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Synthesis, *in vitro* biological evaluation and molecular docking study of coumarin-1,4-dihydropyridine derivatives as potent anti-inflammatory agents

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The green chemistry approach provides for the synthesis of coumarin-1,4-dihydropyridine scaffolds **6a-o** *via* sequential multicomponent reaction using catalytic amount of triethylamine (TEA). These new coumarin scaffolds have been successfully explored for the effective inflammatory as well as microbial infection inhibitors. The antimicrobial activity results of the title compounds have shown potent activity against both gram positive and gram negative bacterial, and fungal stains. Additionally, anti-inflammatory activity of all the compounds has been found to be quite promising in comparison with standard Diclofenac sodium. Furthermore, the *in silico* docking study has been performed for all the compounds with *S. aureus* DNA gyrase and cyclooxygenase-2 (PDB ID 4PH9). The computational results are in good agreement with the *in vitro* antibacterial and anti-inflammatory experimental results.

Keywords: Coumarin-1,4-dihydropyridine, antimicrobial activity, anti-inflammatory activity, molecular docking study, green protocol

Green chemistry an approach to prevent the pollution during the synthesis of chemical products provides environment friendly protocols to the pharmaceuticals[1]. On other hand one pot sequential multicomponent reactions have improved efficiency of multiple bond formation makes atom economy, energy, time saving, avoiding waste and pollution are the major contributions to the field of green chemistry, so it has become an important area of research in organic chemistry[2-5].

In medicinal chemistry, the synthesis of bioactive heterocycles is the challenging goal. While, heterocyclic skeletons are the attractive framework for synthetic organic chemist[6]. Among various heterocycles, pyridine and their hydrogenated derivatives are more significant, possessing diverse biological activities and found in naturally occurring compounds. Dihydropyridine nucleus is the most attractive structural framework present in many drugs and pharmaceuticals[7,8]. Dihydropyridine nucleus containing molecules reveal various biological activities like, antimicrobial[9], anti-inflammatory[10], anticancer[11], antioxidant[12], anti-hypertension[13] and in pharmacology as calcium channel blockers[14]. The commercially available dihydropyridine nucleus having drug molecules such as, Felodipine, Amlodipine, Nifedipine and Nimodipine (Figure 1) are used for the treatment of cardiac disease, hypertension, angina pectoris and congestive heart failure[15,16]. This remarkable drug activity of dihydropyridines (DHP's) attracted many chemists and has become interesting research area[17].

Coumarin nucleus having scaffolds are well cited in literature due to their pronounced anti-inflammatory activity[18] and the structural modification on coumarin nucleus have showed influenced antimicrobial activity[19]. Design concept of the present scaffolds are derived from our earlier work on coumarinyldihydropyrimidinones (Figure 1, C), they exhibited promising antimicrobial and anti-inflammatory activity[20,21]. Attention has made both heterocycles towards various biological activities, hence much microbial infection has been treating with antibiotics and these antibiotics also served as anti-

inflammatory agents[22]. Therefore, the above mentioned results and our continuation efforts have made to synthesize more potent and less toxic new candidates of antimicrobial and anti-inflammatory agents by multicomponent reaction using green chemical techniques. The present report gives an account for the synthesis of coumarin substituted 1,4-dihydropyridine derivatives (Figure 1, D) and their biological screening studies such as antimicrobial, anti-inflammatory and molecular docking study.

Results and Discussion

Chemistry

We describe here the design and synthesis of new coumarin-1, 4-dihydropyridine scaffolds (**6**) represented in Scheme I. Initially, the required substituted 4-formylcoumarin (**2**)[23] was synthesized from 4-bromomethylcoumarin[24]. Further, the target compound **6** was obtained using compound **2** *via* one pot multicomponent approach under ecofriendly condition.

Our attempt was to synthesize the target compound (**6**) by one pot multicomponent reaction (MCRs) under green protocol taking 6-methyl-4-formylcoumarin (**2**), aniline (**3**), dimethyl acetylene dicarboxylate (DMAD) (**4**) and malononitrile (**5**) as model example in basic condition at room temperature (RT). Initially, four component reaction was performed using TEA as base in ethanol at RT for 24 h, this reaction resulted very poor yield of desired product **6** along with identified two major products such as Schiff base (**7**) and coumarinyl malononitrile (**8**) (Entry 1, Table I). Further, in order to obtain desired product **6** in good yield at optimized reaction condition, a series of experiments were performed using different base, but results are not satisfactory (Entry 2 to 4, Table I). By examining the above reaction, we thought of modifying the reaction condition in terms of addition of reagents sequentially

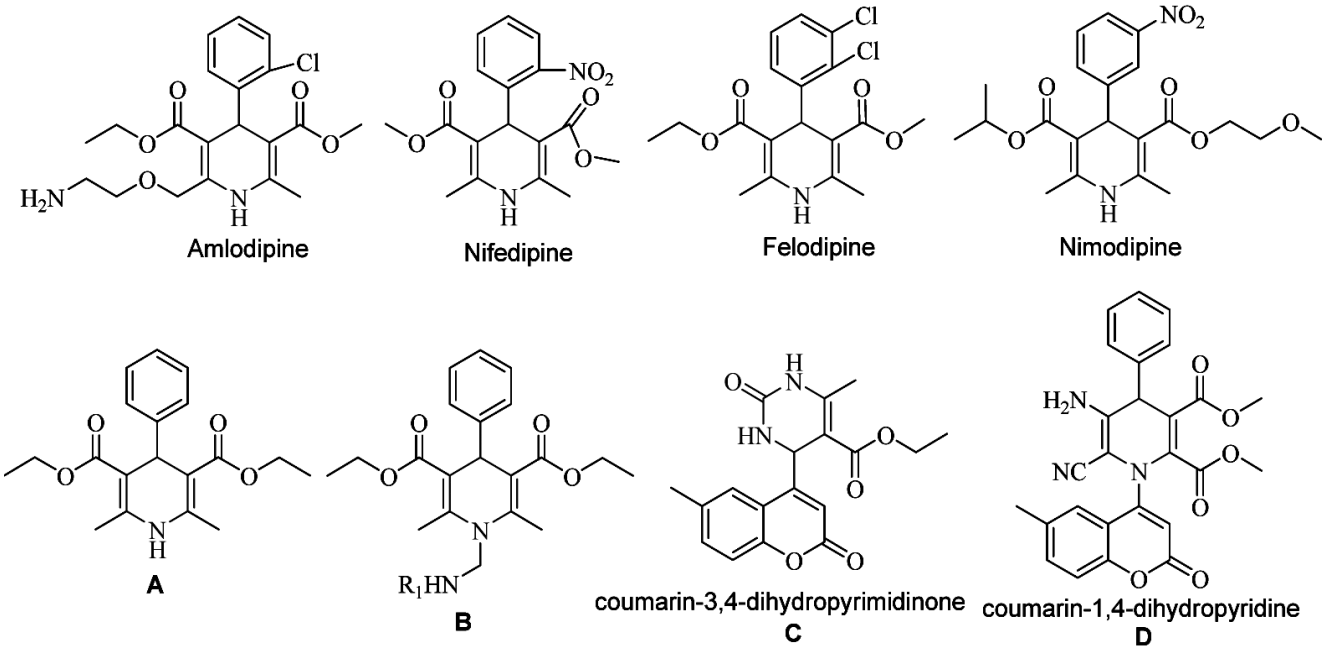
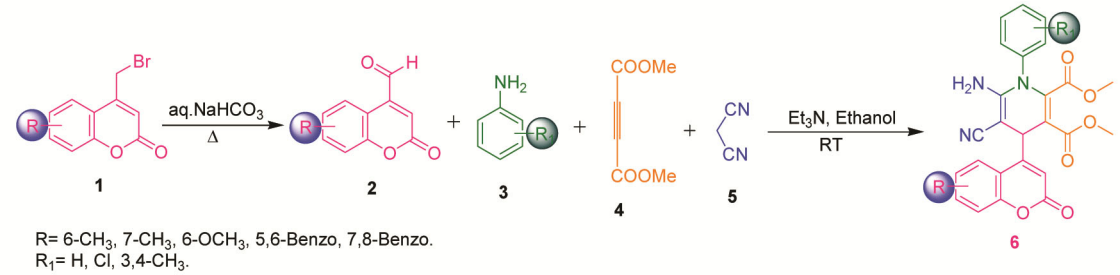


Figure 1 — Biologically active and pharmaceuticals important scaffolds of 1,4-dihydropyridines (1,4-DHP) and 1,4-dipyrimidinones



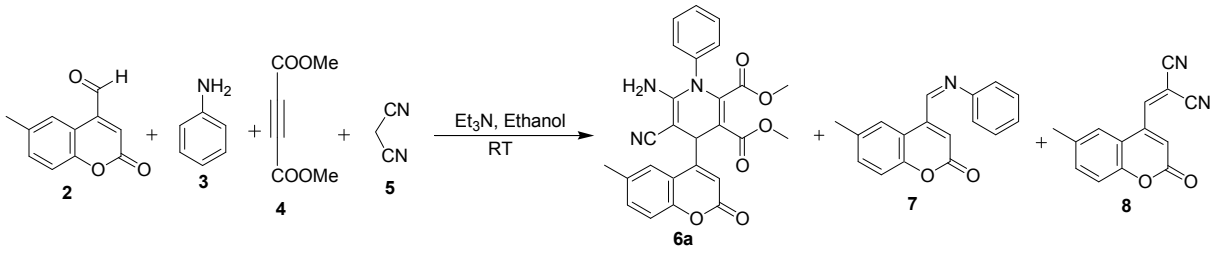
Scheme I — Synthesis of coumarin-1,4-dihydropyridine derivatives **6a-o**

instead of mixing all the reagents at once. The performed reaction by taking aniline (**3**) and DMAD (**4**) in ethanol stirred at RT for 10 min, in this ethanolic solution 4-formylcoumarin (**2**), malononitrile (5) and TEA was added and stirred for about 8-10 h, in this method we noticed the desired product **6** with improved yield (Entry 5, Table I). Moreover, to get better yield, additional optimization was carried out using different base, but not much progress was observed in the yield (Entry **6** and **7**, Table I). From the above discussed conditions, we noticed that a 30-35% starting material remains in the reaction, due to benzaldehyde reacts with malononitrile and aniline to lead corresponding identified intermediates **7** and **8** respectively. In order to increase the reactivity of aniline (**3**) and DMAD (4) we performed reaction by mixing DMAD (**4**) and aniline (**3**) without solvent at RT under stirring for 3 to 4 h. Meanwhile, 4-formylcoumarin (**2**), malononitrile (**5**) with catalytic amount of TEA in ethanol was prepared under stirring for 7 h. The separately prepared reaction mixture was mixed and stirred for 1h. Surprisingly, under this condition, we obtained the desired product in excellent yield (Entry 8, Table I). Using this standard protocol, different substituted coumarin-1,4-dihydropyridine scaffolds were synthesized in good yield. The lists of synthesized compounds are given in Figure 2.

