



SYNTHESIS OF NOVEL BIS PYRAZOLONES

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ABSTRACT

The mixture of acetamide **7(a-f)** and with in ethanol, and ethylacetoacetate were added and the mixture was refluxed for 10-12 hours in presence of catalytical amount glacial acetic acid to get the compounds (**8a-f**) in good yields. The structures of these newly synthesized compounds were characterized by ¹H-NMR, Mass, IR and elemental analysis.

Key words : Pyrazolones, Bis pyrazolones, Ethylacetoacetate

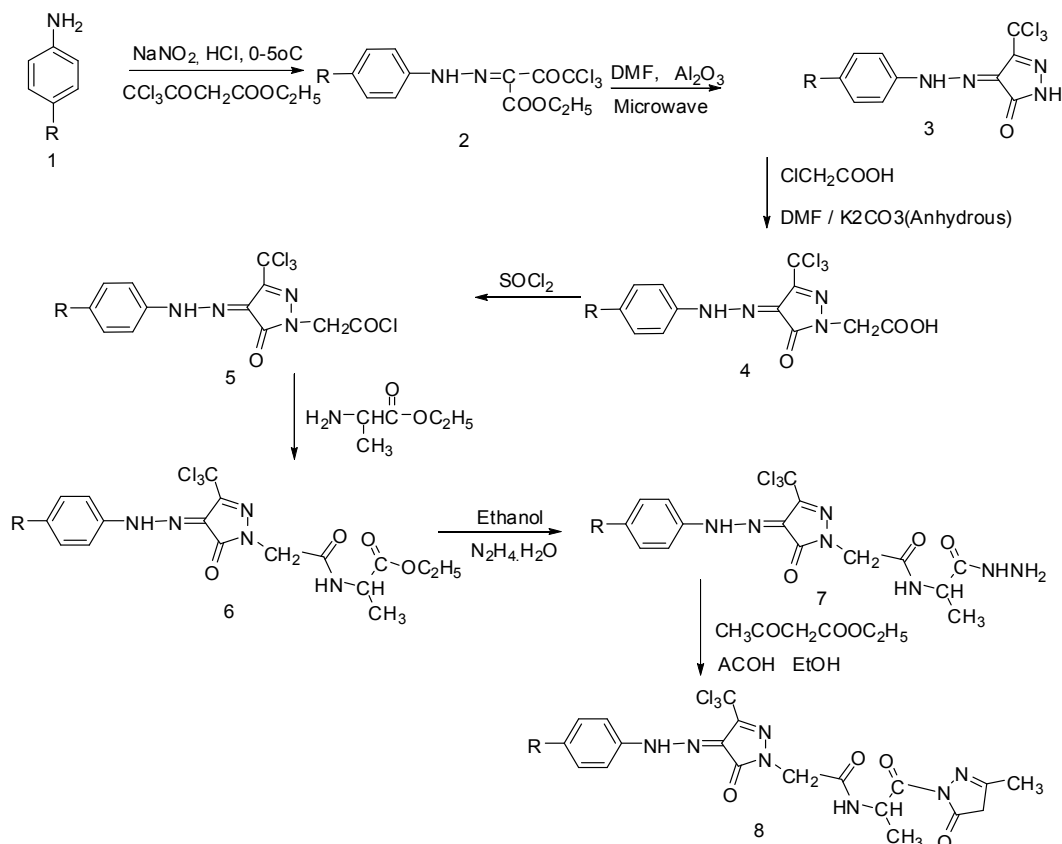
INTRODUCTION

Heterocyclic compounds represents an important class of biologically active molecules specifically, those containing the pyrazolone nucleus have been shown to posses high biological activities such as tranquillizing, muscle relaxant, psycho analeptic, anticonvulsant, antihypertensive, antidepressant activities. The derivatives of pyrazolone are

important class of antipyretic and analgesic Compounds ¹⁻⁷

Some substituted pyrazolines and their derivatives are used as antitumor¹¹ anti bacterial, antifungal, antiviral, anti parasitic, anti-tubercular and insecticidal agents⁸⁻¹²

SCHEME-1



Comp	8a	8b	8c	8d	8e	8f
R	H	4-CH ₃	4-OCH ₃	4-OC ₂ H ₅	4-Cl	4-Br

EXPERIMENTAL

All the chemicals were used as received without further purification. Melting points were determined in open capillary tubes in Buchi 530 circulating oil apparatus and are not corrected. Reactions monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ¹H NMR spectra were determined in DMSO-d₆ solution on JOEL AL300 spectrometers. ¹³CNMR spectra were determined in DMSO-d₆ solution on AMX400 spectrometers. Chemical shifts are relative to tetramethylsilane as internal standard and expressed in ppm.

