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Research Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF NEWER HETEROCYCLIC NITROGEN CONTAINING COMPOUNDS

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ABSTRACT

Nitrogen containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. Pyrimidine and their derivatives are considered to be important for medicinal drugs. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities. Numerous reports have appeared in the literature that highlights chemistry and uses of pyrimidines, and their derivatives like Sulfadiazine, Sulfamerazine, and Sulfamethazine. These agents are inhibitors of folic acid biosynthesis in microorganism. Aldolic condensation (clasien-schmidt condensation reaction) of equimolar quantities of substituted acetophenone with appropriate quantity of substituted aromatic aldehyde in presence of aqueous alcoholic alkali was used for formation of α, β – unsaturated ketones (i.e. chalcones). Equimolar portions of the substituted acetophenone (10mmol, 1 equiv) and substituted benzaldehyde (10mmol, 1 equiv) were dissolved in 15ml of ethanol. The mixture was allowed to stirr for several minutes at 5-10 ºC. Aliquot of a 40% aqueous NaOH solution was then slowly added to the reaction flask. The reaction mixture was allowed to stirr in ice bath for approximately 4-6hrs. All the crude products were washed first with cold water until washings were neutral to pH paper and precipitate formed was then collected and recrystallized from ethanol to give chalcone derivatives. To chalcone (10mmol) obtained from step 1, added guanidine nitrate then reflux for 2 hr The precipitate formed washed with cold water until it turns neutral to pH paper, filtered and recrystallized from ethanol to give Pyrimidine derivatives. Structure of final compounds was confirmed by IR, ^{1}H NMR, and Mass spectral data.

Keywords: Pyrimidine, antifungal activity, antibacterial activity, analgesic activity.

INTRODUCTION

Nitrogen containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. Pyrimidine and their derivatives are considered to be important for medicinal drugs. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities. Pyridine, a heterocyclic nucleus, played a pivotal role in the development of different medicinal agents. It is seen from the current literature that pyridine congeners are associated with different biological activities like pesticidal, fungicidal and antibacterial activity. Pyrimidines and pyridines have contributed to the diverse library of compounds demonstrating selective affinity to the 5-HT7 receptor. Pyrimidines are the most important six member heterocyclic, containing two nitrogen atoms on 1, 3 positions as shown in fig 1.

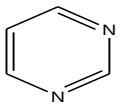
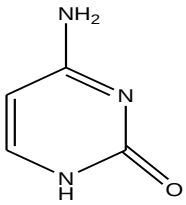
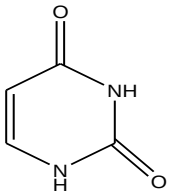


Fig. 1:

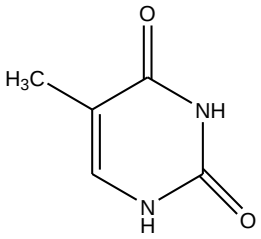
Pyrimidines are present among the three isomeric diazines. Several pyrimidines mainly cytosine (I), uracil (II) and thymine (III) have been isolated from the nucleic acid hydrolysis as shown in Fig 2. The nucleic acid are essential constituent of all cell and thus of all living matter cytosine is found to be present in both types of nucleic acid i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA)[1].



Cytosine
(I)



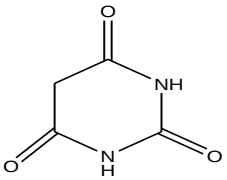
Uracil
(II)



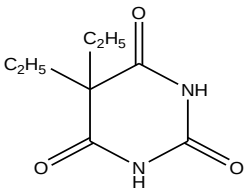
Thymine
(III)

Fig. 2:

In addition to this, Pyrimidines ring is also found in Vitamin B_1, Barbituric acid (IV) and its several derivatives e.g. Veranal (V) which are used as hypnotics (fig. 3)[2].



Barbituric acid
(IV)



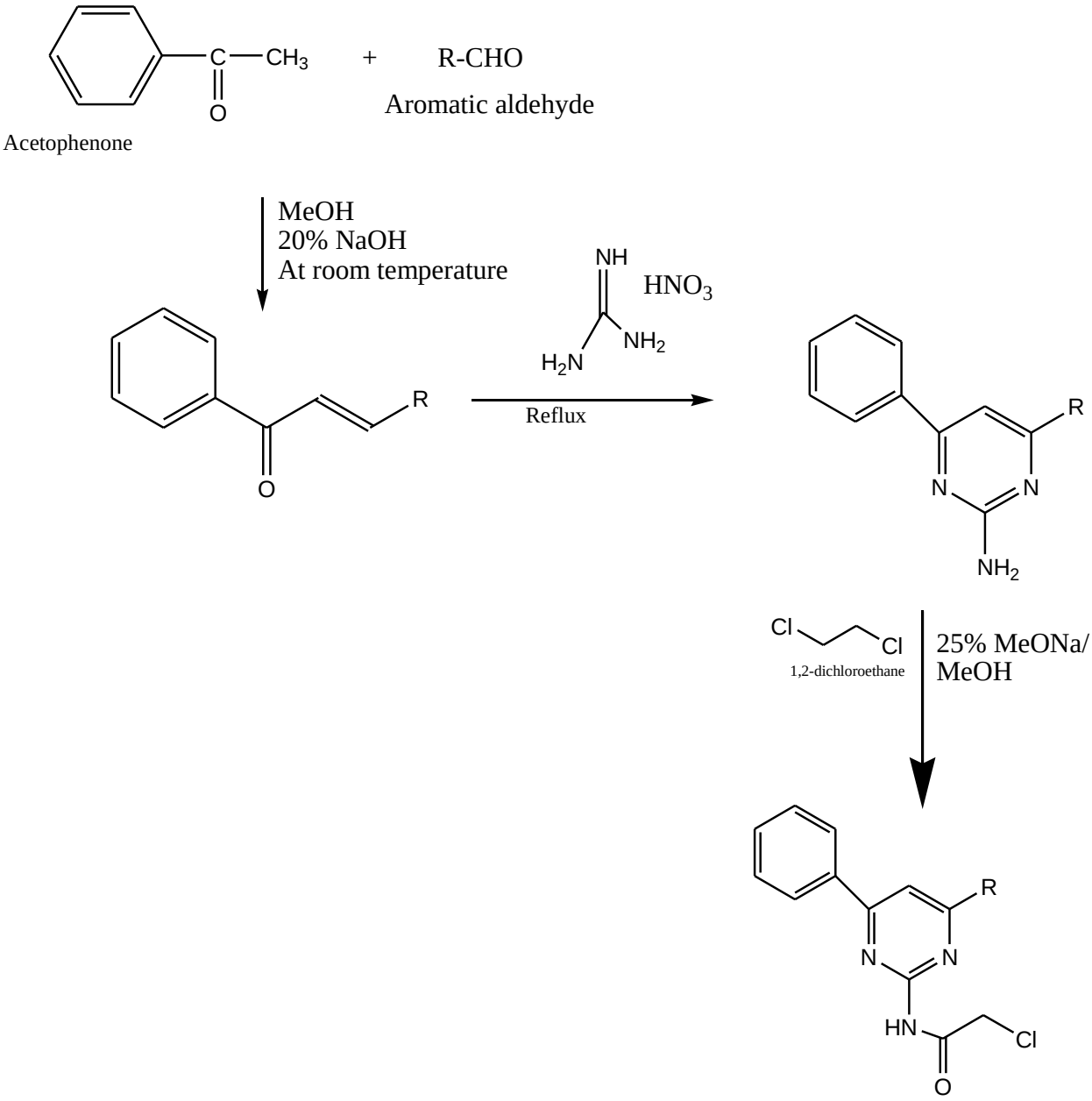
Veranal
(V)

Fig. 3:

Numerous reports have appeared in the literature that highlights chemistry and uses of pyrimidines, and their derivatives like Sulfadiazine, Sulfamerazine, and Sulfamethazine. These agents are inhibitors of folic acid biosynthesis in microorganism. Pyridine is a ubiquitous chemical compound. The aromatic, monocyclic azine is utilized as a reagent or as a polar aprotic solvent. It is salient in a number of biological systems and industrial applications. Naturally occurring pyridines include the nicotinamides, a component of the vitamin B group. Pyridines are precursors to various pharmaceuticals, adhesives, agrichemicals, and synthetic pigments.

A pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier[3].

2. Reaction scheme



3. SYNTHETIC WORK

3.1 MATERIAL AND METHODS

The purified pyrimidine derivatives were obtained in yields of 45-95%. The synthetic route is illustrated in scheme 1. Thin layer chromatography was used to reach completion of reaction and purity of compounds synthesized, using silica gel as stationary phase and Toulene:ethyl acetate:formic acid as solvent system (4:2:1) and visualized by U.V. visualizing cabinet.

