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# Designing rapid onset selective serotonin re-uptake inhibitors. 2: Structure–activity relationships of substituted (aryl)benzylamines

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ABSTRACT

A series of substituted benzylamines **2–48** were prepared as part of a strategy to identify structurally differentiated and synthetically more accessible selective serotonin reuptake inhibitors, relative to clinical candidate **1**. In particular, **44** and **48**; demonstrated low nanomolar potency and good selectivity, in a structurally simplified template and, in vivo, very low Vdu, significantly lower than **l**, and a more rapid $T_{max}$, consistent with our clinical objectives.



Selective serotonin re-uptake inhibitors (SSRIs) have emerged in the last 20 years as a highly important mechanistic class in the management of depression[1] and more recently have emerged as potentially beneficial in numerous other areas[2] including anxiety, panic disorders, and phobia.

In an earlier communication[3] we described our strategy to access SSRIs which demonstrated very rapid elevation of central 5-HT levels, to support rapid onset of efficacy, for use in acute therapy-compatible indications including, for example, pre-menstrual syndrome, obesity and male sexual dysfunction. This work led to the successful identification of our first clinical candidate **1**, which possessed excellent potency, selectivity and pre-clinical pharmacokinetic properties, consistent with our target profile.

As part of our back-up programme to **1**, we wished to identify a compound in alternative chemical space to mitigate the risk of encountering structure-related toxicological issues with the prototype during clinical evaluation. In addition, we wished to identify an alternative lead series with improved synthetic accessibility to more readily allow us to investigate the effect of substitution on potency, selectivity and permeability, as measured in our Caco-2 assay.

In this communication, we wish to describe the successful execution of this plan which involved the design and exploration of a series of substituted (aryl)benzylamines **2–48**, Figure 1. Compounds **2–48** were designed to be structurally less complex expression of **1**, possessing no stereogenic centres, while retaining the key structural features we believed were needed for potency.

Our overall target was to identify an orally bioavailable SSRI ($IC_{50}$) < 10 nM, >100-fold selectivity over dopamine re-uptake inhibition (DRI) and noradrenaline re-uptake inhibition (NRI) possessing high permeability to support both oral delivery and CNS penetration. In addition we were seeking a low Vd compound to support our objectives of rapid $T_{max}$.[4]

While much analysis has been reported on properties which afford good oral absorption,[5] properties which define good passive diffusion across the blood brain barrier (BBB) appear less clearly characterised, though they are generally regarded to be more stringent.[6] Our overall design criteria to support our goals of both good oral bioavailability and high CNS penetration were, therefore; (1) MWt < 400, (2) moderate lipophilicity (log*D* 2–3), (3) low H-bond donor (HBD) count ⩽ 3, (4) low Topological Polar Surface Area (TPSA) < 80Å$^2$, consistent with the parameters applied in the discovery of **1**.

Our first goal, Table 1, was to establish whether high potency[7] and target selectivity, similar to that observed in the conformationally restricted series exemplified by **1** and could be achieved in

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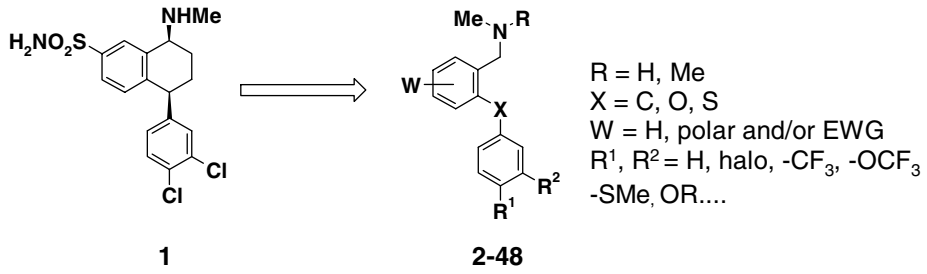
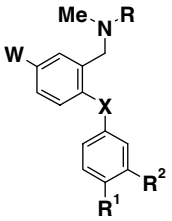



