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Original article

# Aqua mediated synthesis of 2-amino-6-benzothiazol-2-ylsulfanyl-chromenes and its in vitro study, explanation of the structure–activity relationships (SARs) as antibacterial agent

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ABSTRACT

Multi-component reaction (MCR) involves coupling of *p*-bromophenol with 2-Benzothiazolethiol, malononitrile and substituted aldehydes in aqueous $K_2CO_3$ as green base to synthesize 2-amino-6-benzothiazol-2-ylsulfanyl-chromenes. This multi-component reaction thus offers a higher yield and versatility in the preparation of densely functionalized oxygen heterocycles. The newly synthesized compounds were screened for their antibacterial activities against positive and gram negative pathogenic strains to bacteria. SAR analysis was performed to explore comprehensive structure–activity relationships and a statistically reliable model to explain their antibacterial activities.



## 1. Introduction

Heteroaromatic compounds have awestruck significant attention in the design of biologically active molecules and advanced organic materials [1,2]. Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry [3]. Among the family of heterocyclic compounds, 4H-chromenes are important class of oxygenated heterocyclic compounds [4]. More recently, there has been increased interest in the synthesis of 4H-chromenes since bioactive natural products containing chromene ring system possess wide spectrum of activities including as antidepressant, antihypertensive, anti-tubulin, antiviral, antioxidative, activator of potassium channels and inhibition of phosphodiesterase IV or dihydrofolate reductase [5–8].

The 2-benzothiazolethiol ring system is important in medicinal chemistry [9] and finds its application in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia and bacterial and HIV infections [10]. Hence the fusion of 2-benzothiazolethiol with chromene could provide superior biological moiety *i.e.* benzothiazol-2-ylsulfanyl-chromenes. Without any shadow of doubt, it is proposed that the development of libraries of 2-amino-6-benzothiazol-2-ylsulfanyl-chromenes might provide additional lead molecules for new drug discovery.

One of the tools of the organic chemist to strive for the ideal synthesis is multi-component reactions (MCRs), which could be broadly defined, regardless of their mechanistic nature, as the process consisting of a number ($\geq$2) of synthetic steps carried out in the same flask without isolation of any intermediate, thus reducing time, saving money, energy and raw materials with both economic and environmental benefits thus leading to a product containing the main parts of all starting materials [11]. The most effective MCRs provide new products with optimal change in structure and functionality from simple substrates in highly atom-economical fashion. The MCRs, described by Strecker in 1850 [12], after having been considered as an exotic variants of organic reactions have become very popular in recent years for the preparation of compounds following environment friendly and cheaper strategies.

As part of our program aimed at developing efficient and environmentally friendly methodologies for the preparation of fine chemicals, we carried out the synthesis of 2-amino-6-benzothiazol-2-ylsulfanyl-chromenes via four-component reaction employing water as the reaction medium [13]. In fact, as clearly stated

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by Sheldon, it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water". The use of water as the reaction medium represents a remarkable benefit since this green solvent is highly polar and therefore immiscible with most organic compounds; moreover the water soluble catalyst resides and operates in the aqueous phase thus separation of the organic materials is easy [14].

The demand for novel chemotherapeutic antibacterial agents remains attractive in the field of medicinal chemistry. So, the judicious use of antibacterial agent is an important approach in an attempt to control the emergence of bacterial resistance. In order to discover more potent inhibitors, we have successfully attempted a novel and green synthesis of benzothiazol-2-ylsulfanyl-chromenes through substitution of chromenes with 2-Benzothiazolethiol [15].

## 2. Results

### 2.1. Chemistry

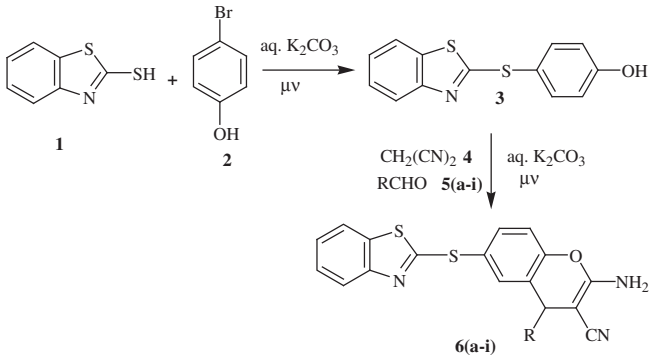
A literature survey has revealed that the reaction of phenol with malononitrile and substituted aldehydes proceeds in ethanolic piperidine to form chromenes derivatives. This classical procedure employs piperidine as a hazardous organic base, refluxing for long hours in organic solvents (ethanol, acetonitrile) and gives low yields of products [16]. In order to study the role of the base used and to modify the classical method to an efficient, clean and economical protocol, aqueous $K_2CO_3$ conditions are used for the reaction. The encouraging results obtained inspired us to synthesize some novel pyrano-coumarin derivatives using heterocyclic aldehydes. The structure of these chromenes derivatives was confirmed on the basis of spectroscopic data (Scheme 1 and Table 1).

Encouraged by these results, we tried to extend the scope of this process to another active thiol compound Benzoimidazole-2-thiol, which is an important synthon for various heterocyclic compounds (Scheme 2) (Table 2). As expected, desired products were obtained in excellent yields in less reaction time.

### 2.2. Evaluation of biological activity and QSAR of compounds

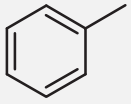
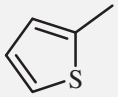
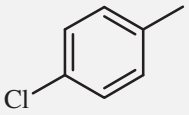
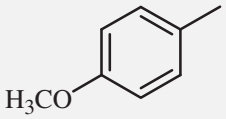
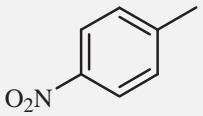
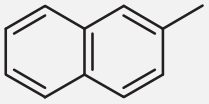
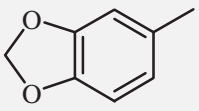
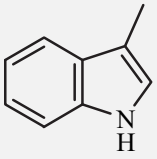
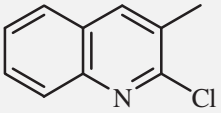
Screening of all the synthesized compounds for their antibacterial activity was performed by employing Broth Microdilution MIC method [17]. Using sterile microtitre plates, 0.2 ml of Mueller Hinton Broth was added to each of the 96 wells. Doubling dilutions of each compound were made in the wells, thus, a plate contained 0.5–100 μg/ml dilutions of 21 different compounds and of ampicillin. In each plate one well was kept as positive control (broth + inoculum) and another as negative control (broth only). The inoculum was adjusted to a turbidity equivalent to McFarland 0.5 turbidity standard. The inoculum was suitably diluted so as to get a final concentration of approximately $5 \times 10^5$ cfu/ml of bacteria in each well. Each well was inoculated with 0.01 ml of the prepared inoculum using a multichannel micropipette and the plates were incubated overnight at 37 °C. The MICs of these compounds and ampicillin were determined by using the standard protocol of NCCLS Broth Microdilution MIC method (Tables 3 and 4).

