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ORIGINAL PAPER

Design, synthesis, bioactivity, and computational studies of some morpholine-clubbed coumarinyl acetamide and cinnamide derivatives

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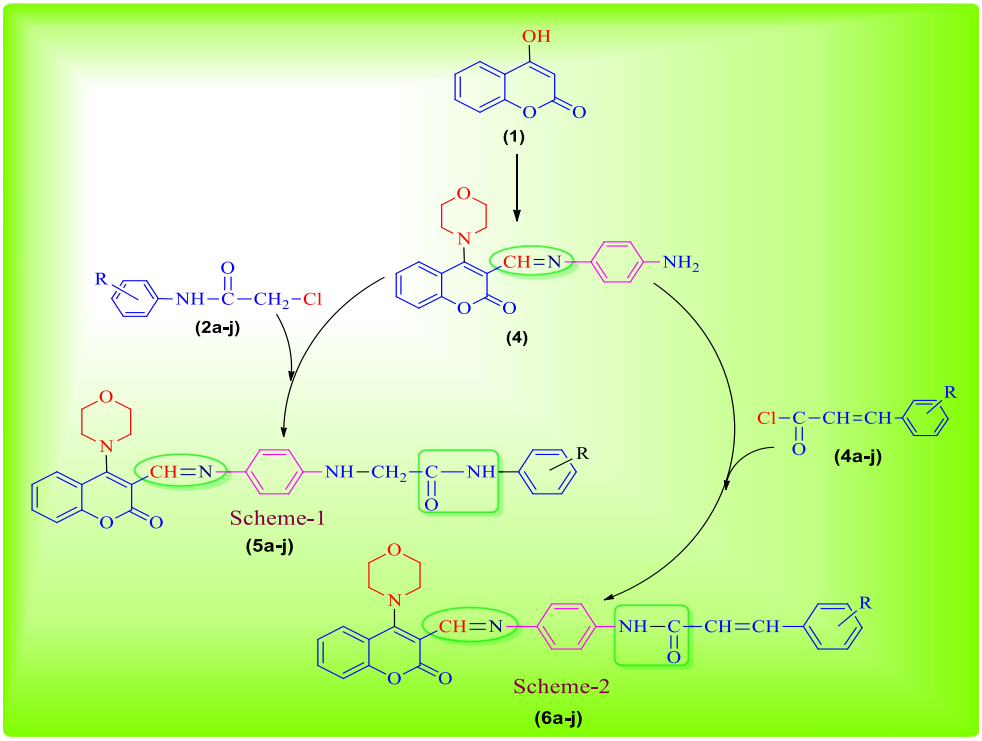
Abstract

The novel derivatives of morpholine-clubbed 3-substituted coumarinyl acetamide and cinnamide derivatives **5a–5j** and **6a–6j** have been synthesized via various 2-chloro-*N*-phenyl acetamide and cinnamoyl chloride derivatives, respectively. The required motif has been generated through Vilsmeier–Haack reaction on 4-hydroxycoumarin annelation of morpholine followed by imine formation and subsequently condensation with various 2-chloro-*N*-phenylacetamide and cinnamoyl chloride to furnish the desired molecule. The synthesized molecules were characterized by various spectroscopic methods viz IR, ^{1}H NMR, ^{13}C NMR. Their antimicrobial activities against various strains of bacteria and fungi have been evaluated, and computational studies have also been performed for all the newly synthesized analogs.

Graphical Abstract



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Extended author information available on the last page of the article

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Keywords Coumarin · Acetamide · Cinnamide · Bioactivity · Computational study

Introduction

In the last few decades, infectious diseases have been emanated dramatically by the bacteria and fungi, resulting in severe threat to health of human being [1]. In spite of availability of various types antibiotics drugs, multidrug resistance (MDR) have been continuously emerged for these drugs in most of the pathogenic bacteria [2]. To overcome such problems, we tempted to design and synthesize some novel antibacterial agents, which might have better antimicrobial potency compare to recent existing drugs. It accentuates the exploitation of novel antimicrobial and antifungal drugs, which can facilitate treatment and prevents disease in a better way.

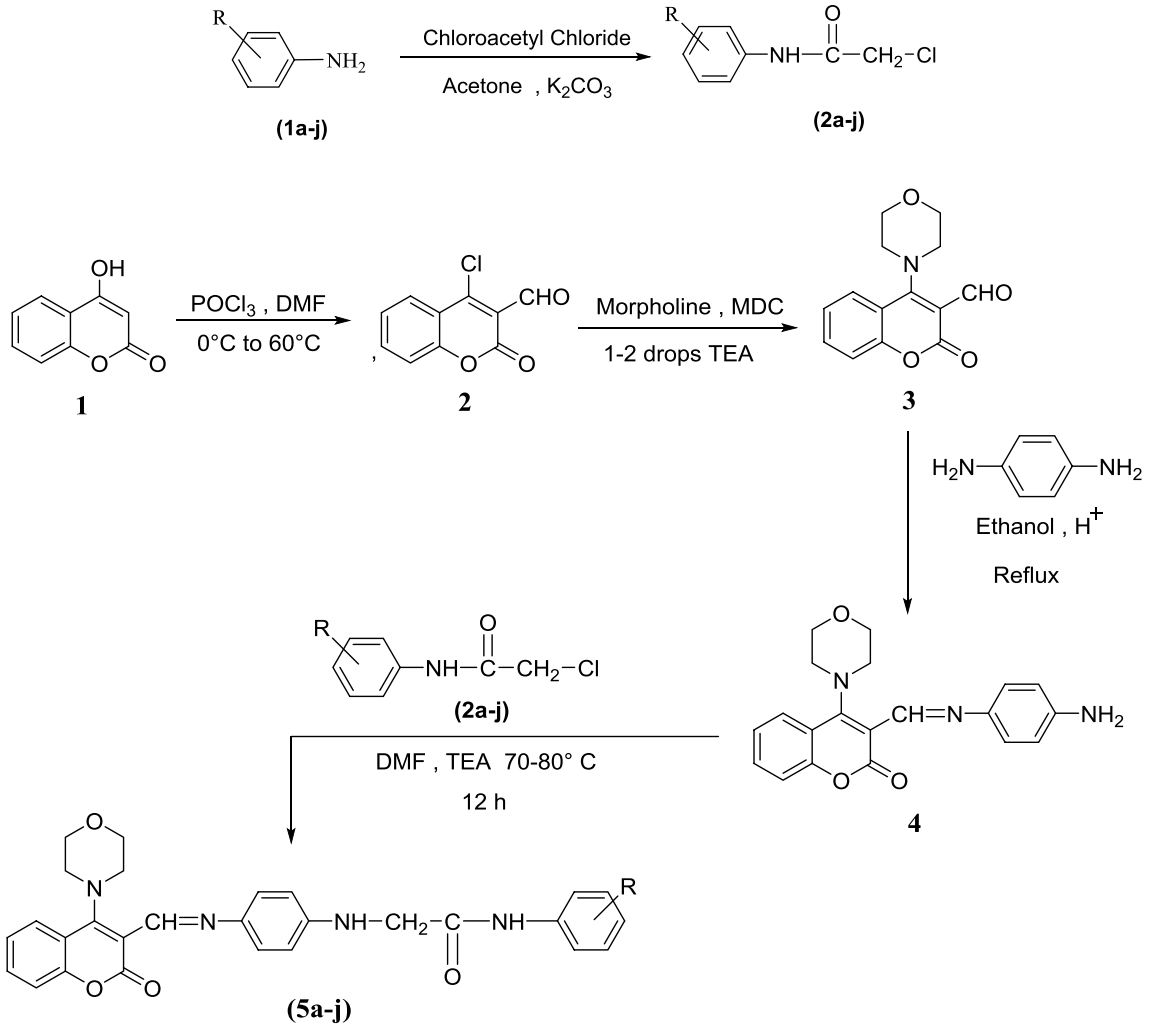
Coumarin, naturally as well as synthetically occurring compound, constitutes a large family of heterocyclic compounds with a benzo-α-pyrone moiety, and its various derivatives have acquired great importance in the field of organic and medicinal chemistry due to its excellent pharmacological properties [3, 4] viz antimicrobial [5], antioxidant [6], antiviral [7], antifungal [8], anti-inflammatory [9], anticancer [10], antiasthmatic [11], and anti-HIV [12, 13] activities. Its extraordinary broad range of biological profile and "immense" therapeutic potential encouraged us to design novel molecule containing coumarin as its core unit with the aim of exploring and modifying its antimicrobial profile. The literature survey reveals that coumarin containing azomethine linkage at C-3 position shows better pharmacological activities which are clinically important [14–17]. Likewise, oxygen- and nitrogen-containing heterocyclic analogs such as morpholine- and morpholine-merged aromatic ring compounds are very vital building blocks in pharmaceutical chemistry. So when morpholine is associated with another heterocyclic or aromatic ring, it stimulates research activity in the field of the medicinal chemistry [18–23].

Furthermore, the significance of amide derivatives is well known due to their biological properties. Amide derivatives were linked with the wide range of pharmacological activities and when they are conjugated with other aromatic and heterocyclic ring exhibits various type of biological activities. They have been reported to possess antitubercular [24], antimicrobial [25], anti-inflammatory [26], antidepressant [27], antitumor [28], antiproliferative [29], anticonvulsant, analgesic, antimalarial, antileukemic, antiviral, and antioxidant activities [30]. The significance of heterocyclic compounds like 4-hydroxycoumarin, morpholine, and analogs which comprise azomethine and amide linkages, in the field of medicinal chemistry and to explore the scope of these motifs, prompted us to develop novel heterocyclic derivatives which comprise all these things in a single molecular framework. So we have developed novel morpholine-clubbed coumarin-based acetamide and cinnamide derivatives via exploration of 3rd position of coumarin with azomethine linkage and examined their antimicrobial and antifungal activity against various Gram-positive and Gram-negative bacterial strains. Moreover, pursuant to thumb rule for physicochemical factor log *P* estimated as hydrophobicity for a drug molecule, it must be underneath "5" to by-pass the cell barrier. To explain the uptake, distribution, biotransformation, and excretion of organic chemicals in biological systems, partition or distribution coefficient is essential factor, and hence in this context, the novel molecules with substantial lipophilic character are offered in order to create remarkable bioactivities [31]. Nowadays, computational studies play an important role in the field of medicinal chemistry with augmented the drug design process, and molecular docking studies of drug molecule provides significant information about the interactions between receptor (target) and drug and becomes helpful in predicting the activity and affinity of drug molecule to their targets [32].

