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DESIGN, SYNTHESIS & MOLECULAR PROPERTIES PREDICTION OF NOVEL HETEROCYCLE DERIVATIVES BY INSILICO METHODS

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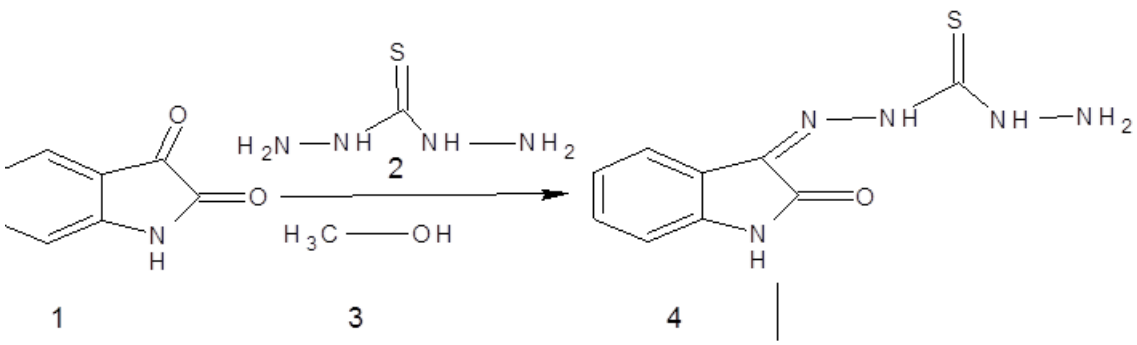
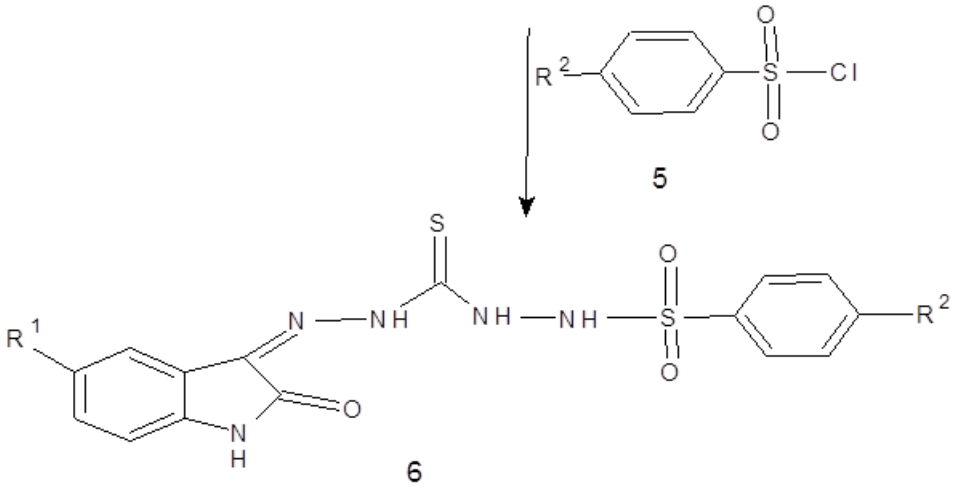
ABSTRACT

Isatin derivatives belongs to heterocyclic compound. Isatins derivatives are synthetically important substrates which can be further used for the synthesis of large variety of heterocyclic compounds. Isatins posses numerous biological properties like anti-inflammatory, anti depressant, anticonvulsant, antihelmintic, antimicrobial, anti allergic and the present study outlines the synthesis, molecular properties prediction, docking studies of noval isatin derivatives. Isatin consist of indole nucleus also known as oxindole and endogenous poly functional heterocyclic compound. So here we synthesized various substituted isatin derivatives by treating with monothiocarbohydrazones and benzene sulphonyl chlorides.

KEYWORDS: Isatin, monothiocarbohydrazones, benzene sulphonyl chlorides, antibacterial, docking.

