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(Research Article)

Synthesis, characterization, and computational evaluation of novel 4-methyl-7-hydroxy coumarin derivatives for potential pharmaceutical applications

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Abstract

A novel class of molecules has been synthesized and characterized in this study using the Pechmann condensation method. These molecules are derived from 4-methyl-7-hydroxycoumarin, 12-substituted benzaldehyde, and imidazole. As a result of their wide range of applications in various industries, it is believed that these compounds hold significant potential, particularly with regard to pharmaceuticals, cosmetics, and agrochemicals. A wide range of analytical techniques, including IR, 1H NMR, and 13C NMR, were employed to thoroughly characterize the synthesized compounds. Furthermore, computational tools were used to analyze their QSAR parameters in silico. The study found that the designed molecules have desirable properties, including high bioavailability, low blood-brain barrier penetrability, and low toxicity. Multi-software programs were used to test the compounds against enzyme targets, including BIOVIA, PYRX, MOLINSPIRATION, SWISS ADME, and PROTOX II. In addition to providing valuable insight into the compounds' potential efficacy and safety profiles, these computational analyses provide additional information as well. The study emphasizes the reliability of ADMET properties prediction by using multiple computational tools, and this study highlights the promise of the synthesized molecules. Developing new therapeutic agents with diverse applications in the pharmaceutical and related industries may be made possible by the results of the study, potentially contributing to ongoing efforts in drug discovery and development.

Keywords: Docking Study; Coumarins Derivatives; Heterocyclic Compounds; Imidazole Derivatives

1. Introduction

The study of heterocycles has dominated organic chemistry for more than a century. By the end of the second millennium, there were about 20 million chemicals identified, and more than two-thirds are aromatic in nature, nearly half of which are heterocyclic [1]. The majority of heterocycles are nitrogen-containing, but there are also heterocycles containing oxygen, phosphorus, and selenium.

There are numerous natural drugs that are heterocyclic in nature, including papaverine, theobromine, quinine, emetine, and morphine. Many synthetic drugs, including diazepam, chlorpromazine, and metronidazole, also fall into this

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category. Diazinon and paraquat are both pesticides and herbicides that contain heterocycles, as are dyes like mauveine and luminophores like acridine orange.

There are a number of therapeutic properties associated with synthetic heterocycles, including antibacterial, antifungal, antiviral, and antiparasitic properties. Additionally, they can reduce inflammation, provide analgesia, counter convulsive activity, and fight cancer [2]. A class of organic compounds known as Coumarins was widely distributed in nature and is readily synthesized. Food and cosmetics, liquid crystal displays, pharmaceuticals, insecticides, rodenticides, and inks, paints, and synthetic rubber use them as fixatives, odor masking agents, and insecticides [3] In addition to antibacterial, anti-inflammatory, antioxidant, anticoagulant, anticancer, and anti-HIV properties, coumarin derivatives show a wide range of therapeutic applications [4,5]. Over the years, numerous synthesis methods have been developed to meet the demand for these versatile compounds [6]. Some of the most well-known methods are Pechmann condensation, Knoevenagel, Perkin, Witting, and Reformatsky reactions, and flash vacuum pyrolysis or carbon suboxide methods. A simple method for synthesis of 4-substituted coumarins, the Pechmann reaction, uses simple and inexpensive starting materials, i.e., phenols and β-ketoesters. [7] There have been several heterogeneous solid acid catalysts recently, including Nafion-H, zeolite H-BEA, montmorillonite clays, ionic liquids, Nafion resin/silica nanocomposites, and silica supported by chloric acid ($HClO4$). Pechmann condensation has been replaced by mesoporous zirconium phosphate (m-ZrP), cellulose sulfuric acid, $ZrOCL2.8H20/SiO2$, and others. As a catalyst for pechmann condensation, concentrated sulfuric acid forms coumarin (2H-1-benzopyran-2-one). In contrast, millemole quantities of the reactants are required for microwave irradiation to accelerate these reactions several-fold and improve product yields [8,9]. Using *insilico* tools, even before their practical synthesis, drugs can be predicted as drug candidates and their ADMET profiles can be built, thereby minimizing the costs incurred during the synthesis, preclinical, and clinical testing phases [10]. It was critical to have quality experimental data under the database for a tool to predict ADMET accurately. The purpose of docking a molecule is to determine whether there is an affinity between the ligands and their targets. The docking study was conducted using Auto Dock Vina through PyRx[11].

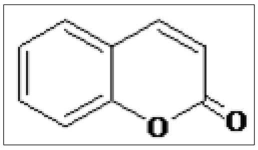


Figure 1 Structure of coumarins

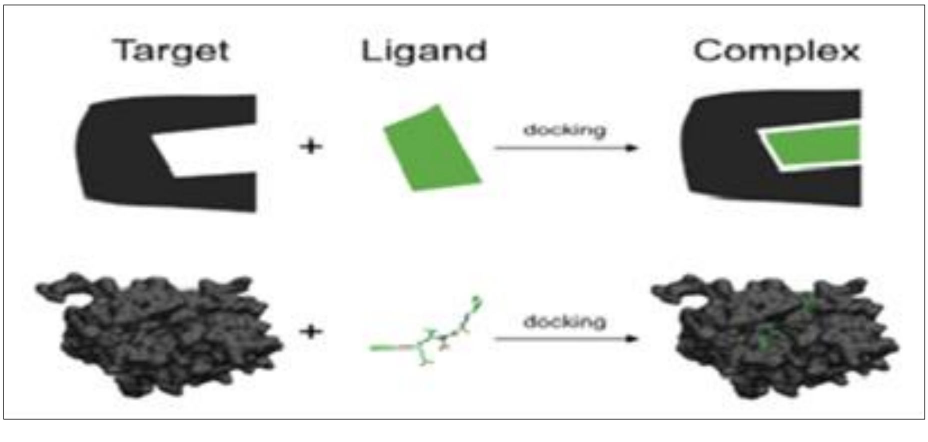


Figure 2 Schematic illustration of docking a small molecule ligand (green) to a protein target (black) producing a stable complex

2. Methodology

2.1. *In-silico* studies of designed compounds

To optimize lead molecules in drug development, computer-based simulations are essential. It is imperative that the formulation (potency, selectivity, and pharmacokinetics), as well as absorption, distribution, metabolism, and excretion (ADME) of a drug, as well as toxicity assessment must all be optimized before clinical trials. According to Lipinski et al., World Drug Index physicochemical properties can help predict oral bioavailability. A combination of Swiss ADME and

PreADMET software was used in this study to assess ADME properties, while ProTox II software was used to assess toxicity.

2.2. ADME Prediction

Several in vitro methods are used to assess intestinal absorption, including Caco2-cell and MDCK cell models. HIA and skin permeability models, along with Caco2-cell and MDCK assays, assist in identifying potential oral and transdermal drug candidates. A distribution analysis includes the penetration of the BBB for CNS drug delivery as well as the binding of plasma protein for disposition and effectiveness. Resilient back-propagation neural networks are used for building QSAR models using genetic approximations.

