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# Design, Synthesis and Biological Evaluation of Some New Piperazine Associated Hydrazone Derivatives

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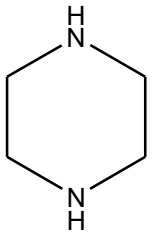
## ABSTRACT
A new series o of compound 2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide derivatives synthesized by the reaction of CetirizineHCl( 2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic acid dihydrochloride ) with $H_2SO_4$ and ethanol followed by esterification reaction in the presence of hydrazine hydrate to give (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan-2-one and its rection with cyclohexane carbaldehyde finally yield compound 2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide with its substituted derivative 4-dimethylamino- benzaldehyde. The compound was demonstrated for in vivo antidepressant activity by tail suspension test on Swiss albino mice. Compound was characterized by 1HNMR along with molecular docking studies. On the basis of evaluations compound have shown significant antidepressant activity as compared to the standarddrugs.
**Key words:** NMR, antidepressant activity, docking.

## Introduction
Piperazine, comprising six membered ring owing two nitrogen atoms in contradictory positions acts as mainstay for piperazine derived compounds and serves as agonist for gamma-amino-butyric acid (GABA) receptor in nematodes delivering remarkable antihelminthic activity. Piperazine showed excellent capacity to produce soluble urate by dissolving uric acid outside the body and became the first used solvent for uric acid[1-4].




Piperazine

In the first instance piperazine was entitled with piperidinefor their chemical resemblance. Piperidine is part of chemical constituent piperine structure found in black pepper. In recent years this scaffold have been redesigned by researchers evaluating its different pharmacological activities[5].In potential and commercially available pharmaceuticals, piperazine and its substituted moieties comes out in additional complex structure compositions. In potential pharmaceuticals, piperazine is available as antidepressants[6-8], neurodegenerative diseases(Alzheimer's disease, Parkinson's diseases)[9], pain suppressors/ moderators[10], antimicrobial agent [11] and for HIV treatment[12-13]. Piperazine moiety is also used

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

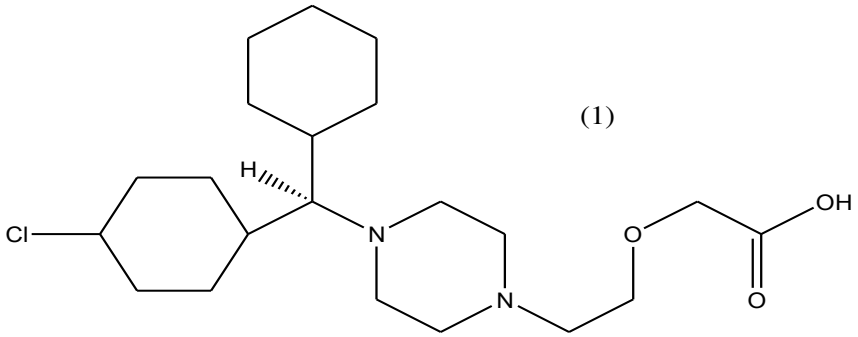
in various anticancer drugs[14-15]. In China, piperazineferulate is used to treat glomerulonephritis. Mechanism of action for this treatment involves the reduction of oxidative stress and inhibition of connective tissue growth factor in glomeruli[16-17]. Piperazineare exploited as principle moiety in several drugs such as ranolazine (antianginal)[18], Buspirone (antidepressant)[19], Zalospirone4 (antidepressant)[20], Ipsapirone5 (antidepressant)[21], Trazodone6 (antidepressant)[22], Cinnarizine7 (antihistamine)[23] , Cetirizine (antihistamine)8[24], Perphenazine (antipsychotic)[25], Quipazine (scientific research)[26], Fipexide (nootropic drug)[27] , 6-Nitroquipazine (selective serotonin reuptake inhibitor)[28], Benzylpiperazine (euphoric, stimulant properties)[29], and Perospirone (atypical antipsychotic)[30].

## Material Method

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), CDH (India) and S.D. Fine were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.25 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 1050C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds. Melting points were determined by using open capillary melting point apparatus and are reported uncorrected. Compounds were placed in one end of the sealed capillary and placed in the caves made for the capillary. Thermometer was placed in the cave. The temperature at which compound starts melting and the temperature at which it completely melts was recorded as a melting point range. FT-IR spectra (KBr) were recorded on a Perkin- Elmer Spectrometer BX-II spectrophotometer.

### General method for the synthesis of piperazine associated hydrazone derivatives-

**Step-1** Synthesis of (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan- Took 19.44 gm of CetrizineHCl( 2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic acid dihydrochloride).




