Bioorganic & Medicinal Chemistry Letters 19 (2009) 4579–4583

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design, synthesis and evaluation of *N*-[(3*S*)-pyrrolidin-3-yl]benzamides as selective noradrenaline reuptake inhibitors: CNS penetration in a more polar template

Paul V. Fish *, Florian Wakenhut, Thomas Ryckmans, Alan Stobie

Discovery Chemistry, Pfizer Global Research and Development, Sandwich Laboratories, Sandwich, Kent CT13 9NJ, UK

ARTICLE INFO

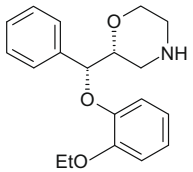
Article history:
Received 8 June 2009
Revised 25 June 2009
Accepted 26 June 2009
Available online 2 July 2009

Keywords:
Noradrenaline reuptake inhibitor
NRI
N-[(3*S*)-Pyrrolidin-3-yl]benzamides
Reduced lipophilicity
CNS penetration

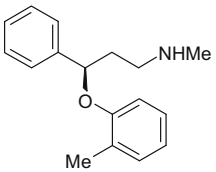
ABSTRACT

Derivatives of *N*-[(3*S*)-pyrrolidin-3-yl]benzamides are disclosed as a new series of noradrenaline reuptake inhibitors (NRI). Structure–activity relationships established that potent NRI activity could be achieved by appropriate substitution at the 2-position of the phenyl ring; consequently, selective NRIs and dual NSRIs were prepared. Benzamide **11e** was identified as a potent NRI with good selectivity over SRI and DRI, good in vitro metabolic stability, weak CYP inhibition and low affinity for ion channels. Evaluation in vivo, in rat microdialysis experiments, showed **11e** increased noradrenaline levels by up to 350% confirming good CNS penetration. Benzamide **11e** was differentiated from previous NRIs as it was significantly less lipophilic (Δclog *P* −0.9).

The identification of noradrenaline (NA) reuptake inhibitors (NRI) continues to be an attractive approach for the treatment of a number of diseases.[1,2] For example, (±)-reboxetine (**1**) is an orally-active, selective NRI developed and launched for the treatment of depression[3,4] and the (+)-(*S,S*)-enantiomer of reboxetine has undergone clinical evaluation as a potential treatment for fibromyalgia and neuropathic pain. Atomoxetine (**2**) is a new therapy for the treatment of child, adolescent and adult attention deficit hyperactivity disorder (ADHD) and was the first non-stimulant marketed for the treatment of ADHD.[5] Furthermore, several small molecule NRIs have been reported to be in clinical development or undergoing preclinical optimisation and evaluation.[6]

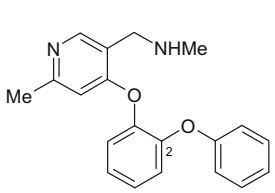


1: (±)-reboxetine
clog *P* = 3.3

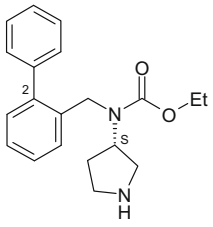


2: atomoxetine
clog *P* = 3.9

We have recently reported several new templates that inhibit NA reuptake[7–11] and two of these compounds were evaluated in preclinical rodent toxicology studies. Pyridinyl phenyl ether **3**[8] and carbamate **4**[11] induced clinical and pathological evidence of hepatotoxicity. Neither compound had an obvious specific liability in vitro as there was minimal off-target pharmacology as measured by Bioprint™ (Cerep). We attributed these findings to the physicochemistry of **3** and **4** as more lipophilic, less polar compounds have an increased risk of in vivo toxicological outcomes and promiscuous off-target pharmacology.[12]



3
clog *P* = 4.4



4
clog *P* = 4.2

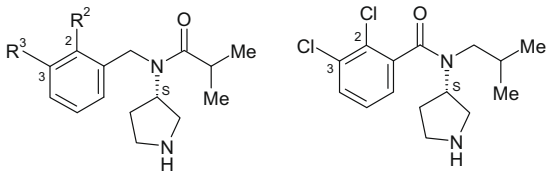
Hence, we proposed that a new NRI template would benefit from a significant decrease in lipophilicity as this would reduce the risk of toxicological outcomes; this reduction in lipophilicity would need to be balanced with retention of good central nervous system (CNS) permeability.

