Synthesis of substituted 2-(1, 3-diphenyl-1H-pyrazol-4-yl)-
1H-benzo[d] imidazoles, benzo[d]thiazoles, malononitriles,
O,O-diethyl,O-(1,3-diphenyl-1H-pyrazol-4-yl)methyl
phosphorothioates
PART-III
3.1. Section A.:
Synthesis of substituted 2-(1, 3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazoles

3.1.1. Introduction:
Heterocyclic compounds possessing two hetero atoms in a ring are of immense biological importance in clinical research field. Some of the naturally occurring heterocycles play an important role in metabolism of all living cells e.g. the essential amino acids like proline, histidine; purine and pyrimidine bases of the genetic material DNA, the vitamins and coenzymes and many other natural products. Among such heterocycles of importance, azoles have occupied a distinct place in medicinal chemistry. Particularly, azoles like pyrazole and imidazole are at centre point as antifungal and anti-microbial activities.

An important azole i.e. benzimidazole have also been studied in detail since last one decade. Benzimidazole is a bicyclic aromatic imidazole system, in which a benzene ring is fused to the 4 and 5- position of imidazole ring [1]. The interest in benzimidazole as chemotherapeutic agent was realized when in 1950 it was found that 5, 6- dimethyl-1-(α-D-ribofuranosyl) benzimidazole was an integral part of the structure of Vitamin B$_{12}$. Benzimidazole compounds have a wide range of biological activities, ranging from widely used human and veterinary anthelmintic [2, 3] to anticancer properties [4]. Several reviews appeared in literature which discusses an array of biological properties of benzimidazole nucleus [5-8]. Along with this, benzimidazole derivatives with different pharmacological properties such as, anti ulcer [9-11], cardiotonic [12], antihypertensive [13] etc., have already been reported.

In literature it was revealed that the substitution at 1, 2, and 5 positions of benzimidazole nucleus is crucial point whereby it can exhibit wide range of pharmacological activities.
A wide range of benzimidazole derivatives found applications in pharmaceutical and veterinary fields. The structures of important benzimidazole derivatives available are shown. (Fig.1)
3.1.2. Common methods for the synthesis of benzimidazoles

Several methods are described in literature for synthesis of benzimidazoles. Wright and Hoffmann reviewed the chemistry of benzimidazoles [14-18].

3.1.2.1. From o-Phenylenediamine

One of the most general and simple method in benzimidazole synthesis is the condensation of o-phenylenediamine with carbonyl compounds [19]. These carbonyl compounds include carboxylic acids and its derivatives like nitriles, amidates and orthoesters.

a) By reaction with carboxylic acid and its derivatives

2-substituted benzimidazoles can be prepared in good yields by the condensation of o-phenylenediamine with carboxylic acids, although, there is necessity of strong acidic conditions and elevated temperature [20]. (Scheme 3.01)

Scheme 3.01

The most prominent method for the synthesis of 2-alkylbenzimidazoles was developed by Phillips [21]. In the Phillips condition, equimolar quantities of the diamine and aliphatic acid refluxed for 3-4 hrs in 4 N HCl. (Scheme 3.02)
Scheme 3.02

Under Phillips condition, aromatic carboxylic acids couldn’t realize the benzimidazoles, hence alternate strategy of using dehydrating agents like polyphosphoric acid (PPA), P$_2$O$_5$ or polyphosphate ester (PPE) was developed [22-26]. (Scheme 3.03)

![Scheme 3.03](image)

Scheme 3.03

In a modified approach, o-phenylenediamine hydrochloride was used for the first time [27]. By this method; corresponding benzimidazole was obtained by condensation of equimolar amount of o-phenylenediamine hydrochloride and ethyl formate in a sealed tube at 225°C for 3h. (Scheme 3.04)

![Scheme 3.04](image)

Scheme 3.04

Niementowski obtained 2- substituted 5-methyl benzimidazole and 2-substituted 6-methylbenzimidazole by heating free base with the corresponding amides [28]. (Scheme 3.05)

![Scheme 3.05](image)

Scheme 3.05

b) By reaction with Imidates (imino-ethers)

In this process o-phenylenediamine on treating with imino-ethers in dilute acidic condition furnishes with benzimidazole with good isolated yields [29]. (Scheme 3.06)

