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Structure-Based Design, Synthesis and Antidepressant-Like Activity of Phenylthiazolyl-1*H*,2*H*,3*H*,4*H*-naphthalene Derivatives

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In recent years, a bacterial homologue of SERT (LeuT) target protein was solved in complex with sertraline and offers promising pathway for the hit identification. Herein, we cover advanced computational methodology for hybrid class 1,2,3,4-tetrahydronaphalene and phenylthiazole derivatives using three two modules. First, these drug-like candidates were filtered by molecular properties from a training set of library. Second, compounds were prioritized according to previously optimized CDocker docking methodology. Finally, synthesized *in silico* actives were demonstrated enhanced antidepressant-like activity with reasonable non-toxicity using standard mice model (s).

Keywords: 1,2,3,4-Tetrahydronaphthalene, Phenylthiazole, Molecular properties, Docking.

INTRODUCTION

Target structure-based drug design (TSBDD) has become increasingly important in the context of drug discovery[1,2]. In practice, identifying potential leads using TSBDD rather than *via* other approaches is faster, more economical and being easier to setup[3]. For this reason, many drugs developed in part by TSBDD are in late-stage clinical trials or have now reached the market, for example tyrosine kinase inhibitors, Canertinib[4]; topoisomerase II inhibitors, Amsacrine[5]; nitrogen mustard pre-prodrug, PR-104[6]; VEGFR2 inhibitors, DMXAA[7], *etc*.

Depressive disorders are one of the most prevalent mental illness worldwide with considerable social impact and economic consequences[8]. In last two decades, the inhibition of serotonin-transporter (SERT) is anticipated to provide an effective treatment of depressive disorders, for instance a selective inhibitor from 1*H*,2*H*,3*H*,4*H*-naphthalene. Sertraline is primarily prescribed in both adults and children[9-11]. Recent crystallographic studies have solved a 3D structure of bacterial homologue of SERT *viz*. leucine transporter (LeuT) in complex with Sertraline (3GWU.pdb) at 2.14 Å resolution[12]. This model explores great opportunities for molecular docking using novel 1*H*,2*H*,3*H*,4*H*-naphthalene ligands.

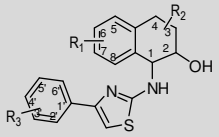
Recent synthetic drug design work in our laboratories has led to design, synthesis and characterization of a novel antidepressant hit, AU-11 from substituted phenylthiazolyl-1*H*,2*H*,3*H*,4*H*-naphthalene class[13]. This work also emphasized that the best correlation R^2 0.77 between CDocker interaction energy and experimental data were obtained by using Discovery Studio Package. Further in an order to improve the efficiency of drug discovery, we decided herein to pre-screen compounds *via* structure variation of AU-11. Each compound was constructed manually by incorporating distinguished alkenyl/alkyl/aryl/hetero alkyl-aryl functionalities. Library of these putative compounds were filtered by molecular properties calculation and ranked according to docking based approach (Table-1).

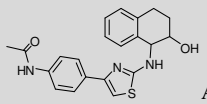
Subsequently, chemical synthesis of these rank-ordered compounds and their antidepressant-like effects were carried out using standard Porsolt's behavioral despair on albino mice, tail suspension and open field tests.

EXPERIMENTAL

Designing of compounds: A library comprising of more than ten thousand compounds were constructed manually by incorporating distinguished alkenyl/alkyl/aryl/hetero alkyl-aryl substituents. Ligands were prepared by Marvin Sketch Tool[14] and finally exported for docking calculations. The calculation of important molecular properties like log P (milog P), topological polar surface area (TPSA), hydrogen bond acceptors-donors, bioactivity score and molecular toxicity was calculated by Molinspiration[15]. Osiris[16], an Java based library layer provides ADMET and reusable cheminformatics functionality. Docking calculation was carried out on HP workstation, NVIDIA Quadro 2000, windows 7 ultimate 64 bit. Docking experiments were

TABLE-1
DOCKING RESULT OF TETRAHYDRONAPTHALENE DERIVATIVES





AU-11

Compounds	R_1	R_2	R_3	Highest cavity (-CDocker energy)
AAP1	6-OCH_3	H	4'-$NHCOCH_3$	48.39
AAP2	6-OCH_3	H	3'-NO_2	48.39
AAP3	6-OCH_3	H	4'-CH_3	47.58
AAP4	H	4-CH_3	3',4'-diCl	46.56
AAP5	6-OCH_3	H	4'-Br	46.45
AAP6	H	4-CH_3	3'-NO_2	46.38
AAP7	6-OCH_3	H	4'-NO_2	46.15
AAP8	H	4-CH_3	4'-CH_3	45.60
AAP9	6-Cl	H	4'-$NHCOCH_3$	45.52

done in compliance with previously validated docking experiments using DS package supplied by Accelrys Software Inc., San Diego USA in CHARMm based CDocker program and highest cavity (x, y, z and Radius 24.7597, 27.4531, 22.7581 and 10 Å) as a binding site. The Cdocker Interaction Energy of each ligand was calculated for ranking.