In this Letter, we disclose derivatives of *N*-[(3*S*)-pyrrolidin-3-yl]benzamides **11** as potent NRIs with good selectivity over serotonin (5-HT) and dopamine (DA) reuptake inhibition (SRI and DRI, respectively). Furthermore, examples of benzamides were identified that were significantly less lipophilic than previous NRIs and

* Corresponding author. Tel.: +44 1304 644589; fax: +44 1304 651987.
E-mail address: paul.fish@pfizer.com (P.V. Fish).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.06.096

the impact of decreasing lipophilicity on in vitro pharmacology, ADME and safety profiles is discussed.



5
5a: $R^2 = R^3 = Cl$
5b: $R^2 = Ph$; $R^3 = H$

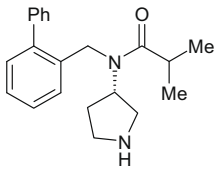
6
clog *P* = 3.6

N-(Benzyl)pyrrolidin-3-amines **5** were first disclosed as selective dual serotonin/noradrenaline reuptake inhibitors (SNRI) (e.g., **5a**)[10] and further modification of the aryl ring furnished selective NRIs (e.g., **5b**).[11] An emerging understanding of the SAR within this 3-aminopyrrolidine scaffold showed that the aryl ring played an important role in modulating NRI and SRI activity; that is, appropriate substitution at the 2-position conferred NRI activity whereas substitution at the 3/4-position gave SRI activity.[7,10,11] In addition, recent reports have shown that transposition of an *i*-propyl amide group to the benzamide motif (i.e., **5a**→**6**) has maintained dual SNRI activity whilst improving CNS penetration.[13] Hence, as an initial venture, we elected to convert the carboxamide of **5b** to the corresponding benzamide **7** with the aim of producing a selective NRI.

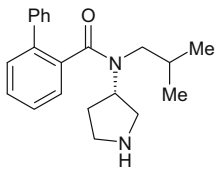
However, benzamide **7** had a significant loss in NRI activity and offered no advantage, compared to **3** and **4**, in reducing the overall lipophilicity of the template (Table 1). Hence, a more detailed investigation of the SAR of the substitution at the 2-position on the benzamide ring (**11**:R^2) and the 3-aminopyrrolidine group (**11**:R) was undertaken with the primary objectives of improving NRI activity whilst simultaneously reducing lipophilicity.

Benzamide target compounds **11** (Table 2) were conveniently prepared in a three-step sequence as described in Scheme 1. Three general methods were used to create the *sec*-amines **9** (Step 1): (a) direct reductive amination of an aldehyde or ketone with 3-aminopyrrolidine **8** under hydride or hydrogenolysis reducing conditions; (b) **8** was coupled with an acid (or activated acid derivative) to give the corresponding amide which was then reduced with borane–THF to yield **9**; (c) palladium catalysed N-arylation of **8** with PhBr.[15] Benzoylation of **9** with either benzoyl chlorides, or benzoic acids under activated coupling conditions, gave benzamides **10** (Step 2). Finally, deprotection of the pyrrolidine *N*-Boc group with either HCl or CF_3CO_2H afforded **11** (Step 3). The corresponding (*R*)-enantiomers **12** were prepared by these methods but starting with *N*-Boc-(3*R*)-aminopyrrolidine. Target compounds **11** were initially prepared by parallel synthesis techniques and preferred examples were resynthesised by standard batch processes; this chemistry proved to be operationally simple to perform on large scale.

Table 1
Physicochemical properties, in vitro inhibition of monoamine reuptake, and ion channel affinities of **5b** and **7**[a,b]



5b



7

	5b	**7**
mw	322	322
clog *P*	3.5	4.1
HBD/HBA count	1/3	1/3
Log $D_{7.4}$	0.8	NT[c]
TPSA, Å^2	32	32
pK_{HB}[d]	2.26	2.23
NRI, K_i (nM)	6	294
SRI, K_i (nM)	960	654
DRI, K_i (nM)	3740	>10,000
K^+, hERG, IC_{50} (nM)	3020	1440

[a] See Ref. 11 for definitions of terms and 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. 14 for the origin of the pK_{HB} values.

