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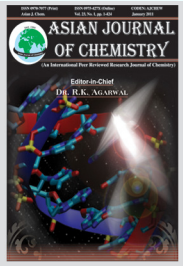

Synthesis and Antitumor Activity of Some Pyrazole Derivatives

FATMA E.M. EL-BAIH[1,*] and HASSAN M. AL-HAZIMI[2]

[1]Women Students-Medical Studies & Sciences Sections, Department of Chemistry, College of Science, King Saud University, P.O. Box 22452, Riyadh 11495, Saudi Arabia
[2]Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia

*Corresponding author: Tel:/Fax: +966 1 4772245; E-mail: zahraa205@yahoo.com

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Vilsmeier-Haack chloroformylation of **1a-e** using DMF and an excess of $POCl_3$ yielded the corresponding pyrazole-4-carbaldehydes **2a-e**. Reaction of **2a,c** with *o*-bromophenol and KOH in DMF gave the target compound 5-phenoxypyrazole-4-carbaldehydes **3a,b** which in turn gave the corresponding oximes **4a,b** by oximation of **3a,b** with hydroxylamine. Condensation of **2b,c** with 1,2-diaminobenzene and 2-aminothiophenol was carried out to give tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine derivatives **5a,b** and benzo[b]pyrazolo[4,3-f][1,4]thiazepine derivatives **6a,b**, respectively. Some of the prepared compounds was examined as cytotoxic agents. The compounds **3a**, **4a**, **5a** and **6a** were proved to be less or more active than the standared doxorubicin depending on the cell lines.

Key Words: Pyrazole carbaldeyhde, Pyrazole carbaldeyhde oxime, Benzopyrazolodiazepine, Benzopyrazolothiazepine.

INTRODUCTION

Pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. Indeed, pyrazole-based derivatives have shown several biological activities such as, insecticidal[1-3], antimicrobial[4-7], antifungal[8], antiviral[9-12] and antitumor[13-15]. These diverse properties prompted us to synthesize pyrazole carbaldeyhde, pyrazole oxime as will as benzopyrazolodiazepine and benzopyrazolothiazepine and evaluate their inhibitory potential against tumor cell lines.

EXPERIMENTAL

Melting points were determined using an electrothermal IA9000 series digital capillary melting point apparatus. IR spectra were obtained as KBr discs on a 1000-Perkin Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol ECP-400 NMR in $CDCl_3$ (or DMSO-d_6) using TMS as an internal standard. Chemical shifts are given in δ ppm and coupling constants (*J*) are given in Hz. The assignments of all carbons are made by comparison to ^{13}C NMR spectra of structurally related compounds[16-18] and theory ground[19-21] and by the aid of modern NMR techniques. Electron impact (EI) MS spectra were acquired with the aid of a Varian MAT 311-A70ev (Varian, Fort Collins, USA), Micro analytical Center Cairo University.

Synthesis of 1,3-disubstituted-1*H*-pyrazol-5(4*H*)-one (1a-e): The starting pyrazolones were readily prepared by the reactions of the appropriate hydrazines with β-ketoesters according to the literature procedures[22].

Synthesis of 5-chloro-1,3-disubstituted-1*H*-pyrazole-4-carbaldehyde (2a-e): The known 5-chloropyrazole-4-carbaldehydes were prepared from the 5-pyrazolones employing Vilsmeier-Haack chloroformylation[23-25].

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (2a): Reddish brown needles, m.p. 140 ºC (from 50 % ethanol); yield 37 %; IR (KBr, ν_{max}, cm^{-1}): 2830, 2776 (CHO), 1678 (C=O); ^{1}H NMR ($CDCl_3$): 2.51 (3H, s, CH_3), 7.49-7.51 (5H, m, Ar-H), 9.95 (1H, s, CHO); ^{13}C NMR: 13.8 (CH_3), 117.4 (C-4), 133.4 (C-5), 151.7 (C-3), 183.8 (CHO), 125.1 (2C), 129.1, 129.2 (2C), 136.9 (sp^2 carbons).