**Figure 1.** Proposed structurally simplified expressions of **1**.

**Table 1**
Human, SRI, DRI, NRI activities and physicochemical properties for phenyl-methanes, ethers and thioethers **2**–**30**




| Compound | R | W | X | $R^1$ | $R^2$ | h-SRI ($IC_{50}$, nM)[a] | h-DRI ($IC_{50}$, nM)[a] | h-NRI ($IC_{50}$, nM)[a] |
|---|---|---|---|---|---|---|---|---|
| **2** | H | H | $CH_2$ | Cl | Cl | 30 | 2000 | 200 |
| **3** | Me | H | $CH_2$ | Cl | Cl | 5 | 320 | 1300 |
| **4**[b] | Me | H | CHMe | Cl | Cl | 40 | NT | NT |
| **5**[b] | Me | H | CHOH | Cl | Cl | 250 | 1800 | 3100 |
| **6**[b] | Me | H | CHOMe | Cl | Cl | >1000 | – | – |
| **7** | Me | H | C=O | Cl | Cl | 50 | 2100 | 8600 |
| **8** | Me | H | $CH_2$ | $-OCF_3$ | H | 45 | – | – |
| **9** | H | H | $CH_2$ | –SMe | H | 4 | 5900 | 7300 |
| **10** | Me | H | $CH_2$ | –SMe | H | 5 | 11,000 | 1300 |
| **11** | H | H | S | $-CF_3$ | H | 70 | 2800 | 6000 |
| **12** | Me | H | S | $-CF_3$ | H | 28 | >10,000 | 9200 |
| **13** | Me | H | S | H | $-CF_3$ | 40 | 9900 | 2000 |
| **14** | Me | H | S | Cl | H | 20 | NT | NT |
| **15** | Me | H | S | H | Cl | 12 | 36 | 50 |
| **16** | Me | H | S | –SMe | H | 22 | 5400 | 640 |
| **17** | Me | H | O | Cl | H | 22 | 100 | 180 |
| **18** | Me | H | O | H | Cl | 190 | 910 | 50 |
| **19** | Me | H | O | Cl | Cl | 11 | 140 | 290 |
| **20** | Me | Br | O | $-CF_3$ | H | 3 | >10,000 | >10,000 |
| **21** | Me | H | O | $-OCF_3$ | H | 7 | 5800 | 6700 |
| **22** | Me | H | O | –OMe | H | 25 | 6400 | 680 |
| **23** | Me | H | O | –OEt | H | 30 | 6400 | 1500 |
| **24** | Me | H | O | –Br | H | 12 | 640 | 760 |
| **25** | Me | H | O | –CN | H | 60 | NT | NT |
| **26** | Me | H | O | –CyP | H | 17 | 4200 | 1400 |
| **27** | Me | H | O | $CH_2$Cyp | H | 660 | 16,000 | 2700 |
| **28** | Me | F | O | –SMe | H | 10 | 7100 | 630 |
| **29** | Me | Cl | O | –SMe | H | 4 | 6100 | 4900 |
| **30** | Me | Br | O | –SMe | H | 2 | 1800 | 7900 |

[a] All assay determination $\geqslant n = 2$. Ref. 7.
[b] Racemate; NT, not tested; Cyp, cyclopropyl.

simple templates, in which there were no stereo centres. Excitingly, the simple diphenymethane[8] analogues **2** and **3** were found to be potent ($IC_{50}$ 30 and 5 nM, respectively). Furthermore, **3** also demonstrated encouraging selectivity over h-DRI (60-fold) and h-NRI (260-fold), demonstrating both high potency and target selectivity over other monoamine transporters could be achieved in this simplified template. Introduction of substitution at the methylene centre **4**–**7** all resulted in a drop in potency. Exploration of the (chloro)phenyl SAR pattern revealed that the 3,4-dichloro substitution pattern, which was generally found to be optimal in **1**,[9] could be replaced with a single 4-substituent. For example, both $-OCF_3$ **8** and –SMe **9**, **10** were found to be well tolerated. In particular, for example, **9** displayed both excellent potency against h-SRI ($IC_{50}$ 4 nM) and selectivity over DRI and NRI (>1000-fold).

A series of phenyl thioethers[10] **11**-**16** were also explored, seeking to develop the SAR from the phenylmethane analogues **2**–**10** in a still more synthetically more accessible series. Disappointingly, however, these analogues tended to be generally less potent or less selective than we ideally sought. For example direct thioether analogue **16**, of phenylmethane **10**, was approximately 5-fold less potent in the SRI assay (22 nM vs 5 nM). Furthermore this phenyl thioether template, in practice, offered only limited additional synthetic accessibility, relative to the phenylmethane series, due to limitations in accessing appropriately substituted thiol precursors.

