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Synthesis, Characterization and Antimicrobial Evaluation of Novel Mannich Bases Containing Pyrazole-5-One Phosphonates

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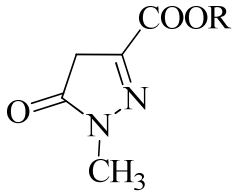
Pyrazole-5-one

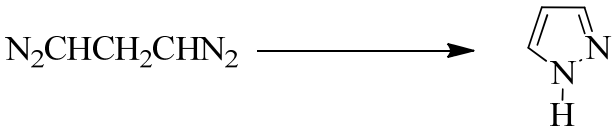
The chemistry of five membered heterocycles having nitrogen atoms has gained importance in recent years, as many of them exhibit pronounced biological activity. Pyrazole constitute an unique class of nitrogen containing heterocycles that received much interest from both chemists and biochemists for their important biological and industrial applications. The synthetic routes to pyrazoles are very interesting and worth studying.

Sucrow *et al* [1] have reported the synthesis of pyrazoles **(1)** by cyclization of mono methyl hydrazones of dialkyl oxalacetates to 5-pyrazolones *via* an enehydrazine.



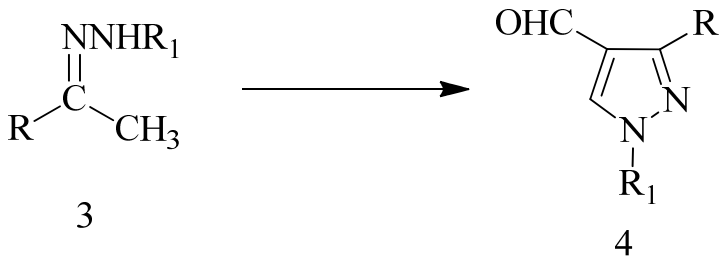
1

Hart and Brewbaker *et al* [2] have described the cyclisation of 1, 3-bis (diazopropane) to pyrazole **(2)** by a concerted, intra molecular 1, 3-dipolar cycloaddition.



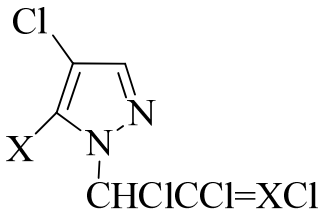
2

Kira *et al* [3] have reported that the Vilsmier-Haack reaction on hydrazones **(3)** affords the corresponding substituted-4-formyl pyrazoles **(4)**.



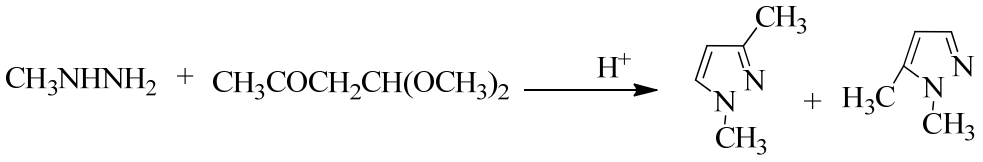
3 4

Freche *et al* [4] have reported the syntheses of pyrazoles **(5)** by thermal cyclisation of azines derived from di- and tri-halogeno acroleins.



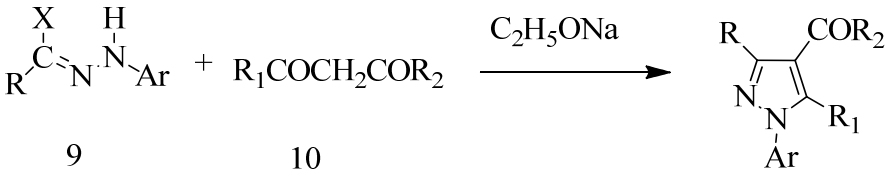
5

The formation of 1, 3- and 1, 5-dimethyl pyrazoles **(8a, 8b)** from the reaction between methyl hydrazine **(7)** and 4, 4-dimethoxy-2-butanone **(6)** were reported in the literature by Lazaro *et al* [5].



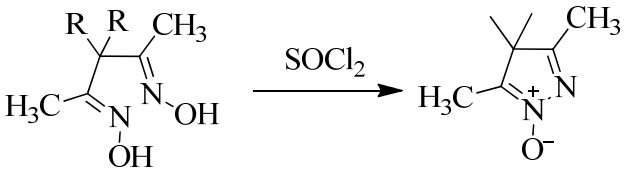
6 7 8a 8b

A series of Schiff bases **(9)** were reacted with 1, 3-diketones **(10)** in presence sodium ethoxide afforded substituted-pyrazoles **(11)** in good yield [6].



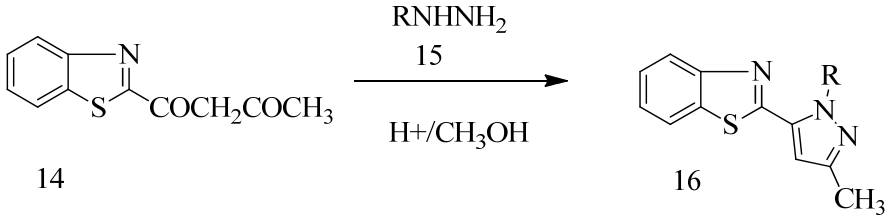
9 10 11

A general method of pyrazole synthesis involving the creation of an N-N bond has been described by Barluenga *et al* [7]. The 1, 3-dioxime **(12)** with thionyl chloride yields the iso-pyrazole N-oxide **(13)**.



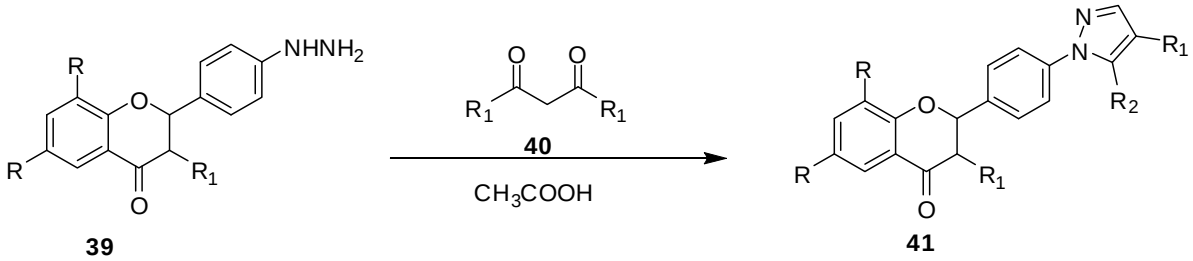
12 13

Singh *et al* [8] have reported the synthesis of 2-(3'-methyl pyrazol-5'-yl) benzthiazoles **(16)** by condensing 2-acetoacetylbenzothiazole **(14)** with hydrazine **(15)**.



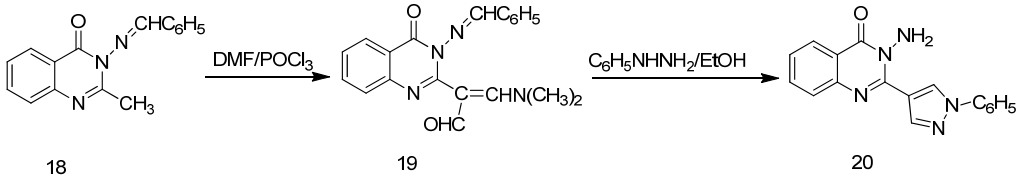
14 16

The synthesis of some new substituted-pyrazoles **(17)** from 4'-aminochromnes and substituted-1, 3-diketones in presence of acetic acid was reported by Mazumdar *et al* [9].



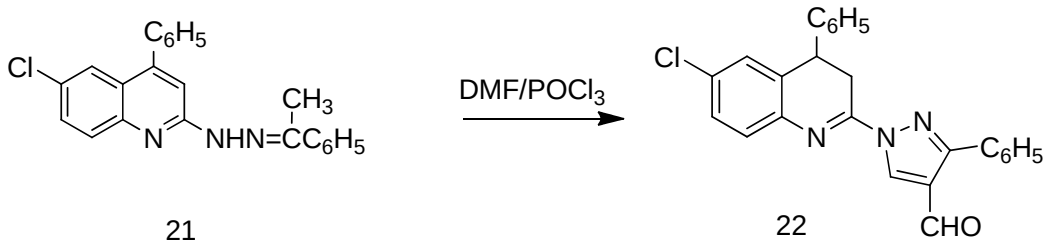
39 **41**

The Vilsmeier reaction on 3-benzalamino-2-methyl-4-quinazolone **(18)** using DMF-$POCl_3$ gave the amino acrolein **(19)** derivative, which was converted into 3-amino-2-(phenyl pyrazol-3'-yl)-4-quinazolone **(20)** by reaction with phenyl hydrazine in ethanol as reported by Barnel *et al* [10]



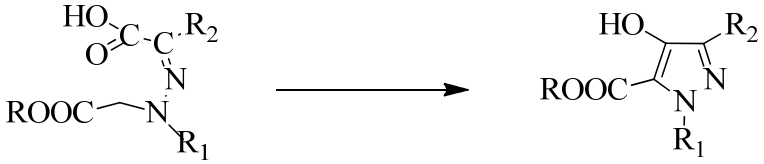
18 19 20

Prabhu *et al* [11] have reported the synthesis of 6-chloro-2-(4-formyl-3-phenyl pyrazol-l-yl)-4-phenylquinoline **(22)** by N'-(6-chloro-4-phenyl quinolin-2-yl) acetophenone hydrazone **(21)** on treatment with Vilsmeier reagent in an excellent yield.



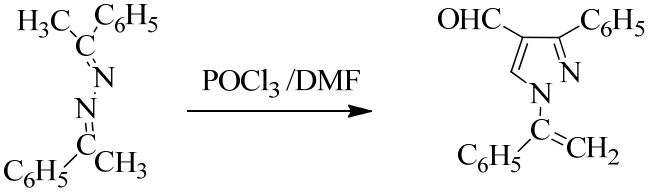
21 22

Farkas *et al* [12] have reported the new synthesis of 4-hydroxypyrazole-5-carboxylic acids **(23)** entails cyclisation of the hydrazones **(24)**.



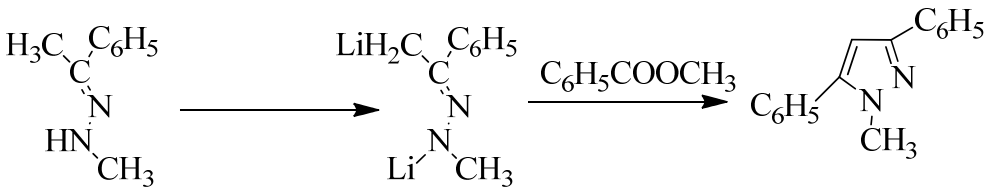
23 24

Kira *et al* [13] have reported the synthesis of pyrazole carboxyl Aldehydes **(26)** by the reaction of acetophenone azine **(25)** with two moles of $POCl_3$-DMF in an almost quantitative yield.



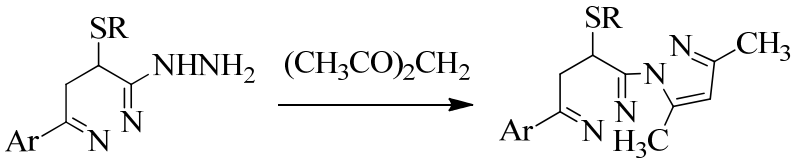
25 26

The methyl hydrazone of acetophenone **(27)** is converted into the dianion **(28)**, which in turn reacts with methyl benzoate to afford the pyrazole **(29)** has been reported in the literature by Beam *et al* [14].



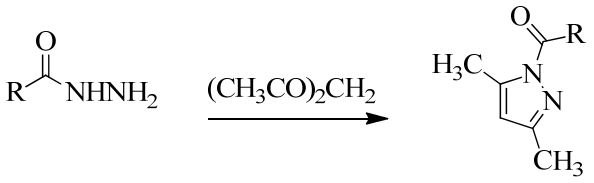
27 28 29

Wasfy *et al* [15] have been reported that 3-hydrazinopyridazine **(30)** on treatment with acetyl acetone undergo cyclisation to afforded 3-(pyrazole-l-yl) pyridazine **(31)** derivatives.



30 31

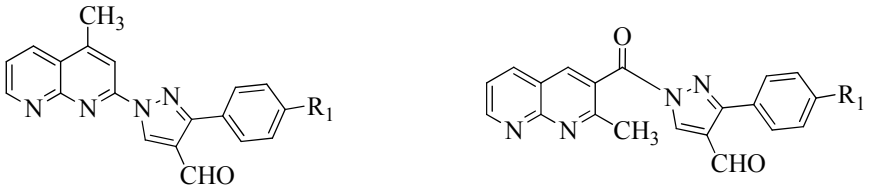
The synthesis of substituted pyrazole **(33)** derivatives from acetyl acetone and substituted carbohydrazides **(32)** and their antimicrobial activity was reported by Bhawsar *et al* [16].



