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Note

Synthesis and antimicrobial screening of 3*H*,11*H*-9-methyl-3-oxopyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazole and its derivatives

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The coupling reaction of the diazonium salt solution of the 6-aminocoumarins **1a-c** with ethylacetoacetate has afforded the corresponding hydrazones **2a-c**, which on further intramolecular cyclisation with PPA yielded the corresponding 3*H*,7*H*,10*H*-9-acetyl-3,10-dioxopyrano[2,3-*f*]cinnolines **3a-c**. Reaction of **3a-c** with hydrazine hydrate has afforded the 3*H*,11*H*-9-methyl-3-oxopyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazoles **4a-c**, which on Mannich condensation with formaldehyde and morpholine yield the corresponding 3*H*-9-methyl-3-oxo-11-(*N*-methylenemorpholino)pyrano[2,3-*f*]cinnolino[3,4-*c*] pyrrazoles **5a-c**. The reaction of **3a-c** with phenyl hydrazine and 4-methyl-7-methoxycoumarin-6-ylhydrazine hydrochloride afforded 3*H*-9-methyl-3-oxo-11-phenyl pyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazoles **6a-c** and 3*H*-9-methyl-3-oxo-11-(4-methyl-7-methoxy-2-oxo-2*H*-[1]-benzopyran-6-yl)pyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazoles **7a-c**, respectively. The structures of the compounds **2-7a-c** have been established on the basis of spectral and analytical data. All the above compounds have been screened for their antimicrobial activities and are found to possess significant antibacterial and antifungal activities.

Keywords: Aminocoumarin, coupling, cyclisation, cinnolino [3,4-*c*]pyrrazoles, antimicrobial activity

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Coumarin derivatives have aroused considerable interest from the viewpoint of their versatile practical applications as well as their wide range of biochemical properties[1]. Several nitrogen mustards synthesized from 6-aminocoumarins are reported as antiviral[2] agents and especially effective against HIV[3]. Also, the cinnolines exhibit biological activity such as antibacterial[4] activity and are used as drugs[5]. The biological importance of the coumarins and the cinnolinones prompted us to synthesize the novel pyranocinnolinones that may possess some biological activity.

For this purpose, the diazonium salt solution of 6-aminocoumarins **1a-c** was coupled with ethylacetoacetate in aqueous ethanol (10%) in the presence of sodium acetate at 0-5°C to yield the corresponding hydrazones **2a-c**. The IR spectrum of **2a** in KBr showed bands at 3448 cm^{-1} for the N-H stretching, 1721 cm^{-1} the carbonyl group, etc. Its ^{1}H NMR spectrum in DMSO-d_6 showed a triplet at δ 1.50 for the three protons of the methyl group of -CH_2-CH_3, a sharp singlet at 2.40 for the three protons of the methyl group at C_6, a singlet at 2.48 for the three protons of the methyl group of -CO-CH_3, a quartet at 4.50 (J= 9.00Hz) for the two protons of the methylene group of -CH_2-CH_3. A singlet was observed at 10.60 for the >N*H* proton which was D_2O exchangeable. The ^{13}C NMR spectrum showed signals at δ 17.00 for the methyl carbon of -CH_2*C*H_3, 18.00 for the methyl carbon, 28.00 for the methyl carbon of -CO-*C*H_3, 65.00 for the methylene carbon of -*C*H_2CH_3, 159.00 for >*C*=N-, 161.01 for the carbonyl of the coumarin ring, 172.01 for the ester carbonyl, 196.20 for the ketonic carbonyl group.

Intramolecular cyclisation of these hydrazones **2a-c** with PPA resulted in the formation of the corresponding 3*H*,7*H*,10*H*-9-acetyl-3,10-dioxopyrano[2,3-*f*]cinnolines **3a-c**. The IR spectrum of **3a** in KBr showed bands at 3433 cm^{-1} for N-H stretching, 1720 cm^{-1} for the carbonyl group, etc. Its ^{1}H NMR spectrum in DMSO-d_6 indicated the absence of the triplet for -CH_3 and quartet for -CH_2 of -CH_2CH_3, which was observed in the ^{1}H NMR spectrum of **2a** thereby confirming the cyclization.

