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# Second generation *N*-(1,2-diphenylethyl)piperazines as dual serotonin and noradrenaline reuptake inhibitors: Improving metabolic stability and reducing ion channel activity

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ABSTRACT

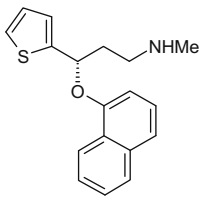
New *N*-(1,2-diphenylethyl)piperazines **6** are disclosed as dual serotonin and noradrenaline reuptake inhibitors (SNRI) which may have potential in treating stress urinary incontinence (SUI). In this Letter, we present new data for SNRI PF-526014 (**4**) including performance in a canine in vivo model of SUI, cardiovascular assessment, pharmacokinetics in dog and determination of the primary routes of metabolism in vitro. Starting from **4**, detailed structure activity relationships established that potent dual SNRIs could be achieved by appropriate substitution of the phenyl rings (**6**: R; $R^1$) combined with a preferred stereochemistry. From this set of compounds, piperazine (−)-**6a** was identified as a potent and selective dual SNRI with improved metabolic stability and reduced ion channel activity when compared to **4**. Based on this profile, (−)-**6a** was selected for further evaluation in a preclinical model of SUI.



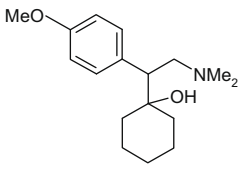
Dual serotonin (5-HT) and noradrenaline (NA) reuptake inhibitors (SNRI) have proven to be an effective treatment for a number of indications including depression, anxiety disorders, fibromyalgia, painful peripheral neuropathy and stress urinary incontinence.[1,2]

Stress urinary incontinence (SUI) is the loss of urine coincident with an increase in intra-abdominal pressure on the bladder that exceeds the urethral resistance. Examples of triggers of involuntary leakage of urine are coughing, sneezing, laughing and physical exercise. There are believed to be 13 million sufferers of SUI in the US and very few seek treatment.[3] Until recently, there were no pharmacotherapies licensed for SUI and treatment was limited to the off-label use of non-selective α-adrenergics (urethral tone), tricyclic antidepressants (urethral tone), β-adrenergics (bladder relaxant) and estrogens (reverses atrophy).[4] In 2004, Eli Lilly introduced dual SNRI duloxetine (**1**) as the first licensed drug therapy specifically for the treatment of moderate to severe SUI. Dual SNRI venlafaxine (**2**) has also shown potential utility as a treatment for SUI.[5]

In the context of treating SUI, SNRIs are believed to work by blocking reuptake of 5-HT and NA in Onuf's nucleus in the sacral spinal cord.[4] Pudendal motor neurons located in Onuf's nucleus regulate the urethral striated muscle sphincter and Onuf's nucleus has a high density of 5-HT and NA receptors.[4] Furthermore, it has been reported that the prevention of urine leakage could be mediated by stimulation of central 5-$HT_2$ and $\alpha_1$ adrenergic receptors resulting in more effective closure of the urethral sphincter.[6]




**1**: duloxetine




**2**: venlafaxine

The search for potent and selective SNRIs has identified duloxetine (**1**),[7] venlafaxine (**2**),[8] desvenlafaxine[9] and milnacipran[10] which are all marketed drugs. Furthermore, several small molecule

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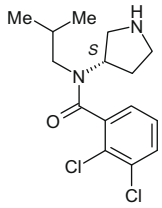
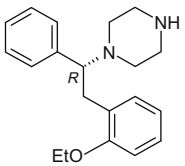
SNRIs have been reported to be in early clinical development or undergoing preclinical optimisation and evaluation.[2,11] Our own efforts have identified PF-184298 (**3**)[12] which demonstrated robust efficacy in a preclinical canine model of SUI and was selected for clinical development.[13] Along with benzamide **3**, we have disclosed additional SNRIs based upon alternative chemical templates[14–19] including PF-526014 (**4**).[20] Piperazine **4** is a potent dual SNRI with excellent selectivity over inhibition of dopamine (DA) reuptake (DRI), weak inhibition of CYP450 enzymes, good central nervous system (CNS) permeability, and minimal binding activity at the hERG channel. However, **4** has moderate metabolic stability in vitro in human liver microsomes (HLM) and modest ion channel activity as measured by binding to representative $Na^+$ and $Ca^{2+}$ channels.




