J. Chem. Sci., Vol. 121, No. 4, July 2009, pp. 485–495.

Synthesis of some new 4-aryloxmethylcoumarins and examination of their antibacterial and antifungal activities

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MS received 27 August 2008; revised 28 May 2009; accepted 3 June 2009

Abstract. A number of new 4-aryloxymethylcoumarins **3** and **5** have been obtained from the reaction of various 4-bromomethylcoumarins with 2-nitro-*p*-cresol **2** and 2,6-dibromo-*p*-cresol **4**. NOE studies have been carried out on two compounds to ascertain their spatial proximity. *p*-cresol ethers **7** have been subjected to bromination in chloroform and the position of bromine has been established by diffraction studies. Cleavage of the ether linkage has been observed during an attempted nitration of ethers **7**. Antimicrobial activity of all the compounds against five bacterial and five fungal species have been reported.

Keywords. 4-Bromomethylcoumarins; NOE; X-ray; electrophilic substitution; fluorescent; antimicrobial.

1. Introduction

Amongst all the naturally occurring oxygen heterocycles, coumarins occupy an important position in view of their wide ranging biological,[1] fluorescent labelling,[2] and protease inhibiting[3] properties. Earlier 4-aryloxymethylcoumarins were screened as models for Claisen rearrangement.[4] Importance of aryl and alkyl ether linkage in coumarins was realized with the discovery of their anti-histaminic activity.[5] Antimicrobial activity, long range coupling[6] and centrosymmetric nature[7] of 4-aryloxymethyl coumarins have been reported from our laboratory. Recently we have also observed that linking of biocompatible fragments like vanillin[8] and paracetamol[9] via an ether linkage at the allylic position in the pyran ring leads to molecular motiffs with potential anti-inflammatory and dual fluorescence properties. It can be seen that 4-aryloxymethyl coumarins are associated with promising biological and structurally interesting properties.

In the present work, we have generated a number of 4-aryloxymethyl coumarins by using 2-nitro-*p*-cresol and 2,6-dibromo-*p*-cresol. NOE studies have been carried out on two compounds to ascertain their spatial proximity. With a view to compare the reactivity of the phenoxy and coumarin moieties, bromination and nitration of *p*-cresol ethers **7** have been carried out. Bromination resulted in 2-bromo-*p*-cresol ethers which has been proved by diffraction studies. Nitration has been found to occur in the coumarin ring with the simultaneous cleavage of the ether linkage.

2. Experimental

2.1 *Materials*

All the starting materials and reagents were purchased from commercial suppliers and used after further purification.

2.2 *Physical measurements*

Melting points were determined by open capillary method and are uncorrected. All the compounds were analysed satisfactorily for C, H and N. IR spectra (KBr disc) were recorded on a Nicolet-5700 FT–IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz spectrometer using $CDCl_3$ as a solvent and TMS as an internal

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standard. The chemical shifts are expressed in δ ppm scale down field from TMS and proton signals are indicated as *s* = singlet, *d* = doublet, *t* = triplet and *m* = multiplet. EI 70 EV and AUTOSPEC electron Impact Mass spectrometer was used to record mass spectra. UV spectra were recorded on U-3310-UV-VIS spectrophotometer and fluorescence spectra were recorded on F-7000 Fluorescence spectrometer. The NOE difference spectra were measured with an Avance Bruker 500 MHz, in $CDCl_3$, against TMS, at 297 K. NOE difference spectra were measured, at concentration 0·01 M, using NOE mul sequence.

2.3 *Synthesis*

2.3a *Synthesis of substituted 4-bromomethyl-coumarins*: The required substituted 4-bromomethylcoumarins[10] **1 (a–g)** have been synthesized by the Pechmann cyclisation of various phenols with 4-bromoethylacetoacetate.[11]

2.3b *Synthesis of 2,6-dibromo-p-cresol* **(4)**[12]: The general procedure for the synthesis of coumarinyl ethers **3(a–g)**, **5(a–g)** and **7(a–g)** are as follows: A mixture of 4-methyl-2-nitro-phenol **2** (1·53 g, 10 mmol) and anhydrous potassium carbonate (1·38 g, 10 mmol) was stirred for 30 min in dry acetone (30 mL). To this, 4-bromomethylcoumarin **1a** (2·53 g, 10 mmol) was added and the stirring was continued for 24 h. Then, the resulting reaction mixture was poured to crushed ice. The separated solid was filtered and washed with 1 : 1 HCl (30 mL) and with water. Then product **3a** was recrystallised from suitable solvent.

Similar procedure was followed for the synthesis of **5(a–g)** and **7(a–g)** by the reaction of the **1(a–g)** with **4** and **6** respectively.

2.3c *6-Methyl-4-(4-methyl-2-nitro-phenoxymethyl)-2H-chromen-2-one* **(3a)**: Blue coloured solid (acetic acid), m.p. 267°C, yield 82%; IR (KBr, ν in cm^{-1}) 1714 (lactone C=O), 1528, 1345 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·40 (*s*, 3H, *p*-CH_3), 2·45 (*s*, 3H, C_6-CH_3), 5·35 (*s*, 2H, C_4-CH_2), 6·72 (*s*, 1H, C_3-H), 7·04–7·74 (*m*, 6H, Ar-H); LCMS *m/z:* 326 [M + 1]; Anal. calc. for $C_{18}H_{15}NO_5$; C, 66·46; H, 4·65; N, 4·31; Found: C, 66·48; H, 4·69; N, 4·36.

2.3d *7-Methyl-4-(4-methyl-2-nitro-phenoxymethyl)-2H-chromen-2-one* **(3b)**: Colourless solid (acetic acid), m.p. 247°C, yield 79%; IR (KBr, ν in cm^{-1}) 1701 (lactone C=O), 1532, 1342 (NO_2); ^{1}H NMR (300MHz, $CDCl_3$): δ 2·40 (*s*, 3H, *p*-CH_3), 2·53 (*s*, 3H, C_6-CH_3), 5·43 (*s*, 2H, C_4-CH_2), 6·91 (*s*, 1H, C_3-H), 7·10–7·81 (*m*, 6H, Ar-H); LCMS *m/z*: 326 [M + 1]; Anal. calc. for $C_{18}H_{15}NO_5$; C, 66·46; H, 4·65; N, 4·31; Found: C, 66·49; H, 4·68; N, 4·37.

2.3e *1-(4-Methyl-2-nitro-phenoxymethyl)-benzo[f] chromen-3-one* **(3c)**: Blue coloured solid (acetic acid), m.p. 261°C, yield 71%; IR (KBr, ν in cm^{-1}) 1716 (lactone C=O), 1531, 1343 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·43 (*s*, 3H, *p*-CH_3), 5·88 (*s*, 2H, C_4-CH_2), 7·34 (*s*, 1H, C_3-H), 7·11–8·18 (*m*, 9H, Ar-H); Anal. calc. for $C_{21}H_{15}NO_5$; C, 69·80; H, 4·18; N, 3·88; Found: C, 69·83; H, 4·22; N, 3·91.

