Open Access Contents
Int. J. Drug Dev. & Res.
I January - March 2014 I Vol. 6 I Issue 1 I ISSN 0975-9344 I
www.ijddr.in

Full Length Original Research Paper

Insilico designing of Pyrazol-1-Yl Azetidin-2-One derivatives as drug like molecules for possible inhibition of Anti Microbial 3GI9, 4AE5, 3FHU and 5COX target Proteins

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Abstract:
Two series of 1- ((3-(substituted phenyl)-5-substituted-4,5-dihydro-1H-Pyrazol-1-yl) Carbonothionyl)-3-chloro-4- (Fuan-2-yl)) Azetidin-2-ones derivates were interacted through inter or intra molecular hydrogen bonding by the enzymatic keys and ADME toxicity, solubility, Drug-score and Biological activities studies, which indicated that the compounds 4(P_1-P_7, P_{11}-P_{77}) have drug likeness properties. The enzymatic keys are the target proteins or receptors of *E.coli* (3GI9), *S.a.* (4AE5), *S.typhi* (3FHU), cyclooxygenase (5COX) and helped for designing of the compounds 4 (P1-P7, P11-P77) for better activities by the MVD-5.0.5 software.

Keywords: LBVS, ADME toxicity study, Biological activity study, Drug-likeness study and Molecular Docking study.

Introduction

Infections are the re-emergency diseases of life threatening, caused by bacteria (parasites) like *E. coli, S. aureus, S. typhi.* Normally *Escherichia coli* is a highly remarkable adapted pathogen which has a capable to produced wide range of infections like gastroenteritis to extra intestinal infections of the urinary tract, bloodstream and central nervous system. Mainly *Escherichia coli* (gram-ve) is remarkable for urinary tract infection (UTI) and various type conterminous infection diseases caused by *Staphylococcus aurous* (gram+ve). While the main causative agent of typhoid is *Salmonella typhi.* The glucocorticoid and prostaglandins are potent mediators of Inflammation in which the body reacts to infection, irritation or other injury were the key feature of redness, warmth, swelling and pain. In the early of 1990th s, the enzymatic key was discovered as a cyclooxygenase which catalyses for the biosynthesis path of arachidonic acid to prostaglandins. The cyclooxygenase enzyme has two isomeric forms likely Cox-1 and Cox-2. The cox-1was produced in many tissues like kidney and GIT, while cox-2 was the inducible and expressed during the inflammation at a site of the injury.

The heterocycles are important components of bio-molecules such as RNA, DNA, protein and

vitamin in which the aromatic rings fused with five member heterocyclic moieties containing N,S,O , exhibited wide range of pharmacological activities like anti-inflammatory, antbacterial, antifungal etc. Keeping in the view of pharmacological activity was emphasized to designing the drug compounds of two series by the interaction of enzymatic keys in MDV5.o.5.

The enzymatic key as receptors (3GI9[5], 4AE5[6], 3FHU[7] and 5COX[8]) of cyclooxygenase, bacteria's and reductase. The cyclooxygenase (COX, also known as PGH synthase) receptor was pharmacological target of NSAIDs. The 5COX pdb (cyclooxygenase inhibitor-2 or COX-2) was also known as PGH synthase-2. The murine structures of COX-2 was unliganded at SC-558 .The murine cox-2 was complexed with compounds to produced exert selective COX-2 inhibitor . While the *E. coli* (3GI9) receptor acts as Amino acid, polyamine, and organocation (APC) transporters which recycling the neurotransmitter to uptake of nutrient and regulate the ionic homeostasis. The *S. aureus* (4AE5) was contained fibrogen –binding clumping factor (ClfB) as like as dermokine peptide binding mode of (ClfB) (glycine-serine-rich, GSR) replication. The main causative agent of typhoid is *Salmonella typhi.* The 3FHUpdb was extracted from native PilS protein (Delta PilS or IVb pilin) of *S.typhi*. The Delta pilS was interacted with extracellular domain of cystic fibrosis trans membrane conductance regulator (CFTR) and forming active site insight on the amino acids for binding. The pilus functions were helped to designing the suitable antibacterial analogs.

MATERIALS AND METHOD:

- Drawing of these structures, energy minimization and docking of 1-((3-(substituted phenyl)-5-substituted-4,5-dihydro-1H-Pyrazol-1-yl)Carbonothionyl)-3-chloro-4-(Fuan-2-yl)) Azetidin-2-ones derivates were done by using Chem. sketch and MVD 5.0.5 .
- The ADME toxicity study of the proposed titled compounds 4(P_{1-7}, P_{11-77}) were done in "Medchem2 Software".
- The Biological Activity study was tested in "Mol inspiration software" by on line submission of the title compounds.
- The Drug-likeness properties were studied in "Osisir Molecular property Explorer software" by online submission of the compounds 4(P_{1-7}, P_{11-77}).
- The target proteins i.e. *E. coli* (3GI9), *S. aurous* (4AE5), *S. typhi* (3FHU) and cyclooxygenase (5COX) were derived from protein data bank (RCBS).
- To finding the best pose energies of Ligands, 4(P_{1-7}, P_{11-77}) and the target proteins interaction through hydrogen bonding were visualized in "Molegro Virtual Docker-5.0.5 software".

COMPUTATIONAL WORK (*INSILICO DESIGNING*)

Computer-based molecular design has been employed in bioinformatics, medicine, biochemistry, Biophysics and other fields. Computational design has speed up research by identifying new molecules with possible medical applications prior to laborious experiments and expensive preclinical studies. However, substantial computational resources and programming proficiencies are usually needed to design computationally molecules with desired biological properties. This precludes researchers who lack computer resources in many countries and small institutions from carrying out studies in the field. A simple, yet effective procedure presented as

ADME toxicity study

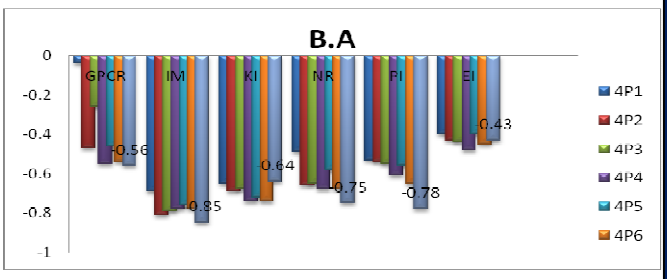
The Five Rules of Lipinski is studied in Medchem2 software to purify and evaluate the drugs as drug-likeness properties for orally active in human. In generally Lipinski's rule says that for an orally active drug have the following criteria:

- Not more than one violation.
- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms).
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms).
- Molecular weight under 500 Daltons.
- The octanol-water partition coefficient log P of less than 5.

