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RESEARCH ARTICLE

SYNTHESIS OF NEW PYRAZOLO[3,4-D]PYRIMIDINE AND THEIR FUSED HETEROCYCLES.

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Abstract

Novel pyrazolo[3,4-.]pyrimidine derivatives were synthesized via various synthetic pathways . Among which were different substituted pyrazole analogues that were synthesized , in addition to various fused dipyrazolo[1,5-*c*:4',3'-*c*]pyrimidine derivatives , imidazo[1,2-*b*]pyrazole and imidazo[1',2':3,4]imidazo[1,2-*b*]pyrazole derivatives .Besides pyrazolo[5,1-*b*]quinazoline dervatives was also synthesized . The structure of the synthesized compounds were confirmed by IR, ^{1}H and ^{13}CNMR, elemental analysis and mass spectra data and all structures of synthesized compounds agree with spectral data and elemental analysis.

Introduction:-

Pyrazolo pyrimidine and related fused Heterocycles are of interest as potential bioactive molecules such as CNS depressant [1] Antiproliferative, antimicrobial and antitumor [2-10]. Also, pyrazolo[3,4-*d*]pyrimidines were identified as general class of adenosine receptor [11]. The present study described the synthesis and characterization of novel triazolopyrimidine and their fused.

Experimental section :

Melting points of all – the compounds are determined in open capillary method and are uncorrected. IR spectra are recorded in KBr pellets on schimadzu FT-IR affinity -1-spectrometer. ^{1}HNMR and ^{13}CNMR spectra in DMSO –d_6 solvent on Bruker High performance Digital FT-NMR Spectrometer. Avance cell 400 MHZ using TMS as internal stander and Mass spectra were done in the regional center for mycology and biotechnology , Al-Azhar University .

Synthesis procedure of ethyl-1- phenyl-5-(1*H*-tetrazol-1-yl)-1*H*- pyrazole-4-carboxylate (2) :

A mixture of **1** (10 mmol), triethyl ortho formate (10 mmol), and sodium azide (10 mmol) in 40 ml glacial acetic acid was stirred under reflux for 2 h . The reaction mixture was cooled and suspended in 7 ml Conc HCl. The solid collected by suction filtration and washed with water . The crude product was recrystallized from ethanol to afford **2** (70 %), m.p:122-124^{o} C ;

Spectroscopic data:-

1. IR data (cm^{-1}) : 3050 (CH-Ar), 2920-2888 (CH-aliph), 1710 (C═O)
2. ^{1}HNMR (DMSO-d_6-δ ppm) : 1.33(t,3H,CH_2CH_3,5.8 HZ), 4.28 (q, 2H, CH_2CH_3,J=7.1 HZ), 7.31-7.88 (m, 5H, Ar-H), 8.23(s, 1H, tetrazole H-5)
3. ^{13} CNMR : 20.2 (CH_3), 60.8 (CH_2),110.5-149.5(Ar-CH), 166.7(C═O)

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Elemental Analysis:-
MS: m/z (%) = 284.11 (5.4). Anal .Calcd for : $C_{13}H_{12}N_6O_2$, [% calculated (%found)]:- C = 54.93 (54.72), H = 4.25 (4.00), N = 29.56 (29.12)

Synthesis procedure of 5.6- Diamino-1-phenyl-1*H*-pyrazolo[3.4-*d*]pyrimidin-4(5*H*)-one (3) :
Compound **2** (10 mmol)in 15 ml hydrazine hydrate was heated under reflux for 7 h. The reaction mixture was cooled and suspended in 50 ml water . The solid was collected by suction filtration , wash with water and recrystallized from ethanol to afford **3** (75%) . m.p : 228-230 ° C

Spectroscopic data:-
1. IR data (cm^{-1}) : 3330,3290($2NH_2$), 3055(CH-Ar), 1680 (C═O), 1580 (C=N)
2. ^{1}HNMR (DMSO- d_6-δppm) : 6.11(br.s, 2H , C-NH_2) ;7.33-7.81(m,5H,Ar-H),11.2(b.r.s.2H,NH_2)
3. ^{13}CNMR : 121.3-149.5 (Ar-CH), 1681 (C═O)

