

Note

Chalcones, pyrazolines and aminopyrimidines as antibacterial agents

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2,4-Bis-ethylamino-6-[4'-{3'-(substitutedphenyl/2''-furanyl)-2''-propanone-1''-yl} phenyl amino]-s-triazine **5a-d** have been prepared by treating ketone **4** with different substituted aromatic and heterocyclic aldehydes in the presence of alkali. These chalcones **5a-d** on cyclisation with hydrazine hydrate and guanidine nitrate to form pyrazolines **6a-d** and aminopyrimidines **7a-d** respectively. The structures of the synthesized compounds have been established on the bases of IR, ¹H NMR and elemental analysis. The compounds have been evaluated for antibacterial activity against *E. coli*, *S. paratyphi-A*, *S. aureus* and *B. subtilis*.

Keywords: Chalcones, pyrazolines, aminopyrimidines, antibacterial activity

The synthesis of α,β -unsaturated carbonyl compounds is one of main structural component in various naturally occurring and biologically essential substance¹. Several strategies for the synthesis of these system based on formation of carbon-carbon bond have been reported and among them the direct Aldol-condensation and Claisen-Schmidt condensation still occupy prominent position². It is well known that most natural or synthetic chalcones are highly active with extensive pharmaceutical and medicinal application³. Chalcones are found to be effective as anticancer⁴, antiviral⁵, cardiovascular⁶ and anti-inflammatory⁷ agents. Synthesis and characterization of pyrazoline derivatives has been a developing field within the realm of heterocyclic chemistry for the past several years because of their ready accessibility through synthesis, wide range of chemical reactivity and broad spectrum of biological activity⁸. Pyrazoline derivatives have been found to be antitumor⁹ and immunosuppressive¹⁰ agents. Survey of literature in the recent past reveals that some pyrazoline derivatives possess cerebroprotective¹¹ effect and CNS-depressant¹² activity. Pyrimidine derivatives play a vital role in many biological processes and in

synthesis of drugs. Pyrimidine derivatives which occur in natural products¹³ like nucleic acid and vitamin B₁ have remarkable pharmaceutical importance because of their biological activities such as anti- HIV¹⁴, antitubercular¹⁵ and antidiabetic¹⁶. These observation led us to synthesize some new s-triazinyl based chalcones and its corresponding pyrazoline and aminopyrimidine derivatives.

In view of the above and in a continuation of earlier work¹⁷⁻²⁰ on chalcones and its derivatives, new series of chalcones **5a-d**, pyrazolines **6a-d** and aminopyrimidines **7a-d** are reported (Scheme I).

