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In-Silico Approaches for the Design and Synthesis of Potent Isatin Sulfonamide of Alpha-Glucosidase Inhibitors Implicated in Treatment of Diabetes

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Abstract:

Heterocyclic chemistry is the branch of chemistry dealing exclusively with synthesis, properties and applications of heterocyclic especially vital to drug design. Isatin and its derivatives have numerous biological properties like Antitumor, Antidiabetic, Anti-inflammatory, Analgesic. Isatin Sulfonamides: C26H24N2O5S, also known as 1-benzyl-5-[(2s)-2-(phenoxy methyl) pyrrolidin-1-yl] sulfonylindole-2,3-dione. Anti-diabetes Marketed Drugs are Acarbose, Miglitol, Voglibose. ACARBOSE AND MIGLITOL-Inhibits alpha-glucosidase in intestinal brush border by Preventing absorption and delay digestion of carbohydrates and Reduce post prandial blood glucose level. In this research, isatin sulfonamides were subjected to Structure-based virtual screening against the alpha-glucosidase inhibitor (PDB ID: 5ZCD). Top lead molecules were studied for molecular docking and pharmacokinetic studies and final Hits were identified by understanding their important pharmacophoric features and novel compounds as 3-Sulfonamido substituted isatin were designed, synthesized and undergo molecular docking and simulation studies. The synthesized compounds are to be characterized by by melting point, TLC, IR, NMR and Mass spectral data. Docking studies were conducted for these derivatives on the PDB ID: 5ZCD by using DOCK THOR software. The molecules are to be evaluated for their possible anti-diabetic activity.

Keywords: Isatin, anti-diabetic, alpha-glucosidase inhibitor, Isatin sulfonamide, nitrogen containing heterocycles, Structure-based Virtual Screening, Molecular Docking

1. INTRODUCTION

1.1 Isatin:

The synthesis of heterocycles may be a noteworthy a part of artificial chemistry, attributable to the broad vary of bioactive heteromolecules.[1] Among N heterocyclic, isatin forms the priority most vital nucleus with N atom towards position one and 2 carbonyl teams towards positions two and three. It contains 2 cyclic rings, one is 6-membered and also the different is membered.[3]

Isatin, therefore known as as tribulin, it's AN compound extracted from indole cluster that showing the formula C8H5NO2. These compounds was 1st noninheritable on the far side Otto Linné Erdman and Auguste Laurent in 1840 as a product from the chemical reaction of indigo dye by aqua fortis and chromic acids.

Isatin derivatives area unit initiated in plants of the dilleniid dicot genus, shown as Couroupita guianensis, wherever as in humans, it's shown as metabolic by-product of Adrenalin.[2]

It is apperaing like AN red-orange solid, and it's sometimes utilized as building block for the synthesis of a good kind of biologically active compounds includes antitumorals activity, antivirals, anti-HIVs, and antituberculars, anti-diabetes, medicine activity.

The isatin and its derivatives is additionally accountable for the look of color of "Maya blue" and "Maya yellow" dyes.

Isatin sulfonamides C26H24N2O5S it conjointly called 1-benzyl-5-[(2s)-2-(phenoxymethyl)pyrrolidin-1-yl]sulfonylindole-2,3-dione.[4]

PHYSICAL PROPERTIES:

Isatin may be a N-based ring heterocyclic entity that contains one nitrogen atom, 2 cyclic rings one is coalesced with six-membered and different is with membered. it's orange-red solid compound having the formula C8H5NO2, the molecular mass of it's 147.1308g/mol. And is typically found in crystalline state.[5]

Isatin sulfonamides compound having the formula C26H24N2O5S.

STRUCTURE OF ISATIN/ ISATIN SULFONAMIDES:

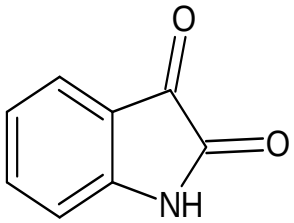


Figure 1: Isatin

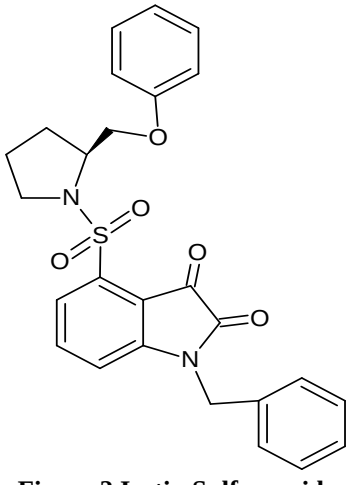


Figure 2 Isatin Sulfonamide

In isatin structure, reactivity behavior of heteroatom six membered ring is significantly affected by the incorporated benzene nucleus.

