STUDIES ON THE SYNTHESIS AND CHEMICAL REACTIONS OF SOME MIXED AND NON - MIXED HETEROCYCLIC COMPOUNDS OF EXPECTED BIOLOGICAL ACTIVITY

BY

MAHMOUD EL-SHAHAT MOHAMED ZAKI ABOU EL-SHAHAT

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Approval Sheet

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CHEMISTRY OF EPOXIDES

BIOLOGICAL ASPECTS:

Oxiranes have physiological properties showing Carcinogenic (Alibaud, 1993; Chemla and Ferreira, 2002), Mutagenic (Bastlova et al., 1993) and Genotoxic (Zeba et al., 1993) effects. Oxiranes are more important in steroid, mammalian biosynthesis for cholesterol (Nelson et al., 1981), marine organisms (Gerwick et al., 1980) and Toxin for some species of fungi (Buchi et al., 1973)

NOMENCLATURE:

Three membered cyclic ethers are important as reactive intermediates in organic synthesis. These substances are often named individually as alkene oxide; collectively they are called oxiranes or epoxides (IUPAC) (Roberts and Caseiro, 1965).

\[
\begin{align*}
\text{Ethylene oxide (oxirane)} & : & \text{H}_2\text{C} = \text{CH}_2 \\
\text{Propylene oxide (2-methyloxirane)} & : & \text{H}_3\text{C} \text{CH} = \text{CH}_2 \\
\text{Styrene oxide (phenyloxirane)} & : & \text{C} = \text{CH}_2 \text{CH} = \text{C} = \text{CH}_2 \\
\text{Cis 2-butene oxide (2,3-dimethyloxirane)} & : & \text{H}_3\text{C} \text{CH} = \text{CH} = \text{CH}_2
\end{align*}
\]

SYNTHESIS OF EPOXIDES:

1- Epoxidation of olefin by oxidation:

Epoxide 1 was prepared stereo specifically by treatment of \(E\)-PhCOCH=CHPh with NaOCl (Hummelen and Wynberg, 1978) at room temperature, 72 hr.
Another oxidation system has been used; NaOCl- Al₂O₃ for the oxidation of the electron-poor enyne 2 (Hopf and Kreutzer, 1990; Chemla and Ferreira, 2002).

2- **Epoxidation of olefin by catalytic oxidation:**

1,3-cyclohexadiene upon treatment with aqueous copper dichloride and palladium dichloride solution gave 2-cyclohexen-1-ol and 2,3-epoxycyclohexen in a 7:2 ratio. The 2-hydroxy-3-cyclohexen-1-yl radical was formed and complexed with Cu²⁺ and epoxide formed when oxygen passed through the solution (Paraskewas et al., 1978). Oxidation of (Z)-disubstituted enynes 3 in presence of manganese (III) catalyst (Kuroki et al., 1995; Nagata et al., 1995) gives alkynyloxiranes in good to excellent yield but as trans/cis mixtures.
3- **Epoxidation of olefin by oxygen:**

Cvetanovic has extensively studied the direct formation of an epoxide from an olefin and oxygen in the gas phase (Cvetanovic, 1958). The mechanism of this reaction in liquid phase has been studied by Brill who showed that intermediate hydroperoxy species were involved and that 50% yields of epoxide were possible (Brill, 1963). Subsequently, Indictor and Brill have shown that t-butylhydroperoxide would work and that epoxidation is catalyzed by metal acetylacetonates (Indictor and Brill, 1965). Others have measured the rates of the oxygen reaction with cyclic olefins (Roch and Balaceanu, 1964), and it appears that the same types of intermediates seem to be involved in the pyrolysis of peroxides (Batt and Benson, 1962). Some of the mechanistic postulates of the previous workers have been supported for a recent isotopic carbon study of the reaction indicated that hydrogen atom shifts do occur in this reaction (white et al., 1965).

This type of method has been found to be especially effective for the synthesis of epoxides of the highly negatively substituted olefins, for it works well for the preparation of tetrafluoroethylene epoxides (Caglioti et al., 1964). In the latter either heat, ultraviolet light or ionizing radiation is effective in initiating the reaction. A similar type of reaction is the photosensitized oxidation of hydroxyl olefins of steroids with hematoporphyrin and oxygen to give an epoxide in stereospecific reaction (Nickon and Mendelson, 1963).

4- **Epoxidation of olefin by using hydrogen peroxide:**

Olefin oxides were prepared by the catalytic epoxidation of olefins at 0-120° by H₂O₂ with continuous removal of H₂O. Epoxide 4 were prepared by oxidizing R-CO-CH=CH-COOH by using hydrogen peroxide (El-Hashash and El-Kady, 1978).
5- **Epoxidation by using alkaline hydrogen peroxide:**

The vinyl chalcones 5 were epoxidized to the benzyl oxiranes 6 by treatment with H$_2$O$_2$ in 4N NaOH at 0°C (Roshke *et al.*, 1974).

![Chemical structure](image)

$$R = \text{Ph; } \text{C}_6\text{H}_4\text{.CH}_3(4); \text{C}_6\text{H}_4\text{.Cl}(4)$$

The α,β-unsaturated ketone react with H$_2$O$_2$ in alkaline media to give α-keto-oxiranes (Zwanenburg and Terwiel, 1970; Coffen and Korzan, 1971) which proceed through an intermediate α-carbonyl anion.

![Chemical mechanism](image)

6- **Epoxidation by using mixture of acetic acid and hydrogen peroxide:**

Unsaturated esters were epoxidized (Utkin and Ermakov, 1975) in AcOH/H$_2$O$_2$ in 1:3:1.5 ratios by heating in the presence of styrene divinyl benzene copolymer as catalyst.

7- **Epoxidation by using hydrogen peroxide and isocyanate:**
Epoxides may be obtained in reasonable yields under neutral conditions by treatment of alkenes with hydrogen peroxide and an aryl isocyanate (Matsumura et al., 1970). Best results were obtained when a non-polar solvent and 2:1 molar ratio of isocyanate to alkene were used.

\[
\begin{align*}
R\equiv R' & + 2R''\text{NCO} + \text{H}_2\text{O}_2 & \rightarrow & \text{O} \\
\ & \ & \ & R\equiv R' \\
\ & \ & \ & R''\text{NH}-\text{NH}-R''+\text{CO}_2
\end{align*}
\]

8- **Epoxidation by using hydrogen peroxide and polyleucine-catalysed:**

The epoxide may also be prepared by polyleucine-catalysed oxidation of enones (Pena and Roberts, 2003) in presences of \( \text{H}_2\text{O}_2 \).

9- **Epoxidation by metalated hydrogen peroxides:**

\( \alpha,\beta \)-Unsaturatedsulfoxides 7 (R'\( ^\prime \)=H) undergo nucleophilic epoxidation by treatment with metalated hydrogen peroxides with complete preservation of double bond geometry and with moderate to excellent facial selectivity to produce enantio- and diastereomerically pure \( \alpha,\beta \)-epoxy sulfoxides 8 (Ferandez de la pradilla et al., 1998).
10- **Epoxidation by tungstic acid:**

It was found that tungstic acid catalyst dispersed on apatite solid phase (H$_2$Wo$_4$/apatite) is effective as the environmentally benign solid catalyst for the epoxidation of alkenes and allylic alcohols with solid urea-hydrogen peroxide complex (Ichihara, 2001).

11- **Epoxidation by peracids:**

Epoxidation rates with per acids appear to be the same in almost every solvent (Schwartz and Blumbergs, 1964) thus suggest intramolecular hydrogen bonding (Suhara, 1964).

*a) By p-chloroperbenzoic acid:*

β,γ-Unsaturated ketones 9 react with p-chloroperbenzoic acid and gave the corresponding β,γ-epoxyketone 10 (Fujita et al., 1977).

\[
\begin{align*}
\text{CH}_3\text{O} & \text{CH}_2\text{CH}_3 \\
\text{R} & \text{Cl} \\
\text{H}_3\text{C} & \text{CO}_3\text{H} \\
9 & + \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{O} & \text{CH}_2\text{CH}_2 \\
\text{R} & \\
\text{H}_3\text{C} & \text{CO}_3\text{H} \\
10 & \\
\end{align*}
\]

R = n-C$_5$H$_{11}$; n-C$_6$H$_{13}$; (CH$_3$)$_2$CHCH$_2$
b) By *m*-chloroperbenzoic acid:

Oxidation of 2-vinylpyridine 11 with excess *m*-chloroperbenzoic acid in methylene chloride at reflux temperature afforded 2-epoxyethylene pyridine-1-oxide 12 (*Abraham et al.*, 1978).

\[
\text{Pyridine} + \text{MCPBA} \rightarrow \text{Epoxide} (60\%)
\]

\[
\text{11} \quad \text{12}
\]

c) By trifluoroperacetic acid:

Trifluoroperacetic acid used to oxidation of enetriyne 13 (*Jones et al.*, 1963).

\[
\text{Enetriyne} + \text{Trifluoroperacetic acid} \rightarrow \text{Epoxide}
\]

\[
\text{13}
\]

d) By *m*-chloroperoxybenzoate anion:

The *m*-chloroperoxybenzoate anion (generated from *m*-CPBA and bases such as K$_2$CO$_3$ or KOH) is a highly efficient nucleophilic epoxidating reagent for strongly deactivated olefins containing two electron-withdrawing groups at the same carbon, under mild condition which affect neither other double bonds nor electrophilic oxidizable centers such as sulfoxides (*Ruano et al.*, 2005).
12- **Epoxidation by dehydrohalogenation:**

Epoxide 14 prepared by dehydrohalogenation (pivawer, 1974) of 2,4,4,4-tetrachloro-1-butanol with aqueous NaOH in presence of an antioxidant (4-tetrbutyl catechol, NaHSO₃) to inhibit emulsion formation.

![Epoxidation by dehydrohalogenation](image)

13- **Epoxidation from α-halocarbonyl compounds:**

A special case of acetal formation in basic media is the well-known action of alcoholates on α-halocarbonyl compounds (Kohler and Addinall, 1930; Stevens and Weinheimer, 1958; Temnikova and Gontarev, 1964). According to the following equation the reaction proceeds through addition of a methoxy group to the carbonyl group followed by intramolecular alkylation to yield the alkoxy epoxide 15.

![Epoxidation from α-halocarbonyl compounds](image)

14- **Epoxidation from carbonyl compounds with Wittig Ylides:**

A large number of special reagents have been applied to the synthesis of epoxides:

a) **Antimony and Arsenic compounds**:

Wittig reagents (Henry and Wittig, 1960) react with an aldehyde or ketone to produce epoxide 16.
b) Sulfonium and oxosulfonium ylides:

Corey and Chaykovsky (Corey and Chaykovsky, 1962) were the first to use dimethyloxosulfonium methylidene 17 and dimethyl sulfonium methylidene 18 for synthesis of epoxides (Franzen and Driesen, 1963; Corey and Chaykovsky, 1965).

It was reported that oxoylide 17 reacted with 3-ketosteriod to form only the α-oxide (axial oxygen) 19 in 79% yield and the ylide react with
the same ketone to form only the $\beta$-oxide (equatorial oxygen) $20$ in 90% yield (Cook et al., 1965).

15- Epoxidation by decomposition reactions:

Early studies had suggested that the rate of thermal decomposition of di-$t$-butylperoxide was the same in the gas phase as in solution, and that the compound was insensitive to induced decomposition. However the accelerate decomposition of the pure liquid with the formation of 1,2-epoxy-2-methylpropane is attributable (Bell et al., 1950) to induced decomposition equation 3 and 4 involving the initially formed $t$-butoxy radicals equation 1 or methyl radicals formed by a fragmentation reaction equation 2.
16- **Epoxidation from carbenes:**

Singlet methylene is comparison to triplet methylene has been shown to add to acetone to give isobutylene oxide (Bradley and Ledwith, 1963). This fact readily explains why diphenylcarbene react with aldehydes to give the corresponding epoxide (Schonberg and Junghans, 1964).

\[
\begin{align*}
\text{H}_3\text{C} - \text{O} - \text{O} - \text{CH}_3 + 2\text{I} & \rightarrow 2\text{H}_3\text{C} - \text{O}. & \quad (1) \\
\text{H}_3\text{C} - \text{O}. & \rightarrow \text{H}_3\text{C} - \text{O} + \text{CH}_3 & \quad (2) \\
\text{H}_3\text{C} - \text{O} \text{ or } \text{CH}_3 + 2\text{I} & \rightarrow \text{H}_3\text{C} - \text{OH} \text{ or } \text{CH}_4 + \text{H}_3\text{C} - \text{O} - \text{O} - \text{CH}_3 & \quad (3) \\
\text{H}_3\text{C} - \text{O} - \text{O} - \text{CH}_3 & \rightarrow \text{H}_3\text{C} - \text{O} \text{ or } \text{CH}_3 + \text{H}_3\text{C} - \text{O}. & \quad (4)
\end{align*}
\]

17- **Epoxidation by nitric acid:**

The use of 90-100% nitric acid on tetra-(p-nitrophenyl) ethylene at 0°C gave the corresponding epoxide (Gorwin, 1963). This is the first
reported case of this type of epoxidation and it is undoubtedly due to the high electrophilicity of the double bond.

**18- Epoxidation by metal-catalyzed:**

Epoxidation of conjugated olefins observed to proceed through a radical intermediate that causes isomerization by rotation about the resulting carbon-carbon single bond so that acyclic conjugated olefins give a mixture of *Cis* and *Trans* epoxides (*Srinivasan et al.*, 1986; *Irie et al.*, 1990).

![Reaction diagram](image)

**19- Epoxidation by tetrakis(dimethylamino)ethylene:**

The reaction of 2,2-dibromomethyl quinoxaline 22 with aromatic aldehyde 23 in presence of TDAE. The reaction leads to a mixture of *Cis/*Trans-isomers of corresponding oxiranes 24 in good yields. The stereoselctivity of the reaction was sensitive to steric hindrance (*Montana et al.*, 2005).

![Reaction diagram](image)

The TDAE is reducing agent which reacts with halogenated derivative to generate an anion under mild condition *via* single electron
transfer (SET) (Giuglio-Tonolo et al., 2003; Giuglio-Tonolo et al., 2004).

20- **Epoxidation by ethyl chloroacetate:**

The reaction of mesityl oxide as an enone with ethyl chloroacetate using methoxide anion as catalyst gave oxirane derivative (Casagrande and Ferrari, 1966).

\[
\begin{align*}
\text{H}_3\text{C} & \text{C=CH} \text{O} + \text{H}_2\text{C} \text{COOEt} \\
& \xrightarrow{} \text{H}_3\text{C} \text{C=CH} \text{O} \text{COOEt}
\end{align*}
\]

21- **Microbial epoxidation:**

Long-chain terminal olefins were oxidized by Caryne-bacterium equivalent (IFO 3730) to give optically pure R- (+)-epoxides (Hiromich and Hatsuki, 1978). Thus 1-hexadecene 25 was incubated with C. equivalent for 48 hr. at 30, 41% of 100% optically pure R- (+)-1,2-epoxyhexadecane 26 was obtained.

\[
\begin{align*}
\text{n-C}_{14}\text{H}_{29} & \text{CH=CH}_2 \\
& \xrightarrow{} \text{n-C}_{14}\text{H}_{29} \text{O}
\end{align*}
\]
PHYSICAL PROPERTIES AND STRUCTURE:

The physical properties of oxiranes such as solubility, dipole moment and electrochemical properties are well known. The optical activity of chiral oxiranes has been investigated by abinitio molecular orbital (Rauk et al., 1981).

The geometry of oxirane has been determined by X-ray diffraction on crystalline natural products.

The strain in this system is mostly angle strain. The conventional ring strain energy of oxirane is 114 KJ mol\(^{-1}\) which can be compared with 115 KJ mol\(^{-1}\) for cyclopropane (Rosowsky, 1964).

The following figure shown the types of oxirane cleavage and reactions (Munavalli et al., 2002).
(1,2) Homolytic cleavages "free radical, photolytic, thermal".

(3) Electrophilic attack on ring oxygen.

(4) Nucleophilic attack on ring carbon.

(5) Nucleophilic attack on ring hydrogen.

(6) Reactions with electrons and surface reactions.

(7) Cycloadditions.

(8) Reactions of the substituents.
REACTIONS OF EPOXIDES:

1- Electrophilic attack on ring oxygen:
   
a) Protonation:
   The α,β-epoxycyclohexanone 27 is converted into 1,3- cycloheptanone 28 in the acidic medium (Hinoue et al., 1971).

\[
\text{O} \quad \text{O} \\
\text{Ph} \quad \text{H} \\
\text{H} \quad \text{Ph}
\]

\[
\text{H}^+ \quad \xrightarrow{\text{H}^-} \quad \text{H} \quad \text{Ph}
\]

\[
\text{O} \quad \text{O} \\
\text{Ph} \quad \text{H} \\
\text{H} \quad \text{Ph}
\]

\[
\rightarrow \quad \text{O} \quad \text{O} \\
\text{Ph} \quad \text{H} \\
\text{H} \quad \text{Ph}
\]

\[
\rightarrow \quad \text{O} \quad \text{O} \\
\text{Ph} \quad \text{H} \\
\text{H} \quad \text{Ph}
\]

\[
27 \quad 28
\]

b) Reaction with Lewis acids:
   The Lewis acids coordination complex of epoxides (Mclaughlin et al., 1960) does not appear to be stable above -80°C. Typical Lewis acid like BF\(_3\) and SbCl\(_5\) coordinates with oxirane 29 to give cyclic oxonium ion 30 which reacts with nucleophiles to give 31.

\[
\text{Cl} \quad \text{SbCl}_5 \quad \text{Et}_2\text{O} \quad \xrightarrow{\text{Cl}} \quad \text{Cl} \quad \text{OEt} \\
\text{O} \quad \text{Cl} \quad \text{Cl} \\
\text{O} \quad \text{Cl} \quad \text{Cl}
\]

\[
\text{O} \quad \text{SbCl}_4
\]

\[
\text{Cl} \quad \text{OEt}
\]

The cyclic ethers are very reactive towards Lewis acids. Ethylene and propylene oxides give ring opening with AsCl\(_3\) (Malinovskii, 1941), BF\(_3\), BCl\(_3\) (Edwards et al., 1955), SnCl\(_4\) (Worsfold and Eastham, 1957) and FeCl\(_3\) through SN2 mechanism.

\[
\text{O} \quad \text{Cl} \quad \text{OBCl}_2
\]

In general

\[
\text{C} \quad \text{C} \quad \text{M}_n \quad \xrightarrow{\text{X}} \quad \text{C} \quad \text{C} \quad \text{OMX}_{n+1}
\]
**c) Reaction with alkyl halides:**

Oxirane 32 reacts with methyl iodide to give 33 formed by electrophilic attack on oxygen by the electrophilic reagent followed by nucleophilic opening of the cyclic oxonium (Rosowsky, 1964).

![Reaction with alkyl halides](image)

The oxirane ring upon treatment with trimethylsilyl halide (TMSX; X=Cl, Br or I) and a mixture of carboxylic acid/ trifluoroacetic anhydride (TFAA), to produce the corresponding C_2-O-acylated vicinal halohydrines in high yields (Stamatov and Stawinski, 2006).

![Reaction with alkyl halides](image)

The reaction of cyano epoxide 34 with TMSX in presence of Mg and hexamethylphosphoric triamide (HMPA) as solvent can be produced β-silylated nitriles 35 (Bolourtchian et al., 2003).