2.3f *4-(4-Methyl-2-nitro-phenoxymethyl)-2H-benzo [h]chromen-2-one* **(3d)**: Green coloured solid (acetic acid), m.p. 266°C, yield 73%; IR (KBr, ν in cm^{-1}) 1705 (lactone C=O), 1533, 1345 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·41 (*s*, 3H, *p*-CH_3), 5·53 (*s*, 2H, C_4-CH_2), 7·14–8·59 (*m*, 10H, Ar-H); Anal. calc. for $C_{21}H_{15}NO_5$; C, 69·80; H, 4·18; N, 3·88; Found: C, 69·82; H, 4·24; N, 3·90.

2.3g *6-Methoxy-4-(4-methyl-2-nitro-henoxymethyl)-2H-chromen-2-one* **(3e)**: Blue coloured solid (acetic acid), m.p. 241°C, yield 76%; IR (KBr, ν in cm^{-1}) 1701 (lactone C=O), 1528, 1346 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·41 (*s*, 3H, *p*-CH_3), 3·95 (*s*, 3H, C_6-OCH_3), 5·41 (*s*, 2H, C_4-CH_2), 6·97 (*s*, 1H, C_3-H), 7·10–7·80 (*m*, 6H, Ar-H); Anal. calc. for $C_{18}H_{15}NO_6$; C, 63·34; H, 4·43; N, 4·05; Found: C, 63·36; H, 4·45; N, 4·09.

2.3h *6-Chloro-4-(4-methyl-2-nitro-phenoxymethyl)-2H-chromen-2-one* **(3f)**: Blue coloured solid (acetic acid), m.p. 256°C, yield 74%; IR (KBr, ν in cm^{-1}) 1715 (lactone C=O), 1528, 1343 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·42 (*s*, 3H, *p*-CH_3), 5·40 (*s*, 2H, C_4-CH_2), 7·04 (*s*, 1H, C_3-H), 7·12–7·68 (*m*, 5H, Ar-H), 7·84 (*s*, 1H, C_5-H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20·4, 66·1, 108·9, 112·6, 115·7 116·4, 119·5, 120·2, 123·6, 127·0, 133·5, 136·1, 149·2, 161·3, 161·9, 162·5; Anal. calc. for $C_{17}H_{12}ClNO_5$; C, 59·06; H, 3·50; N, 4·05; Found: C, 59·10; H, 3·57; N, 4·07.

2.3i *6-Bromo-4-(4-methyl-2-nitro-phenoxymethyl)-2H-chromen-2-one* **(3g)**: Blue coloured solid (acetic acid), m.p. 256°C, yield 72%; IR (KBr, ν in cm^{-1})

1731 (lactone C=O), 1533, 1340 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (*s*, 3H, *p*-CH_3), 5·40 (*s*, 2H, C_4-CH_2), 7·04–7·83 (*m*, 7H, Ar-H); Anal. calc. for $C_{17}H_{12}BrNO_5$; C, 52·33; H, 3·10; N, 3·59; Found: C, 52·37; H, 3·14; N, 3·62.

2.3j *6-Methyl-4-(2,6-dibromo-4-methyl-phenoxy-methyl)-2H-chromen-2-one* (**5a**): Colourless solid (ethylacetate), m.p. 212°C, yield 90%; IR (KBr, ν in cm^{-1}) 1731 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·34 (*s*, 3H, *p*-CH_3), 2·42 (*s*, 3H, C_6-CH_3), 5·18 (*s*, 2H, C_4-CH_2), 6·89 (*s*, 1H, C_3-H), 7·28–7·39 (*m*, 5H, Ar-H); LCMS *m/z*: 439 [M + 1]; Anal. calc. for $C_{18}H_{14}Br_2O_3$; C, 49·35; H, 3·22; Found: C, 49·40; H, 3·30.

2.3k *7-Methyl-4-(2,6-dibromo-4-methyl-phenoxy-methyl)-2H-chromen-2-one* (**5b**): Colourless solid (ethylacetate), m.p. 185°C, yield 92%; IR (KBr, ν in cm^{-1}) 1729 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 2·47 (*s*, 3H, C_6-CH_3), 5·17 (*s*, 2H, C_4-CH_2), 6·84 (*s*, 1H, C_3-H), 7·10 (*d*, 1H, J = 8·0 Hz, C_6-H), 7·21 (*s*, 1H, C_8-H), 7·39 (*s*, 2H, Ar-H) 7·47 (*d*, 1H, J = 8·0 Hz, C_5-H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20·7, 22·0, 70·0, 113·3, 115·3, 117·8, 118·0, 123·7, 125·8, 133·7, 138·0, 143·4, 149·9, 150·5, 154·1, 161·4; LCMS *m/z*: 439 [M + 1]; Anal. calc. for $C_{18}H_{14}Br_2O_3$; C, 49·35; H, 3·22; Found: C, 49·42; H, 3·33.

2.3l *1-(2,6-Dibromo-4-methyl-phenoxymethyl)-benzo[f]chromen-3-one* (**5c**): Colourless solid (ethylacetate), m.p. 236°C, yield 71%; IR (KBr, ν in cm^{-1}) 1727 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·36 (*s*, 3H, *p*-CH_3), 5·61 (*s*, 2H, C_4-CH_2), 7·24 (*s*, 1H, C_3-H), 7·42 (*s*, 2H, Ar-H), 7·53–8·09 (*m*, 6H, Ar-H); Anal. calc. for $C_{21}H_{14}Br_2O_3$; C, 53·20; H, 2·98; Found: C, 53·30; H, 3·05.

2.3m *4-(2,6-Dibromo-4-methyl-phenoxymethyl)-2H-benzo[h]chromen-2-one* (**5d**): Colourless solid (ethylacetate), m.p. 191°C, yield 74%; IR (KBr, ν in cm^{-1}) 1718 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·34 (*s*, 3H, *p*-CH_3), 5·29 (*s*, 2H, C_4-CH_2), 7·00 (*s*, 1H, C_3-H), 7·37–7·89 (*m*, 8H, Ar-H); Anal. calc. for $C_{21}H_{14}Br_2O_3$; C, 53·20; H, 2·98; Found: C, 53·32; H, 3·09.

2.3n *6-Methoxy-4-(2,6-Dibromo-4-methyl-phenoxy-methyl)-2H-chromen-2-one* (**5e**): Colourless solid (ethylacetate), m.p. 180°C, yield 85%; IR (KBr, ν in cm^{-1}) 1710 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·34 (*s*, 3H, *p*-CH_3), 3·86 (*s*, 3H, C_6-OCH_3), 5·14 (*s*, 2H, C_4-CH_2), 6·87 (*s*, 1H, C_3-H), 7·15–7·39 (*m*, 5H, Ar-H); Anal. calc. for $C_{18}H_{14}Br_2O_4$; C, 47·61; H, 3·11; Found: C, 47·71; H, 3·23.

2.3o *6-Chloro-4-(2,6-dibromo-4-methyl-phenoxy-methyl)-2H-chromen-2-one* (**5f**): Colourless solid (ethylacetate), m.p. 218°C, yield 81%; IR (KBr, ν in cm^{-1}) 1755 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·34 (*s*, 3H, *p*-CH_3), 5·14 (*s*, 2H, C_4-CH_2), 6·92 (*s*, 1H, C_3-H), 7·33–7·65 (*m*, 5H, Ar-H); Anal. calc. for $C_{17}H_{11}Br_2ClO_3$; C, 44·53; H, 2·42; Found: C, 44·56; H, 2·46.