1.2 Alpha-Glucosidase inhibitors:

Introduction:

Alpha-glucosidase inhibitors are used as pills for type 2 diabetes milletus and aslo called as oral diabetes drugs that worked by preventing the digestion of carbohydrates-such as starch and table sugar. Carbohydrates are normally translated to simple sugars by alpha-glucosidase enzymes obtained on cells lining on the intestine, enabling monosaccharides to be absorbed through the intestine. Moreover, alpha-glucosidase inhibitors diminished the impact of dietary carbohydrates on blood sugar.[6]

Examples of alpha-glucosidase inhibitors include:[7]

Acarbose, Miglitol, Voglibose

Even though these drugs having a typical mechanism of action, there are subtle similarity between acarbose and miglitol. Acarbose is an oligobase saccharide, and miglitol resembles a monosaccharide. Miglitol is slowly well absorbed by the body, as against acarbose. Futhermore, pancreatic alpha-amylase in addition to alpha-glucosidase[8] are inhibited by Acarbose.

Here, Natural alpha glucosidase inhibitors

There are an outsized number of natural products with alpha-glucosidase inhibitor action.[9]

For example, research shown the culinary activity in mushroom Maitake also called as Grifola frondosa which has a hypoglycemic activity. The reason behind the Maitake lowers blood sugar is because the mushroom naturally contains an alpha glucosidase inhibitory. Another plant attracting tons of attention is Salacia oblonga.[10]

Clinical use

Alpha-glucosidase inhibitors are used to establish greater glycemic control over hyperglycemia effects in DM type 2, particularly with regards to postprandial hyperglycemia. They may be used as monotherapy in conjunction with an appropriate diet and exercise, or they'll be utilized in conjunction with other anti-diabetic drugs.[11]

In patients with DM type 1, Alpha-glucosidase inhibitors use has not been officially approved by the Food and Drug Administration but some data exists on the effectiveness during this population[12], showing potential benefits weighted against an growing up risk factor of hypoglycemia.

1.3 Mechanism of action:[13]

ACARBOSE AND MIGLITOL

Inhibits alpha-glucosidase in intestinal brush border.

Prevents absorption and delay digestion of carbohydrates.

Reduce post prandial blood glucose level.

Alpha-glucosidase inhibitors are oligosaccharides that act as competitive inhibitors of enzymes which needed to digest carbohydrates:[14] specifically alpha-glucosidase enzymes within the brush border of the tiny intestines. The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides within the intestine .

Acarbose also stops pancreatic alpha-amylase additionally to inhibiting membrane-bound alpha-glucosidases. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides within the lumen of the tiny intestine.[15] Inhibition of those enzyme systems reduces the speed of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates aren't weakened into glucose molecules. In diabetic patients, the short-term effect of those drugs therapies is to decrease current blood sugar levels: the long-term effect may be a small reduction in hemoglobin A1c level.[18]

1.4 MARKETED DRUGS OF ALPHA-GlUCOSIDASE INHIBITORS :

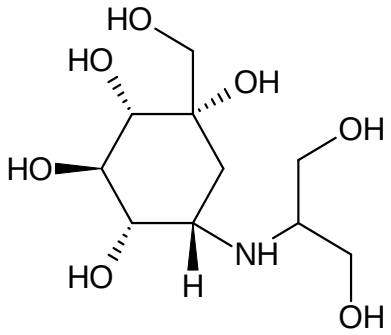


Figure 3 : VOGLIBOSE

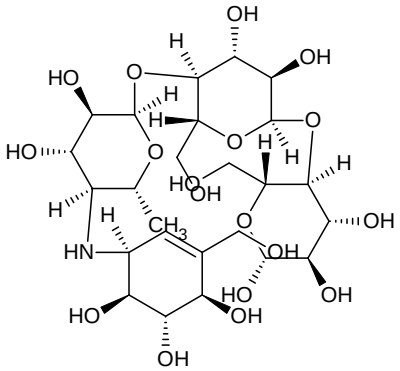


Figure 4 : ACARBOSE

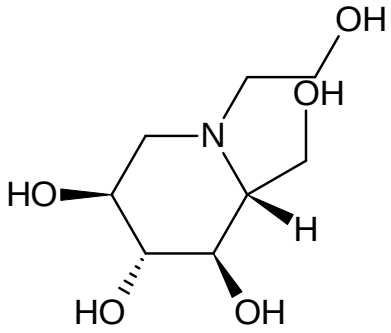


Figure 5 : MIGLITOL

2. MATERIALS AND METHODS:

2.1 Materials:

Table-1 Chemicals and reagents:

Indole-2,3-dione (Isatin)	Ethanol
Benzyl bromide	Hexane
Dimethyl Formamide (DMF)	Ethyl acetate
Potassium Carbonate	Dioxane
Hydrazine hydrate	Triethylamine
Benzene sulfonyl chloride	Bromo benzyl bromide
Toluene sulfonyl chloride	Nitro benzyl bromide
Conc. Hydrochloric acid	Silica gel

All the chemicals (reagents and solvents) were purchased from commercial suppliers (Merck grade) Sigma Aldrich, Avra, and SD Fine Chem. Ltd and they were used further without purification.[19]

2.2 Methods:

Melting Point Apparatus:

The melting points of the synthesized compounds were taken in the open capillary tubes using Chemline company CL726 melting apparatus.

Thin Layer Chromatography:

Purity of the compounds was checked by TLC using silica gel G (0.5mm thickness) coated over glass plate (12 x 20 cm). For the determination Rf value the dried silica gel G coated over glass plate were used.

