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Discovery of chromen-2-one based hybrid molecules as potential anti-tubercular agents and their docking for MTB

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Abstract

Tuberculosis (TB) remains a critical global health challenge, as identified by the World Health Organization (WHO), which names it the world's leading infectious killer. Caused by *Mycobacterium tuberculosis*, TB primarily affects the lungs, leading to symptoms such as chronic cough, weight loss, and fatigue, though it can also impact other organs, including the brain, kidneys, and spine. Transmission occurs when individuals inhale droplets containing the bacteria, allowing it to reach the alveoli after passing through the respiratory tract. Currently, the FDA-approved medications for TB treatment include rifampin, isoniazid, pyrazinamide, and ethambutol. This study aims to develop a naturally occurring compound through synthetic chemistry, targeting TB with modifications at side chains to achieve lower IC₅₀ values compared to existing drugs. For the Synthesized of substituted amide Derivatives (3a - 3j) to achieve this, a library of amides was synthesized and coupled with a chromen molecule is Compound 4a - 4 j. the final synthesized compound was subjected to pharmacokinetic studies and molecular docking to evaluate its efficacy.

Keywords: Tuberculosis, anticancer, antidiabetic activities, umbelliferone (7-hydroxy 4 methyl coumarin), amides

Introduction

For the millennia, human civilizations have relied on nature and its products as medicine, with traditional healing practices across cultures drawing on the therapeutic properties of plants, animals, fungi, and microorganisms (Fokunang CN et.al, 2011) ^[1]. The diverse array of natural products they produce contains biologically active compounds that have been harnessed for treating various ailments and enhancing overall health and wellness (Ekiz E et.al, 2023) ^[2]. Plants have been a primary source of medicinal compounds. Plant species contain chemical compounds known as phytochemicals (Altemimi et.al, 2017) ^[3]. More than a thousand phytochemicals have been identified to date, and they can be obtained from a variety of sources including whole grains, fruits, vegetables, nuts, and herbs. They are plant-derived chemical with bioactive properties for example quinones, flavonoids, polyphenols, tannins, terpenoids, alkaloids, polypeptides, steroids, saponins, coumarins. These phytochemicals display antibacterial, antidiarrheal, anthelmintic, antiallergic, antispasmodic, and antiviral properties as well as significant antioxidant activity (Kumar A et al, 2023) ^[4]. Of these phytochemicals mentioned coumarin is widespread in nature and more than 1300 coumarins have been identified as secondary metabolites from plants, bacteria, and fungi (Tsivileva et.al, 2022) ^[5]. Coumarin is a colorless, crystalline substance that tastes bitter and has a sweet, vanilla-like aroma. It is utilized as a flavoring agent in food products such baked goods, alcoholic beverages, and tobacco as well as in the fragrance industry (Lončar et.al, 2020) ^[6]. It has wide range of pharmacological properties such as anti-inflammatory, anticoagulant, antibacterial, antifungal, antiviral, anticancer, antihypertensive, antitubercular, anticonvulsant, antiadipogenic, antihyperglycemic, antioxidant, and neuroprotective properties (Venugopala et.al, 2013) ^[7]. 'Coumarin', the name is derived from the plant Coumarouna odorata and was isolated by Vogel in 1820 (Lončar et.al, 2020) ^[6]. Coumarins belong to the benzopyrone family commonly found in many medicinal plants.

In this work, a total of 10 Amides are synthesized from anilines, pyridines and chloroacetyl chloride, Triethylamine and Dichloromethane (DCM).

