SYNTHESIS AND CHARACTERIZATION OF NOVEL TRISUBSTITUTED PYRIMIDINE DERIVATIVES FROM CHALCONES

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ABSTRACT: ***The present study aims to focus on account of important chemical moiety, pyrimidine and its various derivatives acts as antimicrobial agents. Trisubstituted pyrimidine derivatives showed antibacterial and antifungal activity Nitrogen containing heterocyclic derivatives synthesized from chalcones have exhibited antiinflammatory,antioxidant, antitubercular, antibacterial activities. Then the mixture was cooled and filtered. All the compounds are purified with ethanol and m.p is noted .The novel trisubstituted pyrimidine derivatives 4a (1-24) were synthesized by urea and thiourea with different chalcones. The structure of the recrystallised compounds were confirmed by IR, [1]H NMR, [13]C NMR, Mass spectral analysis.***

KEYWORDS: Chalcones, Urea, Thiourea , antibacterial and antifungal activity , reflux.

1. INTRODUCTION

Heterocyclic compounds particularly these possessing N-or S- containing moieties, have attracted significant interest due to their useful biological and pharmaceutical properties. Chalcones have been very attractive starting materials in medicinal chemistry from the beginning. They are easy to prepare with large variability at the two aromatic rings and the enone provides a bifunctional site for 1, 3 dinucleophiles affording several heterocyclic ring systems while incorporating other diversity elements. The wide occurrence of the heterocyclic molecules in bioactive natural products and pharmaceuticals has made them as important synthetic targets. Chalcones are of paramount interest for both synthetic and medicinal chemists because of their synthetic utility ,and hence their extensively usage for the development of novel lead molecules[1].

Chalcones have been reported to present various biological activities such as anti-inflammatory, antioxidant, antitubercular, antibacterial activities. It is a basic moiety of many heterocyclic systems containing oxygen, sulphur and nitrogen. Nitrogen containing heterocyclic derivatives synthesized from chalcones have exhibited antiinflammatory,antioxidant, antitubercular, antibacterial activities [2, 3]. The chemistry of pyrimidines has become increasingly important as a result of recent developments in medicinal chemistry. Pyrimidine derivatives are one of the most prominent structures found in nucleic acid including uracil, thymine,cytosine,adenine,and guanine.They are fundamental building blocks for DNA and RNA . The literature indicated that compound having pyrimidine nucleus shows promising antitumor activity ,as there are large numbers of pyrimidine-based anti-metabolites as well as the presence of electron rich nitrogen atoms[5- 8]. Thiourea derivatives are useful compounds and precursors for the synthesis of different classes of acyclic and hetrocyclic compounds as well as they are highly biologically active compounds themselves [9].The pyrimidine ring system being present in various natural compounds such as nucleic acids, vitamins, coenzymes,uric acid, purines, some marine microorganisms[10]. The therapeuticimportance of pyrimidine moti-derivatives such as barbituricacid and thiobarbituric acid play vital role among various heterocyclic compounds due to their anti-neoplastic[11,12] , antiviral[13] ,antibiotic , and anti-inflammatory activity[14]. Many synthetic drugs of barbituric and thiobarbituric acid modified derivatives are and chemotherapeutic agents [15] . Chalcones are the products of the condensation of a simple or substituted aromatic moiety with simple or substituted acetophenone in presence of base. This group of compounds is widely used in anticancer research, and antimicrobial or an antitubercular [16]. Several pyrimidine derivatives are among the major drugs used to combat several human diseases caused by protozoan organisms. These diseases include malaria, leishmaniasis and trypanosomiasis[17-19].