SCHEME

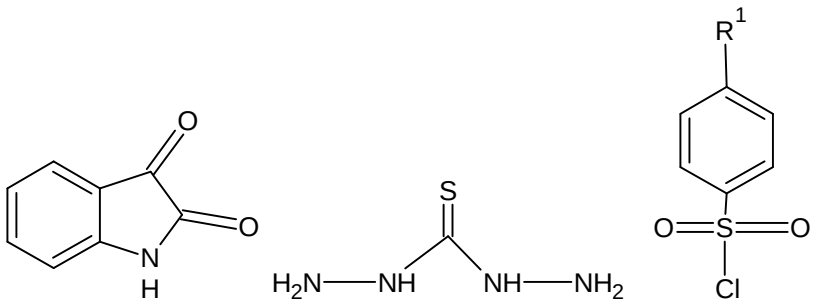




R1	R2	R1	R2
H	H	H	$NHC0CH_3$
Cl	H	Cl	$NHC0CH_3$
Br	H	Br	$NHC0CH_3$
F	H	F	$NHC0CH_3$
CH3	H	CH3	$NHC0CH_3$

1. INTRODUTION

Heterocyclic compounds are widely distributed in nature, play a diverse and important role in the field of Pharmaceutical chemistry. The earliest compounds known to mankind were of heterocyclic origin. Today, the heterocyclic chemistry delivers reagents and synthetic methods of its own traditional activity in synthesis of drugs, pesticides and detergents as well as into the related fields such as biochemistry, polymers and material sciences. They have been also used as optical brightening agents, antioxidants, copolymers, solvents, photographic sensitizers, corrosion inhibitors and additives, dye stuffs and pigments. Heterocyclic compounds are also finding an increasing use as an intermediates in organic synthesis. Heterocyclic compounds like Isatin derivatives, monothiocarbohydrazides, benzene sulfonyl derivatives are with several of its derivatives exhibited diversified biological activity.



(a) (b) (c)

2. Pharmacological activity of 2-oxo-1,2-dihydro-3H-3-ylidene)hydrazinyl-carbothioyl)benzene sulfonohydrtazine derivatives

Isatin derivatives and benzene sulfonyl chlorides have wide spectrum of activities such as antibacterial, antifungal, antitumor, antioxidant, antihelmenthic and Insecticidal activities. So in present investigation all the synthesized 2-oxo-1,2-dihydro-3H-3-ylidene)hydrazinyl-carbothioyl)benzene sulfonohydrtazine derivatives are evaluated and expected to have , anti-bacterial activities.

3. EXPERIMENTAL PROCEDURES

STEP-1: Substituted Isatin (0.01M) and Monothiocarbohydrazine(0.01M) are dissolved in 50 ml Methanol and refluxed for four hours and then cooled to room temperature and filtered, dried and recrystallized from Ethanol.

STEP-2: Step-1 product is treated with Benzyle sulfonyl chloride(0.01M) and again refluxed for five hours and then cooled to room temperature and later filtered ,dried and recrystallized which results in the formation of final product.

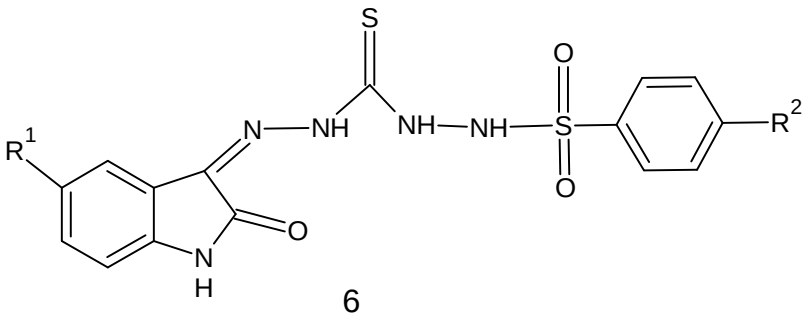


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Table 1: Physical data of (2-oxo-1,2-dihydro-3H-3-ylidene)hydrazinyl-carbothioyl) benzene sulfonohydrtazine derivatives.

