Synthesis and Biological Evaluation of Pyrrole Derivatives Bearing Coumarin Scaffold

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Abstract:
Synthesis of pyrrole derivatives clubbed with coumarin scaffold was achieved by one pot multi-component cyclocondensation of 1,3 dicarbonyl compound, nitromethane, amine, and substituted aldehyde using lewis acid as catalyst. The structures of synthesized derivatives were elucidated by FT-IR, Mass and ^{1}H NMR spectroscopy. The newly synthesized compounds were subjected to antimicrobial evaluation.

Keywords: Pyrrole derivatives, coumarin, multi-component, antimicrobial evaluation.

1. Introduction

Pyrroles and their derivatives are one of the most important classes of heterocyclic compounds. They exhibit extensive biological and pharmacological properties (Bellur and Langer, 2006). Many pyrrole derivatives have shown interesting biological properties such as antibacterial (Daidone, Maggio and Schillaci, 1990), anti-inflammatory (Mohamed, Kamel and Fathallah, 2011), antioxidant (Demir, Akhmedov and Sesenoglu, 2002), antitumor (Yang et al., 2013), antifungal (Meshram, Prasad & Aravind Kumar, 2010) and immune suppressant activities (Davis et al., 2008). Highly functionalized pyrroles are subunits of heme, chlorophyll, bile pigments, vitamin B12 and pyrrole alkaloids isolated from marine source (Reisser & Maas, 2004). Atrovastatin (Lipitor) is a drug for lowering cholesterol (Mathew and Asokan, 2006).

On the other hand, it is well known that coumarin derivatives are widely found in nature. They belong to the family of lactones having 1-benzopyran-2-one system that can be isolated from plants as well as total synthesis can be carried out in the laboratory (Ajani and Nwinyi, 2010). Many coumarins have been isolated from the plants, and are reported to possess many pharmacological activities like anti-inflammatory & antipyretic (Backhouse et al., 2001), antioxidant (Piao et al., 2004), bronchodilator (Ramanitrahasimbola et al., 2005), vasodilator (Dongmo et al., 2007), antiamoebic (Iqbal, Bhat and Azam, 2009), antibacterial (Tadaa et al., 2002) and antifungal (Stein et al., 2006) activities.

Keeping in mind above facts, it was thought worthwhile to incorporate both the biologically active heterocycles in a single molecule, and evaluate them for various antimicrobial activities. To achieve this task, we set upon a program which incorporated the one pot multicomponent cyclocondensation of 1,3 dicarbonyl compound bearing coumarin motif, primary amine, nitromethane, and appropriate aromatic aldehyde in presence of lewis acid as catalyst.

2. Material and Methods

2.1 Experimental

Melting points were determined in open glass capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded shimadzu FT-IR-8400 instrument using potassium

bromide (KBr) pellet method. Mass spectra were recorded on shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on elemental vario EL III Carlo erba 1108 model and the results are in agreements with the structures assigned.

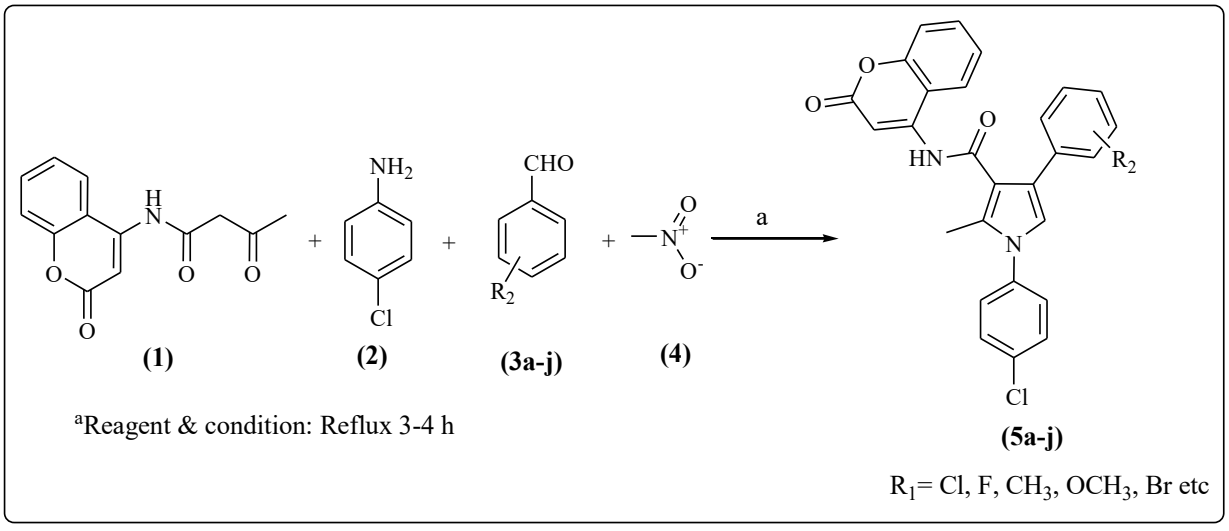
3. Preparation of 1,3-dicarbonyl compound bearing coumarin motif