32 33

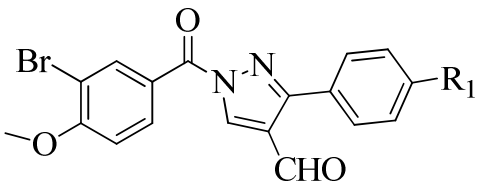
Kidwai *et al* [17] have reported the microwave assisted synthesis and antifungal activity of 4-memyl-2- 3'-substituted phenyl-4'-formyl pyrazolyl quinolines **(34)**.

Mogalaiah *et al* [18] have reported the synthesis and antibacterial activity of 3-(3-aryl-4-formylpyrazole-l-carbonyl)-2-methyl-l, 8-naphthyridines **(35)**.



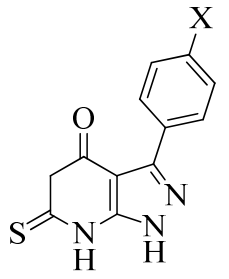
34 35

Havaldar *et al* [19] have reported the synthesis and biological activity of l-(3'- bromo-4'-methoxybenzyl)-4-formyl-3-(substituted-phenyl) pyrazoles **(36)**.



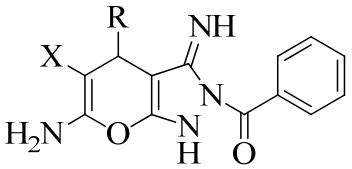
36

Youssif *et al* [20] have reported a facile one-pot synthesis of fused pyrazole pyrimidines **(37)**.



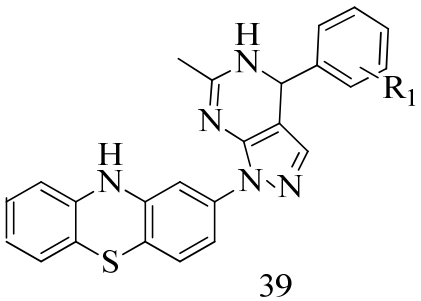
37

Shams *et al* [21] have reported the synthesis and biological evaluation of some fused pyrazole **(38)** derivatives.



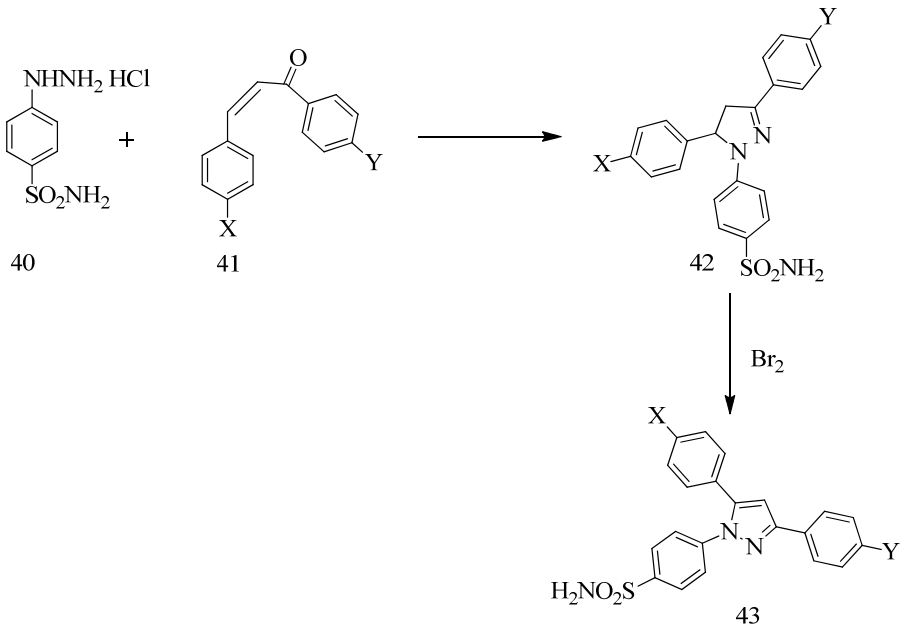
38

Design, synthesis, characterization and antitubercular activity of pyrazoles **(39)** were reported by Shah and coworkers [22].



39

Condensation of *p*-sulphamidephenyl hydrazine hydrochloride **40** with different chalcones **41** afforded 3, 5-disubstituted-l-(*p*-sulphamidephenyl-2-pyrazolines) **42**, which on oxidation with bromine water furnished the corresponding 3, 5-disubstituted-l-(sulphamidephenyl-2-pyrazoles) **43** as reported in the literature by Faid *et al* [23].



40 41 42 43

Prompted by these biological and pharmacological of pyrazole, it would be interesting to prepare pyrazole-5-one derivatives. Thus, Chapter VI describes our work on the synthesis, characterization, antibacterial and antifungal activity studies of some mannich bases containing pyrazole-5-one phosphonates.

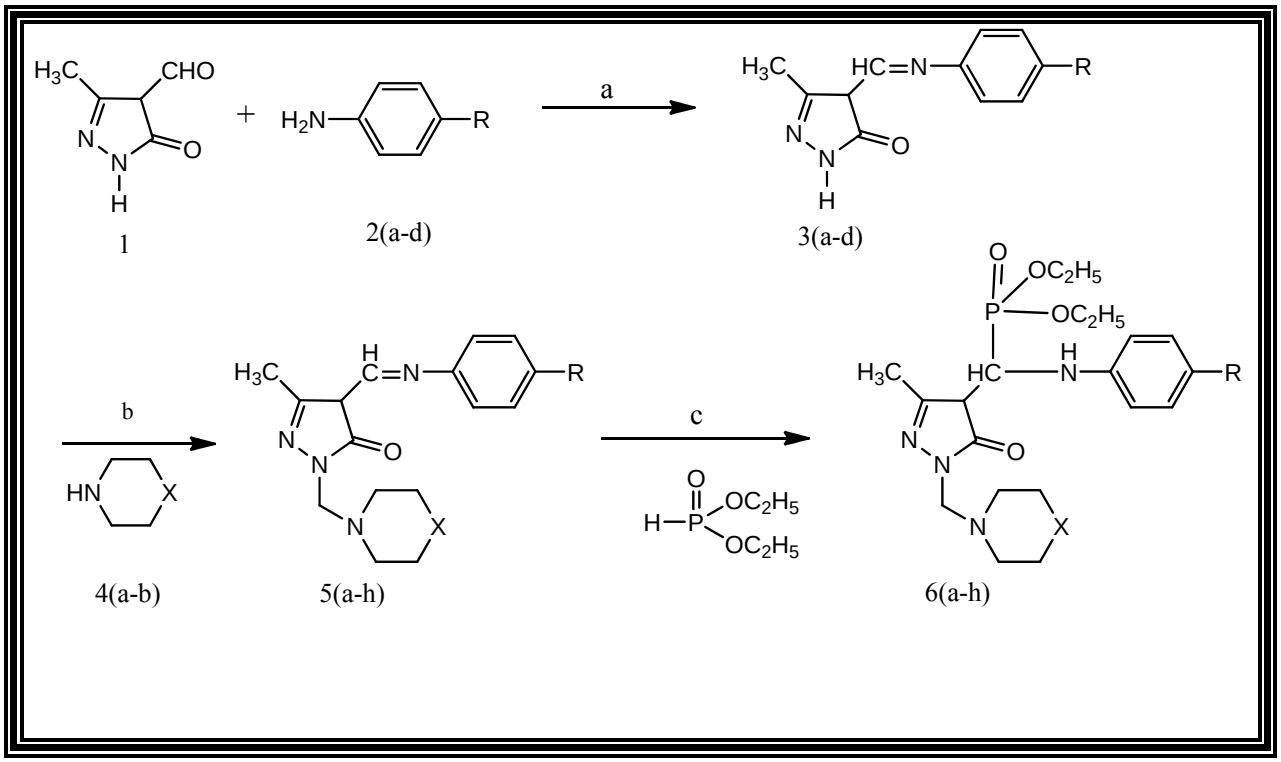
PRESENT WORK

Mannich bases possessing Pyrazole-5-one Phosphonate moiety have gained importance due to their applications as pesticides, insecticides and pharmaceutical industry [24]. They have been encountered with analgesic [25], anti-inflammatory, anticonvulsant [26], anti malarial, antiviral and CNS depressant activities.

Pyrazole-5-one containing Phosphonate moiety possesses various types of biological activities. It is due to their wide use in medicinal chemistry some of them possess anti tuberculosis, anti neoplastic, anti diabatic, anti fertility, anti thyroid and anti microbial activity [27 - 30].

In **Chapter-VI**, we report the synthesis and characterization of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **6(a-h)**. The synthesis route was depicted in the **Scheme -VI**. In this chapter, we report the synthesis and characterization of

1. Synthesis 4-(((4 - fluorophenyl) / (4 - chlorophenyl) / (4 - bromophenyl) / 4-(trifluoromethyl) phenyl) imino) methyl) – 3 – methyl - 1H – pyrazol – 5 - (4H) - one **3(a-d)**.
2. Synthesis of 4-(((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / 4-(trifluoromethyl) phenyl) imino) methyl)-3-methyl-1-(morpholinomethyl) / (4-methyl piperazin-1-yl) methyl)-1H- pyrazol-5(4H)-one **5(a-h)**.
3. Synthesis of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **6(a-h)**.



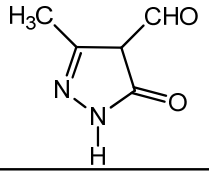
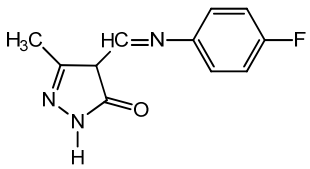
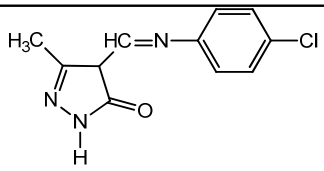
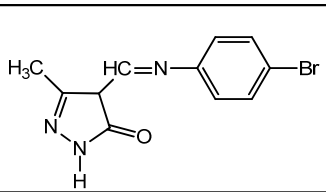
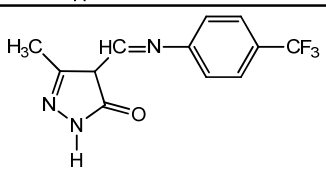
Scheme-VI.1. Proposed synthetic route for the preparation of 6(a-h).

Reagents and conditions: (a) Addition of alcohol, acetic acid and heated on a steam bath for 5-6 hrs at 100^0C, after standing for 24 hrs at R.T., **(b)** Addition of HCHO, DMF in ice cold condition and stirred for 2 hrs and left over night at R.T., **(c)** Anhydrous toluene, stirred at R.T., for 0.5 hr, the reaction mixture heated under refluxed for 4-6 hrs.

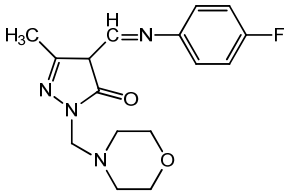
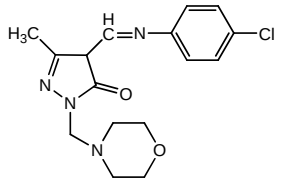
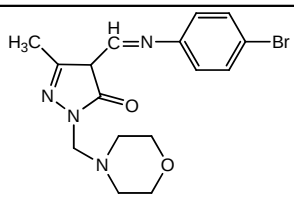
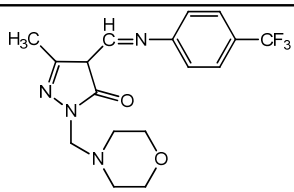
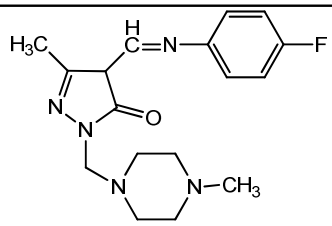
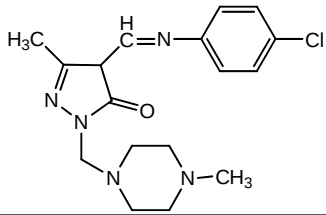
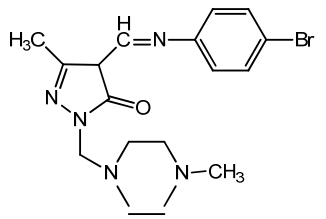
COMP	3a	3b	3c	3d
R	F	Cl	Br	CF3

COMP	5a	5b	5c	5d	5e	5f	5g	5h
	6a	6b	6c	6d	6e	6f	6g	6h
R	-F	-Cl	-Br	-CF3	-F	-Cl	-Br	-CF3
X	O	O	O	O	N-CH3	N-CH3	N-CH3	N-CH3

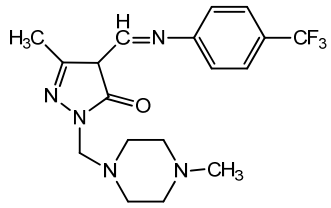
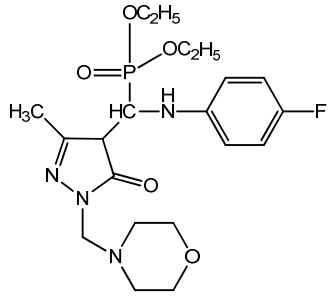
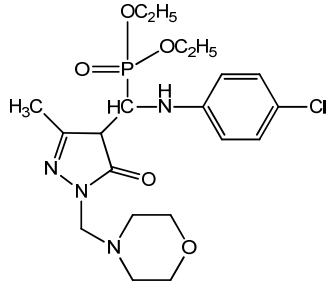
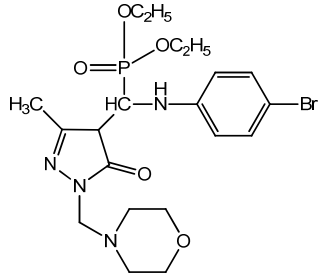
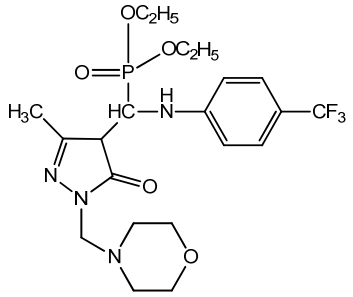
Chart-VI.1. Nomenclature and Molecular formulaes of Pyrazolones.