QSAR methods are widely used in drug design because they allow rapid generation of QSAR models, from which biological

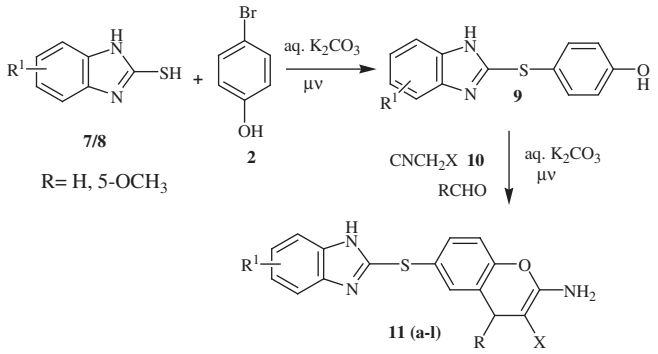



**Scheme 1.** Synthesis of 2-amino-3-cyano-6-benzothiazole-2-ylsulfanyl-chromene.

**Table 1**
Reaction times and yields for the synthesis of 2-amino-4-aryl-6-thiazole-2-chromene (**6a**–**i**).

| S. No. | Entry No. | R | Yield%[a] | Time (min) |
|---|---|---|---|---|
| 1 | a |  | 72 | 22–22.5 |
| 2 | b |  | 63 | 24–24.5 |
| 3 | c |  | 65 | 25–25.5 |
| 4 | d |  | 55 | 23–23.5 |
| 5 | e |  | 25 | 27–27.5 |
| 6 | f |  | 73 | 26–26.5 |
| 7 | g |  | 84 | 25.5–26 |
| 8 | h |  | 52 | 23.5–24 |
| 9 | i |  | 64 | 24–24.5 |

[a] Isolated and unoptimized yields.




**Scheme 2.** Synthesis of 2-amino-2-ylsulfanyl-(6-benzoimidazole)-chromene.

activity of newly designed molecules can be predicted. In this study, 21 compounds with available MIC on four different bacteria were employed for the WINKS SDA 6 analysis. For QSAR analyses, all 21 compounds were selected and the chemical properties were estimated with ChemDraw Ultra. The MIC values of these compounds were used as dependent variables. The WINKS SDA 6 results are summarized in Table 3. These statistical indexes were reasonably high, indicating that this WINKS SDA 6 model had a strong predictive ability. As it can be seen in Table 3, the theoretical results of 21 compounds on four different bacteria were in good agreement with the experimental values, suggesting that the new WINKS SDA 6 model was reliable.

The QSAR methods have been used successfully in pharmaceutical applications and in this work we calculated some molecular properties of compounds in order to correlate them with their antibacterial activity. The calculated descriptors were selected so that they could represent electronic and hydrophobic features of the compounds studied, as they are supposed to be important for their antibacterial activity (Table 4).

The calculated descriptors were:

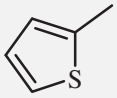
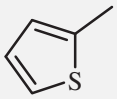
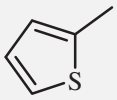
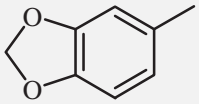
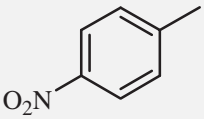
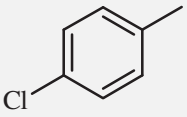
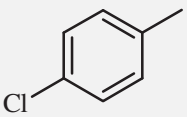
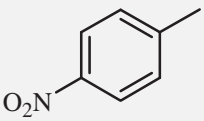
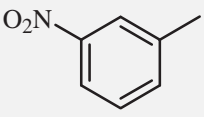
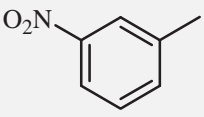
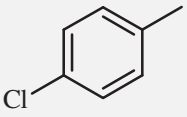
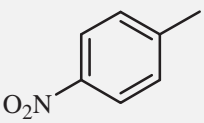
- Electronic properties: $E_{HOMO}$ (the highest occupied molecular orbital energy), $E_{LUMO}$ (the lowest unoccupied molecular orbital energy)
- Hydrophobic property: log *P* (partition coefficient).

## 3. Discussion

The complete process represents an example of the one-pot and sequential steps reaction (often referred to as tandem or cascade reaction) where reagents and catalysts are mixed together and experimental conditions are set up in such a way to promote the reaction cascade. Thus the benzylidenemalononitrile **7**(a–i) containing the electron-poor C=C double bond is quantitatively produced by fast Knoevenagel addition of malononitrile to the aromatic aldehyde. As we previously reported, the reaction easily occurs in protic solvents including water without using catalyst, although it results in net dehydration [18]. The second step that requires the presence of $K_2CO_3$ as base presumably involves the phenol ortho C-alkylation by reaction with the electrophilic C=C double bond giving the intermediate **8**(a–i). Successively the phenolic OH group undergoes fast nucleophilic addition to the CN producing the final 2-amino-2-chromene 6 (Scheme 3).

Quick plot HOMO and LUMO surface and the three-dimensional SCF maps of 9 compounds (4 active (**6d**, **6h**, **6e** and **6g**) + 4 inactive (**6a**, **6c**, **6i** and **6b**) and **11b**) superimposed onto total electron density accounts for the interpretation of short-range interactions between molecules. At each point of the map in SCF, the electrostatic potential expresses the value of the electrostatic energy of

**Table 2**
Reaction times and yields for the synthesis of 2-amino-4-aryl-(6-benzoimidazole)-chromene (**11a**–**l**).

| S. No. | $R^1$ | R | X | Product | Yields[a] (%) | Time (min) |
|---|---|---|---|---|---|---|
| 1 | H |  | COOEt | **11a** | 77 | 17–17.5 |
| 2 | $OCH_3$ |  | COOEt | **11b** | 65 | 15.5–16 |
| 3 | $OCH_3$ |  | CN | **11c** | 46 | 17.5–18 |
| 4 | $OCH_3$ |  | COOEt | **11d** | 53 | 16–16.5 |
| 5 | $OCH_3$ |  | COOEt | **11e** | 68 | 13–13.5 |
| 6 | H |  | COOEt | **11f** | 71 | 16.5–17 |
| 7 | H |  | CN | **11g** | 63 | 15–15.5 |
| 8 | H |  | COOEt | **11h** | 78 | 12–12.5 |
| 9 | H |  | COOEt | **11i** | 65 | 12.5–13 |
| 10 | $OCH_3$ |  | COOEt | **11j** | 73 | 13–13.5 |
| 11 | $OCH_3$ |  | COOEt | **11k** | 77 | 16–16.5 |
| 12 | $OCH_3$ |  | CN | **11l** | 74 | 12.5–13 |

[a] Isolated and unoptimized yields.

