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Research Article

CHEMISTRY

Some Chemical Aspects of 1,2,4-triazine derivatives

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ABSTRACT Condensation of **3a,b** with some aromatic aldehydes afforded the Schiff bases (**4a-f**). Reaction of **3a,b** with aromatic aldehydes and alkyl phosphites gave the corresponding amino phosphonates (**5a-d**). Heating **3a,b** with **6a-f** in $POCl_3$ at 85 °C furnished the amino sulphonamides (**7a- l**). Acid hydrolysis of compounds **7a,b and 7k)** furnished the amines (**8a-c**). Condensation of **3a, b** with **9a,b** afforded the cyclized product **(10a,b).** Reaction of **3a** with halo esters afforded **12** and **13**. Heating **3a,b** with **14a-c** afforded **15a-f.** Hydrolysis of **15a,b** afforded **16a,b.** Fusion of **3a,b** with 1,4-butane sultone gave sultams (**18a**,**b**). The antimicrobial activity o9f some products was tried

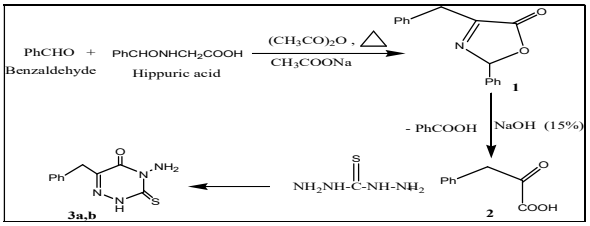
Key words: 1, 2, 4-triazines, aldehydes, aminophosphonates, sultams, biological activity.

Introduction:

1,2,4-Triazines were known to have many biological activities as antihypertensive,[1] anticonvulsant agents,[2] antiinflamatory,[3] muscle relaxants[4] and antibacterial agents.[5] . As we occupied several years ago with the chemistry of 1,2,4-triazines, we felt prompt that preparation of new type of these compounds have the triazine moiety gives at a diverse biological activity. So, it is our goal to extend our study in this direction to explore their reactivity towards different reagents to synthesize some new derivatives for testing their biological activates.

RESULTS AND DISCUSSION

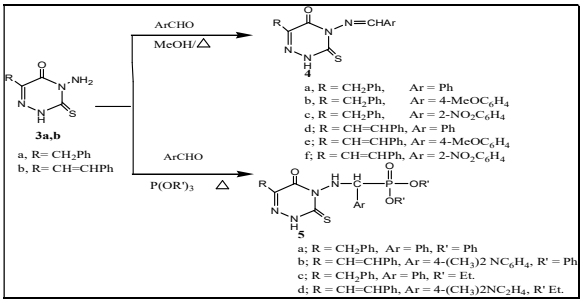
Refluxing benzaldehyde with hippuric acid in acetic anhydride in presence of sodium acetate anhydrous for 2 hr afforded 4-benzyl-2-phenyloxazol-5(2H)-one (**1**),[6] which on boiling in sodium hydroxide solution for 3 hr, afforded phenylpyruvic acid (**2**),[7] which on boiling in 80% aqueous methanol with thiocarbohydrazide for 5 hr afforded **(3a) (**Scheme **1).** Its IR spectrum showed the (C=S) at 1284 cm^{-1} and (C=O) at 1607 cm^{-1}, its ^{1}H-NMR spectrum showed a singlet (CH_2) at 2.41 ppm and its **MS** spectrum showed the (EI) m/z at 233.9. Compound **3b** was prepared according to literature method.[8,9]



Scheme **1**

Condensation of compounds **3a,b** with some aromatic aldehydes namely: benzaldehyde, 4-methoxybenzaldehyde and/or 2-nitrobenzaldehyde in boiling glacial acetic acid afforded the corresponding Schiff bases (**4a-f**) (Scheme 2). The ^{1}H-NMR spectrum of **4b** showed a singlet (3H, CH_3) at 1.80 and a singlet NH at 8.51 ppm. Aminophosphonates are phosphonic analogs of naturally occurring α-amino acids and have attracted much attention due to their biological activities and extensive application in organic chemistry.[10] So, we now report a facile and efficient one step synthesis (one pot) of α-

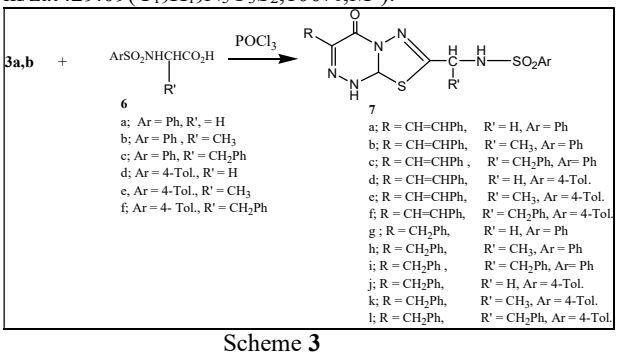
aminophosphonate derivatives of 1,2,4-triazines by a three component condensation reaction. Accordingly, compounds **3a,b** were allowed to react with triethyl- and/or triphenyl–phosphite and an aromatic aldehyde (either benzaldehyde and/or 4-N-dimethyl



Scheme **2**

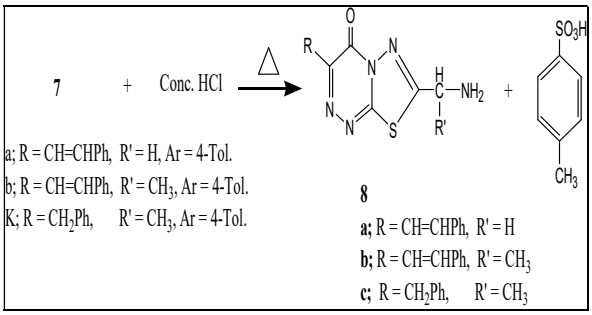
aminobenzaldehyde) in boiling glacial acetic acid for 5-6 hr to give the corresponding amino phosphonates (**5a-d**) in good yields (Scheme **2**). The IR spectrum of **5b** showed the (P=O) at 1250 cm^{-1}, Its ^{1}H-NMR spectrum showed a singlet (6H, 2 CH_3) at 1.42 and 1.80 ppm and Its **MS**: m/z at 611.9 ($C_{32}H_{30}N_5O_4PS$, 99 %, M^+).

Heating **3a,b** with (benzene and/or toluene) sulphonyl amino- (acetic and / or propionic)-acids (**6a-f**) in phosphorus oxychloride at 85 °C for 6-8 hr furnished the corresponding heterocyclic amino sulphonamides (**7a- l**) (Scheme **3**). The IR spectrum of compound **7e** showed the C=O at 1699 cm^{-1} and CH at 2914 cm^{-1} , its ^{1}H-NMR spectrum showed a singlet (3H, CH_3) at 2.41 and a singlet (1H, NH) at 7.99 ppm. Its **MS** spectrum showed the (EI) m/z at 453.09 ($C_{21}H_{19}N_5O_3S_2$, 4.89 %, M^+). The IR spectrum of compound **7h** showed the CH_2 at 2861 cm^{-1} and CH at 2985 cm^{-1} , its ^{1}H-NMR spectrum showed a singlet (3H, CH_3) at 1.97 and a singlet CH_2 at 4.41ppm and Its **MS** spectrum (EI) showed m/zat429.09($C_{19}H_{19}N_5O_3S_2$,100%,M^+).



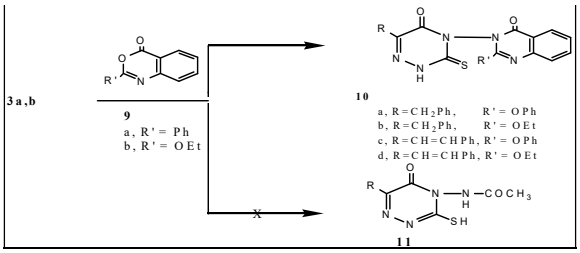
Scheme **3**

Acid hydrolysis of compounds **(7a,b and k)** could be achieved by their refluxing with conc. HCl for 3-5 hr and led to the formation of new type of amines (**8a-c**) in addition to 4-toluenesulphonic acid **(**Scheme **4)**. The IR spectrum of compound **8a** showed the $NH_{2\ sym}$ at 3368 cm^{-1} and $NH_{2\ antisym}$ at 3475 cm^{-1}, its ^{1}H-NMR spectrum showed the single CH_2 at 2.35 and a single NH_2 at 4.16 ppm. Condensation of compounds **3a, b** with 2-(phenyl and/or ethoxy)-1,3-benzoxazin-4H-ones (**9a,b**) in boiling glacial acetic acid afforded the cyclized product **(10a,b)** through the elimination of one molecule of water as the sole product (tlc.) and not



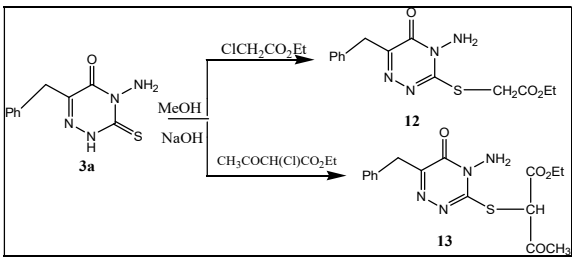
Scheme **4**

the open structure N-(3-mercapto-5-oxo-6-styryl-1,2,4-triazin-4(5H)-yl)acetamide (**11**) (Scheme **5**). The IR spectrum of compound **10b** showed the NH at 3375 cm^{-1} and its ^{13}C-NMR spectrum showed the CH_3 at 14.17, CH_2 at 39.29 and C=S at 193.50 ppm.