5-Chloro-3-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehyde (2b): Pale yellow powder, m.p. 110 ºC (from 50 % ethanol); yield 48 %; IR (KBr, ν_{max}, cm^{-1}): 2840, 2742 (CHO), 1679 (C=O); ^{1}H NMR ($CDCl_3$): 2.54 (3H, s, CH_3), 7.38 (1H, td, ^3J = 6.0, ^4J = 1.8, H-5'), 7.71 (1H, d, J = 8.4, H-3'), 7.90 (1H, td, ^3J = 7.5, ^4J = 1.8, H-4') 8.23 (1H, d, ^3J = 5.9, H-6'), 10.00 (1H, s, CHO); ^{13}C NMR: 13.8 (CH_3), 118.2 (C-4), 118.4 (C-3'), 123.5 (C-5'), 133.0 (C-5), 138.6 (C-4'), 148.5 (C-6'), 150.2 (C-2'), 151.9 (C-3); MS: m/z (%) 221 (10) [M$^+$] ($C_{10}H_8{}^{35}ClN_3O$), 223 (10) [M + 2] ($C_{10}H_8{}^{37}ClN_3O$), 206 (4) [M-CH_3], 186 (18) [M-Cl], 78 (100) [C_5H_4N]$^+$.

5-Chloro-3-phenyl-1*H*-pyrazole-4-carbaldehyde (2c): Beige powder, m.p. 191 ºC (from ethanol); yield 26 %; IR (KBr, ν_{max}, cm^{-1}): 2836, 2778 (CHO), 1646 (C=O); ^{1}H NMR (DMSO-d_6): 7.56-7.57 (3H, m, H-3',4',5'), 7.74-7.75 (2H, m, H-2',6'), 9.83 (1H, s, CHO), 14.12 (1H, s, NH); ^{13}C NMR: 114.5 (C-4), 133.1 (C-5), 148.7 (C-3), 184.0 (CHO), 129.46

(2C), 129.53 (2C), 131.0 (sp^2 carbons); MS: m/z (%) 206 (58) [M^+] ($C_{10}H_7{}^{35}ClN_2O$), 208(20) [M + 2] ($C_{10}H_7{}^{37}ClN_2O$), 205 (83) [M-H], 126 (67) [M-Ph-H].

5-Chloro-1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (2d): Pale yellow needles, m.p. 78 ºC (from ethanol); yield 64 %; IR (KBr, ν_{max}, cm^{-1}): 2809, 2729 (CHO), 1685 (C=O); ^{1}H NMR ($CDCl_3$): 2.42 (3H, s, CH_3 at position 3), 3.79 (3H, s, CH_3 at position 1) 9.82 (1H, s, CHO); ^{13}C NMR: 13.7 (CH_3 at position 3), 35.9 (CH_3 at position 1), 116.3 (C-4), 133.7 (C-5), 150.9 (C-3), 183.4 (CHO); MS: m/z (%)158 (54) [M^+] ($C_6H_7{}^{35}ClN_2O$), 159 (40) [M + 1], 160(17) [M + 2] ($C_6H_7{}^{37}ClN_2O$), 157 (100) [M-H], 143 (2) [M-CH_3].

5-Chloro-1-methyl-3-phenyl-1*H*-pyrazole-4-carbaldehyde (2e): Colourless scales, m.p. 61 ºC (from ethanol); yield 74 %; IR (KBr, ν_{max}, cm^{-1}): 2829, 2779 (CHO), 1666 (C=O); ^{1}H NMR ($CDCl_3$): 3.94 (3H, s, CH_3), 7.44-7.48 (3H, m, H-3,4,5), 7.72-7.74 (2H, m, H-2,6), 9.95 (1H, s, CHO); ^{13}C NMR: 36.4 (CH_3), 115.6 (C-4), 133.3 (C-5), 153.7 (C-3), 183.7 (CHO), 128.7 (2C), 128.8 (2C), 129.5, 131.1 (sp^2 carbons); MS: m/z (%) 220 (100) [M^+] ($C_{11}H_9{}^{35}ClN_2O$), 221 (44) [M + 1], 222 (34) [M + 2] ($C_{11}H_9N_2{}^{37}ClO$), 219 (97) [M-H], 205 (6) [M-CH_3], 192 (6) [M-N_2], 185 (11) [M-Cl], 156 (18) [185-CHO].