**Table 3**
Comparison of experimental ($MIC_{Exp}$), predicted ($MIC_{Cal}$) and cross-validated ($MIC_{Res}$).

| Comp | *P. aeruginosa* | | | *E. coli* | | | *S. aureus* | | | *S. epidermidis* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $MIC_{Exp}$ | $MIC_{Cal}$ | $MIC_{Res}$ | $MIC_{Exp}$ | $MIC_{Cal}$ | $MIC_{Res}$ | $MIC_{Exp}$ | $MIC_{Cal}$ | $MIC_{Res}$ | $MIC_{Exp}$ | $MIC_{Cal}$ | $MIC_{Res}$ |
| **6a** | 32 | 45.5 | 13.5 | 16 | 10.0 | 6 | 4 | 9.3 | 5.3 | 8 | 9.6 | 1.6 |
| **6b** | 32 | 58.5 | 26.5 | 2 | 0.4 | 1.6 | 2 | 0.4 | 1.6 | 64 | 93.9 | 29.9 |
| **6c** | 16 | 21.9 | 5.9 | 32 | 29.7 | 2.3 | 4 | 11.5 | 7.5 | 32 | 31.5 | 0.5 |
| **6d** | 2 | 1.8 | 0.2 | 32 | 38.8 | 6.8 | 8 | 14 | 6 | 16 | 12.8 | 3.2 |
| **6e**[a] | 16 | – | – | 4 | – | – | 0.5 | – | – | 32 | – | – |
| **6f** | 8 | 10 | 2 | 16 | 23.6 | 7.6 | 16 | 4.7 | 11.3 | 32 | 11.5 | 20.5 |
| **6g** | 8 | 6.7 | 1.3 | 1 | 1.8 | 0.2 | 8 | 17.8 | 9.8 | 4 | 0.3 | 3.7 |
| **6h**[a] | 16 | – | – | 0.5 | – | – | 2 | – | – | 32 | – | – |
| **6i** | 16 | 11.7 | 4.3 | 16 | 12.9 | 3.1 | 16 | 8.9 | 7.1 | 64 | 27.5 | 36.5 |
| **11a** | 125 | 133.4 | 12.4 | 125 | 125.4 | 0.4 | 125 | 125.4 | 0.4 | 125 | 114.8 | −10.2 |
| **11b** | 125 | 131.2 | 6.2 | 125 | 124.0 | −1.0 | 125 | 124.0 | −01.0 | 125 | 137.9 | −12.9 |
| **11c** | 125 | 123.8 | −1.2 | 125 | 125.4 | 0.4 | 250 | 125.4 | 0.4 | 250 | 247.7 | 2.3 |
| **11d** | 125 | 176.8 | 51.8 | 125 | 125.0 | 0 | 125 | 125.0 | 0 | 125 | 124.0 | −1.0 |
| **11e** | 32 | – | – | 64 | – | – | 64 | – | – | 64 | – | – |
| **11f** | 8 | 4.3 | 3.7 | 64 | 54.8 | 9.2 | 32 | 42 | 42 | 64 | 51.3 | 12.7 |
| **11g** | 16 | 25.8 | 9.8 | 16 | 19.2 | 3.2 | 16 | 9.9 | 6.1 | 16 | 11.3 | 4.7 |
| **11h** | 8 | – | – | 16 | – | – | 16 | – | – | 32 | – | – |
| **11i** | 32 | – | – | 32 | – | – | 64 | – | – | 64 | – | – |
| **11j** | 125 | – | – | 125 | – | – | 125 | – | – | 125 | – | – |
| **11k** | 64 | 67.0 | 3 | 64 | 53.6 | 10.4 | 32 | 46.0 | 14 | 64 | 30.9 | 33.1 |
| **11l** | 8 | – | – | 16 | – | – | 16 | – | – | 16 | – | – |
| | $r^2 = 0.7538$, $q^2 = 0.918$ | | | $r^2 = 0.8997$, $q^2 = 0.980$ | | | $r^2 = 0.9097$, $q^2 = 0.721$ | | | $r^2 = 0.9931$, $q^2 = 0.930$ | | |

[a] Calculator value cannot be calculated.

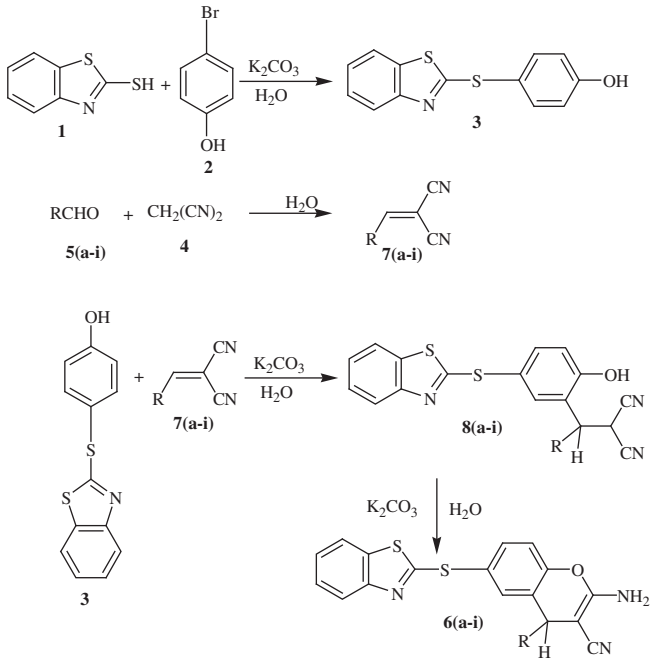
interaction with a unitary positive charge which can account for the determination of an electrostatic pattern for the compounds with same activity and interpretation of long-range interactions with the receptor [19]. This color-coded surface provides a measure of the overall size of the molecule as well as the location of negative or positive electrostatic potentials. The regions of positive electrostatic potential indicate excess positive charge, leading to repulsion of the positively charged test probe, while regions of negative potential indicate excess negative charge. These positive and negative orbitals of HOMO and LUMO lobes have been determined at values of −10 and 10 kcal $mol^{-1}$ (structural representations can be viewed in Fig. 1).

Fig. 1 shows HOMO and LUMO of all 9 compounds, red color shows LUMO while blue color shows HOMO with energy 10 kcal $mol^{-1}$. In Fig. 2, Electron density is shown in which red color shows high electron density while light blue for zero electron density and white color for positive density. Nitrogen in benzothiazole moiety and Oxygen in chromene moiety have high electron density while slightly less electron density in all the aromatic ring (Figs. 1 and 2).

For 9 compounds the SCF superimposed on the electron density shows that a negative potential is located over the oxygen atoms and a null to positive potential is located in the remaining parts of the structure. Through the three-dimensional MEP isosurfaces, it can be observed that all compounds present a negative potential located over the benzothiazole ring, with the chromene moiety showing positive values. Peripheral points of positive potential can also be seen around the aromatic area. In the benzothiazole and benzimidazole area the electrostatic profile is similar for all compounds. The electron potential along with HOMO and LUMO vary negligibly on changing from benzothiazole to benzimidazole but electron potential is higher in case **11b** as compared to **6b**. Similarly by changing CN to COOEt group, there is a decrease in electron density. Compound **6d** showed maximum MIC against *Pseudomonas aeruginosa*, while **6a** showed minimum MIC for the same. Interestingly, **6d** vary by **6a** only due to methoxy group, both compounds have

