



## Original article

# Microwave assisted synthesis of dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones; synthesis, *in vitro* antimicrobial and anticancer activities of novel coumarin substituted dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones



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## ABSTRACT

The present article describes the synthesis of dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one (**2a–h**) under microwave irradiation. The product was obtained in excellent yield (74–94%) in a shorter reaction time (2 min). These molecules (**2a, b**) further reacted with various substituted 4-bromomethylcoumarins (**3a–f**) to yield a new series of coumarin substituted dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones (**4a–h**). The structure of all the synthesized compounds were confirmed by spectral studies and screened for their *in vitro* antibacterial activity against three Gram-positive bacteria viz., *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus mutans* and three Gram-negative bacteria viz., *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans*, *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Fusarium oxysporum*, *Penicillium chrysogenum* and anticancer activity against Dalton's Ascitic Lymphoma (DAL) cell line.

In general, all the compounds possessed better antifungal properties than antibacterial properties. The coumarin substituted dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one (**4g**) (R = *i*-Pr, R<sub>1</sub> = 6-Cl) was found to be the most potent cytotoxic compound (88%) against Dalton's Ascitic Lymphoma cell line at the concentration of 100 µg/mL.

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## 1. Introduction

Dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one is a class of fused tricyclic system having three nitrogen atoms. The design concept of dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones has arisen from the broad spectrum and the wide range of biological activities of the benzimidazole and pyrimidine.

Benzimidazole derivatives [1] exhibited high cytotoxicity against HepG-2 cells and good EGFR inhibitory activity. 2-Substituted-5-amino-benzimidazoles [2] possessed significant cytotoxicity against breast cancer cell line MCF-7. 1,2,5-Trisubstituted benzimidazoles [3] and benzimidazole pyrimidine conjugates [4] were found to be antitumor agents against

Melanoma cell lines. QSAR analyses of 2-aminobenzimidazole derivatives [5] were studied on the relation between acute toxicity and the octanol/water partition coefficient.

6-Butylfuro[2,3-*d*]pyrimidine derivatives [6] showed the highest cytostatic activity against Malignant leukemia and T-lymphocyte cells. 5-Benzylidene barbiturate derivatives [7] inhibited the growth of mushroom tyrosinase and Gram-positive bacteria *Staphylococcus aureus*. Pyrimidine bases [8] exerted pronounced antiproliferative activity against the HeLa and MiaPaCa-2 cell lines. 1-Adamantyl thiopyrimidines [9] displayed the significant cytotoxic activity particularly against H69AR cell line. Pyrimidine analogs of indane-1,3-diones [10] showed significant reduction in ulcerogenic activity when compared to standard drug *Indomethacin*.

The fusion of benzimidazole and pyrimidine pharmacophores in a single molecular framework and the study of subsequent influence on the biological activities are of current interest.

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The known synthetic method of dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one derivatives [11] had many demerits such as long reaction time, drastic condition, tedious experimental procedure and low yield. Hence, there is a need for a simple and straight forward method for the synthesis of dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one derivatives. On the otherhand, to date, neither the synthesis nor the biological evaluation of dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones has been reported in the literature. For all these reasons, we have done laboratory work on the synthesis of fused dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones.

Coumarins are known to be biologically versatile compounds possessing several biological properties. Coumarin Mannich bases [12] inhibited carrageenin-induced hind paw edema and found to possess protective properties against adjuvant-induced arthritis in rats. 4-Amino-3-(2-methylbenzyl)coumarin derivatives [13] exhibited potent estrogenic activity on the estrogen receptor positive (ER<sup>+</sup>) human MCF-7 breast cancer cell line. 4-Hydroxy coumarin derivatives [14] showed pronounced prolongation of prothrombin time with anticoagulant values similar to that of warfarin. Benzothiazolyl coumarin acetamide derivatives [15] exhibited strong *in vitro* anti-HIV effect against the wild-type HIV-1 cell line. The *in vitro* antioxidant activities of 4-schiff bases-7-benzoyloxy coumarin derivatives [16] revealed that DPPH and ABTS<sup>+</sup> radical scavenging activities were better than that of the commercial antioxidant BHT.

Based on the survey of recent literature studies on benzimidazoles, pyrimidines and coumarins and in our effort to discover novel antimicrobial and anticancer agents, the aim of our work is synthesis of coumarin substituted dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones and to evaluate them for their therapeutic importance.

## 2. Chemistry

The synthesis of compounds (**2a–h**) (R: a; *i*-Pr, b; 4-FC<sub>6</sub>H<sub>4</sub>, c; 3-FC<sub>6</sub>H<sub>4</sub>, d; CF<sub>3</sub>, e; C<sub>6</sub>H<sub>5</sub>, f; 4-FC<sub>6</sub>H<sub>4</sub>, g; 3-ClC<sub>6</sub>H<sub>4</sub>, h; 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) was accomplished by synthetic sequence shown in Scheme 1. The preparation of dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones was carried out by the condensation of β-ketoesters (**1a–h**) with 2-aminobenzimidazole under microwave irradiation. The best conditions to obtain these compounds were achieved at 130 °C using DMF as a reaction media. This method gave the higher yield (74–94%) and required a shorter reaction time (3 min). The compounds (**2d–h**) have already been reported by the thermal method (Table 1) in the literature [11].

4-Bromomethyl coumarins [17] (**3a–f**) were synthesized by Pechmann cyclization of phenols with 4-bromoethylacetoacetate [18] using conc. H<sub>2</sub>SO<sub>4</sub> as a cyclizing agent. The synthesis of coumarin substituted dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones (Scheme 2) were carried out by reaction of 4-bromomethyl

**Table 1**

Synthesis of reported compounds (**2d–h**) under microwave irradiation.

| Compounds | Thermal (reported) |             |           | Microwave |             |           |
|-----------|--------------------|-------------|-----------|-----------|-------------|-----------|
|           | Time               | Temperature | Yield (%) | Time      | Temperature | Yield (%) |
| <b>2d</b> | 60 min             | 140 °C      | 55        | 3 min     | 130 °C      | 74        |
| <b>2e</b> | 60 min             | 140 °C      | 75        | 3 min     | 130 °C      | 87        |
| <b>2f</b> | 60 min             | 140 °C      | 87        | 3 min     | 130 °C      | 91        |
| <b>2g</b> | 60 min             | 140 °C      | 80        | 3 min     | 130 °C      | 90        |
| <b>2h</b> | 60 min             | 140 °C      | 87        | 3 min     | 130 °C      | 94        |

