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Original Research Paper

DESIGNING, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL PYRIDAZINONE DERIVATIVES

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ABSTRACT

The designing and synthesis of selected 6-(4-methylphenyl)-4,5-dihydropyridazin-3(2*H*)-one, 6-(4-benzylphenyl)-4,5-dihydropyridazin-3(2H)-one and 6-(4-phenoxyphenyl)-4,5-dihydropyridazin-3(2H)-one derivatives was carried out starting from succinic anhydride and aroylpropionic acids using substituted phenylhydrazines guide by computational approach. Estimation of pharmacotherapeutic potential, possible molecular mechanism of action, toxic/side effects and interaction with drug-metabolizing enzymes was also achieved by computational & suitable *in-vitro* studies. The *in-silico* docking results showed that compound no. III *l* & III *c* were best with analgesic potential while III *u* & III *l* were found to be best for anti-inflammatory activity. The results of *in-vivo* anti-inflammatory studies by carrageenan induced rat paw edema method also revealed that the compound no. III *u* showed maximum inhibition in paw edema volume followed by compound no. III *l* while the compound no. III *l* showed maximum analgesic effect determined by Acetic acid induced writhing method and inhibited the writhes to 69.99 % followed by the compound no. III *c*. The compound no. III *l* also showed good analgesic effect determined by Tail immersion method and increased the reaction time to 90 minutes followed by the compound no. III *c*. In *in-vitro* anti-bacterial studies, compound no. III *j* was found to be most effective against Gram positive strain *S. aureus* and *B. cereus* showing the maximum zone of inhibition of 32 mm and 33 mm, respectively whereas compound no. III *n* was found to be most effective against Gram negative strain *E. coli* and *S. flexveri* showing maximum zone of inhibition of 29 mm and 30 mm respectively. The compound no. III *u* was found to have maximum anti-oxidant potential i.e. 89.393 % at concentrations of 1000, 500 and 250 µg/ml. From above results, it is concluded that compound III *u* has maximum anti-inflammatory and anti-oxidant potential followed by III *l*. Also anti-oxidant activity has a parallel association with inflammatory process and can be regarded base for anti-inflammatory activity. So, *in-vitro* results along with *in-silico* findings strengthens the research findings of these studies.

Keywords: Pyridazinones, Analgesic, Anti-inflammatory, Antimicrobial activity, Molegro virtual docker.

INTRODUCTION

Pyridazinones are the derivatives of pyridazine, an important group of heterocyclic compounds, containing two nitrogen atoms at 1 and 2 positions in a six membered ring. Pyridazin-3-one, saturated or unsaturated form with carbonyl group on third carbon, has been considered as a magic moiety, which posses diverse set of biological activities.[1] The pyridazine nucleus represents a versatile scaffold to develop new pharmacologically active compounds. Some common biological activities reported are analgesic (Asif *et al*., 2011), anti-inflammatory (Gokce *et al*., 2009, Sahin *et al*., 2004), antidepressant (Coelho *et al*., 2003),

antihypertensive (Demirayak *et al*., 2004, Anees Siddiqui *et al*., 2011), antithrombic (Monge *et al*., 1987), diuretics (Akahane *et al*., 1999), and anti-HIV (Livermone *et al*., 1993).[2] In addition, pyridazinones act as core nucleus in various drugs e.g. Sulmazole, Levosimendan, Amipizone, Indolidan, Imazodan, Pimobendan, Emorfazone, Zardaverine, Milrinone etc.[3] These observations contemplated us to synthesize some new derivatives of pyridazinones with a view to explore their potency as good analgesic and anti-inflammatory agents. Computer assisted drug designing involves all computational techniques to discover, design and optimize biologically active compounds with desired structure and properties with a putative use as drugs. Docking is a tool in structural molecular biology to perform virtual screening on large libraries of compounds, and propose the structural hypotheses of how the ligands inhibit the targets. The goal of ligand protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three dimensional structures.[4] So, molecular docking has been performed to pre-access anti-inflammatory and analgesic significance of target compounds and applications in drug discovery.[5,6] Taking in to consideration the docking results, it was felt worthwhile to carry out the synthesis of some novel pyridazinone derivatives.

MATERIAL AND METHODS

Docking

To pre-asses the analgesic and anti-inflammatory activity of substituted pyridazinones and their derivatives on the structural basis, auto-mated docking studies were carried out using Molegro Virtual Docker, the scoring functions and hydrogen bonds formed with the surrounding amino acids were used to predict their binding modes, their binding affinities and orientation of these compounds. Since it is impossible to synthesize all the possible compounds and to test all the available ones so molecular modelling makes this approach easier and limits to some fixed number of compounds. On the basis of literature data, we selected sixty hypothetical compounds and docking studies were performed using (PDB ID 6 COX) for anti-inflammatory & (PDB ID 2 OOX) for analgesic activity using Molegro Virtual Docker. But, out of sixty compounds twenty one compounds (III *a*-III *u*) were selected and docking studies were performed on the same and were found to possess best results for analgesic and anti-inflammatory activity.

Binding Affinities of the Synthesized Compounds into Receptor

The hypothetical compounds were selected based on literature. The ligand molecules were prepared using Marvin 5. 11. 4, converted to 3D structure from the 2D using build and optimization method & finally clean in 3D. The resulting structures were saved in MDL Molfile (*. mol) format. A single, low energy, 3D structure with correct chiralities for each successfully proposed input structure were generated. Then the generated structures were imported into the workspace of docking software Molegro virtual docker 4.0.2. Molecule can be incorporated into MVD using MDL (sdf/sd/mol/mdl) file format which contains bonding information. Then the protien file was imported and ligands were prepared with the help of software MVD. The protien preparation was done and cavities of protien molecule were detected. Then with the help of docking wizard panel docking was executed. The poses of protien-ligand complex were determined. The Mol Dock score and Docking score were calculated. Different types of interactions between receptor and ligand like Vanderwaal's interaction, electrostatic & aromatic interactions were considered to calculate the binding energy. The number of protein receptors (PDBs) used in this study was PBD ID: 6 COX (cyclooxygenase-2 inhibitors) and 2OOX. The PDB's used for docking were procured from RCSB (Protien Data Bank).

Synthesis

6-(4-Methylphenyl)-4,5-dihydropyridazin-3(2H)-one (III a)

The requisite amount of hydrazine hydrate (2.14 mmol) was added to a stirred and refluxing solution of 4-(4-methylphenyl)-4-oxobutanoic acid (2.13 mmol,) in aldehyde free ethanol (40

ml). The reaction mixture was refluxed for 8h at 100^0 C under continuous stirring. The reaction mixture was concentrated to half the volume and left overnight in refrigerator for crystallisation. The crystals were collected on a filter paper and washed with cold ethanol, dried.

2-Substituted-4,5-dihydropyridazin-3(2H)-one) (III b – III u)

The requisite amount of various substituted phenyl hydrazines (2.14 mmol) were added to a stirred and refluxing solution of aroylpropionic acid (II*a*- II *c*) (2.13 mmol,) in aldehyde free ethanol (40 ml). The reaction mixture was refluxed for 8h at 100^0 C under continuous stirring. The reaction mixture was concentrated to half the volume and left overnight in refrigerator for crystallisation. The crystals were collected on a filter paper and washed with cold ethanol, dried.

In-Vitro Activity

Antibacterial Activity

A total four microbial strains were selected on the basis of their clinical importance in causing diseases in humans. Two Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538 P) and *Bacillus cereus* ATCC 11770), and two Gram-negative bacteria (*Escherichia coli* 01547 NCTC 12980 & *Shigella flexveri* ATCC 9199), [7] were used in the present study for evaluation of antimicrobial activity of the chemical compounds. The bacteria were subcultured on Nutrient agar at 37°C. DMSO was used as a negative control whereas Levofloxacin, Maropenem and Vancomycin were used as a positive control (standard).[8-10]

Minimum Inhibitory Concentration (MIC) Studies

Minimum inhibitory Concentration (MIC) is the lowest concentration of an antimicrobial compound that will inhibit the visible growth of a microorganism after overnight incubation. MIC of the various compounds against bacterial strains was tested through a microdilution tube method as recommended by NCCLS.

Antioxidant Activity

Evaluation method of scavenging of hydrogen peroxide (H_2O_2)

A solution of hydrogen peroxide (40 nM) was prepared in phosphate buffer (pH 7.4) Different concentrations (10, 30 and 50 µg/mL) of all the synthesized compounds in DMSO were prepared. Hydrogen peroxide solution (0.6mL, 40mM) was added in the test and standard solutions of different concentrations. Absorbance of hydrogen peroxide at 230 nm was determined after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide.[11]

DPPH free radical scavenging activity

A stock solution of DPHH (33 mg in 1L) was prepared in methanol, and 5ml of this stock solution was added to 1 ml of test solution at different conc. (100, 250, 500, 1000 µg/ml). After 30 min, absorbance was measured at 517 nm and compared with standard at different conc. (100, 250, 500, 1000 µg/ml). Ascorbic acid was used as reference compound. The free-radical scavenging activity of test sample was measured by decrease in the absorbance of methanol solution of DPHH.[12]

In-Vivo Pharmacological Activity

In-vivo study is essential because responses observed *in-vitro* can be diminished or totally different in more complex integrated system.[13]

Determination of Anti-Inflammatory Activity

Swiss albino rats of weight between 180-250 gm were used in the study. They were weighed and marked. Groups of five animals each were used for control, standard and test drugs. A mark was made on the left hind paw near tibio-tarsus junction so that every time the paw was dipped in the 0.5% NaCl solution column up to the fixed mark to ensure constant paw volume. Initial paw volume of all the animals was recorded. After 30 min. of administration of test (10 mg/kg) and standard drug (Indomethacin, (10 mg/kg), carrageenan (10 ml/kg) was injected subcutaneously into the subplantar region of left hind paw of all animals. The volume of paw was measured by displacement of 0.5% NaCl in plethysmograph at 30, 60, 90, 120 minutes after carrageenan injection.[14,15] Thus the edema volume in control group (Vc) and edema volume in groups treated with test compounds (Vt) was

measured and the % inhibition of edema was calculated using the formula.

$$\% \text{ Inhibition} = \frac{(Vc-Vt)}{Vc} * 100$$

Determination of Analgesic Activity

The analgesic study was determined by writhing tests for peripheral analgesic activity and tail immersion method for central analgesic activity.[16,17]

Writhing test

Swiss albino mice of either sex weight between 20-25gm were used in the study. Acetic acid in a concentration of 1% v/v and 10 ml/kg/ *i.p.* was administered to induce writhes. The groups of five animals each were used for control (10 ml/Kg), standard drug (Indomethacin 10 mg/kg) and test(10 mg/Kg). First group of 5 animals were administered acetic acid solution alone, which served as negative control. The test and standard groups of animals were administered the test drug and the standard drug 30 minutes prior to acetic acid administration respectively. The mice were then observed for ten minutes and the numbers of writhes for each animal were recorded during that time period. For scoring purposes, writhes were indicated by stretching of the abdomen with simultaneously stretching of at least one hind limb.