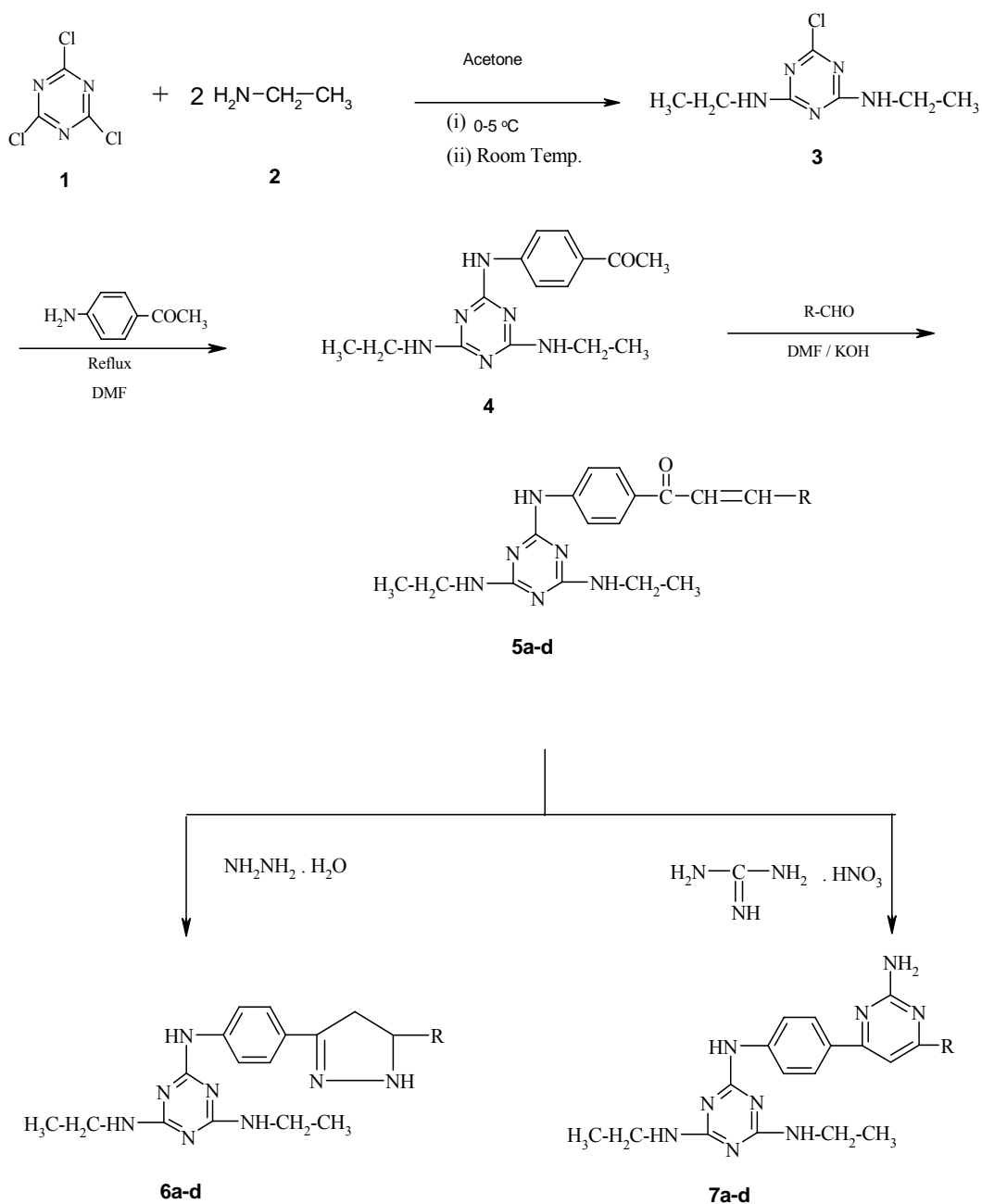
Results and Discussion

The IR spectra of compounds **5a-d** show the characteristic band in the region of 1700-1647 cm⁻¹ which indicate the presence of -C=O group. The IR spectra of compounds **6a-d** show characteristic band in region the of 1650-1580 cm⁻¹ due to -C=N group. The IR spectra of compounds **7a-d** show the characteristic band in the region of 3400-3350 cm⁻¹ which indicate the presence of (-NH₂) primary amine. The IR spectra of compounds **6a-d** and compounds **7a-d** do not show any absorption band in the region of 1700- 1647 cm⁻¹ which indicate the absence of -C=O group. ¹H NMR spectra of compounds **5a-d** show doublet of -CO-CH= near about δ 6.8 confirmed the presence of chalcone moiety. The ¹H NMR spectra of compounds **6a-d** show multiplate of -CH₂ near about δ 3.8 confirmed the cyclisation in pyrazoline moiety. The ¹H NMR spectra of compounds **7a-d** show a sharp singlet near about δ 5.5 due to -NH₂ protons, they also show a sharp singlet of -CH near about δ 6.3.

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method²¹ against *S. aureus* and *B. subtilis* Gram-positive bacteria and *E. coli*, *S. paratyphi A* Gram-negative bacteria in nutrient agar medium. Ciprofloxacin was used as standard drugs for the comparison of antibacterial activity.

By visualizing activity data, it could be observed that compounds **5b**, **6b**, **6d**, **7b** and **7d** were found to be less active against *S. aureus*, whereas remaining



Scheme I

compounds **5a**, **5c**, **5d**, **6a**, **6c**, **7a** and **7c** were found to be inactive against *S. aureus*. Compounds **5d** and **6a** were found to be less active against *B. subtilis*, whereas remaining compounds **5a**, **5b**, **5c**, **6b**, **6c**, **6d**, **7a**, **7b**, **7c** and **7d** were found to be inactive against *B. subtilis*. Compound **5b** was found to be moderately active against *E. coli*, whereas remaining compounds **5a**, **5c**, **5d**, **6a**, **6b**, **6c**, **6d**, **7a**, **7b**, **7c** and **7d** were found to be inactive against *E. coli*. Compound **6a** was found to be

moderately active against *S. paratyphi-A*. Compounds **5a**, **5b**, **5c**, **5d**, **6b**, **6c**, **6d**, **7a**, **7b**, **7c** and **7d** were found to be inactive against *S. paratyphi-A*.