The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME). The compounds ($4P_{1-7}$, P_{11-77}) used in this study satisfy the rule (see Table -01) and are efficiently analyzed. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bonds, and a higher lipophilicity.

Biological activity study[9]

The biological activity scoring is an Expert system of Molinspiration technology for calculation of drug likeness score towards GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors studies furnished the 1- ((3-(substituted phenyl)-5-substituted-4,5-dihydro-1H-Pyrazol-1-yl) Carbonothionyl)-3-chloro-4- (Fuan-2-yl)) Azetidin-2-ones derivates as "average drug-like molecule" and the larger value of the BA score will be highly active molecule. As compared to the standard drugs, ciprofloxacin, indomethacin and aspirin, all compounds have shown good affinity toward these six inhibitors and were shown in table-02.



Drug-likeness study[10]

Drug likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.

The diversity of possible drug targets is so enormous, that it is possible to find a common denominator for all of them and to express molecule drug-likeness by a single "magic number" i.e molecular weight, logP, or number of hydrogen bond donors or acceptors.

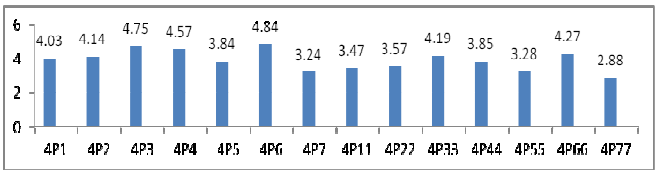
(1)Toxicity Risk Assessment

The drawing structures ($4P_{1-7}$, P_{11-77}) of the toxicity risk predictor will be validated on Osisir explorer due to toxicity risk alerts may be harmful the drawn structure and concerning the specified risk category. In order to assess the toxicity prediction's the precomputed set of structural fragments were encountered the shreddering of any molecule by RTECS database. These in turn were used to reconstruct all possible bigger fragments being a substructure of the original

molecule. Afterwards, a substructure search process determined the occurrence frequency of any fragment (core and constructed fragments) within all compounds of that toxicity class. Based on the assumption that traded drugs are largely free of toxic effects, any fragment was considered a risk factor if it occurred often as substructure of harmful compounds but never or rarely in traded drugs.The proposed titled compounds were tested the toxicity studies in osisir property Explorer which indicates that, all the compounds have no toxic in nature toward the mutagenicity and are shown in table-03.

(2) C Log P Calculation

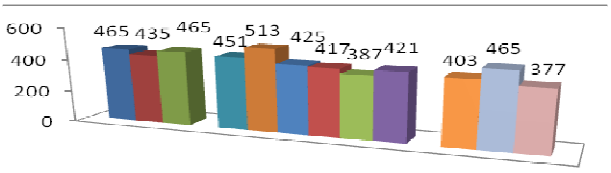
The log P value of a compound, which is the logarithm of its partition coefficient between n-octanol and water log(c $_{octanol}$ /c $_{water}$), is a well established measure of the compound's hydrophilicity. Low hydrophilicities and therefore high log P values cause poor absorption or permeation. It has been shown for compounds to have a reasonable probability of being well absorb their log P value must not be greater than 5.0. The distribution of calculated log P values of compounds (4P$_{1-7}$, P$_{11-77}$) were shown below.



(3) Solubility (log S) Calculation

The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds. Our estimated log S value is a unit stripped logarithm (base 10) of the solubility measured in mol/liter.

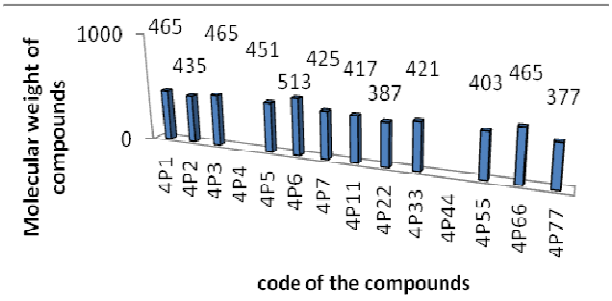
- The solubility via an increment system by adding atom contributions depending on their atom types.
- The solubility of a compound is also depending on the arrangement of molecule in the crystal.
- The logs of the compound depend on pH.



In the following diagram you can see that more than 90% of the compounds 4(P$_1$-P$_{77}$) have a (estimated) logS value greater than 4.

(4) Molecular Weight

Optimizing compounds for high activity on a biological target almost often goes along with increased molecular weights. However, compounds with higher weights are less likely to be absorbed and therefore to ever reach the place of action. Thus, trying to keep molecular weights as low as possible should be the desire of every drug forger.



The diagram shows that more than 96 % of compounds have a molecular weight below 450.

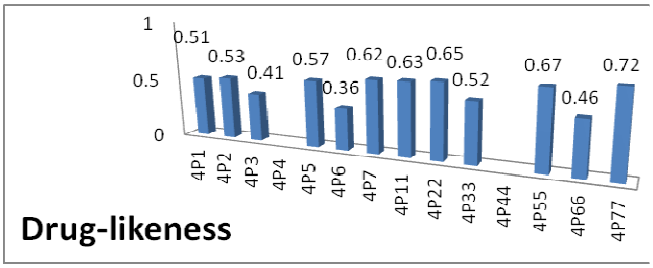
(5) Drug likeness

There are many approaches around that assess a compound's drug likeness partially based on topological descriptors, fingerprints of MDL

structure keys or other properties as cLog P and molecular weights. The drug likeness is calculated with the following equation summing up score values of those fragments that are present in the molecule under investigation.

$$d = \frac{\sum v_i}{\sqrt{n}}$$

The way fragment substitution patterns list were created by shreddering, cut of rotatable bonds or retained of fragment atoms in the original compounds and these properties were analyzed in compounds 4(P_1-P_{77}).