COMP NO	**STRUCTURE**	**NAME**	**MOLECULAR FORMULA**
1		3-Methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carbaldehyde	$C_5H_6N_2O_2$
3a		4-(((4-fluorophenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one	$C_{11}H_{10}FN_3O$
3b		4-(((4-chlorophenyl) imino) methyl)-3-methyl-1H- pyrazol-5(4H)-one	$C_{11}H_{10}ClN_3O$
3c		4-(((4-bromophenyl) imino) methyl) -3- methyl-1H- pyrazol-5(4H)-one	$C_{11}H_{10}BrN_3O$
3d		3- methyl – 4 - (((4 - trifluoromethyl) phenyl) imino) methyl)-1H-pyrazol-5(4H)-one	$C_{12}H_{10}F_3N_3O$

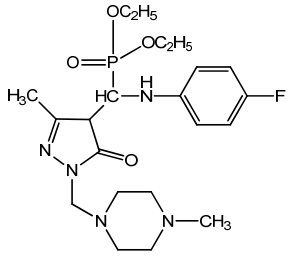
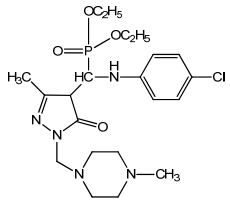
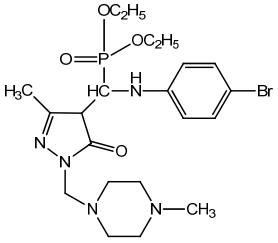
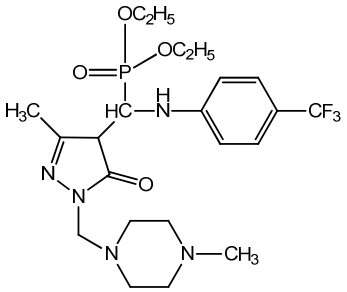
(Chart VI.1) contd.....

COMP NO	STRUCTURE	NAME	MOLECULAR FORMULA
5a		4-(((4-fluorophenyl) imino) methyl) – 3 - methyl-1-(morpholinomethyl)-1H-pyrazol-5(4H)-one	$C_{16}H_{19}FN_4O_2$
5b		4-(((4-chlorophenyl) imino) methyl) – 3 - methyl -1-(morpholinomethyl)-1H- pyrazol-5(4H)-one	$C_{16}H_{19}ClN_4O_2$
5c		4-(((4-bromophenyl) imino) methyl) – 3 - methyl -1-(morpholinomethyl) -1H – pyrazol - 5(4H) - one	$C_{16}H_{19}BrN_4O_2$
5d		3-methyl-1-(morpholinomethyl) – 4 - (((4-(trifluoromethyl) phenyl) imino) methyl)-1H- pyrazol-5(4H)-one	$C_{17}H_{19}F_3N_4O_2$
5e		4-(((4-fluorophenyl) imino) methyl) - 3-methyl -1-(4-methylpiperazin-1-yl) methyl)-1H- pyrazol-5(4H)-one	$C_{17}H_{22}FN_5O$
5f		4-(((4-chlorophenyl) imino) methyl) - 3-methyl -1-(4-methylpiperazin-1-yl) methyl)-1H- pyrazol-5(4H)-one	$C_{17}H_{22}ClN_5O$
5g		4-(((4-bromophenyl) imino) methyl)- 3-methyl -1-(4-methylpiperazin-1-yl) methyl)-1H- pyrazol-5(4H)-one	$C_{17}H_{22}BrN_5O$

(Chart VI.1) contd.....

COMP NO	STRUCTURE	NAME	MOLECULAR FORMULA
5h		3-methyl – 1 - ((4-methylpiperazin – 1 - yl) methyl) – 4 - (((4-(trifluoromethyl) phenyl) imino) methyl-1H- pyrazol-5(4H)-one	$C_{18}H_{22}F_3N_5O$
6a		Diethyl (((4-fluorophenyl) amino) (3 – methyl – 1 - (morpholinomethyl) – 5 – oxo - 4, 5 - dihydro-1H-pyrazol-4-yl) methyl) phosphonates	$C_{20}H_{30}FN_4O_5P$
6b		Diethyl (((4 - chorophenyl) amino) (3 – methyl – 1 - (morpholinomethyl)-5-oxo-4, 5 - dihydro-1H-pyrazol-4-yl) methyl) phosphonates	$C_{20}H_{30}ClN_4O_5P$
6c		Diethyl (((4 - bromophenyl) amino) (3 - methyl-1- (morpholinomethyl) – 5 – oxo - 4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates	$C_{20}H_{30}BrN_4O_5P$
6d		Diethyl ((3 – methyl – 1 - (morpholinomethyl) – 5 – oxo - 4, 5-dihydro - 1H - pyrazol – 4 - yl) ((4-(trifluoromethyl) phenyl) amino) methyl) phosphonates	$C_{21}H_{30}F_3N_4O_5P$

(Chart VI.1) contd.....

COMP NO	STRUCTURE	NAME	MOLECULAR FORMULA
6e		Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (4-methyl piperazin-1-yl) methyl) – 5 – oxo - 4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates	$C_{21}H_{33}FN_5O_4P$
6f		Diethyl (((4 - chlorophenyl) amino) (3 – methyl – 1 - (4-methyl piperazin-1-yl) methyl) – 5 - oxo - 4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates	$C_{21}H_{33}ClN_5O_4P$
6g		Diethyl (((4-bromophenyl) amino) (3 – methyl – 1 - (4-methyl piperazin-1-yl) methyl) - 5 - oxo - 4, 5 - dihydro-1H-pyrazol-4-yl) methyl) phosphonates	$C_{21}H_{33}BrN_5O_4P$
6h		Diethyl ((3-methyl – 1 - (4 -methyl piperazin – 1 - yl) –methyl – 5 – oxo - 4, 5 -dihydro-1H-pyrazol – 4 - yl) ((4 - (trifluoromethyl) phenyl) amino) methyl) phosphonates	$C_{22}H_{33}F_3N_5O_4P$

1. Synthesis 4-(((4-Fluorophenyl) / (4-Chlorophenyl) / (4-Bromophenyl) / 4-(Trifluoromethyl) Phenyl) Imino) Methyl)-3-Methyl-1H-Pyrazol-5(4H)-one (3a-d):

The quantity of 4-fluoro aniline (2.2gr, 0.020 mole) **(2a)** and 3-Methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carbaldehyde (1.746gr, 0.014mole) **(1)** were dissolved in absolute alcohol, to this three drops of acetic acid is added then heated on a steam bath for 5-6 hours at 100°C. After standing for 24 hours at room temperature, the crude product was purified by column chromatography (60-120 mesh silica gel,eluent: 10% EtoAc pet ether). Finally, the product compound 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one **(3a)** which was recrystallized from warm absolute alcohol. Yield 75%, m p 153-155°C.

The similar procedure was adopted to synthesize 3(b-d) by condensing 3-Methyl-5-oxo-4, 5-dihydro-1H-pyrazole-4-carbaldehyde **(1)** with 4-chloro aniline **(2b)**, 4-bromo aniline **(2c)** and 4-trifluoro aniline **(2d)** respectively. The structures of **3(a-d)** were established by IR, ^{1}H-NMR and elemental analysis. The analytical data was shown in the Table **VI.11**.

IR Spectra (ῡ / δ, cm-1)

The IR spectra of 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one **(3a)** recorded in the 4000-400 cm^{-1} range in KBr pellets reflect the molecular structure and showed the characteristic bands around

3418-3384 (N-H), 3052 (stretching of Ar-H), 2940 and 2895 (CH_3 of aliphatic-CH), 1670 (C=O), 1619 (C=N), 1478-1375 (stretching vibrations of pyrazole ring) and 1100 cm^{-1} (C-F). The IR data of **3(a-d)** was shown in the Table **VI.1**

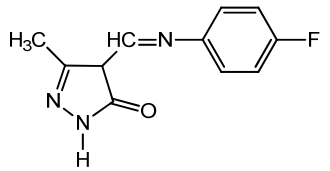
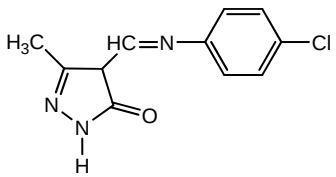
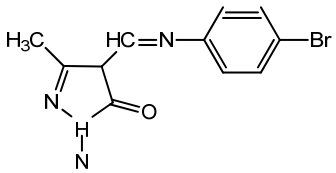
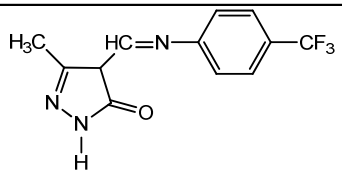
Table VI.1. The IR (KBr) spectra of 4-(((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / 4-(trifluoromethyl) phenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one 3(a-d) ($\bar{\upsilon}/\delta$, cm^{-1}):

COMP	R	N-H	Ar-H	C=O	C=N	PYRAZOLE	C-F	C-Cl	C-Br
3a	F	3418-3384	3052	1670	1619	1478-1375	1100	-	-
3b	Cl	3420-3386	3055	1675	1621	1478-1375	-	730	-
3c	Br	3420-3390	3065	1680	1622	1478-1375	-	-	650
3d	CF3	3422-3392	3067	1685	1624	1478-1375	1100	-	-

^{1}H-NMR (δ, PPM)

The ^{1}H-NMR (400MHz) spectra of 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one **(3a)** was recorded in DMSO d_6 showed the following signals at δ_{PPM}. 1.94 (s, 3H, of CH_3 group), 2.4 (d, 1H, CH of pyrazole ring), 7.0 (s, 1H, NH of pyrazole ring), 7.50 (d, 1H, CH of imine) and 7.24-7.31 (m, 4H, of phenyl group). The ^{1}H-NMR data of **3(a-d)** was shown in the Table **VI.2**.

Table VI.2. The ^{1}H NMR (400MHz) spectra of 4-(((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / 4-(trifluoromethyl) phenyl) vCLTPs

COMP	STRUCTURE	^{1}H-NMR(DMSO-d_6)(δ_{PPM})
3a		1.94 (s, 3H, of CH_3 group), 2.4 (d, 1H, CH of pyrazolone ring), 7.0 (s, 1H, NH of pyrazole ring), 7.50 (d, 1H, CH of imine) and 7.24-7.31 (m, 4H, of phenyl group).
3b		1.94 (s, 3H, of CH_3 group), 2.38 (d, 1H, CH of pyrazole ring), 7.0 (s, 1H, NH of pyrazole ring), 7.48 (d, 1H, CH of imine) and 7.02-7.25 (m, 4H, of phenyl group).
3c		1.94 (s, 3H, of CH_3 group), 2.35 (d, 1H, CH of pyrazolone ring), 7.0 (s, 1H, NH of pyrazole ring), 7.43 (d, 1H, CH of imine) and 7.0-7.20 (m, 4H, of phenyl group).
3d		1.94 (s, 3H, of CH_3 group), 2.30 (d, 1H, CH of pyrazolone ring), 7.0 (s, 1H, NH of pyrazole ring), 7.53 (d, 1H, CH of imine) and 7.25-7.60 (m, 4H, of phenyl group).

