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Studies on synthesis and characterization of bio-active 1,3,5-triazine derivatives

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ABSTRACT

Series of compounds containing *s*-triazine derivatives were synthesized. The synthetic strategy utilizes cyanuric chloride as a starting material to obtain the several Schiff's base A(1-5), azetidinone B(1-5) and thiazolidinone C(1-5) *viz.* condensations and cyclizations. All newly synthesized compounds have been characterized by physical processes (melting points, Thin layer chromatography, elemental analysis, IR and NMR spectra) and have been tested for their antimicrobial activity against gram (+)ve and gram (-)ve bacteria and also on different stains of fungi in which some of these derivatives exhibited potential antibacterial and antifungal activity.

Introduction

Among a wide variety of heterocyclic that have been explored for developing pharmaceutical important molecules such as 1,3,5-triazine, Schiff's base, azetidinone, thiazolidinone have played an important role in medicinal chemistry. As a reagent in organic synthesis, 1,3,5-triazine is used as the equivalent of hydrogen cyanide (HCN). One application is in the Gattermann reaction, used to attach the formyl group to aromatic substrates.[1] It is a common reagent, and readily forms derivatives, which are used as herbicides, dyes, polymers but pharmacological applications are most important.[2,3] Several derivatives of s-triazine show antimicrobial[4,5], antitubercular[6] and anti-HIV activity[7]. They are used as a potential hormone receptor antagonists, anti-tryposomal drugs[8], anti-malarial activity[9], antitumor activity[10], Cyclin Dependent Kinase (CDK) inhibitor[11] and photosynthesis inhibiting activity[12]. In this entire work deals with studies on synthesis and characterization of bio-active 1,3,5-triazine derivatives having the route shown in experimental section.

Experimental

All the melting points reported are uncorrected and were recorded using an electro thermal melting point apparatus. Thin layer chromatography was performed on Merck precoated 60 F_{254} plates. Ethyl acetate : Benzene (7.5 : 2.5) was used as solvent for the TLC and the spots were rendered visible by exposing to UV light. IR spectra were recorded on Shimadzu FT-IR (Japan) instrument. ^{1}H NMR spectra were recorded on Brucker Avance II NMR spectrometer. Chemical shifts (δ ppm) reported are referred to internal reference TMS. Elemental analyses were obtained using a Carlo-Erba CHNS-O EA 1108 elemental analyzer. 1,3,5-triazine was received from Atul limited, Valsad (Gujarat) India. Synthetic route are described in Scheme-I and Scheme-II.

Synthesis of 2,4-dichloro-6-(4-methylphenoxy)-1,3,5-triazine (I)

To a stirred solution of 1,3,5-triazine (0.01mole, 1.81gm) in acetone (25 ml) at 0-5 °C, the solution of 4 - cresol (0.01mole, 1.09gm) in acetone (5 ml) was added and pH was maintained neutral by the addition of 10 % sodium carbonate solution. The stirring was continued at 0-5 °C for 4 hrs. After the completion of reaction, mixture was poured on ice cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from acetone to give 2,4-dichloro-6-(4-methylphenoxy)-1,3,5-triazine.

Synthesis of 6-(4-methylphenoxy)-4-[4-(4-methoxyphenyl)-piperazine-1-yl]-2-(chloro)- 1,3,5-triazine (II)

To a stirred solution of 2,4-dichloro-6-(4-methylphenoxy)-1,3,5-triazine (I) (0.01mole, 2.56gm) in acetone (10 ml) at 30-35 °C, the solution of 4-methoxy *N*-phenyl piperazine (0.01mole, 1.92gm) in acetone (5 ml) was added drop wise maintaining the temperature 35 °C. The pH was adjusted neutral by the addition of 10 % sodium bicarbonate solution. The temperature was gradually raised to 45°C during 2 hrs. After the completion of reaction, the resultant content was poured into ice cold water. The solid product obtained was filtered and dried to give 6-(4-methylphenoxy)-4-[4-(4-methoxyphenyl) piperazine-1-yl]-2-(chloro)-1,3,5-triazine (II).

