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Synthesis and molecular docking studies of coumarin-imidazole conjugates as potential antimicrobial agents

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One-pot multi-component synthesis of tri and tetra-substituted coumarin-imidazole conjugates have been achieved in good to excellent yield under conventional and microwave methods in optimized catalyst condition. Further, they have been evaluated for antimicrobial activity against Gram positive *Bacillus flexus* and Gram negative *Pseudomonas Spp.* bacterial strains and two strains of fungi *Scopulariopsis spp.* and *Aspergillus tereus organisms*. The results of microbial activity are promising against tested organisms. The molecular docking study has been performed for all the compounds and docking scores are excellent. Synthesized compounds have been characterized by IR, NMR, mass and a few of them by single crystal X-ray analysis.

Keywords: Tetra-substituted, coumarin-imidazole, docking, crystal, biological activity

Imidazole ring system is known for active scaffold in biomolecules and is the integral part of some naturally occurring molecules such as histadine, histamines, amino acids, component of DNA base and Vit-B_{12}, *etc*. Generally, this class of compounds attracted importance towards inhibitory activities against p38α[1]. cyclooxygenase-2[2], transfer growth factor β1 (TGF-β1), type I active receptor like kinase[3], and also against biosynthesis of inter-leukine-I[4]. Imidazole derivative also exhibit wide range of biological activities such as fungicides, herbicides[5], plant growth regulators[6] and therapeutic agents[7]. The N-substituted imidazoles are class of heterocyclic scaffolds having important pharmacological properties such as antimicrobial[8-10], antiparasitic[11], antimalarial[12], antihistaminic[13], anti-inflammatory[14], analgesic[15], antitubercular[16], antiprotozoal[17] and anthelmintics[18]. On the other hand imidazole nucleus is essential moiety for the most ionic liquids[19], chiral auxiliaries[20,21] and chiral ligands[22-24].

Natural products exhibit several biological activities that can be of therapeutic actions in treatment of various diseases. Coumarin is one of such natural product which has been isolated from a variety of plant sources to assess their potential therapeutic uses[25]. Thus, the biological investigation of coumarin derivatives shows the engrossment of several path ways by which it showed several biological activities including: anticancer[26,27], anti-HIV[28,29], anticoagulant[30], antimicrobial[31], antioxidant[32] and anti-inflammatory[33] activities. Recently, many conjugate molecules with coumarin ring system have been designed and synthesized. In this line the coumarin derivatives conjugated with nitrogen containing heterocyclic moieties, such as triazolo and pyridine were synthesized and these hybrids proved to possess antibacterial and antifungal activities[34,35]. The promising therapeutic perspectives of both the heterocycles, we have considered molecular hybridization strategy for the synthesis of target compounds.

In this article we have developed a simple, efficient and general method for the synthesis of coumarin conjugate structures under conventional as well as microwave (MW) methods and carried out pharmacological activities as well as molecular docking study.

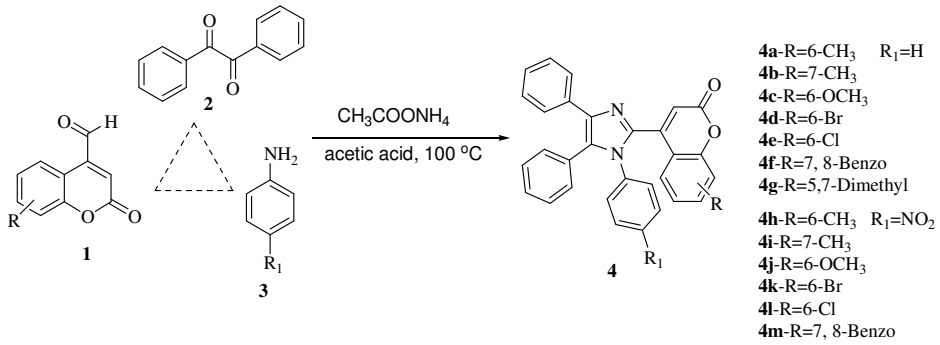
Results and Discussion

Chemistry

In literature there are many synthetic methods for the synthesis of imidazoles, among these microwave assisted method has driven considerable much attention[36,37]. The C-4 position of coumarin ring bearing five membered imidazole derivatives are not available in the literature. Here, we have designed and synthesized C4-coumarin directly linked with C2-imidazole *via* multi-component reaction. The synthetic strategy followed for the synthesis of coumarin-imidazole conjugates are out lined in Scheme I. Reaction of 4-formylcoumarins **1**[38], 1, 2-diketone **2**, substituted anilines **3** with ammonium acetate in presence of acid catalysts to furnished desired coumarin-imidazole conjugates **4a-m** in good yield (>65%) under conventional as well as microwave methods. Among two methods, MW method afforded excellent results in terms of yield and time. Further, the reaction was performed in different solvents and catalysts to optimize the condition to afford compound **4**. The optimization results have shown that acetic acid alone as catalyst and solvent afforded excellent yield as well as purity (Table I). Similarly, compounds **6a-f** were synthesized by using above optimized reaction condition in good to excellent yield and synthetic pathway is outlined in Scheme II. Further, compounds **6a-f** were converted to corresponding esters **7a-f** by the reaction of methanol in sulphuric acid. Structures of all the synthesized compounds **4a-m**, **6a-f** and **7a-f** given in Table II confirmed by spectral analysis and some of them by single X-ray crystal study.

X-ray diffraction studies

The two coumarin imidazole hybrids single crystals **4b** (Figure 1) and **7f** (Figure 2) were grown in dichloromethane (DCM). The crystals of suitable quality were mounted in glass capillaries, cooled to 0 and 100 K. The intensity data were collected on a Bruker Nonius SMART APEX CCD detector system with Mo-sealed Siemens ceramic diffraction tube (λ = 0.71073) and a highly oriented graphite monochromator operating at 50 kV and 30 mA. The data was collected on a hemisphere mode and processed with SAINT-Plus, while the empirical absorption corrections were made using SADABS[39]. The structures were solved by direct method using