2.3p *6-Bromo-4-(2,6-dibromo-4-methyl-phenoxy-methyl)-2H-chromen-2-one* (**5g**): Colourless solid (ethylacetate), m.p. 221°C, yield 78%; IR (KBr, ν in cm^{-1}) 1755 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 5·13 (*s*, 2H, C_4-CH_2), 6·90 (*s*, 1H, C_3-H), 7·27–7·80 (*m*, 5H, Ar-H); Anal. calc. for $C_{17}H_{11}Br_3O_3$; C, 40·59; H, 2·20; Found: C, 40·70; H, 2·28.

2.3q *6-Methyl-4-p-tolyloxymethyl-2H-chromen-2-one* (**7a**): Colourless solid (ethanol + ethylacetate), m.p. 180°C, yield 87%; IR (KBr, ν in cm^{-1}) 1718 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 2·45 (*s*, 3H, C_6-CH_3), 5·21 (*s*, 2H, C_4-CH_2), 6·67 (*s*, 1H, C_3-H), 6·90 (*d*, 2H, J = 8·4 Hz, Ar-H), 7·13 (*d*, 2H, J = 8·3 Hz, Ar-H), 7·31–7·40 (*m*, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20·8, 21·4, 66·1, 113·9, 115·1, 117·4, 117·5, 123·6, 130·5, 131·7, 133·3, 134·4, 150·4, 152·2, 156·0, 161·2, 182·0; LCMS *m/z*: 281 [M + 1]; Anal. calc. for $C_{18}H_{16}O_3$; C, 77·12; H, 5·75; Found: C, 77·16; H, 5·78.

2.3r *7-Methyl-4-p-tolyloxymethyl-2H-chromen-2-one* (**7b**): Colourless solid (ethanol + ethylacetate), m.p. 142°C, yield 85%; IR (KBr, ν in cm^{-1}) 1713 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·32 (*s*, 3H, *p*-CH_3), 2·48 (*s*, 3H, C_6-CH_3), 5·20 (*s*, 2H, C_4-CH_2), 6·62 (*s*, 1H, C_3-H), 6·89 (*d*, 2H, J = 8·1 Hz, Ar-H), 7·12 (*d*, 2H, J = 8·0 Hz, Ar-H), 7·20 (*s*, 1H, C_8-H), 7·28–7·49 (*m*, 2H, Ar-H); LCMS *m/z*: 281 [M + 1]; Anal. calc. for $C_{18}H_{16}O_3$; C, 77·12; H, 5·75; Found: C, 77·18; H, 5·77.

2.3s *1-(4-Tolyloxymethyl)-benzo[f]chromen-3-one* (**7c**): Golden yellow Coloured solid, (ethanol +

ethylacetate), m.p. 146°C, yield 89%; IR (KBr, ν in cm^{-1}) 1722 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 5·57 (*s*, 2H, C_4-CH_2), 6·91 (*m*, 3H, C_3-H and Ar-H), 7·14 (*d*, 2H, J = 8·3 Hz, Ar-H), 7·51–8·18 (*m*, 6H, Ar-H); Anal. calc. for $C_{21}H_{16}O_3$; C, 79·73; H, 5·10; Found: C, 79·78; H, 5·14.

2.3t *4-p-Tolyloxymethyl-2H-benzo[h]chromen-2-one* (**7d**): Colourless solid (ethanol + ethylacetate), m.p. 190°C, yield 84%; IR (KBr, ν in cm^{-1}) 1717 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 5·32 (*s*, 2H, C_4-CH_2), 6·78 (*s*, 1H, C_3-H), 6·93 (*d*, 2H, J = 8·3 Hz, Ar-H), 7·14 (*d*, 2H, J = 8·0 Hz, Ar-H), 7·58–8·62 (*m*, 6H, Ar-H); Anal. calc. for $C_{21}H_{16}O_3$; C, 79·73; H, 5·10; Found: C, 79·76; H, 5·15.

2.3u *6-Methoxy-4-p-tolyloxymethyl-2H-chromen-2-one* (**7e**): Colourless solid (ethanol + ethylacetate), m.p. 150°C, yield 91%; IR (KBr, ν in cm^{-1}) 1707 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 3·87 (*s*, 3H, C_6-OCH_3), 5·19 (*s*, 2H, C_4-CH_2), 6·68 (*s*, 1H, C_3-H), 6·89–7·35 (*m*, 7H, Ar-H); Anal. calc. for $C_{18}H_{16}O_4$; C, 72·96; H, 5·44; Found: C, 73·02; H, 5·47.

2.3v *6-Chloro-4-p-tolyloxymethyl-2H-chromen-2-one* (**7f**): Colourless solid (ethanol + ethylacetate), m.p. 180°C, yield 87%; IR (KBr, ν in cm^{-1}) 1718 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 5·17 (*s*, 2H, C_4-CH_2), 6·73 (*s*, 1H, C_3-H), 6·90 (*d*, 2H, J = 8·5 Hz, Ar-H), 7·14 (*d*, 2H, J = 8·4 Hz, Ar-H), 7·33–7·59 (*m*, 3H, Ar-H); Anal. calc. for $C_{17}H_{13}ClO_3$; C, 67·89; H, 4·36; Found: C, 67·97; H, 4·40.

2.3w *6-Bromo-4-p-tolyloxymethyl-2H-chromen-2-one* (**7g**): Colourless solid (ethanol + ethylacetate), m.p. 173°C, yield 79%; IR (KBr, ν in cm^{-1}) 1713 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 5·17 (*s*, 2H, C_4-CH_2), 6·72 (*s*, 1H, C_3-H), 6·90 (*d*, 2H, J = 6·3 Hz, Ar-H), 7·14 (*d*, 2H, J = 8·5 Hz, Ar-H), 7·28–7·73 (*m*, 3H, Ar-H); Anal. calc. for $C_{17}H_{13}BrO_3$; C, 59·15; H, 3·80; Found: C, 59·28; H, 3·84.

2.4 *Bromination of* **7(a–g)***: General procedure*

Compound **7a** (2·80 g, 10 mmol) was dissolved in 25 mL of chloroform or acetic acid, and to this bromine (0·52 mL, 10 mmol) in 25 mL of chloroform or acetic acid was added with stirring, and stirring was continued for 6 h (reaction was monitored by TLC), the solid separated **10a** was filtered, dried, and recrystallised from suitable solvent.

2.4a *6-Methyl-4-(2-bromo-4-methyl-phenoxymethyl)-2H-chromen-2-one* (**10a**): Colourless solid (ethylacetate), m.p. 228°C, yield 80%; IR (KBr, ν in cm^{-1}) 1716 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·31 (*s*, 3H, *p*-CH_3), 2·45 (*s*, 3H, C_6-CH_3), 5·26 (*s*, 2H, C_4-CH_2), 6·80 (*s*, 1H, C_3-H), 6·87 (*d*, 1H, J = 8·2 Hz, Ar-H), 7·07 (*d*, 1H, J = 8·1 Hz, Ar-H), 7·31 (*s*, 1H, Ar-H), 7·34–7·43 (*m*, 3H, Ar-H); LCMS *m/z*: 361 [M + 2]; Anal. calc. for $C_{18}H_{15}BrO_3$; C, 60·18; H, 4·21; Found: C, 60·21; H, 4·25.

