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Original Article

Coumarinthiopropionic Acids: Syntheses, Characterization, and Comparison of Docking-DFT Studies on their Antimicrobial Activity

P. Palanisamy[1], R. Subramanian[2], S. Sankari[3], S. Kumaresan[4]*

[1]Department of Chemistry, Pioneer Kumaraswamy College, Nagercoil-629 003, Tamilnadu, India
[2]Centre for Scientific and Applied Research, PSN College of Engineering and Technology, Melathediyoor, Tirunelveli – 627 152, Tamilnadu, India
[3]Department of Chemistry, Manonmaniam Sundaranar University, Tirunelveli-627 012, Tamilnadu, India
[*4]Department of Biotechnology, Manonmaniam Sundaranar University, Tirunelveli-627 012, Tamilnadu, India

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ABSTRACT

Three coumarinthiopropionic acid (**4**, **7**, and **10**) derivatives have been synthesized from the key-intermediates 4-(chloromethyl)-6-methyl-2H-chromen-2-one (**3**), 4-(chloromethyl)-6-hydroxy-2H-chromen-2-one (**6**), and 4-(chloromethyl)-2H-benzo[g]chromen-2-one (**9**). These compounds have been characterized by IR, ^{1}H-NMR, ^{13}C-NMR, Mass, and CHN analysis. These are subjected to antimicrobial-, anticancer-, and DNA cleaving studies. The docking patterns for the above derivatives **4**, **7**, and **10** with **1FIQ** protein have been studied. Compound **4** has a lower binding energy (-225.46 Kcal/mol) as compared to that of other derivatives (**7** and **10**). DFT calculations were performed using Gaussian 09 software. Compound **4** showed the highest antimicrobial activity. DFT and docking studies agreed well with the experimental antimicrobial activity.

Key words: Coumarinthiopropionic acids, antimicrobial, docking, and DFT studies

INTRODUCTION

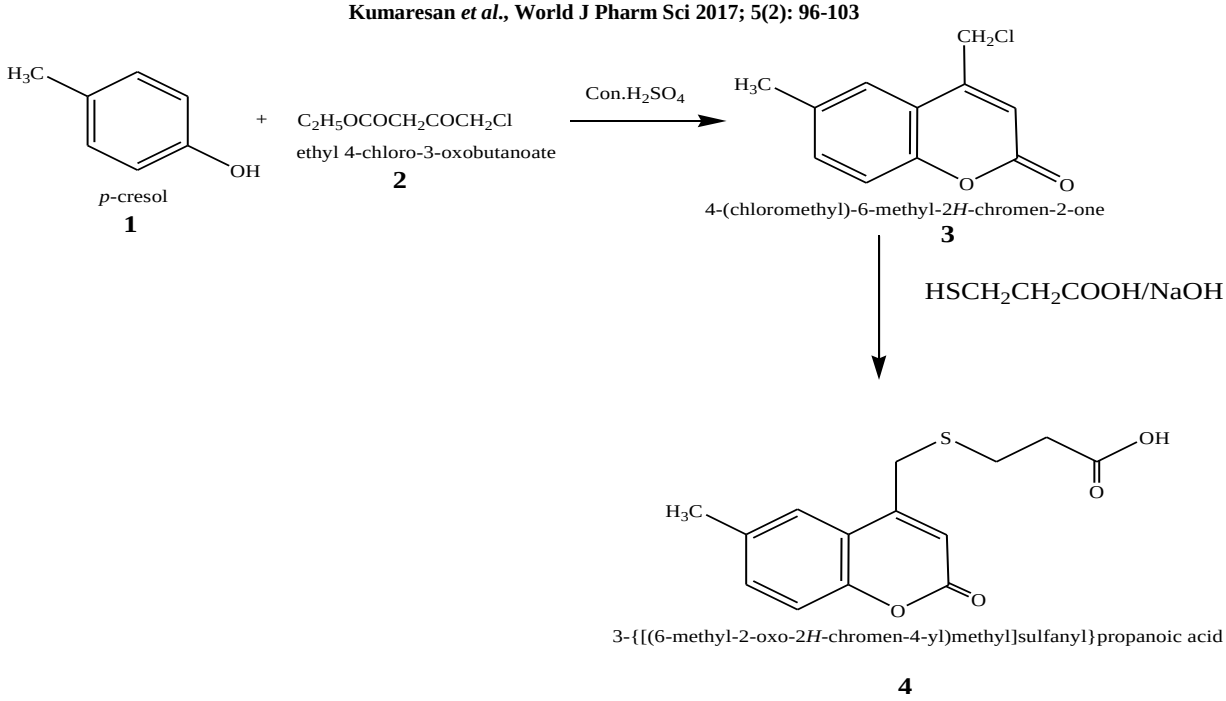
Coumarins are an important group of organic compounds that are used as additives to food and cosmetics, optical brightening agents, dispersed fluorescent-, laser dyes [1-2], fragrances, pharmaceuticals, anticoagulants, bioactive compounds, agrochemical product [3], pesticide intermediates, drugs, insect antifeedants [4-5], intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, 2-acylresorcinol *etc* [6-8]. They are also used as antioxidant and antimicrobial agents, HIV protease inhibitors, acetylcholinesterase (AChE) inhibitors, antifungal, anthelminths, non-nucleoside reverse transcriptase inhibitor (calanolides A), lipid lowering agents [8], tumornecrosis factor-α (TNF-α) inhibitor, serine protease inhibitor, antimicrobial-, antitumor-, anti-HIV-, and antioxidation agents [9]. On the other hand, coumarins with diamino functionality also display interesting physicochemical properties, especially in the sense of design of new drugs and new materials and biological activities [10].