![Scheme 3.06](image)
c) Reaction with carbonyl compounds

i) Reaction with aldehydes

Weidenhagen’s method is extensively used for the preparation of 2- aryl/ alkyl substituted benzimidazoles. Various 2- substituted benzimidazoles were synthesized by condensation of diamine with different substituted alkyl or aryl aldehydes in the presence of oxidizing agents like cupric acetate (Weidenhagen procedure) [30], mercuric oxide [31], chloronil [32], lead tetraacetate [33], manganese oxide[34], nitrobenzene [35], polyphosphoric acid [36], nickle peroxide [37], sodium bisulfite [38], CAN [39], CAN/ H₂O₂ [40] (Scheme 3.07)

Scheme 3.07

ii) By reaction with ketones

The reaction of o-phenylenediamine with ketones in the presence of HCl at 250-300°C can yield benzimidazoles by the aromatization of intermediate benzimidazoline; their use has been rather limited due to formation of mixture of products after dehydrogenation [41-42]. (Scheme 3.08)

Scheme 3.08
d) By reaction with Nitriles

The reaction of nitriles with arylenediamine at 200-250\(^\circ\)C in the presence of HCl or by using the hydrochloride of diamine could afford 2-substituted benzimidazoles [43]. (Scheme 3.09)

![Reaction Scheme 3.09](attachment:reaction_scheme_3.09.png)

**Scheme 3.09**

3.1.2.2. From o-(N-acylamino and N-aroylamino) arylamines and Nitroarenes

The conversion of o-(N-acylamino and N-aroylamino) arylamines to benzimidazole has been discussed in literature. The method is not so much attractive from synthetic point of view. Another protocol of using nitroarenes requires reduction of nitro group by using one of many possible reagents (e.g., zinc, Iron, tin (II) chloride, H\(_2\)/ Pd/C or Raney Ni) [44]. In second step ring closure performed with aldehydes or carboxylic acids. (Scheme 3.10)

![Reaction Scheme 3.10](attachment:reaction_scheme_3.10.png)

**Scheme 3.10**
3.1.2.3. From o-nitroarylamines and o-dinitroarenes

Single step synthesis of benzimidazoles can be achieved by reduction of nitro compounds with reducing agents such as NaHSO$_3$ [45], BaSO$_4$/Pd/H$_2$ [46], Zn [47], Na$_2$S$_2$O$_4$, Na$_2$SO$_3$. [48] (Scheme 3.11)

Scheme 3.11

3.1.2.4. From Amidines

Preparation of benzimidazoles from N-aryl-N’-hydroxylamidines and benzene sulphonyl chloride in pyridine or TEA in good yields have been achieved. [49] (Scheme 3.12)

Scheme 3.12

3.1.3. Present work

Taking into account the importance of benzimidazole, we have decided to synthesize benzimidazole derivatives of pyrazole and investigate their antimicrobial activities. This section describes synthesis of 2-(1,3-diphenyl-1$_H$-pyrazol-4-yl)-1$_H$-benzo[d]imidazoles (17a-h) under Phillips condition by condensation of substituted 4-formyl pyrazoles (15a-h) with o-phenylenediamine in 2$_N$ HCl.

(15a-h) + (16) → (17a-h)
3.1.4. Experimental:

Synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole (17a)

The mixture of an aldehyde 15a (0.5 gm, 0.002 mol) and 1, 2-phenylenediamine 16 (0.22 gm, 0.002 mol) in 2N HCl (5ml) was refluxed at 110°C for 5-6h and was monitored by using TLC. After completion of reaction, the reaction mass was cooled to room temperature and then to 5-10°C, stirred for 15-20 min. The solid material filtered through buchner funnel and washed with chilled toluene. The solid obtained was triturated by diethyl ether, filtered and dried.

The derivatives of the substituted 4-formyl pyrazoles were synthesized according to the above representative procedure.