2. Synthesis of 4-(((4-Fluorophenyl) / (4-Chlorophenyl) / (4-Bromophenyl) / 4-(Trifluoromethyl) Phenyl) Imino) Methyl)-3-Methyl-1-(Morpholinomethyl) / (4-Methyl Piperazin-1-yl) Methyl)-1H- Pyrazol-5(4H)-one 5(a-h):

A mixture of 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one (0.87gr, 0.004mol) **(3a)**, (0.78gr, 0.09mol) morpholine **(4a)** (0.15 mol) and water 20 ml was stirred to obtained a clear solution. To this solution, HCHO (0.05 mol) and DMF were added in ice cold condition and stirred for 2 hours in an ice bath and left over night at room temperature. The progress of the reaction was monitored by TLC using cyclohexane and ethylacetate (7:3) solvent

mixture as a mobile phase. At the end of the reaction, the mixture was taken in a 30 ml dichloromethane and neutralized with 50 ml 1N NaOH solution, after neutralization the mixture was extracted with CH_2Cl_2 (3(25 ml). The combined extract was dried on Na_2SO_4. After filtration, the solvent was removed with rota evaporator. The residue was purified by column chromatography, using 60-120 mesh silica and $CHCl_3$ solvent was used as an elutent. Finally the product compound 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1-(morpholinomethyl)-1H- pyrazol-5(4H)-one (5a) was purified from aqueous dimethyl formamide. Yield 70%, m p 162-164°C.

The similar procedure was adopted to synthesise **5(b-h)** by condensing **3(a-d)** with morpholine (4a) N-methylpiperazine **(4b)** respectively. The structures of **5(a-h)** were established by IR, ^{1}H-NMR and elemental analysis. The analytical data was shown in the Table **VI.11**.

IR Spectra ($\bar{\upsilon}$ / δ, cm-1)

The IR spectra of 4-(((4-fluorophenyl) imino) methyl) – 3 – methyl – 1 -(morpholinomethyl) - 1H - pyrazol-5(4H)-one **(5a)** was recorded in the 4000-400 cm^{-1} range in KBr pellets reflect the molecular structure and showed the characteristic bands around 3052 (stretching of Ar-H), 2940 and 2895 (CH_3 of aliphatic-CH), 1670 (C=O), 1619 (C=N), 1478-1375 (stretching vibrations of pyrazolone ring), 1140 (C-O) and 1100 cm^{-1} (C-F). The IR data of 5(a-h) was shown in the Table **VI.3**

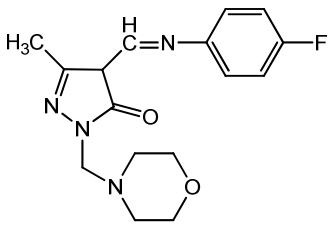
Table VI.3. The IR (KBr) spectra of 4-(((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / 4-(trifluoromethyl) phenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one 3(a-d) ($\bar{\upsilon}$/δ, cm^{-1}):

COMP	R	X	Ar-H	C=O	C=N	PYRAZOLONE	C-O	C-F	C-Cl	C-Br
5a	F	O	3052	1670	1619	1478-1375	1140	1100	-	-
5b	Cl	O	3055	1675	1621	1478-1375	1145	-	730	-
5c	Br	O	3065	1676	1622	1478-1375	1148	-	-	650
5d	CF_3	O	3067	1680	1624	1478-1375	1150	1100	-	-
5e	F	N-CH_3	3052	1685	1620	1478-1375	-	1100	-	-
5f	Cl	N-CH_3	3055	1678	1624	1478-1375	-	-	730	-
5g	Br	N-CH_3	3065	1673	1625	1478-1375	-	-	-	650
5h	CF_3	N-CH_3	3067	1676	1628	1478-1375	-	1100	-	-

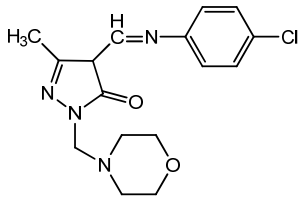
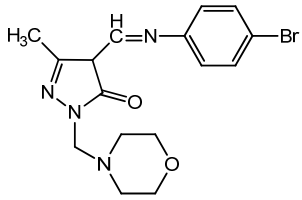
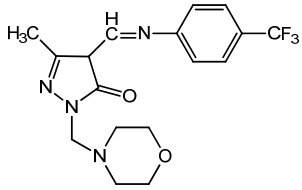
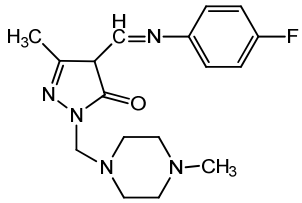
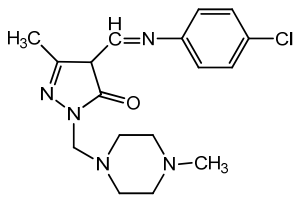
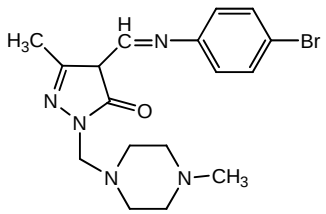
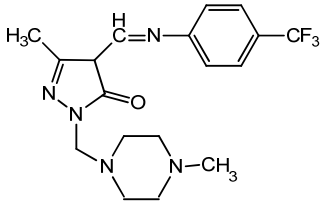
^{1}H-NMR (δ, PPM)

The ^{1}H-NMR (400MHz) spectra of 4-(((4-fluorophenyl) imino) methyl) – 3 - methyl-1-(morpholinomethyl)-1H-pyrazol-5(4H)-one **(5a)** was recorded in DMSO d_6 showed the following signals at δ_{PPM}. 1.94 (s, 3H, of CH_3 group), 2.4 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7Hz), 4.27 (s, 2H, N-CH_2-N of morpholine ring), 7.50 (d, 1H, CH of imine) and 7.24-7.31 (m, 4H, of phenyl group). The ^{1}H-NMR data of **5(a-h)** was shown in the Table **VI.4**.

Table VI.4. The ^{1}H-NMR (400MHz) spectra of 4-(((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / 4-(trifluoromethyl) phenyl) imino) methyl)-3-methyl-1-(morpholinomethyl) / (4-methyl piperazin-1-yl) methyl)-1H- pyrazol-5(4H)-one 5(a-h) (δ_{PPM}):

COMP	STRUCTURE	^{1}H-NMR(DMSO-d6)(δ_{PPM})
5a		1.94 (s, 3H, of CH_3 group), 2.4 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7Hz), 4.27 (s, 2H, N-CH_2-N of morpholine ring), 7.50 (d, 1H, CH of imine) and 7.24-7.31 (m, 4H, of phenyl group).

(Table VI.4) contd.....

COMP	STRUCTURE	^{1}H-NMR(DMSO-d6)(δ_{PPM})
5b		1.94 (s, 3H, of CH_3 group), 2.45 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7Hz), 4.27 (s, 2H, N-CH_2-N of morpholine ring), 7.55 (d, 1H, CH of imine) and 7.02-7.25 (m, 4H, of phenyl group).
5c		1.94 (s, 3H, of CH_3 group), 2.38 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7Hz), 4.27 (s, 2H, N-CH_2-N of morpholine ring), 7.48 (d, 1H, CH of imine) and 7.0-7.20 (m, 4H, of phenyl group).
5d		1.94 (s, 3H, of CH_3 group), 2.48 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7Hz), 4.27 (s, 2H, N-CH_2-N of morpholine ring), 7.58 (d, 1H, CH of imine) and 7.25-7.60 (m, 4H, of phenyl group).
5e		1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 group attached to piperazine ring), 2.35 (m, 8H, $(CH_2)_4$ of piperazine ring), 2.4 (d, 1H, CH of pyrazolone ring), 4.27 (s, 2H, N-CH_2-N of piperazine ring), 7.50 (d, 1H, CH of imine) and 7.24-7.31 (m, 4H, of phenyl group).
5f		1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 group attached to piperazine ring), 2.35 (m, 8H, $(CH_2)_4$ of piperazine ring), 2.4 (d, 1H, CH of pyrazole ring), 4.27 (s, 2H, N-CH_2-N of piperazine ring), 7.50 (d, 1H, CH of imine) and 7.02-7.49 (m, 4H, of phenyl group).
5g		1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 group attached to piperazine ring), 2.35 (m, 8H, $(CH_2)_4$ of piperazine ring), 2.45 (d, 1H, CH of pyrazolone ring), 4.27 (s, 2H, N-CH_2-N of piperazine ring), 7.55 (d, 1H, CH of imine) and 7.0-7.20 (m, 4H, of phenyl group).
5h		1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 group attached to piperazine ring), 2.35 (m, 8H, $(CH_2)_4$ of piperazine ring), 2.48 (d, 1H, CH of pyrazolone ring), 4.27 (s, 2H, N-CH_2-N of piperazine ring), 7.58 (d, 1H, CH of imine) and 7.25-7.60 (m, 4H, of phenyl group).

3. Synthesis of Diethyl ((4-Fluorophenyl) / (4-Chlorophenyl) / (4-Bromophenyl) / (4-(Trifluoromethyl) Phenyl) Amino) (3-Methyl-1-(Morpholino methyl) / (4-Methylpiperazin-1-Yl)-5-oxo-4, 5-Dihydro-1H-Pyrazol-4-yl) Methyl) Phosphonates 6(a-h):

A mixture of 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1-(morpholinomethyl)-1H- pyrazol-5(4H)-one (0.95gr, 0.003mol) **(5a)** and Diethyl phosphite (1.24 ml, 0.009 mol) in an hydrous toluene (15ml) was added dropwise. Stirring was continued at room temperature for another 0.5 hour, after which the mixture was heated under reflux for 4-6 hours. The reaction was monitored by TLC on silica gel using petroleum ether-ethyl acetate (1:2 v/v). After completion of the reaction, the solvent was removed by rota evaporator and the resulting residue was purified by column chromatography on silicagel (100-200 mesh) and ethyl acetae-hexane, (3:7 ratio) as an eluent to afford pure Diethyl (((4-fluorophenyl)amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4,5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)**, was purified from aqueous dimethyl formamide. Yield 70%, m p 176-178°C.

The similar procedure was adopted to synthesise **6(b-h)** by the reaction between **5(b-h)** with Diethyl phosphite. The structure of these newly synthesized compounds of **6(a-h)** were established by IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, mass data and elemental analysis. The analytical data was shown in the Table **VI.11**.

IR Spectra (ῡ / δ, cm-1)

The IR spectra of Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4,5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)** was recorded in the 4000-400 cm^{-1} range in KBr pellets reflect the molecular structure and showed the characteristic bands around 3418-3384 (N-H), 3052 (stretching of Ar-H), 2940 and 2895 (CH_3 & CH_2 of aliphatic-CH), 1670 (C=O), 1478-1375 (stretching vibrations of pyrazolone ring), 1140 (C-O), 1245 (P=O), 1100 (C-F) and 745 cm^{-1}(P-O). The IR spectra of **(6a)** was shown in Fig. (**VI.1**) and IR data of **6(a-h)** was shown in the Table **VI.5**.