This work reports the syntheses, characterization, antimicrobial activity, docking- and DFT studies of three coumarinthiopropionic acids.

CHEMISTRY

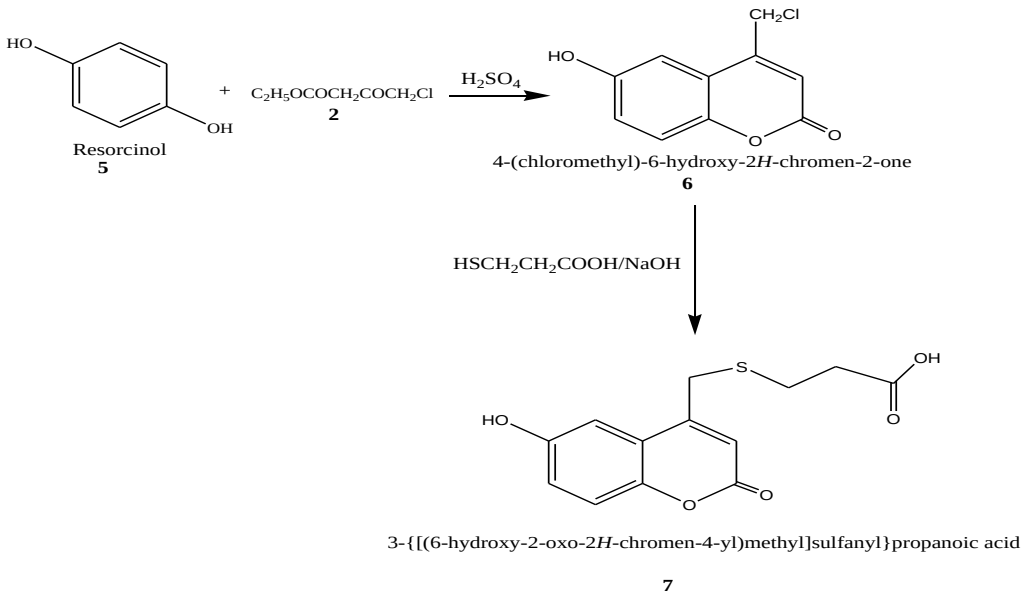
The syntheses of the three coumarinthiopropionic acids (**4**, **7**, and **10**) are depicted in Schemes **2. 1**, **2. 2**, and **2. 3**. The intermediates **3**, **6** and **9** were prepared as per the reported methods [11-12]. 4-(Chloromethyl)-6-methyl-*2H*-chromen-2-one (**3**) was stirred with the sodium salt of mercaptopropionic acid in acetone for 24h (Scheme **2.1**). Colorless 3-{[(6-methyl-2-oxo-*2H*-chromen-4-yl) methyl]sulfanyl}propionicacid (**4**) was obtained in 80% yield. The IR spectrum of **4** showed the acid and lactone carbonyls absorption bands merged together at 1715 cm^{-1}. ^{1}H-NMR spectrum showed a singlet at δ 2.4 ppm (-C<u>H</u>$_3$ group), two triplets at δ 2.6 and 2.7 ppm (-S-CH$_2$-C<u>H</u>$_2$ and -S-C<u>H</u>$_2$-CH$_2$ group), two singlets at δ 3.9 and 6.4 ppm (benzylic-CH$_2$ and C=C<u>H</u>), and a multiplet in the region δ 7.2-7.5 ppm (aromatic protons).