Reaction of **3a-c** with hydrazine hydrate in boiling ethanol furnished the 3*H*,11*H*-9-methyl-3-oxopyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazoles **4a-c**. The IR spectrum of **4a** in KBr showed bands at 3419 cm^{-1} for N-H stretching, 1722 cm^{-1} for the carbonyl group, etc. Its ^{1}H NMR spectrum in DMSO-d_6 showed a sharp singlet at δ 2.30 for the three protons of the methyl group at C_6, a singlet at 2.45 for the three protons of the methyl group at C_9. A singlet appeared at 10.30 for the >N*H* proton which was D_2O exchangeable. The ^{13}C NMR spectrum indicated the absence of signals for the carbonyl groups at δ 170.01 and 195.50 seen in the ^{13}C NMR spectrum of **3a** and showed the signal for the methyl group at C_6 at δ 17.00, 18.00 for the methyl group at C_9, 161.20 for the carbonyl group

at C_3. Compound **4a-c** on Mannich condensation with formaldehyde and morpholine yielded the corresponding 3*H*-9-methyl-3-oxo-11-(*N*-methylenemorpholino)pyrano[2,3-*f*]cinnolino [3,4-*c*]pyrrazoles **5a-c**. The IR spectrum of **5a** in KBr suggested the absence >N-H group due to the absence of any band beyond 3047, other bands were observed at 1722 for the carbonyl group, 1616, 1553, 1445, 1400 cm^{-1}, etc. Its ^1H NMR spectrum in DMSO-d_6 showed a singlet at δ 2.30 for the three protons of the methyl group at C_6, a singlet at 2.37 for three protons of the methyl group at C_9. A triplet appeared at 2.90 for the four protons of the two methylene groups of -C*H*$_2$-N-C*H*$_2$- of the morpholine ring; another triplet was observed at 3.65 for the four protons of the two methylene groups of -C*H*$_2$-O-C*H*$_2$- of the morpholine ring. A singlet was prominent at 3.83 for the two protons of the methylene group of >N-C*H*$_2$-N<. It indicated the absence of peak due to the >NH proton which was observed in the ^1H NMR spectrum of **4a**. The ^{13}C NMR spectrum showed signals at δ 18.00 for the methyl carbon at C_6, 19.00 for the carbon of the methyl group at C_9, 48.10 for the methylene carbons of -*C*H$_2$-N-*C*H$_2$- of the morpholine ring, 60.00 for the methylene carbon of >N-*C*H$_2$-N<, 67.55 for the methylene carbon of -*C*H$_2$-O-*C*H$_2$- of the morpholine ring, 161.00 for the carbonyl at C_3. Its mass spectrum showed molecular ion peak M^+ 365 (46).

Similarly, the reaction of **3a-c** with phenyl hydrazine gave the corresponding 3*H*-9-methyl-3-oxo-11-phenyl pyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazoles **6a-c**. The structure of the compounds was in agreement with the spectral and analytical data.

Also, the 4-methyl-7-methoxycoumarin-6-ylhydrazine hydrochloride[6] on reaction *in situ* with the compound **3a-c** in boiling ethanol afforded the corresponding 3*H*-9-methyl-3-oxo-11-(4-methyl-7-methoxy-2-oxo-2*H*-[1]-benzopyran-6-yl)pyrano[2, 3-*f*]cinnolino[3,4-*c*]pyrrazoles **7a-c** (**Scheme I**). The IR spectrum of **7a** in KBr indicated the absence of >N-H or -NH_2 due to the absence of prominent bands beyond 3057 cm^{-1}, other bands were observed at 1724 cm^{-1} for the carbonyl group, etc. Its ^1H NMR spectrum in DMSO-d_6 showed a sharp singlet at δ 2.30 for three protons of the methyl group at C_6, a singlet at 2.38 for three protons of the methyl group at $C_{4'}$. A singlet appeared at 2.42 for the three protons of the methyl group at C_9; another singlet was observed at 3.80 for the three protons of the methoxy group. The disappearance of the peak due to >NH proton seen in the ^1H NMR spectrum of **3a** also proved the product formation. The ^{13}C NMR spectrum indicated the absence of signals for the carbonyl groups at δ 170.01 and 195.50 seen in the ^{13}C NMR spectrum of **3a**; the signal for the methyl group at C_6 appeared at δ 17.00, 17.50 for the methyl carbon at C_4', 18.00 for the carbon of the methyl group at C_9, 56.55 for the methoxy carbon, 161.20 for the carbonyl at C_3, 162.00 for the carbonyl at $C_{2'}$. Mass spectrum showed molecular ion peak M^+ 454 (32).