Elemental Analysis:-
MS: M/Z (%) = 243.01 [M^+] (14.1). Anal. Calcd for : $C_{11}H_{10}N_6O$, [% calculated (%found)]:- C = 54.54 (54.33), H = 4.16 (4.00), N = 34.69 (34.50)

Synthesis procedure of ethyl-5-(2-(dicyano methylene)-1-phenyl-1*H*-pyrazole-4-carboxylate (4) :
A solution of compound 1 in Conc HCl (2 mmol in 5 ml) was kept in in an ice bath at 0-5 ° C for 10 min . An aqueous solution of sodium nitrite (2.1 mmol in 5 ml) was added drop wise with stirring to the amine hydrochloride salt solution over period of 20-25 min at 0 ° C . A yellow precipitated of diazonium hydrochloride salt was formed . The reaction mixture was stirred for an additional 15 min . While maintaining the temperature at 0 ° C . Malononitrile (2 mmol) was added to a solution of the amine hydrochloride salt and 5 g anhydrous sodium acetate in 100 ml ethanol with stirring at 0-5 ° C .Stirring was continued for an additional 3 h . The mixture was left overnight in the refrigerator . Water (250 ml) was added to the reaction mixture and the solid product was collected by filtration and recrystallized from ethanol to afford **4** (60%); m.p: 150-152 ° C .

Spectroscopic data:-
1. ^{1}HNMR (DMSO- d_6-δppm) : 1.30 (t, 3H, CH_3, J=6.8 HZ), 4.30 (q, 2H, CH_2CH_3, J=7.8 HZ), 7.40-7.90 (m, 5H, Ar-H), 11.80 (s, 1H, NH)
2. ^{13}CNMR : 17.1 (CH_3), 52.4 (CH_2), 102.4-144.2 (Ar-CH), 172.5 (C═O)

Elemental Analysis:-
MS: m/z (%) = 308.12 (8.11%). Anal.Calcd. for : $C_{15}H_{12}N_6O_2$, [% calculated (%found)]:- C = 58.44 (58.10), H = 3.92 (3.50), N = 27.26 (27.00)

Synthesis procedure of E-5-[(3,5-Diamino-1H-pyrazol-4-yl-)diazo-nyl]-1-phenyl-1H-pyrazole-4-carbohydrazide (5):
A mixture of **4** (10mmol) and hydrazine hydrate (15 mmol) in 30 ml ethanol was heated under reflux for 6 h . The solid precipitated after concentration was filtrated , dried ,and recrystallized from ethanol to afforded **5** (55%) ; m.p: 278-280 ° C .

Spectroscopic data:-
^{1}HNMR (DMSO- d_6-δppm) : 2.60,2.85 ,4.20 (3s,6H , $3NH_2$), 7.40-7.91 (m, 5H, Ar-H), 9.80 (br.s, 1H, NH), 10.12(br.s,1H, NH)

Elemental Analysis:-
MS: m/z (%) = 326.1 (4.1); Anal. Calcd .for : $C_{13}H_{14}N_{10}O$, [% calculated (%found)]:- C = 47.85 (47.50), H = 4.32 (4.00), N = 42.92 (42.54)

Synthesis procedure of 1-phenylbenzo[4,5]thiazolo[3,2-*a*]pyrazolo[3,4-*d*]pyrimidine (6) :
A solution of ortho –amino ester **1** (5mmol) and 2-mercaptobenzo thiazole (5mmol) was heated to reflux temperature in dry acetic acid (6 ml) for 6 h. After cooling to room temperature ,crushed ice was added , and the mixture stirred for 1 h . The separated product was collected and filtration and crystallized from methanol to afford **6** (50%) ; m.p: >360° C .

Spectroscopic data:-
IR data (cm^{-1}) : 3033 (CH-Ar), 1685 (C═O), 1580 (C═N)

Elemental Analysis:-
MS: m/z (%) = 319.0 (12.1); Anal.Calcd. for : $C_{17}H_{10}N_4OS$, [% calculated (%found)]:- C = 64.14 (64.00), H = 3.17 (3.12), N = 17.60 (17.22), S = 10.07 (10.12)

Synthesis procedure of amino-6-(chloromethyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrmidin-4-(5*H*)one (8):
A mixture of compound 7 (0.01mol) and 2-chloroacetyl chloride (10mmol) were heated under reflux for 12 h. The reaction mixture was cooled to room temperature and then poured on crushed ice with scratching , the mixture was acidified by 10% HCl and allowed to stand overnight , the separated solid was filtrated off, washed thoroughly with water , dried and crystallized from ethanol to afford **8** (55%); m.p: >360° C .