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Synthesis of 2-hydrazinyl-6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazine[13] (III)

Take a compound 6-(4-methylphenoxy)-4-[4-(4-methoxyphenyl)piperazine-1-yl]-2-(chloro)-1,3,5-triazine (0.01mole, 4.27gm) and hydrazine hydrate (0.05mole, 2.50gm) in alcohol (25 ml) was refluxed in a water bath. The temperature was gradually raised to 80-90 °C during 3 hrs. The pH was adjusted neutral by the addition of 10 % sodium bicarbonate solution. After the completion of reaction, the refluxed content was added to cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol.

Synthesis of 2-(2-substituted benzylidenehydrazinyl)-6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazine[14] (A_1 to A_5)

A mixture of 2-(methylphenoxy)-6-[4-(4-methoxy phenyl)piperazine 1-yl]-4-(hydrazino)-1,3,5-triazine (III) (0.01mole, 4.23gm) and substituted benzaldehyde (0.01mole) was dissolved in absolute ethanol (25 ml) and add few drops of glacial acetic acid. The reaction mixture was refluxed for 8 hrs in a water bath then cooled and poured into ice cold water, solid product obtained was filtered and dried.

2-(2-(4-choloro)benzylidenehydrazinyl)-6-(4-(4-methoxy phenyl)piperazin-1-yl)-4-(*p*-tolyl oxy)-1,3,5-triazine (A_1)

Yield 82%; m.p. 148-150 °C; Anal. Calcd. for $C_{28}H_{28}O_2N_7Cl$ (530.0 gm/mole): C, 63.45; H, 5.32; N, 18.50. Found: C, 63.51; H, 5.38; N, 18.59. IR (KBr, cm^{-1}): 784 (C-Cl), 815, 1365, 1440, 1580, 1620, 2980, 3150, 3200. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (s, 3H, -CH_3), 3.10 (t, 4H, -N-CH_2), 3.78 (s, 3H, -OCH_3), 3.98 (t, 4H, -N-CH_2), 6.75-7.75 (m, 12H, Ar-H), 8.43 (s,1H, -N-CH), 10.55 (s, 1H, -NH).

2-(2-(4-hydroxy)benzylidenehydrazinyl)-6-(4-(4-methoxy phenyl)piperazin-1-yl)-4-(*p*-tolyl oxy)-1,3,5-triazine (A_2)

Yield 79%; m.p. 165-167 °C; Anal. Calcd. for $C_{28}H_{29}O_3N_7$ (511.57 gm/mole): C, 65.74; H, 5.71; N, 19.17. Found: C, 65.82; H, 5.64; N, 19.26. IR (KBr, cm^{-1}): 817, 1361, 1439, 1585, 1622, 2976, 3148, 3205, 3260 (O-H). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.41 (s, 3H, -CH_3), 3.20 (t, 4H, -N-CH_2), 3.65 (s, 3H, -OCH_3), 3.88 (t, 4H, -N-CH_2), 5.42 (s, 1H, -OH), 6.70-7.70 (m, 12H, Ar-H), 8.39 (s,1H, -N-CH), 10.61 (s, 1H, -NH).

2-(2-(4-methoxy)benzylidenehydrazinyl)-6-(4-(4-methoxy phenyl)piperazin-1-yl)-4-(*p*-tolyl oxy)-1,3,5-triazine (A_3)

Yield 77%; m.p. 164-166 °C; Anal. Calcd. for $C_{29}H_{31}O_3N_7$ (525.60 gm/mole): C, 66.27; H, 5.94; N, 18.65. Found: C, 66.39; H, 5.87; N, 18.58. IR (KBr, cm^{-1}): 820, 1369, 1445 (C-O-C), 1582, 1615, 2978, 3151, 3212. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.39 (s, 3H, -CH_3), 3.19 (t, 4H, -N-CH_2), 3.70 (s, 3H, -OCH_3), 3.95 (t, 4H, -N-CH_2), 4.02 (s, 3H, -OCH_3), 6.75-7.80 (m, 12H, Ar-H), 8.40 (s,1H, -N-CH), 10.58 (s, 1H, -NH).

