RESEARCH ARTICLE

Synthesis of New Substituted Coumarin Derivatives containing Schiff-Base as Potential Antimicrobial and Antioxidant Agents

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ABSTRACT

By unusual method for separating two isomers of a substituted nitro-coumarin using a soxhlet extractor and in controlling temperature to get a selective nitration reaction, several new Schiff base coumarins were synthesized from nitro coumarins as starting material, which were reduced by Fe in glacial acetic acid to produce corresponding amino coumarin derivatives. Then the latter was reacted with different aromatic aldehydes to produce the desired Schiff bases derivatives. After characterization by Fourier transform infrared (FT-IR), Proton nuclear magnetic resonance (^{1}HNMR) and Carbon-13 nuclear magnetic resonance (C-NMR), all these compounds were evaluated as potential Antimicrobial and Antioxidant Agents.

Keywords: Coumarins, Schiff base, Antioxidants.

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Conflict of interest: None

INTRODUCTION

Coumarins are heterocyclic-like compounds[1] with a biological significance which consists of benzene attachment with a lactone ring by two carbons. Coumarins are found as biosynthesis and biochemical and very important compounds as heterocyclic which using as Antitumor screening[2], Antibacterial activity[3], Antioxidant Activities, Anti-Inflammatory[4], Antihypertensive[5], Anticoagulant[6], Anti-HIV[7], Anti-adipogenic[8], Anti-convulsant[9], Anti-abiogenic.[10]

EXPERIMENTAL

The following methods were used to synthesize Schiff bases from 4,7-dimethyl-6-amino-coumarin (scheme 1)

Preparation of 6- nitro-4,7- dimethyl -coumarin(2) 8- nitro-4,7-dimethyl- coumarin was synthesized (3) by using the same method in literature[11] with some modification by using nitric acid and Sulphuric acid under very cold condition (0-4)°C in preparation of compound (2) at (15) m.p 255-257°C

While the preparation of compound (3) was under very cold conditions (0-4)°C for overnight m.p 189-190°C

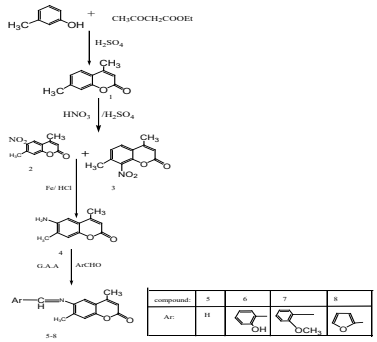
Synthesis of 6-amino- 4,7-di methyl-chromen-2–one (4) A mixture of 2g from Amino-4,7-dimethyl-coumarin, 1.6 g of iron, 2.5 mL G.A.A and 5 mL H_2O in 30 mL dioxan was refluxed for 8 hours. Then the solution was filtered, neutralized the filtrate to pH=7 then the solution was added to the ice bath, to formed precipitate was filtered and recrystallized from benzene m.p 209-210°C, FT-IR (KBr, cm^{-1}): 3446 and 3363(NH_2) 1693 (C=O), ^{1}HNMR(ppm): 2.3 and 2.4 for (S, S, 6H, 2CH_3), 6.2 (s,1H,3-H), 8.19 and 8.12 ppm for (S, S, 2H, for benzene ring).

Synthesis of Schiff base derivatives [5-8]

A mixture of 6- Amino-4,7-di methyl-chromen-2 -one(0.013 mole, aromatic aldehydes (0.013 mole) and few drops from glacial acetic acid in 15 mL ethanol was reflux about (6 hours) to complete the reaction, the product was filtered.

6-(Benzylidene-amino)-4,7-dimethyl-chromen-2-one : m.p: 181-182°C FT-IR (KBr, cm^{-1}):1730 (C=O), 1629 (C=N); ^{1}HNMR: 6.3-7.9 (m, 7H-Ar-H), 8.64(S, 1H, CH=N), 2.4 and 2.52(ss, 6H, 2CH^3)

6-[(2-Hydroxy-benzylidene)-amino]-4,7-dimethyl-chromen-2-one m.p: 183-184°C FTIR (KBr, cm-1):1699 (C=O), 1622(C=N) ; 1HNMR: 6.38-7.1(m, 7H, Ar-H), 9.02(S,