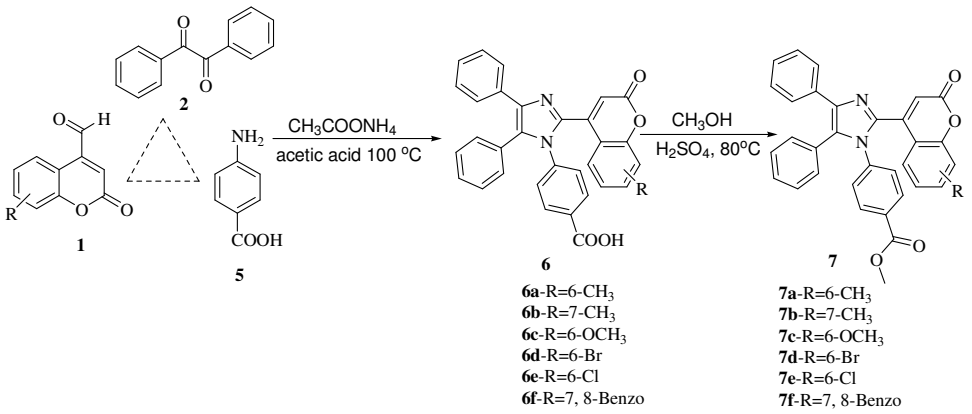


Scheme I — Synthesis of coumarin conjugates **4a-m**

Table I — Optimized condition for the synthesis of compound **4a**

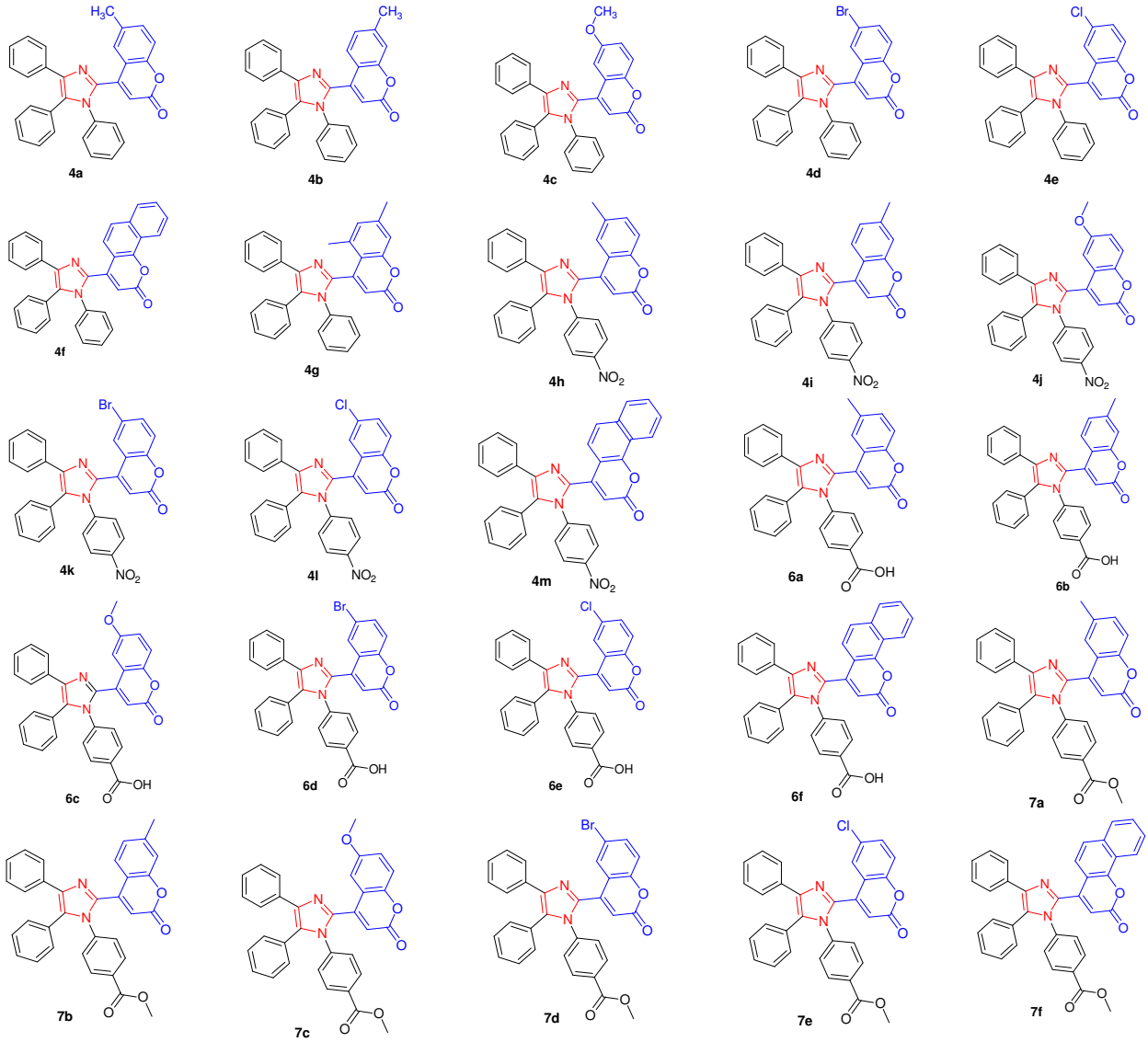
Entry	Catalysts	Solvent	Ratio	Conventional			Microwave		
				Temp. (°C)	Time (h)	Yield (%)	Temp. (°C)	Time (min)	Yield (%)[a]
1	Acetic acid	Ethanol	1:1	80	8	55	70	5	83
2	Acetic acid	PEG-400	1:2	100	8	62	120	5	78
3	Acetic acid	DMF	1:1	80	8	64	100	5	85
4	Acetic acid	Acetic acid	–	90	8	85	100	5	93
5	Silica H_2SO_4	Ethanol	1:1	80	5	54	70	4	69
6	Silica H_2SO_4	PEG-400	1:2	100	5	60	120	4	75
7	Silica H_2SO_4	DMF	1:1	80	5	62	100	3	75
8	Zinc Oxide	Ethanol	2:1	110	8	45	100	6	56
9	Zinc Oxide	PEG-400	2:2	120	8	52	120	6	60
10	Zinc Oxide	DMF	2:1	100	8	55	100	6	55

[a]Isolated yields



Scheme II — Synthesis of coumarin conjugates **6a-f** and **7a-f**

Table II — Synthesized coumarin-imidazole conjugates **4a-m**, **6a-f** and **7a-f**



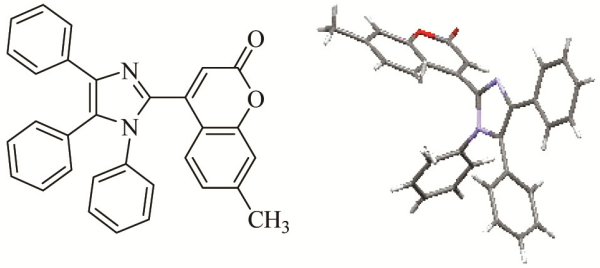


Figure 1 — ORTEP diagram of compound **4b**

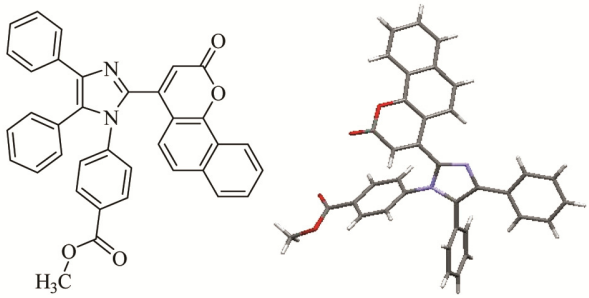


Figure 2 — ORTEP diagram of compound **7f**

SHELXTL package and refined by full matrix least-squares method based on F^2 using SHELX97 program[40]. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the ideal positions with fixed isotropic U values and were riding with their respective non-hydrogen atoms.

Substitution on the coumarin ring may affect the molecular arrangement of coumarin imidazole conjugates because of the steric repulsion. The coumarin is planar but exhibits slightly wave deformation. In particular compound **4b** structure is found in triclinic setting, space group P-1, with Z=8. Its asymmetric unit contains a coumarin ring, imidazole and two phenyl groups. As shown in Figure 1 and Figure 2, three phenyl groups are oriented in slightly perpendicular geometry. Similarly, structure **7f** is found in the monoclinic setting, space group P121/c1, with Z=4.Crystal data and structure refinement parameters of compounds **4b** and **7f** are summarized in Table III.

Table III — The crystal data and structure refinement parameters of compounds **4b** and **7f**

Compd	**4b**	**7f**
Formula	$C_{31}H_{22}N_2O_2$	$C_{36}H_{24}N_2O_4$
M	454	548.59
T/K	296(2) K	296(2) K
Crystal system	triclinic	monoclinic
Space group	P -1	P 1 21/c 1
a/Å	14.4026(3)	12.8057(4)
b/Å	18.2380(4)	28.4281(10)
c/Å	19.8452(5)	7.9865(3)
α/(°)	93.9030(10)	90°
β/(°)	110.3220(10)	101.402(2)°
γ/(°)	99.9650(10)	90°
V/Å^3	4768.03(19)	2850.04(17)
Z, *d*calcd /(g cm^{-3})	8, 1.207	4, 1.281 Mg/cm^3
μ/mm^{-1}	0.077	0.084
F(000)	1736	1148
θ range/(°)	1.14 to 26.18	1.43 to 30.15°
Index ranges	−17<=h<=17	−17<=h<=15
	−22<=k<=22	−39<=k<=37
	−24<=l<=24	−10<=l<=11
Reflections collected	70762	31805
Independent	70762	31805
Completeness	98.45%	97.6%
Data/restraints/parameters	18968 / 0 / 1266	8228 / 0 / 381
Goodness-of-fit onF^2	0.848	0.683
R1, *wR2* [*I*>2*σ*(*I*)]	0.0471, 0.1492	R1 = 0.0564,wR2 = 0.1203
R1, *wR2* (all data)	0.1545, 0.2418	R1 = 0.2088,wR2 = 0.1506
Largest diff. peak,hole/ (e A^{-3})	0.234, −0.157 eÅ^{-3}	d −0.238

Biological Screening

Antimicrobial Activity

Coumarin and imidazole derivatives are promising target compounds for antibacterial as well antifungal activity. Thus, all the synthesized scaffolds **4a-m**, **6a-f** and **7a-f** were screened for their antibacterial activity against Gram positive *Bacillus flexus* and Gram negative *Pseudomonas Spp.* bacterial strains. Similarly, two strains of fungi *Scopulariopsis spp*. and *Aspergillustereus via* agar well diffusion method.*Ciprofloxacin* and *Nystatin* are most effective antimicrobial agents and were used as reference drugs. All the strains were incubated at 37°C for about 48 h by inoculation into nutrient broth (Difco). The molten nutrient agar was inoculated with 100 µL of the inoculums and poured into the petri plate. The diameter of inhibition zones (in mm) was determined and MIC of the tested compounds was statistically determined by Turkey's fair wise test. A stock solution of the newly synthesized compounds in DMSO was prepared and incorporated in sterilized liquid medium. After medium was solidified, a well was made in the plates with the help of cup-borer (0.85 cm) after 48 h.

SAR Study

Several important structural features of coumarin and imidazole derivatives are identified and constructed as coumarin-imidazole skeleton. The various substituent's on coumarin exhibits better antimicrobial activity as a result the SAR study was deduced by scrutinizing their results.

Antibacterial Assay

Imidazole nucleus at C-4 position of the coumarin conjugates **4a-m** were screened for their antibacterial activity. The MIC results (Table IV) indicated that most of the compounds exhibited promising activity against both bacterial strains. Compounds **4a-g** having N-1-phenyl substation on imidazole and different substitution on coumarin nucleus showed excellent antibacterial activity with MIC values 0.1 to 0.4 µg/mL, except compound **4b** (C7 methyl group substitution on coumarin nucleus) have not exhibited activity at a selected standard MIC values. Whereas, in the case of nitrobenzene substitution on N-1 imidazoles **4h-m** have exhibited higher activity at selected standard MIC. The structural modification on N-1 of imidazoles that is N-1-benzoic acid – imidazolo-coumarins **6a-f** was screened for their antibacterial activity. The results showed slight decrease in the antibacterial activity against both bacterial strains.

Further, N-benzoic acid imidazolo-coumarin conjugates **6a-f** were converted into corresponding methyl esters pharmacophores **7a-f**. The results obtained are discussed in Table IV; it reveals the improvements in their active compared to compounds **6a-f**. Thus, the comparative evidence of the all series, compounds **7a-f** showed promising antibacterial activity against Gram positive and Gram negative bacterial strains at low concentrations. The brief antibacterial study is drawn in Figure 3.