Synthesis of compounds: Synthesis of 1,2-epoxy-1,2,3,4-tetrahydronaphthalene was done as per previously described methodology[17]. The synthesized 1,2-epoxy-1,2,3,4-tetrahydronaphthalene (0.1 mol) and different substituted phenyl-2-amino thiazole (0.1 mol) were refluxed under acetone (5 mL) at 70 °C for 5-6 h. The reaction mixture was washed with hexane (5 mL) to furnish semisolid matter and again with ethyl acetate (2 mL). Finally, the mixture was re-crystallized with hexane to afford nine compounds (AAP 1-9).

Melting points were uncorrected. Thin-layer chromatography was performed using silica gel-G (0.5 mm thickness, Hexane and ethyl acetate solvent system) and spots were visualized under iodine chamber. FTIR spectra were recorded on Fourier transform infrared spectrometer-Spectrum 2 (Perkin Elmer, USA). Spectra were recorded in KBr and expressed in cm^{-1}. The ^1H and ^{13}C NMR spectra were recorded on Bruker Avance II 400 and 100 NMR spectrometers (Bruker, USA) in $CDCl_3$ and chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane. The mass spectra were recorded on a Micromass Q-Tof spectrometer. Elemental analysis was carried out on a Vario EL III elemental analyzer (Elementar Analysensysteme, GmbH, Germany).

6-Methoxy-1-[4-(4-acetamidophenyl)thiazol-2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 1): Physical state white crystals; Yield 54 %; m.p. 235-237 °C; R_f value 0.6415 (hexane: ethylacetate 95:5); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (s, 3H, acetamido) 2.07-2.13 (m, 2H, 3-CH_2 naphthalene), 2.90-2.93 (t, 2H, 4-CH_2 naphthalene), 3.34 (m, 1H, 2-CH naphthalene), 3.69 (d, 1H, 2-OH naphthalene), 3.71-3.77 (s, 3H, CH_3-O phenyl), 3.84-3.86 (t, 1H, 1-CH naphthalene), 4.11 (d, 1H, NH-thiazole), 4.13 (d, 1H, 1-CH naphthalene, *J* = 7.16 Hz), 6.67-6.81 (m, 3H, 5,7&8-CH-naphthalene), 7.26 (s, 1H, NH-acetamido), 7.36 (s, 1H, 4-CH thiazole), 7.76 (d, 2H, 3, 5-CH phenyl), 7.99-8.03 (d, 2H, 2,6-CH phenyl); ^{13}C NMR (100 MHz) δ: 20.2 (CH_3-CO); 22.4, 26.5 (CH_2 naphthalene); 55.4 (CH_3-O); 61.3 (C-NH); 80.6 (C-OH); 100.2, 162.4 (C-S thiazole); 121.6, 128.5, 139.2, 127.4, 121.6, 148.4 (phenylthiazole); 112.4, 112.3, 129.5, 135.9, 155.9 (naphthalene); 164.7 (CO-CH_3); FTIR (KBr, ν_{max}, cm^{-1}): 1611 (C=0), 1663 (N-H bending), 875 and 995 (C-H bending), 1364 (C-N), 2842 (aliphatic C-H), 1542 (C=C aromatic), 3446 (Sec. N-H); MS *m/z* 409.2; Anal. Calcd for $C_{22}H_{23}N_3O_3S$: C 64.53, H 5.66, N 10.26; found C 64.43, H 5.60, N 10.12.

6-Methoxy-1-[4-(3-nitrophenyl)thiazol-2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 2): Physical state yellow crystals; Yield 76 %; m.p. 284-286 °C; R_f value 0.5914 (hexane: ethyl acetate 95:5); ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.63-0.65 (m, 1H, 3-CH_2 naphthalene), 0.66-0.69 (m, 1H, 3-CH_2 naphthalene), 1.64 (t, 1H, 4-CH_2 naphthalene), 2.19 (t, 1H, 4-CH_2 naphthalene), 2.46 (t, 1H, 2-OH naphthalene), 2.94 (m, 3H, 6-methoxy), 3.79 (m, 1H, 2-CH naphthalene), 4.17 (d, 1H, NH-thiazole), 4.19 (d, 1H, 1-CH naphthalene, *J* = 7.16 Hz), 6.47 (s, 1H, 4-CH thiazole), 6.96 (d, 4H, 5,6,7&8-CH-naphthalene), 7.50 (d, 2H, 3, 5-CH phenyl), 7.79 (d, 2H, 2, 6-CH phenyl); ^{13}C NMR (100 MHz) δ: 20.2, 22.2 (CH_2-naphthalene); 53.5 (CH_3-O); 59.2 (C-NH); 78.7 (C-OH); 98.0, 162.4 (C-S thiazole); 126.5, 133.9, 126.5, 137.2, 146.4 (phenylthiazole); 110.4, 111.3, 119.6, 119.6, 155.8 (naphthalene); FTIR (KBr, ν_{max}, cm^{-1}): 1651 (N-H bending); 1536 (N-O stretch); 1368 (C-N); 2841 (aliphatic C-H); 781 (C-H aromatic bending); 3435 (Sec. N-H); Mass (70 ev *m/z*): 397.0; Anal. Calcd for $C_{20}H_{19}N_3O_4S$: C 60.44, H 4.82, N 10.57; found: C 60.56, H 4.76, N 10.45.

