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Regioselective Green Synthesis and Antimicrobial properties of full fused non mixed Heterocyclic Systems

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ABSTRACT

One pot synthesis and reaction of triazinthione and triazinohydrazide derivatives with different electrophilic reagents in ordered to synthesis of some interesting non-mixed heterocyclic compounds. Structures of thiazolotriazine, triazolotriazine, pyrimidinyltriazine, and triazinotriazine derivatives were established via spectroscopic data and elemental analysis. The synthesized compounds were screened for their antimicrobial activity.

KEYWORDS: 1,2,4-Triazine, thiazole, arylidine pyrimidine, pyrazine, grinding, green organic synthesis

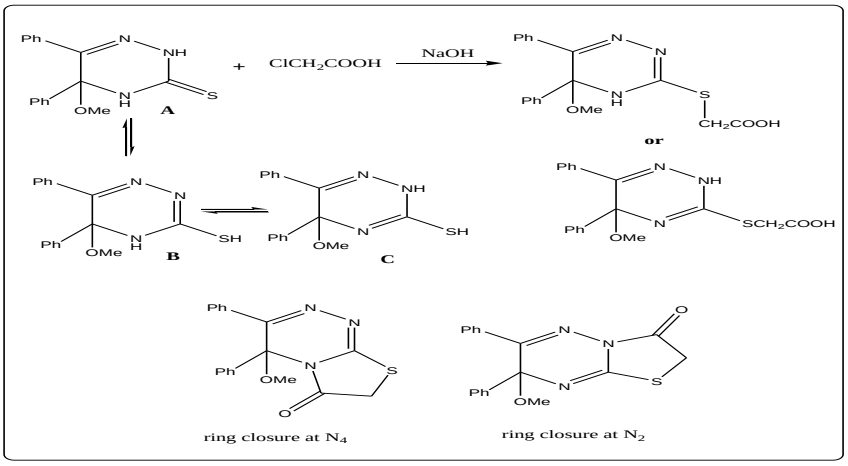
INTRODUCTION

Presently, green chemistry is a pro-active approach to pollution prevention. Additionally, enhancing the efficiency of organic synthesis, lowering the consumption of chemicals. Green Chemistry is designing chemical products and processes that reduce time, chemical, solvents, reduced hazards and obtaining heterocyclic compounds from simple starting materials which are fundamental goals in organic synthesis[1-5]. Grinding considered as simplest green chemistry protocol which has proven to be an efficient, economical and environmentally benign process. 1,2,4-Triazines play an essential task in various biological routes and in synthesis of drugs. Therefore, a lot of heterocyclic systems attitude 1,2,4-triazines are found to have significant pharmacological effects[6-13]. That targets have anti-AIDS[14,15], antiviral[16], anticancer[17-20], antimicrobial[21-24], antitumor[25], antithelmintic drugs[26]. The nature of substituent in 1,2,4-triazines have prompt affect on the orientation of cyclization reaction[27], so that the substituted at position 6 of 3-hydrazino-5-hydroxy-1,2,4-triazine effect on the orientation of cyclization to form 1,2,4-triazolo[1,2,4]triazines. When the substituent was an electron with drawing group, 1,2,4-triazolo[3,4-c][1,2,4]triazines were created in neutral or acidic medium, while, when substituted was an electron donating group and the reagent was acidic 1,2,4-triazolo[4,3-b][1,2,4]triazines were produced.

MATERIAL AND METHODS

Chemistry

This work deals with regiospecificity alkylation of compound **1**[28,29] which has two nucleophilic center NH or SH and present in three isomers **A, B, C** (Scheme 1). Thus, the triazinthione derivatives **1** was allowed to react with a variety of α,β-bifunctional halogen compounds (e.g. choloroacetic acid). Initially, the sulphur of the triazinthione attacks the more reactive center in the, β-bifunctional halogen compounds, followed by ring closure. The closure takes place at N_4 rather N_2, this is due to the product obtained via ring closure at N_4 is more thermodynamically stable than that obtained via ring closure at N_2. This presented on (Scheme 1) and the sole product obtained is 5,6-diphenyl-5-methoxythiazolo[2,3C]-4,5-dihydro[1,2,4]triazine and not the isomer 5,6-diphenyl-5-methoxytthiazolo[3,2C]-4,5-dihydro[1,2,4]triazine (Scheme 1).

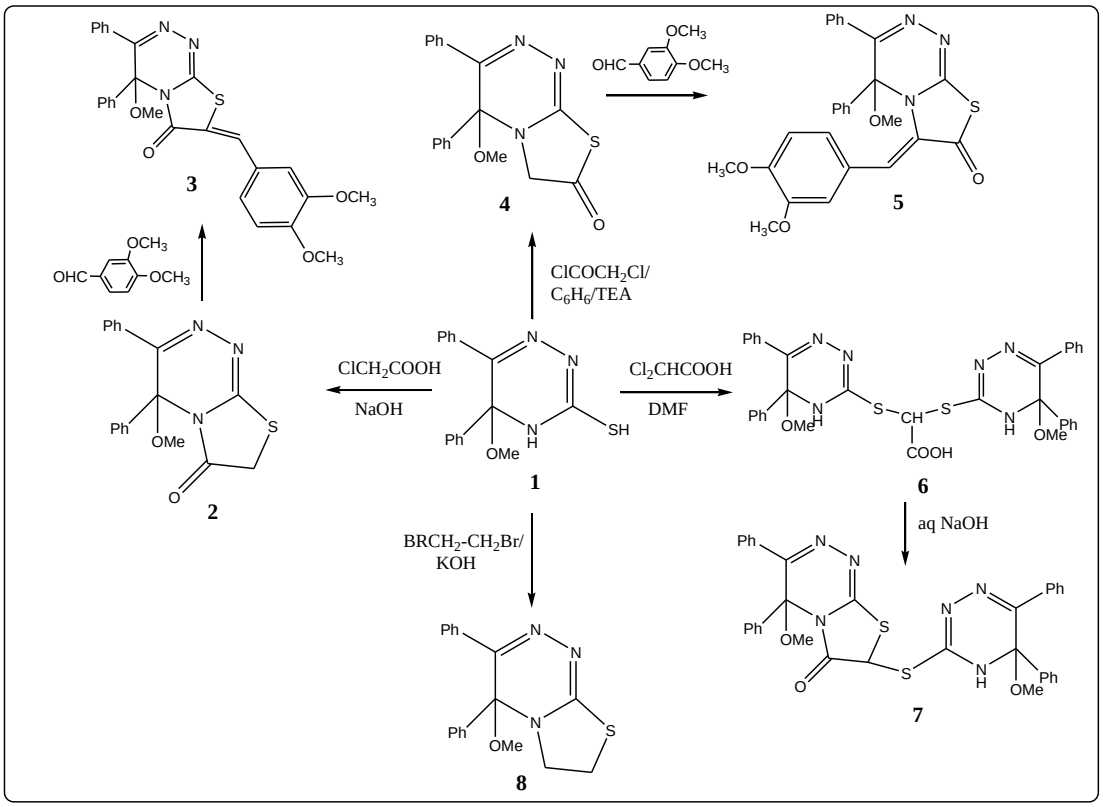


Scheme 1

The activities of the thioamide and iminothiol tautomers based on their thermodynamic and kinetic control under experimental conditions have been explained[4]. The conjugate base of the iminothiol tautomer has been found to be thermodynamically more stable than the conjugate base of the thioamide tautomer (basicity is thermodynamic control) due to back donation involving the vacant d-orbital of the sulfur atom. Further, the sulphur anion is strong nucleophile than the nitrogen anion (the nucleophilicity is kinetically controlling). Thus, the iminothiol tautomer is kinetically more stable or more reactive than the thioamide tautomer. Thus, under the experimental conditions used the iminothiol tautomer is more

thermodynamically and kinetically favored than the thioamide tautomer, which practically spells out the reactivity of the iminothiol tautomer.

Interaction of compound **2** with 3,4-dimethyl benzaldehyde in boiling acetic acid yielded the corresponding benzylidene derivative **3** (Scheme 2).



Scheme 2

When compound **1** was allowed to react with choloroacetyl choloride in warming benzene in the presence of TEA(triethyl amine) afforded 4,5-dihydro-5,6-diphenyl-5-methoxy-5-oxothiazolo[2,3-C][1,2,4]triazine **4**.

The reaction takes place via nucleophilic substitution of sulphur anion on acyl moiety of choloracetyl chloride through tetrahedral mechanism [T.H.M] in which the S-C bond is formed before C-Cl bond is broken and the energy evolved accumulate in the reaction medium and enhance the rate of the reaction followed by intrabimolecular nucleophilic substitution by lone pair of nitrogen atom on the alkyl moiety to afford compound **4**.