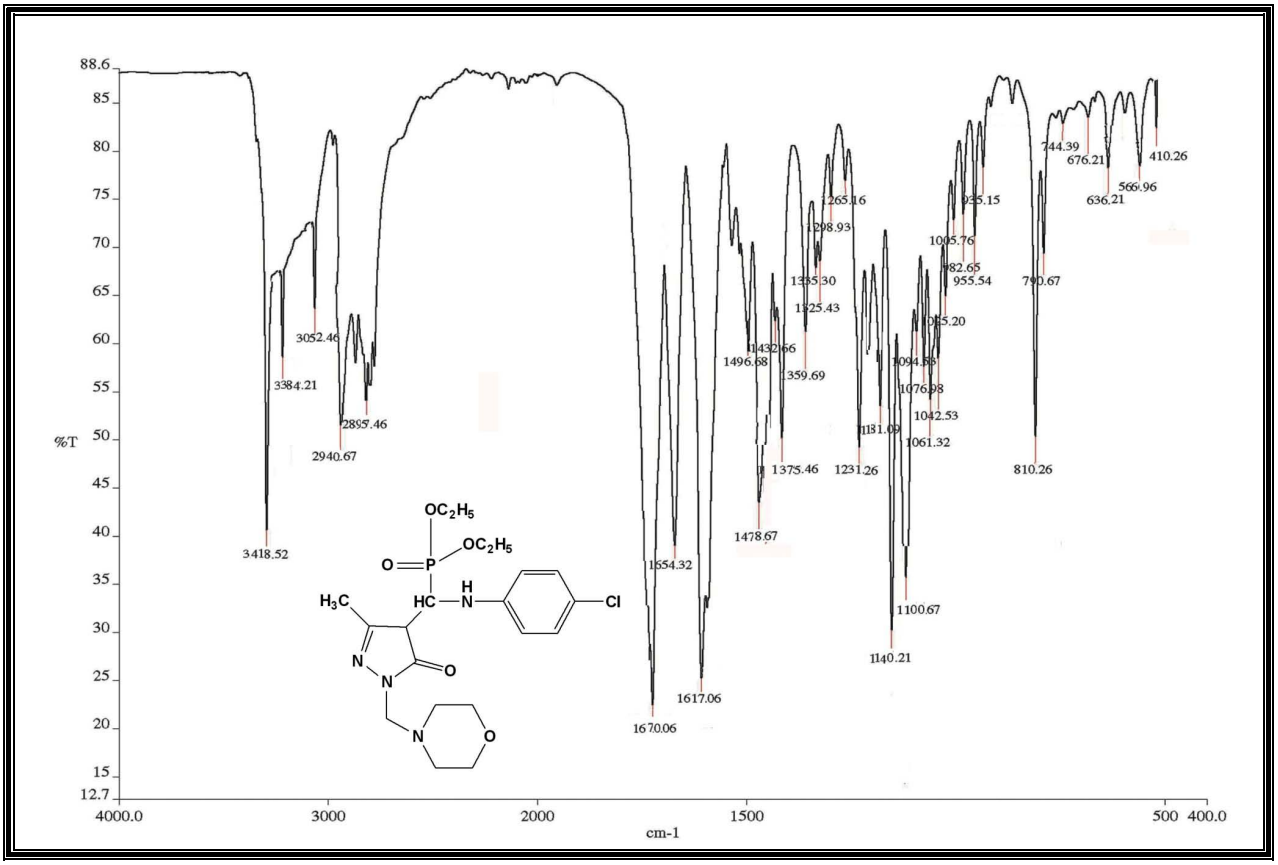


Fig. (VI.1). IR Spectrum of Diethyl (((4-fluorophenyl) amino) (3 – methyl – 1 - (morpholinomethyl) – 5 – oxo - 4, 5 – dihydro - 1H - pyrazol – 4 - yl) methyl) phosphonates 6(a)

Table VI.5. The IR (KBr) spectra of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl) -5- oxo - 4, 5 - dihydro-1H-pyrazol-4-yl) methyl) phosphonates 6(a-h) ($\bar{\upsilon}/\delta$, cm^{-1}):

COMP	R	X	N-H	Ar-H	C=O	PYRAZOLONE	P=O	P-O-C(ali)	C-F	C-Cl	C-Br
6a	F	O	3418-3384	3052	1670	1478-1375	1245	744	1100	-	-
6b	Cl	O	3420-3386	3055	1675	1478-1375	1254	740	-	730	-
6c	Br	O	3420-3390	3065	1680	1478-1375	1259	752	-	-	650
6d	CF3	O	3422-3392	3067	1673	1478-1375	1256	755	1110	-	-
6e	F	N-CH_3	3418-3384	3052	1674	1478-1375	1254	756	1108	-	-
6f	Cl	N-CH_3	3420-3386	3055	1676	1478-1375	1259	747	-	735	-
6g	Br	N-CH_3	3420-3390	3065	1678	1478-1375	1256	743	-	-	655
6h	CF_3	N-CH_3	3422-3392	3067	1680	1478-1375	1254	758	1115	-	-

^{1}H-NMR (δ, PPM)

The ^{1}H-NMR (400MHz) spectra of Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates (6a) was recorded in DMSO d_6 showed the following signals at δ_{PPM}. 1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.40 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2-of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2-of morpholine ring J=7Hz), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.72 (s, 1H, P-C-H), 6.03 (s, 1H, NH) and 7.24-7.31 (m, 4H, of flourophenyl group). The ^{1}H-NMR spectra of **(6a)** was shown in the Fig. **V1.2**) and ^{1}H NMR data of **6(a-h)** was shown in the Table **VI.6**.

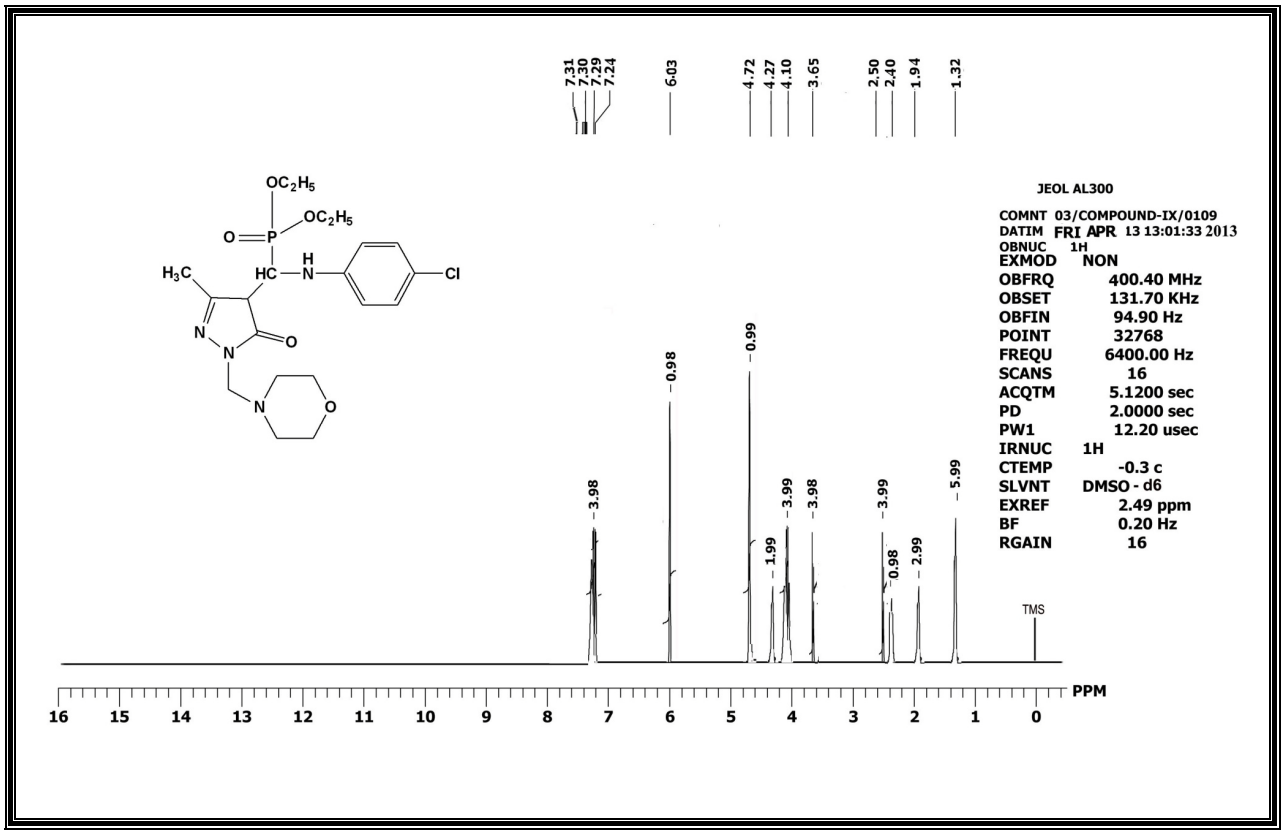
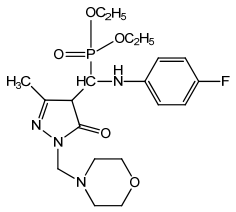
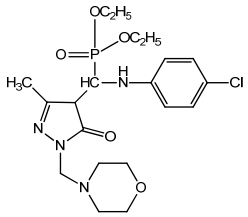
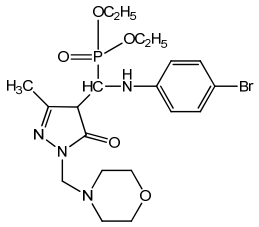
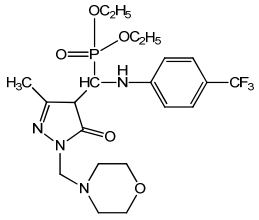
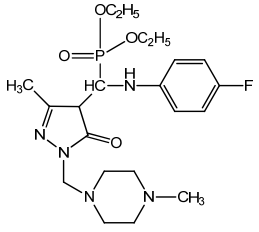
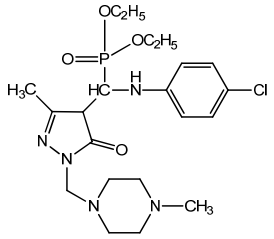
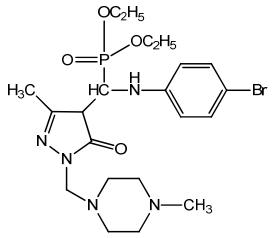
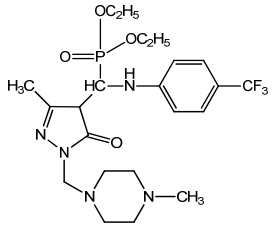


Fig. (V1.2). ^{1}H - NMR Spectrum of Diethyl (((4-fluorophenyl) amino) (3 – methyl – 1 - (morpholinomethyl) – 5 – oxo - 4, 5 – dihydro - 1H - pyrazol – 4 - yl) methyl) phosphonates 6(a)

Table VI.6. The ^{1}H-NMR (400MHz) spectra of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates 6(a-h) (δ, PPM) :

COMP	STRUCTURE	^{1}H-NMR(DMSO-d^{6})(δ_{PPM})
6a		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.40 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2-of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2-of morpholine ring J=7Hz), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.72 (s, 1H, P-C-H), 6.03 (s, 1H, NH) and 7.24-7.31 (m, 4H, of fluorophenyl group).
6b		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.40 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2-of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2-of morpholine ring J=7Hz), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.65 (s, 1H, P-C-H), 5.95 (s, 1H, NH) and 7.02-7.25 (m, 4H, of chlorophenyl group).
6c		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.40 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2-of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2-of morpholine ring J=7Hz), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.60 (s, 1H, P-C-H), 5.90 (s, 1H, NH) and 7.0-7.20 (m, 4H, of bromophenyl group).
6d		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.40 (d, 1H, CH of pyrazolone ring), 2.50 (t, 4H, -CH_2-N-CH_2-of morpholine ring J=7Hz), 3.65 (t, 4H, -CH_2-O-CH_2-of morpholine ring J=7Hz), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.80 (s, 1H, P-C-H), 6.15 (s, 1H, NH) and 7.25-7.60 (m, 4H, of triflouromethylphenyl group).
6e		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 attached to piperazin ring), 2.40 (d, 1H, CH of pyrazolone ring), 2.65 (m, 8H, (CH_2)4 of piperazine ring), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.72 (s, 1H, P-C-H), 6.03 (s, 1H, NH) and 7.24-7.31 (m, 4H, of flourophenyl group).

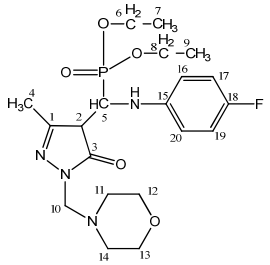
(Table VI.6) contd.....

COMP	STRUCTURE	^{1}H-NMR(DMSO-d^{6})(δ_{PPM})
6f		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 attached to piperazin ring), 2.40 (d, 1H, CH of pyrazolone ring), 2.65 (m, 8H, (CH_2)4 of piperazine ring), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.65 (s, 1H, NH), 5.95 (s, 1H, P-C-H) and 7.02-7.20 (m, 4H, of chlorophenyl group).
6g		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 attached to piperazin ring), 2.40 (d, 1H, CH of pyrazolone ring), 2.65 (m, 8H, (CH_2)4 of piperazine ring), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.65 (s, 1H, NH), 5.95 (s, 1H, P-C-H) and 7.0-7.20 (m, 4H, of bromophenyl group).
6h		1.32 (t, 6H, 2x P-O-CH_2-CH_3 J=7Hz), 1.94 (s, 3H, of CH_3 group), 2.26 (s, 3H, CH_3 attached to piperazin ring), 2.40 (d, 1H, CH of pyrazolone ring), 2.65 (m, 8H, (CH_2)4 of piperazine ring), 4.10 (q, 4H, 2x OCH_2, J=7Hz), 4.27 (s, 2H, -N-CH_2-N- of morpholine ring), 4.65 (s, 1H, NH), 5.95 (s, 1H, P-C-H) and 7.25-7.60 (m, 4H, of triflouromethyl phenyl group).