All solvents used were analytical grade. The chemicals used were obtained from sigma –Aldrich (St. Louis Mossuri, USA). The structures of compounds were identified using infrared spectroscopy, Mass spectroscopy and proton nuclear magnetic resonance studies. Elemental proportions for 'C', 'N' and 'S' were determined by instrument Elementar vario EL III-C, Elementar vario EL III-N, Elementar vario EL III-S, Respectively. IR Spectra were recorded by KBR pellet technique using FTIR-84005 shimadzu spectrophotometer. ^{1}HNMR Spectra were obtained on Bruker model DRX (300MHzNMR)

Spectrometer in DMSO-d6/CDCl as solvent and using tetramethylsilane as internal standard. Mass were recorded on API 2000 triple quadrapole mass spectrophotometer. The purity of the synthesized compounds was analyzed by thin-layer chromatography.

3.2 General syntheses of derivatives

3.2.1 General Synthesis of chalcone compounds (Step 1): (IS1-5)

Aldolic condensation (clasien-schmidt condensation reaction) of equimolar quantities of substituted acetophenone with appropriate quantity of substituted aromatic aldehyde in presence of aqueous alcoholic alkali was used for formation of α, β – unsaturated ketones (i.e. chalcones). Equimolar portions of the substituted acetophenone (10mmol, 1 equiv) and substituted benzaldehyde (10mmol, 1 equiv) were dissolved in 15ml of ethanol. The mixture was allowed to stirr for several minutes at 5-10 ºC. Aliquot of a 40% aqueous NaOH solution was then slowly added to the reaction flask. The reaction mixture was allowed to stirr in ice bath for approximately 4-6 hrs. All the crude products were washed first with cold water until washings were neutral to pH paper and precipitate formed was then collected and recrystallized from ethanol to give chalcone derivatives.

3.2.2 General synthesis (Step 2) (S1-5)

To chalcone (10mmol) obtained from step 1, added guanidine nitrate then reflux for 2 hr The precipitate formed washed with cold water until it turns neutral to pH paper, filtered and recrystallized from ethanol to give derivatives.

3.2.3 General synthetic procedure of pyrimidine compounds (Step 3): (P1-5)

To mixture of derivatives **(P1-5)** (10mmol), 1,3-dichloroethane (10mmol) and 25% NaOH (0.025 mol, 10 ml) was refluxed in methanol(25 ml) for 8-12 h. The resulting mixture (III) was poured into ice-water and stirred. The crude product (III) were separated and recrystallized from Acetone.

Table 1: Physiochemical Properties of Synthesized compounds Intermediate series

[a]Compounds	R_1	R_2	Mol. Formula (Mol.Wt.)	[b]R_f value	Yield (%)	m.p. (ºC)
IS1	2,4,di-Cl	-3,4,5,tri-OCH_3	$C_{18}H_{16}Cl_2O_4$ (438.32)	0.80	90.20	103-105
IS2	2-OCH_3	-2,4,di-Cl	$C_{16}H_{12}Cl_2O_2$ (307.17)	0.67	68.57	166-168
IS3	-2,5,di-OCH_3	-2,NO_2	$C_{17}H_{15}NO_5$ (313.30)	0.74	89.91	86-88
IS4	-H	-2,NO_2	$C_{15}H_{11}NO_3$ (313.30)	0.65	91.34	111-113
IS5	-4Cl	-H	$C_{15}H_{11}ClO$ (242.70)	0.86	86.80	114-116

[a] Products were characterized by IR, NMR, MS. [b] 1; Toulene : EthylAcetate : Formic Acid (4:2:1), 2; EthylAcetate : n-Hexane (3:7), 3; Pet. Ether : EthylAcetate (2:1)

Table 2: Physiochemical properties of second step derivatives (S1-5)

[a]Compounds	R_1	R_2	Mol. Formula (Mol.Wt.)	[b]R_f value	Yield (%)	m.p. (ºC)
S1	2,4,di-Cl	-3,4,5,tri-OCH_3	$C_{18}H_{16}Cl_2O4$ (366.04)	0.73^1	93.50	113-115
S2	2-OCH_3	-2,4,di-Cl	$C_{16}H_{12}Cl_2O_2$	0.66^2	65.40	185-187
S3	-2,5,di-OCH_3	-2,NO_2	$C_{17}H_{15}NO_5$ (313)	0.75^2	47.00	98-100
S4	-H	-2,NO_2	$C_{30}H_{24}N_2O_7$ (524)	0.87^3	83.74	125-127
S5	-4Cl	-H	$C_{30}H_{24}Cl_2O_3$ (503)	0.87^3	75.90	128-130

[a] Products were characterized by IR, NMR, MS.
[b] 1; Toulene : EthylAcetate : Formic Acid (4:2:1), 2; EthylAcetate : n-Hexane (3:7), 3; Pet. Ether : EthylAcetate (2:1)

Table 3: Physiochemical properties of third step derivatives (P1-30)

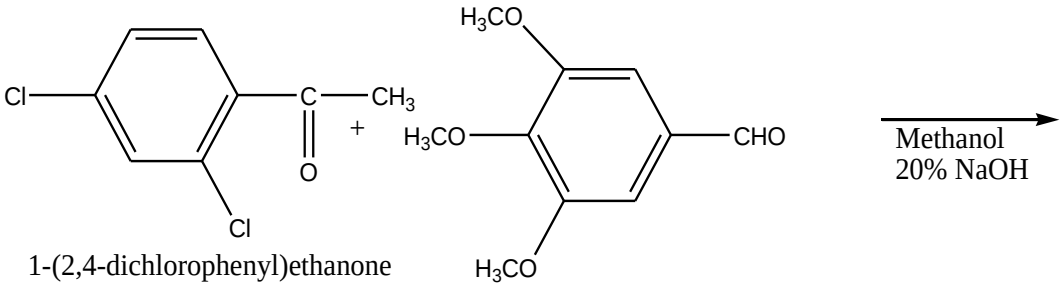
[a]Compounds	R_1	R_2	Mol. Formula (Mol.Wt.)	[b]R_f value	Yield (%)	m.p. (ºC)
P1	2,4,di-Cl	-3,4,5,tri-OCH_3	$C_{20}H_{16}Cl_3N_3O_4$ (467.02)	0.73[1]	93.50	113-115
P2	2-OCH_3	-2,4,di-Cl	$C_{18}H_{12}Cl_3N_3O_2$ (408)	0.66[2]	45.40	185-187
P3	-2,5,di-OCH_3	-2,NO_2	$C_{19}H_{15}ClN_4O_5$ (414)	0.75[2]	77.00	98-100
P4	-H	-2,NO_2	$C_{17}H_{11}ClN_4O_3$ (354)	0.87[3]	83.74	125-127
P5	-4Cl	-H	$C_{17}H_{10}Cl_3N_3O$ (343)	0.87[3]	75.90	128-130

[a] Products were characterized by IR, NMR, MS.
[b] 1; Toulene : EthylAcetate : Formic Acid (4:2:1), 2; EthylAcetate : n-Hexane (3:7), 3; Pet. Ether : EthylAcetate (2:1)

Synthesis of Intermediate Compound

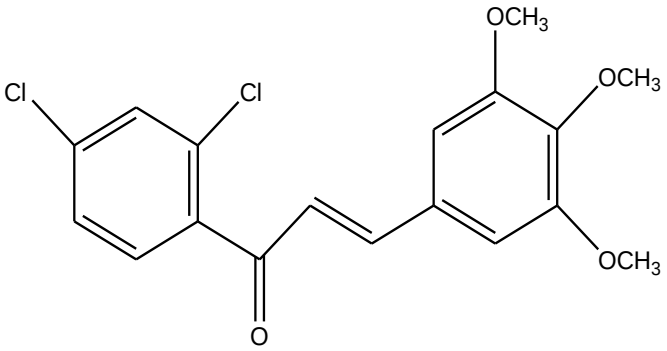
3.2.1.1. Synthesis of *(E)*-1-(2,4-dichloro)-3-(3,4,5-trimethoxyphenyl)lprop-2-en-1-one (IS1)

Aldolic condensation (clasien-schmidt condensation reaction) of equimolar quantities of 2,4-dichloro acetophenone with appropriate quantity of 3,4,5-trimethoxy benzaldehyde in presence of aqueous alcoholic alkali was used for formation of α, β – unsaturated ketones (i.e. chalcones). Equimolar portions of the acetophenone (10mmol, 1 equivalent) and 3,4,5-trimethoxy benzaldehyde (10mmol, 1 equivalent) were dissolved in 15ml of ethanol. The mixture was allowed to stirr for several minutes at 5-10 ºC. Aliquot of a 40% aqueous NaOH solution was then slowly added to the reaction flask. The reaction mixture was allowed to stirr in ice bath for approximately 4-6hrs. All the crude products were washed first with cold water until washings were neutral to pH paper and precipitate formed was then collected and recrystallized from ethanol to give chalcone derivatives of *(E)*-1-(2,4-dichloro)-3-(3,4,5-trimethoxyphenyl)lprop-2-en-1-one.