Preparation of TLC plate:

By using distilled water silica gel G slurry is prepared and poured on to a glass plate which is maintained on a level surface.[20] The slurry is spread uniformly on the surface of the glass plate. After setting, the plates are dried in an oven at 50ºC or 15 minutes for activating the TLC plate. Chromatogram was developed by ascending technique when solvent front travelled appropriate distance; plates were taken out and dried. The location of spot was detected using iodine chamber.

Rf = Distance travelled by solute / Distance travelled by solvent

Infrared Spectroscopy:

The IR Spectra of the synthesized compounds were recorded at RBVRR women's College of Pharmacy by Shimadzu-FT/IR spectrophotometer in KBr disc. The IR value was measured in cm-1.

Nuclear Magnetic Resonance:

The H-NMR Spectra of the synthesized compounds were recorded at Central Facilities for Research and Development, Osmania University, Hyderabad by Bruker 300 MHz FT- NMR using CDCl3(Deuteriated Chloroform) as internal standard. The PMR (Proton Magnetic Resonance) spectroscopic values are measured in δ ppm in DMSO-d6. [21]

Mass Spectroscopy: Mass spectra was recorded in Schimadzu Mass Spectrometer

3. RESULTS AND DISCUSSION:

3.1 Virtual Screening:

100 isatin sulfonamides structures were extracted from the CHEMBL database using various filters and these were subjected to virtual screening against Alpha-glucosidase inhibitor (PDB ID: 5ZCD) by using **PyRx** software.[22]

Table 2: Virtual screening results of Alpha-Glucosidase inhibitors for with Isatin Sulfonamide.

S. No:	CHEMBL ID	Alpha Glucosidase inhibitors (PDB ID: 5ZCD)
1.	CHEMBL9913141	-10.3
2.	CHEMBL25179324	-10.1
3.	CHEMBL9934739	-9.8
4.	CHEMBL25178948	-9.7
5.	CHEMBL15184836	-9.7
6.	CHEMBL42618277	-9.6

Therefore, from the above results by virtual screening of Isatin moieties with Alpha-glucosidase inhibitor, it is understood that the following 6 hit molecules are having possible activity against diabetes. Figure5 illustrates the structure of the six hit molecules obtained from virtual screening results:[23]

Molecular Docking

As the binding affinity studies between ligands and their receptors from the basis of physiological activity and pharmacological effects of chemical compounds. We carried out docking studies to investigate the correct binding pose of the novel molecules with Alpha glucosidase inhibitors by using **DOCK THOR** software. (Table 3)[25]

Molecular docking of 6 hit molecules with Alpha-glucosidase inhibitor exhibit satisfactory results and so the essential pharmacophoric features from these molecules which are responsible for the basic antidiabetic activity were understood and incorporated on the basic isatin moiety to design a new lead molecule with its derivatives. The designed lead and its derivatives were made to undergo molecular properties and toxicity prediction using OSIRIS Property Explorer software and bioactivity prediction using Molinspiration software.[26]

On the basis of drug likeness, compounds were predicted to be promising druggable candidates.[28] The toxicity of the compounds was also predicted using Osiris, most of the compounds amongst the synthesized ones showed non-tumorigenic and non-reproductive effects, which further supports the drug features in the molecules. This toxicity prediction would be useful for the selection of compounds to test in animal models.[29]