General Reaction

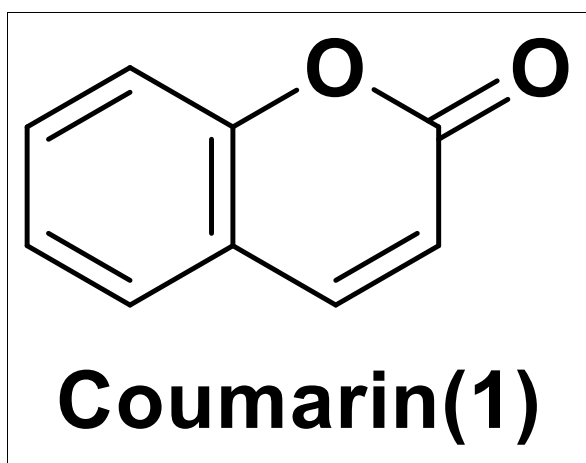
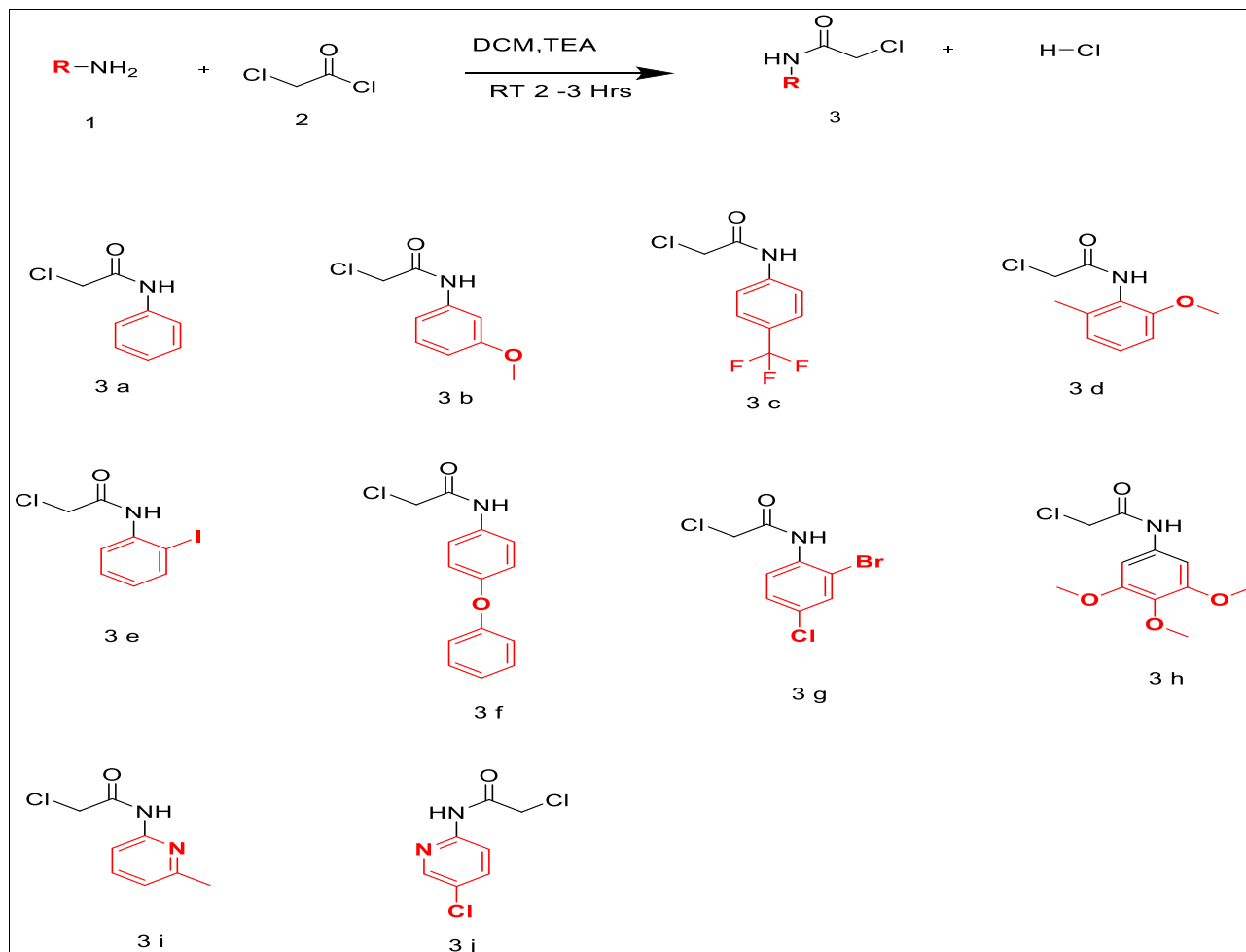
Respective Aniline to N Phenyl Acetamide

Respective Aniline/pyridine is taken as starting material the reagent used is chloroacetyl chloride, Triethyl amine and the

solvent used is Dichloromethane (DCM). The progress of the reaction is checked through thin layer chromatography

Synthesis of chloroacetamides

Amides- These are functional groups in which a carbonyl carbon atom is connected to a nitrogen atom, an H-atom, or a C-atom by a single bond.



Materials and Methods

Tuberculosis (TB) is caused by bacterium *Mycobacterium tuberculosis*. TB affects the lungs, it can also affect other parts of the body like brain, the kidneys or the spine. TB is treated with a combination of antibiotics for a period of six to

nine months or longer. The most common drugs used for TB treatment include isoniazid, rifampicin, pyrazinamide, and ethambutol.

Here, our study is to find molecule which is more effective than the marketly available drugs. Chromen-2-one is a naturally occurring compound which has anticancer, anticonvulsant, antimicrobial, anticholinesterase, antituberculosis, and antidiabetic activities. Chromen-2-one is synthetically modified to produce 7-hydroxy-4-methyl-2H-chromen-2-one (7-Hydroxy-4-methyl-coumarin) to get a better antituberculosis activity. Series of amide was prepared and set of amide was coupled with 7-hydroxy-4-methyl-2H-chromen-2-one.

The objective is to check the biological activity of the coupled molecule and to know if it is a promising drug candidate. Insilico studies is to be done.

