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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW NITROGEN HETEROCYCLIC SYSTEMS BEARING 1, 2, 4-TIAZINE MOIETY

Strictly as per the compliance and regulations of :

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Keywords : 1,2,4-triazines, nitrogen heterocycles, antimicrobial activity.

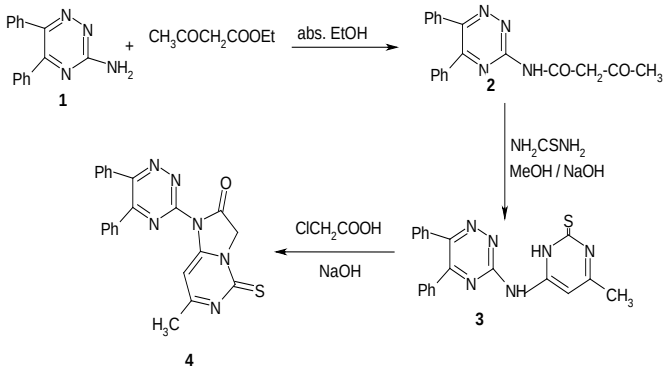
I. Introduction

Substituted 1,2,4-triazines represent an important class of nitrogen containing heterocyclis systems. The 1,2,4-triazine nucleus has been considered as a source of great interest to organic, medicinal and materials scientists over many years, which is present in a number of biologically active organic compounds which exhibit , antibacterial [1], anticancer [2], antimicrobial [3], antifungal [4], [5], anti-inflammatory [6], antibiotic [7], anti HIV [8] activities. Various condensed 1,2,4-triazines found applications as pharmaceuticals, herbicides [9], pesticides [10], and dyes [11].

Nitrogen heterocycles such as pyrimidines, 1,2,4-triazoles, 1,2,4-triazines, 1,3-thiazoles are found to be endowed with potential therapeutic activities such as antitumor [12], antiviral [13], antimycobacterial [14], anticancer [15], and analgesic [16], [17], antimicrobial [18], antiproliferate [19], antihistaminic [20] activities.

The systematic propagation of heterocyclic rings in 1,2,4 triazines precursors with the installation of biologically active heterocyclic units such as pyrimidines, 1,2,4-triazoles, 1,2,4-triazines, 1,3-thiazoles is the major focal point of the present investigation which would be expected to afford interesting biologically active series of compounds.

The synthetic routes followed for the preparation of compounds are outlined in schemes 1-4. The staring compound 3-amino-5,6-diphenyl-1,2,4-triazine (1) [21] reacted with ethyl acetoacetate to afford the *N*-triazinyloxobutamide 2 , which underwent cyclocondensation on treatment with thiourea in MeOH/NaOH to afford the substituted triazinylpyrmidinethione derivative 3 (Scheme1). Structure of compound 3 was established based on analytical and spectral data. The ^{1}H NMR spectrum revealed the appearance of two singlets at δ 8.32 and 9.55 ppm corresponding to NH protons, and two singlets at δ 3.23 and 6.18 ppm attributed to methyl protons and the C_5-$H_{pyrimidinethione}$, respectively. Treatment of compound 3 with chloroacetic acid in NaOH solution afforded the 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-7-methyl-2-oxo-3*H*-imidazo [3,2-*c*] pyrimidine-5-thione (4) (Scheme 1). The IR spectrum of compound 4 confirmed disappearance absorption bands of NH groups in compound 3. It's ^{1}H NMR spectrum revealed the appearance of three singlets at δ 2.53, 2.79 and 6.43 ppm assigned to methyl, $COCH_2$ and the C_5-$H_{pyrimidinethione}$ protons, respectively.



Scheme 1 : Synthetic pathway for the preparation of compounds 1 – 4.

On the other hand, the important synthon *N*-(5,6-diphenyl -1,2,4-triazin-3-yl)formamide (5) was obtained from formylation of 3-amino-5,6-diphenyl-1,2,4-triazine (1) with Ac_2O/HCO_2H. [22] The reaction of compound 5 with thiourea in the presence of sodium ethoxide, via addition reaction gave 1-{[(5,6-diphenyl-1,2,4-triazin-3-yl)amino] hydroxy methyl }thiourea (6) (Scheme 2). Cyclocondensation reaction of 6 by boiling in glacial acetic acid /fused sodium acetate gave 5-(5,6-diphenyl -1,2,4-triazin-3-yl) -4-methyl-1,3,5-triazine-2-thione (7) (Scheme 2). The analytical and spectral data