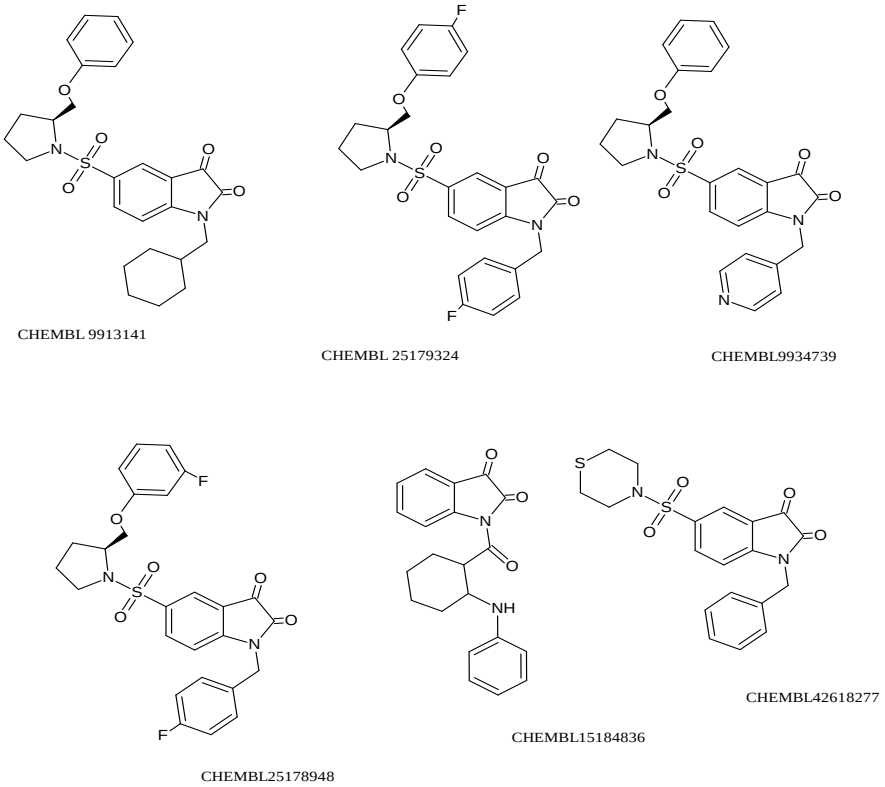
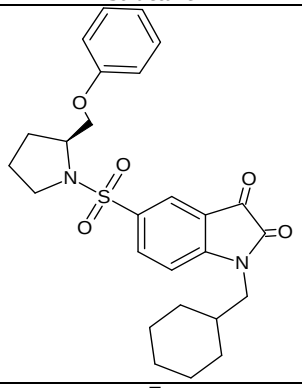
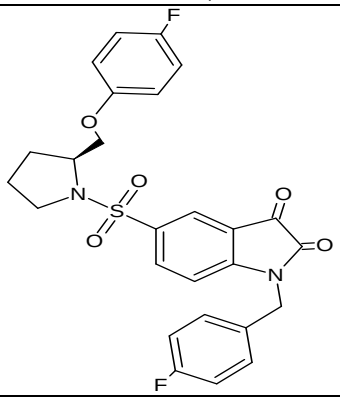
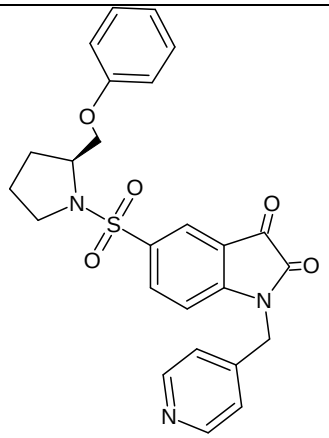
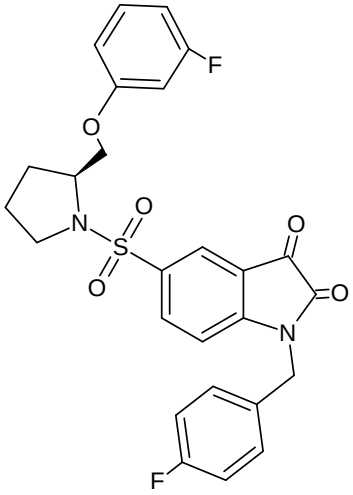
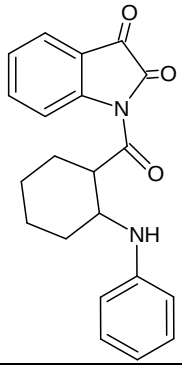
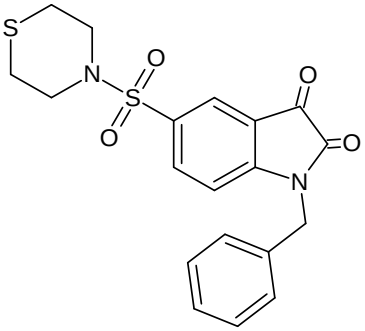


Figure 6: Structures of selected 6hit molecules with their CHEMBL ID's

Table 3: Molecular Docking interactions of 6 hit molecules obtained from virtual screening results

S.No	Pubchem ID	Structure	Interactions	Binding scores
1.	CHEMBL 9913141		**HYDROGEN BOND INTERACTIONS** ASN A:255, ARG A:194 **VANDERWAAL INTERACTIONS** GLN A:253, ASP A:196, PHE A:222, MET A:282 **OTHER INTERACTION** PHE A:141, ASP A:319	**-8.74**
2.	25179324		**HYDROGEN BOND INTERACTIONS** ARG A:403 **VANDERWAAL INTERACTIONS** GLN A:164, ASP A:57, TRP A:285, **OTHER INTERACTION** PHE A:222, ILE A:140, TYR A:60	**-8.52**

S.No	Pubchem ID	Structure	Interactions	Binding scores
3.	9934739		**HYDROGEN BOND INTERACTIONS** GLN A:320 **VANDERWAAL INTERACTIONS** ASP A:196, PHE A:141, MET A:282, TRP A:285 GLU A:280 **OTHER INTERACTION** ALA A:197, PHE A:222, PHE A:160	**-8.35**
4.	25178948		**HYDROGEN BOND INTERACTIONS** HIS A:200, ASN A:255 **HYDROPHOBIC INTERACTION** GLN A:164, HIS A:100 **VANDERWAAL INTERACTIONS** GLN A:320, TYR A:60, TRP A:285, ALA A:197 **OTHER INTERACTIONS** PHE A:279, ILE A:140, ASP A:57	**-9.40**
5.	15184836		**HYDROGEN BOND INTERACTIONS** HIS A:200, ASN A:255 **VANDERWAALS INTERACTION** ASP A:196, ASP A:374, PHE A:222 **OTHER INTERACTIONS** ALA A:197, PHE A:279	**-8.17**
6.	42618277		**HYDROGEN BOND INTERACTIONS** GLN A:320 **HYDROPHOBIC INTERACTION** ARG A:194, MET A:282, ALA A:197 **VANDERWAAL INTERACTIONS** HIS A:200, PHE A:141, ARG A:403 **OTHER INTERACTIONS** ASP A:319, PHE A:279	**-7.75**

