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MICROWAVE ASSISTED SOLVENT-FREE SYNTHESIS OF PYRAZOLO [4,3-C] QUINOLINES USING MONTMORILLONITE K-10 CLAY: AN ENVIRONMENTAL BENIGN APPROACH

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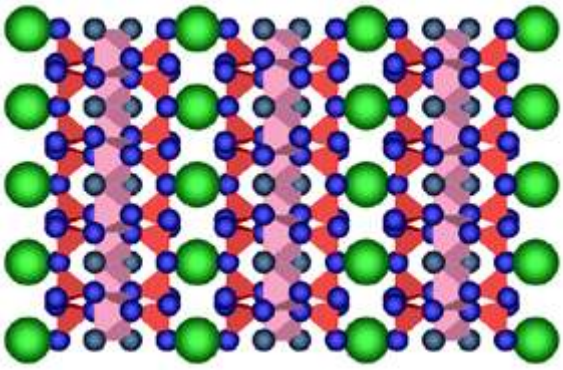
Abstract: A series of novel pyrazolo[4,3-c]quinolines have been synthesized in good to excellent yields by environmental benign solvent free microwave -induced technique involving condensation of ethyl-4-chloroquinoline-3-carboxylates **5 (a-d)** with different hydrazines using montmorillonite K-10 clay as a catalyst. All new compounds were characterized by spectral and analytical methods.

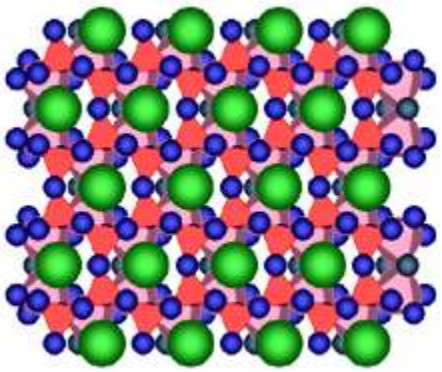
Key words: 4-chloro-quinoline-3-carboxylates, pyrazolo [4,3-c] quinolines , Gould-Jacobs reaction, K-10 clay, microwave irradiation.

Introduction :

Quinolines and their derivatives are an important class of organic molecules that have attracted much attention from synthetic and medicinal chemists, because of their wide range of physiological activity[1]. Pyrazoles and their derivatives are also important constituents of biologically active synthetic compounds[2]. Because these systems have been associated with useful biological activities for example antiviral[3], antimalarial[4,5], antibacterial[6], anticancer[7], and antimicrobial[8] activity. Pyrazolo[4,3-c]quinolines were found to be highly fluorescent materials in the blue region of the spectrum[9]. These literature reports prompted us to develop a new synthetic route to novel quinoline fused heterocyclics.



Montmorillonite Layers (horizontal)

