SYNTHESIS AND CHARACTERIZATION OF NEW TRIAZOLE AND COUMARIN-DERIVED HETEROCYCLIC COMPOUNDS PART II

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In the present article our research work is focused on the synthesis of coumarin, triazole drieved Schiff bases as well as to synthesize the variety of metal complexes with various transition metal ions. Starting from the synthesis of 4-amino-2-[(5-amino-1,3,4-oxadiazol-2-yl)methyl]-5-(2-furoyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (2) which was performed by using 2-[4-amino-3-(2-furoyl)-5-oxo-4,5-dihydro-1*H* -1,2,4-triazol-1-yl] acetohydrazide (1) as starting metarial. The treatment of (2) with divers coumarin aldehydes (5, 9, 12, 15 and 19) afforded the corresponding Schiff bases (6, 10, 1 3, 16, and 20). Newly synthesized *N*'-[(1*Z*)-(7,8-dimethoxy-2-oxo-2*H*-chromen-4-yl)methylene]-4-{[(1*Z*)-(7,8-dimethoxy-2-oxo-2*H*-chromen-3-yl)methylene]amino}-3-(2-furoyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-carbohydrazide derivatives, have been characterized by spectroscopic measurements (IR, ^{1}H-NMR, ^{13}C-NMR).

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1. Introduction

Substituted 1,2,4-triazoles as highly potential antimicrobial agents having diverse biological activities such as fungicidal, antimicrobial, antiviral activities are among the large number of heterocyclic compounds that have been studied very attentively in last two decades. [1, 2]. A wide variety of therapeutically fascinating drugs, including H1/H2 histamine receptor blockers, antianxiety agents, active agents of Cholinesterase, CNS stimulants, and sedatives which contains 1,2,4-triazole nucleus [3]. Mercapto derivatives of substituted 4-amino-l, 2,4-triazoles are specifically remarkable as complexing agents beacause of the presence of four potential donor atoms (three nitrogen and one sulphur), as a result a wide variety of metal derivatives ligands has been synthesized [4].

Coumarin (2*H*-chromen-2-one, 2*H*-1-benzopyran-2-one) structurally the least complex member of well known benzopyrones class, moreover they are amongst the best known oxygen heterocycle with a d-lactone ring which consist the enormous class of compounds found throughout the plant kingdom [5]. Furthermore, coumarin derivatives have several biological activities i.e. antithrombotic, antimicrobial, antiallergic, anti-inflammatory [6], antitumor and anticoagulants [7]. Coumarin derivatives are also known to retain significant antifungal as well as antibacterial properties. İt has also been reported that several coumarins from plants sources as well as their synthetic analogues possess good antifungal and antibacterial properties [8]. Preliminary structure– activity relationship studies has also been proved that hydroxyl or carboxylic groups on the coumarin nucleus are the main cause for antimicrobial activities [9]. Antibiotics, such as novobiocin, clorobiocin and coumermycin A1 also consist of coumarin nucleus. Despite pharmacologically potent property of these compounds, the use of these in antibiotics has been limited due to their poor water solubility, low activity against Gram-negative bacteria and the rapid emergence of resistance [10].

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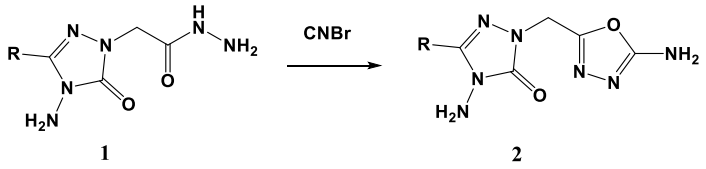

1 2

Fig. 1. General Synthetic pathway for the preparation of compound 2.