2.3. ProTox II

The ProTox II virtual lab was designed to predict toxicities of small molecules, a critical part of drug design and development. It offers speed and reduces the requirement for animal experiments thanks to its computational estimations. As a result of the incorporation of fragment propensities, similarity, and machine learning, ProTox II predicts acute toxicity, hepatotoxicity, cytotoxicity, carcinogenesis, mutagenesis, immunotoxicity, Tox21 pathways, and toxicity targets.

2.4. Molecular docking

PyRx software was used in this study to conduct docking studies. This study focused on the active site of COX (PDB ID: 6F86). In order to analyze docking, RCSB's protein structure was obtained. [11, 12]

2.4.1. Scheme of Work

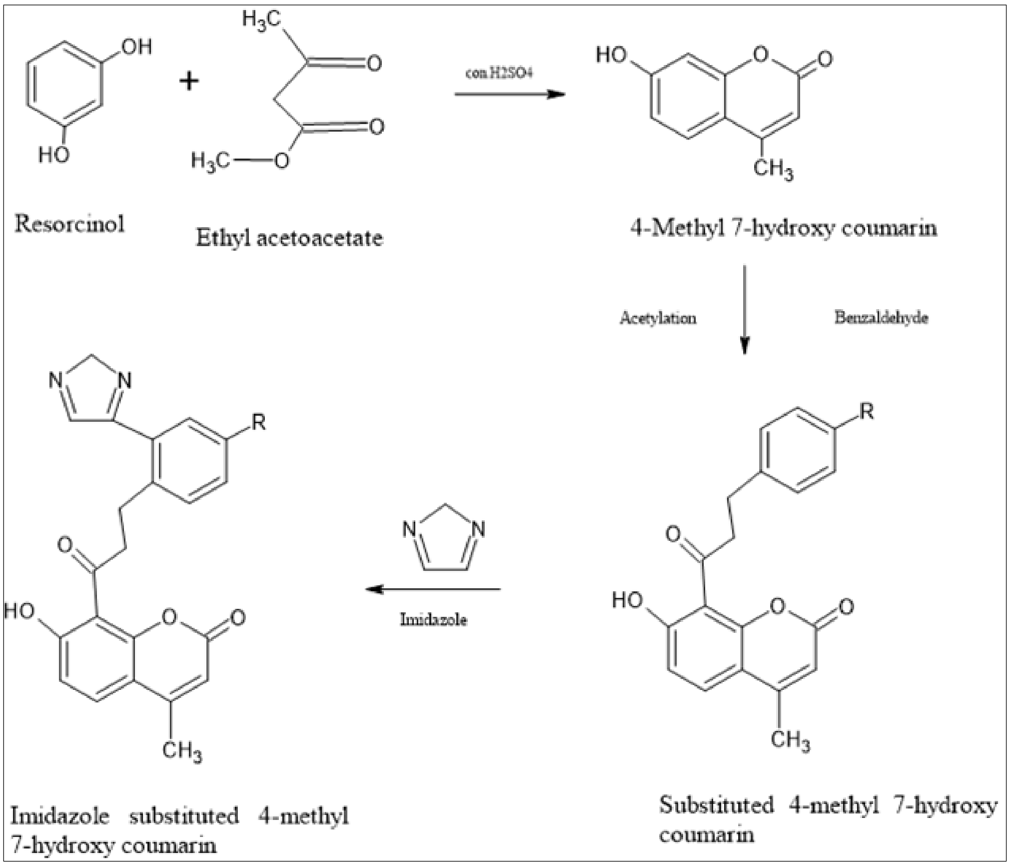


Figure 3 Work Scheme

2.5. Synthesis procedures

2.5.1. Step: 1 Synthesis of 4-Methyl-7- Hydroxy Coumarin

Nine ml of concentrated sulphuric acid were chilled and placed into a suitable container to start the synthesis process. 2.2 grams of resorcinol powder were gently added to chilled sulfuric acid with continuous mechanical stirring. Temperatures must not exceed 10 degrees Celsius during this process. To facilitate the condensation reaction, stirring is continued for 30 to 40 minutes. In order to separate the product, the resulting mixture is carefully transferred into a container filled with crushed ice water. After the separated product has been filtered using suction, it is thoroughly rinsed with cold water to remove any impurities.

2.5.2. Step:2 Condensation of product

Using an ethanol solution containing a catalytic amount of potassium hydroxide (KOH) (0.1 ml), a mixture containing acetyl coumarin and the corresponding aromatic aldehyde (5 mmol) was prepared. A one-hour irradiation was then performed on the prepared mixture.

2.5.3. Step: 3 Final Product formation (Substituted Imidazole coumarins)

Sodium hydroxide (0.045 mol, 0.40 g), coumarin (4-methyl-7-hydroxy-8-acetyl) (0.01 mol), as well as thiourea (0.015 mol, 0.96 g) were meticulously mixed in a small quantity of water. Irradiating the resulting mixture for approximately 30 minutes initiated the condensation process. Cooling the mixture until it acquired a dark-yellow hue was followed by a reduction in temperature. Afterwards, ethanol solvent was used to perform recrystallization.

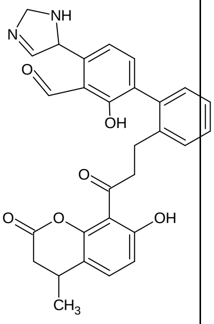
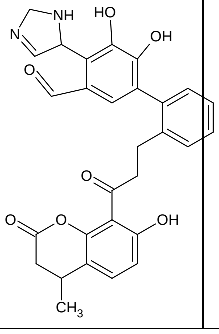
2.5.4. Characterisation of Synthesized compounds

A variety of spectroscopy techniques were used to characterize the synthesized compounds, including FT-IR, 1H-NMR, 13C-NMR, and MASS Spectroscopy.

3. Results and discussion

3.1. *In-silico* modelling

Table 1 Substituted Chemical Constituents

S.no	**Chemical constituents**	**Structure**	**Smiles**
1	Imidazole substituted 2-hydroxybenzaldehyde 4-methyl -7-hydroxy coumarin		O=Cc1c(ccc(c1O)c1ccccc1CCC(=O)c1c(O)ccc2c1OC(=O)CC2C)C1C=NCN1
2	Imidazole substituted 2,3-dihydroxybenzaldehyde 4-methyl -7-hydroxy coumarin		O=Cc1cc(c(O)c(O)c1C1C=NCN1)c1ccccc1CCC(=O)c1c(O)ccc2c1OC(=O)CC2C