Scheme **5**

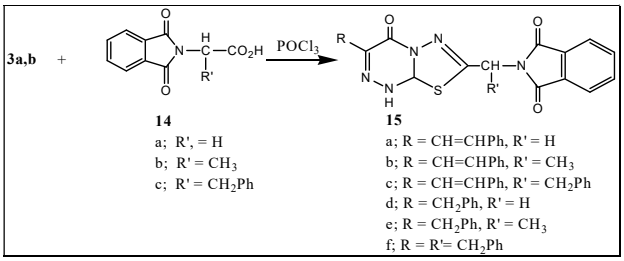
Reaction of compound **3a** with ethyl chloro -(acetate and /or acetoacetate) in boiling methanol in the presence of sodium hydroxide for 3-4 hr afforded the corresponding alkyl derivatives **12** and **13**, respectively (Scheme **6**). The IR spectrum of compound **12** showed the $NH_{2\ sym}$ at 3452 cm^{-1} and $NH_{2assym.}$ at 3461 cm^{-1} and its ^{1}H-NMR spectrum showed the triplet CH_3 at 1.54 and a quartet CH_2 at 2.41 ppm. Its IR spectrum of compound **13** showed the NH_{2sym} at 3338 cm^{-1} and $NH_{2\ assym.}$ at 3453 cm^{-1} and its ^{1}H-NMR spectrum showed the triplet CH_3 at 1.60, a quartet CH_2 at 2.50 and a single CH at 8.33ppm



Scheme **6**

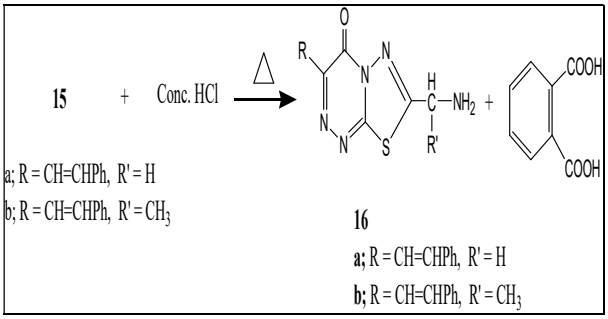
Heating a mixture of **3a,b** with (1,3-dioxo-1,3-dihydroisoindol-2-yl)(methyl-, phenyl- and / or benzyl-)acetic acid (**14a-c**)[11] in phosphorus oxychloride at 85 °C for 5-6 hr yielded **15a-f** after cooling and neutralization

with 1N NaOH (Scheme **7**). The IR spectrum of compound **15b** showed the disappearance of NH_2 at 3453 cm^{-1} and the presence of CH_3 at 2925 cm^{-1}, its ^{1}H-NMR spectrum showed the single CH_3 at 2.31ppm. The MS spectrum of compound **15f** showed the (EI) m/z at 493.12 ($C_{27}H_{19}N_5O_3S$, 1.41 %, M^+).



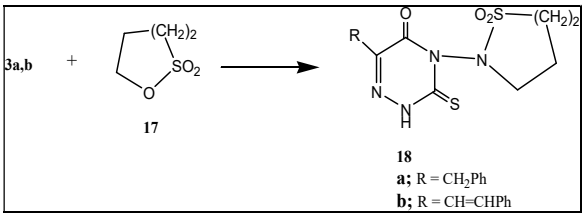
Scheme **7**

Acid hydrolysis of **15a,b** could be achieved by their refluxing with conc. HCl for 8-10 hr and led to the formation of a new type of amine **16a,b** in addition to phthalic acid (Scheme **8**). The IR spectrum of compound **16a** showed the presence of $NH_{2\ sym}$ at 3368 cm^{-1} and $NH_{2\ antisym}$ at 3475 cm-1. The MS spectrum of compound **16b** showed the (EI) m/z at 299.08 ($C_{14}H_{13}N_5OS$, 100 %, M^+).



Scheme **8**

Fusion of compounds **3a,b** with 1,4-butanesultone (**17**) at 180 °C for 6-8 hr afforded the corresponding sultams (**18a**,**b**), respectively (Scheme **9**). The IR spectrum of compound **18a** showed the appearance of S=O at 1162 cm^{-1} and 1351 cm^{-1}. The MS spectrum of compound **18b** showed the (EI) m/z at 364.07 ($C_{15}H_{16}N_4O_3S_2$, 80.12 %, M^+).



Scheme **9**

EXPERIMENTAL

All melting points were uncorrected and performed by the open capillary melting point apparatus. Microanalyses performed by Microanalysis Unit, Central Laboratory, Tanta University, Tanta, Egypt. IR spectra were recorded with a perkin-Elmer 1720 spectrometer. The NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C,Varian UNITY 500 NMR spectrometer at 500 MHz for ^{1}H or 125.7 MHz for ^{13}C, Bruker 200 MHz And Bruker 90 MHz spectrometer using TMS as an internal standard, DMSO and $CHCl_3$ as solvents. Chemical shifts (δ) are reported in parts per million (ppm) and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). Mass spectra (MS) were recorded using electron ionization (E.I.) on a Varian Mat 311A spectrometer.

Preparation of 4-amino-6-benzyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (3a).

Compound 4-benzyl-2-phenyloxazol-5(2H)-one **(1)**[6] and phenylpyruvic acid **(2)**[7] were prepared according to known methods. Refluxing **2** (1.3 g, 0.01 mol) in aqueous methanol 80% with thiocarbohydrazide (1.06 g, 0.01 mol) for 5 hr (tlc.), cooled the reaction mixture at r. t. The solid obtained was filtered off, dried and recrystallized from ethanol to afford **(3a)** yield: 74%, m.p. 195 °C**.**

4-Amino-6-benzyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (3a).

IR (KBr): *ν* (cm^{-1}) = 1284 (C=S), 1748 (C=O), 3287 ($NH_{2\ asym.}$), 3446 ($NH_{2\ sym.}$). **^{1}H-NMR** (DMSO-d_6) = δ 2.41 (s, 2H, CH_2), 3.84 (s, 2H, NH_2), 9.92 (s, 1H, NH), 7.88 - 8.71 (m, 5H, $H_{ar.}$) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 24.23 (CH_2), 127.38, 128.65, 129,73, 134.28 and 142.16 ($C_{ar.}$), 176.87 ($C{=}O_{cyclic}$), 181.47 ($C{=}S_{cyclic}$) ppm. **MS** (EI): *m/z* 233.9 ($C_{10}H_{10}N_4OS$, 90.6 %, M^+).

Compound **3b** was prepared according to literature method.[8, 9]

Condensation of compounds 3a,b with some aromatic aldehydes. Formation of Schiff bases (4a-f).

The compounds **3a or 3b (**0.01mol) and some aromatic aldehydes namely: benzaldehyde, 4-methoxybenzaldehyde and/or 2-nitro- benzaldehyde (0.01mol) were mixed. The reaction mixture was refluxed in glacial acetic acid (15 ml) for 4-6 hr (tlc), cooled to r. t. and poured onto ice water. The solid obtained was filtered off, dried and recrystallized from DMF/water to afforded the corresponding Schiff bases (**4a-f**).

6-Benzyl-4-(benzylideneamino)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (**4a**).

IR (KBr): υ (cm^{-1}) = 1350 (C=S), 1605 (C=N), 1640 (C=O), 3007 (Ph CH)**,** 3203 (NH). **^{1}H-NMR** ($CDCl_3$) = δ 3.81 (s, 2H, CH_2), 4.63 (s, 1H, $CH_{ar.}$), 6.85-7.3 (m, 5H, $H_{ar.}$), 7.47-8.4 (m, 5H, $H_{ar.}$), 8.53 (s, 1H, N=CH), 10.12 (s, 1H, NH) ppm.