S.no	Compound	R_1	R_2	Melting point	%Yield	Molecular weight
1.	1A	H	H	185^0C	79%	248.26
2.	2A	Cl	H	205 ^{0}C	73.5%	282.71
3.	3A	Br	H	247^0C	72%	326.16
4.	4A	F	H	222^0C	76%	266.26
5.	5A	CH_3	H	182^0C	77.5%	262.26
6.	6A	H	$NHCOCH_3$	268^0C	74%	374.25
7.	7A	Cl	$NHCOCH_3$	248^0C	80%	373.16
8.	8A	Br	$NHCOCH_3$	249^0C	75.4%	293.26
9.	9A	F	$NHCOCH_3$	245^0C	81.5%	327.15
10.	10A	CH_3	$NHCOCH_3$	232^0C	69%	316.71

4. MOLECULAR PROPERTY PREDICTION

4.1 Molinspiration

1. Molinspiration Cheminformatics provides calculation of molecular physicochemical properties relevant to drug design and QSAR including log P, polar surface area (PSA), nrotb, HBA/HBD counts and the rule of five descriptors.

2. It also offers tools to calculate other properties, such as volume and total number of atoms in the molecule.

3. Lipinski's "Rule of Five":-"Rule of 5" properties are a set of simple molecular descriptors.

4. The rule states, that most "drug-like" molecules have logP<= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability

Table 2: Physicochemical properties of few substituted novel Isatin derivatives.

compound	R1	R2	TPSA(A)	No .of atoms	M.Wt	nON	nOHNH	No.of violations	No. of rotable bonds	Volume
1A	H	H	115.45	25	375.44	8	4	0	6	295.76
2A	Cl	H	115.45	26	409.88	8	4	0	6	309.29
3A	Br	H	115.45	26	426.00	8	4	0	6	313.64
4A	F	H	115.45	26	393.43	8	4	0	6	300.69
5A	CH3	H	115.45	25	375.44	8	4	0	6	295.76
6A	H	-NHCOCH3	158.45	29	432.49	10	6	1	7	342.59
7A	Cl	-NHCOCH3	158.45	29	452.90	10	6	1	7	339.56
8A	Br	-NHCOCH3	158.45	29	497.36	10	6	1	7	343.91
9A	F	-NHCOCH3	158.45	29	436.45	10	6	1	7	330.96
10A	CH3	-NHCOCH3	184.87	30	447.50	11	8	2	8	354.12

Table 3: Prediction pf bioactivity of few substituted novelnIsatin derivatives.

compound	MI Bioactivity score	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
1A	0.55	-0.70	-0.95	-0.54	-1.23	-0.64	-0.41
2A	0.55	-0.69	-0.93	-0.54	-1.21	-0.65	-0.42
3A	0.55	-0.89	-1.30	-0.57	-1.33	-0.76	-0.48
4A	0.55	-0.66	-0.90	-0.49	-1.15	-0.65	-0.39
5A	0.55	-0.70	-0.95	-0.54	-1.23	-0.64	-0.41
6A	0.55	-0.64	-0.97	-0.41	-1.18	-0.54	-0.37
7A	0.55	-0.61	-0.91	-0.39	-1.17	-0.52	-0.35
8A	0.55	-0.72	-1.00	-0.42	-1.29	-0.61	-0.41
9A	0.55	-0.58	-0.91	-0.35	-1.23	-0.52	-0.33
10A	0.55	-0.52	-0.81	-0.29	-1.23	-0.33	-0.24

4.2. SWISS ADME

Swiss ADME online tool calculates the properties like Molecular formula, Molecular weight, Number of hydrogen bond acceptors (HBA), Number of hydrogen bond donors (HBD), mol LogP (octanol /water partition coefficient), mol logS (water solubility), Polar surface area.

