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Structural Exploration of (3*S*,6*S*)-6-Benzhydryl-*N*-benzyltetrahydro-2*H*-pyran-3-amine Analogues: Identification of Potent Triple Monoamine Reuptake Inhibitors as Potential Antidepressants

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Keywords

Monoamine Transporters; Triple reuptake inhibitors; Pyran; Antidepressants

Unipolar depression is ranked as number one before all other somatic and psychiatric illnesses. In spite of its prevalence, the underlying causes of depression are still unclear [1]. This disorder is a significant health problem and 10-20% of all adults suffer from this disease[1]. Different classes of antidepressants have been developed over the past decades. Antidepressants are traditionally thought to elicit their therapeutic effects by increasing extraneuronal concentrations of serotonin and norepinephrine [2]. Earlier tricyclic antidepressants displayed variable norepinephrine and serotonin uptake inhibitory activity, while exhibiting considerable side effects in addition to antidepressant effects due to non-specific interactions in the central nervous system (CNS) [3] Subsequent development of selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are second generation antidepressants which provided drugs with much more selective interaction at serotonin and norepinephrine systems [4-7]. By virtue of their interaction with the SERT and NET only, these drugs had appreciable less unwanted side effects than tricyclic antidepressants [8-9]. An SNRI such as Venlafaxine exhibits antidepressant activity in clinical trials and displays somewhat greater response and remission rates compared to SSRIs [10]. However, a significant unmet need for more improved therapy still exists, as large numbers of depressed people are still refractory to the current existing therapies. In addition, a significant number of people suffer from relapse after treatment with current therapies [11].

Dopaminergic activity has not been included in the current pharmacotherapy of depression even though there are ample evidences pointing towards an important involvement of dopaminergic neurotransmission in depression [12-13]. Inclusion of dopamine activity should act to reduce anhedonia which is associated with a deficit in dopaminergic transmission and is a central component of the depressed state of mind. A successful adjunct therapy approach involving use of dopamine transporter blocker bupropion and SSRI was found to be more

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efficacious in patients refractory to SSRI.[14-15] Furthermore, the D3 dopamine receptor preferring drug pramipexole was effective in both unipolar and bipolar depression.[16]

This prompted the design of triple uptake inhibitors (TUIs). However, from drug development point of view it is difficult to optimize three uptake inhibition activities in a single molecule. In recent years a number of TUIs, e.g. DOV 216,303, PRC200-SS, JNJ-7925476 and GSK-372,475 have been developed (Figure 1) and have been characterized in animal depression models.[17-18] DOV 216,303 was studied in a human clinical trial for pharmacokinetic properties and efficacy.[18-19] In severe to major depressive disorder, DOV 216,303 was found to be as efficacious as Citalopram.[18]

In our effort to develop triple uptake inhibitors, we embarked on developing molecules based on asymmetric pyran derivatives. CNS-active pyran compounds are relatively rare. In our recent reports, we have demonstrated the development of asymmetric 3,6-disubstituted and 2,4,5-trisubstituted pyran derivatives targeting monoamine transporter systems.[20-22] Compounds with various profiles were developed. Thus, a number of TUIs were identified as well as compounds with an SSRI, SNRI and dopamine/norepinephrine reuptake inhibitor (DNRI) profile. Two of our lead TUIs **1a** (D-142) and **1b** (D-161) (Figure 1, Table 1) were shown to be efficacious in animal models of depression.[23-24]

Reductive amination of the amines **1** (disubstituted pyran) and **3** (trisubstituted pyran) with various aldehydes in the presence of $NaCNBH_3$ afforded the target compounds **2a-2f**, **4a-4e** (Scheme 1 and Scheme 2 respectively) in appreciable yields. Nucleophilic displacement of corresponding halides by the amines **1** and **3** in the presence of a weak base (K_2CO_3 or Et_3N) provided compounds **2g-2h** and **4f** (Scheme 1 and Scheme 2, respectively).

The synthesis of the intermediate (*R*)-epoxide **10** is depicted in Scheme 3 and Scheme 4. Commercially available bis(4-fluorophenyl)methane (**5**) was converted to the corresponding ketone **6** *via* oxidation in the presence of $KMnO_4$. Wittig reaction of ketone **6** with (methoxymethyl)triphenylphosphonium bromide in the presence of sodium amide under the Schlosser conditions afforded the desired vinyl ether **7** in excellent yield.[25] Compound **7** was converted to the corresponding aldehyde **8** in the presence of glacial acetic acid and concentrated sulfuric acid.[26] Without further purification, the aldehyde **8** was immediately utilized to obtain the racemic epoxide **9** *via* the Corey-Chakovsky method.[27] The racemate **9** was then subjected to the kinetic hydrolytic resolution in the presence of Jacobsen's catalyst to obtain the (*R*)-epoxide **10** and diol **11** in 48% yield (over 99% ee). Selective protection of the primary hydroxyl group of the diol **11** in the presence of TBDMSCl and catalytic imidazole afforded compound **12**. Mesylation of compound **12** followed by the deprotection of TBDMS group by TBAF furnished compound **14**. Intramolecular S_N2 displacement of the OMs group by the primary alcohol group of compound **14** in anhydrous methanol, catalyzed by anhydrous K_2CO_3 afforded the desired (*R*)-epoxide **10** in excellent yield.