Plausible reaction mechanism is given in Scheme II. Firstly, the aza-Michael addition takes place between DMAD (**4**) and substituted aryl amines (**3**) to produce the intermediate **A,** this is rate determining step. Next, catalytic amount of triethylamine act as a base to induce the Knoevenagel condensation reaction between 4-formylcoumarin (**2**), malononitrile (**5**) providing the compound **8**. Further, by adding intermediate **A** and **8,** Michael addition take place to form the adduct **B,** then **B** transferred to **C** by the shift of proton. The intermediate **C** further undergoes intramolecular cyclization with nitrile carbon to form intermediate **D** and led the targeted product coumarin-1, 4-dihydropyridineby tautomerization of imino group to amino group.

In case of compound **6a** the IR shows NH_2 asymmetric and symmetric stretching bands at 3423 and 3367 cm^{-1} respectively. The nitrile stretching band exhibited at 2180 cm^{-1} and stretching bands of ester carbonyl group of dihydropyridine and lactone carbonyl group of coumarin are observed at 1753 and 1712 cm^{-1} respectively. Compound **6a** was confirmed by the GC-MS, which shows mass at *m*/*z* 471 correspond to the molecular ion peak of compound. Further, ^{1}H NMR spectral data supports the formation of compound **6a**, the three singlets were resonated at δ 2.45, δ 3.51 and δ 3.41 corresponds to methyl group of coumarin and two ester methyl group of dihydropyridine respectively. The two singlets resonated at δ 5.87 and δ 5.18 are due to NH_2 and methine protons of dihydropyridine respectively. Coumarin C_3-H appeared as a singlet at δ 6.20 and C_7H of coumarin resonated as doublet at δ 7.55 (*J*=8Hz) and C_5-H of coumarin resonated as a singlet at δ 7.46. C_8-H of coumarin resonated as doublet at δ

Table I — Optimization of the reaction conditions for the synthesis of coumarin-1,4- dihydropyridine



Entry	Catalyst	Solvent	Condition	Time (h)	Yield (**6a**) (%)	Yield (**7**) (%)	Yield (**8**) (%)
1	TEA	Ethanol	RT	24	10	18	37
2	K_2CO_3	Ethanol	RT	24	7	17	35
3	Piperidine	Ethanol	RT	24	5	12	27
4	DBU	Ethanol	RT	24	5	15	25
5	TEA	Ethanol	RT	12	38	12	23
6	Piperidine	Ethanol	RT	12	22	7	16
7	DBU	Ethanol	RT	12	18	5	12
8	TEA	(Ethanol)	RT	12	87	–	5

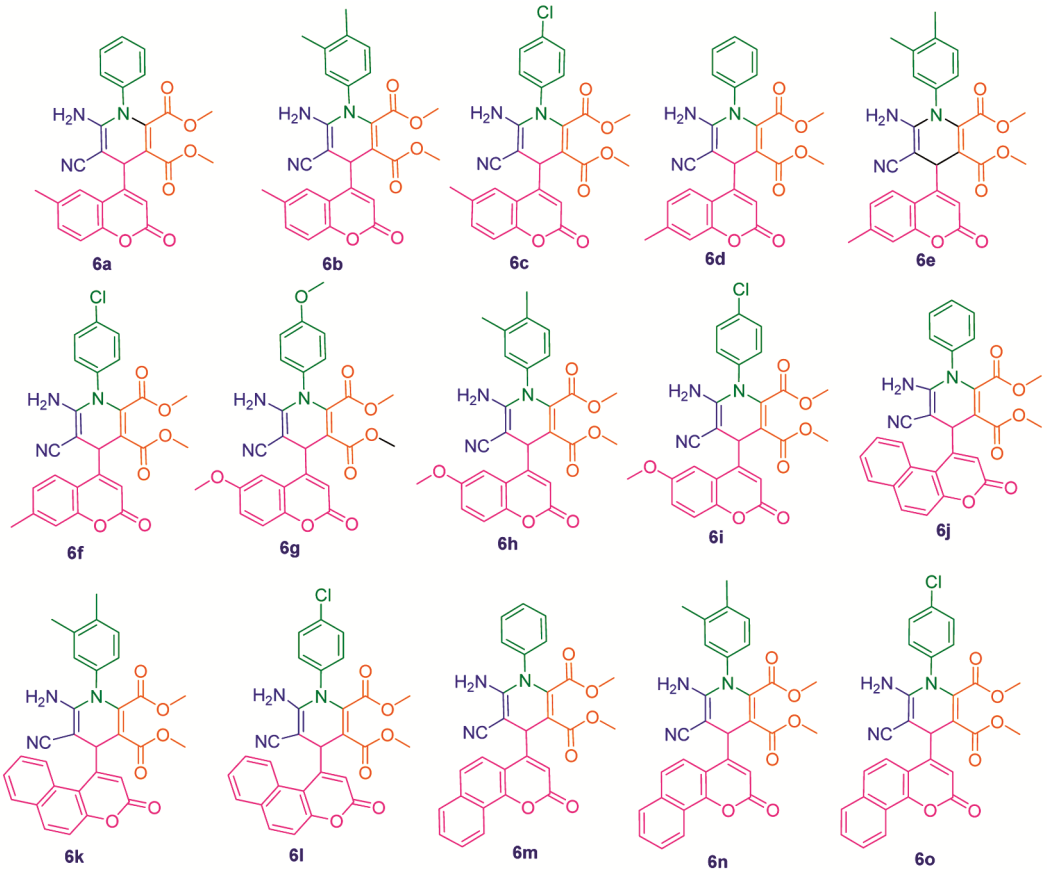
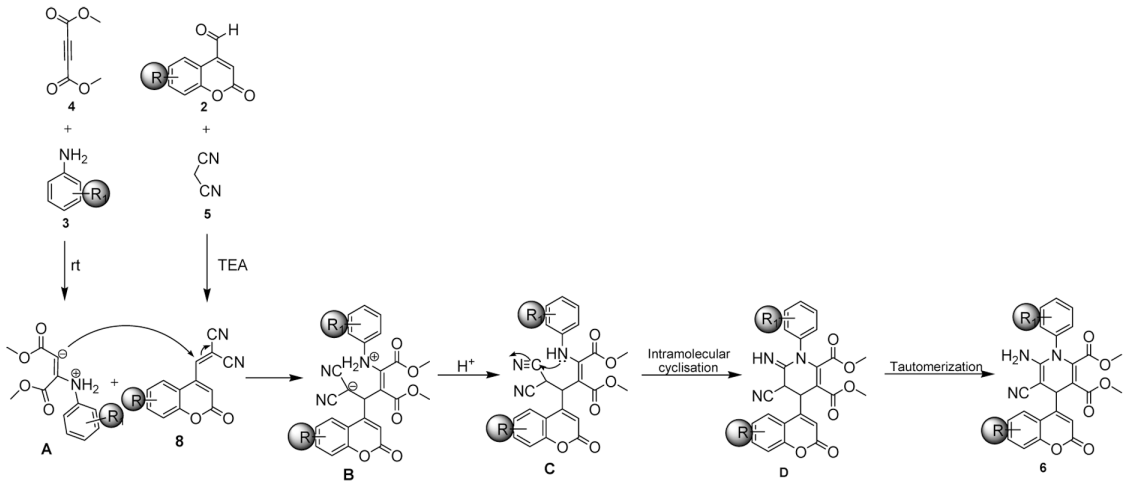


Figure 2 — Structures of all synthesized coumarin-1,4-dihydropyridine derivatives **6a-o**



Scheme II — Plausible mechanism for the synthesis of coumarin substituted 1, 4-dihydropyridine derivatives **6a-o**

8.07 (*J*=8Hz) and phenyl proton appeared as a multiplet in the region δ 7.32 respectively.

Biological screening

In vitro antibacterial study

Novel coumarin-1,4-dihydropyridine derivatives **6(a-o)** were assessed for their *in vitro* antibacterial activity against Gram positive bacterial strains *S. aureus*, *B. subtilis* and Gram-negative bacterial strains *E. coli* and *P. aeruginosa* respectively. Whereas, two references drugs gentamycin and ampicillin were used

and determined the minimum inhibitory concentration (MIC) of all the compounds, the antibacterial MIC results of all the compounds are tabulated in Table II.