**3**: PF-184298




**4**: PF-526014

In this Letter, we present previously undisclosed data for **4** including performance in a canine in vivo model of SUI, cardiovascular (CV) assessment, pharmacokinetics in dog and determination of the primary routes of metabolism in vitro. In addition, we disclose our efforts to identify second generation dual SNRIs from this *N*-(1,2-diphenylethyl)piperazine template **6** which have improved metabolic stability and reduced ion channel activity.

The evaluation of **4** in a preclinical in vivo canine model of SUI showed a robust dose-dependant response in improving urethral tone that was at least as equivalent to duloxetine (**1**)[13] and PF-184298 (**3**)[12] at similar free plasma concentration of drug.[21] Piperazine **4** increased peak urethral pressure (PUP) by 38 ± 4% at a free plasma concentration of 2.7 nM (Fig. 1). The haemodynamic and electrophysiological effects of **4** were examined in the isoflurane anaesthetised dog ($n = 4$) using a stepped intravenous infusion regimen which achieved free plasma concentrations of 30, 150, 400 and 1710 nM. The observed effects were consistent with the primary mode of action of an SNRI in this model.[22]

The metabolic stability of **4** was determined in HLM where **4** has a half-life ($T_{1/2}$) stability of 70 min. The major metabolite was identified as O-deethylation of the 2-OEt group to give phenol **5** (Fig. 2).[23] Several minor metabolites were due to mono-oxidation of the piperazine ring. The metabolism of **4** was investigated in

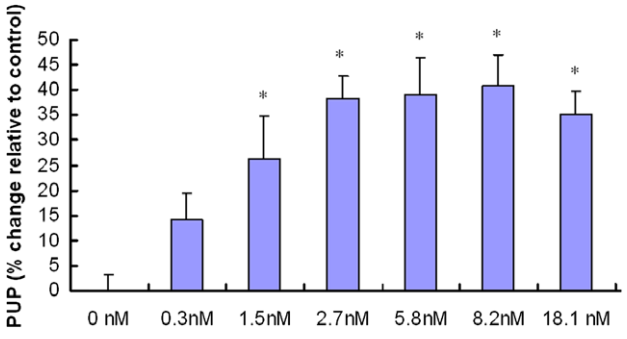
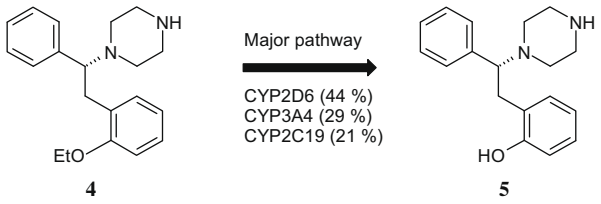



**Figure 1.** The effect of **4** on peak urethral pressure (PUP) as percent change relative to control in the female anaesthetised dog ($n = 5$; iv infusion to steady state plasma concentration). Each bar represents the mean response ± SEM versus mean free plasma concentration. Significance relative to control noted thus $^*P$ <0.05. Dog functional potency for **4**: dSRI $IC_{50}$ = 13 nM (platelet, $n = 13$); dNRI $IC_{50}$ = 27 nM (carotid artery, $n = 16$).