**Table 4**
Calculated values of the three most important variables (log *P*, $E_{HOMO}$, $E_{LUMO}$ and $\Delta E$).

| Comp | *P. aeruginosa* | *E. coli* | *S. aureus* | *S. epidermidis* | log *P* | $E_{HOMO}$ | $E_{LUMO}$ | $\Delta E$ |
|---|---|---|---|---|---|---|---|---|
| **6a** | 32 | 16 | 4 | 8 | 6.05 | −4.47 | −4.47 | 0 |
| **6b** | 32 | 2 | 2 | 64 | 5.72 | 4.32 | 5.23 | −0.91 |
| **6c** | 16 | 32 | 4 | 32 | 6.64 | −4.12 | −3.79 | −0.33 |
| **6d** | 2 | 32 | 8 | 16 | 5.96 | 4.33 | 5.19 | −0.86 |
| **6e** | 16 | 4 | 0.5 | 32 | 5.78 | −5.06 | −5.06 | 0 |
| **6f** | 8 | 16 | 16 | 32 | 7.28 | 4.35 | 4.55 | −0.2 |
| **6g** | 8 | 1 | 8 | 4 | 5.91 | 5.55 | 6.03 | −0.48 |
| **6h** | 16 | 0.5 | 2 | 32 | 5.97 | −4.14 | −4.13 | −0.01 |
| **6i** | 16 | 16 | 16 | 64 | 6.54 | −4.59 | −4.24 | −0.35 |
| **11a** | 125 | 125 | 125 | 125 | 5.28 | −5.16 | −5.16 | 0 |
| **11b** | 125 | 125 | 125 | 125 | 5.19 | −5.64 | −5.64 | 0 |
| **11e** | 125 | 125 | 250 | 250 | 5.43 | −5.00 | −4.72 | −0.28 |
| **11f** | 125 | 125 | 125 | 125 | 5.38 | −5.55 | −4.77 | −0.78 |
| **11g** | 32 | 64 | 64 | 64 | 5.25 | −5.49 | −5.50 | 0.01 |
| **11h** | 16 | 32 | 32 | 32 | 6.2 | −4.77 | −4.64 | −0.13 |
| **11i** | 16 | 16 | 16 | 16 | 5.81 | −4.85 | −4.86 | 0.01 |
| **11j** | 8 | 16 | 16 | 32 | 5.33 | −5.20 | −5.28 | 0.08 |
| **11k** | 32 | 32 | 64 | 64 | 5.33 | −5.26 | −5.22 | −0.04 |
| **11l** | 125 | 125 | 125 | 125 | 5.25 | −6.56 | −6.56 | 0 |




**Scheme 3.** Supposed reaction mechanism for the synthesis of 2-amino-3-cyano-2-ylsulfanyl-(6-benzoimidazole)-chromene.

similar HOMO and LUMO but vary in SCF, probably because of higher electron potential at oxygen of methoxy group. Likewise, **6h** showed maximum MIC against *Escherichia coli* and **6c** showed less due to presence of indole ring which has positive and negative HOMO orbitals in indole ring. For *Staphylococcus aureus*, **6e** has maximum while **6i** has minimum MIC, due to presence of a strong electro-withdrawing $-NO_2$ group which lowers electron density in chromene ring. Similarly for *Staphylococcus epidermidis* **6g** has highest MIC while **6b** has lowest MIC, in **6g** there is similarity between HOMO and LUMO orbitals at $NH_2$ and CN positions which indicate that the energy difference is less. It concludes that comparison of electron density among various compounds could predict the extent of interaction with the bio-receptor.

Analyzing the values of $E_{HOMO}$; $E_{LUMO}$; $\Delta E$ and log *P* presented in Table 4, we can obtain important informations on the antibacterial activity of compounds studied:

- For *P. aeruginosa*, $E_{HOMO}$ and $E_{LUMO}$ are positive, $\Delta E$ is high further more Log *P* is also high *i.e.* compound should be hydrophobic in nature.
- For *E. coli*, $\Delta E$ is low, Log *P* is high *i.e.* compound should be hydrophobic in nature.
- For *S. aureus*, $\Delta E$ is low, Log *P* is low *i.e.* compound should be hydrophilic in nature.
- For *S. epidermidis*, $E_{HOMO}$ and $E_{LUMO}$ are positive, Log *P* is also high *i.e.* compound should be hydrophobic in nature.

In conclusion, 2-amino-6-benzothiazol-2-ylsulfanyl-chromenes were synthesized via one-pot four-component coupling of *p*-bromophenol with 2-Benzothiazolethiol, malononitrile and substituted aldehydes in aqueous $K_2CO_3$. The method serves as a facile construction of 2-amino-6-benzothiazol-2-ylsulfanyl-chromenes starting from readily and widely available simple substrates, which shall be widely applicable for the synthesis of biologically active molecules and advanced materials. All the synthesized compounds were screened for their *in vitro* antibacterial activity against standard strains of *P aeruginosa*, *E. coli*, *S. aureus*, and *S. epidermidis*. QSAR analysis was performed to explore comprehensive structure–activity relationships and a statistically reliable model with good predictive power on the basis of the common substructure-based alignment.

## 4. Experimental section

### 4.1. General

$^1H$ NMR and $^{13}C$ NMR were recorded on Burker TOP SPIN 300 MHz and 75.6 MHz spectrometer with chemical shift values ($\delta$) in ppm downfield from TMS using DMSO as solvent. IR spectra of samples were recorded on a model Perkin–Elmer FTIR-1710 spectrometer using KBr. Elemental analysis was performed using Heraeus CHN-Rapid Analyzer. EI mass spectra were recorded on TOF MS mass spectrometer. The purity of compounds was checked on silica gel coated aluminum plates (Merck TLC: mass particle size 10–12 μm; particle distribution 5–20 μm; layer thickness 250 μm; plate height 30 μm).

### 4.2. Microwave reactor

The studies were carried out in a microwave reactor (Discover, model CEM-SP1245). The reactor was a fully baffled, cylindrical

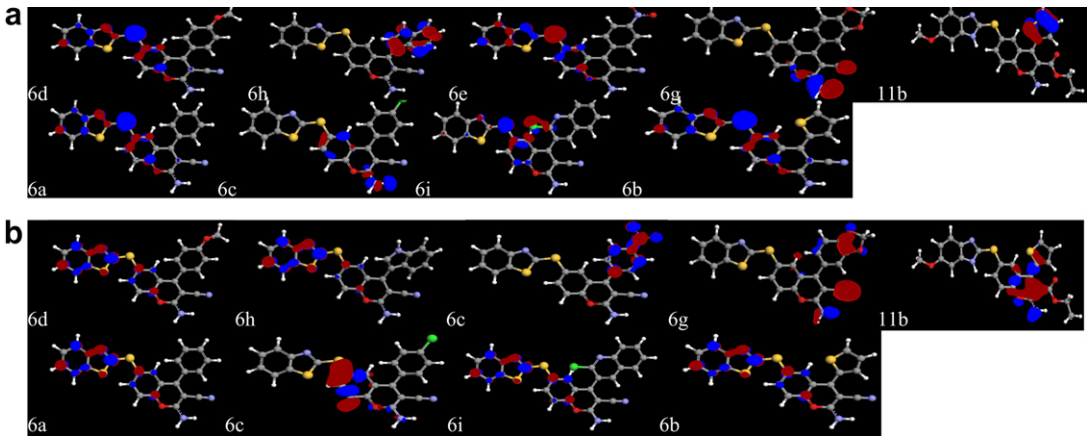



**Fig. 1.** a. HOMO of three-dimensional electrostatic potential isosurfaces at $-10$ kcal mol$^{-1}$ (Red color) and 10 kcal mol$^{-1}$ (Blue color) for compounds **6d**, **6h**, **6c**, **6g**, **11b**, **6a**, **6c**, **6i** and **6b**. b. LUMO of three-dimensional electrostatic potential isosurfaces at $-10$ kcal mol$^{-1}$ (Red color) and 10 kcal mol$^{-1}$ (Blue color) for compounds **6d**, **6h**, **6c**, **6g**, **11b**, **6a**, **6c**, **6i** and **6b**. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