Nowadays coumarin are well known key group of organic compounds that are widely used as food additives, in cosmetics, optical brightening agents, dispersed putrescent and laser dyes [11]. Coumarin derivatives are found usually as secondary metabolites present in seeds, roots and leaves of many plant species, although their function is not well understood yet, though suggestions include as waste products, plant growth regulators, fungi stats and bacterio stats. It is therefore the synthesis of coumarin and its derivatives became extremly important to be achieved by a simple and efficient synthetic method. Coumarins have already been synthesized by some different methods such as Von Pechman, Knovenagel and Reformatsky reactions. Neverthless, renewed interest in these antibiotics has arisen after finding that they are potent catalytic inhibitors of DNA gyrase enzyme. Futhermore these antibiotics have been shown to be active against Gram positive bacteri especially against Methicillin-resistant Staphylococcusaureus (MRSA) [12]. Further derivatisation of novobiocin, clorobiocin, and coumermycin A1 has produced novel coumarin antibiotics which shows excellent inhibition of DNA supercoiling by DNA gyrase B and superb antibacterial activity against vancomycin, teicoplanin and novobiocinresistant *Enterococci* species [13]. A part from the biological significance, Schiff bases and their metal complexes find applications in various other fields. Some aromatic Schiff bases have been used as stabilizers [14] for a wide variety of compounds such as jet fuels, fuel oils, lubricating oils etc., Schiff bases have been combined in several polymers [15] to produce required characteristics final products, Such as includes süper conducting property, resistance towards heat, light and oxidation, hardness and vulcanisation. For the catalytic oxidation of ascorbic acid and cysteine some specific Schiff bases metal complex have been used, furthermore for the catalytic decomposition of hydrogen peroxide Some Schiff base complexes have been used [16]. Aromatic Schiff bases and their metal complexes are found to have strong catalytic influence [17] on reactions like oxidation, decomposition and polymerisation. Many Schiff base complexes can also be usee as dyes and as electrographic materials. Several Schiff bases have been used as analytical reagents, corrosion inhibitors, flocculants, medicines and therapeutic agents [18]. Some Schiff bases shows obstruction in root development in detached cabbage leaves [19]. Copper azomethane complexes found application as pigments. There is suggestive proof that, the visual pigment rhodospin contains azomethane linkages. It is well known that chelation of metal ions with organic ligands acts synergistically to increase their biological activities [20].

Beacause of this all above mentioned fascinating structural and biological features of coumarins, recently hydroxy substituted formyl coumarins have been used for the preparation of various Schiff bases.

2. Experimental work

Melting points were determined on a Buchi B-540 melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured on potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer.

2.1 General Method for the Synthesis of 4-Amino-2-[(5-amino-1,3,4-oxadiazol-2-yl)methyl]-5-(2-furoyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (2)

2-[4-amino-3-(2-furoyl)-5-oxo-4,5- dihydro-1*H*-1,2,4-triazol-1-yl] acetohydrazide **(1)** (0.01 mol) and CNBr (0.55 mL, 0.01 mol) were added to a solution of KOH (0.56 g, 0.01 mol) in 50 mL of H_2O and 50 mL of ethanol. The reaction mixture was refluxed for 3 h. After evaporating the solvents under reduced pressure to dryness, a solid was obtained. It was dissolved in 300 mL of H_2O and acidified with conc. HCl. The precipitate was filtered off, washed with H_2O, and recrystallized from ethanol to afford the desired compound. Yield 78%, mp 218-220° C; IR (KBr,υ, cm^{-1}): 3323 and 3210 (2 NH_2), 1676 (C=O), 1519, 1505 and 1601 (C=N); ^{1}H-NMR (DMSO-$d_6\delta$ ppm): 5.12 (2H, s, CH_2), 5.56 (4H, bs, NH_2), 7.30 (2H, d, *j*=8.0 Hz, arH), 7.88 (2H, d, *j* =8.0 Hz, arH); ^{13}C-NMR (DMSO-$d_6\delta$ ppm): arC: 127.45 (2CH), 128.78 (2CH), 139.88 (C)], 145.73 (C-3, triazole), 153.06 (C-5, triazole), 158.85 (C-2, oxadiazole), 177.86 (C-5, oxadiazole).

