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Bioorganic & Medicinal Chemistry Letters 16 (2006) 1434–1439
Bioorganic & Medicinal Chemistry Letters

Designing rapid onset selective serotonin re-uptake inhibitors. Part 1: Structure–activity relationships of substituted (1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydro-1-naphthaleneamine

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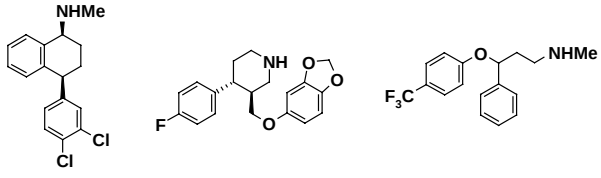
Received 3 October 2005; revised 1 November 2005; accepted 9 November 2005
Available online 28 November 2005

Abstract—A series of sertraline analogues **4**–**39** which possess polar groups on the fused tetrahydronaphthalene ring, targeting reduced V_d as a strategy to reduce T_{max} and increase rate of elevation of central 5-HT levels, were prepared. These studies led to the successful identification of **22a**, which demonstrated equivalent pharmacology and metabolic stability to **1**, but which possessed greatly reduced V_d leading to significantly shorter T_{max}, in rat pharmacokinetic studies.

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] In particular, sertraline (zoloft®) (**1**), paroxetine (paxil®) (**2**) and fluoxetine (prozac®) (**3**), amongst others, have found widespread clinical application in the treatment of this debilitating condition. More recently these agents have emerged as potentially beneficial in numerous other areas[2] including anxiety and panic disorders, obsessive compulsive disorder and phobia (Fig. 1).



(**1**) (**2**) (**3**)

Figure 1. Structures of marketed SSRIs, sertraline (**1**), paroxetine (**2**) and fluoxetine (**3**).

Our own interests in this area lay in targeting SSRIs which demonstrated very rapid elevation of central 5-HT levels, to support rapid onset of efficacy, for use in potentially acute therapy-compatible indications including, for example, pre-menstrual syndrome, obesity and male sexual dysfunction. Pharmacokinetically, current SSRIs tend to be characterised by high volume of distribution (V_d), which results in relatively long T_{max} in the clinic (typically 4–8 h).[1,3] In addition, and key, in-house oral CNS microdialysis studies in rodent demonstrated that systemic T_{max} broadly correlated with time to peak central 5-HT levels[4], suggesting that reducing T_{max} could lead to more rapid elevation in central 5-HT, consistent with our goals in this area.

We reasoned that the key to achieving short T_{max} lay in targeting reduced V_d, which would result in reduced hepatic transit time, and hence shorter T_{max}. Our medicinal chemistry strategy, Figure 2, to achieve lower V_d, focussed on incorporation of small polar groups into

Keyword: Selective serotonin re-uptake inhibitors.
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doi:10.1016/j.bmcl.2005.11.031

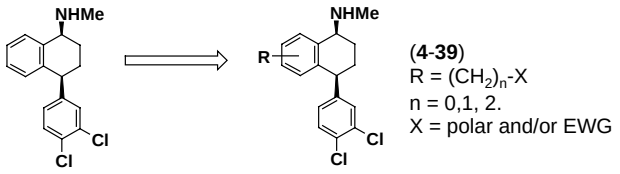


Figure 2. Medicinal chemistry strategy to lower V_d in lead **1**.

lead **1** as a strategy to: (a) reduce intrinsic lipophilicity, (b) disrupt any lipophilic–lipophilic interactions between the membrane phospholipids and the lipophilic region of the fused aryl ring in the tetrahydronaphthalene region of **1** and (c) attenuate pK_a, to reduce the energetically favourable ionic interaction, at physiological pH, between the protonated amine and the negatively charged phospholipid phosphate head-group.

The choice of **1** as our lead was driven by several factors. First, we reasoned that starting with a marketed drug, most of the properties we would ultimately require (e.g., potency, selectivity and CNS penetration) would already be inherent in the structure. Second, starting with a clinically precedented chemotype could diminish the potential for adverse toxicological findings. Third, the compound possessed very attractive physicochemistry; low MWt (~300) low hydrogen bond donor (HBD) count (1) and topographical polar surface area (TPSA) (12 Å^2), providing potential scope to execute our medicinal chemistry strategy to lower V_d without compromising oral absorption or CNS penetration. Fourth, a detailed in-house SAR was available to guide medicinal chemistry design.[5]

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 rapid systemic T_{max} ($\leqslant$1 h) and high CNS penetration.

