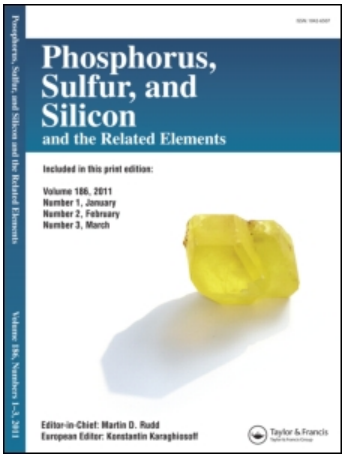


## Phosphorus, Sulfur, and Silicon and the Related Elements

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# The Synthesis and Biological Evaluation of Regioisomeric Benzothiazolyl Coumarins

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*Various 4-aryloxymethylcoumarins have been obtained by the r.t. allylic substitution with formylphenols. These have been further reacted with o-aminothiophenol resulting in the formation of a benzothiazole skeleton. These compounds have been synthesised with a view to study their potential as microbial growth inhibitors. Comparative studies on the spectral and antimicrobial activities have also been carried out.*

**Keywords** 4-Bromomethylcoumarins; antimicrobial; benzothiazole; coumarin

## INTRODUCTION

The 1,3-benzothiazole moiety has been the seat of diverse biological properties through its innumerable derivatives.[1–3] 2-arylbenzothiazoles have been found to be useful as topoisomerase inhibitors,[4,5] in vivo imaging agents,[6] lysophosphatidic acid acyltransfer agents,[7] and prodrugs.[8] The introduction of an aryloxy moiety in the pyran ring of coumarin leads to compounds with potential antitubercular[9] and antimicrobial[10] activities. Recently,

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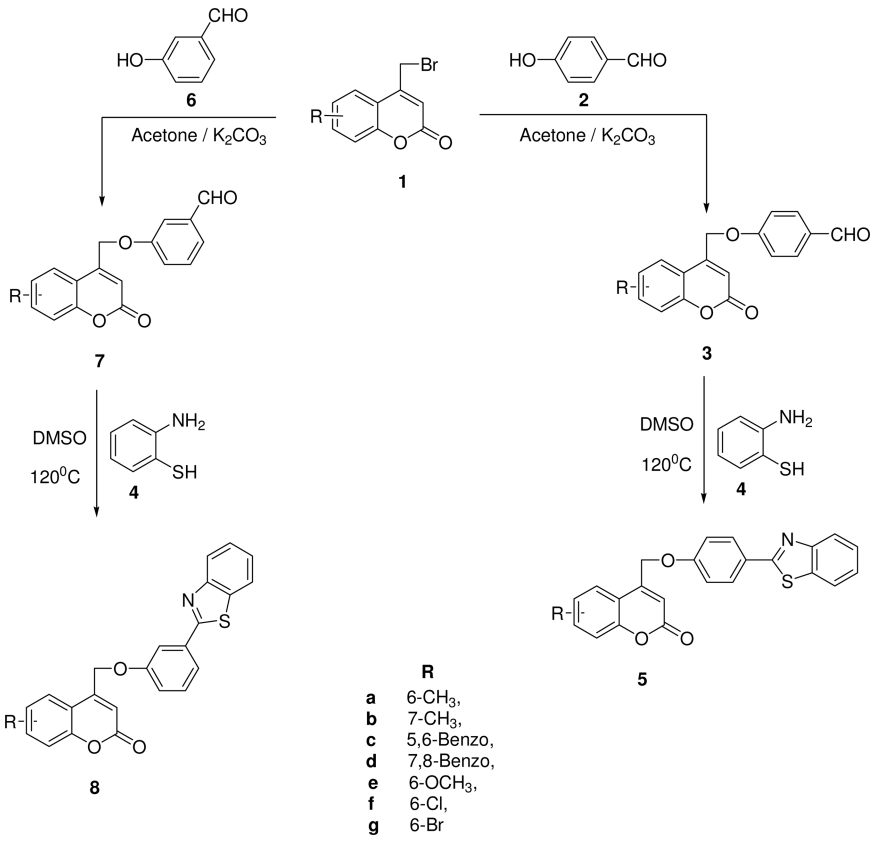
we have observed that a linking of biocompatible fragments like Vanillin and Paracetamol leads to molecular entities with enhanced antiinflammatory[11] and antimicrobial activities.[12] Further, benzothiazoles with a phenolic hydroxyl function have been isolated from marine sponges.[13] The biodegradation of coumarin leads to a generation of similar polar groups.[14] In view of this, the present article reports the synthesis of benzothiazolyl coumarins (Scheme 1) **5** and **8** via the formyl-4-aryloxy methyl coumarins **3** and **7**. The intermediates **3** and **7** possessing a formyl group have been reacted with *o*-aminothiophenol **4**, resulting in the formation of regioisomeric benzothiazolyl coumarins **5** and **8** respectively. The present synthetic strategy is illustrative of the 4+1 approach for the synthesis of five-membered heterocycles utilizing the double nucleophilicity of *o*-aminothiophenol and the electrophilic aldehydic carbon. All compounds have been subjected to a preliminary






**SCHEME 1**

antimicrobial screening against both Gram positive and Gram negative species.