Tail immersion method

Mice were held in position in a suitable restrainer with the tail protruding out. The tail up to 5 cm was dipped in a beaker of water at 55 $^{\circ}$C. The drug used as standard was indomethacin, (10 mg /kg body weight i.e. 28g). The test compounds were given orally (10 mg/kg body weight). All the dose of standard and test drugs was prepared in 0.5% w/v Tween-80 which served as drug vehicle. The time taken by the mice to withdraw the tail clearly out of water was recorded as the reaction time. The reaction time was measured after 30, 60, 90, and 120 minutes respectively.

RESULTS AND DISCUSSION

Docking Studies

All hypothetical compounds were found to possess good results for anti-inflammatory and analgesic activity. But, out of sixty compounds, only twenty one compounds (III *a*-III *u*) were found to possess best results for analgesic and anti-inflammatory activity and were reported in the Table I. Docking studies revealed the following information with respect to anti-inflammatory on **pdb - 6COX (Table I).** The standard drug, 2-benzyl-4-(5-methylpyridin-3-yl)-5-(4-(methylsulfonyl)phenyl)pyridazin-3(2H)-one showed Mol dock score -143.627 and docking score -149.991 and formed 5 hydrogen bonds, between N-N, N-N, N-N, O-N, N- O, with distance of 3.30 A$^{\circ}$, 2.53 A$^{\circ}$, 3.59 A$^{\circ}$, 3.04 A$^{\circ}$, 2.75 A$^{\circ}$ respectively as shown in Figure- A. The compound **III *u*,** showed very good binding affinity towards the receptor with highest Mol dock score -132.964 and docking score- 138.101 and formed 5 hydrogen bonds, between O of Biphenyl with N, N of NO_2 with N, O of NO_2 with N, O of NO_2 with N, N of NO_2 with N with distance of 3.23 A°, 3.18 A°, 3.10 A°, 3.12 A°, 3.55 A° respectively as presented in Figure-B. The analgesic docking results are presented in Table II **using pdb - 2OOX,** the standard drug, **Emorfazone** bound with the hydrophobic pocket of the receptor. It showed Mol dock score -86.155 and docking score- 87.0387 and formed 3 hydrogen bonds, between N of N, N of N, N of N with distance of 3.10 A°, 3.19 A°, 3.56 A° respectively as shown in Figure- C. Compound **III *l*** showed very good affinity towards the receptor with highest Mol dock score -135.769 and docking score -143.709 and form 9 hydrogen bonds shown as blue lines, between O of NO_2 with N, O of NO_2 with N, O of NO_2 with N, N of NO_2 with N, N of NO_2 with N, N of NO_2 with O, O of NO_2 with O, O of NO_2 with N and O of NO_2 with N with distance of 3.09 A°, 2.82 A°, 3.05 A°, 2.60 A°, 2.98 A°, 3.57 A°, 2.37 A°, 2.85 A° respectively as shown in Figure- D.

Physical Characterization of Synthesized Compounds:

All chemicals were commercially purchased from various chemical units- E. Merck India Ltd, CDH, SD Fines Chem. Ltd. and Qualigens Fine Chemicals. These solvents and reagents were of L.R. grade and purified before their use. Melting points were taken on slides in an electrical

apparatus Labindia visual melting range apparatus and were uncorrected. IR spectra were recorded on Hitachi spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ & DMSO on Bruker Nuclear Magnetic Resonance (NMR) spectrometer at 300MHz using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in delta.

6-(4-methylphenyl)-4,5-dihydropyridazin-3(2H)-one (III a)

$C_{11}H_{12}N_2O$, Yield – 30.7 %, m.p.- 224-226^{o}C, Molecular Weight – 188.23, TLC(T:E:F-5:4:1) : R_f – 0.49, IR (KBr) ν_{max} (cm^{-1}): 1674(C=O), 1643(-C=N), 3364 (-N−H), 3387(-N−H) ^{1}HNMR (DMSO): δ 1.19 (s, 3H, CH_3), 9.20(bs, 1H, NH), 1.99-2.38(t, 2H, CH_2), 1.63-1.71(t, 2H, CH_2), 7.31-7.34(d, 1H, Ar), 7.11-7.14(d, 1H, Ar), 7.42-7.46 (d, 1H, Ar), 7.77-7.91(d, 1H, Ar). ^{13}C-NMR (DMSO) δ 140.7 (C of C-1), 129.2 (C-H of C-2,C-6), 129.1 (C-H of C-3), 131 (C of C-4), 146.6(C of C-7), 24.2 (CH_2 of C-8), 35.1 (CH_2 of C-9).

6-(4-methylphenyl)-2-phenylpyridazin-3(2H)-one (III b)

$C_{17}H_{16}N_2O$, Yield –20.93 %, m.p. 366^{o}C, Molecular Weight- 264.32,TLC(T:E:F-5:4:1) : R_f – 0.51, IR (KBr) ν_{max} (cm^{-1}): 1674(-C=N), 1713(C=O), 1589,1450, 1350(Ar, str), 3387 (Ar-H str) ^{1}HNMR (DMSO): δ 1.23(s, 3H, CH_3), 1.64-1.72(t, 2H, CH_2), 1.99-2.38(t, 2H, CH_2), 7.31-7.34 (d, 1H, Ar), 7.11-7.14(d, 1H, Ar), 7.46-7.48(d, 1H, Ar), 7.88-7.93(d, 1H, Ar), 7.96-8.05 (d, 1H, Ar), 7.32-7.34(t, 1H, Ar), 7.42-7.48(t, 2H, Ar). ^{13}C-NMR (DMSO) δ 140.7 (C of C-1), 129.2 (CH of C-2, C-6), 129.1 (CH of C-3, C-5, 131(C of C-4), 145.3(C of C-7), 24.5 (CH_2 of C-8), 32.5(CH_2 of C-9), 173 (C of C-10).

2-(2,4-dinitrophenyl)-6-p-tolyl-4,5-dihydropyridazin-3(2H)-one (III c)

$C_{17}H_{14}N_4O_5$, Yield – 40.89 %, m.p.- 375^{o}C, Molecular Weight- 354.32, TLC(T:E:F-5:4:1) : R_f – 0.45, IR (KBr) ν_{max} (cm^{-1}): 1705(C=O), 1589,1420,1335(Ar-str), 1504(Ar-NO_2), 1335(Ar-NO_2) ^{1}HNMR (DMSO): δ 1.53-1.69(t, 2H, CH_2), 1.91-2.22(t, 2H, CH_3), 1.16(s, 3H, CH_3), 7.13-7.29(d, 1H, Ar), 7.09-7.12(d, 1H, Ar), 7.23-7.42(d, 1H, Ar), 7.82-7.91(d, 1H, Ar), 8.12(s, 1H, Ar), 7.93-8.04(d, 1H, Ar), 7.86-7.93(d, 1H, Ar). ^{13}C-NMR (DMSO) δ 139.2 (C of C-1), 127.5 (CH of C-2, C-6), 125.6 (CH of C-3, C-5), 132 (C of C-4), 143.7 (C of C-7), 23.7 (CH_2 of C-8), 31.8 (CH_2 of C-9), 171 (C of C-10).

2-(4-methylquinolin-2-yl)-6-p-tolyl-4,5-dihydropyridazin-3(2H)-one (III d)

$C_{21}H_{19}N_3O$, Yield – 35.23 % m.p. - 362^{o}C, Molecular Weight – 329.4, TLC(T:E:F-5:4:1) : R_f – 0.49, IR (KBr) ν_{max} (cm^{-1}) : 1713(C=O), 1612(-C=N), 1504,1412,1296(Ar-H), 3410 (Ar-CH_3) ^{1}HNMR (DMSO): δ2.34(s, 3H, CH_3), 2.63(s, 3H, CH_3), 1.62-1.71(t, 2H, CH_3), 1.89-2.12(t, 2H, CH_2), 7.29-7.31(d, 1H, Ar), 7.10-7.13(d, 1H, Ar), 7.42-7.49(d, 1H, Ar), 7.86-7.91(d, 1H, Ar), 7.74-7.78(t, 1H, Ar), 7.23-7.25(d, 1H, Ar), 7.29-7.31(d, 1H, Ar), 7.38-7.39(d, 1H, Ar) ^{13}C-NMR (DMSO) δ 141.6 (C of C-1), 128.1 (CH of C-2, C-6), 124.7 (CH of C-3, C-5), 130.5 (C of C-4), 142.9(C of C-7), 24.3 (CH_2 of C-8), 32.1 (CH_2 of C-9), 173 (C of C-10).