4-(4-Methoxybenzylideneamino)-6-benzyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (**4b**).

IR (KBr): υ (cm^{-1}) = 1246 (C=S), 1557 (C=N), 1685 (C=O), 3066 (CH, Ph)**,** 3139 (NH). **^{1}H-NMR** (DMSO-d_6)

= δ 1.80 (s, 3H, CH_3), 2.18 (s, 2H, CH_2), 4.15 (s, 1H, N=CH), 7.56, 7.92 (m, 9H, $H_{ar.}$), 8.51 (s, 1H, NH) ppm.

4-(2-Nitrobenzylideneamino)-6-benzyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (4c).

IR (KBr): υ (cm^{-1}) = 1587 (C=N), 1250 (C=S), 1695 (C=O), 3083 (CH, Ph), 3250 (NH), 1520 (NO_2).

4-(Benzylideneamino)-6-styryl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-on (4d).

IR (KBr) υ (cm^{-1}) = 1250 (C=S), 1561 (C=N), 1699 (C=O), 3074 (CH, Ph), 3148 (NH).

4-(2-Nitrobenzylideneamino)-6-styryl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (4e).

IR (KBr) υ (cm^{-1}) = 1250 (C=S), 1545 (C=N), 1684 (C=O), 3009 (CH, Ph), 3274 (NH). **^{1}H-NMR** ($CDCl_3$) = δ 3.25 (s, 3H, CH_3), 3.72 (d, 2H, *J* = 2.97 Hz, CH=CH), 6.84-7.10 (m, 5H, $H_{ar.}$), 7.42-7.85 (m, 4H, $H_{ar.}$), 7.25 (s, 1H, N=CH), 10.25 (s, 1H, NH) ppm.

4-(4-Methoxybenzylideneamino)-6-styryl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (4f).

IR (KBr) υ (cm^{-1}) = 1352 (C=S), 1489 (NO_2), 1502 (C=N), 1603 (C=O), 2920 (CH). **^{1}H-NMR** (DMSO-d_6) = δ 4.03 (s, 1H, CH), 7.83 (d, 2H, *J* = 3.0 Hz, CH=CH), 8.22 - 8.94 (m, 7H, $H_{ar.}$), 11.01 (s, 1H, NH) ppm.

Table **1**: Physical and analytical data of compounds **4a-f**.

Cpd	M.P. (ºC)	Yield (%)	M. F. (M. W.)	M.A. (%); Calcd/Found C%	H%	N%
4a	244-6	73	$C_{17}H_{14}N_4OS$ (322.38)	63.33 62.97	4.38 3.92	17.38 16.94
4b	271-3	93	$C_{18}H_{16}N_4O_2S$ (352.41)	61.35 61.06	4.58 4.22	15.90 15.72
4c	264-6	72	$C_{17}H_{13}N_5O_3S$ (367.38)	55.58 55.17	3.57 3.31	19.06 18.84
4d	302-4	53	$C_{18}H_{14}N_4OS$ (334.39)	64.65 64.24	4.22 3.93	16.75 16.53
4e	283-5	74	$C_{19}H_{16}N_4O_2S$ (364.42)	62.62 62.37	4.43 3.99	15.37 15.14
4f	295-7	82	$C_{18}H_{13}N_5O_3S$ (379.39)	56.98 56.79	3.45 3.14	18.46 18.12

Reaction of compounds 3a,b with some aromatic aldehydes and triethyl- and / or triphenyl-phosphite. Formation of 5a-d

A mixture of **3a,b** (0.01 mol), some aromatic aldehydes namely: benzaldehyde and/or 4-N-dimethyl aminobenzaldehyde)[12] (0.01 mol) and triethyl- and/or triphenyl–phosphite (0.02 mol) in glacial acetic acid (30 ml) was heated at 100º C for 5 – 6 hr (tlc.). The reaction mixture was concentrated to 1/4 volume and poured onto ice. The solid formed was filtered off, washed by petroleum ether followed by recrystallization from methanol to give the corresponding amino phosphonates (**5a-d**) in good yields (Scheme **2**). The data are listed in Table **2**.

Diphenyl(6-benzyl-5-oxo-3-thioxo-2,3-dihydro-1,2,4tr-iazin-4(5*H*)-ylimino)-(phenyl)methylphosphonate (5a).

IR (KBr) υ (cm^{-1}) = 1224 (C=S), 1305 (P=O), 1641 (C=N), 1708 (C=O), 2256 (CH_2), 3055 ($CH_{ar.}$), 3436 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.51 (s, 1H, $NH_{acyclic}$), 3.45 (s, 1H, CHPh), 6.08 (s, 2H, CH_2Ph), 7.1-7.3 (m, 20H, H_{ar}), 7.62 (s, 1H, NH_{cyclic}) ppm.

Diphenyl(4-(dimethylamino)phenyl)(5-oxo-6-styryl-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5*H*)ylimino)methy-lphosphonate (5b).

IR (KBr) υ (cm^{-1}) = 1197 (C=S), 1308 (P=O), 1631 (C=N), 1723 (C=O), 2981 (CH), 3086 ($CH_{ar.}$), 3427 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 1.35 (s, 6H, $2CH_3$), 2.60 (s, 1H, $NH_{acyclic}$), 3.65 (s, 1H, CHPh), 6.55-7.05 (d, 2H, *J* = 2.85 Hz, CH=CH), 7.5-8.8 (m, 19H, H_{ar}), 9.15 (s, 1H, NH_{cyclic}) ppm. **MS** (EI) m/z = 611.9 (M^+, $C_{32}H_{30}N_5O_4PS$, 99 %).

Diethyl(6-benzyl-5-oxo-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5*H*)-ylamino)-

(phenyl)methylphosphonate (5c).

IR (KBr) υ (cm^{-1}) = 1250 (C=S), 1350 (P=O), 1520 (C=N), 1640 (C=O), 2951 (CH_2), 3057 ($CH_{ar.}$), 3465 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.51 (t, 6H, *J* = 4.12 Hz, $2CH_3$) 2.72 (s, 1H, $NH_{acyclic}$), 3.72 (s, 1H, CHPh), 4.52 (q, 4H, *J* = 2.43 Hz, $2CH_2$), 5.26 (s, 2H, CH_2Ph), 7.33-9.27 (m, 10H, H_{ar}), 9.72 (s, 1H, NH_{cyclic}) ppm.

Diethyl(4-(dimethylamino)phenyl)(5-oxo-6-styryl-3thi-oxo-2,3-di-hydro-1,2,4-triazin-4(5*H*)ylamino)methyl-phosphonate (5d).

IR (KBr) υ (cm^{-1}) = 1222 (C=S), 1337 (P=O), 1520 (C=N), 1641 (C=O), 2961 (CH), 3087 ($CH_{ar.}$), 3152 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 1.81 (t, 6H, *J* = 4.13 Hz, $2CH_3$), 2.23 (s, 1H, $NH_{acyclic}$), 2.53 (s, 6H, $2CH_3$, $N(CH_3)_2$), 2.55 (s, 1H, CHPh), 4.22 (q, 4H, *J* = 2.81 Hz, $2CH_2CH_3$), 7.55-7.61 (d, 2H, *J* = 3.10 Hz, CH=CH), 7.7-7.9 (m, 9H, H_{ar}), 8.54 (s, 1H, NH_{cyclic}). **^{13}C-NMR** (DMSO-d_6) = δ 12.81 ($2CH_3$), 21.00 ($2CH_3$), 39.70 (CH), 126.25, 126.65, 126.84, 129.76, 137.14 and 137.25 ($C_{ar.}$), 165.28 ($C=O_{cyclic}$), 181.48 ($C=S_{cyclic}$) ppm.

Table **2**: Physical and analytical data of compounds **5a-d**

Cpd	M.P. (ºC)	Yield (%)	M. F. (M. W.)	M.A. (%); Calcd/Found C%	H%	N%
5a	244-6	73	$C_{29}H_{25}N_4O_4PS$ (556.57)	62.58 62.61	4.53 4.64	10.07 10.21

5b	271-3	93	$C_{32}H_{30}N_5O_4PS$ (611.65)	62.84 62.56	4.94 4.72	11.45 11.17
5c	264-6	72	$C_{21}H_{25}N_4O_4PS$ (460.49)	54.77 54.46	5.47 5.29	12.17 11.90
5d	302-4	53	$C_{24}H_{30}N_5O_4PS$ (515.56)	55.91 55.68	5.87 5.59	13.58 13.30

Reaction of 3a,b with (benzene- and/or 4-toluene)-sulphonyl amino acids. Formation of the amino sulphonamides (7a-l).