Results and discussion

Chemistry

To accomplish the synthesis of desired compound (**5a**–**5j**) and (**6a**–**6j**), the tracks outlined in Schemes 1 and 2 were implemented. It can be observed from the topography of 4-hydroxycoumarin that it has both nucleophilic and electrophilic properties. The most reactive site of 4-hydroxycoumarin at 3rd position is carbon atom due to its nucleophilicity. So to explore the 3rd position of coumarin nucleus, it is required that motif 3-formyl-4-chlorocoumarin **2** was generated through Vilsmeier–Haack reaction from commercially available 4-hydroxycoumarin [33, 34]. Then compound **2** on treatment with morpholine in dichloromethane as solvent and few drops of triethylamine as catalyst, afforded compound **3** [35, 36]. Further, imine linkage was introduced on 3rd position by treatment of compound **3** with *p*-phenylenediamine in ethanol and few drops of acetic acid as catalyst to get compound **4** [37, 38]. Then compound **4** was condensed with the 2-chloro-*N*-phenyl acetamide in DMF and with cinnamoylchloride in pyridine to get desired compounds (**5a**–**5j**) and (**6a**–**6j**), respectively. The entire synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral studies, and elemental analysis.



Scheme 1 Synthetic strategy of finally synthesized compounds **5a**–**j**

Characterization

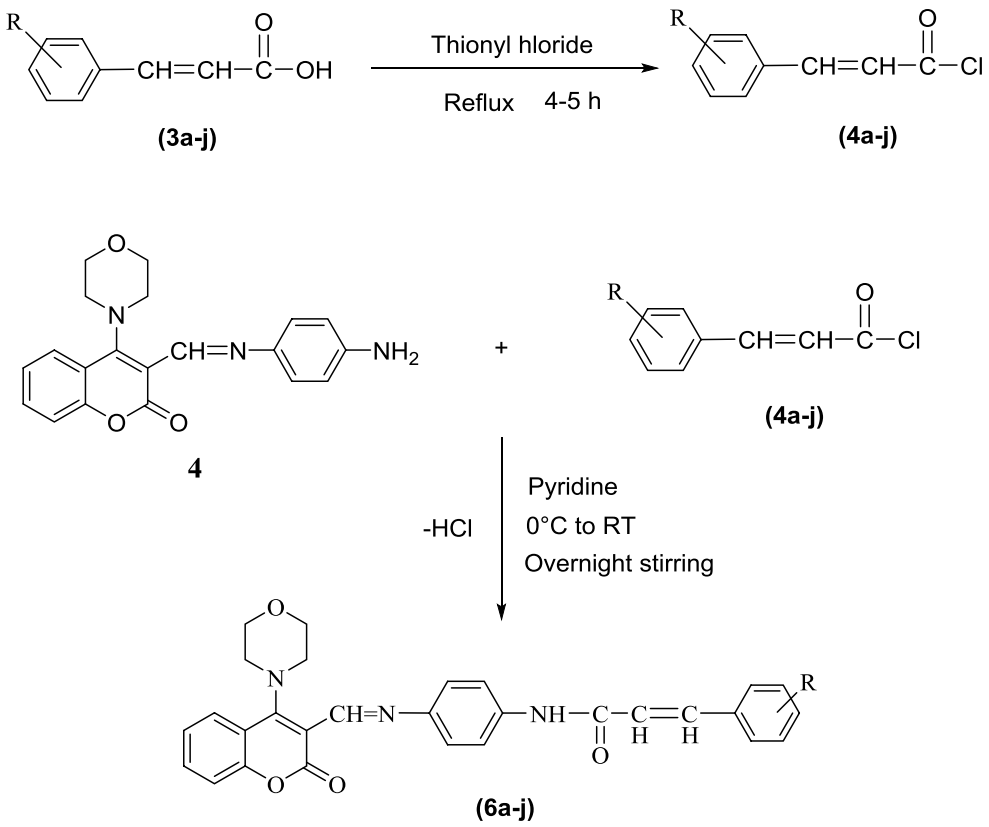
IR spectra

IR spectra of all the newly synthesized compounds **5a**–**5j** and **6a**–**6j** showed a very broad peak of amide formation between 3400 and 3500 cm^{-1} for (–NH) stretching, 1625–1700 cm^{-1} for carbonyl (–C=O) stretching vibrations in pyran nucleus, and 1715–1730 cm^{-1} for carbonyl (–C=O) stretching vibrations in amide. The strong bands for (–C=N) and (–C–O–C–)stretching vibrations were observed between 1690 and 1915 and between 1280 and 1380 cm^{-1} in morpholine, respectively. The aromatic C–H stretching vibrations were observed among 3060–3170 cm^{-1} in the form of a medium band.

^{1}H NMR

^{1}H NMR spectra of all the newly synthesized compound **5a**–**5j** and **6a**–**6j** showed sharp singlet of (–C<u>H</u>=N) proton of imine and proton of (–N<u>H</u>–CO–) amide linkage at 8.50–9.00 δ ppm and 8.00–8.50 δ ppm, respectively. And the multiplet of aromatic region proton lies in the range of 6.30–7.90 δ ppm and the two set of triplet (4H and 4H) proton of morpholine appeared in the range 3.20–3.90 δ ppm and 4.00–4.80 δ ppm, respectively. Further the singlet of proton (–N<u>H</u>) in acetamide derivatives **5a**–**5j** resonates at 6.30–6.90 δ ppm, and doublet of proton (–C<u>H</u>=CH) in cinnamide derivatives appeared between range of 6.20–6.60 δ ppm, and another doublet of proton (–CH=C<u>H</u>–) was inserted into the aromatic region 6.30–7.90 δ ppm.

Scheme 2 Synthetic strategy for finally synthesized compounds **6a**–**j**



Where R =various substituent.

^{13}C NMR

^{13}C NMR spectra of all the newly synthesized compound **5a**–**5j** and **6a**–**6j** showed around 163–170 δ ppm due to the carbonyl (–C=O) carbon of lactone in coumarin, amide group, and (–C–O–) of pyran ring which is attached with morpholine ring and around 150–155 δ ppm which is due to the (–CH=N) imine carbon, while the signals around range between 115 and 155 δ ppm due to the aromatic region carbon and (–C=C–) of cinnamide derivatives. Further the most higher field signal at around 44, 48, and 66 δ ppm can be attributed to methylene group of acetamide derivative carbon (–C–N–C–) and (–C–O–C–) of morpholine ring, respectively.

Biological evaluation

All the newly synthesized morpholine-clubbed 3-substituted coumarinyl acetamide (**5a**–**5j**) and cinnamide derivatives (**6a**–**6j**) were examined for their antibacterial and antifungal activity against different bacterial strains by employing broth microdilution method. The minimum inhibitory concentration (MIC) was determined for each compound along with ciprofloxacin for antibacterial activity and nystatin for antifungal as standard drugs.

Antibacterial activity

The antimicrobial potency in terms of MIC values is summarized in Table 1. It reveals that in general the values of compounds are observed in the varied range (62.5–500 µg/ml) for antibacterial activities against Gram-positive bacterial strain *Staphylococcus aureus* and *Streptococcus pyogenes* and (31.25–500 µg/ml) for antibacterial activities against Gram-negative bacterial strain *Pseudomonas aeruginosa* and *Escherichia coli*, respectively. All the newly synthesized coumarinyl amide derivatives with weakly electron-withdrawing halogen substitution and electron-donating substitution on 4th position of phenyl nucleus were found to be more potent than the remaining ultimate analogs against all the bacterial strains. Compound **5g** and **5j** with 4-chloro and 4-methoxy substituents at the phenyl nucleus of entire coumarin core showed good potency against all the bacterial strains, but among these strains specifically they were more potent against *S. aureus* and *S. pyogenes* with 62.5 and 31.25 µg/ml of MIC, respectively. It can be evidently seen that the compound **5g** (Log $P = 2.78$) and **5j** (Log $P = 2.00$) with lipophilicity displayed higher activity. In addition to this, the compound **5d** (Log $P = 2.21$) and **5f** (Log $P = 2.76$) substituted with electron-withdrawing nitro group at the 4th position of phenyl nucleus and weakly electron-donating

Table 1 In vitro antibacterial and antifungal activities of finally synthesized compounds (**5a**–**j**) and (**6a**–**j**)

Comp. No.	Antibacterial activity						Antifungal activity		
	Minimum inhibitory concentration in µg/ml								
	R	Log *P*	Gram positive		Gram negative		Fungi		
			S. aureus	*S. pyogenes*	*P. aeruginosa*	*E. coli*	*C. albicans*	*A. niger*	*A. clavatus*
5a	–H	2.25	250	250	500	500	500	1000	500
5b	2-NO_2	2.21	500	500	250	250	1000	> 1000	1000
5c	3-NO_2	2.22	500	500	200	200	> 1000	500	1000
5d	4-NO_2	2.21	200	250	500	100	500	> 1000	500
5e	2-Cl	2.77	250	250	500	500	250	500	1000
5f	3-Cl	2.76	200	250	125	200	200	250	500
5g	4-Cl	2.78	62.5	100	100	100	100	500	> 1000
5h	2-CH_3	2.72	200	250	125	100	500	> 1000	> 1000
5i	2-OCH_3	2.00	250	200	250	250	500	500	500
5j	4-OCH_3	2.01	100	100	31.25	250	250	500	500
6a	–H	3.49	250	250	500	500	500	250	100
6b	2-NO_2	3.43	500	500	250	250	250	100	1000
6c	3-NO_2	3.46	500	500	500	250	500	500	1000
6d	4-NO_2	3.45	200	250	200	250	500	500	500
6e	2-CH_3	3.96	100	125	500	500	1000	500	1000
6f	4-CH_3	3.97	200	250	250	250	1000	250	500
6g	2-OCH_3	3.24	250	500	200	250	250	> 1000	> 1000
6h	3-OCH_3	3.22	200	250	250	200	250	> 1000	> 1000
6i	4-OCH_3	3.25	125	125	31.25	100	250	500	500
6j	3,4,5-OCH_3	2.73	62.5	100	125	125	100	> 1000	250
Standard drug	Ciprofloxacin	–	50	50	25	25	–	–	–
	Nystatin	–	–	–	–		100	100	100