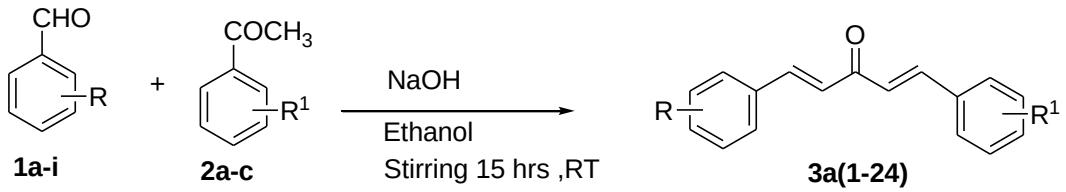
2. MATERIAL AND METHODS

All the chemicals and the reagents used in the study were of synthesis grade purity. Aldehyde , ketones , ethanol , methanol , Urea, thiourea and chloroform are purchased from Qualigents Fine Chemicals Company. Solvents used were purified by distillation. All the compounds synthesized were purified by crystallization using appropriate solvents and established procedures. Melting points were measured on a sigma melting point apparatus using capillary tubes. Analytical TLC was performed on procoated sheets of silica gel to monitor the process of the reaction as well as to check the purity. The spots were visualized by using iodine vapour.IR spectra were recorded on FTIR-8300 shimadzu spectrometer. 1H&13C NMR spectra were recorded on Jeol GSX (400 MHz) and DPX 200 (200MHz). Mass spectra were recorded on Jeol-JMS-DX 30hf.

3. RESULTS AND DISCUSSION

Synthesis of substituted chalcones :

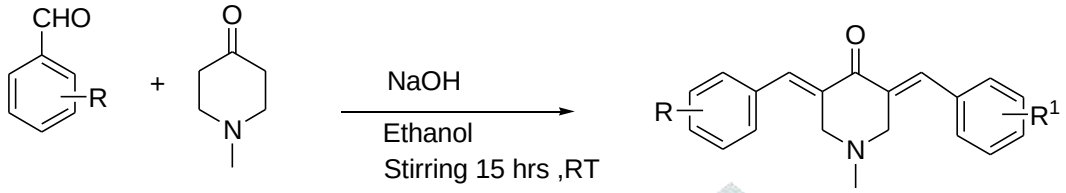
A mixture of subtituted aldehydes (0.01 mol) and substituted ketones (0.01 mol) in the presence of 10% NaOH along with 50ml ethanol was prepared and the solution of reaction mixture was constant stirring for 15hrs at room temperature of stirring the solution was poured in to ice cubes to enhance the precipitation .The precipitate was then collected and washed with distilled water for draining excess sodium hydroxide from the product**3a(1-24)** . The compound is purified and recrystallised with ethanol.



1a-i **2a-c** **3a(1-24)**

R=H,4-Cl, CH_3 ,$N(CH_3)_2$, $N(C_2H_5)_2$, 4-Br,3-NO_2 ,4-OH, OCH_3

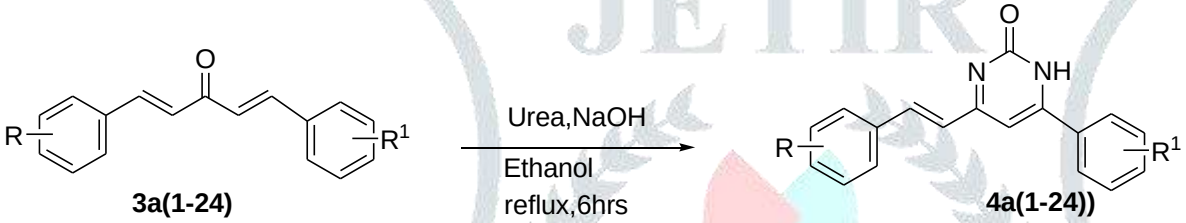
R^1=H,CH_3 ,3-NH_2



R=H,4-Cl, CH_3 ,$N(CH_3)_2$, $N(C_2H_5)_2$,

Synthesis of substituted pyrimidine derivates;

Equal moles of substituted chalcone and Urea with 10% sodium hydroxide were refluxed at 80°C in a heating mantle for 6hrs produced, substituted pyrimidine **4a(1-24).** All the compounds are purified by recrystallisied in ethanol.