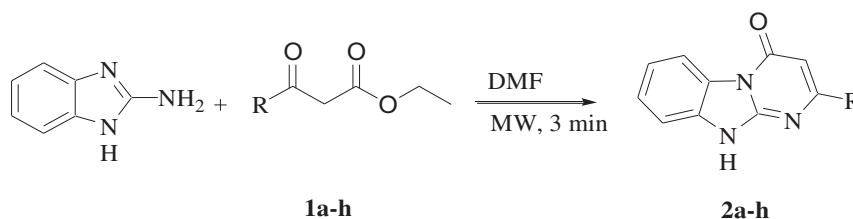
Synthesis of reported compounds (**2d–h**) under microwave irradiation.

coumarins (**3a–f**) (R<sub>1</sub> = a; 6-OMe, b; 6-F, c; 6-CH<sub>3</sub>, d; 6,8-dimethyl, e; 6-Cl, f; 6-Br) with dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones (**2a, b**) (R = a; *i*-Pr, b; 4-FC<sub>6</sub>H<sub>4</sub>) in the presence of anhydrous K<sub>2</sub>CO<sub>3</sub> in dry acetone at room temperature for 24 h. Removal of solvents under reduced pressure afforded the title compounds (**4a–h**) as solids which were purified by routine methods. The numbering of the skeleton is shown in Fig. 1.

### 2.1. Result and discussion

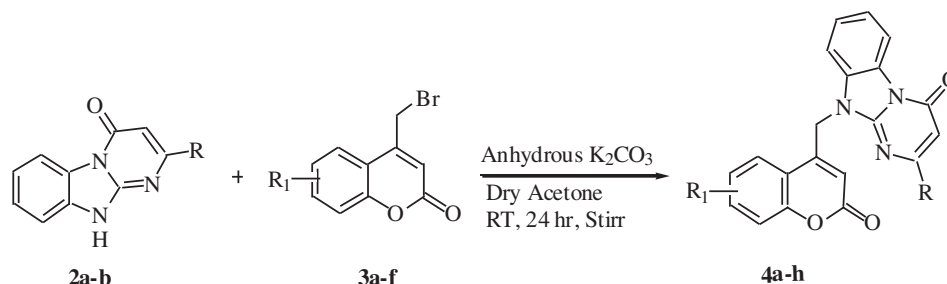
In the IR spectrum of the compound 2-isopropyl-10*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one (**2a**) (R = *i*-Pr), the carbonyl stretching frequency was observed at 1664 cm<sup>−1</sup>, where as the N–H stretching frequency showed a strong absorption band at 3230 cm<sup>−1</sup>. The <sup>1</sup>H NMR spectrum of compound (**2a**) exhibited a singlet in the region δ 5.87 due to presence of C<sub>3</sub>–H proton. A multiplet was observed at δ 2.79 due to methine proton of isopropyl group. The methyl protons of isopropyl group and C<sub>7</sub>–H proton were found to be a doublet at δ 1.22 (*J* = 9 Hz) and 8.38 (*J* = 9 Hz) respectively. A triplet was appeared at δ 7.27 (*J* = 6 Hz) due to the presence of C<sub>8</sub>–H proton. The multiplet was observed in the region between δ 7.42–7.50 due to the presence of C<sub>9</sub>–H and C<sub>10</sub>–H protons. The N–H proton was resonated as a singlet at δ 12.88 which was further confirmed by its D<sub>2</sub>O exchange. The mass spectrum (ESI-MS) of the compound (**2a**) showed a [M + 1] peak at 228. The <sup>13</sup>C NMR spectral data of all the compounds is given in Experimental section.

The IR spectrum of the compound 10-(6-methoxy-2-oxo-2*H*-chromen-4-ylmethyl)-2-trifluoromethyl-10*H*-benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-one (**4a**) (R = CF<sub>3</sub> & R<sub>1</sub> = 6-OCH<sub>3</sub>) displayed the benzimidazopyrimidine carbonyl stretching frequency at 1685 cm<sup>−1</sup>, where as the lactone carbonyl stretching frequency appeared at 1712 cm<sup>−1</sup>. The <sup>1</sup>H NMR spectrum of the compound (**4a**) showed a singlet at δ 3.50, 5.82, 6.02 and 6.26 due to 6-OCH<sub>3</sub>, N–CH<sub>2</sub>, C<sub>3</sub>–H of coumarin and C<sub>3</sub>–H of benzimidazopyrimidine protons respectively. The aromatic protons resonated as a multiplet in the range of δ 7.45–8.32. The mass spectrum (ESI-MS) of the compound (**4a**) displayed a [M + 1] peak at 442. The <sup>13</sup>C NMR spectral data of all the compounds is given in Experimental section.



R; a; *i*-Pr, b; 4-FC<sub>6</sub>H<sub>4</sub>, c; 3-FC<sub>6</sub>H<sub>4</sub>, d; CF<sub>3</sub>, e; C<sub>6</sub>H<sub>5</sub>, f; 4-FC<sub>6</sub>H<sub>4</sub>, g; 3-ClC<sub>6</sub>H<sub>4</sub>, h; 4-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>

**Scheme 1.**



| Compounds      | 4a              | 4b              | 4c                | 4d              | 4e           | 4f           | 4g           | 4h           |
|----------------|-----------------|-----------------|-------------------|-----------------|--------------|--------------|--------------|--------------|
| R              | CF <sub>3</sub> | CF <sub>3</sub> | CF <sub>3</sub>   | CF <sub>3</sub> | <i>i</i> -Pr | <i>i</i> -Pr | <i>i</i> -Pr | <i>i</i> -Pr |
| R <sub>1</sub> | 6-OMe           | 6-F             | 6-CH <sub>3</sub> | 6,8-dimethyl    | 6-F          | 6-OMe        | 6-Cl         | 6-Br         |

Scheme 2.

The molecular structure of the compound (**4b**) is also established by single crystal analysis [19] as shown in Fig. 2.