As the serotonin transporter target is located in the CNS, we recognised the critical need to balance our strategy of incorporation of polar groups to moderate V_d with ensuring this did not compromise the excellent CNS penetration of **1**. While several analyses have been reported on properties which afford good oral absorption,[6] 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.[7] Our overall design criteria to support our goals of both good oral bioavailability and excellent CNS penetration were, therefore; (1) MWt < 400, (2) moderate lipophilicity ($\log D$ 2–3), (3) low HBD count $\leqslant$ 2 and (4) low TPSA < 80 Å^2.

In this first communication,[8] we wish to report the successful application of this strategy, to deliver compounds with significantly lower V_d and shorter T_{max} than the lead compound **1**.

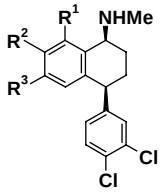
Compounds **4**–**39** were prepared by the methods described previously.[9] Human serotonin, dopamine and noradrenaline transporters were stably expressed in HEK-293 cells. The inhibitory potency at each transporter was quantified through measurement of its ability to inhibit transport and subsequent intracellular accumulation of radiolabelled ligand using an in vitro radiometric assay.

We were excited to find that preliminary SAR investigation of **1** by substitutions at C-8 **4**–**7**, Table 1, showed that polar substitution was relatively well tolerated with high levels of inhibitory activity retained against the serotonin re-uptake transporter (SRI), relative to lead **1**. For example, primary carboxamide **5** was found to be highly potent (SRI, IC_{50} 8 nM), although a small erosion in selectivity over NRI was observed, relative to **1**. Further amide substitution to give the secondary and tertiary amides **6** and **7**, respectively, resulted in a sequential drop in potency relative to the primary carboxamide **5**. Interestingly, the zwitterionic compound **4** also showed respectable SRI activity (IC_{50} 31 nM). Our interest in zwitterionic compounds was principally driven by our belief that such agents would, due to their physicochemistry, possess inherently low V_d, a key aspect of our target profile. Disappointingly, however, despite positional isomerisation of the acid in this series, (**4**, **9** and **36**) we were ultimately unable to identify an agent from this class which possessed our target potency.

Introduction of substitution at C-7 **8**–**29**, Table 1, proved still more encouraging than C-8 substitution, with many analogues identified which possessed our target activity against SRI (<10 nM). For example, methyl ester **8** (IC_{50} 5 nM), nitro analogue **12** (SRI, IC_{50} 2 nM), primary carboxamide **13** (SRI, IC_{50} 2 nM) and secondary carboxamide **14** (SRI, IC_{50} 3 nM) all possessed equivalent primary activity to **1**, with acceptable levels of selectivity over DRI and NRI. Homologation of the primary carboxamide **13**, to **16**, resulted in a small drop in potency against SRI (IC_{50} 10 nM) and an increase in activity against DRI (IC_{50} 29 nM), relative to **13** to give a compound balanced against both SRI and DRI. N-Linked sulfonamide **17** (SRI, IC_{50} 3 nM) was also found to be potent, however, selectivity over DRI and NRI was poor. Homologation gave **18** which demonstrated an approximately equivalent potency against SRI (IC_{50} 10 nM), though still poor selectivity over NRI (ca. 10-fold). Sulfoxide **19** (SRI, IC_{50} 2 nM) and sulfone **20** (SRI, IC_{50} 6 nM) were both highly potent though, again, neither met our selectivity target over DRI. Homologation of the sulfoxide **21** resulted in the >100-fold drop in potency against SRI (IC_{50} 340 nM) relative to **19**, though the level of DRI activity was retained. Primary sulfonamide **22a** showed excellent potency against SRI (IC_{50} 1 nM) and acceptable selectivity over DRI and NRI. Preparation and screening of all four diastereomers of the 7-sulfonamido analogue **22a**–**22d**, Table 2 showed the (1*S*,4*S*)-isomer to possess the highest potency against SRI and selectivity over DRI and NRI activity.[5]