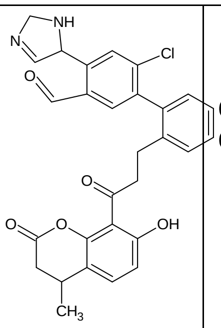
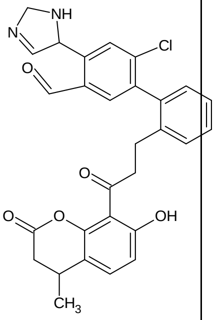
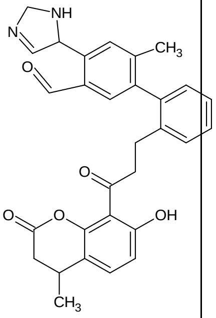
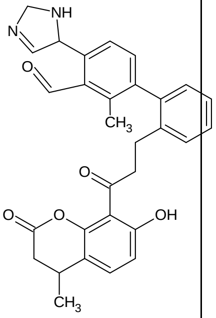
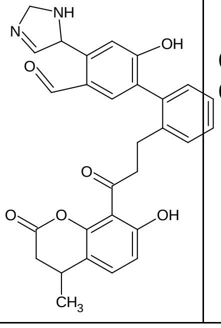
3	Imidazole orthochloro benzaldehyde 4-methyl -7-hydroxy coumarin		O=Cc1cc(c(Cl)cc1C1C=NCN1)c1ccccc1CCC(=O)c1c(O)ccc2c1OC(=O)CC2C
4	Imidazole substituted parachlorobenzaldehyde 4-methyl -7-hydroxy coumarin		O=Cc1cc(c(Cl)cc1C1C=NCN1)c1ccccc1CCC(=O)c1c(O)ccc2c1OC(=O)CC2C
5	Imidazole 4-methylbenzaldehyde 4-methyl -7-hydroxy coumarin		O=Cc1cc(c(C)cc1C1C=NCN1)c1ccccc1CCC(=O)c1c(O)ccc2c1OC(=O)CC2C
6	Imidazole substituted 2-methylbenzaldehyde 4-methyl -7-hydroxy coumarin		O=Cc1c(ccc(c1C)c1ccccc1CCC(=O)c1c(O)ccc2c1OC(=O)CC2C)C1C=NCN1
7	Imidazole substituted 4-hydroxybenzaldehyde 4-methyl -7-hydroxy coumarin		O=Cc1cc(c(O)cc1C1C=NCN1)c1ccccc1CCC(=O)c1c(O)ccc2c1OC(=O)CC2C

Table 2 MOLINSPIRATION of designed Compounds

Compound	**MilogP**	**TPSA Å**	**N Atom**	**Molecular Weight**	**No. of violation**	**No Of rotatable bonds**	**Volume**
4A	2.44	125.29	37	498.54	0	7	440.23
4B	2.15	135.52	38	446.67	0	7	448.25
4C	3.34	105.07	38	478.27	0	7	445.75
4D	3.34	105.07	38	478.27	0	7	445.75
4E	3.11	105.07	37	496.56	0	7	448.78
4F	3.11	105.07	37	496.56	0	7	448.78
4G	2.44	125.29	37	498.54	0	7	440.23

Table 3 SWISS ADME Results

Compound No	**Lipinski**	**Ghose**	**Veber**	**Egan**	**Muegge**	**Bioavailability score**	**GI absorption**	**BBB permeation**	**P-gp substrate**	**Log kP cm/s**	**Synthetic accessibility score**
4A	Yes	No	Yes	Yes	Yes	0.55	High	No	Yes	-6.56 cm/s	4.80
4B	Yes	No	Yes	Yes	Yes	0.55	Low	No	Yes	-7.31 cm/s	4.94
4C	Yes	No	Yes	Yes	Yes	0.55	Low	No	Yes	-7.31 cm/s	4.94
4D	Yes	No	Yes	Yes	Yes	0.55	High	No	Yes	-6.37 cm/s	4.79
4E	Yes	No	Yes	Yes	Yes	0.55	High	No	Yes	-6.37 cm/s	4.79
4F	Yes	No	Yes	Yes	Yes	0.55	High	No	Yes	-6.43 cm/s	4.84
4G	Yes	No	Yes	Yes	Yes	0.55	High	No	Yes	-6.56 cm/s	4.80

Table 4 PROTOXII Analysis

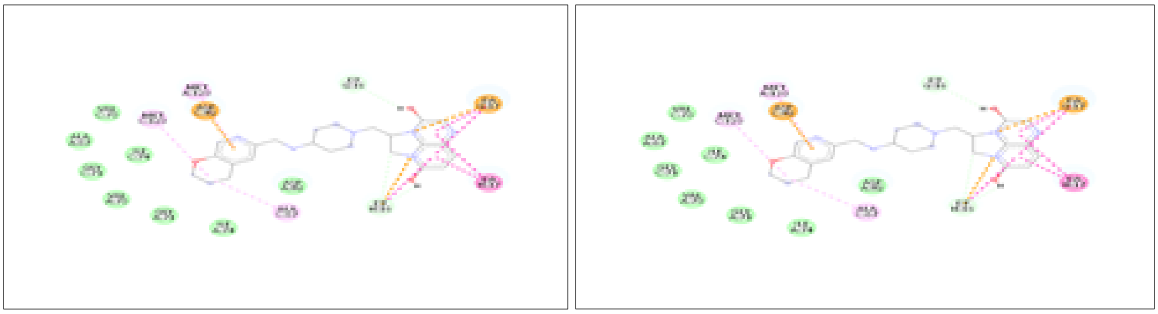
Compound No	**Predicted LD50 mg/kg**	**Predicted toxicity class**	**Carcinogenicity**	**Hepatotoxicity**	**Mutagenicity**	**Cytotoxicity**
4A	5000mg/kg	4	Inactive 0.72	Inactive 0.50	Inactive 0.59	Inactive 0.64
4B	5000mg/kg	4	Inactive 0.72	Inactive 0.51	Inactive 0.57	Inactive 0.64

4C	5000mg/kg	4	Inactive 0.72	Inactive	Inactive	Inactive
4D	5000mg/kg	4	Inactive 0.72	Inactive	Inactive	Inactive
4E	4000mg/kg	4	Inactive 0.72	Inactive 0.50	Inactive 0.59	Inactive 0.63
4F	4800mg/kg	4	Inactive 0.72	Inactive 0.50	Inactive 0.59	Inactive 0.64
4G	5000mg/kg	4	Inactive 0.72	Inactive 0.50	Inactive 0.59	Inactive 0.64

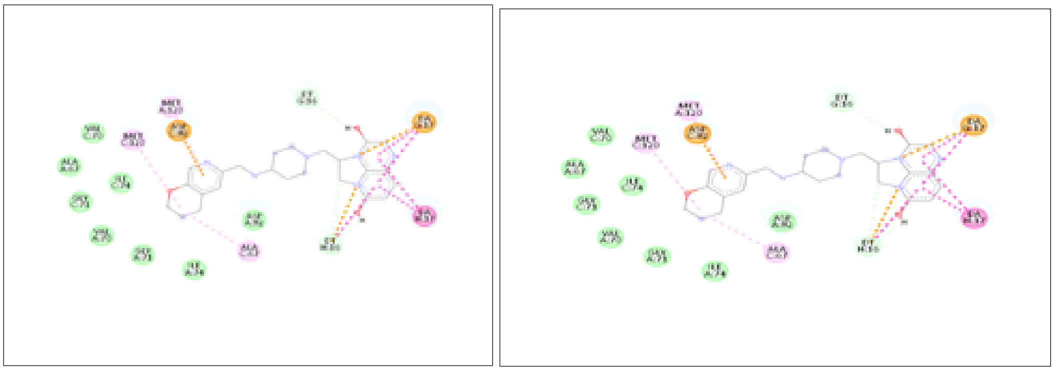
Table 5 Ligand Against Target Enzyme COX I