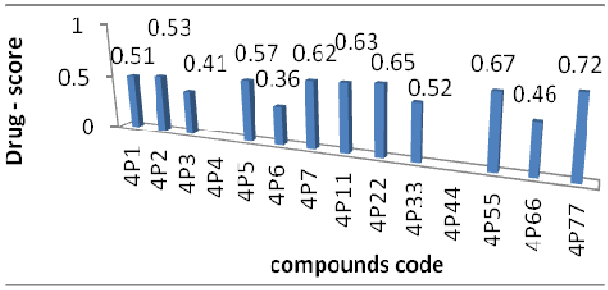
(6) Drug Score

Drug score was the combination of sum, drug likeness, c Log P, log S, molecular weight and drug toxicity risk. This value is calculated by multiplying contributions of the individual properties with the first equation.

$$ds = \prod \left(\frac{1}{2} + \frac{1}{2} s_i\right) \cdot \prod t_i$$

$$s = \frac{1}{1 + e^{ap+b}}$$

ds: the drug score, s_i : are the contributions calculated directly from of cLogP, logS, molecular weight and druglikeness (p_i) via the second equation which describes a spline curve. Parameters *a* and *b* are (1, -5), (1, 5), (0.012, -6) and (1, 0) for c Log P, log S, mol weight and drug likeness, respectively. t_i are the contributions taken from the 4 toxicity risk types. The t_i values are 1.0, 0.8 and 0.6 for no risk, medium risk and high risk, respectively. Thus most of the compounds 4(P_1-P_{77}) were shown good drug-scoring due to all of their scoring value was 0.6.



Molecular docking (MVD-5.0.5)[1-4]

Computational methods are now a ubiquitous part of modern drug design. Being able to predict and visualized drug candidates and their interactions with the target receptor makes it possible to rationally optimize the potential drugs is an important advantage in a competitive area of researched field. Molegro virual Docker is a highly accuracy molecular docking software which predicted the small flexible of ligands (4P_1-P_{77}) linked through intra and inter molecular H-bonding with protein receptors during the time of protein –ligand docking. The protein-Ligand docking results were shown in table-01 and steps of the docking are -

- Import and export of standard file formats (PDB, Mol2, and SDF).
- Displaceable water model.
- Automated preparation of input structures.
- Predict potential binding sites.
- Protein binding pocket flexibility.
- Repair, mutate, or minimize side chains before docking.
- Visually inspect docking predictions with relevant interactions.

The docking energies of proposed compounds 4$P_{1\text{-}7}$, $P_{11\text{-}77}$ were given in tables-03-06.

RESULTS AND DISCUSSION:

The insilico designing has been an important part of solid phase chemistry to purifying and minimized the cost of NCE. The proposed two novel series of compounds have good tolerating efficacy in ADME toxicity studies. While the intra-inter molecular attraction of compounds through hydrogen bonding with six receptors were Scaffold the promised biological activities (BA). The drug –likeness properties like solubility, drug-score and drug-liking score was guided by "Osisir molecular Explorer" which has made these compounds free from toxicity risk into therapeutically active analogs.

Molecular docking is an interesting part of attraction of ligands and target proteins to find out the active site of receptor as well as the biological activity compounds through the best pose energy. The docking results reveal that all the selected title compounds inside target proteins (three bacterial and one cox) were outlined by different amino acids and the hydrophobic pockets. Small ligand molecules were bound to 3GI9, 4AE5, 3FHU and 5COX by four binding modes such as hydrogen bonds, Vander Waals, electrostatic and hydrophobic interactions. The total energy of four binding modes and different energies, interacting surfaces between designed compounds comparison with standard drugs were given in Tables-04-07.

Calculated free energy of binding for compounds $4P_{1\text{-}77}$ and ciprofloxacin, indomethacin and aspirin in the binding sites were -148.767, -144.124, -142.640, -144.667,-94.489, -130.670, and -72.660 kcal/mol respectively in their best pose. The highest free energy of binding and lowest interactive surface is observed with Compound $4P_1$, $4P_{11}$ and $4P_{77}$ than other docked molecules ($4P_2$-P_{66}). Therefore, among all docked molecules, $4P_{1\text{-}77}$ possess highest probability of interaction with binding site of target proteins and it is comparable with that of standard antagonist. Furthermore, the present data showed that the substituent like Cl and furfuryl present in lactum ring resulted in improvement ability of binding was increased. Therefore it was observed that the in vitro insilico method revealed that the compounds of pyrazol-1-yl azetidin-2-one derivatives acted as an anti-antibacterial as well as anti-inflammatory agents.

Table 1: ADME toxicity study of compounds ($4P_1$-P_{77})

Compound Code	Molecular weight	S + logP	S + logD	MlogP	OH NH	ON	TPSA	Violation	No. of Rotable Bonds
$4P_1$	464.974	4.826	2.270	3.385	00	05	55.047	00	06
$4P_2$	434.947	4.547	2.133	3.70	00	05	49.051	00	05
$4P_3$	469.392	5.262	2.765	4.172	00	05	49.05	00	05
$4P_4$	479.945	4.345	2.251	3.747	00	08	94.87	00	06
$4P_5$	450.464	4.464	2.440	3.693	01	06	89.279	00	05
$4P_6$	514.832	4.912	4.912	4.868	00	05	49.051	02	05
$4P_7$	425.897	3.403	3.403	3.092	00	06	62.191	00	05
$4P_{11}$	417.918	4.090	4.090	3.363	00	06	58.285	00	06
$4P_{22}$	387.893	3.861	3.861	3.644	00	05	49.051	00	05
$4P_{33}$	422.337	4.449	4.449	4.135	00	05	49.051	00	05
$4P_{44}$	432.889	3.709	3.709	3.731	00	08	94.875	00	06
$4P_{55}$	403.891	3.771	3.765	3.651	01	06	69.279	00	05
$4P_{66}$	466.788	4.441	4.441	4.245	00	05	49.051	00	00
$4P_{77}$	376.865	2.834	2.834	2.412	00	06	58.953	00	05
Ciprofloxacin	331.347	-1.366	-1.384	0.786	02	06	74.569	00	03
Indomethacin	343.766	2.937	-0.034	2.327	01	05	68.538	00	03
Aspirin	180.159	1.431	-1.938	1.400	01	04	63.604	00	03