![Reaction with alkyl halides](image)

**d) Reaction with dihalotris(hexafluoroisopropoxy)phosphoranes:**

The interaction of trimethylsilyl epoxide 36 with phosphorane 37 has been found to give the phospholane 38 or phosphate 39 depending on the

---
nature of substituent X at low temperature and the initial opening of epoxide occurs (Mironov et al., 2002).

\[ \text{O} \text{SiMe}_3 + (\text{RFO})_3\text{PX}_2 \rightarrow \text{X} \]

\[ \text{RF=CF}_3, \text{X=Cl, Br} \]

**e) Reaction with peroxy acids:**

Peroxy acids as oxygen donors, coordinated with oxirane 40 to give peroxide 41 (Rosowsk, 1964).

\[ \begin{array}{c}
\text{Ph} \text{O} \text{Ph} \\
\text{Ph} \text{Ph} \\
\text{Ph} \text{Ph}
\end{array}
\begin{array}{c}
+ \text{CH}_3\text{CO}_2\text{H}
\end{array}
\begin{array}{c}
\text{Ph} \text{O} \text{Ph} \\
\text{Ph} \text{Ph} \\
\text{Ph} \text{Ph}
\end{array}
\begin{array}{c}
\rightarrow \text{Ph} \text{O} \text{Ph} \\
\text{Ph} \text{Ph} \\
\text{Ph} \text{Ph}
\end{array}
\begin{array}{c}
\rightarrow \text{Ph} \text{O} \text{Ph} \\
\text{Ph} \text{Ph} \\
\text{Ph} \text{Ph}
\end{array}
\begin{array}{c}
\rightarrow 2 \text{Ph}_2\text{Co}
\end{array}
\]

**f) Reaction with carbonyl compound:**

Aldehydes and ketones react with oxiranes to form the five membered heterocycles ring (Rosowsk, 1964).

\[ \begin{array}{c}
\text{O} \\
+ \text{RCHO}
\end{array}
\begin{array}{c}
\rightarrow \text{R} \text{O} \\
\rightarrow \text{R} \text{O}
\end{array}
\]

Miller has shown that the reaction of trans bis-(chloromethyl)ethylene oxide 42 proceeds with inversion to give compounds 43 (Miller, 1960).
g) Reaction with carbon dioxide:

Carbon dioxide reacts with oxiranes to form the five membered ring heterocycles (Nerdel et al., 1967). A straightforward for chemical fixation of CO$_2$ onto epoxides by simply dissolving these compounds in molten Tetrabutylammonium bromide (TBAB) as solvent, in the presence of CO$_2$ at atmospheric pressure. Once the reaction was complete, pure cyclic carbonates was isolated by vacuum distillation or extraction with ethyl acetate in which the ionic liquid is insoluble (Calo et al., 2002).

![Reaction mechanism](image)

A plausible mechanism for this reaction is the ring opening of the epoxide by means of a nucleophilic attack by the bromide ion, which leads to an oxy anion species affording the corresponding cyclic carbonate after reaction with CO$_2$ (Calo et al., 2002).


**h) Deoxygenation:**

Planka and Skell reported the stereochemical consequences of epoxide Deoxygenation by vapour deposited carbon atoms. When *trans* but-2-one oxide and carbon vapour are codeposited at a liquid nitrogen cooled surface carbon monoxide is liberated and *cis* but-2-ene and *trans* but-2-ene are formed in a *trans*: *cis* ratio as 1.4: 1 (Planka and Skell, 1970).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{CH}_3 \\
+ \quad \text{C} & \quad \rightarrow \quad \text{CO} \quad + \quad \text{H}_3\text{C} \quad \text{CH}_3 \\
& \quad \text{cis} \quad \text{trans} \\
\end{align*}
\]


2- **Nucleophilic attack on ring carbon:**

The reaction of nucleophiles with oxirane depends on electronic factors beside the medium of the reaction; it occurs *via* SN2 transition state under non-acidic conditions, alkyl group sterically deflects from the C-α, but under acidic conditions this steric effect is to some extent offset by an electronic one. Thus electronic factors favor cleavage at the more substituted carbon. The nucleophilic ring opening gives primary or secondary alcohols.

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\quad \text{Nu} & \quad \rightarrow \quad \text{R} \quad \text{H} \quad \text{CH}_2\text{O} \quad \text{Primary alcohols} \\
\quad & \quad \text{Nu} \\
\quad & \quad \rightarrow \quad \text{R} \quad \text{H} \quad \text{CH}_2\text{Nu} \quad \text{Secondary alcohols}
\end{align*}
\]

**a) Reaction with bases as nucleophiles:**

1) **Hydroxylamine and hydrazine hydrate:**

The reaction of chalcone epoxide with hydroxyl amine gives the oxime which readily changes into isoxazole (Oskar, 1917).
The reaction of chalcone epoxide with hydrazine hydrate gives pyrazolone derivative (Oskar, 1917; Coffen and Korzan, 1971).

**ii) Ammonia:**

Oxiranes reacts with ammonia to give a mixture of mono ethanol amine 44 and biethanol amine 45 according to the concentration of oxirane and the time of reflux with ammonia (Reynold et al., 1961).

We have developed new, highly region- and diastereoselective way of synthesis of 2-amino-1-hydroxy-2-arylethylphosphoric esters (Cristau et al., 2000) and acids by opening of trans 1,2-epoxy-2-arylethylphosphoric esters with 28% NH₃ in methanol.
Concerning the diastereoselectivity, the obtained esters and acids are probably the unlike diastereoisomers. Conformational studies confirm SN\textsuperscript{2} mechanism and show the formation of hydrogen bond between NH\textsubscript{2} and OH moieties in case of esters, whereas for acids formation of hydrogen bond between NH\textsubscript{2} and P=O predominate (Latajka et al., 2002). In case of trisubstituted epoxyphosphonates we observe rearrangement reaction instead of expected SN2 reaction (Drag et al., 2002).

\textit{iii) Amines:}

Oxirane react with primary or secondary amines to yield β-hydroxy primary or secondary amines (Reynold et al., 1961; Chang, 1993).

\begin{equation}
\text{C} - \text{C} \quad \text{R} \quad \text{N} \quad \text{H}_2 \quad \text{R}_2 \quad \text{N} \quad \text{H} \quad \text{C} - \text{C} \quad \text{O} \quad \text{H} \\
\text{C} - \text{C} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{R} \quad \text{N} \quad \text{H} \quad \text{R}_2
\end{equation}

\textit{iv) Amino acids:}

The amino acid opening of epoxides with short reaction times catalyzed by calcium trifluoromethanesulfonate Ca(OTf)\textsubscript{2} for the preparation of hydroxyethylamine dipeptide isosteres (Babic et al., 2006).

\begin{equation}
\text{R}_1 \quad \text{O} \quad \text{C} - \text{O} \quad \text{R}_3 \quad \text{Ca(OTf)}_2 \quad \text{CH}_3\text{CN} \quad \text{R}_1 \quad \text{H} \quad \text{N} \quad \text{A} \quad \text{C} \quad \text{O} \quad \text{R}_3 \quad \text{R}_2
\end{equation}
v) Alkalies:

The chalcone epoxide in presence of base is converted to 2-hydroxycarboxilic acids (Mouk *et al.*, 1973).

Oxirane 46 undergoes nucleophilic displacement followed by elimination to give 47 in alkaline medium (Mouk *et al.*, 1973).

![Reaction scheme](image)

vi) Alcohols:

The reaction of epoxides with primary, secondary and tertiary alcohols in the presence of 0.01-0.2 molar equivalents of silica sulfuric acid was investigated and the corresponding β-alkoxy alcohols were obtained in good to excellent yields with high degree of region- and chemo selectivity (Salehi *et al.*, 2004).

![Reaction scheme](image)

b) Reaction with azide nucleophile:

Azide anion reacts with oxiranes to yield aziridine via an intermediate β-hydroxy azide (Schwesinger *et al.*, 1980).
Oxiranes undergo ring opening rapidly with sodium azide in a 
BF$_4$/H$_2$O or PF$_6$/H$_2$O (2:1) solvent system under mild and normal reaction 
condition to afford the corresponding 2-azidoalcohols (Yadav et al., 
2005).

The reaction of styrene oxide with sodium azide supported on silica 
gel was completed under solvent free condition in 80 °C after 15 min and 
produced 94% of 1,2-azidoalcohol as a mixture of two isomers. The ratio 
of α-attack to β-attack was found to be 90:10 (Kiasat and Kazemi, 
2003).

Epoxides carrying electron-withdrawing groups react under similar 
reaction conditions and their corresponding 1,2-azido alcohols were 
produced in excellent yields and regioselectivity. In this case, with the 
attack of the azide ion on the less substituted oxirane carbon, the 
regioselectivity is reversed and the 1,2-azido alcohol of β-attack is 
obtained. While epoxides carrying electron- withdrawing groups, it is the 
steric factor which predominates and the nucleophilic attack of azide ion 
is strongly favored on the less substituted carbon atom of epoxide (Kiasat 
c) Reaction with sulfur nucleophile:

i) Thiourea:

Thiourea reacts with methyloxirane in acid medium to give methylthirane (Bordwell and Anderson, 1953) via the following mechanism.

\[
\begin{align*}
\text{NH}_2\text{S} + \text{CH}_3\text{O} &\rightarrow \text{NH}_2\text{S} - \text{H}_2\text{O} \\
\text{H}_2\text{N} &\rightarrow \text{H}_2\text{O} \\
\text{NH}_2\text{S} - \text{CH}_3\text{O} &\rightarrow \text{H}_2\text{N} - \text{H}_2\text{O}
\end{align*}
\]

ii) Sulfides:

Oxirane react with sulfide to yield β-hydroxy mercaptan.

\[
\begin{align*}
\text{C} - \text{C} + \text{SH} &\rightarrow \text{C} - \text{SH} \\
\text{O} &\rightarrow \text{OH}
\end{align*}
\]

Triphenyl silanethiol added to the less hindered side of substituted epoxide to form hydroxythioles after desilylation (Brittain and Gareau, 1993).
**iii) Bisulfite:**

Bisulfite reacts with oxiranes to give the $\beta$-hydroxy sulfonate (Gilbert, 1965).

\[ \text{O} \quad \text{C} \quad \text{C} \quad \text{H}_2\text{O} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{SO}_3^- \]

\[ \text{C} \quad \text{C} \quad \text{O} \quad \text{SO}_3^- \]

**iv) Triphenylphosphine sulfide:**

Triphenylphosphine sulfide converts oxiranes to thiiranes (Calo et al., 1975).

\[ \text{Ph}_3\text{PS} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \]

\[ \text{Ph} \quad \text{S} \quad \text{Ph} \quad \text{Ph} \]

**v) Carbon disulphide:**

Carbon disulphide and KOH react with epoxides in methanol lead to trithiocarbonate via unisolated intermediate (Culvenor et al., 1946).

\[ \text{O} \quad \text{C} \quad \text{O} \quad \text{CS}_2 \quad \text{KOH} \quad \text{MeO} \quad \text{S} \quad \text{S} \quad \text{S} \]

\[ \text{S} \quad \text{S} \quad \text{S} \]

**vi) Thione compounds:**

The thermal ring isomerization and reactions with epoxides of 2-substituted imino-1,3-dithiolanes 48 where found to give the corresponding oxazolidenes 49 (Ueno et al., 1970).
There are two possible mechanisms for the formation of 49.

1\textsuperscript{st} mechanism:

\[ \begin{align*}
\text{S-S} & \overset{\text{NR}}{\longrightarrow} \text{R-NCS} + \overset{\text{O}}{\text{R'}} \rightarrow \text{S-S} \overset{\text{NR'}}{\longrightarrow} \text{R-NCO} + \overset{\text{O}}{\text{R'}} \\
49 & \overset{\text{O}}{\text{O}} \overset{\text{NR}}{\longrightarrow} \\
\end{align*} \]

2\textsuperscript{nd} mechanism:

\[ \begin{align*}
\text{S-S} & \overset{\text{NR}}{\longrightarrow} \text{R'} \overset{\text{O}}{\text{O}} \rightarrow \text{S-S} \overset{\text{N-R'}}{\longrightarrow} \text{O-S} \rightarrow \text{S-S} \overset{\text{O}}{\text{O}} \overset{\text{NR}}{\longrightarrow} \\
49 & \overset{\text{O}}{\text{O}} \overset{\text{NR}}{\longrightarrow} \\
\end{align*} \]

vii) Ortho-aminothiophenol derivatives:

Oxirane derivative react with ortho-aminothiophenol in presences of xylene to produce thiazepin derivative (Singh et al., 2002).
viii) Thiophenols:

The epoxides react with Thiophenols derivative to afford ring opening of epoxide (Zhou et al., 2003).

\[
\text{H}_3\text{C} - \text{C} - \text{SH} + \text{O} \xrightarrow{\text{n-hexane}} \text{H}_3\text{C} - \text{C} - \text{SH} + \text{OH}
\]
**d) Reaction with carbanion as nucleophile:**

**i) Grignard reagent:**

The reaction of Grignard reagent with an epoxide occur in such manner that either the organo magnesium bond may be attacked by the epoxide (1:2). The resulting products are mixture of an alcohol and halohydrine (Evans and Huston, 1959; Stevens and Holland, 1958).

\[
\text{RMgX} + \text{O} \rightarrow \text{R} \text{OMgX} \quad \text{H}_2\text{O} \rightarrow \text{R} \text{OH}
\]

\[
\text{RMgO} \text{X} \quad \text{H}_2\text{O} \rightarrow \text{HO} \text{X}
\]

Oxiranes react with Grignard reagent in complicated manner arising from isomerization or cleavage into magnesium halides to yield primary alcohol or alcohols (Rosowsky, 1964).

\[
\text{O} + \text{RMgX} \quad \text{H}_2\text{O} \rightarrow \text{R} \text{OH}
\]

\[
\text{R} \text{O} \text{R} \text{R} + \text{MgX}_2 \rightarrow \text{R} \text{OH}
\]

**ii) Diethylmalonate:**

Oxirane reacts with diethylmalonate to yield the lactone 50 (Rosowsky, 1964).
3- **Nucleophilic attack on ring hydrogen:**

When oxirane ring opened by organolithium compounds the primary carbon atom is attacked in the case of propylene and styrene (Cristol *et al.*, 1951). The reaction between epichlorohydrin and phenyl lithium is shown by following reaction (Gilman *et al.*, 1952).

\[
\text{O} + \text{PhLi} + \text{H}_2\text{O} \rightarrow \text{Cl} + \text{PhOH}
\]

The reaction with butyl lithium result in the formation of α,β-unsaturated alcohols and not the saturated ones. The proton in the chloromethyl group is attacked and the carbanion intermediate is transformed into the stable trans-alkoxide via stereospecific ring opening (Hoeg *et al.*, 1964).

The oxirane is deprotonated by t-butyllitium to yield oxiranyl lithium 51 which reacts with alkyl halide or trimethylsilyl chloride and/or deuterium oxide to give alkyl, trimethylsilyl and deuterated oxiranes 52, 53, 54 respectively (Eischand and Galle, 1976).
The reaction of oxirane 55 with lithiumdibenzylphosphide produces the aminohydroxyphosphine 56 (Krawiecka and Jeziorna, 2005).

### 4- Thermolysis and photolysis:

Substituted oxiranes on thermolysis both of C-O and C-C cleavage is observed (Flowers and Parker, 1971; Watson and Young, 1974).

Photolysis of epoxides in solution with light of wave length 2537 A° lead to C-O bond cleavage (Gritter and Sabatino, 1964).
5- Reduction:

The reduction of many hindered and unstable bicyclic epoxides with lithium aluminiumhydride is very slow and is often accompanied by rearrangement (Brown et al., 1970). e.g; norbornene oxide 57 on reduction gives 16% of rearranged 7-norbornanol 58 and 84% of expected 2-norbornanol 59 (Brown et al., 1970).
When oxiranes react with LiAlH$_4$ it gave alcohols while when AlCl$_3$ is added to LiAlH$_4$ the result is different (Kwart and Takeshita, 1963).

The AlCl$_3$ coordinate with epoxide and favours an SN$^1$ like opening of epoxide ring with subsequent attack of hydride at the more substituted carbon which bears the positive charge on the incipient carbonium ion.

The reduction of epoxides derived from primary and secondary alcohols with LiAlH$_4$ takes place primarily at C$_2$ but the regioselectivity is not high (Takeshita et al., 1993). Better regioselectivity for production of alkyl-1,3-diols is observed when the reduction is effected by red Al (Viti, 1982; Marotta et al., 2001).

Recently a novel reagent has been introduced for the stereocontrolled reduction of relatively simple epoxy alcohols at C$_3$ (Kawakami et al., 1995). This reducing system joins several other, more established protocols for the production of 1,2-diols, including the
combination of lithium borohydride and Ti(O\textit{i}Pr)\textit{4} \textit{(Dai et al.,1986 ;Pena and Roberts, 2003)}.

6- **Oxidation:**
Epoxides have been found to give $\alpha$-hydroxy ketones when they are oxidized with dimethylsulfoxide in presence of BF$_3$ \textit{(Cohen and Tsuji, 1961)}.

7- **Miscellaneous reactions:**
\textit{a) Hydrolysis:}
Oxiranes are hydrolyzed with water to give dihydroxy compounds \textit{(Suschitzky and Scriven, 1992)}.

Oxiranes such as propylene oxide react in aqueous solvent of HCl and HBr i.e acid-catalyzed cleavage \textit{(Stewart and VanderWerf, 1954)}.

Cis and Trans oxiranes \textit{(Wassermann and Aubry, 1956)} undergo cleavage with retention of configuration. Cis and Trans stibene oxides yield the expected threo- and erythro-chlorohydrin through an oxonium lone-pair intermediate as following.
The base-catalyzed splitting of oxirane an anionic mechanism was suggested by Ingold (Ingold, 1953).

\[ \text{O} + \text{OH} \rightarrow \text{OH} \rightarrow \text{OH} + \text{OH} \]

**b) Reaction with phosphorous ylides:**

Oxiranes react with phosphorus ylides to produce the cyclopropane (Denny et al., 1962).

The reaction proceeds via the following mechanism:
c) Reaction with cyanide, nitrile, thiocyanate:

Treatment of epoxides with potassium cyanide yield cyano alkene (Umbach, 1971).

\[
\begin{align*}
\text{R} \quad & + \quad \text{KCN} \quad \rightarrow \quad \text{H} \quad \text{H} \\
\text{O} & \\
\end{align*}
\]

The reaction of phenyl cyanide with p-chloro-2,2-dimethyl-styrene epoxide give oxazoline derivative (Temnikova and Yandovskii, 1968).