Table VIII. Physical data of the compounds 17(a-h).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>M. P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td></td>
<td>84</td>
<td>178-180</td>
</tr>
<tr>
<td>17b</td>
<td>H3C</td>
<td>78</td>
<td>184-176</td>
</tr>
<tr>
<td>17c</td>
<td>O2N</td>
<td>60</td>
<td>190-192</td>
</tr>
<tr>
<td>17d</td>
<td>F</td>
<td>68</td>
<td>164-166</td>
</tr>
<tr>
<td>17e</td>
<td>Br</td>
<td>69</td>
<td>170-172</td>
</tr>
<tr>
<td>17f</td>
<td>Cl</td>
<td>63</td>
<td>158-160</td>
</tr>
<tr>
<td>17g</td>
<td>H3CO</td>
<td>71</td>
<td>180-182</td>
</tr>
<tr>
<td>17h</td>
<td></td>
<td>75</td>
<td>168-170</td>
</tr>
</tbody>
</table>
3.1.5. Spectral analysis:

![Chemical Structure](image)

**H\textsuperscript{1}NMR:** \textsuperscript{1}H NMR spectra were recorded in DMSO-d\textsubscript{6} on a Varian AS 400 MHz spectrometer TMS as an internal standard.

Comp. (17a): δ ppm 6.87 (d, J = 3.2 Hz, 1H); 6.97 (d, J = 4.4 Hz, 1H); 7.1 (d, J = 8 Hz, 2H); 7.24 (m, 2H); 7.45 (d, J = 10.4 Hz, 4H); 7.48-7.66 (m, 3H); 7.81 (t, 1H); 7.95 (s, 1H, pyrazole proton)

**I.R.:** IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

Comp. (17a): (KBr disc) cm\textsuperscript{-1}: 3316 (NH), 1599 (C=N), 1509.

**Mass:** Mass spectra were recorded on Water-Macromass Quattro-II mass spectrometer.

Comp. (3a): Mass (m/z) 337.2 (M+1)
$^1$H NMR (Comp. 17a).

I. R. (Comp. 17a)
Mass (Comp. 17a)
3.1.6. References:

20. Ladenburg, A. Ber. 1875, 8, 677.
PART-III
3.2. Section B.:

Synthesis of substituted 2-(1, 3-diphenyl-1H-pyrazol-4-yl) benzo[d]thiazoles

3.2.1. Introduction:
Among various known heterocyclic systems, benzothiazole is one of the privileged structures. Heterocycles containing the thiazole moiety are present in many natural as well as synthetic products. Natural products that contain thiazole as a part includes bleomycin, epothilone A, lyngbyabellin A and dolastin [1]. Also, the benzothiazole ring is present in various marine and terrestrial natural compounds, which have useful biological importance. In case of synthetic products, a large number of therapeutic agents are synthesized with the help of benzothiazole nucleus. The small and simple benzothiazole is present in synthetic molecules which aimed at evaluating new products that possess interesting biological activities like antitumor [2-5], antimicrobial [6-8], antitubercular [10], anticonvulsant [11, 12], antihelminthic [13], analgesic and anti-inflammatory activity [14, 15].

During recent years there have been some major developments in the biological activities of benzothiazole derivatives, since these compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. Due to important utilities of these compounds, the synthesis and evaluation of therapeutic activities is of considerable interest.

Some of the benzothiazole derivatives which are used now days are shown below in Fig. 1.

![Fig.1: Benzothiazole derivatives as therapeutic agents available in market.](image-url)
3.2.2. Synthetic routes to benzothiazole rings:

2-arylbenzothiazoles are most commonly synthesized via one of the two major routes. By analogy to the synthesis of benzoxazoles and benzimidazoles; benzothiazoles are obtained by cyclocondensation of o-aminothiophenols or their salts with carboxylic acids, their derivatives or with aldehydes. The method involves the condensation of ortho aminothiophenols with substituted aldehydes, carboxylic acids, acyl chlorides, esters and nitriles [16]. Another route called Jacobsen’s method is based on oxidative cyclization of thiobenzanilides or N-arylthioamides by potassium ferricyanide in sodium hydroxide [17].