Spectroscopic data:-
1. IR data (cm^{-1}) : 3300,3214 (NH_2), 3055 (CH-Ar), 1680 (C═O), 1580 (C═N)
2. ^{1}HNMR (DMSO- d_6-δppm) : 3.70 (s,2H ,CH_2),6.20 (s,2H ,NH_2) exchangeable D_2O), 7.28-7.85 (m,5H ,Ar-H), 8.27 (s,1H ,CH-pyrazole)

Elemental Analysis:-
MS: m/z(%) = 277(5.56); Anal. Calcd : $C_{12}H_{10}ClN_5O$(275.69), [% calculated (%found)]: C = 58.28 (52.18), H = 3.66 (3.78), N = 25.40 (25.30)

Synthesis procedure of 8-amino-5-(chloromethyl)-3-phenyl-3*H*-dipyrazolo[1,5-*c*:4',3'-*e*]pyrimidin-9-carbonitrile (9) :
Synthesis procedure of ethyl-5-(chloromethyl)-8-oxo-3-phenyl-7,8-dihydro-3*H*-*di*pyrazolo[1,5-*c*:4',3'-*e*]pyramidin-9-carboxylate (10):
A equimolar of **8** (10mmol)and malononitrile /or diethylmalonate (10mmol) was heated until the contents melted , the reaction mixture was maintained at temperature 180 ° C for 4h, the fused mass thus obtained was treated with ethanol, collected by filtration and recrystallized by Dioxane . Compound **9** (62%); m.p:285-287° C

Spectroscopic data:-
1. IR data(cm^{-1}) : 3330,3280 (NH_2),3032 (CH-Ar), 2920 (CH-aliph), 2222 (C≡N),1640 (C═N)
2. ^{1}HNMR (DMSO- d_6-δppm) : 3.80(s,2H ,CH_2), 5.80 (s,2H , NH_2, exchangeable with D_2O), 7.33-8.11(m, 5H, Ar-H);^{13}CNMR 55.1(CH_2), 122 (C≡N), 114-146(Ar-CH)

Elemental Analysis:-
MS: m/z (%) = 323 (1.1); Anal. Calcd : $C_{15}H_{10}ClN_7$, [% calculated (%found)]: C = 55.65 (55.30), H = 3.11 (3.00), N = 30.29 (30.00)
Compound **10** (60%) ; m.p:240-242 ° C.

Spectroscopic data:-
1. IR data (cm^{-1}) : 3280(NH), 3032(CH-Ar), 2980(CH-aliph), 1710,1660(2C═O)
2. ^{1}HNMR (DMSO- d_6-δppm) 1.28(t, 3H, CH_2CH_3, J=5.88 HZ), 4.30(q, 2H, CH_2CH_3, J=7.23 HZ), 7.31-7.81(M, 5H, Ar-H), 9.88 (s,1H, NH, exchangeable with D_2O); ^{13}CNMR 18.1(CH_3), 56.8(CH_2), 62.4(CH_2), 168,162 (2C═O),114-144 (Ar-CH)

Elemental Analysis:-
MS: m/z (%) = 374.08 (4.0), 373.08 (1.0). Anal. Calcd : Anal. Calcd : $C_{17}H_{14}ClN_5O_3$, [% calculated (%found)]: C = 54.92 (54.50), H = 3.80 (3.60) , N = 18.84 (18.50)

Synthesis procedure of 2-(Cyanomethyl)-5-methyl-7-phenyl-pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (12):
Synthesis procedure of 2-Amine -6-(cyanomethyl)-1*H*-imidazo[1,2-*b*]pyrazolo-7-carnonitrile (13) *:*
An equimolar amount of 11 (10mmol) and benzoylacetone / or chloro acetonitrile (10mmol)in ethanolic sodium ethoxide solution [(prepared by dissolving sodium metal (0.24 g,10mmol) in absolute ethanol(30 ml)] was heated under reflux for 12 h. The reaction mixture was cooled to room temperature and then poured onto crushed ice with

scratching , the mixture was acidified by 10% HCl and allowed to stand overnight , the separated solid was filtered , washed with water , dried and crystallized from proper solvent .Compound **12** (70%) ; m.p: 300-302 ◦ C .