2.4b *7-Methyl-4-(2-bromo-4-methyl-phenoxymethyl)-2H-chromen-2-one* (**10b**): Colourless solid (ethylacetate), m.p. 196°C, yield 73%; IR (KBr, ν in cm^{-1}) 1712 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·31 (*s*, 3H, *p*-CH_3), 2·48 (*s*, 3H, C_7-CH_3), 5·25 (*s*, 2H, C_4-CH_2), 6·75 (*s*, 1H, C_3-H), 6·85 (*d*, 1H, J = 8·3 Hz, Ar-H), 7·07 (*d*, 1H, J = 8·2 Hz, Ar-H), 7·13 (*d*, 1H, J = 8·3 Hz, C_6-H), 7·21 (*s*, 1H, Ar-H), 7·43 (*s*, 1H, C_8-H), 7·47 (*d*, 1H, J = 8·1 Hz, C_5-H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20·6, 22·0, 66·2, 113·1, 114·1, 115·1, 117·9, 123·4, 125·9, 129·3, 133·5, 134·6, 149·8, 151·2, 156·2, 160·92, 181·2; LCMS *m/z*: 361 [M + 2]; Anal. calc. for $C_{18}H_{15}BrO_3$; C, 60·18; H, 4·21; Found: C, 60·21; H, 4·25.

2.4c *1-(2-Bromo-4-methyl-phenoxymethyl)-benzo[f]chromen-3-one* (**10c**): Colourless solid (ethylacetate), m.p. 206°C, yield 71%; IR (KBr, ν in cm^{-1}) 1718 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·33 (*s*, 3H, *p*-CH_3), 5·32 (*s*, 2H, C_4-CH_2), 6·93 (*m*, 2H, C_3-H and Ar-H), 7·19 (*d*, 1H, J = 7·2 Hz, Ar-H), 7·48 (*s*, 1H, Ar-H), 7·77–8·68 (*m*, 6H, Ar-H); Anal. calc. for $C_{21}H_{15}BrO_3$; C, 63·81; H, 3·83; Found: C, 63·84; H, 3·85.

2.4d *4-(2-Bromo-4-methyl-phenoxymethyl)-2H-benzo[h]chromen-2-one* (**10d**): Colourless solid (ethylacetate), m.p. 234°C, yield 76%; IR (KBr, ν in cm^{-1}) 1714 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·31 (*s*, 3H, *p*-CH_3), 5·33 (*s*, 2H, C_4-CH_2), 6·94 (*m*, 2H, C_3-H and Ar-H), 7·11 (*d*, 1H, J = 7·2 Hz, Ar-H), 7·45 (*s*, 1H, Ar-H), 7·74–8·65 (*m*,

6H, Ar-H); Anal. calc. for $C_{21}H_{15}BrO_3$; C, 63·81; H, 3·83; Found: C, 63·86; H, 3·86.

2.4e *6-Methoxy-4-(2-bromo-4-methyl-phenoxy-methyl)-2H-chromen-2-one* (**10e**): Colourless solid (ethylacetate), m.p. 201°C, yield 69%; IR (KBr, ν in cm^{-1}) 1706 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·31 (*s*, 3H, *p*-CH_3), 3·88 (*s*, 3H, C_6-OCH_3), 5·24 (*s*, 2H, C_4-CH_2), 6·80 (*s*, 1H, C_3-H), 6·86 (*d*, 1H, J = 8·3 Hz, Ar-H), 7·05–7·35 (*m*, 4H, Ar-H), 7·43 (*s*, 1H, C_5-H); LCMS *m/z*: 377 [M + 2]; Anal. calc. for $C_{18}H_{15}BrO_4$; C, 57·62; H, 4·03; Found: C, 57·67; H, 4·08.

2.4f *6-Chloro-4-(2-bromo-4-methyl-phenoxy-methyl)-2H-chromen-2-one* (**10f**): Colourless solid (ethanol + ethylacetate), m.p. 202°C, yield 76%; IR (KBr, ν in cm^{-1}) 1713 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·31 (*s*, 3H, *p*-CH_3), 5·36 (*s*, 2H, C_4-CH_2), 6·81 (*s*, 1H, C_3-H), 6·93 (*d*, 1H, J = 8·1 Hz, Ar-H), 7·12–7·38 (*m*, 4H, Ar-H), 7·48 (*s*, 1H, C_5-H); Anal. calc. for $C_{17}H_{12}BrClO_3$; C, 53·78; H, 3·19; Found: C, 53·83; H, 3·27.

2.4g *6-Bromo-4-(2-bromo-4-methyl-phenoxymethyll)-2H-chromen-2-one* (**10g**): Colourless solid (ethanol + ethylacetate), m.p. 189°C, yield 72%; IR (KBr, ν in cm^{-1}) 1709 (lactone C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2·36 (*s*, 3H, *p*-CH_3), 5·22 (*s*, 2H, C_4-CH_2), 6·79 (*s*, 1H, C_3-H), 6·96 (*d*, 1H, J = 8·2 Hz, Ar-H), 7·30–7·76 (*m*, 4H, Ar-H), 7·51 (*s*, 1H, C_5-H); Anal. calc. for $C_{17}H_{12}Br_2O_3$; C, 48·15; H, 2·85; Found: C, 48·19; H, 2·94.

2.5 *Nitration of* **7(a–b)***: General procedure*

Compound **7a** (2·80 g, 10 mmol) was taken in 5 mL of concentrated sulfuric acid and cooled to 0°C. To this, 6 mL of cold nitrating mixture (2 mL of conc. HNO_3 and 4 mL of conc. H_2SO_4) was added dropwise with stirring. Then resultant reaction mixture was poured to crushed ice and separated reddish brown colored solid **11a** was filtered, washed with cold water, dried and recrystallised from ethanol.

2.5a *4-Hydroxymethyl-6-methyl-5,8-dinitro-2H-chromen-2-one* (**11a**): Yellow Coloured solid (ethanol), m.p. 160°C, yield 80%; IR (KBr, ν in cm^{-1}): 3492 (–OH), 1738 (lactone C=O), 1540, 1345 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2·49 (*s*, 3H, C_6-CH_3), 4·80 (*s*, 2H, C_4-CH_2), 5·67 (*s*, 1H, OH, D_2O exchangeable), 6·65 (*s*, 1H, C_3-H), 8·52 (*s*, 1H, C_7-H); LCMS *m/z*: 279 [M–1]; Anal. calc. for $C_{11}H_8N_2O_7$; C, 47·15; H, 2·88, N, 10·00; Found: C, 47·18; H, 2·91, N, 10·07.