Rosini and Medici [18] have achieved the synthesis of benzothiazole derivatives by cyclization of o-(Methylthio)-anilides with phosphodinitrile dichloride. (Scheme 3.13)

![Scheme 3.13](image)

R. H. Tale [19] developed a new protocol using ceric ammonium nitrate. The oxidative coupling of thiophenols and aromatic nitriles leads to free radical formation which on cyclization yields wide range of 2-arylbenzothiazoles. (Scheme 3.14)

![Scheme 3.14](image)

Ranu and co-workers [20] described the synthesis of benzothiazole derivatives from inexpensive ionic liquid, 1-pentyl-3-methylimidazolium bromide ([pmIm]-Br) by microwave irradiation under solvent and catalyst free condition. (Scheme 3.15)

![Scheme 3.15](image)
Edward R. Biehl [21] and co-workers reported an important method in which microwave heating the aromatic and aliphatic \( \beta \)-ketoesters and o-aminothiophenols proceeds smoothly to benzothiazole derivatives. (Scheme 3.16)

\[
\begin{align*}
\text{NH}_2 \quad \text{SH} & \quad \text{Heat} \\
\begin{array}{c}
\text{O} \\
\text{Et}
\end{array} & \quad \text{MW, 240°C} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Scheme 3.16

D. Subhash Bose and Mohd. Idrees [22] reported a novel method for preparation of 2-substituted benzothiazoles using iodine reagent Dess-Martin periodinane in DCM from thiobenzanilides via intramolecular cyclization. (Scheme 3.17)

\[
\begin{align*}
\text{NH} & \quad \text{S} \\
\text{R} & \quad \text{DMP, CH}_2\text{Cl}_2 \\
\text{RT} & \quad \text{RT}
\end{align*}
\]

Scheme 3.17

A series of benzothiazoles were synthesized from the reaction of o-substituted thiophenols with orthoesters in the presence of catalytic amounts of Bi (III) salts under solvent free conditions [23]. (Scheme 3.18)

\[
\begin{align*}
\text{NH}_2 \quad \text{SH} & \quad \text{Bi(III)salts} \\
\begin{array}{c}
\text{R'} \quad \text{OCH}_2\text{CH}_2\text{CH}_3
\end{array} & \quad \text{R'}
\end{align*}
\]

Scheme 3.18

A convenient and clean “on water” mediated synthesis of benzothiazoles/benzothiazolines is reported by Chakraborti et al. [24] as Green protocol in benzothiazole synthesis. (Scheme 3.19)

\[
\begin{align*}
\text{NH}_2 \quad \text{SH} & \quad \text{H}_2\text{O} \\
\begin{array}{c}
\text{Ar}
\end{array} & \quad \text{Ar}
\end{align*}
\]

Scheme 3.19

The condensation of o-aminothiophenol and carboxylic acid in ionic liquid 1-butyl 3-methyl imidazolium tetrafluoroborate [(bmim)BF_4] at elevated temperature was described by Chandramouli and co-workers [25]. (Scheme 3.20)
Scheme 3.20

2-substituted benzothiazole and benzoxazole in presence of CAN/ H₂O₂ was developed by Bahrami et al. [26] under solvent-free conditions. (Scheme 3.21)

Scheme 3.21

In an attempt to synthesize fluorescent compounds, Raposo et al. [27] reported 2-(2”, 2”-bithienyl)-1, 3-benzothiazoles as novel molecules using oxidizing property of DMSO. (Scheme 3.22)

Scheme 3.22

In an attempt to explore the use of enzymatic system, the Baker’s yeast was used to carry out this synthesis [28].

Scheme 3.23

3.2.3. Present work:

Due to the important biological properties associated with pyrazole and benzothiazole, we thought it worthwhile to combine these two moieties in a single molecule to synthesize pyrazolo-benzothiazole molecule.

This section describes synthesis of 2-(1, 3-diphenyl-1H-pyrazol-4-yl) benzo[d]thiazoles (19a-h) by condensation of substituted 4-formyl pyrazoles (15a-h) and o-aminothiophenol (18) in DMSO as oxidant.
3.2.4. Experimental:

Synthesis of 2-(1, 3-diphenyl-1H-pyrazol-4-yl) benzo[d]thiazole (19a)

The mixture of 4-formyl pyrazole 15a (0.5gm, 0.002mol) and o-aminobenzenethiol 18 (0.25gm, 0.002mol) was heated in DMSO (5ml) at 120°C for 30 min. and the reaction was monitored by TLC. After completion of the reaction, it was cooled to room temperature and poured into water and extracted with ethyl acetate. The organic layer was dried with magnesium sulphate and evaporated under vacuum. The crude compound was crystallized from acetonitrile to furnish the pure compound.

