INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SYNTHESIS AND ANTI-BACTERIAL STUDIES OF NEW SULFONYL BENZOCOUMARIN DERIVATIVES

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ABSTRACT

A series of new coumarins (1-10) were prepared by pechmann condensation of 1- naphthol and ethylacetoacetate followed by sulfonation and amination with various amines. The synthesised coumarin derivatives were characterised by means of IR,^{1}H-NMR,^{13}C-NMR spectral data. These coumarins were evaluated for antibacterial activity against both gram positive and gram negative organisms. They possess significant activity when compared with standard Benzyl penicillin.

Keywords: Benzocoumarin, synthesis, antibacterial activity.

INTRODUCTION

The synthesis and biological activities of benzocoumarins derivatives occupy an important position in heterocyclic chemistry as well as in medicinal chemistry. Coumarin (2H-Lbenzopyran-2-one) and its derivatives possess a wide range of various biological and pharmaceutical activities. They have a wide range of applications as antitumor[1,2], anti-HIV[3,4], anticoagulant[5,6], antimicrobial[7,8], antioxidant [9, 10], and anti-inflammatory [11, 12] agents. The antitumor activities of coumarin compounds have been extensively examined[13–16]. Although most of the existing natural coumarins have been isolated from higher plants, some of them have been discovered in microorganisms, for example, aminocoumarin antibiotics: novobiocin, coumermycin A1, and chlorobiocin (produced by the actinomycete Streptomyces niveus)[17].

Experimental

General details

The chemicals used for the synthesis were supplied by LOBA chemicals. Purity of the compounds was checked on thin layer chromatography (TLC) plates (Silica Gel G) using the solvent systems ethyl acetate: hexane (1:1). The spots were located under UV light (254 and 365 nm). Melting points were determined on GallenKamp (MFB-600) melting point apparatus and were uncorrected. The IR spectra of the compounds were recorded on a shimadzu FTIR-8300 spectrometer as KBr disk. The ^{1}H-NMR and ^{13}C-NMR spectra (solvent CD_3OD) were recorded on Bruker 400 MHz spectrophotometer using TMS as internal standard.

General synthesis (1-10)

The synthesis was illustrated in **Scheme 1.**Chlorosulphonic acid was added slowly to 4-methyl benzocoumarins synthesized by pechmann condensation of equimoles of 1-naphthol and ethyl aceto acetate under acidic conditions. The reaction mixture was allowed to cool and the product was precipitated in crushed ice, filtered and dried. The dried 4-methyl benzocoumarins- 8-sulfonylchloride was treated with various amines and refluxed for 30 min .The reaction mixture was allowed to cool , the product obtained was filtered,recrystalissed from ethanol.

4-methyl-2H-benzo[h]chromen-2-one (1)

%yield:40%;R_f:0.566(ethylacetate:hexane1:1); M.P(^{0}c):150-155^{0}C;IR(KBr,V_{max},Cm^{-1}):3734(-NH),3433(-OH),3087(-C=C-), 2812(CH_3), 1665(C=O),1244(C-O),1210(C-O-C), 1600(C=C-aromatic), 1384(assymetricSO_2)1132(SymmetricSO_2).;^{1}H NMR(400MHZ,MeOD)2.4(CH_3(M)),7.38,7.35,7.

68,8.08,7.26,7.21(CH-protons-1.71(S), ^{13}CNMR(500MHZ,MeOD):21.2(CH_3(S)),126.8, 126.2,127.5,134.1,126,121.7,121.1, 122.6,124.8,154.8,152.8,112.5,160.(basic ring carbons).

4-methyl-2-oxo-2H-benzo[h]chromene-8-sulfonyl chloride (2)

%yield: 45% ;R_f: 0.6(ethyl acetate:hexane1:1); M.P:150^{0}C ;IR (KBr,V_{max}, Cm^{-1}): 3733 (NH),3423(-OH),3085(-C=C-), 2810(CH_3), 1669(C=O),1238(C-O),1208(C-O-C), 1600(C=C Aromatic),1383(assymetric SO_2) ,1132(Symmetric SO_2). ; ^{1}H NMR(400MHZ,MeOD): 0.9,1.71,2.46 (CH_3(T)),7.24,7.47,8.02,7.23,7.20 (CH-protons), ;^{13}C NMR (500MHZ,MeOD): 34,21.2,24.6(CH_3(T), 136.3,126.8,134, 124,120,120.5,122.4,123.7,154.3,152.8,112.5, 160.9(basic ring carbons).

