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N-Alkyl-*N*-arylmethylpiperidin-4-amines: Novel dual inhibitors of serotonin and norepinephrine reuptake

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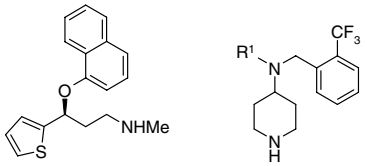
Abstract—A series of *N*-alkyl-*N*-arylmethylpiperidin-4-amines have been prepared and are demonstrated to be inhibitors of both serotonin and norepinephrine reuptake.

Major depressive disorder is currently the fourth leading cause of disease or disability world wide and is projected to rise to second by 2020.[1] Furthermore it has been suggested that dual serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors offer the potential for superior anti-depressant activity.[2] That enhancing both serotonergic and noradrenergic neurotransmission results in anti-depressant efficacy is now supported by clinical experience with duloxetine (Cymbalta™) (**1**), a dual 5-HT and NE uptake inhibitor.[3,4]



Duloxetine 1 **2**

Figure 1.

As part of a program seeking to identify new dual uptake inhibitors a series of alkylaminopiperidines that possess potent dual 5-HT and NE transport inhibition properties have now been identified (Fig. 1).[5,6]

The initial compounds synthesized for this SAR were analogues of **2** where R1 was varied to investigate which alkyl, cycloalkyl and substituted alkyl groups maintained dual 5-HT and NE transport inhibition.

Alkylated 4-aminopiperidines were straightforwardly synthesised by two general routes from *N*-Boc-piperidone (**3**) by reductive amination with either 2-trifluoromethylbenzylamine (**4**) or an alkylamine (**7**) to give amines (**5**) and (**8**), respectively, in good yields (Scheme 1).[7,8] Benzylamino piperidine (**5**) was reductively aminated with either aldehyde or ketone (**6**). Conversely alkylaminopiperidine (**8**) was reductively aminated with either 2-trifluoromethylbenzaldehyde (**9**) or benzylated with 2-trifluoromethylbenzyl bromide (**10**). Both routes provided compounds (**11**–**23**) whose transporter affinity is tabulated below (Table 1). Tartrate or fumarate salts of the secondary amines were routinely prepared and affinity data has been generated on these salts (Tables 1–4).

Taking advantage of the availability of 4-bromobutyronitrile and trifluoro-methanesulfonic acid 2-trifluoromethoxy-ethyl ester,[9] benzylamino piperidine (**5**) was

Keywords: Serotonin; Norepinephrine; Reuptake; Transporter; Inhibitors; Aminopiperidines.
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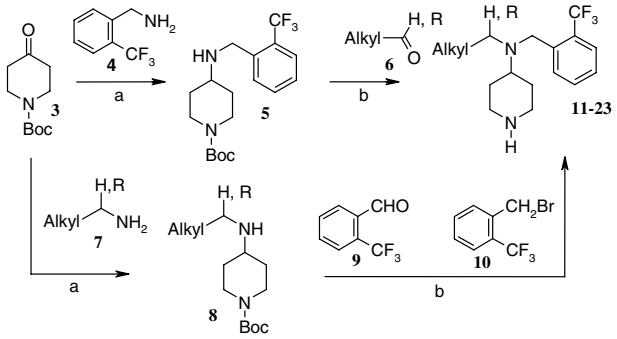


Scheme 1. Reagents: (a) H_2, EtOH, 10% Pd/C, 45–80%, (b) i—RCHO, $Na(AcO)_3BH$, DMF, $ClCH_2CH_2Cl$; ii—TFA, CH_2Cl_2; iii—tartaric acid or fumaric acid MeOH, 15–75%.

alkylated under basic conditions to give the cyano and trifluoromethoxy analogues (**25** and **26**) (Table 1). The trifluoroethyl analogue was made by trifluoroacetylation with trifluoroacetic anhydride, followed by reduction of the trifluoroacetamide (**28**) with borane-THF to give (**27**) (Scheme 2).