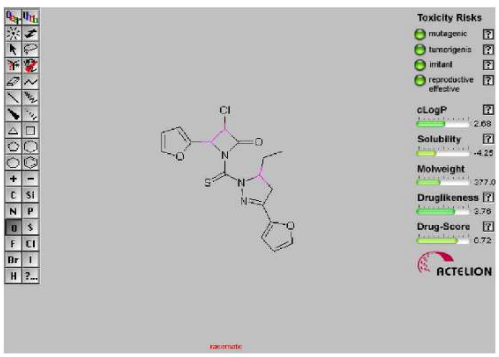
Table 2: Biological Activity of compounds ($4P_1$-P_{77})

Compound Code	Molecular weight	GPCR	IM	KI	NR	PI	EI
$4P_1$	464.974	-0.39	-0.69	-0.65	-0.49	-0.53	-0.40
$4P_2$	434.947	-0.47	-0.81	-0.69	-0.66	-0.54	-0.43
$4P_3$	469.392	-0.26	-0.79	-0.68-	-0.65	-0.55	-0.44
$4P_4$	479.945	-0.55	-0.78	-0.74	-0.68	-0.61	-0.48
$4P_5$	450.464	-0.46	-0.76	-0.72	-0.58	-0.56-	-0.40
$4P_6$	514.832	-0.54	-0.84	-0.71	-0.73	-0.61	-0.47
$4P_7$	425.897	-0.52	-0.85	-0.80	-0.83	-0.65	-0.47
$4P_{11}$	417.918	-0.35	-0.76	-0.-76	-0.44	-0.42	-0.49
$4P_{22}$	387.892	-0.33	-0.75	-0.79	-0.47	-0.39	-0.48
$4P_{33}$	422.337	-0.32	-0.73	-0.77	-0.47	-0.42	-0.49
$4P_{44}$	432.889	-0.44	-0.72	-0.83	-0.51	-0.49	-0.54
$4P_{55}$	403.891	-0.32	-0.69	-0.82	-0.39	-0.43	-0.45
$4P_{66}$	466.788	-0.41	-0.79	-0.80	-0.55	-0.49	-0.54
$4P_{77}$	376.865	-0.32	-0.68	-0.83	-0.52	-0.55	-0.44
Ciprofloxacin	331.347	0.12	-0.04	-0.07	-0.19	-0.21	-0.28
Indomethacin	343.766	0.10	-0.48	-0.18	0.23	-0.30	0.21
Aspirin	180.159	-0.76	-0.32	-01.06	-0.44	-0.82	-0.28

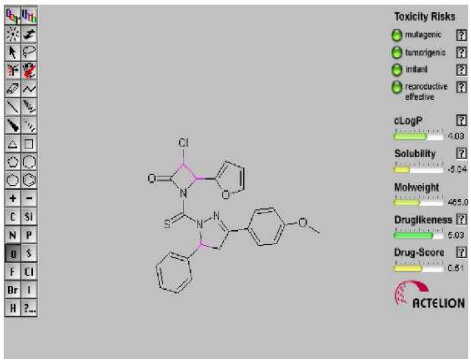
GPCR: G- Protein couple Receptor, IM: Ion channel Modulator, KI: Kinase Inhibitor, NR: Nuclear Receptor, PI: Protease Inhibitor, EI: Enzymatic Inhibitor

Table 3: Drug-likeness study of compounds (4 $P_{1\text{-}77}$)

Compound code	Solubility(log S)	Drug-likeness	Drug-score
$4P_1$	-5.04	5.03	0.51
$4P_2$	-5.02	4.34	0.53
$4P_3$	-5.075	6.42	0.41
$4P_4$	----- ----------	Toxicity	----------
$4P_5$	-4.72	5.19	0.57
$4P_6$	-5.85	3.54	0.36
$4P_7$	-4.70	4.07	0.62
$4P_{11}$	-4.59	4.75	0.63
$4P_{22}$	-4.57	4.7	0.65
$4P_{33}$	-5.31	6.18	0.52
$4P_{44}$	----------	Toxicity	----------
$4P_{55}$	-4.28	3.83	0.67
$4P_{66}$	-5.41	3.25	0.46
$4P_{77}$	-4.25	3.76	0.72
ciprofloxacin	-1.72	2.42	0.71
indomethacin	-3.6	4.92	0.73
Aspirin	-1.93	-0.48	0.24



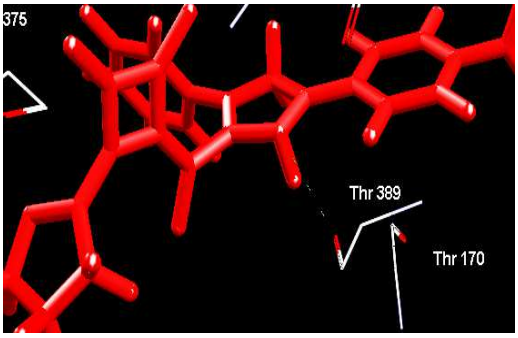
$4P_{77}$



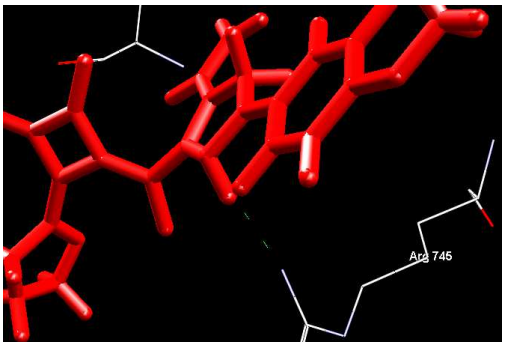
$4P_1$

Table 4: Docking energies of compounds ($4p_1$-p_{77}) against *E.coli* (3GI9)