**4** **5**

**Figure 2.** In vitro metabolism of **4** in HLM.

individual CYP450 recombinant enzymes which identified that CYPs 2D6, 3A4 and 2C19 ($T_{1/2}$ 2, 20, 60 min, respectively) should be the major CYP450 enzymes contributing to the CYP-mediated clearance of **4**. Phenol **5** was subsequently shown to be a potent dual SNRI (Table 1) although single dose pharmacokinetics in dog showed minimal systemic exposure compared to parent (**4**:**5**, ratio of $C_{max}$ >100:1).

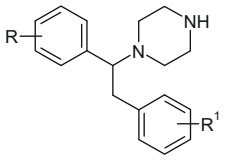
We proposed that second generation 4-piperazines **6** would benefit from the blocking of sites vulnerable to metabolism as this would help to improve metabolic stability. Suitable modifications of this template **6** would be to exchange the 2-OEt group of **4** for groups less prone to oxidative O-dealkylation and to introduce F-atoms to prevent aromatic hydroxylation. In addition, a decrease in compound lipophilicity was also likely to improve metabolic stability and decrease ion channel activity; this reduction in lipophilicity would need to be balanced with retaining good CNS permeability. Hence, a detailed investigation of the structure activity relationships (SAR) of the 4-piperazines **6** was undertaken with the primary objective of retaining dual SNRI activity whilst optimising metabolic stability and reducing ion channel affinity.

4-Piperazines **6** (Table 1) were conveniently prepared in a three-step sequence as described previously (Scheme 1).[20] Condensation of benzaldehydes **7**, 1-Boc-piperazine **8** and benzotriazole in refluxing PhMe with azeotropic removal of water gave intermediate **9**, which was not isolated, but added directly as a solution to the relevant benzylic Grignard or zinc reagent to afford **10**.[24] Deprotection of the *N*-Boc amines **10** with TFA furnished the target compounds **6**. Aryl ethers **6e** and **6j** were prepared from the corresponding aryl iodides **11** by copper-catalysed coupling with the appropriate aliphatic alcohol to give **12**.[25] The four pairs of single enantiomers (Table 1) were prepared by separation of the corresponding racemic piperazines **6a**, **6g**, **6r** and **6t** by chiral HPLC. Phenol **5** was prepared from **4** by chemical O-deethylation with $BBr_3$.

Target compounds **4**–**6** (Table 1) 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.[16] Compound lipophilicity was assessed by calculation of partition coefficients ($c \log P$; BioByte software v4.3). Selected compounds were then screened for metabolic stability in HLM, for CYP2D6 inhibition, and binding to the potassium hERG and sodium TTX-S channels as a measure of ion channel activity.

The SARs were initially focused around replacing the 2-OEt of **4** with alternative 2-alkyloxy groups **6a–e**. Only the 2-OMe ether **6a** retained good dual SNRI activity along with minimal ion channel activity. Cyclising the ethoxy group into a ring as 2,3-dihydrobenzofuran **6f** also possessed minimal hERG activity but was accompanied by an erosion in NRI activity; hence **6f** was a potent SRI with >40-fold selectivity over NRI. Further SAR was directed at exploring the introduction of F-atoms both onto the group at the 2-position **6g–h**, directly onto the ring as a second substituent **6i–j**, and as a combination of these two strategies **6k**. Several groups were accommodated with 2-$OCHF_2$ **6g** being superior. Substitution on

**Table 1**
In vitro inhibition of monoamine reuptake,[a,b] human liver microsomal stability,[c] CYP2D6 inhibition, sodium (TTX-S) and potassium (hERG) binding activity for piperazines **4**–**6**[d]