Antibacterial activity results of all the targeted compounds reveals that; most of the compounds **6(a-o)** are exhibiting low activity. Compounds **6a** (C_6-CH_3 substitution on coumarin) and **6e** (C_7-CH_3 substitution on coumarin and C_3,C_4-di-CH_3 on phenyl ring) are found to be encourageable antibacterial agents against Gram positive *S.aureus* and *B.subtilis* bacterial strain with MIC 32 µM/mL which shows equipotent activity with standard drug Gentamycin (32 µM/mL). Further, compounds **6c** (C_6-CH_3 substitution on coumarin and C_4-Cl on phenyl ring), **6h** (C_6-OCH_3 on coumarin and C_3, C_4-di-CH_3 substitution on phenyl ring) and **6n** (7,8-benzo substitution on coumarin and C_3, C_4-di-CH_3 on phenyl ring) showed good activity against both Gram positive bacterial strains with MIC value ranging 32-64 µM/mL over the standard drug Gentamycin (32 µM/mL) and found to be least active compared with standard drugAmpicillin (MIC=8 and 4 µM/mL) respectively. Wherein, other compounds showed moderate activity. Moreover, the results showed that, all synthesized compounds are less active against both gram –ve bacterial strains. The activity results of all compounds are represented in Figure 3.

From the above discussion, antibacterial activity of all compounds reveals that, coumarin dihydropyridines having H, C_3, C_4-di-CH_3 substitution on phenyl ring are found to be promising antibacterial agents. Most of the compounds having C_4-Cl on phenyl ring showed moderate activity. The novel coumarin-1,4-dihydropyridines are considered to be promising structural templates for the development of more efficient antibacterial agent in future.

In vitro antifungal study

In vitro antifungal activity results of all newly synthesized scaffolds are summarized in Table III. Minimum inhibitory concentration (MIC) value of all compounds against two fungal stains *C. albicans* and *A. niger*were determinedtheMIC measured in µM/mL using Amphotericin-B as standard drug.

Table III reveals that, most of the compounds are less active against both fungal strains compared to

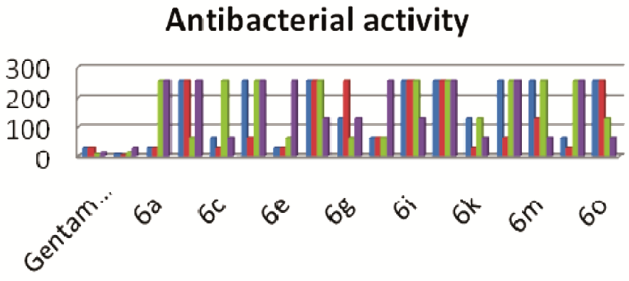


Figure 3 — Graphical representation of all the compounds minimum inhibitory concentration (MIC) (µM/mL) against *B.subtilis*, *S.aureus*, *P.aeruginosa* and *E.coli*.

Table II — *In vitro* antibacterial activity of coumarin-1,4-dihydropyridine derivatives **6a-o**

Compd	R	R_1	Minimum inhibitory concentrations (MIC) in µM/mL			
			Gram positive		Gram negative	
			B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
6a	6-CH_3	H	32	32	≥256	≥256
6b	6-CH_3	3,4-di-CH_3	≥256	≥256	64	≥256
6c	6-CH_3	4-Cl	64	32	≥256	64
6d	7-CH_3	H	≥256	64	≥256	≥256
6e	7-CH_3	3,4-di-CH_3	32	32	64	≥256
6f	7-CH_3	4-Cl	≥256	≥256	≥256	128
6g	6-OCH_3	H	128	≥256	64	128
6h	6-OCH_3	3,4-di-CH_3	64	64	64	≥256
6i	6-OCH_3	4-Cl	≥256	≥256	≥256	128
6j	5,6-Benzo	H	≥256	≥256	≥256	≥256
6k	5,6-Benzo	3,4-di-CH_3	128	32	128	64
6l	5,6-Benzo	4-Cl	≥256	64	≥256	≥256
6m	7,8-Benzo	H	≥256	128	≥256	64
6n	7,8-Benzo	3,4-di-CH_3	64	32	≥256	≥256
6o	7,8-Benzo	4-Cl	≥256	≥256	128	64
Gentamycin			32	32	8	16
Ampicillin			8	4	16	32

Table III — *In vitro* antifungal activity of coumarin-1,4-dihydropyridine derivatives **6a-o**

Compd	R	R_1	Minimum Inhibitory Concentrations (MIC) in μM/mL	
			C. albicans	*A. niger*
6a	6-CH_3	H	≥256	128
6b	6-CH_3	3,4-di-CH_3	128	≥256
6c	6-CH_3	4-Cl	≥256	≥256
6d	7-CH_3	H	64	128
6e	7-CH_3	3,4-di-CH_3	64	64
6f	7-CH_3	4-Cl	≥256	128
6g	6-OCH_3	4-OCH_3	64	≥256
6h	6-OCH_3	3,4-di-CH_3	≥256	128
6i	6-OCH_3	4-Cl	128	≥256
6j	5,6-Benzo	H	64	64
6k	5,6-Benzo	3,4-di-CH_3	128	64
6l	5,6-Benzo	4-Cl	≥256	≥256
6m	7,8-Benzo	H	64	128
6n	7,8-Benzo	3,4-di-CH_3	≥256	128
6o	7,8-Benzo	4-Cl	≥256	≥256
Amphotericin-B			4	≥2

standard drug molecules. Among all compounds, **6e** (C_7-CH_3 substitution on coumarin and C_3,C_4-di-CH_3 substitution on phenyl ring) and **6j** (5,6-benzo substitution on coumarin) have showed activity towards both fungi *C. albicans* and *A. niger* with MIC 64 μM/mL.

From the results, we observe that, dihydropyridines with C_4-Cl substitution on phenyl ring shows least activity against both fungal strains compared to other substitution on phenyl ring. Different substitution on coumarin nucleus and phenyl ring has not shown much effects on the fungal strains. Figure 4 shows graphical representation of minimum inhibitory concentration of all the compounds.

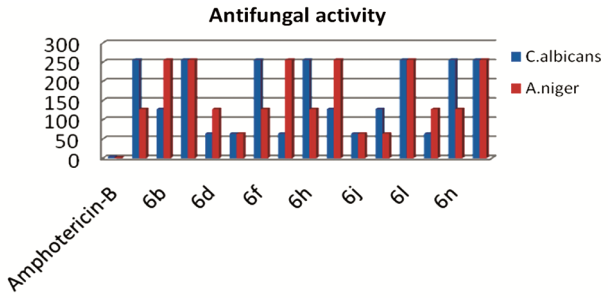


Figure 4 — Graphical representation of minimum inhibitory concentration (MIC) (μM/mL) against *C. albicans* and *A. niger*.

In vitro anti-inflammatory study

In vitro anti-inflammatory activity evaluation of title compounds was determined by egg albumin denaturation method using Diclofenac sodium as a standard, the results obtained are presented in Table IV. Figure 5 shows the percentage inhibition of all the compounds, which showed remarkable activity against denaturation of protein over standard Diclofenac sodium. Compound **6i** (C_6-OCH_3 substitution on coumarin and C_4-Cl on phenyl ring) shows highest inhibition (89.33%), whereas, **6c** (C_6-CH_3 substitution on coumarin and C_4-Cl on phenyl ring) shows least inhibition (39.33%) compared with standard Diclofenac sodium. While, compounds **6d** (C_7-CH_3 on coumarin), **6e** (C_7-CH_3 on coumarin and C_3, C_4-di-CH_3 on phenyl ring), **6g** (C_6-OCH_3 on coumarin and C_4-OCH_3 on phenyl ring), **6h** (C_6-OCH_3 on coumarin and phenyl ring), **6n** (7, 8-benzo on coumarin and C_3,C_4-di-CH_3 on phenyl ring), **6k** (5,6-benzo on coumarin and C_3,C_4-di-CH_3 on phenyl ring) and **6m** (7,8-benzo on coumarin and phenyl ring, C_3,C_4-di-CH_3 on phenyl ring) shows good activity with inhibition range from 74.16-85.26%. Further, compounds **6a, 6b, 6c, 6f, 6j, 6l** and **6o** showed least activity with inhibition ranges from 39.33-70.00%. From the above discussion we observe that, compounds with C_6-OCH_3 substitution on coumarin exhibited good anti-inflammatory activity with maximum inhibition range from 82.16-89.33%. Whereas, compounds having C_6-CH_3 substitution on coumarin and C_4-Cl substitution on phenyl ring are considered as least active compared with standard Diclofenac sodium.

Computational study

To demonstrate the mechanism of antibacterial activity and information of intermolecular interactions of the synthesized scaffold, we performed molecular docking studies on the crystal structure of twinned 3.35A structure of *S. aureus* Gyrase complex with ciprofloxacin and DNA (PDB ID: 2XCT) using the surflex-dock programme of sybyl-X 2.0 software. All the synthesized 15 inhibitors were docked into the active site of enzyme and the identified binding energies of the targets are listed in supplementary file (Fig. S4 Table S1). The docking study revealed that all the compounds have exhibited good docking score.

As presented in Figure 6, the compound **6a** makes four hydrogen bonding interactions at the active site of the enzyme (PDB ID: 2XCT). The oxygen atoms of carboxylate group present at the 3rd position of dihydropyridine ring makes two hydrogen bonding interactions with hydrogen's of U/SER1084 (O···H-U/SER1084, 1.75 Å and 2.74 Å). Oxygen atom present in the coumarin ring makes a hydrogen bonding interaction with hydrogen of W/DA7 (O···H-W/DA7, 2.74 Å) and remaining hydrogen bonding interaction raised from the hydrogen atom of amino group present on the 6th position of dihydropyridine ring with nitrogen of W/DG8 (NH···N-W/DG8, 2.47 Å) amino acid residue respectively.