To a solution of **3a,b** (0.01 mol) in phosphorus oxychloride (15 ml) , (benzene- and / or toluene)-sulphonyl amino –(acetic and / or propionic)-acids (**6a-f**) (0.005 mol) [6] were added, in portions. The reaction mixture was heated at 85 °C for 6-8 hr (tlc) and cooled. Sodium hydroxide solution (1%, 50 ml) was added until a solid product was formed. It was filtered off, washed with water, dried and recrystallized from methanol and furnished the corresponding amino sulphonamides (**7a-l**).

N-((4-Oxo-3-styryl-4,8a-dihydro-1*H*[1,3,4]thiadiazolo[2,3c]|-1,2,4]-triazin-7-yl)methyl)benzenesulfonamide (7-a).

IR (KBr) υ (cm^{-1}) = 1335, 1375 (SO_2), 1592 (C=N), 1710 (C=O), 2981 (CH), 3020 ($CH_{ar.}$), 3335 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 3.31 (s, 2H, CH_2), 7.21-7.40 (d, 2H, *J* = 3.02 Hz, CH=CH), 7.51-8.82 (m, 10H, $H_{ar.}$), 11.73 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 34.00 (CH_2), 113.94, 116.20, 117.69, 119.81, 128.61, 128.87, 129.40, 130.96, 137.78, 138.54 and 139.02 ($C_{ar.}$), 159.80 (C=N), 167.08 ($C{=}O_{cyclic.}$) ppm.

N-(1-(4-Oxo-3-styryl-4,8adihydro1*H*[1,3,4]thiadiazolo-[2,3c][1,2,4]triazin-7-yl)ethyl)benzenesulfonamide (7b).

IR (KBr) υ (cm^{-1}) = 1332, 1373 (SO_2), 1553 (C=N), 1695 (C=O), 2932 (CH), 3070 ($CH_{ar.}$), 3218 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.21 (s, 3H, CH_3), 3.25 (s, 1H, CH), 7.55-7.63 (d, 2H, *J* = 2.92 Hz, CH=CH), 7.75-7.82 (m, 10H, H_{ar}). **^{13}C-NMR** (DMSO-d_6) = δ 17.11 (CH_3), 31.15 ($\underline{C}H_3CH$), 40.94 ($\underline{C}HCH_3$), 153.49 (C-7), 159.89 (C-3), 161.73 (C-4), 126.44, 129.24, 132.52, 139.95, 148.52 ($C_{ar.}$), 159.02 (C=N), 169.77 ($C{=}O_{cyclic}$) ppm.

N-(1-(4-Oxo-3-styryl-4,8a-dihydro-1*H*-[1,3,4]thiadiazo-lo[2,3-c][1,2,4]triazin-7-yl)-2phenylethyl)benzenesulfo-namide (7c).

IR (KBr) υ (cm^{-1}) = 1345, 1368 (SO_2), 1605 (C=N), 1717 (C=O), 2978 (CH_2), 3102 (CH), 3189 ($CH_{ar.}$), 3319 (NH) ppm. **^{1}H-NMR** (DMSO-d_6) = δ 2.51 (s, 2H, CH_2), 4.11 (s, 1H, CH), 7.41 -7.55 (d, 2H, *J* = 2.43 Hz, CH=CH), 7.61-7.92 (m, 15H, H_{ar}), 8.55 (s, 1H, NH). **^{13}C-NMR** (DMSO-d_6) = δ 35.62 (CH_2), 64.42 (CH), 124.73, 127.25, 129.98, 130.15, 131.32, 132.84, 137.10 and 139.73 ($C_{ar.}$), 158.15 (C=N), 167.81 ($C{=}O_{cyclic}$) ppm.

4-Methyl-N-((4-oxo-3-styryl-4,8a-dihydro-1*H*[1,3,4]th-iadiazolo[2,3-c]|[1,2,4]-triazin-7-yl)methyl)benzenesulf-onamide (7d).

IR (KBr) υ (cm^{-1}) = 1351, 1374 (SO_2), 1613 (C=N), 1718 (C=O), 2935 (CH), 3110 ($CH_{ar.}$), 3465 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.43 (s, 3H, CH_3), 3.41 (s, 2H, CH_2), 4.50-7.55 (d, 2H, *J* = 3.53 Hz, CH=CH), 7.56-7.90 (m, 9H, H_{ar}), 8.95 (s, 1H, NH). **^{13}C-NMR** (DMSO-d_6) = δ 19.31 (CH_3), 38.32 (CH_2), 42.69 (CH), 153.19, 158.62, 164.91, 128.16, 131.12, 138.08, 142.78, 147.93 ($C_{ar.}$), 158.11 (C=N), 168.93 ($C{=}O_{cyclic}$) ppm. **MS** (EI) m/z = 439.07 (M^+, $C_{20}H_{17}N_5O_3S_2$, 7.52 %).

4-Methyl-N-(1-(4-oxo-3-styryl-4,8a-dihydro-1*H*-[1,3,4]thiadiazolo[2,3-c]|[1,2,4]-triazin-7-yl)ethyl-)benzenesulfonamide (7e).

IR (KBr) υ (cm^{-1}) = 1333, 1372 (SO_2), 1598 (C=N), 1699 (C=O), 2914 (CH), 3139 ($CH_{ar.}$), 3558 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.45 (s, 3H, CH_3CH), 3.21 (s, 3H, CH_3Ph) 3.42 (s, 1H, $CHCH_3$), 7.35-7.45 (d, 2H, *J* = 2.64 Hz, CH=CH) 7.72-7.90 (m, 9H, H_{ar}), 9.95 (s, 1H, NH). **^{13}C-NMR** (DMSO-d_6) = δ 17.10 (CH_3), 31.12 ($\underline{C}H_3CH$), 40.93 ($\underline{C}HCH_3$), 153.44, 159.89, 161.78, 126.50, 129.60, 137.13, 142.83, 148.28 ($C_{ar.}$), 156.39 (C=N), 170.12 ($C{=}O_{cyclic}$) ppm. **MS** (EI) m/z = 453.09 (M^+, $C_{21}H_{19}N_5O_3S_2$, 4.89 %).

4-Methyl-N-((4-oxo-3-styryl-4,8a-dihydro-1H-[1,3,4-]thiadiazolo[2,3-c][1,2,4]-triazin-7-yl)(ph-enyl)methyl)-benzenesulfonamide (7f).

IR (KBr) υ (cm^{-1}) = 1330, 1367 (SO_2), 1611 (C=N), 1705 (C=O), 2981 (CH_2), 2991 (CH), 3064 ($CH_{ar.}$), 3411 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 1.34 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 4.12 (s, 1H, CH), 7.40-7.55 (d, 2H, *J* = 3.13 Hz, CH=CH), 7.60-7.92 (m, 14H, H_{ar}), 8.55(s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 16.20 (CH_3), 38.31 (CH_2), 63.25 (CH), 124.50, 128.14, 129.08, 129.85, 131.19, 131.59, 136.70 and 139.49 ($C_{ar.}$), 157.75 (C=N), 169.14 ($C{=}O_{cyclic}$) ppm.

N-((3-Benzyl-4-oxo-4,8a-dihydro-1H-[1,3,4]-thiadiaz-olo[2,3-c][1,2,4]-triazin-7-yl)methyl)-benzenesulfona-mide (7g).

IR (KBr) υ (cm^{-1}) = 1334, 1365 (SO_2), 1617 (C=N), 1709 (C=O), 2922 (CH_2), 2922 (CH), 3056 ($CH_{ar.}$), 3554 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.41 (s, 2H, CH_2NH), 4.46 (s, 2H, CH_2Ph), 7.6-7.91 (m, 10H, H_{ar}), 8.95 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 18.44 (CH_3), 29.52 (CH_2), 42.42 (CH), 154.16, 159.72, 163.95, 126.96, 129.71, 133.33, 139.95, 148.67 ($C_{ar.}$), 158.35 (C=N), 169.22 ($C{=}O_{cyclic}$) ppm.

N-(1-(3-Benzyl-4-oxo-4,8a-dihydro-1H-[1,3,4]-thiad-iazolo[2,3-c][1,2,4]triazin-7-yl)ethyl)benze-neesulfon-amide (7h).