Spectroscopic data:-
1. IR data (cm^{-1}) : 3050 (CH-Ar), 2993-2888(CH-aliph), 2222(2C≡N)
2. ^{1}HNMR (DMSO- d_6-δppm) : 1.14(s, 3H, CH_3), 4.28(s, 2H, CH_2), 7.28-7.71 (m,5H,Ar-H), ^{13}CNMR . 20.1(CH_3), 56.7(CH_2), 124.2, 115.7 (2C≡N),128.3-144.1(Ar-CH)

Elemental Analysis:-
MS: m/z (%) =273.29 (17.4); Anal.Calcd: $C_{16}H_{11}N_5$, [% calculated (%found)]: C = 70.32 (70.00), H = 4.06 (4.01), N = 25.63 (25.30)

Compound **13** (52%) ; m.p: 280-282 ◦ C.

Spectroscopic data:-
1. IR data (cm^{-1}) : 3340,3300 (NH, NH_2), 2220 (2C≡N)
2. ^{1}HNMR (DMSO- d_6-δppm) : 5.82(s, 2H, NH_2, exchangeable with D_2O), 4.11(s, 2H, CH_2), 8.12 (s, 1H, CH-imidazole), 12.18 (s, 1H, NH, exchangeable with D_2O)

Elemental Analysis:-
MS: m/z (%) = 186.1(7.7); Anal.Calcd: $C_8H_6N_6$, [% calculated (%found)]: C = 51.61 (51.30), H = 3.25 (3.00), N = 45.14 (45.00)

Synthesis procedure of 6-(cyanomethyl)-2-methyl-3-oxo-3*H*-imidazo[1',2':3,4]imidazo[1,2-*b*]pyrazole-5-carbonitrile (14)*:*
A equimolar mixture of **13** (10mmol) and pyruvic acid (10mmol) was heated until the contents melt . The reaction mixture was maintained at temperature 200 ◦ C for 4 h. The fused mass thus obtained was treated with ethanol , collected by filtration and recrystallized from dioxane to afford **14** (55%); ; m.p:>360 ◦ C .

Spectroscopic data:-
1. IR data (cm^{-1}) : 2988 (CH-aliph), 2211 (2CN),1670 (C═O)
2. ^{1}HNMR (DMSO- d_6-δppm) : 1.82(s, 3H, CH_3), 4.28(s, 2H, CH_2), 8.22 (s, 1H, CH-imidazole)

Elemental Analysis:-
MS: m/z (%)= 239..20[M^+] (8.21); Anal.Calcd: $C_{11}H_6N_6O$, [% calculated (%found)]: C = 55.46 (55.30) , H = 2.54 (2.50) , N = 35.28 (35.20)