Table IV — *In vitro* anti-microbial activity of compounds **4a-g**, **4h-m**, **6a-f** and **7a-f**

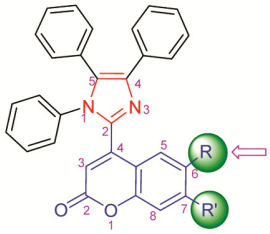
Compd	Minimum inhibitory concentration (MIC) in µg/mL			
	Gram +ve	Gram –ve	Antifungal	
	B. flexus	*P. Spp.*	*S. spp.*	*A. tereus*
4a	0.1	0.1	0.2	0.2
4b	–	–	–	–
4c	0.1	0.1	0.2	0.2
4d	0.2	0.2	0.4	0.4
4e	0.2	0.2	0.1	0.1
4f	0.1	0.1	0.2	0.2
4g	0.4	0.4	0.1	0.2
4h	–	–	–	–
4i	0.7	0.7	0.1	0.1
4j	0.5	0.4	0.4	0.2
4k	0.6	0.6	–	–
4l	0.5	0.5	0.3	0.3
4m	0.2	0.2	0.3	0.3
6a	0.4	0.4	0.1	0.2
6b	0.2	0.1	0.4	0.4
6c	0.1	0.1	–	–
6d	–	–	–	0.2
6e	0.4	0.4	0.1	0.2
6f	–	–	0.2	0.2
7a	0.2	0.2	03	02
7b	0.1	0.1	0.1	0.2
7c	0.2	0.1	0.2	0.2
7d	0.2	0.1	0.2	0.2
7e	0.2	0.1	0.1	0.2
7f	0.2	0.1	0.2	0.1
Ciprofloxacin	0.7	0.7	–	–
Nystatin	–	–	0.7	0.7

Antifungal Assay

All the synthesized compounds **4a-g**, **4h-m**, **6a-f** and **7a-f** were screened for their antifungal activity against *Scopulariopsis spp*. and *Aspergillustereu*s organisms. The results obtained are summarized in Table IV, which indicates that all the compounds are excellent antifungal agents and the antifungal results are very similar to antibacterial activity results. The brief antifungal study is drawn in Figure 3.

Imidazole -N-phenyl group with various substitutions on coumarin ring **4a-g.** Introducing an electron withdrawing nitro group on *para*-position of N-1-phenyl ring and various substitutions on coumarin nucleus **4h-m** and in the case of COOH and $COOCH_3$ as electron withdrawing groups on N-1 of compounds **6a-f** and **7a-f** led to following antibacterial and antifungal structure activity relationship (SAR).

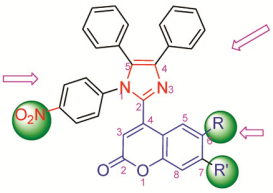
The SAR study reveals that, in the series **4a-g**, compounds **4b** (R^1 =CH_3, R= H) N-1-phenyl substitution is found to be inactive, while introducing an electron withdrawing groups (EWGs) of the series **4h-m**, **6a-f** and **7a-f**: such as NO_2 (**4i**), COOH (**6b**) and $COOCH_3$ (**7b**) on N-1-phenyl ring at *para*-position displayed promising antibacterial and fungal activity. This indicates that coumarin nucleus with C7 substitution and EWGs on N-1-phenyl ring at *para*-position is necessary.



Substituent R= CH_3, OCH_3, Cl and Br (R'=H) are found to be highly active against tested bacterial and fungal strains. C7-C8 benzo and C5, C7-dimethy substitutions also exhibited excellent activity.

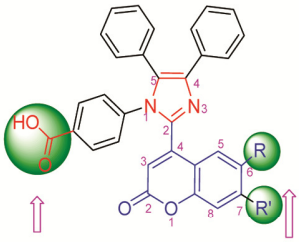
R= H and R' = CH_3 is found to be inactive against tested bacterial and fungal strains.

R = Br (R' = H) is found to be inactive against both tested bacterial strains and S.spp fungal strain, while active against A. tereus fungal strain.

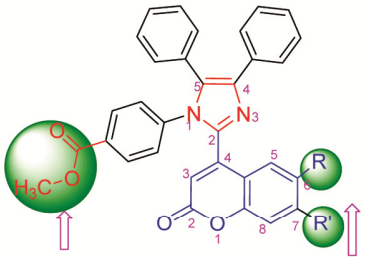


R= CH_3, Cl (R' = H) and R' = CH_3 (R =H) are found to be active against both tested fungal and bacterial strain.

R = OCH_3 (R' = H) is active against both bacterial strains while inactive against both fungal strains. Similarly, C7-C8 benzo substitution on coumarin is found to be inactive against both tested bacterial stains, but active against tested both fungal strains.



R = CH_3 (R' = H) (6a) is found to be inactive against both bacterial and fungal strains. Whereas, R = OCH_3, Cl (R' =H) and C7-C8 benzo showed promising antibacterial and antifungal activity against tested bacterial and fungal strains. But R = Br (R' = H) is found to be active against bacterial strains, while inactive against fungal strains. R' = CH_3 (R = H) showed antibacterial and antifungal activity.



R = CH_3, OCH_3, Br, Cl (R' = H) and R'= CH_3 (R = H) exhibited higher activity against both tested bacterial and fungal strains compared to 6a-f series. Whereas, C7-C8 benzo substitution is also found to be active against bacterial and fungal strains.

Figure 3 — Antibacterial and antifungal SAR study of coumarin-imidazole conjugates

Docking Study

The crystal structures used were *Aspergillus fumigates N*-myristoyltransferase in complex with myristoyl CoA and pyrazolesulphonamide ligand (PDB ID: 4CAW; A-Chain) and *Candida albicans* dihydrofolatereductase (PDB ID: 1AI9) was obtained from the Protein Data Bank. The proteins were prepared for docking by adding polar hydrogen atom with Gasteiger-Huckel charges and water molecules were removed. The 3D structure of the ligands was generated by the SKETCH module implemented in the SYBYL program (Tripos Inc., St. Louis, USA). The energy-minimized conformation was obtained with the help of the Tripos force field using Gasteiger-Huckel[41] charges and molecular docking was performed with Surflex-Dock program that is interfaced with Sybyl-X 2.0[42] and other miscellaneous parameters were assigned with the default values given by the software. The molecular docking was performed on PDB 1AI9 and presented in the Figure 4, compound **4a**, makes two hydrogen bonding interaction at the active site of the enzyme, oxygen atom of carbonyl group present at the 2nd position of the coumarin ring makes an hydrogen bonding interaction with hydrogen atom of the amino acid subunit TRP27 at the active site of the enzyme (C=O-----H-TRP27; 2.10 Å) and another interaction was raised from the oxygen atom of coumarin ring

with hydrogen atom of amino acid residue ALA11 (O-----H-ALA11; 2.49 Å). As depicted in the Figure 5, compound **7f**, makes two hydrogen bonding interaction at the active site of the enzyme (PDB ID: 1AI9), oxygen atom of the carbonyl group present at the 2nd position of the coumarin ring makes an hydrogen bonding interaction with hydrogen atom of the amino acid subunit GLU116 at the active site of

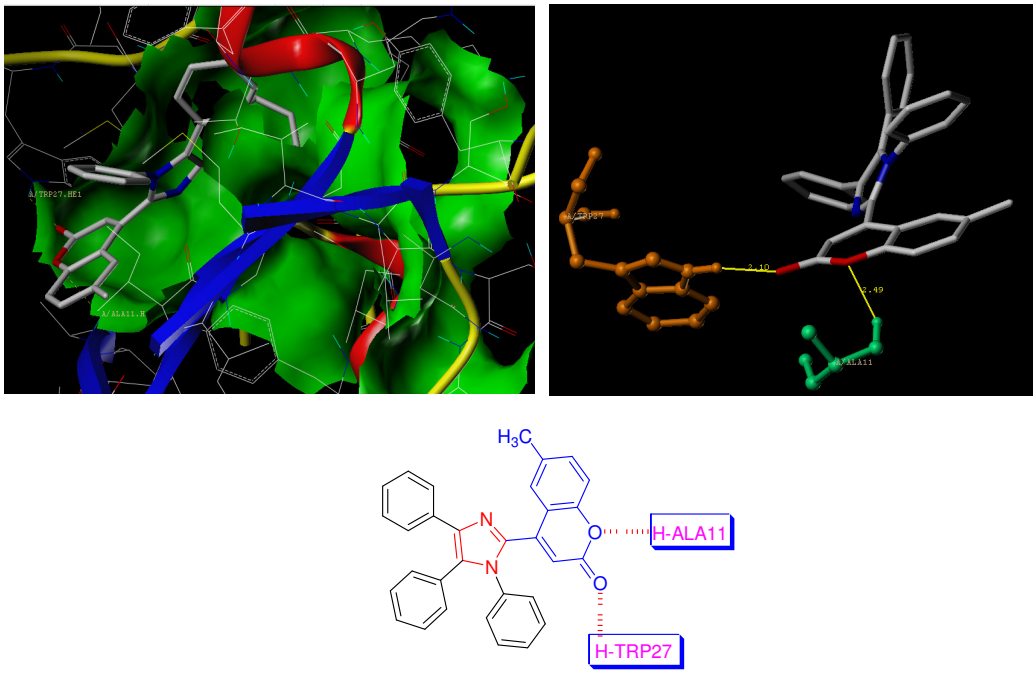


Figure 4 — Docked view of compound **4a** at the active site of the enzyme (PDB ID: 1AI9)