IR (KBr) υ (cm^{-1}) = 1337, 1372 (SO_2), 1562 (C=N), 1703 (C=O), 2861 (CH_2), 2985 (CH), 3092 ($CH_{ar.}$), 3235 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.45 (s, 3H, CH_3), 2.51 (s, 1H, CH), 3.25 (s, 2H, CH_2) 7.61-7.88 (m, 10H, $H_{ar.}$), 8.00 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 18.44 (CH_3), 29.54 (CH_2), 42.91 (CH), 155.19, 158.74, 164.15, 127.01,

129.83, 134.38, 139.40, 149.57 ($C_{ar.}$), 159.23 (C=N), 168.93 ($C=O_{cyclic}$) ppm. **MS** (EI) m/z = 429.09 (M^+, $C_{19}H_{19}N_5O_3S_2$, 100.0 %).

N-((3-Benzyl-4-oxo-4,8a-dihydro-1H-[1,3,4]thiadiazolo[2,3c][1,2,4]triazin-7-yl)(phenyl)methyl)benzenesulfonamide (7i).

IR (KBr) υ (cm^{-1}) = 1338, 1360 (SO_2), 1650 (C=N), 1711 (C=O), 2843 (CH_2), 3053 ($CH_{ar.}$), 3323 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.51 (s, 1H, CH), 3.92 (s, 2H, $CHCH_2$), 4.20 (s, 2H, CH_2Ph), 7.41-7.92 (m, 10H, $H_{ar.}$), 8.55 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 39.25 (CH_2), 62.11 (CH), 127.14, 128.01, 129.23, 129.89, 130.19, 131.56, 136.57 and 139.84 ($C_{ar.}$), 158.10 (C=N), 169.03 ($C=O_{cyclic}$) ppm.

N-((3-Benzyl-4-oxo-4,8a-dihydro-1H-[1,3,4]thiadiazolo[2,3c][1,2,4]-triazin-7-yl)methyl)-4-methylbenzenesulfonamide (7j).

IR (KBr) υ (cm^{-1}) = 1338, 1370 (SO_2), 1632 (C=N), 1705 (C=O), 2932 (CH_2), 3126 ($CH_{ar.}$), 3398 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.51 (s, 3H, CH_3Ph), 3.2 (s, 1H, CH), 3.35 (s, 2H, CH_2NH), 4.53 (s, 2H, $C\underline{H}_2Ph$), 7.32-7.75 (m, 9H, $H_{ar.}$), 8.91 (s, 1H, N<u>H</u>) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 21.25 (CH_3), 42.41 (CH_2), 154.13, 159.73, 163.93, 127.07, 130.06, 137.08, 143.73, 148.65 ($C_{ar.}$), 158.92 (C=N), 170.02 ($C=O_{cyclic}$) ppm.

N-(1-(3-Benzyl-4-oxo-4,8a-dihydro-1*H*-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl)ethyl)-4-met-hylbenzene sulfonamide (7k).

IR (KBr) υ (cm^{-1}) = 1332, 1371 (SO_2), 1563 (C=N), 1715 (C=O), 2995 (CH), 3107 ($CH_{ar.}$), 3395 (NH)**. ^{1}H-NMR** (DMSO-d_6) = δ 2.31 (s, 3H, CH_3CH), 2.52 (s, 3H, CH_3Ph), 3.22 (s, 1H, CH), 3.45 (s, 2H, CH_2), 7.32-7.75 (m, 9H, $H_{ar.}$), 7.95 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 17.30 (CH_3), 26.13 ($\underline{C}H_3CH$), 39.35 (CH_2), 154.46, 160.81, 162.56, 127.51, 129.54, 138.14, 143.52, 149.34 ($C_{ar.}$), 159.31 (C=N), 169.62 ($C=O_{cyclic}$) ppm.

N-(1-(3-Benzyl-4-oxo-4,8a-dihydro-1*H*-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl)-2-phenyleth-yl)-4methylbenzenesulfonamide (7l).

IR (KBr) υ (cm^{-1}) = 1338, 1368 (SO_2), 1646 (C=N), 1718 (C=O), 2851 (CH_2), 3063 ($CH_{ar.}$), 3352 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 1.31 (s, 3H, CH_3CH), 2.53 (s, 2H, CH_2CH), 4.01 (s, 1H, CH), 4.20 (s, 2H, CH_2Ph), 7.41-7.90 (m, 14H, $H_{ar.}$), 8.55 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ14.17 (CH_3), 39.29 (CH_2), 61.12 (CH), 126.59, 127.44, 129.00, 129.96, 130.15, 130.50, 135.50 and 139.93 ($C_{ar.}$), 156.30 (C=N), 168.20 ($C=O_{cyclic}$) ppm.

Table **3**: Physical and analytical data of compounds **7a-l.**

Cpd	M.P. (ºC)	Yield (%)	M. F. (M. W.)	M.A. (%); Calcd/Found C%	H%	N%
7a	176-8	83	$C_{19}H_{17}N_5O_3S_2$ (427.5)	53.38 53.09	4.01 3.92	16.38 15.98
7b	183-5	71	$C_{20}H_{19}N_5O_3S_2$ (441.53)	54.41 54.12	4.34 3.97	15.86 15.57
7c	179-81	78	$C_{26}H_{22}N_5O_3S_2$ (516.61)	60.45 60.15	4.29 3.07	13.56 13.27
7d	197-9	85	$C_{20}H_{19}N_5O_3S_2$ (441.53)	54.41 54.22	4.34 3.97	15.86 15.45
7e	158-60	69	$C_{21}H_{21}N_5O_3S_2$ (455.55)	55.37 55.18	4.65 4.24	15.37 15.08
7f	202-4	74	$C_{27}H_{25}N_5O_3S_2$ (531.65)	61.00 60.14	4.74 4.38	13.17 12.98
7g	232-4	58	$C_{18}H_{17}N_5O_3S_2$ (415.49)	52.03 51.81	4.12 3.93	16.86 16.57
7h	165-7	67	$C_{19}H_{19}N_5O_3S_2$ (429.52)	53.13 52.95	4.46 4.17	16.31 16.10
7i	191-3	79	$C_{25}H_{22}N_5O_3S_2$ (504.6)	59.51 59.32	4.39 4.08	13.88 13.59
7j	218-20	61	$C_{19}H_{19}N_5O_3S_2$ (429.52)	53.13 52.83	4.46 4.27	16.31 15.92
7k	189-91	82	$C_{20}H_{21}N_5O_3S_2$ (443.54)	54.16 53.96	4.77 4.35	15.79 15.41
7l	199-01	89	$C_{26}H_{25}N_5O_3S_2$ (519.64)	60.10 59.97	4.85 4.58	13.48 13.17

<u>Hydrolysis of compounds (7a,b and k). Formation of 8a-c</u>.

Compounds **(7a,b and k)** (0.003 mol) was refluxed in conc. hydrochloric acid[13] (25 ml) for 3-5 hr (tlc). The reaction mixture was cooled to r. t. and neutralized with sodium hydroxide solution (10 %, 25– 30 ml). The precipitate formed was filtered off, dried, and recrystallized from methanol to form **8a-c**. The filtrate was acidified by dil. HCl to give a white precipitate of 4-toluensulphonic acid.

7-(Aminomethyl)-3-styryl-1H-[1,3,4]thiadiazolo-2,3-c][1,2,4]triazin-4(H)-one (8a).

IR (KBr) *v* (cm^{-1}) = 1510 (C=N), 1623 (C=O, cylic), 2781 (CH), 3368 ($NH_{2\ sym}$), 3475 ($NH_{2\ asym}$). **^{1}H-NMR** (DMSO-d_6) = δ 2.35 (s, 2H, NH_2), 3.40 (s, 2H, CH_2), 4.21-7.35 (d, 2H, *J* = 2.97 Hz, CH=CH), 7.65-8.52 (m, 5H, $H_{ar.}$), 7.95 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 31.03 (CH_2), 39.70 (CH=CH), 126.50, 126.65, 126.84, 129.76, 137.14 and 137.25 ($C_{ar.}$), 156.12 (C=N), 167.68 (C=O) ppm.

7-(1-Aminoethyl)-3-styryl-1H-[1,3,4]thiadiazolo-[2,3-c][1,2,4]triazin-4(H)-one (8b).

IR (KBr) *v* (cm^{-1}) = 1585 (C=N), 1630 (C=O, cylic), 2818 (CH), 3228 ($NH_{2\ sym}$), 3398 ($NH_{2\ asym}$). **^{1}H-NMR** (DMSO-d_6) = δ 2.23 (s, 3H, CH_3), 2.55 (s, 1H, CH), 4.34 (s, 2H, NH_2), 4.62-7.43 (d, 2H, *J* =3.41 Hz, CH=CH), 7.6-8.45 (m, 5H, $H_{ar.}$), 7.95 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 21.01 (CH_3), 39.70 and 39.91 (CH=CH), 110.81, 126.43, 126.62, 128.91, 129.67, 134.20 and 138.09 ($C_{ar.}$), 158.12 (C=N), 169.32 (C=O) ppm.