2.5b *4-Hydroxymethyl-6-methoxy-5,8-dinitro-2H-chromen-2-one* (**11b**): Yellow colourered solid (ethanol), m.p. 150°C, yield 74%; IR (KBr, ν in cm^{-1}) 3474 (–OH), 1739 (lactone C=O), 1537, 1343 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3·50 (*s*, 1H, –OH, D_2O exchangeable), 3·90 (*s*, 3H, C_6-OCH_3), 4·43 (*s*, 2H, C_4-CH_2), 6·89 (*s*, 1H, C_3-H), 8·47 (*s*, 1H, C_7-H); Anal. calc. for $C_{11}H_8N_2O_8$; C, 44·61; H, 2·72, N, 9·46; Found: C, 44·68; H, 2·76, N, 10·02.

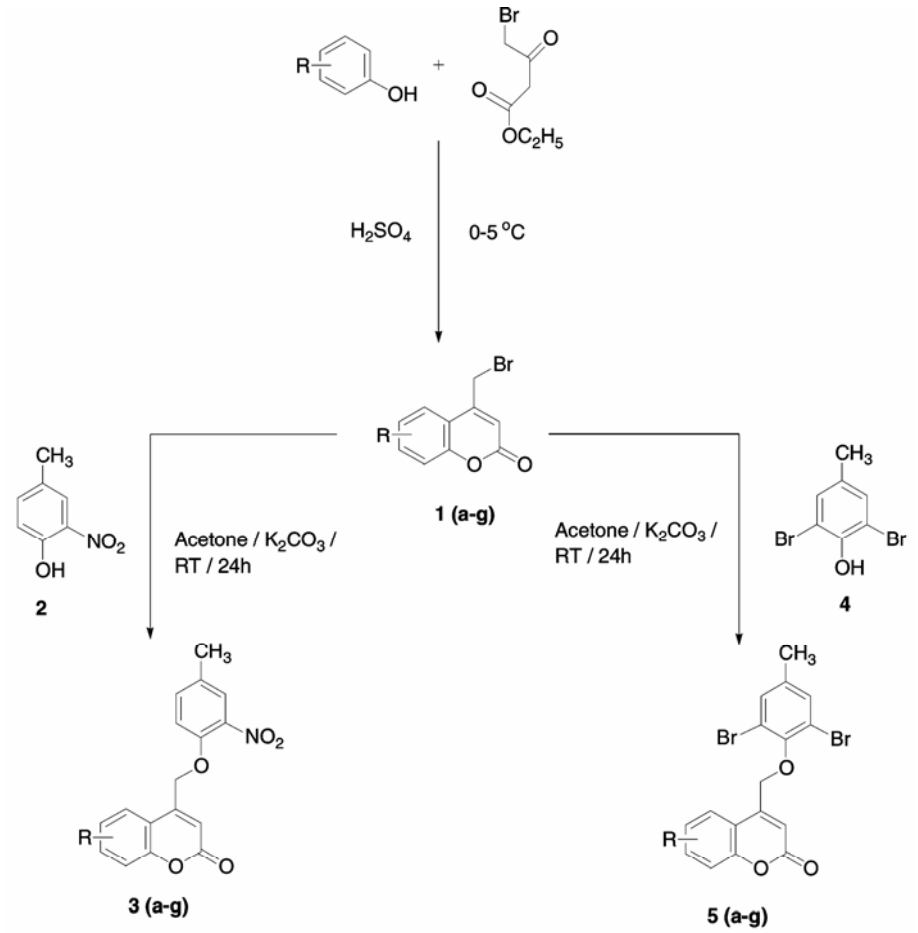
3. Results and discussion

3.1 *Synthesis*

The required 4-bromomethylcoumarins **1** were prepared by the Pechmann cyclisation of substituted phenols with 4-bromoethylacetoacetate using sulphuric acid as the condensing agent. 2-nitro-*p*-cresol **2** and 2,6-dibromo-*p*-cresol **4** were used during the present work and the ethers **3** and **5** respectively were obtained under standard acetone-potassium carbonate conditions at room temperature (scheme 1). Formation of ethers was indicated by the difference in ^{1}H-NMR. The methylene protons in 4-bromomethylcoumarins resonated at 4·6 ppm where as the corresponding 4-aryloxymethylcoumarins exhibited this peak around 5·2 ppm.

The IR spectrum of 6-methyl-4-(4-methyl-2-nitrophenoxymethyl)-2*H*-chromen-2-one (**3a**) (R=6-CH_3) showed lactone carbonyl at 1714 cm^{-1}. The ^{1}H-NMR spectrum exhibited singlets at 2·40, 2·45, 5·35 and 6·72 δ ppm due to *p*-CH_3, C_6-CH_3, C_4-CH_2 and C_3-H respectively. The aromatic protons resonated as multiplet in the range of 7·04–7·74 δ ppm. This is further confirmed by its mass spectrum that shows the molecular ion peak *m/z* 326 (M + 1) which agrees with the molecular weight of the compound.

The IR spectrum of 6-Methyl-4-(2,6-dibromo-4-methyl-phenoxymethyl)-2*H*-chromen-2-one (**5a**) (R=6-CH_3) exhibited lactone carbonyl at 1731 cm^{-1}. The ^{1}H-NMR spectrum showed singlets at 2·34, 2·42, 5·18 and 6·89 δ ppm due to *p*-CH_3, C_6-CH_3, C_4-CH_2 and C_3-H respectively. The remaining protons resonated as a multiplet in the range of 7·28–7·39 δ ppm. The LCMS of the compound showed a



Scheme 1. Synthesis of 4-Aryloxymethylcoumarins **3** and **5**.

peak at *m/z* 439 (M + 1) confirming its molecular weight.

The IR spectrum of 6-methyl-4-p-tolyloxymethyl-2*H*-chromen-2-one (**7a**)[13] (R=6-CH_3) exhibited lactone carbonyl at 1718 cm^{-1}. The ^{1}H-NMR spectrum showed singlets at 2·33, 2·45, 5·21 and 6·67 δ ppm due to *p*-CH_3, C_6-CH_3, C_4-CH_2 and C_3-H respectively. The remaining aromatic protons resonated as a multiplet in the range of 6·97–7·40 δ ppm. The LCMS of compound showed a peak at *m/z* 281 (M + 1) confirming its molecular weight.

3.2 *NOE studies*

Unambiguous assignments of methyl and aromatic protons in 4-aryloxymethylcoumarins are difficult in view of the close chemical shift values. The *peri* relationship between H_5 and CH_2 proton and the difference in multiplicity of the *ortho* protons related to the CH_3 groups have been used to account for all the proton chemical shifts. NOE has also revealed spatial proximity between the CH_2 and the *ortho* protons in the phenoxy moiety.

NOE studies have been carried out on two compounds **3b** and **5a**. The CH_2, two CH_3 groups, aromatic protons were saturated and relative enhancements are listed in tables 1 and 2.

In the nitro cresol ether **3b** (figure 1), saturation of $C_{4'}$-CH_3 at 2·37 δ ppm resulted strong enhancement of two signals H (3′) (7·71, *s*; 18·45%) and H (5′) (7·35, *d*, *J* = 8·5 Hz; 22·74%). Saturation of C_7-CH_3 at 2·46 δ ppm resulted a strong enhancement of 32·02% corresponding to two signals H (6) (7·13, *d*, *J* = 8·0 Hz) and H (8) (7·18, *s*). Saturation of CH_2 at 5·31 δ ppm resulted significant enhancement of three signals H (3) (6·65, *s*; 21·81%), H (5) (7·46, *d*, *J* = 8·0 Hz; 23·28%) and H (6′) (7·02, *d*, *J* = 8·5 Hz; 20·48%), and similarly saturation of aromatic protons resulted a weak enhancement of two signals, one signal of 9·84% corresponding to two methyl

Table 1. Results of NOE difference spectra of the compound **3b**.