Phenyl ethers[11] **17**–**30** were next explored, with this series being found to be synthetically the most accessible of those investigated. Generally, 3,4- or 4-substitution on the distal ring was found to give the best balance of potency against SRI and selectiv-

ity over DRI and NRI. For example, p-$CF_3$ **20**, p-$OCF_3$ **21** and p-SMe **28**–**30** all showed excellent potency against SRI and selectivity over DRI and NRI. Other *p*-substituents explored **22**–**27** showed a range of activities with generally good potency retained. As with the phenylmethane analogues **9** and **10** and the phenyl thioether analogue **16**, *p*-SMe substitution on the distal phenyl ring, relative to the amino methyl group, retained excellent potency against SRI and good selectivity, **28**–**30**. In addition, simple lipophilic substitution (W) was also found to be tolerated at C-4 in these analogues.

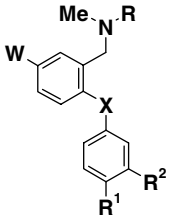
With several low MWt, potent and selective serotonin reuptake inhibitors identified, we next explored introduction of polar substitution, Table 2, (retaining the distal ring substitution patterns which generally afforded the best pharmacology), to attenuate lipophilicity and optimise potency, as described previously.[3] Pleasingly, polar substitution at C-5 was generally well tolerated in the phenyl methane template **31**–**34** with nanomolar potency against SRI observed and good permeability in the Caco-2 assay, despite introduction of primary sulfonamide and carboxamide groups. Unfortunately, selectivity over DRI and NRI was generally only moderate.

Thioethers **35–42** generally showed high levels of potency and selectivity. For example, **38**, **41** and **42** all showed low nM SRI activity and excellent selectivity over both DRI and NRI. Unfortunately, this phenyl thioether series in practice, offered only limited additional synthetic accessibility, relative to the phenylmethane template, due to limitations in readily accessing appropriately substituted thiol precursors.

Overall, substituted phenyl ethers **43**–**48** were generally found to offer the best balance of potency, selectivity and synthetic accessibility. For example, **44**, was found to show excellent potency (SRI $IC_{50}$ 5 nM) and retained target selectivity over both DRI and NRI. The compound also demonstrated excellent permeability in the Caco-2 assay. While we found that, generally, C-5 polar substitution provided the best balance of potency and selectivity in this series, substitution at C-4 was also found to be well tolerated.[12] Progression of **44** and **48** to in vivo PK studies, to benchmark the phenyl ether series against clinical agent **1**, for Vd and $T_{max}$, is shown in Table 3.

Excitingly, both **44** and **48** showed not just equivalent, but significantly reduced, Vd (6 L/Kg vs 19 L/Kg) and Vdu (60 L/Kg and 88 L/Kg vs 1050 L/Kg) relative to **1**. Furthermore, both compounds showed a shorter $T_{max}$ (0.5 h) relative to **1** (2 h) in this study, again, consistent with our clinical objectives of rapid elevation of 5-HT levels. The Vd differences between these two series of compounds

**Table 2**
Human, SRI, DRI, NRI activities and physicochemical properties for amide and sulphonamide-substituted biaryl amines **31–48**