6-p-tolyl-2-(4-(trifluoromethoxy)phenyl)-4,5-dihydropyridazin-3(2H)-one (III e)

$C_{18}H_{15}F_3N_2O_2$, Yield – 20.25 % , m.p.351 ^{o}C, Molecular Weight – 348.32, TLC(T:E:F-5:4:1) : R_f – 0.42, IR (KBr) ν_{max} (cm^{-1}): 1723(C=O), 1660,1525, 1432,1286(Ar-H), 1612(-C=N), 3409(Ar-CH_3), 1132(C-F str) ^{1}HNMR (DMSO): δ 2.35(s, 3H, CH_3), 1.63-1.72(t, 3H, CH_3), 1.90-2.12(t, 3H, CH_3)7.30-7.32(d, 1H, Ar), 7.13-7.15(d, 1H, Ar), 7.43-7.48(d, 1H, Ar), 7.46-7.50(d, 2H, Ar), 7.39-7.42(d, 2H, Ar) ^{13}C-NMR (DMSO) δ 140.7(C of C-1), 129.2 (CH of C-2, C-6), 129.1 (CH of C-3, C-5), 131(C of C-4), 146.3 (C of C-7), 20.5(CH_2 of C-8), 16.5 (CH_2 of C-9), 173 (C of C-10).

2-(2,4-difluorophenyl)-6-p-tolyl-4,5-dihydropyridazin-3(2H)-one (III f)

$C_{17}H_{14}F_2N_2O$, Yield – 20.90 % , m.p 369^{o}C , Molecular Weight- 300.3, TLC(T:E:F-5:4:1) : R_f – 0.53, IR (KBr) ν_{max} (cm^{-1}): 1713(C=O), 3402(Ar-CH_3), 1443(C-F str) ^{1}HNMR (DMSO): δ 2.33(s, 3H, CH_3), 1.7-1.8(t, 3H, CH_3), 2.30-2.32(t, 3H, CH_3), 7.28-7.31(d, 1H, Ar), 7.14-7.16(d, 1H,

Ar), 7.42-7.47(d, 1H, Ar), 7.36-7.40(d, 2H, Ar), 8.10(s, 1H, Ar), 7.60-7.62(d, 1H, Ar), 7.69-7.42(d, 1H, Ar) ^{13}C-NMR (DMSO) δ 136.8(C of C-1), 128.3(CH of C-2, C-6), 128.1 (CH of C-3, C-5), 131 (C of C-4), 143.9(C of C-7), 24.3(CH_2 of C-8), 32.1(CH_2 of C-9), 172.9 (C of C-10).

2-(2-fluorophenyl)-6-p-tolyl-4,5-dihydropyridazin-3(2H)-one (III g)

$C_{17}H_{15}FN_{2O}$, Yield – 20.30 %, m.p. 453°, Molecular Weight – 282.31, TLC(T:E:F-5:4:1) : R_f – 0.56, IR (KBr) ν_{max} (cm^{-1}): 1720(C=O), 1203(Ar-(C-F str) ^{1}HNMR (DMSO): δ 2.35(s, 3H, CH_3), 1.63-1.72(t, 3H, CH_3), 1.90-2.12(t, 3H, CH_3)7.30-7.32(d, 1H, Ar), 7.13-7.15(d, 1H, Ar), 7.43-7.48(d, 1H, Ar), 7.46-7.50(d, 2H, Ar), 7.74-7.75(d, 1H, Ar), 7.74-7.75(d, 2H, Ar) ^{13}C-NMR (DMSO) δ 135.7(C of C-1), 127.5(CH of C-2, C-6), 126.8 (CH of C-3, C-5), 130.7(C of C-4), 142.5(C of C-7), 24.2(CH_2 of C-8), 31.9(CH_2 of C-9), 170.3 (C of C-10).

4-(6-oxo-3-p-tolyl-5,6-dihydropyridazin-1 (4H)-yl) benzonitrile (III h)

$C_{18}H_{15}N_{3O}$, Yield – 45.30 %, m.p. 433°C, Molecular Weight- 289.33, TLC(T:E:F-5:4:1) : R_f – 0.42, IR (KBr) ν_{max} (cm^{-1}): 2232(Ar-CN), 1690 (C=O) ^{1}HNMR (DMSO)= δ 2.35(s, 3H, CH_3), 1.63-1.72(t, 3H, CH_3), 1.90-2.12(t, 3H, CH_3)7.30-7.32(d, 1H, Ar), 7.13-7.15(d, 1H, Ar), 7.43-7.48(d, 1H, Ar), 7.46-7.50(d, 2H, Ar), 7.39-7.42(d, 2H, Ar) ^{13}C-NMR (DMSO) δ 140.6 (C of C-1), 128.5(CH of C-3, C-5), 129.6(C of C-4), 146.4(C of C-7), 24.1(CH_2 of C-8), 32.4(CH_2 of C-9), 172.9 (C of C-10).

2-(4-chlorophenyl-6-p-tolyl-4,5-dihydropyridazin-3(2H)-one (III i)

$C_{17}H_{15}ClN_2O$, Yield – 34.06 %, m.p. 338°C, Molecular Weight- 298.77, TLC(T:E:F-5:4:1) : R_f – 0.52, IR (KBr) ν_{max} (cm^{-1}): 2210(Ar-CN), 760(C-Cl str) ^{1}HNMR (DMSO): δ 2.12(s, 3H, CH_3), 1.56-1.62(t, 3H, CH_3), 7.28-7.31(d, 1H, Ar), 7.14-7.16(d, 1H, Ar), 7.42-7.47(d, 1H, Ar), 7.36-7.40(d, 1H, Ar), 7.58(d, 2H, Ar) ^{13}C-NMR (DMSO) δ 140.5(C of C-1), 129.1 (CH of C-2, C-6), 128.9(CH of C-3, C-5), 130.7(C of C-4), 146.4(C of C-7), 24.2(CH_2 of C-8), 32.6(CH_2 of C-9), 173(C of C-10).

6-(4-benzylphenyl)-4,5-dihydropyridazin-3(2H)-one (III j)

$C_{16}H_{14}N_2O$, Yield – 30.66 % , m.p. 369.52°, Molecular Weight- 250.3, TLC(T:E:F-5:4:1) : R_f – 0.61, IR (KBr) ν_{max} (cm^{-1}): 3202(-N−H), 1674(C=O),1342(-C=N),1612,1481,1381(Ar-H) ^{1}HNMR (DMSO): δ 2.32-2.50(m, 2H, CH_2), 2.88-2.95(m, 2H, CH_2), 7.206(d, 2H, Ar), 7.59-7.62(d, 2H, Ar), 7.35-7.39(m, t, Ar), 7.44-7.48(d, 1H, Ar), 7.64-7.68(d, 1H, Ar) ^{13}C-NMR (DMSO) δ 127.7(CH of C-1), 129.3(CH of C-2, C-6), 127.9(CH of C-3, C-5), 136.5(C of C-4), 138.8(C of C-7), 128.0(CH of C-8, C-12), 129.7(CH of C-9, C-11), 132.9(C of C-10).

6-(4-benzylphenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (III k)

$C_{22}H_{18}N_2O$**,** Yield – 35.13 %, , m.p. 354.63°C, Molecular Weight: 326.39, TLC(T:E:F-5:4:1) : R_f – 0.58, IR (KBr) ν_{max} (cm^{-1}): 3402(-N−H), 1690(C=O), 1335(-C=N), ^{1}HNMR (DMSO)= δ 2.55-2.61(t, 2H, CH_2, 3.22-3.25(t, 2H, CH_2), 7.36-7.48(m, 3H, Ar), 7.66-7.68(d, 2H, Ar), 7.74-7.76(d, 2H, Ar), 8.02-8.05(d, 2H, Ar), 6.95-6.97(m, 3H, Ar), 7.71-7.72(d, 1H, Ar), 7.57-7.58(d, 1H, Ar) ^{13}C-NMR (DMSO) δ 126.9(CH of C-1), 129.2(CH of C-2, C-6), 125.7(CH of C-3, C-5), 134.8(C of C-4), 137.5(C of C-7), 127.9(CH of C-8, C-12), 128.6(CH of C-9, C-11), 132.7(C of C-10).

6-(4-benzylphenyl)-2-(2,4-dinitrophenyl)-4,5-dihydropyridazin-3(2H)-one (III l)

$C_{22}H_{16}N_4O_5$, Yield – 40.18 %, m.p 412°C, Molecular Weight- 416.39, TLC(T:E:F-5:4:1) : R_f – 0.53, IR (KBr) ν_{max} (cm^{-1}): 3317(-N−H), 1612(C=O), 1327(C=N),1728,1489,1330(Ar-H) ^{1}HNMR (DMSO)= δ 3.16-3.18(t, 2H, CH_2), 4.06-4.09(t, 2H, Ar), 9.98(s, 1H, Ar), 8.92(d, 1H, Ar), 8.82(d, 1H, Ar), 8.10-8.11(d, 1H, Ar), 8.06-8.08(d, 1H, Ar), 8.41-8.42(d, 1H, Ar), 8.23-8.24(d, 1H, Ar), 7.35-7.39(m, 3H, Ar), 7.44-7.48(d, 1H, Ar), 7.64-7.68(d, 1H, Ar) ^{13}C-NMR (DMSO) δ All aromatic protons are same except 173 (C of C-15).