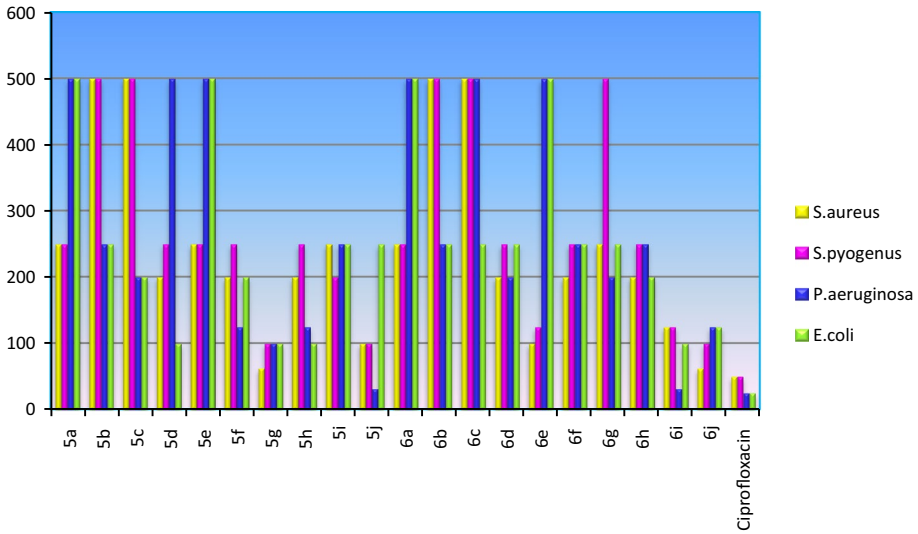
S. aureus, *Staphylococcus aureus*; *S. pyogenes, Streptococcus pyogenes*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *E. coli, Escherichia coli*; *C. albicans, Candida albicans*; *A. niger, Aspergillus niger*; *A. clavatus, Aspergillus clavatus*

chloro group at the 3rd position of phenyl nucleus of acetamide derivatives showed better activity to some extent against Gram-negative bacteria *E. coli* and *P. aeruginosa*, respectively. Other analogs of acetamide **5h** (Log $P = 2.72$) with methyl substituent at the 2nd position of phenyl ring showed good lipophilic value and better activity to some extent against both the Gram-negative bacilli. Rest of the compounds appeared with moderate-to-good activity profile. Furthermore, the coumarinyl cinnamide derivatives also showed diversified activity against different bacterial strains. Final compound **6i** (Log $P = 3.25$) substituted with electron-donating methoxy group at 4th position of phenyl ring of coumarinyl cinnamide derivatives showed good activity against all the *Bacillus*, but among these particularly against Gram-negative *P. aeruginosa*, it showed most prominent activity with 31.25 µg/ml of MIC with higher value of lipophilicity. Another analogs of cinnamide **6j** (Log $P = 2.73$) tri-substituted with electron-donating methoxy group exhibited good activity against both the bacterial strains, but specifically against *S. aureus* it showed promising activity with 62.5 µg/ml of MIC, while the compound **6e** (Log $P = 3.96$) substituted at 2nd position with methyl group and with higher lipophilic parameter showed good activity against Gram-positive bacteria compared to other compounds. Rest of other coumarinyl cinnamide derivatives appeared with moderate-to-good activity profile. None of the compound has reached up to the level of standard drug ciprofloxacin.

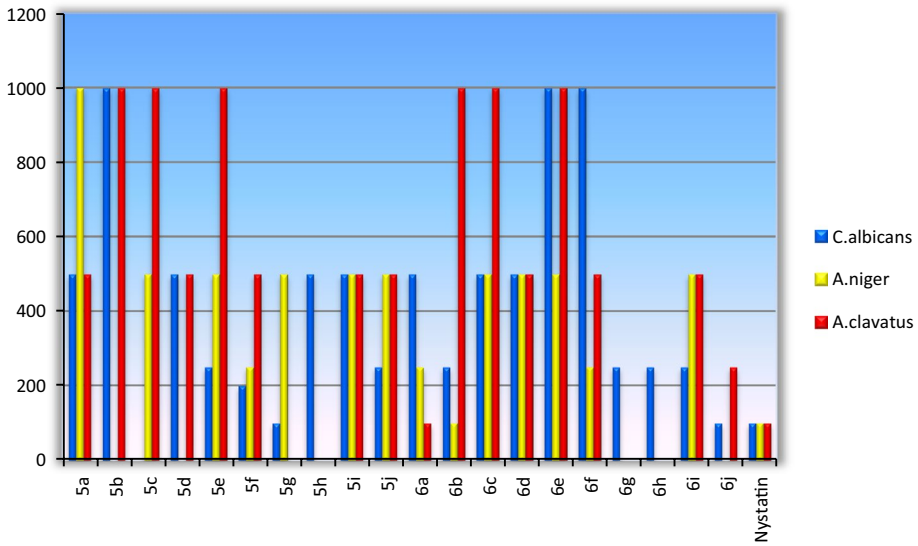
Antifungal Activity

All the synthesized novel derivatives were screened for their in vitro antifungal activity using nystatin as reference drug. The antifungal potency in terms of MIC values is summarized in Table 1. Results of the MIC values of the coumarinyl acetamide derivatives are found in the range (100 to > 1000 µg/ml) against studied fungal strains. Final analogs of coumarinyl acetamide derivative **5g** (Log $P = 2.78$) with electron-donating chloro substituent at the 4th position of phenyl nucleus exhibited better inhibition against *Candida albicans* with 100 µg/

Graphical representation of antibacterial activity of synthesized compounds (**5a**–**5j**) and (**6a**–**6j**)



Graphical representation of antifungal activity of synthesized compounds (**5a**–**5j**) and (**6a**–**6j**)



ml MIC value equivalent to nystatin drug, while none of the acetamide derivatives were reached at the level of standard drug. On the other hand, unsubstituted coumarinyl cinnamide derivatives **6a** (Log $P = 3.49$) with higher lipophilicity showed the best activity against *Aspergillus clavatus* with 100 µg/ml MIC value, while compound **6b** (Log $P = 3.43$) substituted on 2nd position of phenyl nucleus with electron-withdrawing nitro group exhibited potent activity against *Aspergillus niger* with 100 µg/ml MIC value, and **6j** (Log $P = 2.73$) substituted on 3, 4, 5 position of phenyl ring of cinnamide with methoxy group also proved better against *C. albicans* with 100 µg/ml MIC value. Rest of the compounds were not reached up to the level of standard drug nystatin.

Structure–activity relationship studies (SAR)

It was examined from the biological evaluation of derivatives (**5a**–**5j**) and (**6a**–**6j**) is that weakly electron-withdrawing and electron-donating groups provided diverse electronic surroundings on the molecules and demonstrated a great influence on their various biological properties. It is absolutely clear from above-mentioned biological activities in Table 1 that the molecule which possesses electron-donating substituent like (4-OCH_3) (3, 4, 5-OCH_3) and weakly electron-withdrawing substituent like (4-Cl) exhibit much better activity than the other derivatives against Gram-positive and Gram-negative bacteria, while substituent like (4-NO_2), (3-Cl) and (3-CH_3) showed to some extent better

activity against only Gram-negative bacilli, and substituent like (2-CH_3) showed in some extent better activity against only Gram-positive bacilli. It was also observed that for antifungal activity, compound with unsubstituted phenyl nucleus, (2-NO_2), (3, 4, 5-OCH_3), and (4-Cl) exhibited excellent activity compared to standard drug nystatin. SAR study leaded toward conclusion that alteration if undertaken by introducing electron-donating and weakly electron-withdrawing functional group can help to increase the antimicrobial activities of the prepared compounds. From this study, we concluded that substitution by electron-donating and weakly electron-withdrawing group on 4th position of phenyl nucleus of acetamide and cinnamide derivatives are more beneficial for the betterment of antimicrobial profile.

Molecular docking

In biochemical process, DNA gyrase is one of the most important bacterial protein which is engaged with process like transcription and replication, and it catalyzes the negative supercoiling of circular DNA bacteria, and it is also a very known object for the antibacterial compound since its blocking causes the death of bacteria [39]. So with a view to understand the binding mode of the newly synthesized compounds (**5a**–**5j**) and (**6a**–**6j**) against DNA gyrase protein receptor (1KZN), docking study was carried out. All the newly synthesized compounds were docked in the protein structure of *E. coli*, which was obtained from the Protein Data Bank (PDB ID-1KZN), and ciprofloxacin was used as a standard for docking study, and it was docked with target receptor 1KZ. All the ligands showed negative docking scores but none of them reached up to the level of standard ciprofloxacin scores. However, the docking scores of compounds **5e**, **5g**, **5i**, **6i** were found to possess highest negative dock score in all the newly synthesized compounds (Table 2).

And some molecular basis interactions with DNA gyrase protein target enzymes and synthesized compounds can be understood from the docking pose. Crystal structure of protein (1KZN) of *E. coli* and ciprofloxacin are represented as below (Fig. 1).

Figure 2 shows the interaction of ciprofloxacin with receptor protein 1KZN. The docking score of ciprofloxacin was − 6.148, and it was taken as standard for newly synthesized compounds. And the pocket site of ciprofloxacin with receptor included SER-121, ALA-96, VAL-120, and GLU-50 amino acid residues which formed four hydrogen bonds, from which SER-121, ALA-96, VAL-120 formed hydrogen bond with backbone, while GLU-50 formed hydrogen bond with side chain.

Figure 3 shows the interaction of **5e** with DNA gyrase protein 1KZN. The docking score of **5e** was − 5.108, and the pocket site of compound **5e** with receptor protein included ALA-96 and ARG-136 amino acid residues which formed two hydrogen bonds. ALA-96 formed hydrogen bond by electrostatic attraction between N atom of (–NH_2) group of backbone and H atom (–NH–CO–) amide linkage, while ARG-136 formed hydrogen bond by electrostatic attraction between H atom of (–NH_2) group of guanidine side chain and O atom of carbonyl (–CO–) group of pyran nucleus.

Figure 4 shows the interaction of **5g** with DNA gyrase protein 1KZN. The docking score of **5g** was − 5.114, and the pocket site of compound **5g** with receptor protein included ARG-136 amino acid residue which formed 2 hydrogen bonds via side chain. One hydrogen bond formed by electrostatic attraction between H atom of (–NH_2) group of guanidine and N atom of (–CH=N–) imine linkage, and another hydrogen bond is formed by electrostatic attraction between H atom of (–NH_2^+) group of side chain and O atom of carbonyl (–CO–) group of pyran nucleus.