S. NO	Compound No	Docking score Kcal/mol	Amino acid interaction with Distance
1	4A	-9	ARG76-3.074 THR165-2.42 ASP73-2.22 ASP49-4.536 PRO79-4.93
2	4B	-8.8	ASN46-2.94 GLY77-2.56 ASP49-2.54 GLU50-2.04
3	4C	-8.1	ARG76-2.77 THR165-2.34 ASN46-2.48 ASP49-4.55
4	4D	-8.8	ARG76-2.78 THR:165-2.32 ASN46-2.68
5	4E	-9.1	ARG76-3.074 THR165-2.42 ASP73-2.22 ASP49-4.536 PRO79-4.93
6	4F	-8.2	ARG76-3.074 THR165-2.42 ASP73-2.22 ASP49-4.536 PRO79-4.93
7	4G	-9.3	ARG76-3.074 THR165-2.42 ASP73-2.22

			ASP49-4.536 PRO79-4.93



Comp 4A **Comp 4B**



Comp 4C **Comp 4D**

Figure 4 Molecular docking (Ligand against Target Enzyme)

3.2. Spectral Characterisation

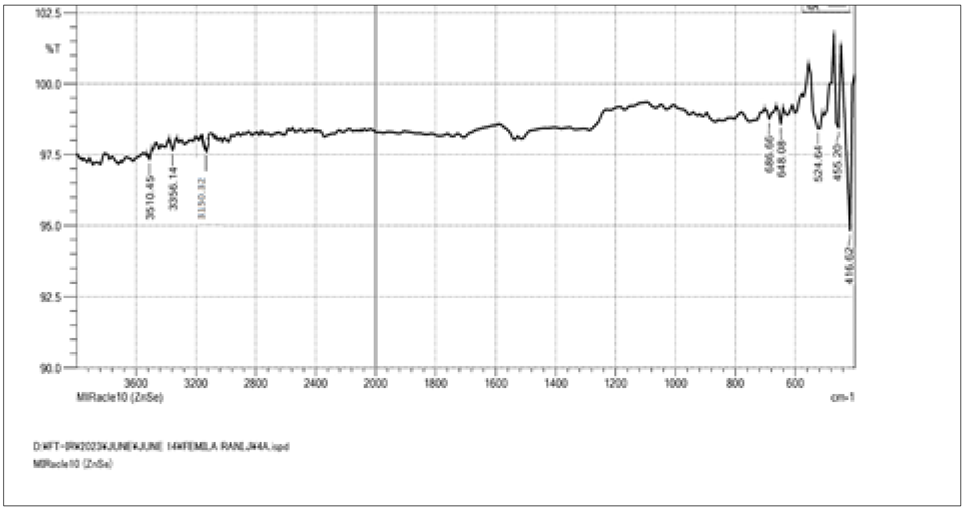


Figure 5 a IR Spectra for Compound 4A

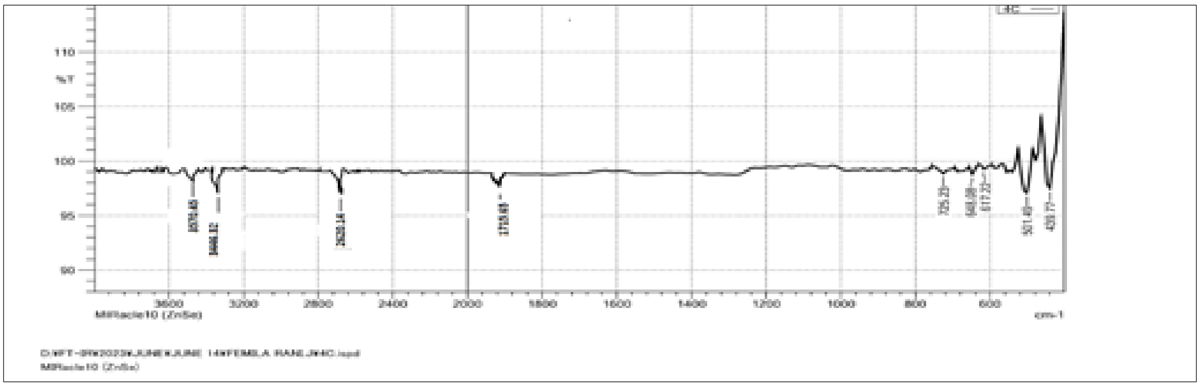


Figure 5 b IR Spectra for Compound 4B

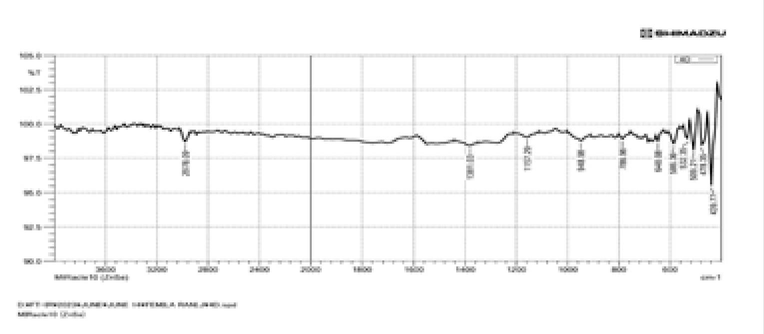


Figure 5 c IR Spectra of Compound 4C

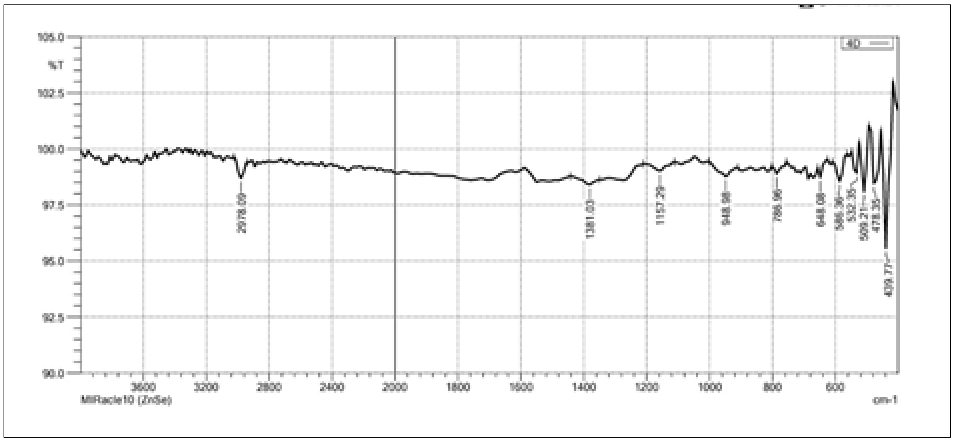


Figure 5 d IR Spectra of Compound 4D

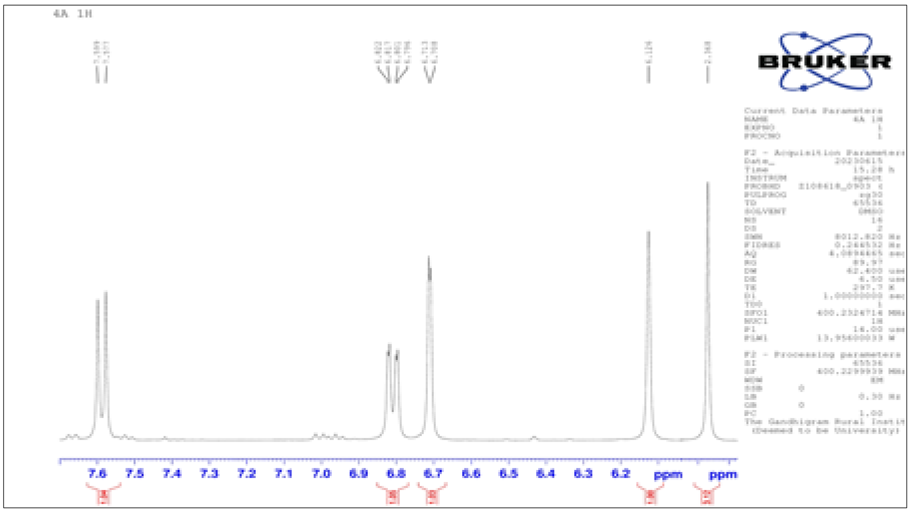


Figure 6 a ^{1}H NMR Spectrum of Compound 4A

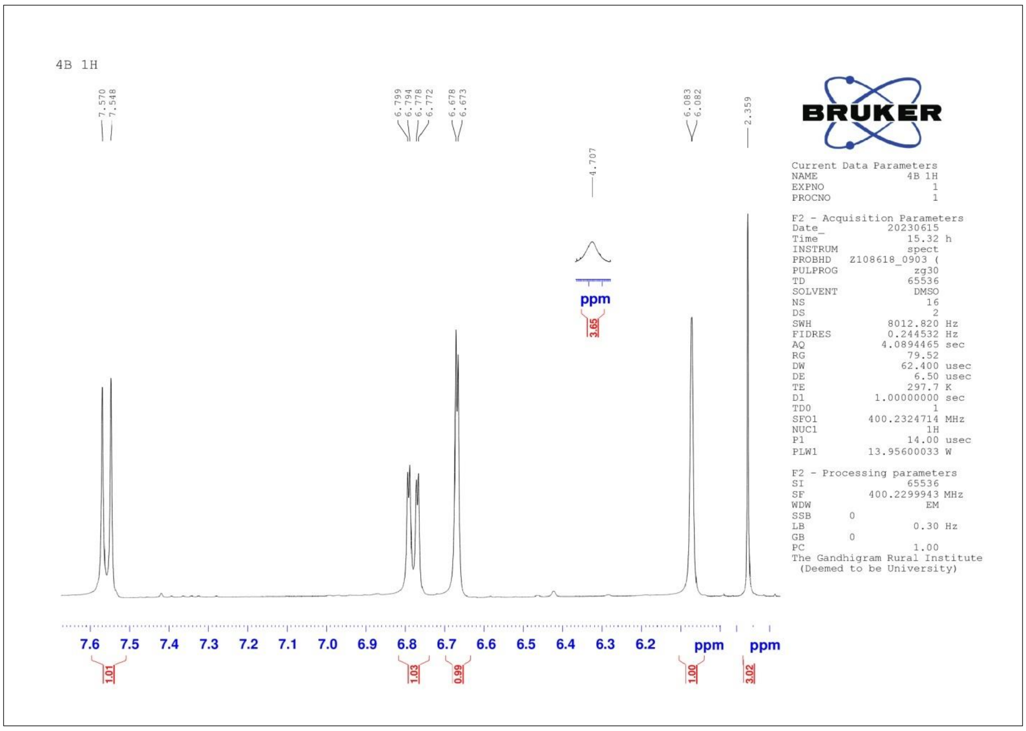


Figure 6 b^{1}H NMR Spectrum of Compound 4B

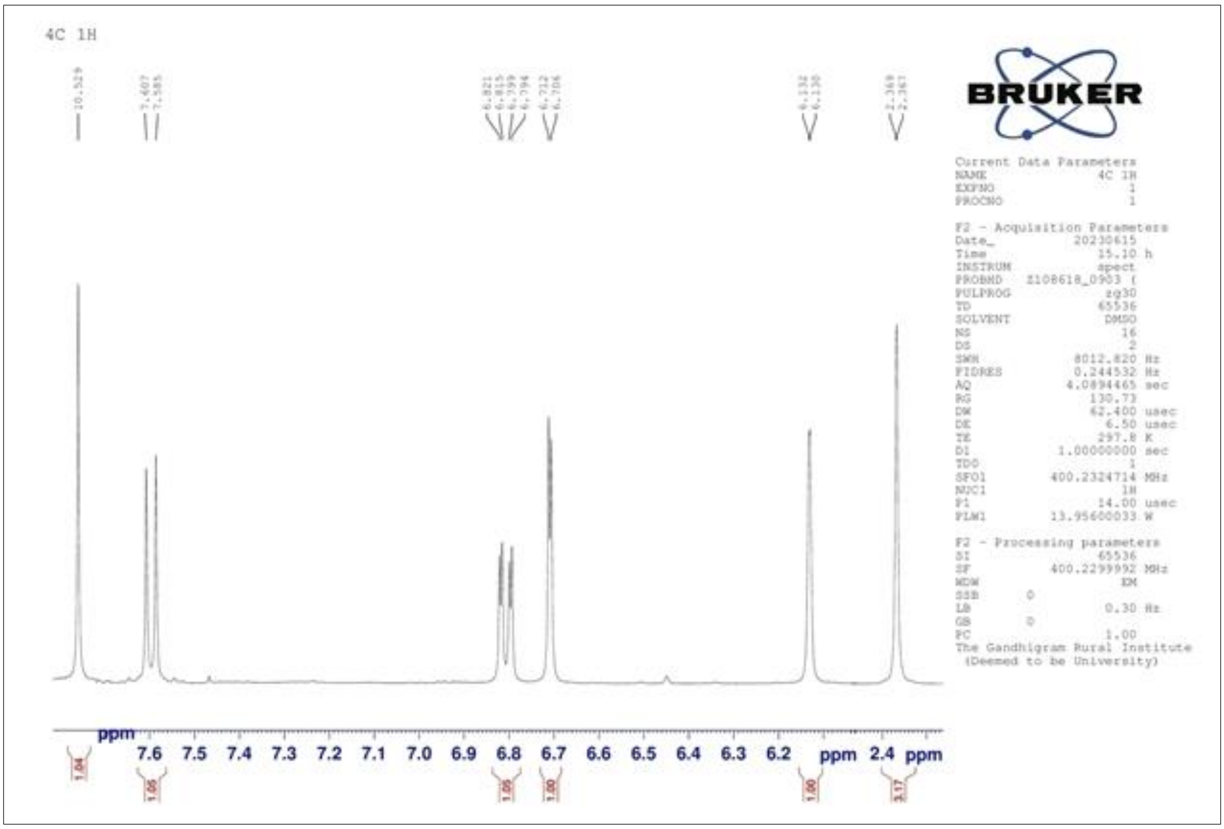


Figure 6 c ^{1}H NMR Spectrum of Compound 4C

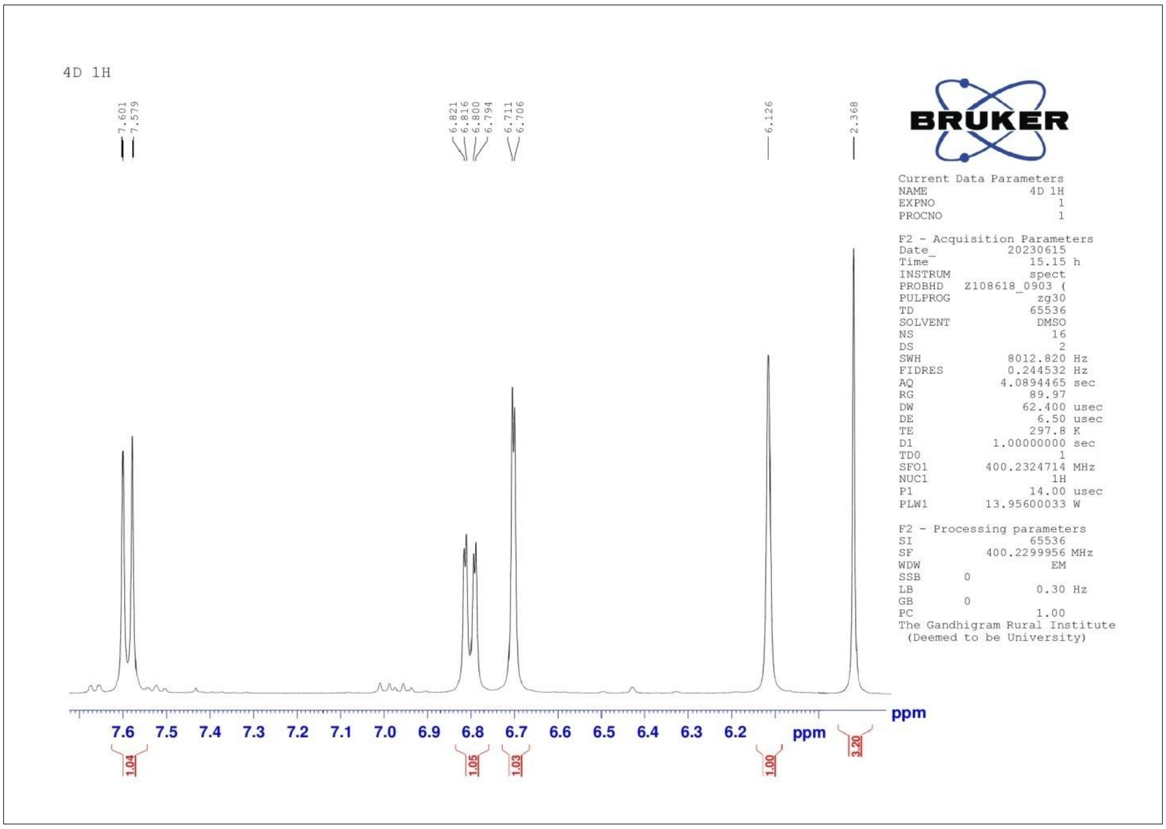


Figure 6 d ^{1}H NMR Spectrum of Compound 4D

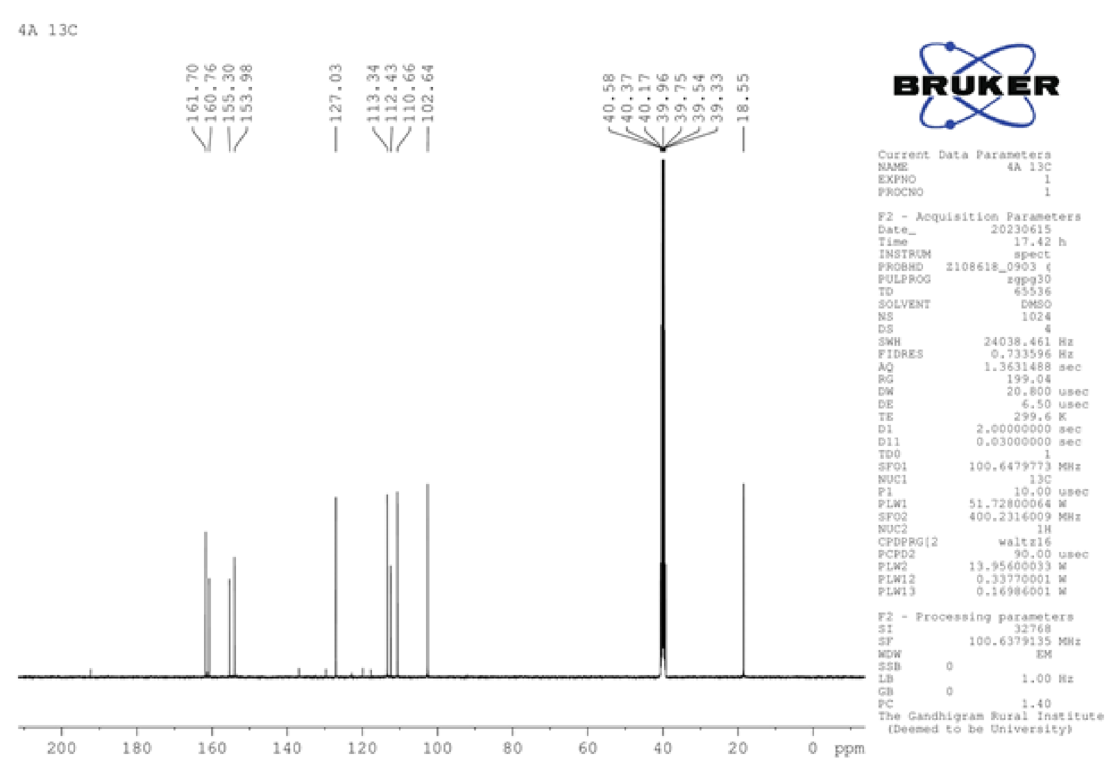


Figure 7 a ^{13}C NMR spectrum of compound 4A

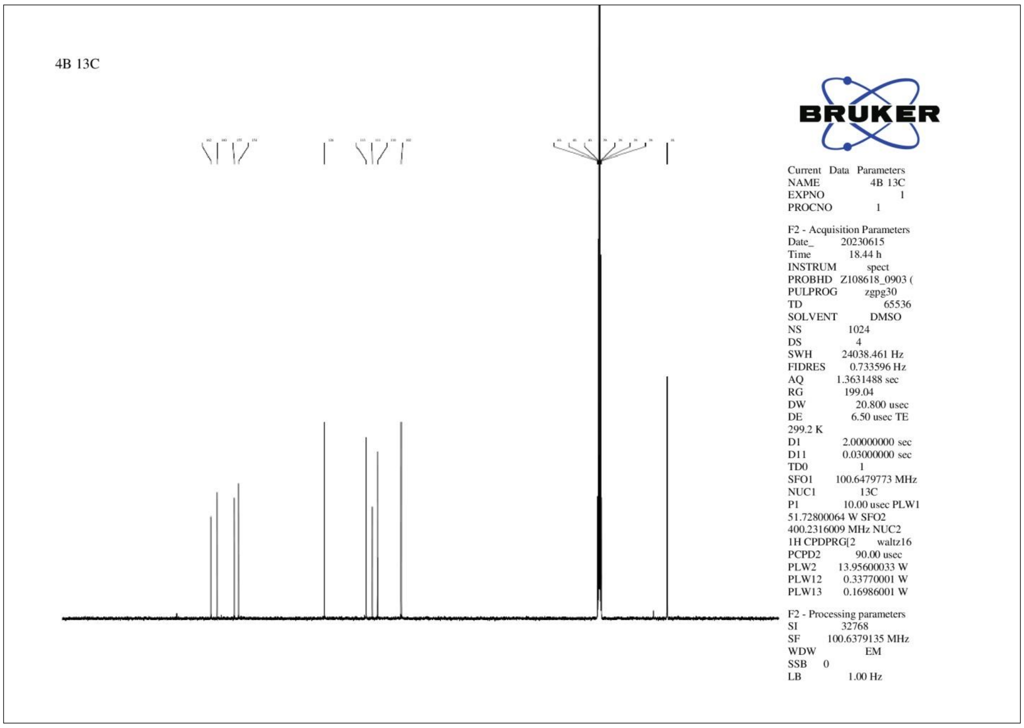


Figure 7 b ^{13}C NMR spectrum of compound 4B

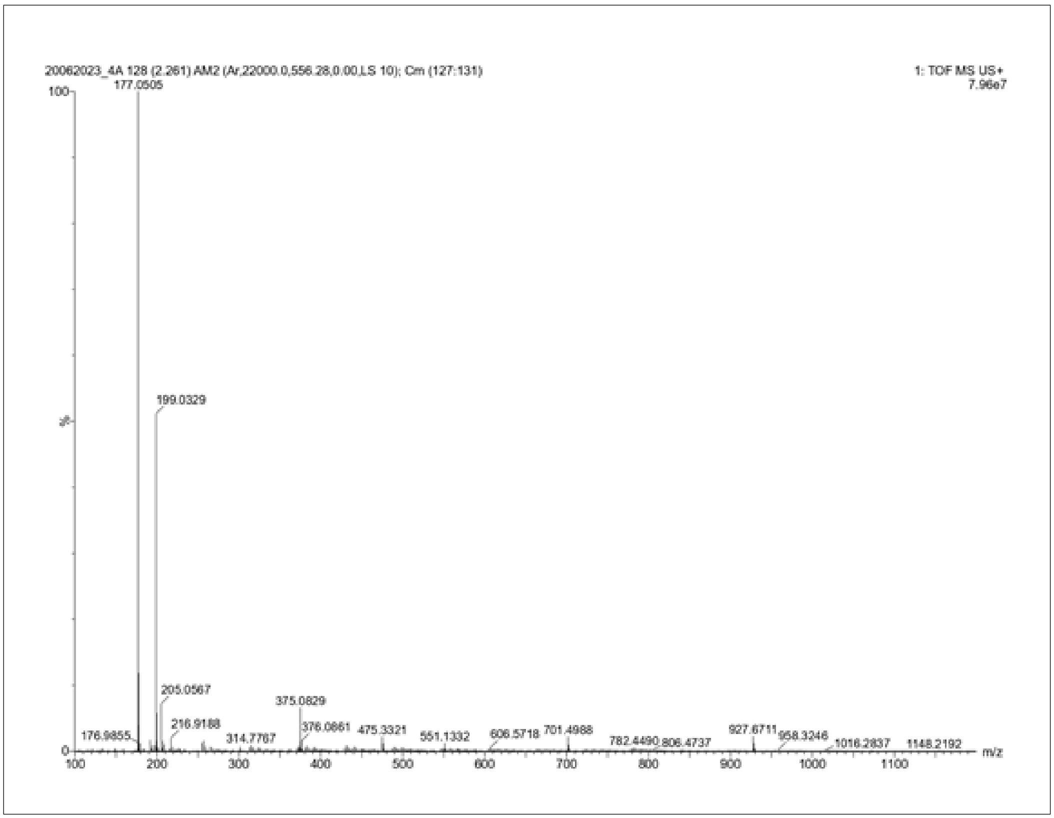


Figure 8 Mass Spectrum of Compound 4A

4. Discussion