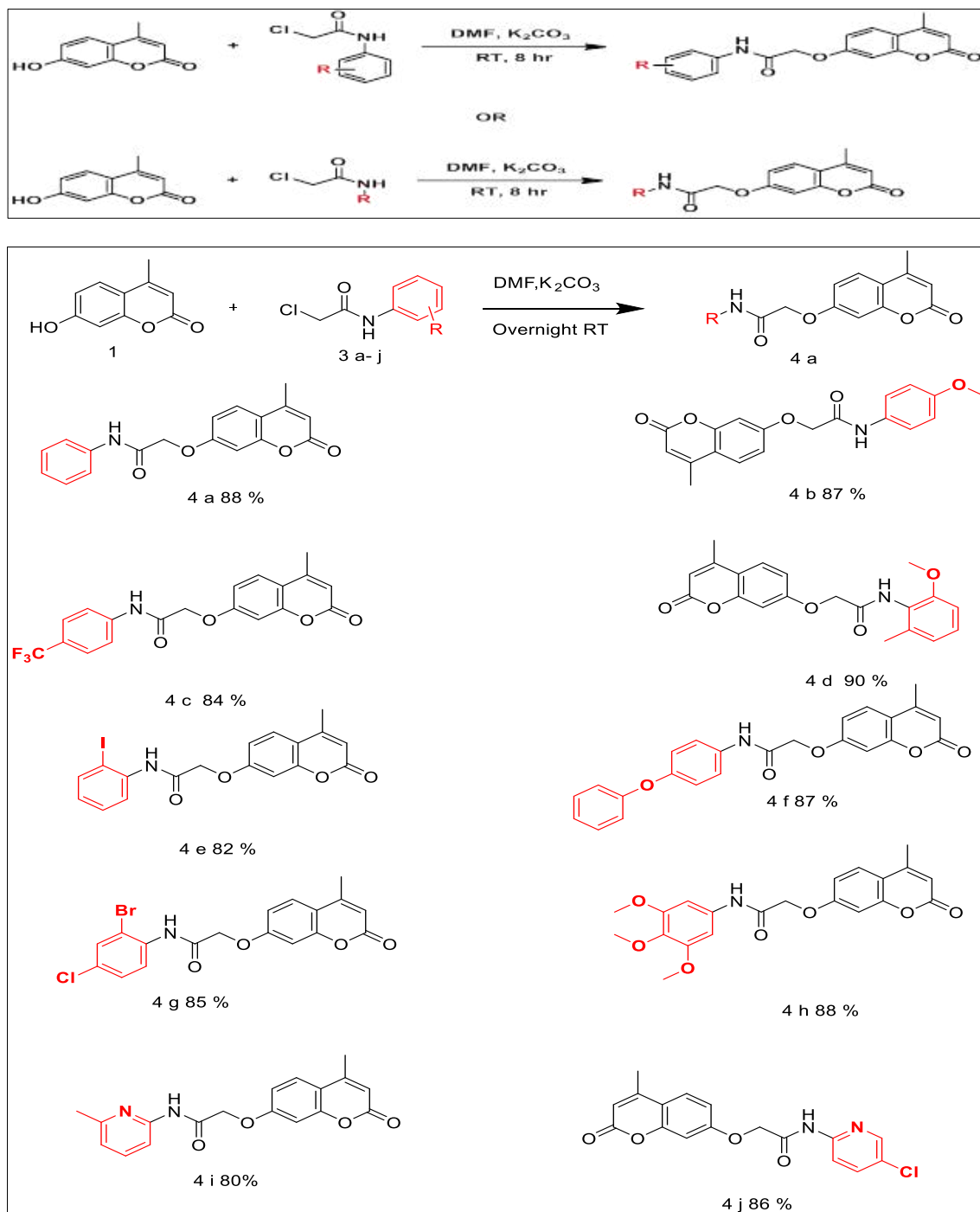
Synthesis of chromen molecule (7-hydroxy-4-methyl-2H-chromen-2-one)

A mixture of resorcinol (1.101 g, 0.01 mole) and ethyl acetoacetate (1.274 ml, 0.01 mole) with 75% H₂SO₄ (10 ml) was heated for one hour. The resulting dark green solution was cooled and poured over crushed ice and filtered using

vacuum pump. The thin-layer chromatography (TLC) was checked with reference, the reference taken is Umbelliferone (7-Hydroxy coumarin). The both compound exhibited fluorescence in UV light chamber. There was slight impurity in the compound formed, so the compound is separated using column chromatography until clear spot is visible in the TLC plate. To identify whether the compound formed is chromen molecule the compound is sent to Mass spectroscopy and ¹H NMR. The compound structure is elucidated. The next step is to couple this pure compound formed (7-hydroxy-4-methyl-2H-chromen-2-one) with the amide which shows best activity towards Tuberculosis (TB).

Experimental: General Reaction: Coupling of chromen molecule with chloroacetamide: In coupling reactions, two similar or different species react together to yield a new product. There is a common intermediate and a metal catalyst.

General Procedure of the synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one molecule N-Phenylacetamide: Here in the coupling reaction, the reactants taken are the 7-hydroxy-4-methyl-2H-chromen-2-one molecule (1eq) and the corresponding amide (1.3 eq) with K₂CO₃ as base and DMF as solvent, the reaction is done at room temperature and kept overnight.



Scheme: 1- 7-hydroxy-4-methyl-2H-chromen-2-one molecule N-Phenylacetamide.