(1)

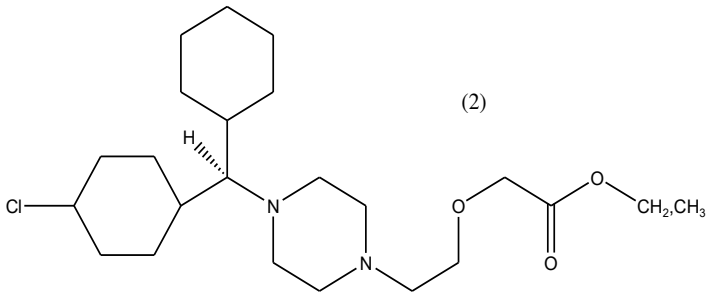
(2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid

Reaction of (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)acetic-acid with ethanol in the presemce of $H_2SO_4$ (few drops) and reflux for 5 to 6 hrs yield esters of (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan.

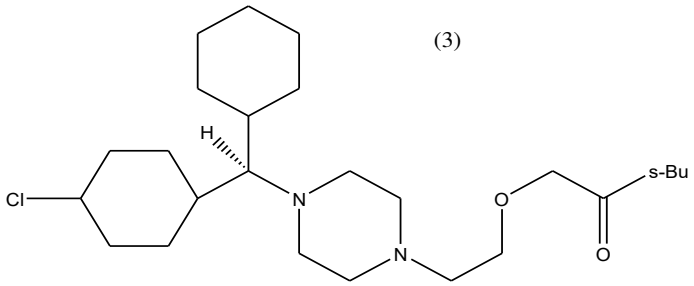
**Step-2 Synthesis of (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan-2-one-** Reaction of esters of (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan with 250mg of hydrazine

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

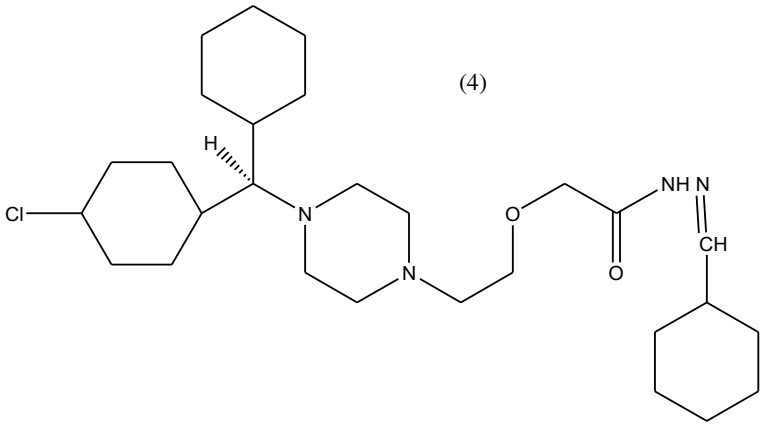
hydrate followed by reflux for 4 to5 hrs yield (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan-2-one.




**Step-3- 4 Synthesis of (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide-** Reaction of 2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan-2-one with cyclohexane carbaldehyde followed by reflux for 3 to 4 minutes yield Synthesis of (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide. Its substitution derivatives are 4-dimethylaminobenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde and 4-bromoacetophenone.




(2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan-2-one



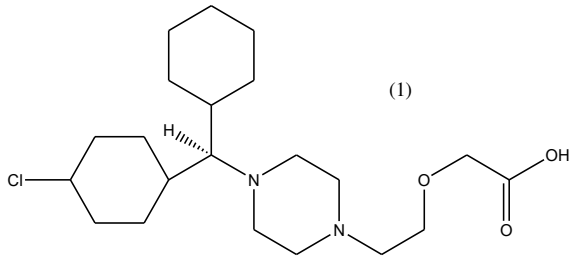

(2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexylmethylene-hydrazide

## Characterization of the synthesized compounds

Compound characterization-Compound no 01AG- (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide )1H NMR-(CDCl3, 300MHz), 6.5-8.5(Aromatic), 2-3 (CH2),1.4-1.7 (R-CH), 0-2(CH3ORCH2),2-3(CH2-Ketone),9-10(Aldehyde),9-10(NH), 0.7-1.3(R-CH3),1.2-1.4(R-CH2-R) Aromatic 22 ; CH2 08; CH03; CH3CH306; NH01

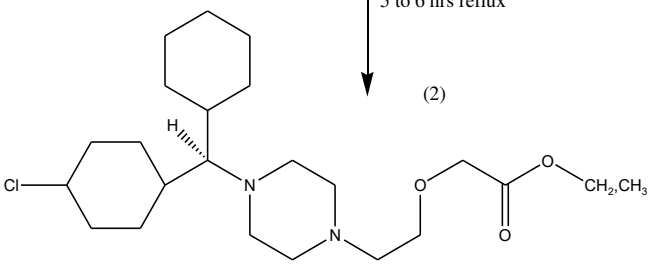
ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