The insilico study of reference drug ciprofloxacin was also performed to camper the synthesized compounds interaction with enzymes. Figure 7 has shown interactions between ciprofloxacin and enzyme. Ciprofloxacin showed four intermolecular hydrogen bonding interactions at the active site of the enzyme (PDB ID: 2XCT). The C4 carbonyl oxygen of quinoline makes hydrogen bonding interaction with hydrogen of X/DC12 (C=O···H-X/DC12, 2.33 Å) amino acid residue and carboxylic acid oxygen atom of carbonyl group makes hydrogen bonding interaction with hydrogen of X/DC12 (C=O···H-X/DC12, 2.69 Å) respectively. Whereas, oxygen atom of hydroxyl group of carboxylic acid raises one bonding interaction with hydrogen of X/DC13 (C=O···H-X/DC13, 1.89 Å) and remaining one bonding interaction raised from the hydrogen atom of NH of piperazine ring with oxygen of Y/DG9 (NH···H-Y/DG9, 1.93 Å). The hydrophobic and hydrophilic interaction of scaffolds **6a** and **6d** are presented in Figure 8.

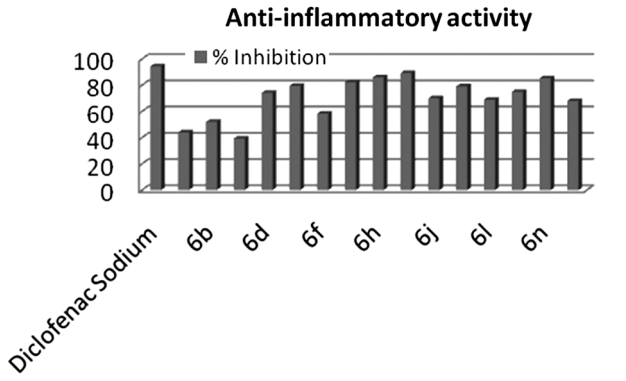


Figure 5 — Graphical representation of % inhibition of egg albuminin100 µg/mL for compounds **6a-o**

Table IV — *In vitro* anti-inflammatory activity results of coumarin-1,4-dihydropyridine derivatives **6a-o**

Compd	R	R_1	% Inhibition of egg albumin in 100 µg/mL
6a	6-CH_3	H	44.0000±0.57735
6b	6-CH_3	3,4-di-CH_3	52.0000±0.57735
6c	6-CH_3	4-Cl	39.3333±0.57735
6d	7-CH_3	H	74.1633±0.58081
6e	7-CH_3	3,4-di-CH_3	79.5233±0.39431
6f	7-CH_3	4-Cl	58.3333±0.88192
6g	6-OCH_3	4-OCH_3	82.1633±0.58081
6h	6-OCH_3	3,4-di-CH_3	86.0000±0.57735
6i	6-OCH_3	4-Cl	89.3333±0.88192
6j	5,6-Benzo	H	70.0000±0.57735
6k	5,6-Benzo	3,4-di-CH_3	79.1200±0.67735
6l	5,6-Benzo	4-Cl	69.0000±0.57735
6m	7,8-Benzo	H	75.1253±0.52318
6n	7,8-Benzo	3,4-di-CH_3	85.2634±0.49829
6o	7,8-Benzo	4-Cl	68.0000±0.57735
Diclofenac Sodium			94.3867±0.63980

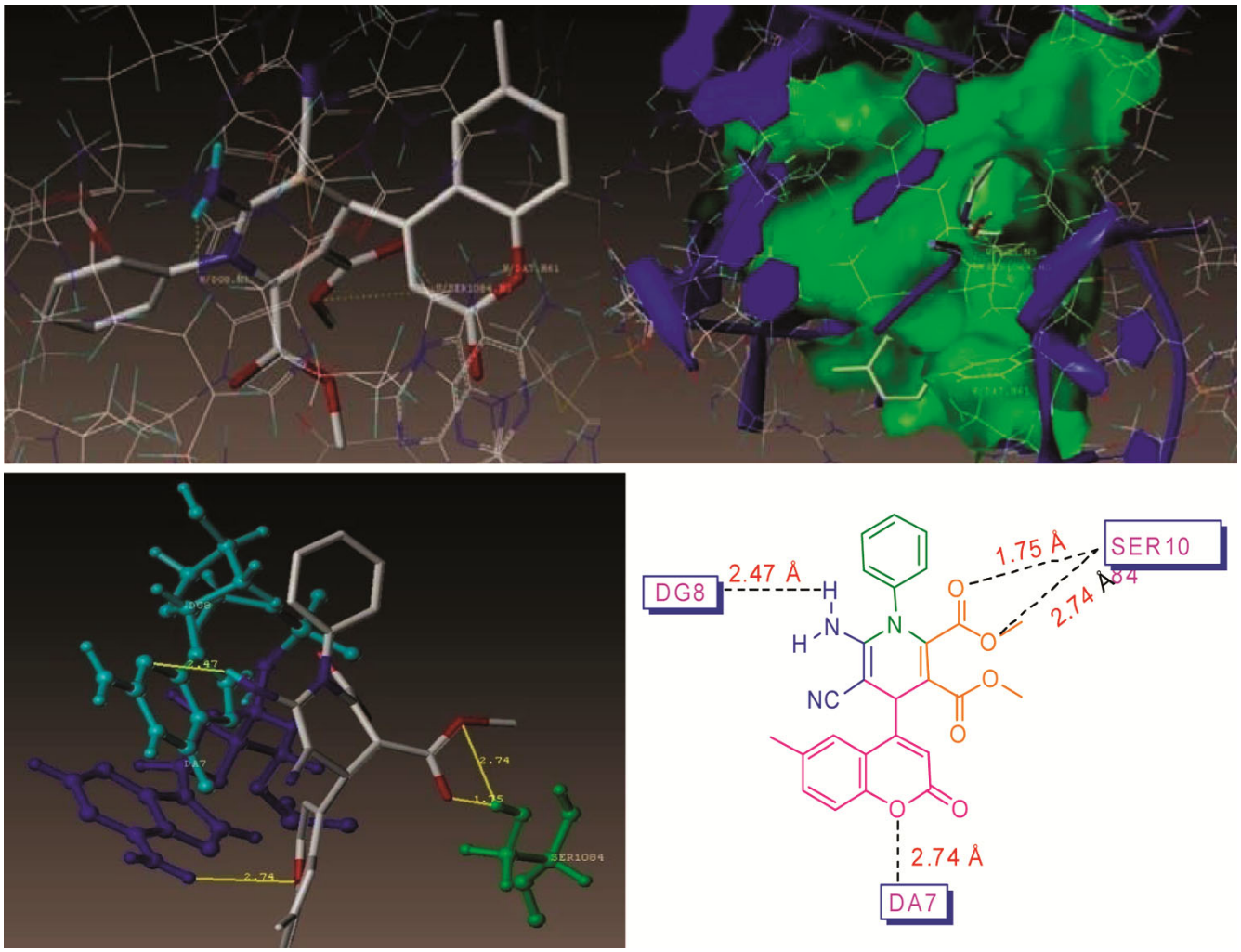


Figure 6 — Docked view of compound **6a** at the active site of the enzyme (PDB ID: 2XCT)

To demonstrate the mechanism of anti-inflammatory activity and its possible intermolecular interactions information between the targets and enzymes, the molecular docking study was performed on the crystal structure of ibuprofen bound to cyclooxygenase-2 (PDB ID 4PH9) using the surflex-dock programme of sybyl-X 2.0 software. All the synthesized fifteen inhibitors were docked into the active site of enzyme and the obtained binding energies of the targets are listed in supplementary file (Figure S6, Table S2). Computational study revealed that all the compounds have exhibited very good docking score.

As presented in the Figure 9 (A-C), compound **6d**, makes four bonding interactions at the active site of the enzyme (PDB ID: 4PH9). The oxygen atom of carboxylate group present at the 3rd position of dihydropyridine ring makes a hydrogen bonding interaction with hydrogen atom of SER354 (C=O----H-SER354, 2.54 Å) amino acid residue, coumarin ring oxygen atom makes a hydrogen bonding interaction with hydrogen atom of TYR356 (O----H-TYR356, 2.594 Å) amino acid residue and remaining tow hydrogen bonding interactions raised from the oxygen atom of carbonyl group of coumarin ring and hydrogen atoms of ARG121 and TYR356 (C=O-----H-ARG121, 2.04 Å, C=O-----H-TYR356, 2.59 Å) amino acid residues respectively.

The comparative molecular docking study results of synthesized compounds and reference drug Ibuprofen noticed that the synthesized compounds exhibited high C-score value. The synthesized scaffolds bind to the active site of enzyme is similar to that of Ibuprofen. Interestingly, the synthesized scaffolds have same H-bonding interactions with same amino acids ARG121 and TYR356 as that of Ibuprofen.