Synthesis of 5-(4-bromophenoxy)-1,3-disubstituted 1*H*-pyrazole-4-carbaldehyde (3a,b): A mixture of **2a** or **2c** (0.18 mmol), 4-bromo phenol (93 mg, 0.54 mmol) and powdered KOH (15 mg, 0.27 mmol) in DMF (5 mL) was stirred at 120 ºC for 2 h. The reaction mixture was diluted with H_2O (40 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed successively with brine and water, dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to give a solid residue which was recrystallized to give **3**.

5-(4-Bromophenoxy)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3a): Pale brown powder, m.p. 122 ºC (from 50 % ethanol); yield 73 %; IR (KBr, ν_{max}, cm^{-1}): 2774, 2826 (CHO), 1663 (C=O); ^{1}H NMR ($CDCl_3$): 2.54 (3H, s, CH_3), 6.88 (2H, d, *J* = 7.7, H-2",6", AA' part of AA'XX' system), 7.32 -7.43 (5H, m, H-2',3',4',5',6'), 7.58 (2H, d, *J* = 7.7, H-3", 5", XX' part of AA'XX' system), 9.65 (1H, s, CHO); ^{13}C NMR: 14.4 (CH_3), 109.0 (C-4), 151.0 (C-3), 156.0 (C-5), 182.7 (CHO), 117.2, 117.7 (2C), 122.8 (2C), 128.2, 129.3 (2C), 133.1 (2C) 136.7, 151.5 (sp^2 carbons); MS: m/z (%) 356(5) [M^+] ($C_{17}H_{13}{}^{79}BrN_2O_2$), 358 (4) [M + 2] ($C_{17}H_{13}{}^{81}BrN_2O_2$), 185 (37) [M], 77(100) [$C_6H_5^+$].

5-(4-Bromophenoxy)-3-phenyl-1*H*-pyrazole-4-carbaldehyde (3b): Brown powder, m.p. 95 ºC (from ethanol); yield 66 %; IR (KBr, ν_{max}, cm^{-1}): 3189 (NH), 2722, 2818 (CHO), 1672 (C=O); ^{1}H NMR ($CDCl_3$): 7.25 (2H, d, *J* = 7.9, H-2",6"), 7.44 (2H, d, *J* = 7.9, H-3",5"), 7.42-7.53 (3H, m H-3',4',5'), 7.73 (2H, d, *J* =7.8, H-2',6'), 9.83 (CHO), 13.40 (br s, NH); ^{13}C NMR: 105.1 (C-4), 127.3 (C-3), 154.6 (C-5), 191.3 (CHO), 119.7, 122.6 (2C), 132.9 (2C), 127.6 (2C), 128.6, 129.5 (2C), 135.92, 151.50 (sp^2 carbons).

Synthesis of 5-(4-bromophenoxy)-1,3-disubstituted-1*H*-pyrazole-4-carbaldehyde oxime (4a,b): A mixture of compound **3a** or **3b** (10 mmol), hydroxylamine hydrochloride (2.78 g, 40 mmol), pyridine (2.4 mL) and ethanol (17 mL) was refluxed for 5 h. Then the mixture was poured onto water (110 mL), the precipitated solid was collected by filtration, washed several times with water, dried and recrystallized to give **4**.