***Corresponding Author Address:** Dr. **S. Kumaresan,** Department of Biotechnology, Manonmaniam Sundaranar University, Tirunelveli-627 012, Tamilnadu, India; E-mail: skumarmsu@yahoo.com*



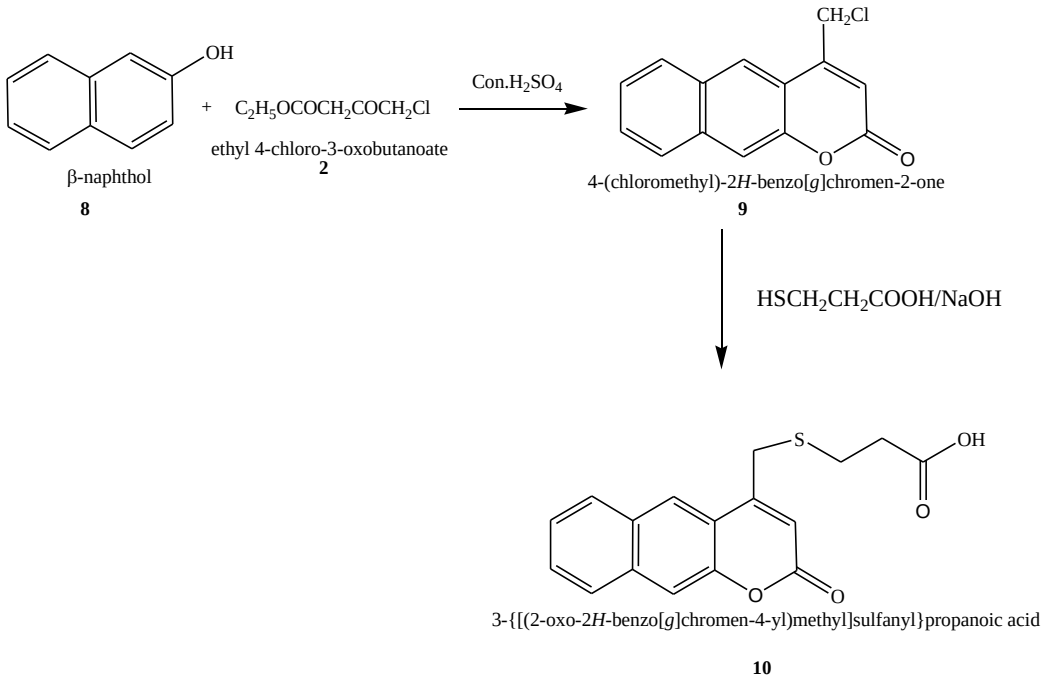
Scheme 2.1

4-(Chloromethyl)-6-hydroxy-*2H*-chromen-2-one (**6**) was stirred with the sodium salt of mercaptopropionic acid in acetone for 24 h (Scheme **2. 2**). Colorless 3-{[(6-hydroxy-2-oxo-*2H*-chromen-4-yl) methyl]sulfanyl}propionic acid (**7**) was obtained in 68% yield. The IR spectrum of **7** showed the acid and lactone carbonyls together at 1705 cm^{-1}. ^{1}H-NMR spectrum showed two triplets at δ 2.0 and 2.2 ppm (-S-CH_2-C$\underline{H}_2$ and -S-C$\underline{H}_2$-CH_2), two singlets at δ 3.2 and 5.6 ppm (benzylic-CH_2 and C=C$\underline{H}$), and a multiplet in the region δ 6.2-7.0 ppm (aromatic protons).



Scheme 2.2

4-(Chloromethyl)-*2H*-benzo[g]chromen-2-one (**9**) was stirred with the sodium salt of mercaptopropionic acid in acetone for 24h (Scheme 2.3). Colorless 3-{[(2-oxo-*2H*-benzo[g]chromen-4-yl)methyl]sulfanyl}propionic acid (**10**) was obtained in 52% yield. The IR spectrum of **10** showed two carbonyl stretching frequencies at 1723 cm^{-1}(lactone carbonyl) and 1716 cm^{-1}(carboxylic acid). ^{1}H-NMR spectrum showed two triplets at δ 2.5 and 2.7 ppm (-S-CH_2-C<u>H</u>$_2$ and -S-C<u>H</u>$_2$-CH_2 group), two singlets at δ 4.3 and 6.6 ppm (benzylic-CH_2 and C=C<u>H</u>), and a multiplet in the region at δ 7.5-8.4 ppm (aromatic protons).