7-(1-Aminoethyl)-3-benzyl-1H-[1,3,4]thiadiazo-lo[2,3-c][1,2,4]triazin-4(H)-one (8c).

IR (KBr) *v* (cm^{-1}) = 1600 (C=N), 1680 ($C=O_{cylic}$), 3105 ($CH_{ar.}$), 3322 (NH_2). **^{1}H-NMR** (DMSO-d_6) = δ 1.03 (s, 3H, CH_3), 2.48 (s, H, CH), 3.49 (s, 2H, CH_2), 4.18 (s, 2H, NH_2), 7.46 – 8.52 (m, 5H, $H_{ar.}$) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 12.81 (CH_3), 20.95 (CH_2), 39.82 (CH), 124.32, 127.15, 127.95, 129.29, 137.18 and 139.95 ($C_{ar.}$), 158.19 (C=N), 169.99 (C=O) ppm.

Table **4**: Physical and analytical data of compounds **8a-c**

Cpd	M.P. (ºC)	Yield (%)	M. F. (M. W.)	M.A. (%); Calcd/Found C%	H%	N%
8a	195-7	81	$C_{13}H_{13}N_5OS$ (287.34)	54.34 53.99	4.56 4.32	24.37 24.01
8b	187-9	75	$C_{14}H_{15}N_5OS$ (301.37)	55.80 55.54	5.02 4.72	23.24 22.81
8c	182-4	78	$C_{13}H_{15}N_5OS$ (289.36)	53.96 53.71	5.23 5.05	24.20 23.97

Reaction of 3a,b with 2-substituted-1,3-benzoxazin-4*H*-one derivatives. Formation of 10a-d.

A mixture of **3a, b** (0.01 mol) and 2-(phenyl and/or ethoxy)-1,3-benzoxazin-4H-ones (**9a,b**) (0.01 mol) was refluxed in glacial acetic acid (20 ml) for 13-15 hr (tlc). The solvent was evaporated till dryness and the solid obtained was recrystallized from (methanol / water) to afford **10a-d**.

3-(6-Benzyl-5-oxo-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5H)-yl)-2-phenylquina-zolin-4(3H)-one (10a).

IR (KBr) υ (cm^{-1}) = 1270 (C=S), 1600 (C=N), 1695, 1730 (2C=O), 2985 ($CH_{aliph.}$), 3088 ($CH_{ar.}$), 3241 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 2.18 (s, 2H, CH_2), 7.20 – 8.55 (m, 14H, $H_{ar.}$), 8.6 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) = δ 23.00 (CH_2), 115.58, 115.9, 125.20, 127.90, 127.95, 128.51, 129.06 and 129.19 ($C_{ar.}$), 131.70 (C-6'), 131.76 (C-2'), 135.23 (C-4'), 135.31(C-5'), 135.73 (C-3'), 162.01 (C=N), 172.81 (C=O), 189.77 (C=S) ppm.

3-(6-Benzyl-5-oxo-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5H)-yl)-2-ethoxyquina-zolin-4(3H)-one (10b).

IR (KBr) υ (cm^{-1}) = 1180 (C=S), 1657 (C=N), 1725 (C=O), 2845 (CH), 3085 ($CH_{ar.}$), 3375 (NH). **^{13}C-NMR** (DMSO-d_6) = δ 14.17 (CH_3), 39.29 (CH_2), 126.21, 128.20, 128.77, 128.93, 129.90, 130.06, 133.47 and 135.28 ($C_{ar.}$), 168.24 (C=N), 188.02 (C=O), 193.50 (C=S) ppm.

3-(5-Oxo-6-styryl-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5H)-yl)-2-phenyl-quinazolin-4(3H)-one (10c).

IR (KBr) υ (cm^{-1}) = 1165 (C=S), 1600 (C=N), 1718 (C=O), 2953 (CH), 3105 ($CH_{ar.}$), 3380 (NH). **^{1}H-NMR** (DMSO-d_6) = δ 3.72-7.25 (d, 2H, *J* = 3.32 Hz, CH=CH), 7.5 – 8.20 (m, 14H, H_{ar}), 8.51 (s, 1H, NH) ppm.

2-Ethoxy-3-(5-oxo-6-styryl-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5H)-yl)-quinazolin-4(3H)-one (10d).

IR (KBr) υ (cm^{-1}) = 1155 (C=S), 1525 (C=N), 1700 (C=O), 2910 (CH), 3012 ($CH_{ar.}$), 3274 (NH).

Table **5**: Physical and analytical data of compounds **10a-d**

Cpd	M.p. (ºC)	Yield (%)	M. F. (M. W.)	M.A. (%); Calcd/Found C%	N%	H%
10a	190-92	55	$C_{25}H_{17}N_5O_2S$ (451.5)	66.50 66.18	3.80 3.71	15.51 15.43
10b	186-8	68	$C_{21}H_{17}N_5O_3S$ (419.46)	60.13 60.01	4.09 3.80	16.70 16.59
10c	157-9	71	$C_{24}H_{17}N_5O_2S$ (439.49)	65.59 65.36	3.90 3.78	15.94 15.85
10d	198-200	57	$C_{20}H_{17}N_5O_3S$ (407.45)	58.96 58.75	4.21 3.92	17.19 16.95

Reaction of 4-amino-6-benzyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (3a) with halo esters. Formation of 12 and 13.

Compound **3a** (2.34 g., 0.01 mol) was fused with ethyl chloro -(acetate and / or acetoacetate) (10 ml.) at 170 °C or refluxed in methanol in the presence of sodium hydroxide for 3-4 hr (tlc). The excess solvent was evaporated till dryness. The residual solid was crystallized from petroleum ether (80-100°C) and filtered to give **12** and **13**, respectively.

Ethyl-2-(4-amino-6-benzyl-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazin-3-ylthio)- acetate (12).

IR (KBr) υ (cm^{-1}) = 1631 (C=N), 1713, 1684 (2C=O), 2954 (CH_2), 3146 ($CH_{ar.}$), 3452 ($NH_{2\ sym}$), 3555 ($NH_{2\ asym.}$). **^{1}H-NMR** (DMSO-d_6) δ = 1.23 (t, 3H, *J* = 3.62 Hz, CH_3), 2.50 (s, 2H, NH_2), 3.30 (s, 2H, CH_2S), 3.55 (s, 2H, CH_2Ph), 4.3 (q, 2H, *J* = 2.57 Hz, CH_2CH_3), 6.90 – 8.21 (m, 5H, $H_{ar.}$) ppm.

Ethyl-2-(4-amino-6-benzyl-5-oxo-2,3,4,5-tetrahyd-ro-1,2,4-triazin-3-ylthio)-3-oxo-butanoate (13).

IR (KBr) υ (cm^{-1}) = 1571 (C=N), 1619 (C=O), 2912 (CH_2), 3001 ($CH_{ar.}$), 3338 ($NH_{2\ sym.}$), 3453 ($NH_{2\ asym.}$). **^{1}H-**

NMR (DMSO-d_6) δ = 1.25 (t, 3H, *J* = 3.42 Hz, CH_3CH_2), 1.65 (s, 3H, CH_3CO), 2.5 (s, 2H, NH_2), 3.2 (s, 2H, CH_2Ph), 3.4 (q, 2H, *J* = 2.51 Hz, CH_2CH_3), 3.55 (s, 1H, CH), 7.11-8.5 (m, 5H, $H_{ar.}$) ppm.

Table **6**. Physical and analytical data of compounds **12** and **13**.

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found C%	N%	H%
12	178-80	74	$C_{14}H_{16}N_4O_3S$ (320.37)	52.49 52.37	5.03 4.62	17.49 17.38
13	205-7	83	$C_{16}H_{18}N_4O_4S$ (362.4)	53.03 52.84	5.01 4.72	15.46 15.37

Reaction of compounds 3a,b with 1,3-dioxoisoindolealkyl acetic acid derivatives. Formation of 15a-f.

A mixture of **3a,b** (0.001mol) and (1,3-dioxo-1,3-dihydroisoindol-2-yl)(methyl-, phenyl- and/or benzyl)acetic acid (**14a-f**) (0.001mol) (prepared by fusion of glycine, alanine and/or phenyl alanine with phthalic anhydride according to Okuda et al)[13-15] was heated in phosphorus oxychloride (20 ml) at 85 °C for 5-6 hr (tlc). The reaction mixture was evaporated till dryness, cooled and neutralized with sodium hydroxide solution (10 %, 30 ml). The precipitate formed was filtered off, dried, and recrystallized from methanol and yielded **15a-f**.