The synthetic scheme for the target molecules was initiated by the Pechmann cyclization of phenols with 4-bromoethylacetoacetate[15] leading to the required 4-bromomethylcoumarins[9] **1**. The r.t. allylic nucleophilic displacement was brought about by using formyl phenols **2** and **6**, resulting in the formation of 4-aryloxymethyl coumarins **3** and **7**. The so-obtained intermediates were refluxed with equimolar quantities of *o*-aminothiophenol in dimethylsulfoxide. The resulting high-melting solids separated in the reaction mixture and were filtered off to obtain compounds **5** and **8** as crystalline solids.

## RESULTS AND DISCUSSION

In the IR Spectrum of 4-(2-oxo-2H-chromen-4-yl-methoxy)-benzaldehyde **3a** (R = 6-$CH_3$), the lactone carbonyl stretching frequency was observed at 1714 $cm^{-1}$, whereas the aldehydic carbonyl stretching appeared at 1696 $cm^{-1}$. In the $^1H$ NMR spectrum of compound **3a** (R = 6-$CH_3$), a singlet was observed at $\delta$ 2.46 due to $C_6$-$CH_3$ protons. The $C_4$-$CH_2$ protons were observed downfield as singlet at $\delta$ 5.34. The $C_3$-H of coumarin appeared at $\delta$ 6.67. $C_5$-H, $C_7$-H and $C_8$-H of coumarin resonated as doublets at $\delta$ 7.33 ($J_{1,3} = 3.3$ Hz), $\delta$ 7.4 ($J_{1,2} = 8.7$ Hz, $J_{1,3} = 3.3$ Hz), and $\delta$ 7.27 ($J_{1,2} = 8.7$ Hz), respectively. Protons in the aryloxy moiety appeared as an *AA'BB'* pattern. Protons *ortho* to the —CHO group appeared as a doublet at $\delta$ 7.90 ($J_{1,2} = 8.4$ Hz), and protons *ortho* to phenolic oxygen appeared as a doublet at $\delta$ 7.14 ($J_{1,2} = 8.4$ Hz). The aldehydic proton appeared as a singlet in the downfield at $\delta$ 9.95. The $^{13}C$ NMR spectral data of compound **3a** is given in the Experimental section, which is confirmed by its 2D-HETERO COSY spectrum. The assignments are in agreement with the literature reports on coumarin[16] and benzaldehyde.[17]

In the IR Spectrum of 3-(2-oxo-2H-chromen-4-yl-methoxy)-benzaldehyde **7a** (R = 6-$CH_3$), the lactone carbonyl stretching frequency was observed at 1707 $cm^{-1}$, whereas the aldehydic carbonyl stretching appeared at 1690 $cm^{-1}$. In the $^1H$ NMR spectrum of compound **7g** (R = 6—Br), a singlet was observed at $\delta$ 5.52 due to $C_4$-$CH_2$ protons. The $C_3$-H of coumarin appeared at $\delta$ 6.66. The $C_5$-H of coumarin appeared as a singlet at $\delta$ 7.71. The $C_7$-H of coumarin resonated as doublets at $\delta$ 7.42 ($J_{1,2} = 8.7$ Hz). The only proton in the aryloxy moiety flanked by a —CHO and —$CH_2O$— group appeared as a singlet at $\delta$ 8.13. The proton *ortho* to —CHO and *para* to the —$CH_2O$ group appeared as a doublet at $\delta$ 7.81 ($J_{1,2} = 8.7$ Hz). The $C_8$-H of coumarin and protons *meta* and *para* to the —CHO group

resonated as a multiplet in the region $\delta$ 7.59–7.60, which was too close for separation. The aldehydic proton appeared in the downfield as a singlet at $\delta$ 10.0 ppm.