Results and Conclusion

The main molecule used in the reaction is Chromen-2-one molecule. A series of intermediates (amides) are made and

are coupled with the Chromen molecule. Insilico studies like molecular docking is performed to determine the receptor-ligand interaction. Drug likeness is validated through

pharmacokinetics and ADME studies. The coupled complex should be validated for their biological activity the complex giving positive results are taken for further studies.

Molecular Docking: Here in this work, the coupled final product is taken as ligand and the receptor used is DNA Gyrase receptor. First we have to prepare protein and ligand.

Preparation of protein (Receptor): Protein was downloaded from Protein Data Bank and is downloaded in PDB format. The downloaded protein is prepared using AutoDock Vina (Version 1.5.7). The heteroatoms, water

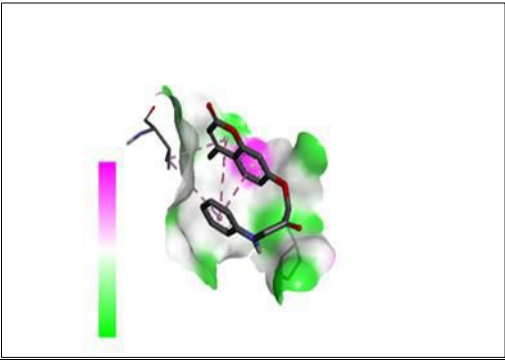
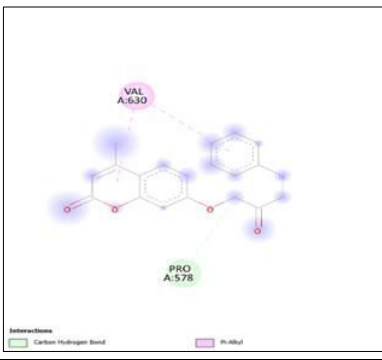
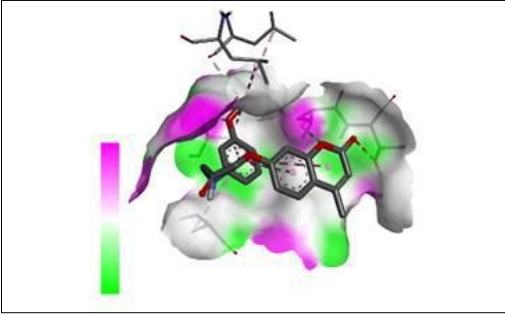
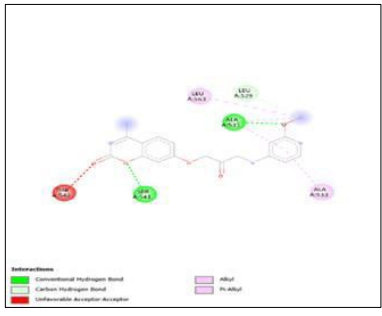
molecules should be removed, Polar H may be added while preparing protein. We can also select grid-box in the target protein and thus prepared protein can be saved as PDBQT (Protein Data Bank, Partial Charge (Q), & Atom Type (T)) format.