The compounds in Scheme 1 were evaluated for their affinity at the 5-HT, NE and dopamine (DA) receptors. neurotransmitter re-uptake (Table 1). Several compounds with nanomolar affinity at SERT and NET were identified. The following SAR conclusions can be drawn: (i) that substitution on an alkyl chain alpha to the 4-amine is detrimental to NE uptake (cf. **19**), however cycloalkyl substitution, for example (**20**) does not impact NE uptake; (ii) branching beta to the 4-amine has less impact and is better tolerated (e.g., **16**, **18** and **21**); (iii) substituting with fluorine at the terminus of an alkyl chain produces compounds with similar activity to the un-fluorinated analogues. An exception to this latter observation is the reduced activity of the trifluoromethoxy analogue (**26**) when compared to the methoxy analogue (**24**).

Having investigated alkyl substituents it was decided to retain a single alkyl chain and investigate the scope of benzyl substitution.

The compounds in Table 2 were synthesized via *N*-Boc-piperidine (**8**) (Scheme 1) and converted to compounds **28–43** by reductive amination with the requisite aryl aldehyde.

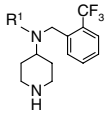
Of the monosubstituted analogues synthesised (Table 2), 3- or 4-substitution (e.g., **29**, **30**, **32**, **33**, **35**, **36**) was detrimental to NE transporter affinity in comparison to **16**. However on replacing the trifluoromethyl with methyl (**34**), chloro (**40**), methylthio (**41**) or trifluormethoxy (**42**) groups, dual inhibition was retained.

Affinity at the dopamine transporter was more prevalent with certain substitution patterns, thus the 3-methyl (**35**), 3-fluoro (**38**) and 2-chloro (**40**) substituents all had inhibition of DA transport of less than 100 nM.

Following the limited success of monosubstitution of the aryl moiety a series of disubstituted analogues were synthesized (Table 3). Disubstituted compounds were synthesized analogously to the compounds in Table 2.

Disubstitution was more rewarding than monosubstitution. Thus maintaining methyl, trifluoromethyl or chloro substituents in the 2-position and substituting with

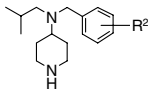
Table 1. Binding affinities at the serotonin, norepinephrine and dopamine transporters compounds **11–27**.



Compound	R1	Salt[a]	5-HT[b,c]	NE[b,c]	DA[b,c]
11	Me–	A	(−40 ± 7%)	(−67% ± 4%)[c]	(3 ± 1%)
12	Et–	A	8 ± 0.2	61 ± 2	(−2 ± 0.2%)
13	*n*-Pr–	A	2.2 ± 0.2	6.5 ± 0.4	(−12 ± 1%)
14	Me_2CH–	A	5.6 ± 0.1	26 ± 2	(−31 ± 3%)
15	*n*-Bu–	A	1.5 ± 0.4	5.1 ± 0.5	(−31 ± 2%)
16	Me_2CHCH_2–	A	1.4 ± 0.1	3.2 ± 0.3	210 ± 30
17	c-$C_3H_5CH_2$–	A	1.5 ± 0.1	6 ± 1	(−27 ± 0.1%)
18	Me_3CCH_2–	A	4.3 ± 0.5	2.7 ± 0.1	160 ± 14
19	Et_2CH–	A	6.8 ± 1.2	86 ± 2	(−41 ± 0.4%)
20	c-C_5H_9–	A	3.6 ± 0.1	4.1 ± 0.1	(−45 ± 0.7%)
21	Et_2CHCH_2–	A	6.9 ± 0.6	6.1 ± 1.5	(−39 ± 1%)
22	$MeO(CH_2)_2$–	A	2.5 ± 0.03	8.3 ± 0.2	(4 ± 3%)
23	$F_3C(CH_2)_2$–	A	2.8 ± 0.1	9.8 ± 0.7	(−35 ± 3%)
24	$MeO(CH_2)_3$–	B	2.2 ± 0.2	6.8 ± 0.7	(−8 ± 2%)
25	$NC(CH_2)_3$–	B	0.58 ± 0.05	21 ± 2	(−15 ± 1%)
26	$F_3CO(CH_2)_2$–	B	17 ± 0.5	51 ± 1	(−8 ± 1%)
27	F_3CCH_2–	B	4.6 ± 0.4	33 ± 2	(−22 ± 2%)