Figure 5 shows the interaction of **5i** with DNA gyrase protein 1KZN. The docking score of compound **5i** was − 5.217, and the pocket site compound **5i** with receptor protein included ASP-46 amino acid residue which formed 2 hydrogen bonds via backbone. Both hydrogen bond formed by electrostatic attraction between 2H atom

Table 2 Docking score of synthesized compounds (**5a**–**j**) and (**6a**–**j**)

Compound No.	*R*	Docking score	Compound No.	*R*	Docking score
Standard	Ciprofloxacin	− 6.148	Standard	Ciprofloxacin	− 6.148
5a	–H	− 3.68	**6a**	–H	− 1.963
5b	2-NO_2	− 2.476	**6b**	2-NO_2	− 3.27
5c	3-NO_2	− 3.441	**6c**	3-NO_2	− 3.732
5d	4-NO_2	− 2.792	**6d**	4-NO_2	− 1.43
5e	2-Cl	− 5.108	**6e**	2-CH_3	− 2.456
5f	3-Cl	− 3.272	**6f**	4-CH_3	− 2.471
5g	4-Cl	− 5.114	**6g**	2-OCH_3	− 3.015
5h	2-CH_3	− 4.311	**6h**	3-OCH_3	− 2.945
5i	2-OCH_3	− 5.217	**6i**	4-OCH_3	− 5.224
5j	4-OCH_3	− 2.391	**6j**	3,4,5-OCH_3	− 2.636

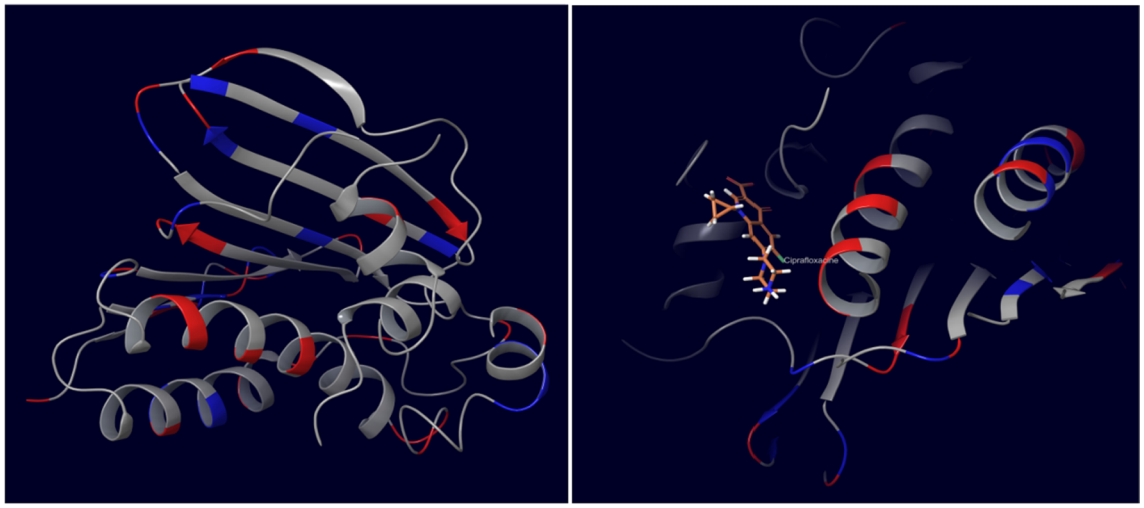


Fig. 1 Crystal structure of target receptor (1KZN) of *E. coli* and standard drug Ciprofloxacin

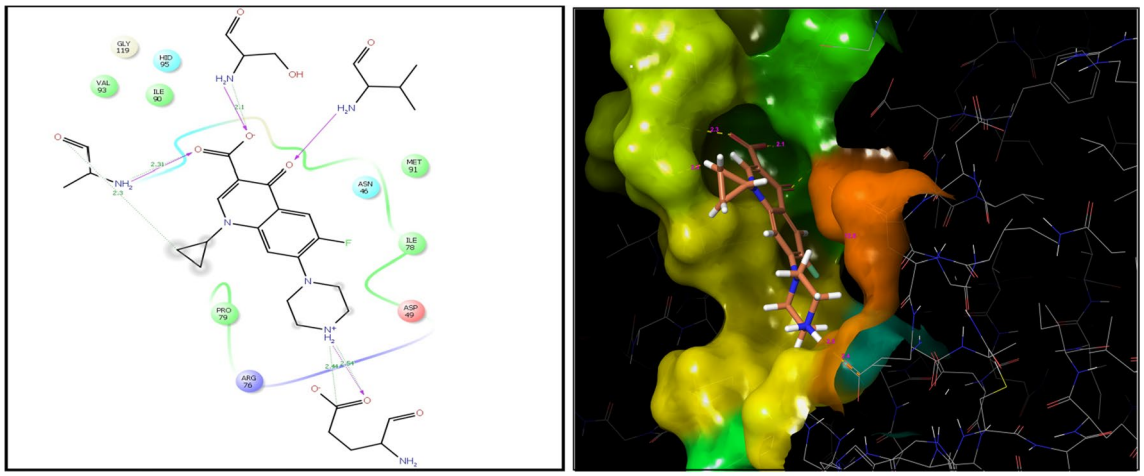


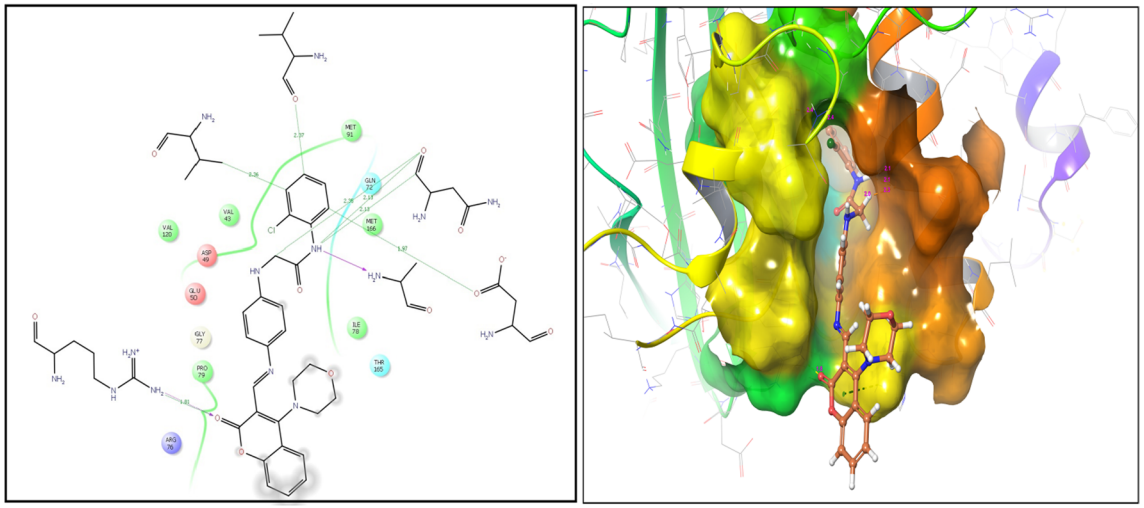
Fig. 2 Binding pose of standard drug ciprofloxacin with receptor protein *E. coli* (1KZN)

of (–NH–CO–NH–) amide linkage and O atom of carbonyl (–CO–) group of pyran nucleus.

Figure 6 shows the interaction of **6i** with DNA gyrase protein 1KZN. The docking score of compound **6i** was − 5.224, and the pocket site of compound **6i** with receptor protein included ARG-76 and ARG-136 amino acid residue from which ARG-136 formed hydrogen bond by electrostatic attraction between H atom of ($-NH_2^+$) group of side chain and O atom of morpholine ring, while another residue ARG-76 showed (π–π stacking) attractive non-covalent interaction with π-bonds of aromatic nucleus which is shown by green line.

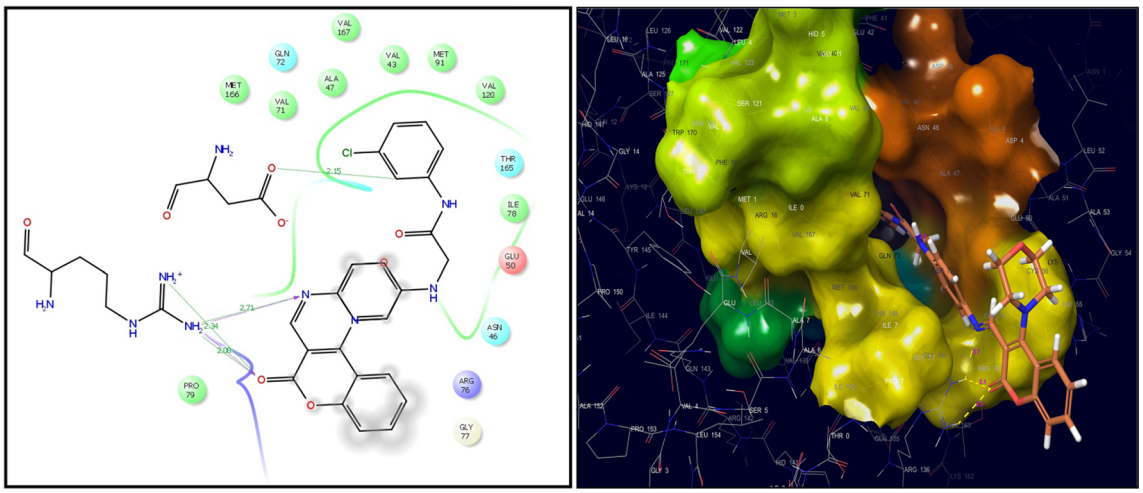
HOMO–LUMO theory (FMO approach)

In frontier molecular orbital theory, "highest occupied molecular orbital" (HOMO) and "lowest unoccupied molecular orbital" (LUMO) are most influential molecular orbital, and the value of their energy gap (E_{HOMO}–E_{LUMO}) reflects the reactivity of molecule. So here we can try to correlate this reactivity with biological activity, and it also reinforces the biological activity [40, 41]. A molecule which possesses a small gap between frontier orbitals is highly polarizable and showed higher chemical reactivity and lower kinetic stability. Generally, the energy of HOMO is directly associated



(Predicted 2D and 3D binding pose of compound 5e)

Fig. 3 Binding pose of compound **5e** with the *E. coli* (1KZN)

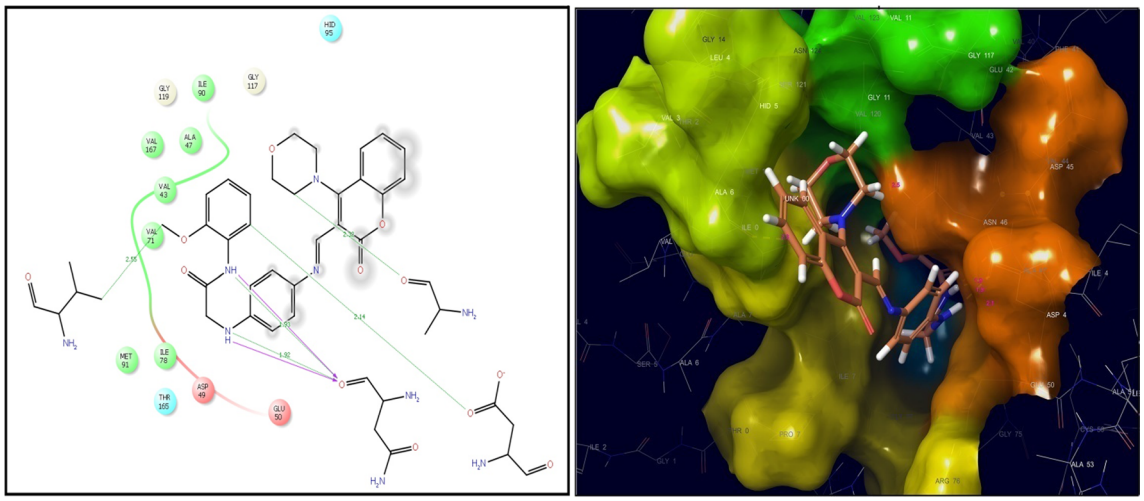


(Predicted 2D and 3D binding pose of compound 5g)

Fig. 4 Binding pose of compound **5g** with the *E. coli* (1KZN)