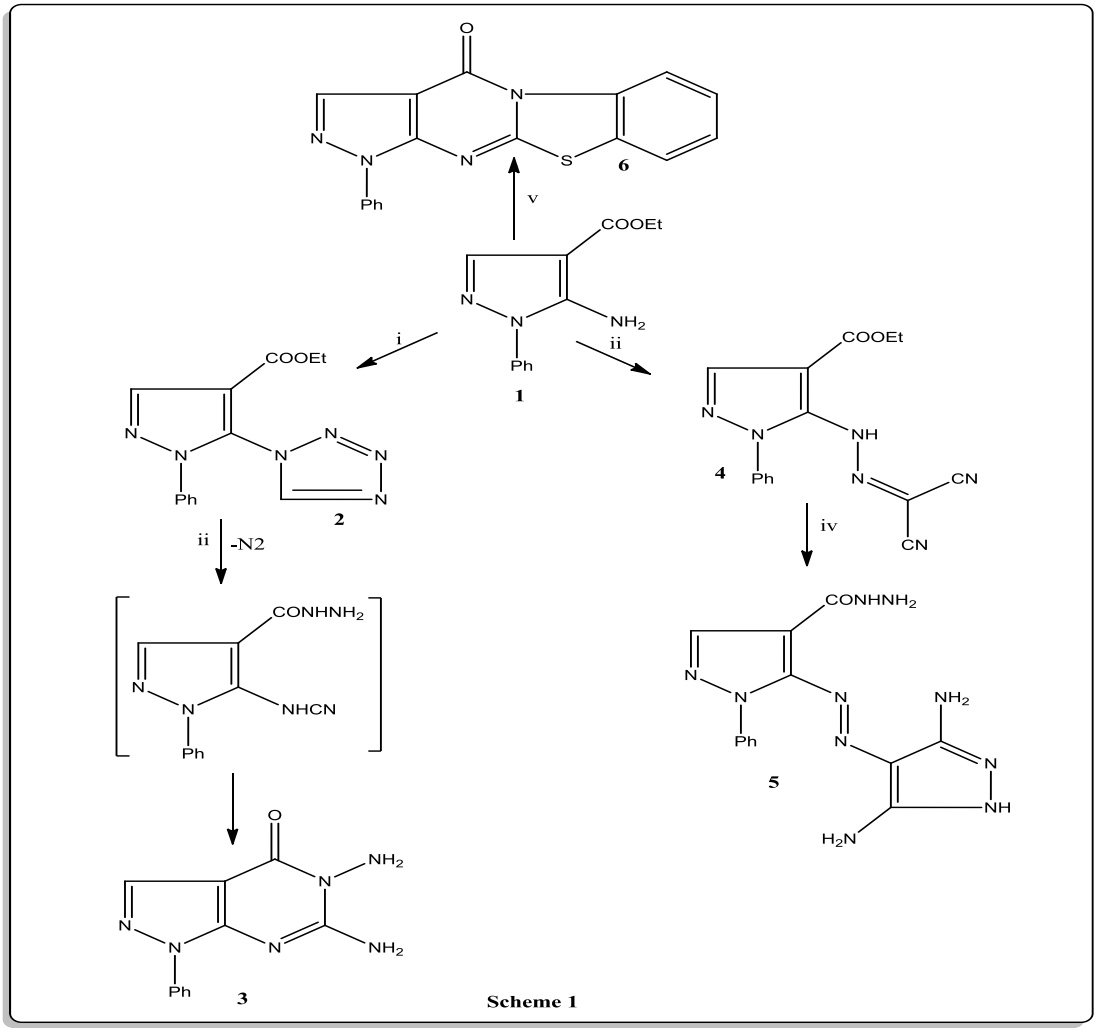
Synthesis procedure of 2-(Cyanomethyl)-9-methyl-5,6,7,8-tetrahydropyrazolo[5,1-*b*]quinazoline-3-carbonitrile (16):
A mixture of 11 (1mmol) and acetylcyclohexanone (1mmol) was added to 5 ml of acetic acid , the solution diluted was reflux for 10 h, cooled to room temperature , evaporated to dryness , the residue was washed with water and alcohol, dried and crystallized from acetic acid to afford **16** (62%); m.p: 234-236 ◦ C
1. IR data (cm^{-1}) : 2981-2833 (CH-aliph), 2218 (2CN),1550 (C═C);
2. ^{1}HNMR (DMSO- d_6-δppm) : 2.32 (s, 2H, CH_2),2.58 (s, 2H,CH_2), 3.01(t, t, CH_2, J=7.3 HZ,J=1.4 HZ), 3.56 (t, t, 2H, CH_2 , J=7.6 HZ, J=2.8 HZ), 4.18(s,2H ,CH_2)
3. ^{13}CNMR : 14.46 (CH_3), 21.91 (CH_2), 22.54 (CH_2) 29.6(CH_2),29.9CH_2) 44.2 (CH_2CN)

Elemental Analysis:-
MS: m/z (%) = 251.22(11.0); Anal.Calcd: $C_{14}H_{13}N_5$, [% calculated (%found)]: C = 66.92 (66.50), H = 5.21 (5.00), N = 27.87 (27.60)