2.2. General method for synthesis of 4-Methyl-hydroxy coumarin derivatives (4, 8, 11, 14 and 18)

4-Methyl-hydroxy coumarin was prepared by the reported method **[21]**. Concentrated H_2SO_4 (500 ml) was cooled to 0^0 C in ice bath. Mixture of ethylacetoacetate (65 ml) and orto or meta-Cresol (55ml) was added in concentrated H_2SO_4 under vigorous stirring at 0-5 ^{0}C over a period of 1-1.5 hrs. Stirring was continued at 5^0C for 2 hrs. Temperature of reaction mixture was then raised slowly to 30^0C and allowed to stand for 24 hrs. The solution was then poured in ice bath and water.The product precipitated was filtered. The crude product was dissolved in 5% NaOH solution and the solution was then clarified with activated charcoal and filtered. Filtrate was acidified with conc. HCl to give 4- Methyl-hydroxy coumarin. The yield of the product was around 95%.

2.3. General method for synthesis of 4-Methyl-hydroxy-formyl coumarin derivatives (5, 9, 12, 15 and 19)

4-Methyl-hydroxy coumarin compaund (0.170 moles) was dissolved in 300 ml glacial acetic acid. Hexamine (60 g, 0.428 moles) was added and heated to 85-90^{o}C for 5 hours. Reaction was monitored for its progress by TLC (30% Ethyl acetate in hexane). After reaction was completed as indicated by TLC, Reaction mixture was quenched in 20% HCl and heated to 60-80^{o}C for 20 minutes. Reaction mixture was cooled to room temperature and product was extracted in methylene chloride (100 ml x 3 times). Combined extract was washed with distilled water and dried over anhydrous Na_2SO_4. Extract was concentrated and crude product was purified by Silica gel column chromatography to get pure 4-Methyl-hydroxy-formyl coumarin. The yield of the product was around 40%.

3.5. General method for synthesis of Schiff bases (6, 10, 13, 16 and 20)

A mixture of 2-[4-amino-3-(2-furoyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl] acetohydrazide (3) and formyl-hydroxy-4-methyl coumarin derivatives(5, 9, 12, 15, 19) in 1:2 molar proportion in an alcoholic medium containing few drops of concentrated HCl was refluxed for 3-4 h. The product separated is filtered, washed with alcohol and recrystallized from EtOH [1] to afford the desired product.

3. Results

In this study, a convenient method was established for the synthesis in good yields of new triazole schiff bases. The syntheses of triazole schiff bases were accomplished according to the reactions shown in figures. First, 4-Amino-2-[(5-amino-1,3,4-oxadiazol-2-yl)methyl]-5-(2-furoyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (2) was synthesized using a published method [22], as indicated in figures. 4-Methyl-hydroxy-formyl coumarin derivatives were prepared by using literature procedures [23]. Finally reactions of compound 2 and coumarin derivatives afforded the desired compounds (6, 10, 13, 16 and 20) (Fig. 1, 2).

