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Bioisosteric replacement of dihydropyrazole of 4*S*-(−)-3-(4-chlorophenyl)-*N*-methyl-*N*′-[(4-chlorophenyl)-sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-caboxamidine (SLV-319) a potent CB1 receptor antagonist by imidazole and oxazole☆

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Abstract—Design, synthesis and conformational analysis of few imidazole and oxazole as bioisosters of 4*S*-(−)-3-(4-chlorophenyl)-*N*-methyl-*N*′-[(4-chlorophenyl)-sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-caboxamidine (SLV-319) **2** is reported. Computer assisted conformational analysis gave a direct clue for the loss of CB1 antagonistic activity of the ligands without a fine docking simulation for the homology model.

CB1 receptor antagonist is a promising approach to treat the obesity by reducing appetite and body weight.[1] Rimonabant hydrochloride (**1**) (SR 141716A) (Fig. 1) is the first therapeutically potent and selective CB1 receptor antagonist, recently approved in Europe as antiobesity drug, which belongs to diaryl pyrazole family.[2]

Since the discovery of Rimonabant, several classes of CB1 receptor antagonists with diverse chemical structures have been disclosed.[3–5] Lange et al. from Solvay Pharmaceuticals have disclosed the 3,4-diaryl dihydropyrazole **2** (SLV-319) (Fig. 1) as a CB1 antagonist, which has elicited potent in vitro[6] and in vivo[7] activities and are currently in Phase IIB.

Bioisosteric replacement is one of the modest methodologies to create therapeutically equivalent surrogates. There are number of reports for the bioisosteric replacement of pyrazole nucleus of rimonabant **1** by pyrazine,[8] imidazole,[9] thiazoles,[10] triazoles[10] and dihydropyrazoles.[11]

More recently, we have synthesized several diaryl dihydropyrazole carboxamide derivatives using bioisosteric replacement in a rational approach in conjunction with

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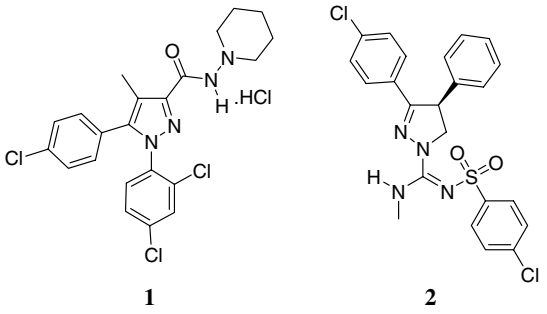


1 **2**

Figure 1. Potent CB1 receptor antagonists.

molecular modeling studies.[12] Wherein the optimization of the diaryl dihydropyrazole-3-carboxamide class of compounds led to the compound as potent CB1 receptor antagonist with significant antiobesity effect in animal model and similar interactions of the diaryl dihydropyrazole-3-carboxamides have been observed in the homology models of CB1 receptor as those with **1** and **2**.[12]

However, no studies have been disclosed towards bioisosteric replacement of dihydropyrazole moiety of sulfonyl carboxamidine derivative **2** by different heterocycles.

In continuation of our cannabinoid research,[12–17] we selected compound **2** for further modification and the dihydropyrazole system of **2** was replaced by isosters such as imidazole and oxazole to afford the compounds **3**–**7** (Fig. 2).[18] Further the compounds **3**–**7** were studied for in vitro (Tables 1 and 2), in vivo pharmacological evaluation in relevant CB1 antagonist models (Table 3) and conformational analyses (Figs. 3 and 4).

The compounds **3**–**7** have been synthesized as depicted in Scheme 1. The oxazole ethyl ester derivative **8** and corresponding imidazole derivatives were synthesized as described in the literature.[9,10,19] Hence, ethyl ester derivative **8** was directly converted into amide **9** using trimethylaluminium and ammonium chloride.[20] Amide derivative **9** was converted to nitrile intermediate **10**

Table 1. In vitro hCB1 functional assay for assessing cAMP activity for compounds **3**–**7**

