REVIEW

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Role of uncondensed 1,2,4-triazine compounds and related heterobicyclic systems as therapeutic agents – a review*

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The role of uncondensed 1,2,4-triazine compounds and related heterobicyclic systems in AIDS and Cancer is reviewed. Their medicinal applications are also reported.

1. Introduction

The 1,2,4-triazine ring has been successfully used as a carrier for several functional groups in the development of antiviral agents [1, 2] various 1,2,4-triazines have been synthesized and most of them have shown biological applications [3–8].

Recently, a great deal of synthetic effort has been spent on uncondensed 1,2,4-triazines searching for new anti HIV and anticancer agents and other medicinal applications.

At present several drugs are used for treatment of AIDS [9]. Some of them fail to maintain adequate drug levels at the site of replication over extended periods due to their relatively short half lives [10–13] and thus fail to stop progression of the disease. The large number of research papers published every year [14–16] indicates that the development of effective drugs for the treatment of AIDS continues to be a challenging problem in medicinal research.

Of all the diseases, cancer is the greatest killer of human race. Though the disease was detected long back, it's cause is still unknown and its complete cure is yet to be achieved. One need hardly dwell on the advantages which might occure if the enormous powers of the human immune system could be mobilized to do battle against cancer [17–20]. It could be imagined that such a recruitment would be helpful in combatting the formation of the cancerous cell, in attacking existing areas of cellular transformation and in resisting metastasis [21].

This concept has often been discussed in the context of futuristic hopes and has been supported by some early success [22–25].

It is believed that cancer (80–90%) results from interactions between host factors and the environment and that only a small percentage of cancer (about 5%) can be attributed to genetic factors alone [26].

In view of the above findings, the antitumor activity of some representative derivatives has been evaluated primarily by growth inhibition assays [27].

2. Synthesis of uncondensed 1,2,4-triazines as antiHIV and/or anticancer agents

Abdel-Rahman et al. take part in the discovery and development of novel uncondensed 1,2,4-triazines for treatment of malignancy and HIV infections.

The procedure used in the National Cancer Institute (USA) to test compounds against HIV is designed to detect agents acting at any stage of the virus reproductive cycle. All compounds tested are compared with a positive (AZT treated) control done at the same time under identical conditions [28]. Most of the newly synthesized compounds have also been evaluated *in vitro* for antitumor activity. A sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth.

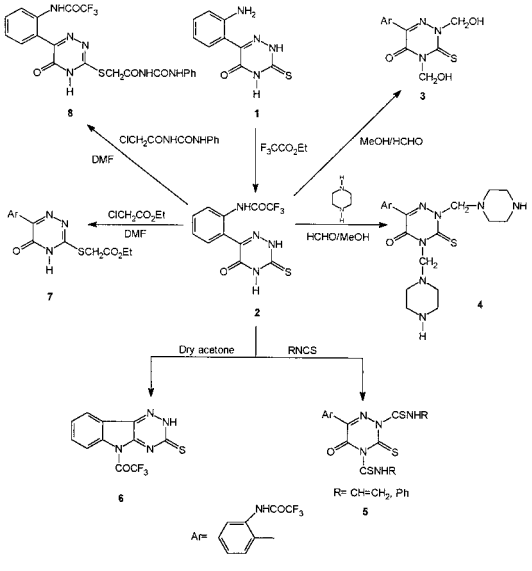
The fluorene bearing 3-thioxo-1,2,4-triazin-5-one (**2**) was obtained by acylation of 6-(2-aminophenyl)-3-thioxo-1,2,4-triazin-5(2*H*,4*H*)one (**1**) with ethyl trifluoroacetate. The targets **2**–**7** displayed a moderate but significant anti HIV activity (Scheme 1) [27]. Compounds **4** and **8** showed a moderate activity against leukemia/lymphoma, small/non small cell lung, colon carinoma and melanoma cells [29].