4-methyl-2-oxo-2hbenzo[h]chromene-8-sulphonamide (3)

%yield: 37.06%;R_f:0.7(ethyl acetate:hexane1:1) M.P(^{0}C) 160^{0}C ;IR (KBr,V_{max}, Cm^{-1}): **:** 2954cm^{-1} (CH stretching),1707cm^{-1}(C=O),3737cm^{-1}(NH stretching),1077cm^{-1}(C-O-C),1370cm^{-1}(SO_2 asymmetric),1162cm^{-1}(SO_2 symmetric),. ;^{1}H NMR(400MHZ,MeOD): 1.71(CH_3(S)),8.05,8.35 ,8.36,7.26,7.21,(CH-protons), ,2(NH_2); ^{13}CNMR(500MHZ,MeOD): 21.2(CH_3(S)),125, 125.5,134.4, 129.2,122,121.122.6,124.8,154.8,152.8,112.5, 160.9,(basic ring carbons)

4-methyl-2-oxo-2hbenzo[h]chromene-8-sulphonamide (4)

%yield: 12.336% ;R_f:0.59(ethyl acetate:hexane1:1); M.P(^{0}c):154-156^{0}C;IR (KBr,V_{max}, Cm^{-1}): 2891cm^{-1}(CH-stretching),1710cm^{-1}(C=O),3740cm^{-1}(NH),1372cm^{-1}(SO_2 asymmetric),1170cm^{-1}(SO_2 symmetric) ;^{1}H NMR(500MHZ,MeOD): 1.71(CH_3(S)),8.05,8.35,8.36,7.26,7.21,(CH-protons), 2(NH,(s)),2(NH(S)) ;^{13}C NMR (500MHZ,MeOD): 21.2(CH_3(S)), 125,125.5, 134.4,129.2,122, 121.1, 122.6,124.8, 154.8,152.8,112.5,160.9,(basic ring carbons),137(NH-side chain carbons).

4-metyhl-2-oxo-N-propyl-2H-benzo[h]chromene-8-sulphonamide (5)

%yield:32.326 ;R_f:0.66 (ethyl acetate:hexane1:1); M.P(^{0}c):159-164;IR (KBr,V_{max}, Cm^{-1}): 2982cm^{-1}(CH-stretching),3736cm^{-1}(NH),1709cm^{-1} (C=O),1079cm^{-1}(C-O-C),1370cm^{-1}(SO_2 asymmetric), 1168cm^{-1}(SO_2symmetric) ;^{1}H NMR(500MHZ,MeOD): 0.96(CH_3(S)),3.16,1.59 (CH_2-protons), 2 (NH_2,(s)),8.05,8.35,8.36,7.26,7.21(CH protons) ;^{13}C NMR (125MHZ,$CDCl_3$): 21.2(CH_3(S)) ,112.5,152.8,124.8,160.9,154.6,19.2,134.4,12 1.1,122.6,125.5,125,122.0 (basic ring carbons),137,45,22.3,11.2(side chain).

N-butyl-4-methyl-2-oxo-2H benzo[h]chromene-8-sulphonamide (6)

%yield:40.06;R_f:0.58(ethyl acetate:hexane1:1); M.P(^{0}c):158-162 ;IR (KBr,V_{max}, Cm^{-1}): : 1557cm^{-1}(CH- aromatic stretching),3739cm^{-1}(NH),1709cm^{-1}(C=O),1081cm^{-1}(C-O-C),1372cm^{-1}(SO_2 asymmetric),1171cm^{-1}(SO_2symmetric) ;^{1}H NMR(500MHZ,MeOD): 1.71,0.96(CH_3(D)),3.16,1.55,1.33 (CH_2-protons), 2(NH_2,(s)), 3.16,1.55,1.33,0.96(side chain protons),;^{13}C NMR (125MHZ,MeOD): 21.2,13.8(CH_3(D)), 112.5, 152.8,124.8,160.9,154.6,19.2,134.4,121.1,122 .6,125.5,125,122.0 (basic ring carbons),137,42.5,31.4,19.9,13.8(side ring carbons).

N-cyclohexyl-4-methly-2-oxo-2Hbenzo[h]chromene-8-sulphonamide (7)

%yield:26.415;R_f:0.58 (ethyl acetate:hexane1:1); M.P(^{0}c):160-165;IR (KBr,V_{max}, Cm^{-1}): 1506cm^{-1}(CH- aromatic stretching),3736cm^{-1}(NH),1711cm^{-1}(C=O),1079cm^{-1}(C-O-C),1371cm^{-1}(SO_2 asymmetric),1170cm^{-1}(SO_2symmetric) ;^{1}H NMR(500MHZ,MeOD): 1.71(CH_3(S)),1.49,1.39,1.46,1.43,1.49,1.39,1. 78,1.53 (CH_2-protons), 7.21,7.26,8.35,8.36,8.05(basic ring protons protons) ;^{13}C NMR (125MHZ,MeOD): 21.2(CH_3(S)), 112.5, 152.8,124.8,160.9,154.6,19.2,134.4,121.1,122 .6,125.5,125,122.0 (basic ring carbons) ;137,32.9,42.7,32.9,22.9,28,22.9,(side ring carbons).