Experimental Section

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 237 spectrometer. ^1H NMR spectra on a Bruker Avance DPX 400 MHz

spectrometer with CDCl_3 as a solvent and tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet) and m (multiplet). Analytical separation was conducted with silica Gel 60 F-254 (Merck) plates of 0.25 mm thickness eluted with toluene : acetone (9 : 2 v/v) and were visualized with UV (254 nm) or iodine to check the purity of the synthesized compounds.

Preparation of 2,4-bis-ethylamino-6-chloro-s-triazine 3. Cyanuric chloride **1** (0.01 mole; 1.845g) was dissolved in acetone (25 mL) and monoethyl amine **2** (0.02 mole; 0.900 g) was added slowly to it at 0-5°C with constant stirring for 6 hr at RT. Periodically, sodium carbonate solution (0.005 mole in 10 mL water) was added dropwise to neutralized HCl evolved during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give **3**. m.p. 144-45°C, yield 81%; IR (KBr): 3370 (N-H str.), 805 (C-N, *s*-triazine), 772 cm^{-1} (C-Cl str.); ^1H NMR (CDCl_3): δ 1.2 [t, 6H, $-(\text{-CH}_2\text{-CH}_3)_2$], 4.1 [q, 4H, $(\text{-CH}_2\text{-CH}_3)_2$], 6.9 [s, 2H, NH].

Preparation of 2,4-bis-ethylamino-6-(4'-acetylphenylamino)-s-triazine 4. 2,4-Bis-ethylamino-6-chloro-*s*-triazine **3** (0.01mole; 2.015 g) and 4-amino acetophenone (0.01 mole; 1.350 g) were dissolved in DMF (40 mL) and the reaction-mixture was refluxed for 12 hr. Periodically, sodium carbonate solution (0.005 in 10 mL water) was added to neutralized HCl evolved during the reaction. Finally the contents were poured in to crushed ice. The solid separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give **4**. m.p. 266°C, yield 78%; IR (KBr): 3366 (N-H str.), 1660 (-C=O), 804 cm^{-1} (C-N, *s*-triazine); ^1H NMR (CDCl_3): δ 1.26 [t, 6H, $-(\text{-CH}_2\text{-CH}_3)_2$], 2.6 (s, 3H, -COCH_3), 4.12 [q, 4H, $(\text{-CH}_2\text{-CH}_3)_2$], 6.9 - 8.8 (m, 7H, Ar-H and NH).

General procedure for the preparation of 2,4-bis-ethylamino-6-[4'-{3''-(substitutedphenyl/furanyl)-2''-propenon-1''-yl}phenyl amino]-s-triazine 5a-d. 2,4-Bis-ethylamino-6-(4'-acetylphenylamino)-*s*-triazine **4** (0.01mole; 3.00 g) was dissolved in DMF (30 mL) different aromatic and heterocyclic aldehydes (0.01 mole) was added to it. Then solution of KOH (5 mL of 40%) was added to the reaction-mixture with constant stirring at RT. After 24 hr the reaction-mixture was poured into crushed ice and neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give **5a-d**.

2,4-Bis-ethylamino-6-[4'-{3''-(3''',4'''-dimethoxyphenyl)-2''-propenon-1''-yl}phenylamino]-s-triazine 5a. m.p. 110°C, yield 74%; IR (KBr): 3385 (N-H str.), 1675 (-C=O , chalcone moiety), 1220 (C-O-C str.), 803 cm^{-1} (C-N, *s*-triazine); ^1H NMR (CDCl_3): δ 1.2 [t, 6H, $-(\text{-CH}_2\text{-CH}_3)_2$], 3.80 (s, 3H, *m*- OCH_3), 3.88 (s, 3H, *p*- OCH_3), 4.1[q, 4H, $(\text{-CH}_2\text{-CH}_3)_2$], 6.80 (d, 1H, -CO-CH= , $J = 16$ Hz), 7.2-7.7 (m, 10H, Ar-H and NH), 7.8 (d, 1H, Ar-CH=, $J = 16$ Hz); Anal. Calcd. for $\text{C}_{24}\text{H}_{28}\text{N}_6\text{O}_3$: C, 64.28; H, 6.29; N, 18.75. Found: C, 64.25; H, 6.22; N, 18.70%.