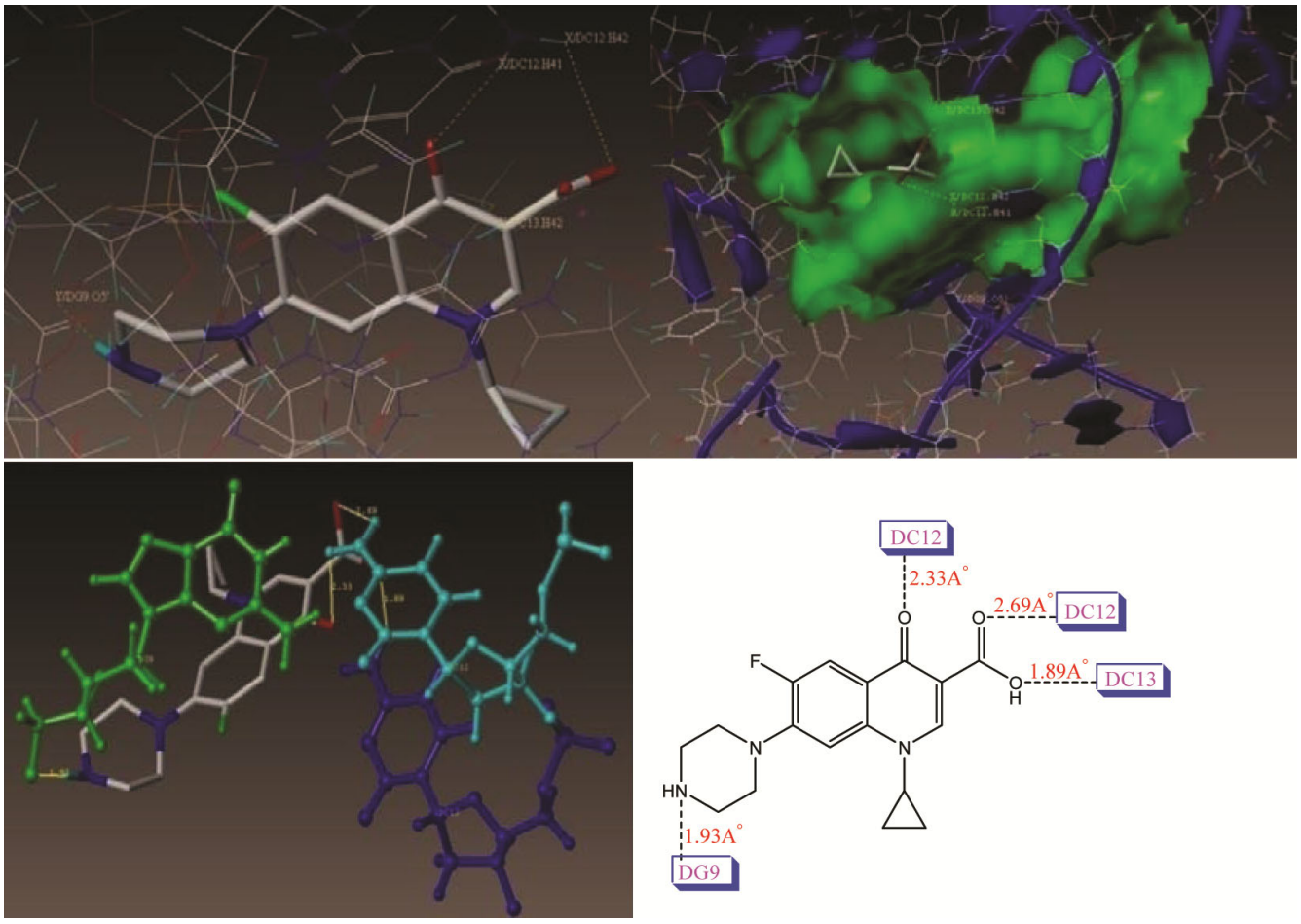


Figure 7 — Interaction of ciprofloxacinat the binding site of the enzyme (PDB ID: 2XCT)

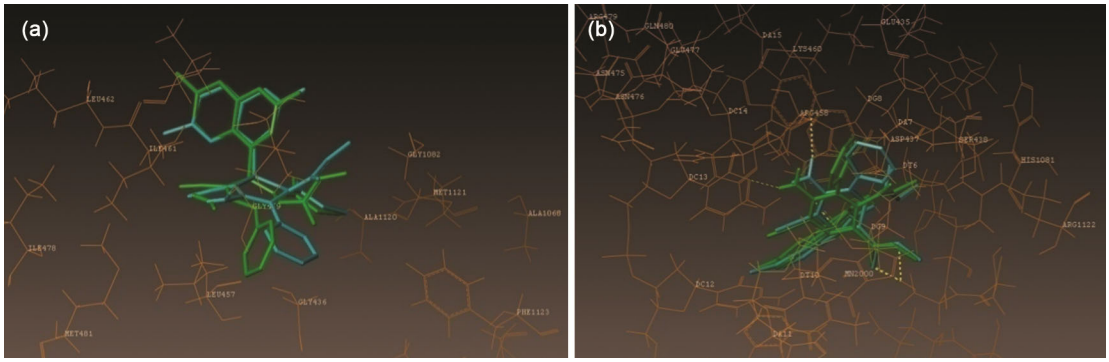


Figure 8 — (A) Hydrophobic amino acids surrounded to compounds **6d** (green color)and **6a** (cyan color). (B) Hydrophilic amino acids surrounded to compounds **6d** and **6a**

As depicted in the Figure 10 (A-C), Ibuprofen, makes four hydrogen bonding interactions at the active site of the enzyme (PDB ID: 4PH9).

Experimental Section

Materials and Method

All the reagents were obtained commercially of analytical grade and were used without further purification unless otherwise stated. The melting points were determined by open capillary method and are uncorrected. The Infrared (IR) spectra (KBr) were recorded on a Nicolet-5700 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer and Jeol 400 MHz using DMSO-d_6, as solvent and tetramethylsilane

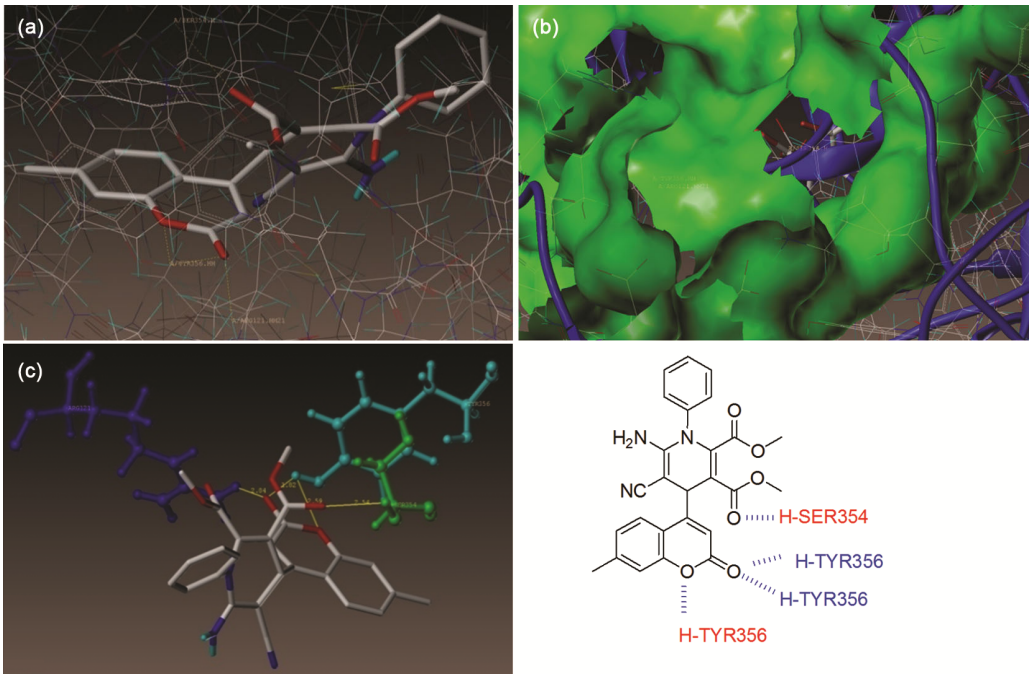


Figure 9 — Docked view of compound **6d** at the active site of the enzyme PDB: 4PH9

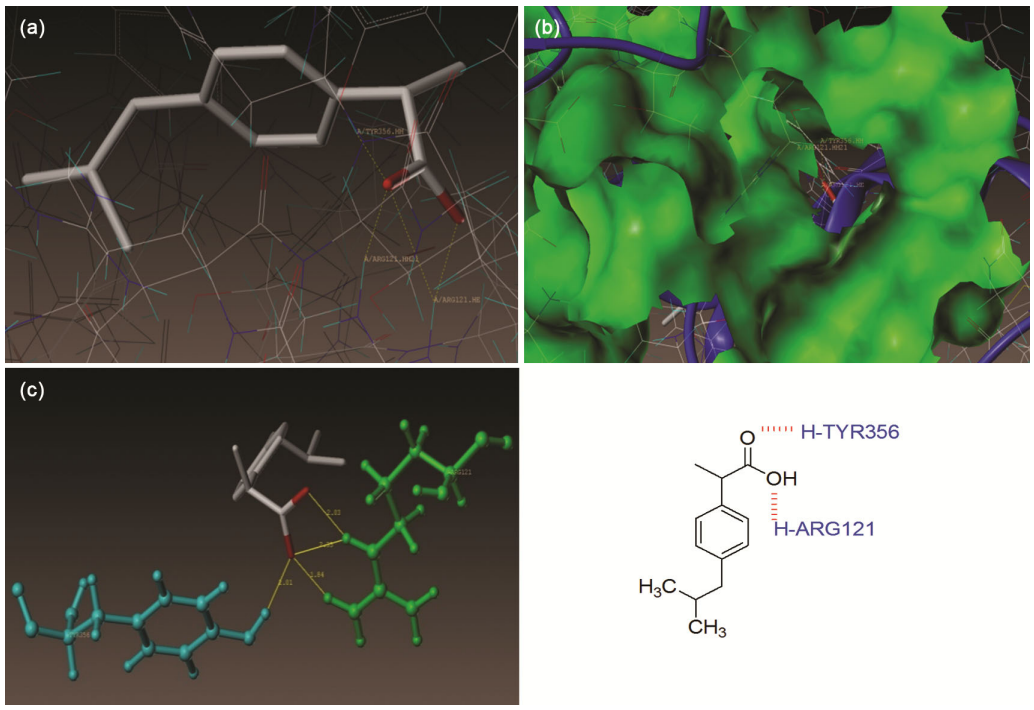


Figure 10 — Interaction of Ibuprofen at the binding site of the enzyme (PDB ID: 4PH9)

(TMS) as an internal standard and the chemical shifts are expressed in ppm (δ-scale). The mass spectra were recorded using Agilent- single Quartz GC-MS. The Purity of compounds is checked by Thin Layer Chromatography (TLC) which was performed on Merck Silica Gel 60 F254 and visualized under UV light chamber.