2-(2-(2,4-dichloro)benzylidenehydrazinyl)-6-(4-(4-methoxy phenyl)piperazin-1-yl)-4-(*p*-tolyl oxy)-1,3,5-triazine (A_4)

Yield 85%; m.p. 180-182 °C; Anal. Calcd. for $C_{28}H_{27}O_2N_7Cl_2$ (546.64 gm/mole): C, 59.58; H, 4.82; N, 17.37. Found: C, 59.66; H, 4.91; N, 17.49. IR (KBr, cm^{-1}): 727 (C-Cl), 812, 1370, 1450, 1570, 1609, 2975, 3140, 3230. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, -CH_3), 3.10 (t, 4H, -N-CH_2), 3.75 (s, 3H, -OCH_3), 3.90 (t, 4H, -N-CH_2), 6.70-7.80 (m, 11H, Ar-H), 8.35 (s,1H, -N-CH), 10.62 (s, 1H, -NH).

2-(2-(3,4-dihydroxy)benzylidenehydrazinyl)-6-(4-(4-methoxy phenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazine (A_5)

Yield 80%; m.p. 103-105 °C; Anal. Calcd. for $C_{28}H_{29}O_4N_7$ (527.57 gm/mole): C, 63.74; H, 5.54; N, 18.58. Found: C, 63.68; H, 5.47; N, 18.49. IR (KBr, cm^{-1}): 816, 1372, 1443, 1575, 1615, 2980, 3145, 3222, 3270 (O-H). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, -CH_3), 3.10 (t, 4H, -N-CH_2), 3.75 (s, 3H, -OCH_3), 3.90 (t, 4H, -N-CH_2), 5.30 (s, 1H, -OH), 5.65 (s, 1H, -OH), 6.70-7.80 (m, 11H, Ar-H), 8.35 (s,1H, -N-CH), 10.62 (s, 1H, -NH).

Synthesis of 3-chloro-1-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-4-(substitutedphenyl)azetidin-2-one (B_1 to B_5)

Take a solution of 2-(2-substituted benzylidenehydrazinyl)-6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazine **(A_1 to A_5)** (0.01 mole) and triethylamine (5-6 drops) as a catalyst in dry benzene (15 ml) was added in chloro acetyl chloride (0.015 mole, 1.18gm) at 50 °C. The reaction mixture was stirred for a half an hour at room temperature and refluxed for 6-7 hrs, then cooled it and poured in ice cold water. The solid thus obtained was recrystallization from alcohol to yield the target compounds (B_1 to B_5).

3-chloro-1-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-4-(4-chlorophenyl)azetidin-2-one (B_1)

Yield 82%; m.p. 138-140 °C; Anal. Calcd. for $C_{30}H_{29}O_3N_7Cl_2$ (602.10 gm/mole): C, 59.41; H, 4.82; N, 16.17. Found: C, 59.26; H, 4.90; N, 16.04. IR (KBr, cm^{-1}): 810 (C-Cl), 835, 1325, 1430, 1510, 1700, 3015, 3240. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.31 (s, 3H, -CH_3), 3.01 (t, 4H, -N-CH_2), 3.61 (s, 3H, -OCH_3), 3.81 (t, 4H, -N-CH_2), 4.61 (s, 1H, -CH-Cl), 5.90 (s,1H, -N-CH), 6.78-7.84 (m, 12H, Ar-H), 9.51 (s, 1H, -NH).

3-chloro-1-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-4-(4-hydroxyphenyl)azetidin-2-one (B_2)

Yield 73%; m.p. 110-112 °C; Anal. Calcd. for $C_{30}H_{30}O_4N_7Cl$ (588.05 gm/mole): C, 61.27; H, 5.14; N, 16.67. Found: C, 61.18; H, 5.01; N, 16.76. IR (KBr, cm^{-1}): 842, 1330, 1440, 1520, 1710 (-C=O Azetidinone), 3015, 3240, 3280 (O-H). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.29 (s, 3H, -CH_3), 3.05 (t, 4H, -N-CH_2), 3.65 (s, 3H, -OCH_3), 3.80 (t, 4H, -N-CH_2), 4.58 (s, 1H, -CH-Cl), 5.38 (s, 1H, -OH), 5.88 (s,1H, -N-CH), 6.72-7.80 (m, 12H, Ar-H), 9.47 (s, 1H, -NH).