6-Methoxy-1-[4-(4-methylphenyl)thiazol-2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 3): Physical state white crystals; Yield 83 %; m.p. 266-268 °C; R_f value 0.7214 (hexane: ethyl acetate 95:5); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.24-1.26 (m, 2H, 3-CH_2 naphthalene), 2.23-2.31 (s, 3H, 4-CH_3 phenyl), 2.40 (t, 2H, 4-CH_2-naphthalene), 3.64 (m,1H, 2-CH naphthalene), 3.67-3.73 (m, 3H, 6-methoxy) 3.76 (d, 1H, 2-OH naphthalene), 4.05 (d, 1H, 1-CH naphthalene), 4.33 (d, 1H, NH-thiazole), 6.55-6.63 (d, 3 × 1H, 5,7&8-CH naphthalene), 7.12 (s, 1H, 4-CH thiazole), 7.23-7.4 (t, 2H, 3, 5-CH phenyl), 7.85-7.96 (d, 2H, 2,6-CH phenyl); ^{13}C NMR (100 MHz) δ: 24.5 (CH_3); 21.6, 25.4 (CH_2 naphthalene); 54.7 (CH_3-O); 60.2 (C-NH); 79.6 (C-OH); 99.4, 163.4 (C-S thiazole); 120.7, 127.5, 138.2, 127.4, 120.7, 147.4 (phenylthiazole); 111.4, 112.4, 129.6, 134.9, 156.9 (naphthalene); FTIR (KBr,

ν_{max}, cm^{-1}): 1637 (N-H bending); 794 (C-H bending); 1309 (C-N); 2853 (aliphatic C-H); 1543 (C=C aromatic); 3447 (sec. N-H); Mass (70 ev *m/z*): 366.1; Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C 68.82, H 6.05, N 7.64; found: C 68.96, H 6.26, N 7.55.

4-Methyl-1-(3,4-dichlorophenylthiazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 4): Physical state brownish yellow crystals; Yield 75 %; m.p. 291-293 °C; R_f value 0.7322 (hexane: ethyl acetate 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28-1.32 (d, 3H, 4-methyl), 1.34 (m, 2H, 3-CH_2 naphthalene), 2.5 (t, 1H, 4-CH_2 naphthalene), 3.56 (m, 1H, 2-CH naphthalene), 3.15 (d, 1H, *J* = 7.2, 2-OH naphthalene), 4.2 (d, 1H, NH thiazole), 4.3 (d, 1H, 1-CH naphthalene, *J* = 7.15 Hz) 7.05-7.17 (d, 4 × 1H, 5,6,7&8-CH-naphthalene), 7.20 (s, 1H, 4-CH thiazole), 7.20 (t, 1H, 5-CH phenyl), 7.31 (d, 1H, 6-CH phenyl), 7.57 (d, 1H, 2-CH phenyl); ^{13}C NMR (100 MHz) δ: 21.8 (CH_3); 28.2, 30.0 (CH_2-naphthalene); 60.8 (C-NH); 80.4 (C-OH); 100.5, 164.2 (C-S thiazole); 130.5, 133.1, 133.1, 132.4, 129.4, 148.2 (phenylthiazole); 128.6, 125.4, 125.4, 128.6 (naphthalene); FTIR (KBr, ν_{max}, cm^{-1}): 1607 (N-H bending), 771 (C-Cl), 1234 (C-N), 2816 (aliphatic C-H), 3436 (sec. N-H); Mass (70 ev *m/z*): 404.4; Anal. Calcd for $C_{20}H_{18}N_2OSCl_2$: C 59.26, H 4.48, N 6.91; found: C 59.32, H 4.59, N 6.67.

6-Methoxy-1-[4-(4-bromophenyl)thiazol-2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 5): Physical state pale white crystals; Yield 79 %; m.p. 297-299 °C; R_f value 0.4615 (hexane: ethyl acetate 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (m, 1H, 3-CH_2 naphthalene), 1.67 (m, 1H, 3-CH_2 naphthalene), 2.54 (t, 1H, 4-CH_2 naphthalene), 2.71 (t, 1H, 4-CH_2 naphthalene), 3.31 (t, 1H, 2-OH naphthalene), 3.70 (m, 3H, 6-methoxy), 3.86 (m, 1H, 2-CH naphthalene), 4.11 (d, 1H, NH-thiazole), 4.13 (d, 1H, 1-CH naphthalene, *J* = 7.16 Hz), 6.67-6.89 (d, 4H, 5,6,7 & 8-CH-naphthalene), 6.81 (s, 1H, 4-CH thiazole), 7.53-7.55 (d, 2H, 3,5-CH phenyl), 8.01-8.02 (d, 2H, 2,6-CH phenyl); ^{13}C NMR (100 MHz) δ: 20.4, 24.4 (CH_2 naphthalene); 53.5 (CH_3-O); 59.2 (C-NH); 78.7 (C-OH); 98.0, 162.4 (C-S thiazole); 119.6, 126.5, 137.2, 126.5, 119.6, 146.4 (phenylthiazole); 110.4, 111.3, 128.6, 134.9, 155.8 (naphthalene); FTIR (KBr, ν_{max}, cm^{-1}): 560 (C-Br), 1638 (N-H bending), 753 (C-H bending), 1243 (C-N), 2842 (aliphatic C-H), 1542 (C=C aromatic), 3445 (sec. N-H); Mass (70 ev *m/z*): 432.0; Anal. Calcd for $C_{20}H_{19}N_2O_2SBr$: C 55.69, H 4.44, N 6.49; found: C 55.46, H 4.52, N 6.62.