SYNTHESIS OF COMPOUNDS

Ethyl 4,4,4-trichloro-3-oxo-2-(2-phenyl hydrazono)butanoate (2) was prepared by the procedure described by H.M.W.Alborsky, M.E.Baum¹³

4-(4-substituted aryl hydrazono)-5-trichloromethyl-2, 4-dihydro-pyrazol-3-one (3)

A mixture of (2) and hydrazine hydrate and Dimethyl formamide (10 drops) was subjected to microwave irradiation at 150W intermittently at 30 seconds intervals for 2 minutes. After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with cold water. The

precipitate 3-methyl 4-(4'-substituted aryl hydrazono) pyrazoline-5-one (**3**) was filtered and recrystallized from ethanol. The yield is 85%.

2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (4)

A mixture of (**3**), 2-chloroacetic acid, anhydrous K_2CO_3 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 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (**4**). Yield 71%, m.p.: $181^\circ C$; 1H -NMR (400 MHz, DMSO- d_6 δ ppm): 3.65(s, 2H, NCH₂CO), 10.56 (s, H, Ar-NH), 12.68 (s, 1H, COOH) 6.81 -7.88 (m, 5H, for C₆H₅ phenyl group); ^{13}C -NMR (400 MHz, DMSO- d_6 δ ppm): 62.5 (CH₂), 114-144 (Ar-C), 135 (NH-N=C), 154 (pyrazole C=O), 92 (CCl₃), 145 (CCl₃-C), 168.4 (Acid C=O); IR (KBr): $\bar{\nu}$ = 1600, 3120, 2967, 1682, 1617 cm^{-1} and these are due to C=N, NH, acid carbonyl and cyclic carbonyl in five membered hetero cyclic ring respectively *Anal.* Calcd. for C₁₂H₉Cl₃N₄O₃ (363.58); C, 39.64; H, 2.50; N, 15.41; found (%); C: 38.23, H: 3.13, N: 22.31.

2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetyl chloride (5)

To a solution of 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (**4**). (900 mg) in toluene (30 mL) was added Thionyl chloride (0.90 mL) at room temperatures. The resulting solution was heated to reflux for 2 h. Then, it was cooled to room temperature and the excess Thionyl chloride and toluene was removed under vacuum. The residue was dissolved one time in toluene and removed again under vacuum to afford 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetyl chloride (**5**). Yield 58%, m.p.: $173^\circ C$; 1H -NMR (400 MHz, DMSO- d_6 δ ppm): 3.81(s, 2H, NCH₂CO), 10.70 (s, H, Ar-NH), 6.78 -7.88 (m, 5H, for C₆H₅ phenyl group); ^{13}C -NMR (400 MHz, DMSO- d_6 δ ppm): 64.1 (CH₂), 18.5 (CH₃), 51.2 (CH) 113-145 (Ar-C), 133 (

NH-N=C), 154 (pyrazole C=O), 92 (CCl₃), 144 (CCl₃-C), 172 (C=ONHN-); IR (KBr): $\bar{\nu}$ = 3180, 1696, 1617, 1651 cm^{-1} and these are due to NH, cyclic carbonyl in five membered hetero cyclic ring $exo > C = N$, acid chloride respectively *Anal.* Calcd. for C₁₂H₈Cl₄N₄O₂ (382.03); C, 37.73; H, 2.11; N, 14.67; found (%); C: 38.23, H: 3.13, N: 22.31.