3a(1-24) **4a(1-24))**

R=H,4-Cl, CH_3 ,$N(CH_3)_2$, $N(C_2H_5)_2$, 4-Br,3-NO_2 ,4-OH, OCH_3

R^1=H,CH_3 ,3-NH_2

4.CHARACTERIZATION:

Synthesis of 6-phenyl-4-styrylpyrimidin-2(1H)-one : $4a_1$

Equal moles of mixture (1E,4E)- 1,5-diphenylpenta-1,4-dien-3-one **3a** are treated with Urea with 10% sodium hydroxide were refluxed at 80°C in a heating mantel for 6hrs produced **4a** was prepared. Yield: 88%,m.p :115-117°C, IR : 1690 cm^{-1} –CN ,3300 cm^{-1} –NH, 1555 cm^{-1}C=C, 1690 cm^{-1}C=O, Aromatic stretching 2925 cm^{-11} HNMR : δ 6.9(S, α CH), 7.5 (d,β CH), 7.25-7.46 (m ,Aromatic H), 8.0 (NH) ^{13} CNMR : δ 95.4 ,116.4,126.4 ,128.7, 135.2, 135.2, 138.2,164.6 Mass :(m/z) :274

Synthesis of 6-phenyl-4-styrylpyrimidin-2(1H)-thione: $4a_2$

Yield: 83%,m.p :120-121°C .IR : 1690 cm^{-1} –CN ,3300 cm^{-1} –NH, 1565 cm^{-1}C=C, 1150 cm^{-1}C=S, Aromatic stretching 2925 cm^{-1} .^{1} HNMR : δ 6.9(S, α CH), 7.5 (d,β CH), 7.25-7.46 (m ,Aromatic H), 8.0 (NH) ^{13} CNMR : δ 95.4 ,116.4,126.4 ,128.7, 135.2, 135.2, 138.2,164.6 ,180.1Mass :(m/z) :290

Synthesis of 4,6-diphenylpyrimidin-2(1H)-one : $4a_3$

Yield: 85%,m.p :107-109°C .IR : 1680 cm^{-1} –CN ,3300 cm^{-1} –NH, 1585 cm^{-1}C=C, 1710 cm^{-1}C=O, Aromatic stretching 2925 cm^{-11} HNMR : δ 4.9(S, β CH), 7.25-7.46 (m ,Aromatic H), 8.0 (NH) ^{13} CNMR : δ 95.4 ,116.4,126.4 ,128.0,128.7, 133.2, 135.2, 138.2,154.6,164.6 Mass :(m/z) :248

Synthesis of 4,6-diphenylpyrimimidin-2(1H)-thione : $4a_4$

Yield: 85%,m.p :107-109°C . IR : 1670 cm^{-1} –CN ,3300 cm^{-1} –NH, 1565 cm^{-1}C=C, 1160 cm^{-1}C=S, Aromatic stretching 2925 cm^{-1}.^{1} HMR : δ 6.9(S, α CH), 7.25-7.46 (m ,Aromatic H),
^{13} CNMR : δ 95.4 ,116.4,126.4 ,128.7, 135.2, 135.2, 138.2,164.6,180.4 Mass :(m/z) :264

Synthesis of 6-(4-chlorophenyl)-4phenylpyrimidin-2(1H)-one: $4a_5$

Yield: 83%,m.p :120-121°C .IR : 1670 cm^{-1} –CN ,3300 cm^{-1} –NH, 1550 cm^{-1}C=C, 1710 cm^{-1}C=O, Aromatic stretching 2925 cm^{-1}.^{1} HNMR : δ 6.9(S, α CH), 7.25-7.46 (m ,Aromatic H), 8.0 (NH) ^{13} CNMR : δ 95.4 ,116.4,126.4 ,127.8,128.7, 133.2,130.1, 135.2, 138.2,164.6 Mass :(m/z) :282

Synthesis of 6-(4-chlorophenyl)-4phenylpyrimidin-2(1H)-thione: $4a_6$

Yield: 83%,m.p :120-121°C . IR : 1680 cm^{-1} –CN ,3300 cm^{-1} –NH, 1560 cm^{-1}C=C, 1180 cm^{-1}C=S, Aromatic stretching 2925 cm^{-1}.^{1} HNMR : δ 6.9(S, α CH), 7.25-7.48 (m ,Aromatic H),
^{13} CNMR : δ 93.4 ,116.4,126.4 ,128.7, 135.2, 135.2, 138.2,164.6 ,180.2 Mass :(m/z) :2984

4-(4-(dimethylamino)styryl-6-(4-dimethylamino)phenyl))pyrimidin-2(1H)-one : $4a_7$