The structure of compound **4** was proved chemically via its interaction with 3,4-dimethoxy benzaldehyde in acetic acid and yielded the benzylidene derivative 5. When compound **1** was allowed to react with dicholoro acetic acid in DMF (2:1 mole respectively), produced 1,1-(diarylthia)-acetic acid **6** which under goes cyclization producing 5-(5-methoxy-5,6-diphenyl-1,2,4-triazin-3-thiaryl)-4,5-dihdro-5-methoxy-5,6-diphenyl-4-oxothiazolo[2,3-C][1,2,4]triazine **7**. Where the sulphur nucleophile attacks the dicholoro acetic acid via bimolecular nucleophilic substitution SN^2 affording the biscompound **6**, which undergoes intramolecular nucleophilic displacement by lone pair of sp^3 hybridized nitrogen to give the cyclized product **7**, (Scheme 3).

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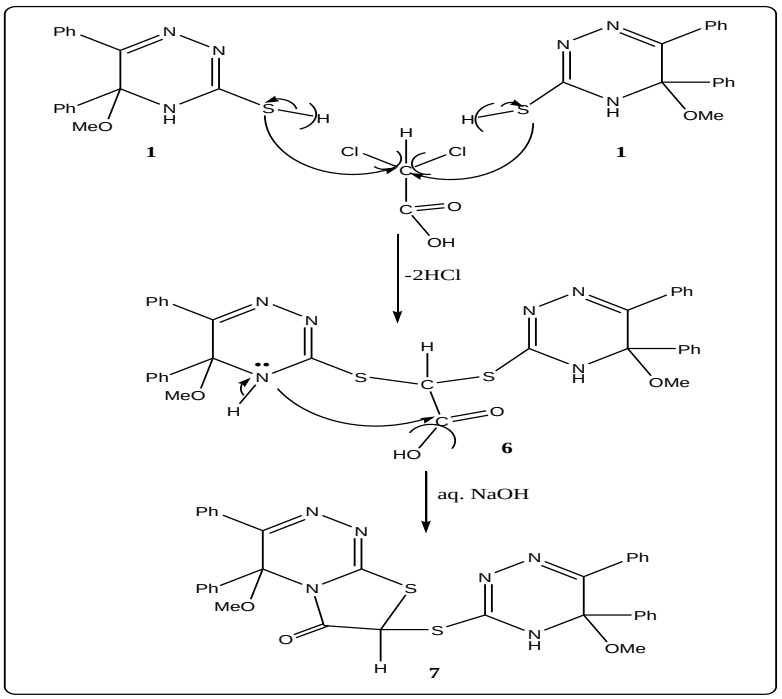
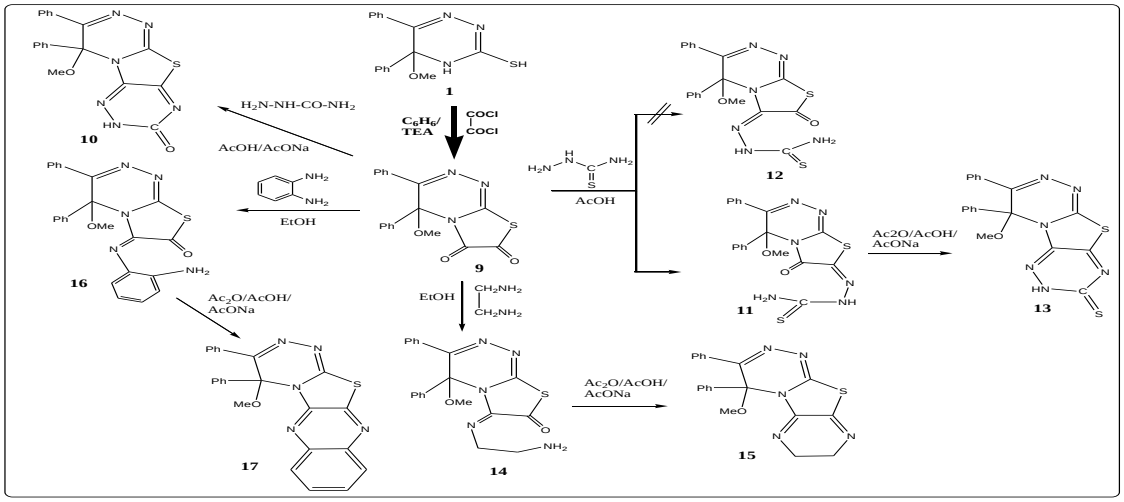
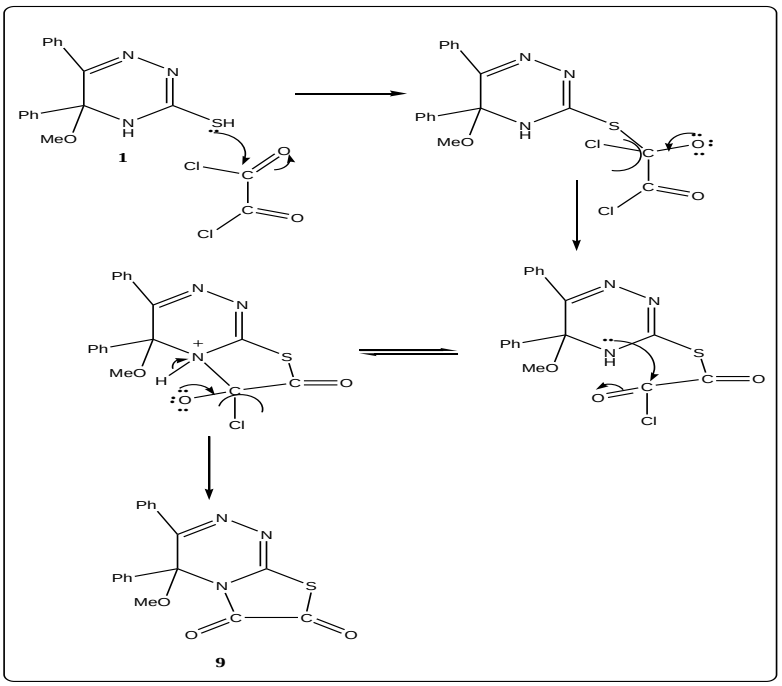


Scheme 3

Interaction of compound 1 with 1,2-dibromoethane in ethanolic KOH afforded 4,5-dihydro-5-methoxy-5,6-diphenyl thiazolo[2,3-C][1,2,4]triazine B. When compound **1** was allowed to react with oxoloyl choloride in dry benzene / TEA yielded 5-methoxy-5,6-diphenyl-4,5-dioxo thiazolo[2,3-C][1,2,4] triazine **9** (Scheme 4), where the reaction of **1** with oxaloyl chloride takes place via tetrahedral mechanism, in which the S-C bond was formed between SH and carbonyl group before C-Cl bonds which started to break and consequently a lot of energy is accumulated in the reaction medium which decreases the activation energy of the reaction and a facile conversion was occurred. The energy barrier that hampers, the reaction is lowered when the reaction proceeds through anions (I and II) for along such a route the system receives much of its (energy payment) from the formation of the new bonds (S-C=O, N-C=O) before having to pay its (energy dept) for the breakage of the C-Cl (Scheme 5).



Scheme 4



Scheme 5

Compound **9** used as key starting material for the building of annulated heterocyclic systems. Thus, interaction of compound **9** with semicarbazide hydrocholoride in glacial acetic acid and in the sodium acetate, yield 3-oxo-1,2,4-triazino[6-5-d]thiazolo[2,3-C][1,2,4]triazine **10**.

On the other hand, compound **9** has been reacted with thiosemicarbazide in boiling glacial acetic acid and yields the thiosemicarbazone derivative **11** and not the isomeric form **12**. Treatment of compound **11** with acetic anhydride and fused sodium acetate, yielded 1,2,4-triazinon thiazolo-triazinthione **13**.

The isomeric **11** is formed and not **12**, this is due to the carboxyl group adjacent to NH, is less reactive because mesmerism occurs between C=O and NH is more predominate than mesmerism between C=O and S (in first case, overlap between 2p of nitrogen with 2p of carbon of carbonyl, which is effective overlap and deactivated the carbonyl group while, in second case overlap occurs between 3p of sulphur and 2p of carbon less effective overlap and activate carbonyl group).

Interaction of dicarbonyl compound **9** with ethylene diamine in boiling ethanol yielded the condensed product **4**, which yielded pyrazino[2,3-C]1,2,4-triazine derivative **15**, when the reaction conducted in boiling glacial acetic acid in the presence of anhydrous sodium acetate.

Similarly, the dicarbonyl compound **9** condensed with o-phenylenediamine in boiling ethanol and yielded the condensed product **16** and when the reaction carried out in boiling glacial acetic acid in the presence of fused sodium acetate yielded benzopyrazino[2,3-d]thiazolo[2,3-C]-1,2,4-triazine.

All data of compounds **1-17** are in Table 1.