DESIGN OF THE LEAD MOLECULE FROM SIMILAR STRUCTURES AND THEIR PHARMACOPHORIC FEATURES

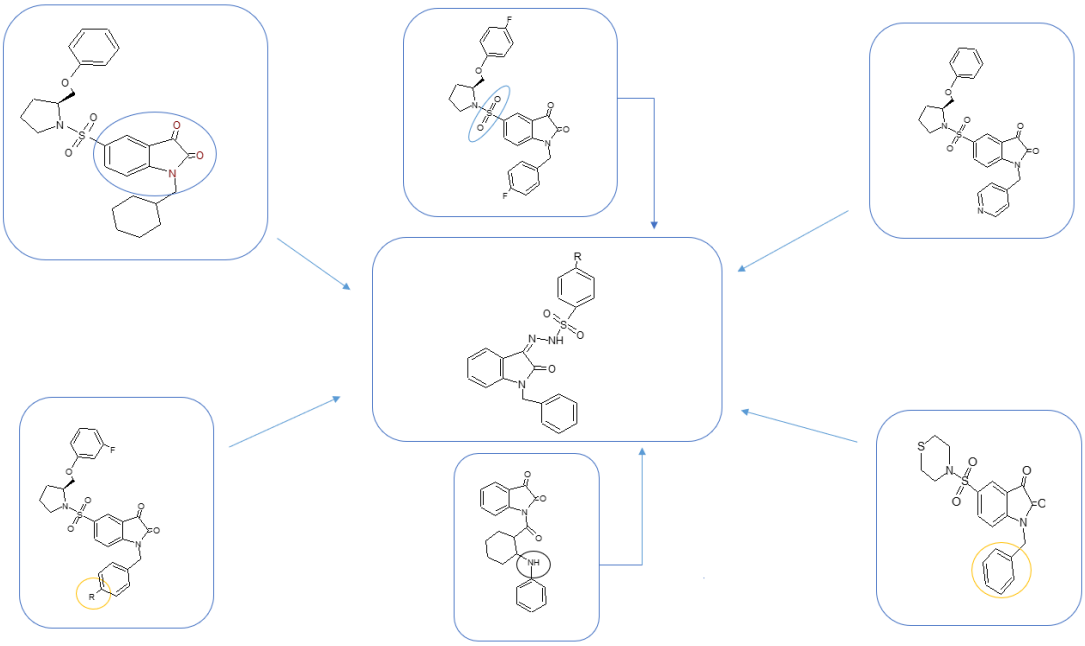
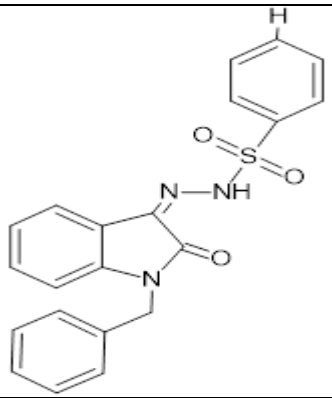
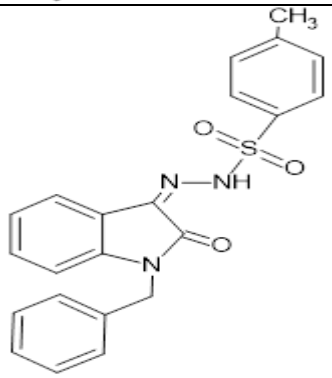
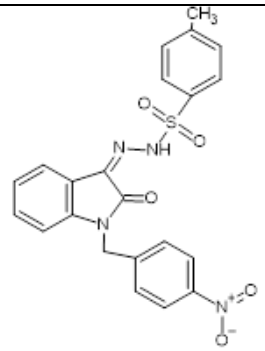
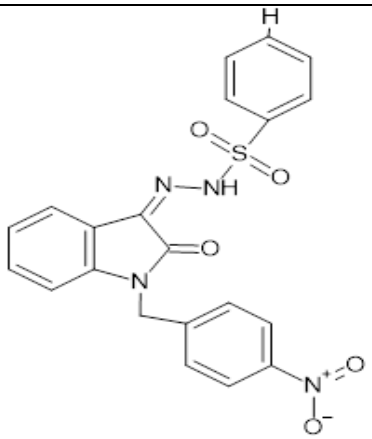
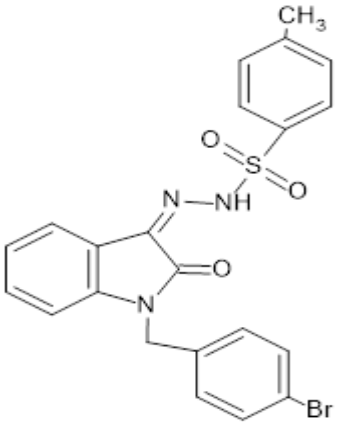
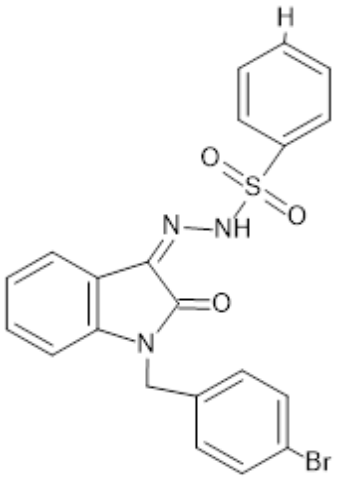