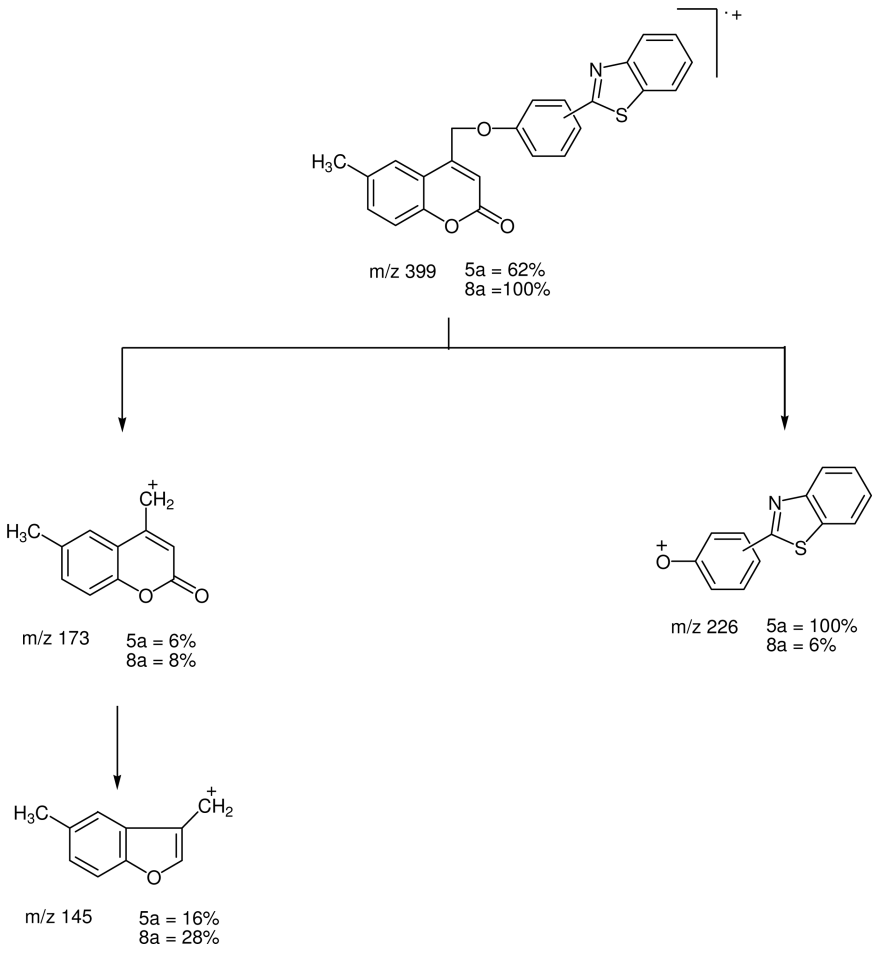
In the IR spectrum of 4-(4-benzothiazol-2-yl-phenoxymethyl)-chromen-2-one **5a** (R = 6-$CH_3$), the lactone carbonyl stretching frequency was observed at 1715 $cm^{-1}$. The absence of a band around 1696 $cm^{-1}$ confirmed the conversion of aldehyde into the benzothiazole. In the $^1$H NMR spectrum of compound **5a** (R = 6-$CH_3$), a singlet was observed at $\delta$ 2.46 due to $C_6$-$CH_3$ protons. The $C_4$-$CH_2$ protons were observed downfield as a singlet at $\delta$ 5.4. The $C_3$-H of coumarin appeared at $\delta$ 6.66, whereas the aromatic protons resonated as a multiplet in the region $\delta$ 7.19–8.10. The absence of a —CHO proton at $\delta$ 9.95 was indicative of the formation of benzothiazole.

In the IR spectrum of 4-(3-benzothiazol-2-yl-phenoxymethyl)-chromen-2-one **8a** (R = 6-$CH_3$), the lactone carbonyl stretching frequency was observed at 1718 $cm^{-1}$. The absence of a band around 1690 $cm^{-1}$ confirmed the conversion of aldehyde into the benzothiazole. In the $^1$H NMR spectrum of compound **8a** (R = 6-$CH_3$), a singlet was observed at $\delta$ 2.43 due to $C_6$-$CH_3$ protons. The $C_4$-$CH_2$ protons were observed downfield as a singlet at $\delta$ 5.43. The $C_3$-H of coumarin appeared at $\delta$ 6.61, whereas the aromatic protons resonated as a multiplet in the region $\delta$ 7.19–8.09. The absence of a —CHO proton at $\delta$ 10.0 confirmed the formation of benzothiazole.

The mass spectrum (EI) of compound **5a** (R = 6-$CH_3$) showed a molecular ion peak itself as a base peak at *m/z* 399 (100%). The mass spectrum (EI) of compound **8a** (R = 6-$CH_3$) showed a molecular ion peak at *m/z* 399 (62%), whereas a base peak appeared at *m/z* 226 (100%) due to homolytic allylic cleavage of the $CH_2$-O bond leading to the formation of aryloxy benzothiazole ion. The minor differences observed in the mass spectral fragmentation of the two-regio isomeric benzothiazoles is depicted in Scheme 2.

## ANTIMICROBIAL ACTIVITY

The antimicrobial screening for all compounds was carried out against Gram positive and Gram negative species with *B. subtilis* and *E. coli*, respectively. *A. niger* and *C. albicans* were employed as fungal strains. DMF was used as a solvent control. The reference drugs used were *Ciprofloxacin* and *Gresiofulvin*. Tests were carried out by the cup plate method[18] at a concentration of 100 $\mu$g $mL^{-1}$. After 48 h of incubation at 37°C, the zone of inhibition was measured in mm. The percent inhibition of test compounds was related to the standard whose zone of inhibition was taken as 100%. Among the formyl ethers **3e** and **7e** (R = 6—$OCH_3$),




**SCHEME 2**

**3g** and **7g** (R = 6-Br) were found to show higher antimicrobial activity. The most effective compounds were **3f** and **7f** (R = 6-Cl), which were equally effective against the two bacterial and fungal species (Table I). Compounds with methyl and benzo substitution were less active.