^{1}H-NMR	$C_{4'}$–CH_3 2.37 (s)	$C_{7'}$–CH_3 2.46 (s)	CH_2 5·31 (s)	H_3 6.65 (s)	H_5 7·46 (*d*, *J* = 8·0 Hz)	H_6 7·13 (*d*, *J* = 8·0 Hz)	H_8 7·18 (*s*)	$H_{3'}$ 7·71 (s)	$H_{5'}$ 7·35 (*d*, *J* = 8·5 Hz)	$H_{6'}$ 7·02 (*d*, *J* = 8·5 Hz)
Irradiate (2·37) $C_{4'}$–CH_3	*	–	–	–	–	–	–	18·45%	22·74%	–
Irradiate $C_{7'}$–CH_3 (2·46)	–	*	–	–	–	32·02%	–	–	–	
Irradiate CH_2 (5·31)	–	–	*	21·81%	23·28%	–	–	–	–	20·48%
Irradiate Ar-H and C_3-H (6·65–7·71)	9·84%		5·62%	*	*	*	*	*	*	*

*Saturated or irradiated; –, No enhancement

Table 2. Results of NOE difference spectra of the compound **5a**.

^{1}H-NMR	$C_{4'}$–CH_3 2·34 (s)	C_6–CH_3 2·42 (s)	CH_2 5·16 (s)	H_3 6·87 (s)	H_5 7·37 (s)	H_7 7·27 (*d*, *J* = 8·5 Hz)	H_8 7·35 (*d*, *J* = 8·5 Hz)	$H_{3'}$ and $H_{5'}$ 7·26 (*s*)
Irradiate $C_{4'}$–CH_3 (2·34)	*	–	–	–	–	–	–	32·13%
Irradiate C_6–CH_3 (2·42)	–	*	–	–	31·46%	–	–	– –
Irradiate CH_2 (5·16)	–	–	*	35·59%	34·18%		–	– –
Irradiate Ar-H and C_3-H (6·87–7·37)	31·45%		25·20%	*	*	*	*	* *

*Saturated or irradiated; –, No enhancement

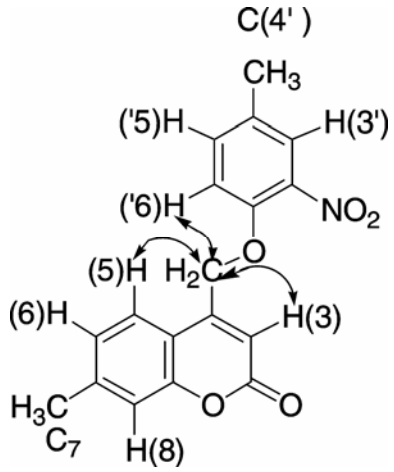


Figure 1. NOE correlation of compound **3b**.

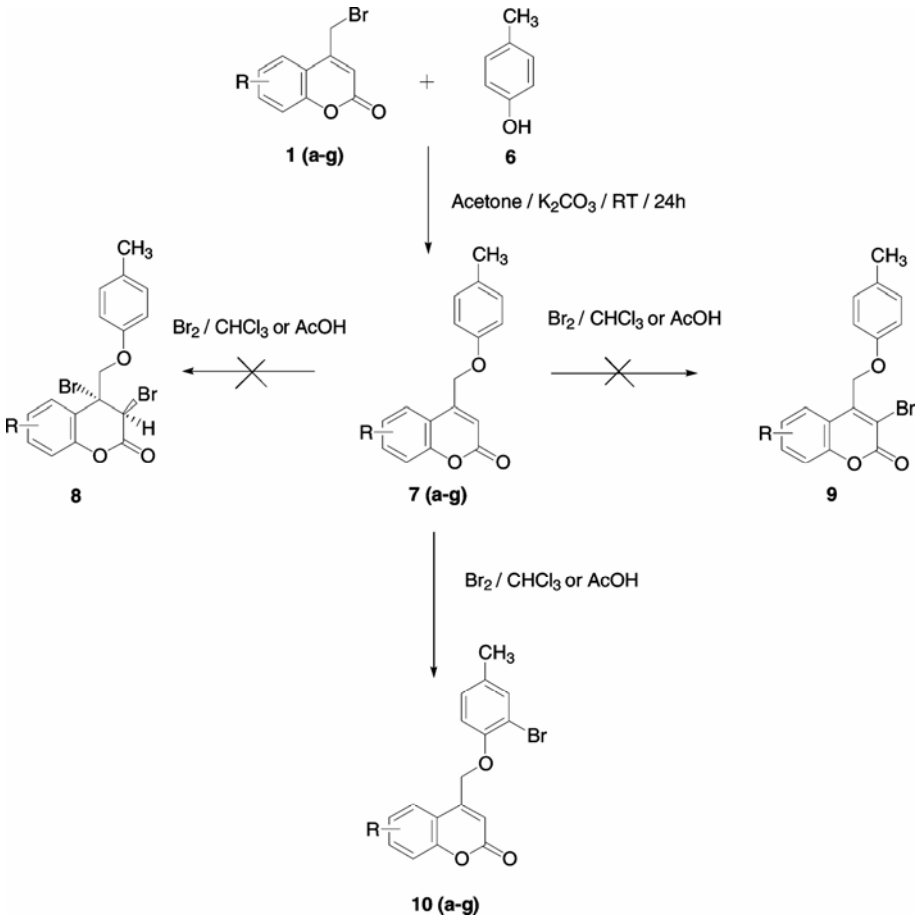
protons ($C_{4'}$-CH_3, C_7-CH_3) and one more signal of 5·62% corresponding to C_4-CH_2 (table 1).

In the dibromo-*p*-cresol ether **5a** (figure 2), saturation of $C_{4'}$-CH_3 at 2·34 δ ppm resulted a strong enhancement of 32·13% corresponding to two signals H (3′) and H (5′) (7·26, *s*). Saturation of C_6-CH_3 at 2·42 δ ppm resulted a strong enhancement of 31·46% corresponding to two signals H (5) (7·37, *s*) and H (7) (7·27, *d*, *J* = 8·5 Hz). Saturation of CH_2 at 5·16 δ ppm resulted strong enhancement of two signals H (3) (6·87, *s*; 35·59%) and H (5) (7·37, *s*; 34·18%) and similarly saturation of aromatic protons resulted in enhancement of two signals, one signal of 31·45% corresponding to two methyl protons ($C_{4'}$-CH_3, C_6-CH_3) and one more signal of 25·20% corresponding to C_4-CH_2 (table 2).

3.3 *Electrophilic substitution*

With a view to compare the reactivity of the phenoxy moiety and the coumarin ring, bromination was attempted on ethers **7** derived from *p*-cresol and 4-bromomethylcoumarins (scheme 2). The reaction in principle can result in addition across the C_3–C_4 double bond or substitution at C-3 position. It can also occupy at C-6 position or enter the phenoxy moiety.