6-(4-benzylphenyl)-2-(4-methylquinolin-2-yl)-4,5-dihydropyridazin-3(2H)-one (III m)

$C_{26}H_{21}N_3O$, Yield –25.87 % , m.p.451°C , Molecular Weight: 391.6, TLC(T:E:F-5:4:1) : R_f – 0.59, IR (KBr) ν_{max} (cm^{-1}):1703(C=O), 1612(-C=N), 1504,1412,1296(Ar-H), 3413 (Ar-CH3) ^{1}HNMR (DMSO): δ 2.50-2.62(t, 2H, CH_2, 3.21-3.23(t, 2H, CH_2), 7.36-7.48(m, 3H, Ar), 7.66-7.68(d, 2H, Ar), 7.74-7.76(d, 2H, Ar), 8.02-8.05(d, 2H, Ar), 7.46-7.52(t, 2H, Ar), 7.89-7.91(d, 1H, Ar), 7.38-7.40(d, 1H, Ar) ^{13}C-NMR (DMSO) δ 24.5 (CH_2 of C-14), 32.5(CH_2 of C-15).

6-(4-benzylphenyl)-2-(trifluoromethoxy)-4,5-dihydropyridazin-3(2H)-one (III n)

$C_{17}H_{13}F_3N_2O_2$, Yield – 30.56 % , m.p. 300.27°C, Molecular Weight- 334.29, TLC(T:E:F-5:4:1) : R_f – 0.58, IR (KBr) ν_{max} (cm^{-1}): 1712(C=O), 1630,15125,1462,1286(Ar-H), 1612(-C=N),), 1232(C-F str) ^{1}HNMR (DMSO): δ 2.75-2.79(t, 2H, CH_2, 3.17-3.21(t, 2H, CH_2), 7.70-7.76(m, 3H, Ar), 7.92-7.94(d, 1H, Ar), 7.04- 7.06(d, 1H, Ar), 7.25-7.28(d, 4H, Ar), 7.46-7.50(d,2H, Ar), 7.39-7.42(d, 2H, Ar)
^{13}C-NMR (DMSO) δ 29.2(CH_2 of C-15).

6-(4-benzylphenyl)-2-(2,4-difluorophenyl)-4,5-dihydropyridazin-3(2H)-one (III o)

$C_{22}H_{16}F_2N_2O$, Yield – 24.23 % , m.p.282.85°C, Molecular Weight- 362.37, TLC(T:E:F-5:4:1) : R_f – 0.45, IR (KBr) ν_{max} (cm^{-1}): 1705(C=O), 3371(-N−H), 1435(C-F str) ^{1}HNMR (DMSO): δ 2.73-2.77(t, 2H, CH_2), 3.17-3.21(t, 2H, CH_2), 8.24(s, 1H, Ar), 7.84-7.86(d, 1H, Ar), 7.55-7.57(d, 1H, Ar), 7.14-7.26(m, 5H, Ar), 6.98-6.99(d, 2H, Ar), 7.66-7.71(dd, 2H, Ar) ^{13}C-NMR (DMSO) δ 146.6(C of C-13).

6-(4-benzylphenyl)-2-(2-fluorophenyl)-4,5-dihydropyridazin-3(2H)-one (III p)

$C_{22}H_{17}FN_2O$, Yield- 30.67 % , m.p. 344.38°C, Molecular Weight- 409.74, TLC(T:E:F-5:4:1) : R_f – 0.56, IR (KBr) ν_{max} (cm^{-1}): 1690(C=O), 3321(-N−H), 1497(C-F str) ^{1}HNMR (DMSO): δ 2.75-2.79(t, 2H, CH_2), 3.18-3.22(t, 2H, CH_3), 7.55-7.74(m, 4H, 2 × CH_2), 7.15-7.20(m, 1H, Ar), 7.86-7.87(t, 2H, Ar), 7.88-7.89(d, 2H, Ar), 7.74-7.75(d, 1H, Ar), 7.74-7.75(d, 2H, Ar) ^{13}C-NMR (DMSO) δ 173(C of C-16)

4-(3-(4-benzylphenyl)-6-oxo-5,6-dihydropyridazin-1 (4H)-yl) benzonitrile (III q)

$C_{23}H_{17}N_3O$, Yield –25.12 % , m.p. 445.41°C , Molecular Weight- 351.4, TLC(T:E:F-5:4:1) : R_f – 0.48, IR (KBr) ν_{max} (cm^{-1}): 2237(-CN−Ar), 3209(-N−H), 1690,1512,1420(Ar-H) ^{1}HNMR (DMSO): δ 2.72-2.74(t, 2H, CH_2, 3.12-3.23(t, 2H, CH_2), 7.69-7.73(m, 3H, Ar), 7.91-7.94(d, 1H, Ar), 7.02- 7.06(d, 1H, Ar), 7.25-7.28(d, 4H, Ar), 7.46-7.50(d,2H, Ar), 7.39-7.42(d, 2H, Ar) ^{13}C-NMR (DMSO) δ 23.9 (CH_2 of C-14), 31.7(CH_2 of C-15).

6-(4-benzylphenyl)-2-(4-chlorophenyl)-4,5-dihydropyridazin-3(2H)-one (III r)

$C_{22}H_{17}ClN_2O$, Yield- 35.45 %, m.p. 339.07°C, Molecular Weight- 360.84, TLC(T:E:F-5:4:1) : R_f – 0.63, IR (KBr) ν_{max} (cm^{-1}): 2237(-CN−Ar), 3044(-N−H), 1690,1512,1420(Ar-H), 825(-Cl-Ar) ^{1}HNMR (DMSO): δ 2.55-2.61(t, 2H, CH_2, 3.22-3.25(t, 2H, CH_2), 7.36-7.48(m, 3H, Ar), 7.66-7.68(d, 2H, Ar), 7.74-7.76(d, 2H, Ar), 8.02-8.05(d, 2H, Ar) ^{13}C-NMR (DMSO) δ 131.7(C of C-10).

6-(4-phenoxyphenyl)-4,5-dihydropyridazin-3(2H)-one (III s)

$C_{16}H_{14}N_2O_2$, Yield- 20.23 %, m.p. 391.75°C, Molecular Weight- 266.29, TLC(T:E:F-5:4:1) : R_f – 0.64, IR (KBr) ν_{max} (cm^{-1}): 1745(C=O), 910(C-O-C str) ^{1}HNMR (DMSO): δ 2.40-2.46(t, 2H, CH_2), 2.90-2.95(t, 2H, CH_2), 7.39-7.44(t, 3H, Ar), 7.00-7.071(m, 2H, Ar), 7.91-7.94(d, 1H, Ar), 7.02- 7.06(d, 1H, Ar), 7.25-7.28(d, 1H, Ar), 7.46-7.50(d,2H, Ar),10.86(s, 1H, N-H) ^{13}C-NMR (DMSO) δ 121.9(CH of C-1), 128.5(CH of C-2, C-6), 117.5(CH of C-3, C-5), 157(C of C-4), 159.3(C of C-7), 117.6(CH of C-8,C-12), 128.9(CH of C-9, C-11), 127.1(C of C-10), 146.6(C of C-13).

6-(4-phenoxyphenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (III t)

$C_{22}H_{18}N_2O_2$, Yield- 30.16 %, m.p. 342.39°C, Molecular Weight- 342.39, TLC(T:E:F-5:4:1) : R_f – 0.61, IR (KBr) ν_{max} (cm^{-1}): 1630(C=O), 895(C-O-C str) ^{1}HNMR (DMSO): δ 2.39-2.42(t, 2H, CH_2), 2.89-2.92(t, 2H, CH_2), 7.36-7.42(t, 3H, Ar), 7.02-7.07(m, 2H, Ar), 7.92-7.94(d, 1H, Ar), 7.03- 7.07(d, 1H, Ar), 7.26-7.27(d, 1H, Ar), 7.43-

7.50(d,2H, Ar), 7.64(d, 2H, Ar),7.24(d, 2H, Ar), 7.00(m, 1H, Ar)

^{13}C-NMR (DMSO) δ All aromatic protons are same except 24.5(CH_2 of C-14), 32.5(CH_2 of C-15).

2-(2,4-dinitrophenyl-6-(4-phenoxyphenyl)-4,5-dihydropyridazin-3(2H)-one III (u)

$C_{22}H_{16}N_4O_6$, Yield – 20.93 %, m.p. 389.02°C, Molecular Weight-432.29, TLC(T:E:F-5:4:1) : R_f – 0.66, IR (KBr) ν_{max} (cm^{-1}): 1455, 1365(-Ar – NO_2), 1615(C=O) ^{1}HNMR (DMSO): δ 2.40-2.46(t, 2H, CH_2), 2.90-2.95(t, 2H, CH_2), 7.39-7.44(t, 3H, Ar), 7.00-7.071(m, 2H, Ar), 7.91-7.94(d, 1H, Ar), 7.02- 7.06(d, 1H, Ar), 7.25-7.28(d, 1H, Ar), 7.46-7.50(d,2H, Ar) ^{13}C-NMR (DMSO) δ 23.9(CH_2 of C-14), 32.7(CH_2 of C-15).

Biological Evaluation (In-Vivo and In-Vitro Study)

Microbiological activity (in-vitro study)

A total of twenty one synthesized compounds were screened for their antibacterial activity. Tested chemical compounds showed zone of inhibition between 10 and 32 mm. On the basis of zone of inhibition produced against the test bacterium, compound **III *j*** was found to be most effective against *S. aureus* and *B. cereus* (Gram-positive) showing the maximum zone of inhibition of 32 mm and 33 mm, respectively and **III *n*** was found to be most effective against *E. coli* and *S. flexveri* (Gram-negative) showing maximum zone of inhibition of 29 mm and 30 mm.

