Synthesis and characterization of Diverse Pyrrole Derivatives clubbed with Coumarin

[A]AMISH P. KHAMAR, [A]NIRUL V. GOTHI, AND [B]DIPAK C. PATEL
[a]Arts, Science & R. A. Patel commerce college, Bhadran, Gujarat.
[b]The H. N. S. B. Ltd. Science College, Himmatnagar, Gujarat.

Abstract:
Pyrrole moiety contacting heterocyclic molecules exhibit significance biological potential. Synthesis of 4-(substituted phenyl)-1-(substituted phenyl)-2-methyl-N-(2-oxo-2H-chromen-4-yl)-1H-pyrrole-3-carboxamide was achieved by one pot multicomponent reaction of acetoacetanilide bearing coumarin motif, nitro methane, substituted aldehydes and primary amine in presence of lewis acid.

Keywords: *Pyrrole, Biological potential, Multicomponent reaction, Acetoacetanilide bearing coumarin motif*

1. Introduction

The pyrrole nucleus is widespread in nature, is the key structural fragment of heme and chlorophyll, two pigments essential for life. Some representative examples of pyrrole-containing secondary metabolites are summarized above. They include some antibacterial 3-halopyrroles such as pentabromopseudodiline and pioluteorine, both isolated from bacterial sources. Pyrrole moieties are particularly prominent in marine natural products, including dimeric structures such as nakamuric acid [1] and the axially chiral marinopyrroles, which showed good activity against metacillin-resistant Staphylococcus aureus strains [2] We will finally mention the storniamide family, isolated from a variety of marine organisms (mollusks, ascidians, sponges) and containing 3,4-diarylpyrrole fragments. A number of O-methylated analogues of storniamide A have shown potent activity as inhibitors of the multidrug resistance (MDR) phenomenon [3] which can be considered as the main obstacle to successful anticancer chemotherapy. For this reason, there is much current interest in the development of new MDR modulators [4-6].

On the other hand, the coumarins are of great interest due to their biological properties. In particular, their physiological, bacteriostatic and anti-tumour activity makes these compounds attractive for further backbone derivatization and screening as novel therapeutic agents. Weber [7] and co-workers have shown that coumarin and its metabolite 7-hydroxycoumarin have antitumour activity against several human tumour cell lines. Both coumarin and coumarin derivatives have shown promise as potential inhibitors of cellular proliferation in various carcinoma cell lines [8]. In addition it has been shown that 4-hydroxycoumarin and 7-hydroxycoumarin inhibited cell proliferation in a gastric carcinoma cell line [9].

Keeping in mind various biological importances of both the heterocycles it was thought worthwhile to design a synthetic program that offers both the heterocycles in single compound. With this aim we achieved synthesis of pyrrole derivatives bearing coumarin motif through one pot multicomponent reaction using lewis acid as catalyst.

2. Experimental Section

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 acetoacetanilide 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.

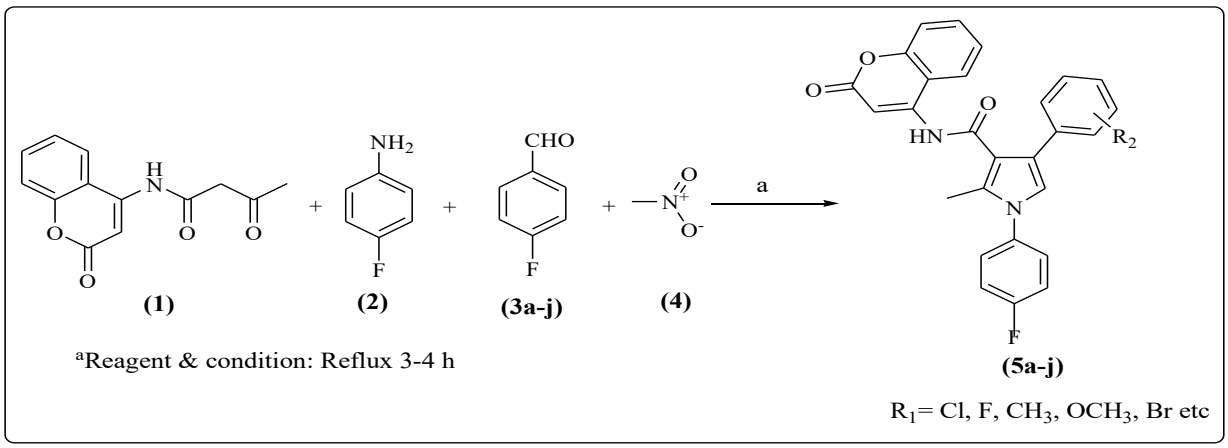

Table 1: Physical data for pyrrole derivatives bearing coumarin motif (5a-o)