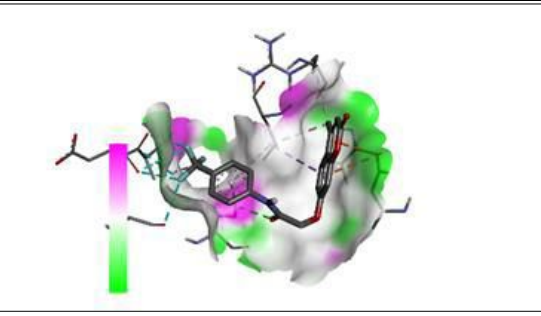
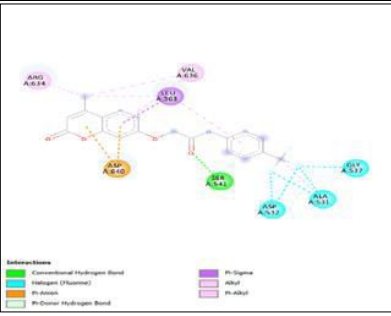
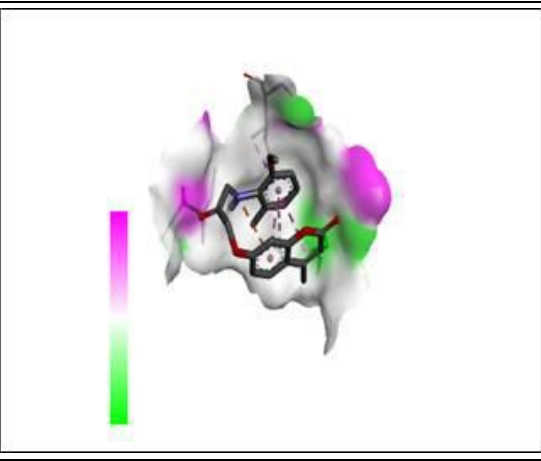
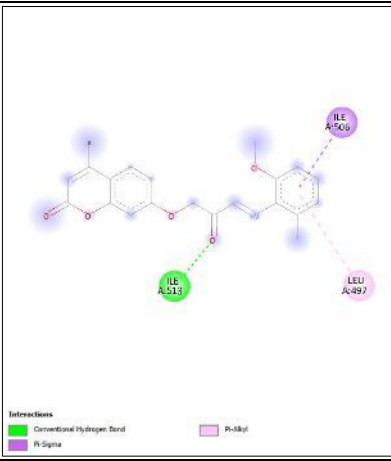
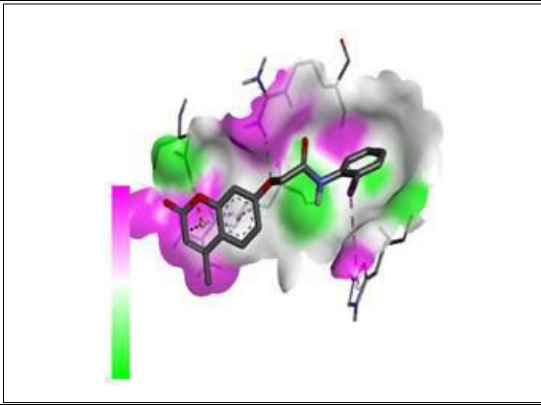
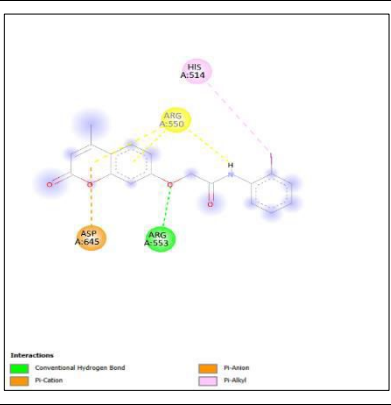
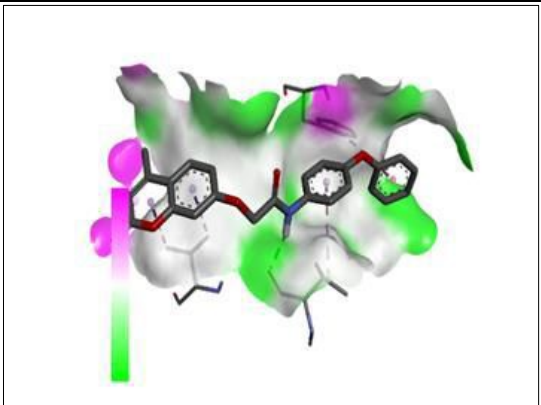
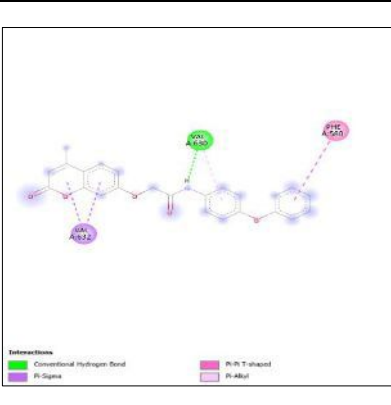
Preparation of Ligand: The ligands taken are the final coupled compound. The structure of the final compound is drawn by ChemBioDraw Ultra 14.0 tool and is saved as "mol" Files. These prepared ligands energy can be minimized by the Open Babel tool in the PyRx Software and these energy minimized ligands can be saved in PDBQT Format.