Scheme 1: Synthesis new Schiff bases from substituted coumarin

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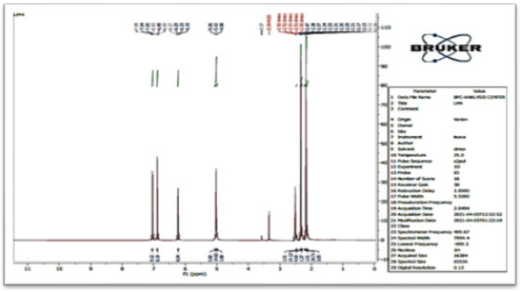

Figure 1: ^{1}HNMR for compound 4

1H, CH=N), 13-09 (s, 1H, OH) 6-[(4-Methoxy-benzylidene)-amino]-4,7-dimethyl-chromen-2-one m.p: 150-151ºC FT-IR (KBr, cm^{-1}): 1737 (C=O), 1627 (C=N), 1257 (C-O-C); ^{1}H-NMR: 6.35-8.3 (m,7H,Ar-H), 8.54(S,1H,CH=N), 3.86 (S, 3H, CH3-O)

6-[(Furan-2-ylmethylene)-amino]-4,7-dimethyl-chromen-2-one m.p: 175-177°C FTIR (KBr, cm^{-1}) 1730, 1159 (C-O-C); ^{1}HNMR: 6.36-8.46 (m, 6H, Ar-H), 8.5 (S, H, CH=N)

RESULTS AND DISCUSSION

In this work, 6- Amino-4,7-di methyl-coumarin (4) was synthesized by reduction of compound 2 in a mixture of Fe, glacial acetic acid and dioxan as solvent. FTIR spectrum for compound (4) showed new absorption band at 3438 and 3363 cm^{-1} due to NH_2 group. The ^{1}H-NMR spectrum of the same compound showed new signals at 5.02 ppm for two protons of NH_2 group and three signals at 8, 8.19 and 8.12 for the protons of the coumarin ring (Figure 1).

Treatment of compound 4 with different aromatic aldehydes to produce Schiff base derivatives [5-8] FTIR spectra for compounds show absorption band at (1622–1629)cm^{-1} for C=N and absorption bands at (1699–1741) cm^{-1} for carbonyl of lactone ring and disappearing of the amino group. The ^{1}H-NMR spectrum for compounds 5-8 showed the disappearing signal of two protons of NH_2 group. And different signal appears according to aldehyde compounds used to produce Schiff base, see (Figure 2 and 5).

Biological Activity

Schiff base is known for the importance of biological activity[12] so by agar well diffusion method. The compounds (4–8) in Dimethyl sulfoxide (DMSO) as solvent were tested for antifungal activity against candida albicans and against antibacterial activity against *Escherichia-coli* and *Staphylococcus aureus*. The compound (4 and 5) show a high antifungal active better than the stander drug Fluconazole. While compound (7) is most effective against *Escherichia coli* more than stander drug cephalexin and Amoxicillin (Table 1).

Antioxidant activity

DPPH Radical Scavenging Activity[13]

DPPH (1,1-Diphenyl-2-picryl-hydrazyl)14 DPPH (4 mg) was dissolved in 100 mL of methanol, various concentrations (6.25,12.5, 25, 50, 100) ppm were prepared in solution for compounds (1–8) in methanol, then the incubation was carried out at 37°C for 1 hour and measured The absorbance with a spectrophotometer at 517 nm, the reference was used

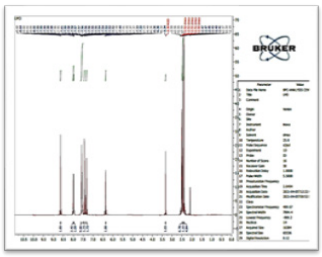

Figure 2: ^{1}HNMR for compound 5

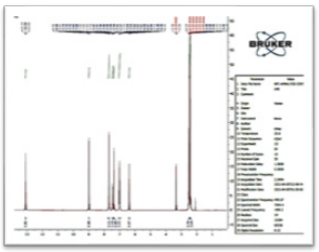

Figure 3: ^{1}HNMR for compound 6

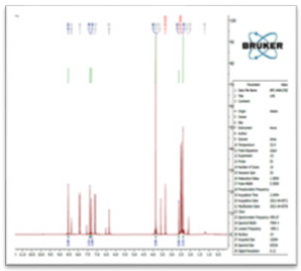

Figure 4: ^{1}HNMR for compound 7

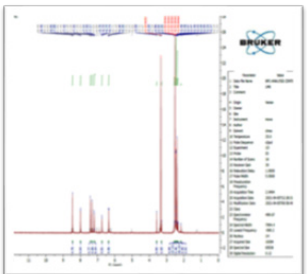

Figure 5: ^{1}HNMR for compound 8

Table 1: Antifungal and antibacterial activity for synthesized compounds 4–8 the conc. of compounds is 10 mg/mL (well diameter was 6mm)