Sr. No.	Code	R_1	M.P.
1	4a	3-Cl	170-172
2	4b	3-Br	214-216
3	4c	4-Cl	236-238
4	4d	4-Br	218-220
5	4e	4-OCH_3	186-188
6	4f	4-CH_3	188-190
7	4g	4-OH	210-212
8	4h	4-F	168-170
9	4i	4-NO_2	196-198
10	4j	3-NO_2	178-180

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

IR (cm^{-1}): 3089, 3064 (aromatic -C-H stretching), 2941 (aliphatic -C-H stretching), 1658 (-C=O stretching), 1309 (-C-N stretching), 1010 (-C-O-C stretching), 966 (-C-H bending), ^{1}H NMR (DMSO-d_6) δ ppm: 2.20 (s, 3H), 5.03 (s, 1H), 7.06 (s, 1H), 7.11-7.18 (m, 2H, H), 7.25-7.38 (m, 5H, H), 7.4920-7.4968 (d, 2H, H), 7.56-7.60 (m, 2H, H), 8.32-8.34 (m, 1H, H), 9.80 (s, 1H, H); MS: *m/z* = 472, Anal. Calcd. for $C_{27}H_{18}ClFN_2O_3$: C, 68.05; H, 3.51; N, 6.10; Found: C, 67.95; H, 3.37; N, 6.01%.

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

IR (cm^{-1}): 3410 (N-H Stretching), 3086 (aromatic -C-H stretching), 2908, (aliphatic -C-H stretching), 1691(-C=O Stretching), 1315 (-C-N stretching), 1003(-C-O-C stretching), 717 (-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.22 (s, 3H, H_a), 5.02 (s, 1H), 7.08 (s, 1H), 7.13-7.20 (m, 2H), 7.27-7.40 (m, 5H, H), 7.4922-7.4970 (d, 2H, H), 7.58-7.62 (m, 2H, H), 8.34-8.36 (m, 1H), 9.82 (s, 1H); MS: *m/z* = 516; Anal. Calcd. for $C_{27}H_{18}FNO_3$: C, 62.04; H, 3.20; N, 5.57; Found: C, 61.95; H, 3.02; N, 5.36%.

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

IR (cm^{-1}): 3415 (N-H Stretching), 3024 (aromatic -C-H stretching), 2984 (aliphatic -C-H stretching), 1690(-C=O Stretching), 1361(-C-N stretching), 1048 (-C-O-C stretching), 699 (-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.21 (s, 3H), 5.06 (s, 1H), 7.08 (s, 1H), 7.13-7.20 (m, 2H), 7.27-7.40 (m, 5H), 7.4918-7.4966 (d, 2H), 7.60-7.64 (m, 2H), 8.36-8.38 (m, 1H), 9.84 (s, 1H); MS: *m/z* = 472, Anal. Calcd. for $C_{27}H_{18}ClFN_2O_3$: C, 68.05; H, 3.51; N, 6.10; Found: C, 67.91; H, 3.30; N, 5.98%.

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

IR (cm^{-1}): 3425 (N-H Stretching), 3062 (aromatic- C-H stretching), 2984 (aliphatic -C-H stretching), 2894(aliphatic -CH stretching), 1693(-C=O stretching), 1263 (-C-N stretching), 1095(-C-O-C stretching), 1082 (-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.18 (s, 3H), 5.01 (s, 1H), 7.01 (s, 1H), 7.12-7.19 (m, 2H), 7.27-7.40 (m, 5H), 7.4925-7.4973 (d, 2H), 7.57-7.61 (m, 2H), 8.35-8.37 (m, 1H), 9.85 (s, 1H, H); MS: *m/z* = 516; Anal. Calcd. for $C_{27}H_{18}FNO_3$: C, 62.04; H, 3.20; N, 5.57; Found: C, 61.91; H, 3.03; N, 5.32%.

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

IR (cm^{-1}): 3425 (N-H Stretching), 3014 (aromatic -C-H stretching), 2961 (aliphatic -C-H stretching), 2823 (aliphatic -CH_2 stretching), 1669 (-C=O stretching), 1382 (-C-H bending), 1262 (-C- N stretching), 1088 (-C-H bending), 1005(-C-O-C stretching), 981 (-C-H bending) ^{1}H NMR (DMSO-d_6) δ ppm: 2.23 (s, 3H), 3.43 (S, 3H), 5.05 (s, 1H), 7.08 (s, 1H), 7.13-7.20 (m, 2H), 7.26-7.43 (m, 5H), 7.49-7.50 (d, 2H), 7.58-7.62 (m, 2H), 8.34-8.36 (m, 1H), 9.88 (s, 1H); MS: *m/z* = 468; Anal. Calcd. for $C_{28}H_{21}FN_2O_4$: C, 71.36; H, 4.21; N, 6.16; Found: C, 71.06; H, 4.01; N, 6.06%.