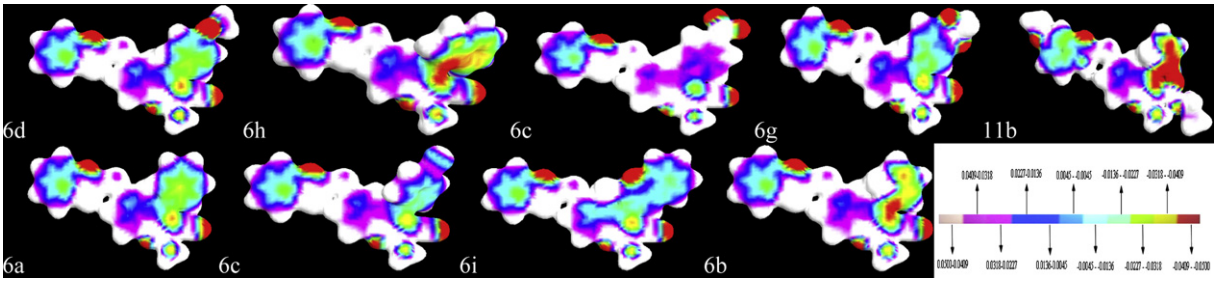



**Fig. 2.** SCFs superimposed onto total electron density at a value of 1.5936e−009 au for compounds **6d**, **6h**, **6c**, **6g**, **11b**, **6a**, **6c**, **6i** and **6b**.

glass vessel (capacity, 120 ml; ID, 4.5 cm) with provision for mechanical stirring. A standard four-blade pitched turbine impeller (diameter, 1.5 cm) was used for agitation. However, the actual reactor volume exposed to the microwave irradiation was 45 ml with 5.5 cm height. There was no bubble formation. Temperature in the reactor was computer controlled.

*4.2.1. General procedure for the synthesis of 2-Amino-4-Aryl-6-(Benzothiazol-2-ylsulfanyl)-4H-chromene-3-carbonitrile (**6a**–**i**)*

A solution of *p*-bromophenol (0.01 mol) and 2-Benzothiazolethiol (0.01 mol) taken in aqueous $K_2CO_3$ (5–10 ml) was microwave irradiated for a specific time at low power (560 W). The progress of the reaction was monitored by TLC examination at an interval of every 30 s. After formation of 4-(Benzothiazol-2-ylsulfanyl)-phenol **3**, aldehyde (0.01 mol) and malononitrile (0.01 mol) were added and again irradiated. Upon completion, the reaction mixture was allowed to cool and then filtered.

*4.2.2. General procedure for the synthesis of 2-Amino-4-aryl-6-(1H-Benzoimidazol/5-methoxy-1H-Benzoimidazol-2-ylsulfanyl)-4H-chromen-3-carbonitrile/carboxylic acid ethyl ester (**11a**–**l**)*

A solution of *p*-bromophenol (0.01 mol) and 1H-Benzoimidazole-2-thiol/5-Methoxy-1H-Benzoimidazole-2-thiol **7/8** (0.01 mol) taken in aqueous $K_2CO_3$ (5–10 ml) was microwave irradiated for a specific time at low power (560 W). The progress of the reaction was monitored by TLC examination at an interval of every 30 s. After formation of 4-(1H-Benzoimidazole-2-ylsulfanyl)-phenol **9**, aldehyde (0.01 mol) and malononitrile/(0.01 mol) were added and again irradiated. Upon completion, the reaction mixture was allowed to cool and then filtered.

*4.2.3. 4-(Benzothiazol-2-ylsulfanyl)-phenol **3***

M.pt. 208–210 °C. HRMS: $M^+$ 259.1245. Anal. Calculated for $C_{13}H_9NOS_2$ C 60.20, H 3.50, N 5.40 and S 24.73%, found C 60.16, H 3.43, N 5.45 and S 24.81%. IR (υ, $cm^{-1}$, KBr pellet) 3444.77 (OH), 1695.65 (C═N). $\delta_H$ ($CDCl_3$ + DMSO-$d_6$, 300 MHz) 6.54 (td, 2H, $C_2$–H Phenol), 7.00 (t, 3H, $C_5$–H MBT + $C_2$–H Phenol), 7.08 (q, 2H, $C_6$–H + $C_7$–H MBT), 7.19 (t, 1H, $C_4$–H MBT), 8.95 (s, 1H, OH). $\delta_C$ (DMSO-$d_6$, 75 MHz) 110.60, 112.41, 117.45, 120.52, 123.66, 126.40, 129.78, 131.99, 141.04, 156.88, 190.23.

*4.2.4. 4-(Benzimidazol-2-ylsulfanyl)-phenol **11a***

M.pt. 223–225 °C. HRMS: $M^+$ 242.1723. Anal. Calculated for $C_{13}H_9N_2OS$ C 64.44, H 4.16, N 11.56 and S 13.23.73%, found C 64.41, H 4.205, N 11.51 and S 13.29%. IR (υ, $cm^{-1}$, KBr pellet) 3461.26 (OH), 1592.76 (C═N). $\delta_H$ ($CD_3CN$ + DMSO-$d_6$, 300 MHz) 6.72(d, 2H, $C_2$–H Phenol), 7.13 (m, 4H, $C_4$–H + $C_5$–H + $C_6$–H + $C_7$–H MMBI), 7.26 (d, 2H, $C_3$–H Phenol), 7.08 (q, 2H, $C_6$–H + $C_7$–H MBT), 7.19 (t, 1H, $C_4$–H MBT), 9.08 (s, 1H, OH), 11.88 (s, 1H, NH). $\delta_C$ (DMSO-$d_6$, 75 MHz) 109.25, 109.42, 110.45, 110.95, 117.52, 122.10, 122.69, 131.37, 132.23, 132.51, 156.90, 157.25, 168.97.

*4.2.5. 4-(5-Meoxy-benzimidazol-2-ylsulfanyl)-phenol **11b***

M.pt. 238–240 °C. HRMS: $M^+$ 259.1245. Anal. Calculated for $C_{14}H_{12}N_2O_2S$ C 61.75, H 4.47, N 10.29 and S 11.77%, found C 61.79, H 3.43, N 10.32 and S 11.75%. IR (υ, $cm^{-1}$, KBr pellet) 3405.14 (OH), 1583.98 (C═N). $\delta_H$ ($CD_3CN$ + DMSO-$d_6$, 300 MHz) 3.66 (s, 3H, $CH_3O$), 6.64 (m, 3H, $C_4$–H MBI + $C_2$–H Phenol), 7.20 (d, 3H, $C_6$–H MBI), 7.22 (m, 3H, $C_7$–H MBI + $C_3$–H Phenol), 9.48 (s, 1H, OH), 12.19 (s, 1H, NH). $\delta_C$ (DMSO-$d_6$, 75 MHz) 55.05, 94.35, 109.47, 110.22, 117.42, 118.34, 125.90, 131.80, 133.01, 155.40, 156.92, 168.02.

*4.2.6. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-phenyl-2-yl-4H-chromene-3-carbonitrile **6a***

M.pt. 220–222 °C. HRMS: $M^+$ 413.1357. Anal. Calculated for $C_{23}H_{15}N_3OS_2$ C 66.80, H 3.66, N 10.16 and S 15.51%, found C 66.89, H 3.73, N 10.11 and S 15.59%. IR (υ, $cm^{-1}$, KBr pellet) 3437.10 ($NH_2$), 2195.13 (C≡N), 1618.38 (C═C), 1566.66 (C═N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 4.78 (s, 1H, $C_4$–H), 6.48 (s, 2H, $NH_2$), 7.23–7.31 (m, 9H, Ar–H). $\delta_C$ (DMSO-$d_6$, 75 MHz) 30.12, 60.78, 112.40, 116.88, 117.59, 120.36, 121.66, 122.31, 122.56, 123.14, 124.12, 125.18, 125.67, 127.06, 128.46, 129.06, 129.34, 133.58, 141.25, 156.25, 157.64, 159.87, 179.57.