Antioxidant Activity

A total of twenty one synthesized compounds were screened for their antioxidant activity. Compound **III *u*** was found to have maximum % anti-radical activity i.e. 89.393 % at different concentration of (1000, 500, 250 µg/ml).

Pharmacological Activities (In-Vivo Study)

Anti-inflammatory activity-

The synthesized compounds were screened for anti-inflammatory activity by Carragennan induced paw edema method. At 60 min, none of the compound was found to be potent. After 90 minutes, some of the compounds were found to have anti-inflammatory activity i.e. III *o*, III *h*, III *u*, III *e*, III *p*, III *q*, III *j*, III *b*, III *i*. At 90 minutes, some of the compounds exhibited more than 60 % percentage inhibition in paw edema volume. At 180 min, none of them remained potent. After 120 min. compound, III *u* was found to be most active followed by III *l*, III *f*, III *e*, III *p*, III *j*, III *h*, III *k*.

Analgesic Activity

Acetic-acid induced writhing method

The synthesized compounds were screened for analgesic activity by Acetic-acid induced writhing method. The compounds III *l*, III *c*, III *s*, III *a* showed good activity comparable to standard. Compound **III *l*** was found to be most potent having % inhibition value = 69.99 %.

Tail immersion method

The synthesized compounds were screened for analgesic activity by Tail immersion method. After 30 minutes of test drug administration, none of the compound were found to be potent. The activity of some compounds (III *u*, III *l*, III *c*, III *h*, III *a*) showed potent activity after 60 minutes, but the maximum potent activity of the compounds (III *l*, III *c*, III *u*, III *h*, III *a*) showed after 90 minutes.

CONCLUSION

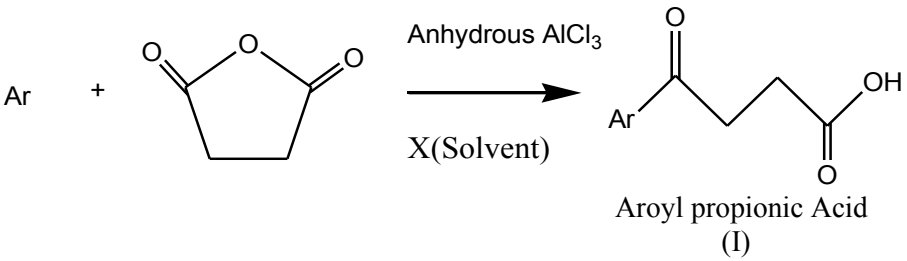
The pyridazinones have diverse potential, further drew attention because of their easy functionalization at various ring positions insisted us to work on designing and development of novel pyridazine as anti-inflammatory and analgesic agents. The computational analysis helped us to synthesize some selected potent derivatives and restricted our study to twenty one compounds. The synthesized compounds showed very encouraging results in *in-vitro* and *in-vivo* models associated with *in-silico*. The synthesized compounds were characterized on the basis of physiochemical data and spectral data.

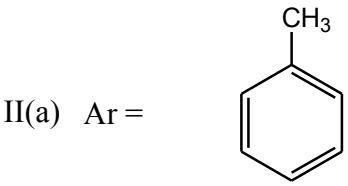
ACKNOWLEDGMENTS

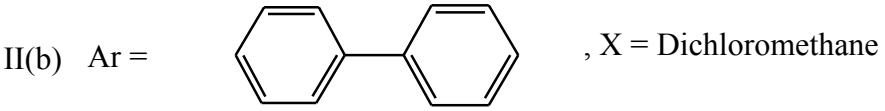
The Authors are thankful to University Institute of Pharmaceutical Sciences, Kurukshetra university, India for providing financial as well as technical support during the research study.

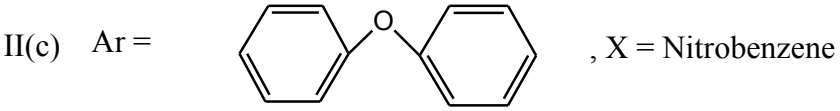
Scheme of Synthesis:

STEP-I

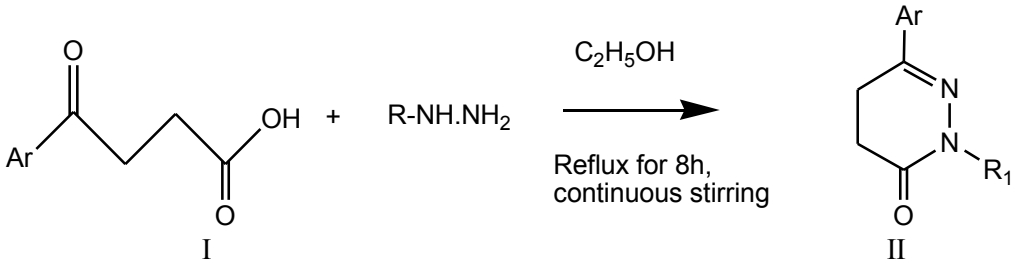








STEP II



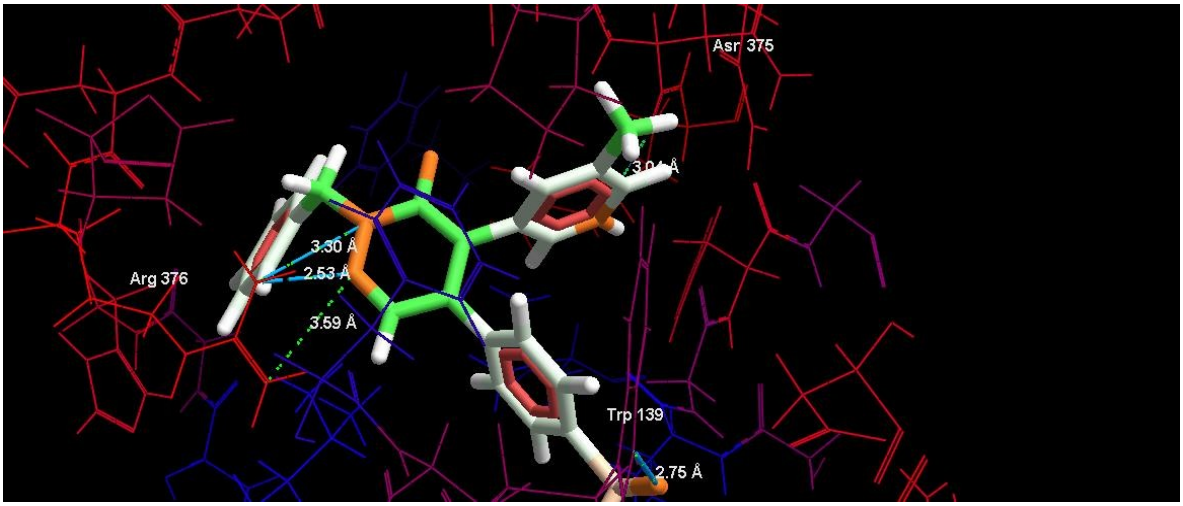


Figure A: Binding mode of standard drug 2-benzyl-4-(5-methylpyridin-3-yl)-5-(4-(methylsulfonyl) phenyl) pyridazin- 3(2H)-one into the binding site of pdb: 6COX