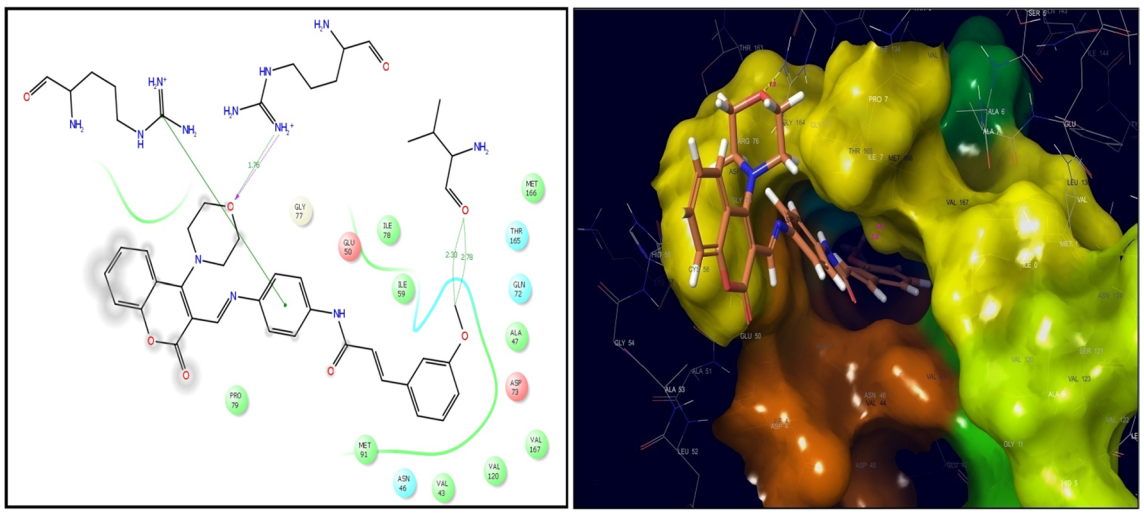
with ionization potential because electrons are weakly held by HOMO, so it loses electrons easily when the molecule is energized. In case of LUMO, it is directly associated with electron affinity because it accepts electrons. The HOMO and LUMO theory was applied on novel synthesized compounds **(5a–5i)** and **(6a–6j)** from these compounds, and some of the substituted compounds like, **5g**, **5j, 6b, 6i, 6j** showed better energy gap when compared to unsubstituted compounds like **5a** and **6a** (Fig. 7).

From Table 3, it is observed that unsubstituted compound **5a** contains HOMO–LUMO Gap (3.565) and further enlisting substituents **5g** and **5j** contain less HOMO–LUMO Gap (3.510) and (3.508), respectively, and exhibited better biological activity. On the other hand, unsubstituted compound **6a** contains HOMO–LUMO Gap (1.347), while substituents **6b** and **6i** contain HOMO–LUMO Gap (0.876) and (0.865), respectively, which were less when compared to unsubstituted compound **6a** and therefore exhibited better biological activity. It can further be concluded that lower the energy gap better activity can be generated.



(Predicted 2D and 3D binding pose of compound 5i)

Fig. 5 Binding pose of compound **5i** with the *E. coli* (1KZN)



(Predicted 2D and 3D binding pose of compound 6i)

Fig. 6 Binding pose of compound **6i** with the *E. coli* (1KZN)

Materials and methods

The melting points of all the newly synthesized compounds were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker AM-400 spectrometer with TMS as internal standard. IR spectra (4000–400 cm^{-1}) of newly synthesized compounds were recorded on a Shimadzu 8400-S FTIR spectrophotometer (Shimadzu India Pvt. Ltd., Mumbai, India) using KBr pellets. The purity of all synthesized compounds was checked using thin layer chromatography (TLC) on silica gel-coated sheets (Merck Kiesel 60 GF-254, 0.2 mm thickness). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz model spectrometer (Varian India Pvt. Ltd., Mumbai, India) using DMSO as a solvent and TMS as internal standard with 1H resonant frequency of 400 MHz and 13C resonant frequency of 100 MHz. The ^{1}H NMR and ^{13}C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS. Mass of the synthesized compound was recorded on GC/MS Shimadzu mass spectrometer, and (M + H) of the compounds was stated in percentage.

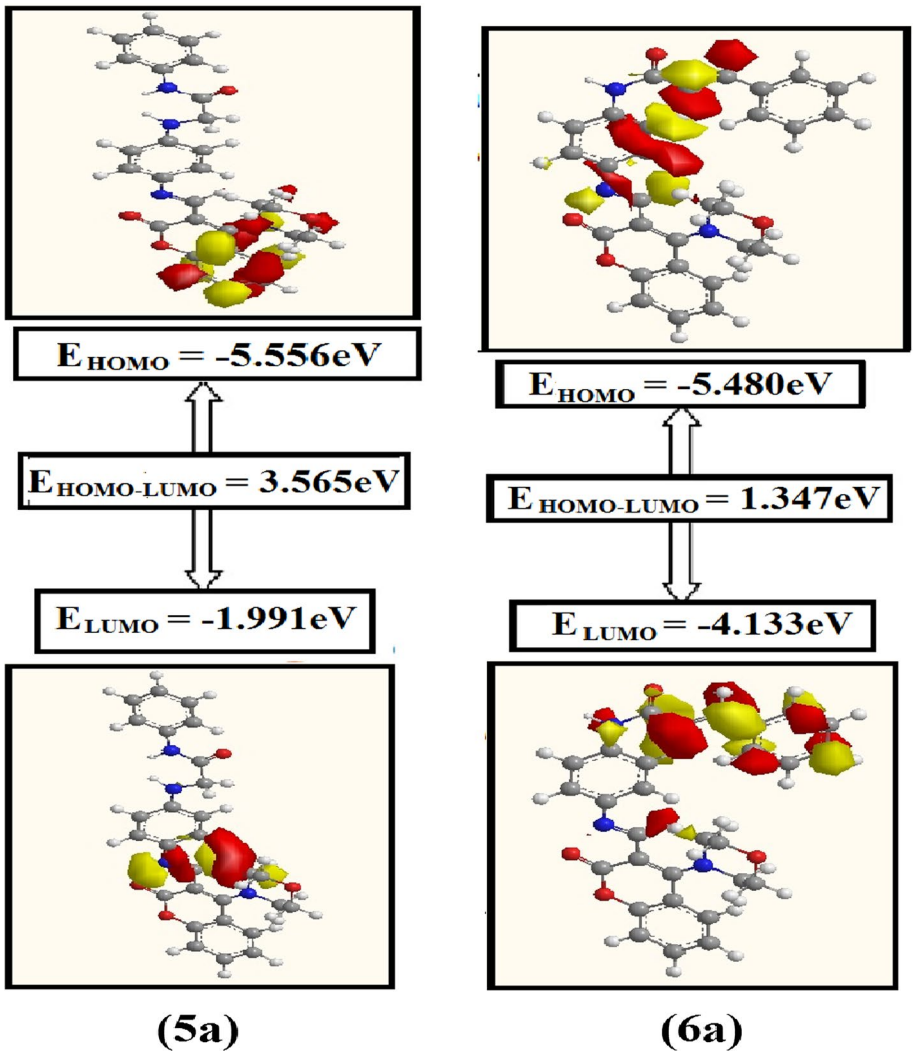


Fig. 7 HOMO–LUMO plot of synthesized compounds **5a** and **6a**

Preparation of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (2)

$POCl_3$ (0.18 mol) was added dropwise to a stirring mixture of 4-hydroxycoumarin **(1)** (0.6 mol) in DMF (46.2 ml), below 0 °C, producing a semisolid mass. A clear solution was appeared after stirring for 1 h at room temperature. Then the temperature was gradually raised up to 60 °C and further stirred for 5–6 h at 60 °C. The progress of reaction was monitored by TLC using ethyl acetate–hexane (6:4) as eluent. After the completion of reaction, it was poured into crushed ice with stirring. The separated solid mass was filtered off and washed thoroughly with water then aqueous Na_2CO_3 (5%). The yellow solid product was obtained. The crude product was purified by crystallization from acetone to get the title compound **(2) M.P.** = 143–148 °C, **Yield** 74%

M.P. = 143 – 148, **Yield** 74%.

Table 3 HOMO–LUMO energy gap of the compounds **5a**, **5g**, **5j** and **6a**, **6b**, **6i**

Compound	E_{HOMO}	E_{LUMO}	HOMO–LUMO gap
5a	– 5.556	– 1.991	3.565
5g	– 5.510	– 2.000	3.510
5j	– 5.509	– 2.001	3.508
6a	– 5.480	– 4.133	1.347
6b	– 5.005	– 4.129	0.876
6i	– 4.964	– 4.099	0.865

Preparation of 4-morpholino-2-oxo-2*H*-chromene-3-carbaldehyde (3)

Morpholine (0.004 mol) in dichloromethane (5 ml) was gradually added with stirring to an ice-cooled mixture of compound **(2)**, (0.002 mol) in dichloromethane (10 ml), and stirred for 30 min at 0–5 °C. The progress of reaction was

monitored by TLC by using chloroform–methanol (9:1) as eluent. After the completion of reaction, the mixture was washed with 3 × 10 ml of water in order to remove unreacted morpholine and its salt. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The dry, flake-like residue was recrystallized from ethanol. The crude product was purified by crystallization from acetone to get the title compound **(3).**

Preparation of 3-(((4-aminophenyl)imino) methyl)-4-morpholino-2*H*-chromen-2-one (4)

A solution of *p*-phenylenediamine (0.002 mol) in ethanol (10 ml) was added to mixture of compound **(3)** (0.002 mol) in ethanol (10 ml) containing 1–2 drops of acetic acid. The reaction mixture was refluxed for 3–4 h. The progress of the reaction was monitored by TLC using ethyl acetate–hexane (4:6) as eluent. After the completion of the reaction, mixture was kept at room temperature for 30 min and then poured into crushed ice. The precipitate obtained was filtered off and washed with water. The crude product was purified by crystallization from absolute alcohol to get the title compound **(4)**.

General synthetic procedure for 2-chloro-*N*-(substituted) phenyl acetamides (2a–2j)

Chloroacetyl chloride (0.06 mol) was added dropwise to a mixture of the appropriate amine (0.05 mol) and K_2CO_3 (0.06 mol) in acetone (50 ml) at room temperature. The reaction mass was refluxed for 4–8 h, and then progress of reaction was monitored by TLC using ethyl acetate–hexane (8:2) solvent system as eluent. Then the reaction mixture was cooled and poured into 100 ml of ice water. The resulting white precipitates were filtered off and dried under the vacuum condition and purified by recrystallization from alcohol. Similarly, other compounds (**5a**–**5j**) were prepared by using various substituted amines.

2-Chloro-*N*-phenyl acetamide (2a): **Yield**: 81%, **M.P.** 110–115 °C. **IR** (KBr) cm^{-1}: 3261 (–NH), 1681 (–C=O).**^{1}H NMR**: (400 MHz, DMSO-d6): δ ppm, 8.46 (br *s*, 1H, –NH), 7.56 (*m*, 2H), 7.40 (*m*, 2H), 7.24 (*m*, 1H), 4.34 (*s*, 2H, $–CH_2–$Cl).