## 2.2. Antimicrobial activity

All the newly synthesized compounds (**2a–h**) and (**4a–h**) were screened for their antibacterial and antifungal activity at different concentrations of 100, 50, 25, 12.5, 6.25, 3.125, 1.6, 0.8, 0.4 and 0.2 µg/mL by the broth micro dilution method. The minimum inhibitory concentrations (MIC) were determined by serial dilution method [20].

Antibacterial activity was carried out against three Gram-positive bacteria viz., *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus mutans* and three Gram-negative bacteria viz., *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. Ciprofloxacin was used as a standard. Antifungal activity was carried out against six fungi viz., *Candida albicans*, *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Fusarium oxysporum* and *Penicillium chrysogenum*. Fluconazole was used as a standard.

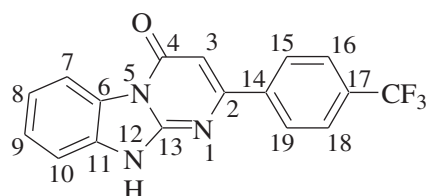
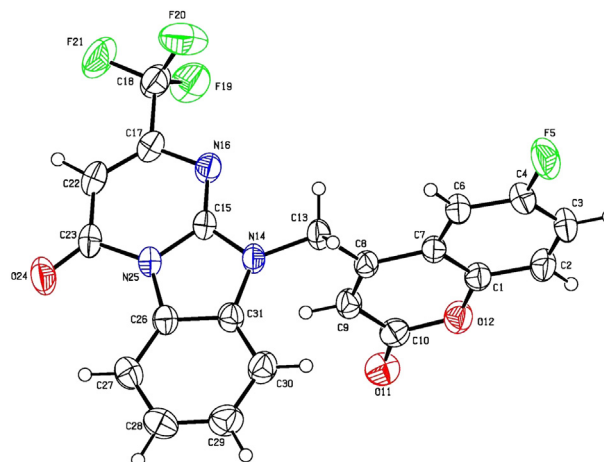
The investigation of antibacterial data (Table 2) showed that most of the tested compounds exhibited good bacterial inhibition. The compounds (**2a–h**) were found to be highly active against *E. faecalis* with MIC of 0.2 µg/mL. The compound (**4d**) (R = CF<sub>3</sub>, R<sub>1</sub> = 6,8-dimethyl) was found to be highly active against *S. mutans* with MIC of 0.2 µg/mL. The compound (**4e**) (R = *i*-Pr, R<sub>1</sub> = 6-F) was found to be most active against *S. mutans* with MIC of 0.8 µg/mL (Fig. 3). It is interesting to note that all the tested compounds were found to be most potent against *E. faecalis* when compared to standard drug Ciprofloxacin. The rest of the compounds were found to be inactive.

The investigation of antifungal data (Table 3) showed that most of the tested compounds exhibited good fungal inhibition. The compounds (**2f**) (R = 4-FC<sub>6</sub>H<sub>4</sub>) and (**2g**) (R = 4-ClC<sub>6</sub>H<sub>4</sub>) were found

to be highly active against *A. fumigatus* and *A. flavus* with MIC of 0.2 µg/mL. The compounds (**2b**) (R = 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>), (**2d**) (R = CF<sub>3</sub>), (**2e**) (R = C<sub>6</sub>H<sub>5</sub>), (**2g**) (R = 3-ClC<sub>6</sub>H<sub>4</sub>), (**2h**) (R = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) and (**4a–h**) were found to be highly active against *F. oxysporum* with MIC of 0.2 µg/mL. The compounds (**2a**) (R = *i*-Pr), (**2b**) (R = 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>), (**2c**) (R = 3-FC<sub>6</sub>H<sub>4</sub>), (**2e**) (R = C<sub>6</sub>H<sub>5</sub>), (**4b**) (R = CF<sub>3</sub>, R<sub>1</sub> = 6-F), (**4c**) (R = CF<sub>3</sub>, R<sub>1</sub> = 6-CH<sub>3</sub>), (**4d**) (R = CF<sub>3</sub>, R<sub>1</sub> = 6,8-dimethyl) and (**4h**) (R = *i*-Pr, R<sub>1</sub> = 6-Br) were found to be highly active against *P. chrysogenum* with MIC of 0.2 µg/mL (Fig. 4). It is interesting to note that all the tested compounds were found to be most potent against *A. fumigatus*, *F. oxysporum* and *P. chrysogenum* when compared to standard drug Fluconazole.

## 2.3. In vitro cell cytotoxicity

The newly synthesized compounds (**2a–h**) and (**4a–h**) were determined *in vitro* cell cytotoxicity by using trypan blue dye exclusion assay method [21]. In this test, only the dead cells took up the dye due to lack of intact membranes. Dalton's Ascitic Lymphoma (DAL) cells (0.2 mL, 10<sup>6</sup> cells/mL), ice cold phosphate buffer saline (1 mL, pH = 7.4) and one of the compounds (**2a–h**) and (**4a–h**) (0.2 mL) were taken in an Eppendorf tube. They were incubated in CO<sub>2</sub> incubator at 37 °C with continuous flow of 5% CO<sub>2</sub> for 3 h.

Fig. 1. Numbering of the compound (**2b**).Fig. 2. ORTEP diagram with the displacement at 50% probability level (**4b**).