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

IR (cm^{-1}): 3411 (N-H Stretching), 3026 (aromatic -C-H stretching), 2956 (aliphatic -C-H stretching), 1662(-C=O stretching), 1323 (-C-N stretching), 1015(-C-O-C stretching), 702 (-C-H bending), 542 (-C-Br stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 2.22 (s, 3H), 2,.30 (S, 3H), 5.05 (s, 1H), 7.10 (s, 1H), 7.15-7.2 (m, 2H), 7.28-7.41 (m, 5H), 7.48-7.49 (d, 2H), 7.60-7.64 (m, 2H), 8.40-8.42 (m, 1H), 9.90 (s, 1H); MS: *m/z* = 452; Anal. Calcd. for $C_{28}H_{21}FN_2O_3$: C, 74.32; H, 4.68; N, 6.19; Found: C, 74.26; H, 4.59; N, 6.11%.

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

IR (cm^{-1}): 3425 (N-H Stretching), 3064 (aromatic -C-H stretching), 2941 (aliphatic -C-H stretching), 1658 (-C=O Stretching), 1500(-C=C- ring strain), 1309 (-C-N stretching), 1124 (-C-O-C stretching), 711(-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.15 (s, 3H), 4.12 (S, 1H), 5.08 (s, 1H), 7.08 (s, 1H), 7.10-7.17 (m, 2H), 7.26-7.39 (m, 5H), 7.47-7.48 (d, 2H), 7.57-7.61 (m, 2H), 8.30-8.32 (m, 1H), 9.81 (s, 1H); MS: *m/z* = 454; Anal. Calcd. for $C_{27}H_{19}FN_2O_4$: C, 71.36; H, 4.21; N, 6.16; Found; C, 71.30; H, 4.15; N, 6.04%.

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

IR (cm^{-1}): 3425 (N-H Stretching), 3012 (Aromatic -C-H stretching), 2956 (Aliphatic -C-H stretching), 1677(-C=O Stretching), 1353(-C-N stretching), 1009 (-C-O-C stretching), 713 (-C-H bending), 653(-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.18 (s, 3H), 5.00 (s, 1H), 7.08 (s, 1H), 7.15-7.21 (m, 2H), 7.27-7.39 (m, 5H), 7.49-7.50 (d, 2H, H), 7.55-7.59 (m, 2H), 8.30-8.32 (m, 1H), 9.81 (s, 1H); MS: *m/z* = 456; Anal. Calcd. for $C_{27}H_{18}F_2N_2O_3$: C, 71.05; H, 3.97; N, 6.14; Found: C, 70.98; H, 3.88; N, 6.01%.

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

IR (cm^{-1}): 3425 (N-H Stretching), 3043 (aromatic -C-H stretching), 2910 (aliphatic -CH_3 stretching), 1689 (-C=O stretching), 1236 (-C-N stretching), 1099 (-C-O-C stretching), 722 (-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.17 (s, 3H), 5.05 (s, 1H), 7.05 (s, 1H), 7.13-7.21 (m, 2H), 7.24-7.37 (m, 5H), 7.48-7.49 (d, 2H), 7.55-7.59 (m, 2H), 8.30-8.32 (m, 1H), 9.81 (s, 1H); MS: *m/z* = 483; Anal. Calcd. for $C_{27}H_{18}FN_3O_5$: C, 67.08; H, 3.75; N, 8.69; Found: C, 67.01; H, 3.68; N, 8.60%.

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

IR (cm^{-1}): 3425 (N-H Stretching), 3023 (Aromatic -C-H stretching), 2924 (Aliphatic -CH_3 stretching), 2854 (Aliphatic -CH_2 Stretching), 1698 (-C=O stretching), 1423, 1397 (-C-H bending), 1223 (-C-N stretching), 988(-C-O-C stretching), 718 (-C-H bending); ^{1}H NMR (DMSO-d_6) δ ppm: 2.24 (s, 3H), 5.07 (s, 1H), 7.09 (s, 1H), 7.15-7.21 (m, 2H), 7.28-7.42 (m, 5H), 7.49-7.50 (d, 2H), 7.57-7.61 (m, 2H), 8.32-8.34 (m, 1H), 9.80 (s, 1H); MS: *m/z* = 483; Anal. Calcd. for $C_{27}H_{18}FN_3O_5$: C, 67.08; H, 3.75; N, 8.69; Found: C, 66.99; H, 3.65; N, 8.57%.

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-2*H*-chromen-4-yl)-1*H*-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 ^{1}H 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.

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