Antimicrobial Screening

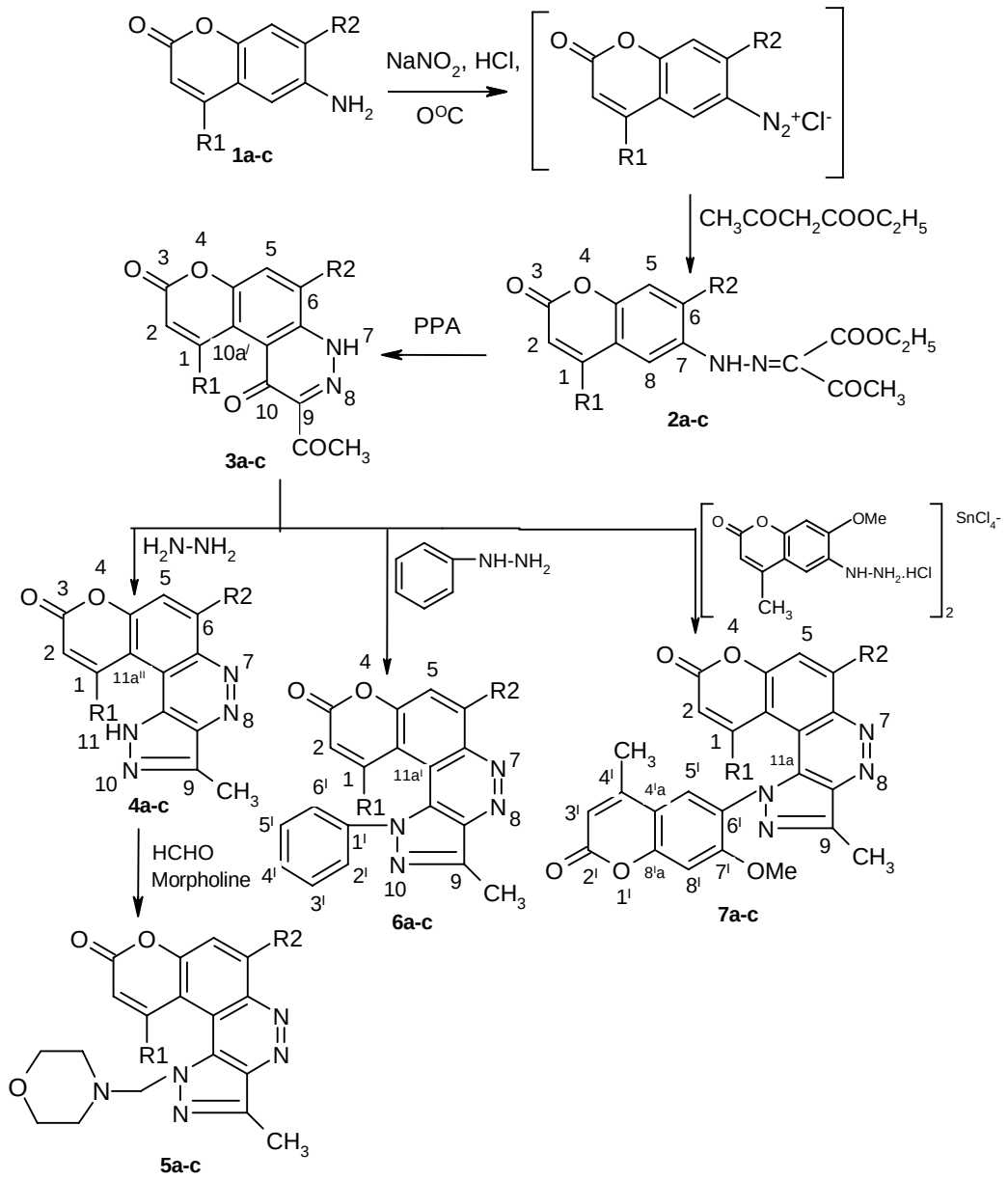
All the above compounds **2-7a-c** were screened for their antibacterial activity against *S. aureus,* and *S. typhi* and antifungal activity against *A. niger* and *C. albicans* **(Table I)**. The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[9]. DMF was used as a solvent and blank. Ciproflxacin and miconazole were used as the antibacterial and antifungal standards respectively. An examination of result reveals that all the compounds showed antimicrobial activity ranging from 50 to 200 μg/mL.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer using KBr (cm^{-1}), ^1H and ^{13}C NMR on a Bruker AMX500 MHz using TMS as an internal standard and DMSO-d_6 as a solvent; mass spectra on a Shimadzu GC-MS. The homogenity of the compounds was determined on the silica gel plates. The spots were developed in the iodine chamber. All the compounds gave satisfactory elemental analysis C, H, N.