Several crucial parameters governing drug likeness were assessed for the designed compounds. Firstly, Total Polar Surface Area (TPSA) is a good indicator of intestinal absorption, with values around 140 Å^2 typically associated with good absorption. In our designed compounds, the TPSA ranged from 79.60 to 122.37 Å^2, falling slightly below the optimal range but still within acceptable limits. In addition, drug candidates should have molecular weights between 160 and 480. It appears that our compounds are similar to drugs in terms of their molecular weights, which indicates favourable drug likeness. As well, the calculated logarithm of the partition coefficient (log P) is considered to be an important factor in determining lipophilicity and membrane permeability, with a value between -0.4 and 5.6 considered ideal. This optimal concentration range for log P values was demonstrated by our designed compounds. There were no violations observed in any of the compound designs, indicating their overall conformity to important drug likeness criteria. As a result of these findings, the designed compounds seem to have favorable properties for potential drug development, including features that are conducive to effective absorption and bioavailability. In order to determine whether a compound will be effective for human oral bioavailability, Lipinski's five-factor rule is applied. According to Lipinski's rule, a compound has fewer than five hydrogen bond donors and has a molecular weight less than 500, an exponent of the partition coefficient (log P) less than 5, as well as a logarithm less than 5. The compound log P value is within a reasonable range and the calculated log S value exceeds -4, as determined by the Ghose filter. Additionally, all designed compounds