## Synthetic Scheme



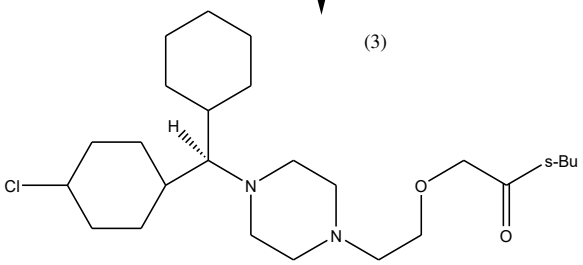

(2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid

C2H5OH(100ML)
few drops (H2SO4)
5 to 6 hrs reflux




`C2H5OH

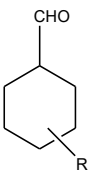
NH2NH2.H2O(250GM)
REFLUX 4 TO 5 HRS

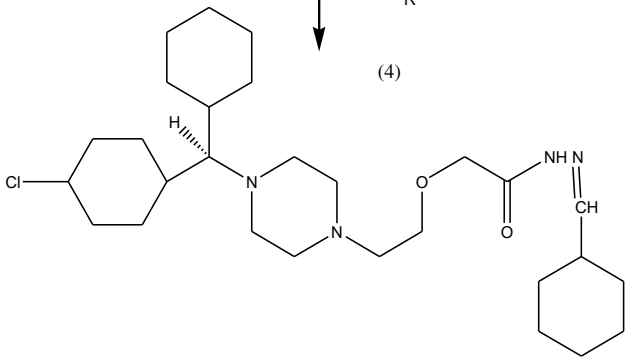



1-(2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-3-methyl-pentan-2-one

10 REFLUX 30 TO 45 MIN

CHO (HYDRAZIDE0




(2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexylmethylene-hydrazide

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

**In vivo Antidepressant Activity Screening**

**By Tail Suspension Test methods**

The In vivo Antidepressant activity was carried out at S. D. College Pharmacy & Vocational Studies, Muzaffarnagar. following the below mentioned procedures.

**Animals**

Swiss albino mice weighing 150-250 gm were attuned to temperature 23 ± 2 °C. Humidity surroundings were controlled (50-55%) followed by 12 h dark and 12 h light cycle as per CPCSEA guidelines. Maximum of two animals were caged in polypropylene cage and fed with water ad libitum and standard food. All the studies conducted were approved by Institutional Animal Ethical Committee according to prescribed guidelines of CPCSEA, Government of India (Reg. No. 876/Po/Re/S/05/CPCSEA).

The rats were divided four groups (n=6). Drugs/ vehicle were administered to the animals 60 min prior to study.

Group I: Negative control, administer saline 2 ml/kg orally.

Group II: Receive standard drug Imipramine (10 mg/kg orally)

Group III: Receive MEAS 30 mg/kg orally

Group IV: Receive MEAS 60 mg/kg orally.

**Procedure**

Tail suspension method was similarly followed as described[31]. All drugs were given 60 min prior to study. All rats were suspended 45 cm above the floor on the table edge and placed 1 cm from tail tip with the help of adhesive tape. The immobility duration caused by tail suspension was recorded during period of 7 min of the 10 min. When animals did not show any body movement, passively hanged these were considered as motionless.

**RESULT AND DISCUSSION**

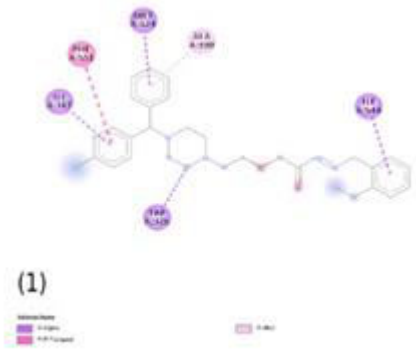
A structure diverse substituted (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide) derivative were synthesized according to general synthetic route as illustrated in scheme. The final product confirmed by 1HNMR,Molecular Docking, In vivo screening.