2,4-Bis-ethylamino-6-[4'-{3''-(2''',4'''-dichlorophenyl)-2''-propenon-1''-yl}phenylamino]-s-triazine 5b. m.p. 138°C, yield 73% ; IR (KBr): 3380 (N-H str.), 1673 (-C=O , chalcone moiety), 1225 (C-O-C str.), 809 (C-N, *s*-triazine), 786 cm^{-1} (C-Cl); ^1H NMR (CDCl_3): δ 1.4 [t, 6H, $-(\text{-CH}_2\text{-CH}_3)_2$], 4.1 [q, 4H, $(\text{-CH}_2\text{-CH}_3)_2$], 6.82 (d, 1H, -CO-CH= , $J = 16$ Hz), 7.1-7.68 (m, 10H, Ar-H and NH), 7.82 (d, 1H, Ar-CH=, $J = 16$ Hz); Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_6\text{OCl}_2$: C, 57.76, H, 4.84; N, 18.38. Found: C, 57.70; H, 4.89; N, 18.30%.

2,4-Bis-ethylamino-6-[4'-{3''-(2''',6'''-dichlorophenyl)-2''-propenon-1''-yl} phenylamino]-s-triazine 5c. m.p. 176°C, yield 73%; IR (KBr): 3378 (N-H str.), 1680 (-C=O , chalcone moiety), 1330 (C-N, aromatic), 1222 (C-O-C str.), 804 (C-N, *s*-triazine), 784 (C-Cl); ^1H NMR (CDCl_3): δ 1.38 [t, 6H, $-(\text{-CH}_2\text{-CH}_3)_2$], 4.12 [q, 4H, $(\text{-CH}_2\text{-CH}_3)_2$], 6.82 (d, 1H, -CO-CH= , $J = 16$ Hz), 7.1-7.68 (m, 10H, Ar-H and NH), 7.82 (d, 1H, Ar-CH=, $J = 16$ Hz); Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_6\text{OCl}_2$: C, 57.76; H, 4.84; N, 18.38. Found: C, 57.65; H, 4.90; N, 18.35%.

2,4-Bis-ethylamino-6-[4'-{3''-(2''-furanyl)-2''-propenon-1''-yl}phenylamino]-s-triazine 5d. m.p. 205°C yield 68%; IR (KBr): 3376 (N-H str.), 1678 (-C=O , chalcone moiety), 1323 (C-N, aromatic), 1220 (C-O-C str.) 805 cm^{-1} (C-N, *s*-triazine); ^1H NMR (CDCl_3): δ 1.28 [t, 6H, $-(\text{-CH}_2\text{-CH}_3)_2$], 4.14[q, 4H, $(\text{-CH}_2\text{-CH}_3)_2$], 6.80 (d, 1H, -CO-CH= , $J = 16$ Hz), δ 6.9 (d, 1H, -CH-furan , $J = 3.5$ Hz), δ 7.1 - 7.7 (m, 10H, Ar-H, NH and CH of furan ring); Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}_2$: C, 63.49; H, 5.85; N, 22.22. Found: C, 63.40; H, 5.80; N, 22.15%.

General procedure for the preparation of 2,4-bis-ethylamino-6-[4'-{5''-(substitutedphenyl / 2-furanyl)-pyrazolin-3''-yl} phenyl amino]-s-triazine 6a-d.

2,4-Bis-ethylamino-6-[4'-{3''-(substitutedphenyl/furanyl)-2''-propenon-1''-yl} phenyl amino]-*s*-triazine **5a-d** (0.01mole) was dissolved in 25 mL dioxane and hydrazine hydrate (0.02mole; 1.0 g) was added to it.

Then the reaction-mixture was refluxed for 15 hr. The reaction-mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give **6a-d**.

2,4-bis-ethylamino-6-[4'-(5''-(3''',4'''-dimethoxyphenyl)-pyrazolin-3''-yl) phenyl amino]-s-triazine 6a; m.p. 155°C, yield 71%; IR (KBr): 3400 (N-H str.), 3320 (N-N, pyrazoline moiety), 1630 (C=N, pyrazoline moiety), 1240 (C-O-C str.) 806 cm⁻¹ (C-N, s-triazine); ¹H NMR (CDCl₃): δ 1.34 [t, 6H, -(-CH₂-CH₃)₂], 3.70 - 3.80 (m, 1H, Ha, Jab=19.0 Hz, Jax = 11.9 Hz), 3.70 - 3.80 (m, 1H, Hb, Jab = 19.0 Hz, Jbx = 4.8 Hz), 3.84 (s, 3H, *m*-OCH₃), 3.88 (s, 3H, *p*-OCH₃), 4.0 [q, 4H, (-CH₂-CH₃)₂], 5.3 (dd, 1H, Hx, Jax = 11.9 Hz, Jbx = 4.8 Hz), 6.9 - 7.8 (m, 11H, Ar-H and NH); Anal. Calcd. for C₂₄H₃₀N₈O₂: C, 62.33; H, 6.53; N, 24.24. Found: C, 62.25; H, 6.49; N, 24.15%.