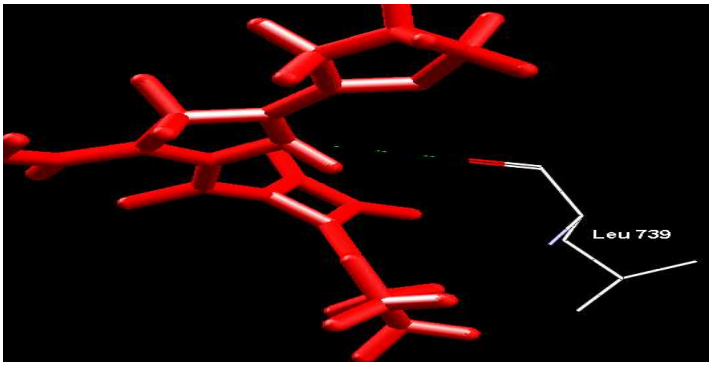
Comp. Code	Molecular volume	Molecular Docking energy Max./ Min	RMSD Max./ Min.	Energy of H –bond Max./ Min.	Best pose Length of H- bond	Torsion
$4P_1$	392.828	-141.232 / -127.298	63.632/ 63.320	-0.5037/ 0.00	3.289	03
$4P_2$	363.239	-124.22/-116.013	-1o4.66/ -100.92	-2.5/-0.150	2.613	03
$4P_3$	376.775	-128.964/ -124.868	80.95/79.96	-2.5/-0.207	3.0475	03
$4P_4$	386.573	-142.709/ -131.062	104.659/ 94.437	-2.485/0.00	2.598	04
$4P_5$	371.237	-130.502/ -115.706	96.467/ 95.824	-1.5589/ -0.111949	3.093	03
$4P_6$	381.124	-137.744/ -125.427	107.429/ 85.780	0.00	0.00	04
$4P_7$	344.807	-138.474/ -125.907	106.824/ 65.299	-1.265/ 0.00	3.352, 3.44	02
$4P_{11}$	350.739	-148.767/ -122.564	64.483/ 64.278	-2.50/ -0.797	2.785	03
$4P_{22}$	325.193	-111.633/ -99.257	62.882/ 63.461	-2.50 / 00	2.953	02
$4P_{33}$	338.729	-111.633/ -99.257	64.457/ 64.262	-2.50/0.0	2.890	03
$4P_{44}$	348.527	-135.468/ -118.97	64.802/ 64.481	-0.355/0.0	2.990	04
$4P_{55}$	333.211	-137.086/ -114.558	78.921/ 80.684	-0.0765/-0.5323	2.559	03
$4P_{66}$	343.078	-136.415/ -125.470	78.832/ 80.711	-0.07901/ 0.00	2.679	03
$4P_{77}$	310.805	-149.475/ -137.113	84.641/ 85.500	-1.559/ -1.616	3.050	03
Ciprofloxacin	285.460	-94.489/ -75.890	45.654/ 30.923	-2.450/ -0.789	2.910	03



$4P_4$: Best pose: -142.709



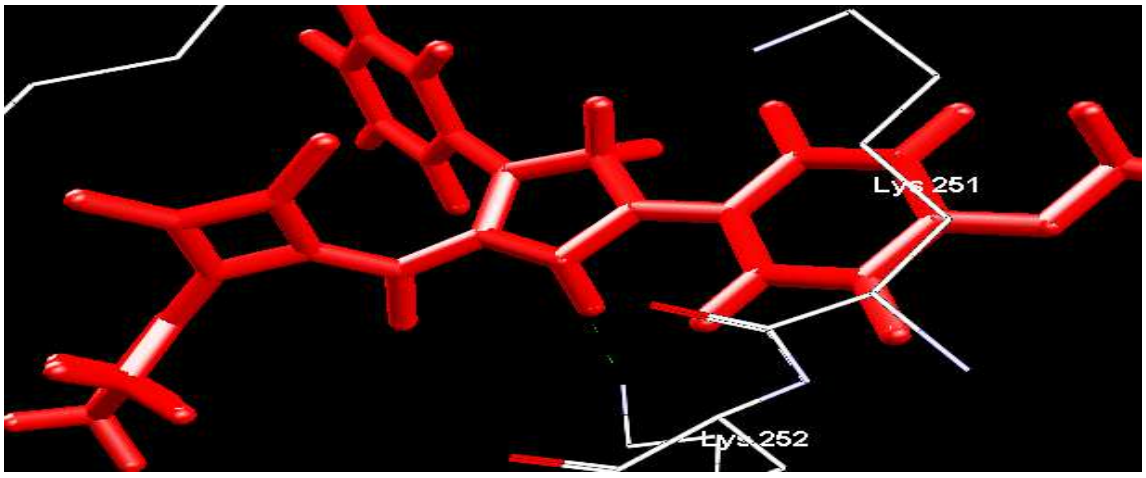
$4P_{11}$: Best pose: -148.767



4P77: Best pose: -149.475

Table 5: Docking energies of compounds ($4p_{1-77}$) against *S.a.* (4AE5)

Comp. Code	Molecular volume	Molecular Docking energy Max./ Min	RMSD Max./ Min.	Energy of H –bond Max./ Min.	Best pose Length of H- bond	Torsion
$4P_1$	392.828	-144.124 / -115.591	51.33/ 44.69	-1.312/ 0.00	3.175	03
$4P_2$	363.239	-140.237/-116.013	-51.906/ -44.841	0.0/-0.686	1.530	03
$4P_3$	376.775	-140.641/ -113.854	51.5906/51.472	-1.954/-0.590	3.307	03
$4P_4$	386.573	-140.658/ -119.571	50.979/ 45.441	-2.5/0.00	2.858	04
$4P_5$	371.237	-134.703/ -108.126	51.797/ 44.447	-2.265/ -0.00	3.146	03
$4P_6$	381.124	-131.185/ -113.438	44.250/ 41.250	-0.5463/0.0	3.2827	04
$4P_7$	344.807	-114.815/ -95.976	40.676/ 35.579	-1.07362	2.759	02
$4P_{11}$	350.739	-114.202/ -104.282	69.481/ 71.780	-0.686/0.00	1.345	03
$4P_{22}$	325.193	-97.697/ -96.426	46.072/ 46.668	-0.397/0.00	1.975	02
$4P_{33}$	338.729	-132.50/ -111.315	50.805/ 47.470	-2.50/0.00	2.015	03
$4P_{44}$	348.527	-131.050/ -113.216	50.185/ 39.730	-2.50/0.00	2.894	04
$4P_{55}$	333.211	-113.048/ -98.152	52.889/ 51.973	-1.220/ -2.50	3.650	03
$4P_{66}$	343.078	-116.011/ -114.214	51.813/ 42.158	-2.50/ -2.366	2.857	03
$4P_{77}$	310.805	-120.279/ -116.118	42.530/ 40.932	-1.423/ -0.138	2.567	03
Ciprofloxacin	285.460	-92.613/ -67.567	70.088/ 45.790	-1.670/ -0.756	3.234	03



