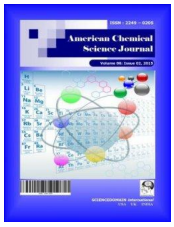

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# Synthesis of Pharmacologically Important Some Novel Pyrimidine and Chalcone Moieties Containing s-triazines

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Author Anupama carried out synthesis, characterization and wrote the first draft of the manuscript. Author BS designed the scheme and protocol for synthetic pathway and wrote the final draft of the manuscript. Both authors read and approved the final manuscript.*

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## ABSTRACT

s-Triazines containing heterocycles have variety of biological activities including anti-cancer, anti-viral, anti-microbial, anti-inflammatory activities. Various heterocycles have been synthesized by annellation methodology using chalcones as base template. A new series of 2-aminopyrimidine substituted chalcones have been synthesized by the temperature controlled reaction of s-triazines. 4,6-Dichloro-N-(pyrimidine-2-yl)-1,3,5-triazine-2-amine and its various derivatives were synthesized at different temperatures. These were further treated with pyridine-2-aldehydes to furnish corresponding chalcones and the newly synthesized compounds were characterized by IR, $^{1}$H-NMR, MS and elemental analysis. s-Traizine containing chalcones have been used as base framework to synthesized five-, six- and seven-membered heterocycles through annellation methodology.

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*Keywords: 2-Aminopyrimidine; s-triazine; 4-aminoacetophenone 4,6-dichloro-N-(pyrimidine-2-yl)-1,3,5-triazine-2-amine; pyridine aldehyde; chalcones.*

## 1. INTRODUCTION

Heterocyclic compounds play important roles in the drug discovery processes and analysis of drugs. It is, therefore, not surprising that research on the synthesis of poly-functionalized heterocyclic compounds have received special attention. Out of these heterocycles, pyrimidine derivatives which are a rarity in nature have been reported to possess a wide range of biological activities. Pyrimidine derivatives have also been the subject of extensive research in the agrochemical areas [1]. It has incidental anti-viral activity against herpes and other infections. Because of the great synthetic potentiality, heterocyclic analogous of chalcones are among the most useful synthons. Chalcones bear very good structural framework so that a variety of novel heterocycles with good pharmaceutical profile can be designed. Chalcones either natural or synthetic are known to exhibit various biological activities [2].

Nitrogen containing heterocycles reveal that these form important constituent of a wide variety of products with plethora of pharmacodynamic applications [3,4,5,6]. 1,3,5-triazines (or s-triazines) are a class of compounds well known from a long time and still continue the subject of considerable research mainly due to their application in different fields including the production of pharmaceuticals, herbicides, polymer photostabilizers [7,8,9], *etc*.1,3,5-Triazines display various biological properties, for example, hexamethyl melamine (HMM & 2-amino-4-morphlino-s-triazine) are used clinically due to their anti-tumor properties for treating lung, breast and ovarian cancer respectively. 2,4,6-trichloro-1,3,5-triazine (TCT) provides a good opportunity to a chemist in the synthesis of its various derivatives by the replacement of its chlorine atom with bioactive pharmacophores at three different temperatures [10,11,12]. s-Triazine or (1,3,5-triazine) derivatives having active 2,4 and 6 positions have been shown in literature to exhibit impressive pharmacological properties such as anti-cancer, anti-malarial, anti-viral, anti-fungal, herbicidal , anti-ulcer , anti-arthritis, local anesthetic, anti-convulsant, anti-bacterial, analgesic, hypoglycemic, anti-inflammatory, anti-helmintic, anti-tubercular activities [13,14,15,16,17,18], *etc*. The replacement of a chlorine atom in s-triazine by basic groups is greatly facilitated by the ring nitrogen atom of the symmetrically built s-triazine nucleus. These considerations prompted us to explore the possibility for the accessibility of novel compounds from 2-aminopyrimidine substituted s-triazines [19,20].