2,4-bis-ethylamino-6-[4'-(5''-(2''',4'''-dichlorophenyl)-pyrazolin-3''-yl)phenyl amino]-s-triazine 6b. m.p. 165°C, yield 69% ; IR (KBr): 3408 (N-H str.), 3318 (N-N, pyrazoline moiety), 1620 (C=N, pyrazoline moiety), 1220 (C-O-C str.) 804 (C-N, s-triazine), 780 cm⁻¹(C-Cl); ¹H NMR (CDCl₃): δ 1.3 [t, 6H, -(-CH₂-CH₃)₂], 3.78-3.82 (m, 1H, Ha, Jab = 19.0 Hz, Jax = 11.9 Hz), 3.78 - 3.82 (m, 1H, Hb, Jab = 19.0 Hz, Jbx = 4.8 Hz), 4.1 [q, 4H, (-CH₂-CH₃)₂], 5.3 (dd, 1H, Hx, Jax = 11.9 Hz, Jbx = 4.8 Hz), 6.92-7.8 (m, 11H, Ar-H and NH); Anal. Calcd. for C₂₂H₂₄N₈Cl₂: C, 56.05; H, 5.13; N, 23.77. Found: C, 56.00; H, 5.19; N, 23.75%.

2,4-Bis-ethylamino-6-[4'-(5''-(2''',6'''-dichlorophenyl)-pyrazolin-3''-yl)phenyl amino]-s-triazine 6c. m.p.148°C, yield 70%; IR (KBr): 3405 (N-H str.), 3321 (N-N, pyrazoline moiety), 1625 (C=N, pyrazoline moiety), 1222 (C-O-C str.) 802 (C-N, s-triazine), 785 cm⁻¹ (C-Cl); ¹H NMR (CDCl₃): δ 1.32 [t, 6H, -(-CH₂-CH₃)₂], 3.78-3.82 (m, 1H, Ha, Jab=19.0 Hz, Jax = 11.9 Hz), 3.78 - 3.82 (m, 1H, Hb, Jab = 19.0 Hz, Jbx = 4.8 Hz), 4.12 [q, 4H, (-CH₂-CH₃)₂], 5.32 (dd, 1H, Hx, Jax = 11.9 Hz, Jbx = 4.8 Hz), 6.89-7.82 (m, 11H, Ar-H and NH); Anal. Calcd. for C₂₂H₂₄N₈Cl₂: C, 56.05; H, 5.13; N, 23.77. Found: C, 55.95; H, 5.20; N, 23.70%.

2,4-Bis-ethylamino-6-[4'-(5''-(2'''-furanyl)-pyrazolin-3''-yl)phenylamino]-s-triazine 6d. m.p. 196°C, yield 66% ; IR (KBr): 3410 (N-H str.), 3315 (N-N, pyrazoline moiety), 1622 (C=N, pyrazoline moiety), 1230 (C-O-C str.) 810 cm⁻¹ (C-N, s-triazine); ¹H NMR (CDCl₃): δ 1.35 [t, 6H, -(-CH₂-CH₃)₂], 3.72 - 3.81 (m, 1H, Ha, Jab = 19.0 Hz, Jax = 11.9 Hz), 3.78 - 3.82

(m, 1H, Hb, Jab = 19.0 Hz, Jbx = 4.8 Hz), 4.05 [q, 4H, (-CH₂-CH₃)₂], 5.3 (dd, 1H, Hx, Jax = 11.9 Hz, Jbx = 4.8 Hz), 6.8 (dd, 1H, -CH furan, J = 3.5 Hz), 6.9-7.85 (m, 11H, Ar-H, NH and -CH of furan ring); Anal. Calcd. for C₂₀H₂₄N₈O₂: C, 61.22; H, 6.16; N, 28.57. Found: C, 61.15; H, 6.10; N, 28.50%.