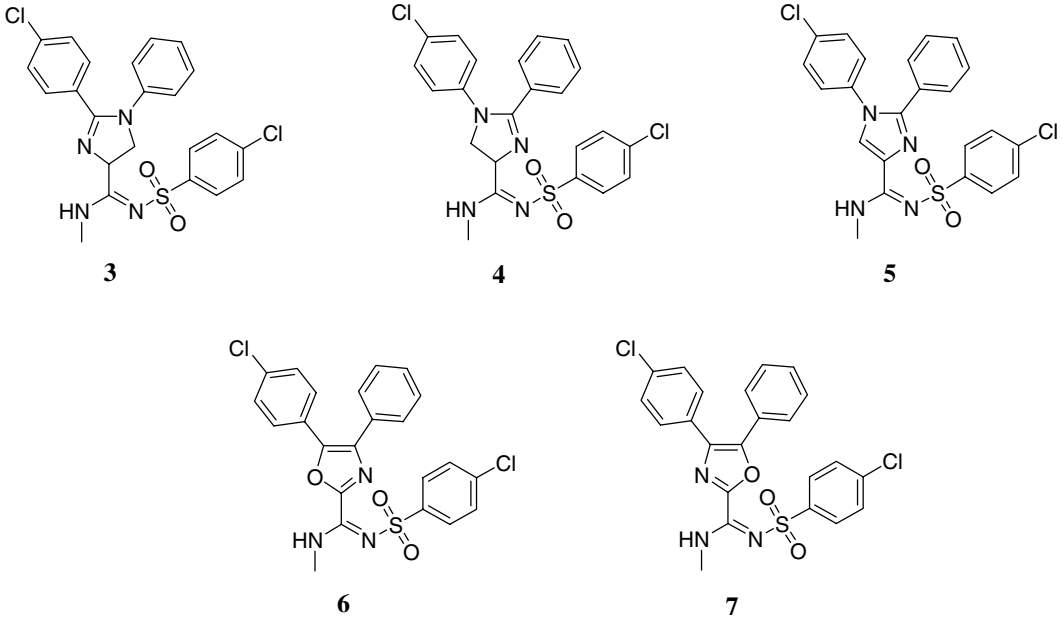
Compound	Concentration (μM)	hCB1 (cAMP)[a] pmol/μg protein
DMSO		0.04 ± 0.00
Forskolin	10	10.12 ± 0.64
WIN-55212-2	100	1.27 ± 0.04
3	10	0.89 ± 0.07
4	10	0.91 ± 0.19
5	10	1.01 ± 0.17
6	10	0.78 ± 0.05
7	10	0.95 ± 0.08
2	10	4.09 ± 0.27
1	10	8.45 ± 1.30

[a] Values indicate mean ± SD performed in duplicate and the results being representative of at least three independent experiments.

Table 2. In vitro hCB1 functional assay for assessing cAMP activity at lower concentrations of WIN-55212-2 for compounds **3**–**7**

Compound	Concentration (μM)	hCB1 (cAMP)[a] pmol/μg protein
DMSO		0.03 ± 0.00
Forskolin	2	1.98 ± 0.23
WIN-55212-2	1	0.69 ± 0.26
3	10	1.22 ± 0.08
4	10	0.94 ± 0.06
5	10	0.55 ± 0.00
6	10	0.60 ± 0.31
7	10	1.3 ± 0.15

[a] Values indicate mean ± SD performed in duplicate and the results being representative of at least three independent experiments.



3 **4** **5**

6 **7**

Figure 2. Novel Imidazole and Oxazole bioisosters of SLV-319.

Table 3. In vivo efficacy of compounds **3**–**7** in 5% sucrose solution intake model in female Zucker fa/fa rats at a single oral dose of 10 mg/kg

Compound	5% Sucrose solution intake in 4 h in gram[a]	% Inhibition in intake of 5% sucrose solution
Control	37.9 ± 3.8	
3	32.4* ± 4.7	14.4 ± 6.8
4	37.1 ± 2.9	2.2 ± 8.5
5	35.4 ± 3.2	6.7 ± 7.3
6	36.3 ± 4.1	4.3 ± 12.1
7	37.7 ± 5.2	0.6 ± 14.1
2	23.6* ± 2.7	37.6 ± 5.3
1	24.2* ± 4.2	36.1 ± 10.5

[a] Values indicate Mean ± SEM for $n = 6$ rats in 4 h.
* $p < 0.05$, when compared with the control group, one way ANOVA followed by Dunnett's multiple comparison test.

using oxalyl chloride and dimethyl formamide.[21] Amidine **11** was conveniently synthesized by reacting nitrile derivative **10** and methylamine hydrochloride using trimethylaluminium.[22] Finally, amidine **11** was reacted with *p*-chlorobenzenesulfonylchloride in the presence of triethylamine affording compound **6**.[23] Employing the similar set of transformations the compounds **3**–**5** and **7** were also synthesized.