$4P_1$: Best pose: -144.124

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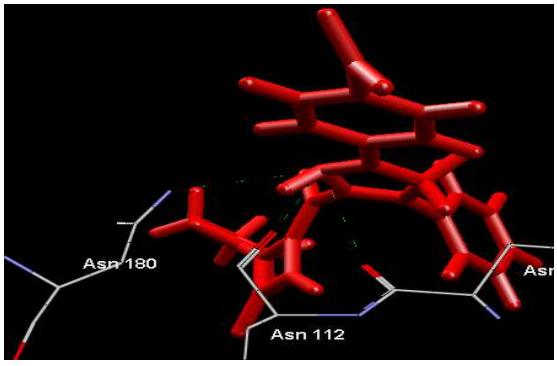
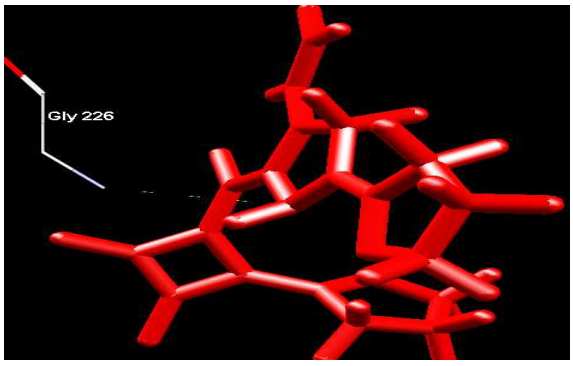
Table 6: Docking energies of compounds ($4p_{1-77}$) against *S.typhi* (3FHU)

Comp. Code	Molecular volume	Molecular Docking energy Max./ Min	RMSD Max./ Min.	Energy of H –bond Max./ Min.	Best pose Length of H- bond	Torsion
$4P_1$	392.828	-77.387 / -67.753	60.354/ 60.429	-0.895/ 0.00	3.376	03
$4P_2$	363.239	-124.288/ -119.193	60.522/ 58.525	-2.325/0.00	2.082 3.292	03
$4P_3$	376.775	-123.325/ -117.256	60.590/ 58.684	-2.450/-0.190	3.593 2.963	03
$4P_4$	386.573	-137.092/ -119.500	45.579/ 45.0302	-1.070/0.00	3.467 3.454	04
$4P_5$	371.237	-134.703/ -108.126	51.797/ 44.447	-2.265/ -0.00	3.146	03
$4P_6$	381.124	-144.292/ -129.405	51.119/ 50.454	-1.9985/ -1.02444	2.6854	04
$4P_7$	344.807	842.406/ 874.258	50.932/ 49.763	-1.72531/ 0.00	2.82962	02
$4P_{11}$	350.739	-121.826/ -111.960	35.925/ 43.832	-2.250/0.00	2.785	03
$4P_{22}$	325.193	-102.534/ -99.0220	44.195/ 44.772	-0.920/ 0.00	3.453	03
$4P_{33}$	338.729	-125.895/ -124.064	60.368/ 55.660	-0.0264/ -1.116	3.853	03
$4P_{44}$	348.527	-128.174/ -108.329	55.407/ 58.183	-1.538/ -1.594	3.567	04
$4P_{55}$	333.211	-112.078/ -103.075	45.101/ 44.210	-3.949/0.00	3.890	03
$4P_{66}$	343.078	-124.349/ -115.156	44.948/ 44.181	-4.203/ 0.00	3.980	03
$4P_{77}$	310.805	-142.640/ -131.259	51.697/ 51.419	-1.741/-2.50	3.520	03
Ciprofloxacin	285.460	-71.919/ -56.765	78.065/ 55.679	-1.354/ -0.780	3.870	03



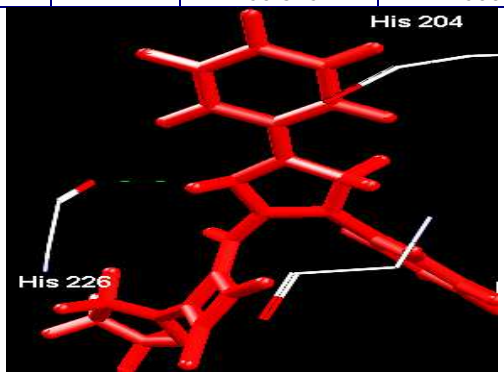
$4P_4$: Best pose: -137.092



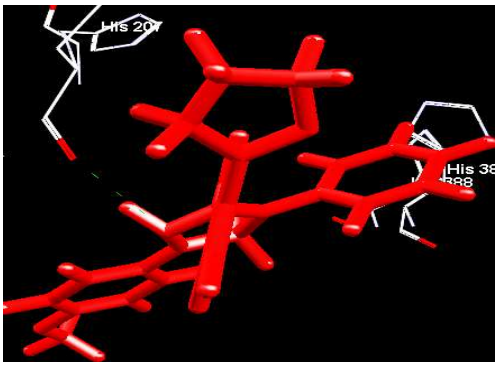
$4P_{77}$: Best pose: --142.640

Table 7: Docking energies of compounds ($4p_{1-77}$) against cyclooxygenase receptor (5COX)