Monomethylation of the primary sulfonamide **23** retained high potency against SRI (IC_{50} 5 nM),

Table 1. Human, SRI, DRI, NRI activities and physicochemical properties for (1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydro-1-naphthaleneamines **1**, **4**–**39**

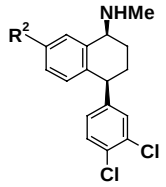


Compounds[a]	R^1	R^2	R^3	h-SRI (IC_{50}, nM)[b]	h-DRI (IC_{50}, nM)[b]	h-NRI (IC_{50}, nM)[b]	MWt	TPSA (Å^2)	HBD	C log *P* (log *D*)
1	H	H	H	3	310	825	306	12	1	5.4 (3.1)
4	$-CO_2H$	H	H	31	540	880	349	49	2	2.8
5	$-CONH_2$	H	H	8	290	1150	348	55	3	3.9
6	–CONHMe	H	H	31	420	1500	362	41	2	4.1
7	$-CONMe_2$	H	H	140	NT	NT	376	32	1	3.8
8	H	$-CO_2Me$	H	5	240	1250	363	38	1	5.3
9	H	$-CO_2H$	H	90	NT	NT	349	49	2	2.8
10	H	$-CH_2CO_2H$	H	30	5100	9600	363	49	2	2.3
11	H	–CN	H	3	100	3200	330	36	1	4.8 (3.4)
12	H	$-NO_2$	H	2	830	2900	350	55	1	5.1
13	H	$-CONH_2$	H	2	170	410	348	55	3	3.9 (2.3)
14	H	–CONHMe	H	3	450	440	363	41	2	4.1 (2.8)
15	H	$-CONMe_2$	H	9	270	270	376	32	1	3.8
16	H	$-CH_2CONH_2$	H	10	29	920	362	55	3	3.7
17	H	$-NHSO_2Me$	H	3	55	60	398	67	2	4.2 (2.2)
18	H	$-CH_2NHSO_2Me$	H	10	90	960	412	67	2	4.0
19[c]	H	–SOMe	H	2	90	2000	367	34	1	4.1 (2.2)
20	H	$-SO_2Me$	H	6	120	2100	383	55	1	3.7
21	H	$-CH_2SOMe$	H	340	89	450	381	34	1	3.9
22a	H	$-SO_2NH_2$	H	1	90	770	384	81	3	3.5 (2.3)
22b[d]	H	$-SO_2NH_2$	H	290	375	310	384	81	3	3.5
22c[e]	H	$-SO_2NH_2$	H	240	90	310	384	81	3	3.5
22d[f]	H	$-SO_2NH_2$	H	25	<1	11	384	81	3	3.5
23	H	$-SO_2NHMe$	H	5	270	1250	398	67	2	4.1 (2.8)
24	H	$-SO_2NMe_2$	H	70	1500	2700	412	58	1	4.5 (3.1)
25	H	*N*(1),2,3-Triazole	H	5	220	650	372	43	1	4.9 (3.2)
26	H	*N*(1),2,4-Triazole	H	4	250	760	372	43	1	4.4 (2.9)
27	H	–OH	H	6	360	680	321	32	2	4.7
28	H	$-CH_2OH$	H	1	20	980	335	32	2	4.3
29	H	$-SO_2NH(CH_2)_2OH$	H	5	100	540	442	87	3	3.9
30	H	H	$-SO_2NH_2$	6	2500	2100	384	81	3	3.5
31[c]	H	H	–SOMe	7	1100	1800	367	34	1	4.1
32	H	H	$-SO_2Me$	54	1400	4200	383	55	1	3.7
33	H	H	$-CONH_2$	13	1300	1100	348	55	3	3.9
34	H	H	–CONHMe	25	3300	5000	376	32	1	3.8
35	H	H	$-CONMe_2$	7	920	11,500	362	41	2	4.1
36	H	H	$-CO_2H$	60	16,700	20,300	349	49	2	2.8
37	$-CONH_2$	H	$-CONH_2$	>1000	NT	NT	391	98	5	
38	H	$-NHSO_2Me$	$-CONH_2$	24	3600	2100	441	110	4	2.6
39	H	$-NHSO_2Me$	$-CO_2H$	65	12,900	9100	442	104	3	2.5