**4-6**

| Compound[d] | R | $R^1$ | *c* log *P* | SRI $K_i$ (nM) | NRI $K_i$ (nM) | DRI $K_i$ (nM) | HLM $T_{1/2}$ (min) | CYP2D6i $IC_{50}$ (nM) | $Na^+$, TTX-S $IC_{50}$ (nM) | $K^+$, hERG $IC_{50}$ (nM) |
|---|---|---|---|---|---|---|---|---|---|---|
| **1**[e] | — | — | 4.3 | 5 | 45 | 435 | | | | |
| **3**[e] | — | — | 3.6 | 6 | 21 | 544 | >120 | >30,000 | 8550 | 20,000 |
| (−)-(*R*)-**4**[e] | H | 2-OEt | 4.2 | 10 | 12 | 2650 | 70 | 30,000 | 790 | 6950 |
| (−)-(*R*)-**5** | H | 2-OH | 3.0 | 8 | 58 | 2070 | | >30,000 | 11,500 | >10,000 |
| **6a** | H | 2-OMe | 3.7 | 4 | 18 | >10,000 | | | 8740 | 41,000 |
| **6b** | H | 2-O*n*Pr | 4.7 | 18 | 31 | 1950 | 46 | | | 5840 |
| **6c** | H | 2-O*i*Pr | 4.5 | 18 | 22 | >3160 | 46 | | | 6370 |
| **6d** | H | 2-OcPr | 4.3 | 19 | 22 | 1390 | | | | 6400 |
| **6e** | H | 2-$OCH_2$cPr | 4.6 | 19 | 25 | 1400 | 84 | | | 2960 |
| **6f** | H | 2,3-$OCH_2CH_2$– | 3.7 | 8 | 340 | >3160 | | | | 21,400 |
| **6g** | H | 2-$OCHF_2$ | 4.1 | 8 | 28 | 6560 | >120 | 30,000 | 4700 | 10,700 |
| **6h** | H | 2-$OCF_3$ | 4.8 | 25 | 77 | >10,000 | 109 | 3600 | 2100 | 10,900 |
| **6i** | H | 2-OMe; 3-F | 3.75 | 2 | 84 | 6810 | >120 | >30,000 | 3810 | 20,800 |
| **6j** | H | 2-OMe; 6-F | 3.95 | 9 | 27 | 2370 | 93 | | | 8550 |
| **6k** | H | 2-$OCHF_2$; 6-F | 4.4 | 19 | 58 | >3160 | | | 1830 | 10,400 |
| **6l** | 2-F | 2-OMe | 3.8 | 10 | 97 | >10,000 | >120 | 17,700 | 3840 | 40,100 |
| **6m** | 3-F | 2-OMe | 3.8 | 8 | 30 | 4060 | >120 | | 4540 | >22,500 |
| **6n** | 4-F | 2-OMe | 3.8 | 8 | 100 | 4870 | >120 | 12,100 | 4830 | 16,000 |
| **6o** | 2-F | 2-$OCHF_2$ | 4.3 | 17 | 46 | >10,000 | 91 | | 3370 | 6500 |
| **6p** | 3-F | 2-$OCHF_2$ | 4.3 | 12 | 26 | 3460 | 117 | | 15,200 | 8240 |
| **6q** | 4-F | 2-$OCHF_2$ | 4.3 | 9 | 40 | 1760 | 92 | | 3660 | 9120 |
| **6r** | 2-F | 2-$OCF_3$ | 4.9 | 21 | 46 | >10,000 | >120 | | 3270 | 7600 |
| **6s** | 3-F | 2-$OCF_3$ | 4.9 | 16 | 30 | 4900 | >120 | | 3990 | 6110 |
| **6t** | 4-F | 2-$OCF_3$ | 4.9 | 15 | 51 | 5090 | >120 | | 3140 | 8050 |
| (+)-**6a** | H | 2-OMe | 3.7 | 16 | 83 | 4950 | >120 | 20,000 | 4470 | 39,000 |
| (−)-**6a** | H | 2-OMe | 3.7 | 2 | 12 | 2940 | >120 | >30,000 | 5400 | 22,900 |
| (+)-**6g** | H | 2-$OCHF_2$ | 4.1 | 6 | 30 | 3290 | 72 | 3000 | 2970 | 12,700 |
| (−)-**6g** | H | 2-$OCHF_2$ | 4.1 | 27 | 180 | 3160 | 44 | 4900 | 4890 | 15,300 |
| (+)-**6r** | 2-F | 2-$OCF_3$ | 4.9 | 34 | 116 | >3160 | 109 | 3100 | 1410 | 2050 |
| (−)-**6r** | 2-F | 2-$OCF_3$ | 4.9 | 24 | 17 | >3160 | >120 | 3500 | | 760 |
| (+)-**6t** | 4-F | 2-$OCF_3$ | 4.9 | 36 | 200 | 2490 | 81 | 1400 | 2960 | 9640 |
| (−)-**6t** | 4-F | 2-$OCF_3$ | 4.9 | 24 | 30 | 2620 | >120 | 3600 | 1420 | 4950 |