Ethylacetoacetate-6-coumarinyl hydrazone derivatives 2a-c. To a well stirred solution of ethylacetoacetate (1.30 g, 0.01 mole) in ethanol (20 mL) and water (2 mL) containing sodium acetate (1 g) was added the diazonium salt solution of 6-aminocoumarins **1a-c** (prepared by diazotisation of 6-aminocoumarin (**1a-c**, 0.01 mole) with conc. HCl (5 mL) and sodium nitrite (0.73 g, 0.01 mole) in water at 0-5°C by usual method) with stirring over a period of 30 min. at 0-5°C. The stirring was continued for further 2 hr after the addition at the same temperature. The product formed was filtered, washed with water, dried and recrystallised from ethanol.

2a: Mol. formula: $C_{16}H_{16}N_2O_5$, m.p. 156°C, yield: 78%; ^1H NMR: δ 1.50 (t, 3H, -CH_2-C*H*$_3$), 2.40 (s, 3H, C_6-C*H*$_3$), 2.48 (s, 3H, -CO-C*H*$_3$), 4.50 (q, *J*= 9.00 Hz, 2H, -C*H*$_2$-CH_3), 6.40 (d, *J*= 9.50Hz, 1H, C_2-*H*), 7.15



1a - 7a: R_1= H, R_2= CH_3
1b - 7b: R_1= CH_3, R_2= CH_3.
1c - 7c: R_1= CH_3, R_2= OCH_3.

Scheme I

(s, 1H, C_5-*H*), 7.80 (s, 1H, C_8-*H*), 8.00 (d, *J*= 9.50Hz, 1H, C_3-*H*), 10.60 (s, 1H, >N*H*, D_2O exchangeable), ^{13}C NMR: δ 17.00 (-CH_2*C*H_3), 18.00 (-*C*H_3), 28.00 (-CO-*C*H_3), 65.00 (-*C*H_2CH$_3$), 116.40 (C_3), 118.80 (C_{4a}), 127.26 (C_5), 137.13 (C_8), 144.00 (C_4), 148.19 (C_6), 153.19 (C_7), 154.00 (C_{8a}), 159.00 (>*C*N), 161.01 (coumarin >*C*=O), 172.01 (ester >*C*=O), 196.20 (-*C*O-CH$_3$). **2b**: Mol. formula: $C_{17}H_{19}N_2O_5$, m.p. 177°C, yield: 85%. **2c**: Mol. formula $C_{17}H_{19}N_2O_6$, m.p. 189°C, yield: 87%**.**

3*H*,7*H*,10*H*-9-Acetyl-3,10-dioxopyrano[2,3-*f*]cinnoline 3a-c. A mixture of **2a-c** (0.01 mole) and PPA was heated for 1 hr. The mixture was then cooled and poured into crushed ice and water, filtered, washed with water, dried and recrystallised from ethanol.