In basic media epoxide reacts with thiocyanate anion with formation of episulfides (Van Tamelen, 1963).

\[
\begin{align*}
\text{H}_3\text{C} \quad & + \quad \text{KCN} \quad \rightarrow \quad \text{KCN} \\
\text{O} & \\
\end{align*}
\]

a variety of epoxides respond rapidly with potassium thiocyanate in PF\textsubscript{6}-H\textsubscript{2}O (2:1) solvent system at room temperature under mild and convenient condition to produce the corresponding thirranrs in high to quantitative yields (Yadav et al., 2003).
Epoxides are efficiently converted to the corresponding thiiranes by ammonium thiocyanate in presence of catalytic amounts of oxalic acid with excellent isolated yields under mild and non-aqueous reaction conditions. This conversion performed under both conventional heating and microwave conditions. Distinct rate enhancement is observed under microwave irradiation (Kazemi and Kiasat, 2003).

\[
\text{Epoxide} + \text{NH}_2\text{SCN, oxalic acid (0.2 equiv.)} \rightarrow \text{Thiirane}
\]

\[
\text{dry CH}_3\text{CN/ reflux condition 0.5-1.75 h}
\]

87-95%

The formation of thiiranes from the reaction of epoxides and thiocyanate ion has proposed to occur through the intermediacy of the corresponding β-hydroxy thiocyanate but this intermediate has not been isolated due to its rapid conversion to the corresponding thiirane (Iranpoor and Kohmareh, 1999). The diamine 2,6-bis[2-(o-aminophenoxy)methyl]-4-bromo-1-methoxybenzene (BABMB) efficiently catalyzed the addition of ammonium thiocyanate to epoxide to form 2-hydroxyethyl thiocyanate (Sharghi et al., 2001; Niknam and Nasehi, 2002).
This reaction occurs according to the following four step mechanism (Niknam, 2004):

1\textsuperscript{st} step: Involves the formation of a 1:1 molecular complex between BABMB and NH\textsubscript{4}SCN in which the thiocyanate ion SCN\textsuperscript{-} exists as a contact ion pair.

\[
diamine + \text{NH}_4\text{SCN} \rightleftharpoons \text{[diamine--NH}_4\text{]SCN}\textsuperscript{-}
\]

2\textsuperscript{nd} step: This complex is further decomposed to release SCN ion into the solution.

\[
\text{[diamine--NH}_4\text{]SCN}\textsuperscript{-} \rightarrow \text{[diamine--NH}_4\text{]} + \text{SCN}\textsuperscript{-}
\]

3\textsuperscript{rd} step: SCN\textsuperscript{-} ion participates in the ring-opening reaction of epoxides.

\[
\text{[diamine--NH}_4\text{]} + \text{SCN}\textsuperscript{-} + \text{R} = \text{RCH(OH)NCS} + \text{NH}_3 + \text{diamine}
\]

4\textsuperscript{th} step: The catalyst is regenerated

\[
\text{[diamine--NH}_4\text{]}
\]

The reaction of 2,3-epoxy esters with acetonitrile in the presence of two equiv. of borontrifluoride etherate at room temperature produced oxazoline in high yield (Rodrigues \textit{et al.}, 2005).
The mechanism pathway to the ring expanded products has been proposed by Zwanenburg (Legters et al., 1992) and also by (Wohi and Cannie, 1973). Initial opening of epoxide by nitrile at C-3 in an SN$^2$ fashion produced a nitrilium ion that undergoes an intramolecular ring closure reaction.

d) Carbonylation:

Reaction of epoxides discovered by Eisenmann involves the reaction of carbonmonoxide, metal carbonyl, alcohol and an epoxide to form β-hydroxy esters (Eisenmann et al., 1961).

\[
\text{H}_3\text{C}\text{O} + \text{CO} + \text{CH}_3\text{OH} + \text{Co}_2(\text{CO})_2 \rightarrow \text{H}_3\text{C}\text{CH}_2\text{COCH}_3
\]

Vinyloxirane 60 undergoes palladium catalyzed carbonylation (Shimizu et al., 1993) on the alkene terminus under an atmosphere of carbonmonoxide to give hydroxyester 61 in high yield (Adam and Balci, 1980).

\[
\text{CH}_2=\text{CHCH}_2\text{Cl} + \text{EtOH} + \text{CO} \rightarrow \text{HOCH}_2\text{CH} = \text{CHCOOEt}
\]

e) Nitration:

Dinitrogen pentaoxide reacts with oxiranes to give the dinitrates 62 (Golding et al., 1993).
f) Polymrization:

The various procedures useful for polymerizing epoxides can be classified into three main categories so far as the mechanism of the propagation step is concerned, namely; anionic, cationic and coordination rearrangement, these mechanisms are represented by reactions (1), (2) and (3) respectively (Price, 1961).

\[ RO......H + \circlearrowleft \rightarrow RO\circlearrowleft \]  
\[ OR\circlearrowleft + \circlearrowleft \rightarrow OR\circlearrowleft \]  
\[ OR\circlearrowleft + \circlearrowleft \rightarrow OR\circlearrowleft \]  

The anionic or base-catalyzed reaction precedes best for ethylene oxide even with propylene oxide (Gee et al., 1961). The chain transfer process intervenes and limits the molecular weight to about 5000 (Simons and Verbanc, 1960).

g) Reaction with cerium V ammonium nitrate (CAN) and NBS:

The CAN and NBS combination has been used for the first time for the synthesis of \( \alpha \)-hydroxy ketones from oxiranes in excellent yields. This method is a direct one-pot, and synthesis under mild condition using acetonitrile-water (9:1) as solvent (Surendra et al., 2005).
h) Reaction with Ferrocene:

Aryl and diaryloxiranes react with ferrocene in methanesulfonic acid (MSA) – dichloromethane (DCM) mixture as solvent to afford (2-arylvinyl) and (2,2-diarylvinyl) ferrocene respectively. The reaction with aryloxiranes is highly stereoselective and gives only the E-isomer. The reaction proceeds via fast isomerization of the protonated oxirane to protonated carbonyl compound which attacks ferrocene (Plazuk and Zakrzewski, 2006).

8- Microwave catalized reaction:

Microwave catalyzed reaction of $H$-dimethylphosphonate with 1,2-epoxydecane; 5,6-epoxy-1-hexene; 1,2-epoxybutane and cyclohexene oxide have been found to cause oxirane ring opening, deoxygenatino and hydrophosphorylation (Munavalli et al., 2002).
The mechanism:

\[
\begin{align*}
\text{PH(O)(OCH}_3)_2 + \text{ } &\xrightarrow{\text{H}} \xrightarrow{\text{+P(O)(OCH}_3)_2} \\
\text{O} &\xrightarrow{\text{+P(O)(OCH}_3)_2} \xrightarrow{\text{O} + \text{P(O)(OCH}_3)_2} \\
\text{+P(O)(OCH}_3)_2 &\xrightarrow{\text{P(O)(OCH}_3)_2} \xrightarrow{\text{+P(O)(OCH}_3)_2} \\
\text{P(O)(OCH}_3)_2 &\xrightarrow{\text{P(O)(OCH}_3)_2} \xrightarrow{\text{P(O)(OCH}_3)_2} \\
\end{align*}
\]

9- **Rearrangement reaction:**

   a) **Super base-promoted rearrangement:**
   All transformation have been carried out making use of super bases (*Schlosser, 1967*) and in particular the equimolar mixtures butyl lithium/ potassium tert-butoxide Schlosser’s base and butyllithium / diisopropylamine / potassium tert-butoxide (*Margot and Schlosser,*
The transformation shown in following scheme (Mordini et al., 2005).

b) 1,2-Group migration of epoxide:

The mechanism of rearrangement of chalcone epoxide explain in following scheme (Joy et al., 2005).
10- **Quantitative chemical method for epoxides:**

The epoxide functional group is quite reactive toward nucleophilic reagents. Useful analytical methods involving this type of reaction include the addition of hydrogen chloride (Swern et al., 1997), thiosulfate (Ross, 1950) and hydrogen bromide (Durbetaki, 1956). Probably the best of these is the method of Durbetaki in which the epoxide is determined by direct titration with anhydrous hydrogen bromide in acetic acid.

\[
\text{HBr} + \text{C} = \text{C} \quad \text{O} \quad \rightarrow \quad \text{C} = \text{C} \quad \text{OH} \quad \text{Br}
\]

The end point in this titration may be determined potentiometrically using glass and calomel electrodes or with a visual indicator such as crystal violet.
CHEMISTRY OF 2-THIOPYRIMIDIES

BIOLOGICAL ASPECTS:

Pyrimidines derivatives are medically important (Tabern and Volwiler, 1935; Atwal et al., 1989; Kappe et al., 1997) for their therapeutic applications (Segal et al., 1962; Cumming et al., 2004).

One possible reason for their activity is presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA and RNA (Calvin and Jorgenson, 1968).

One important class of pyrimidine is the 2-thiopyrimidine and its derivatives which are also well known as 2-mercaptopyrimidine compound (Chung et al., 1999).

Various mono-, di-, tri- and tetra-cyclic, di/tetrahydro-2-thiopyrimidine derivatives have been synthesized and evaluated for anti-inflammatory and analgesic activity both in vivo and in vitro (Sondhi et al., 2004).

Pyrimidine and fused pyrimidine derivatives are of great biological interest especially as antibacterial (Gupta et al., 1993; Kuyper et al., 1996), antiviral (Kappe, 1993; Pratap and Yarovenkom, 2000; Rashad and Ali, 2006), antiherps (Ram et al., 1989; Verheggen et al., 1993; Shigeta et al., 2002), antianalgesic (Dave et al., 1986; Dave et al., 1989), anticancer (Sharma et al., 1996; Bar et al., 1997; El-Gaby et al., 1999; Holla et al., 2004), anti-inflammatory (El-Slager et al., 1972; Chaykovsky et al., 1973; Leistner et al., 1986; Kappe, 1993;
Tozkoparan et al., 1999), anticonvulsant (Sladowska, 1993; Shafik et al., 1995), antihypertensive (Monge et al., 1991; Atwal et al., 1991; Rovnyak et al., 1992; Grover et al., 1995), antipyretic (Bousquet et al., 1984; Bousquet et al., 1985), antianaphylactic (Vieweg et al., 1989), antitumor (Kappe, 1993; Tomita et al., 1996), antiallergic (Madding and Thompson, 1972), hypocholesterolenic (Shishoo et al., 1984), calcium channel blockers (Cho et al., 1989), cardiovascular agents (Khania et al., 1978), antiulcer (Brown et al., 1991), antifungal (Singh et al., 1998; Singh et al., 2000), anti-AIDS (Bowlin, 1992), antineuplastic (Whi-Gun et al., 1998), antimicrobial (Richardson and McCarty, 1972), antiparkinsonian (Naithani et al., 1991).

Nucleosides of pyrimidine base have been used extensively as antiviral and anticancer agents (Szumski and Goodman, 1957), the thiopyrimidine nucleosides are antiherbs activities (Shigeta et al., 2002), attractive antitubercular drug target (Kantardjieff et al., 2005) and a new class of specific inhibitors of human immunodeficiency virus Type 1 [HIV-1] (Mai et al., 1995).
SYNTHESIS OF 2-THIOPYRIMIDINES:

The synthesis of 2-thiopyrimidines including the synthesis of substituted 2-thiopyrimidines and fused ring 2-thiopyrimidine derivatives.

1-From thiourea and its derivatives:

Thiourea and its derivatives used to provide the –N-CS-N- moiety when allowed to react with:

a) Alkenyne derivative:

4-methoxybutyne 63 condensed with isothiourea to gave 4-methyl-2-thiopyrimidine 64 (Hunt et al., 1959).

\[
\begin{align*}
\text{MeO} & \quad \text{HN} \quad \text{SH} \\
& \quad \text{MeO} \quad \text{H}_3\text{C} \\
\end{align*}
\]

b) 1,2-dicarbonyl compound:

Reaction similar to the Michael-Type nucleophilic cycloaddition of the 4-\(p\)-anisyl-5-\(p\)-anisyl-2,3-furandione 65 with monosubstituted thioureas gave \(N\)-alkyl-2-thiopyrimidine derivatives 66 with lose of carbon dioxide and water (Yildirim et al., 2002).
The reaction mechanism studies of another furandione derivative similar to compound 65 with thiourea derivatives have shown that the final product should be 66 (Yildirim et al., 1995).

The confirmation of 2-thiopyrimidine skeleton 66 was based on X-ray studies, thus excluding the possible isomer 67 (Akcamur et al., 1988; Ozbey et al., 1991; Akkurt and Hiller, 1993).

c) 1,3-dicarbonyl compound:

Acetylacetone react with N-methylthiourea to give 1,2-dihydro-1,4,5-trimethyl-2-thiopyrimidine 68 (Marshall and Walker, 1951). Also acetylacetone condensed with S-alkylisothiourea gave 4,6-dimethyl-2-alkylthiopyrimidine 69 (Mervin, 1966).
Heterocyclization of N-azidomethylthiourea 70 with enolate of 1,3-dicarbonyl derivative afforded hydroxyhexahydropyrimidinethione 71 upon dehydration afforded tetrahydropyrimidinethione 72 (Shutalev and Kuksa, 1995).

\[
\text{H}_2\text{N} \quad \text{CH}_3 \quad \text{CHO} + \text{H}_2\text{N} \quad \text{S} \quad \text{NH}_2 \quad \text{S} \quad \text{NH}_2 \quad \text{N} \quad \text{CH}_3 \quad \text{S} \quad \text{NH} \quad \text{NH} \quad \text{S} \quad \text{CH}_3 \quad \text{COR} \quad \text{OH} \quad \text{dehydration} \quad \text{NH} \quad \text{NH} \quad \text{S} \quad \text{CH}_3 \quad \text{COR} 
\]

Benzyloacetone react with thiourea in acidic ethanol gave 6-methyl-4-phenyl-2-(1H)-pyrimidinethione 73 (Brown et al., 1984).

\[
\text{Ph} \quad \text{CO} \quad \text{H}_3\text{C} + \text{H}_2\text{N} \quad \text{S} \quad \text{NH}_2 \quad \text{Acidic ethanol} \quad \text{NH} \quad \text{NH} \quad \text{S} \quad \text{Ph} 
\]

Reaction of benzaldehyde derivative 74 with thiourea and acetoacetate derivative in presence of HCl according to Biginelli reaction gave thiopyrimidine derivative 75 (Jani et al., 1990; Ertan et al., 1991; Jain et al., 1991).

\[
\begin{align*}
\text{CHO} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^4 & + \text{H}_2\text{N} \quad \text{S} + \text{H}_3\text{C} \quad \text{COR} \quad \text{COOR} \\
\text{74} & \rightarrow \text{R}^2 \quad \text{R}^3 \quad \text{R}^4 \\
\text{75} & \quad \text{R}^1 \\
\end{align*}
\]

A mixture of aldehyde, 1,3-dicarbonyl compound, thiourea and 12-tungstophosporic acid was refluxed in glacial acetic acid produced 4-aryl-3,4-dihydropyrimidin-2(1H)-thione 76 (Heravi et al., 2005).
The suggested mechanism is illustrated as following:

Reaction of $\beta$-ketoester or $\beta$-diketone 77, appropriate aldehyde and thiourea in THF under irradiation with a 100 W electrical lamp afforded 2-thiopyrimidine derivatives 78 in high yields (Foroughifar et al., 2003).

2-Thiopyrimidine derivatives 79 were synthesized in high yield using a newly developed microwave-assisted cyclocondensation. Mixture of $\beta$-ketoester, aryl aldehyde and thiourea were subjected to microwave
irradiation by using polyphosphate ester (PPE) as a reaction moderator (Foroughifar et al., 2003).

Reaction of N-alkylthiourea, aldehyde and p-toluesulfinic acid produced α-tosyl substituted thiourea 80 which reacted with enolates of α-functionally substituted ketones 81 produced 2-thiopyrimidine derivatives 82 (Shutalev, 2000).

Ethylacetoacetate condensed with isothiourea in aqueous potassium carbonate (Fischer and Roch, 1952) gave 2-mercaptopyrimidine derivatives 83.
Condensation of acetoacetate derivative \( 84 \) with 2-chloro-3-nitrobenzoic acid and methylisothiourea (Rovnyak and Kimball, 1993) gave \( 85 \).

\[
\begin{align*}
\text{OEt} & \quad \text{Et} & \quad \text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{CO} \\
\text{CH}_2 \text{SiMe}_3 & \quad \text{CH}_2 \text{SiMe}_3 & \quad \text{CH}_2 \text{SiMe}_3 & \quad \text{CH}_2 \text{SiMe}_3
\end{align*}
\]

\( 84 \) + \( 85 \)

Reaction of \( \beta \)-ketoester \( 86 \) with 2-methyl-2-thiopseudourea sulphate \( 87 \) in presence of sodium acetate (Rovnyak and Kimball, 1992) afforded \( 88 \).

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{NO}_2 & \quad \text{MeS} & \quad \text{MeS} & \quad \text{MeS} \\
\text{C}_6\text{H}_4 & \quad \text{C}_6\text{H}_4 & \quad \text{C}_6\text{H}_4 & \quad \text{C}_6\text{H}_4 \\
\text{SCH}_3 & \quad \text{SCH}_3 & \quad \text{SCH}_3 & \quad \text{SCH}_3 \\
\text{COOEt} & \quad \text{COOEt} & \quad \text{COOEt} & \quad \text{COOEt} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} \\
\text{R} = \text{SCH}_3 & \quad \text{R} = \text{SCH}_3 & \quad \text{R} = \text{SCH}_3 & \quad \text{R} = \text{SCH}_3
\end{align*}
\]

\( 86 \) + \( 87 \)

Malonic acid condensed with thiourea in AcOH/Ac\(_2\)O to produce 2-thiopyrimidine derivative \( 89 \) (Ziegler and Steiner, 1965).
Treatment of malonic acid with thiozolylthiourea derivative 90 in presence of acetylchloride (El-Subbagh, 1990) gave 2-thiopyrimidine derivative 91.

\[
\text{HOOC-CH}_2\text{-COOH} + \text{H}_3\text{C-}\text{N-}\text{H-} + \text{S-} \xrightarrow{\text{AcCl}} \text{N=S-CH}_2\text{-CO}_2\text{Et}
\]

Diethylmalonate react with isothiourea in presence of sodium ethoxide gave 4,6-dihydroxy-2-mercaptopyrimidine 92 (Dox and Plaisance, 1916).

\[
\text{OEt-CH}_2\text{-COOEt} + \text{NH-} + \text{S-} \xrightarrow{\text{NaOEt}} \text{HO-N=S-CH}_2\text{-OH}
\]

Ethoxymethylenediethyl malonate 93 condensed with S-alkylthiourea 94 gave 2-thioxopyrimidine derivative 95 (Steinbech et al., 1986).

\[
\text{EtO-CH=CH-CH}_2\text{-COOEt} + \text{NH-} + \text{S-} \xrightarrow{\text{Me}_{2}\text{CHCH}_2\text{Br}} \text{HO-N=S-CH}_2\text{-CHMe}_2\text{-COOEt}
\]

Reaction of 1,1-cycloalkanedicarboxylic acid diethyl ester (96) with thiourea (Youssef et al., 1996) afforded 97.
Condensation of 98 with thiourea in presence of anhydrous potassium carbonate in methanol under reflux, produced the potassium salt of 2-mercaptopuridine derivative 99 which dissolved in water and acidifying with 2N HCl led to formation of 2-mercaptopuridine derivative 100 (El-Deen and Ibrahim, 2000; El-Deen and Ibrahim, 2002).

\[
\text{NH}_2\text{S} = \text{NH}_2 \text{(CH}_2\text{)}_n\text{COOEt} + \text{H}_2\text{N} - \text{NH}_2 \rightarrow \text{NH}_2\text{SH} + \text{K}_2\text{CO}_3/\text{MeOH}
\]

\[
\text{O} \text{O} \text{O} \text{OEt} + \text{K}_2\text{CO}_3/\text{MeOH} \rightarrow \text{O} \text{O} \text{O} \text{O}_2\text{Et} + \text{SH}
\]

\[
\text{d) Acetate derivatives:}
\]
Cyclocondensation of methyl methoxyacetate 101, S-methylisothiourea sulphate and ethyl formate (Binet and Defosse, 1993) gave 2-methylthio-5-methoxy-3,4-dihydropyrimidin-4-one 102.

\[
\text{HCOOEt} + \text{S} - \text{NH}_2\text{CH}_3 + \text{NH}_2\text{H}_2\text{S}_4 \rightarrow \text{HN} \text{C} \text{O} \text{OMe} \text{CH}_3\text{S}
\]

Ethyl cyanoacetate and thiourea undergo cyclization in alkaline media via the intermediate of the open form 103 afforded 2-mercaptopuridine derivative 104 (Rupe et al., 1925; Bergmann and Johnson, 1933).
Heating a mixture of ethyl cyanoacetate with aldehyde and S-methylisothiourea gave the corresponding 4-aryl-5-cyano-2-methylthio-6-oxopyrimidine derivative 105 (Hussain et al., 1985).