4-Methyl-1-(3-nitrophenylthiazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 6): Physical state yellow crystals; Yield 68 %; m.p. 262-265 °C; R_f value 0.6213 (hexane: ethylacetate 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29-1.30 (d, 3H, 4-CH_3 napthalene) 1.99-2.04 (m, 2H, 3-CH_2 naphthalene), 3.01 (t, 2H, 4-CH_2 naphthalene), 3.16-3.20 (m, 1H, 2-CH naphthalene), 3.62 (d, 1H, *J* = 7.3, 2-OH naphthalene), 4.27 (d, 1H, NH-thiazole), 4.30 (d, 1H, 1-CH naphthalene, *J* = 7.14 Hz), 7.08-7.14 (m, 4 × 1H, 5,6,7&8-CH-naphthalene), 7.24-7.26 (s, 1H, 4-CH thiazole), 7.35-7.38 (m, 2H, 5,6-CH phenyl), 7.53 (s, 1H, 2-CH phenyl); ^{13}C NMR (100 MHz) δ: 21.8 (CH_3); 24.6, 25.3 (CH_2 naphthalene); 60.8 (C-NH); 80.4 (C-OH); 100.5, 164.7 (C-S thiazole); 121.8, 128.6, 139.7, 128.6, 121.8, 148.9 (phenylthiazole); 130.2, 133.2, 129.4, 135.7, 156.4 (naphthalene); FTIR (KBr, ν_{max}, cm^{-1}): 1608 (N-H bending); 1542 (N-O stretch); 1164 (C-N); 2841 (aliphatic C-H); 780, 828 (C-H aromatic bending); 3445 (sec. N-H); Mass (70 ev *m/z*): 381.6; Anal. Calcd for $C_{20}H_{19}N_3O_3S$: C 62.97, H 5.02, N 11.02; found: C 62.86, H 5.15, N 11.05.

6-Methoxy-1-[4-(4-nitrophenyl)thiazol-2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 7): Physical state light yellow crystals; Yield 65 %; m.p. 287-289 °C; R_f value 0.8772 (hexane: ethyl acetate 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.62-0.64 (m, 1H, 3-CH_2 naphthalene), 0.66-0.68 (m, 1H, 3-CH_2 naphthalene), 1.64 (t, 1H, 4-CH_2 naphthalene), 2.19 (t, 1H, 4-CH_2 naphthalene), 2.45 (t, 1H, 2-OH naphthalene), 2.93 (m, 3H, 6-methoxy), 3.78 (m, 1H, 2-CH naphthalene), 4.21 (d, 1H, NH-thiazole), 6.47 (s, 1H, 4-CH thiazole), 6.95 (d, 4H, 5,6,7&8-CH-naphthalene), 7.50 (d, 2H, 3,5-CH phenyl), 7.78 (d, 2H, 2,6-CH phenyl); ^{13}C NMR (100 MHz): 25.7, 26.4 (CH_2 naphthalene); 55.8 (CH_3-O); 60.9 (C-NH); 80.5 (C-OH); 100.5, 164.7 (C-S thiazole); 121.7, 128.6, 137.3, 128.6, 121.7, 148.6 (phenylthiazole); 112.4, 113.3, 130.5, 136.6, 157.5 (naphthalene); FTIR (KBr, ν_{max}, cm^{-1}): 1641 (N-H bending); 1542 (N-O stretch); 1108, 1338 (C-N); 2842 (aliphatic C-H); 3160 (C-H aromatic stretching); 3446 (sec. N-H); 3400 (-OH); Mass (70 ev *m/z*): 397.1; Anal. Calcd for $C_{20}H_{19}N_3O_4S$: C 60.44, H 4.82, N 10.57; Found: C 60.19, H 4.98, N 10.46.