Scheme 2.3

Antimicrobial evaluation: All the three newly synthesized compounds were evaluated for their *in vitro* antibacterial activity against *Staphylococcus aureus*, and *Streptococcus pneumoniae*, as examples of Gram-positive bacteria and *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* as examples of Gram-negative bacteria. They were also evaluated for their *in vitro* antifungal potential against *Candida albicans*, *Aspergillus flavus*, and *Aspergillus niger* fungal strains. Agar-diffusion method was used for the determination of the preliminary antibacterial and antifungal activity. *Ampicillin* was used as a reference drug. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the discs in mm and the inhibition zone diameter values are recorded in Table 1.

Table 1 Antibacterial activity and antifungal activity of compounds 4, 7, and 10 [zone of inhibition (mm)]

Name of the bacteria and fungi	Compounds			Ampicillin (Reference drug)
	4	**7**	**10**	
Staphylococcus aureus (bacteria)	07-10	05-08	02-05	12-15
Streptococcus pneumoniae (bacteria)	24-27	21-24	18-21	20-23
Klebsiella pneumoniae (bacteria)	08-11	06-09	04-07	10-13
Pseudomonas aeruginosa (bacteria)	25-28	20-23	17-20	23-26
Escherichia coli(bacteria)	05-08	02-05	01-03	08-12
Candida albicans (fungi)	24-27	19-23	16-19	21-24
Aspergillus flavus (fungi)	08-11	05-08	06-09	12-15
Aspergillus niger (fungi)	10-13	08-11	07-10	11-14

The results depicted in Table 1 revealed that the tested compounds displayed variable inhibitory effects on the growth of the tested bacterial strains, and also against antifungal strains. It would also be noticed that the compound **4** exhibited better antibacterial potentials than compounds **7** and **10**. In this view, 3-{[(6-hydroxy-2-oxo-2H-chromen-4-yl)methyl]sulfanyl}propionic acid (**4**) was found to exhibit higher activity (24-27 mm and 25-28 mm) than that of ampicillin (20-23 mm and 23-26 mm) against *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. The highest antifungal activity against *Candida albicans* (24-27mm) was noticed for compound **4**.

Docking studies of compounds 4, 7, and 10 on 1FIQ proteins: The interpretation of molecular surfaces is considered important in molecular interaction and reactions since they play a significant role in drug design and docking experiments [13]. Docking explores ways in which two molecules, such as drugs and an enzyme/protein receptor fit together and dock to each other well. The molecules binding to a receptor, inhibit its function, and thus act as drug. The interaction of a drug and receptor molecule is identified *via* docking and their relative stabilities evaluated using molecular dynamics and their binding affinities, using free energy simulations [14]. From the docking results, the best scoring (*i.e.* with the lowest docking energy) docked model of a compound is chosen to represent its most favorable binding mode predicted by AutoDock [15, 16]. The protein-ligand interactions are also studied in web server. Based on the score value against the activity, the molecules are represented as active, moderately active and inactive [17]. Docking calculations were carried out using docking server [18]. The MMFF94 force field [19] was used for energy minimization of the ligand molecules (compounds **4, 7,** and **10)** using the docking server. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged and rotatable bonds were defined. Docking calculations were carried out on '**1FIQ-REPLICATION** protein model' [19a] (Fig. 1). Essential hydrogen atoms, Kollman united atom type charges and salvation parameters were added with the help of AutoDock tools [20]. AutoDock parameters set- and distance- dependent dielectric functions were used in the calculations of the van der Walls and the electrostatic terms respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Soils and Wets local search method [21]. Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 2,50,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2Å and quaternion and torsion step of 5 were applied (Figs. 2, 3 and 4). The estimated free energy of binding and the interacting surface of the compounds **4**, **7**, and **10** are given in Table 2.

Table 2 Docking results for compounds 4, 7, and 10

Compound	Est. binding energy (Kcal/mol)	Est. inhibition constant, KI	Interacting surface A^{o2}	Interaction Residue/s
4	-225.46	16.34µM	824.631	VAL43, ALA47, PRO79
7	-174.98	20.25µM	689.361	ASN46, ASP73, PRO79
10	-104.54	25.63µM	528.94	VAL43, ALA47, PRO79