## 2. EXPERIMENTAL DETAILS

### 2.1 General Conditions

Structures of all the compounds were established on the basis of elemental analysis, IR and $^{1}$H NMR, $^{13}$C NMR spectra and mass spectra data. Physical data of all the compounds were found to be consistent to the structures assigned to these molecules. Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on FTIR-8400S (Schimadzu). $^{1}$H NMR &$^{13}$C NMR spectra were recorded on model AVANCE II 400 (Bruker**)** using DMSO as solvent and TMS as an internal reference. Chemical shift are expressed in δ ppm. All chemicals and reagents were purchased from commercial sources.

### 2.2 Synthesis

All the compounds discussed here, are synthesized according to the given methods [11-20].

#### 2.2.1 Preparation of 4, 6-dichloro-N-(pyrimidine-2-yl)-1,3,5-triazine-2-amine (1.1)

To a stirred solution of cyanuric chloride (1.845 g, 0.01 mole) in acetone at low temperature (0-5ºC), the solution of 2-aminopyrimidine (0.905 g, 0.01 mole) in acetone was added slowly while stirring and neutral *p*H was maintained by adding $Na_2CO_3$ solution (0.53 g, 0.005 mole in 20mL water). The stirring was continued at the same temperature for four hours. Then stirring was stopped and progress of the reaction was checked by TLC until the completion of the reaction. Later on the solution was poured on crushed ice. The product obtained was filtered and dried. The crude product was purified by re-crystallization from alcohol to give 82% yield. Melting point-172ºC. IR (KBr, cm$^{-1}$): 3413 [N-H str.], 3088 [C-H str.], 2225 [C-N str.], 1710 [C=O str.], 1610 [N-H bend.], 1580 [C=C bend.],1428 [C=N str.], 710 [C-H bend.]. $^{1}$H NMR (DMSO-*d6*)

δ 8.42 [s, 2H, pyrimidine], 6.91 [t,1H, pyrimidine], 4.01 [s,1H, NH]. $^{13}$C NMR (DMSO-*d6)* δ111.12, 111.21, 132.08, 132.09 (benzene), 127.07, 144.08 (ethylene), 189.01 (carbonyl), 123.01, 123.03, 144.04, 145.36, 145.42 (pyridine), 115.68, 115.98, 148.19, 148.20, 156.29, 156.48, 156.50, 156.58 (pyrimidine ring), 169.01, 169.25, 169.89 (1,3,5-triazine). MS (m/z %): 184.2 (100.0%), 244.2 (21.05), 185.1 (12.0%), 242.1 ($M^+$, 12.8%), 246.1 (4.1%). Anal. Calcd. for $C_7H_4Cl_2N_6$ (243.05): C, 34.59; H,1.66; N, 34.58%.Found:C, 34.60; H, 1.59; N, 34.60%.

### 2.2.2 Preparation of 6-chloro-2,4-di(pyrimidine-2-yl)-1,3,5-triazine-2,4-diamine (1.2)

To a stirred solution of compound **(1.1)** (2.41 g, 0.01 mole) in acetone at 25ºC, the solution of 2-aminopyrimidine (0.905 g, 0.01 mole) in acetone was added drop wise with constant stirring. A neutral *p*H was maintained by adding $Na_2CO_3$ solution (0.53 g 0.005 mole in 20 mL water). The temperature was gradually raised to 30ºC and content was stirred for 6 hours and progress of the reaction was monitored by TLC until the completion of the reaction. Then stirring was stopped and solution was poured to cold water. The solid product thus obtained was filtered and dried. The crude product was purified by re-crystallization from ethanol to give 73% yield. Melting point-173-176ºC. IR (KBr, cm$^{-1}$): 3404 [N-H str.], 3110 [C-H str.], 2225 [C-N str.], 1685 [C=O str.], 1600 [C=C str.], 1585 [N=H bend.], 1521 [C=C bend.], 1409 [C=N str.], 804 [C-Cl str.], 710 [C-H bend.]. $^1$H NMR (DMSO-*d6*) δ 8.20-8.26 [m, 4H, pyrimidine], 6.51-6.53 [t, 2H, pyrimidine] 4.01 [s, 2H, NH]. $^{13}$C NMR (DMSO-*d6*) δ8 δ=118.08, 118.09, 158.02, 158.02, 158.01, 158.01, 161.09, 162.02 (pyrimidine), 162.01, 164.21, 168.05 (1,3,5-triazine) MS (m/z%): 284.2 (100.0%), 285.3 (14.5%), 302.2 ($M^{+\cdot}$11.4%), 303.1 (9.0%). Anal. calcd. for $C_{11}H_8ClN_9$ (301.69): C, 43.79; H, 2.67; N, 41.78% Found: C, 43.78; H, 2.62; N , 41.80%.

