



SYNTHESIS, CHARACTERIZATION OF (R)-N-(1-HYDRAZINYL-1-OXOPROPAN-2-YL)-2-(2-(4-(3-METHYL-5-OXO-4-(2-PHENYLHADRAZONO)-4, 5-DIHYDRO-1H-PYRAZOL-1-YL) PHENOXY) ACETAMIDO) ACETAMIDE

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ABSTRACT

A Solution of (R)-methyl 2-(2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamido)propanoate and hydrazine hydrate in ethanol was refluxed for 5 hours. The reaction mixture was cooled and poured into ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhadrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamide. The synthesized compound is (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhadrazono)-4, 5-dihydro-1H-pyrazol-1-yl) phenoxy)acetamido)acetamide have been characterized by IR, ¹HNMR and elemental analysis.

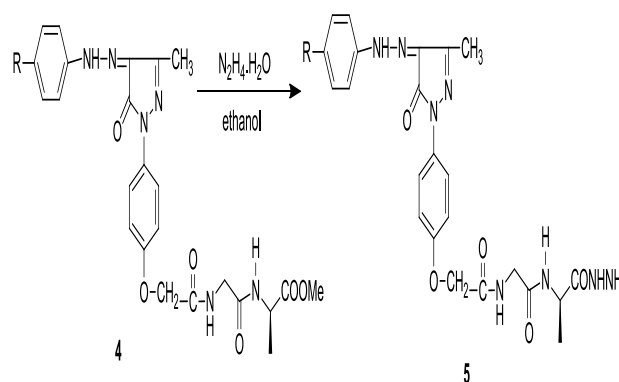
KEYWORDS: Hydrazine hydrate, Pyrazole, Elemental Analysis, IR and ¹HNMR.

INTRODUCTION

Heterocyclic compounds represents an important class of biologically active molecules specifically, those containing the pyrazole nucleus have been shown to posses high biological activities such as tranquilizing, muscle relaxant, psycho analeptic, anticonvulsant, antihypertensive, antidepressant activities. The derivatives of pyrazole are important class of antipyretic and analgesic compounds.^[1-7]

Experimental Section: A solution of (R)-methyl 2-(2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamido)propanoate (0.01M) and hydrazine hydrate (0.015M) in ethanol (20ml) was refluxed for 5 hours. The reaction mixture was cooled and poured into ice cold water with stirring. The separated solid was filtered washed with water and recrystallized from ethanol to afford (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-

phenylhadrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamide. The yield was (2.24g) 60%. Elemental analysis found C: 55.87%, H: 5.26%, N: 22.67%, O: 16.19%.Calcd: C: 55.92%, H: 5.39%, N: 22.73%, O: 16.27%.



Scheme-I.

Compound	5a	5b	5c	5d	5e	5f	5G
R	4-H	4-CH ₃	4-OCH ₃	4-OC ₂ H ₅	4-Cl	4-Br	4-NO ₂

Synthesis of ethyl 2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetate

(a). Substituted phenyl diazonium chloride (A)

The required primary amine is dissolved in a suitable volume of water containing 2.5–3.0 equivalents of hydrochloric acid (sulphuric acid) by the application of heat if necessary. The solution thus obtained is cooled to 0°C when the amine hydrochloride (or sulphate) usually crystallizes. The temperature is maintained at 0 to 5°C, and the aqueous solution of sodium nitrite is added portion wise till there is free nitrous acid. The solution is tested for the later with an external indicator (moist potassium iodide starch paper). An excess of acid is always maintained to stabilize the diazonium acid is harmful, the concentration of the acid is reduced to optimum value. The similar procedure is adopted for the preparation of other substituted phenyl diazonium chlorides.

(b). 3-(2-phenylhydrazono) pentane-2, 4-dione (C)

A solution of sodium acetate (1.0g) in 100 ml of aqueous alcohol (50%) is added to a solution of pentane 2, 4-dione (0.1M) in 50 ml of ethanol and the mixture is added to 0°C. To this cold mixture, the corresponding diazonium chloride is added gradually till turbidity is observed. The addition is continued till yellow crystals separated out. These crystals are filtered, washed with water and dried.

(c). 1-(4-hydroxyphenyl)-3-methyl-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one.