| Compound | R | W | X | $R^1$ | $R^2$ | h-SRI ($IC_{50}$, nM)[a] | h-DRI ($IC_{50}$, nM)[a] | h-NRI ($IC_{50}$, nM)[a] | clog*P* (log*D*) | HBD (TPSA (Å$^2$)) | Caco-2 (%/h) (A-B/B-A) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | | $-SO_2NH_2$ | | | | 1 | 90 | 770 | (2.3) | 3 (83) | 18/7 |
| **31** | H | $H_2NCO$ | $CH_2$ | Cl | Cl | 4 | 105 | 50 | (1.7) | 3 (55) | 31/28 |
| **32** | Me | $H_2NCO-$ | $CH_2$ | Cl | Cl | 3 | 260 | 430 | (3.0) | 2 (46) | >42/>42 |
| **33**[b] | H | $H_2NO_2S-$ | $CH_2$ | Cl | Cl | 6 | 85 | 130 | (2.9) | 3 (81) | 36/31 |
| **34**[b] | Me | $H_2NO_2S-$ | $CH_2$ | Cl | Cl | 60 | 200 | 1050 | 3.5 | 2 (72) | 14/18 |
| **35** | Me | $H_2NO_2S-$ | S | $-CF_3$ | H | 26 | >10,000 | >10,000 | (2.6) | 2 (97) | >42/>42 |
| **36** | Me | $H_2NO_2S-$ | S | H | $-CF_3$ | 30 | >10,000 | 3000 | 3.5 | 2 (97) | NT |
| **37**[c] | Me | $H_2NO_2S-$ | S=O | $-CF_3$ | H | 1900 | >10,000 | >10,000 | 1.6 | 2 (94) | NT |
| **38** | Me | $MeO_2SHN-$ | S | $-CF_3$ | H | 3 | 6900 | 6400 | 4.1 | 1 (83) | NT |
| **39** | Me | $H_2NO_2S-$ | S | –SMe | H | 20 | NT | NT | 3.1 | 2 (122) | NT |
| **40** | H | $MeO_2SHN-$ | S | –SMe | H | 10 | 3800 | 2000 | 3.2 | 2 (117) | 21/22 |
| **41** | Me | $MeO_2SHN-$ | S | –SMe | H | 3 | 1500 | 530 | (2.5) | 1 (108) | 27/41 |
| **42** | Me | $MeO_2S(Me)N-$ | S | –SMe | H | 5 | 3600 | 70 | 3.8 | 0 (99) | NT |
| **43** | Me | $H_2NO_2S-$ | O | $-OCF_3$ | H | 9 | 8000 | >10,000 | 3.3 | 2 (90) | NT |
| **44** | Me | $MeO_2SHN-$ | O | $-CF_3$ | H | 5 | >10,000 | 770 | (2.3) | 3 (67) | 27/31 |
| **45** | Me | $H_2NCO-$ | O | $-OCF_3$ | H | 3 | >10,000 | 4200 | (2.3) | 2 (65) | 27/27 |
| **46** | Me | –CONHMe | O | $-OCF_3$ | H | 10 | >10,000 | 2900 | 3.8 | 1 (51) | NT |
| **47** | Me | $-CONMe_2$ | O | $-OCF_3$ | H | 100 | >10,000 | 510 | 3.6 | 0 (42) | NT |
| **48** | Me | $CH_2NHSO_2Me$ | O | $-OCF_3$ | H | 11 | 5800 | 5600 | 2.1 | 1 (76) | 23/31 |

[a] All assay determination $\geqslant n = 2$. Ref. 7.
[b] C-5 substitution confirmed by NMR studies.
[c] Racemate; NT, not tested.

**Table 3**
Dog pharmacokinetic data for **1**, **44** and **48**

| | h-SRI ($IC_{50}$, nM) | Selectivity over DRI and NRI | Caco-2 (A-B/B-A) (%/h) | log*D* | Amine p$K_a$ | Dog pharmacokinetics (i.v 0.5 mg/kg ($n = 3$), p.o. 1 mg/kg ($n = 3$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cl (ml/min/kg) | Vd (Vdu) (L/Kg) | $T_{1/2}$ (h) | *F* (%) | $T_{max}$ (h) |
| **1** | 1 | 90/770 | 18/7 | 2.3 | 8.5 | 31 | 19 (1050) | 7 | 66 | 2 |
| **44** | 5 | 2200/150 | 27/31 | 2.3 | 9 | 14 | 6 (60) | 4 | — | 0.5 |
| **48** | 11 | 530/520 | 23/31 | 2.1 | 8.5-9[a] | 16 | 6 (88) | 4 | 60 | 0.5 |

[a] estimated value, calculated using experimentally measured data from within phenyl ether series.

is noteworthy. Many factors are known to influence Vd,[13] including lipophilicity and the nature and degree of ionization at physiologically relevant pH. Given their similar physicochemical properties (Log *D* and p$K_a$, Table 3) the magnitude of the Vd differences is perhaps surprising and indicates chemical structure plays a significant, if less predictable, role in influencing Vd.

In summary, a series of non-chiral substituted (aryl)benzylamines have been identified which possess excellent potency in our serotonin transporter assay. These were found to be synthetically more accessible than lead **1**, which allowed rapid exploration of SAR. Overall, the phenyl ether series offered the best balance of target pharmacology, synthetic accessibility, permeability and physicochemistry. In particular, **44** and **48**; demonstrated low nanomolar potency and selectivity in a structurally simplified template, relative to **1**. In vivo, **44** and **48** demonstrated very low Vdu, significantly lower than clinical agent **l**, and a more rapid $T_{max}$. Our work describing the identification of a clinical candidate from within this template will be the subject of our next communication.

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