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Synthesis, Characterization and *anti*-HIV Activity of 4-hydroxy-3-(5-methyl-1-phenyl-1*H*-pyrazol-3-yl)pyrano[3,2-*c*]chromene-2,5-dione

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ABSTRACT

Substituted 4-hydroxy -2H,5H pyrano (3,2-C) chromene – 2,5 – dione (I) have been prepared by 4-Hydroxy coumarin when treated with phosphorus oxychloride and zinc chloride. (I) on reaction with acetic acid and phosphorous oxychloride to give 3- acetyl 4-hydroxy -2H,5H pyrano (3,2-C) chromene – 2,5 – dione (II). Which on heating with ethyl acetate and pulverized sodium metal for several hours afforded 4-hydroxy-3-(3-oxobutanoyl)2H,5H pyrano(3,2-c)chromene-2,5-dione (III) . (III) when treated with ethanol and phenyl hydrazine afforded to give 4-hydroxy-3-(5-methyl-1-phenyl-1H-pyrazol-3-yl)pyrano[3,2-c]chromene-2,5-dione (IV). Several of similar derivatives were also synthesized. The structures of the synthesised compounds have been assigned on the basis of elemental analyses, IR, NMR and mass spectral studies.

Introduction

During the last two decades, the study of the biological activities of pyrano chromene derivatives has been interest of many scientists [1-4]. Natural and synthetic coumarin derivatives reported as diverse biological activities like anticoagulants and antithrombotics are well known [5]. Some of the coumarin derivatives are also reported as triplet sensitizers [6], anti-HIVagents [7], lipid-lowering agents [8], and antioxidants [9].

Current stage of investigation has proved that various substituted 4-hydroxy pyrano benzopyran derivatives showed anti-HIV and other chemotherapeutic activity [10]. Pommier [11-13] and other researchers established the role of dimeric as well as tetrameric 4-hydroxy pyranobenzopyran as integrase inhibitor, one of the key enzyme responsible for HIV-I and HIV-II.

In the present work, few newly substituted 4-hydroxy-3-(5-methyl-1-phenyl-1*H*-pyrazol-3-yl)pyrano[3,2-*c*]chromene-2,5-dione were synthesized and characterized by different spectroscopic methods. All the synthesized compounds were sent for study against replication of HIV-1(III_B Strain).

Experimental

All the melting points were determined in open glass capillaries in a liquid- paraffin-bath and are uncorrected. Purity of the compounds was checked by TLC using silica gel-G as adsorbent and visualization was accomplished by UV light or iodine. IR spectra were recorded on FT-IR spectrophotometer and PMR spectra in DMSO-d_6 on a BRUKER AC(300 MHz) FT NMR spectrometer using TMS as internal standard (chemical shifts in δ ppm). Elemental analysis was carried out in the Saurashtra University, Rajkot on Perkin Elmer Elemental Analyser.

General procedure for the preparation of 4-hydroxy -2H,5H pyrano (3,2-C) chromene – 2,5 –dione. (1a-d)

Substituted 4-hydroxy coumarins (0.1 M) and malonic acid (0.1 M) were added to a mixture of phosphorous oxychloride (40 ml) and anhydrous zinc chloride (30 g) which was preheated to 60–70 ^{o}C for 6 hrs, it was then cooled to room temperature and decomposed with ice and water to afford solid, which was filtered and washed with water. It was then treated with diluted hydrochloric acid. At the neutral point, the precipitates obtained were washed with water and dried. The product was recrystallised from ethanol as light yellow needles. Crystallized from suitable solvent.

General method of substituted 3- acetyl 4-hydroxy -2H,5H pyrano (3,2-C) chromene – 2,5 –dione. (2a-d)

The mixture of substituted 4-hydroxy -2H,5H pyrano (3,2-C) chromene – 2,5 - dione(0.1 M) was dissolved in acetic acid (5 ml) and phosphorous oxychloride (4 ml) and the reaction mixture was refluxed gently for 60-70 minutes, and then added to ice water. The product was filtered, washed with water and crystallized from suitable solvent.