**1HNMR Characterization of the synthesized compounds**

Compound characterization-Compound no 01AG- (2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide )1H NMR-(CDCl3, 300MHz), 6.5-8.5(Aromatic), 2-3 (CH2),1.4-1.7 (R-CH), 0-2(CH3ORCH2),2-3(CH2-Ketone),9-10(Aldehyde),9-10(NH), 0.7-1.3(R-CH3),1.2-1.4(R-CH2-R) Aromatic 22 ; CH2 08; CH03; CH3CH306; NH01

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

**Docking Analysis of some Noval structure**



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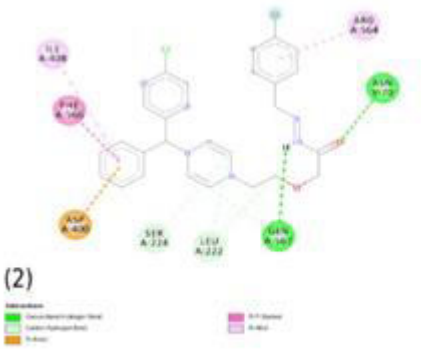

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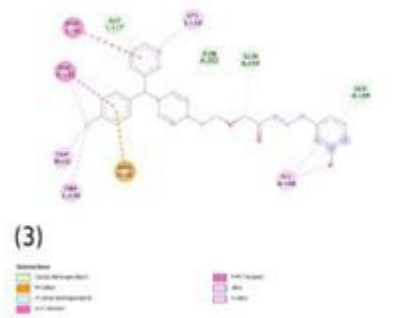

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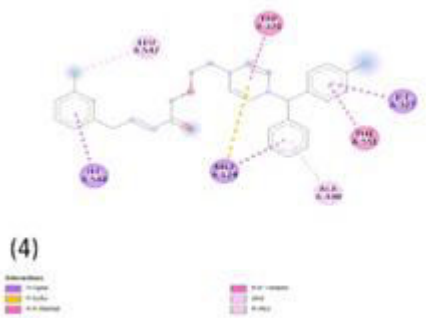

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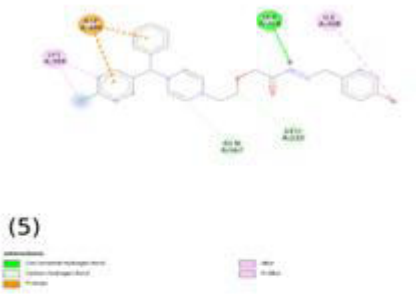

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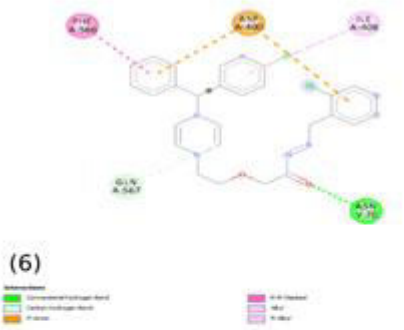

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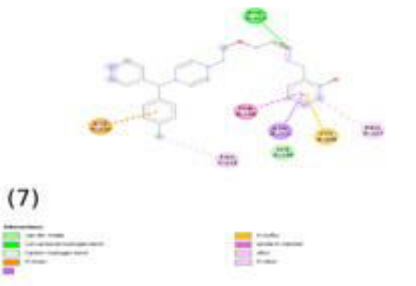

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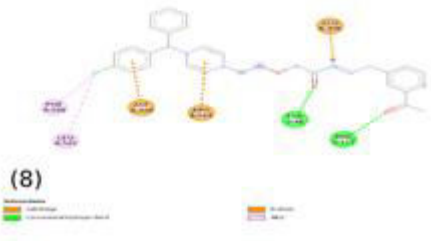