Ethyl 2-(2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamido) propanoate (6)

A solution of acid chloride (**5a-f**) (2.47 mol) in dichloromethane (30 mL) were added L-Alanine ethyl ester hydrochloride (735 mg, 2.5 mol) and Di isopropyl ethylamine (1.3 mL, 7.5 mol) at $0^\circ C$. Then, the solution warmed to room temperature and it was stirred overnight. Then, it was diluted with water (50 mL) and dichloromethane (50 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layer was washed with brine solution and dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the solvent gave the crude residue which was purified by using column chromatography to give ethyl 2-(2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl) acetamido) propanoate (**6a-f**) (1.5 g) as a colorless oil. Yield 65%, m.p.: $184^\circ C$; 1H -NMR (400 MHz, DMSO- d_6 δ ppm): 1.28 (t, 3H, CH₃ of CH₂CH₃), 2.15(d, 3H, CH₃ of CHCH₃), 3.51(s, 2H, NCH₂), 4.27(q, 2H OCH₂ of CH₂CH₃) 5.25(q, 1H, CH of CHCH₃), 10.72 (s, H, CONH), 12.58 (s, H, Ar-NH), 6.82 -7.94 (m, 5H, for C₆H₅ of phenyl group); ^{13}C -NMR (400 MHz, DMSO- d_6 δ ppm): 64.3 (CH₂), 18.1 (CH₃), 51.2 (CH), 113-144 (Ar-C), 133 (NH-N=C), 154 (pyrazole C=O), 92 (CCl₃), 146 (CCl₃-C), 178 (C=ONH) 50 (CHC=O), 17.6 (CH₃CH), 62 (CH₂C=O) 15 (CH₂CH₃); IR (KBr): $\bar{\nu}$ = 3164, 3120, 1592, 1617, 1689, 1732 cm^{-1} and these are due to $>NH$, CO-NH $exo > C = N$, cyclic carbonyl in five membered heterocyclic ring, carbonyl group, ester carbonyl group respectively; *Anal.* Calcd. for C₁₇H₁₈Cl₃N₅O₄ (462.71); C, 44.13; H, 3.92; N, 15.14; found (%); C: 44.20, H: 4.21, N: 22.31.

(E)-N-(1-(hydrazinyloxy)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide (7)

A solution of (6) (0.01M) and hydrazine hydrate (0.015M) in ethanol 20 mL was refluxed for 5 hours. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford (7) Yield 64%, m.p. 132⁰C; ¹H-NMR (400 MHz,DMSO-d₆ δ ppm): 2.10 (d,3H, CHCH₃), 3.78(s,2H, NCH₂CO), 4.31(s, 2H, NH₂),4.77-4.82(q, H CH₃ CH), 9.72 (s, H, CONH), 11.16 (s, H, NH), 10.75(s, H, Ar-NH), 6.82 -7.98 (m, 5H, for C₆H₅ of phenyl group); ¹³C-NMR (400 MHz,DMSO-d₆ δ ppm): 64.5 (CH₂), 18.2 (CH₃), 51.0 (CH), 113-143 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl₃), 145 (CCl₃ - C), 177 (C=ONH) 49(CHC=O); IR (KBr): $\bar{\nu}$ = 3420, 3380, 3198, 3132, 3108, 1720, 1680, 1615 and these are due to -NH₂, CO-NH, >NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, *Anal.* Calcd. for C₁₅H₁₆Cl₃N₇O₃ (448.69); C: 40.15, H: 3.59, N: 21.85 found (%); C: 40.17, H: 3.62, N: 21.88.

N-(1-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide (8 a-f)

In a solution of N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide (7a-f) (0.01 mol) in ethanol (10mL), ethylacetoacetate (0.01 mol) were added and the mixture was refluxed for 12 hours in presence of catalytical amount glacial acetic acid. Excess of ethanol was removed by distillation and crystalline residue obtained was filtered, washed with ethanol, dried and recrystallized to get the compounds (8a-f) in good yields.

N-(1-(3-amino-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8a

Yield 65%, m.p. 142⁰C; ¹H-NMR (400 MHz,DMSO-d₆ δ ppm): 1.46-1.48 (d,3H, CH₃), 2.15(s,2H,CH₂CH₃), 3.12(s,2H, NCH₂CO), 4.35 (s, H,