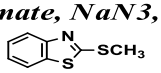
Results and discussion:-

Treatment of Ethyl-5-amino-1- phenyl -1H- pyrazole-4-carboxylate
[11] with tri ethyl ortho formate and sodium azide afforded ethyl-1-phenyl-5-(1*H*-tetrazol-1-*yl*)-1*H*-pyrazole-4-carboxylate **2** in good yield . The ^{1}HNMR of **2** showed a singlet signal at δ 8.23 ppm characteristic of tetrazole

proton , and a lack of the amino proton signal detected for the parent **1** , Pyrazolopyrimidine derivatives **3** was obtained by refluxing **2** with hydrazine hydrate . The reaction sequence and mechanism are outlined in scheme **1** [12] .The ^{1}HNMR of **3** revealed two exchangeable broad singlet signals at δ 6.11 and 11.12 ppm for two amino groups, without the ester proton signals detected for the parent **2** .Compound **1** was diazotized hydrochloric acid and sodium nitrile .The desired diazonium chloride was then coupled with malononitrile to yield the corresponding azo derivatives **4 .** ^{1}HNMR of **4** showed the absence of an amino signal and the presence of signals at δ 1.30 and 4.30 ppm for ethyl ester group and δ11.30 ppm for an exchangeable NH proton. Hydrazone **4** reacted with hydrazine hydrate in ethanol under reflux to afford hydrazide **5** . ^{1}HNMR of **5** exhibited signals at δ 2.60, 2.85 and 4.20 ppm (exchangeable NH_2 and NH protons) **.** Tetracyclic condensed systems in one step via a double displacement process [13] using 2-methylthio-benzothiazole with ortho amino ester **1** gave **6.** The mass spectrum of **6** showed the ion peak at m/z (%)=319.0(12.1) in accordance with the molecular weight ($C_{17}H_{10}N_4OS$) .