[a] A, fumarate; B, tartrate.
[b] K_i, nM.
[c] % inhibition at 1 μM. Binding affinities and displacement measurements were done in triplicate.[4]

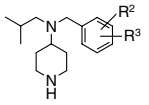
Table 2. Binding affinities at the serotonin, norepinephrine and dopamine transporters



Compound	R2	Salt[a]	5-HT[b,c]	NE[b,c]	DA[b,c]
16	2-CF3	A	1.4 ± 0.1	3.1 ± 0.3	200 ± 30
28	H	FB[d]	8.4 ± 0.6	91 ± 6.4	(−60.4 ± 0.8%)
29	3-CF_3	A	0.26 ± 0.02	255 ± 13	(−63.9 ± 0.6%)
30	4-CF_3	A	0.07 ± 0.01	300 ± 7	(−28.5 ± 2.2%)
31	2-CN	A	1.2 ± 0.04	42 ± 2	(−10.3 ± 1.6%)
32	3-CN	A	0.48 ± 0.07	690 ± 22	201 ± 32
33	4-CN	A	0.28 ± 0.01	190 ± 2	(−24.2 ± 0.6%)
34	2-Me	A	1.5 ± 0.4	3.3 ± 0.2	240 ± 19
35	3-Me	A	2.2 ± 0.1	150 ± 21	98 ± 2.9
36	4-Me	FB	0.99 ± 0.10	69 ± 3	(−60.4 ± 1.4%)
37	2-F	A	(−43.9 ± 4.9%)	15 ± 0.1	330 ± 5.7
38	3-F	A	(−39 ± 3.7%)	43 ± 1	86.5 ± 2.8
39	4-F	A	1.9 ± 0.2	78 ± 12	200 ± 7.2
40	2-Cl	A	1.6 ± 0.1	1.4 ± 0.1	83 ± 3
41	2-MeS	A	1.1 ± 0.2	3.3 ± 0.2	(−17.5 ± 0.1%)
42	2-OCF_3	A	2.2 ± 0.2	7.1 ± 0.3	(−16.4 ± 0.3%)
43	2-MeO	A	15 ± 1	145 ± 10	(4.0 ± 4.0%)

[a] A, fumarate; B, tartrate.
[b] K_i, nM.
[c] % inhibition at 1 μM. Binding affinities and displacement measurements were done in triplicate.[4]
[d] Free base.

Table 3. Binding affinities at the serotonin, norepinephrine and dopamine transporters



Compound	R2	R3	Salt[a]	5-HT[b,c]	NE[b,c]	DA[b,c]
16	2-CF_3	H	A	1.4 ± 0.1	3.2 ± 0.3	210 ± 30
44	2-CF_3	5-F	A	7.9 ± 0.9	3.4 ± 0.1	(−19 ± 2%)
45	2-MeO	4-MeO	A	2.2 ± 0.2	1060 ± 30	(1.8 ± 1.6%)
46	2-F	4-F	A	3.1 ± 0.40	20 ± 2.3	580 ± 40
47	2-Me	4-Me	A	0.39 ± 0.12	4.8 ± 0.3	(−16 ± 1%)
48	2-CF_3	6-F	A	4.1 ± 0.40	6.0 ± 0.8	(−18 ± 2%)
49	2-MeO	5-F	A	1.4 ± 0.14	42.1 ± 2	(−2 ± 1.8%)
50	2-CF_3	4-F	A	0.30 ± 0.1	1.8 ± 0.3	190 ± 20
51	2-Cl	4-Cl	A	0.96 ± 0.1	2.0 ± 0.2	230 ± 20
52	2-Cl	3-CF_3	A	0.48 ± 0.1	420 ± 18	(−37 ± 3%)
53	2-Cl	5-Cl	A	2.1 ± 0.2	5.5 ± 0.30	(−22 ± 3%)
54	2-Cl	5-CF_3	A	9.6 ± 1	175 ± 9	(−11 ± 3%)
55	2-F	4-CF_3	A	5.8 ± 1	2.2 ± 0.1	120 ± 20