3-chloro-1-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-4-(4-methoxyphenyl)azetidin-2-one (B_3)

Yield 72%; m.p. 154-156 °C; Anal. Calcd. for $C_{31}H_{32}O_4N_7Cl$ (602.10 gm/mole): C, 61.84; H, 5.36; N, 16.28. Found: C, 61.74; H, 5.44; N, 16.36. IR (KBr, cm^{-1}): 835, 1334, 1445, 1521, 1730 (-C=O Azetidinone), 3020, 3238. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.31 (s, 3H, -CH_3), 3.13 (t, 4H, -N-CH_2), 3.52 (s, 3H, -OCH_3), 3.70 (s, 3H, -OCH_3), 3.95 (t, 4H, -N-CH_2), 4.63 (s, 1H, -CH-Cl), 5.95 (s,1H, -N-CH), 6.71-7.81 (m, 12H, Ar-H), 9.58 (s, 1H, -NH).

3-chloro-1-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-4-(2,4-dichlorophenyl) azetidin-2-one (B_4)

Yield 80%; m.p. 144-146 °C; Anal. Calcd. for $C_{30}H_{28}O_3N_7Cl_3$ (640.94 gm/mole): C, 56.22; H, 4.40; N, 15.30. Found: C, 56.30; H, 4.24; N, 15.39. IR (KBr, cm^{-1}): 830 (C-Cl), 830, 1340, 1452, 1523, 1727 (-C=O Azetidinone), 3013, 3240. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, -CH_3), 3.07 (t, 4H, -N-CH_2), 3.48 (s, 3H, -OCH_3), 3.92 (t, 4H, -N-CH_2), 4.70 (s, 1H, -CH-Cl), 5.86 (s,1H, -N-CH), 6.65-7.75 (m, 11H, Ar-H), 9.60 (s, 1H, -NH).

3-chloro-1-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-4-(3,4-dihydroxyphenyl)azetidin-2-one (B_5)

Yield 75%; m.p. 218-220 °C; Anal. Calcd. for $C_{30}H_{30}O_5N_7Cl$ (604.05 gm/mole): C, 59.65; H, 5.10; N, 16.23. Found: C, 56.59; H, 5.18; N, 16.03. IR (KBr, cm^{-1}): 832, 1341, 1456, 1525, 1732 (-C=O Azetidinone), 3015, 3253, 3270 (O-H). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.51 (s, 3H, -CH_3), 3.05 (t, 4H, -N-CH_2), 3.53 (s, 3H, -OCH_3), 3.89 (t, 4H, -N-CH_2), 4.71 (s, 1H, -CH-Cl), 5.15 (s, 1H, -OH), 5.45 (s, 1H, -OH), 5.90 (s,1H, -N-CH), 6.70-7.84 (m, 11H, Ar-H), 9.65 (s, 1H, -NH).

Synthesis of 3-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-2-(substitutedphenyl) thiazolidin-4-one (C_1 to C_5)

To a solution of 2-(2-substituted benzylidenehydrazinyl)-6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazine (A_1 to A_5) (0.01mole) and 1gm of anhydrous zinc chloride as a catalyst in dry benzene (15 ml), thioglycolic acid (0.02mole, 1.84gm) was added by dropping funnel with stirring at constant temperature and refluxed it for 8-9 hrs, then cooled it and poured in sodium bicarbonate solution (10%) to get neutralized. The solid thus obtained was recrystalized from alcohol to yield target compounds (C_1 to C_5).