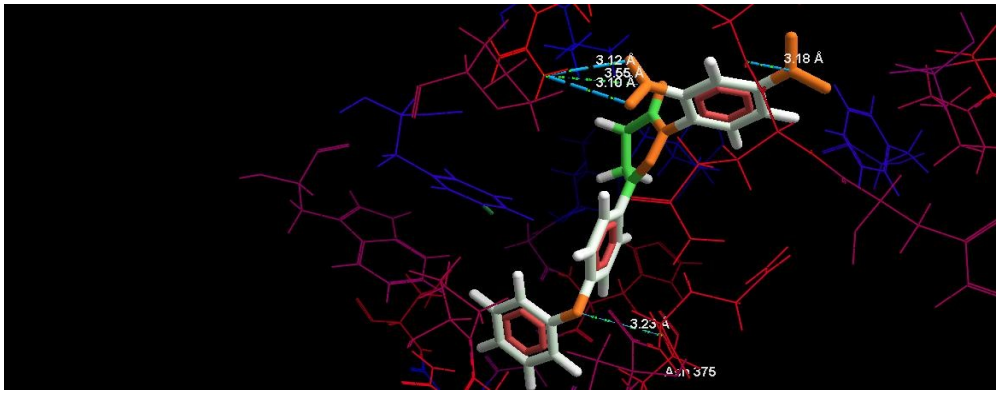


Figure B: Binding mode of III-u into the binding site of pdb: 6COX

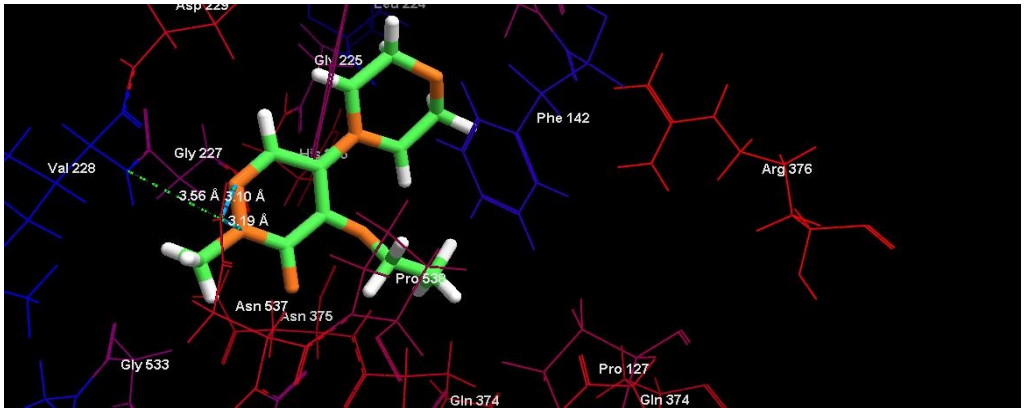


Figure C: Binding mode of Emorfazone into the binding site of pdb: 2OOX

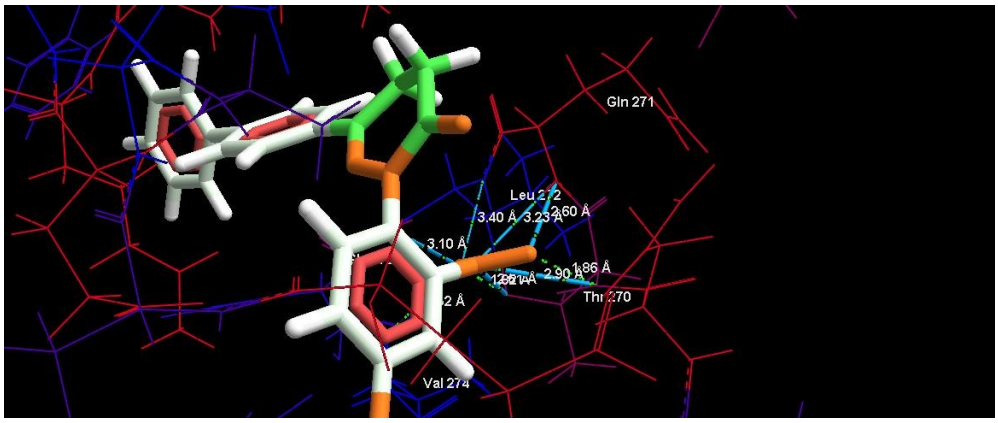


Figure D: Binding mode of III l into the binding site of pdb: 2OOX

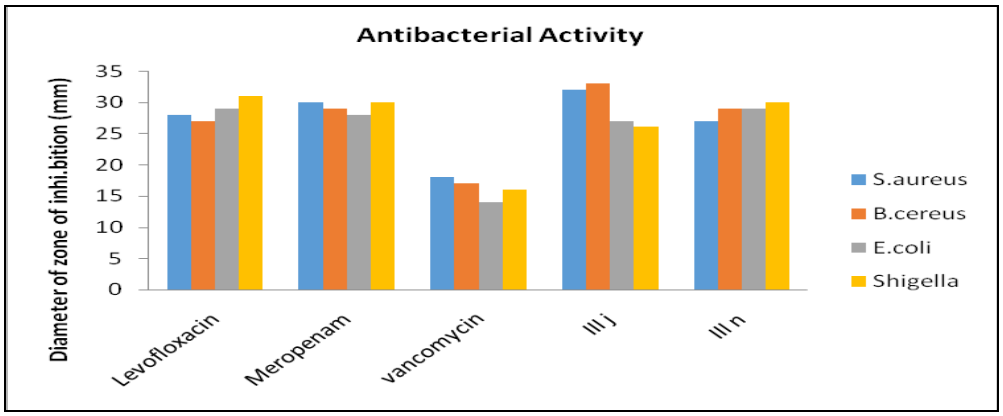


Figure-E: Results of antibacterial activity of compounds with best results

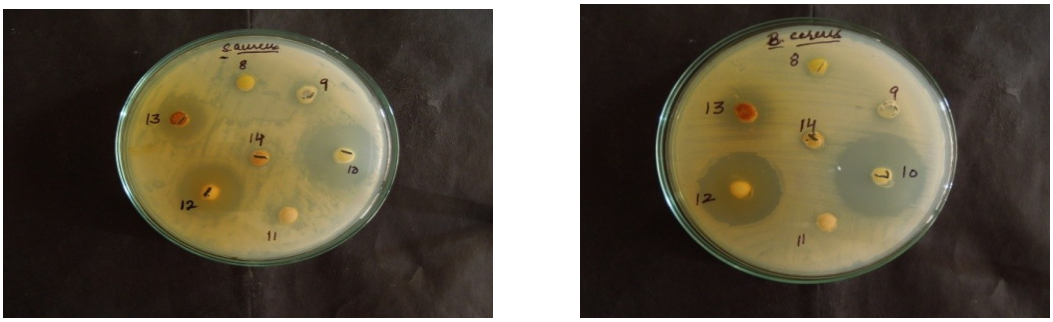


Figure F: Antibacterial activity of synthesized compounds against gram + ve strain i.e. *Staphylococcus aureus* and *Bacillus cereus*

Figure G: Antibacterial activity of synthesized compounds against gram - ve strain i.e. *Escherichia coli* and *Shigella flexveri*

Figure H: Minimum inhibitory cosncentration (MIC) of most potent compound III *j* against gram + ve bacteria i.e. *Staphylococcus aureus* and *Bacillus cereus.*

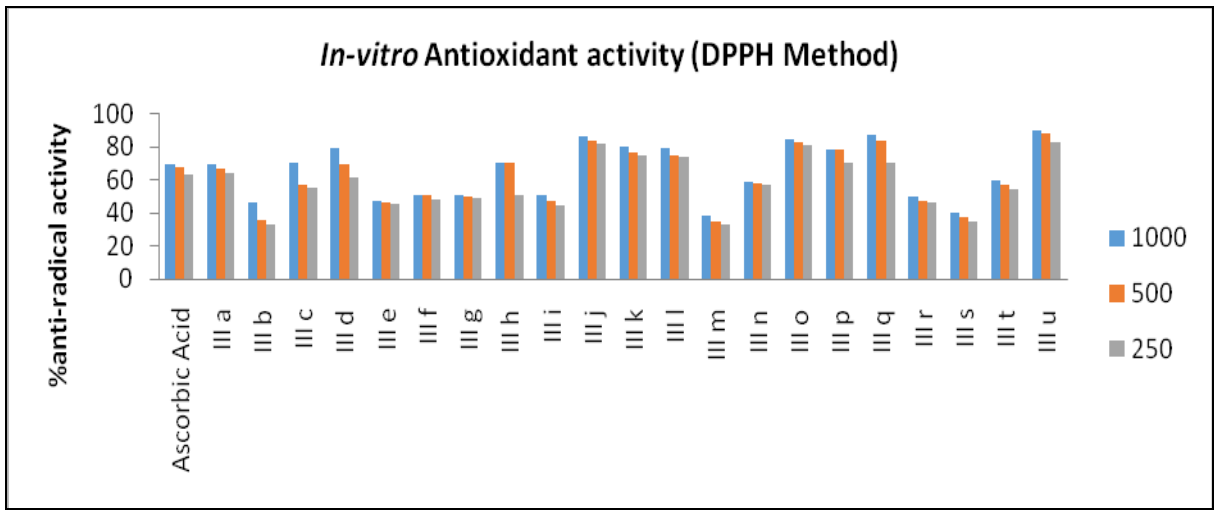


Figure I: *In vitro* antioxidant activity of test compounds by DPPH antioxidant assay

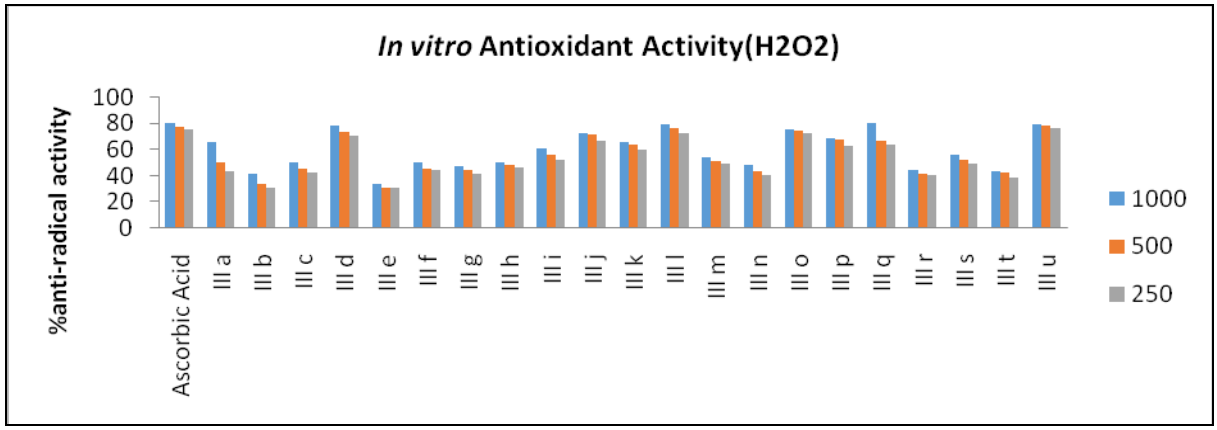


Figure J: *In vitro* antioxidant activity of test compounds by H_2O_2 scavenging activity