**Table 2**  
Results of antibacterial activities of compounds **2a–h** and **4a–h** MICs ( $\mu\text{g/mL}$ ).

| Compounds     | Gram-positive    |                    |                  | Gram-negative  |                      |                      |
|---------------|------------------|--------------------|------------------|----------------|----------------------|----------------------|
|               | <i>S. aureus</i> | <i>E. faecalis</i> | <i>S. mutans</i> | <i>E. coli</i> | <i>K. pneumoniae</i> | <i>P. aeruginosa</i> |
| <b>2a</b>     | 100              | 0.2                | 25               | 12.5           | 100                  | 12.5                 |
| <b>2b</b>     | >100             | 0.2                | >100             | >100           | >100                 | >100                 |
| <b>2c</b>     | 100              | 0.2                | 12.5             | 100            | 100                  | 25                   |
| <b>2d</b>     | 100              | 0.2                | 50               | 100            | 100                  | 100                  |
| <b>2e</b>     | 100              | 0.2                | 100              | 100            | 100                  | 100                  |
| <b>2f</b>     | 100              | 0.2                | 12.5             | 100            | 100                  | 100                  |
| <b>2g</b>     | 100              | 0.2                | 25               | 100            | 100                  | 100                  |
| <b>2h</b>     | 100              | 0.2                | 100              | 100            | 100                  | 100                  |
| <b>4a</b>     | 100              | 0.4                | 12.5             | 100            | 100                  | >100                 |
| <b>4b</b>     | 100              | 0.8                | 12.5             | 100            | 100                  | 100                  |
| <b>4c</b>     | 100              | 0.4                | 12.5             | 100            | 100                  | >100                 |
| <b>4d</b>     | 100              | 0.4                | 0.2              | 100            | 100                  | 100                  |
| <b>4e</b>     | 100              | 0.4                | 0.8              | 100            | 100                  | 100                  |
| <b>4f</b>     | 100              | 0.4                | 3.16             | 100            | 100                  | >100                 |
| <b>4g</b>     | 100              | 0.4                | 12.5             | 100            | 100                  | 100                  |
| <b>4h</b>     | >100             | 0.8                | >100             | 100            | >100                 | >100                 |
| Ciprofloxacin | 2                | 2                  | 2                | 1              | 1                    | 2                    |

Then, previous mixture (0.2 mL), ice cold phosphate buffer saline (0.3 mL,  $\text{pH} = 7.4$ ) and trypan blue solution (0.5 mL, 0.4% in normal saline) were taken in an Eppendorf tube and kept for 5–15 min at room temperature. The percentage of dead cells was calculated with the following formula using Neubauer chamber.

$$\% \text{ Dead cell} = \frac{\text{Number of dead cells}}{\text{Sum of dead cells and living cells}} \times 100$$

The investigation of *in vitro* cell cytotoxicity (Table 4) revealed that most of the tested compounds exhibited good activity. The compounds (**2b**) ( $\text{R} = 4\text{-CF}_3\text{C}_6\text{H}_4$ ), (**2d**) ( $\text{R} = \text{CF}_3$ ), (**2fb**) ( $\text{R} = 4\text{-FC}_6\text{H}_4$ ), (**2g**) ( $\text{R} = 4\text{-ClC}_6\text{H}_4$ ), (**4b**) ( $\text{R} = \text{CF}_3$ ,  $\text{R}_1 = 6\text{-F}$ ), (**4d**) ( $\text{R} = \text{CF}_3$ ,  $\text{R}_1 = 6,8\text{-dimethyl}$ ), (**4e**) ( $\text{R} = i\text{-Pr}$ ,  $\text{R}_1 = 6\text{-F}$ ) and (**4g**) ( $\text{R} = i\text{-Pr}$ ,  $\text{R}_1 = 6\text{-Cl}$ ) were found to be highly active (>70%) against DAL cell at the concentration of 100  $\mu\text{g/mL}$ . The rest of the compounds were found to be moderately active (>40%) against DAL cell at the concentration of 100  $\mu\text{g/mL}$  (Fig. 5).

### 3. Experimental section

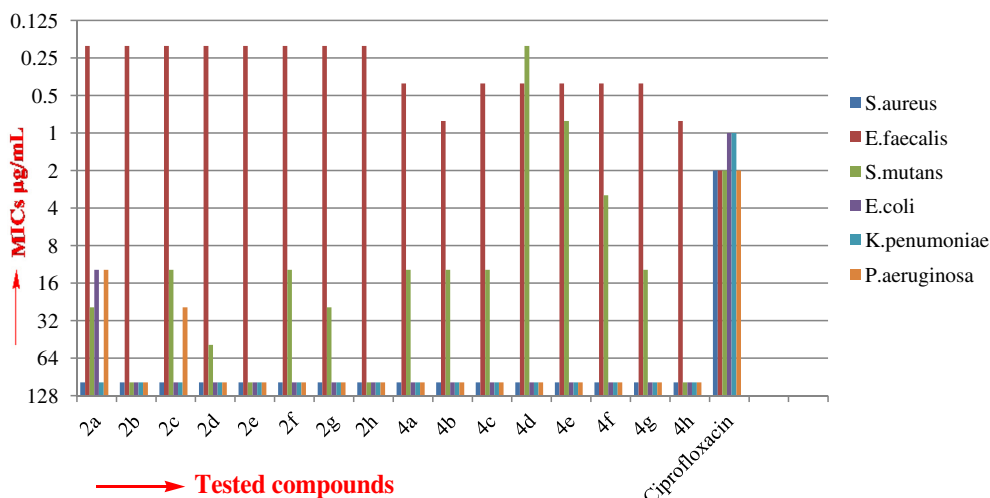
The melting points were determined by open capillary method using electric melting point apparatus and are uncorrected. The IR

spectra (KBr disc) were recorded on a Shimadzu-8400S FT-IR Spectrophotometer.  $^1\text{H}$  NMR spectra were recorded on Bruker 300 MHz spectrometer.  $^{13}\text{C}$  NMR, H–H Cosy, HSQC and  $^{19}\text{F}$  NMR spectra were recorded on Bruker 400 MHz spectrometer by using  $\text{DMSO}-d_6$  as a solvent and TMS as an internal standard. The chemical shifts are expressed in  $\delta$  ppm. The mass spectra were recorded using Agilent-Single Quartz ESI-MS and Agilent-Single Quartz LC-MS. The purity of the compounds was checked by TLC. Milestone laboratory's microwave reactor was used to carry out the microwave reactions. The elemental analyses were carried out using Elemental Vario Micro Cube CHN Rapid Analyzer. All the compounds gave satisfactory elemental analysis.