Table IX. Physical data of the compounds 19(a-j)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>M. P. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>19a</td>
<td></td>
<td>75</td>
<td>190-192</td>
</tr>
<tr>
<td>19b</td>
<td>H3C</td>
<td>70</td>
<td>158-160</td>
</tr>
<tr>
<td>19c</td>
<td>O2N</td>
<td>54</td>
<td>178-180</td>
</tr>
<tr>
<td>19d</td>
<td>F</td>
<td>64</td>
<td>160-162</td>
</tr>
<tr>
<td>19e</td>
<td>Br</td>
<td>74</td>
<td>154-156</td>
</tr>
<tr>
<td>19f</td>
<td>Cl</td>
<td>59</td>
<td>184-186</td>
</tr>
<tr>
<td>19g</td>
<td>H3CO</td>
<td>58</td>
<td>188-190</td>
</tr>
<tr>
<td>19h</td>
<td></td>
<td>74</td>
<td>171-174</td>
</tr>
</tbody>
</table>
3.2.5. Spectral analysis:

![Chemical structure](image)

**H$^1$NMR:** $^1$H NMR spectra were recorded in CDCl$_3$ on a Varian AS 400 MHz instrument using TMS as an internal standard.

Comp. (19a): $\delta$ ppm 7.34 - 7.38 (dd, $J= 8$ & 7.2 Hz, 2H); 7.45 - 7.52 (m, 6H); 7.75 - 7.79 (dd, $J= 1.2$ & 6 Hz, 3H); 7.84 (d, $J= 8.4$ Hz, 2H); 8.0 (d, $J= 8$ Hz, 1H); 8.7 (s, 1H, pyrazole proton)

**I.R.:** IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

Comp. (3a): (KBr disc) cm$^{-1}$: 1618 (aromatic ring); 1595 (C=N).

**Mass:** Mass spectra were recorded on Water-Macromass Quattro-II mass spectrometer.

Comp. (3a): Mass (m/z) 354.2 (M+1)
$^1$H NMR (Comp. 19a)

I. R. (Comp. 19a)
Mass (Comp. 19a)
3.2.6. References:


PART-III
3.3. Section C.:
Synthesis of 2-((1, 3-diphenyl-1H-pyrazol-4-yl) methylene) malononitriles

3.3.1. Introduction:
The condensation of aldehydes or ketones, usually possessing $\alpha$-hydrogen, with compounds of the form $Z$-$CH_2$-$Z'$ or $Z$-$CH_2$-$Z$ where $Z$ and $Z'$ are electron withdrawing groups is called the Knoevenagel reaction [1]. Knoevenagel condensation is a classic reaction in organic synthesis [2], for its significant synthetic utility in C-C bond formation reactions, which is pivotal in organic chemistry [3]. Knoevenagel condensation has numerous applications in the elegant synthesis of the fine chemicals, speciality chemicals drugs, dyes etc. [4].

3.3.2. Synthetic methods in Knoevenagel condensation:
Knoevenagel condensation is base catalyzed reaction and sometimes reported in acid catalysis. In literature, the most of the synthetic protocols are being described in basic catalysts and organic/ aqueous medium. Various catalysts are known to effect the knoevenagel condensation reactions using NaOH, KOH, AlPO$_4$-Al$_2$O$_3$ [5], BiCl$_3$ [6], ZnCl$_2$ [7] etc. Several other methods include P$_2$O$_5$-piperidine [8-9], modified hydrotalcite [10], KF-Al$_2$O$_3$ [11], graphite [12], IR irradiation [13] and solvent free reactions using mechanochemical grinding, ball milling, MWI and ultrasound sonication irradiation.

One of the important catalyst in Knoevenagel condensation is 1, 8 Diazabicyclo (5, 4, 0) undecene-7 or DBU. DBU is a bicyclic amine which is a clear light yellow liquid of relatively low volatility. DBU has been widely used as a catalyst in many reactions such as Michael addition reaction of $\beta$-ketoesters to acrylates and enones [14], conjugate addition of acylsilanes to unsaturated esters and ketones [15], for intramolecular aldehyde-ketone benzoin reactions [16] and in combination with other catalysts for oxidation of aldehydes to methyl esters [17].