1-(2,4-dichlorophenyl)ethanone

3,4,5-trimethoxybenzaldehyde

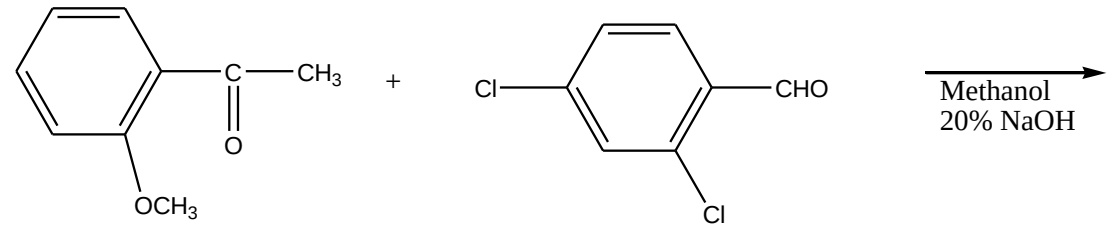


(*E*)-1-(2,4-dichlorophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

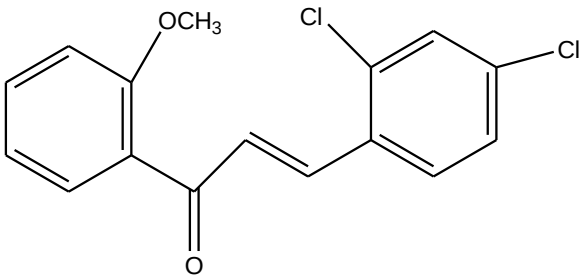
3.2.1.2. Synthesis of *(E)*-1-(2,4-dichlorophenyl)-1-(2-methoxyphenyl)lprop-2-en-1-one: (IS2)

Aldolic condensation (clasien-schmidt condensation reaction) of equimolar quantities of 2-methoxy acetophenone with appropriate quantity of 2,4-dichloro benzaldehyde in presence of aqueous alcoholic alkali was used for formation of α, β – unsaturated ketones (i.e. chalcones). Equimolar portions of the 2-methoxy acetophenone (10mmol, 1 equivalent) and 2,4-dichloro benzaldehyde (10mmol, 1 equivalent) were dissolved in 15ml of ethanol. The mixture was allowed to stirr for several

minutes at 5-10 ºC. Aliquot of a 40% aqueous NaOH solution was then slowly added to the reaction flask. The reaction mixture was allowed to stirr in ice bath for approximately 4-6hrs. All the crude products were washed first with cold water until washings were neutral to pH paper and precipitate formed was then collected and recrystallized from ethanol to give chalcone derivatives of *(E)*-1-(2,4-dichlorophenyl)-1-(2-methoxyphenyl)lprop-2-en-1-one:

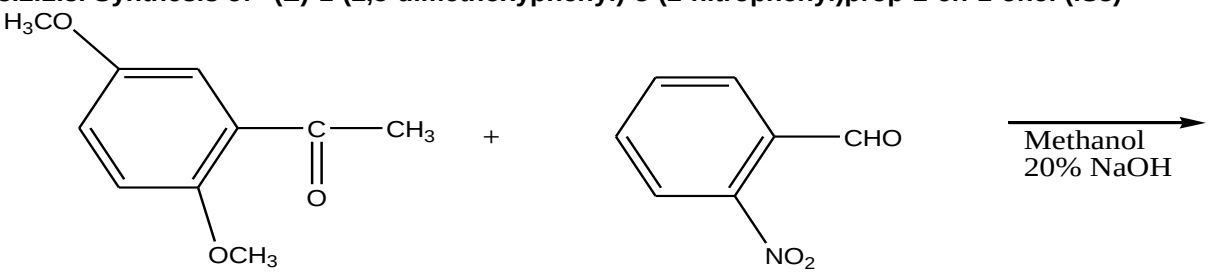


1-(2-methoxyphenyl)ethanone 2,4-dichlorobenzaldehyde

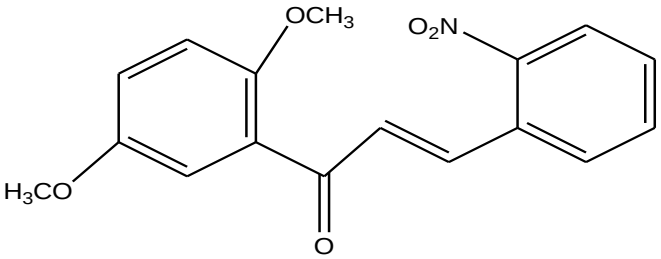


(*E*)-3-(2,4-dichlorophenyl)-1-(2-methoxyphenyl)prop-2-en-1-one

3.2.1.3. Synthesis of (E)-1-(2,5-dimethoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one: (IS3)



1-(2,5-dimethoxyphenyl)ethanone



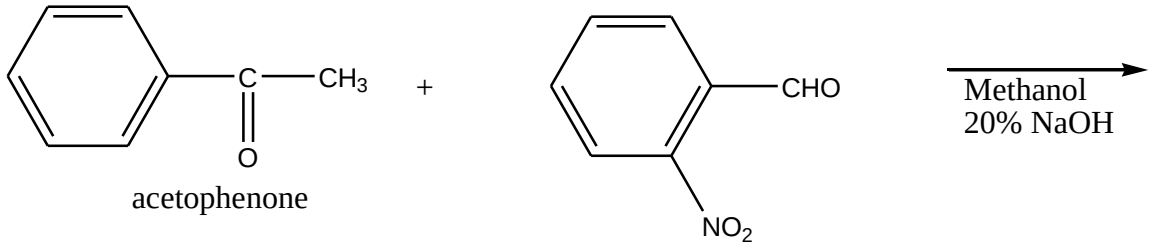
(*E*)-1-(2,5-dimethoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one

Aldolic condensation (clasien-schmidt condensation reaction) of equimolar quantities of 2,4-dimethoxy acetophenone with appropriate quantity of 2,4-nitrobenzaldehyde in presence of aqueous alcoholic alkali was used for formation of α, β – unsaturated ketones (i.e. chalcones). Equimolar portions of the

2,4-dimethoxy acetophenone (10mmol, 1 equivalent) and 2,4-nitrobenzaldehyde (10mmol, 1 equivalent) were dissolved in 15ml of ethanol. The mixture was allowed to stirr for several minutes at 5-10 ºC. Aliquot of a 40% aqueous NaOH solution was then slowly added to the reaction flask. The reaction mixture was allowed to stirr in ice bath for approximately 4-6hrs. All the crude products were washed first with cold water until washings were neutral to pH paper and precipitate formed was then collected and recrystallized from ethanol to give chalcone derivatives of (*E)*-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one.

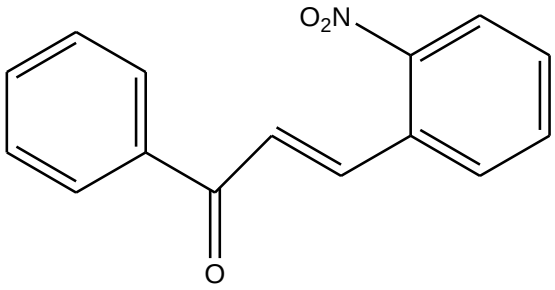
3.2.1.4. Synthesis of *(E)*-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one (IS4)

Aldolic condensation (clasien-schmidt condensation reaction) of equimolar quantities of acetophenone with appropriate quantity of 2-nitrobenzaldehyde in presence of aqueous alcoholic alkali was used for formation of α, β – unsaturated ketones (i.e. chalcones). Equimolar portions of the 2,4-dimethoxy acetophenone (10mmol, 1 equivalent) and benzaldehyde (10mmol, 1 equivalent) were dissolved in 15ml of ethanol. The mixture was allowed to stirr for several minutes at 5-10 ºC. Aliquot of a 40% aqueous NaOH solution was then slowly added to the reaction flask. The reaction mixture was allowed to stirr in ice bath for approximately 4-6hrs. All the crude products were washed first with cold water until washings were neutral to pH paper and precipitate formed was then collected and recrystallized from ethanol to give chalcone derivatives of (*E)*-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one**-**(2-nitrophenyl)-1-phenylprop-2-en-1-one.