3a: Mol. formula $C_{14}H_{10}N_2O_4$, m.p. 172°C, yield 73%; ^{1}H NMR: δ 2.30 (s, 3H, C_6-C*H*$_3$), 2.45 (s, 3H, -CO-C*H*$_3$), 6.44 (d, *J*= 9.50Hz, 1H, C_2-*H*), 7.90 (s, 1H, C_5-*H*), 8.10 (d, *J*= 9.50Hz, 1H, C_1-*H*), 10.60 (s, 1H, >N*H*, D_2O exchangeable); ^{13}C NMR: δ 18.00 (-*C*H$_3$),

Table I — Antimicrobial activity data (MIC μg/mL) of **2-7a-c**.

Compd	Antibacterial activity		Antifungal activity		Compd	Antibacterial activity		Antifungal activity	
	S. aureus	*S. typhi*	*A. niger*	*C. albicans*		*S. aureus*	*S. typhi*	*A. niger*	*C. albicans*
2a	++	+++	+++	+	**5b**	++	-	+	++
2b	+++	+++	+++	++	**5c**	++	+	+	+++
2c	+++	++++	++++	+++	**6a**	++	+	++	++
3a	++	++	+	+	**6b**	++	++	++	++
3b	+++	++	++	+++	**6c**	+++	++	+++	++
3c	+++	+++	+++	++++	**7a**	++	++	++	+
4a	+	-	+	++	**7b**	++	+++	++	++
4b	++	+	+	++	**7c**	+++	++++	++	+++
4c	+++	+	++	+++	C	*	*		
5a	+	-	-	+	M			*	*

Note**:** C = ciprofloxacin, M = miconazole, 200 μg/mL= +, 150 μg/mL= ++, 100 μg/mL= +++, 50 μg/mL= ++++, - = No activity upto 200 μg/mL, * = 5 μg/mL

28.00 (-CO-*C*H$_3$), 116.25 (C$_2$), 118.50 (C$_{10a'}$), 130.00 (C$_{10a}$), 137.13 (C$_5$), 143.45 (C$_1$), 148.02 (C$_{6a}$), 153.80 (C$_6$), 154.00 (C$_{4a}$), 159.00 (C$_9$), 161.20 (C$_3$ >*C*O), 170.01 (C$_{10}$ >*C*O), 195.50 (-*C*O-CH$_3$); **3b**: Mol. formula: $C_{15}H_{12}N_2O_4$, m.p. 169°C, yield: 74%; **3c**: Mol. formula $C_{15}H_{12}N_2O_5$, m.p. 180°C, yield: 70%.

3*H*,11*H*-9-Methyl-3-oxopyrano[2,3-*f*]cinnolino-[3,4-*c*]pyrrazole 4a-c: To the solution of compound **3a-c** (0.01 mole) in ethanol (25 mL) was added hydrazine hydrate (0.01 mole) and refluxed for 3 hr. The product formed was filtered, dried and recrystallised from ethanol.