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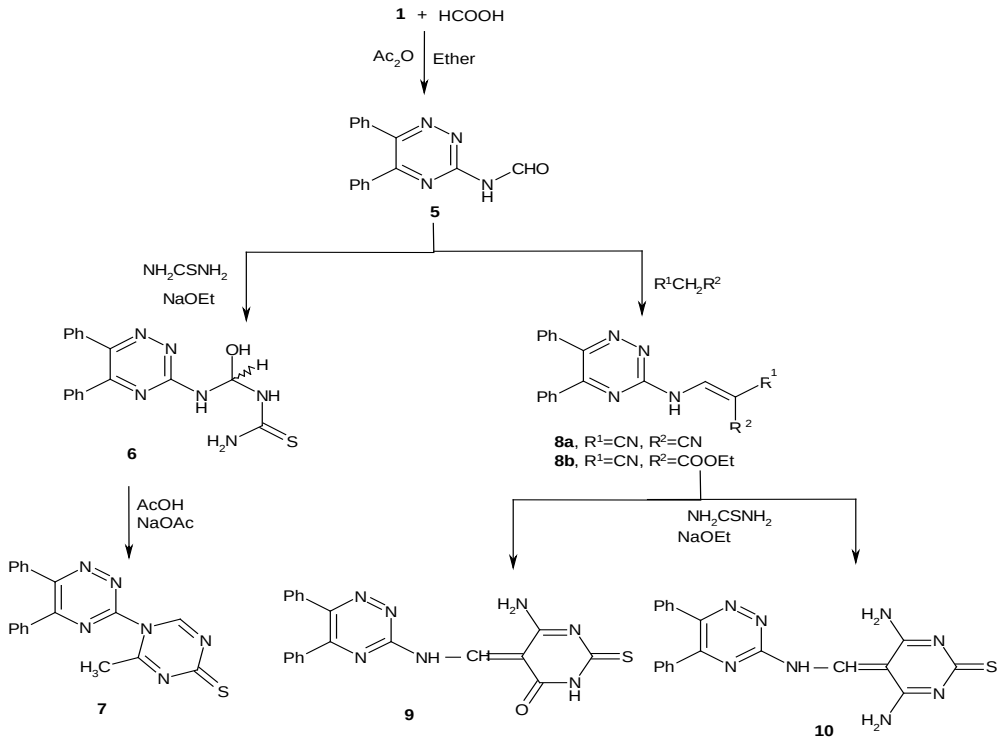
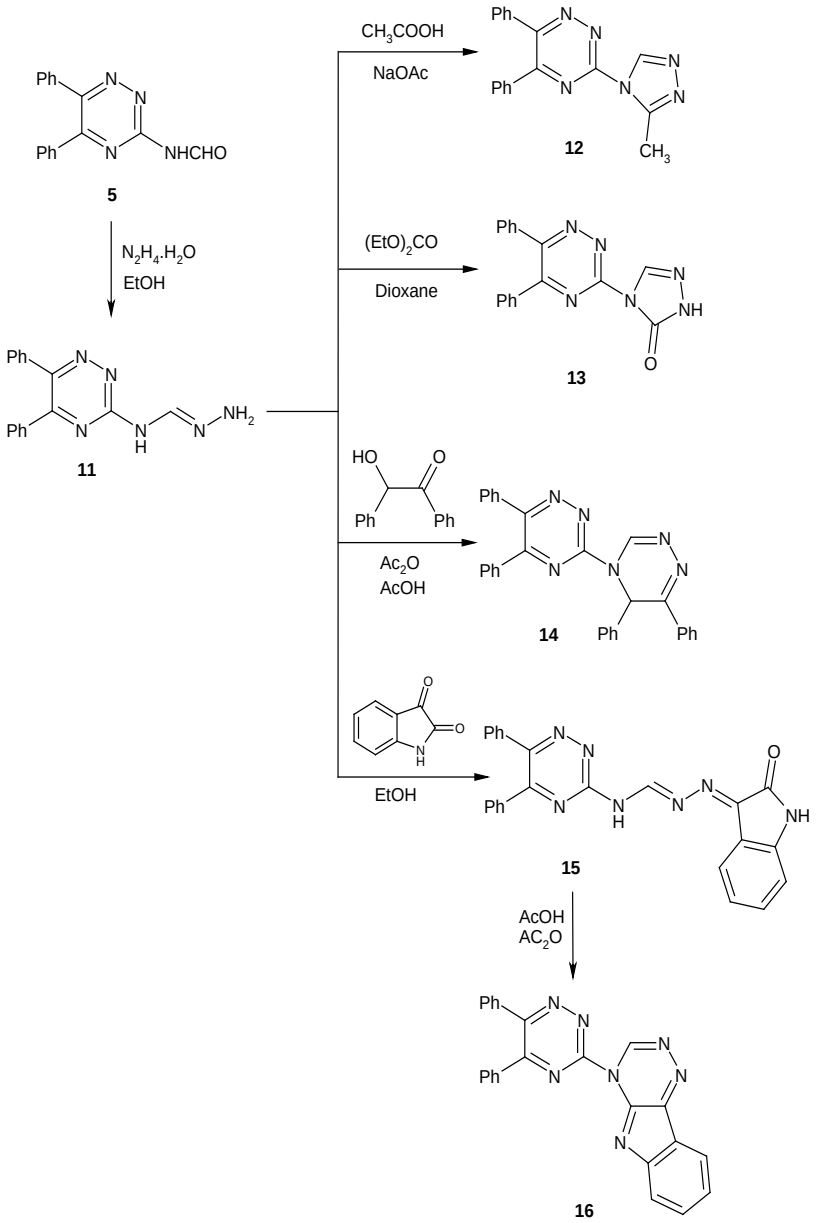
are in agreement with proposed structure. Thus, its ^{1}H NMR spectrum showed signals at δ 1.96 ppm due to CH_3 protons, 7.25–7.59 ppm corresponding to aromatic protons. Also, condensation of compound 5 with active methylene compounds such as malononitrile and ethyl cyanoacetate in refluxing ethanolic sodium ethoxide afforded 8a and 8b, respectively. Cyclocondensation of 8a,b with thiourea on boiling with sodium ethoxide furnished the methylidenaminopyrimidinethiones 9 and 10, respectively (Scheme 2). The IR spectrum of compound 9 showed three characteristic absorption bands at 3479, 3365 and 3228 cm^{-1} due to two NH_2 functions and NH groups. It's ^{1}H NMR spectrum showed three characteristic signals at δ 4.59, 5.19 and 8.87 ppm assigned to two NH_2 and NH protons. Also, its mass spectrum showed the molecular ion peak at m/z 340 [M+1] and the base peak at m/z 178. Also, the IR spectrum of compound 10 showed two characteristic absorption bands at 1668 and 1274 cm^{-1} due to C=O and C=S groups. It's ^{1}H NMR spectrum showed two characteristic signals at δ 5.19, 9.17 ppm assigned to NH_2 and NH protons.



Scheme 2 : Synthetic pathway for the preparation of compounds 5 – 10

Derivatives of 1, 2, 4-triazole and 1, 2, 4-triazine have been found to possess wide spectrum of pharmacological, medicinal and biological activities. [23], [24] Thus, condensation of compound 5 with hydrazine hydrate in absolute ethanol produced the amidrazone 11 which upon heterocyclization by refluxing with glacial acetic acid in the presence of fused sodium acetate and/or diethyl carbonate in dry dioxin [25] afforded 3-(3-methyl-1,2,4-triazol-4-yl)-5,6-diphenyl-1,2,4-triazine (12) and 3-[3-oxo-1H-1,2,4-triazol-3-yl]5,6- diphenyl-1,2,4-triazine 13, respectively (Scheme 3). Structures of compounds 11–13 were established on the basis of analytical and spectral data. Thus, the IR spectrum of compound 11 showed absorption bands at 3300,3220 and 3150 cm^{-1} due to NH_2 and NH groups, which were disappeared in compound 12, in addition compound 13 revealed the absorption bands at 3050 and 1680 cm^{-1} due to cyclic NH and C=O groups. On the other hand, the ^{1}H NMR spectrum of 11 showed signals at δ 2.92, 7.64, 7.76–7.97 and 9.85 ppm due to NH_2, CH=N, aromatic and NH while that of 12 showed the presence of two signals due to CH_3 and the C_3-$H_{triazole}$ at δ 3.45 and 7.32 ppm. Some new 1,2,4-triazine derivatives bearing other 1,2,4-triazine moieties have been deduced from cyclization of amidrazone 11 with 1,2-bioxo-compounds. Thus, triazinyltriazine 14 was prepared from cyclocondensation of amidazone 11 with benzoin in the presence of glacial acetic acid and fused sodium acetate. The structure of compound 14 was established on the basis of analytical and spectral data. The IR spectrum showed the disappearance of NH_2 and NH groups. While condensation of compound 11 with isatin in methanol yielded the isatin-3-hydrazone 15, which on refluxing in glacial acetic acid and fused sodium acetate furnished 4-(5,6-diphenyl-1,2,4-triazin-3-yl)-4H-[1,2,4] triazino[5,6-b]indole 16. The structure of compound 16

was established on the basis of analytical and spectral data. Its IR spectrum showed the disappearance of the NH, OH and C=O groups. Also, the mass spectrum showed the molecular ion peak at *m/z* 401 which agreed with its molecular formula.



Scheme 3 : Synthetic pathway for the preparation of compounds 11 – 16.