General method of substituted 4-hydroxy-3-(3-oxobutanoyl)2H,5Hpyrano(3,2-c)chromene-2,5-dione. (3a-d)

Substituted 3- acetyl 4-hydroxy -2H,5H pyrano (3,2-C) chromene – 2,5 – dione (0.1 M) in freshly distilled ethyl acetate (25 ml) and sodium metal was heated on a waterbath and decomposed with ice and extracted with ether and acidification to give the acetoacetyl moiety. The product was filtered, washed with water and crystallized from suitable solvent.

General method of substituted 4-hydroxy-3-(5-methyl-1-phenyl-1*H*-pyrazol-3-yl) pyrano [3,2-*c*]chromene-2,5-dione. (4a-d)

The substituted 4-hydroxy-3-(3-oxobutanoyl)2H,5H pyrano(3,2-c)chromene-2,5-dione (0.1 M) was added in Phenyl hydrazine(0.05 M) and 30 ml ethanol. It was shaken vigorously at room temperature for 24 hours. On refluxing this mixture for 2-3 hrs the solid separated, it was filtered and washed with water, crystallized from suitable solvent.

The physical data of the compounds synthesized by above methods are given in Table 1.

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Spectral data

4-hydroxy -2H,5H pyrano (3,2-C) chromene – 2,5 – dione(1a). Yield-68%, ^{1}H-NMR ($CDCl_3$), δ ppm: 7.71-6.25 (m, 5H, Ar-H). EI-MS (m/z): 230(m^+), 214, 186, 176, 162, 144, 121, 105, 91, 77. IR (KBr, cm^{-1}): 3380, 2955, 2898, 1720, 1615, 1452, 1360, 1260, 1244, 1201, 845. Anal. Calcd. For $C_{12}H_6O_5$: C 62.62; H 2.63; Found:C 62.64; H 2.61.

3-acetyl-4-hydroxy-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-dione(2a). Yield-80%, ^{1}H-NMR($CDCl_3$), δ ppm: 2.78 (S, 3H, -$COCH_3$), 7.84-6.89 (m, 4H, Ar-H). EI-MS (m/z): 272(m^+), 230, 214, 186, 162, 144, 122, 105, 91. IR (KBr, cm^{-1}): 3385, 2955, 2898, 1728, 1715, 1615, 1452, 1360, 1260, 1244, 1210, 840. Anal. Calcd. For $C_{14}H_8O_6$: C, 61.77; H, 2.96.Found: C, 61.75; H, 2.97.

4-hydroxy-3-(3-oxobutanoyl)-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-dione (3a). Yield-67%, ^{1}H NMR ($CDCl_3$), δ ppm: 3.12 (S, 2H, -CH_2), 2.83 (S, 3H, -$COCH_3$), 7.82-6.82 (m, 4H, Ar-H). EI-MS (m/z): 314(m^+), 272, 186, 176, 163, 144, 121, 105, 91, 77. IR (KBr, cm^{-1}): 3380, 2955, 2930, 2898, 1730, 1710, 1610, 1455, 1365, 1260, 1244, 1210, 850. Anal. Calcd. For $C_{16}H_{10}O_7$: C, 61.15; H,3.21; . Found: C, 61.17; H, 3.20.

4-hydroxy-3-(5-methyl-1-phenyl-1*H*-pyrazol-3-yl)pyrano[3,2-*c*]chromene-2,5-dione (4a).
Yield-67%, ^{1}H NMR ($CDCl_3$), δ ppm: 2.51 (S, 3H, -CH_3), 8.00-6.71 (m, 10H, Ar-H). EI-MS (m/z): 386(m^+), 372, 356, 296, 281, 266, 214, 176, 144, 105, 91.IR (KBr, cm^{-1}): 3391, 2958, 2895, 1728, 1615, 1460, 1315, 1248, 855. Anal. Calcd. For $C_{22}H_{14}O_5N_2$: C,68.39; H, 3.95; N, 7.25. Found: C,68.37; H, 3.97; N, 7.24.

Conclusion

Total 16 heterocyclic compounds were synthesized in this work. The compounds are characterized by IR, ^{1}H NMR, Mass spectral data and elemental analysis.

Results are shown in Table-1 and Table-2.