NCH₂ N), 4.76(q,1H CH₃CH) 9.82 (s, H, CONH), 12.51 (s, H, Ar-NH), 6.99 -7.80 (m, 5H, for C₆H₅ of phenyl group). ¹³C-NMR (400 MHz,DMSO-d₆ δ ppm): 62.5 (CH₂), 115-142.6 (Ar-C), 133 (NH-N=C), 154 (pyrazole C=O), 162 (NH-N=C), 91 (CCl₃), 146 (CCl₃ - C), 167(CH₂C=O), 49.2 (CH), 17.9 (CHCH₃), 165.8 (C=O) 15.9 (CH₃), 158.5 (C=N) 173.4 (CHC=O) 53.5 (CH₂); IR (KBr): $\bar{\nu}$ = 3228,3132,1608,1792,1760,1730,and 1622 these are due to -CO-NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, *Anal.* Calcd. for C₁₉H₁₈Cl₃N₇O₄ (513.05); C: 44.33, H: 3.52, N: 19.05 found (%); C: 44.01, H: 3.01, N: 19.00.

N-(1-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8b

Yield 62%, m.p. 153⁰C; ¹H-NMR (400 MHz,DMSO-d₆ δ ppm): 3.1 (s, 3H, Ar - CH₃), 1.46-1.49 (d, 3H, CH₃), 2.16(s,2H,CH₂CH₃), 3.15(s,2H, NCH₂CO), 4.38 (s, H, NCH₂ N), 4.78(q,1H CH₃CH) 9.84 (s, H, CONH), 12.53 (s, H, Ar-NH), 6.97 -7.82 (m, 4H, for C₆H₅ of phenyl group); ¹³C-NMR (400 MHz,DMSO-d₆ δ ppm): 21.3 (Ar-CH₃), 66.2 (CH₂), 117-144.3 (Ar-C), 135 (NH-N=C), 155 (pyrazole C=O), 163 (NH-N=C), 93 (CCl₃), 147 (CCl₃ - C), 169 (CH₂C=O), 50.1 (CH), 18.1 (CHCH₃), 166.2 (C=O) 16.2(CH₃), 158.8 (C=N) 175.4 (CHC=O) 53.8 (CH₂); IR (KBr): $\bar{\nu}$ = 3221,3135,1603,1790,1766,1731,and 1620 these are due to -CO-NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, *Anal.* Calcd. for C₂₀H₂₀Cl₃N₇O₄ (527.06); C: 45.43, H: 3.81, N: 18.54; found (%); C: 45.00, H: 3.58 N: 18.51.

2-(4-(2-(4-methoxyphenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-1-oxopropan-2-yl)acetamide 8c

Yield 68%, m.p. 154⁰C; ¹H-NMR (400 MHz,DMSO-d₆ δ ppm): 3.24 (s, 3H, OCH₃), 1.46-1.51 (d, 3H, CH₃), 2.19(s,2H,CH₂CH₃), 3.16(s,2H, NCH₂CO), 4.37 (s, H, NCH₂ N), 4.79(q,1H CH₃CH) 9.85 (s, H, CONH), 12.55 (s, H, Ar-NH), 6.98 -7.81 (m, 4H, for C₆H₅ of phenyl group); ¹³C-NMR (400

MHz,DMSO- d_6 δ ppm): 56.4 (O-CH₃), 69 (CH₂), 118-145.2 (Ar-C), 137 (NH-N=C), 156 (pyrazole C=O), 165 (NH-N=C), 94 (CCl₃), 148 (CCl₃-C), 169 (CH₂C=O), 51.2 (CH), 19.2 (CHCH₃), 168.4 (C=O) 16.6 (CH₃), 159.2 (C=N) 175.2 (CHC=O) 54.2 (CH₂); IR (KBr): $\bar{\nu}$ = 3224, 3134, 1605, 1793, 1763, 1734, and 1626 these are due to -CO-NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, *Anal.* Calcd. for C₂₀H₂₀Cl₃N₇O₅ (543.06); C: 44.09, H: 3.70, N: 18.00 found (%); C: 44.02, H: 3.26, N: 17.79.

