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# Synthesis of 4-(2'-Alkyl/Aryl Benzimidazolo N-1-Yl-Methyl) – 7-Hydroxy Coumarins

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## ABSTRACT

The synthesis of a number of 4-(2'-alkyl/aryl benzimidazolo N-1-yl-methyl) -7 hydroxycoumarins containing pharmacophores of the coumarin and benzimidazole in a single molecule has been achieved. 4-Chloromethyl coumarins is used as N-alkylating (N-alkylation of benzimidazole) agent which is prepared by Pechmann condensation. 2-Substituted benzimidazoles were prepared by interaction of carboxylic acids and o-phenylenediamine. The structures of synthesized compounds have been assigned on the basis of chemical tests, IR, $^{1}$H NMR, and Mass spectral data.

**Keywords:** 4-Chloromethyl coumarin, 7-hydroxy coumarin, N-alkylation, benzimidazole.

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## INTRODUCTION

Coumarins (2H-1-benzopyran-2-ones) are important oxygen containing fused heterocycles used in drugs and dyes[1]. They are the family of lactones containing benzo α-pyrone skeletal framework that have enjoyed isolation from plants as well as total synthesis in the laboratory [2]. The incorporation of group as a fused component into parent coumarin alters its activities and converts it into a more useful product [3]. The pharmacological, biochemical properties and therapeutic application of coumarins depend upon the pattern of substitution. Coumarins have attracted intense interest in recent years because of their diverse pharmacological properties. They exhibit diuretic, analgesic, myorelaxant [4], antifungal [5], anthelmintic [6], anti-inflammatory [7], antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities. Coumarin derivatives possessing sulfonamide moiety are found to have antimicrobial [8, 9], antifungal [10], and antitubercular [11] activities. Benzimidazole derivatives possess antimicrobial [12, 13], analgesic and anti-inflammatory activities [14, 15], also they are known to have activities against HIV and cancer [16, 17]. In view of these activities, a series of novel 4-(2'-alkyl/aryl benzimidazolo N-1-yl-methyl)-7-hydroxy coumarins have been synthesized.

4-Chloromethyl-7-hydroxy coumarin**2** was prepared by the reaction of resorcinol with 4-chloroacetoacetic ester in the presence of $H_2SO_4$ (Pechmann condensation) 18,19. It was used for N-alkylation of benzimidazols to yield several new 4-(2'-alkyl/aryl benzimidazolo N-1-yl-methyl-) 7-hydroxy coumarins**3(a-f).**

## MATERIALS AND METHODS

All chemicals and solvents were obtained from Merck (Germany) and used as supplied. Melting points were determined in open glass capillaries and are uncorrected. FT-IR spectra were recorded using (KBr) disc on a Perkin – Elmer FT-IR infrared spectrophotometer. $^1$H NMR spectra were recorded on a Bruker II-400 NMR spectrometer by using DMSO-$d_6$ and $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra were recorded on a 70s mass spectrometer.

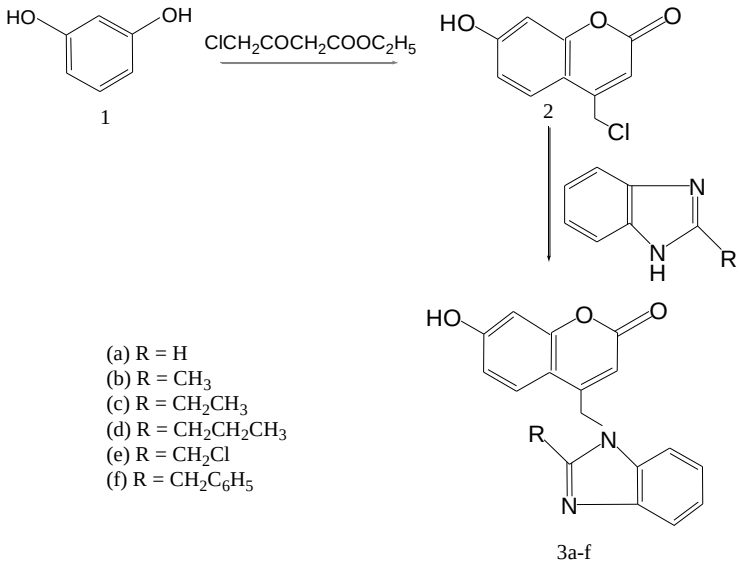
**4 –Chloromethyl 7-hydroxy coumarin**

A mixture of 4-chloroacetoacetic ester (0.1mol) and resorcinol (0.1mol) was added to $H_2SO_4$ (50 ml, 73%) in portion with stirring (18-24 hrs.) at room temp. The reaction mixture was poured onto crushed ice(50g), the yellowish solid obtained was washed with cold water, filtered, dried and crystallized from dioxane, m.p. 215 $^0$C.

