligands at the human 5-HT, NA and DA transporters utilising scintillation proximity assay (SPA) technology and cellular membrane preparations generated from recombinant HEK293 cells expressing a single monoamine transporter.[9] Selected compounds were then screened for metabolic stability in human liver microsomes (HLM) and for CYP2D6 inhibition.[15]

The *sec*-amine **8** had weak NRI activity showing that a second *N*-substituent was required for activity. A series of carboxamides **9a**–**9f** with alkyl groups of increasing size identified **9e** with the isopropyl group as the optimum *N*-substituent for NRI activity (K_i 6 nM). In addition, **9e** had excellent selectivity over SRI and DRI, good in vitro metabolic stability and weak CYP inhibition. Further SAR was directed at improving NRI activity by exploring a broader set of 2-substituents on the aryl ring **9g**–**9k**. However, when compared to **9e** (i.e., $R^2 \neq Ph$), there was an erosion of NRI activity and introduction of SRI activity leading to compounds with modest dual SNRI activity (e.g., **9j**). No compound demonstrated any significant DRI activity. The carboxamide group was successfully exchanged for a carbamate **11a**–**11g** with the Et group giving a slight advantage in NRI activity and the preferred aryl substituent was again the 2-Ph (**11b**). In contrast to the carbamates, the ureas **12a,b** failed to yield a compound with potent NRI activity and were

not pursued. The sulfonamide derivatives **13a**–**13e** showed good NRI activity, and this SAR was more tolerant of different alkyl groups. However, as the alkyl group increased in size and lipophilicity, there was a decrease in metabolic stability and the introduction of potent CYP2D6 inhibition (**13a**,**b** vs **13c**,**d**). Sulfonyl urea **14** was a potent NRI but exhibited CYP2D6 inhibition and was not pursued. Additional noteworthy NRI SARs was that N-methylation on the pyrrolidine ring significantly reduced NRI activity (**13a**,**b** vs **15a**,**b**) and the (*R*)-stereochemistry was slightly inferior to the (*S*) (**16a** vs **11b**, **16b** vs **13a**). A plot of NRI activity versus clog*P* showed that excellent NRI activity could be achieved over a range of lipophilicity (Fig. 1) as reduction of compound lipophilicity was an important selection criteria.[16] In conclusion, the (3*S*)-amino group of **8** proved to be a versatile site to prepare amino derivatives with potent NRI activity, excellent selectivity over SRI and DRI, good in vitro metabolic stability and weak CYP inhibition.

From these experiments, carboxamide **9e**, carbamate **11b** and sulfonamide **13a** emerged as having a superior combination of NRI activity (K_i < 10 nM) combined with selectivity over SRI and DRI (>100-fold).

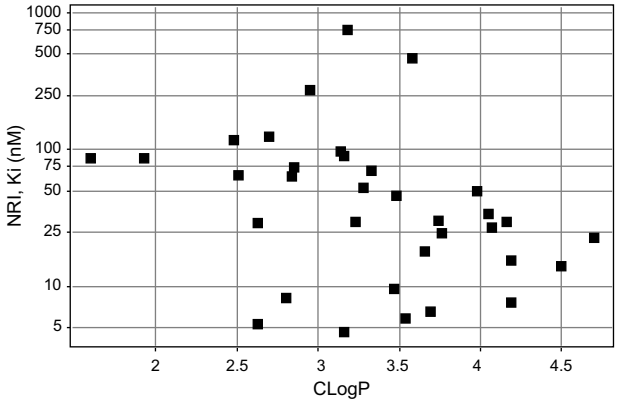


Figure 1. Plot of NRI activity versus clog*P* for all 34 compounds in Table 2.

Table 3
Physicochemical properties, ADME profiles and ion channel affinities of **9e**, **11b** and **13a**[a,b]

	9e	11b	13a
Physicochemical properties			
mw	322	324	330
clog*P*	3.5	4.2	2.6
HBD/HBA count	1/3	1/4	1/4
log$D_{7.4}$	0.8	1.1	0.6
pK_a	NT[c]	9.6	8.9
TPSA (Å^2)	32	42	58
ADME profiles			
HLM, Cl_i (μL/min/mg)	<7	<7	7
h.heps, Cl_i (μL/min/mg)	NT	<5	<5
CYP1A2 inhib., IC_{50} (nM)	>3000	>3000	>3000
CYP2C9 inhib., IC_{50} (nM)	>3000	>3000	>3000
CYP2D6 inhib., IC_{50} (nM)	1860	1210	3100
CYP3A4 inhib., IC_{50} (nM)	>3000	>3000	>3000
CaCO-2, AB/BA	NT	27/28	NT
MDCK-mdr1, AB/BA	11/68	22/44	10/51
MDCK-mdr1, ER	6.1	2.0	5.1
Ion channel affinities			
K^+, hERG, K_i (nM)	2840	2830	>2700
Ca^{2+}, L-type, K_i (nM)	>10,000	1500	1900
Na^+, site 2, K_i (nM)	1200	1100	1900

[a] See Ref. 15 for definitions of terms and assays.
[b] NT denotes not tested.
[c] pK_a ~ 9.4 by analogy with the measured value for **4**.