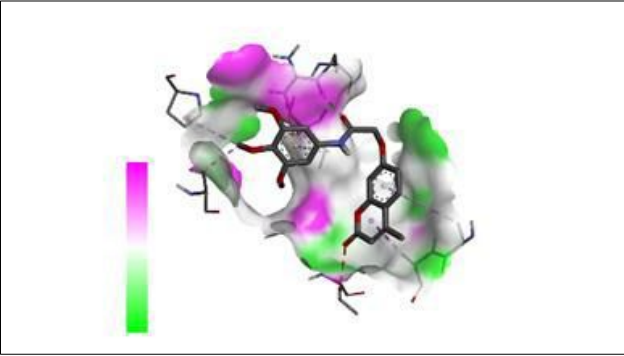
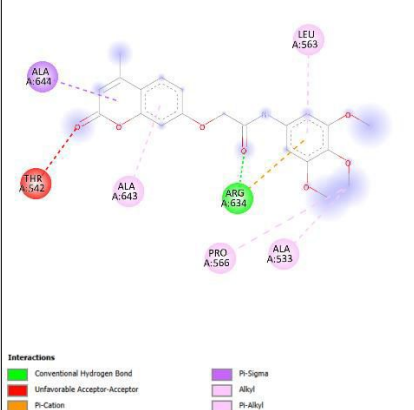
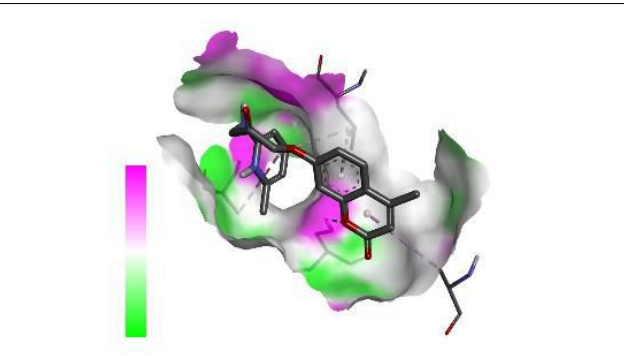
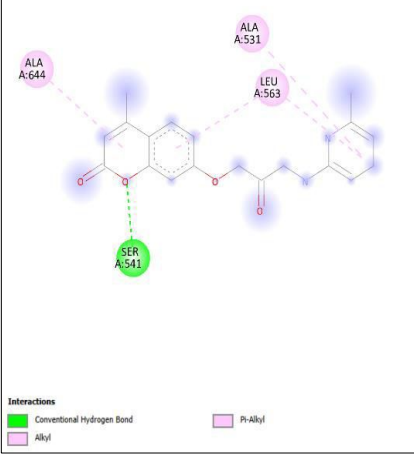
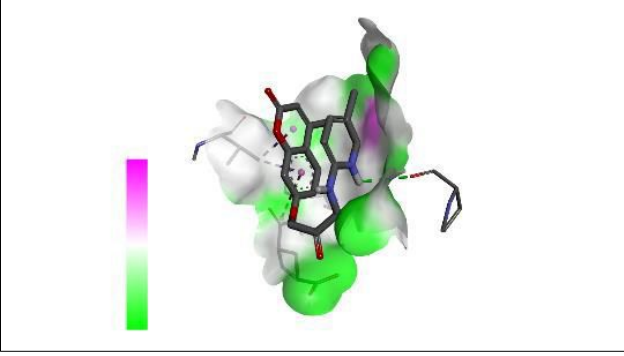
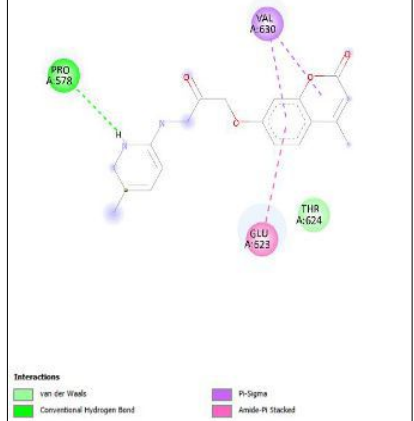
Table 1: Interaction of Ligands with the receptor

Protein	Ligand	Docking score	Interacting residue	Interactions
3IG0	4 - A	-5.7	VAL A:630, PRO A:578	Hydrogen Bond, Hydrophobic Interaction (Pi-Pi stacked, Pi-alkyl)
3IG0	4 - B	-6.5	SER A:541, ALA A:531, LEU A:529, LEU A:563, ALA A:533, THR A:542	Hydrogen Bond (conventional hydrogen bond, carbon hydrogen bond), Hydrophobic interactions (Pi-Pi stacked, Alkyl, Pi-Alkyl)
3IG0	4 - C	-7.2	SER A:541, ASP A:532, ALA A:531, GLY A:537, ARG A:634, VAL A:636, ASP A:640, LEU A:563	Hydrogen Bond (Conventional Hydrogen Bond, Pi-Donor Hydrogen Bond), Halogen (Halogen (Fluorine)), Electrostatic (Pi-anion.)
3IG0	4 - D	-5.4	ILE A:513, ILE A:506, LEU A:497	Hydrogen Bond (Conventional Hydrogen Bond), Electrostatic (Pi-cation), Hydrophobic (Pi-Pi stacked, Pi-alkyl)
3IG0	4 - E	-6.8	ARG A:550, ARG A:553, ASP A:645, HIS A:514	Hydrogen Bond (Conventional Hydrogen Bond), Electrostatic (Pi-Anion), Hydrophobic (Pi-alkyl)
3IG0	4 - F	-7.5	VAL A:630, PHE A:580, VAL A:632	Hydrogen Bond (Conventional Hydrogen Bond), Hydrophobic (Pi-alkyl, Pi-Pi T shaped, Pi-sigma)
3IG0	4 - G	-7.2		
3IG0	4 - H	-6.7	ARG A:634, ALA A:644, ALA A:563, ALA A:643, ALA A:566, ALA A:533	Hydrogen Bond (Conventional Hydrogen Bond), Electrostatic (Pi-cation), Hydrophobic (Pi-sigma, Alkyl, Pi-alkyl)
3IG0	4 - I	-6.4	SER A:541, ALA A:644, ALA A:531, ALA A:563	Hydrogen Bond (Conventional Hydrogen Bond), Hydrophobic (Alkyl, Pi-Alkyl)
3IG0	4 - J	-5.8	PRO A:578, THR A:624, VAL A:630, GLU A:623	Hydrogen Bond (Conventional Hydrogen Bond), Hydrophobic (Pi-sigma, Amide-Pi stacked)

Table 2: Docking results of 10 compounds

Compound	3-D Interaction with receptor	2-D interaction
4 - A		
4 - B		

4 - C		
4 - D		
4 - E		
4 - F		
4 - G		

4 - H		
4 - I		
4 - J		

Pharmacokinetics studies

Pharmacokinetic study is done using SWISS-ADME. It helps to compute physicochemical descriptors as well as to predict ADME parameters, pharmacokinetic properties, drug-likeness and medicinal chemistry friendliness of one or multiple small

molecules to support drug discovery. For the lead molecule to be drug-like molecule it should pass Lipinski's rule of five.