The product obtained upon bromination showed the presence of C_3-H in the ^{1}H-NMR spectrum and no change in the IR carbonyl group of the lactone, hence addition across the C_3–C_4 double bond (**8**) and



Scheme 2. Bromination of 4-Aryloxymethylcoumarins **7**.

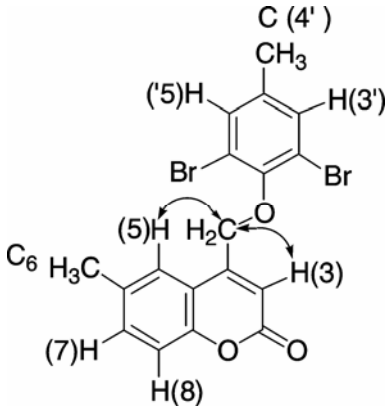


Figure 2. NOE correlation of compound **5a**.

substitution at C-3 (**9**) were ruled out. The mass spectrum of **10b** correspond to a mono brominated compound, the position of which was confirmed by diffraction studies.

Nitration of *p*-cresol ethers **7** using excess of nitrating mixture under ice-cold conditions and aqueous work-up, resulted in the formation of yellow crystalline solids. The ^{1}H-NMR of these compounds showed the absence of one methyl group and lesser number of aromatic protons, which indicated cleavage of the ether linkage.[14]

The ^{1}H-NMR of the ether **7a** shows two CH_3 groups at 2·33 and 2·45 δ ppm whereas its corresponding nitrated product shows the absence of one CH_3 group. The two singlets observed at 6·65 (6·44) and 8·52 (8·44) correspond to C_3-H and C_7-H respectively, which agrees with the predicted values given in parenthesis.

Nitration at C-8 is expected based on the reactivity pattern of coumarin whereas C-5 is activated because of the electron donating groups at C-6. The products **11a** and **11b** correspond to 6-substituted-5,8-dinitro-4-hydroxymethyl-*2H*-chromen-2-one (scheme 3), which is supported by the mass spectral data.

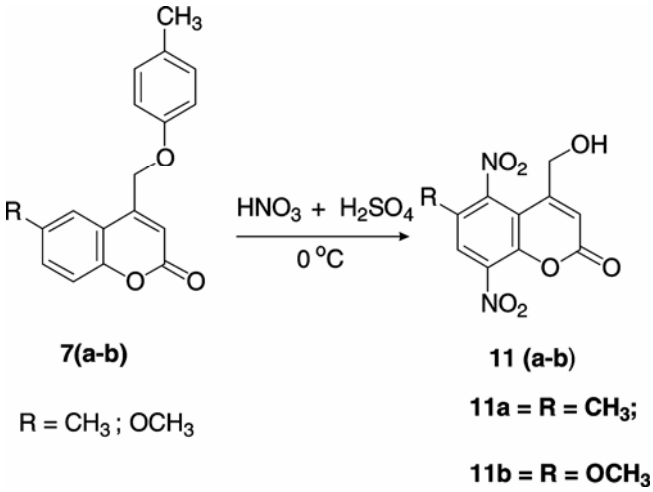
3.4 *Diffraction studies*

In order to ascertain the position of bromine formed during the bromination of ethers 7, one of the com-

pounds was subjected to X-ray studies. Crystals suitable for diffraction studies were grown by slow evaporation technique using ethyl acetate as the solvent. The ORTEP diagram is shown in figure 3. The structure unambiguously shows that the bromination occurs at *ortho* position with respect to the ether linkage which is also expected based on the inductive effects (CCDC-695895).

3.5 *UV and fluorescence studies*

The UV and fluorescence properties of the synthesized compounds **3 (a–g)**, **5 (a–g)** and **7 (a–g)** were studied in chloroform. In the UV spectra, these exhibited three bands in the regions 234–246, 266–280 and 315–355 nm, which are characteristics of 4-aryloxymethyl coumarins. Introduction of bromo and nitro groups in the phenoxy moiety has not caused any significant changes in the position and intensities of the bands. In the fluorescence spectra, all the compounds showed a single band in the region of 389–443 nm, methyl compound **(7b)** exhibits less fluorescent with 389 nm, whereas benzo **(3d)** and methoxy **(3e)** compounds more fluorescent with 443 nm each. All the compounds exhibit a Stokes shift in the range of 68–121 nm. Among these, minimum (68 nm) and maximum (121 nm) Stoke shifts were observed for benzo **(5c)** and methoxy **(5e)** compounds respectively. In general, the maximum Stokes shift has been observed with methoxy, chloro and bromo substituents at C-6 position.



Scheme 3. Nitration of 4-Aryloxymethylcoumarins **7** (**a**, **e**).

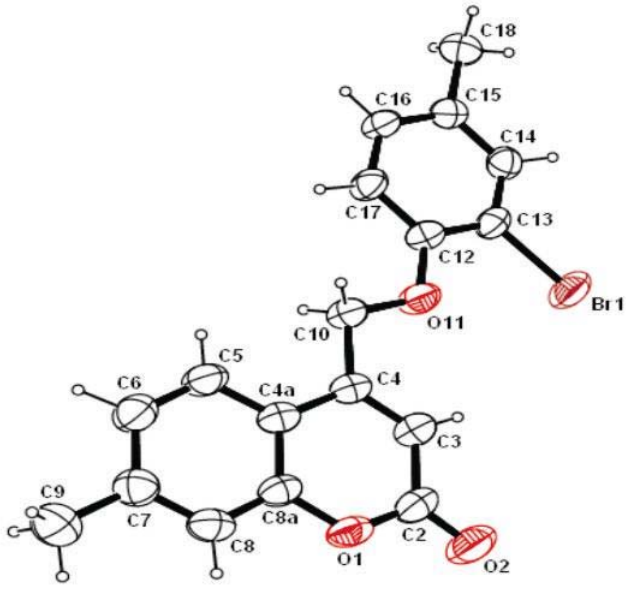


Figure 3. ORTEP diagram of compound **10b**.

3.6 *Antimicrobial studies*

All the newly synthesized compounds **3(a–g)**, **5(a–g)** and **7(a–g)** were screened for their antibacterial and antifungal activity at different concentrations of 500, 250, 100 and 50 μg/disc by the disc diffusion method.[15] The minimum inhibitory concentration (MIC) were determined by serial dilution method.

Antibacterial activity was carried out against three Gram-negative bacteria, viz. *Escherichia coli*, *Psuedomonus aeruginosa, Klebsiella pneumoniae*, and two Gram-positive bacteria, viz. *Staphylococcus aureus,* and *Streptococcus faecalis.* Ciprofloxacin was used as standard.

Antifungal activity was carried out against five fungi, viz. *Aspergilus flavus*, *Aspergilus fumigatus*, *Candida albicans*, *Penicillium notatum* and *Rhizopus.* Fluconazole was used as standard.