[a] A, fumarate; B, tartrate.
[b] K_i, nM.
[c] % inhibition at 1 μM. Binding affinities and displacement measurements were done in triplicate.[4]

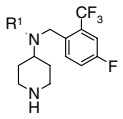
fluorine, methyl or chlorine produced potent dual inhibitors (e.g., **47**, **50**). Notable exceptions are the 2,4-dimethoxy analogue (**45**) which retained SERT affinity (K_i vs SERT = 2.2 nm) but had much reduced NET affinity (K_i vs NET > 1 μM) and the trifluoromethyl analogues (**52** and **54**) which also had reduced NET affinity of K_i = 419 nm and 175 nm, respectively.

From this exercise the 4-fluoro-2-trifluoromethyl substitution pattern was selected for optimization towards dual SERT and NET inhibition and tolerance to alkyl chain modification was reinvestigated.

Alkyl and alkoxy alkyl analogues (**65**–**72**) were synthesized by reductive amination with *N*-Boc protected benzylamine (**60**) with selected carboxaldehydes followed by deprotection.

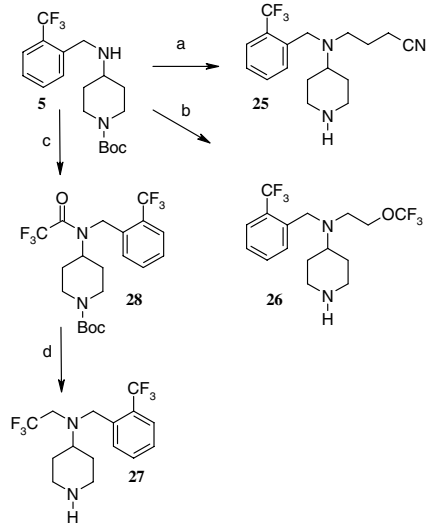
Additional nitrile analogues (Scheme 3) were synthesized to improve upon the NET affinity of **25**. The

Table 4. Binding affinities at the serotonin, norepinephrine and dopamine transporters