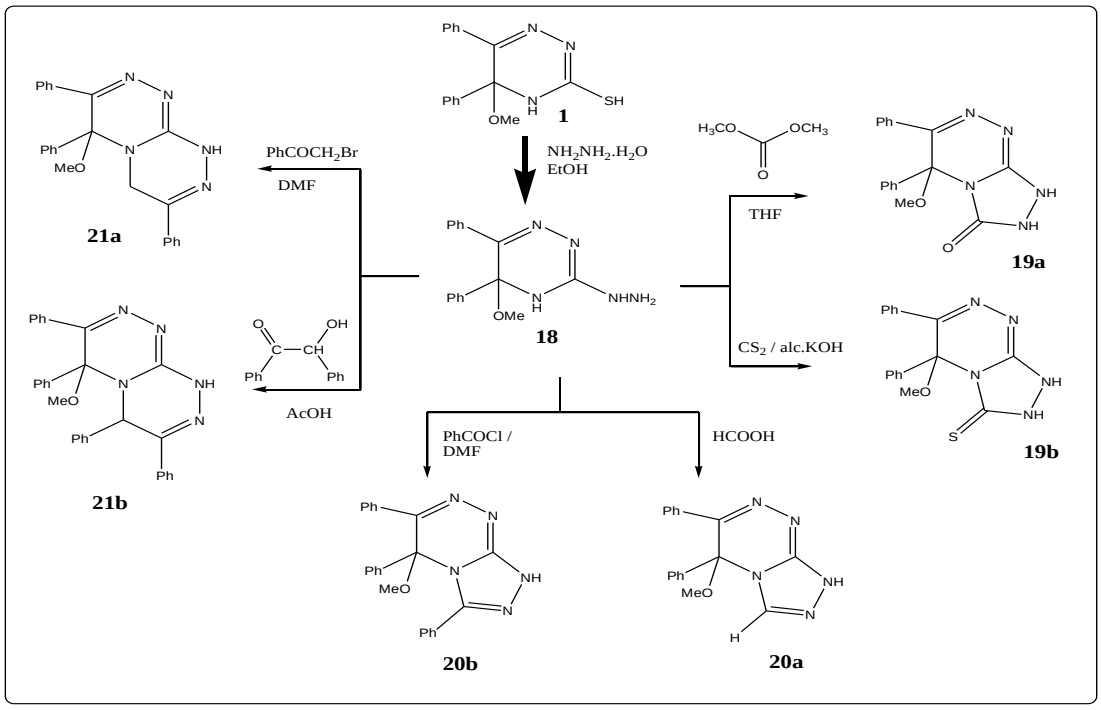
Table 1: Data of the compounds 1-17

No.	Time		Solvent of crystallization	m.p.^{0}C	Yield%		U.V.data	
	T(hrs)	G(min.)			T	G	λ_{max}	Abs.
1	8	10	DMF	232-3	80	56	311	1.9
							214	1.6
2	6	4	MeOH	191-2	97	85	-	-
3	4	3	DMF	182-4	95	74	306	1.0
							209	1.3

4	6	3	MeOH	202-4	81	80	-	-
5	4	3	DMF	177-9	80	87	306	0.5
							252	0.6
							208	1.0
6	2	7	DMF	90-2	64	65	-	-
7	4	4	DMF	190-3	61	45	-	-
8	2	3	DMF	118-0	80	72	-	-
9	4	4	DMF	209-1	83	69	-	-
10	6	5	MeOH	190-2	66	75	-	-
11	2	3	MeOH	188-0	74	84	-	-
13	4	3	MeOH	112-4	67	54	-	-
14	3	3	EtOH	156-7	84	64	-	-
15	6	6	MeOH	144-5	59	72	-	-
16	2	2	EtOH	198-9	86	82	-	-
17	4	2	MeOH	122-3	60	74	-	-

T = traditional, G = grinding, Abs.= absorpance

Hydrazinolysis of **1** afforded the corresponding 3-hydrazino-derivative **18** which used for synthesis of some more bioactive fused and/or isolated nitrogen heterobicyclic systems via ring closure reactions with α,β-bifunctional halogen and oxygen compounds in view of their biocidal effects (Scheme 6).



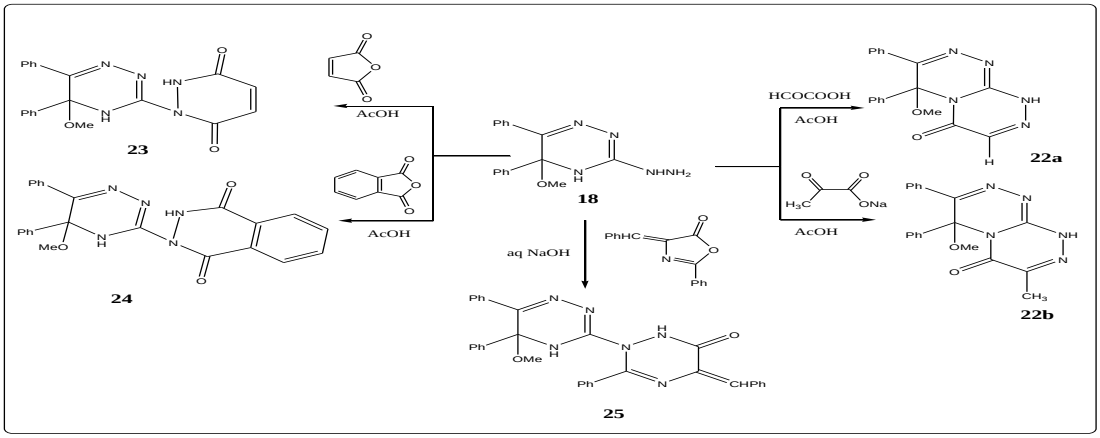
Scheme 6

Treatment of compound **18** with dimethyl carbonate in THF and/or with carbon disulphide in alcoholic potassium hydroxide afforded 5,6-diphenyl-1,2-dihydro-3-oxo/thioxo-5-methoxy-1,2,4-triazolo [3,4-c] [1,2,4]triazines **19a,b**, respectively (Scheme 6).

Reaction of compound **18** with formic acid and/or with benzoyl chloride in DMF produced the triazolo-triazines **20a,b**, respectively (Scheme 6).

Some new 1,2,4-triazino[3,4-c][1,2,4]triazine **21a,b** have been isolated from reaction of compound **18** with phenacyl bromide in DMF and/or with benzoin in glacial acetic acid, respectively (Scheme 6).

1H-3-Un/substituted-4-oxo-6-methoxy-6,7-diphenyl-1,2,4-triazino[3,4-c][1,2,4]-triazines **22a,b** were synthesized from cyclocondensation of compound **18** with glyoxalic acid and/or sodium pyruvate in glacial acetic acid , respectively (Scheme 7).

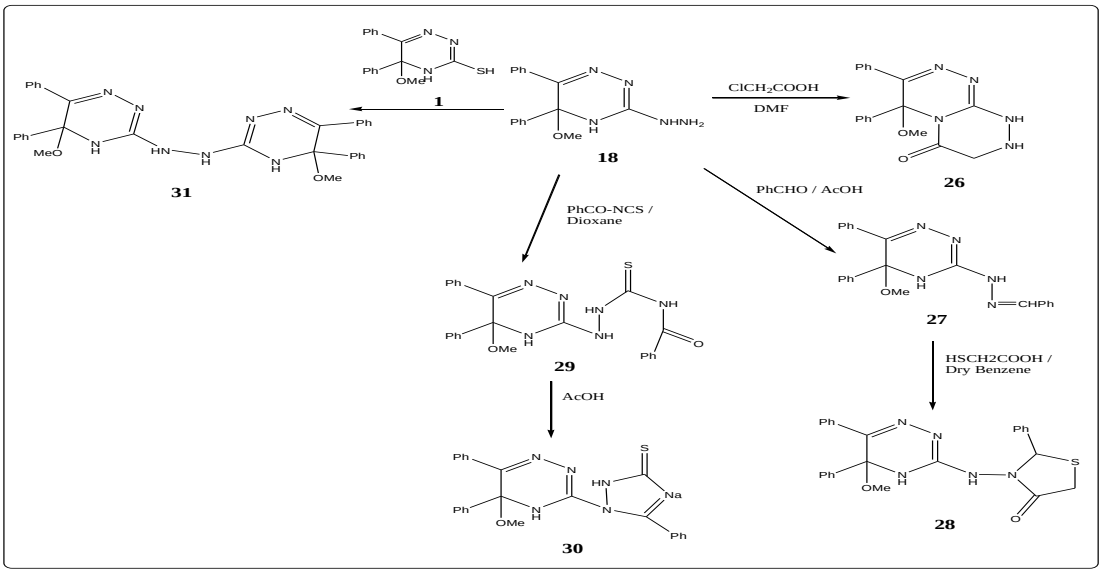


Scheme 7

Cyclocondensation of **18** with maleic and phthalic anhydride in glacial acetic acid afforded the pyrazidinyl **23** and phthalazinyl **24**, respectively (Scheme 7).