Mechanochemical grinding and ball milling are useful tools in organic synthesis that allows a highly efficient mixing of reagents under solvent free conditions [18, 19]. In organic chemistry it found numerous applications including C-C bond formations [20], amine condensations, in syntheses of heterocycles [21] and fullerene
modifications [22]. In grinding, efficient mixing is particularly important in solid-solid reactions which continuously develop fresh contacts between the reacting components. Grinding and ball milling, in particular, milling generates new contact sites between the solids more efficiently. Due to high reagent concentrations and the efficient mixing, the reactions between solids with intermediate local melting and those with at least one liquid reagent gets benefited from such techniques. In chemical synthesis, these tools modify the reaction conditions and enhance the reactivity of the reagents (mechanical activation). This is due to induced mechanical breaking of molecular bonds (mechanochemistry) and efficient mixing and the enormous increase of the reagent surfaces which both lead to a close contact between starting components on an almost molecular scale. Besides this, the factors like temperature and pressure have a significant role for such change in reactivities of the components. For example, during the milling, extreme conditions occur on the surfaces of two colliding bodies for times in the order of microseconds. According to a model developed by Urakaev and Boldyrev, local temperatures of 400-1500 K and pressures of thousand atmospheres can be part of typical conditions in the ball mill [23].

3.3.3. Background of the work:
Condensation reactions of aldehydes with active methylene compounds in organic chemistry are well explored and thoroughly studied but in pyrazole chemistry the reaction is not exploited as such. In case of pyrazole, 4-formyl pyrazole was condensed with few active methylene compounds.
Hangarge et al. [24] have carried out the reaction of 4-formyl pyrazoles with 3-methyl-1-phenyl pyrazolin-5-(4H)-one in Dioxane by using basic hydrotalcite at room temperature. (Scheme 3.24)

Scheme 3.24
Shindalkar and co-workers [25] reported the same reaction using heterogeneous borate-zirconia catalyst. (Scheme 3.25)

![Scheme 3.25](image)

Shingare et al. [26] have reported the Knoevenagel condensation of 4-formyl pyrazoles with 1, 2-dihydro-3-methyl-1-phenylpyrazol-5-one. (Scheme 3.26)

![Scheme 3.26](image)

DBU catalyzed Knoevenagel condensation has been described by Ware and co-workers [27] by reacting aromatic aldehydes and active methylene compounds like cyano ethylacetate, cyanoacetamide and malononitrile. (Scheme 3.27)

![Scheme 3.27](image)

A range of novel pyrazole derivatives has been prepared in moderate to good yield from substituted formyl pyrazole by Knoevenagel condensation with acylglycine, benzamidine hydrochloride, malononitrile and azidoacetate giving different products shown below. [28] (Scheme 3.28)
3.3.4. Present work:
Though in literature the reaction was studied in case of pyrazole aldehyde, the scope of the reaction is not explored and only two derivatives were synthesized by Knoevenagel condensation of 4-formyl pyrazole with malononitrile. In present work, condensation of various 4-formyl pyrazoles with malononitrile is carried out by Knoevenagel condensation by DBU catalyst by mechanochemical grinding.
3.3.5. Experimental:

Synthesis of the 2-((1, 3-diphenyl-1H-pyrazol-4-yl) methylene) malononitrile (21a)

To a mixture of 4-formyl pyrazole 15a (0.5gm, 0.002mol) and malononitrile 20 (0.132gm 0.002mol) was added DBU (mol) as catalyst in mortar. Following this, it was grounded by pestle till the completion of reaction (checked by TLC after 5 min.). The whole reaction mixture then transferred into water to separate out the product. The compound was filtered, dried and crystallized using alcohol.

Other derivatives of the series were synthesized by the above representative procedure and yield and physical constant of compounds were recorded as in Table X.