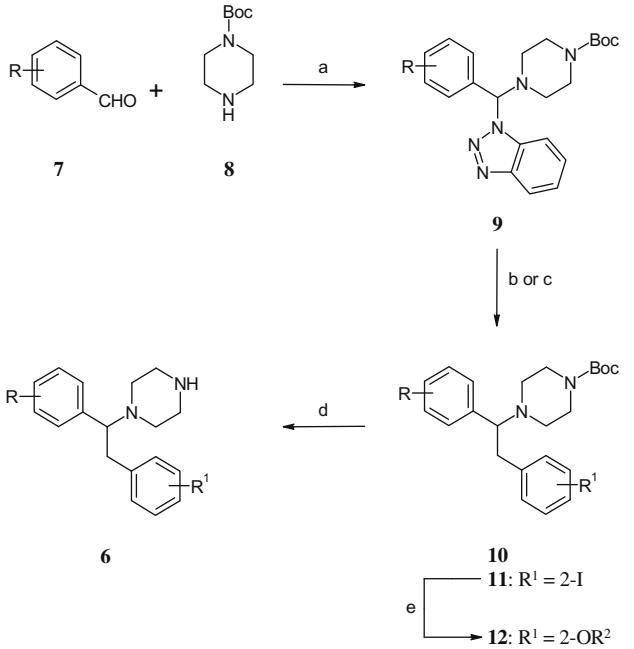
[a] See Ref. 16 for details of assay conditions.
[b] Monoamine reuptake $K_i$ values are geometric means of typically 2–8 experiments. Differences of <2-fold should not be considered significant.
[c] Maximum measurable half-life was 120 min.
[d] Compounds **6** are racemic unless defined otherwise. Single enantiomers are designated by the sign of optical rotation, $[\alpha]_D$.
[e] Data is presented for comparison in a common assay format.

the aryl ring (R) was investigated by the introduction of a F-atom at the 2-, 3- and 4-positions in combination with preferred 2-aryloxy groups ($R^1$ = OMe; $OCHF_2$) to give **6l**–**q**. However, these offered little advantage compared to the parent structures (**6a** vs **6l–n** and **6g** vs **6o–q**). Although the 2-$OCF_3$ group had modest SNRI activity as a single substituent **6h**, this activity could be boosted by up to 2-fold when combined with a F-atom on the distal aryl ring (**6h** vs **6r–t**).

Analysis of the multiple SARs from this compound set highlighted some general trends: (1) All compounds had good SRI activity (**6a–t**: $K_i \leqslant 25$ nM); (2) Good NRI activity could be obtained (**6a**, **c**–**e**,: $K_i \leqslant 25$ nM) but this activity was more sensitive to both the nature and the position of the $R^1$ groups (e.g., **6f**, **6i**), and other substituents on the molecule (R) (e.g., **6l**, **6n**); (3) No compound demonstrated any significant DRI activity (**6a–t**: $K_i$ >1000 nM); (4) CYP2D6 inhibition and binding to the hERG channel was minimal for the more polar examples and generally tracked with increasing lipophilicity; (5) good HLM stability could be achieved through either lowering lipophilicity (e.g., **6a**, **6g**, **6i**, **6l–n**)(**6a** vs **4** vs **6b**) or by blocking sites vulnerable to metabolism (e.g., **6r–t**).