2-((4-Oxo-3-styryl-4,8a-dihydro-1H-[1,3,4]thiadiazolo[2,3-c]-[1,2,4]triazin-7-yl)methyl)isoindo-line-1,3-dione (15a).

IR (KBr) υ (cm^{-1}) = 1460 (CH_2) 1538 (C=$C_{ar.}$), 1642 (C=N), 1721(C=O, NCO), 1772 (C=O, CONCO), 2997 (CH), 3099 ($CH_{ar.}$), 3445 (NH). **^{1}H-NMR** (DMSO-d_6) δ = 3.55 (s, 2H, CH_2), 5.21-5.42 (d, 1H, *J* = 3.12 Hz, CH=CH), 7.82 - 9.75 (m, 9H, $H_{ar.}$), 10.15 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) δ = 32.18 (CH_2), 51.65 (CH), 146.52, 153.18, 124.39, 131.59 and 134.73 ($C_{ar.}$), 165.61 (C=N), 175.37 (CONCO) ppm.

2-(1-(4-Oxo-3-styryl-4,8a-dihydro-1H[1,3,4]thiadiazolo[2,3-c][1,2,4]-triazin-7-yl)ethyl)isoind-oline-1,3-dione (15b).

IR (KBr) υ (cm^{-1}) = 1495 (C=$C_{ar.}$), 1626 (C=N), 1714 (C=O), 2925 (CH, CH_3), 3028 ($CH_{ar.}$), 3425 (NH). **^{1}H-NMR** (DMSO-d_6) δ = 2.15 (s, 3H, CH_3), 2.25, (s, 1H, CH), 4.36-4.63 (d, 2H, *J* = 2.98 Hz, CH=CH), 7.78 - 8.03 (m, 9H, $H_{ar.}$) ppm. **^{13}C-NMR** (DMSO-d_6) δ = 16.75 (CH_3), 52.63 (CH), 125.37, 131.69, 134.74, 148.55 and 157.27 ($C_{ar.}$), 167.61 (C=N), 174.47 (CONCO) ppm.

2-(1-(4-Oxo-3-styryl-4,8a-dihydro-1H-[1,3,4-]thiadiazolo[2,3-c][1,2,4]-triazin-7-yl)-2-phenyle-thyl)isoindoline-1,3-dione (15c).

IR (KBr) υ (cm^{-1}) = 1491 (CH_2), 1515 (C=C_{ar}), 1622 (C=N), 1725 (C=O), 3020 ($CH_{ar.}$), 3315 (NH). **^{1}H-NMR** (DMSO-d_6) δ = 3.11 (s, 2H, CH_2), 3.73 (s, 1H, CH), 7.15-7.35 (d, 2H, *J* = 3.50 Hz, CH=CHPh), 7.85-10.50 (m, 14H, $H_{ar.}$), 10.92 (s, 1H, NH.) ppm. **^{13}C-NMR** (DMSO-d_6) δ = 37.45 (CH_2), 61.15 (CH), 121.54, 124.89, 127.59, 129.14, 131.72, 135.73 148.78 and 157.18 ($C_{ar.}$), 161.55 (C=N), 169.93 (CONCO) ppm.

2-((3-Benzyl-4-oxo-4,8a-dihydro-1H-[1,3,4]thiadiazolo-[2,3-c][1,2,4]-triazin-7-yl)-methyl)isoindo-line-1,3-dione (15d).

IR (KBr) υ (cm^{-1}) = 1511 (CH_2), 1562 (C=$C_{ar.}$), 1595 (C=N), 1660, 1720 (2C=O), 2989 (CH), 3015 ($CH_{ar.}$), 3496 (NH). **^{1}H-NMR** (DMSO-d_6) δ = 2.11 (s, 2H, CH_2N), 3.63 (s, 2H, CH_2Ph), 7.25 – 9.85 (m, 9H, $H_{ar.}$), 10.47 (s, 1H, NH) ppm. **^{13}C-NMR** (DMSO-d_6) δ = 27.18 (CH_2), 33.39 (CH_2Ph), 145.47, 154.94, 125.41, 131.19, 135.71 ($C_{ar.}$), 164.45 (C=N), 174.52 (CONCO) ppm.

2-(1-(3-Benzyl-4-oxo-4,8a-dihydro-1H-[1,3,4]thiadiazo-lo[2,3-c][1,2,4]triazin-7-yl) ethyl)iso-indoline-1,3-dione (15e).

IR (KBr) υ (cm^{-1}) = 1496 (C=C_{ar}), 1571 (CH_2), 1605 (C=N), 1718, 1783 (2C=O), 2894 (CH, CH_3), 3458 (NH). **^{1}H-NMR** (DMSO-d_6) δ = 1.25 (s, 3H, CH_3), 2.55 (s, 1H, CH), 2.61 (s, 2H, CH_2), 7.87 – 9.82 (m, 9H, $H_{ar.}$) ppm. **^{13}C-NMR** (DMSO-d_6) δ = 17.81 (CH_3), 28.41(CH_2), 37.01 (CH), 126.41, 131.69, 135.34, 148.05 and 158.94 ($C_{ar.}$), 169.22 (C=N), 177.93 (CONCO) ppm.

2-(1-(3-Benzyl-4-oxo-4,8a-dihydro-1H-[1,3,4]thiadia-zolo[2,3-c][1,2,4]triazin-7-yl)-2-phenylethyl)isoindoli-ne-1,3-dione (15f).

IR (KBr) υ (cm^{-1}) = 1497 (C=$C_{ar.}$), 1555 (C=N), 1618 (CH_2), 1615, 1660 (2C=O), 3113 ($CH_{ar.}$), 3410 (NH). **^{1}H-NMR** (DMSO-d_6) δ = 3.61-3.82 (s, 4H, $2CH_2$ and H, CH), 7.8 – 9.4 (m, 14H, $H_{ar.}$), 9.94 (s, 1H, NH.) ppm. **MS** (EI) m/z = 493.12 (M^+, $C_{27}H_{19}N_5O_3S$, 1.41 %).

Table **7**. Physical and analytical data of compounds **15 a-f.**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found C%	N%	H%
15a	172-4	89	$C_{21}H_{15}N_5O_3S$ (417.44)	60.42 60.2	3.62 3.4	16.78 16.6

				4	5	0
15b	193-5	52	$C_{22}H_{17}N_5O_3S$ (431.47)	61.24 60.92	3.97 3.89	16.23 16.12
15c	185-7	68	$C_{28}H_{21}N_5O_3S$ (507.56)	66.26 66.14	4.17 4.03	13.80 13.72
15d	205-7	71	$C_{20}H_{15}N_5O_3S$ (405.43)	59.25 59.08	3.73 3.61	17.27 17.14
15e	220-2	86	$C_{21}H_{17}N_5O_3S$ (419.46)	60.13 60.05	4.09 3.81	16.70 16.64
15f	197-9	59	$C_{27}H_{21}N_5O_3S$ (495.55)	65.44 65.36	4.27 4.12	14.13 14.01

Hydrolysis of compounds 15a,b. Formation of 16a,b.

A mixture of **15a,b** (0.0001 mol) was boiled in conc. HCl (25 ml) for 8-10 hr (tlc). The reaction mixture was cooled to r. t. and neutralized with sodium hydroxide solution (10 %, 30 ml). The precipitate formed was filtered off, dried, and recrystallized from methanol to form **16a**,**b.**

7-(Aminomethyl)-3-styryl-1H-[1,3,4]thiadiazol-o[2,3-c][1,2,4]triazin-4(8aH)-one (**16a**).

IR (KBr) υ (cm^{-1}) = 1483 (C=$C_{ar.}$), 1514 (C=N), 1573 (CH_2), 1635 (C=O), 3075 (CH=CH), 3368 ($NH_{2\ sym}$), 3475 ($NH_{2\ asym}$). **^{1}H-NMR** (DMSO-d_6) δ = 1.97 (s, 2H, CH_2), 2.21 (s, 2H, N<u>H</u>$_2$), 5.55-5.75 (d, 2H, *J* = 3.31 Hz, CH=CH), 6.31-6.46 (m, 5H, H_{ar}) ppm.

7-(1-Aminoethyl)-3-styryl-1H[1,3,4]thiadiazo-lo[2,3-c][1,2,4]triazin-4(8aH)-one (16b).