2-Chloro-*N*-(2-nitrophenyl) acetamide (2b): **Yield**: 73%, **M.P.** 165–170 °C. **IR** (KBr) cm^{-1}: 3263 (–NH), 1679 (–C=O). **^{1}H NMR**: (400 MHz, DMSO-d6): δ 8.43 (br *s*, 1H, –NH), 7.63–7.51 (*m*, 4H), 4.28 (*s*, 2H, $–CH_2–$Cl).

2-Chloro-*N*-(3-nitrophenyl) acetamide (2c): Yield: 71%, mp 160–165 °C. **IR** (KBr) cm^{-1}: 3265 (–NH), 1675 (–C=O). **^{1}H NMR**: (400 MHz, DMSO-d6): δ 8.51 (br *s*, 1H, –NH), 7.68–7.52 (*m*, 4H), 4.25 (*s*, 2H, $–CH_2–$Cl).

2-Chloro-*N*-(4-nitrophenyl) acetamide (2d): Yield: 76%, **M.P.** 168–170 °C. **IR** (KBr), cm^{-1}: 3273 (–NH), 1667 (–C=O). **^{1}H NMR**: (400 MHz, DMSO-d6): δ 8.61 (br *s*, 1H, –NH), 7.63–7.450 (*m*, 4H), 4.32 (*s*, 2H,$–CH_2–$Cl).

2-Chloro-*N*-(2-chlorophenyl) acetamide (2e): Yield: 79%, **M.P.** 151–154 °C. **IR** (KBr), cm^{-1}: 3282 (–NH), 1668 (–C=O). **^{1}H NMR**: (400 MHz, DMSO-d6): δ *d* 8.45 (br *s*, 1H, –NH), 7.68–7.21 (*m*, 4H), 4.28 (*s*, 2H, $–CH_2–$Cl).

2-Chloro-*N*-(3-chlorophenyl) acetamide (2f): Yield: 83%, **M.P.** 140–143 °C. **IR** (KBr), cm^{-1}: 3293 (–NH), 1675 (–C=O). **^{1}H NMR**: (400 MHz, DMSO-d6): δ *d* 8.46 (br *s*, 1H, –NH), 7.73 (*s*, 1H), 7.58–7.29 (*m*, 3H), 4.31 (*s*, 2H, $–CH_2–$Cl).

2-Chloro-*N*-(4-chlorophenyl) acetamide (2g): **Yield**: 85%, **M.P.** 145–147 °C. **IR** (KBr), cm^{-1}: 3297 (–NH), 1681 (–C=O). **^{1}H NMR**: (400 MHz, DMSO-d6): δ *d* 8.51 (br *s*, 1H, –NH), 7.72–7.25 (*m*, 4H), 4.27 (*s*, 2H, $–CH_2–$Cl).

2-Chloro-*N*-*p*-tolylacetamide (2h): Yield: 82%, **M.P.** 162–164 °C. **IR** (KBr), cm^{-1}: 3294 (–NH), 1675 (–C=O). **^{1}H NMR** (400 MHz, DMSOd6): δ 8.36 (br *s*, 1H, –NH), 7.53–7.48 (*m*, 2H), 7.37–7.36 (*m*, 2H), 4.29 (*s*, 2H, $–CH_2–$Cl), 2.15 (*s*, 3H, $–CH_3$).

2-Chloro-*N*-(2-methoxyphenyl)acetamide (2i): **Yield**: 80%, Limpid. **IR** (KBr), cm^{-1}: 3318 (–NH), 1658 (–C=O). **^{1}H NMR**: (400 MHz, DMSOd6): δ 8.28 (br *s*, 1H, –NH), 7.66 (*d*, $J = 7.5$ Hz, 2H), 7.45 (*d*, $J = 7.1$ Hz, 2H), 4.28 (*s*, 2H, $–CH_2–$Cl), 3.79 (*s*, 3H, $–OCH_3$).

2-Chloro-*N*-(4-methoxyphenyl)acetamide (2j): **Yield**: 78%, **M.P.** 121–122 °C. **IR** (KBr), cm^{-1}: 3331 (–NH), 1661 (–C=O). **^{1}H NMR**: (400 MHz, DMSOd6): δ 8.37 (br *s*, 1H, –NH), 7.58 (*d*, $J = 7.5$ Hz, 2H), 7.38 (*d*, $J = 7.1$ Hz, 2H), 4.21 (*s*, 2H, $–CH_2–$Cl), 3.67 (*s*, 3H, $–OCH_3$).

General synthetic procedure for 2-((4-(((4-morpholino-2-oxo-2*H*-chromene-3-yl)methylene) amino)phenyl)amino)-*N*-phenylacetamide (5a–5j)

A mixture of compound **(4)** (0.0014 mol) and K_2CO_3 (0.0021 mol) in anhydrous dimethylformamide (10 ml) was stirred for 1 h at room temperature. Then the solution of 2-chloro-*N*-phenyl acetamide **(5)** (0.0014 mol) in 5 ml DMF solvent and appropriate catalytic amount of triethylamine was added to this reaction mixture and refluxed for 3–12 h. The progress of reaction was monitored by TLC using ethyl acetate–hexane (6:4) as eluent. After the completion of reaction, the reaction mixture was poured into ice-cold water. The crude product was filtered and washed

thoroughly with cold water for several times and purified by absolute alcohol to get the title compound (**5**). Similarly, other final compounds (**5a**–**5j**) were prepared from intermediate (**4**) with various substituted aryl acetamide.

2-((4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl) methylene)amino)phenyl)amino)-*N*-phenyl acetamide-(5a) Yield: 75%, **M.P.** 234 °C. **IR** (KBr), cm^{-1}: 3413 (–NH), 3067 (–CH), 1718 (–C=O), 1692 (–C=O), 1625 (–C=N), 1593 (–C=C–Ar), 1287 (–C–O–C–morphine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.33 (*t*, 4H *J* = 4.1 Hz), 4.05 (*t*, 4H *J* = 4.1 Hz), 4.34 (*s*, 2H), 7.60–6.54 (a set of signals 14H, aromatic protons and Ar–N<u>H</u>–), 8.58 (*s*, 1H), 8.88 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 483.0. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.5, 48.5, 66.1, 84.8, 117.3, 117.9, 121.4, 123.7, 125.1, 126.9, 127.9, 129.3, 130.3, 137.7, 143.3, 148.1, 150.6, 151.9, 164.3, 165.5, 167.9, **Elemental Analysis**: Calcd. for $C_{28}H_{26}N_4O_4$: C, 69.70; H, 5.43; N, 11.61. Found: C, 69.67; H, 5.39; N, 11.58.

2-((4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)amino)-*N*-(2-nitrophenyl)acetamide-(5b) Yield: 62%, **M.P.** 248 °C. **IR** (KBr), cm^{-1}: 3415 (–NH), 3069 (–CH), 1720 (–C=O), 1695 (–C=O), 1627 (–C=N), 1596 (–C=C–Ar), 1538, 1343 (Ar–NO_2), 1285 (–C–O–C–morphine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.80 (*t*, 4H *J* = 4.1 Hz), 4.35 (*t*, 4H *J* = 4.1 Hz), 4.68 (*s*, 2H), 7.84–6.38 (a set of signals 13H, aromatic protons and Ar–N<u>H</u>–), 8.28 (*s*, 1H), 8.78 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 528.1. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.5, 48.5, 66.1, 84.8, 117.3, 117.9, 124.0, 125.1, 126.9, 127.9, 133.6, 136.5, 143.3, 148.1, 150.6, 151.9, 164.3, 165.5, 167.7. **Elemental Analysis**: Calcd. for $C_{28}H_{25}N_5O_6$: C, 63.75; H, 4.78; N, 13.28. Found: C, 63.72; H, 4.76; N, 13.25.

2-((4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)amino)-*N*-(3-nitrophenyl)acetamide-(5c) Yield: 64%, **M.P.** 240 °C. IR (KBr), cm^{-1}: 3411 (–NH), 3066 (–CH), 1720 (–C=O), 1691 (–C=O), 1622 (–C=N), 1592 (–C=C–Ar), 1551, 1338 (Ar–NO_2), 1283 (–C–O–C–morphine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.60 (*t*, 4H *J* = 4.2 Hz), 4.31 (*t*, 4H *J* = 4.2 Hz), 4.67 (*s*, 2H), 7.84–6.38 (a set of signals 13H, aromatic protons and Ar–N<u>H</u>–)), 8.28 (*s*, 1H), 8.63 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 528.0. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.5, 48.5, 66.1, 84.8, 115.8, 117.3, 117.9, 120.2, 125.1, 126.9, 127.0, 127.9, 129.2, 130.3, 139.6, 143.3, 148.1, 148.7, 150.6, 151.8, 164.3, 165.5, 167.8. **Elemental Analysis**: Calcd. for $C_{28}H_{25}N_5O_6$: C, 63.75; H, 4.78; N, 13.28. Found: C, 63.78; H, 4.77; N, 13.26.

2-((4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)amino)-*N*-(4-nitrophenyl)acetamide-(5d) Yield: 71%, **M.P.** 239 °C. **IR** (KBr), cm^{-1}: 3411 (–NH), 3058 (–CH), 1716 (–C=O), 1688 (–C=O), 1618 (–C=N), 1587 (–C=C–Ar), 1559, 1352 (Ar–NO_2), 1284 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.80 (*t*, 4H *J* = 3.9 Hz), 4.30 (*t*, 4H *J* = 3.9 Hz), 4.65 (*s*, 2H), 8.21–6.38 (a set of signals 13H, aromatic protons and Ar–N<u>H</u>–), 8.22 (*s*, 1H), 8.75 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 528.2. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.6, 48.5, 66.1, 84.6, 117.3, 117.9, 120.6, 125.1, 125.5, 126.9, 127.9, 130.3, 143.3, 148.1, 145.4, 148.1, 150.6, 151.9, 164.3, 165.5, 167.9. **Elemental Analysis**: Calcd. for $C_{28}H_{25}N_5O_6$: C, 63.75; H, 4.78; N, 13.28. Found: C, 63.72; H, 4.79; N, 13.31.

***N*-(2-chlorophenyl)-2-((4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)amino)acetamide-(5e) Yield**: 72%, **M.P.** 225 °C. **IR** (KBr),cm^{-1}: 3411 (–NH), 3057 (–CH), 1716 (–C=O), 1685 (–C=O), 1616 (–C=N), 1584 (–C=C–Ar), 1282 (–C–O–C–morpholine). **MS** (ESI): *m/z* ([M + H] +); 517.0. **^{1}H NMR**:(400 MHz, DMSO-d_6): δ 3.82 (*t*, 4H *J* = 4.1 Hz) 4.30 (*t*, 4H *J* = 4.1 Hz), 4.60 (*s*, 2H), 7.72–6.30 (a set of signals 13H, aromatic protons and Ar–N<u>H</u>–), 8.22 (*s*, 1H), 8.80 (*s*, 1H).**^{13}C NMR** (100 MHz, DMSO-d_6): δ 44.5, 48.5, 66.1, 84.8, 117.3, 117.9, 120.3, 120.4, 124.8, 125.1, 126.9, 127.9, 129.9, 130.6, 134.3, 139.5, 143.3, 148.1, 150.6, 151.9, 164.8, 165.5, 167.9. **Elemental Analysis**: Calcd. for $C_{28}H_{25}ClN_4O_4$: C, 65.05; H, 4.87; N, 10.84. Found: C, 65.08; H, 4.86; N, 10.82.