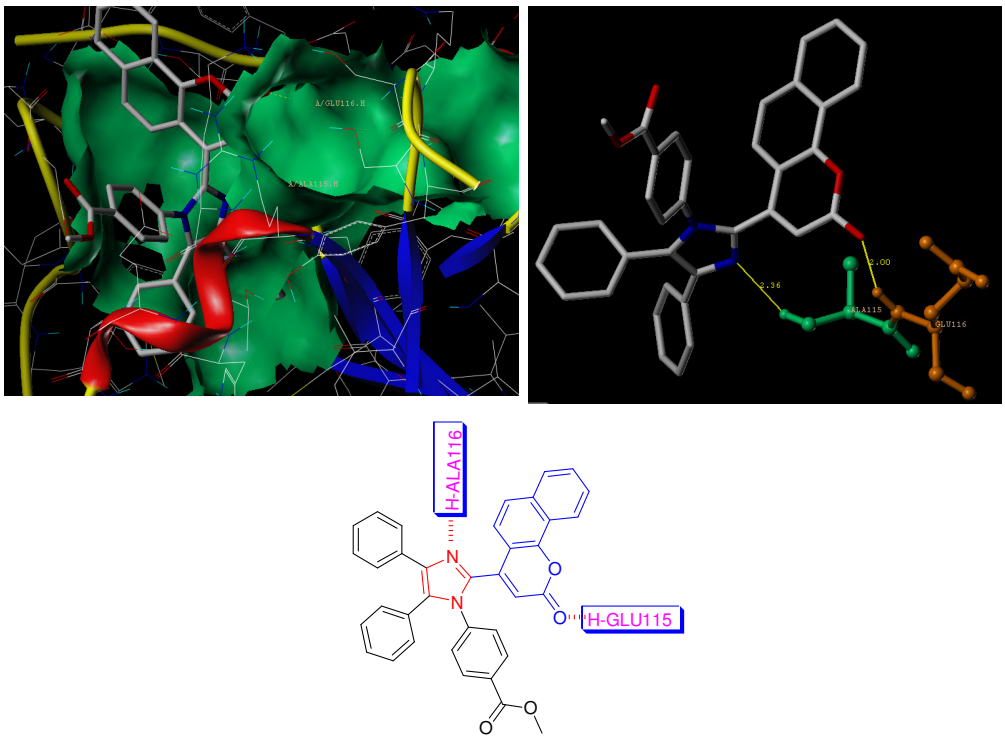


Figure 5 — Docked view of compound **7f** at the active site of the enzyme (PDB ID: 1AI9)

the enzyme (C=O-----H-GLU115; 2.00 Å) and another interaction was raised from the nitrogen atom of imidazoline ring with hydrogen atom of amino acid residue ALA115 (N-----H-ALA116; 2.36 Å). Whereas, molecular docking was performed on PDB 4CAW, as depicted in Figure 6, compound **7b** makes an hydrogen bonding interaction with hydrogen atom of amino acid residue GLY455 at the active site of the enzyme (O-----H-GLY455; 2.05 Å). Docking score results are listed in Table V and Table VI respectively. It reveals that insilico docking studies supports the *in vitro* antibacterial study.

Experimental Section

Reagents were obtained from commercial sources and used without further purification until stated. Melting points were determined in open capillary tube on a Sheetal Scientific instrument, presented in degree centigrade and are incorrect. Infrared spectra were recorded on a Nicolet 410 Fourier transform (FT) infrared Spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz instruments and further, chemical shifts are measured in terms of parts per million with TMS as the internal standard.

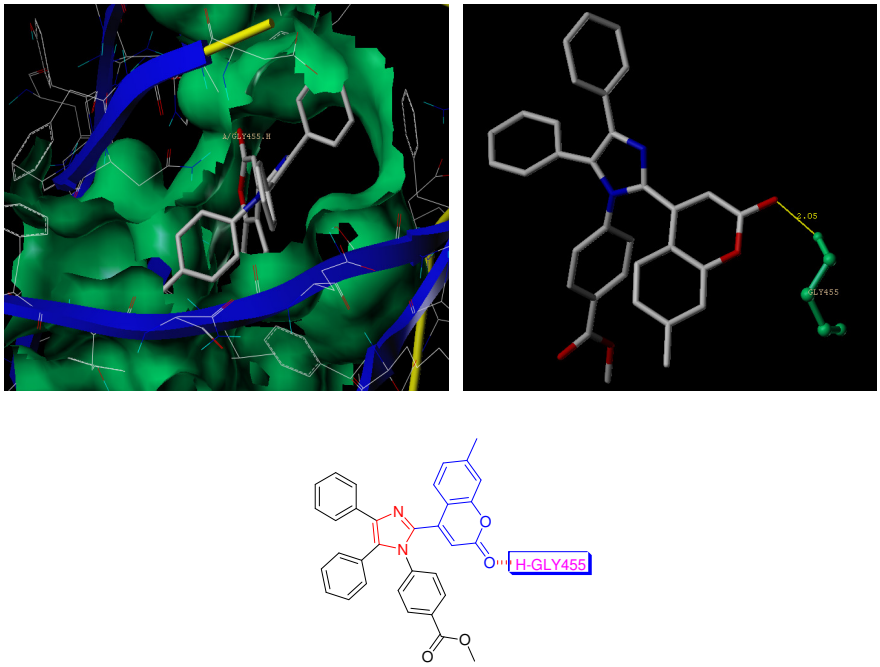


Figure 6 — Docked view of compound **7b** at the active site of the enzyme (PDB ID: 4CAW)

Table V — Surflex docking score (kcal/mol) of the coumarin imidazole conjugates for *Candida albicans* (PDB ID: 1AI9)

Compd	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	ChemScore[g]
4a*	5.20	−1.88	0.86	−2057.47	8.16	−245.53	−45.56
4b	3.89	−3.88	0.02	−1536.08	51.14	−252.74	−35.01
4c	4.15	−0.79	0.13	−1874.35	14.26	−200.96	−35.82
4d	5.13	−1.84	0.00	−1359.24	30.36	−243.26	−32.96
4e	4.30	−0.79	0.81	−1710.17	11.53	−190.67	−39.89
4f	4.99	−3.32	0.00	−1488.53	38.34	−248.64	−33.66
4h	4.52	−1.32	0.69	−1794.80	23.71	−206.03	−40.31
4i	3.21	−2.45	0.56	−1980.34	7.53	−227.30	−43.59
4j	1.59	−9.88	2.87	−1542.95	28.74	−346.49	−50.19
4k	2.96	−1.58	1.23	−1907.48	16.85	−206.32	−38.26
4l	3.45	−0.53	0.82	−1771.01	−0.21	−198.24	−38.51
4m	4.36	−2.64	0.02	−2045.28	23.41	−274.81	−49.49
7a	2.42	−9.64	2.60	−1436.73	47.82	−366.82	−49.67

(*Contd.*)

Table V — Surflex docking score (kcal/mol) of the coumarin imidazole conjugates for *Candida albicans* (PDB ID: 1AI9) (*Contd.*)

Compd	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	ChemScore[g]
7b	3.24	−5.17	0.00	−1567.77	47.48	−272.38	−32.24
7c	2.87	−5.05	0.00	−1599.11	45.12	−260.84	−31.86
7d	0.79	−1.07	1.16	−702.33	−46.75	−108.22	−14.75
7e	0.45	−11.80	0.12	−1092.36	18.13	−260.08	−26.75
7f*	5.63	−0.75	1.24	−1778.78	27.50	−211.18	−38.53

[a]C Score (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.
[b] Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate penetration.
[c] Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.
[d] D-score for charge and van der Waals interactions between the protein and the ligand.
[e] PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs (Potential of Mean Force, PMF).
[f] G-score showing hydrogen bonding, complex (ligand-protein), and internal (ligand-ligand) energies.
[g]Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term.

Table VI — Surflex docking scores (kcal/mol) of the coumarin imidazole conjugates for *Aspergillus fumigates* (PDB ID: 4CAW)

Compd	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	ChemScore[g]
4a	3.97	−1.86	0.00	−1801.92	−45.46	−225.26	−46.19
4b	4.05	−1.41	−0.03	−1821.38	−65.78	−230.17	−46.47
4c	5.01	−1.72	0.00	−1979.33	−72.70	−219.34	−44.99
4d	4.57	−2.18	0.00	−1779.62	−29.45	−240.74	−46.46
4e	4.60	−0.35	0.81	−1556.30	−33.51	−196.09	39.20
4f*	5.11	−1.03	1.15	−1608.48	−54.02	−209.12	−46.28
4h	3.52	−1.48	0.99	−1931.89	−105.37	−210.97	−45.94
4i	3.67	−1.73	1.12	−1860.13	−83.76	−194.91	−48.51
4j	4.95	−1.45	0.53	−2080.10	−50.69	−216.51	−42.22
4k	4.87	−1.25	1.22	−1835.55	−94.96	−238.60	−47.73
4l	2.13	−2.00	0.00	−1657.04	−11.86	−194.93	−36.63
4m	4.64	−1.70	1.11	−1921.34	−108.76	−231.98	−51.12
7a	4.90	−1.19	0.87	−1732.99	−87.83	−230.61	−45.56
7b*	6.08	−1.20	1.13	−2007.77	−109.51	−235.32	−46.59
7c	5.08	−1.43	1.18	−2069.57	−112.56	−225.30	−45.82
7d	4.80	−1.24	0.94	−1868.53	−107.69	−210.90	−44.24
7e	4.29	−1.47	2.02	−1716.87	−87.22	−227.26	−47.97
7f*	5.23	−1.10	0.01	−1968.02	−90.04	−240.99	−42.10

General procedure for synthesis of 4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 4a-m, 6a-f

Conventional Method

Substituted 4-formylcoumarin **1** (0.00049 mol, 100 mg) was added slowly into the reaction mixture of benzil **2** (0.00049 mol, 100 mg), ammonium acetate (0.00049 mol, 37 mg) and aniline/*p*-amino benzoic acid/*p*-nitro aniline (0.00049 mol) in acetic acid as a solvent (10 mL). The reaction mixture was stirred for 20 min at RT and heated at 90°C for 8 h, after completion (monitored by TLC) reaction was cooled to RT and quenched with ice water, the residues obtained was extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous Na_2SO_4. After concentration the crude product was purified by column chromatography (hexane: ethyl acetate) to obtain the desired product **4a-m**, **6a-f**.

Microwave Method

Substituted 4-formylcoumarin **1** (0.00049 mol, 100 mg) was added slowly into the reaction mixture of benzil **2** (0.00049 mol, 100 mg), ammonium acetate (0.00049 mol, 37 mg) and aniline/*p*-amino benzoic acid/*p*-nitro aniline (0.00049 mol) in acetic acid as a solvent (2 mL). The reaction mixture was stirred for 20 min at RT and heated at 100°C for 5 min, after completion (monitored by TLC) reaction was cooled to RT and quenched with ice water, the residues obtained was extracted with ethyl acetate.