### 2.2.3 Preparation of 2, 4, 6-tris-(2-aminopyrimidine)-s-triazine (1.3)

To a stirred solution of compound **(1.2)** (3.017 g, 0.01 mole), 2-aminopyrimidine (0.905 g, 0.01 mole) was added while stirring. Later on the reaction mixture was refluxed for 4 hours at 60-80ºC temperature. In between progress of the reaction was monitored by TLC till completion. A neutral *p*H was maintained by adding $Na_2CO_3$ solution (0.53 g, 0.005 mole in 20 mL water). The content was cooled and added in crushed ice. The crude product was purified by re-crystallization from ethanol to give 75% yield. Melting point-178-180ºC. IR (KBr, cm$^{-1}$): 3407 [N-H str.], 3030 [C-H str.], 2240 [C-N str.], 1584 [C=C bend], 1409 [C=N str.], 855 [C-H bend.].$^1$H NMR (DMSO-*d6*) δ 8.45 [m, 6H, pyrimidine], 6.93 [t, 3H, pyrimidine], 4.00 [s, 3H, NH]. Anal. calcd. for $C_{15}H_{12}N_{12}$ (360.54): C, 50; H, 3.36; N,46.65%. Found: C, 49.98; H, 3.32; N, 46.62%.

### 2.2.4 Preparation of 2,4-bis-(2-aminopyrimidine)-6-(4-acetylphenylamino)-s-triazine (1.4)

To a stirred solution of **(1.2)** (3.017 g, 0.01 mole) in acetone 4-aminoacetophenone (1.35 g, 0.01 mole) was added in lots while stirring. Then the reaction mixture was refluxed at the temperature 60-80ºC for 5 hours. Periodically $Na_2CO_3$ solution (0.53 g, 0.005 mole in 20 mL water) was added drop wise to neutralize HCl evolved during the reaction. Finally the reaction mixture was cooled and poured in crushed ice. The solid separated was filtered, washed twice with water and re-crystallized from DMF to give light buff colored compound with 62% yield. Melting point-225-230ºC. IR (KBr cm$^{-1}$): 3413 [N-H str.], 2924 [C-H str.], 2225 [C-N str.], 1720 [C=O str.],1610 [N-H bend.], 1550 [C=C bend.], 1428 [C=C str.], 870 [C-H bend.] . $^1$H NMR (DMSO-*d6*) δ 8.45 [m, 4H, pyrimidine], 8.01 [d, 2H, benzene], 7.63 [d, 2H, benzene], 6.93 [t, 2H, pyrimidine], 4.0 [s, 3H, NH], 2.4 [s, 3H, $CH_3$]. Anal. calcd. for $C_{19}H_{16}N_{10}O$ (400.40):C, 56.99; H, 4.03; N, 34.98%. Found: C, 56.82; H, 4.09; N, 34.96%.