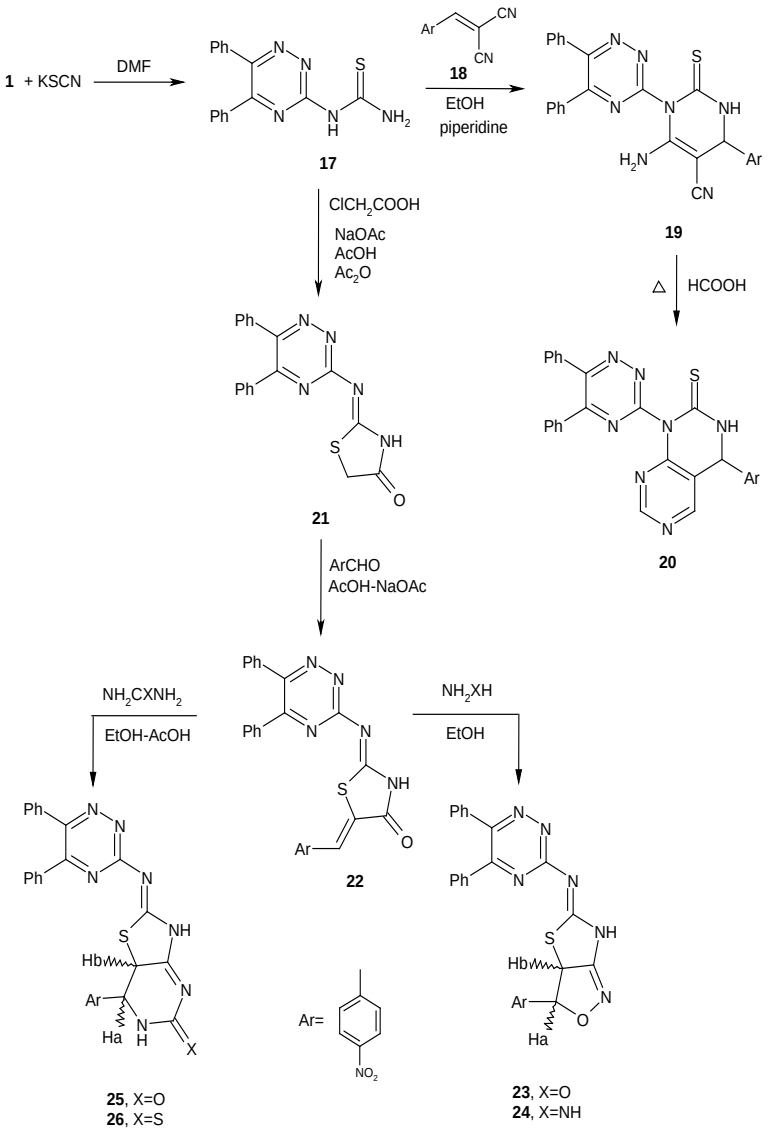
Isoxazoles are widely investigated for therapeutic uses, especially as tranquillizing agent and central nervous systems (CNS) regulation and are reported to have bactericidal and fungicidal activities. [26] Pyrazoles display a number of antimicrobial activities like antitumor [27], immunosuppressive [28], antibacterial [29], anticancer [30], antidiabetic and antidepressants. [31] The imidazolinone moiety is a useful functionality for development of biologically interesting molecules such as hypertensive [32], antimalarial [33], antihypnotic [34] and antihypertensive [35]activities.

In view of continuous and widespread interest in the design of a new heterocyclic derivatives containing 1, 2, 4-triazine moiety, particularly on account of fused 1,2,4-triazine aryl derivatives containing isoxazole, pyrimidine and pyrazole derivatives. Thiourea plays a vital role in many biological processes and is used as intermediates for the synthesis of drugs [36]. Thus, the reaction of 1 with potassium thiocyanate in DMF afforded 1-(5,6-diphenyl-1,2,4-triazin-3-yl)thiourea 17, which upon heterocyclization by refluxing with arylidene malonlonitrile 18 in boiling absolute ethanol containing a catalytic amount of piperidine, afforded 6-amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-(4-nitrophenyl)-2-thioxo 1,2,3,4-tetrahydropyrimidine-5-carbonitrile (19) (Scheme 4). Compound 19 underwent treatment with formic acid to

yield 8-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-(4-nitrophenyl)-7-thioxo-5,6,7,8-trihydropyrimido[4,5 *d*]pyrimidin-2(1*H*)-one (20) (Scheme 4). The ^{1}H NMR spectrum of 19 showed two characteristic signals at **δ** 6.15, 8.93 ppm assigned to NH_2 and NH protons. While the ^{1}H NMR spectrum of 20 showed characteristic signals at **δ** 9.25 ppm assigned to NH proton.

The reaction between key intermediate 17 with chloroacetic acid and sodium acetate in acetic anhydride afforded 1,3-thiazolidinones 21. The ^{1}H NMR of 21 showed a sharp singlet at **δ** 3.45 due to two protons of the CH_2S group. Its IR spectra showed the disappearance of the coupled vibrations and appearance of bands for C=O and NH at around 1730 and 3350 cm^{-1}, respectively (Scheme 4). The thiazolidinone 21 undergoes condensation with aromatic aldehyde like 3-nitrobenzaldehyde to give the cyclic chalcone 22 (Scheme 4). The formation of compound 22 was confirmed by the absence of CH_2 protons it its ^{1}H NMR spectrum.

Treatment of 22 with various *bi*-nucleophiles such as hydroxylamine, hydrazine hydrate, urea and thiourea afforded their respective in *situ* oxidized products 23, 24, 25 and 26 (Scheme 4). The driving force for this in situ oxidation is the formation of new heterocyclic rings. The disappearance of the carbonyl frequency in IR spectrum for 23 and 24 confirms the installation of isoxazole and pyrazole moieties. In case of 25 the band at around 1725 cm^{-1} was assigned to the new amidic C=O group. However, the ^{1}H NMR spectrum of 24 showed additional signal at **δ** 5.56 and 6.48 ppm for two NH, similarly in the ^{1}H NMR of compound 26 the amidic NH proton at **δ** 8.49 ppm.



Scheme 4 : Synthetic pathway for the preparation of compounds 17 – 26.

II. Antimicrobial Activity

Some new synthesized compounds were screened for their antimicrobial activities against two species of bacteria *Bacillus subtilis* and *Escherichia coli* and two species of fungi *Alternaria alternata* and *Aspergillus niger* using the disc diffusion method [37–39], spore suspension 0.5 ml (10^6–10^7 spore/ml) of each of the investigated microorganisms was added to a sterile agar medium just before solidification then poured into sterile Petri dishes (9 cm in diameter) and left to solidify. By using sterile cork borer (6 mm in diameter), three holes (wells) were made in each dish, then 0.1 ml of the tested compounds dissolved in DMF (100 µg /ml) were poured into these holes. Finally the dishes were incubated at 37°C for 48 hr (for bacteria) and at 30°C for 72 hr (for fungi), where clear or inhibition zones were detected around each hole. 0.1 ml of DMF alone was used as a control under the same conditions for each microorganism and by subtracting the diameter of inhibition zone resulting with DMF alone from that obtained from that obtained in each case, both antibacterial and antifungal activities can be calculated as a mean of three replicates. Terbinafin used as a standard agent (antifungal) and chloramphenicol used as a standard agent (antibacterial) (Table 1). The results for antibacterial activities depicted in Table1 revealed that most of the synthesized compounds were found to possess various antimicrobial activities towards all the microorganisms tested.

III. Conclusion

In this report easy, a simple and convenient route for the synthesis of biologically active 1,2,4-triazine aryl derivatives containing pyrimidines, 1,2,4-triazoles, 1,2,4-triazines, 1,3-thiazoles and related compounds. The microbial evaluation of these compounds indicated that they are good potent antimicrobial agents in comparison with the standard drug.

Table 1 : Antimicrobial activity of some of the prepared compounds.

Compound No	Bacteria		Fungi	
	Gram +ve	Gram -ve	*Alternaria alternata*	*Aspergillus niger*
	Bacillus subtilis	*Escherichia coli*		
1	+	++	+	+
2	+	+	+	++
4	+	++	+	++
5	++	++	++	++
7	++	+	++	++
9	++	++	++	++
10	+	+	++	+
11	+	+	+	+
12	+++	++	+++	++
13	++	++	++	++
14	+++	++	++	++
16	++	+++	+	++
20	+	++	+	++
21	+++	++	++	++
22	+	++	+	++
23	+	++	+	++
24	+	+	+	+
25	++	+	++	+
26	+++	+++	++	++
Terbinafin	-	-	+++	++
Chloramphenicol	+++	+++	-	-