No. of sample	*E. coli*	*S. aureus*	*C. albicans*
4	1 6	2 1	1 7
5	18	16	17
6	19	20	16
7	22	18	16
8	19	19	13
Amoxillin	20 mm	24	-
Cephalexin	21mm	20	-
fluconazole	-	-	16

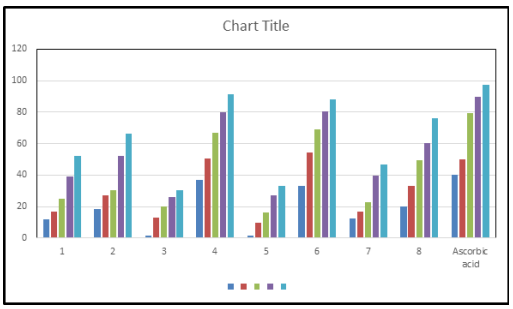

Figure 6: DPPH Scavenging Activity of all compounds

(vitamin C). Triplicate measure made by the following equation to scavenge (DPPH) (Figure 6).

$$\% \text{ inhibition} = (A_0 - A_t) \times 100$$

$$A_t$$

Inhibitory concentrations (IC_{50}) values were recorded for compounds that showed antioxidant activity and good scavenging percentage (Table 2).

Table 2: Antioxidant activities for synthesized compounds (1-8)

Com. No.	*Scavenging %*					*liner eq.*	*R2*	*IC_{50}*
	6.25 µg/mL	*12.5 µg/mL*	*25 µg/mL*	*50 µg/mL*	*100 µg/mL*			
1	12.1	16.9	24.8	39.1	52.1	y = 0.422x + 12.646	R^2 = 0.954	88.5
2	18.3	26.9	30.4	52.4	66.3	y = 0.5043x + 19.317	R^2 = 0.9395	56.5
3	1.3	12.9	20.1	26.2	30.3	y = 0.2569x + 8.2042	R^2 = 0.7271	162.7
4	36.8	50.3	67	80.1	91.2	y = 0.5246x + 44.75	R^2 = 0.8291	10
5	1.3	9.7	16.1	27.2	33.4	y = 0.3154x + 5.3167	R^2 = 0.8605	141.7
6	33.1	54.3	69.1	80.4	88.1	y = 0.4902x + 46.004	R^2 = 0.7276	8.2
7	12.2	16.9	22.9	39.9	46.9	y = 0.3727x + 13.317	R^2 = 0.8999	110.2
8	20.1	33.1	49.3	60.3	75.9	y = 0.538x + 26.892	R^2 = 0.8711	42.9
Ascorbic acid	40.4	50.1	79.6	89.9	97.3	y = 0.5589x + 49.804	R^2 = 0.7276	0.351

The highest antioxidant activity and the lowest IC_{50} values were found for compounds (6) and (4).

In Table 2, compounds (4), (6), and (8) possess strong antioxidant activity. While compounds (1) and (2) possess intermediate antioxidant activity, but compounds (3), (5), and (7) possess weak antioxidant activity.

CONCLUSION

The condensation reaction between aromatic amine compound and various aromatic aldehydes consists of a nucleophile, adding compounds containing amine (NH_2) group coumarins to carbonyl (C=O) group producing to afford Schiff base. Several new Schiff base coumarins were synthesized from nitro coumarins which were separated by an unusual method for separating two isomers of substituted nitrocoumarin by soxhlete extractor and in controlling temperature to get selective nitration reaction, under room temperature the reaction gave the isomer (2), but under very cold condition the isomer (3) was prepared in a good percentage yield. All these compounds were evaluated as potential antimicrobial and antioxidant agents. These compounds have very large applications in the field of chemistry because (C=N) group have a lone pair of electrons on the nitrogen atom. The study also showed that compound (7) was found to be most effect against *E. coli* and the compounds(4 and 5) show a high antifungal activity and are better than the stander drug, while compounds (4), (6) and (8) possess strong antioxidant activity as compared with ascorbic acid as stander.

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