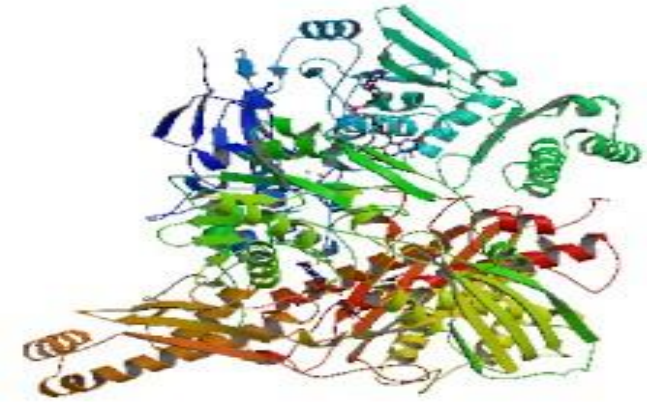


Fig. 1 Structure of 1FIQ replication protein

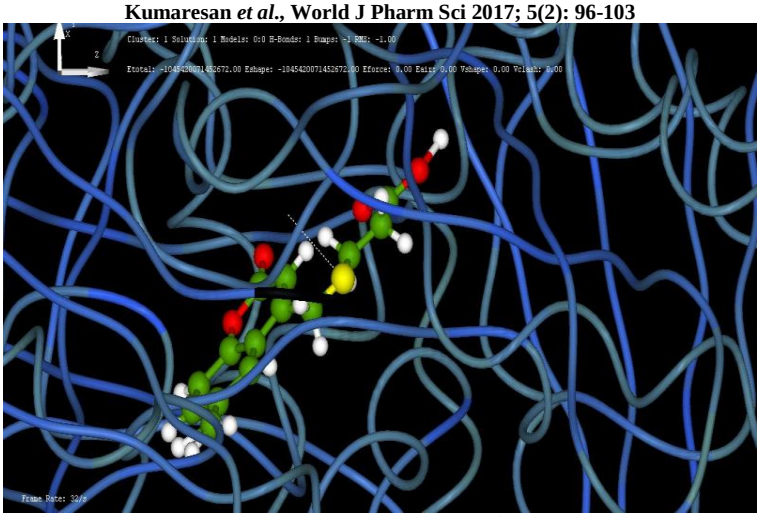


Fig. 2 Docking of 3-{[(6-methyl-2-oxo-*2H*-chromen-4-yl)methyl]sulfanyl}propionicacid 4) with 1FIQ protein

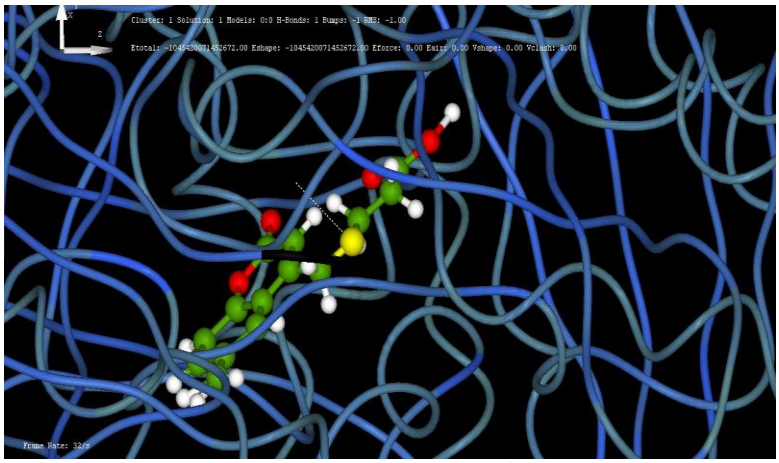


Fig. 3 Docking of 3-{[(6-hydroxy-2-oxo-*2H*-chromen-4-yl)methyl]sulfanyl}propionic acid (7) with 1FIQ protein

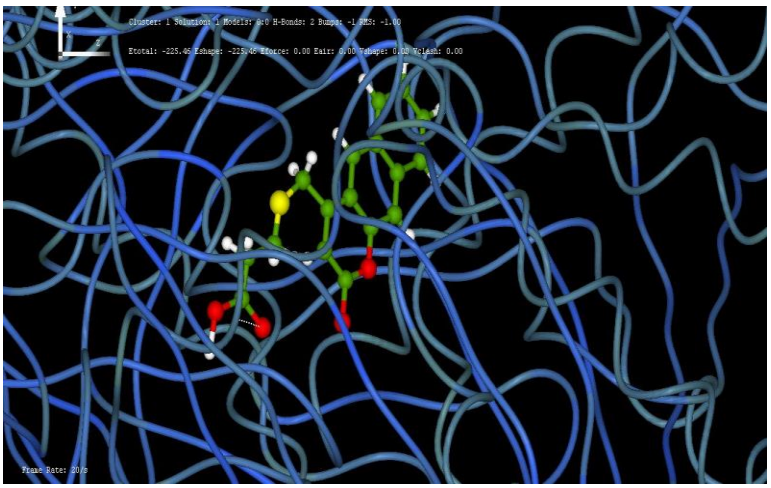


Fig. 4 Docking of 3-{[(2-oxo-2H-benzo[g]chromen-4-yl)methyl]sulfanyl}propionic acid (10) with 1FIQ protein