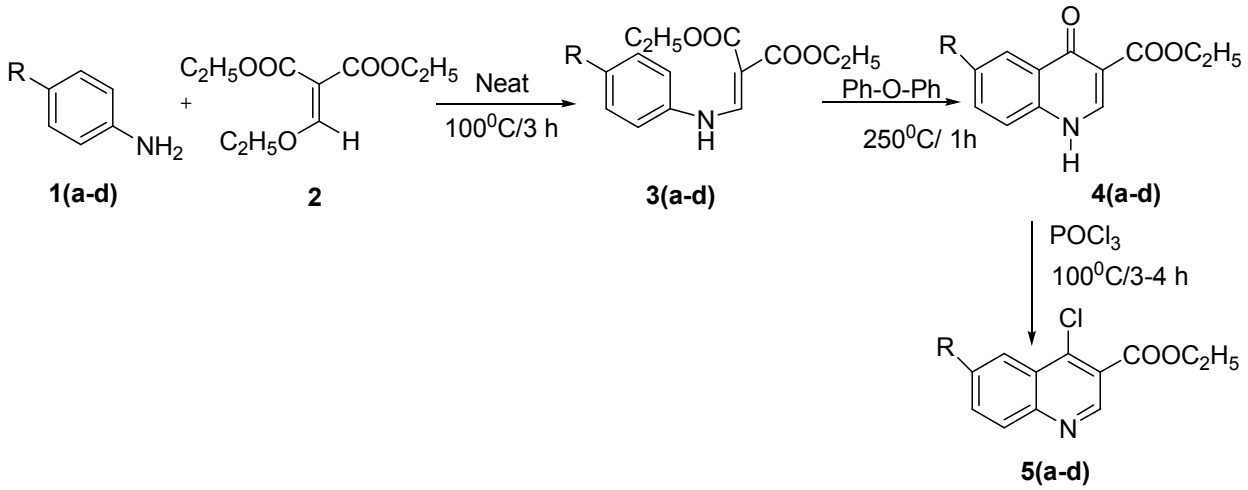


Montmorillonite Layers (vertical)

Microwave irradiation using commercial oven has emerged as an important synthetic tool to accelerate organic reactions, because the high heating efficiency gives remarkable rate enhancement and dramatic reduction in reaction time[10]. Montmorillonite clays have been extensively used as efficient catalyst for a variety of organic reactions[11]. Clay catalyzed organic reactions are gaining importance owing to their inexpensive nature and special catalytic attributes in heterogeneous reactions[12].

Results and Discussion:

SCHEME-I

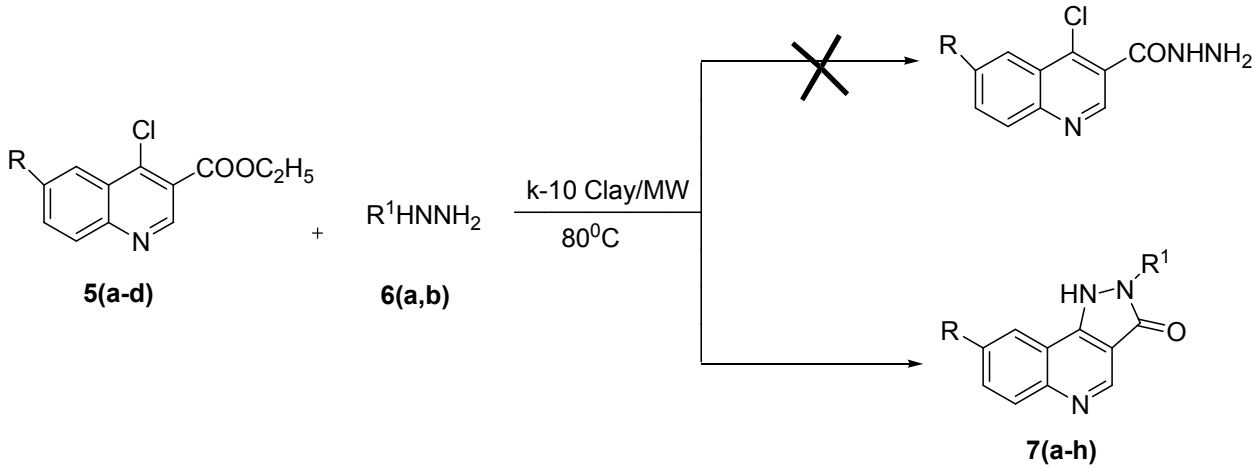


The intermediate ethyl-4-chloroquinoline-3-carboxylates 5 **(a-d)** required for the synthesis of quinoline fused heterocycles were synthesized by Gould-Jacob reaction between primary aromatic amines **1 (a-d)** and diethyl ethoxymethylenemalonate **2** via a chlorination reaction using phosphorus oxychloride[13]. The bifunctional compounds **5 (a-d)** were then used as precursors for the synthesis of pyrazolo[4,3-c]quinolines .