### 2.2.5 Preparation of (E)-1-(4-(4,6-bis(pyrimidine-2-ylamino)-1,3,5-triazine-2-ylamino)phenyl)-3 (pyridine-2-yl)prop-2-en-1-one (1.5)

Compound **(1.4)** (4.001g, 0.01mole) was dissolved in 30mL DMF then 40% KOH solution and pyridine-2-aldehyde (0.01 mole) in DMF were added to the reaction mixture with constant stirring at room temperature. Progress of the reaction was monitored by TLC until the completion of the reaction. After 24h the reaction mixture was poured in crushed ice and *p*H 7-8 was maintained by adding HCl. The product separated out was filtered, washed with water and re-crystallized from ethanol to give dark mustard colored compound with yield 65%. Melting point- >300ºC. IR (KBr cm$^{-1}$): 3413 [N-H str.], 3088 [C-H str.], 2225 [C-N str.], 1710 [-C=O str.], 1610 [N-H bend], 1580 [C=C bend.], 1428

[C=N str.], 710 [C-H bend.]. $^1$H NMR (DMSO-*d6*) δ 8.40-8.56 [d, 4H, pyrimidine], 8.41 [s,2H, 1-ethylene], 7.45-7.46 [m, 4H, pyridine], 7.47-7.69 [m,4H, benzene], 6.80-6.81 [d, 2H, pyrimidine], 4.02-4.13 [s, 3H, NH]. $^{13}$C NMR (DMSO-*d6*) δ111.12, 111.21, 132.08, 132.09 (benzene), 127.07, 144.08 (1-ethylene), 189.01 (carbonyl), 123.01, 123.03,144.04,145.36,145.42 (pyridine), 115.68, 115.98, 148.19, 148.20, 156.29, 156.48, 156.50, 156.58 (pyrimidine ring), 169.01, 169.25, 169.89 (1,3,5-triazine). MS (m/z%): 311.3 (100.0%), 361.3 (35.0%), 489.2 ($M^+$,11.1%), 490.3 (8.6%) Anal. calcd. for $C_{25}H_{19}N_{11}O$ (489.49):C, 61.34; H,3.91; N, 31.48%. Found: C, 61.36; H, 3.95; N, 31.39%.

#### 2.2.6 Preparation of 1-(4-(4-(chloromethyl)-6-(pyrimidine-2-ylamino)-1,3,5-triazine-2-ylamino) phenyl)ethanone (1.6 )

To a stirred solution of compound **(1.1)** (2.41 g, 0.01 mole) in acetone, a solution of 4-aminoacetophenone (1.35 g, 0.01 mole) in acetone was added drop wise. Reaction mixture was stirred for 6 hours at 25-30ºC. Periodically $Na_2CO_3$ solution (0.53 g, 0.005 mole in 20mL water) was added drop wise to neutralize HCl evolved during the reaction. In between progress of the reaction was checked by TLC until the completion of the reaction. Later on reaction was stopped by adding crushed ice in the reaction mixture. The crude product so obtained was slurry like and it was washed with water and re-crystallized from ethanol to get compound with 72% yield. Melting point-160-165ºC. IR (KBr $cm^{-1}$): 3404 [N-H str.], 3110 [C-H str.], 2225 [C-N str.], 1685 [C=O str.], 1600 [C=C str.], 1585 [N=H bend.], 1521 [C=C bend.], 1409 [C=N str.], 804 [C-Cl str.], 710 [CH bend.]. $^1$H NMR (DMSO-*d6*) δ 8.49-8.50 [d,2H, pyrimidine], 8.01-8.20 [d, 2H, benzene], 7.65-7.91 [ d, 2H, 1-benzene], 6.93 [d,1H, 2-pyrimidine], 4.01 [s, 2H, NH], 2.50 [s,3H, methyl]. MS (m/z%): 284.1 (100.0%), 286.3 (13.0%), 349.2 (7.9%), 306.5 (6.2%), 356.1 ($M^+$,5.1%). Anal. calcd. for $C_{15}H_{12}ClN_7O$ (341.08): C, 52.72; H, 3.54; N, 28.69. Found: C, 51.06; H, 3.24; N, 27.54%.