A similar trend was observed in the benzothiazolyl coumarins **5** and **8**, where **5e** and **8e** (R = 6-$OCH_3$) and **5g** and **8g** (R = 6—Br) showed percent inhibition in the range 78–88% specifically for *C. albicans.* The highest activity against all strains was associated with chloro substitution and in particular, the compounds **5f** and **8f** showed growth inhibition of all the species, comparable to the standard (Table I).

**TABLE I Results of Antimicrobial Assay**

| | | *B. subtilis* | | *E. coli* | | *A.niger* | | *C.albicans* | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | R | Zone of inhibition (mm) | Relative inhibition (%) | Zone of inhibition (mm) | Relative inhibition (%) | Zone of inhibition (mm) | Relative inhibition (%) | Zone of inhibition (mm) | Relative inhibition (%) |
| **3a** | 6-$CH_3$ | 16 | 55.5 | 18 | 66.6 | 19 | 72.2 | 19 | 77.7 |
| **3b** | 7-$CH_3$ | 16 | 55.5 | 18 | 66.6 | 19 | 72.2 | 20 | 72.2 |
| **3c** | 5,6-Benzo | 15 | 50.0 | 17 | 61.1 | 17 | 61.1 | 19 | 72.2 |
| **3d** | 7,8-Benzo | 15 | 50.0 | 17 | 61.1 | 17 | 61.1 | 18 | 66.6 |
| **3e** | 6-$OCH_3$ | 17 | 61.1 | 19 | 72.2 | 20 | 77.7 | 20 | 77.7 |
| **3f** | 6-Cl | 21 | 83.33 | 22 | 88.8 | 22 | 88.8 | 23 | 94.4 |
| **3g** | 6-Br | 18 | 66.6 | 20 | 77.7 | 21 | 83.33 | 21 | 83.33 |
| **5a** | 6-$CH_3$ | 17 | 61.1 | 16 | 55.5 | 17 | 61.6 | 20 | 77.7 |
| **5b** | 7-$CH_3$ | 17 | 61.1 | 16 | 55.5 | 16 | 55.5 | 20 | 77.7 |
| **5c** | 5,6-Benzo | 15 | 50.0 | 15 | 50.0 | 16 | 55.5 | 19 | 72.2 |
| **5d** | 7,8-Benzo | 15 | 50.0 | 15 | 50.0 | 15 | 50.0 | 18 | 66.6 |
| **5e** | 6-$OCH_3$ | 18 | 66.6 | 18 | 66.6 | 18 | 66.6 | 21 | 83.33 |
| **5f** | 6-Cl | 23 | 94.4 | 22 | 88.8 | 21 | 83.33 | 22 | 88.8 |
| **5g** | 6-Br | 22 | 88.8 | 19 | 72.2 | 19 | 72.2 | 22 | 88.8 |
| **7a** | 6-$CH_3$ | 21 | 83.33 | 19 | 72.2 | 20 | 77.2 | 19 | 72.2 |
| **7b** | 7-$CH_3$ | 18 | 66.66 | 17 | 61.1 | 19 | 72.2 | 19 | 72.2 |
| **7c** | 5,6-Benzo | 18 | 66.66 | 17 | 61.1 | 19 | 72.2 | 18 | 66.6 |
| **7d** | 7,8-Benzo | 18 | 66.66 | 17 | 61.1 | 19 | 72.2 | 18 | 66.6 |
| **7e** | 6-$OCH_3$ | 22 | 88.8 | 20 | 77.7 | 21 | 83.33 | 21 | 83.33 |
| **7f** | 6-Cl | 23 | 94.4 | 22 | 88.8 | 22 | 88.8 | 22 | 88.8 |
| **7g** | 6-Br | 21 | 83.33 | 19 | 72.2 | 20 | 77.7 | 20 | 77.7 |
| **8a** | 6-$CH_3$ | 18 | 66.6 | 19 | 72.2 | 19 | 72.2 | 20 | 77.7 |
| **8b** | 7-$CH_3$ | 18 | 66.6 | 19 | 72.2 | 19 | 72.2 | 20 | 77.7 |
| **8c** | 5,6-Benzo | 17 | 61.1 | 18 | 66.6 | 18 | 66.6 | 19 | 72.2 |
| **8d** | 7,8-Benzo | 17 | 61.1 | 18 | 66.6 | 18 | 66.6 | 18 | 66.6 |
| **8e** | 6-$OCH_3$ | 19 | 72.2 | 20 | 77.7 | 20 | 77.7 | 20 | 77.7 |
| **8f** | 6-Cl | 22 | 88.8 | 23 | 94.4 | 22 | 88.8 | 22 | 88.8 |
| **8g** | 6-Br | 20 | 77.7 | 22 | 88.8 | 20 | 77.7 | 22 | 88.8 |
| DMF | | 6 | — | 6 | — | 6 | — | 6 | — |
| Ciprofloxacin | | 24 | 100 | 24 | 100 | — | — | — | — |
| Gresiofulvin | | — | — | — | — | 24 | 100 | 24 | 100 |

## EXPERIMENTAL

Melting points were determined using an electric melting point apparatus (Shital scientific industries, Mumbai) and are uncorrected. IR spectra (KBr) were run on a Nicolet impact 410 FT-IR spectrometer ($\nu_{max}$ in $cm^{-1}$). $^1H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ with TMS as an internal standard (chemical shift in $\delta$ ppm and $J$ values in Hz) on a Brucker 300 MHz FTNMR spectrometer. A 2D-heterocosy spectrum was recorded on a 500 MHz NMR at the Indian Institute of Science, Bangalore. Elemental analyses were carried out on a Heraus CHN rapid analyzer. The purity of the compound was checked by TLC. Nomenclature was made using Chem. Draw ultra version 6.0. All reagents were of laboratory reagent quality, were purchased from SD.fine-Chem, and were used after purification.