***N*-(3-chlorophenyl)-2-((4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)amino)acetamide-(5f) Yield**: 73%, **M.P.** 229 °C. **IR** (KBr), cm^{-1}: 3413 (–NH), 3059 (–CH), 1718 (–C=O), 1681 (–C=O), 1611 (–C=N), 1587 (–C=C–Ar), 1286 (–C–O–C–morpholine).**^{1}H NMR**:(400 MHz, DMSO-d_6): δ 3.79 (*t*, 4H *J* = 4.2 Hz), 4.10 (*t*, 4H *J* = 4.2 Hz), 4.51 (*s*, 2H), 7.72–6.40 (a set of signals 13H, aromatic protons and Ar–N<u>H</u>–), 8.21 (*s*, 1H), 8.75 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 517.2. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.5, 48.5, 66.1, 84.8, 117.3, 117.9, 120.2, 124.8, 125.1, 126.9, 127.95, 129.9, 130.3, 134.3, 139.5, 143.3, 148.3, 150.5, 151.9, 164.3, 165.1, 167.6. **Elemental Analysis**: Calcd. for $C_{28}H_{25}ClN_4O_4$: C, 65.05; H, 4.87; N, 10.84. Found: C, 65.03; H, 4.85; N, 10.85.

***N*-(4-chlorophenyl)-2-((4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene amino)phenyl)amino)acetamide-(5g) Yield:** 76%, **M.P.** 228 °C. **IR** (KBr), cm^{-1}: 3415 (–NH), 3059 (–CH), 1716 (–C=O), 1683 (–C=O), 1616 (–C=N), 1582 (–C=C–Ar), 1283 (–C–O–C–morpholine). **^{1}H NMR:** (400 MHz, DMSO-d_6): δ 3.70 (*t*, 4H *J* = 4.1 Hz), 4.09 (*t*, 4H *J* = 4.1 Hz), 4.50 (*s*, 2H), 7.74–6.55 (a set of

signals 13H, aromatic protons and Ar–NH–), 8.20 (*s*, 1H), 8.73 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 517.1.**^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.5, 48.5, 66.1, 84.7, 117.3, 117.9, 122.2, 125.1, 126.9, 127.9, 128.6, 129.2, 130.3, 134.5, 139.5, 143.3, 148.1, 150.6, 151.9, 164.3, 165.5, 167.9. **Elemental Analysis**: Calcd. for $C_{28}H_{25}ClN_4O_4$: C, 65.05; H, 4.87; N, 10.84. Found: C, 65.07; H, 4.88; N, 10.83.

2-((4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl) methylene)amino)phenyl)amino)-*N*-(o-tolyl)acetamide-(5h) Yield: 69%, **M.P. 274** °C. **IR** (KBr), cm^{-1}: 3418 (–NH), 3053 (–CH), 1714 (–C=O), 1689 (–C=O), 1618 (–C=N), 1586 (–C=C–Ar), 1282 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 2.42 (*s*, 3H), 3.70 (*t*, 4H *J* = 4.1 Hz), 4.09 (*t*, 4H *J* = 4.1 Hz), 4.31 (*s*, 2H), 7.69–6.33 (a set of signals 13H, aromatic protons and Ar–NH–), 8.21 (*s*, 1H), 8.71 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 497.2.**^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.5, 48.5, 56.7, 66.1, 84.8, 112.6, 117.3, 117.9, 121.50 122.2, 125.0, 126.9, 130.0, 130.3, 143.3, 147.9, 148.1, 150.6, 151.9, 164.3, 165.5, 167.7. **Elemental Analysis**: Calcd. for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28. Found: C, 70.12; H, 5.70; N, 11.25.

***N*-(2-methoxyphenyl)-2-((4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)amino)acetamide-(5i) Yield**: 71%, **M.P.** 240 °C. **IR** (KBr), cm^{-1}: 3421 (–NH), 3053 (–CH), 1711 (–C=O), 1681 (–C=O), 1615 (–C=N), 1591 (–C=C–Ar), 1279 (–C–O–C–morpholine). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.77 (*t*, 4H *J* = 3.9 Hz), 3.95 (*s*, 3H), 4.17 (*t*, 4H *J* = 3.9 Hz), 4.38 (*s*, 2H), 7.71–6.34 (a set of signals 13H, aromatic protons and Ar–NH–), 8.16 (*s*, 1H), 8.70 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 513.0.**^{13}C NMR** (100 MHz, DMSO-d_6): δ, 44.5, 48.5, 56.0, 66.1, 84.8, 112.6, 117.3, 117.9, 117.9, 122.7, 124.9, 125.1, 126.9, 127.9, 130.3, 131.8, 137.4, 143.3, 148.1, 150.6, 151.9, 164.3, 165.56 167.7. **Elemental Analysis**: Calcd. for $C_{29}H_{28}N_4O_5$: C, 67.96; H, 5.51; N, 10.93. Found: C, 67.98; H, 5.50; N, 10.90.

***N*-(4-methoxyphenyl)-2-((4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)amino)acetamide-(5j) Yield**: 78%, **M.P.**: 239 °C. IR (KBr), cm^{-1}: 3424 (–NH), 3053 (–CH), 1719 (–C=O), 1681 (–C=O), 1614 (–C=N), 1586 (–C=C–Ar), 1277 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.50 (*t*, 4H *J* = 4.2 Hz), 3.97 (*s*, 3H), 4.09 (*t*, 4H *J* = 4.2 Hz), 4.33 (*s*, 2H), 7.66–6.33 (a set of signals 13H, aromatic protons and Ar–NH–), 8.27 (*s*, 1H), 8.70 (*s*, 1H). **MS** (ESI).: *m/z* ([M + H] +); 513.2.**^{13}C NMR**: (100 MHz, DMSO-d_6): δ 44.5, 48.5, 56.0, 66.2, 84.8, 114.5, 117.3, 117.9, 122.0, 125.1, 126.9, 127.9, 130.0, 131.2, 131.8, 143.3, 148.1, 150.6, 151.9, 156.4, 164.3, 165.5, 167.9. **Elemental Analysis**: Calcd. for $C_{29}H_{28}N_4O_5$: C, 67.96; H, 5.51; N, 10.93. Found: C, 67.99; H, 5.49; N, 10.90.

General synthetic procedure for 3-phenyl acryloyl-chloride (4a–4j)

A mixture of various substituted cinnamic acid (0.01 mol) and thionylchloride (10.0 ml) was heated under reflux condition and stirred for 4–5 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the unreacted thionylchloride was removed under reduced pressure by distillation, and then remaining residue was used for further step without recrystallization. Similarly, other compounds were also prepared.

General synthetic procedure for *N*-(4-(((-morpholino-2-oxo-2*H*-chromene-3-yl)methylene) amino)phenyl)-3-(substituted)phenyl acrylamide (6a–6j)

A solution of compound **(4)** (0.003 mol) in 10 ml of pyridine was slowly added to a freshly prepared 3-phenyl acryloyl chloride **(5)** (0.003 mol) at (0–5 °C), and it was further stirred to 30 min. After addition, the temperature was gradually raised up to room temperature and further stirred for 15 h. The progress of reaction was monitored by TLC using hexane–ethylacetate (7:3) as eluent. After the completion of reaction, it was poured into ice-cold water. The crude product was filtered off and washed thoroughly with water in several times. This crude product was purified by recrystallization from absolute alcohol to get title compound **(6)**. Similarly, other compounds (**6a**–**6j**) were prepared from intermediate **(4)** with various substituted cinnamoyl chloride.

***N*-(4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)-3-phenylacrylamide-(6a) Yield**: 67% **M.P.** 244 °C. **IR** (KBr), cm^{-1}: 3457 (–NH), 3167 (–CH), 1725 (–C=O), 1696 (–C=O), 1900 (–C=N), 1610 (–C=C–Ar), 1375 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.26 (*t*, 4H *J* = 4.1 Hz), 4.18 (*t*, 4H *J* = 4.1 Hz), 6.42 (*d*, 1H, *J* = 12.1 Hz, =CH); 7.67–7.24 (a set of signals 14H, aromatic protons and =CH–); 8.15 (*s*, 1H), 8.98 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 480.2. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.6, 66.5, 84.8, 117.3, 117.9, 123.6, 125.1, 126.4, 127.9, 128.0, 129.0, 129.4, 130.3, 131.8, 135.8, 135.9, 142.0, 144.7, 150.6, 151.9, 164.6, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{29}H_{25}N_3O_4$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.61; H, 5.23; N, 8.73.

***N*-(4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl) methylene)amino)phenyl)-3-(2-nitrophenyl)acrylamide-(6b) Yield**: 59% **M.P.** 255 °C. **IR** (KBr), cm^{-1}: 3461

(–NH), 3169 (–CH), 1732 (–C=O), 1692 (–C=O), 1905 (–C=N), 1614 (–C=C–Ar), 1545, 1335 (Ar–NO_2), 1378 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.70 (*t*, 4H *J* = 4.0 Hz), 4.15 (*t*, 4H *J* = 4.0 Hz), 6.50 (*d*, 1H, *J* = 12.0 Hz, =CH); 7.50–6.68 (a set of signals 13H, aromatic protons and =C<u>H</u>–); 8.28 (*s*, 1H), 8.75 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 525.1. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.5, 66.6, 84.8, 117.3, 117.9, 123.6, 125.0, 125.1, 126.4, 127.9, 130.3, 130.4, 131.8, 133.2, 135.9, 141.0, 147.7, 147.9, 150.6, 151.9, 164.3, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{29}H_{24}N_4O_6$: C, 66.41; H, 4.61; N, 10.68. Found: C, 66.38; H, 4.62; N, 10.65.

***N*-(4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl) methylene)amino)phenyl)-3-(3-nitrophenyl)acrylamide-(6c) Yield**: 56% **M.P.** 252 °C. **IR** (KBr), cm^{-1}: 3454 (–NH), 3163 (–CH), 1718 (–C=O), 1691 (–C=O), 1898 (–C=N), 1612 (–C=C–Ar), 1532, 1331 (Ar–NO_2), 1378 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.60 (*t*, 4H *J* = 4.1 Hz), 4.45 (*t*, 4H *J* = 4.1 Hz), 6.40 (*d*, 1H, *J* = 12.1 Hz, =CH), 7.73–6.90 (a set of signals 13H, aromatic protons and =C<u>H</u>–), 8.28 (*s*, 1H), 8.75 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 525.0. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.5, 66.4, 84.7, 117.3, 117.9, 123.6, 123.9, 125.1, 125.5, 126.4, 127.9, 129.2, 130.3, 131.8, 135.4, 135.9, 137.9, 141.8, 144.7, 148.1, 150.6, 151.9, 164.3, 165.4, 166.6. **Elemental Analysis**: Calcd. for $C_{29}H_{24}N_4O_6$: C, 66.41; H, 4.61; N, 10.68. Found: C, 66.39; H, 4.60; N, 10.66.