*4.2.7. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-thiophen-2-yl-4H-chromene-3-carbonitrile **6b***

M.pt. 160–163 °C. HRMS: $M^+$ 419.0642. Anal. Calculated for $C_{21}H_{13}N_3OS_3$ C 60.12, H 3.12, N 10.02 and S 22.93%, found C 60.18, H 3.19, N 10.10 and S 22.81%. IR (υ, $cm^{-1}$, KBr pellet) 3444.77 ($NH_2$), 2225.12 (C≡N), 1573.83 (C═N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 4.65 (s, 1H, $C_4$–H), 6.54–8.92 (m, 13H, Ar + $NH_2$). $\delta_C$ (DMSO-$d_6$, 75 MHz) 29.46, 58.64.

*4.2.8. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-(4-chloro-phenyl)-2-yl-4H-chromene-3-carbonitrile **6c***

M.pt. 228–230 °C. HRMS: $M^+$ 447.4551. Anal. Calculated for $C_{23}H_{14}ClN_3OS_2$ C 61.67, H 3.15, Cl 7.91, N 9.38 and S 14.32%, found C 60.18, H 3.15, Cl 7.98, N 9.30 and S 14.40%. IR (υ, $cm^{-1}$, KBr pellet) 3368.48 ($NH_2$), 2198.82 (C≡N), 1614.28 (C═C), 1577.76 (C═N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 4.89 (s, 1H, $C_4$–H), 6.54–8.92 (m, 13H, Ar + $NH_2$). $\delta_C$ (DMSO-$d_6$, 75 MHz) 29.64, 59.79.

*4.2.9. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-(4-methoxy-phe)-2-yl-4H-chromene-3-carbonitrile **6d***

M.pt. 240–242 °C (Decompose). HRMS: $M^+$ 443.7618. Anal. Calculated for $C_{24}H_{17}N_3O_2S_2$ C 64.99, H 3.86, N 9.47 and S 14.46%, found C 64.88, H 3.81, N 9.39 and S 14.41%. IR (υ, $cm^{-1}$, KBr pellet) 3384.55 ($NH_2$), 2197.02 (C≡N), 1619.97 (C═C), 1589.52 (C═N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 3.56 (s, 3H, $OCH_3$), 4.12 (s, 1H, $C_4$–H), 6.54–8.92 (m, 13H, Ar + $NH_2$). $\delta_C$ (DMSO-$d_6$, 75 MHz) 35.69, 62.68.

*4.2.10. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-(3-nitro-phenyl)-2-yl-4H-chromene-3-carbonitrile **6e***

M.pt. 140–142 °C. HRMS: $M^+$ 458.4521. Anal. Calculated for $C_{23}H_{14}N_4O_3S_2$ C 60.25, H 3.08, N 12.22 and S 13.99%, found C 60.32,

H 3.11, N 12.29 and S 14.06%. IR (υ, $cm^{-1}$, KBr pellet) 3433.63 ($NH_2$), 2193.65 (C≡N), 1602.71 (C=C), 1515.35 (C=N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 4.65 (s, 1H, $C_4$–H), 6.54–8.92 (m, 13H, Ar + $NH_2$). $\delta_C$ (DMSO-$d_6$, 75 MHz) 32.64, 64.69.

*4.2.11. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-naphthalen-2yl-4H-chromene-3-carbonitrile* ***6f***

M.pt. 168–170 °C. HRMS: $M^+$ 463.3558. Anal. Calculated for $C_{27}H_{17}N_3OS_2$ C 69.95, H 3.70, N 9.06 and S 13.83%, found C 69.89, H 3.79, N 9.06 and S 13.91%. IR (υ, $cm^{-1}$, KBr pellet) 3433.59 ($NH_2$), 2225.61 (C≡N), 1653.53 (C=C), 1687.82 (C=N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 4.23 (s, 1H, $C_4$–H), 6.54–8.92 (m, 16H, Ar + $NH_2$). $\delta_C$ (DMSO-$d_6$, 75 MHz) 30.54, 63.87.

*4.2.12. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-(benzo[1,3] dioxol-phenyl)-2-yl-4H-chromene-3-carbonitrile* ***6g***

M.pt. 188–190 °C. HRMS: $M^+$ 457.4564. Anal. Calculated for $C_{24}H_{15}N_3O_3S_2$ C 63.00, H 3.30, N 9.18 and S 14.02%, found C 63.08, H 3.38, N 9.16 and S 13.95%. IR (υ, $cm^{-1}$, KBr pellet) 3433.63 ($NH_2$), 2193.65 (C≡N), 1602.71 (C=C), 1515.35 (C=N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 4.98 (s, 1H, $C_4$–H), 5.42 (s, 2H, $CH_2$), 6.34–8.15 (m, 12H, Ar + $NH_2$). $\delta_C$ (DMSO-$d_6$, 75 MHz) 29.45, 65.97.

*4.2.13. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-(2H-indol-3-yl)-2-yl-4H-chromene-3-carbonitrile* ***6h***

M.pt. 215–217 °C. HRMS: $M^+$ 452.4853. Anal. Calculated for $C_{25}H_{16}N_4OS_2$ C 66.35, H 3.56, N 12.38 and S 14.17%, found C 66.41, H 3.49, N 12.45 and S 14.15%. IR (υ, $cm^{-1}$, KBr pellet) 3281.49 ($NH_2$), 2222.31 (C≡N), 1625.78 (C=C), 1589.67 (C=C), 1569.25 (C=N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 5.56 (s, 1H, $C_4$–H), 6.22–9.45 (m, 15H, Ar + $NH_2$ + NH). $\delta_C$ (DMSO-$d_6$, 75 MHz) 28.19, 65.26, 109.44, 111.00, 113.07, 115.92, 115.97, 118.96, 120.36,121.96, 122.50, 123.21, 123.87, 124.14, 124.65, 125.12, 126.35, 125.63, 126.72, 133.44, 136.33, 152.33, 154.39, 163.47, 182.46.

*4.2.14. 2-Amino-6-(Benzothiazol-2-ylsulfanyl)-4-(2-chloroquinolin-3-yl)-2-yl-4H-chromene-3-carbonitrile* ***6i***

M.pt. 170–172 °C. HRMS: $M^+$ 498.4515. Anal. Calculated for $C_{26}H_{15}ClN_4OS_2$ C 62.58, H 3.03, Cl 7.10, N 11.23 and S 12.85%, found C 62.64, H 3.11, Cl 7.16, N 11.29 and S 12.96%. IR (υ, $cm^{-1}$, KBr pellet) 3281.49 ($NH_2$), 2222.31 (C≡N), 1625.78 (C=C), 1589.67 (C=C), 1569.25 (C=N). $\delta_H$ (DMSO-$d_6$, 300 MHz) 5.42 (s, 1H, $C_4$–H), 7.22–8.31 (m, 13H, Ar + $NH_2$). $\delta_C$ (DMSO-$d_6$, 75 MHz) 29.45, 68.97, 109.44, 111.00, 113.07, 115.92, 115.97, 120.36,121.96, 122.50, 123.21, 123.87, 124.14, 124.65, 125.12, 133.44, 136.33, 154.39, 163.47, 164.52, 183.45.