General procedure for the synthesis of coumarin-1,4-dihydropyridine, 6a-o

A solution of dimethyl acetylenedicarboxylate (DMAD) (1.0 mmol,) and substituted aniline (1.0 mmol) was taken in round bottom flask and stirred for 4 h at RT. Meanwhile, substituted 4-

formylcoumarin (1.0 mmol,) and malononitrile (1.0 mmol,) in 2 mL of ethanol was added to it with catalytic amount of triethylamine and stirred the reaction mixture for another 8 h at RT. The reaction mixture was stirred until the reaction was completed and confirmed by TLC. After completion, the resulting precipitate was collected by filtration and washed with cold ethanol to obtain the pure product.

Spectral Data

Dimethy 6-amino-5-cyano-4-(6-methyl-2-oxo-2*H*-chromen-4-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate, 6a: The compound **6a** obtained from 6-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Yellow solid. Yield 85%. m.p.268-270°C; IR (KBr): 3423, 2180, 1753 and 1712 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.41(s, 3H, C_6-CH_3 of coumarin), 3.35(s, 3H, -OCH_3 of ester), 3.45(s, 3H, -OCH_3 of ester), 5.12(s, 1H, CH of dihydropyridine), 5.84(s, 2H, NH_2), 6.18(s, 1H, C_3-H of coumarin), 7.26(dd, 1H, *J*=9.2 Hz, *J*=2 Hz, C_7-H of coumarin), 7.25-7.27 (m, 3H, CH of phenyl ring), 7.49(s, 1H, C_5-H of coumarin), 7.49-7.50(m, 2H, CH of phenyl ring), 8.02 (d, 1H, *J*=8.4 Hz, C_8-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.55 (C_6-CH_3), 33.73 (C_4-CH of DHP), 52.75 (OCH_3 of ester), 53.14 (OCH_3 of ester), 57.46, 102.71, 111.80, 114.62, 115.65, 117.47 (CN), 120.88, 125.66, 126.05, 130.33, 130.75, 135.04, 135.49, 144.02, 144.17, 152.54, 154.24, 159.11, 159.49, 161.10 (CO of coumarin), 163.13 (CO of ester), 164.90 (CO of ester); GC-MS: *m/z* 471 (M^+).

Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(6-methyl-2-oxo-2*H*-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate, 6b: The compound **6b** obtained from 6-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid. Yield 87%. m.p.268-270°C; IR (KBr): 3413, 2185, 1750 and 1711 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 6H, C_3 and C_4-CH_3 of phenyl ring), 2.45 (s, 3H, C_6-CH_3 of coumarin), 3.47(s, 3H, -OCH_3 of ester), 3.55(s, 3H, -OCH_3 of ester), 4.24(s, 2H, NH_2), 5.12(s, 1H, CH of dihydropyridine), 6.36(s, 1H, C_3-H of coumarin), 7.04(dd, 1H, *J*=8 Hz, *J*=2 Hz, C_7-H of coumarin), 7.07(s, 1H, C_5-H of coumarin), 7.19(m, 3H, CH of phenyl ring), 7.91(d, 1H, *J*=8 Hz, C_8-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.74(C_3- CH_3 of phenyl), 19.86 ((C_4- CH_3 of phenyl)), 21.73(C_6-CH_3), 32.87(C_4-CH of DHP), 52.50(OCH_3 of ester), 52.88(OCH_3 of ester), 59.15, 99.99, 102.43, 112.81, 115.52, 117.55(CN), 120.13, 124.50, 125.77, 127.45, 130.74, 131.15, 140.12, 143.66, 143.88, 151.36, 153.11, 154.28, 158.61, 162.25(CO of coumarin), 162.94(CO of ester), 164.83(CO of ester). Anal. Calcd for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N, 8.41. Found: C, 67.36; H, 5.02; N, 8.44%. GC-MS: *m/z* 499 (M^+).

Dimethyl-6-amino-1-(4-chlorophenyl)-5-cyano-4-(6-methyl-2-oxo-2*H*-chromen-4-yl)-1,4-dihydro py ridine-2,3-dicarboxylate, 6c: The compound **6c** obtained from 6-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chlorobenzenamine (1.0mmol). Gray solid. Yield 83%. m.p.252-254°C; IR (KBr): 3346, 2185, 1750 and 1700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, C_6-CH_3 of coumarin), 3.43(s, 3H, -OCH_3 of ester), 3.62(s, 3H, -OCH_3 of ester), 4.21(s, 2H, NH_2), 5.21(s, 1H, CH of dihydropyridine), 6.23(s, 1H, C_3-H of coumarin), 7.15(dd, 1H, *J* = 8 Hz, *J* = 2 Hz, C_7-H of coumarin), 7.22(d, 1H, *J*=7.2 Hz, C_5-H of coumarin), 7.27(d, 4H, *J* = 8 Hz, CH of phenyl ring), 7.87(d, 1H, *J*=8 Hz, C_8-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.54(C_6-CH_3), 33.27(C_4-CH of DHP), 51.91(OCH_3 of ester), 52.31(OCH_3 of ester), 58.25, 100.19, 105.23, 115.57, 117.02, 117.85(CN), 119.34, 123.21, 125.37, 130.64, 132.27, 139.45, 141.27, 144.67, 151.36, 155.04, 157.11, 161.24(CO of coumarin), 163.17(CO of ester), 165.23(CO of ester). Anal. Calcd for $C_{26}H_{20}ClN_3O_6$: C, 61.73; H, 3.98; N, 8.31. Found: C, 61.78; H, 3.96; N, 8.36%. GC-MS: *m/z* 505 (M^+).

Dimethyl 6-amino-5-cyano-4-(7-methyl-2-oxo-2*H*-chromen-4-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate, 6d: The compound **6d** obtained from 7-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Cream solid. Yield 86%. m.p.238-232°C; IR (KBr): 3432, 2178, 1749 and 1710 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, C_7-CH_3 of coumarin), 3.42(s, 3H, -OCH_3 of ester), 3.48(s, 3H, -OCH_3 of ester), 5.18(s, 1H, CH of dihydropyridine), 5.64(s, 2H, NH_2), 6.24(s, 1H, C_3-H of coumarin), 7.21(dd, 1H, *J*=8 Hz, *J*=2 Hz, C_6-H of coumarin), 7.23-7.29(m, 3H, CH of phenyl ring),

7.51(s, 1H, C_8-H of coumarin), 7.52-7.55(m, 2H, CH of phenyl ring), 7.89(d, 1H, *J*=8.4 Hz, C_5-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.13(C_7-CH_3), 35.02(C_4-CH of DHP), 53.17(OCH_3 of ester), 54.35(OCH_3 of ester), 56.08, 101.11, 113.20, 113.87, 115.67, 116.46(CN), 119.14, 121.76, 128.15, 131.47, 133.27, 135.19, 137.49, 142.49, 143.07, 151.62, 155.17, 157.22, 158.45, 162.87(CO of coumarin), 163.72(CO of ester), 165.49(CO of ester). Anal. Calcd for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91. Found: C, 66.26; H, 4.48; N, 8.94%. GC-MS: *m/z* 471 (M^+).

Dimethyl 6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(7-methyl-2-oxo-2*H*-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate, 6e: The compound **6e** obtained from 7-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid. Yield 89%. m.p.222-224°C; IR (KBr): 3432, 2175, 1754 and 1718 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 6H, C_3 and C_4-CH_3 of phenyl ring), 2.45(s, 3H, C_7-CH_3 of coumarin), 3.48(s, 3H, -OCH_3 of ester), 3.57(s, 3H, -OCH_3 of ester), 4.25(s, 2H, NH_2), 5.12(s, 1H, CH of dihydropyridine), 6.40(s, 1H, C_3-H of coumarin), 7.05(d, 2H, *J*=8.4 Hz, CH of phenyl ring), 7.22(d, 1H, *J*=8 Hz, C_5-H of coumarin), 7.26(s, 1H, CH of phenyl ring), 7.37(d, 1H, *J*=8 Hz, C_6-H of coumarin), 7.82 (s, 1H, C_8-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ19.74(C_3- CH3 of phenyl), 19.86(C_4- CH3 of phenyl), 21.27, 32.89(C_4-CH of DHP), 52.52(OCH_3 of ester), 52.89(OCH_3 of ester), 59.03, 102.44, 113.79, 117.05(CN), 117.60, 120.10, 124.81, 127.23, 130.75, 131.16, 131.83, 133.30, 134.18, 139.20, 140.12, 143.90, 151.48, 152.31, 158.21, 162.13(CO of coumarin), 162.94(CO of ester), 164.83(CO of ester). Anal. Calcd for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N, 8.41. Found: C, 67.35; H, 5.06; N, 8.46%. GC-MS: *m/z* 499 (M^+).

Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(7-methyl-2-oxo-2*H*-chromen-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate, 6f: The compound **6f** obtained from 7-methyl-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chlorobenzamine (1.0mmol). White solid. Yield 78%. m.p.232-234°C; IR (KBr): 3438, 3337, 2277, 1748 and 1726 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, C_7-CH_3 of coumarin), 3.58(s, 3H, -OCH_3 of ester), 3.62(s, 3H, -OCH_3 of ester), 4.19(s, 2H, NH_2), 5.60(s,1H, CH of dihydropyridine), 6.26(s, 1H, C_3-H of coumarin), 7.35(d, 2H, *J*=7.8 Hz, C_6-H of coumarin), 7.47(dd, 3H, *J*=8.4 Hz, C_5-H of coumarin), 7.82(d, 4H, *J*=8 Hz, CH of phenyl ring), 8.23(s, 1H, C_8-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.83, 45.64(C_4-CH of DHP), 53.53(OCH_3 of ester), 54.65(OCH_3 of ester), 61.30, 102.30, 105.23, 108.21, 116.87, 118.10 (CN), 118.94, 120.07, 122.19, 125.43, 129.63, 131.37, 134.03, 140.96, 143.27, 147.38, 153.74, 156.34, 159.70, 160.29(CO of coumarin), 163.06(CO of ester), 167.58(CO of ester). Anal. Calcd for $C_{26}H_{20}ClN_3O_6$: C, 61.73; H, 3.98; N, 8.31. Found: C, 61.75; H, 3.96; N, 8.35%. GC-MS: *m/z* 505 (M^+).

Dimethyl-6-amino-5-cyano-4-(6-methoxy-2-oxo-2*H*-chromen-4-yl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate, 6g: The compound **6g** obtained from 6-methoxy-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-methoxybenzenamine (1.0mmol). Light yellow solid. Yield 78%. m.p.218-220°C; IR (KBr): 3401, 3334, 2220, 1745 and 1725 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.49 (s, 3H, -OCH_3 of ester), 3.59 (s, 3H, -OCH_3 of ester), 3.80 (s, 6H, C_6-OCH_3), 5.03 (s, 1H, CH of dihydropyridine), 5.76(s, 2H, NH_2), 6.23(s, 1H, C_3-H of coumarin), 7.01-7.03(m, 2H, Ar-H), 7.24-7.32(m, 3H, Ar-H), 7.85 (t, 2H Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.13, 35.02(C_4-CH of DHP), 53.17(OCH_3 of ester), 54.35(OCH_3 of ester), 56.08, 101.11, 113.87, 115.67, 116.46(CN), 119.14, 121.76, 124.43, 128.15, 131.47, 133.27, 135.19, 137.49, 142.49, 143.07, 151.62, 155.17, 157.22, 158.45, 160.37(CO of coumarin), 163.72(CO of ester), 165.49(CO of ester). Anal. Calcd for $C_{27}H_{23}N_3O_8$: C, 62.67; H, 4.48; N, 8.12. Found: C, 62.69; H, 4.45; N, 8.16. LC-MS *m/z* 517 (M^+).

Dimethyl-6-amino-5-cyano-1-(3,4-dimethylphenyl) -4-(6-methoxy-2-oxo-2*H*-chromen-4-yl)-1,4-dihyd ropyridine-2,3-dicarboxylate, 6h: The compound **6h** obtained from 6-methoxy-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid. Yield 84%. m.p.232-234°C; IR (KBr): 3431, 2179, 1748 and 1707 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29(s, 6H, C_3 and C_4-CH_3 of phenyl ring), 3.94(s, 3H, C_6-OCH_3 of coumarin), 3.49(s, 3H, -OCH_3 of ester), 3.59(s, 3H,

-OCH_3 of ester), 4.26(s, 2H, NH_2), 5.08(s, 1H, CH of dihydropyridine), 6.42 (s, 1H, C_3-H of coumarin), 7.06(d, 2H, *J*=8 Hz, CH of phenyl ring), 7.21(s, 1H, CH of phenyl ring), 7.15(dd, 1H, *J*=8.8 Hz, *J*=2.8 Hz, C_7-H of coumarin), 7.30(d, 1H, *J*=8.8 Hz, C_8-H of coumarin), 7.47(d, 1H, *J*=2.8 Hz, C_5-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.74(C_3- CH3 of phenyl), 19.86(C_4- CH3 of phenyl), 21.27, 32.89(C_4-CH of DHP), 52.52(OCH_3 of ester), 52.89(OCH_3 of ester), 59.03, 102.44, 113.79, 117.05, 117.60(CN), 120.10, 124.81, 127.23, 130.75, 131.16, 131.83, 133.30, 134.18, 139.20, 140.12, 143.90, 151.48, 152.31, 158.21, 162.13(CO of coumarin), 162.94(CO of ester), 164.83(CO of ester). Anal. Calcd for $C_{28}H_{25}N_3O_7$: C, 65.24; H, 4.89; N, 8.15. Found: C, 65.28; H, 4.85; N, 8.19%. GC-MS: *m/z* 515 (M^+).

Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(6-methoxy-2-oxo-2*H*-chromen-4-yl)-1,4-dihydrop yridine-2,3-dicarboxylate, 6i: The compound **6i** obtained from 6-methoxy-2-oxo-2H-chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chlorobenzamine (1.0mmol). Gray solid. Yield 82%. m.p.230-232°C; IR (KBr): 3414, 3334, 2219, 1748 and 1726 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71(s, 3H, -OCH_3 of ester), 3.73(s, 3H, -OCH_3 of ester), 3.88(s, 3H, C_6-OCH_3 of coumarin), 4.27(s, 2H, NH_2), 5.21(s, 1H, CH of dihydropyridine), 6.14(s, 1H, C_3-H of coumarin), 7.10(t, 2H, *J*=8.7 and Hz, *J*= 8.5 Hz, Ar-H), 7.19(m, 3H,Ar-H), 7.29(d, 2H, *J* =4.2 Hz, Ar-H), 7.80(d, 1H, J= 8.6Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.19, 47.06(C_4-CH of DHP), 52.37(OCH_3 of ester), 55.73(OCH_3 of ester), 60.01,100.30, 105.77, 110.16, 117.34, 117.90(CN), 119.46, 121.03, 123.00, 127.88, 130.63, 132.07, 136.47, 142.23, 145.82, 150.18, 155.04, 157.38, 159.64, 162.86(CO of coumarin), 165.67(CO of ester), 169.78(CO of ester). Anal. Calcd for $C_{26}H_{20}ClN_3O_7$: C, 59.83; H, 3.86; N, 8.05. Found: C, 59.86; H, 3.85; N, 8.09%. GC-MS: *m/z* 521 (M^+).

Dimethyl-6-amino-5-cyano-4-(3-oxo-3*H*-benzo[f]chromen-1-yl)-1-phenyl-1,4-dihydropyridine-2,3-dicarboxylate, 6j: The compound **6j** obtained from 3-oxo-3H-benzo[f]chromene-1-carbaldehyde1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Pink solid. Yield 74%. m.p.247-249°C; IR (KBr): 3393, 2219, 1732 and 1695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.67(s, 3H, -OCH_3 of ester), 3.93(s, 3H, -OCH_3 of ester), 4.32(s, 1H, CH of dihydropyridine), 5.18(s, 2H, NH_2), 6.00(s, 1H, C_3-H of coumarin), 7.60-6.70(m, 5H, of phenyl ring), 7.80(dd, 2H, *J*=8.4 Hz, *J*=1.2 Hz, C_6 and C_7-H of coumarin), 8.11(d, 2H, *J*=7.2 Hz, C_9 and C_{10}-H of coumarin), 8.29(d, 1H, *J*=8.8Hz, C_5-H of coumarin), 8.65(d, 1H, *J*=8.4 Hz, C_8-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.14(C_4-CH of DHP), 53.66(OCH_3 of ester), 56.09(OCH_3 of ester), 57.34, 113., 115.33, 117.94(CN), 120.54, 121.39, 123.77, 124.84, 125.76, 126.29, 126.73, 129.23, 130.62, 131.49, 134.68, 139.67, 141.77, 144.00, 153.16, 155.23, 157.01, 159.42, 160.72(CO of coumarin), 161.97, 162.04(CO of ester), 163.88(CO of ester). Anal. Calcd for $C_{29}H_{21}N_3O_6$: C, 68.63; H, 4.17; N, 8.28. Found: C, 68.68; H, 4.15; N, 8.31%. GC-MS: *m/z* 507 (M^+).

Dimethyl-6-amino-5-cyano-1-(3,4-dimethylphenyl)-4-(3-oxo-3*H*-benzo[f]chromen-1-yl)-1,4-dihydropyridine-2,3-dicarboxylate, 6k: The compound **6k** obtained from 3-oxo-3H-benzo[f]chromene-1-carbaldehyde1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Pink solid. Yield 76%. m.p.248-250°C; IR (KBr): 3426, 3337, 2225, 1746 and 1726 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 and 2.43 (s, 6H, C_3 and C_4-CH_3 of phenyl ring), 3.53(s, 3H, -OCH_3 of ester), 3.65(s, 3H, -OCH_3 of ester), 4.78(s, 2H, NH_2), 5.19(s,1H, 1H, CH of dihydropyridine), 6.21(s, 1H, C_3-H of coumarin), 7.31(d, 1H, Ar-H, *J*=8.0 Hz), 7.43(t, 2H, Ar-H), 7.67(m, 4H, Ar-H), 7.64(t, 1H, Ar-H), 7.72(d, 2H, *J*=6.4 Hz, Ar-H), 7.91(s, 1H, Ar-H), 8.04(d, 1H, *J*=4 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.76(C_3- CH3 of phenyl), 23.17(C_4- CH3 of phenyl), 36.12(C_4-CH of DHP), 54.03(OCH_3 of ester), 55.43(OCH_3 of ester), 57.18, 100.26, 111.45, 112.19, 114.34, 117.44(CN), 118.69, 122.31, 123.08, 124.77, 126.25, 129.11, 130.37, 134.18, 137.02, 137.46, 140.76, 142.83, 152.81, 155.27, 155.92, 157.94, 159.42, 161.53(CO of coumarin), 162.89(CO of ester), 165.75(CO of ester). Anal. Calcd for $C_{31}H_{25}N_3O_6$: C, 69.52; H, 4.71; N, 7.85. Found: C, 69.58; H, 4.65; N, 7.87%. GC-MS: *m/z* 535 (M^+).