#### 3.1. General procedure for the preparation of compounds

##### 3.1.1. Synthesis of 10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-ones (**2a–h**)

An equimolar mixture of 2-aminobenzimidazole (0.5 g, 3.75 mmol) and  $\beta$ -ketoesters (**1a–h**) (3.75 mmol) in DMF (10 mL) was added to a microwave tube equipped with a magnetic stir bar. The microwave tube was fitted with a reflux condenser and irradiated in a microwave reactor at a temperature of 130  $^\circ\text{C}$  for 3 min



**Fig. 3.** Antibacterial activity of compounds (**2a–h**) and (**4a–h**).

**Table 3**Results of antifungal activities of compounds (**2a–h**) and (**4a–h**) MICs ( $\mu\text{g/mL}$ ).

| Compounds   | <i>C. albicans</i> | <i>A. niger</i> | <i>A. fumigatus</i> | <i>A. flavus</i> | <i>F. oxysporum</i> | <i>P. chrysogenum</i> |
|-------------|--------------------|-----------------|---------------------|------------------|---------------------|-----------------------|
| <b>2a</b>   | 3.12               | 25              | 1.6                 | 1.6              | 0.4                 | 0.2                   |
| <b>2b</b>   | 6.25               | 100             | 1.6                 | 1.6              | 0.2                 | 0.2                   |
| <b>2c</b>   | 1.6                | 12.5            | 0.8                 | 0.8              | 0.4                 | 0.2                   |
| <b>2d</b>   | 1.6                | 6.25            | 0.8                 | 0.8              | 0.2                 | 0.4                   |
| <b>2e</b>   | 1.6                | 6.25            | 0.8                 | 0.8              | 0.2                 | 0.2                   |
| <b>2f</b>   | 1.6                | 1.6             | 0.2                 | 0.2              | 0.4                 | 0.4                   |
| <b>2g</b>   | 1.6                | 25              | 0.2                 | 0.2              | 0.2                 | 0.4                   |
| <b>2h</b>   | 6.25               | 25              | 1.6                 | 0.8              | 0.2                 | 0.4                   |
| <b>4a</b>   | 50                 | 25              | 6.25                | 3.12             | 0.2                 | 0.4                   |
| <b>4b</b>   | 50                 | 25              | 1.6                 | 1.6              | 0.2                 | 0.2                   |
| <b>4c</b>   | 50                 | 12.5            | 25                  | 12.5             | 0.2                 | 0.2                   |
| <b>4d</b>   | 50                 | 3.12            | 1.6                 | 3.12             | 0.2                 | 0.2                   |
| <b>4e</b>   | 25                 | 1.6             | 0.8                 | 1.6              | 0.2                 | 0.4                   |
| <b>4f</b>   | 25                 | 50              | 0.8                 | 0.8              | 0.2                 | 0.8                   |
| <b>4g</b>   | 50                 | 12.5            | 0.8                 | 1.6              | 0.2                 | 0.4                   |
| <b>4h</b>   | 50                 | 25              | 0.8                 | 0.8              | 0.2                 | 0.2                   |
| Fluconazole | 16                 | 8               | 8                   | 8                | 8                   | 8                     |

at a maximum power of 320 W. Then, the reaction mixture was poured on to crushed ice. The solid was filtered and washed with 100 mL of cold water. The crude product was dried and recrystallized from 1:3 ethyl acetate and chloroform.

**3.1.1.1. 2-Isopropyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (2a).** Colorless solid, Yield: 93%. Mp: 189–191 °C, IR (KBr,  $\text{cm}^{-1}$ ): 3230  $\text{cm}^{-1}$  (N–H), 1664  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  1.22 (d, 6H, 2-CH<sub>3</sub> of *i*-Pr,  $J$  = 6.9 Hz), 2.79 (m, 1H, CH of *i*-Pr), 5.87 (s, 1H, C<sub>3</sub>–H), 7.27 (t, 1H, C<sub>8</sub>–H,  $J$  = 7.8 Hz), 7.42–7.50 (m, 2H, C<sub>9</sub>–H & C<sub>10</sub>–H), 8.38 (d, 1H, C<sub>7</sub>–H,  $J$  = 8.1 Hz), 12.88 (s, 1H, N–H, D<sub>2</sub>O exchangeable) ppm;  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  21.65, 34.87, 98.42, 113.59, 115.08, 121.28, 125.92, 126.81, 135.16, 148.25, 158.95, 159.22 ppm; ESI-MS:  $m/z$  [ $M + 1$ ] 228; Anal. C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O. Calcd for: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.60; H, 5.71; N, 18.37.

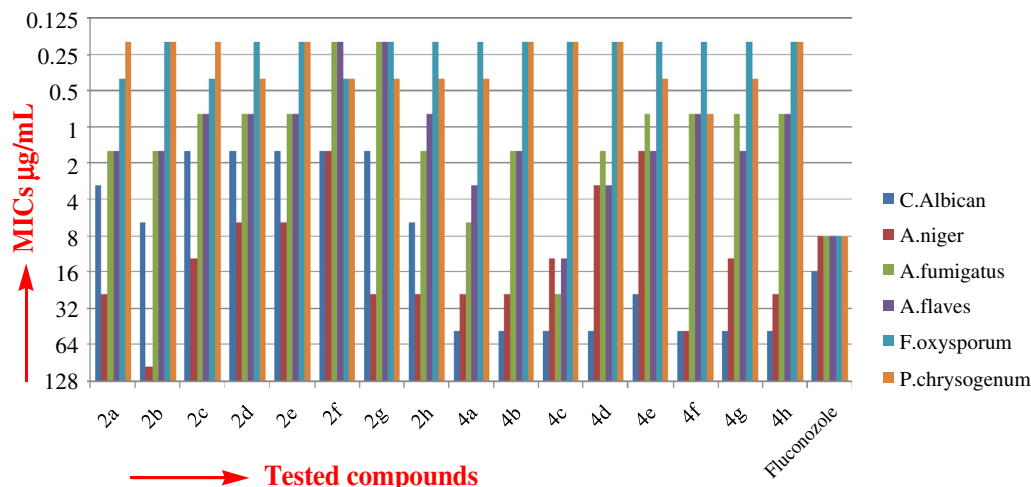
**3.1.1.2. 2-(4-Trifluoromethyl-phenyl)-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (2b).** Colorless solid, Yield: 87%. Mp: 233–235 °C, IR (KBr,  $\text{cm}^{-1}$ ): 3236  $\text{cm}^{-1}$  (N–H), 1687  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.82 (s, 1H, C<sub>3</sub>–H), 7.34–7.39 (m, 1H, C<sub>10</sub>–H), 7.51–7.53 (d, 2H, C<sub>8</sub>–H & C<sub>9</sub>–H,  $J$  = 3.9 Hz), 8.05 (d, 2H, C<sub>15</sub>–H & C<sub>19</sub>–H,  $J$  = 6.0 Hz), 8.48 (d, 1H, C<sub>7</sub>–H,  $J$  = 8.1 Hz), 8.73 (d, 2H, C<sub>16</sub>–H & C<sub>18</sub>–H,  $J$  = 3.6 Hz), 13.14 (s, 1H, N–H) ppm;  $^{13}\text{C}$  NMR (100 MHz,