While, reaction of compound **18** with oxazolone in aqeuos sodium hydroxide was afforded a triazinyl triazine **25** (Scheme 7).

Perhydro 1,2,4-triazino[3,4-c][1,2,4]triazine **26** was obtained from alkylation of compound **18** with monochloroacetic acid in DMF (Scheme 8).



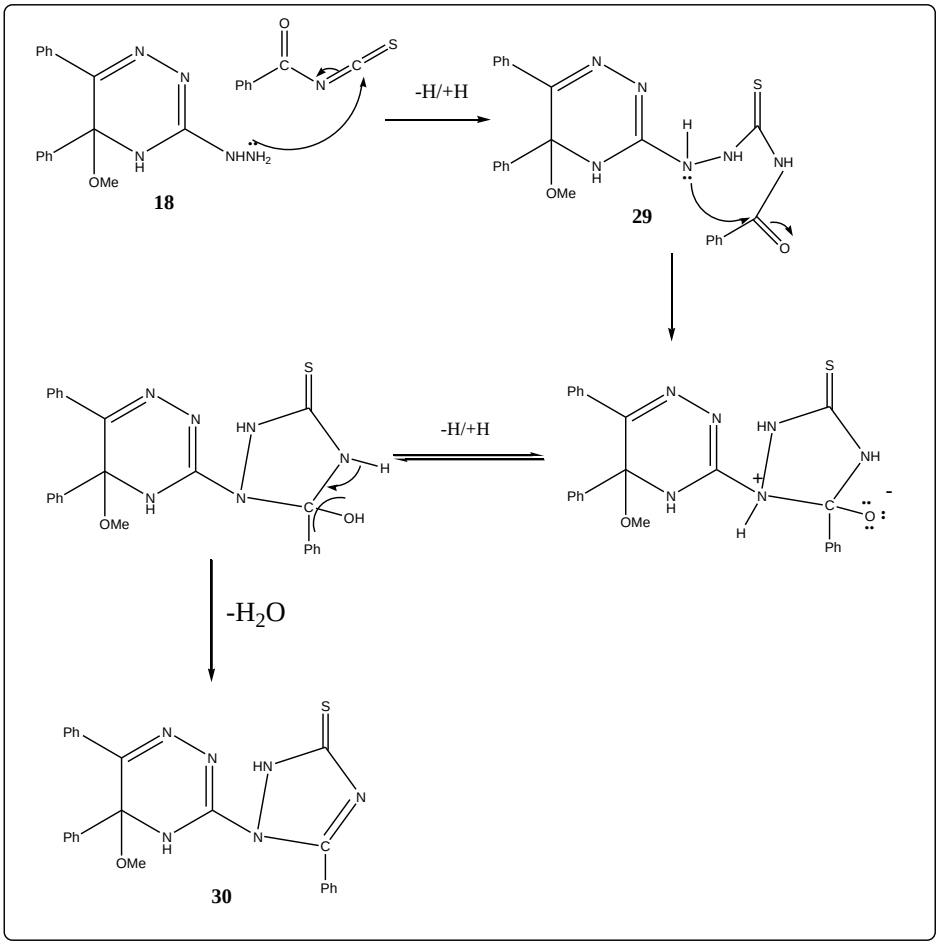
Scheme 8

Synthetic of isolated heterobicyclic systems, to achieve a better biologically active, is one of the main aims of the present work. Thus, condensation of compound **18** with benzaldehyde produced the hydrazone **27**, which reacted with mercaptoacetic acid via cycloaddition to give 3-(4-thioxo-2-phenylthiazolidin-3-yl)amino-5-methoxy-5,6-diphenyl-4,5-dihydro-1,2,4-triazine **28** (Scheme 8).

On the other hand, addition of compound **18** to benzoyl isothiocyanate in dry solvent such as dioxane, yielded **29**, which underwent ring closure, to yield 3-(2H-3-thioxo-5-phenyl-1,2,4-triazol-1-yl)-4,5- dihydro -5- methoxy -5,6- diphenyl -1,2,4-triazine **30** (Scheme 8). In that mechanism, the author offer a speculation to explain why nitrogen nucleophile of hydrazine moiety attacked carbon atom of N=C=S and not carbon atom of carbonyl group of benzoyl moiety. The state of

hybridization of carbon N=C=S is sp hybridized (more electronegativity and easily accept nucleophile), while state of hybridization of carbon of carbonyl group is sp^2 which (less electronegativity and accept nucleophile more difficult) (Scheme 9).

A simple nucleophile displacement of mercapto group is compound **1**, which upon reaction of **1** with a good nucleophile hydrazine derivative **18** afforded the bis compound **31** (Scheme 8).



Scheme 9

All data of compounds 18-31 are in Table 2.

Table 2: Data of the compounds 18-31

No.	Time		Solvent of crystallization	m.p.^{0}C	Yield%		U.V.data	
	T(hrs)	G(min.)			T	G	λ_{max}	Abs.
18	6	4	EtOH	160-2	90	84	-	-
19a	4	4	EtOH	85-6	81	74	-	-
19b	4	3	EtOH	70-2	79	54	-	-
20a	4	4	DMF	143-5	97	89	-	-
20b	4	5	DMF	150-1	66	70	-	-
21a	4	6	DMF	177-8	72	65	-	-
21b	4	3	DMF	191-3	70	75	-	-

22a	4	3	EtOH	125-7	57	69	-	-
22b	6	3	EtOH	138-9	60	61	-	-
23	4	3	DMF	173-5	70	65	-	-
24	4	2	DMF	187-9	82	84	-	-
25	6	4	DMF	198-0-5	53	41	-	-
26	6	4	DMF	112-7	59	64	-	-
27	4	4	DMF	134-0	75	78	-	-
28	10	4	DMF	219-6	57	78	402	0.175
							314	2.395
							269	1.212
							254	1.161
							218	1.822
29	6	4	DMF	214-5	75	65	-	-
30	4	4	DMF	232-9	90	87	-	-
31	6	4	DMF	247	85	87	-	-

T = traditional, G = grinding, Abs.= absorpance

Antimicrobial Activity

The standardized disc-agar diffusion method[30] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphylococcus aureus* (ATCC 25923) and *Streptococcus pyogenes* (ATCC 19615) as Gram - positive bacteria, *Pseudomonas fluorescens* (S 97) and *Pseudomomas phaseolicola* (GSPB 2828) as Gram-negative bacteria and the fungi *Fusarium oxysporum* and *Aspergillus fumigatus*.

The antibiotic chloramphencol was used as standard reference in the case of Gram- negative bacteria, Cephalothin was used as standard reference in the case of Gram – positive bacteria and cicloheximide was used as standard antifugal reference.

The tested compounds were dissolved in DMF [di methyl formamide] (which has no inhibition activity) to get concentration of 2mg/ml and 1mg/ml. The test was performed on medium potato dextrose agar (PDA) which contain infusion of 200g potatoes, 6g dextrose and 15g agar[31].

Uniform size filter paper disks (in triplicate) were impregnated by equal volume (10µL) from the specific concentration of dissolved tested compounds and carefully placed on inoculated agar surface. After incubation for 36h at 37 ^{0}C in the case of bacteria and for 3-5 days at 25-29 ^{0}C in case of fungi inhibition of the organisms which evidenced by clear zone surround each disk was measured and used to calculate mean of inhibition zones (Table 3).

The activity of tested compounds was categorized as follows:

Low activity = Mean of zone diameter ≤ 1/3 of mean zone diameter of contril.

Intermediate activity = Mean of zone diameter ≤ 2/3 of mean zone diameter of contril.

High activity = Mean of zone diameter > 2/3 of mean zone diameter of contril.