2-(4-(2-(4-ethoxyphenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-1-oxopropan-2-yl)acetamide 8d

Yield 74%, m.p. 164°C; ¹H-NMR (400 MHz,DMSO- d_6 δ ppm): 1.32 (t, 3H, CH₃), 3.44 (q, 2H, O - CH₂), 1.51-1.52 (d, 3H, CH₃), 2.16(s, 2H, CH₂CH₃), 3.15(s, 2H, NCH₂CO), 4.37 (s, H, NCH₂N), 4.76(q, 1H CH₃CH) 9.87 (s, H, CONH), 12.57 (s, H, Ar-NH), 6.98 -7.83 (m, 4H, for C₆H₅ of phenyl group); ¹³C-NMR (400 MHz,DMSO- d_6 δ ppm): 64.8 (CH₂), 16 (CH₃), 69 (CH₂), 118-145.2 (Ar-C), 137 (NH-N=C), 156 (pyrazole C=O), 169 (NH-N=C), 94 (CCl₃), 148 (CCl₃-C), 167.4 (CH₂C=O), 51.2 (CH), 19.2 (CHCH₃), 168.4 (C=O) 16.6 (CH₃), 159.2 (C=N) 175.3 (CHC=O) 54.2 (CH₂); IR (KBr): $\bar{\nu}$ = 3226, 3131, 1601, 1795, 1762, 1736, and 1624 these are due to -CO-NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, *Anal.* Calcd. for C₂₁H₂₂Cl₃N₇O₅ (557.07); C: 45.14, H: 3.97, N: 17.54 found (%); C: 45.08, H: 3.60, N: 17.31.

2-(4-(2-(4-chlorophenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-1-oxopropan-2-yl)acetamide 8e

Yield 70%, m.p. 154°C; ¹H-NMR (400 MHz,DMSO- d_6 δ ppm): 1.51-1.53 (d, 3H, CH₃), 2.17(s, 2H, CH₂CH₃), 3.18(s, 2H, NCH₂CO), 4.37 (s, H, NCH₂N), 4.79(q, 1H CH₃CH) 9.89 (s, H, CONH), 12.57 (s, H, Ar-NH), 6.97 -7.80 (m, 4H, for C₆H₅ of phenyl group); ¹³C-NMR (400 MHz,DMSO- d_6 δ ppm): 73.2 (CH₂), 119-146.6 (Ar-C), 138 (NH-N=C), 158 (pyrazole C=O), 168 (NH-N=C), 96 (CCl₃), 149 (CCl₃-C), 170 (CH₂C=O), 52.4 (CH), 17.9 (CHCH₃), 169.6 (C=O) 19.8 (CH₃), 160.1 (C=N) 176.8 (CHC=O) 56.4 (CH₂); IR (KBr): $\bar{\nu}$ = 3225, 3130, 1607, 1796, 1764, 1735, and 1625 these are due to -CO-NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, *Anal.* Calcd. for C₁₉H₁₇Cl₄N₇O₄ (547.01); C: 41.55, H: 3.12, N: 17.85; found (%); C: 41.21, H: 2.88, N: 17.61.

2-(4-(2-(4-bromophenyl)hydrazono)-5-oxo-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(1-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-1-oxopropan-2-yl)acetamide 8f

Yield 61%, m.p. 159°C; ¹H-NMR (400 MHz,DMSO- d_6 δ ppm): 1.52-1.54(d, 3H, CH₃), 2.18(s, 2H, CH₂CH₃), 3.17(s, 2H, NCH₂CO), 4.38 (s, H, NCH₂N), 4.78(q, 1H CH₃CH) 9.88 (s, H, CONH), 12.58 (s, H, Ar-NH), 6.98 -7.82 (m, 4H, for C₆H₅ of phenyl group); ¹³C-NMR (400 MHz,DMSO- d_6 δ ppm): 73.2 (CH₂), 119-146.6 (Ar-C), 138 (NH-N=C), 158 (pyrazole C=O), 168 (NH-N=C), 96 (CCl₃), 149 (CCl₃-C), 170 (CH₂C=O), 52.4 (CH), 17.9 (CHCH₃), 169.6 (C=O) 19.8 (CH₃), 160.1 (C=N) 176.8 (CHC=O) 56.4 (CH₂); IR (KBr): $\bar{\nu}$ = 3227, 3138, 1607, 1799, 1764, 1735, and 1625 these are due to -CO-NH, Ar-NH exo > C = N, cyclic carbonyl in five membered hetero cyclic ring respectively, *Anal.* Calcd. for C₁₉H₁₇Cl₃N₇O₄Br (590.96); C: 38.44, H: 2.89, N: 16.52; found (%); C: 38.03, H: 2.49, N: 16.20.

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