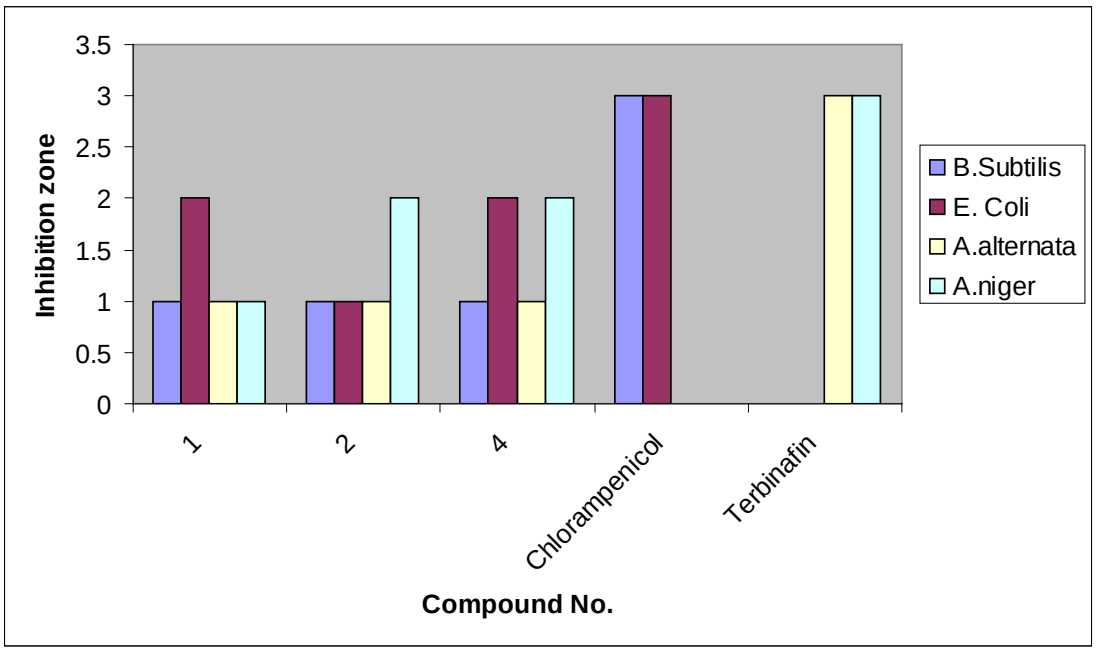
The test done using the diffusion agar technique

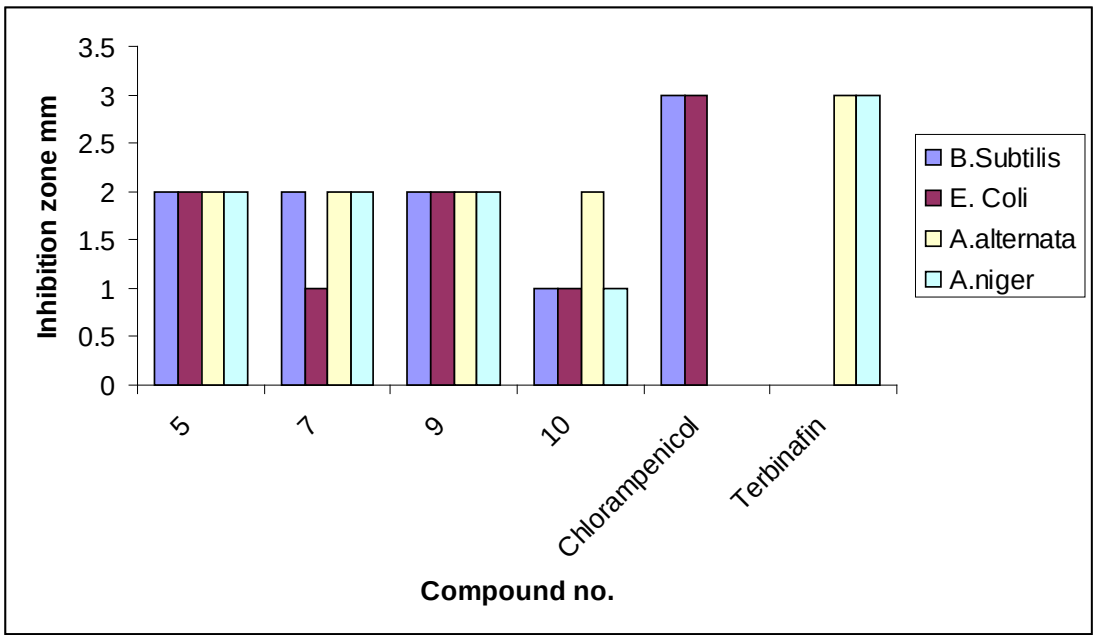
Well diameter = 0.06 cm

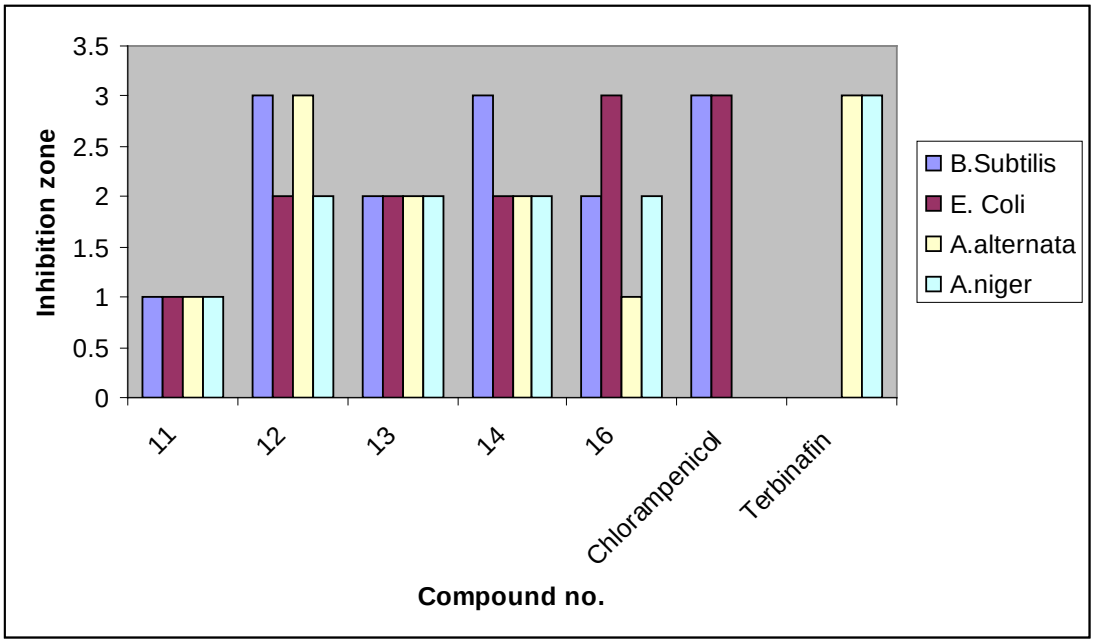
Inhibition values = 0.1 – 0.5 cm beyond control = + (less active)

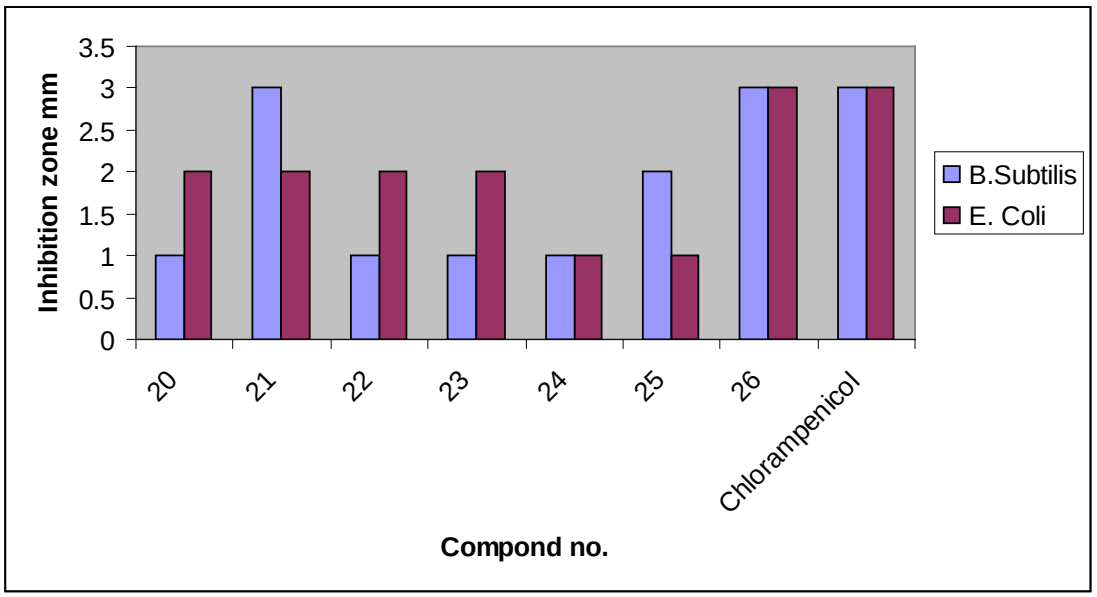
Inhibition values = 0.6 – 1.0 cm beyond control = ++ (moderate active)