The synthesis of the key amine intermediate **21** (disubstituted pyran) is described in Scheme 5. The δ,ε-unsaturated alcohol **15** was obtained by the regioselctive ring opening of the (*R*)-epoxide **10** in the presence of allylmagnesium chloride and catalytic amount of copper(I) iodide. Compound **15** was converted to the corresponding vinyl ether **16** via *trans*-vinylation with ethyl vinyl ether using catalytic amount of mercury (II) trifluoroacetate. Compound **16** was immediately subjected to ring-closing metathesis in the presence of Grubb's catalyst (1st genetaion) to afford the cyclic olefin **17**. Compound **17** was then subjected to hydroborylation in the presence of 9-BBN in anhydrous THF, followed by oxidation to obtain an inseparable mixture of distereomers exclusively in favor of the *trans*-isomer **18a**. We have established the stereochemistry of the product **18a** in our recent and earlier

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publications.[20-22] The diastereomeric mixture was mesylated with methanesulfonyl chloride and separated by gradient column chromatography to afford **19a** as the major isomer in 77% yield. The azide **20** was obtained by nucleophilic S_N2 substitution of **19a** with sodium azide in anhydrous DMF. Hydrogenation of compound **20** in the presence of 10% Pd/C in methanol provided quantitative yield of the key intermediate *cis*-amine **21**. Compounds **22**, **23b-d** were obtained by reductive amination with corresponding aldehydes. Compound **23a** was obtained by hydrogenation of compound **22** in the presence of 10% Pd/C in methanol for 1 h.

Scheme 6 describes the synthesis of the other key intermediate amine **30** (trisubstituted pyran). The (*R*)-epoxide **10** was treated with vinylmagnesium chloride and catalytic amount of copper(I) iodide in anhydrous THF to obtain the homoallylic alcohol **24** in a regioselective fashion. *O*-Allylation of compound **24** followed by ring-closing metathesis in the presence of Grubb's catalyst (1st generation) afforded the cyclic olefin **26**. Regioselective bromohydrin formation of the olefin **26** in the presence of *N*-bromoacetamide provided compound **27** which was converted to the *trans*-epoxide **28** in the presence of 20% NaOH in dioxane. The stereochemistry of *trans*-epoxide was comprehensively determined in our recent publication.[28] The *trans*-epoxide **28** was regioselectively converted to the corresponding azide **29** which upon hydrogenation in the presence of 10% Pd/C in methanol afforded the key intermediate amine **30** in a quantitative yield. Reductive amination of the amine **30** with various aldehydes provided the target compounds **31a-b**.

Expanding on SAR studies with asymmetric pyran derivatives, we report here on structural modifications of both di- and trisubstituted pyran derivatives. One of our main goals is to develop suitable TUIs and to further understand the effect of structural modifications on the activity profile for the three monoamine transporters. Our recent communication explored a number of disubstituted pyran derivatives, producing a lead TUI exhibiting balanced activity at all three monoamine transporters and exhibited significant effectiveness in reducing immobility in the forced swim test (FST).[21] In this regard, FST is a well recognized animal model for preclinical screening of potential antidepressant.[21-29] In addition, in our recent report we were able to demonstrate potent in vivo activity of a tri-substituted pyran derivative D-142 in both FST and mouse tail suspension tests.[24]

In our current study, we have further expanded our SAR studies with 3,6-disubstituted compounds. Compounds **2a-h** were synthesized and characterized to evaluate their uptake inhibition profile. Several different *N*-benzyl substitutions were introduced to evaluate their effect on profile of uptake inhibition. To follow up on our previous SAR studies, several different phenyl-alkoxy related derivatives were synthesized. Thus, compounds **2a**, **2c**, **2e** and **2f** were made. Out of these compounds, **2c** showed exceptional uptake inhibition potency at SERT and moderate to weak potency at NET and DAT (K_i; 152, 1.05 and 47.3 nM for DAT, SERT and NET, respectively), i.e. exhibited an SSRI profile. In this context, compound **2c** was 11.6 times more potent than fluoxetine for its interaction with SERT. Thus, compound **2c** might qualify as one of the most potent SERT-selective inhibitors known to date. Compound **2f** similarly exhibited very high uptake inhibitory potency at SERT, but also had a good affinity for NET (K_i; 160, 1.07 and 15.8 nM for DAT, SERT and NET, respectively) and thus, exhibited a SNRI type profile. Compound **2a**, however, did not display appreciable inhibitory activity at either SERT or NET but was potent at DAT. Dioxy compound **2e** was potent at NET and moderately potent at both SERT and DAT (K_i; 87.7, 52.6 and 8.58 nM for DAT, SERT and NET, respectively), exhibiting a profile similar to that of a TUI. The precursor to compound **2e**, derivative **2d** did not show much activity for any one of the three transporters. We next synthesized several sulfonamide derivatives to explore their activity. Compound **2b** showed moderate potency at DAT and NET but weaker

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potency at SERT. Compound **2g** showed comparable potency at all three transporters (K_i; 60, 79 and 70 nM for DAT, SERT and NET, respectively) and thus, was a balanced TUI.