#### 2.2.7 Preparation of 1,1'-(4,4'-(6-(pyrimidine-2-ylamino)-1,3,5-triazine-2,4-diyl)bis(azanediyl) bis(4,1-phenylene)diethanone (1.7)

A mixture of compound **(1.6)** (3.55 g, 0.01 mole) and 4-aminoacetophenone (1.35 g, 0.01 mole) in acetone was refluxed for 5 hours at 60-80ºC temperature. Periodically $Na_2CO_3$ solution (0.53 g, 0.005 mole in 20 mL water) was added drop wise to neutralize HCl evolved during the reaction and to maintain the neutral pH during the reaction. Progress of the reaction was monitored by TLC. At the completion of the reaction content was added to the crushed ice. Compound was washed with water and re-crystallized from DMF to get pure compound with 74% yield. Melting point-182-189ºC IR (KBr $cm^{-1}$): 3404 [N-H str.], 3110 [C-H str.], 2225 [C-N str.], 1680 [C=O str.], 1610 [C=C str.], 1585 [N=H bend.], 1521 [C=C bend.], 1406 [C=N str.], 810 [C-Cl str.], 715 [C-H bend.]. $^1$H NMR (DMSO-*d6*) δ 8.45 [d, 2H, pyrimidine], 8.01 [m, 4H, benzene], 7.63 [m, 4H, benzene], 6.93 [t,1H, pyrimidine], 4 [s, 3H, NH ], 2.50 [s, 6H,$CH_3$]. Anal. calcd. for $C_{23}H_{20}N_8O_2$ (440.46): C, 62.72; H, 4.58; N, 25.44%. Found: C, 62.69; H, 4.52; N, 25.42%.

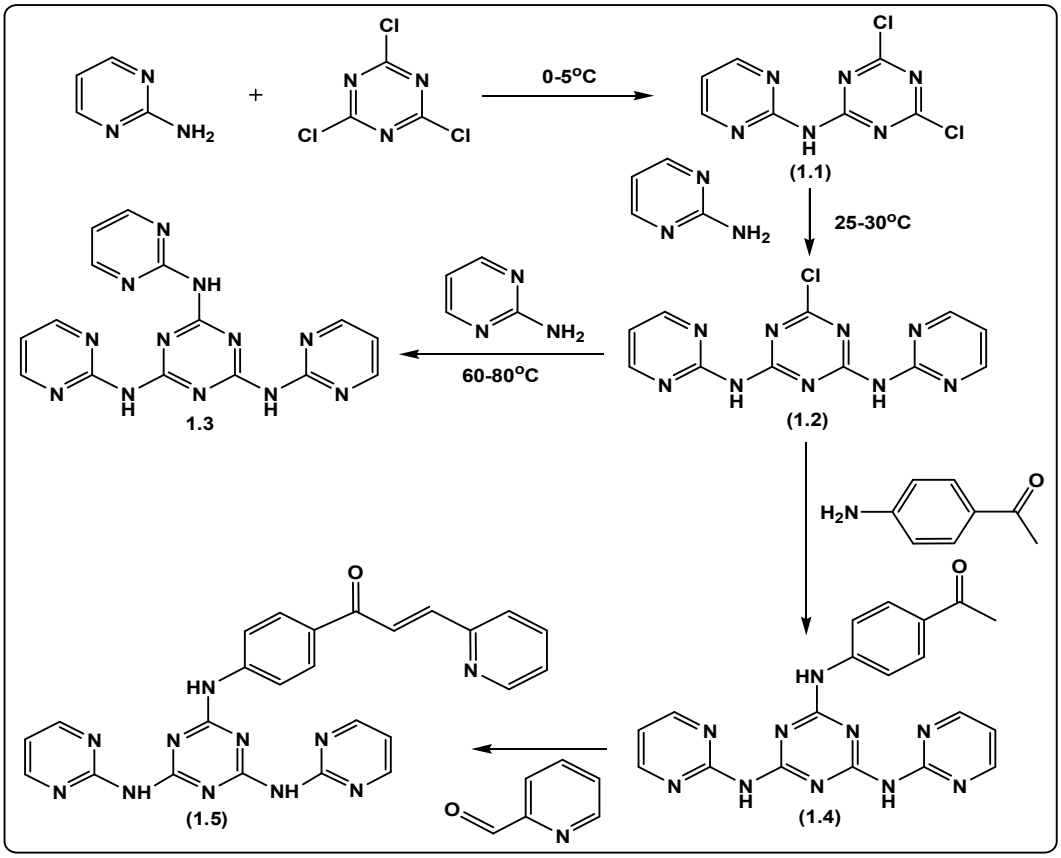
#### 2.2.8 Preparation of (E)-3-(pyridine-3-yl)-1-(4-(4-(4-(E)-3-(pyridine-4-yl)acryloyl) phenylamino)-6-(pyrimdine-2-ylamino)-1,3,5-triazine-2-ylamino)phenyl)prop-2-en-1-one (1.8)