The reaction of ethyl cyanoacetate, thiourea and 5-(4-bromophenyl)oxazole-4-carboxaldehyde 106 in presence of K$_2$CO$_3$ and EtOH as solvent produced 2-thioxopyrimidine derivative 107 (Aly, 2004).

e) β-Aminoester:
Ethyl-β-aminocrotonate 108 react with isothiourea gave 2-mercaptopyrimidine derivative 109 with elimination of ammonia (Polonivski et al., 1948).
Cyano and nitrile derivative:
The reaction of cyanolefine \( \text{110} \) with thiourea gave the corresponding 4-amino-2-mercaptopyrimidine derivative \( \text{111} \) (Lorente et al., 1985).

\[
\text{H} = \text{CN} + \text{S} + \text{H}_2\text{N} - \text{NH}_2 \rightarrow \text{R} \quad \text{R'} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \quad \text{NH}_2 \\
\text{110} \quad \text{111}
\]

Reaction of acrylonitrile derivative \( \text{112} \) with thiourea produced 2-mercaptopyrimidine derivative \( \text{113} \) (Jachak et al., 1993).

\[
\text{Me}_2\text{N} = \text{CHO} + \text{S} + \text{H}_2\text{N} - \text{NH}_2 \rightarrow \text{N} \quad \text{NH}_2 \quad \text{CHO} \\
\text{112} \quad \text{113}
\]

Malononitrile react with thiourea gave 4,6-diamino-2-mercaptopyrimidine derivative \( \text{114} \) (Bendich et al., 1948) and also react with thiosemicarbazide (N-aminothiourea) gave 1,4,6-tri amino-2(1H)-pyrimidinethione \( \text{115} \) (Talyor and Morrison, 1967).
g) \(\alpha,\beta\)-unsaturated carbonyl compounds:

4-Ethoxy-3-formyl-3-buten-2-one 116 condensed with S-methylthiourea gave 5-formyl-4-methyl-2-methylthiopyrimidine 117 (Tore and Kjell, 1982).

\[
\begin{array}{c}
\text{CN} \\
\text{CN}
\end{array}
\xrightarrow{\text{H}_2\text{N} - \text{N}} 
\begin{array}{c}
\text{NH}_2 \\
\text{NH}_2
\end{array}
\]

\[\text{114}\]

2-Arylmethylene cyclohexanone 118 was refluxed with thiourea in ethanolic potassiumhydroxide gave 4-aryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones 119 (Hammam et al., 1983).

\[
\begin{array}{c}
\text{H}_2\text{C} \\
\text{O}
\end{array}
\xrightarrow{\text{H}_2\text{N} - \text{SCH}_3} 
\begin{array}{c}
\text{H}_3\text{C} \\
\text{N}
\end{array}
\]

\[\text{116} \xrightarrow{\text{119}} \text{117}\]

The enone derivatives 120 react with thiourea in ethanolic potassium hydroxide produced 4,6-diaryl-2-thiopyrimidine derivative 121 (Soliman et al., 1996; El-Emary et al., 2002; Soleiman et al., 2002; Holla et al., 2004; Amr et al., 2006).
2-From isothiocyanate derivatives:

Ethyl enaminonitrile 122 reacted with isothiocyanate derivative to gave the corresponding 2-thiopyrimidine derivative 123 (Mohamed et al., 1987).

\[
\text{NC} \quad \text{COOEt} \quad + \quad \text{RNCS} \quad \rightarrow \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{S} \quad \text{R} 
\]

Reaction of cinnamoyl isothiocyanate with cyanothioacetamide 124 afforded 2-thiopyrimidine derivative 125 ( Assy and Moustafa, 1995).

\[
\text{R} \quad \text{N} \quad \text{O} \quad \text{S} \quad \text{N} \quad \text{F} \quad \text{F} \quad \text{CN} \quad + \quad \text{RNCS} \quad \rightarrow \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{S} \quad \text{R} 
\]

Condensation of isothiocyanate derivative with methylamino acrylate derivative 126 gave 2-thiopyrimidine derivative 127 (Andree et al., 1995).
Reaction of N-aminothiocarbonyl 128 with malononitriles, methyl cyanoacetate or diethyl malonate by refluxing in alkoxide gave the corresponding 2-thiopyrimidine derivative 129, 130, and 131 respectively (Krech et al., 1988).

\[
R'\text{NH}\overset{\text{OMe}}{\text{O}} + \text{RNCS} \rightarrow \text{R'CH}_3\text{O}\overset{\text{NH}}{\text{N}}\text{S}
\]

128

\[
\text{CN} \overset{\text{CN}}{\text{MeONa}} \rightarrow \text{R'NC} \overset{\text{N}}{\text{N}} \overset{\text{R}}{\text{S}} \overset{\text{H}_2\text{N}}{\text{N}} \overset{\text{R}}{\text{S}}
\]

129

\[
\text{CN} \overset{\text{CN}}{\text{COOMe}} \rightarrow \text{R'NC} \overset{\text{N}}{\text{N}} \overset{\text{R}}{\text{S}} \overset{\text{O}}{\text{N}} \overset{\text{R}}{\text{S}}
\]

130

\[
\text{COOEt} \overset{\text{COOEt}}{\text{EtONa}} \rightarrow \text{R'NC} \overset{\text{N}}{\text{N}} \overset{\text{R}}{\text{S}} \overset{\text{O}}{\text{N}} \overset{\text{R}}{\text{S}}
\]

131

On condensation of anthranilic acid 132 with 4-isothiocyanato-4-methyl-2-pentanone 133 afforded 134 (Singh and Kumar, 1987).

\[
\text{COOH} \overset{\text{H}_2\text{N}}{\text{N}} \overset{\text{S}}{\text{N}} \overset{\text{O}}{\text{O}} \overset{\text{CH}_3}{\text{C}} \overset{\text{COOMe}}{\text{COOMe}} \rightarrow \overset{\text{O}}{\text{H}} \overset{\text{C}}{\text{H}} \overset{\text{C}}{\text{H}} \overset{\text{C}}{\text{O}} \overset{\text{O}}{\text{O}} \overset{\text{Me}}{\text{C}} \overset{\text{C}}{\text{O}} \overset{\text{Me}}{\text{C}}
\]

132 133 134

Various 2-thiopyrimidine derivatives 137 and 138 have been synthesized in reasonable yields by the one-pot reaction of β-Keto/aldo isothiocyanate derivative 135 with commercially available functionalized
amines 136 in absolute methanol. Temperature and PH conditions play an important role in these reactions (Sondhi et al., 2005).

General mechanism (Singh and Kumar, 1987) for condensation of the functionalized amine with β-keto/aldo-isothiocyanate is presented as:
Isothiocyanate derivative 139 reacted with hydrazine hydrate in benzene gave the corresponding 2-thiopyrimidine derivative 140 (Ahmed, 2002). While when reacted with hydrazine hydrate in methylene chloride then treated with alcoholic potassium hydroxide, gave the potassium salt of 2-thiopyrimidine derivative. Finally by acidification gave the same 2-thiopyrimidine derivative 140 (Ahmed, 2002; Ahmed, 2003).

The reaction of 1,1-dimethyl-3-oxobutyl-isothiocyanate (DMO-ITC) 141 with an excess of NH₄OH gave pyrimidine-2-thione 142 (Mathes et al., 1948).

The reaction of DMO-ITC with aliphatic amines produced different 2-thiopyrimidine derivative DMO-ITC (141) condensed with alkyl amine at 5-8°C gave 143 (Unkovskii et al., 1970; Verma, 2003) but by reflux gave 144 (Mathes, 1953).
Condensation of DMO-ITC 141 with aromatic amine in presence of an acid afforded 145 (Ovechkin et al., 1972).

Reaction of DMO-ITC 141 with heterocyclic amines afforded 146 and 147 (Sondhi et al., 1996).
Reaction of DMO-ITC 141 with 2-aminoethanol as amino alcohols gave 148 (Sahu et al., 1994; Zigeuner et al., 1976).

\[
\begin{align*}
\text{Reaction} & \quad \text{Product} \\
\text{DMO-ITC} & \quad \text{2-aminoethanol} \\
141 & \quad 148
\end{align*}
\]

Condensation of o, m, or p-aminobenzonitriles 148) with DMO-ITC 141 gave 150 (Ovechkin et al., 1972).

Amino acids having a primary amino group [e.g. glycine (151a, R=CH₂), β-alanine (151b, R=CH₂CH₂) and dL-α-alanine (151c, R=CHCH₃)] when heated with DMO-ITC 141 in presence of water gave respective pyrimidine-2-thiol 152a-c, having an acid substituent at position-1 (Mathes and Stewart, 1950).

\[
\begin{align*}
\text{Reaction} & \quad \text{Product} \\
\text{DMO-ITC} & \quad \text{Amino acid} \\
141 & \quad 152a-c
\end{align*}
\]

The reaction of DMO-ITC 141 with NH₄OH, aliphatic amines, aromaticamines, heterocyclic amines, amino alcohols,
aminobenzonitriles and amino acids have been reported by Verma (Verma, 2003).

The reaction of $\beta$-amino esters 153 with phenyl isothiocyanate gave the corresponding pyrimidine-2-thione derivatives 154 (Khodairy and Abdel-Ghany, 2000; Khodairy, 2003; Abass, 2003; Amr et al., 2006).

\[ \text{NH}_2\text{COOEt} + \text{PhNCS} \rightarrow \text{154} \]

The reaction of $\beta$-amino cyano derivatives 155 with isothiocyanate gave the corresponding pyrimidine-2-thione derivative 156 (Khatoon and Yadav, 2004).

\[ \text{R}_1\text{R}_2\text{CN} + \text{R}_3\text{NCS} \rightarrow \text{156} \]

3-From carbon disulphide:

Carbon disulphide used to prepared 2-thiopyrimidine derivatives when allowed to react with:

a) $\beta$-aminocarboxamide:

The treatment of $\beta$-aminocarboxamide derivatives 157 with carbon disulphide yielded 2-thiopyrimidine derivatives 158 (El-Sharief et al., 2003; Moustafa et al., 2003; Bakkite et al., 2004).

\[ \text{157} + \text{CS}_2 \rightarrow \text{Pyridine} \]
b) \( \beta \)-aminoester:

The \( \beta \)-aminoester 159 reacts with carbon disulphide and potassium hydroxide, then the anion that formed was S-methylated by methyl iodide and subsequently the process was completed by insitu treatment with hydrazine hydrate to produced 2-thiopyrimidine derivative 160 (Pathak et al., 1986; Abass, 2003).

\[
\begin{align*}
\text{OEt} & \quad \xrightarrow{\text{1-} \text{CS}_2/ \text{MeI/KOH or CS}_2/\text{K}_2\text{CO}_3}\quad \xrightarrow{\text{2-} \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}}
\end{align*}
\]

\( \text{159} \quad \rightarrow \quad \text{160} \)

\( \text{NH}_2\text{O} \quad \text{OEt} \quad \text{N} \quad \text{NH}_2\text{O} \quad \text{S} \quad \text{NH}_2\text{OH}_2\text{O} \quad \text{CS}_2 \quad \text{MeI/KOH or CS}_2/\text{K}_2\text{CO}_3 \quad \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \quad \text{NH}_2\text{CN} \quad \text{N} \quad \text{NH}_2\text{S} \quad \text{159} \quad \text{160} \)

\( \text{CS}_2 \quad \text{KOH, EtOH} \quad \Delta \)

\( \text{NH}_2\text{CN} \quad \text{CS}_2 \quad \text{KOH, EtOH} \quad \Delta \)

\( \text{161} \quad \rightarrow \quad \text{162} \)

c) \( \beta \)-aminocyano:

The reaction of \( \beta \)-aminocyano derivative 161 with carbon disulphide in presence of aqueous potassium hydroxide (Swelam et al., 1999; El-Gazzar et al., 2002; Rashad et al., 2005) to gave (162).
REACTION OF 2-THIOPYRIMIDIES:

2-Thiopyrimidine is \( m \)-diazine derivative, the electrophilic substitution take place at C\(_5\) while nucleophilic substitution takes place at C\(_2\), C\(_4\) and C\(_6\).

1-**Electrophilic substitution reaction:**

\textit{a) Halogenation:}

2-Methylthiopyrimidin-6-one 163 is bromonated with \( \text{Br}_2 \) in dioxane in presence of \( \text{NaBr/KOH} \) gave 5-bromo-2-methylthiopyrimidin-6-one 164 (Barrett et al., 1948).

\begin{equation*}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{SCH}_3 \\
\text{Br} \\
\text{2-Methylthiopyrimidin-6-one 163} \\
\text{Br}_2/\text{dioxane} \\
\text{NaBr/KOH} \\
\text{5-bromo-2-methylthiopyrimidin-6-one 164} \\
\end{array}
\end{equation*}

\textit{b) Nitrosation:}

Nitrosation of 1,2-dihydro-2-thiopyrimidin-4-(3H)one derivative 165 with sodium nitrite in acetic acid yielded the corresponding 5-nitroso-1,2-dihydro-2-thiopyrimidin-4-(3H)one 166 (Hubsch and Pfleiderer, 1988; Hassaneen et al., 2001).

\begin{equation*}
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{S} \\
\text{NPh} \\
\text{N} \\
\text{H} \\
\text{165} \\
\text{NaNO}_2/\text{AcOH} \\
\text{166} \\
\end{array}
\end{equation*}

\textit{c) Diazotization:}

Reaction of 1,2-dihydro-2-thiopyrimidin-4-(3H)one derivative 165 with diazotized aniline gave 5-phenylazo-1,2-dihydro-2-thiopyrimidin-4-(3H)one derivative 167 (Hubsch and Pfleiderer, 1988; Hassaneen et al., 2001).
d) Isocyanation:

The thiopyrimidine derivative 168 reacted with phenyl isocyanate in presence of pyridine to gave 169 (Minatelli and Brewer, 1986).

2- Nucleophilic substitution reaction:

a) Alkylation:

i) With Grignard reagent:

The reaction of 2-methylthiopyrimidine derivative 170 with Grignard reagent gave dihydro derivative 171 (Rise et al., 1984; Remennikov et al., 1989).

ii) With alkyl halide:

The reaction of 2-thiopyrimidine derivative 172 with alkyl halide gave 2-alkylthiopyrimidine 173 (Khalil et al., 1989; Hammam et al., 1996; El-Gazzar et al., 2001; Wyrzkiewicz and Szponar, 2003; Aly, 2004).
iii) With isothiocyanate:

The reaction of 2-mercaptopyrimidine derivative 174 with phenyl isothiocyanate gave 175 (El-Deen and Ibrahim, 2002).

iv) With monohalo compounds:

The reaction of 2-thiopyrimidine derivative 176 with 2-chloroethyl methyl ether 177 in presence of alcoholic sodium hydroxide solution gave the S-alkylated derivative 178 (Sayed et al., 2006).

The reaction 2-thiopyrimidine derivative 179 with 2,3,4,5-tetra-O-acetyl-α-D-glucopyranosyl bromide (α-ABG) in presence of aqueous potassium hydroxide gave alkylated derivative 180 (Abdel-Megeid et al., 1998).
While the reaction of 2-thiopyrimidine derivative 181 with 2 mole of α-ABG gave N- and S-alkylated derivative 182 (Aly et al., 2004).

The 2-thiopyrimidine derivative 183 undergoes alkylation with bromoester followed by heating in H₂O gave thiazolopyrimidine derivatives 184 (Wyrzkiewicy et al., 1982).

The 2-thiopyrimidine derivative 185 undergoes alkylation with bromoester followed by heating in sodiumethoxide gave 186 (Ahmed, 2002).
2-Thiopyrimidine derivative 187 heated with chloro/bromoacetic acid, α-bromopropionic acid and β- bromopropionic acid in acetic acid/ acetic anhydride and fused sodium acetate (Hammam et al., 1987; El-Gazzar et al., 2002; El-Sharief et al., 2003; Rashad et al., 2005; Sayed et al., 2006) or in dioxane (Mobinikhaledi et al., 2003; Mobinikhaledi et al., 2004). First S-alkylated then cyclized and gave thiazolopyrimidine-3-ones 188, 2-methylthiazolopyrimidine-3-ones 189 and thiazolopyrimidine-4-ones 190 respectively.

When 2-thiopyrimidine derivative 187 reacted with an aldehyde and chloro/bromoacetic acid in acetic acid/ acetic anhydride and fused sodium acetate under reflux (El-Gazzar et al., 2002; El-Sharief et al., 2003; Holla et al., 2004; Sayed et al., 2006) or in sodium acetate under microwave irradiation (Mobinikhaledi and Foroughifar, 2004) gave 191.
When 2-thiopyrimidine derivative (192) reacted with an aldehyde and β-bromopropionic acid in acetic acid/ acetic anhydride and fused sodium acetate under reflux (Rashad et al., 2005) to give (193).

2-Thiopyrimidine derivative 194 reacted with chloroacetic acid in alcoholic potassium hydroxide caused alkylation on thiol group (El-Sharief et al., 2003) and gave 195.