In our next exploration, selected tri-substituted pyran derivatives corresponding to their already characterized disubstituted compounds were synthesized. Thus, compounds **4a-f** were synthesized and characterized. Compound **4a** which is a trisubstituted derivative of **2e**, showed an interesting profile of triple uptake inhibition (K_i; 135, 14.7 and 25.9 nM for DAT, SERT and NET). Compound **4a** exhibited higher inhibition potency at SERT compared to its corresponding disubstituted version **2e** (K_i; 14.7 vs. 52.6 nM for SERT for **4a** and **2e**, respectively). Compounds **4b** and **4c** were in general weakly active at all three transporters, indicating low tolerance of hydroxyl substitution on the aromatic ring. Similar to its disubstituted counterpart **2c**, compound **4d** exhibited high uptake inhibition activity for SERT and was an SSRI (K_i; 401, 1.99 and 57.2 nM for DAT, SERT and NET, respectively). Thus, it seems that *N*-benzyl aryl substitutions carrying tetrahydrofuran or methoxy moieties (in particular tetrahydrofuran) conveye high affinity for SERT. Compounds **4e** and **4f** were not active at the three transporters targets.

In our next goal, we wanted to evaluate the effect of introduction of fluorine atoms in the aromatic rings of pyran derivatives on uptake inhibitory potency. Another rationale behind introducing fluorine is to increase possible metabolic stability in the lead compounds which will have an impact in improving their pharmacokinetical properties. A fluorinated version of a previous lead molecule, **23a** exhibited a dopamine and norepinephrine reuptake inhibitory profile (DNRI) with more potent inhibition of dopamine and norepinephrine transporters compared to SERT (K_i; 32.5, 69 and 8.5 nM, for DAT, SERT and NET, respectively). The unsubstituted version of **23a,** compound **1c** (Table 1), was more potent at SERT and less potent at DAT compared to **23a**.[20] Compound **23b** which is a fluorinated version of D-161, exhibited a DNRI-type profile (K_i; 28.8, 334 and 13.4 nM for DAT, SERT and NET, respectively). In this regard, it is important to mention that there are only few compounds which are known to exhibit a DNRI-type profile. One well known example of this is bupropion, used as an antidepressant agent in the clinic.[15, 30] Disubstituted fluorinated indole compound **23c** exhibited good potency at DAT and NET but was weaker at SERT. Compound **23d**, which is a fluorinated version of **2c**, exhibited high uptake inhibition potency at all three transporters (K_i; 11, 3.1 and 6.2 nM for DAT, SERT and NET, respectively). Thus, compound **23d** is one of the most potent TUIs that we have developed so far.

Followed by synthesis of disubstituted fluorinated compounds, two trisubstituted fluorinated derivatives **31a** and **31b** were made. Compound **31a** exhibited a triple uptake inhibitory profile with highest uptake inhibition shown for NET and DAT (K_i; 4.2 and 38.4 nM, respectively for NET and DAT), exhibiting a profile similar to a DNRI. Compound **31b** was modestly potent at SERT and weak at DAT and NET transporters. Overall, it seems that fluorinated versions of compounds showed propensity for higher activity at DAT and NET giving rise to a more DNRI-type profile. We have incorporated the current SAR results along with our earlier findings into the pharmacophore model we presented previously (ref 20). This updated pharmacophore model is shown in Figure 2.

Finally, we carried out an in vivo study with one of our lead TUIs, **2g**. Based on physiochemical properties calculated by using Molecular Operating Environment (MOE) 2011.10 version program, of three lead TUIs (Table 2), this compound was chosen for in vivo rat FST experiment over **4a** and **23d** as it was expected to provide more favorable bioavailability. Based on our previous experience with transporter inhibitors with comparable affinities, a dose of 10 mg/kg (ip) was selected to evaluate the effect on immobility and was compared with vehicle. Imipramine was used as a positive control.

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Compound **2g** was able to reduce the immobility significantly compared to vehicle (Figure 3). The in vivo activity of **2g** was similar to structurally different PRC200-SS (Figure 1) under the same ip drug administration conditions.[17] With respect to other, structurally different, compounds, DOV 21,947 and DOV 216,303 (Figure 1), no direct correlation could be made as the DOV compounds were administered orally.[31-32] In regards to our own results, it appears compound **2g** is marginally more efficacious in reducing immobility compared to D-142 (Ref. 24) but was similar to D-391 (compound **10f** in ref. 21).[21, 24] We plan to carry out a broad spectrum screening of compound **2g** in the near future to assess its interaction with CNS receptors. Based on core pyran structural similarity with our previous lead molecules, it is expected that similar selectivity for monoamine transporters would be exhibited by compound **2g** as found for our disubstituted and trisubstituted pyran derivatives D-161, D-391 and D-142.[21, 23, 24]

In our goal to determine whether the efficacy of **2g** originated, in part or in full, from locomotor activation, we carried out locomotor activity studies with the 10 mg/kg dose of **2g** as applied in the FST. The results indicate that 10 mg/kg of **2g** was ineffective in producing locomotor activity as tested under same experimental protocol applied in rat FST (Figure 4a). Additionally, determination of total locomotor activity for a period of one and a half an hour post administration of drugs indicated no significant difference of activity between **2g** and vehicle (Figure 4b). Thus, the reduction of immobility by **2g** in these animal models was not due to increased locomotor activity.