The organic phase was washed with water and dried over anhydrous Na_2SO_4. After concentration the crude product was purified by column chromatography (hexane:ethyl acetate) to obtain the desired product **4a-m**, **6a-f**.

6-Methyl-4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 4a: White solid. Yield 86%. m.p.210-212°C. IR (KBr): 1728 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, *J* = 1.2 Hz, 1H), 7.51 (dd, *J* = 1.2 & 5.2 Hz, 2H), 7.44 (dd, *J* = 2 Hz, 1H), 7.29 (m, 14H), 6.21 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.08 (C_2 of coumarin), 151.48 (C_4 of coumarin), 142.93 (C_9 of coumarin), 140.39 (C_2 of imidazole), 137.80 (C_6 of coumarin), 135.48 (Ar-C), 133.75 (Ar-C), 133.66 (Ar-C), 133.22 (Ar-C), 132.19 (C_4 of imidazole), 131.55 (Ar-C), 130.97 (Ar-C), 129.64 (Ar-C), 129.01 (Ar-C), 128.89 (Ar-C), 128.73 (C_7 of coumarin), 128.53 (Ar-C), 128.29 (Ar-C), 128.15 (Ar-C), 127.87 (C_5 of coumarin), 127.48 (Ar-C), 126.86 (C_5 of imidazole), 126.41 (Ar-C), 126.11 (Ar-C), 122.43 (C_8 of coumarin), 121.65 (C_{10} of coumarin) 121.21 (Ar-C) 120.35 (Ar-C), 119.19 (Ar-C), 119.39 (C_3 of coumarin), 20.41 (CH_3 of coumarin); GC-MS: *m/z* Calcd for $C_{31}H_{22}N_2O_5$: 454.17. Found: 454.

7-Methyl-4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 4b: White solid. Yield 86%. m.p.205-207°C. IR (KBr): 1728 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, *J* = 1.2 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.44 (dd, *J* = 8.4 Hz, 1H), 7.27 (m, 22), 6.215 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.08 (C_2 of coumarin), 151.48 (C_4 of coumarin), 142.93 (C_9 of coumarin), 140.39 (C_2 of imidazole), 137.80 (C_6 of coumarin), 135.48 (Ar-C), 133.75 (Ar-C), 133.66 (Ar-C), 133.22 (Ar-C), 132.19 (C_4 of imidazole), 130.97 (Ar-C), 127.79 (Ar-C), 129.64 (Ar-C), 129.33 (Ar-C), 129.01 (Ar-C), 128.89 (Ar-C), 128.73 (C_7 of coumarin), 128.53 (Ar-C), 128.29 (Ar-C), 128.15 (Ar-C), 127.48 (C_5 of coumarin),127.54 (Ar-C), 126.41 (C_5 of imidazole), 122.21 (Ar-C), 121.56 (Ar-C), 121.22 (C_{10} of coumarin), 120.35 (Ar-C), 117.35 (C_8 of coumarin), 117.19 (Ar-C), 116.39 (C_3 of coumarin) 20.41(CH_3 of coumarin); GC-MS: *m/z* Calcd for $C_{31}H_{22}N_2O_5$ 454.17. Found: 454.

6-Methoxy-4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 4c: White solid. Yield 78%. m.p.212-214°C. IR (KBr): 1730 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (d, *J* = 1.2 Hz, 1H), 7.54 (dd, *J* = 1.2 & 5.2 Hz, 2H), 7.38 (dd, *J* = 2 Hz, 1H), 7.30 (m, 14H), 6.18 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.00 (C_2 of coumarin), 151.55 (C_4 of coumarin), 142.94 (C_9 of coumarin), 140.38 (C_2 of imidazole), 137.82 (C_6 of coumarin), 135.41 (Ar-C), 133.76 (Ar-C), 133.68 (Ar-C), 133.19 (Ar-C), 132.18 (C_4 of imidazole), 130.96 (Ar-C), 129.66 (Ar-C), 129.00 (Ar-C), 128.84 (Ar-C), 128.74 (C_7 of coumarin), 128.58 (Ar-C), 128.32 (Ar-C), 128.16 (Ar-C), 127.92 (Ar-C), 127.73 (Ar-C), 127.52 (C_5 of coumarin), 126.87 (Ar-C), 126.42 (C_{10} of coumarin), 124.21 (Ar-C), 123.68 (C_5 of imidazole), 122.45 (Ar-C), 120.87 (Ar-C) 120.33 (C_8 of coumarin), 119.19 (Ar-C), 118.39 (C_3 of coumarin), 52.04 (OCH_3 of coumarin); GC-MS: *m/z* Calcd for $C_{31}H_{22}N_2O_3$:470.52. Found: 470.

6-Bromo-4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 4d: White solid. Yield 80%. m.p.214-216°C. IR (KBr): 1718 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (d, *J* = 1.2 Hz, 1H), 7.52 (dd, *J* = 1.2 & 5.2 Hz, 2H), 7.38 (dd, *J* = 2 Hz, 1H), 7.30 (m, 14H), 6.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.00 (C_2 of coumarin), 151.49 (C_4 of coumarin), 142.91 (C_9 of coumarin), 140.33 (C_2 of imidazole), 137.78 (C_6 of coumarin), 135.49 (Ar-C), 133.76 (Ar-C), 133.68 (Ar-C), 133.24 (Ar-C), 132.20 (C_4 of imidazole), 130.98 (Ar-C), 129.78 (Ar-C), 129.51 (Ar-C), 129.21 (Ar-C), 128.83 (Ar-C), 128.74 (C_7 of coumarin), 128.55 (Ar-C), 128.30 (Ar-C), 128.16 (Ar-C), 127.52 (C_5 of coumarin), 127.42 (Ar-C), 126.82 (Ar-C), 126.40 (C_5 of imidazole), 122.33 (Ar-C), 121.48 (Ar-C), 121.35 (Ar-C), 121.02 (C_8 of coumarin), 120.34 ($C_{10}$of coumarin), 119.90 (Ar-C), 119.40 (C_3 of coumarin); GC-MS: *m/z* Calcd for $C_{30}H_{19}BrN_2O_2$:519.39. Found: 519.

6-Chloro-4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 4e: White solid. Yield 74%. m.p.218-220°C. IR (KBr): 1720 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (d, *J* = 1.2 Hz, 1H), 7.54 (dd, *J* = 1.2 & 5.2 Hz, 2H), 7.41 (dd, *J* = 2 Hz, 1H), 7.27 (m, 14H), 6.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.08 (C_2 of coumarin), 151.38 (C_4 of coumarin), 142.92 (C_9 of coumarin), 140.34 (C_2 of imidazole), 137.82 (C_6 of coumarin), 135.46 (Ar-C), 133.72 (Ar-C), 133.56 (Ar-C), 133.22 (Ar-C), 132.21 (C_4 of imidazole), 130.86 (Ar-C), 130.00 (Ar-C), 129.02 (Ar-C), 128.88 (Ar-C), 128.62 (C_7 of coumarin), 128.52 (Ar-C), 128.28 (Ar-C), 128.11 (Ar-C), 128.88 (Ar-C), 127.92 (Ar-C), 127.36 (C_5 of coumarin), 126.80 (Ar-C), 126.42 (C_5 of imidazole), 122.73 (C_{10} of coumarin) 122.21 (Ar-C), 121.56 (Ar-C), 120.35 (Ar-C), 118.33 (C_8 of coumarin), 117.16 (Ar-C),

116.42 (C_3 of coumarin); GC-MS: *m/z* Calcd for $C_{30}H_{19}ClN_2O_2$:474.94. Found: 474.

4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-benzo[h] chromen-2-one 4f: White solid. Yield 75%. m.p.220-218°C. IR (KBr): 1725 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, *J* = 1.2 Hz, 1H), 7.52 (dd, *J* = 1.2 & 5.2 Hz, 3H), 7.44 (dd, *J* = 2 Hz, 3H), 7.28 (m, 14H), 6.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.00 (C_2 of coumarin), 151.38 (C_4 of coumarin), 142.94 (C_9 of coumarin), 140.34 (C_2 of imidazole), 137.82 (C_6 of coumarin), 135.46 (Ar-C), 133.72 (Ar-C), 133.56 (Ar-C), 133.22 (Ar-C), 132.21 (C_4 of imidazole), 130.86 (Ar-C), 130.60 (Ar-C), 130.54 (Ar-C) 129.84 (Ar-C), 129.34 (Ar-C), 129.22 (Ar-C), 129.09 (Ar-C), 128.88 (C_7 of coumarin), 128.59 (Ar-C), 128.50 (Ar-C), 128.31 (Ar-C), 128.21 (Ar-C), 127.74 (C_{14} of coumarin), 127.54 (C_{11} of coumarin), 127.13 (C_{12} of coumarin), 126.78 (C_5 of coumarin), 126.41 (C_5 of imidazole), 125.83 (C_8 of coumarin), 124.52 (C_{13} of coumarin), 122.98 (Ar-C), 122.13 (Ar-C), 121.85 (Ar-C), 121.03 (C_{10} of coumarin), 118.45 (C_3 of coumarin); GC-MS: *m/z* Calcd for $C_{34}H_{21}N_2O_2$:490.55. Found: 490.