Table 4: Swiss ADME dta of few substituted novel Isatin derivatives.

compound	PHYSICOCHEMICAL PROPERTIES				LIPOPHILICITY mlogP	PHARMA COKINETICS			LIPINS-KIRULE	LEADLIK-ENESS
	N-rotb	H-accepters	H-donar	TPSA		GI	BBB	P-gp		
1A	6	5	4	152.16A0	0.72	LOW	NO	NO	YES	NO
2A	6	5	4	152.16A	1.24	LOW	NO	NO	YES	NO
3A	6	5	4	152.16A²	1.36	LOW	NO	NO	YES	NO
4A	6	6	4	152.16A²	1.11	LOW	NO	NO	YES	NO
5A	6	6	4	152.16A²	0.44	LOW	NO	NO	YES	NO
6A	7	6	5	195.25A²	0.27	LOW	NO	YES	YES	NO
7A	7	6	5	195.25A²	0.54	LOW	NO	YES	YES	NO
8A	7	6	5	195.25A²	0.66	LOW	NO	YES	YES	NO
9A	7	7	5	195.25A²	0.42	LOW	NO	YES	YES	NO
10A	8	7	6	221.27A²	0.49	LOW	NO	YES	YES	NO

5. RESULTS AND DISCUSSION

SPECTRAL INTERPRETATION

1A Compound (2-oxo-1,2-dihydro-3H-3-ylidene)hydrazinyl-carbothioyl)benzene sulfonohydrazine

Yield (%) : 79, M.P(ºC) : 105ºC, IR (KBr, cm-1):1652(C=O); 1596(C=C of Ar); 1509(-CH=CH-683(C-S). ^{1}HNMR (CDCl3): δ2.30[s, 3H, C-S-CH3]; 2.40[s, 3H, C-S-

CH3];2.65[s,3H,Ar-CH_3]; 7.21[s, 1H, Ar-H]; 7.25[d, 1H, CO-CH=]; 7.46[d, 1H, =CH-Ar-H]; 7.60 [dd, 2H, Ar-H]; 7.80[dd, 2H, Ar-H]; MS m/z: 248.

2A Compound (2-oxo-1,2-dihydro-3H-3-ylidene) chloro hydrazinyl-carbothioyl)benzene sulfonohydrazine

Yield (%) : 73.5; M.P(ºC) : 151; IR (KBr, cm^{-1}):(C-S) 744.52; (C =N) 1597; (C-N) 1122.57;(C-Cl) 827.46 .^{1}HNMR ($CDCl_3$): δ2.38 (s, 3H,CH_3) ; δ2.68 (s, 3H,CH_3) ; δ7.16(s, 1H,-Ar,) ; δ6.9 (t, 3H,-Ar) ; δ7.23 (m, 5H,-Ar) ; δ7.6 (s, 2H,-Ar) . MS m/z =282 (m-1).

3A Compound (2-oxo-1,2-dihydro-3H-3-ylidene) bromo hydrazinyl-carbothioyl)benzene sulfonohydrazine

Yield (%) : 77.5; M.P(ºC) : 151; IR (KBr, cm^{-1}):(C-S) 744.52; (C =N) 1597; (C-N) 1122.57;(C-Cl) 827.46 .^{1}HNMR ($CDCl_3$): δ2.38 (s, 3H,CH_3) ; δ2.68 (s, 3H,CH_3) ; δ7.16(s, 1H,-Ar,) ; δ6.9 (t, 3H,-Ar) ; δ7.23 (m, 5H,-Ar) ; δ7.6 (s, 2H,-Ar) . MS m/z =326 (m-1).

4A Compound (2-oxo-1,2-dihydro-3H-3-ylidene) fluoro hydrazinyl-carbothioyl)benzene sulfonohydrazine

Yield (%) : 76; M.P(ºC) : 151; IR (KBr, cm^{-1}):(C-S) 744.52; (C =N) 1597; (C-N) 1122.57;(C-Cl) 827.46 .^{1}HNMR ($CDCl_3$): δ2.38 (s, 3H,CH_3) ; δ2.68 (s, 3H,CH_3) ; δ7.16(s, 1H,-Ar,) ; δ6.9 (t, 3H,-Ar) ; δ7.23 (m, 5H,-Ar) ; δ7.6 (s, 2H,-Ar) . MS m/z =266 (m-1).