4-Methyl-1-(4-methylphenylthiazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 8): Physical state white crystals; Yield 62 %; m.p. 250-252 °C; R_f value 0.5449 (hexane: ethyl acetate 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.26 (d, 2H, 4-CH_3 naphthalene), 2.32-2.34 (m, 2H, 3-CH_2), 2.35 (s, 3H, 4-CH_3 phenyl), 2.36-2.39 (t, 1H, 4-CH_2 naphthalene), 3, 54-3.56 (m, 1H, 2-CH naphthalene), 3.57-3.62 (m, 3H, 6-methoxy), 3.63-3.65 (m, 1H, 2-OH naphthalene), 4.05 (d, 1H, NH-thiazole), 4.33 (d, 1H, 1-CH naphthalene, *J* = 7.16 Hz), 6.67 (d, 4 × 1H, 5,6,7&8-CH naphthalene), 7.26 (s, 1H, 4-CH thiazole), 7.51-7.53 (t, 2H, 3,5-CH phenyl), 8.01-8.02 (d, 2H, 2,6-CH phenyl); ^{13}C NMR (100MHz) δ: 21.7 (CH_3); 24.3 (CH_3 phenyl), 28.3, 30.2 (CH_2 naphthalene); 60.6 (C-NH); 80.2 (C-OH); 100.1, 164.7 (C-S thiazole); 129.6, 127.4, 129.6, 127.4, 130.5, 138.4, 148.9, (phenylthiazole); 125.8, 128.9, 125.8, 128.9, 156.4 (naphthalene); FTIR ((KBr, ν_{max}, cm^{-1}): 1641 (N-H bending); 830 (C-H bending); 1365 (C-N); 2850 (aliphatic C-H); 3160 (C-H aromatic stretching); 3231 (-OH); 3445 (sec. N-H); Mass (70 ev *m/z*): 350.1; Anal. Calcd for $C_{21}H_{22}N_2OS$: C 71.97, H 6.33, N 7.99; found: C 71.85, H 6.25, N 7.91.

6-Chloro-1-[4-(4-acetamidophenyl)thiazol-2-ylamino]-1,2,3,4-tetrahydronaphthalen-2-ol (AAP 9): Physical state white crystals; Yield 81 %; m.p. 272-275 °C; R_f value 0.8545 (hexane: ethyl acetate 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (s, 3H, acetamido), 2.09-2.12 (m, 2H, 3-CH_2 naphthalene), 2.90-2.92 (t, 2H, 4-CH_2 naphthalene), 3.31-3.33 (m, 1H, 2-CH naphthalene), 3.63 (d, 1H, 2-OH naphthalene), 3.67-3.68 (t, 1H, 1-CH naphthalene), 4.11 (d, 1H, NH-thiazole), 4.13 (d, 1H, 1-CH naphthalene, *J* = 7.16 Hz), 6.78-6.81 (m, 3H, 5,7&8-CH-naphthalene), 7.26 (s, 1H, 4-CH thiazole), 7.55 (d, 2H, 3, 5-CH phenyl), 7.99-8.02 (d, 2H, 2, 6-CHphenyl), 10.02 (s, 1H, NH-acetamido); ^{13}C NMR (100 MHz) δ: 22.8 (CH_3-CO); 22.5, 26.9 (CH_2 naphthalene); 60.8 (C-NH); 80.9 (C-OH); 100.9, 162.3 (C-S thiazole); 127.6, 128.9, 139.8, 127.6, 122.7, 149.1 (phenylthiazole); 125.9, 127.6, 129.5, 135.9,

156.5 (naphthalene); 131.7 (C-Cl); 164.3 (CO-CH_3); FTIR (KBr, ν_{max}, cm^{-1}): 1591 (N-H bending); 675 (C-Cl); 829 (C-H aromatic bending); 1333 (C-N); 1635 (C=O); 2968 (aliphatic C-H); 3139 (C-H aromatic stretching); 3436 (sec. N-H); Mass (70 ev *m/z*): 413.2; Anal. Calcd for $C_{21}H_{20}N_3O_2SCl$: C 60.94, H 4.87, N 10.15; Found: C 60.88, H 4.78, N 10.22.

Biological activity: Five Swiss albino mice (20-25 g) of either sex, aged 6-8 weeks were housed in groups of eleven. All experiments using animals were conducted in accordance with the CPCSEA Guideline for the Care and Use of Laboratory Animals and approved by the Institutional Animal Ethics Committee of Shri Guru Ram Rai Institute of Science and Technology (RS/IAEC/01/2011/EEC-4). Mice were supplied with test compounds (AAP1-9) 30 mg/kg orally to first 9 groups and remaining groups were assigned for Sertraline at dose 15 mg/kg and control, respectively. The standard Porsolt forced swimming test (FST)[18], Tail suspension test (TST)[19], Open field test (OFT)[20] were used to evaluate the antidepressant-like effect. The results are presented as means, standard error of means (SEM). Differences between data sets were considered as significant when p value was less than 0.05.

Acute toxicity: Healthy female mice (6-7 weeks old), weighed between 25 and 30 g, 3 animals in one cage was used to determine LD_{50} cut off values of two key hits from starting dose 50 mg/kg according to the Organisation for Economic Co-operation and Development (OECD) 423 guideline[21] and animals were observed after dosing at least once during 0.5, 24 and 36 h.

RESULTS AND DISCUSSION

A straightforward approach was applied to the filter out drug like candidates using Molinspiration and Osiris online services from a large set of ten thousand compounds. Each compound having distinguished alkenyl/alkyl/aryl/hetero alkyl-aryl substituent demonstrated different physico-chemical properties. Ninety five analogues that were in accordance with minimum violations using lipinske rule of five, are selected for docking studies.