The bioisosters **3**–**7** have been synthesized and evaluated in two CB1 antagonist assays.[24,25] There are number of in vitro assay employed to explore the functionality of CB1 ligands. The cAMP quantification is one of the most commonly used methods.[26] The in vitro screening of the compounds **3**–**7** was done in hCB1 (cAMP) assay[24] and to our surprise, the compounds **3**–**7** did not response significantly in the forskolin-stimulated cAMP assay as compared to positive controls **1** and **2** (Table 1). Unlike **1** and **2** none of the compounds rescued 100 μM WIN-55212-2 mediated decrease of forskolin induced cyclic AMP generation. We further tested the antagonism of the compounds against 1 μM WIN-55212-2, where compounds **3** and **7** showed partial reversal of cyclic AMP decrease induced by 1 μM of the agonist (Table 2). In order to confirm this loss of responsiveness as CB1 antagonist, the same set of molecules was evaluated against appetite suppression model in

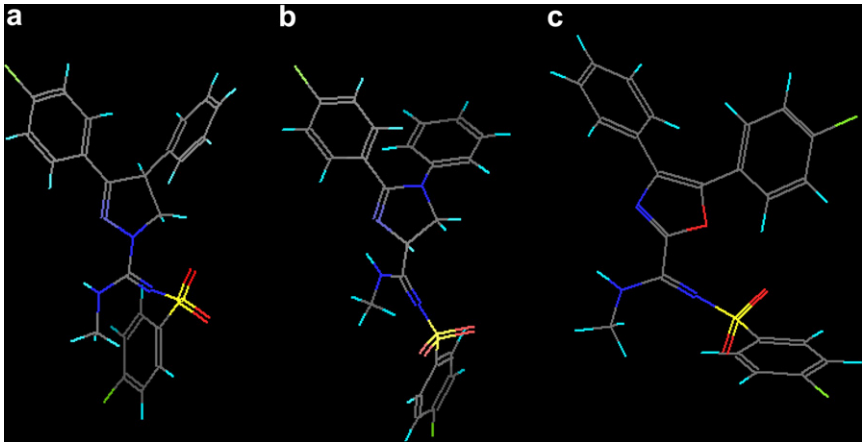


Figure 3. (a) Energy-minimized structure of compound **2**. (b) Energy-minimized structure of compound **3**. (c) Energy minimized structure of compound **6**.