5A Compound (2-oxo-1,2-dihydro-3H-3-ylidene) fluoro hydrazinyl-carbothioyl)benzene sulfonohydrazine

Yield (%) : 77.5; M.P(ºC) : 151; IR (KBr, cm^{-1}):(C-S) 744.52; (C =N) 1597; (C-N) 1122.57;(C-Cl) 827.46 .^{1}HNMR ($CDCl_3$): δ2.38 (s, 3H,CH_3) ; δ2.68 (s, 3H,CH_3) ; δ7.16(s, 1H,-Ar,) ; δ6.9 (t, 3H,-Ar) ; δ7.23 (m, 5H,-Ar) ; δ7.6 (s, 2H,-Ar) . MS m/z =262 (m-1).

6. PHARMACOLOGICAL ACTIVITY-ANTI BACTERIAL ACTIVITY

Antibacterial activity

The antibacterial activity is tested by agar-cup plate method. The antibacterial activity of 2-mercaptobenzothiazoletrithiocarbonate derivatives were tested and compared with the standard Ampicillin at concentration of 100µg/ml and 200µg/ml. The following organisms were used.

Test organisms

Gram negative bacteria

Escherichia coli.

Experimental procedure for antibacterial activity

The antifungal activity of test compounds is evaluated by cup plate method taking drug at concentration of 100µg/ml against three fungal organisms *A.niger, C.albicans, R.oryzae*. The zone of inhibition (ZOI) is taken as parameter for antifungal activity. The ZOI of test compound is compared to that of standard drug i.e. flucanazole. Chloroform is taken as control.

Potato dextrose agar medium is dissolved and distributed in 25 ml quantities in 100ml conical flasks and are sterilized in an autoclave 121ºC(15lbs/sq.in) for 20 minutes.

The medium is inoculated at using 48hrs old cultures of test organisms mentioned above aseptically into sterile petridishes and allowed to settle at room temperatures for about 30 minutes.

In a size of 4 inches petridishes, 4 cups of 8mm diameter at equal distance are made in each plate. In each plate, 1 cup is used for standard i.e. flucanazole with 100 µg/ml, other cup for chloroform, other 2 cups with concentrations of test compounds i.e. 50 µg/ml and 100 µg/ml solutions.

The plates thus prepared are left for 90 minutes in a refrigerator for diffusion. After incubation for 72hrs at 27ºc, the plates are examined for inhibition zone (in mm). The zone of inhibition is measured using antibiotic zone reader.

Table-5 zone of inhibition.

S No	Compound	Zone of inhibition (in mm)	
		Gram negative organism	
		E.coli	
		200µg	100µg
IA	C15H13O3N5S2	5.2	5.0
2A	C15H13O3N5S2Cl	4.1	3.7
3A	C15H13O3N5S2Br	5.8	5.1
4A	C15H13O3N5S2F	3.6	3.0
5A	C15H13O3N5S2CH3	4	3.8
6A	C17H17O4N6S2	5.3	4.2
7A	C17H17O4N6S2Cl	3.3	2.4

8A	**C17H17O4N6S2Br**	**5.4**	**5.0**
9A	**C17H17O4N6S2F**	**3.2**	**3.0**
10A	**C17H17O4N6S2CH3**	**3.9**	**4.0**
*****	**AMOXYCILLIN**	**6.7**	**6.2**

7. DOCKING

Computer aided drug design

The development of new drugs is undoubtedly one of the most challenging tasks of today's science. Human genome project that gave 30,000 or so genes encoded within the human genome, it was expected that a large number of new drug targets would be found expeditiously. But it did not turn out to offer a direct source for drug development, because it is the proteins encoded by the genes are the usual drug targets.