In this present study the molecular interactions of SERT inhibitors were based upon CDocker docking and CDocker interaction energy calculations. The results from *in silico* assays conformationally defined 9 compounds with un-substituted or methoxy, chloro substituent in tetrahydronaphthalene at position 6 and unsubstituted or methyl at position 4 (Table-1). This compute-intensive method revealed that ligands AAP1 and 2 have exhibited the highest CDocker energy 48.39. Visual analysis of the pose explained that 5 resides Gly-24, Asn-27, Ser-355, Gly-408, Asp-404 forms hydrogen bonding with AAP 1 (Table-2).

These residues snugly fitted ligand inside the receptor molecular surface. In addition, we found π-π stacking interactions between ligand AAP 1 and protein residues, Arg-30 and Try-108 (Fig. 1). The common feature of these ligands is connectivity Tween tetrahydronaphthalene and phenylthiazole ring through NH bridge. The synthetic strategy used for construction of these *in silico* actives was described previously[13] and is shown in **Scheme-I**.

Structure of these title ligands was confirmed on behalf of their spectrometric and CHN data analysis. All synthesized compounds were evaluated for antidepressant-like activity in mice and two actives AAP 1 and AAP 2 have shown the highest biological activity in both computational and *in vivo* procedures (Table-3).

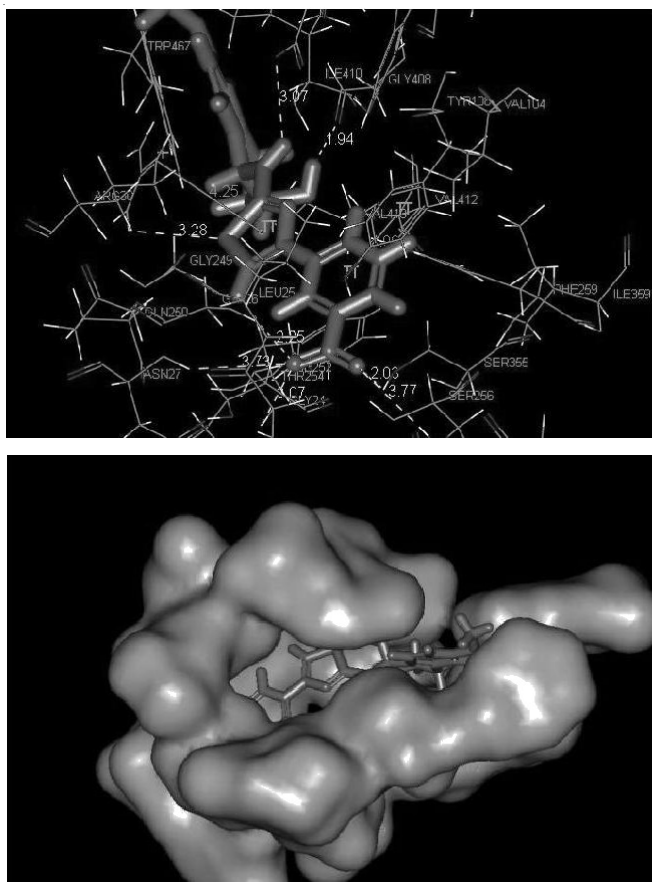


Fig. 1. Predicted AAP 1 contact

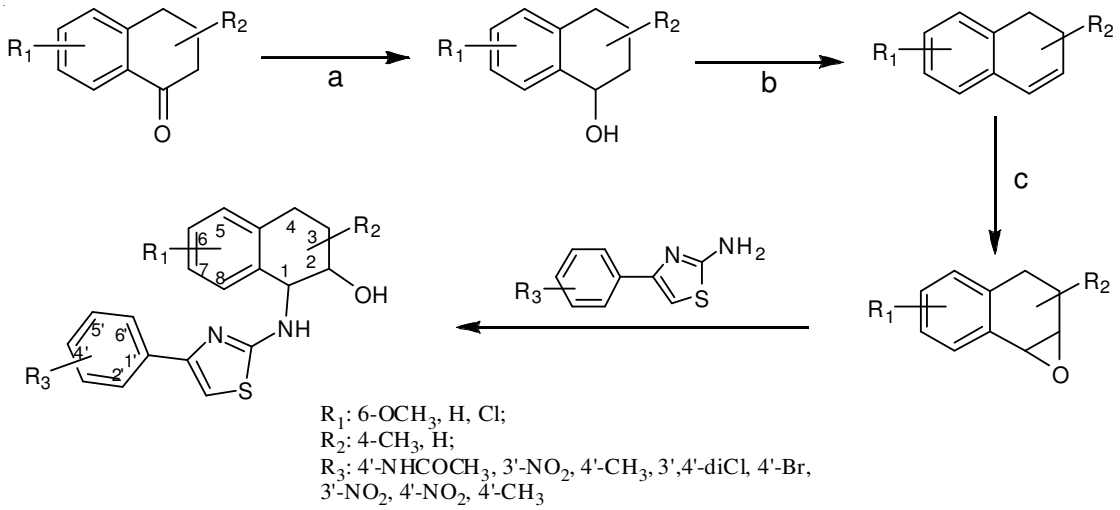
TABLE-2
KEY INTERACTION IN SEROTONIN RECEPTOR WITH LIGAND AAP 1

Hydrogen bond interaction	Distance (Å)	Angle DHA	Angle HAY
A:GLY24:HN-AAP1:O28	3.0725	113	128
A:ASN27:HN-AAP1:O28	3.7259	133	153
A:SER355:HG-AAP1:O27	2.0327	122	153
AAP1:H35-A: GLY408:O	1.9417	151	119
AAP1:H36-A:ASP404:OD2	3.0655	134	119
Pi interaction			
AAP1-A:ARG30:NE	4.2480	Pi Cation monitor	
AAP1-A:TYR108	4.9862	PiPi monitor	

TABLE-3
ANTIDEPRESSANT-LIKE ACTIVITY OF COMPOUNDS

Compounds	FST Duration of immobility# (s)	TST Duration of immobility# (s)	OFT no. of crossings in the square
AAP 1	39.6 ± 3.73	48.2 ± 2.67	102.0 ± 3.34
AAP 2	37.8 ± 3.59	50.0 ± 2.81	96.0 ± 2.29
AAP 3	61.6 ± 2.13	105.2 ± 3.39	117.2 ± 2.57
AAP 4	64.8 ± 1.65	148.4 ± 3.16	107.6 ± 2.07
AAP 5	63.2 ± 1.01	103.0 ± 3.35	112.8 ± 1.92
AAP 6	65.2 ± 2.84	105.8 ± 2.35	113.6 ± 2.91
AAP 7	69.4 ± 2.47	96.0 ± 2.78	107.8 ± 2.25
AAP 8	74.0 ± 2.33	95.2 ± 2.02	116.2 ± 2.47
AAP 9	77.4 ± 2.14	114.4 ± 2.76	108.4 ± 2.75
Sertraline	58.2 ± 1.47	87.6 ± 2.34	80.1 ± 2.83
Control	117.2 ± 1.15	140.8 ± 1.98	107.6 ± 3.88

#Values represent the mean ± S.E.M., *Significantly compared to control (Dunnet's test; $p < 0.05$)