5-(4-Bromophenoxy)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime (4a): Pale brown needle crystals, m.p. 131 ºC (from 50 % ethanol); yield 88 %; IR (KBr, ν_{max}, cm^{-1}): 3183 (OH); ^{1}H NMR ($CDCl_3$): 2.46 (3H, s, CH_3), 6.78 (2H, d, *J* = 8.0, H-2",6", AA' part of AA'XX' system), 7.28-7.37 (5H, m, H-2',3',4',5',6'), 7.54 (2H, d, *J* = 8.0, H-3",5", XX' part of AA'XX' system), 7.88 (1H, s, CH=NOH), 8.54 (1H, s, OH); ^{13}C NMR: 14.7 (CH_3), 102.4 (C-4), 146.2 (C-3), 149.0 (CH=NOH), 155.5 (C-5), 116.0, 117.1 (2C), 122.1 (2C), 127.3, 129.1 (2C), 132.7 (2C), 140.7, 148.2, (sp^2 carbons); MS: m/z (%) 338 (38) [M-NH2OH], 93 (31) [M-C_6H_4OBr-C_6H_5-CH_3-H_2O + 3H], 51(100) [$C_4H_3^+$].

5-(4-Bromophenoxy)-3-phenyl-1*H*-pyrazole-4-carbaldehyde oxime (4b): Yellowish needles, m.p. 134 ºC (from ethanol); yield 85 %; IR (KBr, ν_{max}, cm^{-1}): 3327 (NH), 3210 (OH); ^{1}H NMR ($CDCl_3$): 7.26 (2H, d, *J* =7.8, H-2",6"), 7.38 (2H, d, *J* =7.8, H-3",5"), 7.43-7.58 (3H, m, H-3',4',5'), 7.82 (2H, d, *J* = 8, H-2',6'), 8.08 (1H, s, CH=N), 12.89, br.s, NH); ^{13}C NMR: 108.2 (C-4), 126.5 (C-3), 148.2 (CH=N), 154.6 (C-5), 118.7, 122.5 (2C), 126.7 (2C), 129.1, 129.4 (2C), 133.0 (2C), 134.0,151.5. (sp^2 carbons).

Method A for synthesis of 5a,b and 6a,b: A solution of compound **2b** or **2c** (10 mmol) and 1,2-diamino benzene or 2-amino thiophenol (10 mmol) in ethanol (30 mL) in the presence of piperidine (0.1 mL) was refluxed for 2 h. The reaction mixture was evaporated to dryness under reduced pressure to give crystals which were washed with 5 mL acetic acid, dried and then dissolved in ether (3 × 20 mL). The combined ethereal solution was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure to afford pure products of **5** and **6**.

Method B for synthesis of 5a: A solution of compound **2b** (2.0 g, 10 mmol) and 1,2-diamino benzene (1 g, 10 mmol) in ethanol (30 mL) in the presence of piperidine (0.1 mL) was irradiated in the water bath of an ultrasonic cleaner for 150 min then treated as in method A.

3-Methyl-1-(pyridin-2-yl)-1,4,5,10-tetrahydrobenzo-[b]pyrazolo[3,4-e][1,4]diazepine (5a): Pale brown powder, m.p. 160 ºC, yield 22 %^{A} 60 %^{B}; IR (KBr, ν_{max}, cm^{-1}): 3229; ^{1}H NMR (DMSO-d_6): 2.11 (3H, s, CH_3), 3.93 (2H, s, CH_2-4), 5.63 (1H, s, NH), 6.75-6.82 (2H, m, H-2", 5"), 6.92-6.98 (2H, m, H-3",4"), 7.38 (1H, t, ^3J = 5.9, H-5'), 7.85 (1H, d, *J* = 8.4, H-3'), 7.96 (1H, td, ^3J = 7.5, ^4J = 1.8, H-4') 8.23 (1H, d, ^3J = 5.9, H-6'), 10.71 (1H, s, NH); ^{13}C NMR: 12.4 (CH_3), 43.2 (C-4), 119.8 (C-3'), 122.1 (C-5'), 139.8 (C-4'), 147.0 (C-6'), 154.4 (C-2'), 101.0, 112.7, 119.9, 121.4, 121.5, 132.1, 140.0, 143.5, 147.5 (sp^2 carbons); MS: m/z (%) 277 (33) [M^+] ($C_{16}H_{15}N_5$), 276 (39) [M-H], 199 (39) [M-C_5H_4N], 170 (44) [199-N_2-H], 78 (100) [$C_5H_4N]^+$.