### The Preparation of (2-Oxo-2*H*-chromen-4-yl-methoxy)-benzaldehydes (3a–g) and (7a–g): General Procedure

Formylphenols **2** or **6** (1.22 g, 10 mmol) and anhydrous $K_2CO_3$ (1.38 g, 10 mmol) were stirred in dry acetone (50 mL) for 30 min. 4-bromomethyl coumarins (**1a–g**) (10 mmol) were added, and stirring was continued for 24 h. The reaction mixture was concentrated and poured into ice-cold water. The solid separated was filtered and washed with 5% HCl (10 mL) to neutralize the excess of potassium carbonate. Then it was washed with 100 mL of cold water and with ethanol. The crude product was dried and recrystallised from DMF.

#### *4-(6-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (3a)*

Colorless crystals from DMF. Yield 80%, m.p. 220–222°C; (found; C, 73.09; H, 4.29. $C_{18}H_{14}O_4$ (294.30) requires C, 73.46; H, 4.76%); IR: $\nu = 1714$ (C=O, lactone), 1696 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 2.46$ (s, 3H, $C_6$-$CH_3$), 5.34 (s, 2H, $CH_2O$), 6.67 (s, 1H, $C_3$-H), 7.14–7.93 (m, 7H, Ar—H), 9.95 (s, 1H, CHO) ppm; $^{13}C$ NMR ($CDCl_3$)$\delta = 161.0$ ($C_2$), 115.0 ($C_3$), 148.0 ($C_4$), 123.0 ($C_5$), 153.0 ($C_6$), 134.0 ($C_7$), 118.0 ($C_8$), 132.0 ($C_9$), 114.0 ($C_{10}$), 66.0 ($C_{11}$), 163.0 ($C_{12}$), 117.0 ($C_{13}$ & $C_{17}$), 133.0 ($C_{14}$ & $C_{16}$), 131.0 ($C_{15}$), 192.0 ($C_{18}$), and 21.0 ($C_{19}$) ppm.

#### *4-(7-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (3b)*

Colorless crystals from DMF. Yield 78%, m.p. 226–228°C; (found; C, 73.16; H, 4.31. $C_{18}H_{14}O_4$ (294.30) requires C, 73.46; H, 4.76%); IR: $\nu = 1701$ (C=O, lactone), 1689 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$):

$\delta = 2.49$ (s, 3H, $C_6$-$CH_3$), 5.32 (s, 2H, $CH_2O$), 6.61 (s, 1H, $C_3$-H), 7.14–7.92 (m, 7H, Ar—H), 9.94 (s, 1H, CHO) ppm.

### *4-(3-Oxo-3H-benzo[f]chromen-1-ylmethoxy)-benzaldehyde) (3c)*

Colorless crystals from DMF. Yield 80%, m.p. 222–224°C; (found; C, 76.09; H, 3.91. $C_{21}H_{14}O4$ (330.33) requires C, 76.36; H, 4.24%); IR: $\nu = 1710$ (C=O, lactone), 1696 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.73$ (s, 2H, $CH_2O$), 6.91 (s, 1H, $C_3$-H), 7.13–8.13 (m, 10H, Ar—H), 9.95 (s, 1H, CHO) ppm.

### *4-(2-Oxo-2H-benzo[h]chromen-4-ylmethoxy)-benzaldehyde) (3d)*

Colorless crystals from DMF. Yield 75%, m.p. 246–248°C; (found; C, 73.04; H, 3.97. $C_{21}H_{14}O_4$ (330.33) requires C, 76.36; H, 4.24%); IR: $\nu = 1714$ (C=O, lactone), 1707 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.47$ (s, 2H, $CH_2O$), 6.74 (s, 1H, $C_3$-H), 7.13–8.67 (m, 10H, Ar—H), 9.93 (s, 1H, CHO) ppm.

### *4-(6-Methoxy-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde) (3e)*

Colorless crystals from DMF. Yield 70%, m.p. 202–204°C; (found; C, 69.31; H, 4.24. $C_{18}H_{14}O_5$ (310.30) requires C, 69.67; H, 4.51%); IR: $\nu = 1712$ (C=O, lactone), 1702 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 3.88$ (s, 3H, $C_6$-$OCH_3$), 5.31 (s, 2H, $CH_2O$), 6.68 (s, 1H, $C_3$-H), 7.00–7.93 (m, 7H, Ar—H), 9.94 (s, 1H, CHO) ppm.