Table 3: The antimicrobial activity of some prepared compounds:

Organism	Gram-positive				Gram-negative				Fungi			
	Staph.aur (ATCC 25923)		***Strepto.pyo. (ATCC 19615)***		***Pseudo.phas. (GSPB 2828)***		***Pseudo.flur. (S 97)***		***Fusar.oxys.***		***Asper.fum.***	
Consent	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Sample	2mg	1mg	2mg	1mg	2mg	1mg	2m	1mg	2m	1mg	2m	1mg

	/ml	/ml	/ml	/ml	/ml	/ml	g /ml	/ml	g /ml	/ml	g /ml	/ml
1	24,I	15,I	17,I	10,L	0.6,L	0.4,L	-	-				
2	20,I	14,I	14,I	0.8, L	-	-	-	-	-	-	-	-
3	30,H	22,H	20,I	14,I	-	0.8,L	16,I	0.9,L	-	-	-	-
4	14,L	0.9, L	17,I	10,L	12,L	-	-	-	-	-	-	-
5	20,I	15,I	22,I	10,L	0.9,L	0.5,L	-	-	-	-	-	-
6	0.9,L	0.4, L	-	16,I	-	-	-	-	-	-	-	-
9	13,L	0.8, L	0.8,L	-	-	-	-	-	-	-	-	-
10	15,L	0.9, L	14,I	0.5, L	-	-	-	-	-	-	-	-
13	0.9,L	0.4, L	0.7,L	10,L	-	-	-	-	-	-	-	-
17	0.8,L	0.4, L	-	0.3, L	-	-	-	-	-	-	-	-
18	40,H	29,H	37,H	25,H	-	-	-	-	-	-	-	-
19b	25,I	17,I	27,H	18,I	-	-	-	-	-	-	-	-
23	20,I	12,I	23,I	12,I	-	-	-	-	-	-	-	-
25	22,I	12,I	20,I	14,I	-	-	-	-	-	-	-	-
27	30,H	-16,I	30,H	19,I	-	-	-	-	-	-	-	-
28	20,I	11,I	15,I	10,I	-	-	-	-	-	-	-	-
30	-	-	-	-	-	-	-	-	-	-	-	-
31	15,I	7,L	12,L	5,L	-	-	-	-	-	-	-	-
Control#	42	28	38	30	36	25	38	30	40	28	40	31

Conclusion

From the results in Table 3, we can be concluded that:

i) All the tested compounds did not active towards both the Gram – negative bacteria *Pseudomonas fluorescens* (S 97) and *Pseudomomas phaseolicola* (GSPB 2828) and the fungi *Fusarium oxysporum* and *Aspergillus fumigatus*.

ii) All the tested compounds exhibited a degree of activity towards *Staphylococcus aureus* (ATCC 25923) and *Streptococcus pyogenes* (ATCC 19615) as Gram - positive bacteria

iii) The compound **3** exhibit a highly effect towards positive bacteria *Staphylococcus aureus* at two concentrations used, in comparison with Chloamphenicol as stander. The more electron delocalization properties of compound **3** increase those effects on the tested organisms via interaction between the vital concentrations of both.

iv) Also the compounds **18**, **27** recorded a highly activity in compare with used control-especially at 2mg/ml towards (Gram- positive bacteria).

v) A highly activity of compound **18** is due to presence of hydrazine group.

Experimental:

All material was obtained from commercial suppliers. Melting points are uncorrected. All reactions were monitored by thin-layer chromatography (TLC). IR spectra in KBr were recorded on Shimadzu 8201FT spectrometer (**υ**cm^{-1}), ^{1}HNMR were recorded on a Varian EM-NMR spectrophotometer 300MHz and TMS as initial reference (δ_{ppm}) and EIMS recorded on a gas chromatographic GCMPS 9P1000ex Shimadzu instrument at 70 eV.:

General method for grinding:

Mixed all reactants (in small scale) as one pot reaction in mortar and pestle then grinded them till reaction was finished (followed the reaction by TLC) and recorded the time.

2,3,4,5-Tetrahydro-5-methoxy-5,6-diphenyl-3-thioxo-1,2,4-triazine 1 has been prepared according to reported procedure[23,24,32-34].:

Also, in one pot reaction, mixture of benzil (0.01mol) and thiosemicarbazide(0.01mol) in presence of sodium methoxide MW (microwave irradiation) gave 1,2,4-triazine **1**, m.p = 232-3 ^{0}C, IR (v cm^{-1}); 3180 (NH),1550 (C=N) . ^{1}HNMR (DMSO-d_6), δ ppm, (*J*, Hz): 4.76 (m, 3H, OCH_3), 7.59–8.33(m, 10H, ArH), 11.32(bs, 2H, 2NH that exchangeable in D_2O). MS (m/e); M^+ at 297 and M^{+1} at 298. Anal. Calcd for $C_{16}H_{15}N_3OS$ (297.3): C, 64.62; H, 5.08; N, 14.13; S, 10.78. Found C, 63.99; H, 4.98; N, 14.00; S, 10.54%.

5-Methoxy-5,6-diphenyl-4,5-dihydro-5-oxothiazolo[2,3-c][1,2,4]triazine 2:

A mixture of triazine **1** (0.01mol) and choloroacetic acid (0.01mol) in aqueous sodium hydroxide (10%, 50mL), was refluxed for 6hs, the reaction mixture after cooling was poured on dilute hydrochloric acid, The solid that separated was filtered off and crystallized from the proper solvent m.p = 191-2 ^{0}C. IR (v cm^{-1}); 1670 (C=O), 1534 (C=N).^{1}HNMR ($CDCl_3$) **(**$\delta\delta_{ppm}$**)**: 2.14 (s, 2H, CH_2), 3.42 (S, 3H, OCH_3), 6.7-7.8 (m, 10H, Ar-H). MS (m/e); (M^+- OCH_3) at 265 and 220, base peak at 178. Anal. Calcd for $C_{18}H_{15}N_3O_2S$ (337): C, 64.09; H, 4.45; N, 12.46; S, 9.49. Found C, 64.38; H, 4.13; N, 12.20; S, 9.21%.

2-(3,4-dimethoxy benzylidene)-4,5-dihydro- 5- methoxy- 5,6 –diphenylthiazolo [2,3-c][1,2,4]triazine 3:

A mixture of triazine derivative **2** (0.01mol) and 3,4-dimethoxybenzaldehyde (0.01mol) in glacial acetic acid (50mL) was heated under reflux for 4hrs, after cooling, the reaction mixture was diluted by ice and water. The solid that separated was filtered and crystallized from the proper solvent to give **3**. m.p = 182-4 ^{0}C, ^{1}HNMR ($CDCl_3$) **(**δ_{ppm}**)**: 3.19, 3.43, 3.66 (s, 3OCH_3 groups), 5.9 (s, 1H, olefinic proton), 7.25-7.52 (m, 13H, Ar-H). Anal. Calcd for $C_{27}H_{23}N_3O_4S$ (485): C, 66.80; H, 4.74; N, 8.66; S, 6.59. Found C; 65.92; H, 4.50; N, 8.32; S, 6.31%.

5-Methoxy-5,6-diphenyl-4,5-dihydro-3-oxothiazolo[2,3-c][1,2,4]triazine 4:

A mixture of triazine derivative **1** (0.01mol) and choloroacetyl chloride (0.01mol) in dry benzene (50mL) and drops TEA (triethyl amine) was heated under reflux for 6hrs. The solid that separated after cooling was filtered off and crystallized from the proper solvent to give **4**, m.p = 202-4 ^{0}C. IR (v cm^{-1}); .1723 (C=O), 1533 (C=N). ^{1}HNMR (DMSO), (δ ppm): 4.1(s, 3H, OCH_3), 4.43 (s, 2H, CH_2), 7.62-8.41 (m, 10H, Ar-H). Anal. Calcd for $C_{18}H_{15}N_3O_2S$ (337): C, 64.09; H, 4.45; N, 12.46; S, 9.49. Found C, 64.00; H, 4.46; N, 12.50; S, 9.00%

5-Methoxy-5,6-diphenyl-4,5-dihydro[4-(3,4-dimethoxybenzylidene)-5-oxothiazolo] [2,3-c][1,2,4]triazine 5:

A mixture of triazine derivative **4** (0.01mol) and 3,4-dimethoxybenzaldehyde (0.01mol) in glacial acetic acid (50mL) was heated under reflux for 4hrs, the reaction mixture was cooled and diluted with ice/H_2O. The solid that separated was filtered and crystallized from the proper solvent to give **5**, m.p. = 177-9 ^{0}C. ^{1}H-NMR (DMSO) (δppm): 3.52-3.74 (s, 3OCH_3 groups), 6.2 (s, 1H, olefinic proton), 6.9-7.7 (m, 13H, Ar-H). MS (m/e); (M^+-3OCH_3) at 393 and 265, 178 (base peak). Anal. Calcd for $C_{27}H_{23}N_3O_4S$ (485): C, 66.80; H, 4.74; N, 8.66; S, 6.59. Found C, 66.64; H, 4.52; N, 8.51; S, 6.20%

Bis(thiatriazin-3-yl) acetic acid 6:

A mixture of triazine derivative **1** (0.02mol) and 1,1-dichloro acetic acid (0.01mol) in DMF (50mL) was refluxed for 2hrs, the reaction mixture after cooling was diluted with water, the solid was obtained, and crystallized from suitable solvent to yield **6**, , m.p = 90-2 ^{0}C. IR (v cm^{-1}); 3421 (OH), 3122 (NH), 1680 (C=O). ^{1}HNMR (DMSO),(δ ppm): 2.44(s, 6H, OCH_3), 4.20(s, 1H, methine proton), 6.9-7.8 (m, 20H, Ar-H), 8.3(s, 1H, COOH exchangeable with D_2O), 9.80(s, 2H, 2NH exchangeable with D_2O)..Anal. Calcd for $C_{34}H_{30}N_6O_4S_2$ (650): C, 62.77; H, 4.62; N, 12.92; S, 9.85. Found C, 62.44; H, 4.55; N, 12.73; S, 9.55%