Molecular Docking

Molecular docking may be defined as an optimization problem, which would describe the best fit orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. In mo9drn structure based drug design the accurate prediction of the binding modes between the ligand and protein is of fundamental importance. The binding of small molecule ligands to large protein targets is central to numerous biological processes. This process is not simple; several entropic and enthalpic factors influence the interactions between them. The mobility of both ligand and receptor, the effect of the protein environment on the charge distribution over the ligand, and the interactions with the surrounding water molecules, further complicate the quantitative description of the process. The idea behind this technique is to generate a comprehensive set of conformations of the receptor complex, and then to rank them according to their stability. Themost popular docking programs include DOCL, AUTO DOCK, FLEX x, GOLD and GLIDE, among others. FLExXandGLIDE programs were utilized in the present work, hence only these will be discussed, before. Molecular docking can be divided into two separate steps, first step is application of search algorithm to create an optimum number of configurations that include the experimentally determined binding modes. In the second step these configurations are evaluated using scoring functions to distinguish the experimental binding modes from all other modes explored through the searching algorithm.

Glide Score

The starting point for Glide scoring is the empirically based ChemScore function of Eldridge et al., which can be written as.

$\Delta G_{bind} = C_o + C_{lipo} f(r_{lr}) + C_{hbond} g(\Delta r) h(\Delta\alpha) + C_{metal} f(r_{lm}) + C_{rotb} H_{rotb}$

Glidescore modifies and extends the Chemscore function as follows:

$\Delta G_{bind} = C_{lipo\text{-}lipo} f(r_{lr}) + C_{hbond\text{-}neut\text{-}neut} g(\Delta r) h(\Delta\alpha) + C_{hbond\text{-}neut\text{-}charged} g(\Delta r) h(\Delta\alpha) + C_{hbond\text{-}charged\text{-}charged} g(\Delta r) h(\Delta\alpha) + C_{max\text{-}metal\text{-}ion} f(r_{lm}) + C_{rotbHrotb} + C_{polar\text{-}phob} V_{polar\text{-}phob} + C_{roul} E_{roul} + C_{vdw} E_{vdw}$ + **Solvation terms**

WORK PLAN

METHODOLOGY

- **Ligand preparation**

Protein preparation

- **Receptor grid generation**

Receptor grid generation facility helps in defining the protein active site to prepare grid for the ligands to be docked in. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The receptor vanderwaals scaling for the non polar atoms to set (the default being 1 for glide) to 0.9 this makes the protein site "roomier" by moving back the surface of non- polar region of the protein and ligand. This kind of adjustment emulates to same extent the effect of breathing motion to the protein site (it is a kind of giving breathing to the receptor). The receptor active site is defined either by selecting the co-crystallized ligand or by mentioning the residues of the active site (amino acid to be included). An enclosing box (the box with in which all the ligand atoms should be incorporated) and a bounding box (acceptable positions of the ligand center must lie within. This box gives a truer measure of the effective size of the search space) are used in glide to organize the calculations.

- **Ligand docking**

The screened low energy conformations of the ligands which are obtained from ligand preparation are docked into the rare receptor grid using standard precision mode. Docking studies give glide score (G-score) which predicts the binding affinity and the ranking order of ligands, is an expanded version of chemscore and Cvdw. Cvdw is the sum of coulomb energy and vanderwaal energy of the non-bonding interactions between the ligand and receptor. E-Model is a combination of Glide score, the ligand-receptor molecular mechanics

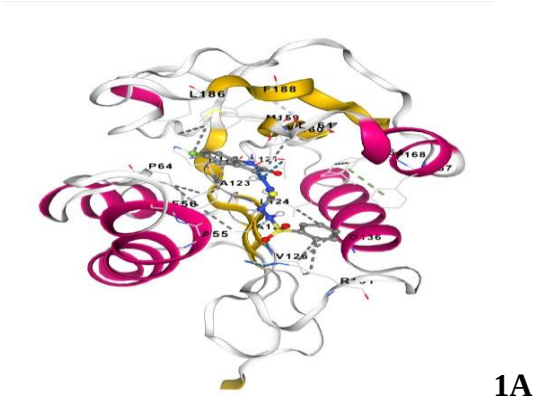
interactions energy and the ligand strain energy to select the correctly docked pose. The ligands with good docking score will be considered as the lead molecules and will be synthesized.