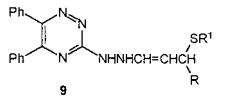
A number of various thioethers derived from 5,6-diphenyl-3-hydrazone-1,2,4-triazine have been synthesized and evaluated for anticancer and anti HIV activities. The results indicated that compounds **9**, **10** and **11** showed a significant activity towards leukemia, **9d** against CNS and **10d** against ovarian cancer. Compounds **9a**, **9c**, **9d**, **10b**, **10c**, **10d** and **11b** showed a significant anti-HIV activity [30].

Some new 1,6-dihydro-3(2*H*)-thioxo-6-spiro(9′-fluorene)-1,2,4-triazin-5(4*H*)ones and related compounds synthesized were **12**–**16** showing significant activity against HIV *in vitro* while only compounds **16** and **17** were moderately active towards tumor cells. Compound **16** was more potent regarding both anti HIV, and antitumor activities [31].

Some new heterobicyclic compounds containing the 1,2,4-triazine moiety have been synthesized and evaluated for anticancer and anti HIV activities. Compounds **18**–**20** proved to be potent antitumor agents activity, while compound **21** possessed only a moderate activity [32].

Scheme 1





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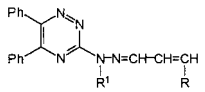
	R	R^1
a	Me	$C_6H_4NH_2$-o
b	Ph	$C_6H_4NH_2$-o
c	Ph	$C_6H_4NHCSNHPh$-o
d	Ph	C_6H_4Me-o
e	Ph	C_6H_4Cl-p



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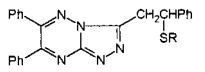
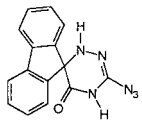
	R	R^1
a	Ph	CSNHPh-o
b	Ph	$COC_6H_3Cl_2$-o,p
c	Me	$SO_2C_6H_4Me$-p
d	Ph	$SO_2C_6H_4Me$-p



11

	R
a	$C_6H_4NH_2$-o
b	C_6H_4Cl-p

The introduction of an azide group in the 1,2,4-triazinone nucleus **22** results in the enhancement of HIV activity. On the other hand, the 1,2-disubstituted hydrazine **23** has a higher sensitivity than other tested compounds [33]. Similarly, compound **24** has shown a lethal activity for antitumor and a moderate activity for anti HIV activity [34].



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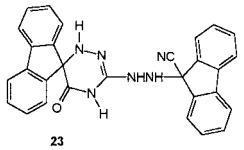

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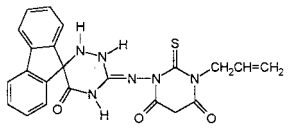

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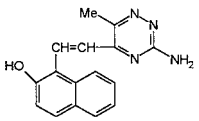

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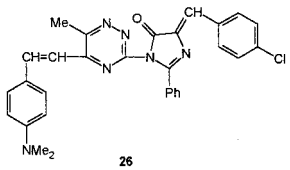

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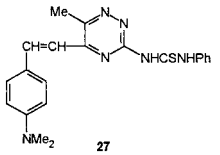

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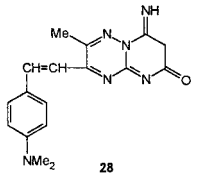

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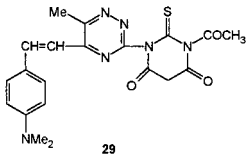

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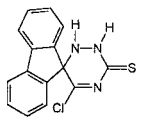

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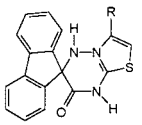

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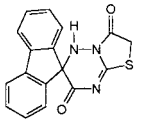
R= NHCSNHPh



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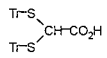

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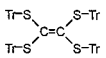

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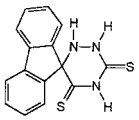

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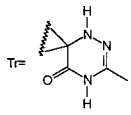
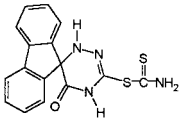


Tr=



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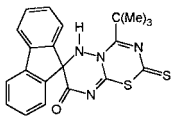