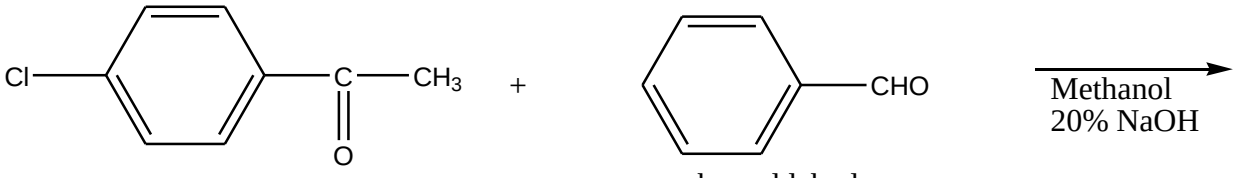
acetophenone

2-nitrobenzaldehyde

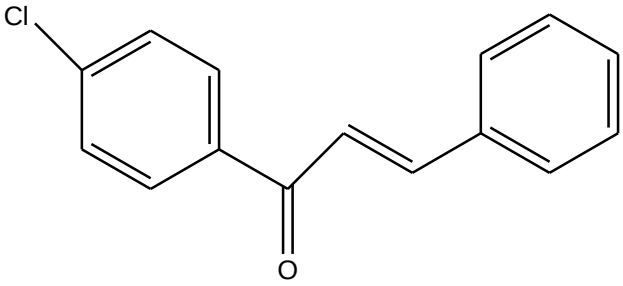


(*E*)-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one

3.2.1.5. Synthesis of (*E)*-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one: **(IS5)** Aldolic condensation (clasien-schmidt condensation reaction) of equimolar quantities of 1-(4-chlorophenyl)ethanone with appropriate quantity of benzaldehyde in presence of aqueous alcoholic alkali was used for formation of *(E)*-1-(4-chlorophenyl)ethanone (10mmol, 1 equivalent) and then (10mmol, 1 equivalent) benzaldehyde were dissolved in 15ml of ethanol. The mixture was allowed to stirr for several minutes at 5-10 ºC. Aliquot of a 40% aqueous NaOH solution was then slowly added to the reaction flask. The reaction mixture was allowed to stirr in ice bath for approximately 4-6hrs. All the crude products were washed first with cold water until washings were neutral to pH paper and precipitate formed was then collected and recrystallized from ethanol to give chalcone derivatives of (*E)*-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one



1-(4-chlorophenyl)ethanone benzaldehyde

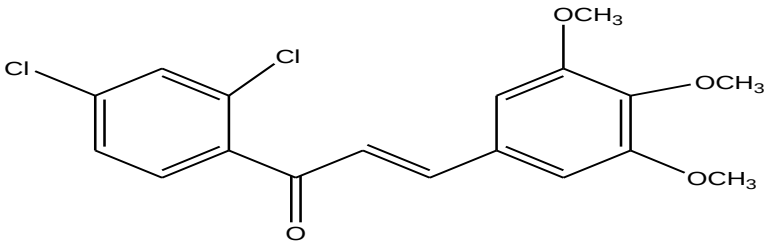


(*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one

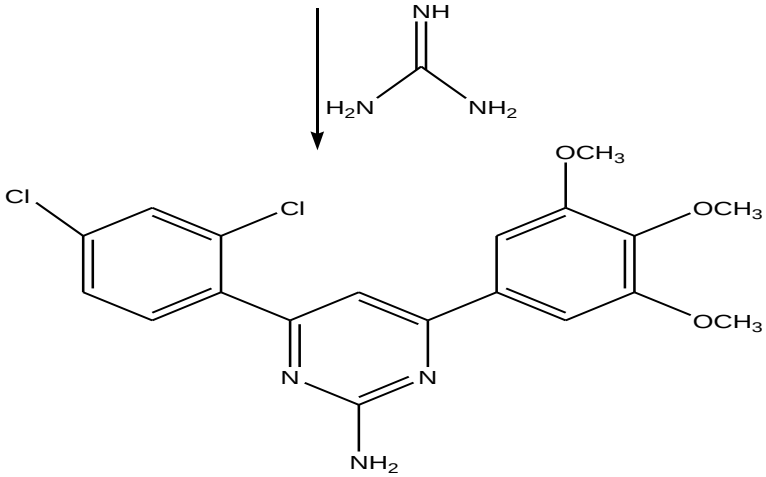
Synthesis of second step derivatives

3.2.2.1. Synthesis of 4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimdine-2-amine (S1)

To *(E)*-1-(2,4-dichlorophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (10mmol) obtained from step 1, added guanidine nitrate then reflux for 2 hr The precipitate formed washed with cold water until it turns neutral to pH paper, filtered an recrystallized from ethanol to give 4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimdine-2-amine.



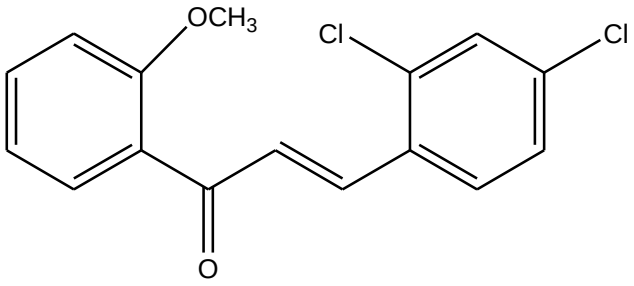
(*E*)-1-(2,4-dichlorophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one



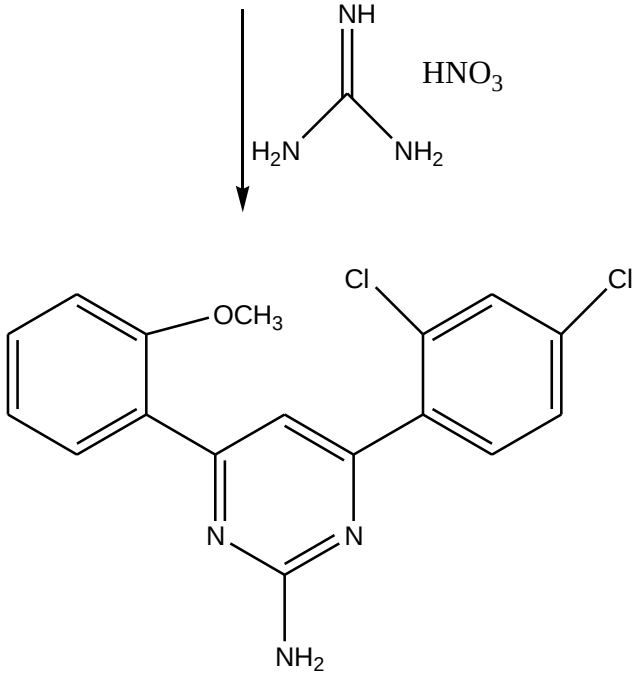
4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine

3.2.2.2. Synthesis of 4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimdine-2-amine (S2)

To *(E)*-3-(2,4-dichlorophenyl)-1-(2-methoxyphenyl)prop-2-en-1-one (10mmol) obtained from step 1, added guanidine nitrate then reflux for 2 hr The precipitate formed washed with cold water until it turns neutral to pH paper, filtered an recrystallized from ethanol to give 4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimdine-2-amine.



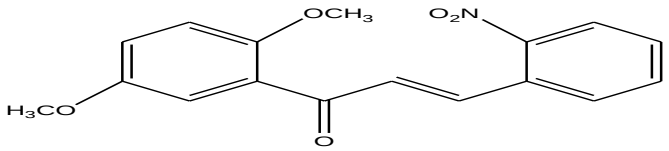
(*E*)-3-(2,4-dichlorophenyl)-1-(2-methoxyphenyl)prop-2-en-1-one



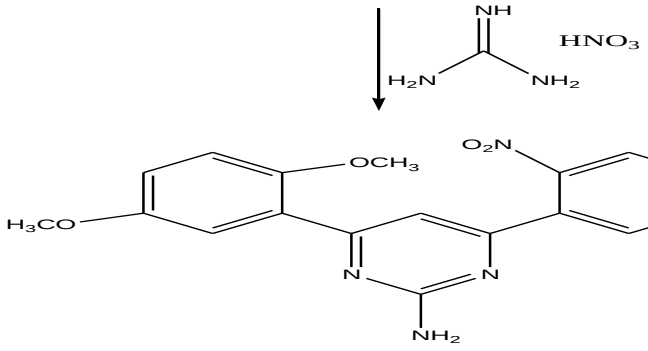
4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimidin-2-amine

3.2.2.3. Synthesis of 4-(2,5-dimethoxyphenyl)-6-(2,nitrophenyl)pyrimdine-2-amine (S3)

To *(E)*-1-(2,5-dimethoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one (10mmol) obtained from step 1, added guanidine nitrate then reflux for 2 hr The precipitate formed washed with cold water until it turns neutral to pH paper, filtered an recrystallized from ethanol to give 4-(2,5-dimethoxyphenyl)-6-(2,nitrophenyl)pyrimdine-2-amine.