NT, not tested.
[a] All compounds are single (1*S*,4*S*)-enantiomers.
[b] All assay determination $\geqslant n = 2$.
[c] Diastereomeric at sulfoxide centre.
[d] (1*S*,4*R*)-isomer.
[e] (1*R*, 4*R*)-isomer.
[f] (1*R*,4*S*)-isomer.

however, dimethylation (unlike in the carboxamide series **13**–**15**) led to an unacceptable dropoff in potency (IC_{50} 70 nM). Heterocycles were also found to be generally tolerated at C-7. For example, both isomeric triazoles **25** and **26** were found to be potent against serotonin re-uptake inhibition (IC_{50} 5 and 4 nM, respectively). Both these N-linked heterocycles also showed low HBD count (1) and a significantly reduced C log *P*,

Table 2. Comparative potency, permeability and CNS penetration profiles for (1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydro-1-naphthaleneamines **1**, **13**, **14**, **22** and **23**



Compounds[a]	R^2	h-SRI (IC_{50}, nM)	Selectivity over DRI	Selectivity over NRI	log *D* (pH 7.4)	pK_a	MWt	TPSA(Å^2)/HBD	Caco-2 (A–B/B–A) (%/h)	Rat CNS studies Brain:blood (CSF:free (blood))
1	H	3	100	275	3.1	9.3	306	12/1	21/8 ER = 0.4	14:1 (1:1)
13	–$CONH_2$	2	85	205	2.3	8.5[b]	348	55/3	NT	ND (1:1)
14	–CONHMe	3	150	150	2.8	8.8	363	41/2	26/11 ER = 0.4	ND 1:1
22a	–SO_2NH_2	1	90	770	2.3	8.4	384	81/3	18/7 ER = 0.4	16:1 (2.6:1)
23	–SO_2NHMe	5	55	250	2.8	NT	398	67/2	NT	ND 0.3:1

NT, not tested; ND, not detected; ER, basolateral–apical (B–A)/apical–basolateral (A–B).
[a] All compounds are single (1*S*,4*S*)-enantiomers.
[b] Calculated value.

relative to lead **1**. Unfortunately, these particular analogues showed unacceptable levels of CYP2D6 inhibition and so were not progressed further.

Substitution was also found to be generally well tolerated at C-6 (**30**–**36**, Table 1). For example, sulfonamide **30**, sulfoxide **31** and carboxamide **33** all displayed good potency against SRI ($IC_{50} \sim 10$ nM), however, all were found to be slightly weaker than their C-7 analogues, albeit often with slightly improved selectivity over DRI. Synthetically, however, these targets proved significantly more difficult to access than their C-7 isomers and as they offered no significant advantage, this series was not pursued further.

Attempts to introduce two polar substituents onto the tetrahydronaphthalene ring **37**–**39**, as a strategy to further reduce C log *P*, gave compounds which ranged from inactive in our primary assay in the case of C(8), C(6) bis-carboxamide **37** to relatively high potency in the case of C(7)sulfonamido-C(6)carboxamido analogue **38** (SRI, IC_{50} 24 nM).

However, this strategy of incorporating two polar groups into the lead **1** was not pursued further, due to a combination of synthetic inaccessibility and unacceptably high penalty in TPSA and HBD count incurred in these targets.

Compounds were then selected for further progression into permeability and CNS penetration studies, Table 2, based on a combination of highest activity in the primary assay, retention of selectivity over DRI and NRI (>50-fold) and synthetic accessibility to support any future development work.

As anticipated, incorporation of polar electron-withdrawing, carboxamide and sulfonamide substitution, resulted in both a reduction in pK_a and log *D*, indicating that our goal of significantly dropping intrinsic lipophilicity had been achieved in each case. Furthermore, and pleasingly, incorporation of polar, HBD containing functionality did not compromise permeability in the Caco-2 assay. Interestingly, all analogues profiled in this assay displayed an ER < 0.5, potentially indicating facilitated transport in these analogues.