***N*-(4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl) methylene)amino)phenyl)-3-(4-nitrophenyl)acrylamide-(6d) Yield**: 61% **M.P.** 259 °C. **IR** (KBr), cm^{-1}: 3459 (–NH), 3163 (–CH), 1712 (–C=O), 1693 (–C=O), 1891 (–C=N), 1616 (–C=C–Ar), 1550, 1342 (Ar–NO_2), 1372 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.72 (*t*, 4H *J* = 4.0 Hz), 4.20 (*t*, 4H *J* = 4.0 Hz), 6.29 (*d*, 1H, *J* = 12.2 Hz, =CH), 7.73–6.90 (a set of signals 13H, aromatic protons and =C<u>H</u>–), 8.23 (*s*, 1H), 8.74 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 525.2.**^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.6, 66.4, 84.8, 117.3, 117.9, 123.6, 124.4, 125.1, 126.4, 127.9, 129.1, 130.3, 131.8, 135.9, 142.0, 142.4, 144.7, 147.8, 150.6, 151.9, 164.3, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{29}H_{24}N_4O_6$: C, 66.41; H, 4.61; N, 10.68. Found: C, 66.37; H, 4.63; N, 10.66.

***N*-(4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)-3-(*o*-tolyl)acrylamide-(6e) Yield**: 62%, **M.P.** 271 °C. **IR** (KBr), cm^{-1}: 3451 (–NH), 3158 (–CH), 1716 (–C=O), 1696 (–C=O), 1886 (–C=N), 1612 (–C=C–Ar), 1379 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 2.22 (*s*, 3H), 3.77 (*t*, 4H *J* = 4.2 Hz), 4.16 (*t*, 4H *J* = 4.2 Hz), 6.57 (*d*, 1H, *J* = 12.0 Hz, =CH), 7.56–7.07 (a set of signals 13H, aromatic protons and =C<u>H</u>–), 8.19 (*s*, 1H), 8.79 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 494.2. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.5, 66.2, 84.7, 117.3, 117.9, 123.6, 125.1, 126.4, 127.6, 127.9, 128.3, 129.4, 130.0, 130.3, 131.8, 135.2, 135.9, 136.0, 139.1, 144.7, 150.6, 151.9, 164.3, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{30}H_{27}N_3O_4$: C, 73.01; H, 5.51; N, 8.51. Found: C, 73.03; H, 5.50; N, 8.49.

***N*-(4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)-3-(*p*-tolyl)acrylamide-(6f) Yield**: 65%, **M.P.** 268 °C. **IR** (KBr), cm^{-1}: 3461 (–NH), 3149 (–CH), 1718 (–C=O), 1688 (–C=O), 1901 (–C=N), 1621 (–C=C–Ar), 1382 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 2.31 (*s*, 3H), 3.72 (*t*, 4H *J* = 4.0 Hz), 4.17 (*t*, 4H *J* = 4.0 Hz), 6.48 (*d*, 1H, *J* = 12.0 Hz, =CH), 7.61–6.82 (a set of signals 13H, aromatic protons and =C<u>H</u>–), 8.09 (*s*, 1H), 8.75 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 494.1. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.5, 66.3, 84.8, 117.4, 117.9, 123.6, 125.1, 126.4, 127.9, 128.1, 129.1, 130.3, 131.8, 133.9, 135.9, 139.3, 142.0, 144.7, 150.6, 151.9, 164.3, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{30}H_{27}N_3O_4$: C, 73.01; H, 5.51; N, 8.51. Found: C, 73.04; H, 5.53; N, 8.52.

3-(2-Methoxyphenyl)-*N*-(4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)acrylamide-(6g) Yield: 69%, **M.P.** 244 °C. IR (KBr), cm^{-1}: 3451 (–NH), 3152 (–CH), 1721 (–C=O), 1684 (–C=O), 1904 (–C=N), 1623 (–C=C–Ar), 1386 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.65 (*t*, 4H *J* = 4.1 Hz), 3.91 (*s*, 3H), 4.15 (*t*, 4H *J* = 4.1 Hz), 6.47 (*d*, 1H, *J* = 12.2 Hz, =CH), 7.52–6.93 (a set of signals 13H, aromatic protons and =C<u>H</u>–), 8.13 (*s*, 1H), 8.75 (*s*, 1H). **MS** (ESI) *m/z*: 510.1 (M + H).**^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.56, 56.79, 66.13, 84.71, 113.51, 117.36, 117.93, 120.84, 123.67, 125.11, 126.47, 127.84, 127.95, 129.59, 130.36, 130.57, 131.86, 135.99, 142.57, 147.21, 151.91, 155.81, 157.36, 164.37, 165.50, 166.67. **Elemental Analysis**: Calcd. for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found:: C, 70.69; H, 5.36; N, 8.23.

3-(3-Methoxyphenyl)-*N*-(4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)acrylamide-(6h) Yield:71%, **M.P.** 240 °C. **IR** (KBr), cm^{-1}: 3459 (–NH), 3161 (–CH), 1728 (–C=O), 1690–(C=O), 1906 (–C=N), 1619 (–C=C–Ar), 1389 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.68 (*t*, 4H *J* = 4.0 Hz), 3.81 (*s*, 3H), 4.11 (*t*, 4H *J* = 4.0 Hz), 6.55 (*d*, 1H, *J* = 12.1 Hz, =CH), 7.48–6.94 (a set of signals 13H, aromatic protons and =C<u>H</u>–); 8.05 (*s*, 1H), 8.81 (*s*, 1H) **MS** (ESI): *m/z* ([M + H] +); 510.0. **^{13}C NMR**: (100 MHz,

DMSO-d_6): δ 48.5, 56.0, 66.1, 84.7, 113.5, 115.6, 117.3, 117.9, 121.0, 123.6, 125.1, 126.4, 127.9, 129.1, 130.3, 130.5, 131.8, 135.9, 137.9, 141.8, 147.2, 151.9, 155.8, 160.7, 164.3, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found: C, 70.68; H, 5.32; N, 8.28.

3-(4-Methoxyphenyl)-*N*-(4-(((4-morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)acrylamide-(6i) Yield: 69%, **M.P.** 238 °C. **IR** (KBr), cm^{-1}: 3450 (–NH), 3152 (–CH), 1719 (–C=O), 1687–(C=O), 1901 (–C=N), 1620 (–C=C–Ar), 1392 (–C–O–C–morpholine); **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.56 (*t*, 4H *J* = 4.0 Hz), 3.83 (*s*, 3H), 4.15 (*t*, 4H *J* = 4.0 Hz), 6.50 (*d*, 1H, *J* = 12.0 Hz, =CH); 7.53–7.03 (a set of signals 14H, aromatic protons and =C<u>H</u>–); 8.07 (*s*, 1H), 8.72 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 510.2. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.5, 56.0, 66.2, 84.8, 114.5, 117.3, 117.9, 123.6, 125.1, 126.4, 127.9, 128.7 129.3, 130.3, 131.8, 135.9, 142.0, 144.7, 150.6, 151.9, 160.8, 164.3, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found:: C, 70.69; H, 5.36; N, 8.27.

***N*-(4-(((4-Morpholino-2-oxo-2*H*-chromen-3-yl)methylene)amino)phenyl)-3-(3, 4, 5-trimethoxyphenyl) acrylamide-(6j) Yield**: 73%, **M.P.** 248 °C. **IR** (KBr), cm^{-1}: 3445 (–NH), 3148 (–CH), 1722 (–C=O), 1681 (–C=O), 1911 (–C=N), 1613 (–C=C–Ar), 1388 (–C–O–C–morpholine). **^{1}H NMR**: (400 MHz, DMSO-d_6): δ 3.71 (*t*, 4H *J* = 4.0 Hz), 3.82 (*s*, 9H), 4.25 (*t*, 4H *J* = 4.0 Hz), 6.55 (*d*, 1H, *J* = 12.1 Hz, =CH), 7.41–6.85 (a set of signals 11H, aromatic protons and =C<u>H</u>–), 8.04 (*s*, 1H), 8.81 (*s*, 1H). **MS** (ESI): *m/z* ([M + H] +); 570.1. **^{13}C NMR**: (100 MHz, DMSO-d_6): δ 48.5, 56.7, 60.6, 66.1, 84.8, 107.9, 117.3, 117.8, 123.6, 125.1, 126.4, 127.9 128.8, 131.8, 135.9, 141.5, 141.9, 144.7, 150.5, 151.9, 154.2, 164.3, 165.5, 166.6. **Elemental Analysis**: Calcd. for $C_{32}H_{31}N_3O_7$: C, 67.48; H, 5.49; N, 7.38. Found: C, 67.45; H, 5.48; N, 7.35.

Conclusion

In summary, the novel series of bioactive morpholine-clubbed 3-substituted coumarinyl acetamide and cinnamide derivatives **5a**–**5j** and **6a**–**6j** were disclosed and characterized by various spectral techniques viz, IR, ^{1}H-NMR, and ^{13}C-NMR. All the synthesized compounds were screened for their antibacterial and antifungal activities which were followed by SAR study. These study leads to a conclusion that compound **5g** (4-Cl), **5j** (4-OCH_3), **6i** (4-OCH_3), and **6j** (3, 4, 5-OCH_3) showed much better antibacterial activity. By observing this, we concluded that substitution on 4th position of these amide derivatives is more beneficial for the antibacterial activity. While in case of antifungal activity, there are no specific positions which were more beneficial for antifungal activity. Compounds **5g** (4-Cl), **6a** (unsubstituted), **6b** (2-NO_2), and **6j** (3, 4, 5-OCH_3) exhibited much better antifungal activity. No significant conclusion in context to the electronic effect of substituents is derived off, but deviation of biological profile shows that basic pharmacophore is responsible for activities. It is worth to pursue further incorporation of more substituents of both electron-donating and electron-withdrawing groups, which may lead to proper conclusion. Molecular docking studies showed that compounds **5g**, **5e**, **5i,** and **6i** showed better docking score, but none of the compounds reached up to the level of standard ciprofloxacin docking score. This study also favoured that 4th position of synthesized compound is the most active on biological point of view, and **5g** and **6i** also showed better dock score, and FMO theory also reinforced this things; compound **5g**, **5j**, **6b**, and **6i** possess better energy gap in compare to unsubstituted compounds like **5a** and **6a** and exhibited better antimicrobial activity correlation with HOMO–LUMO and bioactivity.

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