4a: Mol. formula $C_{14}H_{14}N_4O_2$, m.p. 183°C, yield: 61%; ^{1}H NMR: δ 2.30 (s, 3H, C$_6$-C*H*$_3$), 2.45 (s, 3H, C$_9$-C*H*$_3$), 6.42 (d, *J*= 9.50Hz, 1H, C$_2$-*H*), 7.80 (s, 1H, C$_5$-*H*), 8.05 (d, *J*= 9.50Hz, 1H, C$_1$-*H*), 10.30 (s, 1H, >N*H*, D$_2$O exchangeable), ^{13}C NMR: δ 17.00 (C$_6$-CH$_3$), 18.00 (C$_9$-CH$_3$), 116.25 (C$_2$), 118.50 (C$_{11a''}$), 132.00 (C$_{11a'}$), 137.13 (C$_5$), 144.20 (C$_1$), 148.02 (C$_{6a}$ & C$_{8a}$), 149.00 (C$_{11a}$), 153.80 (C$_6$), 154.00 (C$_{4a}$), 159.00 (C$_9$), 161.20 (C$_3$ >*C*O); **4b**: Mol. formula: $C_{15}H_{16}N_4O_2$, m.p. 181°C, yield: 60%. **4c**: Mol. formula: $C_{15}H_{16}N_4O_3$, m.p. 185°C, yield: 60%.

3*H*-9-Methyl-3-oxo-11-(*N*-methylenemorpholino)-pyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazole 5a-c. To the mixture of compound **4a-c** (0.01 mole) and formaldehyde (0.2 g, 0.01 mole) was added morpholine (1.74 g, 0.02 mole) and the mixture was stirred at rt for 2 days. The reaction mixture was then poured into ice-water containing small amount of conc HCl. The product thus obtained was filtered, washed well with water, dried and recrystallised from ethanol.

5a: Mol. formula: $C_{19}H_{19}N_5O_3$, m.p. 193°C, yield: 70%; ^{1}H NMR: δ 2.30 (s, 3H, C$_6$-C*H*$_3$), 2.37 (s, 3H, C$_9$-C*H*$_3$), 2.90 (t, 4H, -C*H*$_2$-N-C*H*$_2$, morpholine ring), 3.65 (t, 4H, -C*H*$_2$-O-C*H*$_2$, morpholine ring), 3.83 (s, 2H, >N-C*H*$_2$-N<), 6.42 (d, *J*= 9.50Hz, 1H, C$_2$-*H*), 7.80 (s, 1H, C$_5$-*H*), 8.05 (d, *J*= 9.50Hz, 1H, C$_1$-*H*); ^{13}C NMR: δ 18.00 (C$_6$-*C*H$_3$), 19.00 (C$_9$-*C*H$_3$), 48.10 (-*C*H$_2$-N-*C*H$_2$-, morpholine ring), 60.00 (>N-*C*H$_2$-N<), 67.55 (-*C*H$_2$-O-*C*H$_2$-, morpholine ring), 116.25 (C$_2$), 143.45 (C$_1$), 148.02 (C$_{6a}$), 153.80 (C$_{4a}$), 159.00 (C$_9$), 161.00 (C$_3$ >*C*O), 118.00-148.00 (6 C-atoms); MS (m/z, %): M$^+$ 365 (46), 237 (23), 236 (38), 210 (15), 182 (44), 154 (17), 153 (04), 128 (19), 125 (40), 100 (100); **5b**: Mol. formula $C_{20}H_{21}N_5O_3$, m.p. 210°C, yield: 70%; **5c**: Mol. formula: $C_{20}H_{21}N_5O_4$, m.p. 198°C, yield: 69%.

3*H*-9-Methyl-3-oxo-11-phenyl pyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazole 6a-c: A mixture of **3a-c** (0.01 mole) and phenyl hydrazine (1.08 g, 0.01 mole) in ethanol (25 mL) was refluxed for 3 hr. The product formed was filtered, dried and recrystallised from ethanol.