comply with Lipinski's rule when it comes to gastrointestinal absorption. Based on these findings, the compounds may be able to deliver and absorb drugs effectively orally in the body. Additionally, the compounds satisfy the criteria of the Veber filter, with a maximum number of rotatable bonds and a polar surface area below 140 Å^2, further supporting their potential as orally active drugs. Additionally, the compounds' suitability for cellular permeation and drug optimization are enhanced by adhering to the Egan rule and having appropriate topological polar surface areas (TPSA) and log P values. A study has been shown that it is possible to synthesize certain important coumarins using a mixture of 1-butyl pyridinium chloroaluminate ionic liquid and also indium chloride in good yields [13]. By coupling various phenolics with ketoesters in an acidic medium, some of the most important industrially important coumarins such as the 7-hydroxy-4-methylcoumarin can be obtained via the Pechmann reaction. A docking study was conducted using Pyrx to assess ligand-protein interactions with the active sites of COX-1 and COX-2 (PDB ID: 1U67), downloaded from RCSB. Validation was based on the co-crystallization structure of the protein complexed with CWW. Its high predicted activity is attributed to strong hydrogen-bond interactions with certain amino acids (ARGA:76, GLUA:50, AspA:73, THRA:165). A potential activity was also indicated by the interactions of ligand 3h and 4E with key amino acids. As a result of their hydrogen bonding relationships with specific amino acids (ARGA:76, ASP:49, GLYA:77, THRA:165, ASNA :46), ligands 4A, 4B, 4C, and 4D showed similar interactions