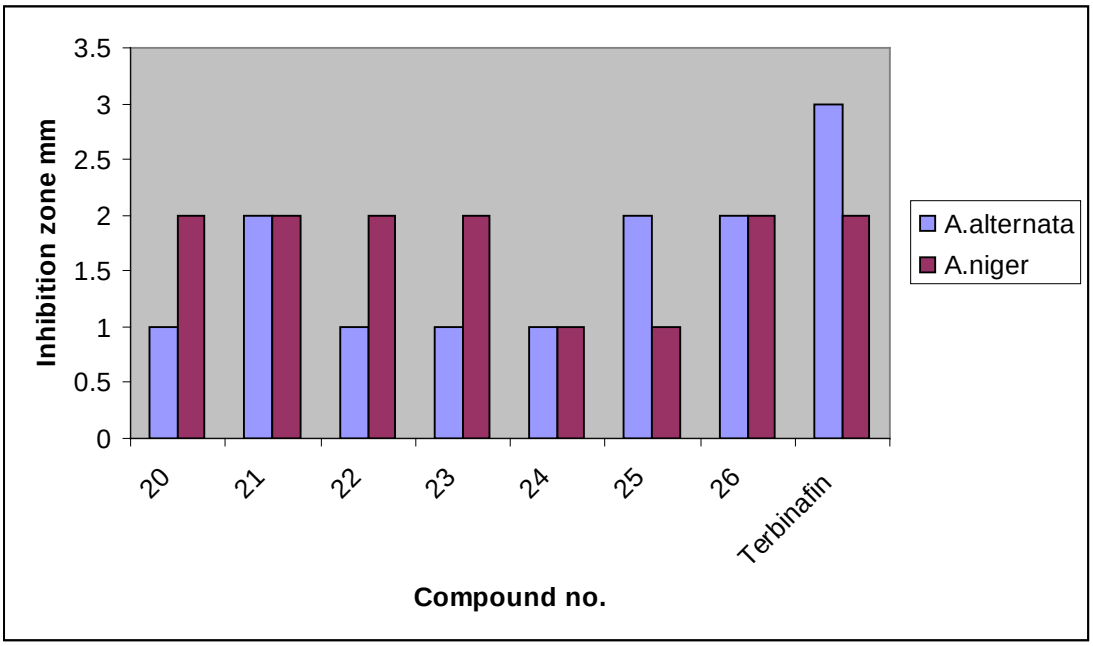
Inhibition values = 1.1 – 1.5 cm beyond control = +++ (highly active)











IV. Experimental Section

Melting points were recorded on a digital Stuart SMP-3 apparatus. Infrared spectra were recorded on FT-IR Bruker Vector 22 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were measured on Gemini spectrometer 200 MH_Z using DMSO-d_6 as solvent and TMS (Chemical sift in δ ppm) as an internal standard. Mass spectra were obtained using as chromatography GCMS qp 1000 ex Schimadzu instrument mass spectrometer (70 eV). Elemental micro-analyses were performed at the Cairo University Microanalytical Center and were in the range of ± 0.4 % for each element analyzed (C, H, N, S). The purity of compounds was checked by thin layer chromatography on silica gel (silica gel, aluminum sheets 60 F254, Merck). 3-Amino-5,6-diphenyl-1,2,4-triazin(1) was prepared according to the previously procedure [21].

N-(5,6-Diphenyl -1,2,4-triazin-3-yl)-3-oxobutanamide (2)

A mixture of compound 1 (0.01 mol) and ethyl acetoacetate (0.01 mol) in absolute ethanol (15 cm^3) containing a few drops of piperidine (3 drop) was refluxed for 6 h. The reaction mixture was cooled and the solid so obtained was filtered off and recrystallized from ethanol. Yield 86%. M.p.:- 194–196 ^{o}C. FT-IR, ν (cm^{-1}): 3295 (NH), 1716, 1662 (2 C=O). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.48 (s, 3H, CH_3), 2.79 (s, 2H, CH_2) 7.24 – 8.43 (m, 10H, Ar-H), 9.23 (s, 1H, NH). Anal. Calcd. for $C_{19}H_{16}N_4O_2$ (332): C, 68.67; H, 4.81; N, 16.86.Found: C, 68.27; H, 4.49; N, 16.51 %.

3-[4-Methyl-2-thioxo-1H-pyrimidinylamino] 5,6- diphenyl-1,2,4-triazine- (3)

To a solution of compound 2 (0.01 mol) in methanolic NaOH (10%, 20 cm^3), thiourea (0.01 mol) was added and the reaction mixture was heated under reflux for 4 h, and then allowed to cool. The precipitate that formed was filtered off, dried and recrystallized from ethanol.Yield 90 %. M.p.: 203 -205 ^{o}C. FT-IR, ν (cm^{-1}): 3200 (NH), 3100 (NH), 1565 (C=N), 1532 (C=N), 1239 (C=S). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.23 (s, 3H, CH_3), 6.18 ($CH_{pyridimidine}$), 7.16–7.96 (m, 11H, Ar-H), 8.92 (s, 1H, NH), 9.25 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{16}N_6S$ (372): C, 64.51; H, 4.30; N, 22.58; S, 8.60.Found: C, 64.83; H, 4.73; N, 22.94; S, 8.24 %.

1-[5,6-Diphenyl-1,2,4-triazin-3-yl]-7-methyl-2-oxo-3H-imidazo[3,2-c]pyrimidine-5-thione (4)

A mixture of compound 3 (0.01 mol) and chloroacetic acid (0.01 mol) in NaOH (5%, 20 cm^3) was refluxed for 6 h. The precipitate obtained was filtered off dried and recrystallized from a mixture of ethanol and DMF (1: 1).Yield 75 %. M.p. 196 -198 ^{o}C.FT-IR, ν (cm^{-1}): 1527, 1538 (2 C=N), 1470 (def. CH_3) 1720 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.53 (s, 3H, CH_3), 2.79(s, 2H, CH_2), 6.43(CH pyridimidine), 7.35-7.29 (m, 11H, Ar-H). Ms (m/z, I %): 412 (M, 2%), 314 (13), 178 (100), 167 (8), 152 (4), 126 (2), 110 (4).Anal. Calcd.for $C_{22}H_{16}N_6OS$ (412): C, 64.07; H, 3.88; N, 20.38; S, 7.76.Found: C, 63.78; H, 4.11; N, 20.03; S, 7.42 %.