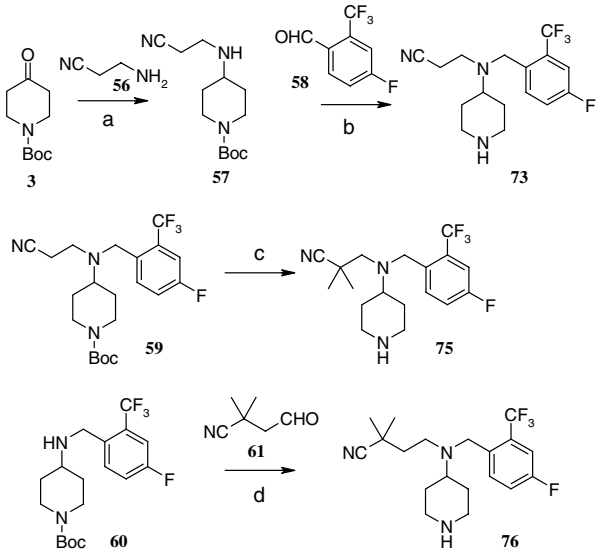


Compound	R1	Salt[a]	5-HT[b,c]	NE[b,c]	DA[b,c]
50	Me_2CHCH_2–	A	0.3 ± 0.1	1.8 ± 0.3	200 ± 20
65	*n*-Pr–	A	0.8 ± 0.2	3.6 ± 0.5	(−21 ± 3%)
66	*n*-Bu–	A	1.3 ± 0.1	8.3 ± 1.4	(−32 ± 2%)
67	c-$C_3H_5CH_2$–	A	0.8 ± 0.1	6.1 ± 0.5	(−26 ± 2%)
68	c-$C_3H_5CH_2$–	B	0.4 ± 0.05	6.5 ± 0.7	(−22 ± 2%)
69	c-$C_4H_7CH_2$–	B	2.5 ± 0.7	3.1 ± 0.5	(−45 ± 2%)
70	$MeO(CH_2)_3$–	B	1.1 ± 0.3	5.4 ± 0.8	(−7 ± 0.2%)
71	$EtO(CH_2)_2$–	B	2.8 ± 0.1	9.6 ± 1.0	(−3 ± 0.1%)
72	$Me_2CHO(CH_2)_2$–	B	3.0 ± 0.6	9.7 ± 0.6	(5 ± 0.5%)
73	$NC(CH_2)_2$–	B	0.4 ± 0.05	13.3 ± 1.5	(−4 ± 0.5%)
74	$NC(CH_2)_3$–	B	0.4 ± 0.05	13.3 ± 1.5	(10 ± 1.2%)
75	$Me_2(CN)CCH_2$–	B	4.2 ± 0.3	15.9 ± 1.2	(−17 ± 0.6%)
76	$Me_2(CN)C(CH_2)_2$–	B	0.7 ± 0.05	6.2 ± 0.4	(−23 ± 2%)
77	$HO(CH_2)_2$–	A	3.1 ± 0.2	95.9 ± 6.3	(−7 ± 1%)
78	$Me_2(OH)CCH_2$–	B	4.0 ± 0.5	4.2 ± 0.3	(−8 ± 1%)
79	$Me_2(OH)C(CH_2)_2$–	B	5.0 ± 0.3	(−23 ± 1.3%)	(1.3 ± 0.9%)

[a] A, fumarate; B, tartrate.
[b] K_i, nM.
[c] % inhibition at 1 μM. Binding affinities and displacement measurements were done in triplicate.[4]



Scheme 2. Reagents: (a)—i $Br(CH_2)_3CN$, K_2CO_3, CH_3CN, 45%; ii—TFA, CH_2Cl_2, 87%, (b) i—$CF_3O(CH_2)_2OSO_2CF_3$, K_2CO_3, CH_3CN 63%; ii—TFA, CH_2Cl_2 96%; iii—tartaric acid, MeOH, 87%, (c) i—$(CF_3CO)_2O$, DMAP, Et_3N, CH_2Cl_2, 81%, (d) i—BH_3, THF, 70%; ii—TFA, CH_2Cl_2, tartaric acid, MeOH, 39%.



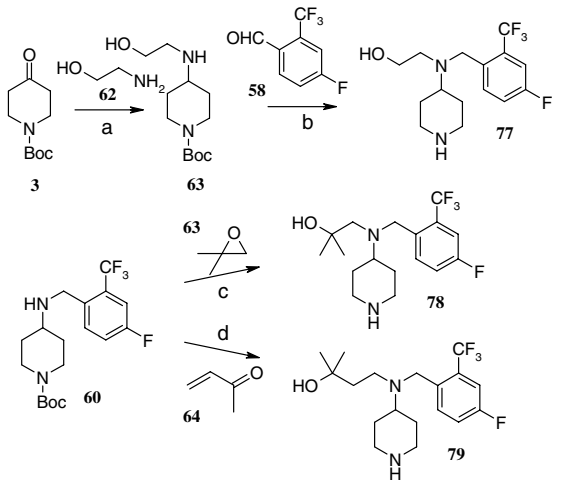
Scheme 3. Reagents: (a) i—**56**, $Na(OAc)_3BH$, THF, 70%, (b) **58**, $Na(OAc)_3BH$, THF; iii–TFA, CH_2Cl_2; iv—tartaric acid, MeOH, 38% for steps ii–iv, (c) i—LDA, MeI, THF, 32%; ii—TFA, CH_2Cl_2; iii—tartaric acid MeOH, 20% for steps ii–iii, (d) i—**61**, $Na(OAc)_3BH$, THF, 97%; ii—TFA, CH_2Cl_2; iii—tartaric acid MeOH, 66% for steps ii–iii.