Scheme-I: Reaction and conditions (a) $NaBH_4$/MeOH, (b) $KHSO_4$, (c) *m*-chloro perbenzoic acid/dichloro methane

in vivo Test utilizes the established phenomenon of receptor mediated inhibition, therefore a marked biological effect was exhibited by these ligands. Literature clearly predicts that tetrahydronaphthalene nucleus is required for antidepressant activity[22,23]. The results indicated that identified compounds AAP 1 and AAP 2 elicited mean immobility time in mice 39.6 and 37.8 sec, respectively at a dose 30 mg/kg body weight in FST model. The mean immobility times were significantly different from the control animals, better than all the other compounds tested and comparable to standard sertraline at a dose 15 mg/kg. Further substitution at 6th position with electron withdrawing methoxy group augmented biological activity and introduction of acetamido group at para position to the phenylthiazole ring caused a increase in the antidepressant-like activity as reflected by AAP 1. The addition of 4-methyl (AAP 3), 4-bromo(AAP 5) and 4-nitro (AAP 7) groups in phenyl ring failed to elicit the reduction in the immobility time. This was different from the standard Sertraline indicate that the methyl, bromo and nitro groups are causing a loss in the antidepressant-like activity. The introduction of 6-chloro group of tetrahydronapthalene nucleus (AAP 9) abolishes the antidepressant-like activity (Fig. 2).

The presence of electron donating 4-methyl group in tetrahydronapthalene nucleus along with 3-nitro and 4-methyl substituted phenylthiazole (AAP 6 and AAP 8) displayed 105.8 and 95.2 sec, respectively of mean immobility time, but this is non-significantly different from the standard Sertraline 87.6 sec in TST model, indicate that the methyl group at 4 position of tetrahydronapthalene is causing a loss in the antidepressant-like activity. Further, 6-methoxy showed the optimal activity in mice behavior model using TST from its ability to cause SERT inhibition. The derivatives comprised of phenylthiazole functionalized, 4-acetamido and 3-nitro substituents have shown prominent biological effects. OFT results addressed that these compounds were practically non-stimulatory and showing no significant effect on locomotion at a dose 30 mg/kg in comparison to Sertraline. As listed in Table-3, there was about three fold improvement in bioactivity from AAP 11 in mice

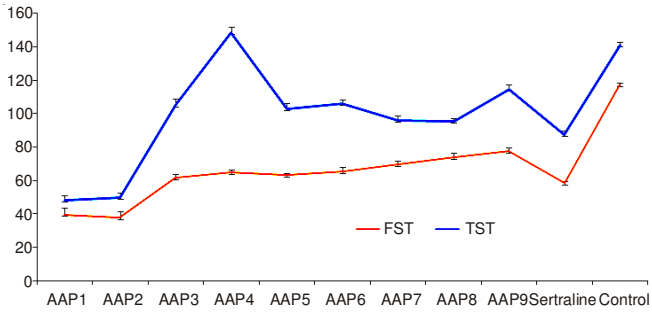


Fig. 2. Mice behavioral model (FST and TST)

behavior model. Therefore, it is obvious that molecular docking dictates not only the orientation of ligand but also prescreens compounds for the finest pharmacological activity.