A mixture of 3-(2-phenylhydrazono) pentane-2, 4-dione (C), hydrazine and dimethyl formamide (10 drops) was subjected to microwave irradiation at 150 W intermittently at 30 sec intervals for 2 minutes. After complete conversion as indicated by TLC, the reaction mixture was cooled and heated with cold water. The precipitate was filtered recrystallized from ethanol M.P. 176°C, yield 88%.

(d). Ethyl 2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl) phenoxy) acetate.

A mixture of 1-(4-hydroxyphenyl)-3-methyl-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (0.02M) and ethyl 2-chloroacetate (0.02M), anhydrous K₂CO₃ (0.03M) and DMF was stirred at room temperature for 8 hours. The reaction mixture was diluted with ice cold water. The separated solid was identified as ethyl 2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl) phenoxy) acetate. This was collected by filtration, and recrystallized from ethanol. M.P 197°C, yield 78%. Elemental analysis found C: 63.15%, H: 5.26%, N: 14.73%, O: 16.84%. Calcd: C: 63.22%, H: 5.34%, N: 14.78%, O: 16.92%.

(e). 2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl) phenoxy) acetic acid (2)

The compound ethyl 2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetate(0.01M) was dissolved in THF and treated with 50ml of aq. 5N NaOH solution, the solute is stirred at room temperature for 4 hours. The completion of reaction monitor by TLC, the THF distilled under reduced pressure and acidified with con HCl at 0°C separated solid was filtered, washed with water to afforded 2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetic acid. Yield: 80%. Elemental analysis found C: 61.36%, H: 4.54%, N: 15.90%, O: 18.18%. Calcd: C: 61.46%, H: 4.62%, N: 15.99%, O: 18.25%.

II. Synthesis of (R)-methyl 2-(2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamido)propanoate

(a). Methyl (2R)-2-(2-aminoacetamido) propionate Hydrochloride.

The synthon, Methyl (2R)-2-(2-aminoacetamido) propionate hydrochloride was prepared by the procedure described by Rajiv DAHIYA.^[42]

(i). ¹Butyloxycoronyl-Glycyl-alanine methyl ester.

The compound of Alanine methyl ester Hydrochloride (0.01mol) was dissolved in Chloroform (CHCl₃) (20ml) and cooled to 0°C then add N-Methylmorpholine (NMM) (2.23ml, 0.021mol) and stirred for 15min. then add N-Boc-Glycine (0.01mol) was dissolved in CHCl₃ (20ml) and dicyclohexylcarbodiimide (DCC) (2.1g, 0.01mol) and stirred for 24 h, the reaction was monitored by TLC. After completion of the reaction the unwanted solid was filtered and separated the filtrate was washed with 5% sodium bicarbonate (NaHCO₃) and saturated sodium chloride solution. Further the solvent was distilled under reduced pressure to give N-Boc-Glycyl-Alanine methyl ester as a crude product. It was recrystallization with chloroform and hexane followed by cooling at 0°C to give semi solid. The yield was 80 %.

(ii). Methyl (2R)-2-(2-aminoacetamido) propionate Hydrochloride.

The compound of ¹Butyloxycoronyl-Glycyl-alanine methyl ester (0.01mol) was dissolved in Dichloromethane (DCM) (20ml) and treated with trifluoroacetic acid (TFA) (0.025mol) and stirred for 2h. The reaction was monitor by TLC. After completion of the reaction it was basified with saturated sodium bicarbonate solution and extracted with dichloromethane and the solvent was distilled off and treated with isopropyl alcohol hydrochloride. The precipitate was filtered to give Methyl (2R)-2-(2-aminoacetamido) propionate hydrochloride. The yield was 61%. Elemental analysis found C: 36.58%, H: 6.60%, N: 14.17%, O: 24.32%, Cl: 17.96. Calcd: C: 36.65%, H: 6.66%, N: 14.25%, O: 24.41%, Cl: 18.03.