cyanoethyl analogue (**73**) was synthesized from *N*-Boc-piperidone (**3**) by consecutive reductive aminations with aminopropionitrile (**56**) to give protected hydroxyethylamino piperidine (**57**) and then 4-fluoro-2-trifluoromethylbenzaldehyde (**58**) and subsequent deprotection.

Di-alkylation alpha to the nitrile group of (**59**) with LDA and methyl iodide, followed by deprotection with trifluoroacetic acid produced (**75**).

The higher homologue of (**75**) was obtained via reductive amination with 2,2-dimethyl-4-oxobutyronitrile[10] (**61**) followed by deprotection to give (**76**) (Scheme 3).

Seeking groups with comparable hydrogen bond accepting capability to the nitrile function, prompted the synthesis of (**77**–**79**) (Scheme 4).[11] These were synthesized according to Scheme 4. Thus *N*-Boc piperidone (**3**) was



Scheme 4. Reagents: (a) i—**62**, $Na(OAc)_3BH$, THF, 70%, (b) **58**, $Na(OAc)_3BH$, THF; iii—TFA, CH_2Cl_2; iv—fumaric acid, MeOH, 38% for steps ii–iv, (c) i—**63**, $LiClO_4$, MeOH, 65 °C, 71%; ii—TFA, anisole, CH_2Cl_2, 92%; iii—tartaric acid, MeOH, 99%, (d) i—**64**, $CHCl_3$, 99%; ii—MeMgCl, THF, 92%; iii—TFA, CH_2Cl_2; iv—tartaric acid, MeOH, 58% for steps iii–iv.

reductively aminated with ethanolamine (**62**) to give **63**, followed by reductive amination with aldehyde **58** and deprotection to give alcohol **77**. Benzylamino piperidine **60** was alkylated with epoxide **63** to give a tertiary alcohol (**78**). The higher homologue of **78** was prepared by conjugate addition to ketone **64** followed by Grignard reaction with methyl magnesium chloride to give (**79**).

Maintaining the aryl substitution as 4-fluoro-2-trifluoromethyl showed that of the alkyl chains examined the activity paralleled that of the analogues in Table 1. Improved NET inhibition was not observed with the analogues in Table 4, however the compound having the closest affinity to the isobutyl side chain was the cyclobutylmethyl analogue (**69**). However (**69**) had weaker SERT inhibition than (**16**).

Of the nitrile analogues synthesized, three showed sub-nanomolar affinity at the 5-HT transporter and one of these (**76**), had the highest NET affinity (K_i vs NET = 6.2 nm) of any nitrile investigated.

The decision to replace the nitrile functionality with an alcohol moiety was also rewarded with good dual activity with (**78**), however the hydroxyethyl (**77**) analogue was one of the least active analogues in this SAR.

As no improvement in NET transporter activity over (**16**) was observed on varying the side chain of the 4-fluoro-2-trifluoromethylbenzyl analogues it was decided to advance (**16**) into in vivo studies. Thus in in vivo microdialysis experiments with (**16**), increases above basal levels of synaptic 5-HT and NE levels of 202 ± 24% and of 249 ± 21%, respectively, at 3 mg/kg po have been demonstrated. Further in vivo studies will be published elsewhere.

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