From the docking analysis, the following data were obtained.

a) The surface area of compound **4** is found to be 824.631Å^2 and that of compound **7** and **10** are 689.361 and 528.94 Å^2 respectively.
b) Compound **4** has a lower binding energy (-225.46 Kcal/mol) as compared with that of compounds **7** (-174.98 Kcal/mol) and **10** (-104.54 Kcal/mol). This suggests that the designed coumarinthiopropionic acid **4** is a moderate promoter of 1FIQ protein.
c) VAL43, ALA47, and PRO79 are the interacting residues with minimum binding energy with compound **4**.

DFT Studies on compounds 4, 7, and 10: DFT calculations often provide the much desirable information on the molecular properties. Choice of a computational procedure, however, depends upon the level of the needed accuracy, size of the molecular system, and the available computational facility. The B3LYP/3-21G(d) method has been successfully used to predict the geometry and electronic structure of a molecule due to its more advantages [22]. All calculations were performed using Gaussian 09 software [23]. Gas phase geometry of **4**, **7**, and **10** was fully optimized at Density Functional Theory (DFT/B3LYP-3-21G (d)) method [24]. The electronic properties were calculated both from the Koopmans' theorem (orbital energy consideration represented by subscript O) and from the total energies denoted with subscript E of the species as reported methods [25-26]. Gas phase geometrical parameters of the optimized structures of coumarinthiopropionic acids **4**, **7**, and **10** at the DFT/3-21G(d) level is listed in Table 3. In total we have investigated the electronic structures of the compounds **4**, **7**, and **10** using the DFT method. Figs. 5, 6, and 7 represent the optimized structures of the coumarinthiopropionic acids **4**, **7**, and **10** respectively.

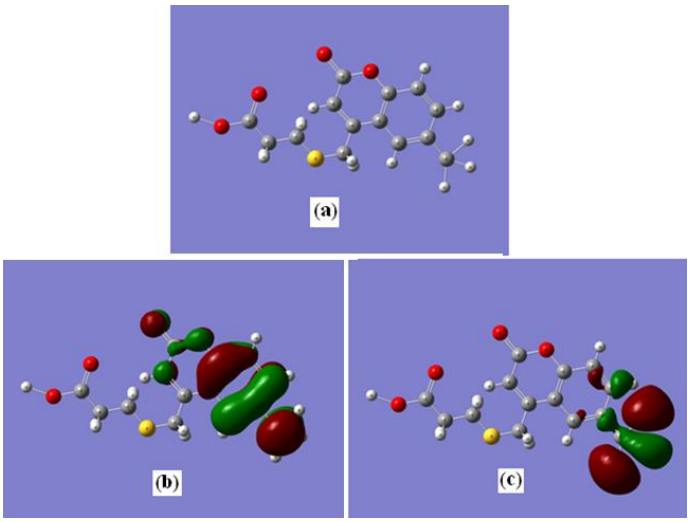


Fig. 5 (a) Optimized structure of 3-{[(6-methyl-2-oxo-*2H*-chromen-4-yl)methyl]sulfanyl}propionic acid (4) (b) HOMO of 4 (c) LUMO of 4

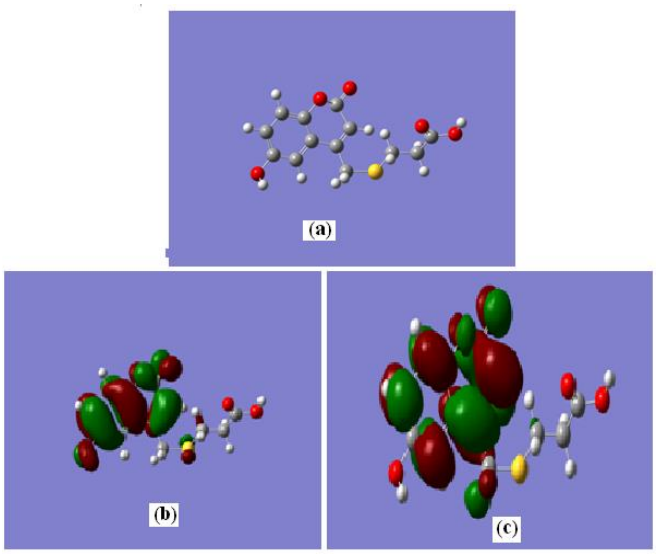


Fig. 6 (a) Optimized structure of 3-{[(6-hydroxy-2-oxo-*2H*-chromen-4-yl)methyl]sulfanyl}propionic acid (7) (b) HOMO of 7 (c) LUMO of 7