3-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-2-(4-chlorophenyl)thiazolidin-4-one (C_1)

Yield 73%; m.p. 179-181 °C; Anal. Calcd. for $C_{30}H_{30}O_3N_7SCl$ (604.12 gm/mole): C, 59.64; H, 5.01; N, 16.23. Found: C, 56.72; H, 5.13; N, 16.35. IR (KBr, cm^{-1}): 690, 750 (C-Cl), 813, 1300, 1380, 1510, 1698, 3050, 3250. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.31 (s, 3H, -CH_3), 2.75 (s, 2H, -S-CH_2), 3.10 (t, 4H, -N-CH_2), 3.75 (s, 3H, -OCH_3), 3.92 (t, 4H, -N-CH_2), 5.90 (s,1H, -N-CH), 6.80-7.50 (m, 12H, Ar-H), 11.01 (s, 1H, -NH).

3-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-2-(4-hydroxyphenyl)thiazolidin-4-one (C_2)

Yield 75%; m.p. 185-187 °C; Anal. Calcd. for $C_{30}H_{31}O_4N_7S$ (604.12 gm/mole): C, 61.52; H, 5.34; N, 16.74. Found: C, 61.63; H, 5.42; N, 16.66. IR (KBr, cm^{-1}): 692, 815, 1305, 1378, 1515, 1690, 3050, 3250, 3275 (O-H). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.28 (s, 3H, -CH_3), 2.70 (s, 2H, -S-CH_2), 3.15 (t, 4H, -N-CH_2), 3.80 (s, 3H, -OCH_3), 3.95 (t, 4H, -N-CH_2), 5.40 (s, 1H, -OH), 5.95 (s,1H, -N-CH), 6.70-7.40 (m, 12H, Ar-H), 11.10 (s, 1H, -NH).

3-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-2-(4-methoxyphenyl)thiazolidin-4-one (C_3)

Yield 81%; m.p. 124-126 °C; Anal. Calcd. for $C_{31}H_{33}O_4N_7S$ (599.70 gm/mole): C, 61.98; H, 5.70; N, 16.32. Found: C, 61.89; H, 5.83; N, 16.46. IR (KBr, cm^{-1}): 710, 825, 1320, 1380, 1525, 1695, 3040, 3205. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.32 (s, 3H, -CH_3), 2.71 (s, 2H, -S-CH_2), 3.20 (t, 4H, -N-CH_2), 3.60 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3), 3.99 (t, 4H, -N-CH_2), 5.90 (s,1H, -N-CH), 6.70-7.50 (m, 12H, Ar-H), 11.05 (s, 1H, -NH).

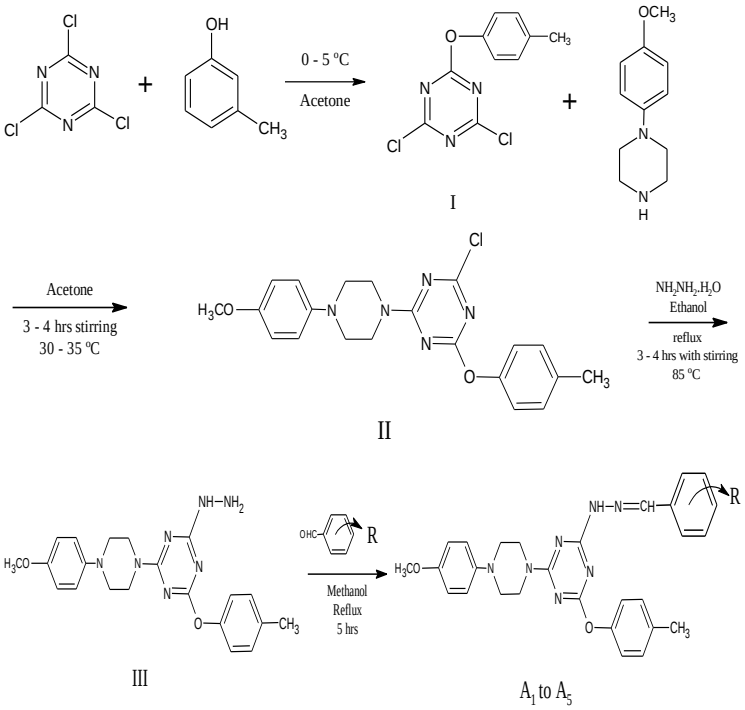
3-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-2-(2,4-dichlorophenyl)thiazolidin-4-one (C_4)