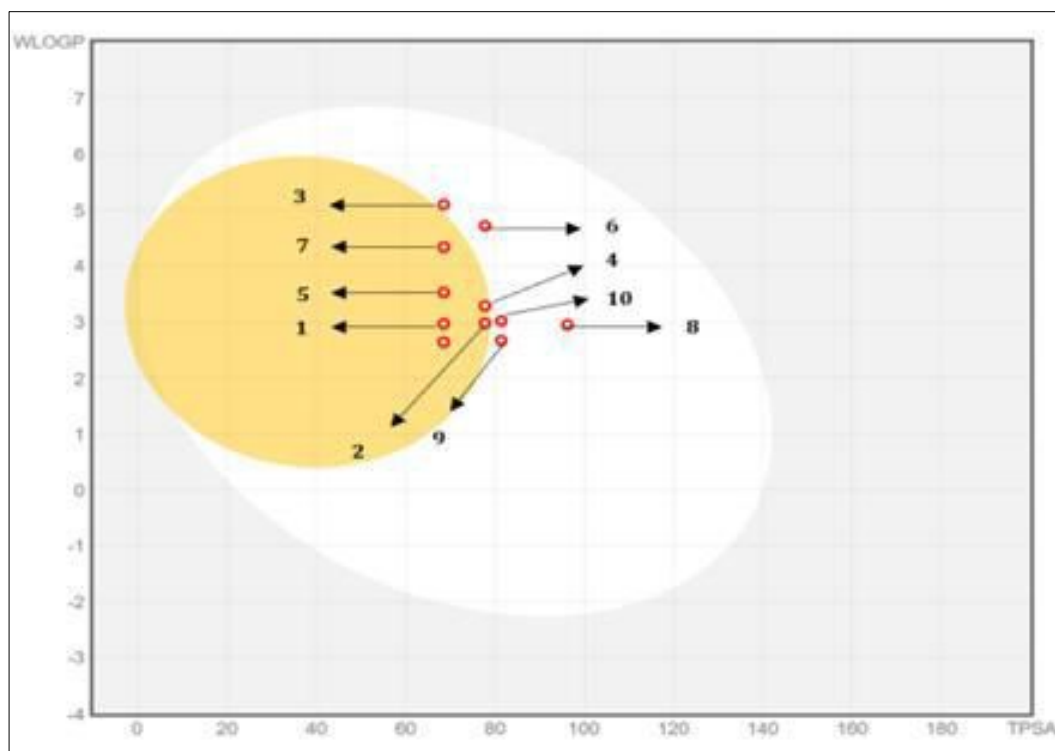
1. hydrogen bond donors not greater than 5
2. hydrogen bond acceptors not greater than 10
3. molecular weight not greater than 500 Da
4. octanol-water partition coefficient (logP)

Table 3: Pharmacokinetic analysis of the final compounds

	4 - A	4 - B	4 - C	4 - D	4 - E	4 - F	4 - G	4 - H	4 - I	4 - J
Mol wt.	323.34	353.37	377.31	367.4	435.21	401.41	422.66	399.4	338.36	358.78
Heavy atoms	24	26	27	27	24	30	25	29	25	25
Aromatic heavy atoms	16	16	16	16	16	22	16	16	16	16
Fraction Csp ³	0.16	0.2	0.16	0.24	0.11	0.08	0.11	0.24	0.21	0.17
Rotatable bonds	6	7	6	7	5	7	5	8	6	6
H Bond acceptor	4	5	7	5	4	5	4	7	5	5
H Bond Donor	1	1	1	1	1	1	1	1	1	1
iLOGP	2.33	2.92	3.05	3.25	3.03	3.38	3.38	3.12	2.81	2.8
XLOGP3	3.69	3.66	4.01	3.59	3.35	4.66	4.02	2.61	2.92	3.15
MLOGP	1.95	1.63	2.97	1.86	2.85	2.96	3.23	1.21	1.5	1.81
Solubility(ESOL LogS)	-4.27	-4.33	-4.75	-4.36	-4.81	-5.35	-5.14	-3.84	-3.86	-4.13
GI Absorption	High	High	High	High	High	High	High	High	High	High
BBB Permeability	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No
Log Kp	-5.65	-5.86	-5.75	-5.99	-6.58	-5.44	-6.02	-6.88	-6.29	-6.25
Lipinski violations	0	0	0	0	0	0	0	0	0	0
PAINS	0	0	0	0	0	0	0	0	0	0

Boiled Egg: The BOILED-Egg in SWISS-ADME is to predict simultaneously two key ADME parameters, i.e. the

passive gastrointestinal absorption (HIA) and brain access (BBB).