Yield: 89%,m.p :128-129ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1567cm^{-1}C=C, 1710 cm^{-1}C=O, Aromatic stretching 2920cm^{-1} .^{1} HNMR : δ 5.0(S, α CH), 6.8(d, β CH) 7.55-7.88 (m ,Aromatic H), 8.0 (NH). ^{13} C NMR : 40.3,95.4,114.2,124.0,127.8,128.0,131.3,133.9,156.3,163.3. Mass :(m/z) :360.45

4-(4-(dimethylamino)styryl-6-(4-dimethylamino)phenyl))pyrimidin-2(1H)-thione: $4a_8$

Yield: 83%,m.p :130-132ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1555cm^{-1}C=C, 1170 cm^{-1}C=S, Aromatic stretching 2930cm^{-1}. ^{1} H NMR : δ 5.2(S, α CH), 6.8(d, β CH) 7.35-7.50 (m ,Aromatic H) . ^{13} C NMR : δ 40.3,95.4,114.2,124.0,127.8, 128.0,131.3,133.9,156.3,176.3,180.4 Mass :(m/z) :376.52

4-(4-(diethylamino)styryl-6-(4-diethylamino)phenyl))pyrimidin-2(1H)-one: $4a_9$

Yield: 89%,m.p :128-129ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1567cm^{-1}C=C, 1710 cm^{-1}C=O, Aromatic stretching 2920cm^{-1} .^{1} HNMR : δ 5.0(S, α CH), 6.8(d, β CH) 7.55-7.88 (m ,Aromatic H),.^{13}CNMR:δ13.4,40.3,95.4,114.2,124.0,127.8,128.0,131.3,133.9,156.3,163.0 Mass :(m/z) :360.45

4-(4-(diethylamino)styryl-6-(4-diethylamino)phenyl))pyrimidin-2(1H)-thione: $4a_{10}$

Yield: 83%,m.p :130-132ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1555cm^{-1}C=C, 1170 cm^{-1}C=S, Aromatic stretching 2930cm^{-1}. ^{1} HNMR : δ 5.2(S, α CH), 6.8(d, β CH) 7.35-7.50 (m ,Aromatic H). ^{13} C NMR δ13.1,40.3,95.4,114.2,124.0,127.8,128.0,131.3,133.9,156.3,176.3,180.4 Mass :(m/z) :416.52

4-(3-nitrostyryl-6-(4-aminophenyl)) pyrimidin-2(1H)-one: $4a_{11}$

Yield: 84%,m.p :138-139ºC,IR : 1650 cm^{-1} –CN ,3300 cm^{-1} –NH, 1557cm^{-1}C=C, 1715 cm^{-1}C=O, Aromatic stretching 2940cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.3(d, β CH) 7.65-7.98 (m ,Aromatic H), 8.0 (NH) ,4.0(NH_2). ^{13} C NMR : δ 95.4,116.2,120.3,124.0,129.8, 138.2,147.6,148.9,156.3. Mass :(m/z) :334.33

4-(3-nitrostyryl-6-(4-aminophenyl)) pyrimidin-2(1H)-thione: $4a_{12}$

Yield: 78%,m.p :142-143ºC,IR : 1660 cm^{-1} –CN ,3300 cm^{-1} –NH, 1547cm^{-1}C=C, 1170 cm^{-1}C=S, Aromatic stretching 2930cm^{-1} .^{1} H NMR : δ 4.0(NH_2), 5.3(S, α CH), 6.6(d, β CH) 7.45-7.60 (m ,Aromatic H) . ^{13} C NMR : δ 95.4,116.2,120.2,124.0,127.8, 128.0,131.3,133.9,156.3,180.4 Mass :(m/z) :350.39

4-(3-hydrotyryl-6-(4-aminophenyl)) pyrimidin-2(1H)-one: $4a_{13}$

Yield: 76%,m.p :117-119ºC,IR : 1650 cm^{-1} –CN ,3300 cm^{-1} –NH, 1547cm^{-1}C=C, 1710 cm^{-1}C=O, Aromatic stretching 2930cm^{-1}. ^{1} H NMR : δ 4.0(NH_2),5.0 (Aromatic OH),5.3(S, α CH), 6.6(d, β CH) 7.45-7.60 (m ,Aromatic H) . ^{13} C NMR : δ 95.4,116.2,120.2,124.0,127.8, 128.0,131.3,133.9,156.3,180.4 Mass :(m/z) :305.2