In a typical experiment an equimolar mixture of **5 (a-d)** and hydrazine hydrate were mixed with montmorillonite K-10 clay and the mixture was exposed to CEM's Discover Bench Mate single-mode microwave irradiation at 180 Watts for 2-5 mins. Work up of the reaction mixture afforded **7 (a-h), 9 (a-d), 11 (a-d)** as a pale yellow powder. Similarly the reaction was extended to methyl hydrazine hydrate, phenyl hydrazine and 2,4,-di nitro phenyl hydrazine. In order to know the role of microwave in the rate enhancement of the reaction, similar reactions were

carried out in ethanol containing triethylamine was heated under reflux for 2-3 hrs[14]. Where the reactions took longer time for completion giving the desired products in poor yield.

SCHEME-II



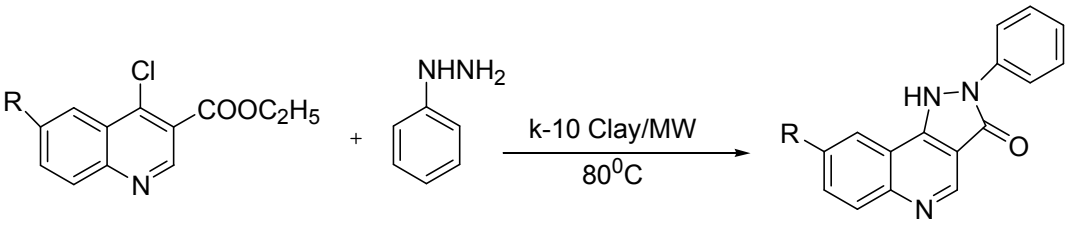
The reaction (between **5 (a-d)** & hydrazine hydrate) has also been carried out without adding any support (neat conditions) which could be expected to be the most economical method. But unfortunately lower yields were obtained (5 min, 36%; 15 min, 42%; 30 min, 50%). Then different solid supports, including silica gel, silica-sulphuric acid, alumina, K-10 clay and p-TsOH were checked to define the most effective reactions conditions (Table-I). From these results it is obvious that K-10 clay is the most adaptable and simplest catalyst for the synthesis of **7 (a-h), 9 (a-d), 11 (a-d)** . As workup is after completion of the reaction methanol was added to the reaction mixture, the clay is filtered off and the filtrate was treated with cold water, the solid separated was filtered and recrystallized from ethanol.

Table:I Comparative study of various catalysts:

Support	**Time (min)**	**Yield(%)**
No	5	36
Silica gel	10	40
SSA[a]	10	46
Alumina	10	42
p-TsOH	10	25
K-10 clay	**2**	**92**

[a]Silica-sulphuric acid (SSA)[15]

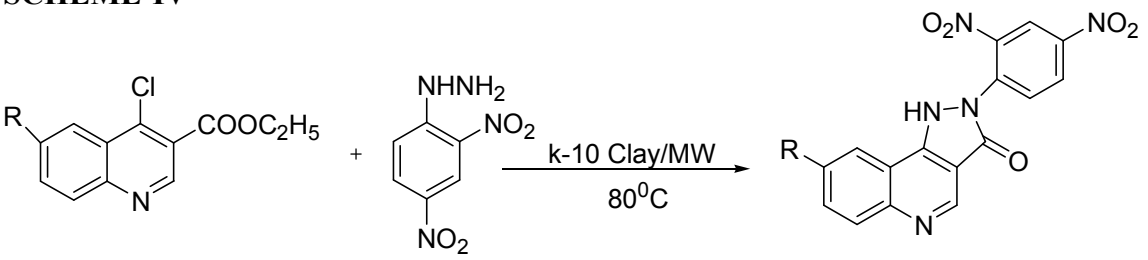
SCHEME-III



5(a-d) **8** **9(a-d)**

9a: R = OCH_3 9b: R = Cl
9c: R = F 9d: R = CH_3

SCHEME-IV



5(a-d) **10** **11(a-d)**

11a: R = OCH_3 11b: R = Cl
11c :R = F 11d: R = CH_3

The products were characterized by IR, ^{1}HNMR, and Mass spectral data. To the best of our knowledge this is the first report for the synthesis of pyrazolo [4,3-c]quinolines using k-10 clay as catalyst under microwave irradiation in solvent-free conditions.