Compound **(1.7)** (4.12 g, 0.01 mole) was dissolved in 30 mL DMF then 40% KOH solution and pyridine-2-aldehyde (0.02 mole) in DMF were added to the reaction mixture with constant stirring at room temperature. Progress of the reaction was monitored by TLC until the completion of the reaction. After 24h the reaction mixture was poured in crushed ice and pH 7-8 was maintained by adding HCl. The product separated out was filtered, washed with water and re-crystallized from ethanol to give dark mustard coloured slurry. Yield-55%, Melting Point->300ºC. IR (KBr $cm^{-1}$): 3318 [N-H str.], 2979 [C-H str.], 2225 [C-N str.], 1685 [C=O str.], 1594 [N-H bend.], 1550 [C=C bend.], 1412 [C=N str.], 1094 [C-H bend.], 686 [C-H bend.]. $^1$H NMR (DMSO-*d6*) δ 8.54-8.96 [d,2H, pyrimidine ring], 8.06-7.42 [m, 4H, ethylene], 7.58-7.87 [m, 8H, pyridine], 7.43-7.51 [dd, 8H, benzene], 6.93 [ s, 1H, 2-pyrimidine], 4.10-4.11 [s, 3H, NH].MS (m/z%): 361.3 (100.0%), 284.3 (81.0%), 368.4 (16.8%), 485.5 (17.0%), 592.6 (6.0%), 619.2 ($M^+$,9.2%), 593.6 (4.1%) Anal. Calcd. for $C_{35}H_{26}N_{10}O_2$ (618.22):C, 67.95; H, 4.24; N, 22.64%. Found: C, 67.94; H, 4.20; N, 22.69%.

## 3. RESULTS AND DISCUSSION

The chlorines of cyanuric chlorides can be replaced in a stepwise process at different temperatures by different neucleophiles containing groups such as –$NH_2$, -NHOH, -CN, -

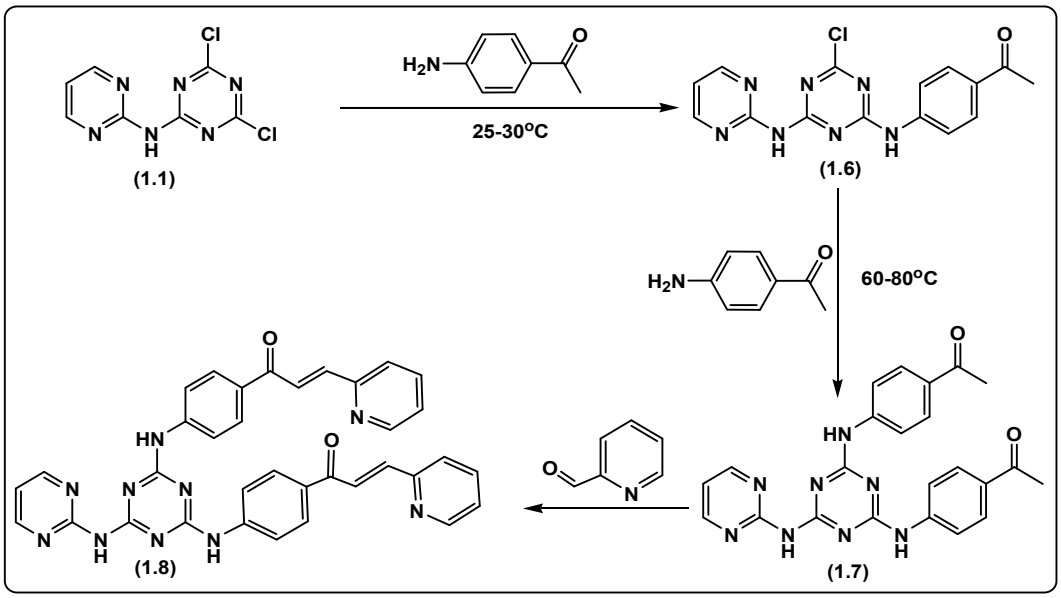
SN, -$N_3$ *etc*. By changing temperature variant, we had synthesized pyrimidine substituted s-triazines (1.1,1.2 & 1.3) from 2-aminopyrimidine and 2,4,6-trichloro-1,3,5-triazene according to reaction **scheme-1** by adopting the methods described in the literature. According to the same reaction scheme, the compound (1.3) reacted with 4-aminoacetophenone at 60-80ºC to give compounds (1.4) which further reacted with pyridine-2-aldehyde to furnish α,β-unsaturated carbonyl compounds (1.5). Similar, strategy is followed to synthesize compound (1.6) from the reaction of compound (1.1) with 4-aminoacetophenone at 25-30ºC. Compound (1.6) is further reacted with 4-aminoacetophenone at 60-80ºC to synthesize compound (1.7) and then compound (1.7) is further reacted with pyridine-2-aldehyde to give compound (1.8) as shown in the reaction **scheme-2**. Formation of all the compounds was confirmed by the IR, $^1$H NMR and MS spectral data.




