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Synthesis, spectral characterization of some new 3-heteroaryl azo 4-hydroxy coumarin derivatives and their antimicrobial evaluation

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Abstract

In the present research study, 3-heteroarylazo 4-hydroxy coumarin derivatives were synthesized and evaluated *in vitro* for their preliminary antibacterial activities against four different pathogenic bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa*. Antibacterial activity of each compound was compared with standard drug, Ampicillin. The compounds were interpreted by UV, IR, ^{1}H NMR, mass spectroscopy and X-ray diffraction studies. Solvatochromic behaviour of these compounds was also investigated by UV–vis spectra. Zone of inhibition and minimum inhibitory concentration revealed that all the products exhibited greater antibacterial potential against all bacterial strains except 4g.3-Thiazolylazo and 3-(4-phenyl thiazolylazo) of 4-hydroxy coumarin, which have been exhibiting good zone of inhibition against both gram +ve strains and gram −ve strains, where as the compound pyrazolone azo analogue 4e has tremendous antibacterial activity. Finally we concluded that the compounds having thiazole, pyrazole and triazole nucleus in individual molecular structure clubbed with potent antibacterial pharmacophore of 4-hydroxy coumain showed antibacterial activities.

Keywords: 4-Hydroxy coumarin (HC); Heteroarylamine; Diazotization; Coupling; Antibacterial activity

1. Introduction

Nowadays, the use of nitrogen bearing heterocyclic intermediates in the synthesis of azo disperse dye is well established and the resultant dyes give higher tinctorial strength and are brighter than those aromatic primary amine based diazo components [1]. Dyes synthesized from heterocyclic amines produce pronounced bathochromic effect, when compared to the corresponding aniline compounds [2]. Azo dyes based on heterocyclic amines have been studied widely due to their excellent thermal [3], optical [4] and medicinal properties, such as antibacterial [5], antiviral [6], antifungal [7] and antioxidant activities [8]. Incorporation of hydrazino and azo group has been reported to enhance the pharmacological activity of heterocyclic compounds [9]. Azo dyes are the most important group of synthetic colourants. Furthermore, thiazoles are important compounds that have many derivatives with wide range of pharmacological properties. 2-Amino thiazole derivatives can be obtained by the reaction of acetophenone with thiourea in the presence of iodine [10]. 4-Hydroxycoumarin is a structurally a Benz[α]pyrone derivative and was an intermediate synthetic precursor

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in the preparation of potent anticoagulant drug such as warfarin. The aryl substitution at C-3 of 4-hydroxy coumarin is very essential for exhibiting broad biological actions such as anti-viral [11], anti-bacterial [12], anticancer [13], anticoagulant [14] and antioxidant activities [15,16]. Insertion of aryl/hetero aryl azo in C-3 of coumarin has been reported to have a good antimicrobial activity [17,18]. The 4-hydroxy 3-hetroaryl coumarin moiety is found in many natural and synthetic products and also could be useful in significant biological actions [19]. A part of our investigation has focused on the synthetic and medicinal utilities of newly prepared heterocyclic azo compounds. According to these medicinal values in the present study, a series of linear azodyes were synthesized by coupling of 4-hydroxy coumarin with diazonium salts of potent antimicrobial pharmacophores of heterocyclic amine moieties, such as derivatives of 2-amino thiazole, 2-amino pyridine, 3-amino triazole and 4-amino pyrazolone.

2. Experimental

2.1. Instruments and methods

The chemicals used in the present studies were of synthetic grade, and some were sourced from Merck Company Ltd. The products were characterised by IR (JASCO FT/IR 4100 Spectrophotometer using K Br disc), ^{1}H NMR (Bruker ^{1}H NMR 400MHZ) using TMS as an internal standard, UV (JASCO V-630 Spectrophotometer), LC–MS (Shimadzu-Mass spectrophotometer) and elemental analysis was carried out by using Perkins Elmer-2400C H N S Analyser system. An X-ray diffraction (XRD) pattern of silica was obtained with Cu Ka X-ray source including and a step of 0.02(2θ) and run $2\theta = 6–80^\circ$ at room temperature. The melting points were determined by open capillary method and remained uncorrected. The purity of prepared compounds was checked by TLC using silica gel with appropriate solvents ethyl acetate and cyclohexane in 1:1. Elemental (C, H, N, S) analysis indicated that the calculated and found values were within the acceptable limits (±0.4%).