Target compounds (Table 2) were tested for their ability to inhibit specific binding of selective radioligands at the human NA, 5-HT and DA transporters utilising scintillation proximity assay (SPA) technology and cellular membrane preparations generated from recombinant HEK293 cells expressing a single monoamine transporter.[11] Selected compounds were then screened for metabolic stability in human liver microsomes (HLM), for CYP2D6 inhibition, and binding to the potassium hERG channel as a measure of ion channel activity. Compound lipophilicity was initially assessed by calculation of partion coefficients (*clog P*; BioByte software v4.3) and then confirmed for selected examples by measurement of octanol-buffer distribution coefficients (log $D_{7.4}$).

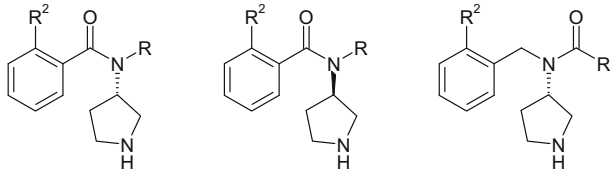
An analysis of NRI, SRI, and DRI activity and the correlation with *clog P* for all the compounds disclosed ($n = 205$) was performed with scatter plots (Fig. 1). Potent NRI activity could be achieved (K_i <10 nM) and, despite substitution at just the aryl ring R^2 position in an attempt to bias the outcome towards NRI activity, it was clear that selective NRIs along with compounds showing dual NRI with SRI activity (NSRI) had been prepared (Fig. 1a). No compound demonstrated any significant DRI activity. A plot of NRI activity versus *clog P* showed that excellent NRI activity could be achieved over a range of lipophilicity dropping as low as *clog P* ~3.0 and gave encouragement that our target profile could be accomplished (Fig. 1b).

A more detailed in vitro evaluation of selected examples, along with HLM stability, CYP2D6 inhibition and ion channel activity, is presented in Table 2. A series of benzamides **11a**–**j** (R = CH_2c-Bu), where the aryl ring was substituted by groups of increasing lipophilicity, showed potent NRI activity could be achieved. Several groups at R^2 were accommodated with SMe, CF_3, SEt, *i*-Pr, and OPh being superior. Retaining these preferred aryl ring substituents (R^2) whilst exploring the 3-aminopyrrolidine substituent, R, identified additional potent NRIs although, in general, exchanging the cyclobutylmethyl group resulted in a loss of NRI potency and decreased selectivity over SRI. One of the most potent dual NSRIs was **11o** (R = *c*-Hex) where the cyclohexyl group had conferred potent SRI activity without significantly eroding NRI activity. Compounds having R^2 = OPh (e.g., **11aa**–**dd**) were exceptions to this general trend as potent NRI activity could be achieved provided that R ≠ Me; however, the 2-OPh group contributed a significant burden to the template in terms of lipophilicity (Rekker fragmental constant, $\pi = 2.08$)[16] and was not pursued. Benzamides **11** had excellent HLM metabolic stability across a range of *clog P*. CYP2D6 inhibition and binding to the hERG ion channel was minimal with the more polar examples (e.g., **11e**) and generally tracked with increasing lipophilicity. Additional noteworthy NRI SAR was that the (*R*)-stereochemistry was inferior to the (*S*) (**12** vs **11**) and the direct carboxamide analogue **13e**[11] of benzamide **11e** had a significant decrease in NRI activity (*cf* **7** vs **5b**).

From these experiments, benzamide **11e** (*clog P* 3.3) emerged as having a superior NRI activity (K_i 6 nM) combined with selectivity over SRI and DRI (>35-fold).

Additional screening in high throughput in vitro ADME and safety screens showed **11e** to have excellent metabolic stability

Table 2
In vitro inhibition of monoamine reuptake, human liver microsomal stability, CYP2D6 inhibition and ion channel activity for compounds **3**, **4**, **7**, **11**, **12** and **13**[a,b,c]