In this report we have shown the development of novel compounds with TUI, DNRI, SNRI, or SSRI profile. Both disubstituted and trisubstituted pyran compounds exhibited such profiles. Compounds **2g, 4a** and **23d** exhibited a TUI profile. Compound **2g** exhibited balanced potency at all three monoamine transporters. Compound **4a** was most potent at SERT and NET with moderate potency at DAT. Disubstituted compound **2c** and trisubstituted compound **4d** exhibited an SSRI-type profile with a nanomolar potency selectively at SERT. Introduction of fluorine atom in general increased activity for the DAT. Compound **23b** exhibited DNRI-type profile. An *in vivo* rat study with balanced TUI **2g** indicated significant reduction of immobility in the FST depression model compared to vehicle, indicating potential antidepressant property.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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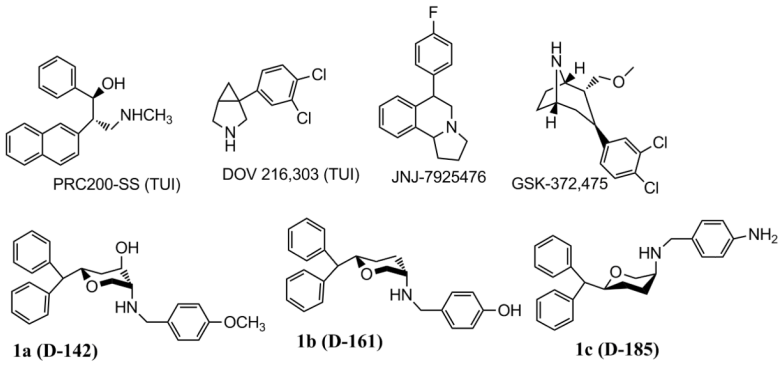

Figure 1.
Molecular structures of known TUIs and pyran molecule-based TUIs.

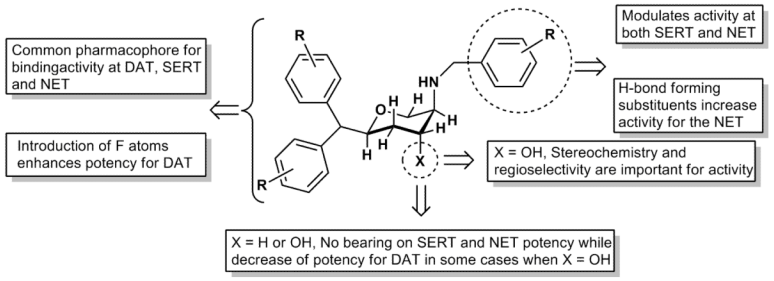

Figure 2.
An updated interaction model of pyran derivatives with monoamine transporters molecules.

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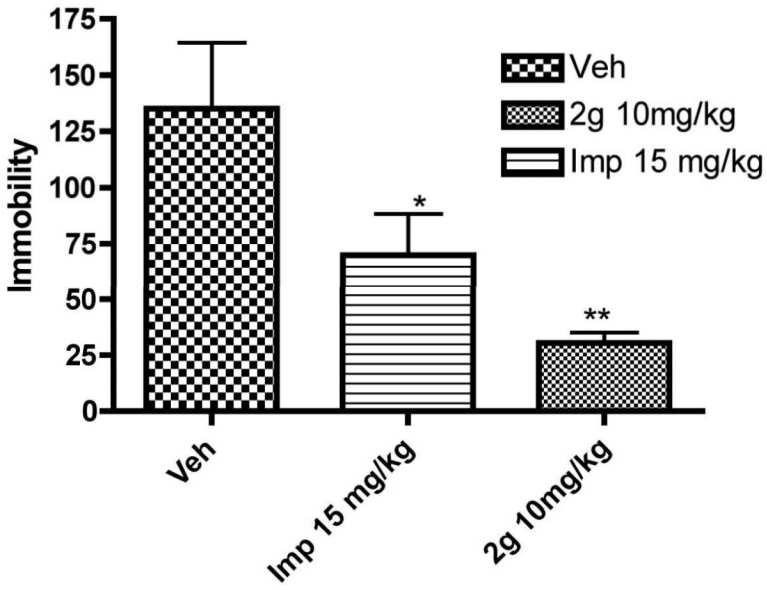

Figure 3.