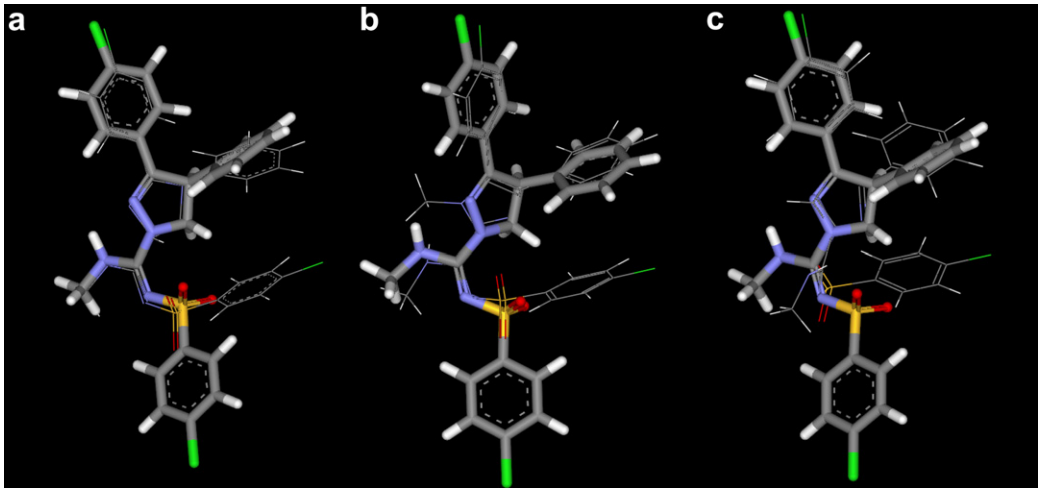
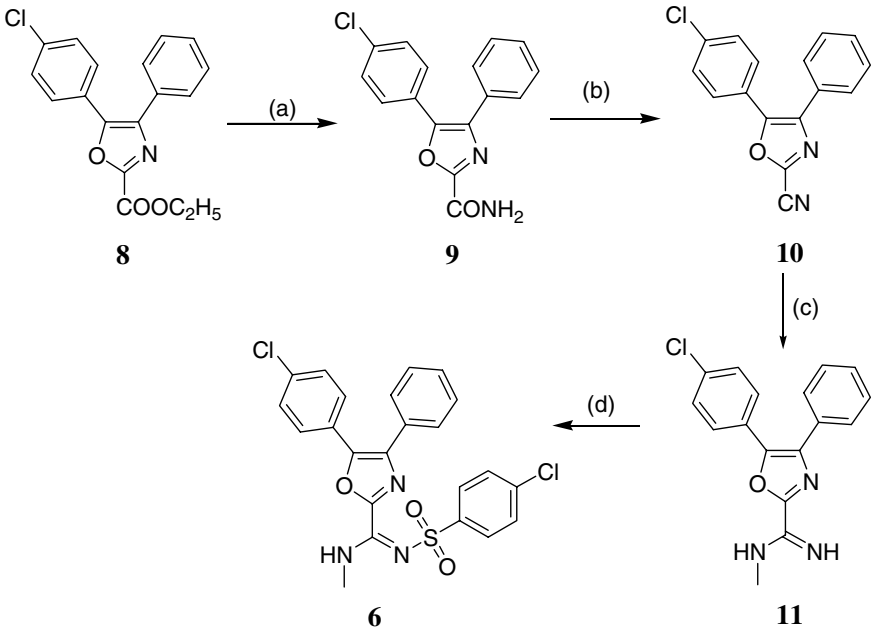


Figure 4. (a) Superimposition of molecule **3** (line mode) with **2** (stick mode). (b) Superimposition of molecule **5** (line mode) with **2** (stick mode). (c) Superimposition of molecule **6** (line mode) with **2** (stick mode).



Scheme 1. Reagents and conditions: (a) $Al(Me)_3$ (2.0 M sol in toluene), NH_4Cl, C_6H_6, 78–80 °C, 2 h, 68%; (b) $(COCl)_2$, DMF, 0–25 °C, 1 h, 77%; (c) $Al(Me)_3$ (2.0 M sol in toluene), $CH_3NH_2{\cdot}HCl$, C_7H_8, 108–110 °C, 2 h, 90%; (d) $4\text{-}ClC_6H_4SO_2Cl$, Ch_2Cl_2, NEt_3, 0–5 °C, 16 h, 45%.

rodents. The CB1 receptor antagonist markedly and selectively reduces sucrose feeding and drinking in rodents and in obese Zucker fa/fa rats,[27,28] thus the in vivo effects of the compounds **3**–**7** were evaluated in 5% sucrose solution intake model in female Zucker fa/fa rats[25] (Table 3). Notably, all the compounds **3**–**7** showed no suppression of sucrose solution consumption while compounds **1** and **2** induced a significant reduction in the solution intake. The in vitro and in vivo results prompted us to further verify the loss in CB1 receptor antagonistic activity. The computer assisted conformational analysis of the compounds **3**–**7** was carried out to establish the correlation between the orientation and biological activity of the molecules.

From the energy-minimized[29] structures of compounds **2**, imidazole isoster **3** and oxazole isoster **6**, large differences have been observed in the orientation of compounds **3** and **6** as compared to compound **2** (Fig. 3), which may be attributed for the loss in CB1 receptor antagonistic activity.