N-(5,6-Diphenyl -1,2,4-triazin-3-yl)formamide (5)

A mixture of formic acid (3.4 cm^3) and acetic anhydride (8.2 cm^3) was refluxed for 2h. The mixture was added drop wise to a solution of compound 1 (0.01mol) in diethyl ether (50 cm^3), the formed solid product was filtered off, dried and recrystallized from ethanol. Yield 55%. M.p.: 182–184 ^{o}C. FT-IR, ν (cm^{-1}): 3189 (NH), 1708(C=O), 1528 (C=N), 1631 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 7.45 – 7.98 (m, 10H, Ar-H), 8.62 (s, 1H, NH), 9.95 (s, 1H, CHO). Ms (m/z, I%): 277 (M^++3, 5%) , 276 (M +2, 7%), 195 (11),

156 (6) , 140 (8) , 178 (100) , 115 (13) , 112 (9.) , 101 (7) , 70 (8).Anal. Calcd.for $C_{16}H_{12}N_4O$ (274): C, 70.07; H, 3.97; N, 20.43.Found: C, 69.73; H, 4.49; N, 20.08 %.

1-{[(5,6-Diphenyl-1,2,4-triazin-3–yl)amino]hydroxylmethyl} thiourea(6)

A mixture of compound 5 (0.01 mol) and thiourea (0.01 mol) in sodium ethoxide (0.23g sodium in 100 cm^3 absolute ethanol) was stirred for 2h at room temperature then neutralized with diluted acetic acid. The formed solid product was collected by filtration, dried and recrystallized from diluted methanol. Yield 65%.M.p.:159–161°C. FT-IR, ν (cm^{-1}): 3475 (OH), 3398, 3290 (NH_2), 3228, 3289 (2NH), 1620 (def. NH_2). 1560 (C=N), 1237 (C=S), 878, 806 (2-phenyl groups). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 6.26 (brs, 2H, NH_2) 7.25 – 7.92 (m, 12H, Ar-H), 8.95 (s. 1H, NH), 9.53 (s, 1H, NH), 10.21 (s, 1H, OH). Ms (m/z, I %): 354 (M+2, 3%), 324(7), 178(12), 174(3), 160(4), 142(6), 141(100), 115(6), 77(4), 65(8).Anal. Calcd. For $C_{17}H_{16}N_6OS$ (352): C, 57.95; H, 4.54; N, 23.86; S, 9.09. Found: C, 57.66; H, 4.31; N, 23.46; S, 8.73 %.

5-(5,6-Diphenyl-1,2,4-triazin-3-yl)-4-methyl-1,3,5-triazine-2-thione (7)

A mixture of 6 (0.01 mol) and glacial acetic acid (30 cm^3) with fused sodium acetate (3 gm) was refluxed for 6 h and then allowed to cool. The precipitate that formed was filtered off, dried and recrystallized from pet. ether (80%).Yield 50%. M.p.: 206-208 °C. FT-IR, ν (cm^{-1}): 1545, 1579 (2 C=N), 1237 (C=S). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.96 (s, 3H, CH_3), 7.25 – 7.59 (m, 11H, Ar-H), Ms (m/z, I %): 359 (M +1, 1.08%), 512 (3), 343 (5.68), 327 (14), 301 (8), 259 (11), 178 (100), 112 (10), 54 (5). Anal. Calcd. for $C_{19}H_{14}N_6S$ (358): C, 64.77; H, 3.97; N, 23.46; S, 8.93.Found: C, 64.54; H, 3.61; N, 23.17; S, 8.69 %.

2-Cyano-3-[(5,6-diphenyl-1,2,4-triazin-3yl)amino] acrylonitrile (8 a) and ethyl 2-cyano-3-[(5,6-diphenyl-1,2,4-triazin-3-yl) amino] acrylate(8b)

A mixture of compound 5 (0.01 mol) and active methylene compounds namely, malononitrile, ethyl cyanoacetate (0.01 mol) in sodium ethoxide (0.23g sodium in 100 cm^3 absolute ethanol) was refluxed for 4h. The reaction mixture was cooled and then poured into a beaker containing ice/water mixture containing few drops of HCl for neutralization. The solid so obtained was filtered off and recrystallized to give compounds 8a, b, respectively.

For compound 8a recrystallized from MeOH. Yield 50%.M.p.: 110–112 °C. FT-IR, ν (cm^{-1}): 3192 (NH), 2219 (C≡N), 2226 (C≡N), 1597 (C=N).Anal. Calcd.for $C_{19}H_{12}N_6$ (324): C, 70.37; H, 3.70; N, 25.92. Found: C, 70.12; H, 3.42; N, 25.61%.

For compound 8b recrystallized from isopropanol.Yield 62 %. M.p.: 132- 134 °C. FT-IR, ν (cm^{-1}): 3245 (NH), 2230 (C≡N), 1675 (C=O), 1578 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.79 (t, 3H, CH_3), 4.15 (q, 2H, CH_2), 7.15 – 7.98 (m, 11H, Ar-H), 9.16 (s, 1H, NH). Anal.Calcd. for $C_{21}H_{17}N_5O_2$ (371): C, 67.92; H, 4.58; N, 18.86.Found: C, 67.57; H, 4.23; N, 18.51 %.

4,6-Diamino-5-{[(5,6-diphenyl-1,2,4-triazin-3yl)methylideneamino] }pyrimidine-2-thione (9)

A mixture of compound 8a (0.01 mol) and thiourea (0.01 mol) and sodium ethoxide (0.02 mol Na in 100 cm^3 absolute ethanol) was refluxed for 4 h, cooled and then poured into ice /water mixture containing few drops of CH_3CO_2H to neutralization. The formed solid product was collected by filteration, dried and recrystallized from DMF.Yield 54 %. M.p.: 236–238 °C. FT-IR, ν (cm^{-1}): 3479, 3365 ($2NH_2$), 3228 (NH), 1557 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 4.59 (brs, 2H, NH_2), 5.19 (brs, 2H, NH_2), 6.95 (s, 1H, =CH), 7.26 – 7.98 (m, 10H, Ar-H), 8.87 (s, 1H, NH). Ms (m/z, I %): 343 (M +2, 12 %), 397 (M -4, 3%), 261(4), 222 (5), 178 (100), 141 (3), 120 (5), 102 (9), 94 (2), 80 (7).Anal. Calcd.for $C_{20}H_{15}N_7OS$ (401): C, 59.85; H, 3.74; N, 24.43; S, 7.98.Found: C, 59.51; H, 3.49; N, 24.07; S, 7.62 %.

6-Amino-5-{[(5,6-diphenyl-1,2,4-triazin-3-yl)methylideneamino]}-2-thioxo-2,5-dihydropyrimidin-4-one (10)

A mixture of compound 8b (0.01 mol) and thiourea (0.01 mol) and sodium ethoxide (0.02 mol Na in 100 cm^3 absolute ethanol) was refluxed for 4 h, cooled and then poured into ice-water mixture containing few drops of acetic acid to neutralization. The formed solid product was collected by filteration, dried and recrystallized from DMF. Yield 55 %. M.p.: 222–224 °C. IR FT-IR, ν (cm^{-1}): 3378, 3223(NH_2), 3192, 3050 (2NH), 1668 (C=O), 1274 (C=S), 1588 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 5.19 (brs, 2H, NH_2), 7.21–7.87 (m, 11H, Ar-H), 9.17 (s, 1H, NH). Ms (m/z, I %): 403 (M +3, 11%), 248 (3), 197 (2), 178 (100 %), 151 (3), 138 (5), 104 (11), 76 (2.).Anal.Calcd. for $C_{20}H_{16}N_8S$ (400): C, 60.00; H, 4.00; N, 28.00; S, 8.00.Found: C, 59.66; H, 3.76; N, 27.73; S, 7.63 %.