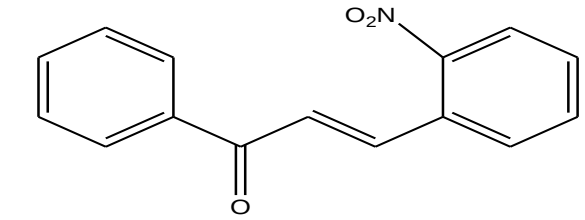
(*E*)-1-(2,5-dimethoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one



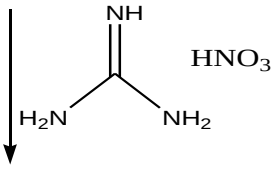
4-(2,5-dimethoxyphenyl)-6-(2-nitrophenyl)pyrimidin-2-amine

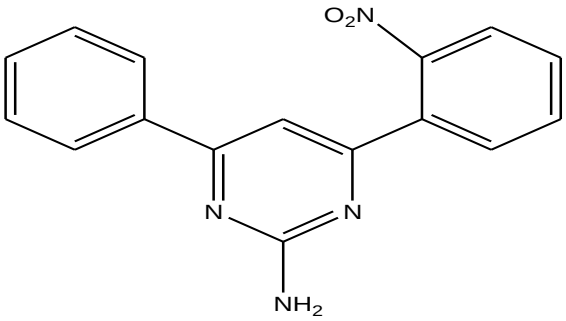
5.2.2.4. Synthesis of 4-(2-nitrophenyl)-6-phenylpyrimdine-2-amine (S4)

To *(E)*-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one (10mmol) obtained from step 1, added guanidine nitrate then reflux for 2 hr The precipitate formed washed with cold water until it turns neutral to pH paper, filtered an recrystallized from ethanol to give 4-(2-nitrophenyl)-6-phenylpyrimdine-2-amine.



(*E*)-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one

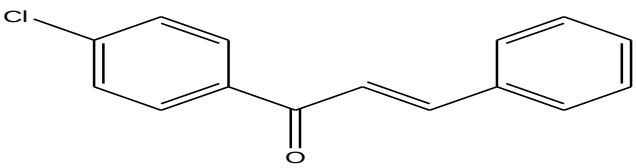




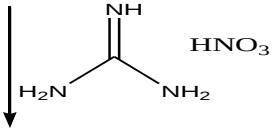
4-(2-nitrophenyl)-6-phenylpyrimidin-2-amine

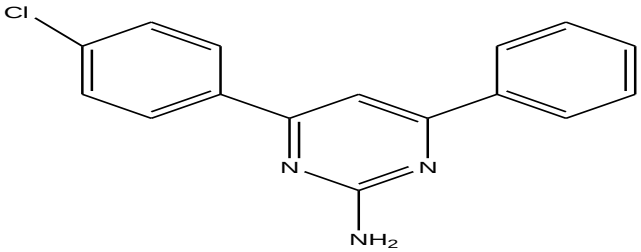
3.2.2.5. Synthesis of 4-(4-chlorophenyl)-6-phenylpyrimdine-2-amine (S5)

To *(E)*-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (10mmol) obtained from step 1, added guanidine nitrate then reflux for 2 hr. The precipitate formed washed with cold water until it turns neutral to pH paper, filtered an recrystallized from ethanol to give 4-(4-chlorohenyl)-6-phenylpyrimdine-2-amine.



(*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one

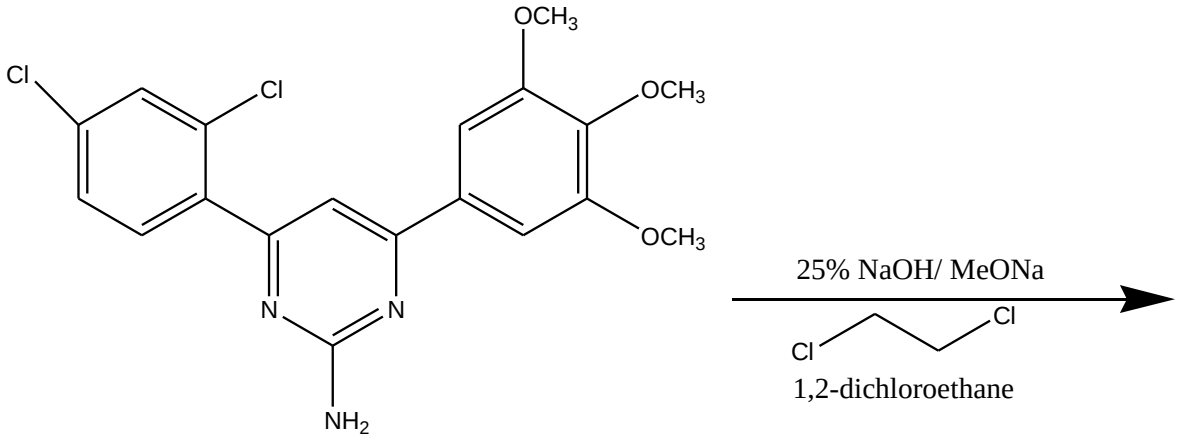




4-(4-chlorophenyl)-6-phenylpyrimidin-2-amine

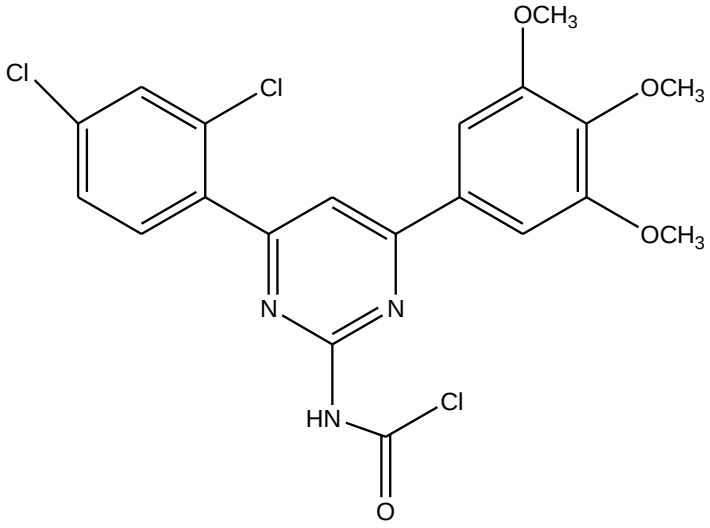
Synthesis of third step derivatives

3.2.3.1. Synthesis of 4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidine-2-yl)carbamic chloride (P_1) : To mixture of derivatives 4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyimidine-2- amine (10mmol), 1,2-dichloroethane (10mmol) and 25% NaOH (0.025 mol, 10 ml) was refluxed in methanol(25 ml) for 8-12 h. The resulting mixture 4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyimidine-2-yl)carbamic chloride (P_6) was poured into ice-water and stirred. The crude product (P_6) 4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyimidine-2-yl)carbamic chloride were (P_6) separated and recrystallized from Acetone.