5,7-Dimethyl-4-(1,4,5-triphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 4g: White solid. Yield 92%, mp: 210-212°C. IR (KBr): 1706 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 4 Hz, 2H), 7.27 (m, 7H), 7.08 (d, *J* = 4 Hz, 2H), 6.97 (3H, m), 6.64 (s, 1H), 6.43 (s, 1H), 6.31 (s, 1H), 2.33 (s. 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.37 (C_2 of coumarin), 152.42 (C_4 of coumarin), 142.94 (C_9 of coumarin), 141.83 (C_2 of imidazole), 136.49 (C_6 of coumarin), 135.00 (Ar-C), 133.90 (Ar-C), 133.45 (Ar-C), 132.25 (Ar-C), 131.03 (C_4 of imidazole), 129.72 (Ar-C), 129.16 (Ar-C), 128.76 (Ar-C), 128.37 (Ar-C), 128.12 (Ar-C), 127.98 (C_7 of coumarin), 127.28 (Ar-C), 127.12 (Ar-C), 126.89 (Ar-C), 126.35 (C_5 of coumarin), 125.88 (Ar-C), 125.03 (C_5 of imidazole), 122.95 (Ar-C), 122.11 (C_{10} of coumarin), 121.44 (Ar-C), 120.35 (Ar-C), 119.71 (Ar-C), 119.42 (C_8 of coumarin), 118.80 (Ar-C), 118.37 (C_3 of coumarin), 23.19 (CH_3 of coumarin), 20.62 (CH_3 of coumarin); GC-MS: *m/z* Calcd for $C_{31}H_{22}N_2O_5$:468.18. Found: 468.

4-(2-(6-Methoxy-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoic acid 4h: White solid. Yield 88%. m.p.196-198°C. IR (KBr) 1728 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.40 (s, 1H), 8.12 (d, *J* = 8 Hz, 2H), 7.85 (d, *J* = 8 Hz, 3H), 7.44 (s, 1H), 7.38 (d, *J* = 4 Hz, 1H), 7.32 (d, *J* = 4 Hz, 2H), 7.24 (m, 6H), 7.28 (d, *J* = 8 Hz, 1H), 7.10 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.02 (C of COOH), 168.12 (C_2 of coumarin), 166.76 (C_4 of coumarin), 159.64 (C_9 of coumarin), 156.01 (C_2 of imidazole), 153.64 (C_6 of coumarin), 148.38 (Ar-C), 142.44 (Ar-C), 140.58 (Ar-C), 138.42 (Ar-C), 134.02 (C_4 of imidazole), 133.84 (Ar-C), 132.52 (Ar-C), 131.67 (Ar-C), 131.55 (Ar-C), 130.23 (C_7 of coumarin), 129.20 (Ar-C), 128.91 (Ar-C), 128.44 (Ar-C), 127.44 (Ar-C), 126.88 (Ar-C), 126.71 (C_5 of coumarin), 126.43 (Ar-C)), 125.21 (C_5 of imidazole), 125.10 (Ar-C), 124.82 (Ar-C), 122.18 (Ar-C), 121.28 (C_8 of coumarin), 120.13 (C_{10} of coumarin), 120.06 (Ar-C), 118.00 (C_3 of coumarin), 20.27 (CH_3 of coumarin),.

4-(2-(7-Methyl-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoic acid 4i: White solid. Yield 90%. m.p.198-200°C. IR (KBr) 1725 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.42 (s, 1H), 8.10 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8 Hz, 3H), 7.44 (s, 1H), 7.36 (d, *J* = 4 Hz, 1H), 7.31 (d, *J* = 4 Hz, 2H), 7.25 (m, 6H), 7.30 (d, *J* = 8 Hz, 1H), 7.12 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.00 (C of COOH), 168.14 (C_2 of coumarin), 166.77 (C_4 of coumarin), 159.65 (C_9 of coumarin), 156.02 (C_2 of imidazole), 153.60 (C_6 of coumarin), 148.40 (Ar-C), 142.45 (Ar-C), 140.56 (Ar-C), 134.00 (Ar-C), 132.85 (C_4 of imidazole), 131.94 (Ar-C), 131.64 (Ar-C), 130.66 (Ar-C), 129.82 (Ar-C), 129.62 (Ar-C), 129.32 (Ar-C), 128.92 (C_7 of coumarin), 128.80 (Ar-C), 128.31 (Ar-C), 127.72 (Ar-C), 127.69 (Ar-C), 127.48 (Ar-C), 127.23 (Ar-C), 126.96 (C_5 of coumarin), 126.68 (Ar-C), 126.45 (Ar-C), 122.82 (C_8 of coumarin), 122.23 (C_5 of imidazole), 120.21 (C_{10} of coumarin), 118.26 (C_3 of coumarin), 20.25 (CH_3 of coumarin).

4-(2-(6-Methoxy-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoicacid 4j: White solid. Yield 82%, mp198-200°C. IR (KBr) 1718 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8 Hz, 2H), 7.45 (s, 1H), 7.43 (d, *J* = 4 Hz, 2H), 7.36 (d, *J* = 4 Hz, 2H), 7.31 (m, 6H), 7.29 (d, *J* = 8 Hz, 2H), 7.01 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.08 (C of COOH), 168.00 (C_2 of coumarin), 166.81 (C_4 of coumarin), 159.63 (C_9 of coumarin), 155.98 (C_2 of imidazole), 153.63 (C_6 of coumarin), 148.36 (Ar-C), 142.42 (Ar-C), 140.66 (Ar-C), 134.05 (Ar-C), 132.85 (C_4 of imidazole), 131.71 (Ar-C), 130.65 (Ar-C), 130.32

(Ar-C), 129.72 (Ar-C), 129.21 (Ar-C), 128.92 (Ar-C), 128.15 (C_7 of coumarin), 127.92 (Ar-C), 127.78 (C_5 of coumarin), 127.56 (Ar-C), 127.22 (Ar-C), 126.86 (Ar-C), 126.57 (Ar-C), 126.27 (Ar-C), 126.12 (Ar-C), 125.92 (Ar-C), 122.37 (C_5 of imidazole), 121.93 (C_8 of coumarin), 121.56 (C_{10} of coumarin), 119.82 (C_3 of coumarin), 56.27 (OCH_3 of coumarin).

4-(2-(6-Bromo-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoic acid 4k: White solid. Yield 78%. m.p.194-196°C. IR (KBr) 1700 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.42 (s, 1H), 8.14 (d, *J* = 8 Hz, 2H), 7.86 (d, *J* = 8 Hz, 3H), 7.40 (s, 1H), 7.41 (d, *J* = 4 Hz, 1H), 7.34 (d, *J* = 4 Hz, 2H), 7.22 (m, 6H), 7.28 (d, *J* = 8 Hz, 1H), 7.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.21 (C of COOH), 168.32 (C_2 of coumarin), 166.77 (C_4 of coumarin), 159.64 (C_9 of coumarin), 156.00 (C_2 of imidazole), 153.65 (C_6 of coumarin), 148.41 (Ar-C), 142.46 (Ar-C), 140.60 (Ar-C), 134.00 (Ar-C), 132.85 (C_4 of imidazole), 131.72 (Ar-C), 130.66 (Ar-C), 130.12 (Ar-C), 129.65 (Ar-C), 129.47 (Ar-C), 129.23 (Ar-C), 128.89 (Ar-C), 128.67 (Ar-C), 128.51 (Ar-C), 128.28 (Ar-C), 127.75 (C_5 of coumarin), 127.36 (Ar-C), 126.86 (C_7 of coumarin), 126.12 (Ar-C), 124.55 (C_5 of imidazole), 122.89 (Ar-C), 122.02 (C_8 of coumarin), 121.56 (Ar-C), 120.12 (C_{10} of coumarin), 119.84 (C_3 of coumarin).

4-(2-(6-Chloro-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoic acid 4l: White solid,yield 74%. m.p.196-198°C. IR (KBr) 1702 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.41 (s, 1H), 8.12 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8 Hz, 3H), 7.42 (s, 1H), 7.40 (d, *J* = 4 Hz, 1H), 7.32 (d, *J* = 4 Hz, 2H), 7.20 (m, 6H), 7.18 (d, *J* = 8 Hz, 1H), 7.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.22 (C of COOH), 168.34 (C_2 of coumarin), 166.76 (C_4 of coumarin), 159.65 (C_9 of coumarin), 156.04 (C_2 of imidazole), 153.68 (C_6 of coumarin), 148.42 (Ar-C), 142.45 (Ar-C), 140.62 (Ar-C), 134.02 (C_4 of imidazole), 132.86 (Ar-C), 131.74 (Ar-C), 130.68 (Ar-C), 129.86 (Ar-C), 129.59 (Ar-C), 129.22 (Ar-C), 128.91 (Ar-C), 128.76 (Ar-C), 128.42 (Ar-C), 127.89 (C_7 of coumarin), 127.54 (C_5 of coumarin), 127.21 (Ar-C), 126.67 (Ar-C), 124.14(Ar-C), 123.33 (C_8 of coumarin). 122.56 (C_5 of imidazole), 121.89 (Ar-C), 121.14 (C_{10} of coumarin), 120.82 (Ar-C), 120.22 (Ar-C), 118.30 (C_3 of coumarin).

4-(2-(2-Oxo-2*H*-benzo[h]chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoic acid 4m: White solid. Yield 90%. m.p.200-202°C. IR (KBr) 1730 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.42 (s, 1H), 8.14 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8 Hz, 4H), 7.42 (s, 1H), 7.36 (d, *J* = 4 Hz, 1H), 7.34 (d, *J* = 4 Hz, 4H), 7.25 (m, 6H), 7.28 (d, *J* = 8 Hz, 1H), 7.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.12 (C of COOH), 168.14 (C_2 of coumarin), 159.66 (C_4 of coumarin), 156.00 (C_{13} of coumarin), 153.62 (Ar-C), 148.41 (C_2 of imidazole), 142.69 (C_{12} of coumarin), 140.62 (Ar-C), 141.58 (Ar-C), 134.00 (C_4 of imidazole), 132.82 (Ar-C), 131.70 (Ar-C), 130.64 (Ar-C), 129.22 (Ar-C), 128.92 (Ar-C), 126.86 (Ar-C), 125.40 (Ar-C),124.23 (Ar-C), 123.59 (Ar-C), 120.12 (Ar-C), 120.04 (Ar-C), 119.86 (Ar-C), 119.20 (Ar-C), 118.27 (Ar-C), 113.15 (Ar-C), 110.07 (C_8 of coumarin), 109.02 (C_9 of coumarin), 108.74 (C_5 of imidazole), 108.66 (C_5 of coumarin), 108.40 (Ar-C), 108.28 (Ar-C), 107.44 (C_6 of coumarin), 107.31 (C_{10} of coumarin), 106.82 (C_3 of coumarin), 105.70 (C_{14} of coumarin).