Yield 72%; m.p. 114-116 °C; Anal. Calcd. for $C_{30}H_{29}O_3N_7Cl_2$ (638.56 gm/mole): C, 56.43; H, 4.58; N, 15.35. Found: C, 56.54; H, 4.66; N, 15.26. IR (KBr, cm^{-1}): 685, 760 (C-Cl), 825, 1305, 1375, 1520, 1695, 3055, 3245. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.34 (s, 3H, -CH_3), 2.65 (s, 2H, -S-CH_2), 3.03 (t, 4H, -N-CH_2), 3.70 (s, 3H, -OCH_3), 3.95 (t, 4H, -N-CH_2), 5.85 (s,1H, -N-CH), 6.85-7.55 (m, 11H, Ar-H), 11.05 (s, 1H, -NH).

3-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazin-2-ylamino)-2-(3,4-dihydroxyphenyl)thiazolidin-4-one (C_5)

Yield 81%; m.p. 120-122 °C; Anal. Calcd. for $C_{30}H_{31}O_5N_7S$ (601.67 gm/mole): C, 59.89; H, 5.19; N, 16.30. Found: C, 59.79; H, 5.31; N, 16.18. IR (KBr, cm^{-1}): 691, 823, 1308, 1385, 1525, 1695, 3045, 3246, 3280 (O-H). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.32 (s, 3H, -CH_3), 2.79 (s, 2H, -S-CH_2), 3.17 (t, 4H, -N-CH_2), 3.83 (s, 3H, -OCH_3), 3.93 (t, 4H, -N-CH_2), 5.35 (s, 1H, -OH), 5.65 (s, 1H, -OH), 5.95 (s,1H, -N-CH), 6.70-7.40 (m, 12H, Ar-H), 11.10 (s, 1H, -NH).

Scheme - I



Scheme - II

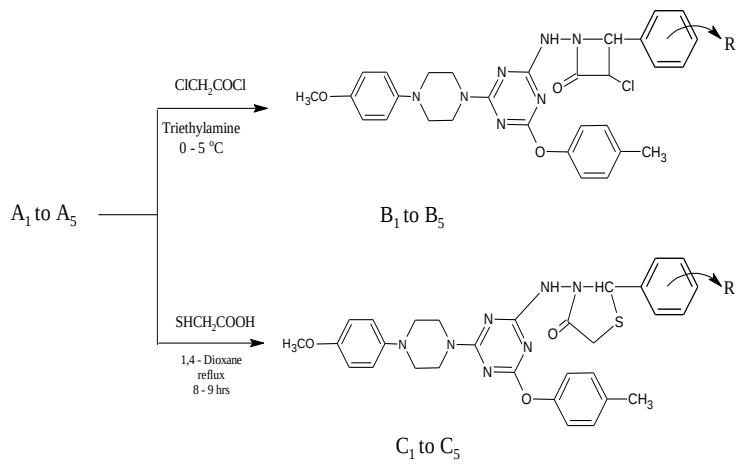


Table-I: Antimicrobial activity of the synthesized compounds

Compound No.	Minimal Inhibitory Concentration (µg/ml)						
	Antibacterial Activity				Antifungal Activity		
	Gram (+ve) bacteria		Gram (-ve) bacteria		Gram (+ve) fungus	Gram (-ve) fungus	
	S. aureus	*S. pyogenus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*A. clavatus*
A_1	25	100	25	50	100	200	100
A_2	50	50	50	25	50	50	100
A_3	100	50	100	50	50	100	25
A_4	25	50	25	100	50	200	50
A_5	50	100	50	50	25	100	100
B_1	50	50	200	200	200	25	100
B_2	100	50	100	50	100	25	50
B_3	200	25	50	50	200	100	200
B_4	25	50	25	100	50	100	200
B_5	50	200	100	200	25	200	100
C_1	50	100	25	50	200	100	50
C_2	100	50	200	25	100	50	100
C_3	200	50	100	100	25	50	50
C_4	25	25	50	200	50	25	25
C_5	50	100	25	50	100	100	100
Gentamycin	25	5	5	25	-	-	-
Nystatin	-	-	-	-	25	5	25