Compounds **6a**, **6g**, **6r** and **6t** were then evaluated as the two single enantiomers (e.g., (+)-**6a** and (−)-**6a**) so as to determine the influence of absolute stereochemistry on SRI, NRI and DRI activity (Table 1). Screening of these separate enantiomers showed one enantiomer possessed more SRI and NRI activity resulting in potent dual SNRI and this trend was observed for all four pairs [(−)-**6a**, (+)-**6g**, (−)-**6r** and (−)-**6t**]. These enantiomers with potent SNRI activity tended to have improved HLM stability but slightly greater affinity for binding to the hERG channel. The SARs for DRI, CYP2D6-i and $Na^+$ channel activity were not dependant on stereochemistry for these compounds.

Pharmacokinetic data for (−)-**6a**, (+)-**6g** and (−)-**6t** was generated in vitro and in vivo in dog (Table 2). These compounds all had some improvement of metabolic stability in vitro in DLM compared to **4**. Following single intravenous administration, plasma clearance of (−)-**6a** and (−)-**6t** was moderate relative to liver blood flow resulting in an elimination half-life of 7.1 and 6.0 h, respectively. The high clearance for (+)-**6g** in excess of liver blood flow was not predicted by DLM stability in vitro and can be attributed to non-microsomal clearance mechanisms. Compounds (−)-**6a**




**Scheme 1.** General synthesis of 4-piperazines **6**. Reagents and conditions: (a) benzotriazole, PhMe, Dean–Stark apparatus, reflux; (b) $ArCH_2MgX$, THF, −78 °C→0 °C, 30 min; (c) $ArCH_2ZnX$, THF, 20 °C; (d) TFA, $CH_2Cl_2$, rt; (e) $R^2OH$, CuI (10 mol %), 1,10-phenanthroline (20 mol %), $Cs_2CO_3$, Reacti-Vial sealed vessel, 90–120 °C.

and (+)-**6g** distribute extensively into tissues as shown by the high volumes of distribution.

Compound (−)-**6a** was then evaluated in additional in vitro pharmacology and pharmacokinetic screens; the results are presented along with the data for **4** (Table 3). Compound (−)-**6a** is a potent dual SNRI with excellent selectivity over DRI (>245-fold). Compound (−)-**6a** had improved metabolic stability in both HLM and human hepatocytes consistent with low predicted clearance, weak CYP450 enzyme inhibition and good membrane permeability as measured by transit performance in Caco-2 cell-line. Compound (−)-**6a** had reduced ion channel activity compared to **4** as measured by binding to representative potassium, sodium and calcium channels. In addition, (−)-**6a** showed minimal off-target activity against a panel of 110 receptors, enzymes and ion channels (Cerep, Bioprint™) with >100-fold selectivity in binding assays for all targets evaluated except for the 5-$HT_7$ ($K_i$ 840 nM) and sigma ($K_i$ 290 nM) receptors. Furthermore, (−)-**6a** was one of the least lipophilic structures of those presented in Table 1.[26] Based on this profile, (−)-**6a** was selected for further evaluation in a preclinical in vivo canine model of SUI.[27]

**Table 2**
In vitro and in vivo[a] dog pharmacokinetic data for **4**, (−)-**6a**, (+)-**6g** and (−)-**6t**

| | **4** ($n$ = 2) | (−)-**6a** ($n$ = 2) | (+)-**6g** ($n$ = 1) | (−)-**6t** ($n$ = 2) |
|---|---|---|---|---|
| DLM, $T_{1/2}$[b] (min) | 4 | 6 | 63 | 17 |
| Dog plasma protein binding (%) | 90 | 75 | 92.5 | 96.5 |
| Intravenous dose (mg/kg) | 0.025 | 0.025 | 0.025 | 0.0075 |
| Elimination half-life, $T_{1/2}$ (h) | 5.1 | 7.1 | 1.8 | 6.0 |
| Plasma clearance, Cl (ml/min/kg) | 30 | 21 | 87 | 19 |
| Volume of distribution, $V_d$ (l/kg) | 13.5 | 13.2 | 13.6 | 7.0 |

[a] Single intravenous administration to male beagle dog.
[b] Dog liver microsomes (DLM). Maximum measurable half-life was 120 min.