6a: Mol. formula $C_{20}H_{14}N_4O_2$, m.p. 184°C, yield: 72%; ^{1}H NMR: δ 2.30 (s, 3H, C$_6$-C*H*$_3$), 2.40 (s, 3H, C$_9$-C*H*$_3$), 6.44 (d, *J*= 9.50Hz, 1H, C$_2$-*H*), 7.00 (d, *J*= 7.90 Hz, 2H, C$_{2'}$ and C$_{6'}$-*H*, Ph), 7.20 (t, 2H, C$_{3'}$-*H* and C$_{5'}$*H*, Ph), 7.35 (t, 1H, C$_4$-*H*, Ph), 7.87 (s, 1H, C$_5$-*H*), 8.07 (d, *J*= 9.50Hz, 1H, C$_1$-*H*); ^{13}C NMR: δ 17.00 (C$_6$-*C*H$_3$), 17.50 (C$_9$-*C*H$_3$), 116.25 (C$_2$), 118.50 (C$_{11a''}$), 132.50 (C$_{11a'}$), 137.13 (C$_5$), 144.20 (C$_1$), 148.02 (C$_{6a}$ and C$_{8a}$), 149.00 (C$_{11a}$), 153.80 (C$_6$), 154.00 (C$_{4a}$), 159.00 (C$_9$), 161.20 (C$_3$ >*C*O), 120.00-130.00 (6 Ar-C), MS (m/z, %): M$^+$ 342 (43), 237 (33), 210 (11),

182 (18), 154 (26), 153 (15), 125 (17), 105 (08), 77 (100); **6b**: Mol. formula: $C_{21}H_{16}N_4O_2$, m.p. 189°C, yield: 70%; **6c**: Mol. formula $C_{21}H_{16}N_4O_3$, m.p. 197°C, yield 63%.

3*H*-9-Methyl-3-oxo-11-(4-methyl-7-methoxy-2-oxo-2*H*-[1]-benzopyran-6-yl) pyrano[2,3-*f*]cinnolino[3,4-*c*]pyrrazole 7a-c: To the suspension of coumarin-6-ylhydrazine hydrochloride in ethanol (30 mL) was added compound **3a-c** (0.01 mole) and refluxed for 3 hr. The reaction mixture was then cooled and poured into crushed ice and water. The product thus obtained was filtered, washed with water, dried and recrystallised from ethanol.

7a: Mol. formula: $C_{25}H_{18}N_4O_5$, m.p. 195°C, yield: 72%; ^{1}H NMR: δ 2.30 (s, 3H, C_6-C*H*$_3$), 2.38 (s, 3H, $C_{4''}$-C*H*$_3$), 2.42 (s, 3H, C_9-C*H*$_3$), 3.80 (s, 3H, -OC*H*$_3$), 6.25 (s, 1H, $C_{3'}$-*H*), 6.44 (d, *J*= 9.50Hz, 1H, C_2-*H*), 7.30 (s, 1H, $C_{5''}$-*H*), 7.60 (s, 1H, C_5-*H*), 7.82 (s, 1H, $C_{8''}$-*H*), 8.05 (d, *J*= 9.50Hz, 1H, C_1-*H*); ^{13}C NMR: δ 17.00 (C_6-*C*H$_3$), 17.50 ($C_{4''}$-*C*H$_3$), 18.00 (C_9-*C*H$_3$), 56.55 (-O*C*H$_3$), 116.25 (C_2), 118.50 ($C_{11a''}$ and $C_{4'a}$), 127.00 ($C_{1'}$), 132.50 ($C_{11a'}$), 137.13 (C_5 and $C_{8'}$), 143.45 (C_1), 144.00 ($C_{4'}$), 148.02 (C_{6a} and C_{8a} and $C_{6''}$, 148.50 ($C_{3'}$), 149.00 (C_{11a}), 153.25 (C_6), 154.00 (C_{4a} and $C_{8'a}$), 155.00 ($C_{7'}$), 159.00 (C_9), 161.20 (C_3 >*C*=O), 162.00 ($C_{2'}$ >*C*=O), MS (m/z, %): M^+ 454 (32), 237 (35), 236 (16), 217 (26), 210 (33), 189 (06), 182 (19), 158 (27), 154 (35), 153 (40), 130 (29), 129 (23), 125 (17), 101 (13), 101 (100); **7b**: Mol. formula $C_{26}H_{20}N_4O_5$, m.p. 214°C, yield: 67%; **7c**: Mol. formula: $C_{26}H_{20}N_4O_6$, m.p. 231°C, yield: 68%.

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