Figure:7 Molecular Properties and Toxicity Prediction of the Isatin-sulfonamide derivatives using OSIRIS Property Explorer[27]

Table 4: Molecular Properties and Toxicity Prediction of the Isatin-sulfonamide derivatives using OSIRIS Property Explorer

S.No	Molecules	Mol.Wt	C LogP	Log S	Druglikeness	Mutagenic	Reproductiveness
1.		391.0	2.68	-4.16	-0.63	none	None
2.		405.0	3.02	-4.01	0.13	none	None

S.No	Molecules	Mol.Wt	C LogP	Log S	Druglikeness	Mutagenic	Reproductive ness
3.		450.0	2.1	-4.27	-10.04	none	None
4.		436.0	1.76	-4.92	-10.79	None	None
5.		483.0	3.75	-4.64	-1.75	none	None
6.		469.0	3.4	-4.3	-2.5	none	None

Pharmacokinetic Property Prediction of the Title compounds

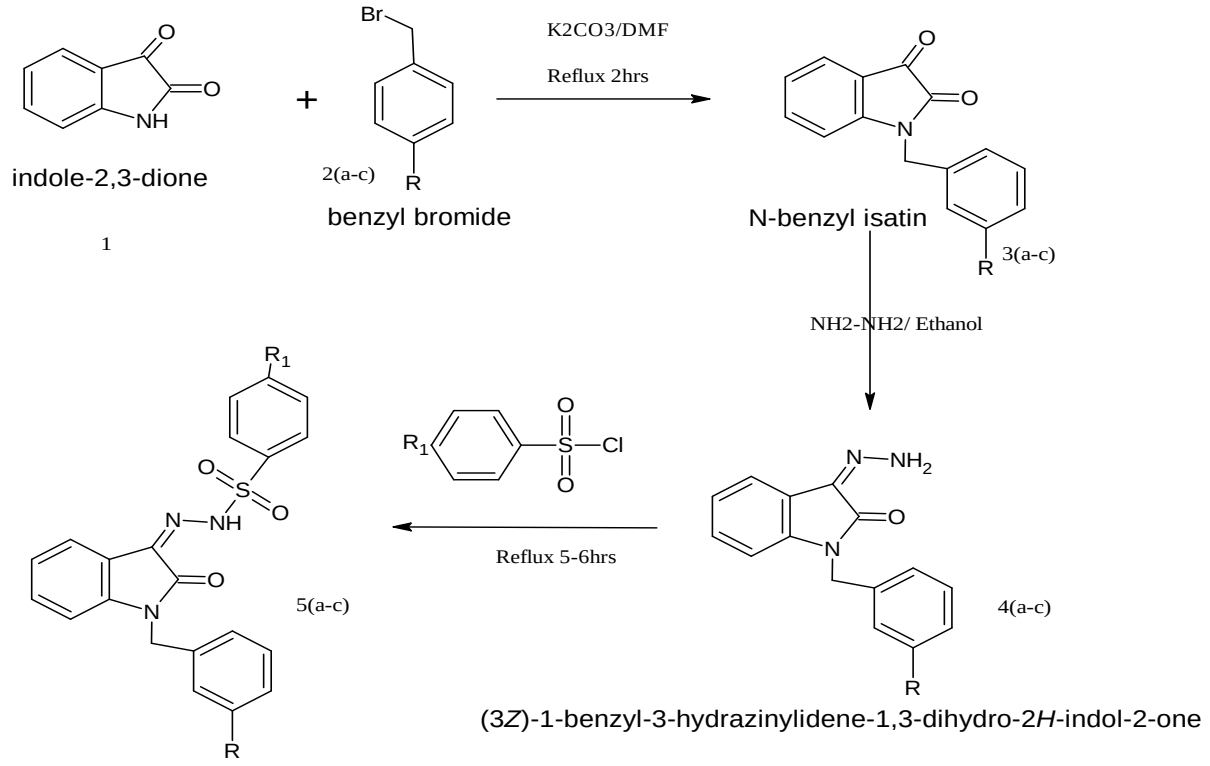
• Pharmacokinetic properties of the title compounds were predicted using an online freeware SwissADME

Table 5: Pharmacokinetics Properties Prediction studies of Isatin-sulfonamide derivatives using SwissADME software.[30]

Molecules	1	2	3	4	5	6
Range						
GI absorption	High	High	High	High	High	High
BBB permeation	No	No	No	No	No	No
P-gp Permeation	Yes	No	Yes	No	No	No
Cyp1a2 inhibitor	No	No	No	No	Yes	No
Cyp2c19inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
Cyp2c9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
Cyp2d6 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
Cyp3a4 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
Log Kp(Skin Permeation)	-5.95 Cm/S	-6.61 Cm/S	-7.30 Cm/S	-6.61 Cm/S	-5.35 Cm /S	-7.36 Cm/S

SYNTHESIS:

New series of 4a-c and 5a-c were synthesized by a known convenient method. The compounds were characterized by IR, NMR and Mass Spectrometry.