Slurry of NaOH (3 gm) in 4 mL water was taken in R.B.F. containing 30 mL toluene. 4-amino coumarin (10 gm) was added to reaction mixture. The reaction mixture was refluxed for 24 h. solvent was removed under mixture and ether (50 mL) was added. The precipitated solid was filtered and washed with ether and subsequently dried over sodium sulfate.

4. Preparation of substituted pyrrole

To a stirred solution of aromatic amine (1.5 mmol), aromatic aldehyde (1 mmol) and acetoacetanilide (1 mmol) in nitromethane (1 ml) was added anhydrous $ZnCl_2$ (0.1 mmol) and the mixture was heated to reflux slowly for 3-4 h and cooled down to room temperature, followed by addition of 5 ml methanol and allowed to reflux for 1 h and cooled down to room temperature, after confirmation from TLC obtain desired compound was filtered and washed with methanol to yield crystalline solid. In some compounds if solid do not precipitates out, the excess solvent was removed under vacuum, and to the residue was added petroleum ether and allowed to crystallize the product at room temperature and isolated in 60-80% yield.

Reaction Scheme



[a]Reagent & condition: Reflux 3-4 h

R_1= Cl, F, CH_3, OCH_3, Br etc

Analytical Data

4-(3-chlorophenyl)-1-(4-chlorophenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5a)

IR (cm^{-1}): 3435 (N-H Stretching), 3013 (Aromatic -C-H stretching), 2941 (Aliphatic -C-H stretching), 1643 (-C=O stretching), 1346 (-C-N stretching), 1068 (-C-O-C stretching), 914 (-C-H bending), 786 (-C-H bending), ^{1}H NMR (DMSO-d_6) δ ppm: 2.02 (s, 3H), 4.38 (s, 1H), 5.45 (s, 1H), 6.85-6.87 (m, 2H), 7.10-7.11 (m, 2H), 7.14-7.19 (m, 2H), 7.38-7.42 (m, 2H), 7.58-7.62 (m, 2H), 7.67-7.72 (m, 2H), 9.45 (s, 1H); MS: m/z = 488; Anal. Calcd. for $C_{27}H_{18}Cl_2N_2O_3$: C, 66.27; H, 3.71; N, 5.72; Found: C, 66.15; H, 3.65; N, 5.65 %.

4-(3-bromophenyl)-1-(4-chlorophenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5b)

IR (cm^{-1}): 3409 (N-H Stretching), 3068 (Aromatic -C-H stretching), 2964, (Aliphatic -C-H stretching), 1693 (-C=O Stretching), 1344 (-C-N stretching), 1003 (-C-O-C stretching), 729 (-C-H bending), ^{1}H NMR (DMSO-d_6) δ ppm: 2.08 (s, 3H), 4.39 (s, 1H), 5.49 (s, 1H), 6.82-6.84 (m, 2H), 7.06-7.08 (m, 2H), 7.15-7.20 (m, 2H), 7.35-7.41 (m, 2H), 7.60-7.64 (m, 2H), 7.70-7.75 (m, 2H), 9.47 (s, 1H); MS: m/z = 532; Anal. Calcd. for $C_{27}H_{18}BrClN_2O_3$: C, 60.75; H, 3.40; N, 5.25; Found: C, 60.66; H, 3.35; N, 5.19 %.

4-(4-chlorophenyl)-1-(4-chlorophenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5c)

IR (cm^{-1}): 3425 (N-H Stretching), 3003 (Aromatic -C-H stretching), 2951 (Aliphatic -C-H stretching), 1653 (-C=O stretching), 1346 (-C-N stretching), 1068 (-C-O-C stretching), 914 (-C-H bending), 786 (-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.00 (s, 3H), 4.37 (s, 1H), 5.40 (s, 1H), 6.80-6.82 (m, 2H), 7.08-7.09 (m, 2H), 7.11-7.17 (m, 2H), 7.31-7.37 (m, 2H), 7.56-7.60 (m, 2H), 7.65-7.70 (m, 2H), 9.42 (s, 1H); MS: m/z = 488; Anal. Calcd. for $C_{27}H_{18}Cl_2N_2O_3$: C, 66.27; H, 3.71; N, 5.72; Found: C, 66.11; H, 3.61; N, 5.63 %.