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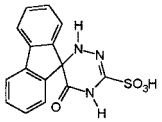

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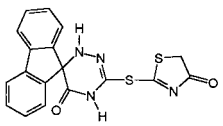

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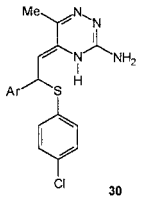


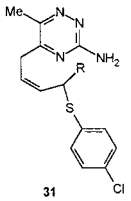
30

Ar

a=

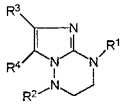
b=

c=



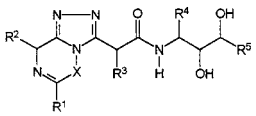
31

a, R= Me
b, R= Ph



32

R^1, R^2= H ; R^3= 4-FC_6H_4 ; R^4= 4-pyridyl



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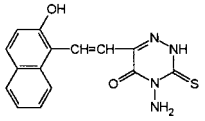

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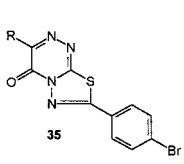

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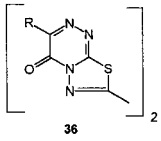

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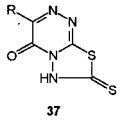
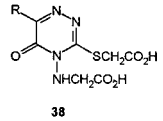


37

R=



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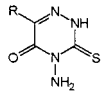

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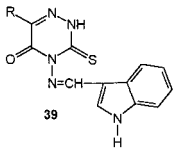

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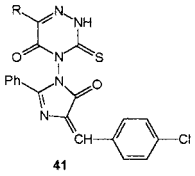

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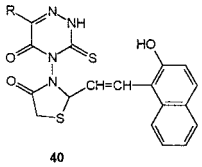

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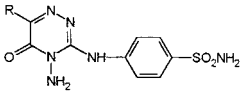
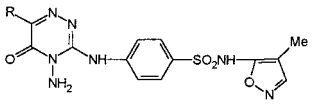
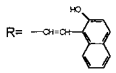


41a



41b



Some new heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety have been synthesized starting from 3-amino-1,2,4-triazines. For compounds **26** > **25** > **27** > **28** > **29** a moderate to lethal anticancer activity, was recorded and compound **28** has a higher sensitivity than other compounds, while compound **26** was found to be more active against HIV activity [35].

Also, compounds **31b** > **30c** > **31a** > **30a** > **30b** showed high to moderate anticancer activity, while compounds **31a** and **31b** were moderately active towards HIV. The skeleton of compound **31b** enhanced both the HIV and anticancer activities [36].

Some new imidazolotriazines **32** have been prepared as inhibitors of interleukin-1 and tumor necrosis factor. Thus, **32** ($R^1 = R^2 = H$, $R^3 = 4\text{-}FC_6H_4$, $R^4 = 4$-pyridyl) had IC_{50} values for the inhibition of interleukin-1 to 1.3 and 1.5×10^{-7} μl [37]. In addition, the triazolo-1,2,4-triazine **33** has been synthesized and tested as renin inhibitors with IC_{50} 20–150 nμ [38].

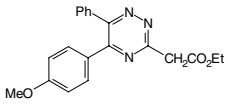
Abdel-Rahman et al. [39], reported 4-amino-3-thioxo-6-styryl-1,2,4-triazin-5-ones and evaluated them for anticancer activity, where compounds **35** > **34** > **37** > **36** > **38** showed more activity against lung, breast and CNS cancer cells.

Moreover, compounds **34**, **39**, **40**, **41**, **42a** and **42b** exhibited moderate activity towards leukemia, ovariar cancer, non-small cell lung cancer cells [40].