Progression of these analogues into rat CNS penetration studies gave varied and unpredictable results, with little apparent correlation with physicochemical properties observed. For example, **1**, as anticipated for this CNS agent, displayed excellent CNS permeability (brain:blood (14:1) and CSF:free (1:1)). Excitingly, primary sulfonamide **22a** showed excellent CNS penetration in both the brain:blood (16:1) and in the CSF:free (1:1) rat assays, with comparable CNS exposure to sertraline **1**, despite being more polar (log *D* 2.3) and possessing a significantly greater H-bond donor capacity (HBD 3) and TPSA (81 Å^2) than **1** (HBD 1, TPSA 12 Å^2), with both these latter parameters being just outside our original ideal target design limits for good CNS penetration (vide supra). Similarly, primary carboxamide **13** also showed excellent CNS penetration (CSF:free, 1:1), despite being significantly more polar (log *D* 2.3) than **1** and, again, possessing a greater H-bond donor capacity (HBD 3) than 'ideal'.

On the other hand, however, *N*-methyl sulfonamide **23** was found to possess poor CNS penetration as assessed in the rat assay (0.3:1), despite possessing both lower HBD count (2) and higher log *D* (2.8) than **22a**.

Table 3. Comparative potency, selectivity and rat pharmacokinetic data for **1** and **22**

Compounds	R^2	h-SRI (IC_{50}, nM)	Selectivity over DRI and NRI	Caco-2 (A–B/B–A) (%/h)	HLM[a] ($T_{1/2}$, min)	RLM[b] ($T_{1/2}$, min)	Rat pharmacokinetics (iv 1 mg/kg ($n = 3$), po 1 mg/kg ($n = 3$) for (**1**)). (iv 3 mg/kg ($n = 3$), po 5 mg/kg ($n = 3$) for (**22**))					Rat CNS data
							Blood Cl (mL/min/kg)	V_d (V_{du}) (L/Kg)	$T_{1/2}$ (h)	F (%)	T_{max} (h)	Brain:blood (CSF:free (blood))
1	H	3	100/275	21/8	>120	23	71	52 (1900)	5	51	4	14:1 (1:1)
22a	$-SO_2NH_2$	1	90/770	18/7	>120	>120	60	19 (600)	4	44	1	16:1[c] (2.6:1)

[a] HLM, human liver microsomes.
[b] RLM, rat liver microsomes.
[c] 3 mg/kg (iv) sampled 1 h post-dose.

Excitingly, full pharmacokinetic profiling of **22a**, Table 3, showed the compound to possess, significantly lower V_d (19 vs 52 L/kg) and V_{du} (660 vs 1900 L/kg) relative to **1**, consistent with its lower log*D* and pK_a. Furthermore, **22a** was found to possess a significantly more rapid T_{max} than lead **1** (1 h vs 4 h), a key objective in our strategy.

Based on these data and further profiling, **22a** (UK-373,911) was selected for clinical development as a potent SSRI with the potential to deliver rapid increases in central 5-HT.

In summary, a series of (1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydro-1-naphthaleneamines were prepared incorporating polar functionality as a strategy to reduce V_d, attenuate T_{max}, and hence deliver rapid elevation of central 5-HT. Polar functionality was found to be generally tolerated at C-6, C-7 and C-8, with variable selectivity, particularly over DRI, observed. Subsequent profiling of preferred analogues in rat showed these compounds to possess variable CNS penetration, which could not be predicted from their physicochemical properties. Overall, **22a** displayed the most attractive profile, combining excellent SRI activity (IC_{50}, 1 nM), selectivity over DRI and NRI, good oral absorption and excellent CNS penetration, comparable to **1**, despite possessing significantly higher HBD count, TPSA and lower log*D*. The reduced lipophilicity and pK_a in this analogue relative to **1** resulted in significantly reduced V_d and T_{max} in rat pharmacokinetic studies, consistent with our target profile.

Our continuing efforts in this field will be the subject of future communications from these laboratories.

Acknowledgments

The authors thank Dr. Willard Welch for advice and support. We also acknowledge the able assistance of Ms. Clare Finnis-Lane, Ms. Isabella Sergides, Mr. Leigh Turner and Ms. Teresa Tyler, for transporter assays, Mr. Richard Mitchell for pharmacokinetic studies and Mrs. Joanne Bennett for Caco-2 permeability studies. We also thank the staff of the Structural and Separation Sciences Department for analytical and spectroscopic data.

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