Effect of sub-chronic administration of vehicle (Veh), 2g, and imipramine (Imp) on the duration of immobility in the forced swimming test in rats. One way ANOVA analysis demonstrates significant effect among treatments: $F(3,95) = 8.93$ ($P < 0.0042$). Dunnett's analysis showed that the effect of 2g at a dose (10 mg/kg) on immobility was statistically significant different compared to vehicle ($P < 0.01$). The effect of reference imipramine (15 mg/kg) on immobility was also statistically significantly different ($P < 0.05$) from vehicle. Asterisks indicate a statistically significant difference toward control group that received saline i.p. **$P < 0.01$. Each treatment group contained six to eight rats.

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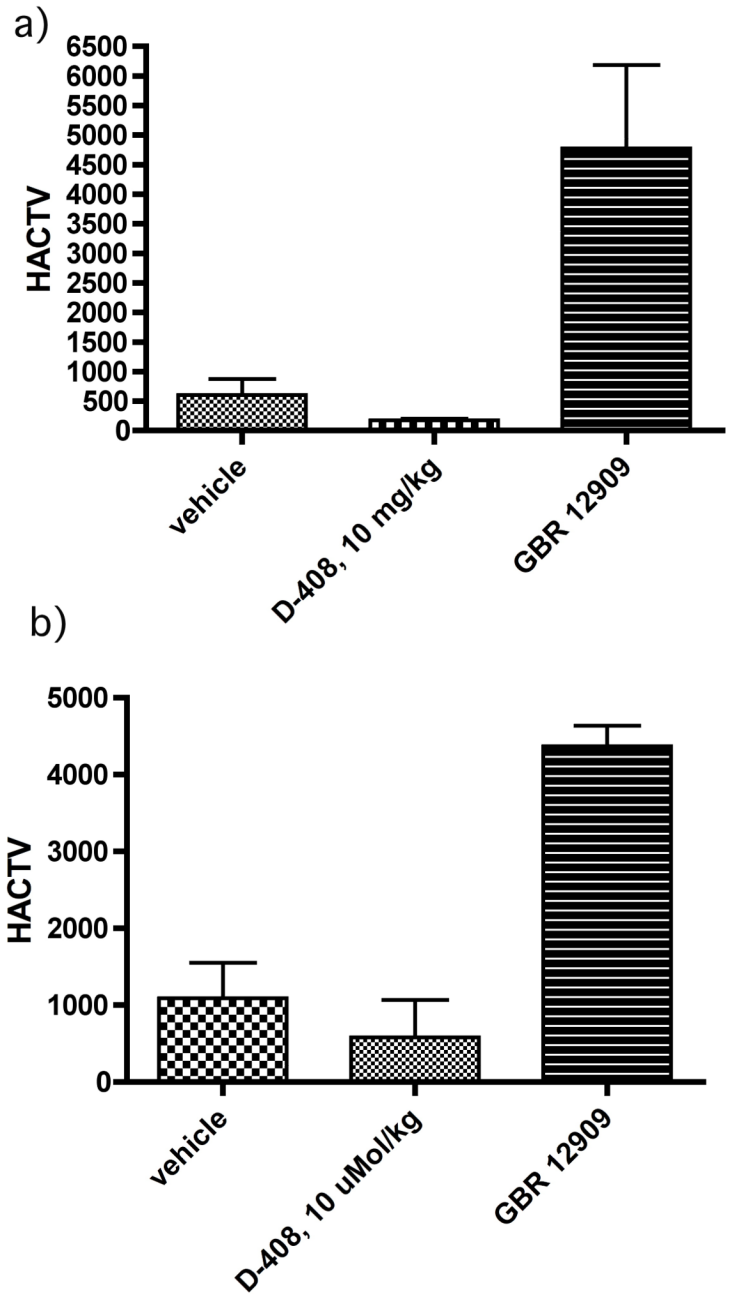

Figure 4.

Effects of drugs, 2g and GBR 12909, on locomotor activity (horizontal activity, HACTV). Rats were injected (i.p.) with either vehicle or 2g followed by measurement of locomotor activity for one and a half an hour post administration of drugs. GBR 12909 is shown for comparison from our previous work (ref). a) This time frame represents measurement of locomotor activity for ½ h after post 1 h of administration of drugs and mimicked the condition of rat FST test. One way ANOVA analysis demonstrates non significant effect between control and the dose of 2g but significant effect between control and GBR 12909 : $F(3,95) = 6.73$ ($P < 0.05$). b) This time frame represents total locomotor activity for one and a half an hour post administration of drugs. One way ANOVA analysis demonstrates non significant effect between control and the dose of 2g but significant effect between control

and GBR 12909 : F (3,95) = 24.21 (P< 0.01). Asterisks indicate a statistically significant difference toward control group that received saline i.p. **P < 0.01. Each treatment group contains three to four rats.