Table X: Physical data of the compounds. 21(a-j)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>M. P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21a</td>
<td><img src="image" alt="Ar" /></td>
<td>86</td>
<td>190-192</td>
</tr>
<tr>
<td>21b</td>
<td><img src="image" alt="Ar" /></td>
<td>88</td>
<td>178-180</td>
</tr>
<tr>
<td>21c</td>
<td><img src="image" alt="Ar" /></td>
<td>70</td>
<td>202-204</td>
</tr>
<tr>
<td>21d</td>
<td><img src="image" alt="Ar" /></td>
<td>78</td>
<td>194-196</td>
</tr>
<tr>
<td>21e</td>
<td><img src="image" alt="Ar" /></td>
<td>82</td>
<td>172-174</td>
</tr>
<tr>
<td>21f</td>
<td><img src="image" alt="Ar" /></td>
<td>80</td>
<td>188-190</td>
</tr>
<tr>
<td>21g</td>
<td><img src="image" alt="Ar" /></td>
<td>75</td>
<td>198-200</td>
</tr>
<tr>
<td>21h</td>
<td><img src="image" alt="Ar" /></td>
<td>90</td>
<td>182-184</td>
</tr>
</tbody>
</table>
3.3.6. Spectral analysis:

![Chemical Structure](image)

**H¹ NMR:** H¹ NMR spectra were recorded in DMSO-d₆ on Varian AS 400 MHz instrument using TMS as an internal standard.

Comp. (21a): δ ppm 7.48-7.68 (m, 8H, aromatic protons); 7.92 (s, 2H, aromatic protons); 8.2 (s, 1H, pyrazole proton); 9.2 (s, 1H, methine proton)

**I.R.:** IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer. Comp. (21a): cm⁻¹ 3035, 2225 (C=N), 2189 (C=N), 1593 (C=N), 1528 (C=C).
H\textsuperscript{1} NMR (Comp. 21a)

I. R. (Comp. 21a)
3.3.7. References:


27. Ware, N. M. Ph. D. Thesis, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, 2007.

3.4. Section D:

Synthesis of substituted O, O-diethyl O-(1, 3-diphenyl-1H-pyrazol-4-yl) methyl phosphorothioates

3.4.1. Introduction:

Pyrazole chemistry has been the focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives appearing as antimicrobial, antiviral, antitumor, anti-inflammatory, antihistaminic, anticoagulant, antidepressant agents [1-7].

On the hand in agrochemistry, organophosphorous compounds comprising phosphates, dithiophosphates and phosphorothioates are used as pesticidal agents [8-13]. The biodegradable nature of these compounds makes them more preferable and safe alternative in comparison with DDT, BHC etc. Synthetic pesticides and nematicides which are phosphorous derivatives are getting importance due to environmental concern and their biodegradable nature.

Phosphorothioates have a broad spectrum of applications such as industrial, agricultural and in medicinal chemistry due to their biological and physical properties as well as their synthetic utility [13]. These phosphorothioates have been prepared as pesticides and thio-analogues of biologically active phosphoric diesters [14]. Some of the derivatives of phosphorothioates have introduced as potential chemotherapeutic agents [15] and inhibitor of different enzymes [16].

In a study, one of major pest of crops Helicoverpa armigera in Indian subcontinent which accounts for loss of US $ 300-500 million per annum to cotton and pulses alone [17], was found to be active against the commercially available pesticides. Cypermethrin, Fenvalerate, Endosulfan, Quinalphos and some methomyl insecticides rapidly losing battle against the pest, however, the pest is still susceptible to Monocrotophos- a phosphorothioate derivative [18-19].

Apart from agricultural chemistry, in medicinal chemistry many phosphonic acids and derivatives thereof have been also shown to exhibit important biological properties including antibiotic, antileukemic depending on the nature of substituent on the phosphonic group [20-21].

Some of the commercially used phosphorothioates have been listed in Fig.1.
Fig.1: Commercially useful phosphorothioates.

In literature, phosphorothioates have been prepared by the reaction of dialkyl phosphates with sulfonyl chlorides [22], sulfonyl cyanides [23], thiosulphonates [24], disulfides [25] and sulfur [26]. Also condensation of phosphorochlorothioates with thiols [27] is a method of choice.