{4-methyl-2-oxo-2H-benzo[h]chromene-8-sulphonyl} urea (8)

%yield: 34.36 ;R_f:0.61 (ethyl acetate:hexane1:1); M.P(^{0}c):158-164;IR (KBr,V_{max}, Cm^{-1}): 1551cm^{-1}(CH- aromatic stretching),3860cm^{-1}(NH),1708cm^{-1}(C=O),1077cm^{-1}(C-O-C),1369cm^{-1}(SO_2 asymmetric),1167cm^{-1}(SO_2symmetric). ;^{1}H NMR(500MHZ,MeOD): 1.71(CH_3(S)),8.05,8.35,8.36,7.26,7.21, (CH-protons),6(NH_2,(s)),6(NH(S));^{13}C NMR (125MHZ,MeOD): 21.2(CH_3(S)), 112.5, 152.8,124.8,160.9,154.6,19.2,134.4,121.1,12 2.6,125.5,125,122.0 (basic ring carbons),137,161(Side chain carbons).

4-methyl-2-oxo-N-(propan-2-yl)-2Hbenzo[h]chromene-8-sulphonamide (9)
%yield:33.35;R_f:0.67(ethyl acetate:hexane1:1); M.P(^{0}c):159-164;IR (KBr,V_{max}, Cm^{-1}): : 1506cm^{-1}(CH- aromatic stretching) , 3735cm^{-1}(NH),1710cm^{-1}(C=O),1077cm^{-1}(C-O-C),1370cm^{-1}(SO_2 asymmetric),1142cm^{-1}(SO_2symmetric). ;^{1}H NMR(500MHZ,MeOD): 1.71,1.05,1.05(CH_3,(T)), 8.05,8.35,8.36,7.26,7.21,2.97(CH-protons), ,2(NH(S)) ;^{13}C NMR (125MHZ,MeOD): 21.2,22.4,22.4(CH_3,(S)), 112.54,152.8,124.8,160.9,154.6,19.2,134.4,121.1,122.6,125.5,125,122.0 (basic ring carbons).

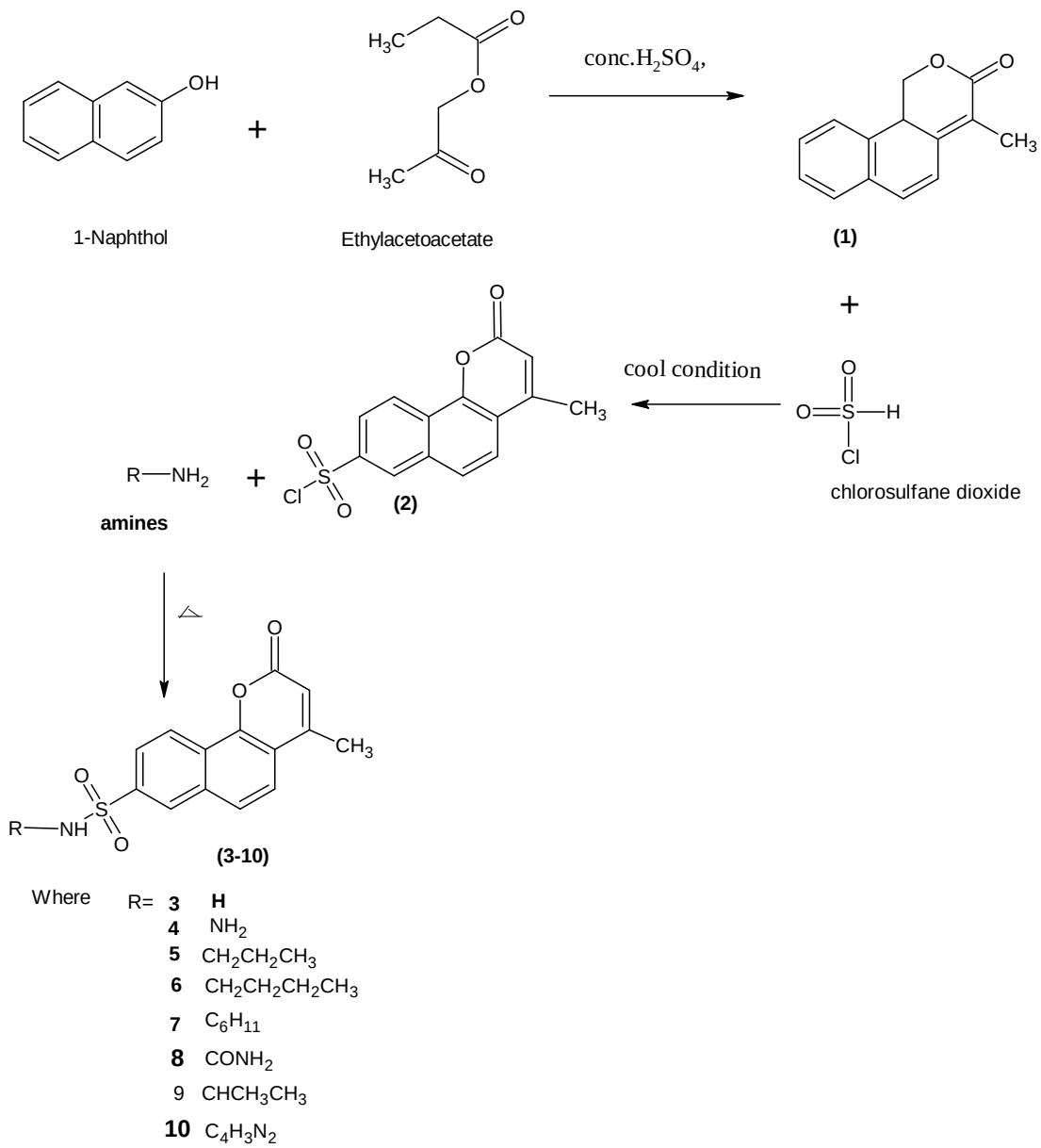
4-methyl -2-oxo-N-(pyrimidin-2-yl)-2H-benzo[h]chromene-8-sulphonamide (10)
%yield:35.23 ;R_f:0.60(ethyl acetate:hexane1:1); M.P(^{0}c):160-165 ;IR (KBr,V_{max}, Cm^{-1}): : 1603cm^{-1}(C=N -stretching),3738cm^{-1}(NH),1709cm^{-1}(C=O),1079cm^{-1}(C-O-C),1371cm^{-1}(SO_2 asymmetric),1170cm^{-1}(SO_2symmetric) ;^{1}H NMR(500MHZ,MeOD): 1.71(CH_3,(S)) 8.05,8.35,8.36,7.26,7.21,2.97,6.58,8.38(CH_2-protons), ,4(NH(S)) ;^{13}C NMR (125MHZ,MeOD): 21.2(CH_3,(S)), 112.54,152.8,124.8,160.9,154.6,19.2,134.4,121.1,122.6,125.5,125,122.0 (basic ring carbons).;169.3,157.9,110.3,157.9 (side ring carbons).