Dimethyl-6-amino-1-(4-chlorophenyl)-5-cyano-4-(3-oxo-3*H*-benzo[f]chromen-1-yl)-1,4-dihydrop yridine-2,3-dicarboxylate, 6l: The compound **6l** obtained from 3-oxo-3H-benzo[f]chromene-1-carbaldehyde10.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 4-chloroaniline (1.0mmol).

Pink solid. Yield 75%. m.p.246-248°C; IR (KBr): 3398, 2198, 1742 and 1724 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.59(s, 3H, -OCH_3 of ester), 3.91(s, 3H, -OCH_3 of ester), 4.23(s, 1H, CH of dihydropyridine), 5.18(s, 2H, NH_2), 5.67(s, 1H, C_3-H of coumarin), 6.63 (d, 2H, *J*=7.2 Hz, CH of phenyl ring), 6.96 (d, 2H, *J*=7.2 Hz, CH of phenyl ring), 7.53-7.74(m, 4H, of coumarin), 8.09 (d, 1H, *J*=8.4 Hz, C_5-H of coumarin), 8.28(d, 1H, *J*=9.2 Hz, C_9-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.93(C_4-CH of DHP), 54.17(OCH_3 of ester), 54.66(OCH_3 of ester), 56.23, 112.11, 112.87, 113.22, 114.37, 117.29(CN), 118.33, 122.41, 122.89, 123.54, 125.02, 127.45, 130.00, 131.24, 133.49, 135.62, 139.88, 142.17, 152.84, 154.31, 155.03, 158.15, 159.28, 161.94(CO of coumarin), 164.68(CO of ester), 165.49(CO of ester). Anal. Calcd for $C_{29}H_{20}ClN_3O_6$: C, 64.27; H, 3.72; N, 7.75. Found: C, 64.30; H, 3.70; N, 7.79%. GC-MS: *m/z* 541.94 (M^+).

Dimethyl-6-amino-5-cyano-4-(2-oxo-2*H*-benzo [h] chromen-4-yl)-1-phenyl-1,4-dihydropy ridine-2,3-dicarboxylate, 6m: The compound **6m** obtained from 2-oxo-2H-benzo[h]chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), aniline (1.0mmol). Gray solid. Yield 74%. m.p.247-249°C; IR (KBr): 3464, 2182, 1751 and 1708 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.36(s, 3H, -OCH_3 of ester), 3.43(s, 3H, -OCH_3 of ester), 4.31(s, 1H, CH of dihydropyridine), 5.30(s, 2H, NH_2), 6.35(s, 1H, C_3-H of coumarin), 7.49-6.54 (m, 5H, of phenyl ring), 7.26-7.30 (m, 2H, of coumarin), 7.71-7.74 (m, 2H, of coumarin), 7.95(d, 1H, *J*=8.8 Hz, C_9-H of coumarin), 8.65 (d, 1H, *J*=9.2 Hz, C_5-H of coumarin); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.14(C_4-CH of DHP), 52.74, 53.15(OCH_3 of ester), 56.54(OCH_3 of ester), 100.39, 102.84, 113.38, 114.63, 117.45(CN), 120.87, 121.61, 122.34, 122.92, 127.11, 129.28, 130.72, 133.77, 135.22, 138.45, 140.78, 141.21, 151.09, 152.51, 154.77, 158.45, 160.37, 162.87(CO of coumarin), 163.62(CO of ester), 164.94(CO of ester). Anal. Calcd for $C_{29}H_{21}N_3O_6$: C, 68.63; H, 4.17; N, 8.28. Found: C, 68.69; H, 4.15; N, 8.30%. GC-MS: *m/z* 507 (M^+).

Dimethyl 6-amino-5-cyano-1-(3,4-dimeth ylphe nyl)-4-(2-oxo-2*H*-benzo[h]chromen-4-yl)-1,4-dihy dropyridine-2,3-dicarboxylate, 6n: The compound **6n** obtained from 2-oxo-2H-benzo[h]chromene-4-carbaldehyde (1.0mmol), DMAD (1.0mmol), malononitrile (1.0mmol), 3,4-dimethylamine (1.0mmol). Gray solid. Yield 74%. m.p.247-249°C; IR (KBr): 3428, 3338, 2260, 1755 and 1728 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.38(s, 3H, C_3-CH_3 of phenyl ring), 2.49(s, 3H, C_4-CH_3 of phenyl ring), 3.53(s, 3H, -OCH_3 of ester), 3.54(s, 3H, -OCH_3 of ester), 5.28(s, 1H, CH of dihydropyridine), 5.49 (s, 2H, NH_2), 6.36(s, 1H, C_3-H of coumarin), 6.65(d, 1H, *J* = 8Hz, Ar-H), 6.97(d, 1H, *J* = 8Hz, Ar-H), 7.12(t, 2H, Ar-H), 7.72-7.30(m, 3H, Ar-H), 7.38(s, 1H,Ar-H), 7.96(d. 1H, *J*=8 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.12(C_3- CH3 of phenyl), 19.84(C_4-CH3 of phenyl), 35.17(C_4-CH of DHP), 53.3(OCH_3 of ester), 54.17(OCH_3 of ester), 57.22, 100.42, 111.01, 113.44, 115.00, 117.26(CN), 120.54, 122.67, 123.49, 124.93, 128.11, 128.75, 130.57, 131.84, 136.27, 139.19, 141.97, 144.58, 150.39, 154.69, 156.12, 159.01, 161.21, 161.94(CO of coumarin), 162.17(CO of ester), 164.94(CO of ester). Anal. Calcd for $C_{31}H_{25}N_3O_6$: C, 69.52; H, 4.71; N, 7.85. Found: C, 69.56; H, 4.67; N, 7.87%. GC-MS: *m/z* 535 (M^+).

Dimethyl 6-amino-1-(4-chlorophenyl)-5-cyano-4-(2-oxo-2*H*-benzo[h]chromen-4-yl)-1,4-dihydro pyridine-2,3-dicarboxylate, 6o: The compound **6o** obtained from 2-oxo-2H-benzo[h]chromene-4-carbaldehyde (1.0 mmol), DMAD (1.0 mmol), malononitrile (1.0 mmol), 4-chloroaniline (1.0 mmol). Gray solid. Yield 75%. m.p.247-249°C; IR (KBr): 3439, 3320, 2232, 1743 and 1722cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.37(s, 3H, -OCH_3 of ester), 3.45(s, 3H, -OCH_3 of ester), 5.18(s, 1H, CH of dihydropyridine), 5.42(s, 2H, NH_2), 6.37(s, 1H, C_3-H of coumarin), 6.91(d, 1H, *J* = 8.0 Hz, Ar-H), 7.32(d, 1H, *J* = 8.0 Hz, Ar-H), 7.41(d, 1H, *J* = 4.0 Hz, Ar-H), 7.48(d, 1H, *J* =8 Hz, Ar-H), 7.56(d, 3H, *J* = 12Hz, Ar-H), 7.78 (m, 2H, Ar-H) 8.29(d,1H, *J*=8.0 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.07(C_4-CH of DHP), 53.38(OCH_3 of ester), 54.12(OCH_3 of ester), 56.47, 101.01, 111.80, 113.25, 116.00, 116.76(CN), 119.37, 122.16, 125.17, 125.84, 126.46, 127.35, 130.49, 133.17, 135.27, 139.23, 141.78, 142.48, 152.07, 155.89, 157.45, 159.46, 160.11, 161.83(CO of coumarin), 162.54(CO of ester), 164.92(CO of ester). Anal. Calcd for $C_{29}H_{20}ClN_3O_6$: C, 64.27; H, 3.72; N, 7.75. Found: C, 64.31; H, 3.70; N, 7.76%. GC-MS: *m/z* 541 (M+).

Conclusions

In summary, we have, synthesized novel coumarin-1,4-dihydropyridines *via* one pot multicomponent

reaction by using activated alkyl and active methylene compound at environmentally friendly reaction condition, with easy workup and time saving. All the compounds are found to be good to moderate antimicrobial agent, wherein compounds **6a, 6e** and **6n** are found low MIC value 32 μM/mL and these are considered to be prime candidate for further development of new class of antibacterial agents. The synthesized novel dihydropyridines exhibited as significant anti-inflammatory activity, among all compound **6i** is found to be highly promising anti-inflammatory agent. Molecular docking study was performed for all the dihydropyridine derivatives with *S. aureus* DNA *gyrase* and*cyclooxygenase-2* (PDB ID 4PH9).Compounds **6a** and **6d** showed better bonding interaction againstDNA *gyrase whereas*, *compounds 6d and 6e found excellent interaction with cyclooxygenase-2* at the active site of the enzyme with maximum CScore value, while all other compounds results obtained were quite promising.

Supplementary Information

Full experimental details, ^{1}H and ^{13}C NMR spectra and elemental analysis are available in the website http://nopr.niscair.res.i n/handle/12345678 9/60.

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