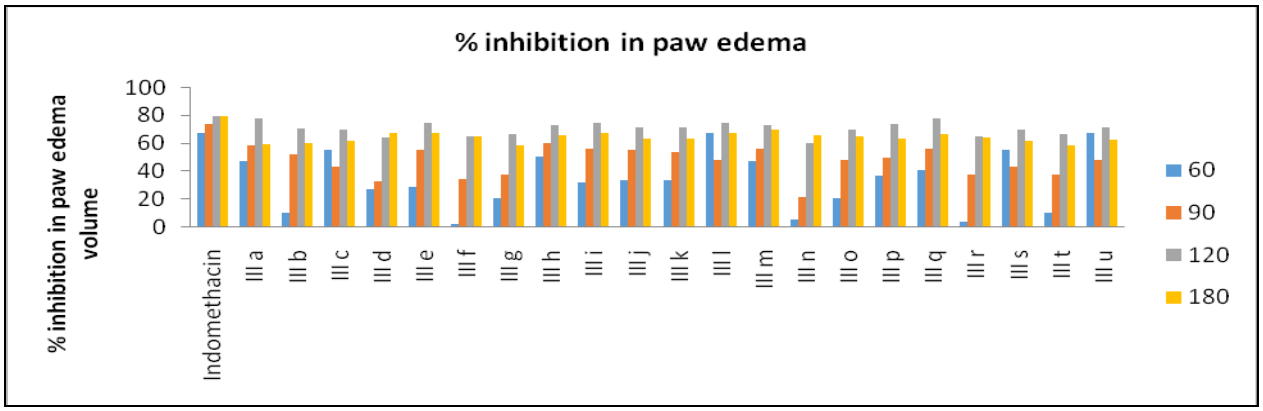


Figure K: Results of % inhibition in paw edema volume

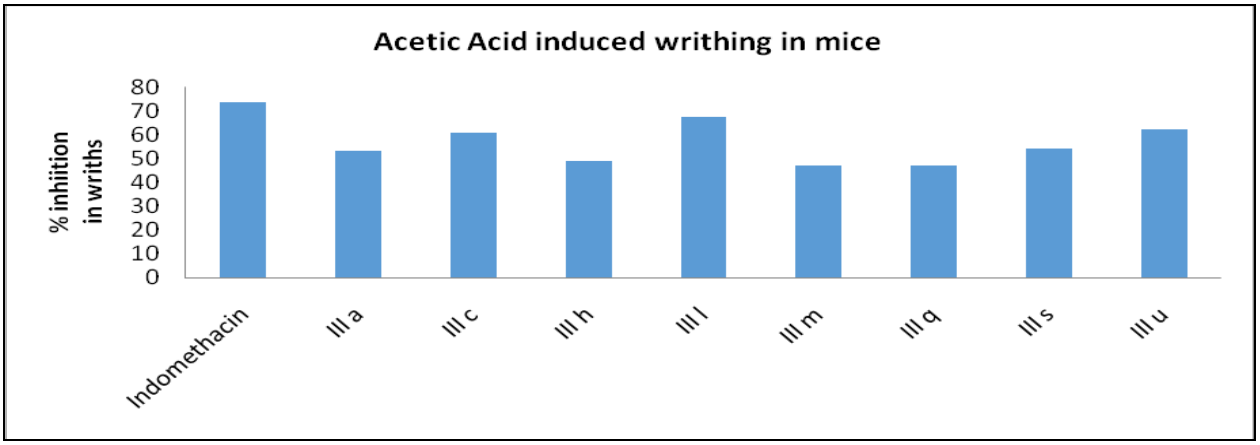


Figure L: Results of analgesic activity by acetic acid induced wriths method

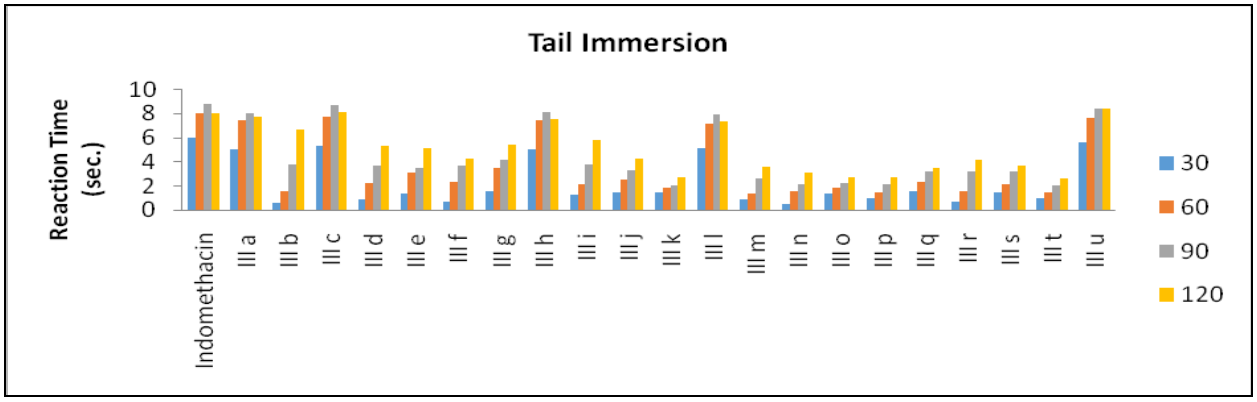
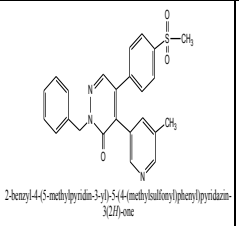
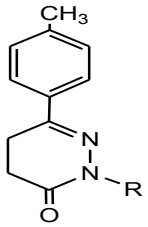
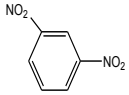
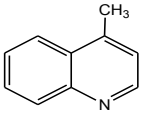
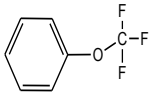
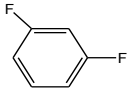
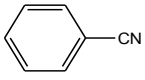
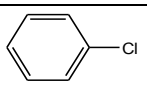
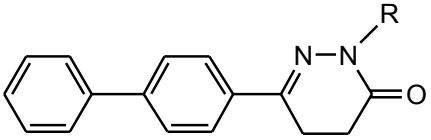
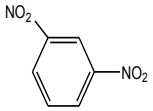
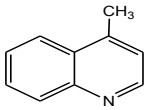
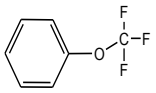
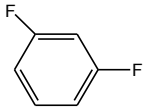
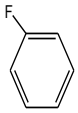
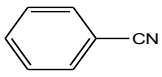
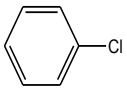
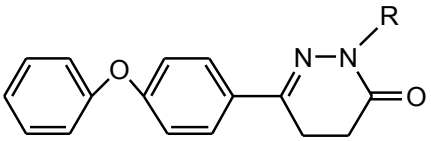


Figure M: Results of analgesic activity by tail Immersion Method

Table I: Docking results of synthesized compounds (III *a*-III *u*) with PDB ID: 6COX for anti-inflammatory activity (Designing, synthesis & biological evaluation of novel pyridazinone derivatives).

S. No.	Compound No	Structure/ R Group	Mol Dock Score	Docking Score	H-Bond Interaction	H-Bond Distance(A°)	Interacting Residue	Interacting Residue
1.	1	 2-benzyl-4-(5-methylpyridin-3-yl)-5-(4-(methylsulfonyl)phenyl)pyridazin-3(2H)-one	-143.627	-149.991	5	3.30 2.53 3.59 3.04 2.75	Arg 376 Arg 376 Arg 376 Asn 375 Trp 139	N-N N-N N-N O-N N-O
								
2.	III *a*	H	-77.5482	-80.6051	2	2.35 2.72	Asn 537 Val 228	N of pyridazinone with H O of pyridazinone with N
3.	III *b*	C_6H_5	-104.374	-102.004	1	2.60	Asn 375	O of pyridazinone with N
4.	III *c*		-124.97	-122.784	3	3.09 3.40 3.54	Asn 537 Val 228 Asn 375	O of NO_2 with N O of NO_2 with N O of NO_2 with N
5.	III *d*		-120.921	-118.281	0	-----	----	-----
6.	III *e*		-114.455	-115.743	2	3.28 3.56	Arg 376 Arg 376	N of pyridazinone with N N of pyridazinone with N
7.	III *f*		-115.54	----	0	----	----	----
8.	III *g*		-112.681	-110.033	2	3.53 3.21	Asn 375 Asn 375	N of pyridazinone with N N of pyridazinone with N
9.	III *h*		-113.037	-117.399	3	3.10 3.08 2.72	Asn 375 Gly 536 Gly 533	O of pyridazinone with N N of CN with O N of CN with O
10.	III *i*		-112.384	-109.862	1	3.34	Asn 375	N of pyridazinone with N

								
11.	III *j*	H	-95.5091	-95.5991	3	3.08 3.22 3.07	Asn 375 Asn 375 His 226	N of pyridazinone with N N of pyridazinone with O N of pyridazinone with O
12.	III *k*	C_6H_5	-104.96	-104.654	1	2.72	Asn 375	O of pyridazinone with N
13.	III *l*		-141.262	-140.163	5	3.47 2.87 3.29 2.62 3.02	Asn 375 Asn 375 Asn 537 Asn 537 Val 228	N of NO_2 with N O of NO_2 with N N of NO_2 with N O of NO_2 with N O of NO_2 with N
14.	III *m*		-118.708	-118.306	2	2.96 2.86	Asn 375 Asn 375	N of Quinoline with O O of pyridazinone with N
15.	III *n*		-101.445	-100.991	1	3.26	Asn 537	O of CF_3 with N
16.	III *o*		-125.156	-119.837	0	----	----	----
17.	III *p*		-124.931	-118.297	3	3.12 3.36 2.59	Trp 139 Lys 333 Lys 333	N of pyridazinone with N N of pyridazinone with N O of pyridazinone with N
18.	III *q*		-118.335	-120.982	3	2.60 2.30 2.10	Glu 140 Asn 375 Trp 139	N of CN with O N of CN with O N of CN with N
19.	III *r*		-150.059	-113.487	1	3.13	Asn 375	O of pyridazinone with N
								
20.	III *s*	H	-94.6208	-95.6732	4	3.37 3.10 3.49 3.10	Asn 375 Asn 375 Gly 225 His 226	N of pyridazinone with O N of pyridazinone with N N of pyridazinone with O N of pyridazinone with O
21.	III *t*	C_6H_5	-135.815	-133.783	1	3.33	Asn 375	O of pyridazinone