Reaction Scheme

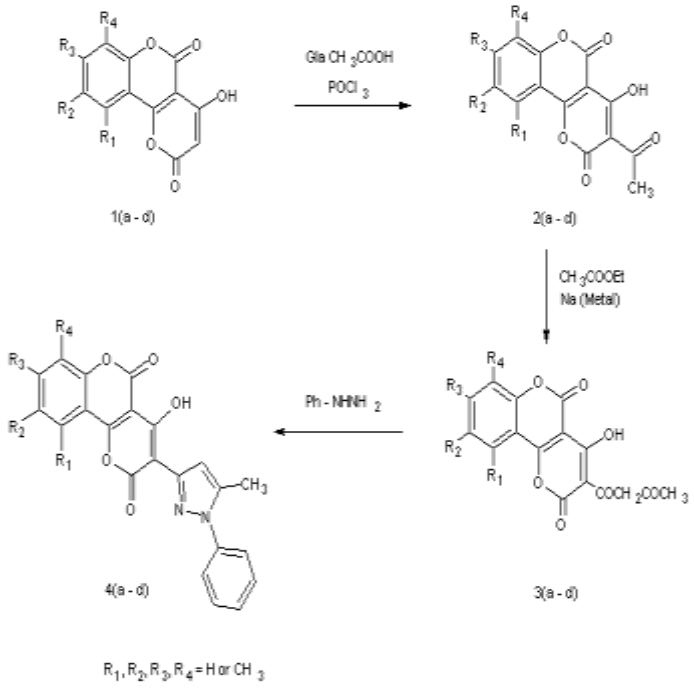

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Table 1. Physical constants of synthesized compounds

No.	Substitution				Mol. Formula	Mol. Weight	Color	M.P.	*R_f Value
	R_1	R_2	R_3	R_4					
1a	H	H	H	H	$C_{12}H_6O_5$	230	Light Yellow	175°C	0.58
1b	H	CH_3	H	H	$C_{13}H_8O_5$	244	Light Brown	225°C	0.81
1c	H	H	CH_3	H	$C_{13}H_8O_5$	244	Buff	120°C	0.57
1d	H	H	H	CH_3	$C_{13}H_8O_5$	244	Yellow	180°C	0.59
2a	H	H	H	H	$C_{14}H_8O_6$	272	Dark Brown	100°C	0.56
2b	H	CH_3	H	H	$C_{15}H_{10}O_6$	286	Light Brown	120°C	0.61
2c	H	H	CH_3	H	$C_{15}H_{10}O_6$	286	Dark Brown	88°C	0.47
2d	H	H	H	CH_3	$C_{15}H_{10}O_6$	286	Dark Brown	90°C	0.58
3a	H	H	H	H	$C_{16}H_{10}O_7$	314	Dark Brown	130°C	0.81
3b	H	CH_3	H	H	$C_{17}H_{12}O_7$	328	Buff	144°C	0.75
3c	H	H	CH_3	H	$C_{17}H_{12}O_7$	328	Dark Brown	105°C	0.79
3d	H	H	H	CH_3	$C_{17}H_{12}O_7$	328	Dark Brown	192°C	0.68
4a	H	H	H	H	$C_{22}H_{14}O_5N_2$	386	Light Yellow	158°C	0.71
4b	H	CH_3	H	H	$C_{22}H_{16}O_5N_2$	400	Buff	177°C	0.65
4c	H	H	CH_3	H	$C_{22}H_{16}O_5N_2$	400	Brown	180°C	0.61
4d	H	H	H	CH_3	$C_{22}H_{16}O_5N_2$	400	Brown	156°C	0.58

* TLC solvent system- Ethyl Acetate: Hexane- 6:4

Table 2. Anti HIV Activity

Compound Code	% Polymerase Inhibition of HIV-1RT at 50 µM concentration	Compound Code	% Polymerase Inhibition of HIV-1RT at 50 µM concentration
DCK-1a	2 ± 1	DCK-3a	1 ± 1
DCK-1b	4 ± 1	DCK-3b	4 ± 2
DCK-1c	14 ± 1	DCK-3c	1 ± 1
DCK-1d	1 ± 2	DCK-3d	7 ± 3
DCK-2a	2 ± 1	DCK-4a	1 ± 1
DCK-2b	32 ± 4	DCK-4b	2 ± 2
DCK-2c	2 ± 3	DCK-4c	6 ± 2
DCK-2d	2 ± 1	DCK-4d	1 ± 4
Efavirenz (Control)	> 99	Efavirenz (Control)	> 99

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