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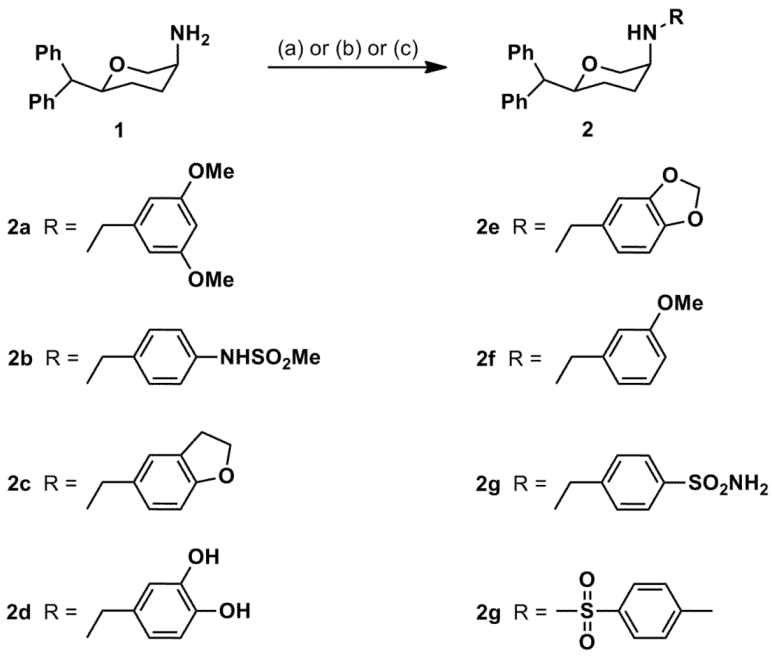

Scheme 1.

Synthesis of **2a-2h**: *Reagents and conditions*: (a) RCHO, $NaCNBH_3$, AcOH, 1,2-dichloroethane, rt, overnight (for compounds **2a-2f**), (b) 4-(bromomethyl)benzenesulfonamide, K_2CO_3, DMT, rt, overnight (for compound **2g**) (c) *p*-Toluenesulfonyl chloride, Et_3N, DCM, rt, overnight (for compound **2h**)

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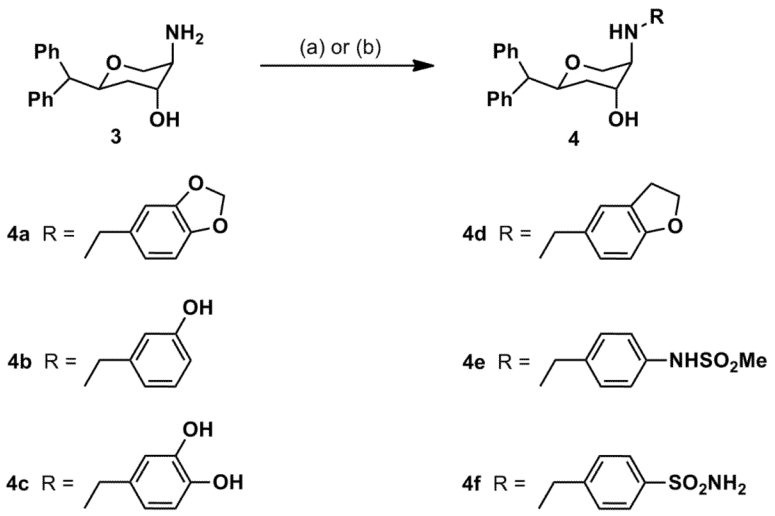
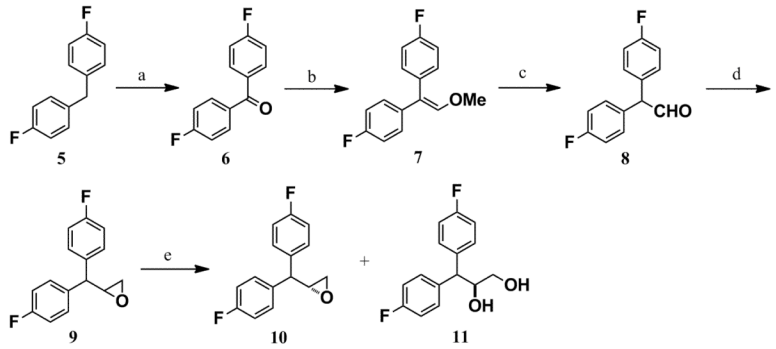


Scheme 2.

Synthesis of **4a-4f**: *Reagents and conditions*: (a) RCHO, $NaCNBH_3$, AcOH, 1,2-dichloroethane, rt, overnight (for compounds **4a-4e**), (b) 4-(bromomethyl)benzenesulfonamide, K_2CO_3, DMT, rt, overnight (for compound **4f**).



Scheme 3.

Synthesis of **10** and **11**: *Reagents and Conditions*: a) $KMnO_4$, CH_3CN, 0 °C-rt, 99%. b) $MeOCH_2PPh_3\ ^+Br^-$, anhyd. THF, anhyd. $NaNH_2$, 0 °C-rt, 97%. c) Conc. H_2SO_4, glacial AcOH, rt, 30 min, 97%. d) trimethylsulfoxonium iodide, anhyd. DMSO, NaH, rt, 1 h, then 60 °C, 2 h 95%. e) (*R,R*)-(−)-*N,N*′-bis(3,5-di-tert-butylsalicylidine)-1,2-cyclohexane diaminocobalt (Jacobsen's catalyst), H_2O, THF, over 99% ee and 48% yield for both **10** and **11**.