4-(3-hydrotyryl-6-(4-aminophenyl)) pyrimidin-2(1H)-thione: $4a_{14}$

Yield: 86%,m.p :121-123ºC,IR : 1650 cm^{-1} –CN ,3300 cm^{-1} –NH, 1547cm^{-1}C=C, 1170 cm^{-1}C=S, Aromatic stretching 2930cm^{-1}. ^{1} H NMR : δ 4.0(NH_2),5.0 (Aromatic OH),5.3(S, α CH), 6.6(d, β CH) 7.45-7.60 (m ,Aromatic H) . ^{13} C NMR : δ 95.4,116.2,120.2,124.0,127.8, 128.0,131.3,133.9,156.3,180.4.Mass :(m/z) :321.4

4-(4-methoxstyryl-6-(4-aminophenyl))pyrimidin-2(1H)-one : $4a_{15}$

Yield: 81%,m.p :134-1395ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1587cm^{-1}C=C, 17150cm^{-1}C=O, Aromatic stretching 2950cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.3(d, β CH) 7.65-7.98 (m ,Aromatic H), 8.0 (NH) ,4.0(NH_2). ^{13} C NMR : δ 55.9,95.4,116.2,120.3,124.0,129.8, 138.2,147.6,148.9,156.3,159.9. Mass :(m/z) :319.36

4-(4-methoxstyryl-6-(4-aminophenyl)) pyrimidin-2(1H)-thione: $4a_{16}$

Yield: 87%,m.p :137-1385ºC,IR : 1650 cm^{-1} –CN ,3300 cm^{-1} –NH, 1587cm^{-1}C=C, 1160cm^{-1}C=O, Aromatic stretching 2950cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.3(d, β CH) 7.65-7.98 (m ,Aromatic H), 8.0 (NH) ,4.0(NH_2). ^{13} C NMR : δ 55.9,95.4,116.2,120.3,124.0,129.8, 138.2,147.6,148.9,,159.9.,180.2.Mass :(m/z) :335.42

(8E)-8-benzylidene-5,6,7,8-tetrahydro-6-methyl-4-phenylpyrido(4,3-d)pyrimidin-2(3H)-one: $4a_{17}$

Yield: 86%,m.p :108-109ºC,IR : 1650 cm^{-1} –CN ,3300 cm^{-1} –NH, 1557cm^{-1}C=C, 1715 cm^{-1}C=O, Aromatic stretching 2920cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.5(d, β CH) 7.25-7.48 (m ,Aromatic H), 8.0 (NH) . ^{13} C NMR : δ 43.9,50.8,53.5, 98.1, 126.4, 128.0,131.3,133.9,156.3 Mass :(m/z) :329.4

(8E)-8-benzylidene-5,6,7,8-tetrahydro-6-methyl-4-phenylpyrido(4,3-d)pyrimidin-2(3H)-thione: $4a_{18}$

Yield: 81%,m.p :110-112ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1555cm^{-1}C=C, 1170 cm^{-1}C=S, Aromatic stretching 2930cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.8(d, β CH) 7.35-7.50 (m ,Aromatic H) . ^{13} CNMR : δ 43.9,50.8,54.5,95.0,123.0,126.4,128.7,135.2,146.9,180.4 Mass :(m/z) :345.46

(8E)-8-(4-chlorobenzylidene-4-(chlorophenyl)-5,6,7,8-tetrahydro-6-methylpyrido(4,3-d)pyrimidin-2(3H)-one: $4a_{19}$

Yield: 89%,m.p :122-134ºC,IR : 1660 cm^{-1} –CN ,3300 cm^{-1} –NH, 1547cm^{-1}C=C, 1725 cm^{-1}C=O, Aromatic stretching 2920cm^{-1} .^{1} HNMR : δ 5.1(S, α CH), 6.8(d, β CH) 7.45-7.78 (m ,Aromatic H), 8.0 (NH) . ^{13} C NMR : δ 43.9,50.8,53.5, 98.0, 126.4, 128.0,131.3,133.5,135.8,156.3.Mass :(m/z) :398.29

(8E)-8-(4-chlorobenzylidene-4-(chlorophenyl)-5,6,7,8-tetrahydro-6-methylpyrido(4,3-d)pyrimidin-2(3H)-thione: $4a_{20}$