Antibacterial Activity
Cup plate method [18,19]using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of **(1-10)** against *Bacillus subtilis* ,*Staphylococcus aureus,Eischerria coli* and *Pseudomonas aeroginosa*.The agar media was purchased from HI-media laboratories limited , Mumbai,India.Preparation of nutrient broth ,subculture ,base layer medium ,agar medium was done as per the standard procedure .Each test compound (5mg)was dissolved in 5ml of dimethyl sulfoxide . Benzyl penicillin was employed as reference standard (1000µg/ml) to compare the results. All the compounds were tested at a concentration of 0.10ml (100µg) level. DMSO as control did not show any inhibition.
The medium was inoculated at one percent level using 18hrs old cultures of the test organism mentioned above aseptically into sterile petridishes and allowed to set at room temperature for about 30 minutes. The test and standard solutions were added into cups, left for 90 minutes in a refrigerator for diffusion. After incubation for 24 hours at 37 ^{0} c , the plates were examined for inhibition zones. The results are represented in **TABLE 1**

RESULTS AND DISCUSSION
The results of antibacterial activity revealed that the compounds **(1 -10)** exhibited moderate to considerable activity when compared to reference standard benzyl penicillin. This may be due to the presence of sulfonamide group at C-8 of benzo coumarin ring. In addition it was found that compound **6** showed maximum activity against gram positive organism *Staphylococcus aureus* and compound **4** showed against *pseudomonas auregenosa* . The compounds showed significant inhibition against gram positive Staphylococcus ***aureus*** when compared to other organisms.
The results clearly revealed the contribution of electron releasing groups like alkyl, amido, thio amide, hydroxyl on the 8-sulfonyl benzocoumarins ring in enhancing the antibacterial activity.

Table1: Antibacterial Activity of Benzocoumarins (1-10)

Zones of inhibition in mm				
Compound	**Bacillus subtilis**	**Staphylococcus aureus**	**E.coli**	**Pseudomonas aeroginosa**
1	10	10	13	15
2	11	9	10	12
3	9	10	12	15
4	10	14	9	20
5	-	10	12	11
6	-	20	13	11
7	9	19	12	-
8	9	12	12	10
9	15	10	9	-
10	-	11	-	10
Benzyl Penicillin	15	22	17	23



Scheme. 1:

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