R	R1
H	H
NO2	CH3
Br	

Table 7: substituents

Experimental:

STEP:1 Synthesis of 1-benzylisatin:

Isatin(1.0mmol) was dissolved in DMF(5ml), K2CO3 was added, then the reaction mixture was stireed under room temperature until isatin anion was obtained and hydrogen was removed. Alkyl halide(CH3I/CH3Br)(4mmol)[31] was added to above reaction mixture. Then the reaction mixture were kept under reflux on 70°c was completed after 1.5-2hrs, then the reaction were cooled overnight and precipitate were formed on ice water, further it was purified and recrystallized from ethanol to give orange red crystals in yield 82%, MP: 133°c–134°c.

STEP:2 preparation of the hydrazino-isatin derivatives:

Hydrazine hydrate (3 ml) is being added to a solution of isatin (1, 5 mmol) or 1-benzylisatin (3, 5 mmol) in ethanol (10 ml). Then heat the above solution and pour the reaction mixture into crushed ice water,[32] the final product was dried and recrystallized from ethanol to give a yellow solid. MP: mp114°c–116°c.

STEP:3 Synthesis of substituted isatin derivatives:

An equimolar quantity of isatin derivative (0.03mole) and benzene sulfonylchloride (0.42ml, 0.003mole)/ toluene sulfonylchloride (0.42ml, 0.003mole) and dioxane 10ml and few drops of trietheylamine was refluxed for 5-6 hours by monitoring the progress with TLC. Then the mixture was poured into ice cold water. A pale yellow coloured solid was obtained and recrystallized by ethanol [33]

1. Synthesis of N'-[(3Z)-1-benzyl-2-oxo-1,2-dihydro-3H-indol-3 ylidene]benzenesulfonohydrazide was characterized by melting point 130.134 o C, pale yellow powder, Mol.wt-391.44 g/mol., Yield: 88% and also by appearance of N-NH2 at 3345.88 cm-1 ; C=O at 1734.08 cm-1; C=N at 2248 cm-1 ; S=O at 1186.21 cm-11. H NMR: δ 5.04 (2H, s), 7.11-7.31 (6H, 7.19 (dddd, J = 7.8, 7.7, 1.9, 0.6 Hz), 7.18 (tt, J = 7.7, 1.5 Hz), 7.22 (dddd, J = 7.8, 1.5, 1.3, 0.6 Hz), 7.24 (ddd, J = 8.8, 7.5, 1.3 Hz)), 7.33-7.81 (8H, 7.40 (ddd, J = 8.7, 1.3, 0.5 Hz), 7.49 (ddd, J = 8.8, 1.4, 0.5 Hz), 7.52 (ddd, J = 8.7, 7.5, 1.4 Hz), 7.55 (dddd, J = 7.9, 7.6, 1.6, 0.4 Hz), 7.64 (tt, J = 7.6, 1.5 Hz), 7.75 (dtd, J = 7.9, 1.5, 0.4 Hz)).

2. Synthesis of N'-[(3Z)-1-benzyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene]-4-methylbenzene-1-sulfonohydrazide was characterised by melting point 128-129 o C, yellowish brown powder, Mol.wt 405.46 g/mol., Yield: 90% and also by appearance of N-NH2 at 3345.88 cm-1 ; C=O at 1734.08 cm-1 ; C-N at 1298.15 cm-1 ;C-H at 2922.28 cm-1 ; C=N at 2248 cm-1 ; S=O at 1186.21 cm-1. 1H NMR: δ 2.33 (3H, s), 5.04 (2H, s), 7.11-7.71 (13H, 7.19 (dddd, J = 7.8, 7.7, 1.9, 0.6 Hz), 7.18 (tt, J = 7.7, 1.5 Hz), 7.22 (dddd, J = 7.8, 1.5, 1.3, 0.6 Hz), 7.24 (ddd, J = 8.8, 7.5, 1.3 Hz), 7.33 (ddd, J = 7.9, 1.8, 0.4 Hz), 7.40 (ddd, J = 8.7, 1.3, 0.5 Hz), 7.49 (ddd, J = 8.8, 1.4, 0.5 Hz), 7.52 (ddd, J = 8.7, 7.5, 1.4 Hz), 7.65 (ddd, J = 7.9, 1.5, 0.4 Hz)).

3. Synthesis of N'-[(3Z)-1-benzyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene]nitro benzenesulfonohydrazide was characterised by melting point 210-240 o C, yellow powder, Mol.wt 436.44 g/mol., Yield: 92% and also by appearance of N-NH2 at 3317.89 cm-1 ; C=O at 1724.30 cm-1 ; C-N at 1275.19 cm-1 ; C-H at 2954.38 cm-1 ; C=N at 2360.01 cm-1 ; S=O at 1186.12 cm-1. 1H NMR: δ 5.21 (2H, s), 6.74-6.92 (4H, 6.80 (ddd, J = 8.2, 1.2, 0.5 Hz), 6.86 (ddd, J = 8.2, 1.8, 0.5 Hz)), 7.24 (1H, ddd, J = 8.8, 7.5, 1.3 Hz), 7.33-7.81 (8H, 7.40 (ddd, J = 8.7, 1.3, 0.5 Hz), 7.49 (ddd, J = 8.8, 1.4, 0.5 Hz), 7.52 (ddd, J = 8.7, 7.5, 1.4 Hz), 7.55 (dddd, J = 7.9, 7.6, 1.6, 0.4 Hz), 7.64 (tt, J = 7.6, 1.5 Hz), 7.75 (dtd, J = 7.9, 1.5, 0.4 Hz)).