(b). (R)-methyl 2-(2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamido)propanoate

The compound of (2R)-2-(2-aminoacetamido)propanoate Hydrochloride (0.01mol) was dissolved in Chloroform (20ml) and cooled to 0°C then add N-Methylmorpholine (NMM) (0.02mol) and stirred for 15min. then add 2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetic acid (0.01mo) in CHCl₃ (20ml) and dicyclohexylcarbodiimide (DCC) (0.01mol) and stirred for 24 h, the reaction was monitored by TLC. After completion of the reaction the unwanted solid was filtered and separated the filtrate was washed with 5% sodium bicarbonate and saturated sodium chloride solution. Further the solvent was distilled under reduced pressure to give crude product it was stirred in hexane to give solid. It was filtered to give (R)-methyl 2-(2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamido)propanoate . The yield was 60%. Elemental analysis found C: 58.29%, H:

5.26%, N: 17.00%, O: 19.43%.Calcd: C: 58. 38%, H: 5.35%, N: 17.09%, O: 19.52%.

III. Synthesis of (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhadrazono)-4, 5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamide

A solution of give (R)-methyl 2-(2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamido)propanoate. (0.01M) and hydrazine hydrate (0.015M) in ethanol (20ml) was refluxed for 5 hours. The reaction mixture was cooled and poured onto ice cold water with stirring. The separated solid was filtered washed with water and recrystallized from ethanol to afford (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhadrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy) acetamido) acetamide. The yield was 60%. Elemental analysis found C: 55.87%, H: 5.26%, N: 22.67%, O: 16.19%.Calcd: C: 55.92%, H: 5.39%, N: 22.73%, O: 16.27%.

The compound synthesized has been characterized by elemental analysis, IR and ¹HNMR.

Compound	R	V _{max} in cm ⁻¹			
		NH ₂	NH	amide NH	C=O
5a	H	3445	3305	1540	1710
		3425			1645
					1636
5b	CH ₃	3420	3285	1510	1690
		3400			1630
					1625
5c	OCH ₃	3425	3200	1530	1700
		3405			1640
					1635
5d	OC ₂ H ₅	3435	3300	1535	1705
		3415			1635
					1700
5e	Cl	3420	3275	1550	1710
		3400			1650
					1630
5f	Br	3444	3290	1560	1725
		3424			1640
					1630

¹H NMR Spectrum: The ¹H NMR (200MHz) spectra of (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhadrazono)-4,5-dihydro-1H-pyrazol-1-yl) phenoxy) acetamido) was recorded in CDCl₃ + DMSO-d₆ δ 7.3-7.40(m, 5H, C₆H₅), 6.22(Br, S, -NH, amide), 4.74-4.6(1H, m, α-H, Ala), 4.67(S, 2H, CH₂, amide), 3.49-3.47(2H, d, CH₂, Gly), 2.8(S, 6H, -CH₃, pyrazole), 2.0(Br, S, -NH₂), 1.29-1.27(3H, d, β-H's, Ala). Anal. Clacd. For C₂₄H₂₄N₆O₆: C, 55.87; H, 5.26; N, 22.67; O, 16.19.

¹H NMR spectral data of (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl) phenoxy) acetamido)acetamide.