3. Medicinal applications of uncondensed 1,2,4-triazines

Synthesis of 5,6-diaryl-1,2,4-triazine derivatives as blood platelet aggregation inhibitors has been reported. Thus, 5,6-diphenyl-3,5-diphenyl-, and 3,6-diphenyl-1,2,4-triazine derivatives were synthesized and evaluated for inhibitory activity towards arachidonic acid-induced aggregation of rabbit blood platelets *in vitro*. Among the isomers, 5,6-diphenyl-1,2,4-triazine derivatives were active, therefore a Ph substituent on the 1,2,4-triazine ring at the 5- and 6-positions were essential for the inhibitory activity. Among these compounds Et 5-(4-methoxyphenyl)-6-phenyl-1,2,4-triazine-3-acetate (**42**) and Et 5,6-bis(4-methoxyphenyl)-1,2,4-triazine-3-acetate (**43**) showed the most potent inhibitory activity, which was almost equal to the activity of antiazafen [41].

Lamotrigin (LTG, **44**) is a novel triazine anticonvulsant. The novel antiarrhythmic LTGN-glucuronide (**45**)



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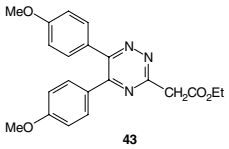

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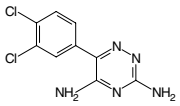

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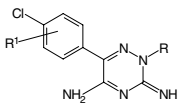


45

($R = Me_2CH$, Et; $R = Et$, $R^1 = Cl$) was ~ 3 times more effective than Bw A_2 **56c** at 1 mg/kg i.v. in rats [42].

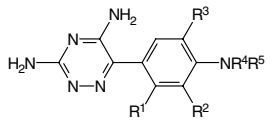
6-Aminophenyl-3,5-diamino-1,2,4-triazines **46** (R^1–R^3 = Cl, and the others = H or Cl; R^4, R^5 = H, alkyl) were prepared as neuroprotective agents. Compound **46** had IC_{50} of 10 μM against glutamate release from rat brain slices [43].

1-Heterocyclylalkyl-3-aryl-1,2,4-triazin-6-ones and analogs **47** [R = substituted (hetero)aryl; $R^1 = (CH_2)nNR^2R^3$ and $R^6R^{16} = O$; R^2, R^3 = H, alkyl; NR^2R^3 = heterocyclyl; n = 2–4; R^1R^6 = bond and $R^{16} = NR^7R^8$; $R^1R^6 = CR^{13}{:}NNR^{17}$ and $R^{16}R^{17}$ = bond; R^5 = H, (cyclo)alkyl, (hetero)aryl; R^7 = H, alkyl; R^8 = aminoalkyl; NR^7R^8 = heterocyclyl; R^{13} = (aryl), alkyl, (hetero)aryl] were prepared as analgesics agents. Compound **48** had a ED50 of 25 mg/kg i.p. against acetic acid-induced writhing in mice [44].

1,2,4-Triazines **49** and **50** (A = CO, CS; B = O, NR^4, CR^5R^6; R^1 = (un)substituted aryl, heteroaryl; R^2, R^5, R^6 = H, NH_2, halo (cyclo)alkyl; R^4 = H, (cyclo)alkyl, OH, alkoxycarbonyl; Z = H, pharmaceutically acceptable cation, metabdically Labile group) were prepared as lipoxygenase inhibitors. Compound **50** gave 85% inhibition of leukotriene biosynthesis in rats at 200 μmol/kg orally [45].

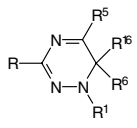
Similarly, some new dihydro-4-methyl-1-phenyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione derivatives **51** (R^1 = H, halo, OH, C_{1-6} alkyl, C_{1-6} alkoxy, (un)substituted phenyl, C_{1-3} alkoxy, R^3O_2C (R^3 = H, C_{1-4} alkyl), R^5R^4NCO (R^4, R^5 = H, C_{1-4} alkyl, or R^5R^4N = saturated 5,7-membered heterocycl; R^2 = H, halo, HO, C_{1-6} alkyl, C_{1-6} alkoxy] were obtained as 5-lipoxygenase inhibitors [46].