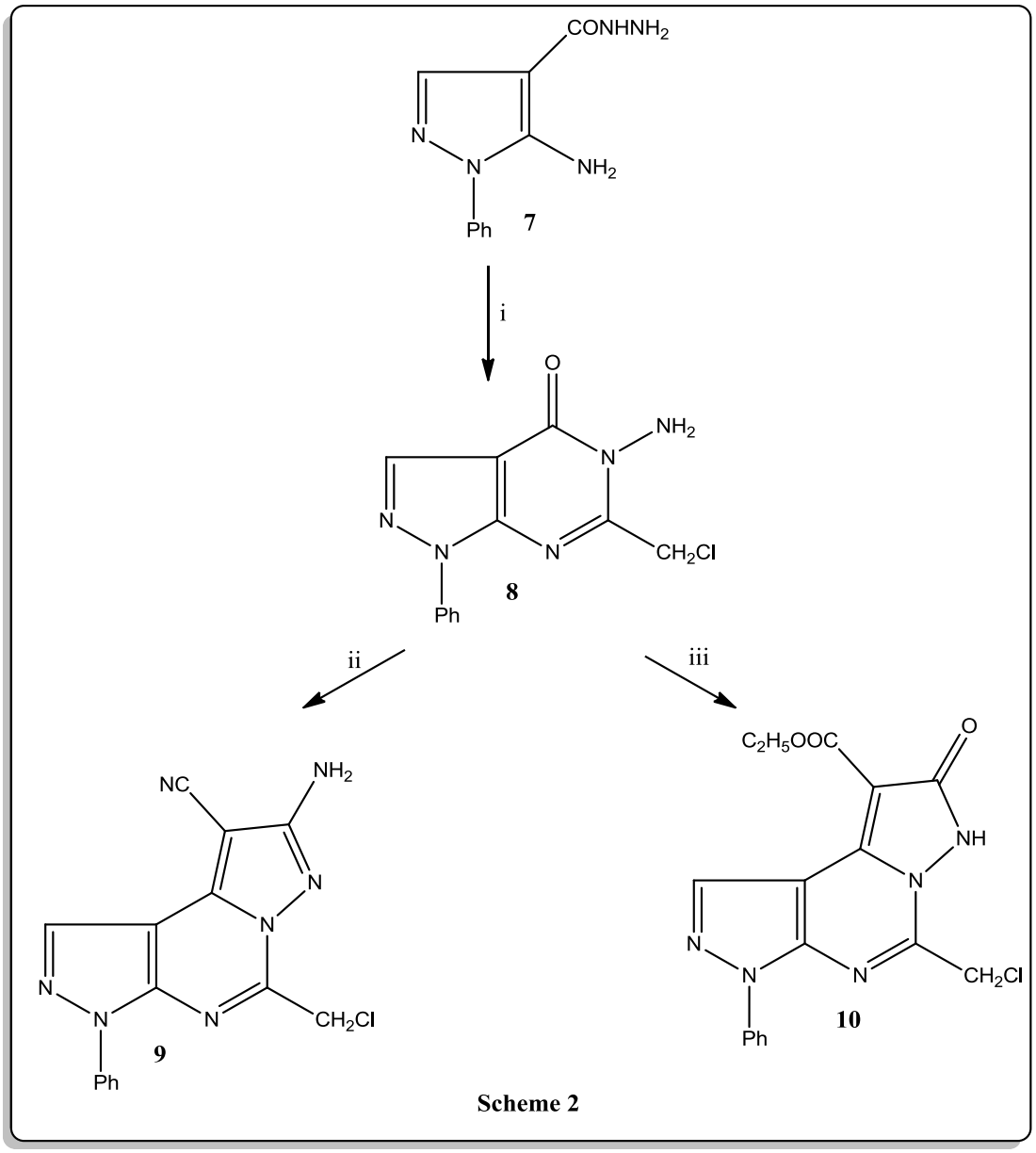


Scheme 1

Reagents and conditions : i)triethylorthoformate, NaN3, gl.AcOH.ii)N2H4 iii)Malononitrile, NaNO2/HCl. iv)N2H4. v) 

Moreover, one-pot cyclocondensation of hydrazide γ **7** [11] with 2-chloroacetyl chloride could be carried out by refluxing in sodium ethoxide to yield pyrazolopyrimidine γ **8** (scheme 2). ^{1}HNMR of **8** showed a singlet at δ 3.70 ppm integrated for two protons of (CH_2) , in addition deuterium oxide exchangeable singlet signal at δ 6.20 ppm due to NH_2 protons . pyrazole-pyrimidine **8** was utilized in preparing the target compounds pyrazoloimiazopyrimidine derivatives **9** and **10** , through fused with malononitrile /or diethylmalonate . ^{1}HNMR of **9** recorded a singlet signal at δ3.80 ppm for (CH_2) and deuterium oxide exchangeable singlet signal at δ 5.80 ppm due to NH2 proton. ^{1}HNMR of **10** showed signals at δ 1.28 and 4.30 ppm corresponding to (CH_2CH_3-ester) and deuterium oxide exchangeable

singlet signals at δ 9.88 ppm corresponding to NH proton , whereas ^{13}CNMR of **10** refers to the presence of CH_2 signals at δ 56.8 ppm and carbonyl group at δ 162.2 ppm and 168.1 ppm .