Table-4 summarizes results for oral toxicity study of two active compounds (AAP 1 and AAP 2) in accordance with OECD guidelines. LD_{50} cut off value was found to be 1000 mg/kg body weight as compared to standard (ibuprofen) value 500 mg/kg. Thus these two compounds were found to be non toxic.

TABLE-4
ACUTE TOXICITY OF COMPOUNDS

Compound	LD_{50} cut off value mg/kg body weight
AAP 1	1000
AAP 2	1000
Ibuprofen (standard)	500

Conclusion

In this paper, we have demonstrated the use of CHARMm docking based design for 1,2,3,4-tetrahydro-naphalene class. These putative ligands were involved in optimal *in silico* activity towards the SERT transporter. Synthesis of 9 actives was achieved in simple and efficient manner. Interestingly, the antidepressant-like effect in mice behavior model identified two hits AAP1 and AAP2, with reasonable non-toxicity using standard OECD guideline.

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REFERENCES

1. C.L.M.L.J. Verlinde and W.G.J. Hol, *Structure*, **2**, 577 (1994).
2. D. Kuntz, *Science*, **257**, 1078 (1992).
3. B.S.P. Romano T. Kroemer, *Curr. Protein Pept. Sci*., **8**, 312 (2007).
4. E. Varkondi, F. Pinter, K. Robert, R. Schwab, N. Breza, L. Orfi, G. Keri and I. Petak, *J. Recept. Signal Transduct. Res*., **28**, 295 (2008).
5. C. Ketron, W.A. Denny, D.E. Graves and N. Osheroff, *Biochemistry*, **51**, 1730 (2012).
6. Q.Z. Zheng, F. Zhang, K. Cheng, Y. Yang, Y. Chen, Y. Qian, H.J. Zhang, H.Q. Li, C.F. Zhou, S.Q. An, Q.C. Jiao and H.L. Zhu, *Bioorg. Med. Chem*., **18**, 880 (2010).
7. M. Buchanan, J.H. Shih, J.W. Astin, G.W. Rewcastle, J.U. Flanagan, P.S. Crosier and P.R. Shepherd, *Clin. Sci.*, **122**, 449 (2012).
8. G.E. Simon, *Biol. Psychiatry*, **54**, 208 (2003).
9. R. Lanzenberger, G.S. Kranz, D. Haeusler, E. Akimova, M. Savli, A. Hahn, M. Mitterhauser, C. Spindelegger, C. Philippe, M. Fink, W. Wadsak, G. Karanikas and S. Kasper, *Neuroimage*, **63**, 874 (2012).
10. L.L. Brunton, D.K. Blumenthal, N. Murri, R.H. Dandan and B.C. Knollmann, Goodman & Gilman's The Pharmacological Basis of Therapeutics. edn. 12, McGraw-Hill, New York, ISBN 978-0-07-162442-8 (2011).
11. J.M. Grohol, Top 25 Psychiatric Medication Prescriptions for 2011 Psych Central (2012); Available from: http://psychcentral.com/lib/2012/top-25-psyciatric-medication-prescriptions-for-2011.
12. Z. Zhou, J. Zhen, N.K. Karpowich, C.J. Law, M.E.A. Reith and D.N. Wang, *Nat. Struct. Mol. Biol*., **16**, 652 (2009).
13. A. Uppal, P. Kothiyal and A. Singh, *J. Heterocycl. Chem.*; doi 10.1002/jhet.2203.
14. http://www.chemaxon.com/marvin/sketch/index.php Retrieved 1 January (2013).
15. Calculated based on the methodology available from: http://www.molinspiration.com/cgi-bin/properties Retrieved 9 January (2013).
16. Calculated based on the methodology available from: http://www.organic-chemistry.org/prog/peo/Retrieved 15 January (2013).
17. K. Bhandari, V.L. Sharma, C.M. Singh, G. Shanker and H.K. Singh, *J. Indian Chem.*, **39B**, 468 (2000).
18. R.D. Porsolt, M. Le Pichon and M. Jalfre, *Nature*, **266**, 730 (1977).
19. L. Steru, R. Chermat, B. Thierry and P. Simon, *Psychopharmacology*, **85**, 367 (1985).
20. C.S. Hall and E. L. Ballachey, *Univ. Calif. Publ. Psych*, **6**, 1 (1932).
21. Test No. 423: Acute Oral Toxicity-Acute Toxic Class Method; OECD Guidelines for the Testing of Chemicals, pp. 1-14(14) (2010).
22. Z. Rogoz, G. Skuza and A. Kodzinska, *Pol. J. Pharmacol*., **56**, 519 (2004).
23. Y. Kitamura, H. Araki, K. Shibata, Y. Gomita and Y. Tanizaki, *Eur. J. Pharmacol*., **481**, 75 (2003).