11 **12** **13**

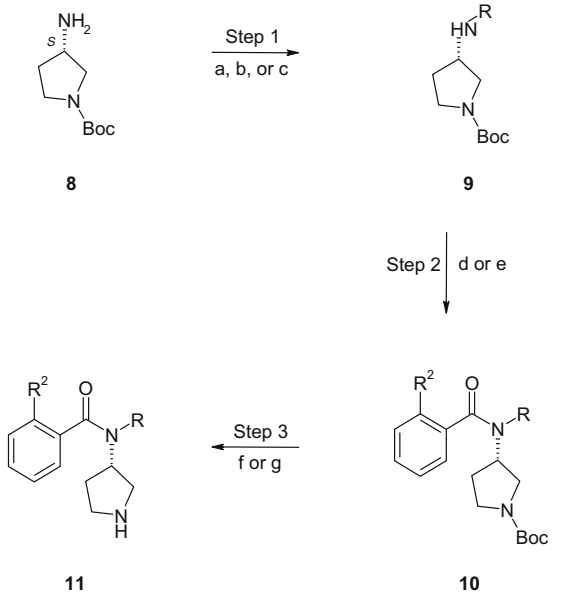
Compound	R^2	R	*c*log *P*	NA K_i (nM)	5-HT K_i (nM)	DA K_i (nM)	HLM, Cl_i (μL/min/mg)	CYP2D6-i IC_{50} (nM)	K^+, hERG IC_{50} (nM)
3	—	—	4.4	10	823	1910	<7	3400	11,200
4	—	—	4.2	8	1110	3030	<7	1210	4980
7	Ph	*i*-Bu	4.1	294	654	>10,000	NT	NT	1440
11a	Me	CH_2*c*-Bu	2.7	72	118	2340	NT	NT	>20,000
11b	SMe	CH_2*c*-Bu	2.9	8	179	3040	<7	NT	>20,000
11c	OEt	CH_2*c*-Bu	3.0	22	348	2650	<7	NT	>16,800
11d	Cl	CH_2*c*-Bu	3.0	19	39	1360	NT	NT	>20,000
11e	CF_3	CH_2*c*-Bu	3.3	6	224	2290	<7	15,100	>20,000
11f	Et	CH_2*c*-Bu	3.3	29	237	2680	NT	NT	>16,300
11g	SEt	CH_2*c*-Bu	3.4	6	266	3670	8	480	7570
11h	*i*-Pr	CH_2*c*-Bu	3.7	10	857	2040	<9	3170	>18,200
11i	*c*-Pent	CH_2*c*-Bu	4.3	18	802	3720	60	430	2210
11j	OPh	CH_2*c*-Bu	4.3	7	151	>10,000	<7	65	760
11k	SMe	*c*-Bu	2.3	16	62	>10,000	<7	>30,000	>20,000
11l	SMe	*n*-Pr	2.4	37	1090	3110	NT	NT	>20,000
11m	SMe	*c*-Pent	2.8	9	36	4770	NT	NT	>18,700
11n	SMe	Ph	3.0	19	64	3440	NT	NT	>20,000
11o	SMe	*c*-Hex	3.4	5	16	2950	NT	NT	2270
11p	CF_3	*i*-Pr	2.6	172	457	>10,000	NT	NT	>20,000
11q	CF_3	*c*-Bu	2.6	60	210	>10,000	<7	NT	>10,000
11r	CF_3	CH_2*c*-Pr	2.7	30	581	>10,000	NT	NT	>20,000
11s	CF_3	Ph	3.3	28	113	3130	<7	>3000	>20,000
11t	CF_3	CH_2*c*-Pent	3.8	24	109	2750	<7	NT	>13,500
11u	*i*-Pr	*c*-Bu	3.0	43	776	>10,000	NT	NT	>19,000
11v	i-Pr	CH_2*c*-Pr	3.1	31	2870	>10,000	NT	NT	>17,600
11w	*i*-Pr	*n*-Pr	3.2	92	5210	>10,000	NT	NT	>20,000
11x	*i*-Pr	*c*-Pent	3.6	32	663	>10,000	NT	>30,000	>18,500
11y	*i*-Pr	CH_2*c*-Pent	4.2	18	330	3470	NT	NT	2350
11z	OPh	Me	2.8	61	661	>3160	NT	NT	9210
11aa	OPh	Et	3.3	9	1610	3570	<7	>30,000	5030
11bb	OPh	*c*-Bu	3.7	13	222	>10,000	<7	3370	2950
11cc	OPh	*i*-Bu	4.2	8	160	>10,000	<7	290	1080
11dd	OPh	Ph	4.4	3	68	4650	<7	5540	2810
12b	SMe	CH_2*c*-Bu	2.9	572	1080	3470	NT	NT	NT
12e	CF_3	CH_2*c*-Bu	3.3	1120	1650	3960	NT	NT	NT
12h	*i*-Pr	CH_2*c*-Bu	3.7	825	1990	>3160	NT	NT	NT
12j	OPh	CH_2*c*-Bu	4.3	38	587	4100	<8	NT	NT
13e	CF_3	*c*-Bu	2.9	148	187	>10,000	<7	NT	>7460