N-(5,6-Diphenyl-1,2,4-triazin-3-yl) hydrazonoformamide (11)

A mixture of 5 (0.01 mol) and hydrazine hydrate (98 %, 0.15 mol) in absolute ethanol (20 cm^3) was refluxed for 30 min., and then allowed to cool. The precipitate that formed was filtered off and recrystallized from EtOH.Yield 72 %. M.p.: 220–222°C. FT-IR, ν (cm^{-1}): 3391, 3250 (NH_2) 3203 (NH), 1516 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.92 (brs, 2H, NH_2), 7.64 (s, 1H, CH=N), 7.76 – 7.97(m, 10H, Ar-H), 9.85 (s, 1H, NH). Anal.Calcd. for $C_{16}H_{14}N_6$ (290): C, 66.20; H, 4.82; N, 28.96. Found: C, 65.86; H, 4.46; N, 28.67 %.

3-(3-Methyl-1,2,4-triazol-4-yl)-5,6-diphenyl-1,2,4-triazine (12)

A mixture of 11 (0.01 mol) and glacial acetic

acid (30 cm^3) with fused sodium acetate (3 g) was refluxed for 4 h, cooled and poured onto ice. The solid obtained was filtered off, and recrystallized from benzene.Yield 78 %. M.p.: 190–192°C. FT-IR, ν (cm^{-1}): 3391 (NH_2) 3203 (NH), 1556 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.45 (s, 3H, CH_3), 7.21 (s, 1H, CH=N), 7.43–7.89 (m, 11H, Ar-H and C_5-H triazole). Anal. Calcd. for $C_{18}H_{14}N_6$ (314): C, 68.78; H, 4.45; N, 26.75.Found: C, 68.44; H, 4.20; N, 26.40 %.

3-[3-Oxo-2H-1,2,4-triazol-4-yl) 5,6-diphenyl-1,2,4- (13)

A mixture of 11 (0.01 mol) and an equimolar amount of diethyl carbonate in dioxan (50 cm^3) was refluxed for 6 h, then concentrated and the separated solid was filtered off, dried and recrystallized from benzene. Yield 59 %. M.p.: 241–243°C. FT-IR, ν (cm^{-1}): 3137 (NH), 1670 (C=O), 1532 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.15–7.98 (m, 11H, Ar-H and C_2-H pyrazole), 8.97 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{12}N_6O$ (316): C, 64.55; H, 3.79; N, 26.58.found: C, 64.21; H, 3.43; N, 26.21 %.

5,5|,6,6|-Tetraphenyl -3,4|-bi-1,2,4-triazine (14)

A mixture of 11 (0.01 mol) and benzoin (0.01 mol) in absolute ethanol (20 cm^3) was refluxed for 12 h, cooled and then the reaction mixture was poured into crushed ice, and the separated solid was filtered off, dried and recrystallized from MeOH.Yield 57 %. M.p.: 189–199 °C. FT-IR, ν (cm^{-1}): 561 (C=N). Ms (m/z, I %): 467 (M +2, 21%), 465 (M, 12%), 205 (12), 178 (8), 105(100), 103 (13), 79 (7), 54 (3). Anal. Calcd. for $C_{30}H_{21}N_6$ (465): C, 77.41; H, 4.51; N, 18.06. Found: C, 77.05; H, 4.14; N, 17.71 %.

N-(5,6-Diphenyl-1,2,4-triazin-3-yl)-N-[2-oxo-1,2-dihydro-indol-3-ylidene]hydrazonoformamide (15)

A mixture of 11 (0.01 mol) and isatin (0.01 mol) in absolute ethanol (30 cm^3) was refluxed for 1h. The reaction mixture was cooled and the solid so obtained was filtered off and recrystallized from MeOH.Yield 75 %. M.p.: 197–198 °C. IR FT-IR, ν (cm^{-1}): 3216, 3174 (2 NH), 3091 (CH aryl), 1725 (C=O), 1549 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.15 – 7.97 (m, 15H, Ar-H and =CH), 8.92 (s, 1H, NH), 9.62 (s, 1H, NH).Anal. Calcd. for $C_{24}H_{17}N_7O$ (419): C, 68.73; H, 4.05; N, 23.38.Found: C, 68.39; H, 3.69; N, 23.02%.

4-(5,6-Diphenyl-1,2,4-triazin-3-yl)-[1,2,4]triazino[5,6-b] indole(16)

A mixture of 15 (1g) and glacial acetic acid (20 cm^3) with fused NaOAc (5g) was refluxed for 4h and then allowed to cool. The precipitate that formed was filtered off, dried and recrystallized from $CHCl_3$.Yield 72 %. M.p.: 272–274 °C. FT-IR, ν (cm^{-1}): 1590 (C=N), 1522 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.25 – 8.2 (m, 15H, Ar-H). Ms (m/z, I %): (M, 401, 12%), 223 (14), 169 (8), 141 (100), 128 (12), 54(8).Anal. Calcd.for $C_{24}H_{15}N_7$ (401): C, 71.82; H, 3.74; N, 24.43. Found: C, 71.44; H, 3.38; N, 24.05 %.

1-(5,6-Diphenyl-1,2,4-triazin-3-yl)thiourea (17)

A mixture of 1 (0.01 mol) and potassium thiocyanate (0.01 mol) in DMF (20 cm^3) and dil. HCl (20%, 2 cm^3 in 10 ml of water) was refluxed for 6h, then the reaction mixture was poured into crushed ice , and the separated solid was filtered off, dried well and recrystallized from ethanol. Yield 73 % . M.p.: 184 – 186 °C. FT-IR, ν (cm^{-1}): 3452, 3340 (NH_2), 3269 (NH), 1529 (C=N), 1228 (C=S), 853, 820 (2-phenyl groups), ^{1}H NMR (200 MHz, DMSO-d_6) δ: 4.33 (s, 1H, NH), 5.92 (brs, 2H, NH_2), 7.15– 8.23 (m, 10H, Ar-H). Anal. Calcd. for $C_{16}H_{13}N_5S$ (307): C, 62.54; H, 4.23; N, 22.80; S, 10.42. Found: C, 62.16; H, 3.88; N, 22.43; S, 10.04 %.

6-Amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-(4-nitroph enyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (19)

A mixture of 17 (0.01 mol) and 3-nitrobenzyliden malononitrile (18) (0.01 mol) in absolute ethanol (20 cm^3) containing piperidine (0.5 cm^3).The reaction mixture was heated under reflux for 4 h and allowed to cool. The precipitate that formed was filtered off, dried and recrystallized from ethanol.Yield 87 %. M.p.: 190–192 °C. IR FT-IR, ν (cm^{-1}): 3423, 3310(NH_2), 3212 (NH), 2218 (CN), 1587 (C=N), 1235 (C=S). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 6.15 (brs, 2H, NH_2), 7.12–8.15 (m,15H, Ar-H andC_4-H pyrimidine), 8.93 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{17}N_8O_2S$ (505): C, 61.78; H, 3.02; N, 22.17; S, 6.33. Found: C, 61.42; H, 3.36; N, 21.79; S, 5.99 %.

8-(5,6-Diphenyl-1,2,4-triazin-3-yl)-5-(4-nitropheny)-7-thioxo-5,6,7- trihydropyrimido[4,5-d]pyrimidin-4-one(20)

A mixture of 17 (0.01 mol) and formic acid (10 cm^3) was refluxed for 24 h. The formed solid product was filtered off, dried and recrystallized from ethanol.Yield 56%. M.p.: 201– 203 °C. FT-IR,ν(cm^{-1}): 3245 (NH), 1579 (C=N), 1215 (C=S). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.15 – 7.98 (m, 16H, Ar-H), 9.25 (s, 1H, NH). Ms (m/z, I %): 493 (12), 315 (4), 263 (2), 197 (13), 178 (100), 111 (3).Anal. Calcd. for $C_{27}H_{17}N_8O_2S$ (517): C, 62.66; H, 3.28; N, 21.66; S, 6.18. Found: C, 62.29; H, 2.90; N, 21.28; S, 5.82 %.