2-(5-methoxy-5,6-diphenyl-4,5-dihydro-3-thiayl)-4,5-dihydro-5-methoxy-5,6-diphenyl-5-oxothiazolo[2,3-c][1,2,4]triazine 7:

A mixture of bis compound **6** (0.01mol) and aqueous NaOH (5%, 50mL) was heated under reflux for 4hrs, after cooling, the reaction mixture was poured on dilute hydrochloric acid. The solid that obtained was crystallized to yield **7**, m.p = 190-3 ^{0}C. IR (v cm^{-1}); 3124 (NH) , 1720 (C=O). ^{1}H-NMR (DMSO), (δ ppm): 2.44(s, 6H, 2OCH_3), 4.7(s, 1H, methine proton), 6.9-7.8 (m, 20H, Ar-H), 9.80(s, 1H, 1NH exchangeable with D_2O). Anal. Calcd for $C_{34}H_{28}N_6O_3S_2$ (632): C, 64.56; H, 4.43; N, 13.29; S, 10.13. Found C, 64.36; H, 4.62; N, 13.01, S, 10.00%

4,5-Dihydro-5-methoxy-5,6-diphenyl-4,5-dihydro-thiazolo[2,3-c][1,2,4]triazine 8:

A mixture of triazine derivative **1** (0.01mol) and 1,2-dibromoethane (0.01mol) in alcoholic KOH (10%, 50mL) was heated under reflux for 2hrs, cooled then diluted with ice/HCl. The solid obtained was crystallized from suitable solvent to yield **8**, m.p = 118-0 ^{0}C. Its IR devoid any band for υ_{N-H}. ^{1}HNMR (DMSO), (δ ppm): 4.1(s, 3H, OCH_3), 3.7(t, 2H, CH_2S), 4.0(t, 2H, CH_2N), 7.65-8.31 (m, 10H, Ar-H). Anal. Calcd for $C_{18}H_{17}N_3OS$ (321): C, 66.87; H, 5.26; N, 13.00; S, 9.90. Found C, 66.50; H, 4.90; N, 13.33; S, 9.28%

4,5-Dihydro-5-methoxy-5,6-diphenyl-4,5-dioxothiazolo[2,3-c][1,2,4]triazine 9:

A mixture of triazine derivative **1** (0.01mol) and oxaloyl chloride (0.01mol) in dry benzene (50mL) in the presence of TEA (few drops) was heated under reflux for 4hrs, the solid obtained after cooling was filtered off and crystallized to give **9,** m.p = 209-1 ^{0}C. IR (v cm^{-1}); 1723 (C=O) and devoid any band for υ_{N-H}. ^{1}HNMR (DMSO), (δ ppm): 4.3(s, 3H, OCH_3), 7.61-8.33 (m, 10H, Ar-H). MS (m/e); M^+ - (OCH3, CO-CO) at 266 and 178 (base peak). Anal. Calcd for $C_{18}H_{13}N_3O_3S$ (351): C, 61.54; H, 3.70; N, 11.97; S, 9.12. Found C, 61.30; H, 4.00; N, 11.90; S, 8.98%

9-Methoxy-8,9-diphenyl-[1,2,4]triazino-[6,5-d]thiazolo-[2,3-c][1,2,4]triazin-3-one 10:

A mixture of **9** (0.01mol) and semicarbazide hydrochloride (0.01mol) in glacial acetic acid (50mL) and anhydrous sodium acetate (0.5g) was heated under reflux for 6hrs, the solid that separated after cooling was crystallized from proper solvent to give **10**, m.p = 190-2 ^{0}C. IR (v cm^{-1}); 3124 (NH), 1656 (C=O), 1535 (C=N). ^{1}HNMR (DMSO), (δ ppm): 4.1(s, 3H, OCH_3), 7.62-8.41 (m, 10H, Ar-H), 9.3(s, 1H, NH exchangeable by D_2O). Anal. Calcd for $C_{19}H_{14}N_6O_2S$ (390): C, 58.46; H, 3.59; N, 21.54; S, 8.21. Found C, 58.14; H, 3.28; N, 21.33; S, 8.01%

Thiosemicarbazone 11:

A mixture of **9** (0.01mol) and thiosemicarbazide (0.01mol) in glacial acetic acid (50mL) was heated under reflux for 4hr. The solid that separated after cooling was crystallized from the proper solvent to give **11**, m.p = 188-0 ^{0}C. IR (v cm^{-1}); 3426 (NH_2), 3125 (NH), 1699 (C=O), 1537 (C=N), 1188 (C=S). ^{1}HNMR (DMSO), (δ ppm): 3.9(s, 3H, OCH_3), 7.55-8.42 (m, 10H, Ar-H), 9.1, 11.2 (bs, 3H, NH&NH_2 exchangeable by D_2O). MS (m/e); 267, 266, 265 and 178 (base peak). Anal. Calcd for $C_{19}H_{16}N_6O_2S_2$ (424): C, 53.77; H, 3.77; N, 19.81; S, 15.09. Found C, 53.90; H, 3.45; N, 19.59; S, 14.86%

7-Methoxy-7,8-diphenyl triazino[6,5-d]thiazolo[2,3-c][1,2,4]triazin-3-thione 13:

A mixture of **11** (0.01mol) in glacial acetic acid (25mL), acetic anhydride (25mL) and anhydrous sodium acetate (0.5g) was heated under reflux for 4hrs. The reaction mixture was diluted with water and the solid separated was crystallized from proper solvent to give **13**, m.p = 112-4 ^{0}C. IR (v cm^{-1}); 3056 (NH), 1507 (C=N), 1213 (C=S), ^{1}HNMR (DMSO), (δ ppm): 3.9(s, 3H, OCH_3), 7.52-8.11 (m, 10H, Ar-H), 9.3(bs, 1H, NH exchangeable by D_2O). MS (m/e); 259, 258, 248 and 178 (base peak). Anal. Calcd for $C_{19}H_{14}N_6OS_2$ (406): C, 56.16; H, 3.45; N, 20.69; S, 15.76. Found C, 55.96; H, 3.11; N, 20.39; S, 15.36%

3-(2-Aminoethylimino-5-methoxy-5,6-diphenyl thiazolo[2,3-c][1,2,4]triazine 14:

A mixture of **9** (0.01mol) and ethylene diamine (0.01mol) in ethanol (50mL) was heated under reflux for 3hrs, and the solid separated was crystallized from the proper solvent to give **14**, m.p = 156-7 ^{0}C . IR (v cm^{-1}); 3443 (NH_2), 1649 (C=O), 1534 (C=N). ^{1}HNMR (DMSO),(δ ppm): 3.5(t, 2H, CH_2N), 3.8(t, 2H, CH_2N=), 4.2(s, 3H, OCH_3), 6.2(bs, 2H, NH_2 exchangeable by D_2O), 7.60-8.21 (m, 10H, Ar-H), Anal. Calcd for $C_{20}H_{19}N_5O_2S$ (393): C, 61.07; H, 4.83; N, 17.81; S, 8.14. Found C, 61.44; H, 4.98; N, 17.92; S, 8.03%

7-Methoxy-7,8-diphenyl pyrazino[3`,2`:4,5]thiazolo[2,3-c][1,2,4]triazine 15:

A solution of **14** (0.01mol) in glacial acetic acid and acetic anhydride (10mL : 10mL) and anhydrous sodium acetate (0.5g) was heated under reflux for 6hrs. The solid that obtained after cooling, was filtered off and crystallized from suitable solvent to yield **15**, m.p = 144-5 ^{0}C , IR spectrum devoid any band for $\upsilon_{C=O}$ and υ_{N-H} , ^{1}HNMR ($CDCl_3$) **(δ_{ppm})** : 2.14 and 2.59 (s, 4H, CH_2-CH_2), 3.43 (s, 3H, OCH_3), 7.19-7.46 (m, 10H, Ar-H). Anal. Calcd for $C_{20}H_{17}N_5OS$ (375): C, 64.00; H, 4.53; N, 18.67; S, 8.53. Found C, 63.342; H, 4.21; N, 18.50; S, 8.33%

3-(2-Aminophenylimino-5-methoxy-5,6-diphenylthiazolo[2,3-c][1,2,4]triazin-2-one 16:

A mixture of **9** (0.01mol) and o-phenylene diamine (0.01mol) in ethanol (50mL) was heated under reflux for 2hrs, the solid that separated after cooling was crystallized to give **16**, m.p = 198-9 ^{0}C, IR (v cm^{-1}); 3431 (NH_2), 1663 (C=O), 1560 (C=N). ^{1}HNMR (DMSO), (δ ppm): 3.7(s, 3H, OCH_3), 7.53-8.33 (m, 14H, Ar-H), 11.2(s, 2H, NH_2 exchangeable by D_2O). Anal. Calcd for $C_{24}H_{19}N_5O_2S$ (441): C, 65.29; H, 4.31; N, 15.81; S, 7.26. Found C, 65.11; H, 4.20; N, 15.78; S, 7.00%