4-(3-bromophenyl)-1-(4-chlorophenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5d)

IR (cm^{-1}): 3425 (N-H Stretching), 3034 (aromatic -C-H stretching), 2923 (aliphatic -C-H stretching), 1698 (-C=O stretching), 1323 (-C-N stretching), 1032 (-C-O-C stretching), 934 (-C-H bending), 2.00 (s, 3H), 4.30 (s, 1H), 5.41 (s, 1H), 6.72-6.79 (m, 2H), 7.08-7.10 (m, 2H), 7.19-7.24 (m, 2H), 7.36-7.46 (m, 2H), 7.62-7.66 (m, 2H), 7.70-7.74 (m, 2H), 9.49 (s, 1H); MS: m/z = 532; Anal. Calcd. for $C_{27}H_{18}BrClN_2O_3$: C, 60.75; H, 3.40; N, 5.25; Found: C, 60.62; H, 3.33; N, 5.14 %.

1-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5e)

IR (cm^{-1}): 3425 (N-H Stretching), 3066 (aromatic -C-H stretching), 2970 (aliphatic -C-H stretching), 1660 (-C=O stretching), 1598, 1566, 1502 (-C=C- ring strain), 1354 (-C-N stretching), 1056 (-C-O-C stretching), 759 (-C-H bending), ^{1}H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H), 4.39 (s, 1H), 5.46 (s, 1H), 6.87 -6.89 (m, 2H), 7.10-7.13 (m, 2H), 7.19-7.21 (m, 2H), 7.31-7.37 (m, 2H), 7.57-7.61 (m, 2H), 7.77-7.87 (m, 2H), 9.50 (s, 1H); MS: m/z = 484; Anal. Calcd. for $C_{28}H_{21}ClN_2O_4$: C, 69.35; H, 4.36; N, 5.78; Found: C, 69.29; H, 4.25; N, 5.67 %.

1-(4-chlorophenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-4-p-tolyl-1H-pyrrole-3-carboxamide (5f)

IR (cm^{-1}): 3413 (N-H Stretching), 3034 (Aromatic -C-H stretching), 2923 (Aliphatic -C-H stretching), 1643 (-C=O stretching), 1334 (-C-N stretching), 1022 (-C-O-C stretching), 932 (-C-H bending), 732 (-C-H bending),), ^{1}H NMR (DMSO-d_6) δ ppm: 2.04 (s, 3H), 2.12 (S, 3H), 4.42 (s, 1H), 5.48 (s, 1H), 6.86 -6.88 (m, 2H), 7.12-7.15 (m, 2H), 7.20-7.23 (m, 2H), 7.34-7.38 (m, 2H), 7.58-7.62 (m, 2H), 7.78-7.88 (m, 2H), 9.52 (s, 1H); MS: m/z = 468; Anal. Calcd. for $C_{28}H_{21}ClN_2O_3$: C, 71.72; H, 4.51; N, 5.97; Found: C, 71.62; H, 4.40; N, 5.85 %.

1-(4-chlorophenyl)-4-(4-hydroxyphenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5g)

IR (cm^{-1}): 3425 (N-H Stretching), 3023 (aromatic -C-H stretching), 2943 (aliphatic -C-H stretching), 1688 (-C=O stretching), 1312 (-C-N stretching), 1002 (-C-O-C stretching), 981 (-C-H bending),), ^{1}H NMR (DMSO-d_6) δ ppm: 2.02 (s, 3H), 3.44 (S, 1H), 4.44 (s, 1H), 5.50 (s, 1H), 6.88 -6.90 (m, 2H), 7.14-7.17 (m, 2H), 7.22-7.25 (m, 2H), 7.36-7.40 (m, 2H), 7.60-7.64 (m, 2H), 7.80-7.86 (m, 2H), 9.48

(s, 1H); MS: m/z = 470; Anal. Calcd. for $C_{27}H_{19}ClN_2O_4$: C, 68.87; H, 4.07; N, 5.95; Found: C, 68.81; H, 4.01; N, 5.82 %.

1-(4-chlorophenyl)-4-(4-fluorophenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5h)

IR (cm^{-1}): 3416 (N-H Stretching), 3074 (aromatic -C-H stretching), 2991 (aliphatic -C-H stretching), 1670 (-C=O Stretching), 1477 (-C=C- ring strain), 1338 (-C-N stretching), 1128 (-C-O-C stretching), 748 (-C-H bending), ^1H NMR (DMSO-d_6) δ ppm: 2.03 (s, 3H), 4.47 (s, 1H), 5.53 (s, 1H), 6.91 -6.94 (m, 2H), 7.17-7.20 (m, 2H), 7.25-7.28 (m, 2H), 7.39-7.43 (m, 2H), 7.63-7.67 (m, 2H), 7.83-7.89 (m, 2H), 9.51 (s, 1H); MS: m/z = 472; Anal. Calcd. for $C_{27}H_{18}ClFN_2O_3$: C, 68.58; H, 3.84; N, 5.92; Found: C, 68.51; H, 3.79; N, 5.86 %.