Yield: 81%,m.p :110-112ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1555cm^{-1}C=C, 1180 cm^{-1}C=S, Aromatic stretching 2930cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.8(d, β CH) 7.35-7.50 (m ,Aromatic H) . ^{13} CNMR : δ 43.9,50.8,54.5,95.0,123.0,126.4,128.7,135.2,137.5,146.9,180.4 Mass :(m/z) :414.36

(8E)-8-(4-(dimethylamino)benzylidene-4-(4-(diamino)phenyl)-5,6,7,8-tetrahydro-6-methylpyrido(4,3-d)pyrimidin-2(3H)-one: $4a_{21}$

Yield: 83%,m.p :130-134ºC,IR : 1650 cm^{-1} –CN ,3300 cm^{-1} –NH, 1567cm^{-1}C=C, 1715 cm^{-1}C=O, Aromatic stretching 2940cm^{-1} .^{1} HNMR : δ

5.1(S, α CH), 6.8(d, β CH) 7.45-7.78 (m ,Aromatic H), 8.0 (NH) . ^{13} C NMR : δ 40.3,43.9,50.8,53.5, 98.0, 126.4, 127.3128.0,131.3,133.5,135.8,148.1,156.3.Mass :(m/z) :415.43

(8E)-8-(4-(dimethylamino)benzylidene-4-(4-(diamino)phenyl)-5,6,7,8-tetrahydro-6-methylpyrido(4,3-d)pyrimidin-2(3H)-thione: 4a$_{22}$
Yield: 84%,m.p :110-112ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1555cm^{-1}C=C, 1180 cm^{-1}C=S, Aromatic stretching 2930cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.8(d, β CH) 7.35-7.50 (m ,Aromatic H) . ^{13} C NMR : δ 40.3,43.9,50.8,53.5, 98.0, 126.4, 127.3128.0,131.3,133.5,135.8,148.1,80.3.Mass :(m/z) :431.6

(8E)-8-(4-(diethylamino)benzylidene-4-(4-(diethylamino)phenyl)-5,6,7,8-tetrahydro-6-methylpyrido(4,3-d)pyrimidin-2(3H)-one: 4a$_{23}$
Yield: 88%,m.p :140-144ºC,IR : 1640 cm^{-1} –CN ,3300 cm^{-1} –NH, 1557cm^{-1}C=C, 1710 cm^{-1}C=O, Aromatic stretching 2940cm^{-1} .^{1} HNMR : δ 5.2(S, α CH), 6.8(d, β CH) 7.25-7.78 (m ,Aromatic H), 8.0 (NH) . ^{13} C NMR : δ13.0, 40.3,43.9,50.8,53.5, 98.0, 126.4, 127.3128.0,131.3,133.5,135.8,148.1,156.3.Mass :(m/z) :471.3

(8E)-8-(4-(diethylamino)benzylidene-4-(4-(diethylamino)phenyl)-5,6,7,8-tetrahydro-6-methylpyrido(4,3-d)pyrimidin-2(3H)-thione: 4a$_{24}$
Yield: 85%,m.p :110-112ºC,IR : 1650 cm^{-1} –CN ,3300 cm^{-1} –NH, 1565cm^{-1}C=C, 1180 cm^{-1}C=S, Aromatic stretching 2930cm^{-1} .^{1} H NMR : δ 5.2(S, α CH), 6.8(d, β CH) 7.25-7.78 (m ,Aromatic H), 8.0 (NH) . ^{13} C NMR : δ13.0, 40.3,43.9,50.8,53.5, 98.0, 126.4, 127.3128.0,131.3,133.5,135.8,148.1,156.3,180.3.Mass :(m/z) :487.0

5.CONCLUSION

The substituted ketones and aldehydes react with sodium hydroxide in ethanol produced substituted chalcones. The starting material chalcones were prepared by claisen Schmidt condensation. Chalcones are treated with urea and thiourea with 10% sodium hydroxide were refluxed for 6hrs produced, trisubstituted pyrimidine derivatives **4a(1-24).** The compounds are recrystallised by ethanol. Purified by coloum chromatography.The structure of the compounds were confirmed by IR, H^{1}NMR, C^{13} NMR, Mass spectral studies. Biological studies are carried out in future studies.

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