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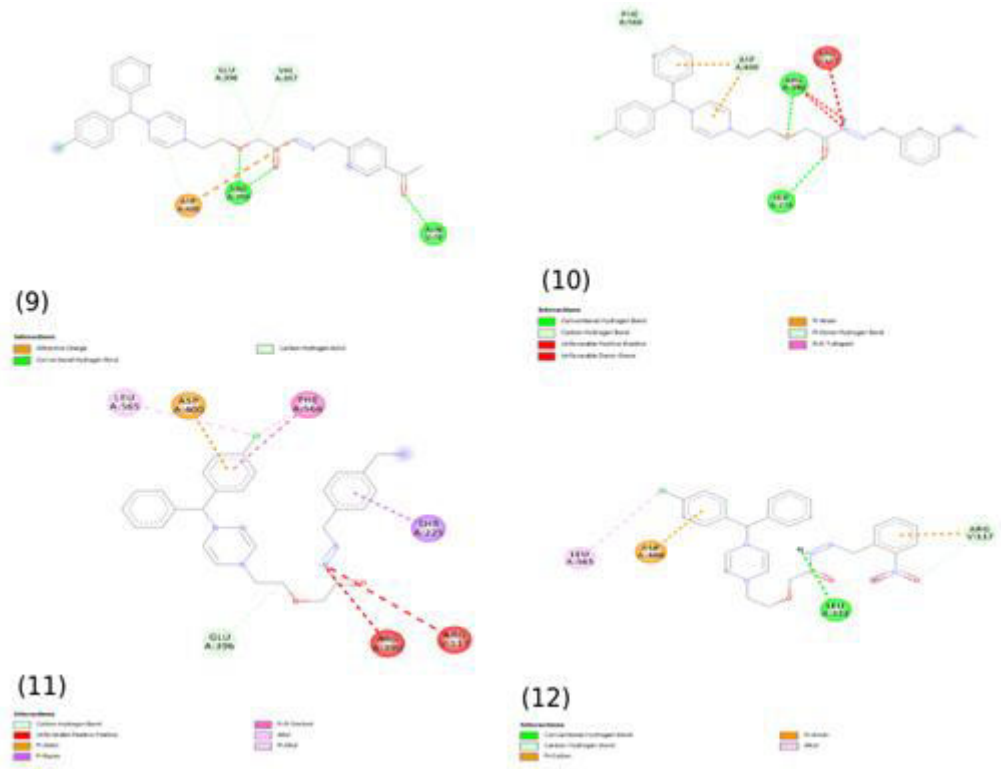
ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021




Results of all possible interaction of noval compound is tabulated in table 1.

**Table: 1 Molecular Docking: 8 Run**

| Ligand | Binding Affinity | Pi-Sigma | PI-PI-TSHAPE | PI-ALKYL | HYDROGEN BOND |
|---|---|---|---|---|---|
| **6dzw 01** | -7.5 | MET-A:124,ILA-A:544,TRP-A:326,ILE-A:327 | PHE-A:551 | ALA-A:330 | |
| **6dzw 02** | -7.3 | | PHE-A:566 | | ASN-V:70,GLN-A:567 |
| **6dzw 03** | -8.5 | | PHE-L:56,PHE-H:125 | ILE-A:188 | GLY-L:117, GLN-A:194 |
| **6dzw 04** | -7.7 | ILE-A:544, ILE-A:327 | PHE-A:551 | ALA-A:330 | |
| **6dzw 05** | -7.0 | | | ILE-A:408 | SER-A:224, GLN-A:567, LEU-A:222 |
| **6dzw 06** | -7.4 | | | ILE- | ASN-V:70, |

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

| | | | | | |
|---|---|---|---|---|---|
| | | | | A:408 | GLN-A:567 |
| **6dzw 07** | -8.2 | ASN-A:211 | | PRO-A:227, PRO-V:118 | PHE-A:213 |
| **6dzw 08** | -7.1 | | | PHE-A:566, LEU-A:565 | TYR-V:48, ARG-V:117 |
| **6dzw 09** | -6.9 | | | | GLE-A:396, VAL-A:397, ARG-A:390, ASN-V:70 |
| **6dzw 10** | -6.9 | | | | ARG-A:390, SER-A:226, PHE-A:566, ASP-A:400 |
| **6dzw 11** | -7.0 | THR-A:225 | | LEU-A:565 | GLU-A:396 |
| **6dzw 12** | -7.6 | | | LEU-A:565 | LEU-A:222 |
| **6dzw 13** | -7.7 | | PHE-A:566 | LEU-A:565 | GLN-A:567, LEU-A:222 |

## IN VIVO ANTIDEPRESSANT ACTIVITY RESULT

**Table 2: Effect of compound on immobility time in Tail Suspension test**

| Treatment | Concentration (mg/kg orally) | Tail Suspension test Duration of Immobility (Sec) |
|---|---|---|
| **Control** | | 45.2 ± 5.1 |
| **Imipramine** | 10 | 90.5 ± 4.15** |
| **Compound-1** | 30 | 60.1 ± 3.33** |
| | 60 | 80.3 ± 3.35** |

Each value represents Mean ± S.E.M., n=6. **p< 0.05 compared with control.
On the basis of results(Molecular Docking, 1HNMR & INVIVO screening study), I found that my compound binding affinity of protein is effective on receptors and responding positively.

## CONCLUSION

Compound 2-{4-[(4-Chloro-cyclohexyl)-cyclohexyl-methyl]-piperazin-1-yl}-ethoxy)-acetic acid cyclohexyl-methylene-hydrazide and its derivatives were synthesized and evaluated for in vivo antidepressant activity along with its characterization and molecular docking. On the

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

basis of these evaluation and former literature surveys it can be concluded that the compound exhibit significant antidepressant activity. In the future more research at this compound with the aid of technical tool can led to novel drug discovery.

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