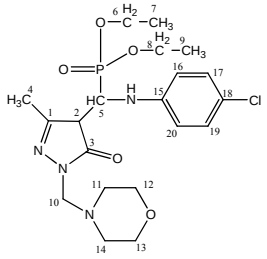
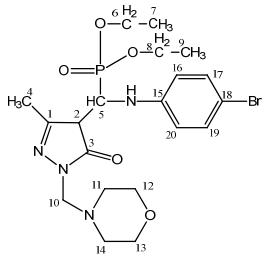
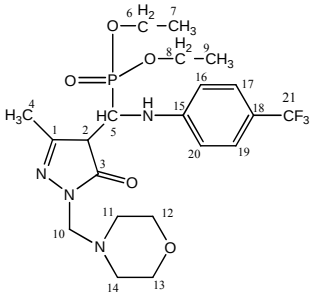
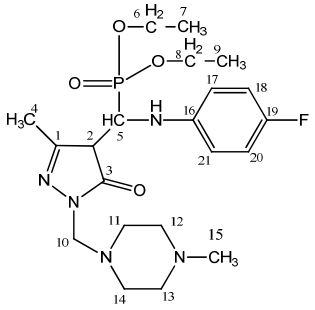
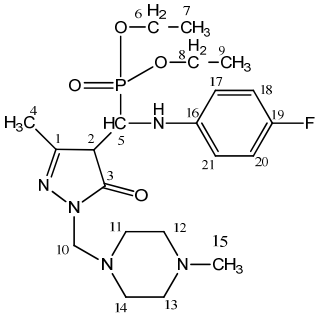
^{13}C-NMR (δ_{PPM})

The ^{13}C-NMR (75MHz) spectra of Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4,5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)** was recorded in DMSO d_6 showed the following signals at δ_{PPM}. 155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.3, 53.2, 66.4, 143.2, 118.9, 116.3 and 155.7 corresponding to C_1, C_2, C_3, C_4, C_5, C_6 &C_8, C_7 & C_9, C_{10}, C_{11}&C_{14}, C_{12} &C_{13}, $C_{15,}$ C_{16} &C_{20}, C_{17} &C_{19} and C_{18} respectively. The ^{13}C NMR spectra of **(6a)** was shown in the Fig. (**VI.3**) and ^{13}C-NMR data of **6(a-h)** was shown in the Table **VI.7**

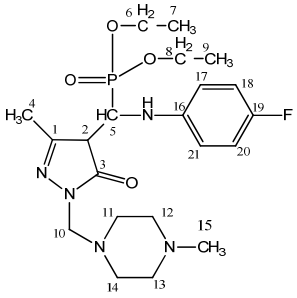
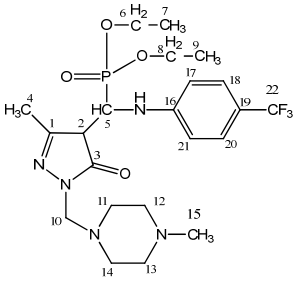
Table VI.7. The ^{13}C-NMR (75MHz) spectra of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates 6(a-h) (δ_{PPM})

COMP	STRUCTURE	^{13}C-NMR(DMSO-d_6)(δ_{PPM})
6a		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.3, 53.2, 66.4, 143.2, 118.9, 116.3 and 155.7 corresponding toC_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11},& C_{14}, C_{12} & C_{13}, C_{15}, C16 & C_{20}, C_{17} & C_{19} and C_{18}.

(Table VI.7) contd.....

COMP	STRUCTURE	^{13}C-NMR(DMSO-d_6)(δ_{PPM})
6b		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.3, 53.2, 66.4, 145.7, 114.9, 129.6 and 126.1 corresponding toC_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11},& C_{14}, C_{12} & C_{13}, C_{15}, C16 & C_{20}, C_{17} & C_{19} and C_{18}.
6c		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.3, 53.2, 66.4, , 146.6, 114.5, 132.4 and 115.1 corresponding toC_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11},& C_{14}, C_{12} & C_{13}, C_{15}, C16 & C_{20}, C_{17} & C_{19} and C_{18}.
6d		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.3, 53.2, 66.4, 150.9, 113.8, 125.9, 124.9 and 124.1 corresponding toC_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11},& C_{14}, C_{12} & C_{13}, C_{15}, C16 & C_{20}, C_{17} & C_{19}, C_{18} and C_{21}.
6e		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.0, 52.2, 57.3, 46.6, 143.2, 118.9, 116.3 and 155.7 corresponding toC_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11}, & C_{14}, C_{12} & C_{13}, C_{15}, C_{16}, C_{17} & C_{21}, C_{18} & C_{20} and C_{19}.
6f		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.0, 52.2, 57.3, 46.6, 145.7, 114.9, 129.C_{18} 126.1 corresponding toC_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11}, & C_{14}, C_{12} & C_{13}, C_{15}, C_{16}, C_{17} & C_{21}, C_{18} & C_{20} and C_{19}.

(Table VI.7) contd.....

COMP	STRUCTURE	^{13}C-NMR(DMSO-d_6)(δ_{PPM})
6g		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.0, 52.2, 57.3, 46.6, 146.6, 114.5, 132.4 and 115.1 corresponding toC_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11}, & C_{14}, C_{12} & C_{13}, C_{15}, C_{16}, C_{17} & C_{21}, C_{18} & C_{20} and C_{19}.
6h		155.6, 33.7, 172.0, 19.3, 57.5, 62.2, 16.3, 70.0, 52.2, 57.3, 46.6, 150.9, 113.8, 125.9, 124.9 and 124.1 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, & C_8, C_7 & C_9, C10, C_{11}, & C_{14}, C_{12} & C_{13}, C_{15}, C_{16}, C_{17} & C_{21}, C_{18} & C_{20}, C_{19} and C_{22}.

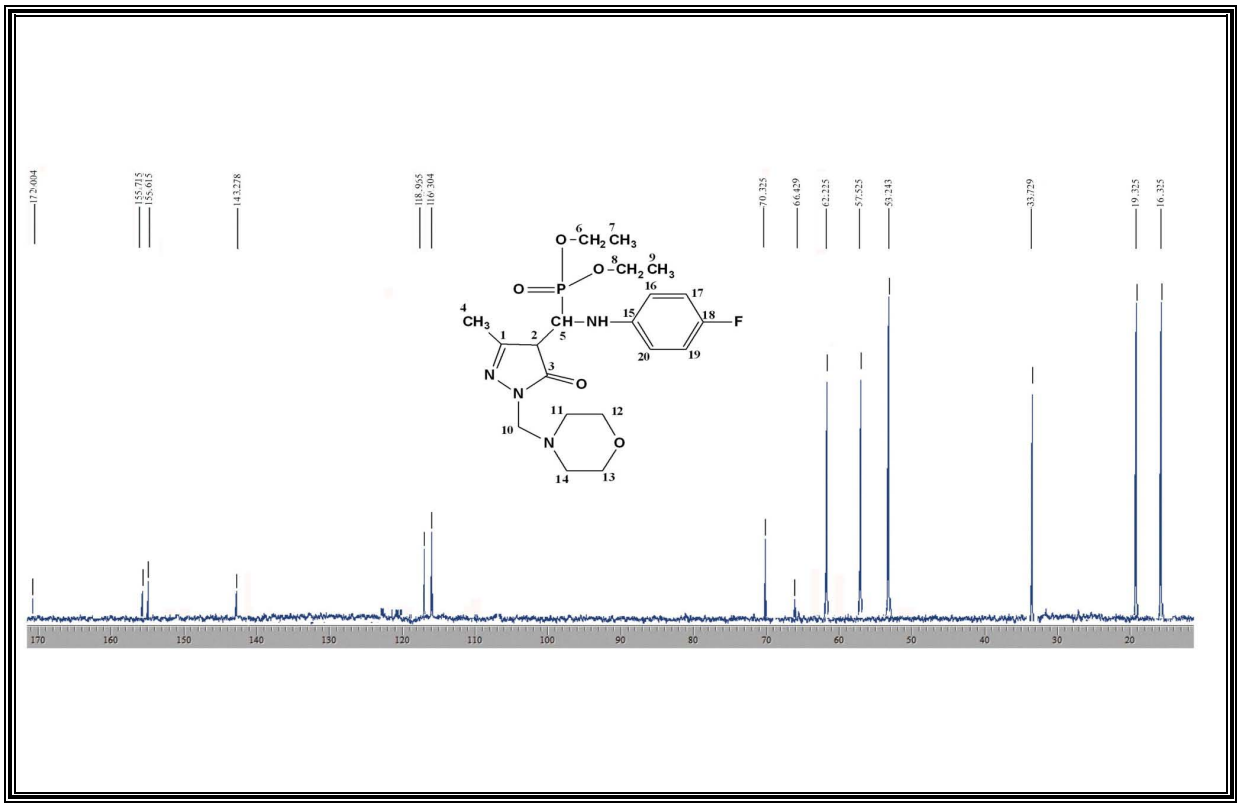


Fig. (V1.3). ^{13}C - NMR Spectrum of Diethyl (((4-fluorophenyl) amino) (3 – methyl – 1 - (morpholinomethyl) – 5 – oxo - 4, 5 – dihydro - 1H - pyrazol – 4 - yl) methyl) phosphonates 6(a)

^{31}P-NMR (δ, PPM)

The ^{31}P-NMR (161.89MHz) spectra of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **6(a-h)** was recorded in DMSO d_6 solvent. The ^{31}P-NMR spectra of **6(a-h)** were recorded by taking 85% H_3PO_4 as reference standard. The title compounds found to exhibit only one signal in ^{31}P-NMR spectrum. Phosphorus resonance signals[31-33] of the title compounds 6(a-h) appeared as a singlet signals in the range of -19-27 PPM. The ^{31}P-NMR data of **6(a-h)** was shown in the Table **VI.8** and ^{31}P-NMR spectrum of Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4,5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)** was shown in the Fig. (**VI.4**).

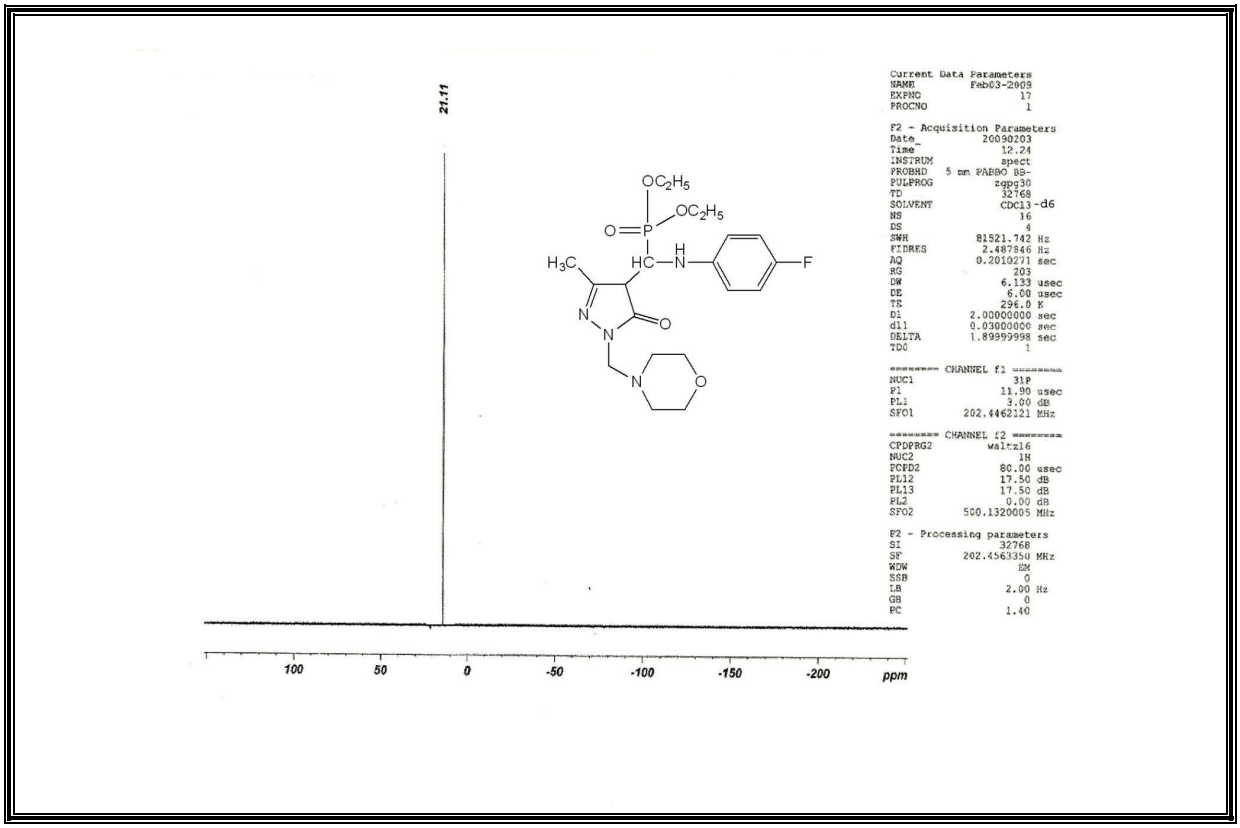
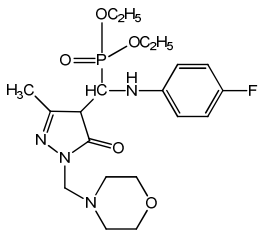
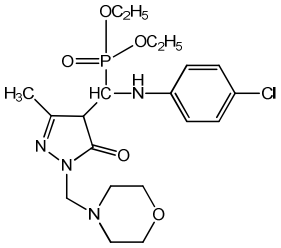
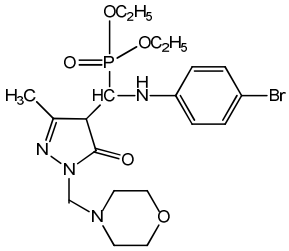
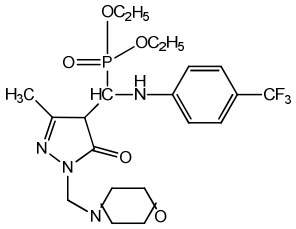
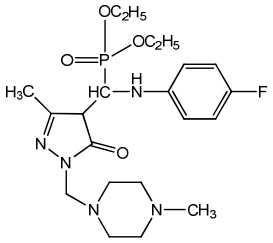
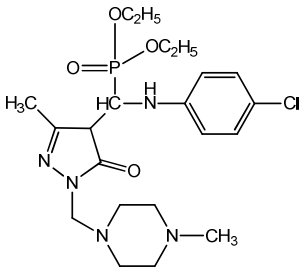