Additional screening of **9e**, **11b** and **13a** in high throughput in vitro ADME and safety screens showed all three compounds to have excellent metabolic stability in HLM and human hepatocytes consistent with low predicted clearance, weak CYP450 enzyme inhibition and modest ion channel activity as measured by binding to representative potassium, sodium and calcium channels (Table 3).[15] An in vitro screen that clearly differentiated **9e**, **11b** and **13a** was transit performance in the MDCK-mdr1 cell line which is commonly used as a model to estimate CNS penetration.[17] All three compounds have good passive permeability but amide **9e** and sulfonamide **13a** demonstrate efflux ratios (ER > 5) which were consistent with recognition and efflux by the P-glycoprotein (P-gp) transporter. Compounds with significant efflux by P-gp tend to have poorer CNS penetration than compounds that are not.[17] Performance in this assay proved to be decisive in selecting carbamate **11b** for in vivo assessments of CNS penetration.

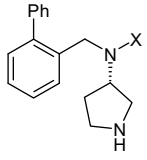
Compounds **9e**, **11b** and **13a** had drug-like physicochemical properties consistent with CNS target space (Table 3).[17,18] Furthermore, many of these properties are quite similar and so the superior performance of **11b** in the MDCK-mdr1 screen was not easy to rationalise.[19] We concluded that carbamate **11b** offered the advantage of slightly increased lipophilicity and lower H-bond acceptor strength resulting in minimal recognition and efflux by the P-gp transporter.[20]

H-bond donor and acceptor profiles are key properties when designing potential CNS drug candidates. However, HBD and HBA counts may be too simplistic to distinguish between close structural analogues as HBD and HBA strengths of different functional groups are not equivalent. We found that H-bond strengths, as measured by Abraham et al.[21] and Laurence,[22] proved to be a valuable guide in ranking the HBA capacity of functional groups and target compounds (Table 4).

Compound **11b** was screened for off-target pharmacology against a panel of 110 receptors, enzymes and ion channels (CEREP, Bioprint) and was found to have binding affinity for the muscarinic (M_3) and 5-$HT_{2A/2B/2C}$ receptors (>80% inhibition at 10 μM). Further evaluation showed **11b** to be 80-fold selective over M_3 (K_i 635 nM) and to have no confirmed functional activity at 5-$HT_{2A/2B/2C}$ (EC_{50} > 10 μM).

Pharmacological evaluation in vivo, in microdialysis experiments,[23] showed **11b** increased NA levels in interstitial fluid of the prefrontal cortex of conscious rats by 400% above pre-drug baseline levels confirming good CNS penetration (Fig. 2).[24]

Table 4
Correlation of MDCK-mdr1 transit properties with HBA strength of the *N*-substituent (X) (pK_{HB}) for **9e**, **11b**, **12b**, **13a** and **14**[a,b]



Compound	X	log$D_{7.4}$	MDCK-mdr1		pK_{HB}[c]
			AB/BA	ER	
9e	–CO*i*-Pr	0.8	11/68	6.1	2.26
11b	–COOEt	1.1	22/44	2.0	1.83
12b	–CON$(CH_2)_4$	0.7	2/53	26	2.44
13a	–SO_2Me	0.6	10/51	5.1	1.30
14	–SO_2NMe_2	1.0	17/68	4.0	1.47

[a] See Ref. 15 for definitions of terms and assays.
[b] Compounds **12b** and **14** have been included in this analysis to expand the structural diversity of this data set.
[c] See Ref. 22 for the origin of the pK_{HB} values.

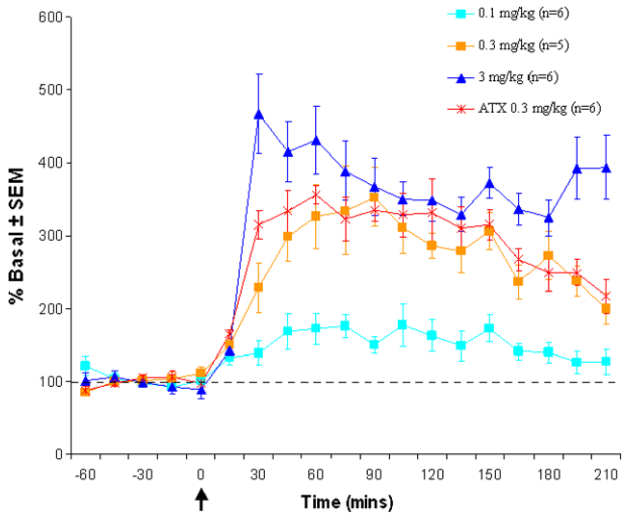


Figure 2. Dose-dependent effects of **11b** on NA levels in microdialysate from the prefrontal cortex of conscious rats. Test compounds were administered sc at time = 0 (n = 5–6). Atomoxetine (ATX, **1**) was used as a positive control.