General procedure for the preparation of 2,4-bis-ethylamino-6-[4'-(2''-amino-6''-(substituted phenyl / 2'''-furanyl)-pyrimidin-4''-yl)-phenylamino]-s-triazine 7a-d. 2,4-Bis-ethylamino-6-[4'-(3''-(substitutedphenyl/furanyl)-2''-propenon-1''-yl)phenyl amino]-s-triazine **5a-d** (0.01mole) was dissolved in 25 mL dioxane and guanidine nitrate (0.01 mole, 1.22g) was added to it. Then solution of KOH (5 mL of 40%) was added to the reaction- mixture and refluxed for 15 hr. The reaction-mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give **7a-d**.

2,4-Bis-ethylamino-6-[4'-(2''-amino-6''-(3''',4'''-dimethoxyphenyl)-pyrimidin-4''-yl)-phenylamino]-s-triazine 7a. m.p. 131°C, yield 73%; IR (KBr): 3410 (-NH₂ pyrimidine moiety), 1645 (C=N str. Pyrimidine moiety), 1255 (C-O-C str.), 803 cm⁻¹ (C-N, s-triazine); ¹H NMR (CDCl₃): δ 1.3 [t, 6H, -(-CH₂-CH₃)₂], 3.78 [q, 4H, (-CH₂-CH₃)₂], 3.91 (s, 3H, *m*-OCH₃), 4.0 (s, 3H, *p*-OCH₃), 5.49 (s, 2H, -NH₂), 6.28 (s, 1H, -CH), 7.2-7.8 (m, 10H, Ar-H and NH); Anal. Calcd. for C₂₅H₂₉N₉O₂: C, 61.60; H, 5.99; N, 25.87. Found: C, 61.52; H, 5.92; N, 25.78%.

2,4-Bis-ethylamino-6-[4'-(2''-amino-6''-(2''',4'''-dichlorophenyl)-pyrimidin-4''-yl)-phenylamino]-s-triazine 7b. m.p. 156°C, yield 68%; IR (KBr): 3390 (-NH₂ pyrimidine moiety), 1640 (C=N str. pyrimidine moiety), 1250 (C-O-C str.), 805 (C-N, s-triazine), 770 cm⁻¹ (C-Cl); ¹H NMR (CDCl₃): δ 1.32 [t, 6H, -(-CH₂-CH₃)₂], 3.81 [q, 4H, (-CH₂-CH₃)₂], 5.52 (s, 2H, -NH₂), 6.30 (s, 1H, -CH), 7.18-7.8 (m, 10H, Ar-H and NH); Anal. Calcd. for C₂₃H₂₃N₉Cl₂: C, 55.64; H, 4.67; N, 25.40. Found: C, 55.60; H, 4.72; N, 25.35%.

2,4-Bis-ethylamino-6-[4'-(2''-amino-6''-(2''',6'''-dichlorophenyl)-pyrimidin-4''-yl)-phenylamino]-s-triazine 7c. m.p. 195°C, yield 68%; IR (KBr): 3395 (-NH₂ pyrimidine moiety), 1644 (C=N str. pyrimidine moiety), 1245 (C-O-C str.), 807 (C-N, s-triazine), 775 cm⁻¹ (C-Cl); ¹H NMR (CDCl₃): δ 1.29 [t, 6H, -(-CH₂-CH₃)₂], 3.80 [q, 4H, (-CH₂-CH₃)₂], 5.50 (s, 2H, -NH₂), 6.32 (s, 1H, -CH), 7.21-7.8 (m, 10H, Ar-H and NH); Anal. Calcd. for C₂₃H₂₃N₉Cl₂: C, 55.64; H, 4.67; N, 25.40. Found: C, 55.55; H, 4.70; N, 25.30%.

2,4-Bis-ethylamino-6-[4'-(2"-amino-6"-(2'''-furan-2-yl)-pyrimidin-4"-yl)-phenyl amino]-s-triazine 7d. m.p. 212°C, yield 69%; IR (KBr): 3405 (-NH₂ pyrimidine moiety), 1642 (-C=N str. pyrimidine moiety), 1240 (C-O-C str.), 806 cm⁻¹ (C-N, s-triazine); ¹H NMR (CDCl₃): δ 1.31 [t, 6H, (-CH₂-CH₃)₂], 3.82 [q, 4H, (-CH₂-CH₃)₂], 5.54 (s, 2H, -NH₂), 6.32 (s, 1H, -CH), 7.22–7.78 (m, 10H, Ar-H+NH and -CH of furan ring); Anal. Calcd. for C₂₁H₂₃N₉O: C, 60.43; H, 5.55; N, 30.21. Found: C, 60.35; H, 5.49; N, 30.15%.

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