**Scheme 1. Formation of Bis(pyrimidyl)-α,β-unsaturated s-triazines**

**Table 1. Physical and analytical data of the compounds**

| S. no. | Comp. no. | Molecular formula | M.W. | M.P. | Yield (%) | Elemental analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (cal. /exp.) C | (cal. / exp.) H | (cal. / exp.) N |
| 1. | 1.1 | $C_7H_4Cl_2N_6$ | 243.05 | 170-172ºC | 82% | 34.59/34.60 | 1.66/1.59 | 34.58/34.60 |
| 2. | 1.2 | $C_{11}H_8ClN_9$ | 301.69 | 173-176ºC | 73% | 43.79/43.78 | 2.67/2.62 | 41.78/41.80 |
| 3. | 1.3 | $C_{15}H_{12}N_{12}$ | 360.54 | 178-180ºC | 75% | 50.0/49.98 | 3.36/3.32 | 46.65/46.62 |
| 4. | 1.4 | $C_{19}H_{16}N_{10}O$ | 400.40 | 225-230ºC | 62% | 56.99/56.82 | 4.03/4.09 | 34.98/34.96 |
| 5. | 1.5 | $C_{25}H_{19}N_{11}O$ | 489.49 | 218-220ºC | 65% | 61.34/61.36 | 3.91/3.95 | 31.48/31.39 |
| 6. | 1.6 | $C_{15}H_{12}ClN_7O$ | 341.08 | 160-165ºC | 72% | 52.72/51.06 | 3.94/3.24 | 28.69/27.54 |
| 7. | 1.7 | $C_{23}H_{20}N_8O_2$ | 440.46 | 182-189ºC | 74% | 62.72/62.69 | 4.58/4.52 | 25.44/25.42 |
| 8. | 1.8 | $C_{35}H_{26}N_{10}O_2$ | 618.22 | >300ºC | 55% | 67.95/67.94 | 4.24/4.20 | 22.64/22.69 |




**Scheme 2. Formation of pyrimidyl-bis(α,β-unsaturated) s-triazines**

## 4. CONCLUSION

2-Aminopyrimidine reacted with cyanuric chloride at different temperatures to provide an intermediate which was further reacted with 4-aminoacetophenone and pyridine-2-aldehyde to provide the products. Both the schemes-1 and 2 proceeded at different temperatures as these reactions of cyanuric chloride are temperature dependent. pH of the reaction was maintained by adding a base sodium bicarbonate and whole process was monitored by TLC. It was concluded from both the reaction schemes that as the temperature increases, nature of the product changed drastically.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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