**General procedure for 3a-f**

A hot solution of 4-chloromethyl-7-hydroxy coumarin**2** (10mmol) in DMF (25ml) was treated

withbenzimidazole (22mmol) and stirred for 24h at room temperature (completion of reaction determined by TLC). The reaction mixture was poured onto cold water (200ml). The solid was filtered off and crystallized from alcohol. A series of novel 4-(2'-alkyl/aryl benzimidazolo N-1-yl-methyl)-7-hydroxy coumarins have been synthesized (**Scheme 1**).




**Scheme 1:4-(2'-alkyl/aryl benzimidazolo N-1-yl-methyl)-7 hydroxycoumarins**

**Agar diffusion method**

Media Used (Nutrient broth): Peptone-10 g, NaCl-10g and Yeast extract 5g, Agar 20g in 1000 ml of distilled water

Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at 37ºC for 18 hrs. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 h old cultures (100 µl, $10^4$cfu) and spread evenly on the plate. After 20 min, the wells were filled with samples. All the plates were incubated at 37ºC for 24 h and the diameter of inhibition zones were noted

## RESULTS AND DISCUSSION

3a: IR (KBr): 3197 (OH), 2945 (-$CH_2$), 1503 (C-H def), 1622 (C=O), 1193 (C-O). $^1$H NMR (400 MHz,DMSO-$d_6$): 7.89 δ (s, 1H, OH, $H_7$), 6.30 δ (s, 1H, $H_8$ ), 2.59 δ (s, 2H, $CH_2$), 7.29-7.63 δ (m, 4H, Aromatic), 6.78 δ (d,2H, $H_5$, $H_6$), 2.35 δ (s,1H, $H_3$). MS (EI, 70eV): m/z (%) 293 (M+1, 100).

3b: IR (KBr): 3220 (OH), 2930 (-$CH_2$), 1491 (C-H def.), 1618 (C=O), 1201 (C-O).$^1$H NMR (400 MHz, DMSO-$d_6$): 7.93 δ (s,1H,OH, $H_7$), 6.35 δ (s, 1H,$H_8$), 4.87 δ (s,3H,$CH_3$), 2.62 δ (d,2H,$CH_2$),7.21-7.58 δ (m, 4H, Aromatic), 6.81δ (d,2H, $H_5$, $H_6$), 2.48 δ (s,1H,$H_3$). MS (EI, 70eV): m/z (%) 307 (M+1,100).

3c: IR (KBr): 3182 (OH), 2936 (-$CH_2$), 1522 (C-H def), 1630 (C=O), 1197 (C-O). $^1$H NMR (400 MHz, DMSO-$d_6$): 8.05 δ (s, 1H, OH, $H_7$ ), 6.20 δ (s,1H,$H_8$), 2.52 δ (s,2H,$CH_2$), 2.65 δ (t, 3H,$CH_3$), 2.96 (m,2H,$CH_2$), 7.28-7.52 δ (m,4H, Aromatic), 6.20 δ (d,2H, $H_5$,$H_6$), 2.45δ (s,1H,$H_3$). MS (EI, 70eV): m/z (%) 321 (M+1,100).

3d: IR (KBr): 3225 (OH), 2948 (-$CH_2$), 1497 (C-H def), 1633 (C=O), 1211 (C-O). $^1$H NMR (400 MHz, DMSO-$d_6$): 7.90 δ (s, 1H, OH, $H_7$ ), 6.11 δ (s,1H, $H_8$), 2.57 δ (s,2H,$CH_2$), 2.55δ (t,3H,$CH_3$), 2.97δ (m,2H,$CH_2$), 2.83δ (t,2H,$CH_2$), 7.42-7.61δ (m,4H,Aromatic), 6.86δ (d,2H,$H_5$,$H_6$), 2.56δ (s,1H,$H_3$). MS (EI, 70eV): m/z (%) 335 (M+1,100).

3e: IR (KBr): 3179 (OH), 2932 (-$CH_2$), 1512 ( C-Hdef), 1615 (C=O), 1195 (C-O), $^1$H NMR (400 MHz, DMSO-$d_6$): 8.02δ (s,1H,OH,$H_7$), 6.28δ (s,1H,$H_8$), 2.51δ (s,2H,$CH_2$), 2.96δ (s,2H,$CH_2$), 7.19-7.55δ(m,4H,Aromatic), 6.57δ(d,2H,$H_5$,$H_6$), 2.76δ (s,1H,$H_3$). MS (EI 70eV): m/z (%) 341 (M+1, 100).