EXPERIMENTAL SECTION:

General Information

Melting points were determined on a Buchi melting-point apparatus and were uncorrected. The progress of the reaction was monitored by Thin-layer chromatography (TLC) performed on silica gel G (Merck), and spots were exposed to iodine vapour or UV light. IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer. 1H NMR spectra were recorded on Brucker DPX-400 at 400-MHz (chemical shifts in δ, ppm) and Mass spectra on an Agilent LC-MS instrument giving only M+ values in Q+1 mode. The MW irradiation was effected using the CEM's Discover Bench Mate single-mode MW synthesis system using safe pressure regulation 10-mL pressurized vials with ''snap-on'' cap.

Preparation of target molecules (General Procedure): 5 (2mmol) and Hydrazine hydrate derivatives (2mmol) were mixed with Montmorillonite K10 clay (1g) and the mixture was placed in a sealed pressure regulation 10-mL pressurized vial with ''snap-on'' cap and was irradiated in the single-mode MW synthesis system at 180 W power and 80^0C temperature for 2–5 min with 60 sec intervals for specified time (Table-II). After completion of reaction (monitored by T.L.C), the reaction mixture was cooled to room temperature. Methanol (10 ml) was added to

reaction mixture. The clay was filtered off, and the filtrate was treated with cold water. The solid separated was filtered and recrystallized from Ethanol to give the target molecules.

1,2-dihydro-8-methoxypyrazolo[4,3-c]quinolin-3-one (7a) :- 92 % Yield, 2 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.73 (s,3H,OCH_3), δ 4.84(s, OH), 6.98-7.98 (m, 3H, Ar-H), 8.70 (s, 1H, C_4-H), 13.7 (s, NH); ^{13}C- NMR (DMSO-d_6): δ 56.0, 99.9, 113.1, 123.4, 124.4, 130.4, 141.9, 143.9, 150.4, 155.9, 167.3.; m/z (M^++1): 216 ; Anal. Calcd. for ($C_{11}H_9N_3O_2$) requires C, 61.39; H, 4.22; N, 19.53; found C,61.43; H, 4.18; N, 19.40 %.

8-chloro-1,2-dihydropyrazolo[4,3-c]quinolin-3-one (7b) :- 84 % Yield, 3 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 4.8(s, OH), 7.60-7.90 (m, 3H, Ar-H), 8.80 (s, 1H, C_4-H), 13.1 (s, NH); m/z (M^++1): 220 ; Anal. Calcd. for ($C_{10}H_6ClN_3O$) requires C, 54.69; H, 2.75; N, 16.14; found C,54.73; H, 2.70; N, 16.19 %.

8-fluoro-1,2-dihydropyrazolo[4,3-c]quinolin-3-one (7c) :- 85 % Yield, 3 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 4.92(s, OH), 7.32-8.03 (m, 3H, Ar-H), 8.75 (s, 1H, C_4-H), 12.9 (s, NH); m/z (M^++1): 204 ; Anal. Calcd. for ($C_{10}H_6FN_3O$) requires C, 59.12; H, 2.98; N, 20.68; found C,59.20; H, 2.94; N, 20.72 %.

1,2-dihydro-8-methylpyrazolo[4,3-c]quinolin-3-one (7d) :- 86 % Yield, 4 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.3 (s, 3H, CH_3), δ 4.84(s, OH), 7.45-7.92 (m, 3H, Ar-H), 8.75 (s, 1H, C_4-H), 12.8 (s, NH); m/z (M^++1): 200 ; Anal. Calcd. for ($C_{11}H_9N_3O$) requires C, 66.32; H, 4.54; N, 21.09; found C, 66.20; H, 4.59; N, 21.12 %.