3-Phenyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (5b): Brown powder, m.p. 137 ºC, yield 41 %; IR (KBr, ν_{max}, cm^{-1}): 3295; ^{1}H NMR (DMSO-d_6): 4.38 (2H, s, CH_2-4), 5.23 and 5.82 (2H, s, 2NH), 6.52-6.72 (4H, m, H-2",3", 4",5"), 7.38 (1H, t, ^3J = 8.2, H-4'), 7.52 (2H, t, *J* = 8.3, H-3',5'), 7.73 (2H, d, *J* = 8.3, H-2', 6'), 12.49 (1H, s, NH); ^{13}C NMR: 46.7 (C-4), 127.6 (C-2',6'), 128.7 (C-4'), 129.2 (C-3',5'),

132.8 (C-1'), 102.0, 116.1, 119.5, 126.5, 130.6, 135.2, 139.8, 139.4, 154.6 (sp^2 carbons); MS: m/z 262 [M^+] ($C_{16}H_{14}N_4$).

3-Methyl-1-(pyridin-2-yl)-1*H*-benzo[b]pyrazolo[4,3-f][1,4]thiazepine (6a): Brown powder, m.p. 140 ºC; yield 31 %; ^{1}H NMR ($CDCl_3$): 2.79 (3H, s, CH_3), 6.75-6.82 (2H, m, H-2", 5"), 6.92-6.98 (2H, m, H-3",4"), 7.35 (1H, t, ^3J = 5.9, H-5'), 7.62 (1H, s, H-4), 7.76 (1H, d, J = 8.4, H-3'), 7.90 (1H, td, ^3J = 7.5, ^4J = 1.8, H-4') 8.23 (1H, d, ^3J = 5.9, H-6'); ^{13}C NMR: 15.3 (CH_3), 118.1 (C-3'), 123.0 (C-5'), 138.5 (C-4'), 148.4 (C-6'), 152.5 (C-2'), 116.5, 117.1, 118.6, 125.6, 126.8, 126.9, 132.3, 148.9, 150.7, 151.8 (sp^2 carbons); MS: m/z (%) 292 (6) [M^+] ($C_{16}H_{12}N_4S$), 293 (6) [M + 1], 250 (5) [M-CH_3-HCN], 78 (100) [C_5H_4N]$^+$.

3-Phenyl-1*H*-benzo[b]pyrazolo[4,3-f][1,4]thiazepine (6b): Brown prisms, m.p. 107-110 ºC; yield 37 %; IR (KBr, ν_{max}, cm^{-1}): 3327; ^{1}H NMR ($CDCl_3$): 7.0-7.22 (4H, m, H-2",3",4",5"), 7.26 (1H, t, J = 8.0, H-4'), 7.35 (2H, t, J = 8.0, H-3',5'), 7.50 (2H, d, J = 8.0, H-2', 6'), 7.56 (1H, s, H-4), 13.28 (1H, s, NH); ^{13}C NMR ($CDCl_3$): 127.2 (C-2',6'), 128.1 (C-4'), 129.0 (C-3',5'), 133.1 (C-1'), 159.5 (C-4), 104.2, 122.8, 126.4, 126.8, 127.0, 127.6, 130.5, 134.0, 149.6; MS: m/z 277 [M^+] ($C_{16}H_{11}N_3S$).