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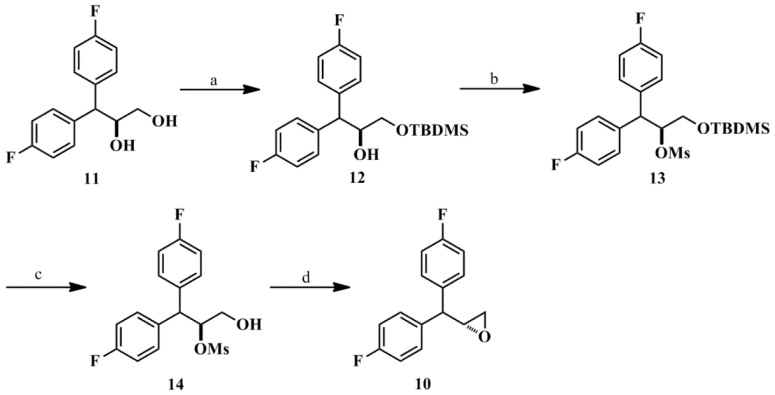

Scheme 4.

Synthesis of **10**: *Reagents and Conditions*: a) TBDMSCl, imidazole, DCM, 0 °C-rt, 1 h. b) CH_3SO_2Cl, Et_3N, DCM, 0 °C-rt, 2 h. c) TBAF, THF, 0 °C-rt, 1 h. d) K_2CO_3, CH_3OH, 0 °C-rt, 5 h.

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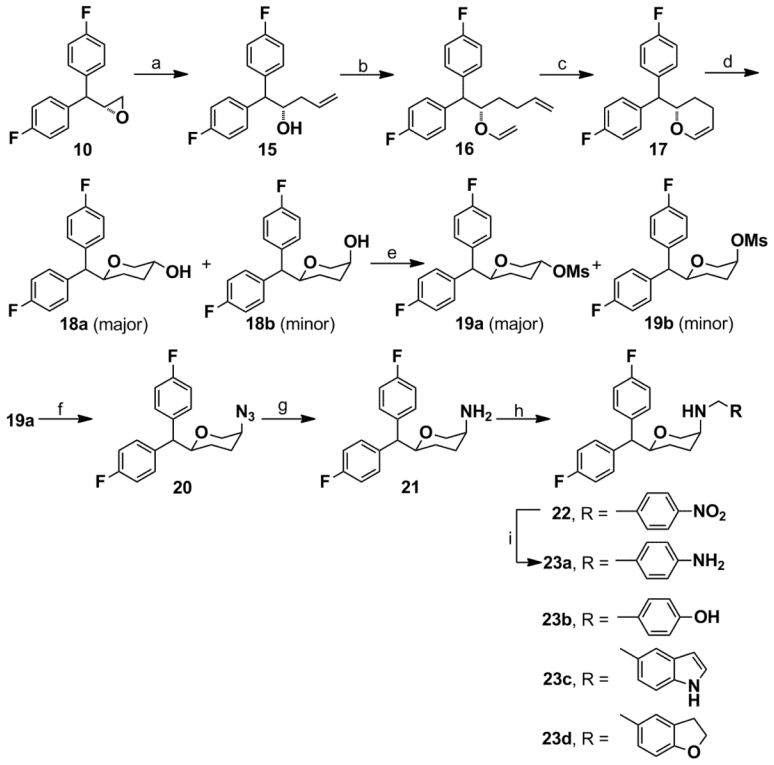

Scheme 5.

Synthesis of **23a-23d**: *Reagents and conditions*: (a) allylmagnesium chloride, anhyd. diethylether, −78 oC to rt, overnight. (b) ethylvinyl ether, $Hg(OCOCF_3)_2$, rt, 4 h. (c) 1st generation Grubb's catalyst, anhyd. benzene, reflux, 2 h. (d) (i) 9-BBN, anhyd. THF, rt, overnight; (ii) 10% NaOH, 30% H_2O_2, 50 °C, 1 h. (e) CH_3SO_2Cl, Et_3N, anhyd. DCM, rt, 2 h. (f) NaN_3, anhyd. DMF, 80 °C, overnight. (g) H_2, Pd/C, MeOH, 50 psi, 2 h. (h) RCHO, $NaCNBH_3$, 1,2-dichloroethane, AcOH rt, overnight. (i) H_2, Pd/H_2, MeOH, 50 psi, 1 h.