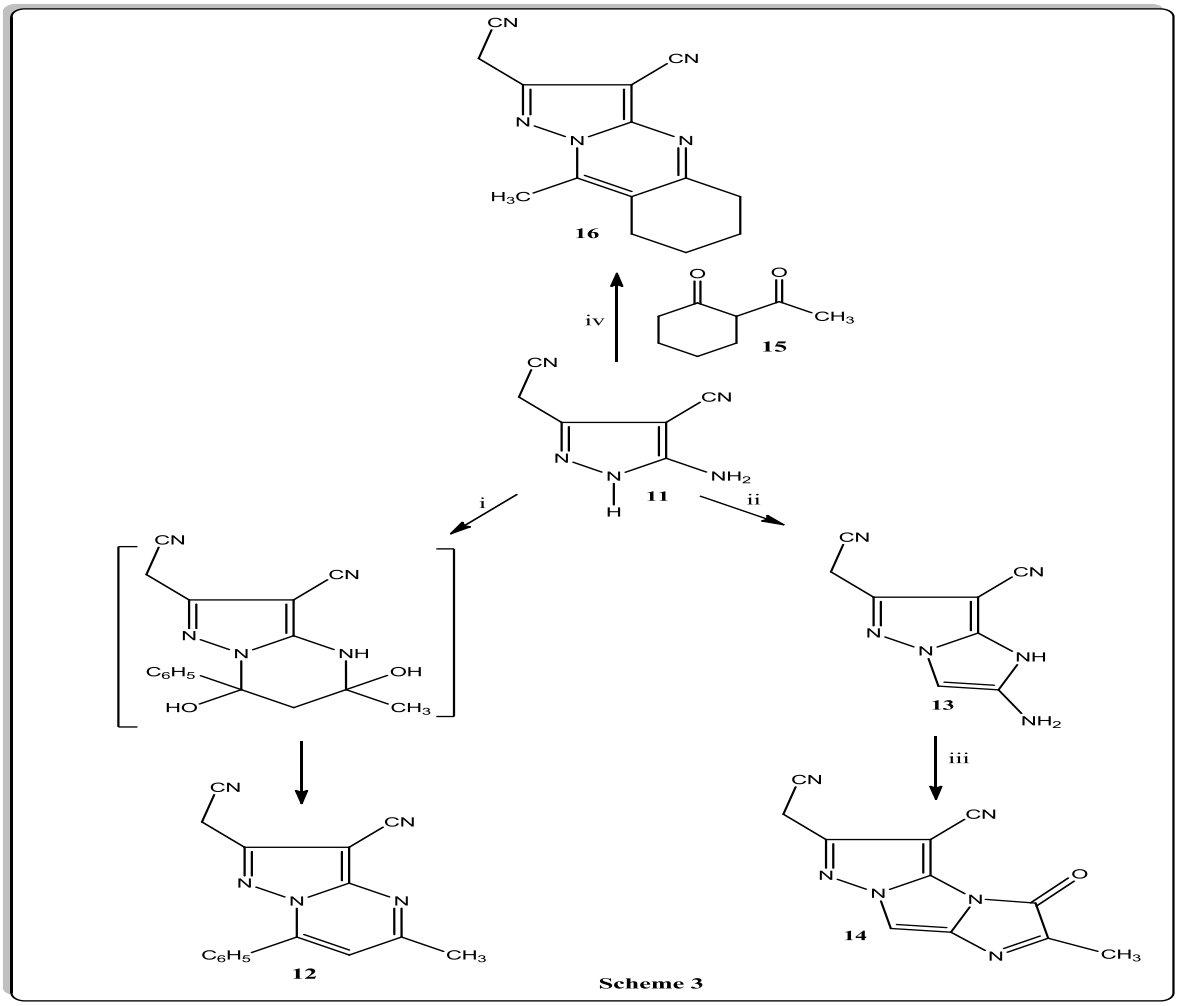


Scheme 2

Reagents and conditions : i) 2- chloroacetyl chloride . ii)Malononitrile . iii) Diethyl malonate.

Our study were extended to synthesis fused azole (scheme 3). Thus, fusion of compound **11**[14] with benzoyl acetone / or chloroacetonitrile furnished pyrazolopyrimidine **12** and pyrazoloimidazole **13** , ^{1}HNMR of **12** revealed the presence of two singlet signals at δ 1.14 and 4.28 ppm for CH_3 and CH_2 groups , while ^{13}CNMR refers to the presence of CH_3,CH_2 and (2CN) groups at δ 20.1,56.7 and (124.7,115.7). ^{1}HNMR of **13** showed the presence of two singlet signals at δ 5.82 and 12.18 ppm due to NH_2 and NH protons .Cyclization of **13** with pyruvic acid afforded imidazo[1',2':3.4]imidazo[1,2-*b*]pyrazole derivatives **14** . ^{1}HNMR of **14** showed the absence of an NH_2 and NH protons , whereas ^{13}CNMR refers to the presence of signals at δ 18.1, 54.6, 115.1, 125.2 and 172.8 ppm for CH_3,CH_2, 2CN and carbonyl groups.

Finally , reaction of 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **11** with 2-acetylcyclohexanone [15] under reflux in presence of acetic acid afforded pyrazolo [5,1-*b*]quinazoline derivatives **16** , ^{1}H and ^{13}C NMR were used to deduce the structure of **16** (see experimental).



Scheme 3

Reagents and conditions :i)$PhCOCH_2COCH_3$.
ii) 2-Chloroacetonitrile .iii) 2-Oxopropanoic acid .

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