Measurement of potential cytotoxicity by SRB assay: The growth suppressing potential compounds **3a**, **4a**, **5a** and **6a** was investigated by determining their IC_{50} value by SBR assay against human tumor cell lines: HEPG2 (hepatocellular carcinoma), HCT116 (colorectal carcinoma) and MCF7 (human breast adenocarcinoma) using the method of Skehan *et al.*[26]. Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compounds under test (0, 5, 12.5, 25 and 50 µg/mL) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the latter for 48 h at 37 ºC and in atmosphere of 5 % CO_2. After 48 h, cells were fixed, washed and stained with sulforhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with tris EDTA buffer. Colour intensity was measured in an ELISA reader. The relation between the surviving fraction and the concentration of the compound is plotted to get the survival curve of each tumor cell line after the specified compound. Doxorubicin was used as a reference drug.

The cytotoxic activities of the prepared compounds **3a**, **4a**, **5a** and **6a** including doxorubicin are summarized in Table-1. In general, compounds **3a** and **4a** show cytotoxic activities. Compound **6a** is as potent as doxorubicin on MCF7, but it has decreased cytotoxicity compared to doxorubicin on HEPG2 and HCT116. Compound **5a** has more potent activity than doxorubicin on HCT116, but it is less active than doxorubicin on HEPG2.

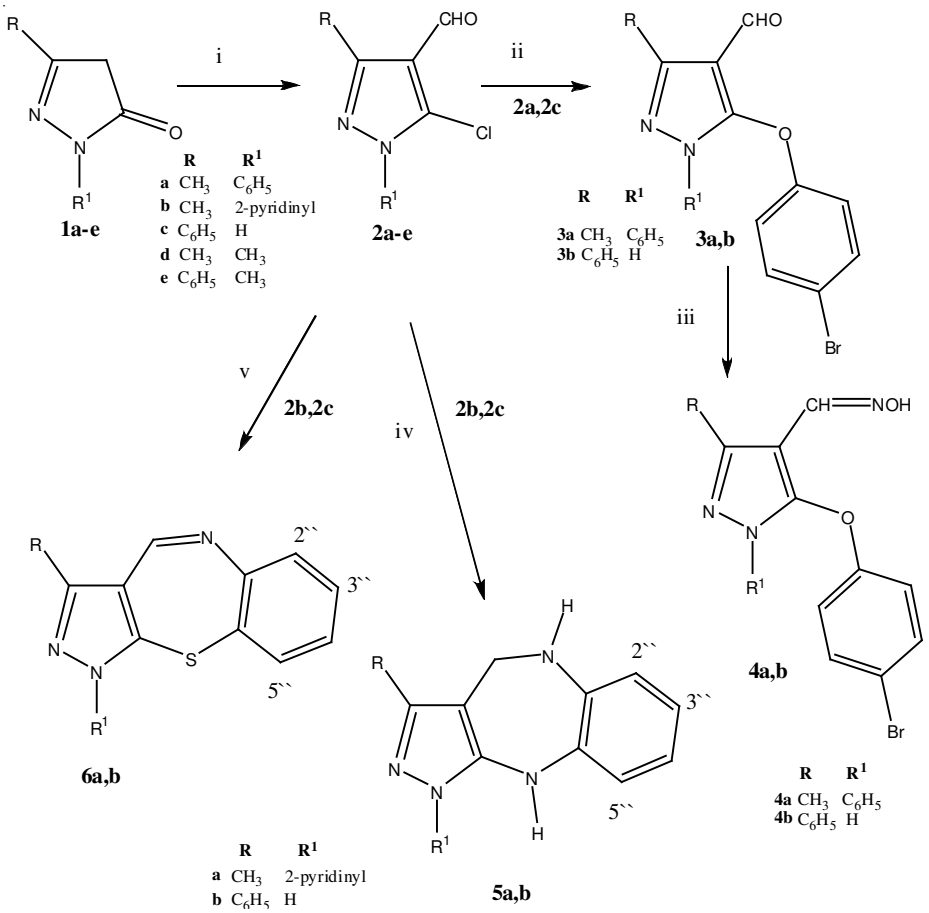
TABLE-1
ANTITUMOR ACTIVITY OF COMPOUNDS **3-6**