6-Methyl-4-(1-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 6a: White solid. Yield 92%. m.p.232-234°C. IR (KBr) 1719 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 1H), 8.25 (d, *J* = 8 Hz, 2H), 8.00 (d, *J* = 8 Hz, 2H), 7.80 (m, 4H), 7.68 (m, 2H), 7.40 (m, 2H), 7.20 (m, 3H), 7.00 (m, 1H), 6.40 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.64 (C_2 of coumarin), 159.50 (C_4 of coumarin), 156.10 (C_9 of coumarin), 155.23 (Ar-C), 152.12 (Ar-C), 147.21 (C_2 of imidazole), 144.76 (C_6 of coumarin), 143.71 (Ar-C), 142.94 (Ar-C), 142.36 (C_4 of imidazole), 140.77 (Ar-C), 139.46 (Ar-C), 136.12 (Ar-C), 133.16 (Ar-C), 131.02 (C_7 of coumarin), 130.37 (Ar-C), 130.22 (Ar-C), 129.97 (Ar-C), 129.29 (Ar-C), 129.14 (Ar-C), 128.56 (Ar-C), 128.02 (C_5 of imidazole), 127.68 (Ar-C), 127.41 (Ar-C), 124.86 (Ar-C), 119.76 (C_8 of coumarin), 116.61 (C_{10} of coumarin), 116.33 (C_3 of coumarin), 115.36 (Ar-C), 115.14 (C_5 of coumarin), 24.12 (CH_3 of coumarin).

7-Methyl-4-(1-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 6b: White solid. Yield 90%. m.p.234-236°C. IR (KBr) 1720 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.24 (d, *J* = 8 Hz, 2H), 8.04 (d, *J* = 8 Hz, 2H), 7.82 (m, 4H), 7.70 (m, 2H), 7.42 (m, 2H), 7.22 (m, 3H), 7.02 (m, 1H), 6.42 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.62 (C_2 of coumarin), 159.50 (C_4 of coumarin), 156.12 (C_9 of coumarin), 155.24 (Ar-C), 152.10 (Ar-C), 147.22 (C_2 of imidazole), 144.78 (C_6 of coumarin), 143.72 (Ar-C), 142.95 (Ar-C),

142.38 (C_4 of imidazole), 140.78 (Ar-C), 139.48 (Ar-C), 136.14 (Ar-C), 133.18 (Ar-C), 131.00 (C_7 of coumarin), 130.38 (Ar-C), 130.24 (Ar-C), 129.98 (Ar-C), 129.31 (Ar-C), 129.15(Ar-C), 128.58 (Ar-C), 128.00 (C_5 of imidazole), 127.72 (Ar-C), 124.88 (Ar-C), 124.55 (Ar-C), 119.78 (C_8 of coumarin), 116.62 (C_{10} of coumarin), 116.34 (C_3 of coumarin), 115.34 (Ar-C), 115.15 (Ar-C), 24.14 (CH_3 of coumarin).

6-Methoxy-4-(1-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 6c: White solid. Yield 88%. m.p.234-236°C. IR (KBr) 1718 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.24 (d, *J* = 8 Hz, 2H), 8.04 (d, *J* = 8 Hz, 2H), 7.82 (m, 4H), 7.70 (m, 2H), 7.42 (m, 2H), 7.22 (m, 3H), 7.08 (m, 1H), 6.42 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.65 (C_2 of coumarin), 159.52 (C_4 of coumarin), 156.14 (C_9 of coumarin), 155.24 (Ar-C), 152.11 (Ar-C), 147.20 (C_2 of imidazole), 144.78 (C_6 of coumarin), 143.72 (Ar-C), 142.96 (Ar-C), 142.38 (C_4 of imidazole), 140.68 (Ar-C), 139.48 (Ar-C), 136.14 (Ar-C), 133.18 (Ar-C), 131.04 (C_7 of coumarin), 130.38 (Ar-C), 130.24 (Ar-C), 129.98 (Ar-C), 129.30 (Ar-C), 129.15 (Ar-C), 128.58 (Ar-C), 128.04 (C_5 of imidazole), 127.69 (Ar-C), 127.42 (Ar-C), 124.78 (Ar-C), 119.72 (Ar-C), 116.62 (C_8 of coumarin), 116.34 (C_{10} of coumarin), 115.38 (C_3 of coumarin), 115.16 (Ar-C), 51.24 (OCH_3 of coumarin).

6-Bromo-4-(1-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 6d: White solid. Yield 80%. m.p.230-232°C. IR (KBr) 1730 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 1H), 8.27 (d, *J* = 8 Hz, 2H), 8.08 (d, *J* = 8 Hz, 2H), 7.84 (m, 4H), 7.66 (m, 2H), 7.42 (m, 2H), 7.22 (m, 3H), 7.04 (m, 1H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.66 (C_2 of coumarin), 159.52 (C_4 of coumarin), 156.12 (C_9 of coumarin), 155.20 (Ar-C), 152.11 (Ar-C), 147.22 (C_2 of imidazole), 144.68 (C_6 of coumarin), 143.70 (Ar-C), 142.92 (Ar-C), 142.35 (C_4 of imidazole), 140.79 (Ar-C), 139.47 (Ar-C), 136.13 (Ar-C), 133.11 (Ar-C), 131.00 (C_7 of coumarin), 130.38 (Ar-C), 130.24 (Ar-C), 129.98 (Ar-C), 129.30 (Ar-C), 129.15 (Ar-C), 128.58 (Ar-C), 128.00 (C_5 of imidazole), 127.69 (Ar-C), 127.42 (Ar-C), 124.88 (Ar-C), 119.77 (Ar-C), 116.62 (C_8 of coumarin), 116.30 (C_{10} of coumarin), 115.34 (C_3 of coumarin), 115.00 (Ar-C).

6-Chloro-4-(1-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-2*H*-chromen-2-one 6e: White solid. Yield 78%. m.p.232-234°C. IR (KBr) 1732 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.26 (d, *J* = 8 Hz, 2H), 8.06 (d, *J* = 8 Hz, 2H), 7.86 (m, 4H), 7.66 (m, 2H), 7.44 (m, 2H), 7.20 (m, 3H), 7.06 (m, 1H), 6.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.64 (C_2 of coumarin), 159.54 (C_4 of coumarin), 156.14 (C_9 of coumarin), 155.22 (Ar-C), 152.12 (Ar-C), 147.24 (C_2 of imidazole), 144.70 (C_6 of coumarin), 143.72 (Ar-C), 142.94 (Ar-C), 142.36 (C_4 of imidazole), 140.80 (Ar-C), 139.48 (Ar-C), 136.14 (Ar-C), 133.12 (Ar-C), 131.04 (Ar-C), 130.40 (Ar-C), 130.25 (C_5 of imidazole), 129.99 (Ar-C), 129.32 (Ar-C), 129.16 (Ar-C), 128.60 (Ar-C), 127.78 (Ar-C), 126.64 (Ar-C), 126.32 (Ar-C), 125.35 (Ar-C), 125.04 (Ar-C) 124.04 (C_8 of coumarin), 123.70 (C_{10} of coumarin), 122.44 (C_3 of coumarin), 121.89 (Ar-C).

4-(1-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-2*H*-benzo[h]chromen-2-one 6f: White solid. Yield 88%. m.p.230-232°C. IR (KBr) 1720 $\nu_{max}cm^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 1H), 8.26 (d, *J* = 8 Hz, 2H), 8.04 (d, *J* = 8 Hz, 3H), 7.80 (m, 4H), 7.72 (m, 4H), 7.42 (m, 2H), 7.21 (m, 3H), 7.02 (m, 1H), 6.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.65 (C_2 of coumarin), 159.52 (C_4 of coumarin), 156.12 (C_{13} of coumarin), 155.24 (Ar-C), 152.14 (Ar-C), 147.22 (C_2 of imidazole), 144.74 (C_{12} of coumarin), 143.72 (Ar-C), 142.95 (Ar-C), 142.38 (C_4 of imidazole), 140.76 (Ar-C), 139.48 (Ar-C), 136.14 (Ar-C), 133.18 (Ar-C), 131.04 (Ar-C), 130.38 (Ar-C), 130.24 (Ar-C), 129.95 (Ar-C), 129.30 (Ar-C), 129.15 (Ar-C), 128.58 (C_7 of coumarin), 128.00 (C_8 of coumarin), 127.72 (C_9 of coumarin), 127.42 (C_{11} of coumarin), 124.88 (C_5 of imidazole), 119.78 (Ar-C), 116.62 (Ar-C), 116.34 (Ar-C), 115.35 (Ar-C), 115.12 (C_{10} of coumarin)114.86 (C_5 of coumarin), 113.22 (C_6 of coumarin), 112.46 (C_3 of coumarin), 112.31 (C_{12} of coumarin).

General procedure for synthesis of methyl 4-(2-(2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl) benzoate 7a-f

Compound **4a** (0.00018 mol, 0.1 gm) was dissolved in 20 mL of dry methanol together with con. H_2SO_4 (5 mL) was added to the cold solution, the mixture was brought to reflux at 80°C for 4 h. After completion (monitored by TLC), the resulting mixture was poured into ice cold water and stirred for 10 min, filtered and washed with water thoroughly to obtain white solid product.