Docking studies are performed against antibacterial activity using protein PDB ID-7OTC Escherichia coli BL21(DE3) of resolution-2.90 A^0

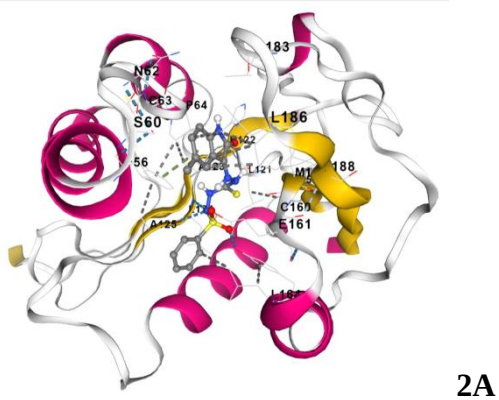
Table 6: glide score of synthesized compounds.

S.NO	GLIDE SCORE(kcal/mole)
1A	-7.4
2A	-7.5
3A	-8.2
4A	-7.9
5A	-7.7
6A	-8.0
7A	-7.9
8A	-8.1
9A	-7.8
10A	-7.6
amoxycillin	-8.3

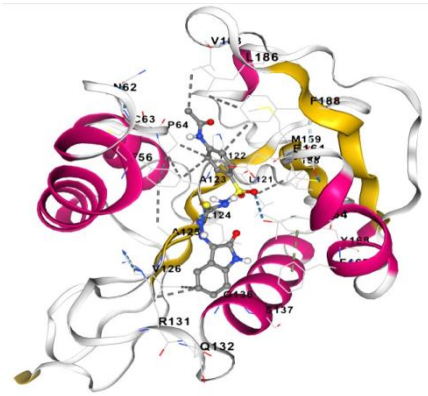
Protein –ligand docking pictures of synthesized compounds



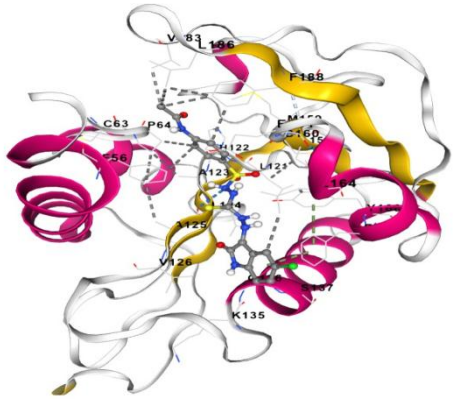
1A



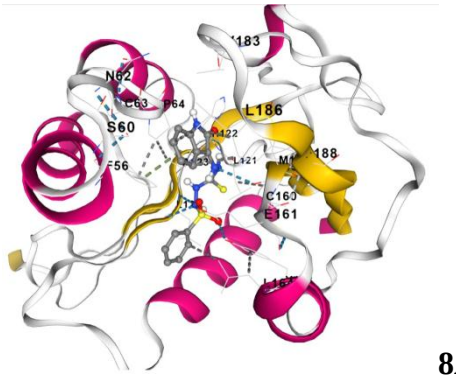
2A



3A



4A



8A

8. CONCLUSION

Research aimed at generation of a new molecular template by linking two pharmacophores i.e., substituted Isatin monothiocarbohydrazide and substituted benzene sulfonyl chloride. A novel series of Isatin monothiocarbohydrazide bearing benzene sulfonyl chloride moieties were designed, characterized and evaluated for anti bacterial activity by molecular docking studies. Physicochemical properties have been predicted using Molinspiration, Swiss ADME and all the compounds were found to obey Lipinski Rule of five. Docking studies were performed to determine antibacterial activity, using 7OTC (pdb protein), using AUTODOCK software. Obtained results suggest that compounds 3A and 8A show good docking score. Antibacterial studies were performed against gram- negative strains. Synthesised compounds found against gram negative bacteria while compounds 3A & 8A shown good antibacterial activity against gram negative strain *E. coli*. These compounds could therefore may have enough potential to be evaluated as antibacterial agent and can make a great impact on those medicinal chemists who work on development of these moieties.

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