and predicted activities against COX-1 and COX-2. The design of the ligands suggests that these compounds may be effective antibacterial agents. The docking approach is a method that is used to predict the preferred orientation of molecules when they are bound together to form stable complexes [14]. This tool provides useful information pertaining to the affinity of a ligand with a protein target by analyzing the molecular docking of the ligand. To carry out the docking analysis, study used Auto Dock Vina under PyRx through the use of Auto Dock Vina. Based on E value (Kcal/mol), docked poses of ligands and targets were found to exhibit the highest affinity. For docked ligands, a binding constant and free energy prediction is provided by the algorithm [15,16]. A variety of analytical techniques were used to characterize the synthesized compounds, which included the use of infrared spectroscopy (IR), proton nuclear magnetic resonance spectroscopy (1H NMR), mass spectrometry (MS), and elemental analysis. According to the IR spectra, the compounds exhibit characteristic stretching vibrations within specific frequency ranges, specifically between 375.85 and 3410 cm-1, between 3320 and 3140 cm-1, and between 3200-3050 cm-1. The presence of a CH2 group within the molecules was also attributed to an absorption peak at 1396 cm-1. According to mass spectrometry, the synthesized compounds have a molecular mass of 145 (100%), which is compatible with the expected molecular mass. Detailed characterization of the synthetic compounds facilitates further understanding of their properties and potential uses by providing valuable information about their structure and integrity.