[a] See Ref. 11 for definitions of terms and 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.

in HLM and human hepatocytes consistent with low predicted clearance, weak CYP450 enzyme inhibition and good membrane permeability (Table 3). There was evidence for some degree of recognition and efflux by the P-glycoprotein (P-gp) transporter as measured by transit performance in the MDCK-mdr1 cell line[17] which prompted further evaluation in vivo. Compound **11e** had modest ion channel activity as measured by binding to representative potassium, sodium and calcium channels and a reduced direct CV risk as **11e** had no significant effect in vitro on either the hERG channel as assessed by functional blockade (48% I @ 10 μM) or binding to the cardiac sodium channel ($NaV_{1.5}$).[18]

Compound **11e** was screened for off-target pharmacology against a panel of 110 receptors, enzymes and ion channels (Bioprint™) and was found to have binding affinity for the human muscarinic M_4 and M_5 receptors (>50% inhibition at 10 μM). Further evaluation showed **11e** to be 700-fold selective over M_4 (K_i 4300 nM) and 300-fold selective over M_5 (K_i 1800 nM).

Pharmacological evaluation in vivo, in microdialysis experiments,[19] showed **11e** produced a rapid increase in NA levels in interstitial fluid of the prefrontal cortex of conscious rats by 200–350% above pre-drug baseline levels (0.3–3.2 mg/kg administered sc, $n = 2$) (Fig. 2).[20] The magnitude and duration of the response for **11e** was similar (by dose) to those observed with **3** and **4** indicating good CNS penetration. These studies also demonstrated that, at doses up to 3.2 mg/kg, **11e** has no significant effect on levels of 5-hydroxyindoleacetic acid (5-HIAA) or dihydroxyphenylacetic



Scheme 1. Reagents and conditions: Step 1: (a) (i) aldehyde/ ketone, MeOH–PhMe, rt, then $NaBH_4$, MeOH, rt; or (ii) aldehyde/ketone, H_2 (60 psi), 10% Pd–C, EtOH, rt; (b) (i) R′COCl, NEt_3, CH_2Cl_2, rt; or (ii) R′CO_2H, 1-propanephosphonic anhydride (T3P), NEt_3, CH_2Cl_2, rt; or (iii) (R′$CO)_2O$, *N*-methylmorpholine, PhMe, rt; then (iv) BH_3·THF, THF, reflux; (c) tris(dibenzylideneacetone)-dipalladium(0) (5 mol %), 1,1′-binaphthalene-2,2′-diylbis-(diphenyl)phosphine (10 mol %), PhBr, PhMe, 100 °C. Step 2: (d) ArCOCl, NEt_3, CH_2Cl_2 or dioxane rt; (e) ArCO_2H, T3P, NEt_3, CH_2Cl_2, rt. Step 3: (f) TFA, CH_2Cl_2, rt; (g) HCl in dioxane, rt.

acid (DOPAC) consistent with selective NA transporter functional blockade.[21]

In ex vivo NA transporter occupancy binding studies to rat neocortical tissue,[22] **11e** achieved 52 ± 12% occupancy at 1 h post dose (3 mg/kg administered sc: mean ± sem, $n = 4$) confirming good CNS penetration.[22]

In summary, derivatives of *N*-[(3*S*)-pyrrolidin-3-yl]benzamides are disclosed as a new series of NRIs. Structure–activity relationships established that potent NRI activity could be achieved by appropriate substitution at the 2-position of the phenyl ring; consequently, selective NRIs and dual NSRIs were prepared. Benzamide **11e** was identified as a potent NRI with good selectivity over SRI and DRI, good in vitro metabolic stability, weak CYP inhibition and low affinity for ion channels. Evaluation in vivo, in rat microdialysis experiments, showed **11e** increased NA levels by up to 350% confirming good CNS penetration. Benzamide **11e** was differentiated from previous NRIs (*cf* **3** and **4**) as it was significantly less lipophilic (Δclog *P* −0.9). Based on this profile, **11e** (PF-3409409)[23] was selected as a candidate for further evaluation in preclinical disease models and toxicology studies.