9-Methoxy-9,10-diphenyl-[1,2,4]triazino[3,4-b]thiazolo[2,3-d]quinoxaline 17:

A mixture of **16** (0.01mol) in glacial acetic acid and acetic anhydride (20mL **1 : 1** by volume) and anhydride sodium acetate (0.5g) was heated under reflux for 4hrs. The solid that separated after cooling was crystallized from suitable solvent to yield **17**, m.p = 122-3 ^{0}C, IR (v cm^{-1}); 1534 (C=N), ^{1}HNMR (DMSO), (δ ppm): 3.8(s, 3H, OCH_3), 7.42-8.22 (m, 14H, Ar-H). MS (m/e); M^+ at 423, and 251, 249, 207 and 178 (base peak). Anal. Calcd for $C_{24}H_{17}N_5OS$ (423): C, 68.09; H, 4.02; N, 16.55; S, 7.57. Found C, 67.87; H, 3.77; N, 16.20; S, 7.82%

5,6-diphenyl-4,5-dihydro-3-hydrazino-5-methoxy-1,2,4-triazines 18:

A mixture of **1** (0.01mol) and hydrazine hydrate (0.02mol) in absolute ethanol (50mL) was refluxed for 6hrs, cooled then poured onto ice. The solid obtained was filtered and crystallized to yield **18**, m.p. = 160-2 ^{0}C, IR (v cm^{-1}); 3318 (NH_2), 3220 (NH). ^{1}HNMR (DMSO-d_6) **(δ_{ppm})** : 3.7 (S, 3H, OCH_3), 5.7 (NH_2), 6.72-7.34 (m, 10H, arH), 8.05, 8.38 (exo- and endo-NH). Anal. Calcd for $C_{16}H_{17}N_5O$ (295): C, 65.08; H, 5.76; N, 23.73; Found C, 64.65; H, 5.47; N, 23.42%.

5,6-Diphenyl-1,2-dihydro-5-methoxy-3-oxo-1,2,4-triazolo[3,4-c][1,2,4]triazine 19a:

A mixture of **18** (0.01mol) and dimethyl carbonate (0.01mol) in THF (20mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to give **19a**, m.p. = 85-6 ^{0}C, IR (v cm^{-1}); 3316, 3195 (cyclic NH-NH), 1665(C=O). ^{1}HNMR (DMSO), (δ ppm): 4.76 (m, 3H, OCH_3), 7.59–8.33(m, 10H, ArH), 11.32(bs, 2H, 2NH that exchangeable in D_2O). Anal. Calcd for $C_{17}H_{15}N_5O_2$ (321): C, 63.55; H, 4.67; N, 21.81; Found C, 63.21; H, 4.32; N, 21.61%.

5,6-Diphenyl-1,2-dihydro-5-methoxy-3-thioxo-1,2,4-triazolo[3,4-c][1,2,4]triazine 19b:

A mixture of **18** (0.01mol) and carbon disulphide (0.02mol) in alcoholic KOH was refluxed for 4hrs, cooled then added on dilute HCl. The solid obtained was filtered and crystallized to give **19b**, m.p. = 70-2 ^{0}C, IR (v cm^{-1}); 3400, 3388 (cyclic NH-NH), 1223(C=S). ^{1}HNMR (DMSO), (δ ppm): 4.56 (m, 3H, OCH_3), 7.59–8.33(m, 10H, ArH), 11.32(bs, 2H, 2NH that exchangeable in D_2O). MS (m/e): (M^+ -CH_3) at 325, 263, 224, 180, 64 (base peak). Anal. Calcd for $C_{17}H_{15}N_5OS$ (337): C, 60.53; H, 4.45; N, 20.77; S; 9.49 Found C, 60.22; H, 4.10; N, 20.46, S; 9.11%.

1-H-5,6-triphenyl-5-methoxy-1,2,4-triazolo[3,4-c][1,2,4]triazine 20a:

A mixture of **18** (0.01mol) and formic acid (10mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **20a**, m.p = 143-5 ^{0}C, IR (v cm^{-1}); 3221 (NH), 1530(C=N). ^{1}HNMR (DMSO), (δ ppm): 4.66 (m, 3H, OCH_3), 7.58–8.23(m, 10H, ArH), 13.0 (bs, H, NH that exchangeable in D_2O). Anal. Calcd for $C_{17}H_{15}N_5O$ (305): C, 66.89; H, 4.92; N, 22.95; Found C, 66.54; H, 4.67; N, 22.64%.

1-H-3,5,6-triphenyl-5-methoxy-1,2,4-triazolo[3,4-c][1,2,4]triazine 20b:

A mixture of **18** (0.01mol) and benzoyl choloride (0.01mol) in DMF (20mL) was refluxed for 4hrs, cooled, then solid obtained was filtered and crystallized to yield **20b**, m.p = 150-1 ^{0}C, IR (v cm^{-1}); 3215 (NH), 1528(C=N). ^{1}HNMR (DMSO) (δ ppm): 4.65 (m, 3H, OCH_3), 7.57–8.22(m, 15H, ArH), 12.8(bs, 1H, 1NH that exchangeable in D_2O). Anal. Calcd for $C_{23}H_{19}N_5O$ (381): C, 72.44; H, 4.99; N, 18.36; Found C, 72.41; H, 4.89; N, 18.22%.

1-H-6-methoxy-3,6,7-triphenyl-1,2,4-triazino[3,4-c][1,2,4]triazine 21a:

A mixture of **18** (0.01mol) and phenacyl bromide (0.01mol) in DMF (20mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **21a**, m.p = 177-8 ^{0}C, IR (v cm^{-1}); 3225 (NH), 2923(aliph. CH_2),. ^{1}HNMR ($CDCl_3$) **(δ_{ppm})** : 2.29 (s, 2H, CH_2), 3.40(s, 3H, OCH_3), 3.65 (s, 1H, NH), 7.07-7.45 (m, 15H, ArH). Anal. Calcd for $C_{24}H_{21}N_5O$ (395): C, 73.09; H, 5.08; N, 17.77; Found C, 72.94; H, 4.98; N, 17.46%.

1-H-6-methoxy-3,4,6,7-tetraphenyl-1,2,4-triazino[3,4-c][1,2,4]triazine 21b:

A mixture of **18** (0.01mol) and benzoin (0.01mol) in glacial acetic acid (30mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **21b**, m.p = 191-3 ^{0}C, IR (v cm^{-1}); 3229 (NH). ^{1}HNMR ($CDCl_3$) **(δ_{ppm})**:3.1 (s, 1H, CH), 3.40(s, 3H, OCH_3), 3.65 (s, 1H, NH), 7.04-7.35 (m, 20H, ArH), MS (m/e): 296 (base peak), 252, 178, 165, Anal. Calcd for $C_{30}H_{25}N_5O$ (471): C, 76.43; H, 5.34; N, 14.86; Found C, 76.10; H, 5.23; N, 14.44%.

1-H-6,7-diphenyl-4-oxo-6-methoxy-1,2,4-triazino[3,4-c][1,2,4]triazine 22a:

A mixture of **18** (0.01mol) and glyoxalic acid (0.01mol) in glacial acetic acid (30mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **22a**, m.p = 125-7 ^{0}C, IR (v cm^{-1}); 3270 (NH), 1714 (C=O), 1608 and 1579 (C=N); MS (m/e): 296 (base peak), 252,178. ^{1}HNMR (DMSO), (δ ppm): 4.4(s, 3H, OCH_3), 7.32–8.12(m, 11H, ArH), 11.7 (bs, H, NH that exchangeable in D_2O). Anal. Calcd for $C_{18}H_{15}N_5O_2$ (333): C, 64.86; H, 4.50; N, 21.02; Found C, 64.21; H, 4.23; N, 20.75%.

1-H-6,7-diphenyl-3-methyl-6-methoxy-4-oxo-1,2,4-triazino[3,4-c][1,2,4]triazine 22b:

A mixture of **18** (0.01mol) and sodium pyruvate (0.01mol) in glacial acetic acid (30mL) was refluxed for 6hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **22b**, m.p = 138-9 ^{0}C, IR (v cm^{-1}); 3162 (NH), 1677 (C=O), 1596 and 1578 (C=N); ^{1}HNMR (DMSO), (δ ppm): 2.8(s, 3H, CH_3), 4.5(s, 3H, OCH_3), 7.4–8.1(m, 10H, ArH), 13.2 (bs, H, NH that exchangeable in D_2O). Anal. Calcd for $C_{19}H_{17}N_5O_2$ (347): C, 65.71; H, 4.89; N, 20.17; Found C, 65.36; H, 4.54; N, 19.96%.