2.2. General method of synthesis of 4-hydroxy-3-(heteroaryl-2-yldiazenyl)-2H-chromen-2-one (4a, 4b, 4c, 4d, 4e, 4g) [20]

A cold solution of sodium nitrite (0.207 g, 3 mmol) was added dropwise into the solution of six different individual substituted hetero aromatic amines (3 mmol) with conc. Sulphuric acid (8–9 mmol) and water (5 ml) were kept on an ice bath. The temperature of the reaction was maintained up to 5 °C. When addition was completed, the solution was kept for 15 min with occasional stirring to complete the diazotization. Then it was poured into an ice-cold solution of 4-hydroxy coumarin (0.543 g, 3 mmol) in 10 ml of acetate buffer solution (pH = 5) in ethanol. Then resultant mixtures were stirred at 0–5 °C and allowed to stand in an ice bath for 1 h. The colour products obtained were filtered and washed with water. Finally the obtained products were dried and recrystallised by ethanol.

2.3. Synthesis of 4-[(4-hydroxy-2-oxo-2H-chromen-3-yl) diazenyl]-N-(5-methylisoxazol-3-yl) benzenesulfonamide (4f)

A cold solution of sodium nitrite (0.207 g, 3 mmol) was added dropwise into the solution of sulfamethoxazole (3 mmol) with conc. Hydrochloric acid (8–9 mmol) and water (5 ml)were kept on an ice bath. The temperature of the reaction was maintained up to 5 °C. When addition was completed, the solution was kept for 15 min with occasional stirring to complete the diazotization. Then it was poured into an ice-cold solution of 4-hydroxy coumarin (0.543 g, 3 mmol) in 20 ml of 10% sodium hydroxide solution. Then resultant mixture was stirred and kept on an ice bath for 30 min at a temperature of 5 °C. The pH was maintained at about 5–6. The obtained products were filtered and washed with cold distilled water. Finally the obtained product was dried and recrystallised by ethanol.

2.3.1. 4-Hydroxy-2H-chromen-2-one

White solid, m.p. (°C): 207–210 (lit. 211–213 °C) [21]; UV–vis (λ_{max}, ethanol): 294 nm; IR (K Br) cm^{-1}: 3417 (O–H str), 2993 (Ar–H), 1698 (C=O str. lactone carbonyl), 1610 (C=C str), 1198 (=C–O–H bending), 1102 (C–O str); ^{1}H NMR (DMSO-d_6) δ: 15.56 (s, 1H, 4-OH) 7.58 (d, 1H, $J = 7.2$ Hz), 7.42–7.58 (m, 1H), 7.15–7.23 (m, 2H), 5.45 (s, coumarin H-3) [22].

2.3.2. 4-Hydroxy-3-(thiazol-2-yldiazenyl)-2H-chromen-2-one (4a)

IR (K Br) cm^{-1}: 3418 (O–H str), 2928 (Ar–H), 1696 (C=O str. lactone carbonyl), 1609 (C=C str), 1554 (–N=N–), 1197 (C–O str), 1198 (=C–O–H bending), 947 (C–S str); ^{1}H NMR (DMSO-d_6) δ: 7.92 (d, coumarin H-5, $J = 8.1$ Hz), 7.59 (m, coumarin H-6), 7.63 (m, coumarin H-7), 7.36 (d, coumarin H-8, $J = 8.1$ Hz), 7.22–7.34 (d, 2H, thiazole-H), 13.56 (s, 1H, 4-OH); analysis calcd% for $C_{12}H_7N_3O_3S$: C, 52.74; H, 2.58; N,