R = 4-Cl (1), 4-OH (2), 4-OCH_3 (3), 2,4-Cl (4), 3,4-OH (5)

Results and Discussion

The synthetic route of the compounds (A, B & C) is outlined in schemes I & II respectively. The synthesis of 2-(2-substituted benzylidenehydrazinyl)-6-(4-(4-methoxyphenyl) piperazin-1-yl)-4-(*p*-tolyloxy)-1,3,5-triazine (A_1 to A_5) as shown in Scheme-I was carried out from *p*-cresol and cyanuric chloride. The compound-I and *N*-phenyl piperazine was refluxed to give compound-II which on refluxed with hydrazine hydrate in alcohol to give compound-III. The compound-III was refluxed with different substituted benzaldehyde to give (A_1 to A_5). The compound (B_1 to B_5) was synthesized by the reaction of (A_1 to A_5) with chloroacetylchloride in presence of base. The Compound (C_1 to C_5) was synthesized by thioglycolic acid and compound (A_1 to A_5) as shown in scheme-II.

The structures of the synthesized compounds were characterized by analytical methods and spectral data (IR and ^{1}H NMR). In the IR spectra, the -N=C bands were observed at 815, 1365, 1580 cm^{-1}. Compounds (A_1 to A_5) have shown -CH=N band in the range of 1600-1670 cm^{-1}. In compound (B_1 to B_5) C-Cl and C=O bands have shown at 780-830 cm^{-1} and 1590-1750 cm^{-1} respectively. In compound (C_1 to C_5) C-S-C bands were observed in the range of 670-720 cm^{-1}. In the ^{1}H NMR spectra range 3.70-4.20 ppm and 9.00-11.00 ppm (singlet) peaks for all compounds confirmed the availability of -OCH_3 and -NH group respectively. In compound (B_1 to B_5)-CH-Cl peaks at 4.58-4.71 ppm (singlet). In (C_1 to C_5) -S-CH_2 peaks at 3.70-3.95 ppm (singlet).

The antimicrobial activities of the synthesized compounds are also shown in the table III. The antimicrobial activities of these compounds active against variety of bacterial stains in which some of these derivatives exhibited potential antibacterial and antifungal activity. The antimicrobial activities of the synthesized compounds are shown in the Table-I which were found moderate to good active against tested organism. Compounds A_1, A_4, B_4 & C_4 showed good activity (25µg/ml) against *S.aureus* compared to Gentamycin which may be due to 4-chloro, and 2,4-dichloro substituents. Compounds B_3 & C_4 showed good acitivity against *S.pyogenus* which may be due to 3-methoxy and 2,4-dichloro substituents. Compound A_1, A_4, B_4, C_1 & C_5 showed good activity (25µg/mL) against *E.coli* which posses due to 4-chloro, 3,4-dihydroxy and 2,4-dichloro substituents. Compounds A_2 & C_2 exibited good activity (25µg/ml) against *P.aeruginosa* which possess due to 2-hydroxy substituent. Compounds A_5, B_5 & C_3 exibited good activity against *C.albicans* compared to Nystatin which may be due to 3-methoxy, 3,4-dihydroxy substituents. Compounds B_1, B_2 & C_4 showed good activity against *A.niger* which may be due to 4-chloro, 4-hydroxy and 2,4-dichloro substituents. Compounds A_3 & C_4 showed good activity against *A.Clavatus* which possess due to 3,4-dihydroxy and 2,4-dichloro substituents. From the antibacterial and antifungal results (table-I) indicated that rest of all compounds moderate to weak activity against these species.