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

	11e
Physicochemical properties	
mw	326
clog *P*	3.3
HBD/HBA count	1/3
log $D_{7.4}$	0.4
pK_a	9.5
TPSA, Å^2	32
ADME profiles[b]	
HLM, Cl_i μL/min/mg	<7
h.heps, Cl_i μL/min/mg	<5
CYP1A2 inhib. (tacrine), IC_{50} (nM)	>30,000
CYP2C9 inhib. (diclofenac), IC_{50} (nM)	>30,000
CYP2C19 inhib. (*S*-methphenytoin), IC_{50} (nM)	>30,000
CYP2D6 inhib. (dextromethorphan), IC_{50} (nM)	11,300
CYP3A4 inhib. (felodipine), IC_{50} (nM)	22,000
CYP3A4 inhib. (midazolam), IC_{50} (nM)	12,200
CYP3A4 inhib. (testosterone), IC_{50} (nM)	31,200
CaCO-2, AB/BA, $P_{app} \times 10^{-6}$ cm s^{-1}	16/33
MDCK-mdr1, AB/BA, $P_{app} \times 10^{-6}$ cm s^{-1}	11/57
MDCK-mdr1, efflux ratio	5.2
Ion channel binding affinities	
K^+, hERG, K_i (nM)	>20,000
Ca^{2+}, L-type, K_i (nM)	4300
Na^+, site 2, K_i (nM)	3700
Na^+, $NaV_{1.5}$, IC_{50} (nM)	>26,000

[a] See Ref. 11 for definitions of terms and assays.
[b] For CYP inhibition studies, the conventional probe is in brackets.

Acknowledgements

We thank Paul Blackwell, Tim Buxton, Russell Cave, Yann Lecouturier, Malcolm Mackenny and Melanie Skerten for compound synthesis. We are grateful to Stephen Phillips (Discovery