Fig. (VI.4). ^{31}P - NMR Spectrum of Diethyl (((4-fluorophenyl) amino) (3 – methyl – 1 - (morpholinomethyl) – 5 – oxo - 4, 5 – dihydro - 1H - pyrazol – 4 - yl) methyl) phosphonates 6(a)

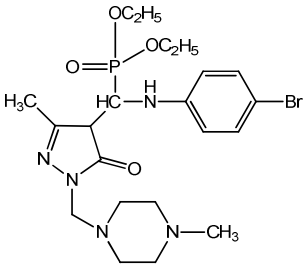
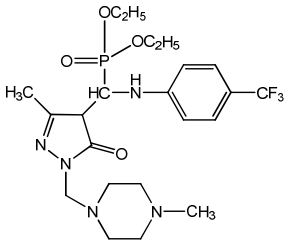
Table VI.8. The ^{13}P-NMR (161.89MHz) spectra of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates 6(a-h) (δ_{PPM})

COMP	STRUCTURE	^{31}P-NMR(DMSO-d_6)(δ^{PPM})
6a		21.11

(Table VI.8) contd.....

COMP	STRUCTURE	^{31}P-NMR(DMSO-d_6)(δ^{PPM})
6b		20.9
6c		19.90
6d		26.5
6e		20.10
6f		19.80

(Table VI.8) contd.....

COMP	STRUCTURE	^{31}P-NMR(DMSO-d_6)(δ^{PPM})
6g		19.60
6h		24.5

Mass Spectra

The electron impact mass spectrum for Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)** was recorded and interpreted. The mass spectrum fragmentation [34] of compound **(6a)** was rationalized in Chart. (**VI.2**) and Chart. (**VI.3**). The mass spectral data of compounds **(6a)** was given in the Table **V1.9** and Table **V1.10**.

Table VI.9. Mass spectral data of primary fragmentation of Diethyl (((4-fluorophenyl) amino) (3-methyl-1-(morpholinomethyl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates (6a):

MOLICULAR ION	LOSTFREE RADICAL/ NEUTRAL	PRIMARY FRAGMENTED ION	M/Z	RELATIVE ABUNDENCE (%)
$C_20H_30FN_4O_5P$(M+) M/z=456.19(100%)	$C_4H_8NO^{\cdot}$	$C_{16}H_{22}FN_3O_4P^+$ (VIb)	370.13	17.7
	$C_{16}H_{22}FN_3O_4P^{\cdot}$	$C_4H_8NO^+$ (VIc)	86.06	4.7
	$C_5H_{10}NO^{\cdot}$	$C_{15}H_20FN_3O_4P^+$ (VId)	356.13	16.6
	$C_{15}H_20FN_3O_4P^{\cdot}$	$C_5H_{10}NO^+$ (VIe)	100.08	5.6
	$C_9H_{14}N_3O_2^{\cdot}$	$C_{11}H_{16}FNO_3P^+$ (VIf)	260.09	12.2
	$C_{11}H_{16}FNO_3P^{\cdot}$	$C_9H_{14}N_3O_2^+$ (VIg)	196.11	11.1
	$C_6H_5FNO^{\cdot}$	$C_{14}H_{25}N_3O_5P$+(VIh)	346.15	15.6
	$C_{11}H_{16}N_4O_6P^{\cdot}$	$C_6H_5FNO^+$ (VIi)	110.04	6.4
	$C_6H_4F^{\cdot}$	$C_{14}H_{26}N_4O_5P^+$ (VIj)	361.16	15.6
	$C_{14}H_{26}N_4O_5P^{\cdot}$	$C_6H_4F^+$ (VIk)	95.03	6.5
	$C_{16}H_{20}FN_4O_2^{\cdot}$	$C_4H_{10}O_3P^+$ (VIl)	137.04	4.6
	$C_4H_{11}FO_3P^{\cdot}$	$C_{16}H_{20}FN_4O_2^+$ (VIm)	319.16	17.6

The mass spectra of Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)** exhibited the molecular ion ($M^{7+\cdot}$) ion peak at m/z = 456.19(100.0%). The m/z value of molecular ion indicates that molecule is having even number of nitrogens. The molecular ion peak **(6a)** at m/z = 456.19(100.0%) is appeared as base peak of the spectrum.

The primary fragmentation pattern of Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)** was presented in the Chart- (VI.2). The other important primary fragmented peaks appeared at different m/z values were shown in the following Table **V1.9**.

The molecular ion signal was obeying nitrogen rule while, the primary fragmented ions derived from molecular ion signal mayor may not obeying nitrogen rule. The primary fragmented ions undergo fragmentation and forms secondary fragmented ions at different m/z values. The secondary fragmented peaks appeared at different m/z values were shown

in the Table **V1.10**. And fragmentation process was shown in the Chart. (**VI.3**).

Table IV1.10. Mass spectral data of secondary fragmentation Diethyl (((4-fluorophenyl) amino) (3-methyl-1-(morpholinomethyl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates (6a):

PRIMARY FRAGMENTED ION	LOSTFREE RADICAL/NUETRAL MOLICULE	SECONDARY FRAGMENTED ION	M/Z	RELATIVE ABUNDENCE %
$C_{16}H_{22}FN_3O_4P^+$ (VIb) m/z= 370.13	$C_4H_{11}O_3P$	$C_{12}H_{11}FN_3O$+(VIb^I)	232.09	14.3
	$C_4H_{12}O_2$	$C_{12}H_{10}FN_3O_2P$+(VIb^{II})	278.05	14.2
$C_{15}H_20FN_3O_4P^+$(VId) m/z=356.13	$C_4H_{11}O_3P$	$C_{11}H_9FN_3O^+$(VId^I)	218.07	12.0
	$C_4H_{12}O_2$	$C_{11}H_8FN_3O_2^+$(VId^{II})	264.03	12.1
$C_{11}H_{16}FNO_3P^+$(VIf) m/z=260.09	$C_4H_{11}O_3P$	C_7H_5FN+(VIf^I)	122.04	7.9
$C_9H_{14}N_3O_2$+(VIg) m/z=196.11	C_5H_9NO	$C_4H_5N_2O$+(VIg^I)	97.04	5.1
$C_{14}H_{25}N_3O_5P$+(VIh) m/z=346.15	C_5H_9NO	$C_9H_{16,3}O_4P^+$ (VIh^I)	261.09	10.1
$C_{14}H_{26}N_4O_5P^+$(VIj) m/z=361.16	C_5H_9NO	$C_9H_{17}N_3O_4P^+$ (VIj^I)	262.10	10.1
$C_{16}H_20FN_4O_2^+$(VIm) m/z=319.16	C_5H_9NO	$C_{11}H_{11}FN_3O^+$(VIm^I)	220.09	13.2

EXPERIMENTAL SECTION

1. Synthesis 4-(((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / 4-(trifluoromethyl) phenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one (3a-d):

Equimolar quatity of 4-fluoro aniline (2a) and 3-Methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carbaldehyde **(1)** were dissolved in absolute alcohol, to this three drops of acetic acid is added then heated on a steam bath for 5-6 hours at 100°C. After standing for 24 hours at room temperature, the crude product was purified by column chromatography (60-120 mesh silica gel,eluent: 10% EtoAc pet ether). Finally, the product compound 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one (3a) which was recrystallized from warm absolute alcohol. Yield 75%, m p 153-155°C.

The similar procedure was adopted to synthesise **3(b-d)** by condensing 3-Methyl-5-oxo-4, 5-dihydro-1H-pyrazole-4-carbaldehyde **(1)** with 4-chloro aniline **(2b)**, 4-bromo aniline **(2c)** and 4-trifluoro aniline **(2d)** respectively. The structures of **3(a-d)** were established by IR, ^{1}H-NMR and elemental analysis. The analytical data was shown in the Table **VI.11**.

2. Synthesis of 4-(((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / 4-(trifluoromethyl) phenyl) imino) methyl)-3-methyl-1-(morpholinomethyl) / (4-methyl piperazin-1-yl) methyl)-1H- pyrazol-5(4H)-one 5(a-h):

A mixture of 0.1 mole 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1H-pyrazol-5(4H)-one (3a), morpholine **(4a)** (0.15 mol) and water 20 ml was stirred to obtained a clear solution. To this solution, HCHO (0.05 mole) and DMF were added in ice cold condition and stirred for 2 hours in an ice bath and left over night at room temperature. The progress of the reaction was monitored by TLC using cyclohexane and ethylacetate (7:3) solvent mixture as a mobile phase. At the end of the reaction, the mixture was taken in a 30 ml dichloromethane and neutralized with 50 ml 1N NaOH solution, after neutralization the mixture was extracted with CH_2Cl_2 (3(25 ml). The combined extract was dried on Na_2SO_4. After filtration, the solvent was removed with rota evaporator. The residue was purified by column chromatography, using 60-120 mesh silica and $CHCl_3$ solvent was used as an elutent. Finally the product compound 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1-(morpholinomethyl)-1H- pyrazol-5(4H)-one (5a) was purified from aqueous dimethyl formamide. M p 162-164°C, yield 70%.

The similar procedure was adopted to synthesise **5(b-h)** by condensing **3(a-d)** with morpholine **(4a)** N-methylpiperazine **(4b)** respectively. The structures of **5(a-h)** were established by IR, ^{1}H-NMR and elemental analysis. The analytical data was shown in the Table **VI.11**.

3. Synthesis of Diethyl ((4-fluorophenyl) / (4-chlorophenyl) / (4-bromophenyl) / (4-(trifluoromethyl) phenyl) amino) (3-methyl-1-(morpholino methyl) / (4-methylpiperazin-1-yl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates 6(a-h):

A mixture of 4-(((4-fluorophenyl) imino) methyl)-3-methyl-1-(morpholinomethyl)-1H- pyrazol-5(4H)-one (5a) and Diethyl phosphite (0.50ml, 0.004 mol) in an hydrous toluene (15ml) was added dropwise. Stirring was continued at room temperature for another 0.5 hour, after which the mixture was heated under reflux for 4-6 hours. The reaction was monitored by TLC on silica gel using petroleum ether-ethyl acetate (1:2 v/v). After completion of the reaction, the solvent was removed by rota evaporator and the resulting residue was purified by column chromatography on silicagel (100-200 mesh) and ethyl acetae-hexane, (3:7 ratio) as an eluent to afford pure Diethyl (((4-fluorophenyl)amino) (3-methyl-1- (morpholinomethyl)-5-oxo-4,5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates **(6a)**, was purified from aqueous dimethyl formamide. Yield 70%, m p 176-178°C.

The similar procedure was adopted to synthesise 6(b-h) by the reaction between 5(b-h) with Diethyl phosphite. The structure of these newly synthesized compounds of 6(a-h) were established by IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, mass data and elemental analysis. The analytical data was shown in the Table **VI.11**.