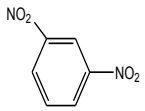
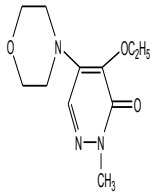
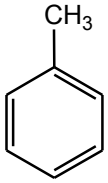
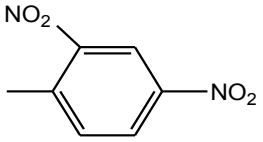
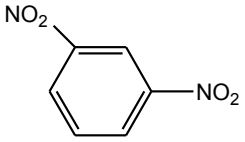
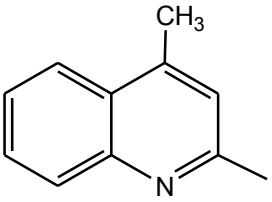
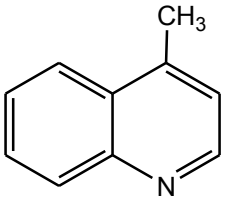
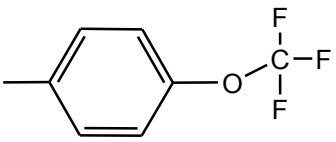
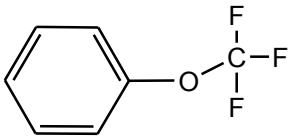
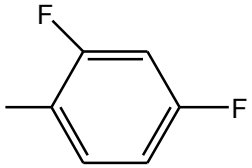
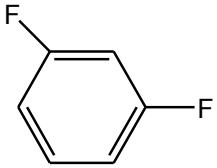
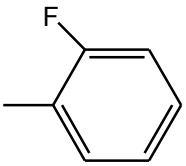
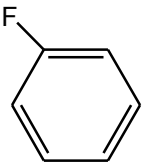
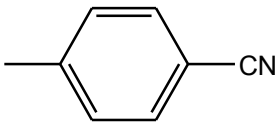
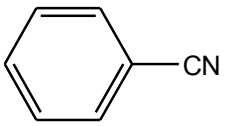
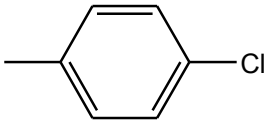
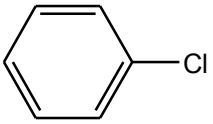
								with N
22.	III *u*		-132.964	-138.101	5	3.23 3.18 3.10 3.12 3.55	Asn 375 Asn 375 Arg 376 Arg 376 Arg 376	O of Biphenyl with N N of NO_2 with N O of NO_2 with N O of NO_2 with N N of NO_2 with N

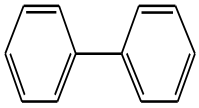
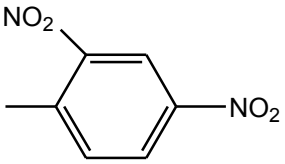
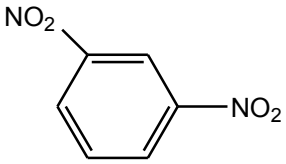
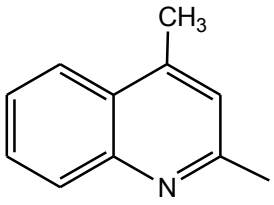
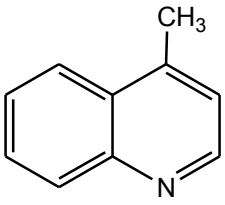
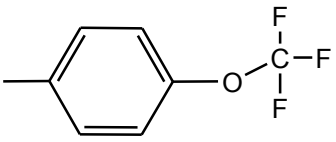
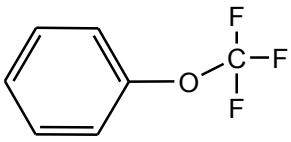
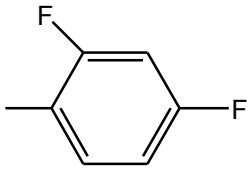
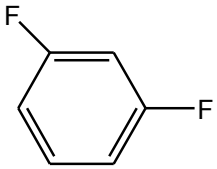
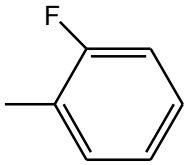
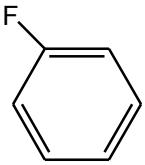
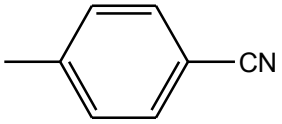
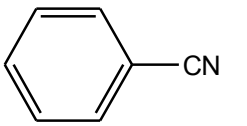
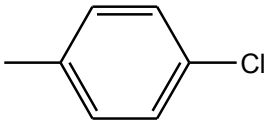
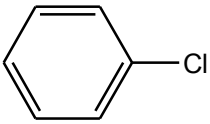
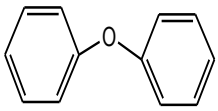
Table II: Docking results of synthesized compounds (III a-III u) with PDB ID: 2OOX for analgesic activity (Designing, synthesis & biological evaluation of novel pyridazinone derivatives).

S. No.	Compound No	Structure	Mol dock score	Docking Score	H-Bond Interaction	H-Bond Distance	Interacting Residue	Interacting Atom
1.	Emorfazone (Std Compund)		-86.155	-87.0387	3	3.10 3.19 3.56	Asn 537 Asn 537 Val 228	N-N N-N N-N
2.	III *a*		-89.087	-91.5335	4	2.75 3.24 3.00 3.27	Ala 268 Thr 270 Thr 270 Ala 276	N of pyridazinone with O N of pyridazinone with O N of pyridazinone with N O of pyridazinone with N
3.	III *b*		-120.556	-117.9	0	----	----	---
4.	III *c*		-104.099	-114.603	8	3.09 2.82 3.05 2.60 2.98 3.57 2.37 2.85	Asn 269 Ser 247 Gln 271 Asn 269 Ser 247 Ser 247 Ser 247 Ala 95	N of NO_2 with N N of NO_2 with O N of NO_2 with N O of NO_2 with N O of NO_2 with N O of NO_2 with N O of NO_2 with O O of NO_2 with N
5.	III *d*		-111.02	-109.39	1	3.07	Leu 272	N of Quinoline with O
6.	III *e*		-112.771	-110.84	1	3.10	Thr 45	O of CF_3 with O
7.	III *f*		-105.758	-102.775	0	----	----	----
8.	III *g*		-108.483	-105.064	0	----	----	----
9.	III *h*		-112.052	-114.56	4	3.01 2.23	Ala 95 Glu 96	N of CN with O N of CN with O Electrostatic Interaction (2)

10.	III *i*		-92.168	-94.1417	1	3.36	Lys 99	O of pyridazinone with N
11.	III *j*		-99.4804	-98.2317	1	2.60	Gly 244	N of NH with O
12.	III *k*		-107.297	-104.137	1	3.33	Thr 45	O of pyridazinone with O
13.	III *l*		-135.769	-143.709	9	2.60 3.10 3.40 3.23 2.90 2.61 1.87 3.52 1.86	Gln 271 Gly 273 Leu 272 Gln 271 Thr 270 Thr 270 Thr 270 Val 274 Thr 270	O of NO_2 with N O of NO_2 with N O of NO_2 with N N of NO_2 with N N of NO_2 with O O of NO_2 with O O of NO_2 with O O of NO_2 with N O of NO_2 with N
14.	III *m*		-105.697	-104.98	2	2.33 3.07	Thr 45 Thr 45	O of pyridazinone with O O of pyridazinone with N
15.	III *n*		-106.692	-82.4956	0	----	----	----
16.	III *o*		-142.679	-139.339	1	3.58	Gly 273	N of pyridazinone with N
17.	III *p*		-134.006	-131.358	1	3.49	Gly 273	N of pyridazinone with N
18.	III *q*		-113.646	-112.789	2	3.48	Ser 48	N of CN with O Electrostatic Interaction (1)
19.	III *r*		-111.807	-110.35	0	----	----	----
20.	III *s*		-86.8399	-91.0378	2	3.47 3.24	Thr 45 Thr 45	N of pyridazinone with O O of pyridazinone with N
21.	III *t*		-130.974	-128.285	1	3.50	Gly 273	N of pyridazinone with N
22.	III *u*		-127.717	-134.544	8	2.99 3.28 3.10 3.21 3.10 3.08 2.36 2.68	Thr 45 Thr 40 Asn 295 Arg 101 Phe 296 Lys 99 Lys 99 Phe 296	O of diphenylether with O O of NO_2 with O O of NO_2 with N O of NO_2 with N N of NO_2 with N N of NO_2 with N O of NO_2 with N O of NO_2 with N

Table III: Structure of Synthesized Compounds (Designing, synthesis & biological evaluation of novel pyridazinone derivatives).

S.No	Synthesized Compounds	Ar	R	R_1
1.	III *a*		H_2O	H
2.	III *b*		C_6H_5	C_6H_5
3.	III *c*			
4.	III *d*			
5.	III *e*			
6.	III *f*			
7.	III *g*			
8.	III *h*			
9.	III *i*			
10.	III *j*		H_2O	H
11.	III *k*		C_6H_5	C_6H_5

12.	III *l*			
13.	III *m*			
14.	III *n*			
15.	III *o*			
16.	III *p*			
17.	III *q*			
18.	III *r*			
19.	III *s*		H_2O	H
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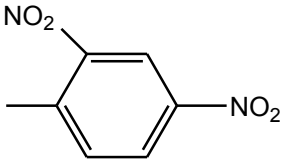
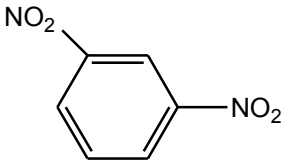
21.	III *u*			

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