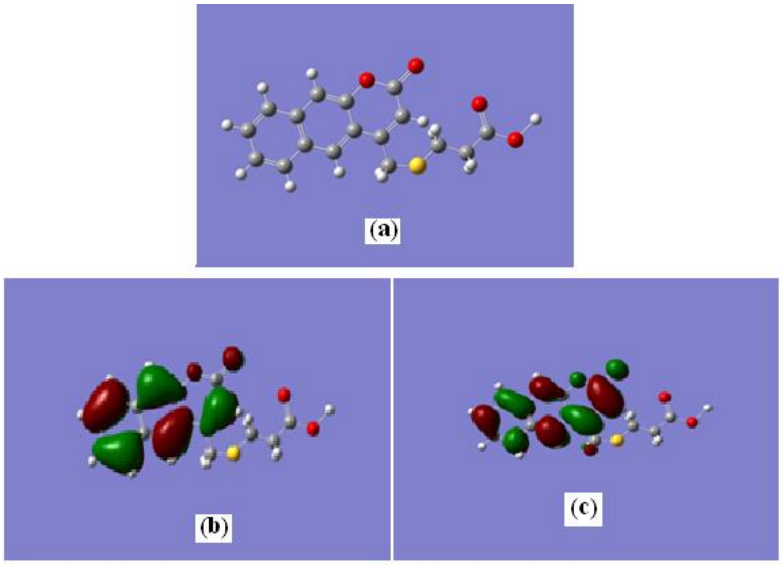


Fig. 7 (a) Optimized structure of 3-{[(2-oxo-*2H*-benzo[g]chromen-4-yl)methyl]sulfanyl}propionic acid (10) (b) HOMO of 10 (c) LUMO of 10

Table 3 DFT results of compounds 4, 7, and 10

DFT Properties	Compound		
	4	7	10
HOMO (eV)	-0.25466	-0.33297	-0.29216
LUMO(eV)	-0.01104	-0.0729	-0.01182
Energy gap, ΔE (eV)	0.24362	0.26007	0.28034
Ionization Potential (eV)	0.25466	0.33297	0.29216
Electron affinity (eV)	0.01104	0.0729	0.01182
Electro negativity, χ (eV)	0.13285	0.202935	0.15199
Electrochemical potential, μ (eV)	-0.13285	-0.20294	-0.15199
Hardness, η (eV)	0.12181	0.130035	0.14017
Softness, σ (eV)	8.209507	7.690237	7.134194
Nucleophilicity (ω)	0.072445	0.158352	0.082403
E_{total} Kcals/mol	-1227.43	-1264.16	-1340.63

Terms involving the frontier molecular orbitals (FMO) could provide dominative contribution, because of the inverse dependence of stabilization energy on orbital energy difference. HOMO-LUMO energy gap (ΔE), molecular hardness (η), ionization energy, electron affinity, and total energy are very important physical parameters for chemical reactivity and biological activities of the compounds under study. E_{HOMO} is often associated with the electron donating ability of a molecule; high values of E_{HOMO} are likely to indicate the tendency of the molecule to donate electrons to appropriate acceptor molecules with lower energy MO. E_{LUMO}, on the other hand, indicates the ability of the molecule to accept electrons. The binding ability of the molecule increases with increasing HOMO and decreasing LUMO energy values. Thus, the lower the value of E_{LUMO}, the most probable it is that the molecule would accept electrons. Figs. **5**, **6**, and **7** reveal the HOMO and LUMO of coumarinthiopropionic acids **4**, **7**, and **10** respectively. From this one can understand that **4** has the highest E_{HOMO} value (-0.25466 eV) making it an electron donor (Lewis base) and **10** has the lowest E_{LUMO} value (-0.01182 eV) and it becomes an electron acceptor (Lewis acid). Moreover, the gap between the HOMO and LUMO energy levels (ΔE) of the molecule is an important parameter that determines the reactivity of the molecule. As ΔE decreases (most especially for the cationic species), the reactivity of the molecule increases leading to a decrease in the stability of the molecule.

Compound **4** has the lowest energy gap and least stability and compound **10** has the highest energy gap and more stability.