2-[(5,6-Diphenyl-1,2,4-triazin-3-yl)imino]-1,3-thiazolididin -4-one(21)

A mixture of 17 (0.01 mol) and chloroacetic acid (0.01 mol) and anhydrous sodium acetate (0.01 mol) in glacial acetic acid (15 cm^3) with a trace of acetic anhydride (0.5 cm^3) was refluxed for 8 h. The reaction mixture was cooled and poured into ice–cold water. The solid that separated out was filtered off and purified by recrystallization from glacial acetic acid.Yield 60 %. M.p.: 191– 93 °C. FT-IR, ν (cm^{-1}): 3292 (NH), 1660 (C=O),

1609, 1575(2 C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.35(s, 2H, CH_2), 5.67 (s, 1H, NH), 7.15 –7.98 (m, 10H, Ar-H). Anal.Calcd.for $C_{18}H_{13}N_5OS$ (347): C, 62.24; H, 3.74; N, 20.17; S, 9.22. Found: C, 61.97; H, 3.36; N, 19.83; S, 8.85 %.

2-[(5,6-Diphenyl-1,2,4-triazin-3-yl)imino]-5-(4-nitrobenz ylidene) -1,3-thiazolidin-4-one(22)

A mixture of 21 (0.01 mol), the 3-nitrobenzaldehyde (0.01 mol) and anhydrous sodium acetate (0.02 mol) in glacial acetic acid (20 cm^3) was refluxed for 5 h. The reaction mixture was allowed to at room temperature and treated with cold water. The solid thus separated was filtered off, washed with water and recrystallized from glacial acetic acid.Yield 82 %. M.p.: 186–188 ^{o}C. FT-IR, ν (cm^{-1}): 3293 (NH), 1608 (C=C), 1673 (C=O), 1563 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 5.67 (s, 1H, NH), 6.58 (s, 1H, CH), 7.16–7.96 (m, 14H, Ar-H).Anal. Calcd.for $C_{25}H_{16}N_6O_3S$ (480): C, 62.50; H, 3.33; N, 17.50; S, 6.66. Found: C, 62.13; H, 2.98; N, 17.13; S, 6.30 %.

2-[5,6-Diphenyl-1,2,4-triazin-3-ylimino]-6-(3-nitrophenyl) 3,6,7-trihydro-1,3-thiazolo[4,5-c]isoxazole (23)

A mixture of 22 (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) was taken in absolute ethanol (20 cm^3) and two drops of KOH (2 %) were added slowly to the solution. It was refluxed for 12 h. The reaction mixture was kept overnight and then the solution was poured into water. The resulting solid was filtered off, dried and recrystallized from EtOH.Yield 53 %. M.p.: 213–215 ^{o}C. FT-IR, ν (cm^{-1}): 3301 (NH), 1617, 1591 (2, C=N), 1075 (C – O), 900 (N–O), 770 (C–Cl). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.30 (d, 1H, CH_b), 4.36 (d, 1H, CH_a), 6.51 (s, 1H, NH), 7.16 – 8.25 (m, 14H, Ar-H). Ms (m/z, I %): 495(M, 11%), 318 (16), 317 (7.), 303 (5.), 203 (13), 191(6), 192 (5), 178 (100).Anal. Calcd.for $C_{25}H_{17}N_7O_3S$ (495): C, 60.60; H, 3.43; N, 19.79; S, 6.46. Found: C, 60.31; H, 3.06; N, 19.42; S, 6.09 %.

2-[5,6-Diphenyl-1,2,4-triazin-3-ylimino]-6-(3-nitrophenyl) 3,5,6,7-tetrahydro-1,3-thiazolo[4,5-c]pyrazole (24)

A mixture of 22 (0.01 mol) and hydrazine hydrate (0.01 mol) were dissolved in ethanol (20 cm^3). After the addition of two drops of pyridine, the reaction mixture was refluxed for 16 h. After evaporating the excess solvent, it was cooled and poured into ice-cold water. The solid obtained was filtered off, dried and recrystallized from EtOH.Yield 64 %. M.p.: 191–193 ^{o}C. FT-IR, ν (cm^{-1}): 3320, 3293 (2NH), 1626, 1568 (2C=N), 770 (C-Cl), 712(C-S-C). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.45 (d, 1H, CH_b), 4.67 (d, 1H, CH_a), 5.56 (s, 1H, NH), 6.48 (s, 1H, NH), 7.22 –8.25 (m, 14H, Ar-H), Ms (m/z, I %) : 495 (M +1, 12%), 392 (21), 330 (7), 316 (22), 269 (21), 254 (2), 178 (100), 115 (7).Anal. Calcd. For $C_{25}H_{18}N_8O_2S$ (494): C, 60.72; H, 3.25; N, 22.67; S, 6.47. Found: C, 60.34; H, 3.64; N, 22.37; S, 6.20 %.

2-[(5,6-Diphenyl-1,2,4-triazin-3-ylimino]-7-(3-nitrophenyl) -6,7,8-trihydro-1,3-thiazolo[4,5-d]pyrimidine-5-(6H) one (25)

A mixture of 2 (0.01 mol) and urea (0.01 mol) in ethanol (20 cm^3) with a trace of acetic acid (0.5 ml) was refluxed for 17 h. After cooling the reaction mixture was neutralized with 5% NaOH solution. The solid that separated out was filtered off, washed several times with water and recrystallized from acetic acid.Yield 63 %. M.p.: 204–206 ^{o}C. FT-IR, ν (cm^{-1}): 3293, 3183 (2, NH), 1667 (C=O), 1556 (2C=N), 747 (C – Cl), 710 (C – S – C). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.50 (d, 1H, CH_b), 4.56 (d, 1H, CH_a), 5.98 (s, 1H, NH), 6.45 (s, 1H, = CH), 7.15 – 7.98 (m,14H, Ar-H), 9.32 (s, 1H, CONH), Ms (m/z, I %): 522 (M, 11%).344 (23), 330 (5), 298 (19), 178 (100), 176 (8), 144 (6), 141 (3).Anal. Calcd.for $C_{26}H_{18}N_8O_3S$ (522): C, 59.77; H, 3.44; N, 21.45; S, 6.13. Found: C, 59.40; H, 3.17; N, 21.17; S, 5.86 %.

2-[(5,6-Diphenyl-1,2,4-triazin-3-ylimino]-7-(3-nitrophenyl) -6,7,8-trihydro[1,3]thiazolo[4,5-d]pyrimidine-5-(6H) thione (26)

A mixture of 22 (0.01 mol) and thiourea (0.01 mol) in ethanol (20 cm^3) with a trace of acetic acid (0.5 ml) was refluxed for 17 h. The solid that separated out was filtered off, washed several times with water and recrystallized from acetic acid.Yield 63 %. M.p.: 215–217 ^{o}C. FT-IR, ν (cm^{-1}): 3330, 3212 (2NH), 1617, 1589 (2C=N), 1235 (C=S), 762 (C–Cl). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.4 (d, 1H, CH_b), 4.50 (d, 1H, CH_a), 5.96 (s, 1H, NH), 6.98 – 7.89 (m, 14H, Ar-H), 8.49 (s, 1H, NH). Ms (m/z, I %): 539 (M +1, 11%). 384 (3), 370 (4), 350 (8), 347 (3), 335 (5), 178 (100), 143(5). Anal. Calcd. for $C_{26}H_{18}N_8O_2S_2$ (538): C, 57.99; H, 3.34; N, 20.81; S, 5.94. Found: C, 57.75; H, 2.97; N, 20.44; S, 5.70 %.

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Graphical Abstract

A series of some new 1,2,4-triazines aryl derivatives containing isoxazoles, pyrimidines, pyrazoles and imidazoles moieties was synthesized and screened for their antimicrobial activity against bacterial and fungal strain. The results suggest that some of these compound to be potent antimicrobial agents.