4. Synthesis of N'-[(3Z)-1-benzyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene]nitro-4-methylbenzene-1-sulfonohydrazide was characterized by molecular weight:450.44g/mol, melting point 174-175 oC, yellowish brown powder, Yield: 96% and also by appearance of N-NH2 at 3312.88 cm-1 ; C=O at 1734.08 cm-1 ; C-N at 1298.15 cm-1 ; C-H at 2922.28 cm-1 ; C=N at 2248 cm-1 ; C=C at 1676.21 cm-1. 1H NMR: δ 2.33 (3H, s), 5.21 (2H, s), 6.74-6.92 (4H, 6.80 (ddd, J = 8.2, 1.2, 0.5 Hz), 6.86 (ddd, J = 8.2, 1.8, 0.5 Hz)), 7.16-7.71 (8H, 7.24 (ddd, J = 8.8, 7.5, 1.3 Hz), 7.33 (ddd, J = 7.9, 1.8, 0.4 Hz), 7.40 (ddd, J = 8.7, 1.3, 0.5 Hz), 7.49 (ddd, J = 8.8, 1.4, 0.5 Hz), 7.52 (ddd, J = 8.7, 7.5, 1.4 Hz), 7.65 (ddd, J = 7.9, 1.5, 0.4 Hz)).

5. Synthesis of N'-[(3Z)-1-benzyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene]bromo benzenesulfonohydrazide was characterized by molecular Weight: 470.33g/mol, melting point 200-210 oC, yellowish brown powder, Yield: 95% and also by appearance of N-NH2 at 3312.88 cm-1 ; C=O at 1734.08 cm-1 ; C-N at 1298.15 cm-1 ; C-H at 2922.28 cm-1 ; C=N at 2248 cm-1 ; C=C at 1676.21 cm-1. 1H NMR: δ 2.33 (3H, s), 5.07 (2H, s), 7.16-7.71 (12H, 7.24 (ddd, J = 8.8, 7.5, 1.3 Hz), 7.33 (ddd, J = 7.9, 1.8, 0.4 Hz), 7.34 (ddd, J = 8.4, 1.3, 0.6 Hz), 7.40 (ddd, J = 8.7, 1.3, 0.5 Hz), 7.46 (ddd, J = 8.4, 1.5, 0.6 Hz), 7.49 (ddd, J = 8.8, 1.4, 0.5 Hz), 7.52 (ddd, J = 8.7, 7.5, 1.4 Hz), 7.65 (ddd, J = 7.9, 1.5, 0.4 Hz)).

6. Synthesis of N'-[(3Z)-1-benzyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene]-4-methyl bromo benzene-1-sulfonohydrazide was characterized by mol.weight:484.36, melting point 165-17+0 oC, yellowish brown powder, Yield: 92% and also by appearance of N-NH2 at 3312.88 cm-1 ; C=O at 1734.08 cm-1; C-N at 1298.15 cm-1 ; C-H at 2922.28 cm-1 ; C=N at 2248 cm-1 ; C=C at 1676.21 cm-1. 1H NMR: δ 5.07 (2H, s), 7.16-7.81 (13H, 7.24 (ddd, J = 8.8, 7.5, 1.3 Hz), 7.34 (ddd, J = 8.4, 1.3, 0.6 Hz), 7.40 (ddd, J = 8.7, 1.3, 0.5 Hz), 7.46 (ddd, J = 8.4, 1.5, 0.6 Hz), 7.49 (ddd, J = 8.8, 1.4, 0.5 Hz), 7.52 (ddd, J = 8.7, 7.5, 1.4 Hz), 7.55 (dddd, J = 7.9, 7.6, 1.6, 0.4 Hz), 7.64 (tt, J = 7.6, 1.5 Hz), 7.75 (dtd, J = 7.9, 1.5)

4. DISCUSSION:

New series of 4a-c and 5a-c were synthesized by a known convenient method. The compounds were characterized by IR, NMR and Mass Spectrometry. 3-Sulfonamido Substituted isatin compounds were synthesized by isosteric replacement of various benzyl bromide with hydrazine hydrate. The synthesized compounds were then evaluated with physical and spectral data.

5. CONCLUSION:

In the present investigation 100 molecules from CHEMBL database were retrieved and subjected to virtual screening against PDB ID:5ZCD. Six HITS with highest scores were

selected and by understanding the basic pharmacophoric features, a new lead molecule was designed and from that a new series of substituted isatins (4a-c, 5a-c) were subjected to molecular docking and toxicity prediction studies. All the title compounds were having anti-diabetic activity and were found to be safe. These molecules were synthesized and all the synthesized compounds characterized by physical and spectral data

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