Antimicrobial activity

All the synthesized compounds (A, B & C) were screened for their antimicrobial activity by agar disc diffusion method[15,16]. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. All the tubes not showing visible growth are subcultured and incubated overnight at 37 °C. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. Prepared stock solution of antibiotics of concentrations 2000 mg/lit, as required. Arrange micro well plate 8×12 well of sterile well in the rack. The lowest concentration inhibiting growth of the organism was recorded as the MIC. The growth, inhibition is measured and compound is applied in the method to determine

the activity in µg/ml concentration. All the compounds were screened against Gram (+ve) bacteria [*Staphylococcus aureus* (MTCC-96) and *Streptococcus pyogenus* (MTCC-443)] and Gram (-ve) bacteria [*Escherichia coli* (MTCC-442) and *Pseudomonas aeruginosa* (MTCC-441)]. The antifungal activity was tested against Gram (+ve) fungus [*Candida albicans* (MTCC-227)] and Gram (-ve) fungi [*Aspergillus niger* (MTCC-282) and *Aspergillus clavatus* (MTCC-1323)]. The results of all the synthesized compounds were compared with Gentamycin and Nystatin as a reference drugs. The results are shown in table-I.

Conclusion

The antimicrobial activity of the synthesized compounds showed that compounds containing 4-hydroxy, 4-chloro and 2,4-dichloro substituents are found active against tested organism. This fact reveals that the activity is not affected due to the electronic properties of the substituents. Compounds A_1 & A_4 Schiff's base, B_4 azetidinone and C_4 thiazolidinone were found more active against these gram (+ve) and gram (-ve) bacterial and fungul species.

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References

1. R. Böhme, Qun Dang "1,3,5-Triazine" in Encyclopedia of Reagents for Organic Synthesis John Wiley & Sons 2008.
2. A. Aksenov, I. Aksenova, *Chemistry of Heterocyclic Compds.* 45(2) (2009) 130.
3. A. Rosowsky and S. Queener, J. Med. Chem., 47 (2004) 1475.
4. C. Zhou, J. Min, Z. Liu, A. Young, H. Desharzer, T. Gao, Y. Chang and N. Kallenbach., *Bioorg. Med. Chem. Lett.*, 18(4) (2008) 1308.
5. M. Saleh, S. Abbott, V. Perron, C. Lauzon, C. Penney, B. Zacharie, *Bioorg. Med. Chem. Lett.*, 20 (2010) 945.
6. H. Tappe and P. Vermehren, *Ullman's Encyclopedia of Industrial Chemistry*, 651 (1989) A22**.**
7. D. Ludovici and R. Kavash, *Bioorg. Med. Chem. Lett.*, 11 (2001) 2229.
8. I. Gilbert and R. Brun, *J. Med. Chem.*, 44 (2001) 3440.
9. A. Agarwal and M. Chauhan, *Bioorg. Med. Chem. Lett.*, 15 (2005) 531.
10. M. Zheng, C. Xu, J. Ma, Y. Sun, F. Du, H. Liu, L. Lin, C. Li, J. Ding, K. Chen and H. Jiang., *Bioorg. Med. Chem.*, 15(4) (2007) 1815.
11. G. Kuo and X. Chen., *J. Med. Chem.*, 48 (2005) 4535.
12. K. Arya and A. Dandia, *Bioorg. Med. Chem. Lett.*, 17 (12) (2007) 3298.
13. J. Dudley, J. Thurston, F. Fchaefer, J. Hull, *J. Med. Chem.*, 73 (1951) 2986.
14. A. Baliani, G. J. Bueno, M. L. Stewart, V. Yardley, R. Brun, M. P. Barrett and I. H. Gilbert, *J. Med. Chem.*, 48 (17) (2005) 5570.
15. A. Rattan, *Antimicrobials in laboratory medicine*, B. I. Churchill, Livingstone, New Delhi (2000) 85–110.
16. R. Patel and K. Patel, *Experimental Microbiology Part 1 & 2;* Aditya Publication, Ahmedabad, 2004.