### *4-(6-Chloro-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (3f)*

Colorless crystals from DMF. Yield 66%, m.p. 220–222°C; (Found; C, 64.65; H, 3.17. $C_{17}H_{11}O_4Cl$ (314.72) requires C, 64.96; H, 3.50%); IR: $\nu = 1720$ (C=O, lactone), 1700 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.28$ (s, 2H, $CH_2O$), 6.71 (s, 1H, $C_3$-H), 7.12–7.93 (m, 7H, Ar—H), 9.90 (s, 1H, CHO) ppm.

### *4-(6-Bromo-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (3g)*

Colorless crystals from DMF. Yield 68%, m.p. 217–219°C; (found; C, 56.47; H, 2.81. $C_{17}H_{11}O_4Br$ (359.17) requires C, 56.82; H, 3.06%); IR: $\nu = 1718$ (C=O, lactone), 1700 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.54$ (s, 2H, $CH_2O$), 6.65 (s, 1H, $C_3$-H), 7.39–7.94 (m, 7H, Ar—H), 9.90 (s, 1H, CHO) ppm.

### *3-(6-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (7a)*

Colorless crystals from DMF. Yield 72%, m.p. 202–204°C; (found; C, 73.11; H, 4.42. $C_{18}H_{14}O_4$ (294.30) requires C, 73.46; H, 4.76%); IR: $\nu = 1707$ (C=O, lactone), 1690 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 2.45$ (s, 3H, $C_6$-$CH_3$), 5.29 (s, 2H, $CH_2O$), 6.67 (s, 1H, $C_3$-H), 7.26–7.53 (m, 7H, Ar—H), 10.01 (s, 1H, CHO) ppm.

### *3-(7-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (7b)*

Colorless crystals from DMF. Yield 70%, m.p. 223–225°C; (found; C, 73.12; H, 4.39. $C_{18}H_{14}O_4$ (294.30) requires C, 73.46; H, 4.76%); IR: $\nu = 1716$ (C=O, lactone), 1687 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 2.49$ (s, 3H, $C_6$-$CH_3$), 5.30 (s, 2H, $CH_2O$), 6.64 (s, 1H, $C_3$-H), 7.15–7.56 (m, 7H, Ar—H), 10.02 (s, 1H, CHO) ppm.



### *3-(3-Oxo-3H-benzo[f]chromen-1-ylmethoxy)-benzaldehyde) (7c)*

Colorless crystals from DMF. Yield 78%, m.p. 168–168°C; (found; C, 76.12; H, 3.89. $C_{21}H_{14}O_4$ (330.33) requires C, 76.36; H, 4.24%); IR: $\nu = 1724$ (C=O, lactone), 1697 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.69$ (s, 2H, $CH_2O$), 6.92 (s, 1H, $C_3$-H), 7.33–8.14 (m, 10H, Ar—H), 10.01 (s, 1H, CHO) ppm.

### *3-(2-Oxo-2H-benzo[h]chromen-4-ylmethoxy)-benzaldehyde) (7d)*

Colorless crystals from DMF. Yield 76%, m.p. 185–187°C; (found; C, 76.01; H, 3. 49. $C_{21}H_{14}O_4$ (330.33) requires C, 76.36; H, 4.24%); IR: $\nu = 1721$ (C=O, lactone), 1684 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.72$ (s, 2H, $CH_2O$), 6.94 (s, 1H, $C_3$-H), 7.27–8.16 (m, 10H, Ar—H), 10.02 (s, 1H, CHO) ppm.

### *3-(6-Methoxy-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde) (7e)*

Colorless crystals from DMF. Yield 70%, m.p. 280–282°C; (found; C, 69.31; H, 4.22. $C_{18}H_{14}O_5$ (310.30) requires C, 69.67; H, 4.51%); IR: $\nu = 1713$ (C=O, lactone), 1688 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 3.88$ (s, 3H, $C_6$-$OCH_3$), 5.28 (s, 2H, $CH_2O$), 6.69 (s, 1H, $C_3$-H), 6.99–7.58 (m, 7H, Ar—H), 10.01 (s, 1H, CHO) ppm.

### *3-(6-Chloro-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (7f)*

Colorless crystals from DMF. Yield 65%, m.p. 230–232°C; (found; C, 64.48; H, 3.17. $C_{17}H_{11}O_4Cl$ (314.72) requires C, 64.96; H, 3.50%); IR: $\nu = 1723$ (C=O, lactone), 1681 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.26$ (s, 2H, $CH_2O$), 6.72 (s, 1H, $C_3$-H), 7.26–7.59 (m, 7H, Ar—H), 10.01 (s, 1H, CHO) ppm.

### *3-(6-Bromo-2-oxo-2H-chromen-4-ylmethoxy)-benzaldehyde (7g)*

Colorless crystals from DMF. Yield 64%, m.p. 224–226°C; (found; C, 56.43; H, 2.79. $C_{17}H_{11}O_4Br$ (359.17) requires C, 56.82; H, 3.06%); IR: $\nu = 1720$ (C=O, lactone), 1688 (C=O, aldehyde) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta = 5.52$ (s, 2H, $CH_2O$), 6.66 (s, 1H, $C_3$-H), 7.42–8.13 (m, 7H, Ar—H), 10.00 (s, 1H, CHO) ppm.