Moreover, some 3,7-disubstituted-4*H*-[1,2,4]triazino[3,4-*a*]-phthalazines **52** [R = OEt, $NMeCH_2CH(OH)Me$, pyrrolidino, R^1 = H, OMe] and 3,7-disubstituted-4*H*-[1,2,4]triazino[3,4-*a*]phthalazine-4-ones **53** [R = same as above,

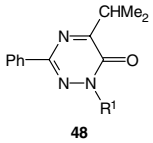


46

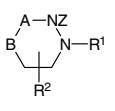
R^1, R^3= Cl, R^5= H



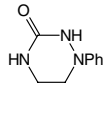
47



48



49



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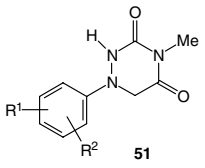

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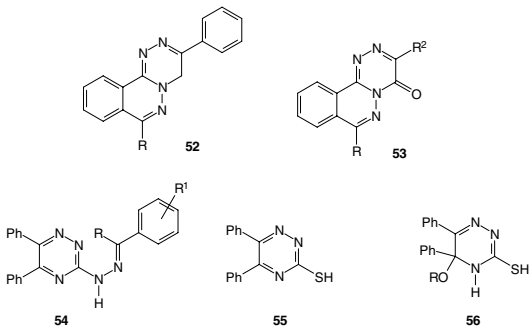
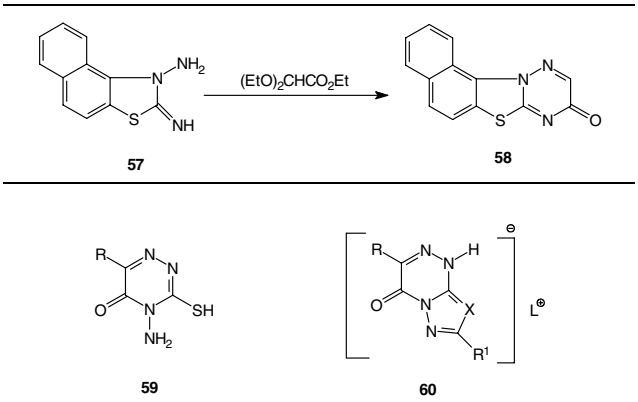


Scheme 2



R^2 = Me, 4-$MeOC_6H_4$] were obtained and tested *in vitro* for inhibition of the H^3-diazepam specific binding to benzodiazepine receptors in rat brain and *in vivo* for their effects on the conditioned behavior in rats. **52** (R = OEt, pyrrolidino, R^1 = H) and **53** (R = $NMeCH_2CH(OH)Me$, R^2 = 4-C_6H_4OMe) showed weak activity [47].

Also, some new 1,2,4-triazine derivatives have been synthesized and used as antiviral agents. Among them, 5,6-Diphenyl-1,2,4-triazine-3-hydrazines **54** (R = H, Me; R^1 = H, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 2-HOC_6H_4) showed antiviral activity [48].

Refluxing 5,6-diphenyl-1,2,4-triazine-3-thiol (**55**) with alcohols (ROH; R = Me, Et) led to the formation of alkoxytriazine **56** in 94% and 77% yields. Compounds **55** and **56** had 5% antiviral inhibitory activity against influenza viruses in concentrations of 12.5–63.1 mg/ml [49].

Cyclocondensation of 3-amino-2-iminonaphtho[1,2-*d*]-thiazole (**57**) with ethyl diethoxyacetate in AcOH yielded thiazolotriazinone the **58** (Scheme 2). Compound **58** showed anti HIV activity [50].

6-Nitro-1-oxo-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines **60**, (R = NO_2, CN, CO_2Et; X = NCH, CN; R^1 = H, Me, Ph, 4-pyridyl, NMe, NHAc, SMe; L = Na, K, Mg, NH_2, Me_2, piperidinium, morpholinium) have been synthesized starting from 4-amino-3-thioxo-1,2,4-triazin-5-one (**59**). Compounds **60** exhibited antiviral activity [51].

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