The investigation of antibacterial screening data (table 3) revealed that all the tested compounds showed moderate to good bacterial inhibition. Compounds **7f** and **7g** were found to be very active against *E. coli*. The benzo compound **(7d)** is highly active against *P. aeruginosa*, whereas the compounds **3e**, **3f**, **7b** and **7g** are more active against *K. pneumoniae*. Compounds with methyl groups **(5b)** and **(7a)** exhibited high activity against *S. aureus*. For *S. faecalis*, **7f** was equipotent compared to standard drug Ciprofloxacin. In general, the compounds possessing methoxy **(e)**, chloro **(f)**, bromo **(g)** substituents at C6-position of coumarin showed higher activity compared to the remaining against both Gram-positive and Gram-negative bacteria.

Table 3. Results of antibacterial activity of the compounds **3** (**a–g**), **5** (**a–g**) and **7** (**a–g**) at concentration of 50 μg/disc.

Compound	Diameter of the zone of inhibition in mm (relative inhibition %)				
	E. coli	*P. aeruginosa*	*K. pneumoniae*	*S. aureus*	*S. faecalis*
3a	8 (44·4)	12 (48)	11 (55)	9 (47·3)	15 (75)
3b	10 (55·6)	16 (64)	12 (60)	12 (63·1)	12 (60)
3c	9 (50)	12 (48)	12 (60)	9 (47·3)	11 (55)
3d	7 (38·9)	12 (48)	12 (60)	8 (42·1)	12 (60)
3e	10 (55·6)	16 (64)	18 (90)	11 (57·9)	12 (60)
3f	9 (50)	12 (48)	17 (85)	10 (52·6)	10 (50)
3g	12 (66·7)	18 (72)	14 (70)	14 (73·7)	12 (60)
5a	9 (50)	12 (48)	11 (55)	10 (52·6)	10 (50)
5b	11 (61·1)	12 (48)	13 (65)	17 (89·5)	13 (65)
5c	8 (44·4)	9 (36)	10 (50)	10 (52·6)	12 (60)
5d	11 (61·1)	10 (40)	14 (70)	15 (78·9)	16 (80)
5e	9 (50)	10 (40)	9 (45)	15 (78·9)	13 (65)
5f	12 (66·7)	16 (64)	16 (80)	11 (57·9)	14 (70)
5g	10 (55·6)	16 (64)	14 (70)	9 (47·3)	15 (75)
7a	9 (50)	18 (72)	16 (80)	16 (84·2)	13 (65)
7b	13 (72·2)	14 (56)	18 (90)	12 (63·1)	12 (60)
7c	11 (61·1)	16 (64)	12 (60)	9 (47·3)	13 (65)
7d	10 (55·6)	20 (80)	14 (70)	9 (47·3)	13 (65)
7e	13 (72·2)	12 (48)	14 (70)	10 (52·6)	15 (75)
7f	14 (77·8)	15 (60)	16 (80)	12 (63·1)	20 (100)
7g	14 (83·3)	15 (60)	18 (90)	13 (68·4)	12 (60)
Ciprofloxacin 10 μg/disc	18 (100)	25 (100)	20 (100)	19 (100)	20 (100)

Table 4. Results of antifungal activity of the compounds **3** (**a–g**), **5** (**a–g**) and **7** (**a–g**) at concentration of 50 μg/disc.

Compound	Diameter of the zone of inhibition in mm at concentration of 50 μg/disc (relative inhibition %)				
	A. flavus	*A. fumigatus*	*C. albicans*	*P. notatum*	*Rhizopus*
3a	12 (40)	16 (66·7)	13 (54·1)	14 (53·8)	18 (69·2)
3b	30 (100)	24 (100)	12 (50)	12 (46·1)	14 (53·8)
3c	16 (53·3)	16 (66·7)	13 (54·1)	20 (76·9)	26 (100)
3d	20 (66·7)	24 (100)	13 (54·1)	12 (46·1)	14 (53·8)
3e	28 (93·3)	22 (91·7)	11 (45·8)	12 (46·1)	13 (50)
3f	20 (66·7)	24 (100)	11 (45·8)	12 (46·1)	14 (53·8)
3g	14 (46·7)	20 (83·3)	12 (50)	14 (53·8)	18 (69·2)
5a	11 (36·7)	12 (50)	10 (41·7)	9 (34·6)	22 (84·6)
5b	10 (33·3)	18 (75)	8 (33·3)	24 (92·3)	14 (53·8)
5c	20 (66·7)	20 (83·3)	14 (58·3)	26 (100)	16 (61·5)
5d	17 (56·7)	24 (100)	18 (75)	23 (88·5)	22 (84·6)
5e	11 (36·7)	12 (50)	16 (66·7)	22 (84·6)	24 (92·3)
5f	13 (43·3)	18 (75)	14 (58·3)	16 (61·5)	22 (84·6)
5g	12 (40)	24 (100)	14 (58·3)	16 (61·5)	20 (76·9)
7a	9 (30)	18 (75)	8 (33·3)	14 (53·8)	14 (53·8)
7b	26 (86·7)	22 (91·7)	16 (66·7)	14 (53·8)	18 (69·2)
7c	12 (40)	24 (100)	11 (45·8)	10 (38·5)	12 (46·1)
7d	9 (30)	20 (83·3)	24 (100)	18 (69·2)	12 (46·1)
7e	10 (33·3)	8 (33·3)	10 (41·7)	12 (46·1)	20 (76·9)
7f	12 (10)	16 (66·7)	12 (50)	9 (34·6)	24 (92·3)
7g	11 (36·7)	14 (58·3)	12 (50)	23 (88·5)	20 (76·9)
Fluconazole 30 μg/disc	30 (100)	24 (100)	24 (100)	26 (100)	26 (100)

Similarly, the screening data of antifungal activity revealed that all the tested compounds showed moderate to good fungicidal activity. Compounds **3b**, **3e** and **7b** were more active against *A. flavus*, among these **3b** was equipotent compared to standard drug. Compounds **3b**, **3d**, **3f**, **5d**, **5g** and **7c** were equipotent to standard drug against *A. fumigatus*. The benzo compound **(7d)** was equipotent compared to standard drug against *C. albicans* whereas for *P. notatum*, **5b** and **5c** were more active, among these **5c** was equipotent compared to standard drug. Compounds **3c**, **5e** and **7f** were more active against *Rhizopus*. In general, the compounds with 5,6-benzo **(c)** and 7,8-benzocoumarins **(d)** have shown equipotent activities compared to standard drug Fluconazole. The results of investigated compounds are summarized in table 4.

4. Conclusion

In conclusion, we have generated a number of nitro and dibromo-4-aryloxymethylcoumarins, the former possessing promising antifungal activity. We have also studied the reactivity of phenoxy and coumarin moieties towards hard and soft electrophiles. Bromination resulted in substitution in the phenoxy moiety whereas nitration occurred in the coumarin ring with simultaneous cleavage of the ether linkage.

Acknowledgements

Authors thank the University Sophisticated Instrumentation Centre (USIC), Karnatak University, Dharwad for the spectral data. Thanks are also due to Professor C M Sun, Department of Applied Chemistry, National Chiao-Tung University, Hsinchu, Taiwan for providing difference NOE spectral data. One of the authors, Mr Mahantesha Basanagouda is grateful to Karnatak University, Dharwad for a University Research Studentship.

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