## The Preparation of 4-(Benzothiazol-2-yl-phenoxymethyl)-chromen-2-ones (5a–g) and (8a–g): General Procedure

(2-Oxo-2*H*-chromen-4-yl-methoxy)-benzaldehydes (**3a–g**) or (**7a–g**) (10 mmol) and *o*-aminothiophenol (1.1 mL, 10 mmol) were refluxed at $120^0$C in an oil bath for 8 h in dimethylsulfoxide (10 mL). The reaction mixture was cooled to r.t., and the separated solid was filtered, washed with ethanol, dried and recrystallized from DMF.

### *4-(4-Benzothiazol-2-yl-phenoxymethyl)-6-methyl-chromen-2-one (5a)*

Colorless crystals from DMF. Yield 92%, m.p. 300–302°C; (found; C, 71.86; H, 3.97; N, 3.19. $C_{24}H_{17}O_3NS$ (399.46) requires C, 72.18; H, 4.26; N, 3.5%); IR: $\nu = 1715$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 2.46$ (s, 3H, $C_6$-$CH_3$), 5.40 (s, 2H, $CH_2O$), 6.66 (s, 1H, $C_3$-H), 7.19–8.10 (m, 11H, Ar—H) ppm; ms: m/z 399 ($M^+$), m/z 371 (15%) (M—CO), m/z 384 (30%) (M—$CH_3$), m/z 356 (5%) (M—$CO_2$).

### *4-(4-Benzothiazol-2-yl-phenoxymethyl)-7-methyl-chromen-2-one (5b)*

Colorless crystals from DMF. Yield 91%, m.p. 226–228°C; (found; C, 71.88; H, 3.94; N, 3.16. $C_{24}H_{17}O_3NS$ (399.46) requires C, 72.18; H, 4.26, N; 3.5%); IR: $\nu = 1708$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 2.46$ (s, 3H, $C_6$-$CH_3$), 5.26 (s, 2H, $CH_2O$), 6.62 (s, 1H, $C_3$-H), 7.07–8.08 (m, 11H, Ar—H) ppm.

### *1-(4-Benzothiazol-2-yl-phenoxymethyl)-benzo[f]chromen-3-one (5c)*

Colorless crystals from DMF. Yield 91%, m.p. 262–264°C; (found; C, 74.16; H, 3.59; N, 2.91. $C_{27}H_{17}O_3NS$ (435.49) requires C, 74.48; H; 3.90; N, 3.21%); IR: $\nu = 1708$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.70$ (s, 2H, $CH_2O$), 6.95 (s, 1H, $C_3$-H), 7.11–8.16 (m, 14H, Ar—H) ppm.

### *4-(4-Benzothiazol-2-yl-phenoxymethyl)-benzo[h]chromen-2-one (5d)*

Colorless crystals from DMF. Yield 93%, m.p. 140–142°C; (found; C, 74.16; H, 3.59; N, 2.91. $C_{27}H_{17}O_3NS$ (435.49) requires C, 74.48; H, 3.90; N, 3.21%); IR: $\nu = 1715$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.39$ (s, 2H, $CH_2O$), 6.99 (s, 1H, $C_3$-H), 7.04–8.03 (m, 14H, Ar—H) ppm.



### *4-(4-Benzothiazol-2-yl-phenoxymethyl)-6-methoxy-chromen-2-one (5e)*

Colorless crystals from DMF. Yield 89%, m.p. 264–266°C; (found; C, 69.03; H, 3.71; N, 3.03. $C_{24}H_{17}O_4NS$ (415.46) requires C, 69.39; H, 4.09; N, 3.37%); IR: $\nu = 1718$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 3.84$ (s, 3H, $C_6$-$OCH_3$), 5.45 (s, 2H, $CH_2O$), 6.60 (s, 1H, $C_3$-H), 7.18–8.05 (m, 11H, Ar—H) ppm.

### *4-(4-Benzothiazol-2-yl-phenoxymethyl)-6-chloro-chromen-2-one (5f)*

Colorless crystals from DMF. Yield 82%, m.p. 300–302°C; (found; C, 65.51; H, 3.01; N, 3.02. $C_{23}H_{14}O_3NSCl$ (419.88) requires C, 65.87; H, 3.34; N, 3.34%); IR: $\nu = 1709$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.38$ (s, 2H, $CH_2O$), 6.84 (s, 1H, $C_3$-H), 7.04–7.86 (m, 11H, Ar—H) ppm.

### *4-(4-Benzothiazol-2-yl-phenoxymethyl)-6-bromo-chromen-2-one (5g)*

Colorless crystals from DMF. Yield 85%, m.p. 295–297°C; (found; C, 59.09; H, 2.69; N, 2.67. $C_{23}H_{14}O_3NSBr$ (464.33) requires C, 59.48; H, 3.01; N, 3.01%); IR: $\nu = 1711$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.36$ (s, 2H, $CH_2O$), 6.74 (s, 1H, $C_3$-H), 7.19–8.10 (m, 11H, Ar—H) ppm.