3.4.2. Background of the work:
Literature survey revealed that attempts were made to couple piperidinyl, pyrazolyl and quinolyl compounds and phosphochlorothioates and evaluate their biological activities.
N. S. Joshi [28] synthesized various O, O- diethyl O-[2-(1H-pyrazole-4-carbonyl)-Phenyl] phosphorothioate from substituted 2-hydroxy phenyl-(1H-pyrazol-4-yl)-methanone and phosphochlorothioate with sodium metal in dry THF. (Scheme 3.29)
In another report, same author reported [29] the condensation of 1-(6-hydroxyphenyl)-3-piperidino-2-propen-1-one with O, O-diethyl phosphochlorothioate to produce O,O-diethyl O-[1-(6-hydroxyphenyl)-3-piperidino-2-propen-1-one] phosphorothioate. (Scheme 3.30)

![Scheme 3.30](image)

Pokalwar et al. [30] have synthesized some of the phosphorothioate derivatives of (2-chloroquinolin-3-yl) methanol with phosphorochlorothioate in NaOH and acetone. (Scheme 3.31)

![Scheme 3.31](image)

3.4.3. Present work:
This section includes synthesis of different substituted O, O-diethyl O-(1, 3-diphenyl-1H-pyrazol-4-yl) methyl phosphorothioates (24a-f) from (1, 3-diphenyl-1H-pyrazol-4-yl) methanol (22a-f) and O, O-diethyl chlorothiophosphate (23) in presence of sodium hydroxide and acetone.

![Scheme 3.31](image)
3.4.4. Experimental:

Synthesis of O, O-diethyl O-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methyl phosphorothioate (24c)

In a round bottom flask, (3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methanol 22c (0.5gm, 0.0017mol) in acetone was taken. To this solution, crushed pellets of NaOH (0.135gm, 0.0034mol) were added and stirred. After 15 min., O, O-diethyl thiochlorophosphate 23 (0.32gm, 0.0017mol) was added in it. On completion of reaction (checked by TLC), the solvent was evaporated under reduced pressure to get the solid which was poured into water. The separated product was filtered, dried and crystallized from alcohol.

Table XI: Physical data of the compounds. (24a-f)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>R₁</th>
<th>Yield (%)</th>
<th>M. P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24a</td>
<td>H</td>
<td>H</td>
<td>73</td>
<td>------*</td>
</tr>
<tr>
<td>24b</td>
<td>CH₃</td>
<td>H</td>
<td>78</td>
<td>200-202</td>
</tr>
<tr>
<td>24c</td>
<td>NO₂</td>
<td>H</td>
<td>67</td>
<td>241-216</td>
</tr>
<tr>
<td>24d</td>
<td>F</td>
<td>H</td>
<td>70</td>
<td>194-196</td>
</tr>
<tr>
<td>24e</td>
<td>Br</td>
<td>H</td>
<td>82</td>
<td>------*</td>
</tr>
<tr>
<td>24f</td>
<td>OCH₃</td>
<td>H</td>
<td>80</td>
<td>210-212</td>
</tr>
</tbody>
</table>

* Colorless oily liquids.
3.4.5. Spectral analysis:

H\textsuperscript{1}NMR: H\textsuperscript{1}NMR spectra were recorded in CDCl\textsubscript{3} on a Varian AS instrument at 400 MHz using TMS as an internal standard.

Comp. (24c): 1.29 (t, 6H, methyl protons); 4.11 (q, 4H, methylene protons); 5.2 (s, 2H); 7.36 (t, $J=7.2$ Hz, 1H); 7.5 (t, $J=7.2$ Hz, 2H); 7.75 (d, $J=8.0$ Hz, 2H); 8.06 (d, $J=8.4$ Hz, 2H); 8.17 (s, 1H, pyrazole proton); 8.32 (d, $J=8.4$ Hz, 2H)

I.R.: IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

Comp. (24c) cm\textsuperscript{-1}: 1597 (C=N), 1528 (NO\textsubscript{2}), 1273 (O-P=S).

Mass: Mass spectra were recorded on Water-Macromass Quattro-II mass spectrometer.

Comp. (24c): Mass (m/z) 448.1 (M\textsuperscript{+})
H$^1$NMR (Comp. 24c)

I. R. (Comp. 24c)
Mass (Comp. 24c)
3.4.6. References:


8. Etom, M. In *Organophosphorous Pesticides, Organic and Biological Chemistry*, CRS Press, Elveland, **1974**.