*4.2.15. 2-Amino-6-(1H-Benzoimidazol-2-ylsulfanyl)-4-thiophen-2-yl-4H-chromen-3-carboxylic acid ethyl ester* ***11a***

M.pt. 182–184 °C. HRMS: $M^+$ 449.3241. Anal. Calculated for $C_{23}H_{19}N_3O_3S_2$ C 61.45, H 4.26, N 9.35 and S 14.27%, found C 61.76, H 4.41, N 9.61 and S 14.41%. IR (υ, $cm^{-1}$, KBr pellet) 3152.50 ($NH_2$), 3089.76 (NH), 1717.82 (C=O), 1632.81 (C=C), 1615.91 (C=C), 1597.87 (C=N), 1251.04(C-O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 2.30 (t, 3H, $CH_3$), 3.73 (q, 2H, $CH_2$-O), 5.42 (s, 1H, $C_4$–H), 6.67 ($NH_2$), 6.70–6.72 (m, 5H, Ar), 7.02–7.04 (m, 5H, Ar), 12.35 (s, 1H, NH). $\delta_C$ (DMSO-$d_6$, 75 MHz) 13.21, 28.56, 55.67, 94.51, 109.80, 126.42, 133.12, 155.81, 164.52, 167.76.

*4.2.16. 2-Amino-6-(5-methoxy-1H-benzoimidazol-2-ylsulfanyl)-4-thiophen-2-yl-4H-chromene-3-carboxylic acid ethyl ester* ***11b***

M.pt. 203–205 °C. HRMS: $M^+$ 479.7309. Anal. Calculated for $C_{24}H_{21}N_3O_4S_2$ C 60.11, H 4.41, N 8.76 and S 13.37%, found C 60.23, H 4.53, N 8.64 and S 13.51%. IR (υ, $cm^{-1}$, KBr pellet) 3126.31 ($NH_2$), 3087.21 (NH), 1717.72 (C=O), 1638.43 (C=C), 1618.91 (C=C), 1597.87 (C=N), 1214.20 (Ar–C–O), 1155.94 (Aliphatic–C–O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 2.32 (t, 3H, $CH_3$), 3.70 (s, 3H, $CH_3O$), 3.77 (q, 2H, $CH_2$–O), 5.64 (s, 1H, $C_4$–H), 6.67 (s, 2H, $NH_2$), 6.74–77 (m, 5H, Ar), 7.13–16 (m, 5H, Ar), 12.39 (s, 1H, NH).

*4.2.17. 2-Amino-(4-benzo[1,3]dioxol-5-yl)-6-(5-methoxy-1H-benzoimidazol-2-ylsulfanyl)-4H-chromene-3-carboxylic acid ethyl ester* ***11d***

M.pt. 122–124 °C. HRMS: $M^+$ 498.4515. Anal. Calculated for $C_{27}H_{23}N_3O_6S$ C 62.66, H 4.48, N 8.12, and S 6.20%, found C 62.71, H 4.53, N 8.23 and S 6.34%. IR (υ, $cm^{-1}$, KBr pellet) 3128.98 ($NH_2$), 3060.82 (NH), 1721.61 (C=O), 1643.97 (C=C), 1621.91 (C=C), 1591.81 (C=N), 1218.12 (Ar–C–O), 1201.91 (Ar–C–O), 1151.71 (Aliphatic–C–O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 2.31 (t, 3H, $CH_3$), 3.65 (s, 3H, $CH_3O$), 3.81 (q, 2H, $CH_2$–O), 5.34 (s, 2H, O–$CH_2$–O), 5.62 (s, 1H, $C_4$–H), 6.61 ($NH_2$), 7.18–21 (m, 5H, Ar), 7.26–7.29 (m, 9H, Ar), 12.05 (s, 1H, NH).

*4.2.18. 2-Amino-6-(5-methoxy-1H-benzoimidazol-2-ylsulfanyl)-4-(4-nitro-phenyl)-4H-chromene-3-carboxylic acid ethyl ester* ***11e***

M.pt. 148–150 °C. HRMS: $M^+$ 518.5498. Anal. Calculated for $C_{26}H_{22}N_4O_6S$ C 60.22, H 4.28, N 10.80 and S 6.18%, found C 60.28, H 4.23, N 10.91 and S 6.24%. IR (υ, $cm^{-1}$, KBr pellet) 3123.16 ($NH_2$), 3065.86 (NH), 1720.42 (C=O), 1617.89 (C=C), 1592.67 (C=N), 1202.50 (Ar–C–O), 1183.22 (Aliphatic–C–O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 1.49 (t, 3H, $CH_3$), 3.78 (s, 3H, $CH_3O$), 4.51 (q, 2H, $CH_2$), 5.21 (s, 1H, $C_4$–H), 6.73 (t, 3H, Ar + $NH_2$), 7.06(d, 1H, Ar), 7.44 (t, 2H, Ar), 8.15 (d, 2H, Ar), 8.38 (d, 3H, Ar), 11.91 (s, 1H, NH).

*4.2.19. 2-Amino-(1H-benzoimidazol-2-ylsulfanyl)-4-(4-chloro-phenyl)-64H-chromene-3-carboxylic acid ethyl ester* ***11f***

M.pt. 80–82 °C. HRMS: $M^+$ 477.9815. Anal. Calculated for $C_{25}H_{20}ClN_3O_3S$ C 62.82, H 4.22, N 8.79, and S 6.71%, found C 62.77, H 4.29, N 8.83 and S 6.88%. IR (υ, $cm^{-1}$, KBr pellet) 3037.48 ($NH_2$), 2990.58 (NH), 1724.31 (C=O), 1646.45 (C=C), 1622.65 (C=C), 1590.44 (C=N), 1200.59 (Ar–C–O), 1155.08 (Aliphatic–C–O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 1.41 (t, 3H, $J = 8.4$, $CH_3$), 4.41 (q, 2H, $J = 4.1$, $CH_2$), 5.02 (s, 1H, $C_4$–H), 7.51 (s, 2H, $NH_2$), 7.53 (d, 2H, Ar), 7.97 (m, 3H, Ar), 8.27 (m, 6H, Ar), 12.01 (s, 1H, NH).

*4.2.20. 2-Amino-6-(1H-benzoimidazol-2-ylsulfanyl)-4-(4-chloro-phenyl)-4H-chromene-3-carbonitrile* ***11g***

M.pt. 156–158 °C. HRMS: $M^+$ 430.9841. Anal. Calculated for $C_{23}H_{15}ClN_4OS$ C 64.11, H 3.51, N 13.00, and S 7.44%, found C 64.15, H 3.53, N 13.09 and S 7.49%. IR (υ, $cm^{-1}$, KBr pellet) 3152.99 ($NH_2$), 3034.71 (NH), 2227.48 (CN), 1654.44 (C=C), 1621.91 (C=C), 1583.97 (C=N), 1215.75 (Ar–O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 5.13 (s, 1H, $C_4$–H), 7.12 (s, 1H, Ar), 7.13 (s, 2H, $NH_2$), 7.55 (m, 6H, Ar), 7.94 (d, 4H, Ar), 12.26 (s, 1H, NH).