Absolute hardness, η, and softness, σ, are important properties to measure the molecular stability and reactivity. A hard molecule has a large energy gap and a soft molecule has a small energy gap. Soft molecules are more reactive than hard ones because they could easily offer electrons to an acceptor. For the simplest transfer of electrons, adsorption could occur at the part of the molecule where σ has the highest magnitude and η has the lowest. The nucleophilicity, ω, measures the electrophilic power of a molecule. It has been reported that the lower the value of χ, the lower the capacity of the molecule to donate electrons [27].

Table 3 shows that compound **4** has the lowest energy gap (ΔE, 0.24362 eV), lowest hardness (0.12181 eV), highest softness (8.209507 eV), lower nucleophilicity (0.072445 eV), and lower energy (-1227.43 kcal/mol). The experimentally observed potent activity of compound **4** matches with the theoretical results obtained from DFT studies.

EXPERIMENTAL

General comments: FT IR spectra were recorded on a JASCO FT-IR Model 410 spectrophotometer. The recording was performed in the 4000-400 cm^{-1} wave number range. ^{1}H-NMR spectra were recorded on a 300 MHz Varian spectrometer using $CDCl_3$/DMSO-d_6 solvent system. All chemicals were purchased commercially and used as such. Each set of reaction was monitored using TLC plates prepared from silica gel (Merck) grade. The products formed were purified by column chromatography using silica gel, 60-120 mesh (Merck).

General procedure for the syntheses of compounds 3, **6**, and **9:** One mmol of p-cresol/resorcinol/β-naphthol was mixed thoroughly with 1 mmol of ethyl 4-chloro-3-oxobutanoate. This mixture was stirred at ice cold condition. To this mixture, 85% con.H_2SO_4 (50 mL) was added dropwise and stirred for 30 minutes. The resulting solution was decomposed with crushed ice. Compounds **3**, **6**, and **9** got separated as colourless solids. They were washed with excess of ice water, dried, and recrystallized from benzene.

General procedure for the syntheses of compound 4, **7**, and **10:** Compounds **3/6/9** (1 mmol) was dissolved in acetone (25mL). 3-Mercaptopropionic acid (1 mmol) was mixed with two equivalents of aqueous NaOH (25mL). The aqueous sodium salt of the acid was added slowly with continuous stirring to the above compounds. The resulting solution was stirred at ambient temperature for 24h. Neutralization was done under ice cold conditions using aqueous 1:1 HCl. The solid compounds of **4**, **7**, and **10** separated were washed with excess of ice water, dried, and recrystallized from ethanol.

Antimicrobial evaluation: Standard sterilized filter paper discs (5 mm diameter) impregnated with a solution of the test compound in DMSO (1 mg/mL) was placed on an agar plate seeded with the appropriate test organism in triplicates. The utilized test organisms were *Staphylococcus aureus,* and *Streptococcus pneumoniae,* as examples of Gram-positive bacteria and *Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Escherichia coli* as examples of Gram-negative bacteria. They were also evaluated for their *in vitro* antifungal potential against *Candida albicans, Aspergillus flavus,* and *Aspergillus niger* strains. Ampicillin was used as a standard antibacterial agent and antifungal agent. DMSO alone was used as a control at the above-mentioned concentration. The plates were incubated at 37^0C for 24h for bacteria and 28^0 C and 48h for fungi.

DFT study: All calculations were performed using Gaussian 09 software [13].

CONCLUSION

We have synthesized three key-intermediates, 4-(chloromethyl)-6-methyl-2H-chromen-2-one (**3**), 4-(chloromethyl)-6-hydroxy-2H-chromen-2-one (**6**), and 4-(chloromethyl)-2H-benzo[h]chromen-2-one (**9**) . The corresponding coumarinthiopropionic acids **4**, **7**, and **10** have been synthesized from the above intermediates. The products have been characterized by IR, and ^{1}H-NMR spectral techniques. Antibacterial and antifungal studies for the new acids (**4**, **7**, and **10**) have also been studied. Compound **4** showed highest antimicrobial activity. Docking patterns for the three acids **4**, **7**, and **10** with **1FIQ** protein have been studied. Compound **4** has a lower binding energy (-25.46 Kcal/mol) as compared with that of compounds **7** (-174.98 Kcal/mol) and **10** (-104.54 Kcal/mol). DFT calculations were performed using Gaussian 09 software. Compound **4** has the lowest energy gap (ΔE, 0.24362eV), lowest hardness (0.12181 eV), highest softness (8.209507 eV), and lower nucleophilicity (0.072445 eV). These results agree with the experimental observations that **4** shows better antimicrobial activity.

Acknowledgements
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