Methyl-4-(2-(6-methyl-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoate 7a: White solid. Yield 89%. m.p.189-191°C. IR (KBr): 1708,

1672 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H), 8.03 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.32 (m, 6H), 7.33 (d, *J* = 8 Hz, 1H), 7.28 (s, 1H), 6.77 (d, *J* = 12 Hz, 1H), 6.52 (d, *J* = 8 Hz, 1H), 4.18 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.91 (C of ester carbonyl), 160.15 (C_2 of coumarin), 153.99 (C_9 of coumarin), 142.78 (C_7 of coumarin), 140.99 (C_2 of imidazole), 140.20 (Ar-C), 138.92 (Ar-C), 134.28 (C_4 of imidazole), 130.31 (Ar-C), 129.91 (Ar-C), 128.69 (Ar-C), 128.60 (Ar-C), 128.43 (Ar-C), 128.36 (C_5 of imidazole), 127.20 (Ar-C), 127.09 (Ar-C), 125.95 (Ar-C), 125.45 (C_5 of coumarin), 124.29 ($C_6$of coumarin), 116.70 (Ar-C), 114.11 (Ar-C), 113.39 (C_8 of coumarin), 111.43 (C_3 of coumarin), 110.81 (C_{10} of coumarin), 58.96 (CH_3 of ester), 20.97 (CH_3 of coumarin).

Methyl-4-(2-(7-methyl-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoate 7b: White solid. Yield 85%. m.p.190-192°C. IR (KBr): 1700, 1668 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.36 (m, 6H), 7.33 (d, *J* = 8 Hz, 1H), 7.26 (s, 1H), 6.78 (d, *J* = 12 Hz, 1H), 6.50 (d, *J* = 8 Hz, 1H), 4.20 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.96 (C of ester carbonyl), 160.16 (C_2 of coumarin), 154.01 (C_9 of coumarin), 142.80 (C_7 of coumarin), 140.98 (C_2 of imidazole), 140.22 (Ar-C), 138.94 (Ar-C), 134.30 (C_4 of imidazole), 130.32 (Ar-C), 129.90 (Ar-C), 128.70 (Ar-C), 128.62 (Ar-C), 128.44 (Ar-C), 128.38 (Ar-C), 128.32 (Ar-C), 128.28 (Ar-C), 127.22 (Ar-C), 127.08 (Ar-C), 125.96 (Ar-C), 125.47 (Ar-C), 124.28 (C_5 of imidazole), 123.47 (Ar-C), 122.46 (Ar-C), 116.72 (Ar-C), 114.14 (C_5 of coumarin), 113.40 (C_6 of coumarin), 112.44 (Ar-C), 112.12 (Ar-C), 112.10 (C_8 of coumarin), 112.05 (C_3 of coumarin), 112.00 (C_{10} of coumarin), 58.94 (CH_3 of ester), 21.02 (CH_3 of coumarin).

Methyl-4-(2-(6-methoxy-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoate 7c: White solid. Yield 90%. m.p.186-188°C. IR (KBr): 1701, 1674 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.34 (m, 6H), 7.28 (d, *J* = 8 Hz, 1H), 7.32 (s, 1H), 6.78 (d, *J* = 12 Hz, 1H), 6.56 (d, *J* = 8 Hz, 1H), 4.20 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.92 (C of ester carbonyl), 160.14 (C_2 of coumarin), 153.98 (C_9 of coumarin), 142.79 (C_7 of coumarin), 140.98 (C_2 of imidazole), 140.22 (Ar-C), 138.94 (Ar-C), 134.30 (C_4 of imidazole), 130.32 (Ar-C), 129.92 (Ar-C), 128.71 (Ar-C), 128.62 (Ar-C), 128.44 (Ar-C), 128.40 (Ar-C), 128.31 (Ar-C), 127.48 (Ar-C), 126.47 (Ar-C), 126.04 (Ar-C), 125.88 (C_5 of imidazole), 124.47 (Ar-C), 124.21 (Ar-C), 123.22 (Ar-C), 123.10 (Ar-C), 122.96 (Ar-C), 125.26 (C_5 of coumarin), 121.30 (C_6 of coumarin), 116.72 (Ar-C), 114.12 (Ar-C), 113.40 (C_8 of coumarin), 111.44 (C_3 of coumarin), 110.82 (C_{10} of coumarin), 58.98 (CH_3 of ester), 52.10 (OCH_3 of coumarin).

Methyl-4-(2-(6–bromo-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoate 7d: White solid. Yield 78%. m.p.192-194°C. IR (KBr): 1702, 1670 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 7H), 7.46 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 7.38 (m, 4H), 7.34 (d, *J* = 8 Hz, 1H), 7.28 (s, 1H), 6.76 (d, *J* = 12 Hz, 1H), 4.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.98 (C of ester carbonyl), 160.18 (C_2 of coumarin), 154.00 (C_9 of coumarin), 142.82 (C_7 of coumarin), 141.00 (C_2 of imidazole), 140.24 (Ar-C), 138.96 (Ar-C), 134.32 (C_4 of imidazole), 130.34 (Ar-C), 129.92 (Ar-C), 128.74 (Ar-C), 128.64 (Ar-C), 128.42 (Ar-C), 128.39 (Ar-C), 127.24 (Ar-C), 127.11 (Ar-C), 127.00 (Ar-C), 125.98 (Ar-C),124.56 (C_4 of imidazole), 124.50 (Ar-C), 124.42 (Ar-C), 124.31 (Ar-C), 123.71 (Ar-C), 123.00 (Ar-C), 122.58 (C_5 of coumarin), 122.30 (C_6 of coumarin), 116.70 (Ar-C), 114.16 (Ar-C), 113.42 (C_8 of coumarin), 111.46 (C_3 of coumarin), 110.84 (C_{10} of coumarin), 58.96 (CH_3 of ester).

Methyl-4-(2-(6-chloro-2-oxo-2*H*-chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoate 7e: White solid. Yield 74%. m.p.190-192°C. IR (KBr): 1700, 1672 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.06 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 7H), 7.44 (d, *J* = 8 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.40 (m, 4H), 7.36 (d, *J* = 8 Hz, 1H), 7.30 (s, 1H), 6.78 (d, *J* = 12 Hz, 1H), 4.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.02 (C of ester carbonyl), 160.20 (C_2 of coumarin), 154.02 (C_9 of coumarin), 142.84 (C_7 of coumarin), 141.02 (C_2 of imidazole), 140.26 (Ar-C), 138.98 (Ar-C), 134.34 (C_4 of imidazole), 130.36 (Ar-C), 129.93 (Ar-C), 128.75 (Ar-C), 128.66 (Ar-C), 128.44 (Ar-C), 128.40 (Ar-C), 127.26 (Ar-C), 127.15 (Ar-C), 127.02 (Ar-C), 125.99 (Ar-C), 124.59 (C_4 of imidazole), 124.51 (Ar-C), 124.42 (Ar-C), 124.32 (Ar-C), 123.71 (Ar-C), 123.00 (Ar-C), 122.58 (C_5 of coumarin), 122.30 (C_6 of coumarin), 116.72 (Ar-C),

114.18 (Ar-C), 113.44 (C_8 of coumarin), 111.45 (C_3 of coumarin), 110.86 (C_{10} of coumarin), 59.02 (CH_3 of ester).

Methyl-4-(2-(2-oxo-2*H*-benzo[h]chromen-4-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)benzoate 7f: White solid. Yield 80%. m.p.194-196°C. IR (KBr): 1700, 1674 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.06 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 7H), 7.45 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 7.40 (m, 4H), 7.36 (d, *J* = 8 Hz, 1H), 7.30 (s, 1H), 6.78 (d, *J* = 12 Hz, 1H), 6.54 (d, *J* = 8 Hz, 1H), 4.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.90 (C of ester carbonyl), 160.22 (C_2 of coumarin), 158.04 (C_4 of coumarin), 154.84 (C_{13} of coumarin), 141.02 (Ar-C), 140.26 (C_2 of imidazole), 138.98 (C_{12} of coumarin), 134.34 (Ar-C), 130.35 (Ar-C), 129.94 (C_2 of imidazole),129.88 (Ar-C), 129.67 (Ar-C), 128.75 (Ar-C), 128.70 (Ar-C), 128. 69 (Ar-C), 128.66 (Ar-C), 128.60 (Ar-C), 128.53 (Ar-C), 128.44 (Ar-C), 128.40 (Ar-C), 128.00 (Ar-C), 127.25 (Ar-C), 127.11 (Ar-C), 127. 09 (Ar-C), 127.02 (Ar-C), 127.00 (Ar-C), 126.96 (C_8 of coumarin), 126.50 (C_9 of coumarin), 125.32 (C_{11} of coumarin), 124.47 (C_2 of imidazole), 116.72 (Ar-C), 114.18 (C_6 of coumarin), 113.44 (C_{10} of coumarin), 111.45 (C_3 of coumarin), 110.85 (C_{14} of coumarin), 59.12 (CH_3 of ester).

Conclusion

Coumarin and its derivatives are key antimicrobial ingredients in several antibiotics, here we have successfully synthesized a pharmacophore library of coumarin-imidazole conjugates **4a-g**, **4h-m**, **6a-f** and **7a-f** both in conventional as well microwave irradiation method. The conjugates were evaluated for their antibacterial and antifungal activities. Most of the compounds exhibited promising activity with MIC values 0.1 to 0.7µg/mL against bacterial and fungal strains, while compounds **4b**, **4k** and **6a** are not active at a selected MIC values. The molecular docking study shows excellent interaction score values in agreement with most active compounds.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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