IR (KBr) υ (cm^{-1}) = 1520 (C=C_{ar}), 1597 (C=N), 1726 (C=O), 3072 (CH=CH), 3310 ($NH_{2\ sym}$), 3435 ($NH_{2\ asym}$). **^{1}H-NMR** (DMSO-d_6) δ = 1.18 (s, 3H, CH_3), 2.5 (s, 2H, NH_2), 4.01-6.40 (d, 2H, *J* = 3.11 Hz, CH=CH), 7.51-8.05 (m, 5H, H_{ar}) ppm. **^{13}C-NMR** (DMSO-d_6) δ = 14.17 (CH_3), 61.12 (CH=CH), 126.59, 127.44, 129.00, 129.96, 130.15, 135.50 and 139.93 ($C_{ar.}$), 156.30 (C=N), 168.20 (C=O) ppm. **MS** (EI) m/z = 299.08 (M^+, $C_{14}H_{13}N_5OS$, 100 %).

<u>Reaction of 3a,b with 1,4-butane Sultone. Formation of 18a,b</u>.

A mixture of **3a,b** (0.001 mol) and 1,4-butanesultone (**17**) (0.136 ml, 0.001 mol) was fused in an oil bath at 140 - 150 °C for 6-8 hr (tlc). The reaction mixture was cooled and the produced mass was treated with dil. HCl. The solid formed was filtered off, and recrystallized from ethanol to give **18a** and **18b**, respectively

Table **8**. Physical and analytical data of compounds **16a,b.**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found C%	N%	H%
16a	175-7	54	$C_{13}H_{13}N_5OS$ (287.34)	54.34 54.21	4.56 4.48	24.37 24.11
16b	197-9	61	$C_{14}H_{15}N_5OS$ (301.37)	55.80 55.63	5.02 4.91	23.24 23.12

6-Benzyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*-)oyl-1-butan-1,4-sultam (18a).

IR (KBr) *ν* (cm^{-1}) = 1170 (C=S), 1162, 1351 (SO_2), 1610 (C=N), 1665 (C=O, $_{cyclic}$), 3472 (NH). **^{13}C-NMR** (DMSO-d_6) δ = 20.89 (CH_2), 22.62 (CH_2), 50.62 (CH_2), 126.43, 126.66, 128.91, 129.67 and 134.20 ($C_{ar.}$), 150.89 (C=N), 168.99 (C=O), 179.99 (C=S) ppm.

6-Styryl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*-)oyl1-butan-1,4-sultam (18b).

IR (KBr) *ν* (cm^{-1}) = 1157 (C=S), 1151, 1358 (SO_2), 1600 (C=N), 1690 (C=O), 3455 (NH). **MS** (EI) m/z = 364.07 (M^+, $C_{15}H_{16}N_4O_3S_2$, 80.12 %).

Table **9.** Physical and analytical data of compounds **18a,b.**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found C%	N%	H%
18a	186-8	52	$C_{14}H_{16}N_4O_3S_2$ (352.43)	47.71 47.42	4.58 4.43	15.90 15.71
18b	174-6	61	$C_{15}H_{16}N_4O_3S_2$ (364.44)	49.43 49.31	4.43 4.31	15.37 15.19

Biological Activity

Experimental

10 g peptone, 20 g glucose, and 20 g agar were dissolved in 1 L distilled water to preparation media of cultural. The

assay were seeded with $5x10^5$ cfu/ml of bacteria and $4x10^5$ cfu/ml of fungi and filled with (10 mg) powder samples for the tested bacteria and fungi, after solidification, they incubated at 37°C for 3 days, after which the diameter of the inhibition zones was measured.

Results and Discussion

Tested microorganisms

The antimicrobial activity of the prepared benzy- and/or styryl-1,2,4-triazine derivatives were determined against *Escherichia coli (NCIM2065)* a*s* gram-negative bacteria, *S. ureus* as gram-positive bacteria and *Candida albicans* as fungi and the inhibition zones were measured in triplicates.

Antimicrobial activity of some selected compounds:

The antimicrobial activity of the prepared benzy- and/or styryl-1,2,4-triazine derivatives **(3a, 5b, 5d, 8b, 8c** and **13)** were determined against the tested organisms by standard methods using Cut plug method**.** [16,17] The inhibition zones were measured and tabulated in the following table.

Table **(10):** Antimicrobial activity of compounds **(3a, 5b, 5d, 8b, 8c** and **13).**

Comp	Inhibition zone (mm)		
	S.areous MARSA	*E. coli*	*C. albicans*
3a	Negative	Negative	Negative
5b	20	Negative	15
5d	25	14	10
8b	16	Negative	Negative
8c	Negative	7	20
13	Negative	6	Negative

In table **10**: CompoundS **5b** and **5d** containing the amino phosphonates group. which might be the responsible group for the inhibitory effect on growth of the three tested microorganisms (*S.areous MARSA, E. coli and C. albicans).* compound. **8b** showed antimicrobial ACTIVITY with *S.areous MARSA,* only. compounds **8C** and **13** were tested against *E. coli and C. albicans.* compound . **8C** showed antimicrobial activities against *E. coli and C. albicans.Whiles* Compound . **13** showed antimicrobial effect with *E. coli* only. Compound . **5d** exhibited the highest inhibition zone.

Determination of Minimal inhibitory concentrations (MICs)

MICs of some synthetic compounds were determined for each antimicrobial agent by using agar dilution method [18]. The inhibition zone was measured in triplicates in different concentrations (0.5, 1.0, 2.0 ug/ml) and the mean values of **MICs** are tabulated in the following table.

Table (**11**): ***(MICs µg/ml)*** **of compounds (3a, 5b, 5d, 8b, 8c** and **13).**

Comp	Inhibition zone (mm)		
	S.areous MARSA	*E. coli*	*C. albicans*
3a	-	-	-
5b	2.0	-	1.0
5d	2.0	1.0	5.0
8b	0.5	-	-
8c	-	1.0	1.0
13	-	1.0	-

In table **11** the MICs of the above compounds were tested against *S.areous MARSA, E. coli and C. albicans* . Compound **5d** yielded MICs 1 µg/ml. It was found that the highest effective MICs was **5d**. The above compounds exhibited *MICs* ranged between 0.5-5 µg/ml.

Conclusion

In this paper. the authors reported the synthesis of some new 1,2,4-triazine derivatives to explore their biological activity. Preliminary results showed that some of them gave antibacterial activity.

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الملخص باللغة العربية

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عند تكاثف المركبين (3a,b) مع عدد من الالدهيدات الأروماتية يعطي قواعد شيف المقابلة .(4a-f). بينما اذا تم تفاعل المركبين 3a,b مع مخلوط من (البنزالدهيد أو -4-ثنائي ميثيل امينو البنزالدهيد) وثلاثي فينيل الفوسفيت فى وجود اوكسي كلوريد الفوسفور عند درجة 100 م° فانه يعطي (5a-d).

عند تسخين المركبين 3a,b مع بعض مشتقات فنيل -4-توليل أمينو حمض الخليك (6a-f) في وجود أوكسي كلوريد الفوسفور عند درجة 85م° فانه يعطي مشتقات الثيادیازولوتریازین المقابلة (7a-l). وبالتحلل المائي للمركبات (7a,b and k) وذلك بتسخينها فى وجود حمض الهيدروكلوريك المركز فانه يعطي الأمينات الجديدة المقابلة (8a – c).

عند غليان المركب 3a,b مع مشتقات البنزواوكزازون (9) فى حمض الخليك الثلجى فانه يعطي المركبيات (10a,b).

بمعالجة المركب 3a مع كلوروايثيل الاسيتات عند درجة الغليان فى وجود هيدروكسيد الصوديوم يتكون مشتق الايثيل اسيتات المقابل 12 وبالمثل عند معالجة المركب 3a بمشتق الكلوروايثيل أسيتوأسيتات فى نفس ظروف التفاعل السابقة فانه يعطي مشتق الاكسو بيوتونات المقابل 13.

عند تسخين المركبين3a,b مع 1،3-داي أوكسو-1،3-داي هيدروايزواندول-2-يل(ميثيل-،فينيل-،أو بينزيل) حمض الخليك (14a-f) فى وجود أوكسي كلوريد الفوسفور عند درجة 85 م° فانه يعطي 15a-f بعد المعادلة بهيدروكسيد الصوديوم. وبالتحلل المائي للمركبات 15a,b بحمض الهيدروكلوريك المركز المغلي فانها تعطي الأمينات المقابلة 16a,b بالاضافة الى حمض الفيثاليك كناتج ثانوي.

عند صهر المركبات 3a,b مع 1،4- بيوتان سالتون عند درجة حرارة 180م° فانه يعطي المركبات (18a,b) المقابلة.

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