4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine

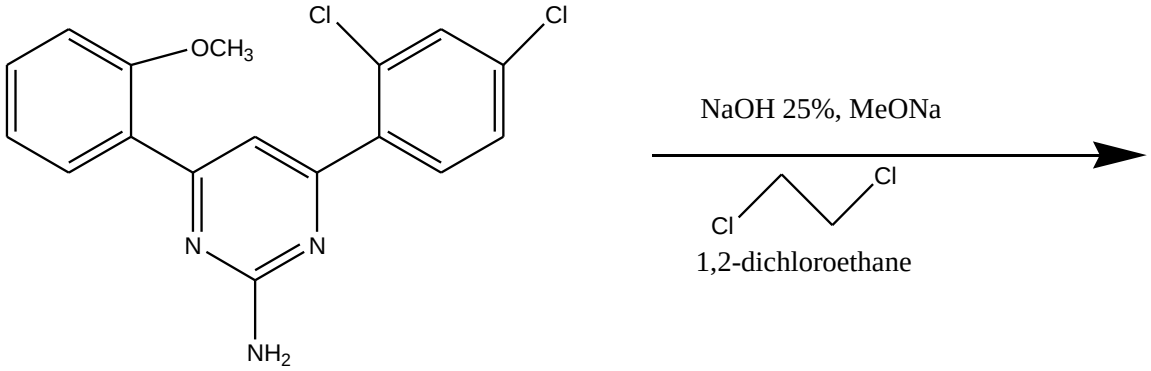
1,2-dichloroethane



(4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)carbamic chloride

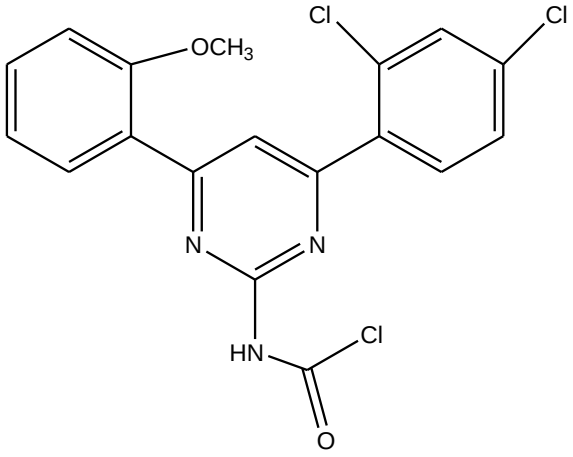
3.2.3.2. Synthesis of 4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimidine-2-yl)carbamic chloride (P_2)

To mixture of derivatives 4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyimidine-2- amine (10mmol), 1,2-dichloroethane (10mmol) and 25% NaOH (0.025 mol, 10 ml) was refluxed in methanol(25 ml) for 8-12 h. The resulting mixture 4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyimidine-2-yl)carbamic chloride (III) was poured into ice-water and stirred. The crude product (P_7) 4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyimidine-2-yl)carbamic chloride (P_7) was separated and recrystallized from Acetone.



1,2-dichloroethane

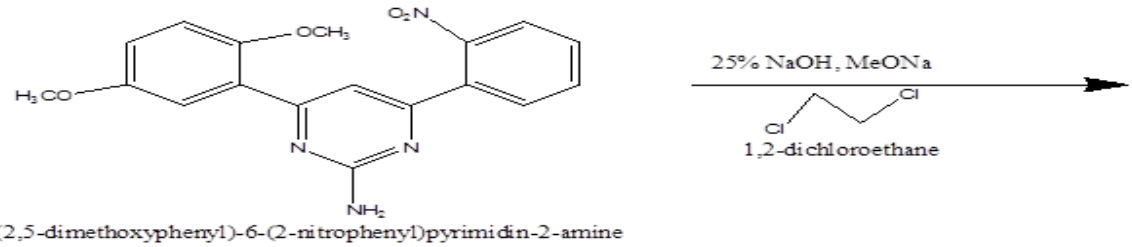
4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimidin-2-amine



(4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimidin-2-yl)carbamic chloride

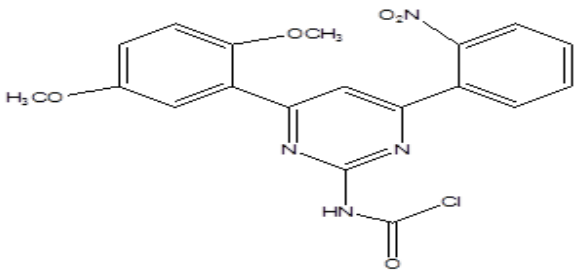
3.2.3.3. Synthesis of 4-(2,5-dimethoxyphenyl)-6-(2-nitrophenyl)pyrimidine-2-yl)carbamic chloride (P_3)

To mixture of derivatives 4-(2,5-dimethoxyphenyl)-6-(2-nitrophenyl)pyimidine-2- amine (10mmol), 1,3-dichloroethane (10mmol) and 25% NaOH (0.025 mol, 10 ml) was refluxed in methanol(25 ml) for 8-12 h. The resulting mixture 4-(2,5-dimethoxyphenyl)-6-(2-nitrophenyl)pyimidine-2-yl)carbamic chloride **(P_8)** was poured into ice-water and stirred. The crude product **(P_8)**4-(2,5-dimethoxyhenyl)-6-(2-nitrophenyl)pyimidine-2-yl)carbamic chloride was separated and recrystallized from Acetone.



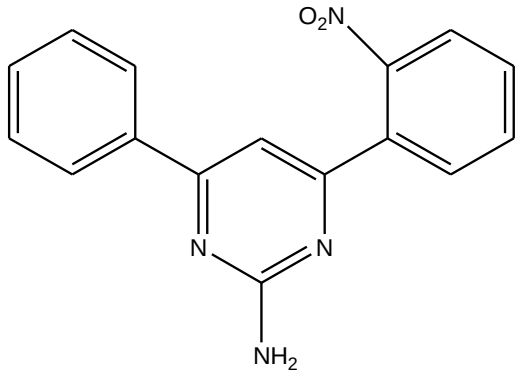
1,2-dichloroethane

4-(2,5-dimethoxyphenyl)-6-(2-nitrophenyl)pyrimidin-2-amine



3.2.3.4. Synthesis of 4-(2-nitrophenyl)-6-phenylpyrimidine-2-yl)carbamic chloride (P_4)

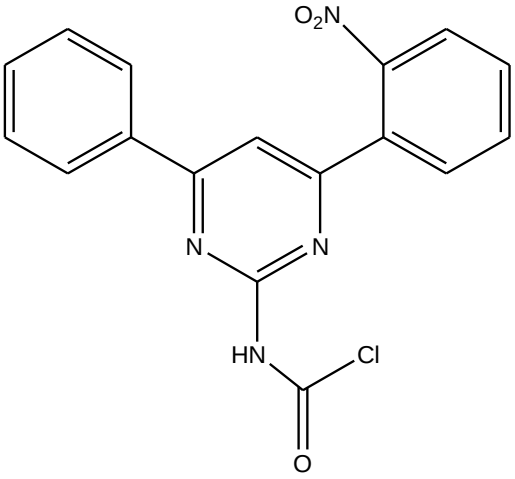
To mixture of derivatives 4-(2-nitrophenyl)-6-phenylpyimidine-2- amine (10mmol), 1,3-dichloroethane (10mmol) and 25% NaOH (0.025 mol, 10 ml) was refluxed in methanol(25 ml) for 8-12 h. The resulting mixture 4-(2-nitrophenyl)-6-phenylpyimidine-2-yl)carbamic chloride (P_9) was poured into ice-water and stirred. The crude product (P_9) 4-(2-nitrophenyl)-6-phenylpyimidine-2-yl)carbamic chloride was separated and recrystallized from Acetone.



4-(2-nitrophenyl)-6-phenylpyrimidin-2-amine

NaOH 25%, MeONa

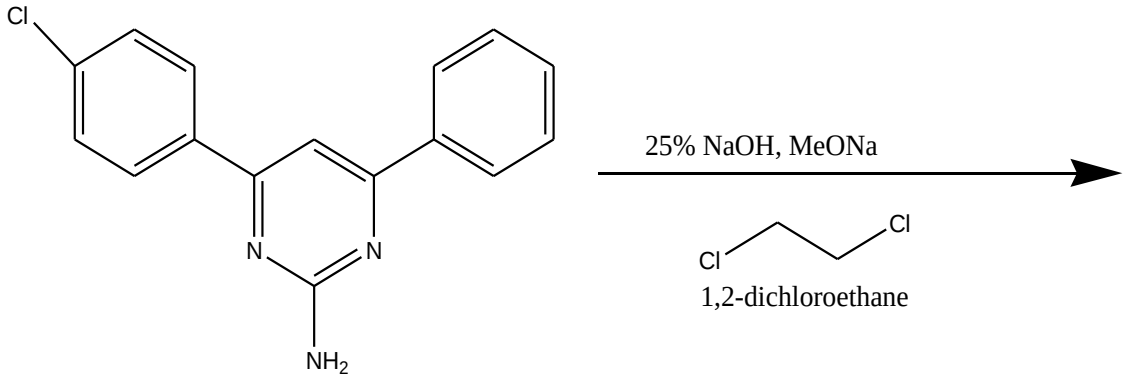
1,2-dichloroethane



(4-(2-nitrophenyl)-6-phenylpyrimidin-2-yl)carbamic chloride

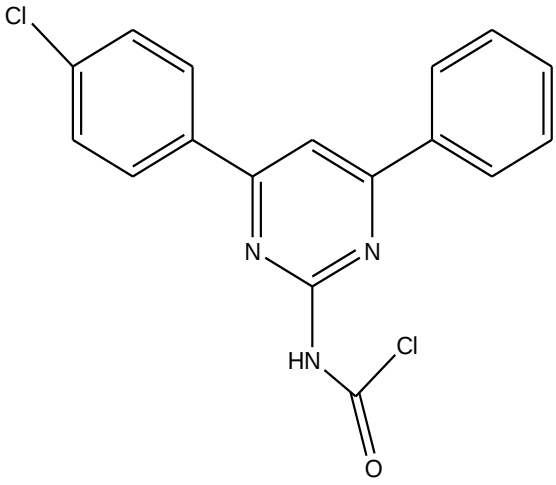
3.2.3.5. Synthesis of 4-(4-chlorophenyl)-6-phenylpyrimidine-2-yl)carbamic chloride (P_5)

To mixture of derivatives 4-(4-chlorophenyl)-6-phenylpyimidine-2- amine (10mmol), 1,2-dichloroethane (10mmol) and 25% NaOH (0.025 mol, 10 ml) was refluxed in methanol(25 ml) for 8-12 h. The resulting mixture 4-(4-chlorophenyl)-6-phenylpyimidine-2-yl)carbamic chloride (P_{10}) was poured into ice-water and stirred. The crude product (P_{10}) 4-(4-chlorophenyl)-6-phenylpyimidine-2-yl)carbamic chloride were separated and recrystallized from Acetone.