Compound	Cytotoxicity IC_{50} (µ/mL)		
	HEPG2	HCT116	MCF7
3a	7.85	4.50	8.00
4a	4.34	8.61	4.50
5a	11.20	2.82	3.12
6a	17.30	10.70	2.97
Doxorubicin	5.50	3.74	2.97

RESULTS AND DISCUSSION

The starting material pyrazolone were readily prepared by the reactions of the appropriate hydrazine with β-ketoesters using microwave irradiation according to the literature procedure[22]. 5-Chloro-1,3-disubstituted-1*H*-pyrazole-4-carbaldehyde (**2a-e**) were prepared from the 5-pyrazolones employing Vilsmeier-Haack chloroformylation[23-25] by heating 5-pyrazolones with an excess phosphorus oxychloride in DMF (**Scheme -I**). The structures of **2a-e** were assigned on the basis of spectroscopic analyses. Thus, IR spectra of **2a-e** showed bands at 2778-2729 cm^{-1} and at 2840-2809 cm^{-1} due to the aldehyde C-H streching and band at 1678 cm^{-1} due to C=O streching. Mass spectral data have been found to be in conformity with the assigned structure. ^{1}H NMR spectrum of **2a** exibited a singlet for the methyl protons at δ 2.51 ppm, a multiplet for the phenyl protons at δ 7.49-7.51 ppm beside the one proton singlet at δ 9.95 ppm for the CHO. The ^{13}C NMR spectrum of **2a** displayed signals at δ: 13.8 ppm for the methyl carbon, 117.4 ppm for C-4, 133.4 ppm for C-5, 151.7 ppm for C-3, 183.8 ppm for CHO and four lines at δ 125.1, 129.1, 129.2, 136.9 ppm for the phenyl carbons. Nucleophilic aromatic substitution[27] by 4-bromophenol was carried out on the carbaldehyde **2a** and **2c** activated by the electon-withdrawing formyl group afforded the phenoxy derivative **3a,b**. The structural identity of **3** was confirmed on the basis of its various spectral data (section 2). Thus, IR spectrum showed band at 1672-1663 cm^{-1} for C=O streching, in addition to two bands in the range 2826-2774 which are characteristic to C-H stretching of the aldehyde group. The ^{1}H NMR spectrum of **3a** is similar to that of **2a**, with additinoal two doublets (J = 7.7 Hz), each integrated for two protons at δ 6.88 and δ 7.58 assigned to H-2",6" and H-3",5", respectively. The chemical shifts of other proton absorptions in the latter spectrum of **3a** as well as the whole carbon signals in the ^{13}C NMR spectrum were in complete consistent with its structure (see experimental). The mass spectrum of **3a** revealed M^+ at m/z 356 as well as at m/z 358 almost with equal intensity as expected for bromine isotopes. Compound **3b** showed also NMR spectral features similar to those of **3a**, except for the absence of methyl resonance in both NMR spectra of **3b**. ^{1}H NMR spectrum of the latter gave a singlet at δ 13.4 for the NH resonance, which disappears on D_2O addition.

Compounds **4a,b** were obtained in very good yield, by the oximation of the aldehydes **3a,b** with hydroxylamine. The structure of the oxime **4a** was confirmed by the analysis of its various spectroscopic data. Its IR spectrum showed an absorption band at 3183 cm^{-1} corresponding to the oxime hydroxyl stretching. The ^{1}H NMR of the latter compound exhibited two singletts, each integrated for one proton at δ 7.88 and δ 8.54 corresponding to the resonances of CH=N and OH, respectively. All other protons in this spectrum appeared at their expected chemical shifts. Further, ^{13}C NMR data of **4a** were consistent completely with its structure. The mass spectrum of **4a** displayed a daughter ion peak at m/z 338 due to [M-NH_2OH IR spectrum of **4b** exhibited two stretching bands at 3210, 3327 cm^{-1} which ascribed to the NH and oxime hydroxyl (=N-OH) groups in its structure. Its ^{1}H NMR spectrum showed almost the same pattern of signals as **4a** in the aromatic