1,2-dihydro-8-methoxy-2-methylpyrazolo[4,3-c]quinolin-3-one (7e) :- 88 % Yield, 2 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.5 (s, 3H, NCH_3), δ 3.75(s, 3H, OCH_3), δ 4.8(s, OH), 6.9-7.7 (m, 3H, Ar-H), 8.6 (s, 1H, C_4-H); m/z (M^++1): 230 ; Anal. Calcd. for ($C_{12}H_{11}N_3O_2$) requires C, 62.87; H, 4.84; N, 18.38; found C, 63.02; H, 4.79; N, 18.42 %.

8-chloro-1,2-dihydro-2-methylpyrazolo[4,3-c]quinolin-3-one (7f) :- 83 % Yield, 4 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.6 (s, 3H, NCH_3), δ 4.9(s, OH), 7.6-7.92 (m, 3H, Ar-H), 8.78 (s, 1H, C_4-H); m/z (M^++1): 234 ; Anal. Calcd. for ($C_{11}H_8ClN_3O$) requires C, 56.54; H, 3.45; N, 17.98; found C, 56.60; H, 3.50; N, 18.02 %.

8-fluoro-1,2-dihydro-2-methylpyrazolo[4,3-c]quinolin-3-one (7g) :- 82 % Yield, 4 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.65 (s, 3H, NCH_3), δ 4.86(s, OH), 7.3-7.80 (m, 3H, Ar-H), 8.8 (s, 1H, C_4-H); m/z (M^++1): 218 ; Anal. Calcd. for ($C_{11}H_8FN_3O$) requires C, 60.83; H, 3.71; N, 19.35; found C, 60.60; H, 3.66; N, 19.73 %.

1,2-dihydro-2,8-dimethylpyrazolo[4,3-c]quinolin-3-one (7h) :- 80 % Yield, 5 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.30 (s, 3H, CH_3), δ 3.75(s, 3H, NCH_3), δ 4.92(s, OH), 7.4-7.6 (m, 3H, Ar-H), 8.5 (s, 1H, C_4-H); m/z (M^++1): 214 ; Anal. Calcd. for ($C_{12}H_{11}N_3O$) requires C, 67.59; H, 5.20; N, 19.71; found C, 67.62; H, 5.19; N, 19.79 %.

1,2-dihydro-8-methoxy-2-phenylpyrazolo[4,3-c]quinolin-3-one (9a) :- 84 % Yield, 3 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.5 (s, 3H, OCH_3), δ 4.86 (s, OH), 7.2-7.4 (m, 5H, Ar-H), 7.4-7.9 (m, 3H,

Ar-H), 8.6 (s, 1H, C_4-H); ^{13}C- NMR (DMSO-d_6): δ 57.0, 99.6, 113.5, 119.4, 122.4, 125.1, 129.3, 131.4, 136.4, 141.9, 144.9, 151.4, 156.8, 159.5, 162.9.; m/z (M^++1): 292 ; Anal. Calcd. for ($C_{17}H_{13}N_3O_2$) requires C, 70.09; H, 4.50; N, 14.42; found C, 71.12; H, 4.54; N, 14.49 %.

8-chloro-1,2-dihydro-2-phenylpyrazolo[4,3-c]quinolin-3-one (9b) :- 83 % Yield, 4 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 4.92 (s, OH), 7.32-7.54 (m, 5H, Ar-H), 7.5-7.99 (m, 3H, Ar-H), 8.81 (s, 1H, C_4-H); m/z (M^++1): 296 ; Anal. Calcd. for ($C_{16}H_{10}Cl\,N_3O$) requires C, 64.98; H, 3.41; N, 14.21; found C, 65.12; H, 3.54; N, 14.33 %.