4-(4-chlorophenyl)-6-phenylpyrimidin-2-amine

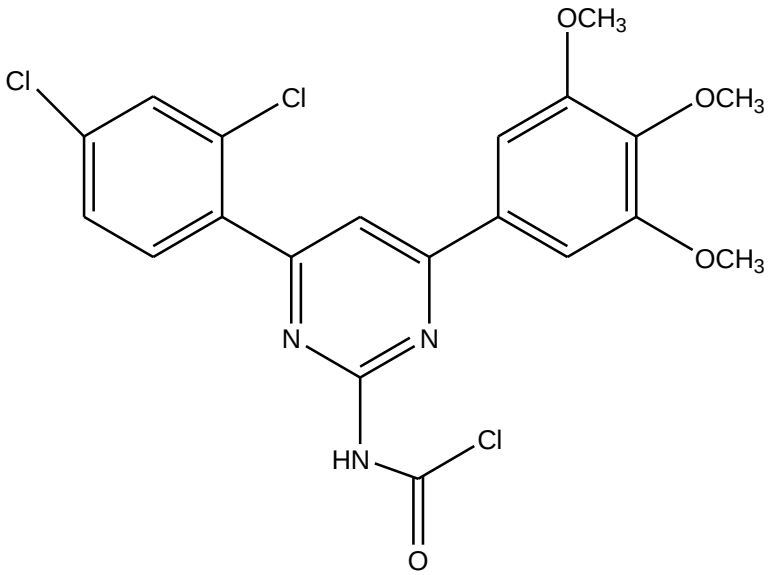
1,2-dichloroethane



(4-(4-chlorophenyl)-6-phenylpyrimidin-2-yl)carbamic chloride

Spectral characterizations of synthesized compounds

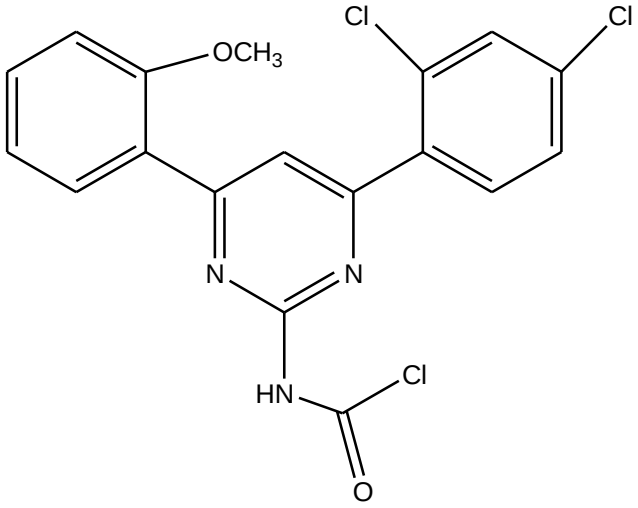
4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyimidine-2-yl)carbamic chloride (P_1):



(4-(2,4-dichlorophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)carbamic chloride

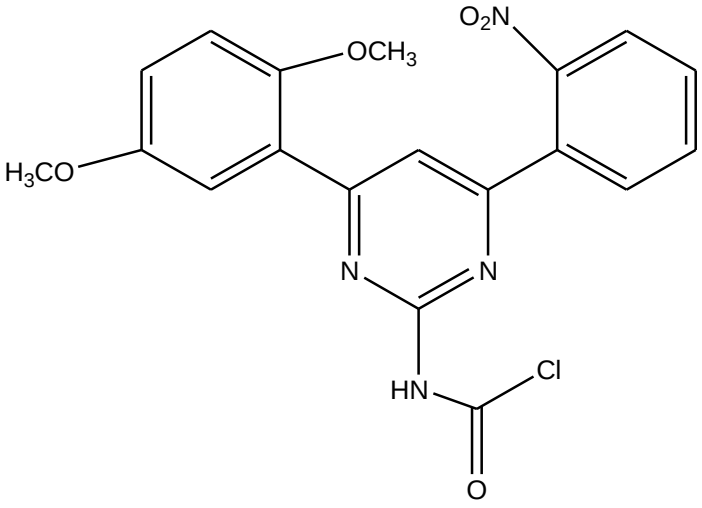
IR (KBr, cm^{-1})
3770 (NH str), 3452 (C-H str), 1677 (C=O of α,β unsaturated ketone) , 1698.00 (C=N str), 1608.77 (Ar C=C) 1706 (C=O str), , 1578 (C=C Ar str), 1545 (C=N str), 1188.20 [C-O-C(-OCH3)], 767 cm-1 (C-Cl str.) ^{1}H NMR: **($CDCl_3$, δ, ppm):** 7.72 (s, 1H, CH of pyrimidine), 7.5-8.0 (m, 5H, Ar-H), 8.8 (s, 1H, NH), 2.50 (s, 3H,-OCH3). MS (*m/z*) : **(**M^+= 468), 430, 366.

4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimidine-2-yl)carbamic chloride (P_2)
IR (KBr, cm^{-1}): 3770 (NH str), 3852 (C-H str), 1678 (C=O of α,β unsaturated ketone) , 1598.00 (C=N str), 1608.77 (Ar C=C) 1706 (C=O str), 1555 (C=N str), 1678 (C=C Ar str), 1108 [C-O-C(-OCH3)], 767.69 cm-1 (C-Cl str.) ^{1}H NMR: **($CDCl_3$, δ, ppm):** 7.72 (s, 1H, CH of pyrimidine), 7.5-8.0 (m, 7H, Ar-H), 8.8 (s, 1H, CH), 2.50 (s, 3H,-OCH3). MS (*m/z*) : **(**M^+= 408), 400, 380.



(4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyrimidin-2-yl)carbamic chloride

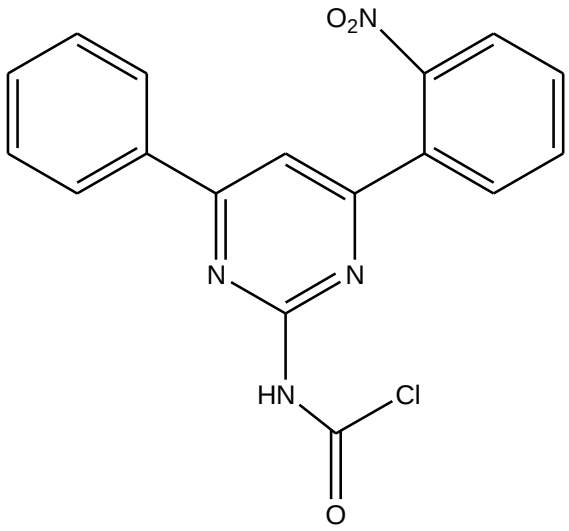
4-(2,4-dichlorophenyl)-6-(2-methoxyphenyl)pyimidine-2-yl)carbamic chloride (P_3)



(4-(2,5-dimethoxyphenyl)-6-(2-nitrophenyl)pyrimidin-2-yl)carbamic chloride

IR (KBr, cm^{-1})
3770 (NH str), 3452 (C-H str), 1677 (C=O of α,β unsaturated ketone) , 1698.00 (C=N str), 1608.77 (Ar C=C) and , 1706 (C=O str), 1545 (C=N str), , 1578 (C=C Ar str), 1188.20 [C-O-C(-OCH3)], 767 cm-1 (C-Cl str.), 709 (*o*- nitro Ar substitution). ^{1}H NMR: **($CDCl_3$, δ, ppm):** 7.72 (s, 1H, CH of pyrimidine), 7.5-8.0 (m, 7H, Ar-H), 8.8 (s, 1H, NH), 2.50 (s, 3H,-OCH3). MS (*m/z*) : **(**M^+= 414), 400, 396.