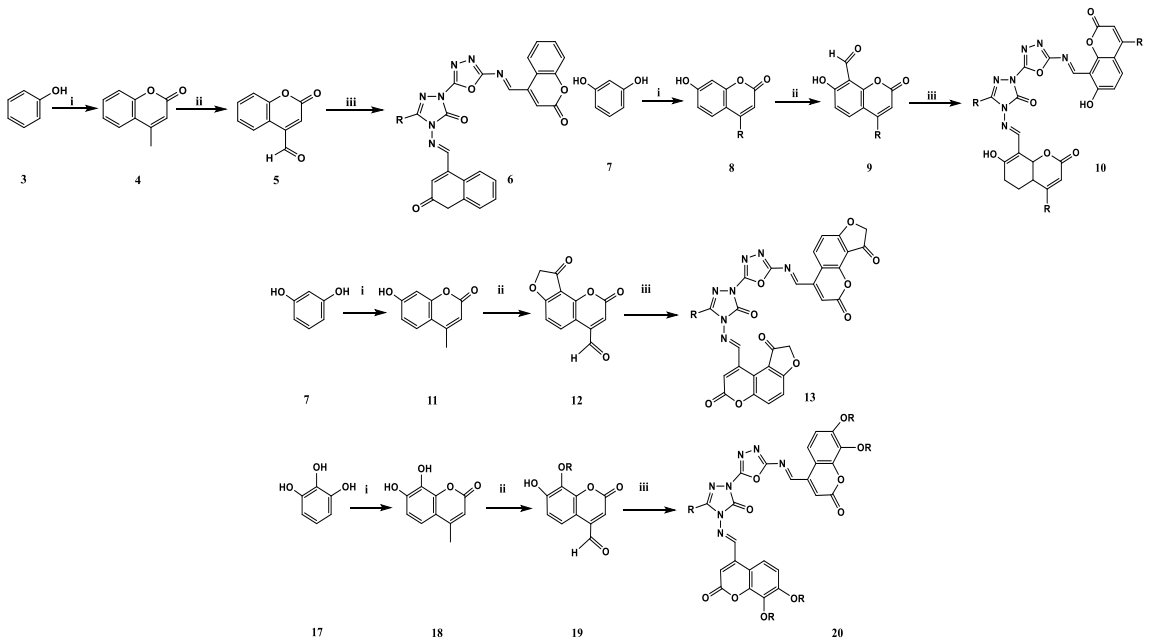

Fig. 2. Synthesized Schiff bases compounds. Reagents and conditions: (i) ethyl acetoacetate, $TiCl_4$, rt, 5 min; (ii) glacial acetic acid, hexamine, rt, 85-90^oC, 5 h; (iii) EtOH/HCL, rt, 4–5 h.

Table 1. Infrared spectral data (cm^{-1}) of the Schiff base Ligands.

Comp.	υC-O	υC=N	Triazole υC=O	Coumarine υC=O	Ar-υOH
6	1053	1644,1560,1500,	1676	1695	_
10	1041	1614,1547,1535	1708	1672	3380
13	1043	1601,1544,1509	1700	1673	_
16	1044	1629,1548,1463	1715	1702	_
20	1238	1623,1569,1507	1721	1665	_

Table 2. ^{1}HNMR data (DMSO-d_6) d (ppm) of the Schiff base Ligands.

Comp.	-CH_3	-OCH_3	-CH_2	Arom-H	-N=CH	OH
6	_	_	_	9.42 (s, 2H), 7.15 (m, 4H), 6.82 (m, 4H), 6.39 (m, 3H)	10.28 **(**s,2H)	_
10		_	_	9.31 (s, 2H), 9.06 (m, 2H), 8.8 (m, 2H), 8.58 (s, 1H), 7.09 (m, 2H)	10.12 **(**s,2H)	13.52 (s, 2H**)**
13	_	_	4.91 (s, 4H)	9.40 (s, 2H), 7.20 (m, 2H), 6.81 (m, 2H), 7.39 (s, 1H), 6.92 (m, 2H)	10.32 **(**s,2H)	_
16	2.84 (s,6H)	_	_	9.39 (s, 2H), 9.06 (m, 2H), 8.18 (m, 2H), 8.58 (s, 1H), 6.78 (m, 2H)	10.21 **(**s,2H)	_
20	_	3.40 (s,3H) 3.64 (s,3H)	_	9.39 (s, 2H), 7.25 (m, 2H), 7.08 (m, 2H), 6.93 (s, 1H), 6.37 (m, 2H)	10.43 **(**s,2H)	_