8-fluoro-1,2-dihydro-2-phenylpyrazolo[4,3-c]quinolin-3-one 9c:- 82 % Yield, 5 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 4.91 (s, OH), 7.33 -7.48 (m, 5H, Ar-H), 7.39 -7.89 (m, 3H, Ar-H), 8.79 (s, 1H, C_4-H); m/z (M^++1): 280 ; Anal. Calcd. for ($C_{16}H_{10}F\,N_3O$) requires C, 68.81; H, 3.61; N, 15.05; found C, 68.89; H, 3.54; N, 15.33 %.

1,2-dihydro-8-methyl-2-phenylpyrazolo[4,3-c]quinolin-3-one (9d) :- 84 % Yield, 5 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.32 (s, 3H, CH_3), δ 4.85 (s, OH), 7.3 -7.45 (m, 5H, Ar-H), 7.47 -7.8 (m, 3H, Ar-H), 8.72 (s, 1H, C_4-H); m/z (M^++1): 276 ; Anal. Calcd. for ($C_{17}H_{13}N_3O$) requires C, 74.17; H, 4.76; N, 15.26; found C, 74.12; H, 4.69; N, 15.39 %.

1,2-dihydro-8-methoxy-2-(2,4-dinitrophenyl)pyrazolo[4,3-c]quinolin-3-one (11a) :- 78 % Yield, 4 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.93 (s, 3H, OCH_3), δ 4.99 (s, OH), 6.9-7.5 (m, 3H, Ar-H), 7.8-8.8 (m, 3H, Ar-H), 8.85 (s, 1H, C_4-H); ^{13}C- NMR (DMSO-d_6): δ 57.6, 98.4, 113.9, 119.2, 123.4, 126.4, 127.4, 130.4, 132.4, 132.9, 139.8, 141.6, 143.4, 151.4, 156.9, 159.5, 163.4; m/z (M^++1): 382 ; Anal. Calcd. for ($C_{17}H_{11}N_5O_6$) requires C, 53.55; H, 2.91; N, 18.37; found C, 53.61; H, 2.85; N, 18.41 %.

8-chloro-1,2-dihydro-2-(2,4-dinitrophenyl)pyrazolo[4,3-c]quinolin-3-one (11b) :- 76 % Yield, 5 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 4.12 (s, OH), 7.6 -7.9 (m, 3H, Ar-H), 7.8 -9.0 (m, 3H, Ar-H), 8.79 (s, 1H, C_4-H); m/z (M^++1): 386 ; Anal. Calcd. for ($C_{16}H_8Cl\,N_5O_5$) requires C, 49.82; H, 2.09; N, 18.16; found C, 49.90; H, 2.13; N, 18.24 %.

8-fluoro-1,2-dihydro-2-(2,4-dinitrophenyl)pyrazolo[4,3-c]quinolin-3-one (11c) :- 77 % Yield, 5 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 4.52 (s, OH), 7.4 -8.0 (m, 3H, Ar-H), 7.9 -9.2 (m, 3H, Ar-H), 8.9 (s, 1H, C_4-H); m/z (M^++1): 370 ; Anal. Calcd. for ($C_{16}H_8F\,N_5O_5$) requires C, 52.04; H, 2.19; N, 18.96; found C, 52.10; H, 2.13; N, 18.84 %.

1,2-dihydro-8-methyl-2-(2,4-dinitrophenyl)pyrazolo[4,3-c]quinolin-3-one (11d) :- 78 % Yield, 5 min, m.p : >250^{0}C, IR (KBr): 1728 and 1674 cm-1(both s, sharp, two -C=O groups); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.43 (s, 3H, CH_3), δ 4.93 (s, OH), 7.47 - 7.99 (m, 3H, Ar-H), 7.7-8.8 (m, 3H, Ar-H), 8.73 (s, 1H, C_4-H); m/z (M^++1): 366 ; Anal. Calcd. for ($C_{17}H_{11}N_5O_5$) requires C, 55.89; H, 3.04; N, 19.17; found C, 55.91; H, 3.13; N, 19.24 %.

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