1-(4-chlorophenyl)-2-methyl-4-(4-nitrophenyl)-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5i)

IR (cm^{-1}): 3425 (N-H Stretching), 3057 (aromatic -C-H stretching), 2953 (aliphatic -C-H stretching), 1696 (-C=O Stretching), 1325 (-C-N stretching), 1034 (-C-O-C stretching), 659 (-C-H bending), ^1H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H), 4.39 (s, 1H), 5.46 (s, 1H), 6.87 -6.89 (m, 2H), 7.10-7.13 (m, 2H), 7.19-7.21 (m, 2H), 7.31-7.37 (m, 2H), 7.57-7.61 (m, 2H), 7.77-7.87 (m, 2H), 9.50 (s, 1H); MS: m/z = 499; Anal. Calcd. for $C_{27}H_{18}ClN_3O_5$: C, 64.87; H, 3.63; N, 8.41; Found: C, 64.81; H, 3.56; N, 8.35 %.

1-(4-chlorophenyl)-2-methyl-4-(3-nitrophenyl)-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide (5j)

IR (cm^{-1}): 3425 (N-H Stretching), 3062 (aromatic -C-H stretching), 2952 (aliphatic -C-H stretching), 1695 (-C=O stretching), 1334 (-C-N stretching), 1014 (-C-O-C stretching), 954 (-C-H bending), ^1H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H), 4.39 (s, 1H), 5.46 (s, 1H), 6.87 -6.89 (m, 2H), 7.10-7.13 (m, 2H), 7.19-7.21 (m, 2H), 7.31-7.37 (m, 2H), 7.57-7.61 (m, 2H), 7.77-7.87 (m, 2H), 9.50 (s, 1H); MS: m/z = 499; Anal. Calcd. for $C_{27}H_{18}ClN_3O_5$: C, 64.87; H, 3.63; N, 8.41; Found: C, 64.78; H, 3.51; N, 8.32 %.

5. Results and Discussion

Extensive literature survey on pyrrole derivatives reveals that pyrrole moiety contacting heterocyclic molecules exhibits significance biological potential. Thus to synthesize novel pyrrole derivatives we utilized acetoacetanilide bearing coumarin motif, nitro methane, substituted aldehydes and primary amine in presence of lewis acid to afford of 4-(substituted phenyl)-1-(substituted phenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide. The characteristic bands of (-C=O) were obtained for stretching at 1650-1750 cm^{-1}. The stretching vibrations (–C-O-C-) group showed in the finger print region of 1100-1050 cm^{-1}. (-C-N-) stretching was observed at 1400-1350 cm^{-1}. It gives aromatic (-C-H-) stretching frequencies between 3200-3000 and ring skeleton (-C=C-) stretching at 1500-1350 cm^{-1} C-H stretching frequencies for methyl and methylene group were obtained near 2950 - 2850 cm^{-1}. The molecular ion peak was found in agreement with molecular weight of the respective compound. Numbers of protons and carbons identified from ^1H NMR spectrum and their chemical shift (δ ppm) were in the agreement of the structure of the molecule. In some cases, aromatic protons were obtained as multiplet.

On evaluation of biological screening data, it can be observed that biological activity is largely affected by the substitution on phenyl ring. Three compounds **5b, 5c,** and **5e** exhibited significant antibacterial and antifungal activity as compare to standard drugs. It can be observed that electron donating group at p-position of the phenyl ring increases the biological activity whereas in rest of the compound the activity was much limited as compare to standard drugs.

Table 1: Antibacterial and antifungal activity of synthesized compounds (4a-j)

Code	Minimum inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	S. p.	E.c.	P.a.	C. a.	A. n.	A.c.
4a	200	500	250	500	1000	500	>1000
4b	50	75	62.5	62.5	100	50	50
4c	62.5	50	75	50	250	>1000	>1000
4d	75	62.5	100	500	50	100	500
4e	200	100	100	500	500	1000	200
4f	250	250	250	250	500	500	1000
4g	100	500	500	1000	250	500	500
4h	500	100	500	100	500	500	>1000
4i	250	500	500	500	200	500	200
4j	500	250	500	500	1000	1000	1000
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

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