A general CB1 inverse agonist pharmacophore model required for crucial receptor–ligand interaction has been proposed on the basis of the CB1 receptor modeling.[4] Furthermore; conformational analysis[29,30] was carried out on compounds **2**, **3**, **5** and **6**. As the position of nitrogen changed, substitution on the central five membered ring also changed because of the change in the hybridization state. As can be seen from Figure 4, orientation of the *p*-chlorophenyl in the ligand **3** has become perpendicular to the *p*-chlorophenyl in **2**. There is also a rotation of the phenyl ring in the 4th position of the pyrazole ring. Similar conformational changes have been observed in the compound **6**. As in both compounds **3** and **6**, it was observed that the change in nitrogen position altered the position of phenyl ring and *p*-chlorophenyl substituent, this could well provide the explanation for bioisosters **3**–**7** did not show CB1 antagonistic activity.

In summary, the bioisosteric replacement of dihydropyrazole nucleus of compound **2** by imidazole and oxazole resulted in the complete loss of required conformation of the molecules, which is suggested to be necessary for CB1 receptor binding. Thus, bioisosters **3**–**7** did not show any pharmacological effect as CB1 receptor antagonist. In the absence of crystallized receptor–ligand complexes and without performing the molecular modeling in the homology model our conformational analysis still gave valuable information on the receptor–ligand interactions.