4-(2-nitrophenyl)-6-phenylpyimidine-2-yl)carbamic chloride (P_4)



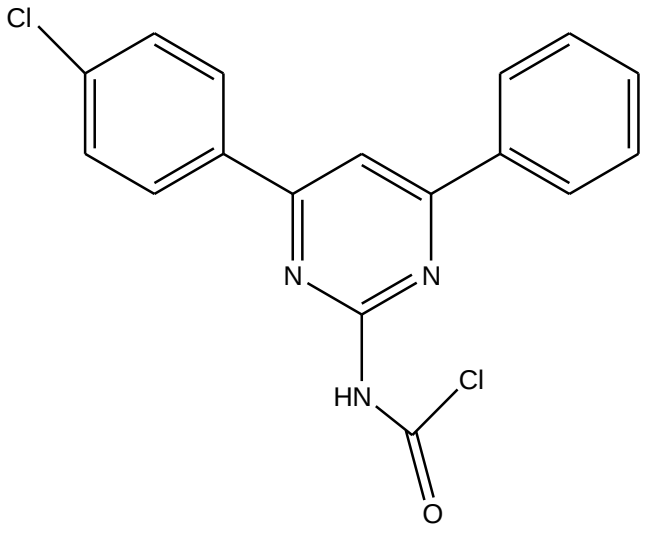
(4-(2-nitrophenyl)-6-phenylpyrimidin-2-yl)carbamic chloride

IR (KBr, cm^{-1})

3770 (NH str), 3452 (C-H str), 1677 (C=O of α,β unsaturated ketone) , 1698 (C=N str), 160 (Ar C=C) and 1706 (C=O str), 1545 (C=N str), , 1578. (C=C Ar str), 1188.20, 767.69, (C-Cl str.), 700 (*o*- nitro Ar substitution). ^{1}H NMR: **($CDCl_3$, δ, ppm):** 7.72 (m, 1H, CH of pyrimidine), 7.5-8.0 (m, 4H, Ar-H), 8.8 (m, 1H, CH), 2.35 [1H, (s, pyrimidine NH], 4.36 (1H, (d, pyrimidine). MS (*m/z)* : **(**M^+= 354), 312, 316.

4-(4-chlorophenyl)-6-phenylpyimidine-2-yl)carbamic chloride (P_5)

IR (KBr, cm^{-1}): 3102.54 (CH str), 2365 (NH str), 1353 (C=C str), 3355.3 (-NH, 2° amide), 3208 (= C-H, aromatic), 1553. (- C=O). ^{1}H NMR: ^{1}H NMR: **($CDCl_3$, δ, ppm):** 7.72 (m, 1H, CH of pyrimidine), 7.5-8.0 (m, 4H, Ar-H), 8.0 (m, 1H, NH), MS (*m/z)* : **(**M^+= 344), 302, 313.



(4-(4-chlorophenyl)-6-phenylpyrimidin-2-yl)carbamic chloride

Pharmacological screening

Table 4: **Antibacterial activity of some synthesized compounds against Gram negative bacteria *Pseudomonas aeruginosa***

Gram-negative bacteria *Pseudomonas aeruginosa* zone of inhibition (mm)									
S.NO	Compounds code	Concentration (µg/ml)							
		ZI	% I	ZI	%I	ZI	% I	ZI	% I
1	Std (Ampicillin)	9	11.11	11	12.22	13	14.44	14	15.55
2	P-1	12	13.33	12	13.33	14	15.56	12	13.33
3	P-2	13	14.44	13	14.44	15	16.67	15	16.67
4	P-3	9	10.00	12	12.22	13	11.11	14	13.33
5	P-4	9	10.00	12	13.33	13	14.44	14	15.56
6	P-5	11	12.22	14	15.56	15	16.67	16	16.67

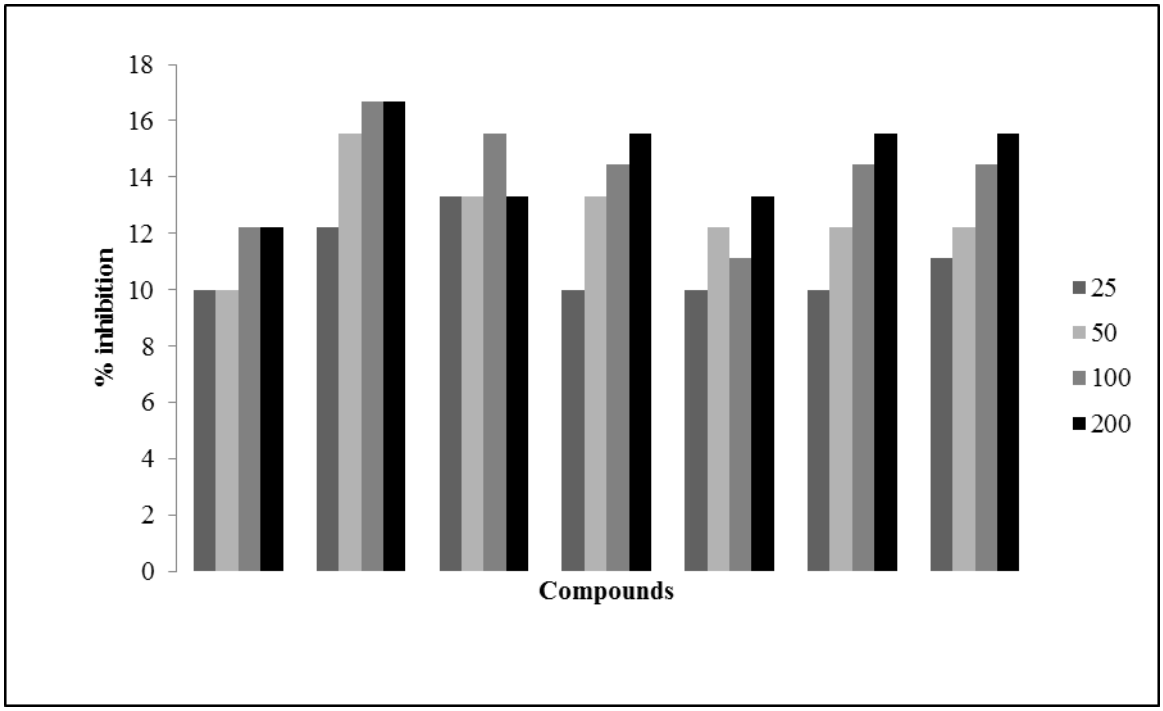


Fig. 9: Graph showing % inhibition and different concentrations of compounds against *Pseudomonas aeruginosa*

CONCLUSION

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. Thepresence of a pyrimidine base in thymine, cytosine and uracil, which are the essential binding blocks of nucleic acids, DNA and RNA is one possible reason for their activity. The literature indicate that compounds having pyrimidine nucleus possess broad range of biological activities, like 5-fluorouracil as anticancer, idoxuridine and trifluoridine as antiviral zidovudine and stavudine as antiHIV, trimethoprim, sulphamethiazine and sulphadiazine as antibacterial, sulphadoxin as antimalarial and antibacterial minoxidil and prazosin as antihypertensive ,barbiturates eg. phenobarbitone as sedative, hypnotics and anticonvulsant propylthiouracil as antithyroid thionzylamine as H1–antihistamine ,and toxoflavin and fervennuline as antibiotics. as they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. As a result of remarkable pharmacological efficiency of pyrimidine derivatives, intensive review has been focused on Pharmacological activity of pyrimidine nucleus. There is still scope for more research work to be done in this field to find a novel pharmacological agent. This study would be useful for the researchers working in this field.

All the newly synthesized substituted Pyrimidine derivatives were evaluate for their pharmacological activity. Agar well diffusion method were used for evaluation of antibacterial activity.

The antibacterial activity evalauated against, gram-negative bacteria *Pseudomonas aeruginosa* agar well diffusion method. All the synthesized compounds and standard drugs were dissolved in DMSO

and the concentrations of test compounds were adjusted to 25, 50, 100, and 200 µg/ml and of standard drug Ampicillin were used as indicated in **Table 4.** The compounds **P-1** (having chloro group at 2th and 4th position) found to be active against *Pseudomonas aeruginosa.*

REFERENCES

1. Singh H and Kapoor VK. Medicinal and pharmaceutical chemistry. 2003;29.
2. Agarwal OP. Organic chemistry, Reaction and Reagent. 2002;735.
3. Jain MK and Sharnevas SC. Organic chemistry. 2006;22:997-999.