4.1. 4-METHYL-7-HYDROXY COUMARIN -2 HYDROXY BENZALDEHYDE IMIDAZOLEIMMIDAZOLE -2- HYDROXY BENZALDEHYDE COUMARIN [4A]:

Benzaldehyde was prepared by condensation for one hour to yield a dark-brown mixture with a yield of 79.6%. The melting point was recorded at between 184 and 185°C. Infrared analysis (KBr, cm-1) revealed characteristic peaks at 3550.45 (aromatic OH stretching), 3356.14 (aromatic N-H stretching), 3150.32 (aromatic C-H stretching), and 686.66 (aromatic C-H bending). 1H NMR spectroscopy exhibited signals at δ 2.368 (3H, s), 6.817 (1H, s), 6.713 (1H, s), 7.599 (1H, d, J = 8.4 Hz), 7.577 (1H, d, J = 8.4 Hz), 6.70 (1H, s), and 6.126 (1H, s). Additionally, 13C NMR spectroscopy displayed signals at δ 39.96, 39.75, 39.54, 40.58, 40.37, 113.34, 112.43, 110.66, 153.98, 155.30, 160.76, and 161.70. This analysis provides comprehensive details about the synthesized sample, allowing for further investigation.

4.2. 4-METHYL-7-HYDROXY COUMARIN 4- HYDROXY BENZALDEHYDE IMIDAZOLE IMMIDAZOLE 4 -HYDROXY BENZALDEHYDE COUMARIN [4B]:

83.5% of the benzaldehyde was converted to a dark-brown mixture after condensation for an hour. The melting point was determined to be within the range of 178-182°C. FT-IR analysis (KBr, cm-1) exhibited characteristic peaks at 3842.20 (aromatic OH stretching), 3718.76 (aromatic OH stretching), 3338.64 (N-H stretching), 2978.09 (C-H stretching), 1527.62 (N-H bending), 14527.62 (C=C stretching), and 725.23 (C-H bending). The 1H NMR spectrum displayed signals at δ 2.359 (3H, s), 4.707 (3H, s), 6.083 (1H, s), 6.673 (1H, s), 6.678 (1H, s), 6.794 (1H, s), 6.799 (1H, s), 7.548 (1H, d, J = 8.3 Hz), and 7.570 (1H, d, J = 8.3 Hz). The 13C NMR spectrum showed signals at δ 39.95, 39.74, 39.54, 40.58, 40.37, 40.16, 102.69, 113.74, 111.86, 110.11, 126.90, 154.05, 155.47, 160.90, and 162.89.

4.3. 4-METHYL-7-HYDROXY COUMARIN ORTHOCHLORO BENZALDEHYDE IMIDAZOLE IMIDAZOLE ORTHOCHLORO BENZALDEHYDE COUMARIN [4C]:

In the condensation of benzaldehyde for an hour, 81.5% yield was obtained as a brown mixture. According to our analysis, the melting point was between 176°C and 179°C. FT-IR analysis (KBr, cm-1) exhibited characteristic peaks at 3570.45 (aromatic OH stretching), 3446.32 (N-H stretching), 3060.57 (aromatic-C-H), 2620.14 (S-H stretching), 1715.65 (C=O stretching), and 725.23 (C-H bending). A 1H NMR spectrum displayed signal at δ 2.369 (1H, s), 6.130, 6.706, 6.712, 6.794, 6.799, 6.815, 6.821, 7.585, 7.607, and 10.529.

4.4. 4-METHYL-7-HYDROXY COUMARIN 4-METHYL BENZALDEHYDE IMIDAZOLEIMIDAZOLE 4-METHYL BENZALDEHYDE COUMARIN [4D]:

After condensation of benzaldehyde for one hour, a brown mixture was obtained with an 82.5% yield. Temperatures between 180°C and 181°C were observed as the melting point. FT-IR analysis (KBr, cm-1) revealed characteristic peaks at 3060.57 (aromatic C-H stretching), 2978.09 (C-H stretching), 1592.55 (N-H bending), 1381.03 (O-H bending), 1157.29 (C-O-C), 948.98 (C-S-C), and 748.96 (C-H bending). The 1H NMR spectrum exhibited signals at δ 2.368 (1H, s), 6.126 (3H, s), 6.706 (3H, s), 6.711 (3H, s), 6.80 (3H, s), 6.821 (3H, s), 7.599, and 7.601.

The major criteria for choosing Insilico tools include their user-friendliness, the type of output they provide (qualitative or quantitative), and the ease of interpretation of their results, as well as the study requirements of the user.

5. Conclusion

The designed compounds exhibit promising drug-like properties based on their adherence to key parameters such as Total Polar Surface Area (TPSA), molecular weight, and logarithmic P-values. In addition to showing potential for effective absorption and bioavailability, these compounds are also viable candidates for future drug development. As a result of docking studies performed using PyRx, favourable ligand-protein interactions were also detected, indicating that the targets of COX-1 and COX-2 may be therapeutically active. Various analytical techniques are used to establish the composition and structure of the synthesized compounds, providing valuable insight into their potential applications. Generally, these compounds are promising for pharmaceutical and industrial applications, paving the way for future research.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Declaration

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