Scheme-I: (i) DMF, $POCl_3$, reflux, 1 h, 130 ºC; (ii) 4-bromophenol, KOH, DMF, stirring, 2 h, 120 ºC; (iii) $NH_2OH.HCl$, pyridine, ethanol , reflux, 5 h; (iv) **a**: 1,2-diaminobenzene, pyridine, ethanol , reflux, 2 h; **b**: 1,2-diaminobenzene, ethanol, piperidine, US, 150 min; (v) 2-aminothiophenol, ethanol, piperidine, reflux, 2 h

region, along with the absence the methyl protons signal in the aliphatic region which shown in the same spectrum of the latter compound. On the other hand, ^{13}C NMR of **4b** displayed 12 distinct resonances in good agreement with its structure and the full assignments of these resonances are given in the experimental part.

Condensation of **2b,c** with 1,2-diamino benzene under refluxing in ethanol for 2 h in the presence of pyridine, yielded compound **5a,b** in moderate yield. Compound **5a** was also obtained following ultrasound procedure under the same condition but in very low yield, although the reaction was much cleaner than the classical heating one. ^1H NMR spectrum of **5a** revealed two singlets in the aliphatic region at δ 2.11 and δ 3.93, integrated for 3 and 2 protons, respectively owing to CH_3 attached to the pyrazole ring and CH_2 group, part of the diazepine ring, in its structure. All other protons in the spectrum of **5a** appeared at their expected chemical shifts. ^{13}C NMR spectrum of the latter showed all carbon signals, including the two signals at δ_C at 12.4 and 43.2 for methyl and methylene carbons. The DEPT experiment for **5** insured the presence of CH_2 group. The mass spectrum of **5a** further confirmed its structure, which gave molecular ion peak [M^+] at m/z 277 for $C_{16}H_{15}N_5$. ^1H NMR of **5b** showed δ_H of CH_2 at position 4 appearing at δ 4.38 ppm, while the carbon signal of this group appeared at δ 46.7 ppm in the ^{13}C NMR spectrum. In this spectrum, a fairly complex multiplet integrated for 4 protons was oberved at 6.52-6.72 ppm for the aromatic protons of the benzene ring fused with triazepine, in addition to the signals of phenyl protons at their respective chemical shifts and with expected multiplicities. The D_2O exchangeable proton at δ 12.49 ppm assigned to the NH in **5b**. The ^{13}C NMR spectral data of this compound was found to be in complete consistence with its structure.

On the other hand, refluxing of **2b,c** with 2-amino thiophenol under the same conditions for obtaining **5** by classical heating method led to the isolation of the expected cyclized imine **6a** and **6b**, in low yield (see experimental). ^1H NMR spectrum of **6a** clearly disclosed the disappearance of any absorption for NH (no exchangeable proton in the aromatic region after addition D_2O) and for CH_2 group; instead, a signal as a singlet integrated for one proton appeared in the aromatic region at δ_H 7.62 which is ascribed to C4-H proton. The assignment of all protons and carbons in **6a** were verified by the aid of the analysis of DEPT and ^1H-^{13}C Cosy techniques. The mass spectrum of **6a** showed a molecular ion peak [M^+] at m/z 292 which is in conformity with its assigned structure. ^1H NMR spectrum of **6b** exhibited a singlet at δ 7.56 ppm readily recognizable for the proton CH=N, along with broad singlet at δ 13.28 attibuted to NH proton. This spectrum also displayed a multiplet at δ 7.02-7.18 integrated for four protons, assigned to the protons of disubstituted aromatic ring, while the protons of phenyl ring appeared at their expected chemical shifts. The ^{13}C NMR spectrum of **6b** exhibited 14 signals in the aromatic region in consistent with its structure which was further

confirmed by its molecular ion at m/z at 277 in the mass spectrum.

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