Compound	R	¹ H NMR (200MHz) (CDCl ₃ + DMSO-d ₆) (δ ppm)
5a	H	δ 7.7(d,2H,C ₆ H ₄), 7.4(d,2H,C ₆ H ₄), 7.1-7.3 (m, 5H, C ₆ H ₅), 7.3-7.40(m, 5H, C ₆ H ₅), 6.22(Br, 2H, S, -NH, amide), 4.74-4.6(1H, m, α-H, Ala), 4.67(S,2H, CH ₂ ,amide), 3.49-3.47(2H, d,CH ₂ ,Gly), 2.8 (S, 6H,-CH ₃ , pyrazole), 2.0 (Br, 2H, S, -NH ₂), 1.29-1.27(3H, d, β-H's, Ala), 1.2(s.3H,CH ₃) ppm
5b	CH ₃	δ 7.7(d,2H,C ₆ H ₄), 7.4(d,2H,C ₆ H ₄), 7.1-7.3 (m, 5H, C ₆ H ₅), 7.3-7.40(m,4H, C ₆ H ₄), 6.22(Br, S, -NH, amide), 4.74-4.6(1H, m, α-H, Ala), 4.67(S,2H, CH ₂ , amide), 3.49-3.47(2H, d,CH ₂ ,Gly), 2.8(S, 6H,-CH ₃ , pyrazole), 2.0(Br, S, -NH ₂), 1.29-1.27(3H, d, β-H's, Ala), 1.2(s.3H,CH ₃) ppm
5c	OCH ₃	δ 7.7(d,2H,C ₆ H ₄), 7.4(d,2H,C ₆ H ₄), 7.1-7.3 (m, 5H, C ₆ H ₅), 7.3-7.40(m, 4H, C ₆ H ₄), 6.22(Br, S, -NH, amide), 4.74-4.6(1H, m,α-H, Ala), 4.67(S,2H, CH ₂ , amide), 3.49-3.47(2H, d,CH ₂ ,Gly), 2.8(S, 6H,-CH ₃ , pyrazole), 2.0(Br, S, -NH ₂), 1.29-1.27(3H, d, β-H's, Ala), 1.2(s.3H,CH ₃) ppm
5d	OC ₂ H ₅	δ 7.7(d,2H,C ₆ H ₄), 7.4(d,2H,C ₆ H ₄), 7.1-7.3 (m, 5H, C ₆ H ₅), 7.3-7.40(m, 4H, C ₆ H ₄), 6.22(Br, S, -NH, amide), 4.74-4.6(1H, m, α-H, Ala), 4.67(S,2H, CH ₂ , amide), 3.49-3.47(2H, d,CH ₂ ,Gly), 2.8(S, 6H,-CH ₃ , pyrazole), 2.0(Br, S, -NH ₂), 1.29-1.27(3H, d, β-H's, Ala), 1.2(s.3H,CH ₃) ppm
5e	Cl	δ 7.7(d,2H,C ₆ H ₄), 7.4(d,2H,C ₆ H ₄), 7.1-7.3 (m, 5H, C ₆ H ₅), 7.3-7.40(m, 4H, C ₆ H ₄), 6.22(Br, S, -NH, amide), 4.74-4.6(1H, m, α-H, Ala), 4.67(S,2H, CH ₂ , amide), 3.49-3.47(2H, d,CH ₂ ,Gly), 2.8(S, 6H,-CH ₃ , pyrazole), 2.0(Br, S, -NH ₂), 1.29-1.27(3H, d, β-H's, Ala), 1.2(s.3H,CH ₃) ppm
5f	Br	δ 7.7(d,2H,C ₆ H ₄), 7.4(d,2H,C ₆ H ₄), 7.1-7.3 (m, 5H, C ₆ H ₅), 7.3-7.40(m, 5H, C ₆ H ₄), 6.22(Br, S, -NH, amide), 4.74-4.6(1H, m,α-H, Ala), 4.67(S,2H, CH ₂ , amide), 3.49-3.47(2H, d,CH ₂ ,Gly), 2.8(S, 6H,-CH ₃ , pyrazole), 2.0(Br, S, -NH ₂), 1.29-1.27(3H, d, β-H's, Ala), 1.2(s.3H,CH ₃) ppm

RESULTS AND DISCUSSION

The IR spectrum of 8a revealed the appearance of bands characteristics of (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamide. The yield was (2.24g) 60%. Elemental analysis found C: 55.87%, H: 5.26%, N: 22.67%, O: 16.19%. Calcd: C: 55.92%, H: 5.39%, N: 22.73%, O: 16.27%. The ¹H NMR (200MHz) spectra of (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl) phenoxy) acetamido) acetamide was recorded in CDCl₃ + DMSO-d₆ δ 7.3-7.40 (m, 5H, C₆H₅), 6.22 (Br, S, -NH, amide), 4.74-4.6(1H, m, α-H, Ala), 4.67(S,2H, CH₂, amide), 3.49-3.47(2H, d, CH₂, Gly), 2.8(S, 6H,-CH₃, pyrazole), 2.0(Br, S, -NH₂), 1.29-1.27(3H, d, β-H's, Ala). Anal. Clacd. For C₂₄H₂₄N₆O₆: C, 55.87; H, 5.26; N, 22.67; O, 16.19.

CONCLUSION

Heterocyclic compounds represents an important class of biologically active molecules specifically Solution of (R)-methyl 2-(2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamido)propanoate and hydrazine hydrate in ethanol was refluxed for 5 hours. The reaction mixture was cooled and poured into ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl)phenoxy)acetamido)acetamide. The

synthesized compound is (R)-N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(2-(4-(3-methyl-5-oxo-4-(2-phenylhydrazono)-4, 5-dihydro-1H-pyrazol-1-yl) phenoxy)acetamido)acetamide have been characterized by IR, ¹H NMR and elemental analysis.

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