2-Thiopyrimidine derivative 196 reacted with bromomalononitrile under microwave irradiation (Foroughifar et al., 2003) lead to formation of 197.
v) With dihalo compounds:

2-Thiopyrimidine derivative \(198\) reacted with 1,2-dibromoethane (Ahmed, 2003; Mobinikhaledi et al., 2003), 1,2-dibromoethylene (Ahmed, 2003), 1,2-dibromopropane (Ahmed, 2003), 1,3-dibromopropane (Ahmed, 2003) and 1,4-dichlorobutane (Mobinikhaledi et al., 2004) in DMF afforded \(199, 200, 201, 202\) and \(203\) respectively.

\[ \begin{align*}
\text{BrCH}_2\text{CH}_2\text{Br} & \rightarrow \text{DMF} \\
\text{BrCH} = \text{CHBr} & \rightarrow \text{DMF} \\
\text{Br-CH}_2\text{CH}_2\text{CH}_3 & \rightarrow \text{DMF} \\
\text{ClCH}_2\text{CH}_2\text{CH}_2\text{Cl} & \rightarrow \text{DMF}
\end{align*} \]

\(198\)

\(199\)

\(200\)

\(201\)

\(202\)

\(203\)

b) Aminolysis:

1,4,6-trisubstituted-2(1H)-pyrimidinethiones \(204\) reacted with hydroxylamine the ring transformation takes place gave 2-aminopyrimidin-1-oxide derivatives \(205\) (Kashima et al., 1982).
c) Ammalysis:

2-Thiopyrimidine derivative 206 was aminated with NH$_3$/MeOH in presence of powdered Cu (Rao, 1982) and gave 2-aminopyrimidine derivative 207.

\[ \text{R} \quad \text{S} \quad \text{N} \quad \text{Ph} \quad \text{Me} \quad \text{Me} \quad \text{HONH}_2 \quad \rightarrow \quad \text{Me} \quad \text{N} \quad \text{NHPh} \]

\[ 204 \quad 205 \]

\[ \text{R} \quad \text{R}' \quad \text{NH}_2/\text{MeOH} \quad \rightarrow \quad \text{R} \quad \text{R}' \quad \text{N} \quad \text{NH}_2 \]

\[ 206 \quad 207 \]

d) Hydrazinolysis:

2-Methylmercaptopyrimidine derivative 208 reacted with hydrazine hydrate produced 2-hydrazinopyrimidine derivative 209 (El-Din and Hamid, 1992; Ahmed, 2002) with evolution of methyl mercaptan.

\[ \text{R} \quad \text{S} \quad \text{CH}_3 \quad \text{N} \quad \text{N} \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{NHNNH}_2 \quad \rightarrow \quad \text{R} \quad \text{R} \quad \text{N} \quad \text{NHNNH}_2 \]

\[ 208 \quad 209 \]

Also, 2-thiopyrimidine derivative 210 reacted with hydrazine hydrate in EtOH (Khalil et al., 1989) or in pyridine (Khodairy, 2003) gave 2-hydrazinopyrimidine derivative 211.
e) **Hydrolysis:**

Hydrolysis of 6-hydroxy-2-mercaptopyrimidie 212 with hydrochloric acid and chloroacetic acid mixture gave a uracil 213 (Brown, 1950).

\[
\text{NH}_2\text{NH}_2 \quad \text{EtOH} \quad \text{or pyridine} \quad \text{NH}_2\text{NH}_2
\]

f) **Desulphurization:**

Desulphurization of 2-thiopyrimidine derivative 214 was achieved under various conditions e.g. with H\(_2\)O\(_2\)/ ClCH\(_2\)COOH or Br\(_2\)/ MeOH/ CH\(_3\)Cl (Samour et al., 1970) produced 1,2-dihydropyrimidine derivative 215.

2-Thiopyrimidine derivative 216 when warmed with Raney nickel, desulphurization takes place (Kashima et al., 1983) and produce 217.
3-Oxidation reaction:

2-methyl thiopyrimidine derivative 218 oxidized with Cl$_2$ water (Rise et al., 1984) gave 219.

4-Reduction reaction:

4,6-diamino-1H-pyrimidine-2-thione 220 reduced by Zn dust (Sayed et al., 2006) produced 4,6-diamino-1,3,4-trihydropyrimidine-2-thione (221).
EXPERIMENTAL

All melting points are uncorrected and were measured using an Electrothermal IA 9100 apparatus. Analytical data were performed by Vario El Mentar apparatus, organic microanalysis section, National Research Centre. The IR spectra (KBr) were recorded on a Pye Unicam Sp-3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. $^1$H spectra were run at 300 MHz and $^{13}$C spectra were run at 75.46 MHz in dimethylsulphoxide (DMSO-d$_6$). Chemical shifts are quoted in δ and were related to that of the solvents. The Mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 ev. The spectroscopic analysis were carried out at micro analytical center, Cairo University.

Synthesis of 1a-c:

A mixture of 3,4-dimethyl-acetophenone (0.01 mole) and aromatic or heterocyclic aldehydes (0.01 mole) in ethanol (30 ml) and 10% NaOH (15 ml) was added drop wise within 15 min. The reaction mixture was stirred for 3 hrs and left overnight at room temperature. The mixture was poured onto ice cold water and the precipitate obtained was filtered off and crystallized from ethanol to give 1a-c.

Compounds 1a (Hassner and Mead, 1962) and 1b (Coffen and Korzen, 1971) were identified via m.p.

Thien-2-yl-formylidene-3,4-dimethyl acetophenone (1c):

80% yield; m.p.75-6°C. IR spectrum (KBr, v, cm$^{-1}$): at 1651 cm$^{-1}$ (C=O) and t 1606 cm$^{-1}$ (C=C). The $^1$H NMR spectrum (DMSO-d$_6$, δ ppm) at 2.29 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$), 7.16-7.31 (m, 2H, olefinic protons), and 7.51-7.90 (m, 6 H, Ar-H). Mass spectrum of showed the molecular ion peak M$^+$ at m/z 242 (100%, C$_{15}$H$_{14}$OS) the parent peak is
the base peak. Analysis for C_{13}H_{14}O S (242): required C, 74.39; H, 5.79; S, 13.22; found C, 74.30; H, 5.67; S, 13.05.

**Synthesis of 2a,b:**

Hydrogen peroxide (5 ml, 30%) was added portion wise to a mixture of 3-(4-chloro-phenyl)-1-(3,4-dimethyl-phenyl)-propenone (1a) or 1-(3,4-dimethyl-phenyl)-3-p-tolyl-propenone (1b) (0.01 mol) in acetone (50 ml), and methanol (15 ml) containing NaOH (1g) at 20-25 °C with stirring. The reaction mixture was left over night, cold water was added and the precipitated solid was filtered off, washed with cold water and crystallized from ethanol to give compounds 2a,b.

**[3-(4-Chloro-phenyl)-oxiranyl]-(3,4-dimethyl-phenyl)-methanone (2a):**

85% yield; m.p 96-7˚C. IR spectrum (KBr, ν, cm^{-1}): at 1655 (C=O). H NMR spectrum (DMSO-d$_6$, δ ppm): 2.27 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 4.13 (d, 1H, epoxy-H), 4.80 (d, 1H, epoxy-H), 7.300-7.780 (m, 7 H, Ar-H); MS, m/z (%): 286 (M$^+$, 41.02), 288(M$^+$+2, 14.61), 133 (100). Analysis for C$_{17}$H$_{15}$ClO$_2$ (286.5): required C, 71.20; H, 5.27; found C, 71.22; H, 5.29.

**(3,4-Dimethyl-phenyl)-(3-p-tolyl-oxiranyl)-methanone (2b):**

80% yield; m.p 80-1˚C. IR spectrum (KBr, ν, cm^{-1}): 1724 (C=O); MS, m/z (%): 266 (M$^+$, 53.25), 242 (100). Analysis for C$_{18}$H$_{18}$O$_2$ (266): required C, 81.17; H, 6.81; found C, 81.30; H, 6.77.

**Synthesis of 3a,b:**
A mixture of compounds (2) (0.01 mole) and thiourea (0.01mol) in ethanolic potassium hydroxide (2g in 100ml ethanol) was refluxed for 4h. The solvent was evaporated and the formed precipitate was washed several time with acidified cold water filtered off and recrystallized from the proper solvent to give compounds 3a,b.

4-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-2-thioxo-tetrahydro-pyrimidin-5-one (3a):

From acetic acid, yield 72%; m.p. 137-8 °C. IR spectrum (KBr, ν, cm\(^{-1}\)): 3128 (2NH), 1245(C=S), 1757 (C=O); \(^1\)H NMR spectrum (DMSO-d\(_6\), δ ppm): 2.22 (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 3.04 (d, 1H, pyrimidine-H), 3.49 (d, 1H, pyrimidine-H), 7.18-7.37 (m, 7 H, Ar-H), 10.66 (s, 1H, NH, D\(_2\)O exchangeable), 11.47 (s, 1H, NH, D\(_2\)O exchangeable); MS, m/z (%): 344 (M\(^+\), 13.23), 346 (M\(^+\)+2, 4.55), 132 (100). Analysis for C\(_{18}\)H\(_{17}\)ClN\(_2\)O\(_5\) (344.5): required C, 62.69; H, 4.97; N, 8.12; S, 9.28; found C, 62.70; H, 4.98; N, 8.11; S, 9.01.

4-(3,4-Dimethyl-phenyl)-2-thioxo-6-p-tolyl-tetrahydro-pyrimidin-5-one (3b):

From benzene, yield 68%; m.p. 170 -1°C. IR spectrum (KBr, ν, cm\(^{-1}\)): 3292, 3396 (2NH), 1263 (C=S), 1725 (C=O); \(^1\)H NMR spectrum (DMSO-d\(_6\), δ ppm): 2.22 (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 2.26 (s, 3H, CH\(_3\)), 3.00 (d, 1H, pyrimidine-H), 3.38 (d, 1H, pyrimidine-H), 7.06-7.35 (m, 7H, Ar-H), 10.63 (s, 1H, NH, D\(_2\)O exchangeable), 11.37 (s, 1H, NH, D\(_2\)O exchangeable); \(^13\)C-NMR spectrum (DMSO-d\(_6\), δ ppm): 42 and 71 \(sp^3\) carbon, 122-136 aromatic carbons, 175 C=S, 181 C=O. MS, m/z (%): 324 (M\(^+\), 38.9), 219 (100). Analysis for C\(_{19}\)H\(_{20}\)N\(_2\)O\(_5\) (324): required C, 70.34; H, 6.25; N, 8.63; S, 9.88; found C, 70.30; H, 6.25; N, 8.50; S, 9.50.
**Synthesis of 4a,b:**

**Method A:**

A mixture of compounds (3) (0.01 mole) with bromoacetic acid (0.01 mole) in acetic acid (30ml) / acetic anhydride (15ml) mixture in the presence of fused anhydrous sodium acetate (2g) was refluxed for 3h. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water, filtered off and recrystallized from acetic acid to give compounds 4a,b.

**Method B:**

A mixture of compounds (3) (0.01 mole) with bromoacetic acid (0.01 mole) in dioxane was refluxed for 3h. The solvent was evaporated and the formed precipitate was filtered off and recrystallized from acetic acid to give compounds identical in all aspects with compounds obtained from method A.

5-(4-Chloro-phenyl)-7-(3,4-dimethyl-phenyl)-tetrahydro-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (4a):

Yield 65%; m.p. 146-7 °C. IR spectrum (KBr, ν, cm⁻¹): 1720 (C=O), 1743(C=O); ¹H NMR spectrum (DMSO-d₆, δ ppm): 2.21 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 3.54 (d, 1H, pyrimidine-H), 3.74 (d, 1H, pyrimidine-H), 4.45 (d, 1H, thiazole-H), 4.56 (d, 1H, thiazole-H), 6.93-7.66 (m, 7H, Ar-H); MS, m/z (%): 384 (M⁺, 19.61), 386 (M⁺+2, 6.33), 132 (100). Analysis for C₂₀H₁₇ClN₂O₂S (384.5): required C, 62.41; H, 4.45; N, 7.28; S, 8.33; found C, 62.50; H, 4.60; N, 7.20; S, 8.20.

7-(3,4-Dimethyl-phenyl)-5-p-tolyl-tetrahydro-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (4b):

Yield 62%; m.p. 185-6 °C. IR spectrum (KBr, ν, cm⁻¹): 1710 (C=O), 1740(C=O); Analysis for C₂₁H₂₀N₂O₂S (364): required C, 69.21; H, 5.53; N, 7.69; S, 8.30; found C, 68.90; H, 5.54; N, 7.70; S, 8.38.
Synthesis of 6:

Method A:

A mixture of compound 3a (0.01 mole) with 2-bromopropionic acid (0.01 mole) in acetic acid (30ml) / acetic anhydride (15ml) mixture in the presence of fused anhydrous sodium acetate (2g) was refluxed for 3h. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water, filtered off and recrystallized from ethanol to give compound 6.

Method B:

A mixture of compound 3a (0.01 mole) with 2-bromopropionic acid (0.01 mole) in dioxane was refluxed for 3h. The solvent was evaporated and the formed precipitate was filtered off and recrystallized from acetic acid to give compound identical in all aspects with compound obtained from method A.

5-(4-Chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-methyl-tetrahydro-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (6):

Yield 63%; m.p. 132-3˚C. IR spectrum (KBr, ν, cm⁻¹): 1700 (C=O), 1756 (C=O); ¹H NMR spectrum (DMSO-d₆, δ ppm): 1.60 (d, 3H, CH₃), 2.23 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 3.05 (d, 1H, pyrimidine-H-7), 3.41 (d, 1H, pyrimidine-H-5), 4.44 (q, 1H, thiazole-H), 7.09-7.33 (m, 7H, Ar-H); MS, m/z (%): 383 (M⁺-15, 23.99), 385 (M⁺-13, 8.02), 125 (100).

Analysis for C₂₁H₁₉ClN₂O₂S (398.5): required C, 63.23; H, 4.87; N, 7.18; S, 8.03; found C, 63.22; H, 4.77; N, 7.17; S, 8.00.

Synthesis of 7a-c:

Method A:

A mixture of compounds 4 (0.01 mole) and equimolar amount of the corresponding aromatic aldehyde in acetic anhydride (30ml) was
refluxed for 3h. The solution was cooled, gradually poured onto cold water and the formed precipitate was filtered off and recrystallized from the proper solvent to give compounds 7a-c.

**Method B:**

A mixture of compounds 3 (0.01 mole), bromoacetic acid (0.01 mole), equimolar amount of the corresponding aromatic aldehyde in acetic acid (30ml) / acetic anhydride (15ml) mixture in the presence of fused anhydrous sodium acetate (2g) was refluxed for 3h. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water, filtered off and recrystallized from the proper solvent to give compounds identical in all aspects with compounds obtained from method A.

5-(4-Chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-(4-fluoro-benzylidene)-tetrahydro-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (7a):

From: benzene / pet. ether, yield 73%; m.p. 190-1°C. IR spectrum (KBr, ν, cm⁻¹): 1702 (C=O), 1737 (C=O); Analysis for C₂₇H₂₀ClFN₂O₂S (490.5): required C, 66.05; H, 4.07; N, 5.70; S, 6.52; found C, 66.05; H, 4.07; N, 5.75; S, 6.60.

7-(3,4-Dimethyl-phenyl)-5-p-tolyl-2-(4-methoxy-benzylidene)-tetrahydro-7H-thiazolo[3,2-a] pyrimidine-3,6-dione (7b):

From: pet. ether as an eluent on silica gel column chromatography, yield 60%; oil. IR spectrum (KBr, ν, cm⁻¹): 1703 (C=O), 1757 (C=O); ¹H NMR spectrum (DMSO-d₆, δ ppm): 2.21 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 3.54 (d, 1H, pyrimidine-H), 3.74 (d, 1H, pyrimidine-H), 3.90 (s, 3H, OCH₃), 6.93-7.66 (m, 7H, Ar-H ), 9.97 (s, 1H, exocyclic vinylic-H)(Holla et al., 2004) ; MS, m/z (%): 482 (M⁺, 75.14), 105 (100).
Analysis for C$_{29}$H$_{26}$N$_2$O$_3$S (482): required C, 79.45; H, 5.43; N, 6.34; S, 7.30; found C, 79.55; H, 5.66; N, 6.29; S, 7.30.

7-(3,4-Dimethyl-phenyl)-5-p-tolyl-2-(4-fluoro-benzylidene)-tetrahydro-7H-thiazolo[3,2-a] pyrimidine-3,6-dione (7c):

From: benzene / pet. ether, yield 68%; m.p. 210-1˚C. IR spectrum (KBr, ν, cm$^{-1}$): 1700 (C=O), 1726 (C=O); MS, m/z (%): 456 (M$^+$-14, 3);

Analysis for C$_{28}$H$_{23}$FN$_2$O$_2$S (470): required C, 71.64; H, 4.90; N, 5.97; S, 6.83; found C, 71.54; H, 4.70; N, 5.23; S, 6.45.

**Synthesis of 8:**

The aromatic amine (0.01 mole) was dissolved in concentrated hydrochloric acid (3 ml) and water (2 ml) cooled to -10˚C and treated with sodium nitrate (0.7g, 5 ml water). The diazotized amine was added gradually while stirring to cooled solution of compound (4a) (0.01 mole) in pyridine (20 ml). The reaction mixture was refrigerator for 1/2 h and then diluted with water and recrystallized from benzene / pet. ether to give compound 8.

5-(4-Chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-(4-nitrophenyl-hydrazono)-tetrahydro-7H-thiazolo [3,2-a]pyrimidine-3,6-dione (8):

Yield 52 %; m.p 152-3˚C. IR spectrum (KBr, ν, cm$^{-1}$): 3296 (NH), 1705 (C=O), 1771 (C=O); $^1$H NMR spectrum (DMSO-d$_6$, δ ppm): 2.23 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 3.05 (d, 1H, pyrimidine-H), 3.41 (d, 1H, pyrimidine-H) , 3.83 (s, 1H, NH, D$_2$O exchangeable), 7.09-7.33 (m, 11 H, Ar-H ); MS, m/z (%): 533 (M$^+$, 40.7), 535 (M$^+$+2, 13.51), 132 (100). Analysis for C$_{26}$H$_{20}$ClN$_5$O$_2$S (533): C, 61.25; H, 4.59; N, 10.20; S, 5.84; found C, 61.00; H, 4.62; N, 10.22; S, 5.85.
**Synthesis of 9a,b:**

Formaldehyde (1ml, 40%) was added to compounds 3 (0.01 mole) in anhydrous ethanol (30ml) the reaction mixture was heated for 5 minutes, then piperidine (0.01 mole) was added to the cold solution and the reaction mixture was stirred for 3h at room temperature. The formed solid filtered off and recrystallized from ethanol to give compounds 9a,b.

6-(4-Chloro-phenyl)-4-(3,4-dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-tetrahydro-pyrimidin-5-one (9a):

Yield 83%; m.p. 215-6°C. IR spectrum (KBr, ν, cm⁻¹): 3279 (NH), 1287 (C=S), 1723 (C=O); ¹H NMR spectrum (DMSO-d₆, δ ppm): 1.20-1.45 (m, 6H, piperidine-H), 1.97 (t, 4H, piperidine-H ), 2.21 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 3.10 (d, 1H, pyrimidine-H), 3.48 (d, 1H, pyrimidine-H), 4.18 (d, 1H, CH₂), 4.57 (d, 1H, CH₂), 7.18-7.37 (m, 7H, Ar-H ), 10.99 (s, 1H, NH, D₂O exchangeable). MS, m/z (%): 441 (M⁺, 1.5) 443 (M⁺+2, 0.47), 98 (100). Analysis for C₂₄H₂₈ClN₃OS (441): required C, 65.21; H, 6.38; N,9.51; S, 7.25; found C, 65.30; H, 6.40; N,9.70; S, 7.30.

4-(3,4-Dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-6-p-tolyl-tetrahydro-pyrimidin-5-one (9b):

Yield 79%; m.p. 205-6°C. IR spectrum (KBr, ν, cm⁻¹): 3293 (NH), 1283 (C=S), 1719 (C=O); ¹H NMR spectrum (DMSO-d₆, δ ppm): 1.09-1.24 (m, 6H, piperidine-H), 1.98 (t, 4H, piperidine-H ), 2.21 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 3.05 (d, 1H, pyrimidine-H), 3.41 (d, 1H, pyrimidine-H), 4.21 (d, 1H, CH₂), 4.44 (d, 1H, CH₂), 7.09-7.33 (m, 7H, Ar-H ). MS, m/z (%): 422 (M⁺+1, 3.3), 98 (100). Analysis for C₂₅H₃₁N₃OS (421): required C, 71.42; H, 7.38; N, 6.66; S, 7.61; found , 71.44; H, 7.40; N, 6.72; S, 7.66.
**Synthesis of 10:**

Formaldehyde (1ml, 40%) was added to compound 4a (0.01 mole) in anhydrous ethanol (30ml) the reaction mixture was heated for 5 minutes, then piperidine (0.01 mole) was added to the cold solution and the reaction mixture was stirred for 3h at room temperature. The formed solid filtered off and recrystallized from ethanol to give compound 10.