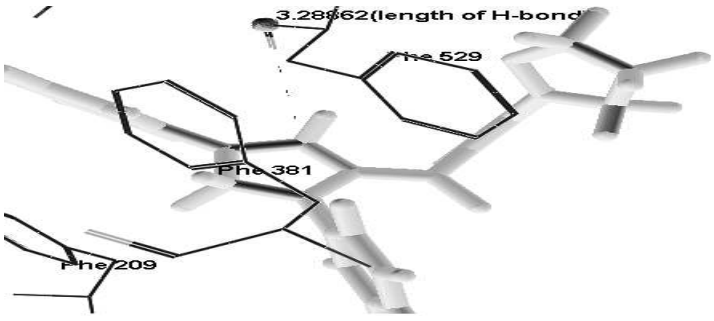
Comp. code	Molecular volume	Molecular Docking energy Max./ Min	RMSD Max./ Min.	Energy of H –bond Max./ Min.	Best pose Length of H- bond	Torsion
$4P_1$	392.828	-144.677/ -121.798	34.457/ 43.192	--1.578/ 0.00	3.129	03
$4P_2$	363.239	-144.425/ -136.002	43.381/ 42.540	-2.081/0.00	2.797	03
$4P_3$	376.775	-144.58/ -113.972	43.381/ 04.541	-2.387/ -0.0997	2.75422	03
$4P_4$	386.573	-144.018/ -138.977	34.491/ 42.5329	-0.070/ -1.3440	0.00	04
$4P_5$	371.237	-141.703/ -123.3979	43.564/ 43.954	-2.170/ 0.00	2. 643	03
$4P_6$	381.124	-149.446/ -138.728	36.5744/ 37.7867	-1.01067/ -0.97798	3.28862	04
$4P_7$	344.807	873.843/ 864.427	38.460/ 36.7671	-2.50/ -1.60453	2.60211	02
$4P_{11}$	350.739	-134.453/ -128.030	43.247/ 40.484	0.00/0.00	0.0	03
$4P_{22}$	325.193	-23.146/ -21.988	13.140/ 13.200	0.00/0.00	0.0	02
$4P_{33}$	338.729	-136.80/ -127.966	43.022/ 41.343	-1.344/0.00	3.137	03
$4P_{44}$	348.527	-133.-130/ -130.085	30.39/ 41.377	-0.522/--1.228	-1.789	04
$4P_{55}$	333.211	-130/,08	43.161/ 33.5	-1.715/ -2.261	3.905	03
4_{66}	343.078	-126.013/ -127.011	42,994	-1.353/ -1.429	3.087	-3
$4P_{77}$	310.805	-128.664/ -120.258	30.270/ 29.409	0.00	0,00	03
indomethacin	286.438	-130.670/ -110.070	38.990/ 34.085	-1.890/ -0.690	3.098	03
Aspirin	155.574	-72.660/ -56.045	58.872/ 47.568	-1.780/ -1.094	-3.941	03