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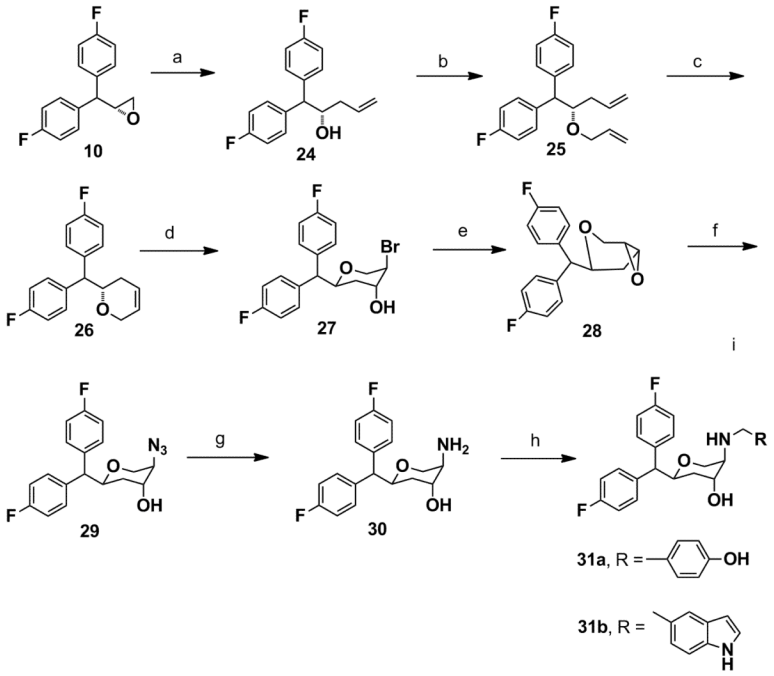

Scheme 6.

Synthesis of **31a-31b**: *Reagents and conditions*: (a) vinylmagnesium bromide, CuI, anhyd. THF, −78 °C-rt, 24 h, 93%. b) NaH, allyl bromide, anhyd. DMF, 1.5 h, 0 °C-rt, 95%. c) 1st generation Grubb's catalyst, anhyd. benzene, reflux, 2 h, 96%. d) *N*-bromoacetamide, Dioxane-H_2O, 0 °C-rt, 4 h, 82%. e) 20% NaOH, Dioxane, 0 °C-rt, 30 min, 90%. f) NaN_3, anhyd. DMF, 80 °C, 24 h, 96%. g) Pd/C, MeOH, H_2, 30 psi, 98%. h) RCHO, $NaCNBH_3$, 1,2-dichloroethane, AcOH, overnight.

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Table 1

Affinity of drugs at DAT, SERT, and NET in rat brain.

Compound	DAT uptake, K_i, nM, [^{3}H]DA[a]	SERT uptake, K_i, nM, [3H]-5-HT[a]	NET uptake, K_i, nM [^{3}H]DA[a]
GBR 12909	9.14 ± 1.94	132 ± 47	38.5 ± 4.9
Reboxetine	> 10,000	503 ± 61	0.694 ± 0.217
Fluoxetine	1092 ± 98	12.2 ± 2.4	158 ± 58
1a	59.3 ± 13.7	14.7 ± 2.1	29.3 ± 7.9
1b	42.0 ± 3.3	29.1 ± 3.5	30.5 ± 7.8
1c	62.4 ± 5.6	16.1 ± 1.6	12.6 ± 3.7
2a	20 ± 14	270 ± 32	658 ± 86
2b	62.1± 4.2	155 ± 53	68.0 ± 15.0
2c	152 ± 11	1.05 ± 0.24	41.3 ± 21.4
2d	344 ± 74	409 ± 52	121 ± 8.1
2e	87.7 ± 3.5	52.6 ± 13.8	8.58 ± 1.29
2f	160 ± 21	1.07 ± 0.12	15.8 ± 3.7
2g	60.0 ± 8.6	79.2 ± 13.8	70.3 ± 18.2
2h	11,795 ± 483	> 100 μm	3288 ± 996
4a	135 ± 6	14.7 ± 3.5	22.6 ± 14.9
4b	334 ± 53	93.2 ± 17.9	244 ± 68
4c	245 ± 47	370 ± 42	193 ± 43
4d	401 ± 87	1.99 ± 0.77	57.2 ± 11.9
4e	303 ± 39	120 ± 21	91.8 ± 16
4f	1393 ± 268	2008 ± 513	4097 ± 661
23a	32.5 ± 4.3	69.1 ± 19.8	8.48 ± 1.73
23b	28.8 ± 2.7	334 ± 126	13.4 ± 5.6
23c	73.0 ± 8.6	187 ± 27	50.5 ± 18.0
23d	11.2 ± 2.8	3.07 ± 0.32	6.19 ± 2.48
31a	38.4 ± 2.6	58.4 ± 4.0	4.20 ± 2.39
31b	424 ± 46	72.8 ± 8.7	89.1 ± 32.3

[a]For uptake by DAT, SERT and NET, [^{3}H]DA, [^{3}H]-5-HT and [^{3}H]DA accumulation was measured. Results are average ± SEM of three to eight independent experiments assayed in triplicate.

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Table 2

Physicochemical parameters of lead TUIs[a]

Compound	Mol. Wt.	Number of H-bond acceptor	Number of H-bond donor	Number of rotatable bonds	TPSA	Log P
2g	421.55	4	2	7	81.42	4.32
4a	417.50	4	1	6	39.72	5.60
23d	435.51	3	1	6	30.49	6.10

[a]Physicochemical parameters were calculated with molecular modelling program MOE 2011.10 version.