7-(3,4-Dimethyl-phenyl)-2-piperidin-1-ylmethyl-5-p-tolyl-tetrahydro-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (10):

Yield 55%; m.p. 210-1˚C. IR spectrum (KBr, ν cm⁻¹): 1500 (C=N), 1715 (C=O), 1740 (C=O); ¹H NMR spectrum (DMSO-d6, δ ppm): 1.09-1.24 (m, 6H, piperidine-H), 1.98 (t, 4H, piperidine-H), 2.21 (s, 3H, CH3), 2.23 (s, 3H, CH3), 2.24 (s, 3H, CH3), 3.05 (d, 1H, pyrimidine-H), 3.41 (d, 1H, pyrimidine-H), 4.32-4.40 (m, 1H, CH2 ), 4.49-4.53 (m, 1H, CH2 ), 5.03-5.12 (m, 1H, thiazole-H ), and 7.09-7.33 (m, 7 H, Ar-H ), MS, m/z (%): 406 (M⁺-55, 3.2), 98 (100). Analysis for C27H31N3O2S (461): required C, 70.28; H, 6.72; N, 9.11; S, 6.94; found C, 70.00; H, 6.11; N, 9.00; S, 6.55.

**Synthesis of 11a,b:**

To a solution of compounds 3 (0.01 mole) in 1ml triethylamine, a solution of 2,3,4,6-teta-O-acetyl-a-glucopyranosyl bromide (0.02 mole) in 5 ml DMF was added then the reaction mixture was stirred for 8h at room temperature, evaporated under reduced pressure at 40˚C, the residue washed with distilled water, filtered off, dried to afford an oily product compounds 11a,b.
4-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-1,3-di-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-thioxo-tetrahydro-pyrimidin-5-one (11a):

Yield 53%, IR spectrum (KBr, ν, cm⁻¹): 1225 (C=S), 1658 (C=O) and 1747 (C=O). ¹H NMR spectrum (DMSO-d₆, δ ppm): 1.98, 2.00, 2.02, 2.03, 2.05, 2.07, 2.08, 2.09 (8s, 24H, 8CH₃CO-), 2.22 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.04 (d, 1H, pyrimidine-H), 3.44 (d, 1H, pyrimidine-H), 4.13-4.21 (m, 6H, 5`-H, 5``-H, 6`-H₂, 6``-H₂), 4.742-4.923 (m, 7H, 2`-H, 2``-H, 3`-H, 3``-H, 4`-H, 4``-H, 1`-H), 5.446 (d, 1H, 1``-H) 7.18-7.37 (m, 7H, Ar-H) (Aly, 2004)

6-(3,4-Dimethyl-phenyl)-4-(4-methyl -phenyl)-1,3-di-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-thioxo-tetrahydro-pyrimidin-5-one (11b):

Yield 56%, IR spectrum (KBr, ν, cm⁻¹): 1220 (C=S), 1663 (C=O) and 1755 (C=O).

Synthesis of 12:

To a solution of compound 4a (0.05 mole) in absolute ethanol (15 ml), hydrazine hydrate (98 %) (0.06 mole) was added and the reaction mixture was refluxed for 2h. The reaction mixture was cooled, poured into water and the solid product formed was washed with little ethanol, filtered off and chromatographed on silica gel column using pet. ether (60-80) as an eluent to give compound 12a .

4-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-5,6-dihydropyrimidin-2-yl-thioacetylhydrazide (12a):

Yield 50% ; m.p 196-7°C. IR spectrum (KBr, ν, cm⁻¹): 3286 (br NHNH₂), 1720 (C=O), 1651 (C=O); ¹H NMR spectrum (DMSO-d₆, δ ppm): 2.22 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.04 (d, 1H, pyrimidine-H), 4.38 (s, 2H, NH₂, D₂O exchangeable), 5.13 (s, 2H, CH₂), 7.18-7.37 (m,
7H, Ar-H), 12.37 (s, 1H, NH, D$_2$O exchangeable. Mass spectrum showed the molecular ion peak M$^+$ at $m/z$ 414 (15.52), 416 (M$^+$+2, 5.11). Analysis for C$_{20}$H$_{19}$ClN$_4$O$_2$S (414): required C, 57.97; H, 4.58; N, 13.52; S, 7.72; found C, 57.23; H, 4.33; N, 13.09; S, 7.60.

**Synthesis of 13:**

A mixture of compound 1c (0.01 mole), ethyl cyanoacetate (0.01 mole) and ammonium acetate (0.08 mole) in ethanol (40 ml) was refluxed for 10 hrs. The precipitate was filtered off and crystallized from ethanol to give 13.

3-Cyano-6-(3,4-dimethyl-phenyl)-4-thien-2-yl-1H-pyridin-2-one (13):

Yield 30%, m.p. 280-1˚C. IR spectrum (KBr, ν, cm$^{-1}$): at 3448 cm$^{-1}$ (br.), 2213 and 1633 cm$^{-1}$ due to NH (keto-enol) (Barnes and Barndon, 1943; Katritzky and Jones, 1960), CN and C=O respectively. The $^1$H NMR spectrum (DMSO-d$_6$, δ ppm) showed signals at 2.28 (s, 3H, CH$_3$), 2.29 (s, 3H, CH$_3$), 3.45 (s, 1H, NH, D$_2$O exchangeable), 6.81 (s, 1H, pyridine-H5), and 7.26-7.97 (m, 6 H, Ar-H). Mass spectrum showed the molecular ion peak M$^+$ at $m/z$ 306 (100%) as the base peak. Analysis for C$_{18}$H$_{14}$N$_2$OS(306): required C, 70.56; H, 4.61; N, 9.14; S, 10.47; found C, 70.13; H, 4.22; N, 8.96; S, 10.21.

**Synthesis of 14:**

A mixture of 3,4-dimethyl-acetophenone (0.01 mole), thiophene-2-carboxaldehyde (0.01 mole) and ethyl cyanoacetate (0.01 mole) and ammonium acetate (0.08 mole) in ethanol (40 ml) was refluxed for 6 hrs. The precipitate was filtered off and crystallized from ethanol to give 14.

4-Cyano-1-(3,4-dimethyl-phenyl)-4-ethoxy-carbonyl-3-thien-2-yl-1-butene (14):
Yield 70%, m.p.90-1°C. IR spectrum (KBr, ν, cm⁻¹): at 1717 cm⁻¹ due to ester group (C=O), and 2216 cm⁻¹ (CN). The ¹H NMR spectrum (DMSO-d₆, δ ppm) showed signals at 1.25-1.28 (t, 3H, CH₃CH₂CO), 2.25 (s, 3H, CH₃), 2.261 (s, 3H, CH₃), 2.269 (d, 1H, CH), 4.27-4.43 (q, 2H, CH₃CH₂CO), 6.85(d, 1H, olefinic H ), 7.31-8.55 (m, 6 H, Ar-H ). Mass spectrum showed the molecular ion peak M⁺ at m/z 306 (100%) as the base peak (M⁺-2CH₃). Analysis for C₂₀H₁₉NO₂S(337): required C, 71.19; H, 5.68; N, 4.15; S, 9.50; found C, 69.90; H, 5.22; N, 4.00; S, 9.21.

**Synthesis of 15:**

A mixture of compound 13 (0.01 mole),ethyl chloroacetate (0.01 mole) and anhydrous potassium carbonate (0.04 mole) in dry acetone 30 ml was refluxed for 20 hrs. the excess of solvent was evaporated then poured onto water. The solid obtained was filtered of and crystallized from ethanol to give 15.

**3-Cyano-6-(3,4-dimethyl-phenyl)-2-ethoxycarbonylmethoxy-4-thien-2-yl-pyridine (15):**

Yield 65%, m.p.170-1°C. IR spectrum (KBr, ν, cm⁻¹): at 2221 cm⁻¹ (CN) and 1751 cm⁻¹ (C=O). The ¹H NMR spectrum (DMSO-d₆, δppm) showed signals at 1.17-1.21 (t, 3H, CH₃CH₂OC=O), 2.28 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 4.15-4.22(q, 2H, CH₃CH₂OC=O), 5.13 (s, 2H, CH₂), and 7.26-8.03 (m, 7 H, Ar-H and pyridine-H5).Mass spectrum showed the molecular ion peak M⁺ at m/z 392 (32.5%) and the base peak at m/z 319 (M⁺-COOC₂H₅) (Nadkarni et al.,1937).Analysis for C₂₂H₂₀N₂O₃S (392) required C, 67.35; H, 5.10; N, 7.14; S, 8.16; found C, 67.22; H, 4.92; N, 7.00; S, 8.02.

**Synthesis of 17:**
A solution of compound 15 (0.01 mole) in ethanol (50 ml) and hydrazine hydrate 98% (0.01 mole) was refluxed for 6 hrs. The separated solid after cooling was crystallized from ethanol to give 17.

3-Cyano-2-hydrazino-6-(3,4-dimethyl-phenyl)-4-thien-2-yl-pyridine (17):

Yield 61%, m.p.185-6°C. IR spectrum (KBr, v, cm\(^{-1}\)): at 3400 and 3295 cm\(^{-1}\) (NH\(_2\), NH), and 2366 (CN). \(^1\)H NMR spectrum (DMSO-d\(_6\), \(\delta\) ppm) showed signals at 2.26 (s, 3H, CH\(_3\)), 2.28 (s, 3H, CH\(_3\)), 4.83 (s, 2H, NH\(_2\), D\(_2\)O exchangeable) 7.47 (s, 1H, pyridine-H5), 7.23-7.94 (m, 6 H, Ar-H), 12.37 (s, 1H, NH, D\(_2\)O exchangeable).Mass spectrum showed the molecular ion peak M\(^+\) at \(m/z\) 320 (100%) which is the base peak. Analysis for C\(_{18}\)H\(_{16}\)N\(_4\)S (320): required C, 67.50; H, 5.00; N, 17.50; S, 10.00 found C, 67.37; H, 4.81; N, 17.29; S, 9.91.

**Synthesis of 18:**

Ethyl acetoacetate (0.01 mole) was added to an ethanolic solution of sodium ethoxide [prepared by dissolving sodium metal (0.03g) in absolute ethanol (15 ml)] and the reaction mixture was stirred for one hour. then 1c (0.01 mole) was added to the reaction mixture and resulting solution was refluxed for 3 hrs then cooled and poured onto ice-dill HCL. The oil product obtained 18

4-(3,4-Dimethyl-phenyl)-2-oxo-6-thien-2-yl-cyclohex-3-enecarboxylate (18):

Yield 65%, IR spectrum (KBr, v, cm\(^{-1}\)): at 1739 cm\(^{-1}\) and 1667 cm\(^{-1}\) (2C=O). Mass spectrum showed the molecular ion peak M\(^+\) at \(m/z\) 354 (9.7%) supporting its molecular formula (C\(_{21}\)H\(_{22}\)O\(_3\)S). Analysis for
\[ C_{21}H_{22}O_3S \] (354): required C, 71.19; H, 6.21; S, 9.04 found C, 71.05; H, 6.16; S, 8.89.

**Synthesis of 19:**

The oil product 18 was added to an ethanolic solution of sodium hydroxide and refluxed for 3 hrs. The reaction mixture was cooled, acidified with dil HCL and extracted with ether. The ether layer was washed with water and dried over anhydrous MgSO\(_4\). The ether was evaporated and the solid obtained was crystallized from ethanol to give 19.

3-(3,4-Dimethyl-phenyl)-5-thien-2-yl-cyclohexa-2,4-dienone (19):

yield 57%, m.p.125-6°C. IR spectrum (KBr, v, cm\(^{-1}\)): at 1701 cm\(^{-1}\) (C=O). \(^1\)H NMR spectrum (DMSO-d\(_6\), \(\delta\) ppm) showed signals at 2.22 (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 4.74 (d, 1H, CH\(_2\)), 4.88 (d, 1H, CH\(_2\)), 6.31 (s, 1H, H-2), 7.13-7.42 (m, 7 H, Ar-H and H-4). Mass spectrum showed the molecular ion peak M\(^+\) at \(m/z\) 280 (13.8%) supporting its molecular formula C\(_{18}\)H\(_{16}\)OS. Analysis for C\(_{18}\)H\(_{16}\)OS (280): required C, 77.14; H, 5.71; S, 11.42 found C, 76.89; H, 5.55; S, 11.30.

**Synthesis of 20:**

A solution of 1c (0.01 mole) and hydrazine hydrate 98% (0.01 mole) in absolute ethanol and drops of triethylamine was heated under reflux for 3 hrs, left to cool then poured onto ice acidified water. The solid obtained was filtered off, washed several times with water and crystallized from ethanol to give 20.

3-(3,4-Dimethyl-phenyl)-5-thien-2-yl-4,5-dihydropyrazolines (20):
Yield 50%, m.p.205-6°C . IR spectrum (KBr, ν, cm\(^{-1}\)): at 3421 cm\(^{-1}\) corresponding to (NH) group. \(^1\)H NMR spectrum (DMSO-d\(_6\), δ ppm) showed signals at 2.22 (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 3.18 (dd, 1H, CH\(_2\)), 3.85 (dd, 1H, CH\(_2\)), 5.76-5.84 (m, 1H, CH), 7.18-7.37 (m, 6H, Ar-H), 11.47 (s, 1H, NH, D\(_2\)O exchangeable). Mass spectrum showed the molecular ion peak M\(^+\) is the base peak at \(m/z\) 254. Analysis for C\(_{15}\)H\(_{16}\)N\(_2\)S (256): required C, 70.31; H, 6.25; N, 10.94; S, 12.50 found C, 69.89; H, 5.89; N, 10.80; S, 12.30.

**Synthesis of 21a,b:**

A solution of 1c (0.01 mole) and hydrazine hydrate 98% (0.01 mole) in formic acid or acetic acid (30 ml) was heated under reflux for 5 hrs. Then left to cool and poured onto ice water. The obtaine precipitate was filtered off, wash several times with water then crystallized from suitable solvent to give 21a,b.

**1-Formyl-3-(3,4-dimethyl-phenyl)-5-thien-2-yl-4,5-dihydropyrazolines (21a):**

Yield 52%, m.p.139-0°C. \(^1\)H NMR spectrum (DMSO-d\(_6\), δ ppm) showed signals at 2.22 (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 3.76 (dd, 1H, CH\(_2\)), 4.42 (dd, 1H, CH\(_2\)), 5.12-5.24 (m, 1H, CH), 7.18-7.37 (m, 6H, Ar-H), 9.06 (s, 1H, CHO). Analysis for C\(_{16}\)H\(_{16}\)N\(_2\)OS (284): required C, 67.61; H, 5.63; N, 9.86; S, 11.27 found C, 67.44; H, 5.56; N, 9.73; S, 11.15.

**1-Acetyl-3-(3,4-dimethyl-phenyl)-5-thien-2-yl-4,5-dihydropyrazolines (21b):**

From acetic acid, yield 56%, m.p.168-9°C. IR spectrum (KBr, ν, cm\(^{-1}\)): at 1663cm\(^{-1}\) (C=O), 1590 (C=N). Mass spectrum showed the
molecular ion peak $M^+$ at $m/z$ 298 ($C_{17}H_{18}N_2SO$) (87%, $C_{17}H_{18}N_2OS$).
Analysis for $C_{17}H_{18}N_2OS$ (298): required C, 68.46; H, 6.04; N, 9.34; S, 10.74 found C, 68.28; H, 5.89; N, 9.11; S, 10.56.

**Synthesis of 22:**
A solution of $1c$ (0.01 mole) and phenyl hydrazine (0.01 mole) in acetic acid (30 ml) was heated under reflux for 5 hrs. Then left to cool and poured onto ice water. The obtained precipitate was filtered off, washed several times with water then crystallized from ethanol to give 22.

3-(3,4-Dimethyl-phenyl)-1-phenyl-5-thien-2-yl-4,5-dihydropyrazoline (22):
Yield 66%; m.p.115-6°C. IR spectrum (KBr, $\nu$, cm$^{-1}$): at 3100, 2923 and 1596 cm$^{-1}$ characteristic to CH aromatic, CH aliphatic and C=N respectively. Analysis for $C_{21}H_{20}N_2S$ (332): required C, 75.87; H, 6.06; N, 8.43; S, 9.64 found C, 75.71; H, 5.87; N, 8.30; S, 9.56.

**Synthesis of 23:**
A solution of $1c$ (0.01 mole), hydroxylamine hydrochloride (0.01 mole) in pyridine (40 ml) was refluxed for 8 hrs then the cooled reaction was acidified with ice cooled dil HCL. The solid separated filtered off, dried and crystallized from ethanol to give 23.

3-(3,4-Dimethyl-phenyl)-5-thien-2-yl-4,5-dihydro isoxazoline (23):
Yield 68%, m.p.173-4°C. IR spectrum (KBr, $\nu$, cm$^{-1}$): at 2937, 1619 and 1590 cm$^{-1}$ characteristic to CH, C=N and C=C respectively. Mass spectrum showed the molecular ion peak $M^+$ is the base peak at $m/z$ 256 ($M^+-1$, 49%). Analysis for $C_{15}H_{15}NOS$ (257): required C, 70.04; H, 5.84; N, 5.45; S, 12.45 found C, 69.71; H, 5.66; N, 5.30; S, 12.22.
RESULTS AND DISCUSSION

Arylidene 3,4-dimethylacetophenone 1a-c could be obtained through Claisen-Schmidt condensation of 3,4-dimethylacetophenone with aromatic aldehydes (Susan and Synden, 1958) namely: 4-chlorobenzaldehyde; 4-methylbenzaldehyde and thien-2-yl formaldehyde in the presence of potassium hydroxide as a catalyst. The enone products 1a-c are useful as key starting material for the preparation of several mixed and non-mixed heterocyclic compounds.

\[
\begin{align*}
\text{H}_3\text{C} &\quad \text{O} \\
\text{H}_3\text{C} &\quad \text{KOH} \\
\text{ArCHO} &\quad \text{H}_3\text{C} \\
\text{O} &\quad \text{Ar} \\
\text{H}_3\text{C} &\quad \text{Ar} \\
\text{H}_3\text{C} &\quad \text{H}_3\text{C} \\
\text{Ar} &\quad (4) \\
\text{a} &\quad \text{C}_6\text{H}_4\text{.Cl} (4) \\
\text{b} &\quad \text{C}_6\text{H}_4\text{.CH}_3 (4) \\
\text{c} &\quad \text{thienyl}
\end{align*}
\]

Compounds 1a (Hassner and Mead, 1962) and 1b (Coffen and Korzen, 1971) were identified via m.p.
Part I: Uses of 1,3-Diaryl-2,3-epoxypropanones in Synthesis of Mixed and Non-Mixed Heterocyclic Compounds

It has been shown that hydrogen peroxide reacts with $\alpha,\beta$-unsaturated carbonyl compounds producing $\alpha,\beta$-epoxy ketones (Coffen and Korzen, 1971; El-Hashash and EL-Kady, 1978) thus hydrogen peroxide reacted with arylidene-3,4-dimethyl acetophenones (1) in alkaline medium to produce 3-aryl-1-(3,4-dimethyl-phenyl)-2,3-epoxypropanones (2).

The reaction possibly takes place via the following mechanism (El-Hashash and EL-Kady, 1978):
Hydrogen peroxide in presence of \( ^\cdot \text{OH} \) behaves as an acid and gives the oxanion (\( :\ddot{\text{O}}\text{O}--\text{H} \)), which in turn attacks the \( \beta \)-carbon of the chalcone to give the fleeting intermediate \( 2^\cdot \) which undergoes intranucleophilic (SN2) attack leading to the desired products \( 2 \).