3f: IR (KBr): 3190 (OH), 2941 (-$CH_2$), 1496 (C-Hdef), 1620 (C=O), 1194 (C-O). $^1$H NMR (400 MHz, DMSO-$d_6$): 7.99δ (s,1H,OH,$H_7$), 6.30δ (s,1H,$H_8$), 2.59δ (s,2H,$CH_2$), 2.99δ (s,2H,$CH_2$), 7.02-7.15δ (m,5H, benzyl proton), 7.25-7.51δ (m,4H,Aromatic), 6.38δ(d,2H,$H_5$,$H_6$), 2.53δ (s,1H,$H_3$) . MS (EI 70eV): m/z (%) 383 (M+1 100).

Thus, resorcinol **1** and 4-chloroacetoacetic ester in Conc.$H_2SO_4$ undergo a smooth reaction at room temperature to produce 4-chloromethyl-7-hydroxy coumarin**2**, which was used as alkylating agent during for N-alkylation of benzimidazoles**3a-f .**

The structures of compounds 3a-f were deduced from their chemical tests, IR, $^1$H NMR and Mass spectra. The IR spectrum of 3b exhibited the absorption band for the hydroxyl group (-OH) at 3220 $cm^{-1}$ ,(-$CH_2$ str) at 2930 $cm^{-1}$, (C=N) at 1570 $cm^{-1}$, and for (C=O) at 1618 $cm^{-1}$.

The $^1$H NMR spectrum of compound 3b exhibited two sharp singlet signals, readily recognized as arising from $CH_2$ and $CH_3$ groups at δ =2.62 and 4.87 ppm respectively. The protons of the CH ($H_3$) were appeared at 2.48 ppm. The protons of the coumarin aromatic ring were observed at7.21-7.58 ppm . The proton of the hydroxyl group appeared at 7.93 ppm($H_7$). The mass spectrum of compound 3b showed M+1 peak at m/z 307 (100%).

**Antibacterial activity**

Antibacterial activities of the synthesized compounds were tested against S.aureus, B. subtilis (Gram-positive) and E. coli, S.typhi (Gram-negative) bacteria using agar diffusion method at a conc.100 µg/ml in DMSO. For antibacterial activity Amoxicillin was used as standard. The results of tested compounds against these bacteria are shown in **Table-2.**

**Table 1: Physical data of compounds 3a-f**

| Compd | R | M.P.($^oC$) | Mol. Formula | Mol.wt | Yield(%) |
|---|---|---|---|---|---|
| 3a | H | 105 | $C_{17}H_{12}O_3N_2$ | 292 | 78 |
| 3b | $CH_3$ | 162 | $C_{18}H_{14}O_3N_2$ | 306 | 64 |
| 3c | $C_2H_5$ | 147 | $C_{19}H_{16}O_3N_2$ | 320 | 70 |
| 3d | $C_3H_7$ | 85 | $C_{20}H_{18}O_3N_2$ | 334 | 69 |
| 3e | $CH_2Cl$ | 185 | $C_{18}H_{13}O_3N_2Cl$ | 340 | 73 |
| 3f | $CH_2C_6H_5$ | 126 | $C_{24}H_{18}O_3N_2$ | 382 | 61 |

**Table 2: Antimicrobial activity of 4-(2'-alkyl/aryl benzimidazolo-N-1-yl-methyl)-7-hydroxy coumarin 3a-e**

| Zone of Inhibition (mm) | | | | |
|---|---|---|---|---|
| **Compd.** | **Antibacterial activity** | | | |
| | **S. aureus** | **B. subtilis** | **E. coli** | **S.typhi** |
| 3a | 3 | - | 6 | 4 |
| 3b | 7 | 4 | 5 | 4 |
| 3c | 5 | 4 | 4 | 3 |
| 3d | - | 5 | 6 | 3 |
| 3e | 5 | 6 | 9 | 8 |
| Std | 14 | 12 | 10 | 10 |

Concentration of test compounds andstandard 100 µg/mL,

Average zone of inhibition in mm,

S. aureus = Staphylococcus aureus

B. subtilis = Bacillus subtilis,

E. coli = Escherichia coli,

S. typhi = Salmonella typhi,

For antibacterial activity: Std. = Amoxicillin

– No zone of inhibition

## CONCLUSION

We have successfully developed an easy and efficient synthesis of 4-(2'-alkyl/aryl benzimidazolo N-1-yl-methyl-) 7-hydroxy coumarins from the 4-chloromethyl-7-hydroxy coumarin and corresponding benzimidazoles at room temperature.

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