Table VI.11. Mass spectral data of secondary fragmentation Diethyl (((4-fluorophenyl) amino) (3-methyl-1-(morpholinomethyl)-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl) methyl) phosphonates (6a):

COMP	MOLECULAR FORMULA	MP(OC)	YIELD(%)	ELEMENTAL ANALYSIS (%)	
				FOUND	CALC
1	$C_5H_6N_2O_2$	153-155	75	C:46.82, H:4.30, N:21.61.	C:47.62, H:4.80, N:22.21.
3a	$C_{11}H_{10}FN_3O$	176-178	70	C:59.47, H:4.10, N:18.57, F:8.07.	C:60.27, H:4.60, N:19.17, F:8.67.
3b	$C_{11}H_{10}ClN_3O$	166-168	65	C:55.26, H:3.78, N:17.23, Cl:14.24.	C:56.06, H:4.28, N:17.83, Cl:15.04.
3c	$C_{11}H_{10}BrN_3O$	157-159	70	C:46.36, H:3.10, N:14.40, Br:27.92.	C:47.16, H:3.60, N:15.00, Br:28.52.
3d	$C_{12}H_{10}F_3N_3O$	183-185	68	C:52.74, H:3.24, N:15.01, F:20.57.	C:53.54, H:3.74, N:15.61, F:21.17.
5a	$C_{16}H_{19}FN_4O_2$	152-154	70	C:59.57, H:5.52, N:17.00, F:5.37.	C:60.37, H:6.02, N:17.60, F:5.97.
5b	$C_{16}H_{19}ClN_4O_2$	192-194	65	C:56.60, H:5.22, N:16.13, Cl:9.79.	C:57.40, H:5.72, N:16.73, Cl:10.59.
5c	$C_{16}H_{19}BrN_4O_2$	143-145	70	C:49.87, H:4.55, N:14.17, Br:20.47.	C:50.67, H:5.05, N:14.77, Br:21.07.
5d	$C_{17}H_{19}F_3N_4O_2$	176-178	70	C:54.63, H:4.70, N:14.61, F:14.87.	C:55.43, H:5.20, N:15.21, F:15.47.
5e	$C_{17}H_{22}FN_5O$	164-166	70	C:60.81, H:6.19, N:20.53, F:5.13.	C:61.61, H:6.69, N:21.13, F:5.73.
5f	$C_{17}H_{22}ClN_5O$	156-158	65	C:57.90, H:5.87, N:19.53, Cl:9.39.	C:58.70, H:6.37, N:20.13, Cl:10.19.
5g	$C_{17}H_{22}BrN_5O$	136-138	70	C:51.25, H:5.15, N:17.25, Br:19.77.	C:52.05, H:5.65, N:17.85, Br:20.37.
5h	$C_{18}H_{22}F_3N_5O$	182-184	75	C:55.88, H:5.31, N:17.76, F:14.34.	C:56.68, H:5.81, N:18.36, F:14.94.
6a	$C_{20}H_{30}FN_4O_5P$	176-178	70	C:51.83, H:6.12, N:11.67, F:3.56, P:6.09.	C:52.63, H:6.62, N:12.27, F:4.16, P:6.79.
6b	$C_{20}H_{30}ClN_4O_5P$	157-159	68	C:50.00, H:5.89, N:11.25, Cl:6.70, P:5.85.	C:50.80, H:6.39, N:11.85, Cl:7.50, P:6.55.
6c	$C_{20}H_{30}BrN_4O_5P$	142-144	67	C:45.63, H:5.34, N:10.23, Br:14.84, P:4.79.	C:46.43, H:5.84, N:10.83, Br:15.44, P:5.49.
6d	$C_{21}H_{30}F_3N_4O_5P$	183-185	65	C:49.00, H:5.47, N:10.46, F:10.65, P:5.42.	C:49.80, H:5.97, N:11.06, F:11.25, P:6.12.
6e	$C_{21}H_{33}FN_5O_4P$	149-151	70	C:52.92, H:6.58, N:14.32, F:3.45, P:6.00.	C:53.72, H:7.08, N:14.92, F:4.05, P:6.60.
6f	$C_{21}H_{33}ClN_5O_4P$	137-139	69	C:51.10, H:6.34, N:13.81, Cl:6.50, P:5.67.	C:51.90, H:6.84, N:14.41, Cl:7.30, P:6.37.
6g	$C_{21}H_{33}BrN_5O_4P$	129-131	65	C:46.75, H:5.77, N:13.60, Br:14.40, P:5.14.	C:47.55, H:6.27, N:13.20, Br:15.00, P:5.84.
6h	$C_{22}H_{33}F_3N_5O_4P$	167-167	75	C:50.06, H:5.90, N:12.78, F:10.37, P:5.26.	C:50.86, H:6.40, N:13.48, F:10.97, P:5.96.

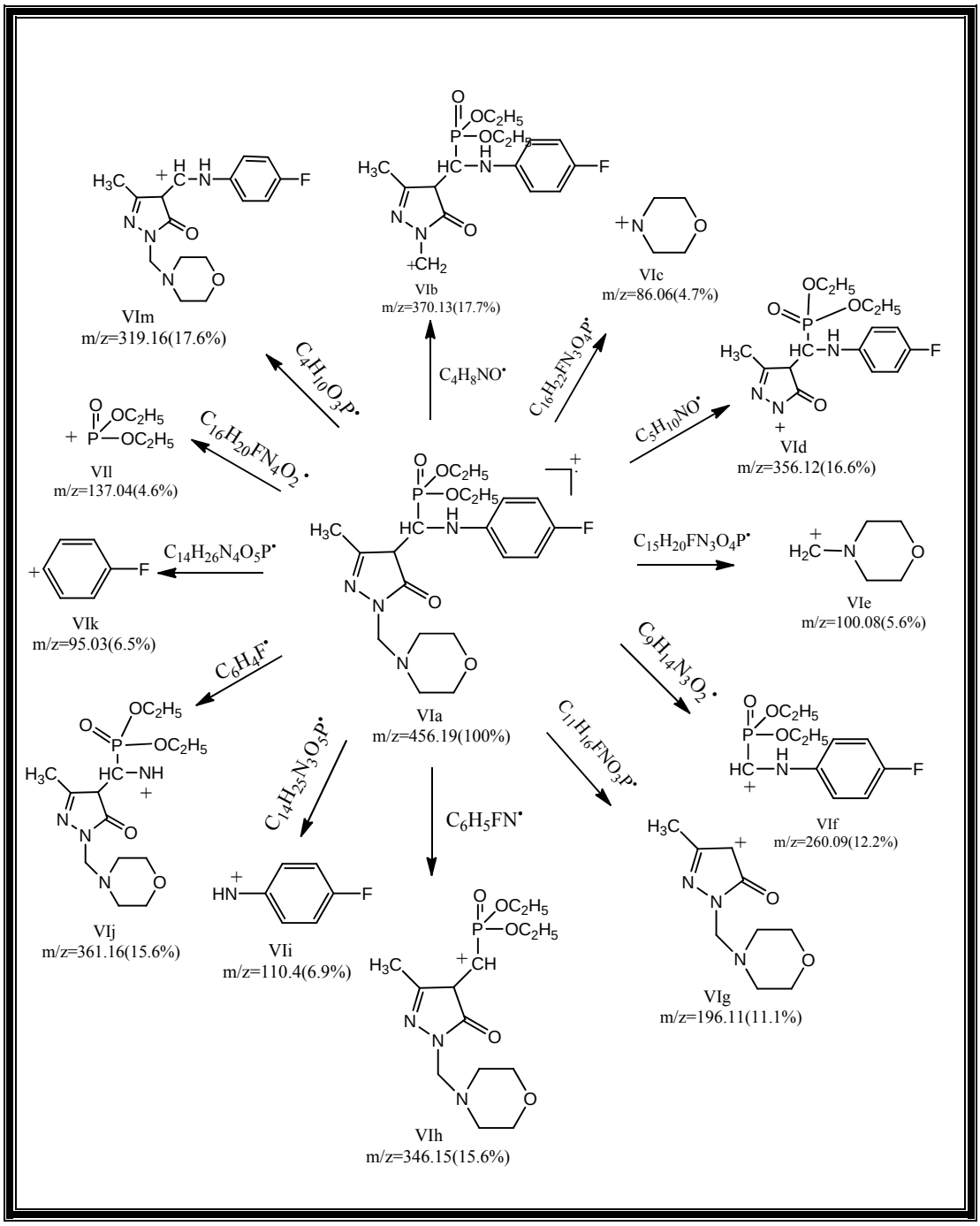


Chart-VI.2. Mass Spectrum of Primary Fragmentation Fragmentation process of Diethyl (((4-fluorophenyl) amino) (3-methyl-1-(morpholinomethyl) -5- oxo -4, 5 – dihydro -1H- pyrazol-4-yl) methyl) phosphonates (6a).

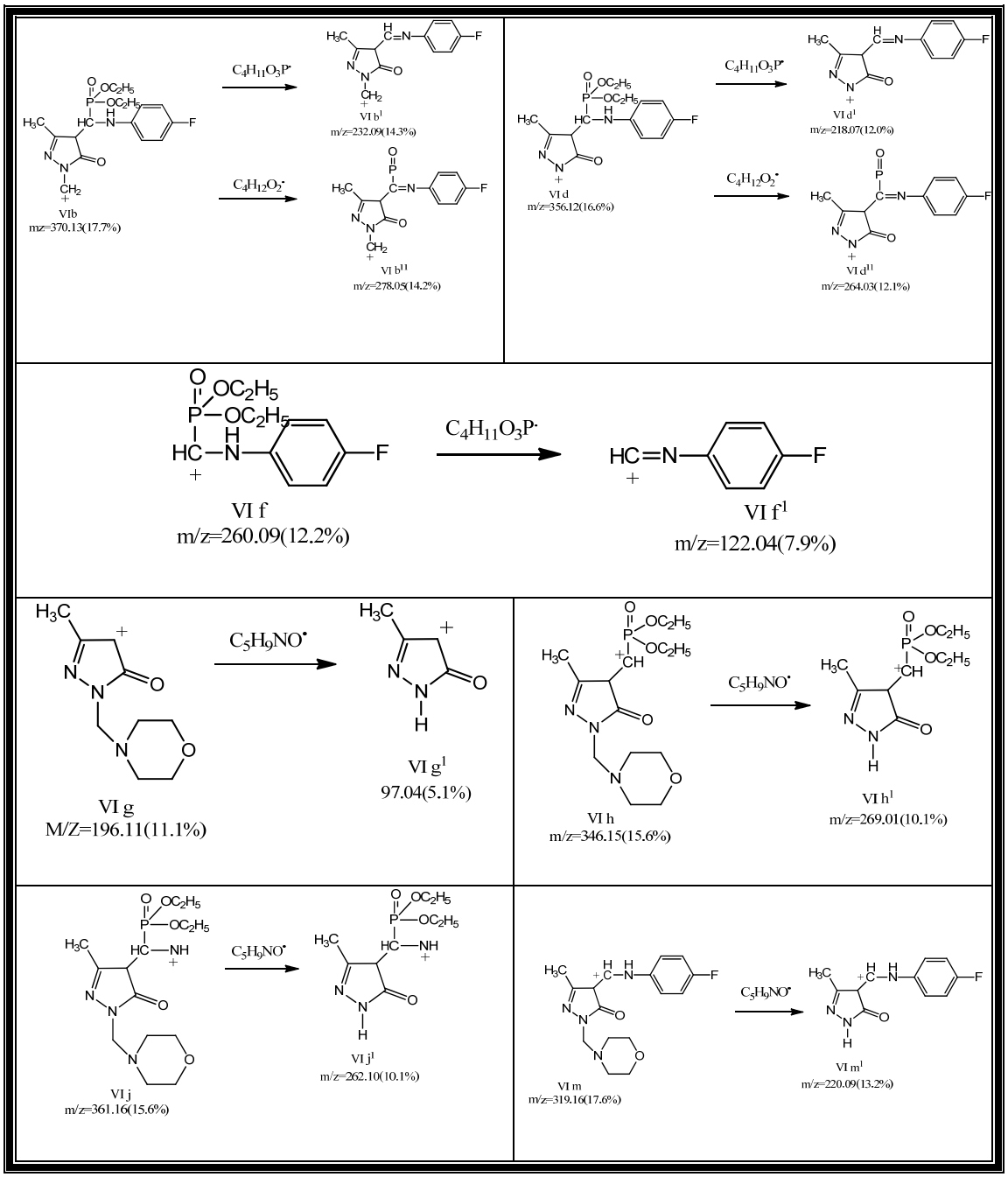


Chart-VI.3. Mass Spectrum of Secondary fragmented ions of Diethyl (((4-fluorophenyl) amino) (3-methyl-1- (morpholinomethyl) – 5 – oxo - 4, 5 – dihydro - 1H – pyrazol – 4 - yl) methyl) phosphonates (6a).

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