3-(2H-3,6-dioxo-pyridazin-1-yl)-5,6-diphenyl-4,5-dihydro-5-methoxy-1,2,4-triazine 23:

A mixture of **18** (0.01mol) and maleic anhydride (0.01mol) in glacial acetic acid (30mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **23**, m.p = 173-5 ^{0}C, IR (v cm^{-1}); 3426 and 3061 (NH), 1736 and 1678 (C=O); ^{1}HNMR (DMSO) **(δ_{ppm})**: 3.7 (s, 3H, OCH_3), 6.22(dd, 2H, CH=CH), 7.1-7.5(m, 10H, ArH), 8.05, 8.38 (bs, 2H, 2NH exchangeable D_2O). Anal. Calcd for $C_{20}H_{17}N_5O_3$ (375): C, 64.00; H, 4.53; N, 18.67; Found C, 63.84; H, 4.22; N, 18.50%.

3-(2H-1,4-dioxo-phthalazin-3-yl)-5,6-diphenyl-4,5-dihydro-5-methoxy-1,2,4-triazine 24:

A mixture of **18** (0.01mol) and phthalic anhydride (0.01mol) in glacial acetic acid (30mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **24**, m.p = 187-9 ^{0}C, IR (v cm^{-1}); 3410 and 3042 (NH), 1730 and 1669 (C=O); ^{1}HNMR (DMSO) (δ_{ppm}): 3.6 (s, 3H, OCH_3), 6.72-7.34 (m, 14H, ArH), 8.1, 8.5(s, 2H, 2NH exchangeable D_2O). Anal. Calcd for $C_{24}H_{19}N_5O_3$ (425): C, 67.76; H, 4.47; N, 16.47; Found C, 67.40 H, 4.21; N, 16.16%.

3-(1H-3phenyl-5-benzyliden-6-oxo-1,2,4-triazin-2-yl)-4,5-dihydro-5,6-diphenyl-5-methoxy-1,2,4-triazine 25:

A mixture of **18** (0.01mol) and oxazolone (0.01mol) in aqueous NaOH (5%, 100mL) was refluxed for 6hrs, cooled then acidified with HCl. The solid obtained was filtered and crystallized to yield **25**, m.p = 198-0 ^{0}C, IR (v cm^{-1}); 3395 (broadNH), 2927 (aliph. CH), 1679 (C=O), 1515 (C=N); ^{1}HNMR (DMSO) **(δ_{ppm})**:4.4(s, CH=), 3.5(s, 3H, OCH_3), 6.72-7.34 (m, 20H, ArH), 8.1, 8.5(s, 2H, 2NH exchangeable D_2O). MS (m/e): 295, 264, 177 (base peak), 102. Anal. Calcd for $C_{32}H_{26}N_6O_2$ (526): C, 73.00; H, 5.04; N, 16.47; Found C, 73.18; H, 5.23; N, 16.76%.

1,2,3,4-tetrahydro-6,7-diphenyl-6-methoxy-4-oxo-1,2,4-triazino[3,4-c][1,2,4]triazine 26:

A mixture of **18** (0.01mol) and choloacetic acid (0.01mol) in DMF (20mL) was refluxed for 6hrs, cooled then added on ice. The *solid* obtained was filtered and crystallized to yield **26**, m.p = 112-5 ^{0}C, IR (v cm^{-1}); 3350-3076 (broadNH), 2992, 2930 (alkyl CH), 1691 (C=O), MS (m/e): 296 (base peak), 265, 252. ^{1}HNMR (DMSO) **(δ_{ppm})**: 2.5 (s, 2H, CH_2C=O), 3.6 (s, 3H, OCH_3),5.70, 8.62 (each s, H, 2NH), 7.80-8.43 (m, 10H, arH). MS (m/e): 296 (base peak), 265, 252.Anal. Calcd for $C_{18}H_{17}N_5O_2$ (335): C, 64.48, H, 5.07; N, 20.89; Found C, 64.21; H, 5.32; N, 20.62%.

3-(benzylidenhydrazino-5,6-diphenyl-5-methoxy-1,2,4-triazine 27:

A mixture of **18** (0.01mol) and benzaldehyde (0.01mol) in glacial acetic acid (30mL) was refluxed for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **27**, m.p = 134-7 ^{0}C, IR (v cm^{-1}); 3319, 3222 (NH),1535 (C=N); ^{1}HNMR (DMSO) **(δ_{ppm})**: 3.9(s, 3H, OCH_3), 5.7 (CH=), 6.9-7.6(m, 15H, ArH), 8.05, 8.38 (bs, 2H,2NH exchangeable D_2O). Anal. Calcd for $C_{23}H_{21}N_5O$ (383): C, 72.06; H, 5.84; N, 18.28; Found C, 71.92; H, 5.50; N, 18.53%.

3-(4-oxo-2-phenyl-thiazolidin-3-yl)amino-5-methoxy-5,6-diphenyl-4,5-dihydro-1,2,4 -triazine 28:

A mixture of **27** (0.01mol) and mercaptoacetic acid (0.01mol) in dry benzene (50mL) was refluxed for 10hrs, cooled then added on petroleum ether (60-80). The solid obtained was filtered and crystallized to yield **28**, m.p = 219-0 ^{0}C, IR (v cm^{-1}); 3323, 3250 (NH), 3056, 3025 (aryl CH), 2966, 2893 (aliph. CH), 1673 (C=O), 1371 (NCS), ^{1}HNMR (DMSO) **(δ_{ppm})** :4.1(s, 2H, CH_2), 3.9 (s, 3H, OCH_3), 5.2(s, 1H, CH), 6.9-7.4 (m, 15H, ArH), 8.9, 9.3 (bs, 2H, 2NH exchangeable D_2O). MS (m/e): 264, 178, 177 (base peak), 176, 175, 99. Anal. Calcd for $C_{25}H_{23}N_5O_2S$ (457): C, 65.65, H, 5.03; N, 15.32, S, 7.00; Found C, 65.00; H, 4.79; N, 15.00, S, 6.57%.

3-(4-benzoyl-thiosemicarbazido-1-yl)-4,5-dihydro-5,6-diphenyl-5-methoxy-1,2,4-triazine 29:

A mixture of **18** (0.01mol) and benzoyl isothiocyanate (0.01mol) in dioxane (20mL) was refluxed for 6hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **29**, m.p = 214-6 ^{0}C, IR (v cm^{-1}); 3482 (enolic OH), 3306, 3202 (NH), 1719 (C=O) [which confirm, the addition of nucleophile takes place at N=C=S and not at C=O), 1180 (C=S), ^{1}HNMR (DMSO) **(δ_{ppm})**:3.7 (s, 3H, OCH_3), 6.9-7.7 (m, 15H, ArH), 8.7, 9.3, 11,2(bs, 4H, 4NH exchangeable by D_2O). Anal. Calcd for $C_{24}H_{22}N_6O_2S$ (458): C, 62.88, H, 4.80; N, 18.34, S, 6.98; Found C, 62.56; H, 4.30; N, 18.10, S, 6.48%.

3-(2H-3-thioxo-5-phenyl-1,2,4-triazolo-1-yl)-4,5-dihydro-5,6-diphenyl-5-methoxy-1,2,4-triazine 30:

Boiling compound **29** in glacial acetic acid (20mL) for 4hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **30**, m.p = 232-5 ^{0}C, IR (v cm^{-1}); 3297, 3141 (NH), 1611, 1552 (C=N), 1218 (C=S), ^{1}HNMR (DMSO) **(δ_{ppm})**:3.7 (s, 3H, OCH_3), 6.8-7.6 (m, 15H, ArH), 9.7, 10,6(bs, 2H, 2NH exchangeable by D_2O). MS (m/e): (M^+ - OCH_3) at 409, 349, 310, 77 (base peak), Anal. Calcd for $C_{24}H_{20}N_6OS$ (440): C, 65.45, H, 4.55; N, 19.09, S, 7.46; Found C, 65.14; H, 4.19; N, 18.96, S, 7.27%.

1,2-bis(4,5-dihydro-5,6-diphenyl-5-methoxy-1,2,4-triazin-3-yl)hydrazine 31:

A mixture of **1** (0.01mol) and **18** (0.01mol) in isopropyl alcohol (20mL) was for 6hrs, cooled then added on ice. The solid obtained was filtered and crystallized to yield **3**1, m.p = 247-9 ^{0}C, IR (v cm^{-1}); 3324, 3189, 3123 (NH), 1536 (C=N), ^{1}HNMR (DMSO), (δ ppm):4.1 (m, 6H, 2OCH_3), 7.59–8.33(m, 20H, ArH), 9.3, 11.32(bs, 4H, 4NH that exchangeable in D_2O). Anal. Calcd for $C_{32}H_{30}N_8O_2$ (558): C, 68.82, H, 5.38; N, 20.07, Found C, 68.43; H, 5.00; N, 19.85%.

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