The proposed structure for \( 2 \) was supported by:

i) Its correct analytical data.

ii) The infrared spectra of compound \( 2a \) showed strong absorption bands at 1655 cm\(^{-1}\) (C=O).

iii) The \( ^1\text{H NMR} \) spectrum (DMSO-d\(_6\), \( \delta \) ppm) of compound \( 2a \) as an example showed signals at 2.27 (s, 3H, CH\(_3\)), 2.29 (s, 3H, CH\(_3\)), 4.13 (d, 1H, epoxy-H), 4.80 (d, 1H, epoxy-H), 7.30-7.82 (m, 7 H, Ar-H).

iv) The mass spectrum of compound \( 2a \) showed the molecular ion peak \( M^+ \) at \( m/z \) 286 (41.02\% C\(_{17}\)H\(_{15}\)ClO\(_2\)), 288 (M\(^+\)+2,14.61\%) which decomposes according to chart I.
Compounds 2 reacted with thiourea in alcoholic potassium hydroxide solution to produce 4-aryl-6-(3,4-dimethyl-phenyl)-2-thioxo-hexahydro-pyrimidin-5-ones (3). The reaction may proceed in a similar manner as a previously reported mechanism (Noyce and Jefraim, 1962).
Compound 3b as an example showed correct values in elemental analysis, IR absorption bands at 3292, 3396 cm$^{-1}$ for (2NH) and 1721 for (C=O); $^1$H NMR spectrum (DMSO-d$_6$, $\delta$ ppm) showed signals at 2.22 (s, 3H, CH$_3$), 2.25 (s, 3H, CH$_3$), 2.26 (s, 3H, CH$_3$), 3.00 (d, 1H, pyrimidine-H), 3.38 (d, 1H, pyrimidine-H), 7.06-7.35 (m, 7H, Ar-H), 10.63 (s, 1H, NH, D$_2$O exchangeable), 11.37 (s, 1H, NH, D$_2$O exchangeable).
exchangeable). $^{13}$C NMR spectrum of compound 3b showed two characteristic signals at 181 ppm for (C=O) and at 175 ppm for (C=S), other two signals corresponding to two $sp^3$ carbon atoms at $\delta$ 42 and 71 besides signals between 122-136ppm corresponding to $sp^2$ carbon atoms were shown .Mass spectrum of compound 3b showed the molecular ion peak M$^+$ at $m/z$ 324 (38.9%, C$_{19}$H$_{20}$N$_2$OS), which decomposes according to chart II.
chart II
The appearance of signals at δ 3.00 and 3.38 ppm in $^1$H NMR spectrum of compound 3b as well as signals at δ 42 and 71 in its $^{13}$C NMR spectrum indicate that the produced pyrimidine ring is in fact alicyclic, not aromatic which takes the shape of a twist boat 3’.

In the twist boat (the observed Raman spectrum of 1,4-cyclohexanedione showed seven bands, all of which showed coincidences in the infrared)(Allinger and Fieiberg, 1961). That so many coincidences are highly improbable to be accidental, but it rather suggests that the compound has the twist boat and not the chair.

Heating compounds 3 under reflux with bromoacetic acid in acetic acid/ acetic anhydride mixture in the presence of anhydrous sodium acetate to produce 5-aryl-7-(3,4-dimethyl-phenyl)-2,3,5,6-tetrahydro-7$H$-thiazolo[3,2-$a$]pyrimidine-3,6-diones (4) or their isomeric structure 5 (Sherif et al., 1993 ; Youssef and Youssef, 2003).
Also compounds 4 were prepared by new method in which bromoacetic acid was used as a cyclocondensation reagent in dioxane (Mobinkhaledi et al., 2003). This method is very easy to give compounds identical in all aspects with compounds 4.

The reaction possibly takes place via the following mechanism:
Compounds 4 gave correct values in elemental analysis besides displaying the expected carbonyl absorption bands in the IR spectra (cf. Experimental). $^1$H NMR spectrum (DMSO-d$_6$, $\delta$ ppm) of compounds 4a showed signals at 2.21 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 3.54 (d, 1H, pyrimidine-H7), 3.49 (d, 1H, pyrimidine-H), 4.45 (d, 1H, thiazole-H), 4.56 (d, 1H, thiazole-H), 6.93-7.66 (m, 7H, Ar-H). The two protons at C-2 are obviously diastereotopic hence they are magnetically non-equivalent and suffer from geminal coupling, resulting in the appearance of two doublets at $\delta$ 4.45 and 4.56 ppm. The mass spectrum of compound 4a showed the molecular ion peak $M^+$ at $m/z$ 384 (19.61%, C$_{20}$H$_{17}$ClN$_2$O$_2$S), 386($M^+$+2, 6.33).
The isomeric product 5 is annelated structure (angular structure) and it is less thermodynamically stable if compared by compound 4 which is annulated structure (linear structure).

Similarly, compound 3a reacted with 2-bromopropionic acid, under the same reaction conditions to produce 5-(4-chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-methyl-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (6) (Youssef and Youssef, 2003).

\[ \text{Ar} \quad \text{a} : C_6H_4Cl (4) \]

The latter compound was prepared also by using 2-bromopropionic acid as a cyclocondensation reagent in dioxane (Mobinikhaldi et al., 2003). \(^1\)H NMR spectrum of compound 6 showed a doublet signal and a quartet signal corresponding to \( \text{CH}_3 \) and proton on C-2, besides the expected signals corresponding to C-5 and C-7 protons, the two phenyl protons and 2 methyl groups (cf. Experimental).

\(^1\)H NMR spectrum (DMSO-d\(_6\), \( \delta \) ppm) of 6 showed signals at 1.60 (d, 3H, \( \text{CH}_3 \)), 2.23 (s, 3H, \( \text{CH}_3 \)), 2.24 (s, 3H, \( \text{CH}_3 \)), 3.05 (d, 1H, pyrimidine-H), 3.41 (d, 1H, pyrimidine-H), 4.44 (q, 1H, thiazole-H), 7.09-7.33(m, 7H, Ar-H). The mass spectrum of compound 6 showed the molecular ion peak at m/z 383 (M\(^+\)-15, 23%, C\(_{21}\)H\(_{19}\)ClN\(_2\)O\(_2\)S), 385 (M\(^+\)-13, 8.02%).
The presence of an active methylene group in compounds 4 could be confirmed by condensation of 4 with different aldehydes in a mixture of acetic acid/ acetic anhydride, in the presence of anhydrous sodium acetate to produce 5-(4-chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-(4-fluoro-benzylidene)-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (7a), 7-(3,4-dimethyl-phenyl)-5-p-tolyl-2-(4-methoxy-benzylidene)-7H-thiazolo[3,2-a] pyrimidine-3,6-dione (7b) and 7-(3,4-dimethyl-phenyl)-5-p-tolyl-2-(4-fluoro-benzylidene)-7H-thiazolo[3,2-a] pyrimidine-3,6-dione (7c).

Compounds 7 could be directly prepared from compound 3 in one step. Thus heating compounds 3 with bromoacetic acid and aromatic aldehydes in acetic acid/ acetic anhydride mixture in the presence of sodium acetate gave product identical in all aspects with compounds 7 ( m.p., mixed m.p., IR, MS and $^1$H NMR ) (c.f. Experimental) (Youssef and Youssef, 2003).

$^1$H NMR spectrum (DMSO-d$_6$, $\delta$ ppm) of 7b as an example revealed the disappearance of two doublets at $\delta$ 4.45 and 4.56 ppm.
(compared with that of 4) belonging to the activated methylene group, besides the appearance of the expected signal representing one OCH$_3$ group at $\delta$ 3.90 ppm. Its mass spectrum showed the molecular ion peak M$^+$ at m/z 482 (75.14%) supporting its molecular formula (C$_{29}$H$_{26}$N$_2$O$_3$S).

Compound 4a coupled with p-nitrobenzenediazonium salt in presence of pyridine to give 5-(4-chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-(4-nitrophenyl-hydrazono)-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (8).

![Chemical structures](image)

The IR spectrum of compound 8 showed absorption bands at $\nu$ 3296 cm$^{-1}$ (NH), $\nu$ 1705 cm$^{-1}$ (C=O), $\nu$ 1771 cm$^{-1}$ (C=O); its $^1$H NMR spectrum (DMSO-d$_6$, $\delta$ ppm) showed signals at 2.23 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 3.05 (d, 1H, pyrimidine-H), 3.41 (d, 1H, pyrimidine-H), 3.83 (s, 1H, NH, D$_2$O exchangeable), 7.09-7.33 (m, 11 H, Ar-H). The mass spectrum of compound 8 showed the molecular ion peak M$^+$ at m/z 533 (40.7%, C$_{26}$H$_{20}$ClN$_5$O$_2$S), 535 (M$^+$+2, 13.51).

Compounds 3 in equilibrium with their 2-mercapto tautomers; they are expected to yield a mixture of two types of products when alkylated,
but under experimental condition of Mannich, only the 3-substituted product was isolated which proved to possess structure of compounds 9. Thus compounds 3 reacted with formaldehyde in the presence of piperidine to give the corresponding Mannich bases namely 6-(4-chlorophenyl)-4-(3,4-dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-tetrahydro-pyrimidin-5-one (9a) and 4-(3,4-dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-6-p-tolyl-tetrahydro-pyrimidin-5-one(9b) successively.

The site of the attack was reached by the study of the IR as well as the $^1$H NMR and mass spectrum. Thus the IR spectrum of compound 9b showed the characteristic absorption bands at 1719, 1262 and 3293 for C=O, C=S, and NH groups successively. Its $^1$H NMR spectrum (DMSO-d$_6$, δ ppm): 1.09-1.24 (m, 6H, piperidine-H), 1.98 (t, 4H, piperidine-H ), 2.21 (s, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$), 2.24(s, 3H, CH$_3$), 3.05 (d, 1H, pyrimidine-H-6), 3.36 (d, 1H, pyrimidine-H-4), 4.21 (d, 1H, CH$_2$), 4.44 (d, 1H, CH$_2$), 7.09-7.33 (m, 7H, Ar-H ) and 10.92(s, 1H, NH, D$_2$O exchangeable).Mass spectrum of compound 9b showed the molecular ion peak at m/z 422 (M$^+$+1, 3.3%) and the base peak at 98 (100%).
Over the years there has been much controversy about the mechanism of the Mannich reaction, especially whether the aldehyde is first attached by the active hydrogen compound or by the amine. It is now generally agreed that the latter path-way is the correct one. Studies of the reaction kinetics have led to the following mechanistic proposals.

Similarly compound 4b reacted with formaldehyde in the presence of piperidine to give 7-(3,4-dimethyl-phenyl)-2-piperidin-1-ylmethyl-5-p-tolyl-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (10).
IR spectrum of compound 10 showed (ν, cm\(^{-1}\)): 1500 (C=N), 1715 (C=O), 1740 (C=O) ; \(^1\)H NMR spectrum (DMSO-d\(_6\), δ ppm): 1.09-1.24 (m, 6H, piperidine-H), 1.98 (t, 4H, piperidine-H), 2.21 (s, 3H, CH\(_3\)), 2.23 (s, 3H, CH\(_3\)), 2.24 (s, 3H, CH\(_3\)), 3.05 (d, 1H, pyrimidine-H), 3.41 (d, 1H, pyrimidine-H), 4.32-4.40 (m, 2H, CH\(_2\)), 4.49-4.53 (m, 2H, CH\(_2\)), 5.03-5.12 (m, 1H, thiazole-H ), and 7.09-7.33 (m, 7 H, Ar-H ) ; MS, m/z (%): 406 (M\(^+\)-55, 3.2), 98 (100) ) which is the base peak .

Additionally, when compounds 3 were glucosidated by coupling with 2,3,4,6-tetra-O-acetyl-\(\alpha\)-glucopyranosyl bromide (\(\alpha\)-ABG) in the presence of triethylamine, Compounds 11 were isolated as judged by tlc analysis 4-(4-chloro-phenyl)-6-(3,4-dimethyl-phenyl)-1,3-di-(2,3,4,6-tetra-O-acetyl-\(\beta\)-D-glucopyranosyl)-2-thioxo-tetrahydro-pyrimidin-5-one (11a) and 6-(3,4-dimethyl-phenyl)-4-(p-tolyl)-1,3-di-(2,3,4,6-tetra-\(O\)-acetyl-\(\beta\)-D-glucopyranosyl)-2-thioxo-tetrahydro-pyrimidin-5-one (11b).
The structures of the new products were established according to its microanalytical and spectroscopic data. Its IR spectrum of 11a reveals the disappearance of (2 NH group) as well as the existence of (C=S group) at 1225 cm$^{-1}$. $^1$H NMR spectrum (DMSO-d$_6$, $\delta$ ppm): 1.98, 2.00, 2.02, 2.03, 2.05, 2.07, 2.08, 2.09 (8s, 24H, CH$_3$CO-), 2.22 (s, 3H, CH$_3$), 2.25 (s, 3H, CH$_3$), 3.04 (d, 1H, pyrimidine-H), 3.44 (d, 1H, pyrimidine-H), 4.13-4.21 (m, 6H, 5`-H, 5``-H, 6`-H$_2$, 6``-H$_2$), 4.74-4.92 (m, 7H, 2`-H, 2``-H, 3`-H, 3``-H, 4`-H, 4``-H, 1`-H), and 5.446 (d, 1H, 1``-H) and 7.18-7.37 (m, 7H, Ar-H) (Aly, 2004).

On the other hand, interaction of compound 4a with hydrazine hydrate afforded a product which its MS revealed two compounds one has $m/z$ ($M^+$ = 414) attributed to 12a and the other compound has $m/z$ ($M^+$ = 475) attributed to 12b in which hydrazine hydrate reacted with 12a via addition and condensation reactions. Further purification using column chromatography, we could isolate only 12a as pure compound.
structure of the new product was established according to its microanalytical and spectroscopic data.

The IR spectrum of compound 12a (ν, cm⁻¹): 3286 (br NHNH₂), 1720 (C=O), 1651 (C=O) ; ¹ H NMR spectrum (DMSO-d₆, δ ppm): 2.22 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.04 (d, 1H, pyrimidine-H), 4.38 (s, 2H, NH₂, D₂O exchangeable), 5.13 (s, 2H, CH₂), 7.18-7.37 (m, 7H, Ar-H), 12.37 (s, 1H, NH, D₂O exchangeable) . Its mass spectrum showed the molecular ion peak at m/z 414 (6% ), 416(M⁺+2, 1.8%) supporting its molecular formula (C₂₉H₁₉ClN₄O₂S).
Part II: Uses of Thien-2-yl-formylidene-3,4-dimethyl acetophenone (1c) in Synthesis of Mixed and Non-Mixed Heterocyclic Compounds

In this part reaction between thien-2-yl-formylidene-3,4-dimethylacetophenone (1c) and some activated methylene compounds, namely ethyl cyanoacetate and ethyl acetoacetate as carbon nucleophiles and hydrazine hydrate, phenyl hydrazine and hydroxylamine as nitrogen nucleophiles are studied aiming to synthesize new different heterocyclic systems with potential biological activity.

The formation of 1c takes place via the plausible mechanism:

The structure of compound 1c was inferred from:

i) Correct analytical data.

ii) IR spectra of compound 1c showed absorption bands at 1651 cm\(^{-1}\) (C=O) and at 1606 cm\(^{-1}\) (C=C)
iii) The $^1$H NMR spectrum (DMSO-d$_6$, $\delta$ ppm) of compound 1c showed signals at 2.29 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$), 7.16-7.31 (m, 2H, olefinic protons), and 7.51-7.90 (m, 6H, Ar-H).

iv) Mass spectrum of compound 1c showed the molecular ion peak M$^+$ at $m/z$ 242 (100%, C$_{15}$H$_{14}$OS) the parent peak is the base peak, the fragmentation is shown in chart III.

![Diagram of fragmentation](image_url)
**Reaction with ethyl cyanoacetate:**

It is well known that enones are excellent starting materials for the synthesis of pyridone derivatives *via* the reaction of enones with ethyl cyanoacetate in the presence of ammonium acetate (Latif et al., 1981). Thus when compound 1c reacted with ethyl cyanoacetate, it afforded 3-cyano-6-(3,4-dimethyl-phenyl)-4-thien-2-yl-1H-pyridin-2-one (13)

![Chemical structure of 1c and 13](chart.png)

Formation of 13 is believed to take place as shown in chart IV, with Michael addition of ethyl cyanoacetate on 1c followed by replacement of enolic OH by NH$_2$ then cyclization with elimination of ethanol and finally dehydrogenation take place.
Chart IV

more thermodynamically stable
The above mentioned method produced a very poor yield of compound 13 (25-30%) which is in agreement with results reported in literature (Sakuria and Midorikawa, 1967). The structure of the pyridone derivative 13 was inferred from the following:

i) Correct analytical data.

ii) IR spectra exhibited absorption bands at 3448 cm\(^{-1}\) (br.), 2213 and 1633 cm\(^{-1}\) due to NH (keto-enol) (Barnes and Barndon, 1943; Katrizky and Jones, 1960), CN and C=O respectively.

iii) The \(^1\)H NMR spectrum (DMSO-d\(_6\), \(\delta\) ppm) showed signals at 2.28 (s, 3H, CH\(_3\)), 2.29 (s, 3H, CH\(_3\)), 3.45 (s, 1H, NH, D\(_2\)O exchangeable), 6.81 (s, 1H, pyridine-H5), and 7.26-7.97 (m, 6 H, Ar-H).

iv) Mass spectrum showed the molecular ion peak M\(^+\) at \(m/z\) 306 (100%) as the base peak.

On the other hand, one step reaction (Kambe et al., 1980) was used to synthesize compound 13, by heating under reflux a mixture of equimolar ratio of 3,4-dimethylacetophenone, thiophene-2-carboxaldehyde and ethyl cyanoacetate in ethanol containing ammonium acetate. The product was isolated identified as 14 which formed by the latter method is produced in high yield (70%).
Formation of 14 from 3,4-dimethyl acetophenone, thiophene-2-carboxaldehyde and ethyl cyanoacrylate is believed to take place as shown in chart V, where the aldehyde condenses with the more reactive methylene group in ethyl cyanoacetate rather than the less reactive methyl group in dimethyl acetophenone. The Michael addition reaction of dimethyl acetophenone on the produced thien-2-yl formylidene ethyl cyanoacetate takes place followed by cyclization of the enolic structure to produce the four member ring 14.
The structure of compound 14 was inferred from the following:

i) Correct analytical data.

ii) IR spectra exhibited absorption bands at 1717 cm\(^{-1}\) due to ester group (C=O), and 2216 cm\(^{-1}\) (CN).

iii) The \(^1\)H NMR spectrum (DMSO-d\(_6\), \(\delta\) ppm) showed signals at 1.25-1.28 (t, 3H, CH\(_3\)CH\(_2\)CO), 2.25 (s, 3H, CH\(_3\)), 2.261 (s, 3H, CH\(_3\)), 2.269(d, 1H, CH), 4.27-4.43 (q, 2H, CH\(_3\)CH\(_2\)CO), 6.85(d, 1H, olefinic H), 7.31-8.55 (m, 6 H, Ar-H) (c.f. Fig. 27).

iv) Mass spectrum showed the molecular ion peak M\(^+\) at \(m/z\) 306 (100\%) as the base peak (M\(^+\)-2CH\(_3\)).