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18. *Characterization data for compounds* **3**–**7**: 4-Chloro-*N*-{[2-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-imidazol-4-yl]-methylamino-methylene} benzenesulfonamide **3**: 70% yield; 99.25% purity by HPLC; mp 98–100 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.34 (d, J = 4.34 Hz, 1H), 7.88–7.85 (dd, J = 6.72 and 1.83 Hz, 2H), 7.62–7.59 (dd, J = 6.78 and 1.87 Hz, 2H), 7.55 (d, J = 8.55 Hz, 2H), 7.43 (d, J = 8.56 Hz, 2H), 7.24 (t, J = 7.76 Hz, 2H), 7.08 (t, J = 7.70 Hz, 1H), 6.91 (d, J = 7.54 Hz, 2H), 5.53–5.46 (dd, J = 11.81 and 9.48 Hz, 1H), 4.54 (t, J = 11.19 Hz, 1H), 3.86 (t, J = 9.90 Hz, 1H), 2.77 (d, J = 4.65 Hz, 3H); IR (KBr) 3332, 1581, 1537 cm^{-1}; ESI-MS: 489 [M+H]$^+$.
4-Chloro-*N*-{[1-(4-chlorophenyl)-2-phenyl-4,5-dihydro-1H-imidazol-4-yl]-methylamino-methylene}-benzenesulfonamide **4**: 65% yield; 99.10% purity by HPLC; mp 95–97 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.92–7.89 (dd, J = 6.75 and 1.83 Hz, 2H), 7.47–7.43 (m, 6H), 7.36–7.31 (t, J = 7.59 Hz, 2H), 7.16–7.14 (dd, J = 6.78 and 2.0 Hz, 2H), 6.75–6.72 (dd, J = 6.84 and 2.0 Hz, 2H), 5.74 (t, J = 10.9 Hz, 1H), 4.69 (t, J = 11.23 Hz, 1H), 4.28 (t, J = 10.32 Hz, 1H), 2.91 (d, J = 4.95 Hz, 3H); IR (KBr) 3328, 1583, 1531 cm^{-1}; ESI-MS: 489.1 [M+H]$^+$.
4-Chloro-*N*-{[1-(4-chlorophenyl)-2-phenyl-1H-imidazol-4-yl]-methylamino-methylene}-benzenesulfonamide **5**: 30% yield; 98.71% purity by HPLC; mp 151–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.09 (d, J = 4.66 Hz, 1H), 8.31 (s, 1H), 7.86 (d, J = 8.50 Hz, 2H), 7.60 (d, J = 8.67 Hz, 4H), 7.40 (d, J = 8.69 Hz, 2H), 7.37 (br s, 5H), 2.87 (d, J = 4.62 Hz, 3H); IR (KBr) 3340, 1577, 1558 cm^{-1}; ESI-MS: 486.0 [M+H]$^+$.
4-Chloro-*N*-{[5-(4-chlorophenyl)-4-phenyl-oxazol-2-yl]-methylamino-methylene}-benzenesulfonamide **6**: 45% yield; 98.95% purity by HPLC; mp 168–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.91 (br s, 1H), 7.82 (d, J = 8.49 Hz, 2H), 7.60–7.57 (m, 4H), 7.55 (d, J = 4.67 Hz, 3H), 7.51–7.44 (m, 4H), 2.92 (d, J = 2.56 Hz, 3H); IR (KBr) 3375, 1593, 1558 cm^{-1}; ESI-MS: 487.1 [M+H]$^+$.
4-Chloro-*N*-{[4-(4-chlorophenyl)-5- phenyl-oxazol-2-yl]-methylamino-methylene}-benzenesulfonamide **7**: 40% yield; 98.64% purity by HPLC; mp 165–167 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.89 (br s, 1H), 7.92 (d, J = 8.55 Hz, 2H), 7.62–7.59 (m, 3H), 7.55 (d, J = 3.76 Hz, 2H), 7.52–7.48 (m, 6H), 2.92 (br s, 3H); IR (KBr) 3373, 1591, 1556 cm^{-1}; ESI-MS: 487.1 [M+H]$^+$.
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24. *In vitro cAMP assay*: Fatty acid-free BSA, IBMX (isobutyl methyl xanthine), RO20-1724 {4-[(3-butoxy-4-methoxyphenyl) methyl]-2-imidazololidinone}, forskolin and DMSO (hybrimax) were purchased from Sigma Chemical Co. cAMP detection ELISA kit was from Assay Designs, USA. Tissue culture reagents were purchased from Sigma and Hi-media. Other reagents used were all of analytical grade. The cAMP assay was carried out in Chinese Hamster Ovarian (CHO) cells (CHOK1) stably expressing human CB1 receptor following the method of Rinaldi-Carmona et al.[26] Cells grown to 80% confluence were maintained in HAM'S F12 medium containing 10% heat inactivated dialyzed fetal bovine serum and 0.8 mg/mL G-418. Cells were seeded at a density of 50,000 cells/well in 24-well plate, grown for 16–18 h, washed once with PBS and incubated for 30 min at 37 °C in plain HAM'S F12 containing 0.25% free fatty acid BSA, IBMX (0.1 mM) and RO20-1724 (0.1 mM). IBMX, the pan phosphodiesterase inhibitor and RO20-1724, the specific phosphodiesterase- 4 inhibitor were added to restore cAMP up to the detection limit. After 5 min incubation with the drugs, forskolin was added at a final concentration of 10 μM and incubation was carried out for another 20 min at 37 °C. The reaction was terminated by washing once with PBS and adding 200 μL lysis buffer comprising 0.1 N HCl and 0.1% Trition X-100. The lysates were centrifuged and aliquotes from supernatants were used for detection of cAMP by ELISA as per the manufacturer's protocol.
25. *5% Sucrose Solution Intake in Zucker falfa rats*: All the animals used in the study were procured from the Animal Breeding Facility of Zydus Research Center. Institutional Animal Ethical Committee approved all the study protocols. Female Zucker fa/fa rats (age of 10–12 weeks and 300–350 g of weight) were used for in vivo experiments, compounds were suspended with 0.5% carboxymethylcellulose sodium salt in distilled water. The test compounds were administered at the dose of 10 mg/kg and by oral route in a volume of 2 mL/kg

body weight. The obese Zucker fa/fa rats were housed individually and subjected to training for consuming 5% sucrose solution over a period of 4 h, by allowing access to the 5% sucrose solution in the bottles. Food and water were withdrawn during this time. This training was given for six consecutive days, at the same time of the day. On seventh day, the animals were randomized into groups of six animals each and treated with the test compounds. After one hour of treatment, the animals were exposed to the 5% sucrose solution for 4 h as that of the training schedule. The amount of sucrose solution consumed by each animal was calculated. Difference between the control and treatment groups were analyzed by performing one way ANOVA followed by Dunnett's test on sucrose solution consumption using Graph pad Prism software.

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29. The energy minimization procedure adopted is smart minimizer protocol in Discovery Studio 1.6, where 100 cycles of minimization are allowed at steepest descent, conjugate gradient and Newton–Raphson methods. All the modeling procedures adopted in the study are molecular mechanics with Charm Force Field.
30. All the computations were carried out on Accelrys Inc. Discovery Studio 1.6. Accelrys Inc., San Diego, CA.