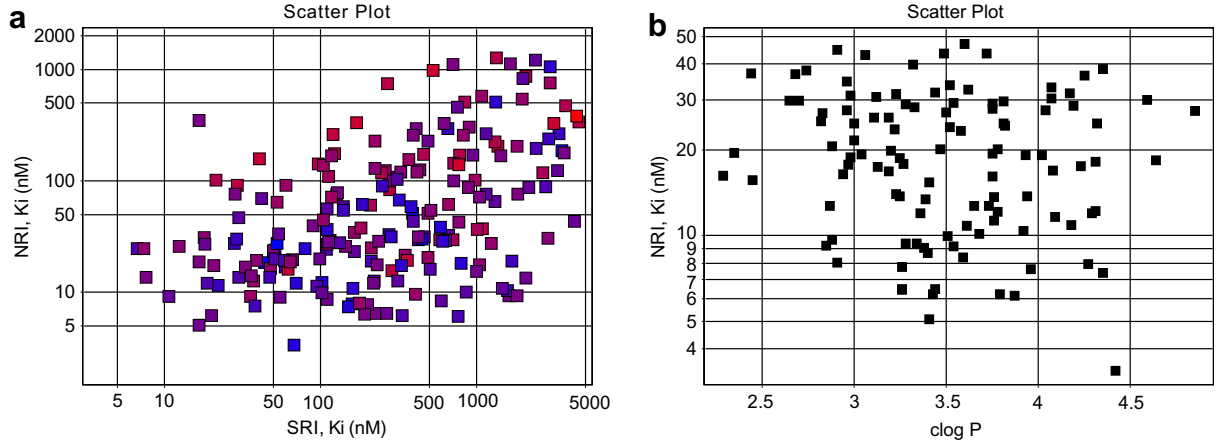


Figure 1. (a) Scatter Plot of NRI activity (K_i <2000 nM) versus SRI activity (K_i <5000 nM) for all compounds disclosed ($n = 205$). Colour code is clog $P = 1.5$ (red) to 4.8 (blue); (b) scatter plot of NRI activity (K_i <50 nM) versus clog *P* ($n = 111$). NRI, SRI, DRI activity and clog *P* values for all compounds in (a) and (b) can be found in the Supplementary data. *Compound key*, where R and R^2 were selected from: ***R*** = Et, *n*-Pr, *n*-Bu, *i*-Pr, *i*-Bu, 2-Bu, CH_2c-Pr, CH_2c-PrMe, CH_2c-Bu, CH_2c-BuMe, CH_2c-Pent, CH_2t-Bu, *c*-Bu, *c*-Pent, *c*-Hex, Ph, CH_2CF_3, CH_2CHF_2, $CH_2CF_2CH_3$, CH_2cPrCF_3, CH_2CH_2cPr, $CH_2CH_2CF_3$, CH_2CH_2OMe; **R^2 =** Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, CH_2c-Pr, *c*-Pr, *c*-Bu, *c*-Pent, Cl, Br, OEt, O*i*-Pr, OCH_2c-Pr, OCH_2c-Bu, SMe, SEt, S-*i*-Pr, CF_3, CH_2CF_3, CF_2CH_3, OCF_3, $OCHF_2$, SCF_3, Ph, CH_2Ph, OPh, SPh.

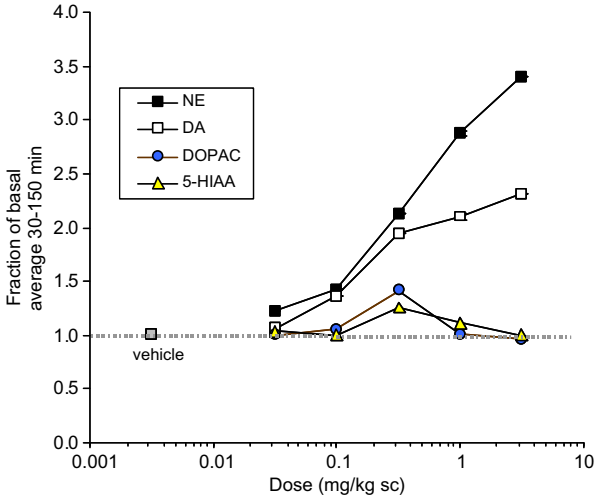


Figure 2. Dose-dependant effects of **11e** on extracellular levels of NA, DA, 5-HIAA and DOPAC in rat prefrontal cortex. Test compounds were administered sc. Data are the average response over 0.5–2.5 h after dosing, expressed as fraction of basal levels ($n = 2$).

Biology), Hans Rollema (Discovery Biology, PGRD Groton), Fidelma Atkinson (PDM) and Robert Webster (PDM) for screening data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.06.096.