DMSO- $d_6$ ): 98.18, 111.02, 115.69, 117.46, 120.56, 121.93, 125.45, 126.30, 126.92, 127.71, 129.12, 129.89 (q,  $^2J_{\text{CF}}$  = 32 Hz), 140.99, 148.14, 149.54, 158.93, 166.44 ppm; ESI-MS:  $m/z$  [ $M + 1$ ] 330; Anal. C<sub>17</sub>H<sub>10</sub>F<sub>3</sub>N<sub>3</sub>O. Calcd for: C, 62.01; H, 3.06; N, 12.76. Found: C, 61.92; H, 2.91; N, 12.60.

**3.1.1.3. 2-(3-Fluoro-phenyl)-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (2c).** Colorless solid, Yield: 94%. Mp: 213–215 °C, IR (KBr,  $\text{cm}^{-1}$ ): 3237  $\text{cm}^{-1}$  (N–H), 1681  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.65 (s, 1H, C<sub>3</sub>–H), 7.31–7.38 (m, 3H, Ar–H), 7.49 (d, 2H,  $J$  = 3.9 Hz), 8.17–8.21 (m, 2H, Ar–H), 8.46 (d, 1H,  $J$  = 8.1 Hz, Ar–H), 13.11 (s, 1H, N–H) ppm;  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  97.62, 110.97, 113.42, (d,  $^2J_{\text{CF}}$  = 23 Hz), 115.67, 116.81, 121.89, 123.0, 125.69, 126.25, 130.47, 130.58, 139.56, 139.64, 149.46, 159.06, 159.71, 161.20, 163.61 ppm; ESI-MS:  $m/z$  [ $M + 1$ ] 280; Anal. C<sub>16</sub>H<sub>10</sub>FN<sub>3</sub>O. Calcd for: C, 68.81; H, 3.61; N, 15.05. Found: C, 68.70; H, 3.55; N, 14.97.

### 3.1.2. Synthesis of 10-(2-oxo-2H-chromen-4-ylmethyl)-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-ones (4a–h)

A mixture of 10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-ones (**2a, b**) (2.20 mmol) and anhydrous K<sub>2</sub>CO<sub>3</sub> (0.6 g, 4.4 mmol) was stirred in 30 mL of dry acetone for 20 min. 4-Bromomethylcoumarins (**3a–f**) (2.20 mmol) was added and

**Fig. 4.** Antifungal activity of compounds (**2a–h**) and (**4a–h**).

**Table 4**  
*In vitro* cytotoxicity of compounds (**2a–h**) and (**4a–h**).

| Type of cancer cell ( $1 \times 10^5$ ) | Concentration of compounds ( $\mu\text{g/ml}$ ) | Number of compounds | Number of cells |      | % of dead cells |
|-----------------------------------------|-------------------------------------------------|---------------------|-----------------|------|-----------------|
|                                         |                                                 |                     | Live            | Dead |                 |
| Dalton's Ascitic Lymphoma               | 100                                             | <b>2a</b>           | 43              | 57   | 57              |
|                                         | 100                                             | <b>2b</b>           | 21              | 79   | 79              |
|                                         | 100                                             | <b>2c</b>           | 46              | 54   | 54              |
|                                         | 100                                             | <b>2d</b>           | 20              | 80   | 80              |
|                                         | 100                                             | <b>2e</b>           | 42              | 58   | 58              |
|                                         | 100                                             | <b>2f</b>           | 17              | 83   | 83              |
|                                         | 100                                             | <b>2g</b>           | 29              | 71   | 71              |
|                                         | 100                                             | <b>2h</b>           | 36              | 64   | 64              |
|                                         | 100                                             | <b>4a</b>           | 42              | 58   | 58              |
|                                         | 100                                             | <b>4b</b>           | 21              | 79   | 79              |
|                                         | 100                                             | <b>4c</b>           | 31              | 69   | 69              |
|                                         | 100                                             | <b>4d</b>           | 22              | 78   | 78              |
|                                         | 100                                             | <b>4e</b>           | 19              | 81   | 81              |
|                                         | 100                                             | <b>4f</b>           | 38              | 62   | 62              |
|                                         | 100                                             | <b>4g</b>           | 12              | 88   | 88              |
|                                         | 100                                             | <b>4h</b>           | 53              | 47   | 47              |
| 5-Fluorouracil                          | 100                                             | —                   | 12              | 88   | 88              |

stirring was continued for 24 h. The reaction mixture was concentrated to one fourth volume and poured on to crushed ice. The solid separated was filtered and washed with 5% HCl (10 mL). Then, it was washed with 50 mL of cold water. The crude product was dried and recrystallized from ethanol.

**3.1.2.1. 10-(6-Methoxy-2-oxo-2H-chromen-4-ylmethyl)-2-trifluoromethyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (**4a**).** Colorless solid, Yield: 93%. Mp: 228–230 °C, IR (KBr,  $\text{cm}^{-1}$ ): 1685  $\text{cm}^{-1}$  (C=O), 1712  $\text{cm}^{-1}$  (lactone C=O);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  3.50 (s, 3H,  $\text{OCH}_3$ ), 5.82 (s, 2H, N-CH<sub>2</sub>), 6.02 (s, 1H, C<sub>3</sub>-H of coumarin), 6.26 (s, 1H, C<sub>3</sub>-H of benzimidazopyrimidine), 7.45–8.32 (m, 7H, Ar-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  42.64, 55.86, 100.84, 107.75, 100.52, 112.32, 116.02, 117.56, 117.70, 119.87, 123.36, 125.36, 126.84, 130.74, 147.37, 148.48, 149.41 (q,  $^2J_{\text{CF}} = 64$  Hz), 150.05, 155.64, 158.96, 159.57 ppm; ESI-MS:  $m/z$  [M + 1] 442; Anal.  $\text{C}_{22}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_4$ . Calcd for: C, 59.87; H, 3.20; N, 9.52. Found: C, 59.68; H, 3.06; N, 9.30.