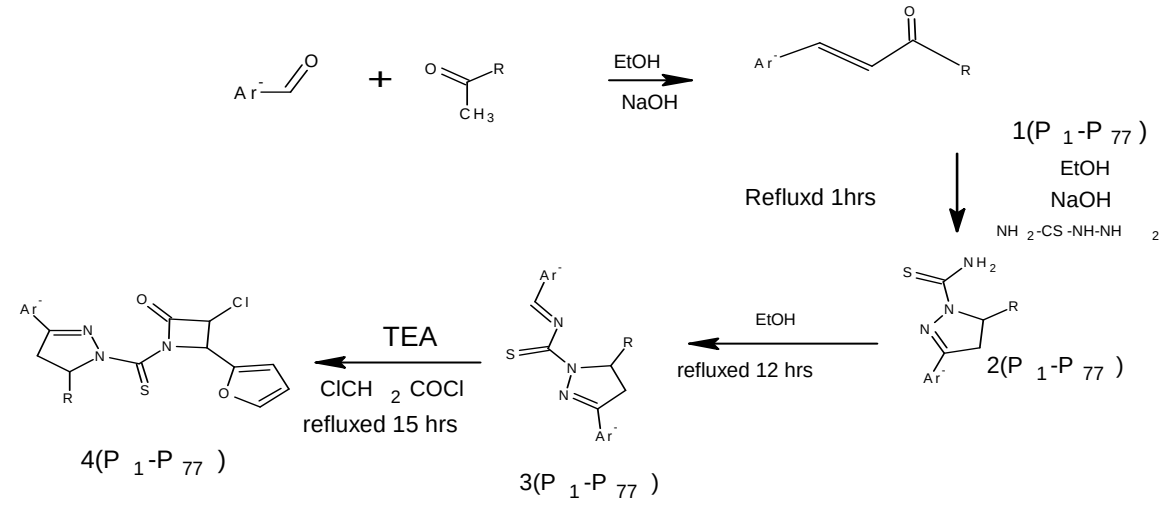
$4P_1$: Best pose: -144.677



$4P_2$: Best pose: -144.425



SCHEME

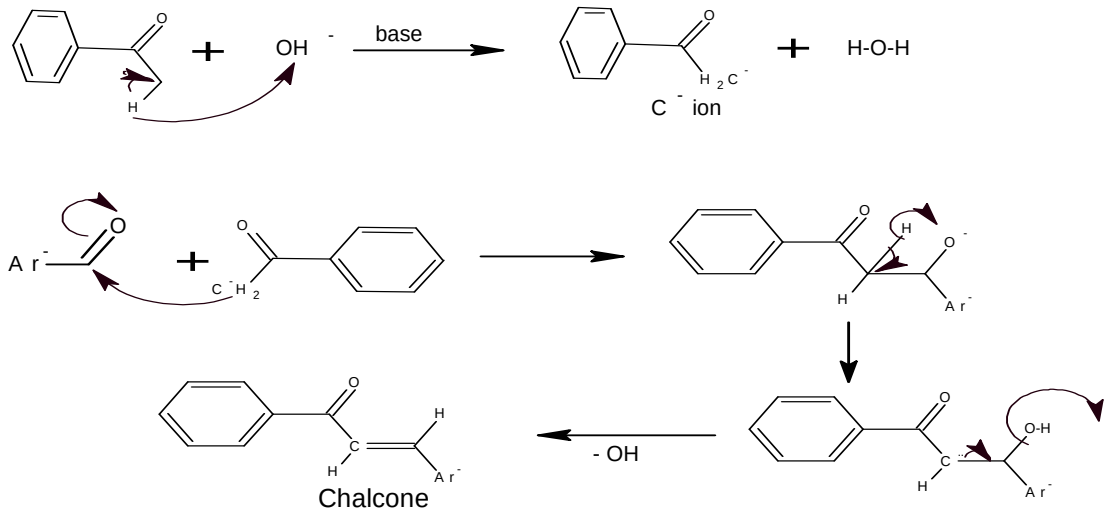


R= Phenyl, ethyl

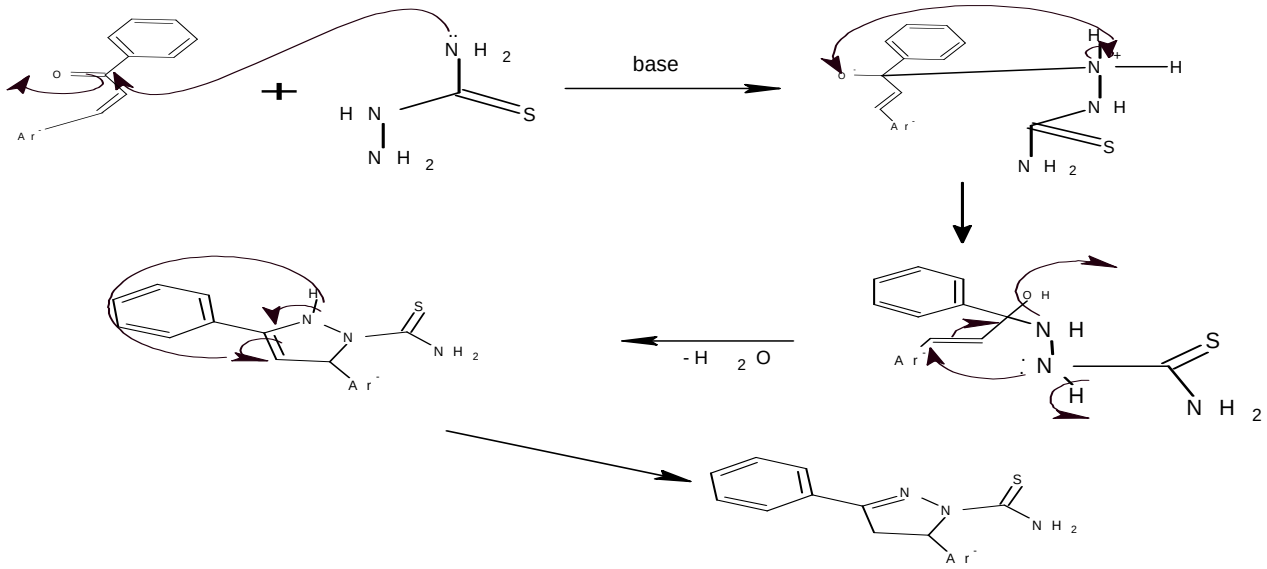
(3, 4) Ar :- $C_6H_4OCH_3$(p), C_6H_5, C_6H_4Cl(p), $C_6H_4NO_2$(p) , C_6H_4OH(o), C_6H_4 Br(p) and 2-Furfuryl.

Mechanism:

Step 1: synthesis of chalcone



Step 2:



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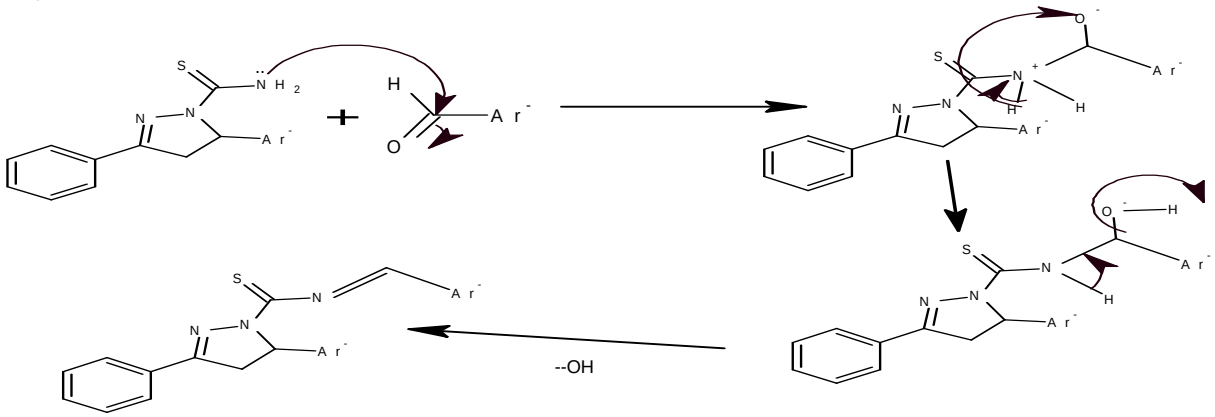
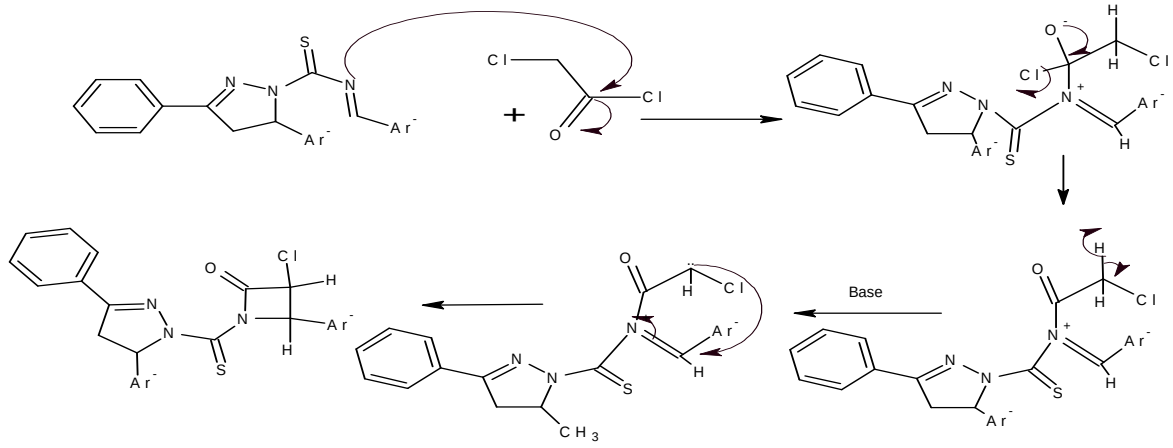
Step 3: synthesis of Schiff bases



Step 4: Synthesis of azetidin-2-one.



Conclusion

In conclusion, the molecular docking study of the title compounds reveals better activity. Indicating the pyrazol-1-yl azetidin-2-one derivatives scaffold influences the pharmacological activity. From the best posed energy, the compounds having electronegative group such as halogens are found to be more activity as compared to others. It is observed that the chloro at 3 position on beta lactum ring increases the activity. However, the difference in activity profile with structural modifications provides further scope to explore these compounds for better bioactivity.

Acknowledgement

The authors thankfully acknowledge to the chairman and Director of Trident Academy of Technology. We also extend our thanks to Mr. R.K. Das for helping hand in entire research at State Drug Testing Laboratory, Bhubaneswar. Finally grate gratitude goes to the HOD,UDPS, Utkal University who has permitted for carrying out this research work.

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Article History: ----------

Date of Submission: 11-11-2013

Date of Acceptance: 29-11-2013

Conflict of Interest: NIL

Source of Support: NONE