*4.2.21. 2-Amino-6-(1H-benzoimidazol-2-ylsulfanyl)-4-(4-nitro-phenyl)-4H-chromene-3-carboxylic acid ethyl ester* ***11h***

M.pt. 181–182 °C. HRMS: $M^+$ 488.5315. Anal. Calculated for $C_{25}H_{20}N_4O_5S$ C 61.47, H 4.13, N 11.47, and S 6.56%, found C 61.51, H 4.18, N 11.54 and S 6.61%. IR (υ, $cm^{-1}$, KBr pellet) 3152.00 ($NH_2$), 2991.86 (NH), 1721.05 (C=O), 1617.38 (C=C), 1594.12 (C=N), 1202.34 (Ar–C–O), 1179.83 (Aliphatic–C–O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 1.44 (t, 3H, $CH_3$), 4.42 (q, 2H, $CH_2$–O), 5.07 (s, 1H, $C_4$–H), 7.11 (s, 2H, $NH_2$), 7.18 (m, 3H, Ar), 7.54 (d, 2h, Ar), 8.19 (d, 2H, Ar), 8.38 (d, 3H, Ar), 12.20 (s, 1H, NH).

*4.2.22. 2-Amino-6-(5-methoxy-1H-benzoimidazol-2-ylsulfanyl)-4-(3-nitro-phenyl)-4H-chromene-3-carboxylic acid ethyl ester* ***11j***

M.pt. 106–108 °C. HRMS: $M^+$ 518.6725. Anal. Calculated for $C_{26}H_{22}N_4O_6S$ C 60.22, H 4.28, N 10.80, and S 6.18%, found C 60.27, H 4.35, N 10.83 and S 6.23%. IR (υ, $cm^{-1}$, KBr pellet) 3152.00 ($NH_2$), 3114.55 (NH), 1721.05 (C=O), 1617.38 (C=C), 1591.12 (C=N), 1202.34 (Ar–C–O). $\delta_H$ (DMSO-$d_6$, 300 MHz) 1.34 (t, 3H, $CH_3$), 3.65

(s, 3H, $CH_3O$), 4.35 (q, 2H, $CH_2$–O), 5.18 (s, 1H, $C_4$–H), 6.62 (s, 2H, $NH_2$), 7.16 (s, 2H, Ar), 7.63 (d, 3H, Ar), 8.21 (d, 4H, Ar), 8.63 (s, 1H, Ar), 10.02 (s, 1H, Ar), 11.53 (s, 1H, NH).

#### *4.2.23. 2-Amino-4-(4-chloro-phenyl)-6-(5-methoxy-1H-benzoimidazol-2-ylsulfanyl)-4H-chromene-3-carboxylic acid ethyl ester* ***11k***

M.pt. 202–204 °C. HRMS: $M^+$ 507.8010. Anal. Calculated for $C_{26}H_{22}ClN_3O_4S$ C 61.47, H 4.37, N 8.27, and S 6.31%, found C 61.54, H 4.42, N 8.23 and S 6.34%. IR (υ, $cm^{-1}$, KBr pellet) 3037.02 ($NH_2$), 2989.92 (NH), 1724.10 (C=O), 1612.45 (C=C), 1589.64 (C=N), 1200.13 (Ar–C–O), 1158.12 (Aliphatic–C–O).

### *4.3. Computational methods*

In QSAR, all the properties (e.g. Critical Temp, Critical Pressure, Critical Volume, Gibbs Energy, Log *P*, MR, Henry's Law, Heat of Form, cLogP, CMR) of compounds were calculated by ChemDraw 7 [20]. All compounds were studied using the quantum mechanical, AMI (NDDO) Hamiltonian. First of all, optimized geometries were done with ACDLABS 12.0 [21]. Its 3D Viewer and then further calculation of the three-dimensional electrostatic potential iso-surfaces (3D-EPI) and molecular electrostatic potential super-imposed onto total electron density (MEP-STED) was done with help of Arugslab (Figs. 1 and 2) [22]. The run type was set at SCF type (RHF) with maximum of 200 cycles. The basic set Minimal Valence Basis is STO 6G. Statistical Data Analysis was done with the help of WINKS SDA [23].

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## Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2010.08.010.

## References

[1] M.S.M. Ahmed, K. Kobayashi, A. Mori, Org. Lett. 7 (2005) 4487–4489.
[2] M. Kidwai, R. Poddar, S. Diwaniyan, R.C. Kuhad, Adv. Synth. Catal. 351 (2009) 589–595.
[3] G.R. Green, J.M. Evans, A.K. Vong, in: A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol. 5, Pergamon Press, Oxford, 1995, p. 469.
[4] S. Abdolmohammadia, S. Balalaieb, Tetrahedron Lett. 48 (2007) 3299–3303.
[5] L.L. Andreani, E. Lapi, Bull. Chim. Farm. 99 (1960) 583–586.
[6] Y.L. Zhang, B.Z. Chen, K.Q. Zheng, M.L. Xu, X.H. Lei, Yao Xue Bao 17 (1982) Chem. Abstr. (1982) 96, 135383e.
[7] L. Bonsignore, G. Loy, D. Secci, A. Calignano, Eur. J. Med. Chem. 28 (1993) 517–520.
[8] E.C. Witte, P. Neubert, A. Roesch, Ger. Offen DE. Chem. Abstr. 104 (1986) 224915f.
[9] V.R. Rao, P.V. Kumar, Syn. Commun. 36 (2006) 2157–2161.
[10] W.C. Patt, H.W. Hamilton, M.D. Taylor, M.J. Ryan, D.G. Taylor Jr., C.J.C. Connoly, A.M. Doherty, S.R. Klutchko, I. Sircar, B.A. Steinbaugh, B.L. Batley, C.A. Painchaud, S.T. Rapundalo, B.M. Michniewiez, S.C.J. Olson, J. Med. Chem. 35 (1992) 2562–2571.
[11] R. Cannella, A. Clerici, N. Pastori, E. Regolini, O. Porta, Org. Lett. 7 (2005) 645–647.
[12] A. Strecker, Liebigs Ann. Chem. 75 (1850) 27–51.
[13] M. Kidwai, R. Poddar, S. Diwaniyan, R.C. Kuhad, Synth. Commun. 40 (2010) Inpress.
[14] R.A. Sheldon, J. Mol. Catal. A 107 (1996) 75–83.
[15] V.V. Shchepin, P.S. Silaychev, A.R. Rakitinb, M.I. Kodess, Tetrahedron Lett. 47 (2006) 557–560.
[16] A.G.A. Elagamay, F.M.A.A. El-Taweel, Indian J. Chem. 29B (1990) 885–889.
[17] M. Kidwai, S. Saxena, M.K.R. Khan, S.S. Thukral, Eur. J. Med. Chem. 40 (2005) 816–819.
[18] M. Kidwai, R. Poddar, Catal Lett. 124 (2008) 311–317.
[19] A.M.A.G. Oliveira, M.M.M. Raposo, A.M.F. Oliveira-Campos, A.E.H. Machado, P. Puapairoj, M. Pedro, M.S.J. Nascimento, C. Portela, C. Afonso, M. Pinto, Eur. J. Med. Chem. 41 (2006) 367–372.
[20] ChemDraw 7 from CambridgeSoft Corporation.
[21] ACDLABS 12.0 from Advanced Chemistry Development.
[22] Arugslab from ArgusLab Molecular Modeling and Drug Docking Software.
[23] WINKS SDA of Statistical Data Analysis from TexaSoft.