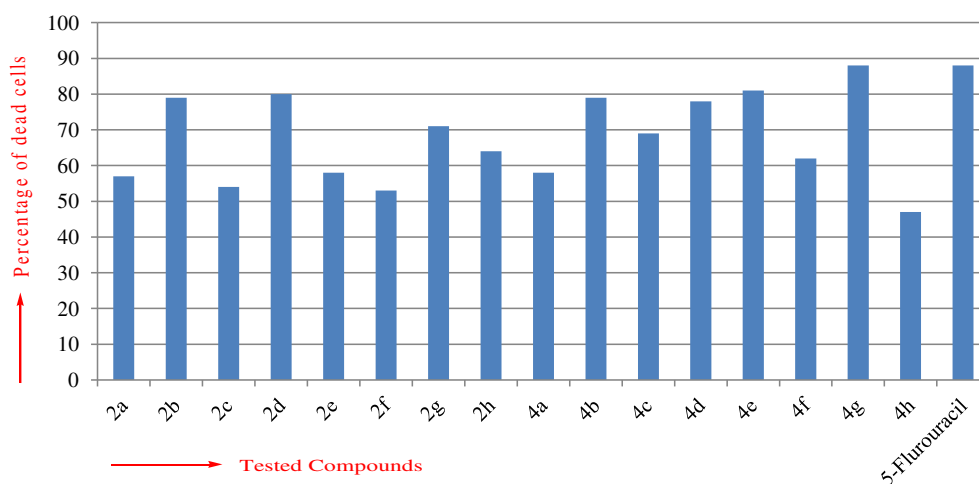
**3.1.2.2. 10-(6-Fluoro-2-oxo-2H-chromen-4-ylmethyl)-2-trifluoromethyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (**4b**).** Colorless solid, Yield: 90%. Mp: 240–245 °C, IR (KBr,  $\text{cm}^{-1}$ ):

1673  $\text{cm}^{-1}$  (C=O), 1738  $\text{cm}^{-1}$  (lactone C=O);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  5.86 (s, 2H, N-CH<sub>2</sub>), 6.28 (s, 1H, C<sub>3</sub>-H of coumarin), 6.64 (s, 1H, C<sub>3</sub>-H of benzimidazopyrimidine), 7.47–8.58 (m, 7H, Ar-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  42.44, 100.88, 110.54, 111.44, 113.12, 116.01, 118.16, 118.46, 118.55, 119.49, 119.74, 123.38, 125.39, 126.83, 130.71, 148.15, 149.44, 150.03 (q,  $^2J_{\text{CF}} = 34$  Hz), 156.91, 158.96, 159.23, 159.30 ppm; ESI-MS:  $m/z$  [M + 1] 430; Anal.  $\text{C}_{21}\text{H}_{11}\text{F}_4\text{N}_3\text{O}_3$ . Calcd for: C, 58.75; H, 2.58; N, 9.79. Found: C, 58.63; H, 2.47; N, 9.56.

**3.1.2.3. 10-(6-Methyl-2-oxo-2H-chromen-4-ylmethyl)-2-trifluoromethyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (**4c**).** Colorless solid, Yield: 92%. Mp: 211–213 °C, IR (KBr,  $\text{cm}^{-1}$ ): 1665  $\text{cm}^{-1}$  (C=O), 1734  $\text{cm}^{-1}$  (lactone C=O);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.45 (s, 3H, CH<sub>3</sub>), 5.86 (s, 2H, N-CH<sub>2</sub>), 6.15 (s, 1H, C<sub>3</sub>-H of coumarin), 6.64 (s, 1H, C<sub>3</sub>-H of benzimidazopyrimidine), 7.37–8.58 (m, 7H, Ar-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  20.31, 42.63, 100.81, 110.23, 111.70, 115.73, 116.63, 119.74, 121.15, 122.32, 123.34, 125.17, 125.32, 125.56, 127.16, 130.81, 133.18, 134.38, 148.81, 150.04 (q,  $^2J_{\text{CF}} = 34$  Hz), 158.93 ppm; ESI-MS:  $m/z$  [M + 1] 426; Anal.  $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_3$ . Calcd for: C, 62.12; H, 3.32; N, 9.88. Found: C, 62.01; H, 3.21; N, 9.74.

**3.1.2.4. 10-(6,8-Dimethyl-2-oxo-2H-chromen-4-ylmethyl)-2-trifluoromethyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (**4d**).** Colorless solid, Yield: 91%. Mp: 216–218 °C, IR (KBr,  $\text{cm}^{-1}$ ): 1670  $\text{cm}^{-1}$  (C=O), 1730  $\text{cm}^{-1}$  (lactone C=O);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.36 (s, 3H, 6-CH<sub>3</sub>), 2.41 (s, 3H, 8-CH<sub>3</sub>), 5.84 (s, 2H, N-CH<sub>2</sub>), 6.13 (s, 1H, C<sub>3</sub>-H of coumarin), 6.64 (s, 1H, C<sub>3</sub>-H of benzimidazopyrimidine), 7.43–8.58 (m, 6H, Ar-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  15.16, 20.30, 42.62, 100.08, 110.52, 111.69, 115.98, 116.62, 122.46, 122.31, 123.33, 125.16, 125.31, 126.86, 130.80, 133.17, 134.37, 148.79, 149.35, 149.46, 150.03 (q,  $^2J_{\text{CF}} = 35$  Hz), 158.92, 159.53 ppm; ESI-MS:  $m/z$  [M + 1] 440; Anal.  $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_3$ . Calcd For: C, 62.87; H, 3.67; N, 9.56. Found: C, 62.67; H, 3.58; N, 9.40.