References and notes

1. Babu, R. P. K.; Maiti, S. N. *Heterocycles* **2006**, *69*, 539.
2. Walter, M. W. *Drug Dev. Res.* **2005**, *65*, 97.
3. Wong, E. H. F.; Sonders, M. S.; Amara, S. G.; Tinbolt, P. M.; Piercey, M. F. P.; Hoffmann, W. P.; Hyslop, D. K.; Franklin, S.; Porsolt, R. D.; Bonsignori, A.; Carfagna, N.; McArthur, R. A. *Biol. Psychiatry* **2000**, *47*, 818.
4. Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23.
5. Ledbetter, M. *Neuropsych. Disease Treatment* **2006**, *2*, 455.
6. For a recent review of new NRI chemical entities, see: Whitlock, G. A.; Andrews, M. D.; Brown, A. D.; Fish, P. V.; Stobie, A.; Wakenhut, F. In *Top. Med. Chem*; Napier, S., Bingham, M., Eds.; Transporters as targets for Drugs; Springer: Berlin, 2009; Vol. 4, Chapter 3, pp 53–94.
7. Fish, P. V.; Fray, M. J.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2022.
8. Fish, P. V.; Ryckmans, T.; Stobie, A.; Wakenhut, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1795.
9. Fish, P. V.; Deur, C.; Gan, X.; Greene, K.; Hoople, D.; Mackenny, M.; Para, K. S.; Reeves, K.; Ryckmans, T.; Stiff, C.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2562.
10. Wakenhut, F.; Fish, P. V.; Fray, M. J.; Gurrell, I.; Mills, J. E. J.; Stobie, A.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4308.
11. Fish, P. V.; Barta, N. S.; Gray, D. L. F.; Ryckmans, T.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4355.
12. For an anlaysis of the influence of drug lipophilicity on off-target pharmacology and in vivo toxicological outcomes, see: (a) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Disc.* **2007**, *6*, 881; (b) Hughes, J. D.; Blagg, J.; Price, D. A.; Bailey, S.; De Crescenzo, G. A.; Dalvie, D.; Devraj, R. V.; Doubovetzky, M.; Ellsworth, E.; Fobian, Y. M.; Gibbs, M. E.; Gilles, R. W.; Grant, D.; Greene, N.; Huang, E.; Kreiger-Burke, T.; Lee, L.; Loesel, J.; Nahas, K.; Wager, T.; Whiteley, L.; Zhang, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4872.
13. Wakenhut, F.; Allan, G; Fish, P. V.; Fray, M. J.; Harrison, A.; McCoy, R.; Phillips, S.; Stobie, A.; Westbrook, D.; Westbrook, S.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2009**, preceeding paper, doi:10.1016/j.bmcl.2009.07.049.
14. The relative H-bond acceptor strengths of the amides were taken by analogy with published values of related compounds (H-bond basicity, pK_{HB}): $Me_2NCOi\text{-}Pr$ (2.26); Me_2NCOPh (2.23). See: Le Questel, J.-Y.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2091.
15. Jean, L.; Rouden, J.; Maddaluno, J.; Lasne, M.-C. *J. Org. Chem.* **2004**, *69*, 8893.
16. The relative lipophilicities of the 2-substituents (R^2) were evaluated by comparison of hydrophobic fragmental constants (π), see: Rekker, R. F.; Mannhold, R. Calculation of drug lipophilicity; VCH: New York. R^2 (π): OEt (0.38); Me (0.56); SMe (0.61); Cl (0.71); CF_3 (0.88) ; Et (1.02); SEt (1.07); *i*-Pr (1.53); *c*-Pent (NA); OPh (2.08).
17. Transit performance in the MDCK-mdr1 cell line is commonly used as a model to estimate CNS penetration, see: Mahar Doan, K. M.; Humphreys, J. E.; Webster, L. O.; Wring, S. A.; Shampine, L. J.; Serabjit-Singh, C. J.; Adkison, K. K.; Polli, J. W. *J. Pharm. Exp. Ther.* **2002**, *303*, 1029.
18. Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. *J. Med. Chem.* **2006**, *49*, 5029.
19. Deecher, D. C.; Beyer, C. E.; Johnston, G.; Bray, J.; Shah, S.; Abou-Gharbia, M.; Andree, T. H. *J. Pharm. Exp. Ther.* **2006**, *318*, 657.
20. Rat NA functional transporter activity was measured in HEK293 cells expressing the rat NA transporter with [^{3}H]-NA as substrate. For **11e**, rNRI, $K_i = 3.9$ nM ($n = 4$).
21. 5-Hydroxyindoleacetic acid (5-HIAA) is the main metabolite of 5-HT and dihydroxyphenylacetic acid (DOPAC) is a major metabolite of DA. The elevation of DA levels reflects blockade of the NA transporter as DA is also a substrate for the NA transporter in the prefontal cortex region of the brain; this effect can also be seen with other selective NRIs such as **1** and **2**. See, Ref. 4 and Bymaster, F. P.; Katner, J. S.; Nelson, D. L.; Hemrick-Luecke, S. K.; Threlkeld, P. G.; Heliigenstein, J. H.; Morin, S. M.; Gehlert, D. R.; Perry, K. W. *Neuropyschopharm* **2002**, *27*, 699.
22. The ex vivo NA binding assay is an index of central in vivo NA occupancy that assesses brain penetration of a NRI in rats after in vivo administration as measured by residual NA transporter binding to homogenized neocortical tissue in an in vitro [^{3}H]-nisoxetine binding assay.
23. For experimental procedures for the preparation of **11e**, see: Fish, P. V.; Ryckmans, T; Stobie, A.; Wakenhut, F.; Whitlock, G. A. US Patent Application 0111429, 2006.