### 4-(3-Benzothiazol-2-yl-phenoxymethyl)-6-methyl-chromen-2-one (8a)

Colorless crystals from DMF. Yield 91%, m.p. 225–227°C; (found; C, 71.82; H, 3.93; N, 3.15. $C_{24}H_{17}O_3NS$ (399.46) requires C, 72.18; H, 4.26; N, 3.5%); IR: $\nu = 1718$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 2.43$ (s, 3H, $C_6$-$CH_3$), 5.43 (s, 2H, $CH_2O$), 6.61 (s, 1H, $C_3$-H), 7.19–8.09 (m, 11H, Ar—H) ppm; ms m/z 399 ($M^+$); m/z 371(3%) (M—CO), m/z 384 (2%) (M—$CH_3$).

### 4-(3-Benzothiazol-2-yl-phenoxymethyl)-7-methyl-chromen-2-one (8b)

Colorless crystals from DMF. Yield 90%, m.p. 214–216°C; (found; C, 71.79; H, 3.89; N, 3.11. $C_{24}H_{17}O_3NS$ (399.46) requires C, 72.18; H, 4.26; N; 3.5%); IR: $\nu = 1721$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 2.43$ (s, 3H, $C_6$-$CH_3$), 5.31 (s, 2H, $CH_2O$), 6.66 (s, 1H, $C_3$-H), 7.11–8.09 (m, 11H, Ar—H) ppm.



### 1-(3-Benzothiazol-2-yl-phenoxymethyl)-benzo[f]chromen-3-one (8c)

Colorless crystals from DMF. Yield 83%, m.p. 200–202°C; (found; C, 74.08; H, 3.51; N, 2.86. $C_{27}H_{17}O_3NS$ (435.49) requires C, 74.48; H; 3.90; N, 3.21%); IR: $\nu = 1717$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.71$ (s, 2H, $CH_2O$) 6.96 (s, 1H, $C_3$-H), 7.13–8.21 (m, 14H, Ar—H) ppm.

### 4-(3-Benzothiazol-2-yl-phenoxymethyl)-benzo[h]chromen-2-one (8d)

Colorless crystals from DMF. Yield 93%, m.p. 180–182°C; (found; C, 74.07; H, 3.49; N, 2.87. $C_{27}H_{17}O_3NS$ (435.49) requires C, 74.48; H; 3.90; N, 3.21%); IR: $\nu = 1711$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.42$ (s, 2H, $CH_2O$), 6.76 (s, 1H, $C_3$-H), 7.13–8.57 (m, 14H, Ar—H) ppm.

### 4-(3-Benzothiazol-2-yl-phenoxymethyl)-6-methoxy-chromen-2-one (8e)

Colorless crystals from DMF. Yield 89%, m.p. 206–208°C; (found; C, 69.02; H, 3.76; N, 3.01. $C_{24}H_{17}O_4NS$ (415.46) requires C, 69.39; H, 4.09; N, 3.37%); IR: $\nu = 1715$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 3.87$ (s, 3H, $C_6$-$OCH_3$), 5.31 (s, 2H, $CH_2O$), 6.73 (s, 1H, $C_3$-H), 7.04–8.09 (m, 11H, Ar—H) ppm.

### *4-(3-Benzothiazol-2-yl-phenoxymethyl)-6-chloro-chromen-2-one (8f)*

Colorless crystals from DMF. Yield 81%, m.p. 180–182°C; (found; C, 65.51; H, 3.02; N, 3.03. $C_{23}H_{14}O_3NSCl$ (419.88) requires C, 65.87; H, 3.34; N, 3.34%); IR: $\nu = 1715$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.39$ (s, 2H, $CH_2O$), 6.77 (s, 1H, $C_3$-H), 7.15–8.58 (m, 11H, Ar—H) ppm.

### *4-(3-Benzothiazol-2-yl-phenoxymethyl)-6-bromo-chromen-2-one (8g)*

Colorless crystals from DMF. Yield 84%, m.p. 230–232°C; (found; C, 59.48; H, 2.66; N, 2.69. $C_{23}H_{14}O_3NSBr$ (464.33) requires C, 59.48; H, 3.01; N, 3.01%); IR: $\nu = 1721$ (C=O, lactone) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 5.42$ (s, 2H, $CH_2O$), 6.76 (s, 1H, $C_3$-H), 7.25–8.07 (m, 11H, Ar—H) ppm.



## CONCLUSION

The 4-(benzothiazol-2-yl-phenoxymethyl)-chromen-2-ones **5** and **8** are more potent than formylethers **3** and **7**. Among regioisomers, the *meta*isomers are more potent than the *para*isomers both in the case of formylethers and benzothiazolyl coumarins. The compounds thatcontain the chloro, bromo, and methoxy substitution at the 6-position in the coumarin ring enhanced the growth inhibition in the following order: methoxy < bromo < chloro.

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