Table 3. ^{13} CNMR Data (DMSO-d_6) d (ppm)of the Schiff base Ligands

Comp.	-C=O	Oxadiazole-C-2/ C-5	Triazole-C-5/ C-3	Arom-C	-OCH_3	-CH_3
6	160.81	165.27/ 154.46	151.85/ 146.54	152.08 (2CH), 150.42 (2CH), 149.93 (4C), 133.13 (4CH), 132.96 (2CH), 114.94 (2C).	–	–
10	160.97	165.19/ 154.11	151.15/ 145.92	153.92 (2C), 153.65 (2CH), 150.42 (2CH), 149.93 (2C), 147.84 (2CH), 133.15 (4C), 118.04 (2C).	–	18.19
13	161.30	165.31/ 154.44	153.10/ 146.41	152.11 (2C), 150.42 (2CH), 144.33 (2CH), 133.14 ($2CH_2$), 132.96 (4C), 116.17 (2CH), 113.03 (4C).	–	
16	161.44	165.33/ 154.13	153.61/ 146.92	153.23 (2C),152.95 (2CH), 151.33 (2C), 151.05 (2CH), 150.75 (2CH), 147.84 (2C), 130.48 (4C), 112.38 (4C).	–	20.83 20.38
20	160.18	164.247 154.23	154.46/ 144.80	117.52 (2C), 115.32 (2CH), 113.05 (2CH), 112.54 (2CH), 111.61 (4C), 107.05 (4C).	55.61 54.70	–

4. Discussions

The Fig. 2 illustrates the method used for the preparation of target compounds. The structures of all the newly synthesized compounds were elucidated by IR, ^{1} H-NMR, and ^{13} C-NMR spectroscopic methods. In the IR spectra of compound 2, C=N bands were observed at about 1629-1463 cm^{-1} . According to the IR spectroscopic data of compound (2), which have a amino structure, the observation of $–NH_2$ function at 3323-3210. The treatment of hydrazides with CNBr in the presence of KOH is a general method leading to the formation of 5-amino-1,3,4-oxadiazole derivatives. As the starting material 2-[4-amino-3-(2-furoyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]aceto-hydrazide (1) was used to produce synthesis of 4-amino-2-[(5-amino-1,3,4-oxadiazol-2-yl)methyl]-5-(2-furoyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (2) (fig. 1). In contrast to compound 1, the ^{1} H-NMR spectrum of compound 2 displayed a signal at 1.65 ppm belonging to the $–NH_2$ group, while the $-NHNH_2$ signals disappeared.

The synthesis of the corresponding schiff base derivatives of compound 2 was performed by the reaction of compound 2 with formyl-hydroxy-4-methyl coumarin derivatives the presence of the catalytic amount of H_2SO_4. In the ^{1}H-NMR spectra additional signals due to a formyl-hydroxy-4-methyl coumarin nucleus were recorded at the aromatic region. The absorption bands due to the 2 –OH groups of coumarin moiety were recorded at 3414 cm^{-1} in the IR spectra of schiff bases. Moreover, the signal recorded at 10.38 ppm in the ^{1}H-NMR spectra of this compounds was assigned to the 2–OH groups.

5. Conclusions

Recently, many scientist are showing a great interest in the synthesis and physico-chemical properties of transition metal complexes with substituted 1,2,4-triazoles. Triazoles and their derivatives have been evidenced to be effective bactericides, pesticides, fungicides and insecticides [24, 25]. Many Schiff bases obained from either heterocyclic amines or aldehydes possess excellent ability to synthesise transition metals complexes [26].

Coumarins since decades known as anti-inflammatory, antioxidant, antithrombtic, antiallergic, hepatoprotective, antiviral and anticarcinogenic [27-30]. The hydroxycoumarins which are typical phenolic compounds are famous as metal chelators and free redical scavengers activity, furthermore hydroxycoumatins are also shows powerful chain-breaking antioxidants activity [31]. The coumarins possess a extra ordinary array of biochemical and pharmacological actions [32], the antitumor effects of coumarin and its major metabolite, 7-hydroxycoumarin,were tested in several human tumor cell lines. Furthermore, cytotoxicity of coumarin derivatives complexes were examined on several neuronal cell lines [33].

Thus the amin idea of our present research work is to synthesize coumarin, triazole drieved Schiff bases as well as to synthisis variety of metal complexes with various transition metal ion.

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