In summary, derivatives of (3*S*)-*N*-(biphenyl-2-ylmethyl)pyrrolidin-3-amine are potent NRIs with good selectivity over SRI and DRI. Carboxamide **9e**, carbamate **11b** and sulfonamide **13a** were identified as potent NRIs with excellent selectivity over SRI and DRI, good in vitro metabolic stability and weak CYP inhibition. Carbamate **11b** demonstrated superior transit performance in MDCK-mdr1 cell lines with minimal P-gp efflux which was attributed to reduced HBA capacity of the carbamate group. Evaluation in vivo, in rat microdialysis experiments, showed **11b** significantly increased NA levels confirming good CNS penetration. Based on this profile, **11b** (PF-3609113)[25] was selected as a candidate for further evaluation in pre-clinical disease models.

Acknowledgments

We thank Paul Blackwell, Tim Buxton, Bradley Caprathe, Russell Cave, Soochal Kim and Yann Lecouturier for compound synthesis. We are grateful to Stephen Phillips (Discovery Biology), Fidelma Atkinson (PDM) and Robert Webster (PDM) for screening data.

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15. *Definitions of terms and assays.* clog*P*: calculated partition coefficient (BioByte software). HBD: H-bond donor count (NH + OH); HBA: H-bond acceptor count (N + O). log$D_{7.4}$: measured octanol-buffer distribution coefficients. TPSA: topological polar surface area. The minimum measurable intrinsic clearance (Cl_i) in human liver microsomes (HLM) and human hepatocytes (h.heps) was 7 and 5 μL/min/mg protein, respectively. CYP: cytochrome P450 enzyme family with isoenzymes 1A2, 2C9, 2D6, 3A4. CaCO-2: human colon adenocarcinoma cell line. MDCK-mdr1: Madin-Darby canine kidney cell line expressing the P-glycoprotein transporter (P-gp). Flux across cells was measured at 10 μM substrate concentrations. Figures quoted correspond to the flux rates ($P_{app} \times 10^{-6}$ cm s^{-1}) for apical to basolateral (AB) and basolateral to apical (BA) directions. Efflux ratio (ER) is the BA/AB value. Ion channel screening: potassium (K^+), hERG ([^{3}H]-dofetilide); sodium (Na^+), (site 2); calcium (Ca^{2+}) (L-type diltiazem site).
16. Preferred examples in Table 2 had calculated properties for ligand efficiency (LE ⩾ 0.45) and ligand-lipophilic efficiency (LLE ⩾ 5.0) consistent with drug-like chemical space. For an analysis of drug-like concepts, especially lipophilicity, see: Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Dis.* **2007**, *6*, 881.
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19. The CNS analysis was limited by an incomplete set of in vivo data and so the correlation was performed against performance in the in vitro MDCK-mdr1 cell line.
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22. The relative H-bond acceptor strengths of the *N*-substituents (X) were taken by analogy with published values of related compounds (pK_{HB}): Me_2NCOi-Pr (2.26); $Me_2NCOOEt$ (1.83); $Me_2NCONMe_2$ (2.44); Me_2NSO_2Me (1.30); $Et_2NSO_2NEt_2$ (1.47). See: (a) Laurence, C.; Berthelot, M. *Persp. Drug Disc. Des.* **2000**, *18*, 39 and references therein; (b) Graton, J.; Berthelot, M.; Laurence, C. *J. Chem. Soc., Perkin Trans.* **2001**, *2*, 2130.
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24. Rat NA functional transporter activity was measured in HEK293 cells expressing the rat NA transporter with [^{3}H]-NA as substrate. For **11b**, rNRI, K_i = 2.5 nM (n = 2).
25. Data for **11b**: $[\alpha]_D = -4.9°$ (MeOH; c 0.19); >99% pure by HPLC; 100% ee by chiral HPLC. For **11b** HCl salt: ^{1}H NMR (CD_3OD, 400 MHz) δ 1.20 (3H, t), 2.10–1.98 (2H, br m), 3.10 (1H, m), 3.25 (1H, m), 3.34 (1H, m), 3.52 (1H, m), 4.06 (2H, d), 4.14–3.92 (1H, br), 4.55 (2H, q), 7.28–7.10 (9H, m); LRMS APCI m/z 325 (MH^+). For **11b** D-tartrate salt: mp 117 °C.