Author Contribution

Siddheshwar B. Lonari: Conceptualization, Experiment, Analysis, Manuscript draft preparation, editing.
Anil S. Kirdant: Conceptualization and Guidance.
Suresh C. Jadhavar: Conceptualization, formal editing, and Guidance.

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Experimental Data

¹H and ¹³C NMR

4- a. 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-phenylacetamide (GO-PhQm): ¹H NMR (400 MHz,

DMSO) δ 10.16 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.66 - 7.61 (m, 2H), 7.36 - 7.30 (m, 2H), 7.12 - 7.02 (m, 3H), 6.24 (t, *J* = 1.2 Hz, 1H), 4.85 (s, 2H), 2.41 (s, 3H).

¹³C NMR (100 MHz, DMSO) δ 166.31, 161.31, 160.55, 155.00, 153.86, 138.76, 129.26, 127.05, 124.26, 120.14, 114.12, 112.87, 111.92, 102.14, 67.75, 18.61.

4-c.N-(3-methoxyphenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (GO-QmAm-6): ¹H NMR (400 MHz, DMSO) δ 10.15 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.33 (t, *J* = 2.2 Hz, 1H), 7.27 - 7.17 (m, 2H), 7.08 - 7.01 (m, 2H), 6.70 - 6.64 (m, 1H), 6.24 (d, *J* = 1.5 Hz, 1H), 4.85 (s, 2H), 3.73 (s, 3H), 2.41 (s, 3H).

¹³C NMR (100MHz, DMSO) δ 166.36, 161.30, 160.55, 159.97, 154.99, 153.87, 139.95, 130.08, 127.05, 114.11,

112.86, 112.31, 111.92, 109.67, 105.85, 102.13, 67.71, 55.48, 18.62.

4-d.N-(2-methoxy-6-methylphenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (GO-QmAm-2): ¹H NMR (400 MHz, DMSO) δ 9.45 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.10 - 7.01 (m, 2H), 6.93 - 6.87 (m, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.25 (d, J = 1.3 Hz, 1H), 4.85 (s, 2H), 3.76 (s, 3H), 2.42 (s, 3H), 2.12 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 171.20, 166.05, 158.65, 141.90, 132.66, 131.65, 127.14, 118.00, 116.64, 114.32, 106.89, 72.38, 60.72, 23.37, 23.05.

4 e. N-(2-iodophenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (GO-QmAm-4): ¹H NMR (400 MHz, DMSO) δ 9.64 (s, 1H), 7.91 (dd, J = 7.9, 1.4 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.67 (dd, J = 8.0, 1.5 Hz, 1H), 7.45 - 7.39 (m, 1H), 7.14 - 7.08 (m, 2H), 7.01 (m, J = 7.6, 1.6 Hz, 1H), 6.25 (d, J = 1.4 Hz, 1H), 4.89 (s, 2H), 2.41 (d, J = 1.2 Hz, 3H).

¹³C NMR (101 MHz, DMSO) δ 166.55, 160.82, 160.54, 154.99, 153.86, 139.45, 138.89, 129.40, 128.17, 127.12, 126.20, 114.34, 112.89, 112.07, 102.43, 95.88, 67.75, 18.64.

4f.2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(4-phenoxyphenyl)acetamide (GO-QmAm-9): ¹H NMR (400 MHz, DMSO) δ 10.20 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.68 - 7.62 (m, 2H), 7.40 - 7.34 (m, 2H), 7.14 - 6.95 (m, 7H), 6.24 (d, J = 1.4 Hz, 1H), 4.85 (s, 2H), 2.41 (s, 3H).

4g.N-(2-bromo-4-chlorophenyl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (GO-QmAm-8): ¹H NMR (400 MHz, DMSO) δ 9.77 (s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 8.6, 6.9 Hz, 2H), 7.50 (dd, J = 8.7, 2.4 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 6.26 (d, J = 1.4 Hz, 1H), 4.92 (s, 2H), 2.42 (s, 3H).

4h. 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(3,4,5-trimethoxyphenyl)acetamide (GO-QmAm-12): ¹H NMR (400 MHz, DMSO) δ 10.09 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.08 - 7.01 (m, 4H), 6.25 (d, J = 1.3 Hz, 1H), 4.83 (s, 2H), 3.74 (s, 6H), 3.62 (s, 3H), 2.41 (d, J = 1.3 Hz, 3H).

4 i.: 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-N-(6-methylpyridin-2-yl)acetamide (GO-QmAm-14): ¹H NMR (400 MHz, DMSO) δ 10.62 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.75 - 7.65 (m, 2H), 7.05 - 6.97 (m, 3H), 6.24 (d, J = 1.3 Hz, 1H), 4.93 (s, 2H), 2.43 (s, 3H), 2.41 (s, 3H).

4j.N-(5-chloropyridin-2-yl)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetamide (GO-QmAm-17): ¹H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.93 (dd, J = 8.9, 2.7 Hz, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.05 - 6.99 (m, 2H), 6.24 (d, J = 1.2 Hz, 1H), 4.96 (s, 2H), 2.41 (s, 3H).

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