The Lactim form of compound 13 contains an OH group that could be utilized as a precursor for building up other rings. Thus, compound 13 reacted with ethyl chloroacetate in dry acetone, in the presence of anhydrous potassium carbonate to produce 3-cyano-6-(3,4-dimethyl-phenyl)-2-ethoxycarbonylmethoxy-4-thien-2-yl-pyridine 15.

\[
\begin{array}{c}
\text{CN} \\
\text{S} \\
\text{CN} \\
\text{H}_3C \\
\text{OCH}_2\text{COOEt}
\end{array}
\]

15

This reaction proves that the nicotinonitrile derivative 13 exists in a Lactam \(\rightleftharpoons\) Lactim dynamic equilibrium and in the presence of acetone the Lactim form is more predominance. The structure of compound 15 was confirmed by:

i) Correct analytical data.
ii) The IR spectrum of the ester 15 revealed the existence of ν (CN) at 2221 cm\(^{-1}\) and 1751 cm\(^{-1}\) (C=O).

iii) The \(^1\)H NMR spectrum (DMSO-d\(_6\), δ ppm) showed signals at 1.17-1.21 (t, 3H, CH\(_3\)CH\(_2\)OC=O), 2.28 (s, 3H, CH\(_3\)), 2.30 (s, 3H, CH\(_3\)), 4.15-4.22 (q, 2H, CH\(_3\)CH\(_2\)OC=O), 5.13 (s, 2H, CH\(_2\)), and 7.26-8.03 (m, 7 H, Ar-H and pyridine-H5) (c.f. Fig. 30).

iv) Its mass spectrum showed the molecular ion peak M\(^+\) at \(m/z\) 392 (32.5%) and the base peak at \(m/z\) 319 (M\(^+\)-COOC\(_2\)H\(_5\)) (Nadkarni et al., 1937).

The reaction possibly takes place \emph{via} the following mechanism:

In acetone the Lactim form is more predominant and consequently the reaction takes place \emph{via} nucleophilic substitution by the lone pair of
oxygen on the primary alkyl halide moiety SN2 (this reaction is regiospecific).

When compound 15 was refluxed with hydrazine hydrate in ethanol, the product obtained was identified as 3-cyano-2-hydrazino-6-(3,4-dimethyl-phenyl)-4-thien-2-yl-pyridine (17) and not the expected hydrazide 16. This is due to position 2 in pyridine nucleus highly reactive towards nucleophiles.

The IR spectrum of compound 17 displayed absorption bands at 3400 and 3295 cm\(^{-1}\) (NH\(_2\), NH), and 2366 (CN). \(^1\)H NMR spectrum (DMSO-d\(_6\), \(\delta\) ppm) showed signals at 2.26 (s, 3H, CH\(_3\)), 2.28 (s, 3H, CH\(_3\)), 4.83 (s, 2H, NH\(_2\), D\(_2\)O exchangeable) 7.47 (s, 1H, pyridine-H5), 7.23-7.94 (m, 6 H, Ar-H), 12.37 (s, 1H, NH, D\(_2\)O exchangeable) and Mass spectrum of 17 showed the molecular ion peak M\(^+\) at \(m/z\) 320 (100%) which is the base peak.
Here the author explains how 17 was formed. Firstly the ethoxycarbonyl group undergoes hydrazinolysis via tetrahedral mechanism (which is more facile than SN2 mechanism, this is due to the energy barrier that hampers, the reaction is lowered when the hydrazinolysis proceeds through anion (I) (T.H.M), for along such a route the system receives much of its "energy payment" from the formation of the new bond (C-NH-NH₂) before having to pay its "energy debt" for the breakage of the (C-OEt) bond [all reactions take place via tetrahedral mechanism have low activation energy].

Secondly, after formation of 16 the reaction takes place via nucleophilic displacement at C₂ of pyridine moiety which is highly electron deficient and reaction proceeded by SN2 mechanism.
Reaction with ethyl acetoacetate:

It is known that the Michael adduct of \(\alpha,\beta\)-unsaturated ketones with ethyl acetoacetate easily undergoes a secondary condensation (Bergmann, 1958) between the terminal methyl group of the adduct and the carbonyl group of the ketone. Thus, the condensation of Thein-2-yl formylidene-3,4-dimethyl acetophenone (1c) in ethanolic sodium ethoxide solution gave 4-(3,4-dimethyl-phenyl)-2-oxo-6-thien-2-yl-cyclohex-3-ene carboxylate (18) which upon decarboxylation (Nadkarni et al., 1937) by heating with ethanolic sodium hydroxide, it afforded 3-(3,4-dimethyl-phenyl)-5-thien-2-yl-cyclohexa-2,4-dienone (19).

The reaction could be represented according to the following mechanism: (ChartVI).
\[ \text{Chart VI} \]

\[ \begin{align*}
18 \quad & \text{β-Keto acid unstable,} \\
& \text{Loses CO}_2 \text{ easily}
\end{align*} \]
The structure of compound 18 was established by the following:

i) Correct analytical data.

ii) The IR spectrum of 18 showed absorption bands at 1739 cm\(^{-1}\) and 1667 cm\(^{-1}\) (2C=O).

iii) Mass spectrum of 18 showed the molecular ion peak M\(^{+}\) at \(m/z\) 354 (9.7%) supporting its molecular formula (C\(_{21}\)H\(_{22}\)O\(_3\)S).

The structure of compound 19 was established by the following:

i) Correct analytical data.

ii) The IR spectrum of 19 showed absorption bands at 1701 cm\(^{-1}\) (C=O).

iii) \(^1\)H NMR spectrum (DMSO-\(d_6\), \(\delta\) ppm) showed signals at 2.22 (s, 3H, CH\(_3\)), 2.25 (s, 3H, CH\(_3\)), 4.74 (d, 1H, CH\(_2\)), 4.88 (d, 1H, CH\(_2\)), 6.31 (s, 1H, H-2), 7.13-7.42 (m, 7 H, Ar-H and H-4).

iv) Mass spectrum of 19 showed the molecular ion peak M\(^{+}\) at \(m/z\) 280 (13.8%) supporting its molecular formula (C\(_{18}\)H\(_{16}\)OS).

Additionally, behavior of \(\alpha,\beta\)–enone 1c towards hydrazine hydrate, phenyl hydrazine and hydroxylamine were studied. Thus when compound 1c was reacted with hydrazine hydrate in basic medium, triethyl amine in ethanol, the product could be formulated as 20.
The structure of compound 20 was established by the following:
i) It gives blue violet color upon treatment with FeCl₃ in concentrated H₂SO₄ which is characteristic of pyrazolines (Mohamed et al., 1985).

ii) The IR spectrum of 20 showed absorption bands at 3421 cm⁻¹ corresponding to (NH) group.

iii) ¹H NMR spectrum (DMSO-d₆, δ ppm) showed signals at 2.22 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.18 (dd, 1H, CH₂), 3.85 (dd, 1H, CH₂), 5.76-5.84 (m, 1H, CH), 7.18-7.37 (m, 6H, Ar-H), 11.47 (s, 1H, NH, D₂O exchangeable).

iv) Mass spectrum of 20 showed the molecular ion peak M⁺ is the base peak at m/z 254.

The reaction possibly takes place via the following mechanism:

There is another route in which hydrazine added 1,4-addition to the enone system:
But the first route is more credible due to it needs less activation energy.

When the above reaction proceeds in either formic or acetic acid, it yields the corresponding 1-acyl-3-(3,4-dimethyl-phenyl)-5-thien-2-yl-4,5-dihydropyrazolines (21)
The structure of compound 21b was established by the following:
i) It gives blue violet color upon treatment with FeCl₃ in concentrated H₂SO₄ which is characteristic of pyrazolines (Mohamed et al., 1985).

ii) The IR spectrum of 21b showed absorption bands at 1663 cm⁻¹ (C=O), 1590 (C=N) and absence of any bands characterized to NH.

iii) Mass spectrum of 21b showed the molecular ion peak M⁺ at m/z 298 (C₁₇H₁₈N₂SO) (87%, C₁₇H₁₈N₂SO).

Fragmentation pattern of mass spectrum of compound 21b:
Similarly, α,β-enone 1c condensed with phenyl hydrazine in boiling acetic acid to yield the corresponding 3-(3,4-dimethyl-phenyl)-1-phenyl-5-thien-2-yl-4,5-dihydropyrazoline (22).
The structure of compound 22 was illustrated from the following:
i) Color test characterized of pyrazolines.
ii) Correct analytical data
iii) The IR spectrum of 22 showed absorption bands at 3100, 2923 and 1596 cm\(^{-1}\) characteristic to CH aromatic, CH aliphatic and C=N respectively.

**Reaction of \(\alpha,\beta\)-enone with hydroxylamine hydrochloride:**

The reaction of the \(\alpha,\beta\)-enone 1c with hydroxylamine in boiling pyridine give 3-(3,4-dimethyl-phenyl)-5-thien-2-yl-4,5-dihydro isoxazoline (23).

The structure of compound 23 be illustrated from the following:
i) correct analytical data.
ii) IR spectrum showed absorption bands at 2937, 1619 and 1590 cm\(^{-1}\) characteristic to CH, C=N and C=C respectively.
iii) Mass spectrum of 23 showed the molecular ion peak $M^+$ is the base peak at $m/z$ 256 ($M^+-1, 49\%$).

The reaction could be represented according to the following mechanism:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{O} & \quad \text{S} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{O} \\
\text{N} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{O} & \quad \text{S} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{O} \\
\text{N} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]
**1-Anticancer Evaluation:**

Five selected new compounds 3a, 3b, 7a, 7b and 7c were tested for cytotoxic activity against the MCF\(_7\) (Breast Carcinoma Cell Line) and H460 (Lung Carcinoma Cell Line).

**Measurement of Potential Cytotoxicity by Sulfurhodamine B. (SRB) Assay:**

- Cells were plated in 96 multiwell plates (10\(^4\) cells/well) for 24h before treatment with the compounds to allow attachment of cell to the wall of the plate.
- Different concentrations of the compounds (1, 2.5, 5 and 10 µg/ml) were added to the cell monolayer.
- Triplicate wells were prepared for each individual dose.
- Monolayer cells were incubated with the compounds for 48h at 37°C and in atmosphere of 5% CO\(_2\).
- After 48h, cells were fixed, washed and stained with SRB stain.
- Excess stain was washed with acetic acid and attached stain was recovered with tris EDTA (Ethylene Diamine Tetra Acetic Acid) buffer.
- Color intensity was measured in an ELISA (Enzyme Linked Immuno Sorbent Assay) Reader.
- The relation between surviving fraction and drug concentrations was plotted to get the survival curve of each tumor cell line of the specified compound Skehan *et al.*, 1990).

All tested compounds were proven to have no cytotoxic activity (not active) against the MCF\(_7\) and H460 at the chosen drug concentrations chart I and chart II respectively.
Chart I
Chart II
2-Antimicrobial Activity:

The target compounds were tested for their antimicrobial activity against Escherichia Coli (Gram-Ve bacteria), Aspergillus Fumigatus and Candida albicans (Fungi). Colimex (colistin oral) and Fluconazole were used as positive controls.

The organisms were exposed to a series of fixed compound concentrations in separate cultures in Nutrient broth media for bacteria and in broth [Nutriren broth for C.albicans and Saboureud broth for A.fumigatus], the different concentration are produced by dilution (using the serial discontinuous concentration method).

The minimum inhibitory concentration (MIC) was readed as the smallest concentration of tested compound or control in the series that prevents the development of visible growth of the test organism (Collee et al., 1989).

a) Antibacterial activity:

Result of the minimum inhibitory concentration (MIC) test against Escherichia coli (Gram-negative bacteria) were not very promising, two compounds out of 18 compounds displayed MIC in range of about 80 and 90 µg/ml while the other tested compounds were generally inefficient (MIC > 100 µg/ml) for each of bacteria and fungi.

b) Antifungal activity:

The prepared compounds 18 were evaluated in vitro against two strains of fungi, Candida albicans and Aspergillus fumigates, the most clinically fungi responsible for the majority of systemic fungi infections.
Result of (MIC) test against *Aspergillus fumigates* were not very promising, two compound out of 18 displayed MIC in range of about 30 and 50 µg/ml while the rest of the series were generally inefficient (MIC >100 µg/ml).

Also the result of (MIC) test against *Candida albicans* were not very promising, three compounds out of 18 displayed MIC in range of about 20, 20 and 40 µg/ml while the rest of the series were generally inefficient (MIC >100 µg/ml).

The different concentrations are produced by dilution (using the serial discontinuous concentration method). The MIC was read as the smallest concentration of tested compound or control in series that prevent the development of visible growth of the test organism (colle. et. al, 1989). The MIC values (µg/ml) of tested compounds together with their structures are illustrated in table I.

**Conclusion:**

The tested compounds were evaluated in vitro against one strains of Gram-negative bacteria (*Escherichia coli*) and two strains of fungi, *Aspergillus fumigates* and *Candida albicans*, Colimex and Floconazole were used as references. Compounds 7c&15 exerted significant antibacterial activity against *Escherichia coli* in range of 90 µg/ml while the rest of the compounds were generally inefficient (MIC >100 µg/ml).

On the other hand compounds 1c&4a showed antifungal activity against *Aspergillus fumigates* in range of 50 µg/ml. Also compounds 1c,4a& 8a exerted significant antifungal activity against *Candida albicans* in range of 20 µg/ml, while the rest of the compounds were
generally inefficient (MIC $>100 \mu g/ml$) against each of *Aspergillus fumigates* and *Candida albicans*.

**Table I: In Vitro Antimicrobial Activity (MIC) of Tested Compounds**

<table>
<thead>
<tr>
<th>Tested compounds &amp; References</th>
<th>Microorganism</th>
<th>Eschericha coli.</th>
<th>Aspergillus fumigates</th>
<th>Candida albicans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colimex</td>
<td>1µg/ml</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>Floconazole</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1c</td>
<td>$&gt;100$</td>
<td>30</td>
<td>40</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>2a</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
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<tr>
<td>2b</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
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<tr>
<td>3a</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
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<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>4a</td>
<td>$&gt;100$</td>
<td>50</td>
<td>20</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>4b</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
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<tr>
<td>7a</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>7b</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>7c</td>
<td>90</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>8a</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>20</td>
<td>$&gt;100$</td>
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<td>9b</td>
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<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>15</td>
<td>80</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
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</tr>
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<td>19</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>21b</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
<td>$&gt;100$</td>
</tr>
</tbody>
</table>

*Acknowledgement*

Thanks to Dr. Seham Y. El-Tablawy, Lecturer at Pharmaceutical Microbiology Department, National Centre for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt. For carrying out the in vitro antimicrobial activity.
3- Analgesic Activity:

I- Materials
A. Experimental animals:

Mature mice of 20-25 g b.wt. each, of both sexes were obtained from The Animal House, NRC, Cairo. Animals were housed under standard environmental conditions (23±1°C, 55±5% humidity and a 12-hr light: 12-hr dark cycle) and maintained on a standard laboratory diet ad libitum with free access to water.

B. Drugs, chemicals and solutions:

- Acetic acid 96%: (ADWIC).
- Acetylsalicylic acid: (Rivo®) (The Arab Drug Co., A.R.E.).

II- Methods
Analgesic effect:

Experimental models used in this study were selected to investigate peripherally mediated analgesic effects of the tested drug. For this purpose; the acetic acid abdominal contraction method was used to elucidate the peripheral effect.

An acetic acid-induced abdominal constriction in mice (Writhing effect) was determined by the method described by Collier et al. (1968).

Sixty six mice were divided into 11 equal groups and pre-treated as follows:

Group 1 which served as a control was orally received distilled water in appropriate volumes. Groups from 2 to 10 received 1c, 11b, 13, 14, 15, 17, 18, 21b and 22 respectively all at oral doses of 15mg/kg body
weight, while group 11 received acetylsalicylic acid at a dose of 100mg/Kg body weight and served as standard.

After 30 minutes, each mouse was administered 0.7% of an aqueous solution of acetic acid (10 ml/kg body weight.) and the mice were then placed in transparent boxes for observation.

The number of writhes was counted for 20 min after acetic acid injection. The number of writhes in each treated group was compared to that of a control un-treated group.

The number of writhings and stretchings was recorded and the percentage protection was calculated using the following ratio:

\[
\text{Percentage of protection} = \frac{\text{Control mean} - \text{Treated mean}}{\text{Control mean}} \times 100
\]
Table II: Analgesic effect of Tested Compounds

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of writhes /20 min.</th>
<th>Protection (%)</th>
<th>Potency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>57.2±2.08 b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1c</td>
<td>27.1±1.20 a</td>
<td>52.6</td>
<td>86.94</td>
</tr>
<tr>
<td>11b</td>
<td>19.6±1.96 a</td>
<td>65.7</td>
<td>108.59</td>
</tr>
<tr>
<td>13</td>
<td>40.1±2.24 a b***</td>
<td>30.0</td>
<td>49.59</td>
</tr>
<tr>
<td>14</td>
<td>33.6±1.29 a b</td>
<td>41.3</td>
<td>68.26</td>
</tr>
<tr>
<td>15</td>
<td>44.0±2.47 a b***</td>
<td>23.1</td>
<td>38.18</td>
</tr>
<tr>
<td>17</td>
<td>56.5±1.09 b***</td>
<td>1.2</td>
<td>1.98</td>
</tr>
<tr>
<td>18</td>
<td>39.1±3.42 a b***</td>
<td>31.7</td>
<td>52.39</td>
</tr>
<tr>
<td>21b</td>
<td>40.0±1.30 a b***</td>
<td>30.1</td>
<td>49.75</td>
</tr>
<tr>
<td>22</td>
<td>26.4±2.29 a</td>
<td>53.8</td>
<td>88.93</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>22.6±1.03 a</td>
<td>60.5</td>
<td>100</td>
</tr>
<tr>
<td>F-value</td>
<td>40.307***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values represent the mean ± S.E. of five animals for each groups.

a P<0.05: Statistically significant from control. (Dunnett's test).
b P< 0.05: Statistically significant from aspirin. (Dunnett's test).
*** Significant at P< 0.001

The potency was calculated compared to the reference drug acetylsalicylic acid.

*The Synthesized Compounds Tested in Pharmacology Research Unit, National Research Center, Cairo, Dokki, Egypt.
SUMMARY AND CONCLUSION

This work deals firstly with the behaviour of aryldene-3,4-dimethylacetophenones toward oxygen nucleophiles e.g., hydrogen peroxide in the presence of sodium hydroxide and yielded the corresponding oxiranes. Interaction of oxirane derivative with thiourea yielded the thioxopyrimidinone derivatives. The behaviour of the thioxopyrimidinone derivatives toward carbon electrophiles e.g., bromoacetic acid and 2-bromopropionic acid has been investigated and yielded the corresponding thiazolopyrimidinone, its behaviour toward aromatic aldehydes, p-nitrobenzene diazonium chloride, piperidine in the presence of formaldehyde under Mannich reaction condition and hydrazine hydrate has been discussed. Also the thioxopyrimidinone has been glycosidated by using 2,3,4,6-tetraacetoxy-α-glucopyranosyl bromide.

Secondly, this investigation involving also the use of thien-2-ylformylidene-3,4-dimethylacetophenone in synthesis of mixed and non-mixed heterocyclic system e.g., cyanopyridine, pyrazole, isoxazol derivatives and some studies with the products.

Biological activity for the synthesized compounds have been studied for anticancer evaluation; antimicrobial activity and analgesic activity.
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