**3.1.2.5. 10-(6-Fluoro-2-oxo-2H-chromen-4-ylmethyl)-2-isopropyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (**4e**).** Colorless solid, Yield: 88%. Mp: 230–232 °C, IR (KBr,  $\text{cm}^{-1}$ ): 1664  $\text{cm}^{-1}$  (C=O), 1736  $\text{cm}^{-1}$  (lactone C=O);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  1.20 (d, 6H, 2CH<sub>3</sub> of *i*-Pr,  $J = 6.0$  Hz), 2.80 (m, 1H, CH of *i*-Pr), 5.82 (s, 2H, N-CH<sub>2</sub>), 6.03 (s, 1H, C<sub>3</sub>-H of coumarin), 6.24 (s, 1H, C<sub>3</sub>-H of benzimidazopyrimidine), 7.45–8.50 (m, 7H, Ar-H) ppm;  $^{13}\text{C}$  NMR

**Fig. 5.** *In vitro* cell cytotoxicity of (**2a–h**) and (**4a–h**).

(100 MHz, DMSO- $d_6$ ):  $\delta$  21.77, 33.95, 42.98, 96.88, 101.97, 110.54, 112.88, 116.92, 117.76, 121.47, 122.76, 123.85, 125.91, 128.52, 131.27, 132.69, 142.60, 144.96, 145.10, 152.93 (d,  $^2J_{CF}$  = 66 Hz), 153.66, 161.23 ppm; LC-MS:  $m/z$  [M + 1] 404; Anal.  $C_{23}H_{18}FN_3O_3$ . Calcd for: C, 68.48; H, 4.50; N, 10.42. Found: C, 68.34; H, 4.40; N, 10.29.

**3.1.2.6. 10-(6-Methoxy-2-oxo-2H-chromen-4-ylmethyl)-2-isopropyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (4f).** Colorless solid, Yield: 94%. Mp: 210–213 °C, IR (KBr,  $cm^{-1}$ ): 1670  $cm^{-1}$  (C=O), 1740  $cm^{-1}$  (lactone C=O);  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  1.20 (d, 6H, 2-CH<sub>3</sub> of *i*-Pr,  $J$  = 6.0 Hz), 2.80 (m, 1H, CH of *i*-Pr), 3.52 (s, 3H, OCH<sub>3</sub>), 5.82 (s, 2H, N=CH<sub>2</sub>), 6.01 (s, 1H, C<sub>3</sub>–H of coumarin), 6.10 (s, 1H, C<sub>3</sub>–H of benzimidazopyrimidine), 7.25–8.52 (m, 7H, Ar–H) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  23.90, 32.27, 42.37, 55.85, 101.49, 110.01, 112.38, 114.46, 115.06, 115.67, 116.20, 117.42, 117.73, 119.86, 122.49, 122.60, 126.01, 130.59, 147.39, 149.04, 155.65, 159.52, 163.87 ppm; ESI-MS:  $m/z$  [M + 1] 416; Anal.  $C_{24}H_{21}N_3O_4$ . Calcd for: C, 69.39; H, 5.10; N, 10.11. Found: C, 69.17; H, 4.86; N, 10.01.

**3.1.2.7. 10-(6-Chloro-2-oxo-2H-chromen-4-ylmethyl)-2-isopropyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (4g).** Colorless solid, Yield: 89%. Mp: 237–239 °C, IR (KBr,  $cm^{-1}$ ): 1669  $cm^{-1}$  (C=O), 1732  $cm^{-1}$  (lactone C=O);  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  1.20 (d, 6H, 2CH<sub>3</sub> of *i*-Pr,  $J$  = 6.0 Hz), 2.78 (m, 1H, CH of *i*-Pr), 5.82 (s, 2H, N=CH<sub>2</sub>), 6.03 (s, 1H, C<sub>3</sub>–H of coumarin), 6.26 (s, 1H, C<sub>3</sub>–H of benzimidazopyrimidine), 7.39–8.51 (m, 7H, Ar–H) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  20.34, 33.33, 42.53, 100.81, 110.56, 111.98, 115.99, 116.39, 116.87, 123.35, 124.80, 125.34, 126.87, 130.83, 133.21, 133.85, 142.81, 148.61, 151.15, 153.36, 158.96 ppm; ESI-MS:  $m/z$  [M + 2] 421; Anal.  $C_{23}H_{18}ClN_3O_3$ . Calcd for: C, 65.79; H, 4.32; N, 10.01. Found: C, 65.65; H, 4.16; N, 9.86.

**3.1.2.8. 10-(6-Bromo-2-oxo-2H-chromen-4-ylmethyl)-2-isopropyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (4h).** Colorless solid, Yield: 95%. Mp: 213–215 °C, IR (KBr,  $cm^{-1}$ ): 1672  $cm^{-1}$  (C=O), 1731  $cm^{-1}$  (lactone C=O);  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  1.24 (d, 6H, 2CH<sub>3</sub> of *i*-Pr,  $J$  = 6.0 Hz), 2.73 (m, 1H, CH of *i*-Pr), 5.80 (s, 2H, N=CH<sub>2</sub>), 6.03 (s, 1H, C<sub>3</sub>–H of coumarin), 6.34 (s, 1H, C<sub>3</sub>–H of benzimidazopyrimidine), 7.32–8.55 (m, 7H, Ar–H) ppm;  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  21.64, 34.87, 40.13, 98.44, 113.60, 115.08, 116.21, 116.85, 118.83, 119.08, 121.30, 125.44, 126.79, 127.73, 134.80, 135.10, 148.22, 150.07, 152.53, 159.04, 159.20 ppm; ESI-MS:  $m/z$  [M + 2] 466; Anal.  $C_{23}H_{18}BrN_3O_3$ . Calcd for: C, 59.50; H, 3.91; N, 9.05. Found: C, 59.38; H, 3.79; N, 8.91.

#### 4. Conclusion

In conclusions, we have developed a simple method for the synthesis of dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones under microwave irradiation giving excellent yields of the products (74–94%) in shorter reaction time (3 min). These molecules further reacted with various substituted 4-bromomethylcoumarins to yield a new series of coumarin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones. The *in vitro* antimicrobial screening revealed that all the tested compounds possessed better antifungal

properties than antibacterial properties. The coumarin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-one (**4g**) (R = *i*-Pr, R<sub>1</sub> = 6-Cl) was found to be the most potent cytotoxic compound (88%) against Dalton's Ascitic Lymphoma cell line at the concentration of 100  $\mu$ g/mL.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejmech.2013.07.015>.

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