**Table 3**
Physicochemical properties, in vitro inhibition of monoamine reuptake, ADME profiles and ion channel affinities of **4** and (−)-**6a**[a]

| | **4** | (−)-**6a** |
|---|---|---|
| *Physicochemical properties* | | |
| Mw | 310 | 296 |
| $c\log P$ | 4.2 | 3.7 |
| $\log D_{7.4}$ | 1.5 | 1.0 |
| TPSA (Å$^2$) | 24 | 24 |
| p$K_a$ | 9.2 and 4.0 | ND[d] |
| *Monoaminine reuptake inhibition*[b] | | |
| SRI, $K_i$ (nM) | 10 | 2 |
| NRI, $K_i$ (nM) | 12 | 12 |
| DRI, $K_i$ (nM) | 2650 | 2940 |
| *ADME profile* | | |
| HLM, $T_{1/2}$ (min) | 70 | >120 |
| H.hepatocytes, $T_{1/2}$ (min) | 80 | 127 |
| CYP2D6 inhibition, $IC_{50}$ (nM) | 30,000 | >30,000 |
| CYP3A4 inhibition, $IC_{50}$ (nM) | 30,000 | 19,400 |
| Caco-2, AB/BA $P_{app} \times 10^{-6}$ cm s$^{-1}$ | 33/36 | 29/37 |
| *Ion channel affinities* | | |
| $K^+$ hERG, $IC_{50}$ (nM) | 6950 | 22,900 |
| $Na^+$ TTX-S, $IC_{50}$ (nM) | 790 | 5400 |
| $Na^+$ site 2, $IC_{50}$[c] (nM) | 450 | 2200 |
| $Ca^{2+}$ L-site (diltiazem), $IC_{50}$[c] (nM) | 730 | ND |
| $Ca^{2+}$ L-site (verapamil), $IC_{50}$[c] (nM) | 5010 | 5900 |
| $Ca^{2+}$ L-site (DHP), $IC_{50}$[c] (nM) | >10,000 | >10,000 |

[a] See Ref. 16 for definition of terms and details of assay conditions.
[b] Monoamine reuptake inhibition $K_i$ values are geometric means of at least four experiments. Differences of <2-fold should not be considered significant.
[c] Data from Cerep (Bioprint™).
[d] ND, not determined.

In conclusion, we have identified second generation dual SNRI *N*-(1,2-diphenylethyl)piperazines **6** which have improved metabolic stability and reduced ion channel activity. Of the strategies explored, reducing overall lipophilicity of the target compounds proved to be more successful in furnishing compounds with an improved balance of in vitro and in vivo activities.

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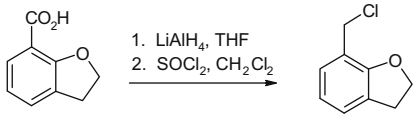
22. Both heart rate (HR) and cardiac contractility (LV+dP/dt) increased at the lowest free plasma concentration (30 nM) by 23 beats/min and 815 mmHg/s, respectively, compared with pre-dose. Thereafter the tachycardia decreased towards pre-dose values and at the highest plasma concentration HR fell rapidly to 27 beats/min below pre-dose values. Similarly, LV+dP/dt fell at free plasma concentrations of 150 and 400 nM and by the highest concentration 1710 nM was 785 mmHg/s below pre-dose levels.
23. Phenol **5** was also the major metabolite in vitro when **4** was incubated with rat and dog liver microsomes.
24. The benzylic halides **13** are commercially available except for **13f** which was prepared as shown.

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