

# 1,2,4-triazine derivatives: Synthesis and biological applications

Mohammad Arshad<sup>1,2\*</sup> Taki Ahmed Khan<sup>2,3</sup> and Meraj Alam Khan<sup>2</sup>

<sup>1</sup>Jamia Millia Islamia, New Delhi-110025, India

<sup>2</sup>Department of chemistry, AMU, Aligarh-202002, India

<sup>3</sup>Applied Biotechnology Department, Sur College of Applied Sciences, Sur, Oman

[mohammadarshad.medchem@gmail.com](mailto:mohammadarshad.medchem@gmail.com)

[mohdarshad1985@gmail.com](mailto:mohdarshad1985@gmail.com)

## Abstract:

1,2,4-Triazines are the six membered heterocyclic compounds possessing three nitrogen in its structure with general formula  $C_3H_3N_3$ . 1,2,4-Triazines and its derivatives have been found to exhibit the variety of biological applications such as antifungal, anti-HIV, anticancer, antiinflammatory, analgesic and antihypertensive, cardiogenic, neuroleptic, nootropic, antihistaminergic, tuberculostatic, antiviral, anti-protozoal, estrogen receptor modulators, antimalarial, cyclin-dependent kinase inhibitors, antimicrobial and antiparasitic activities.

**Key words:** 1,2,4-Triazine derivatives, synthesis, biological activity

## 1. Introduction:

Heterocyclic chemistry is fundamental to biology and medicine. It is not implausible to say that we are living in the age of heterocyclic chemistry. It constitutes a large group of organic molecules exhibiting a wide range of biological activities which is basis of life and society. The majority of pharmaceutical products that mimic natural products with biological activity are heterocyclic in nature.

The triazine structure is a heterocyclic ring, analogous to the six-membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine<sup>1</sup> [Figure-1].

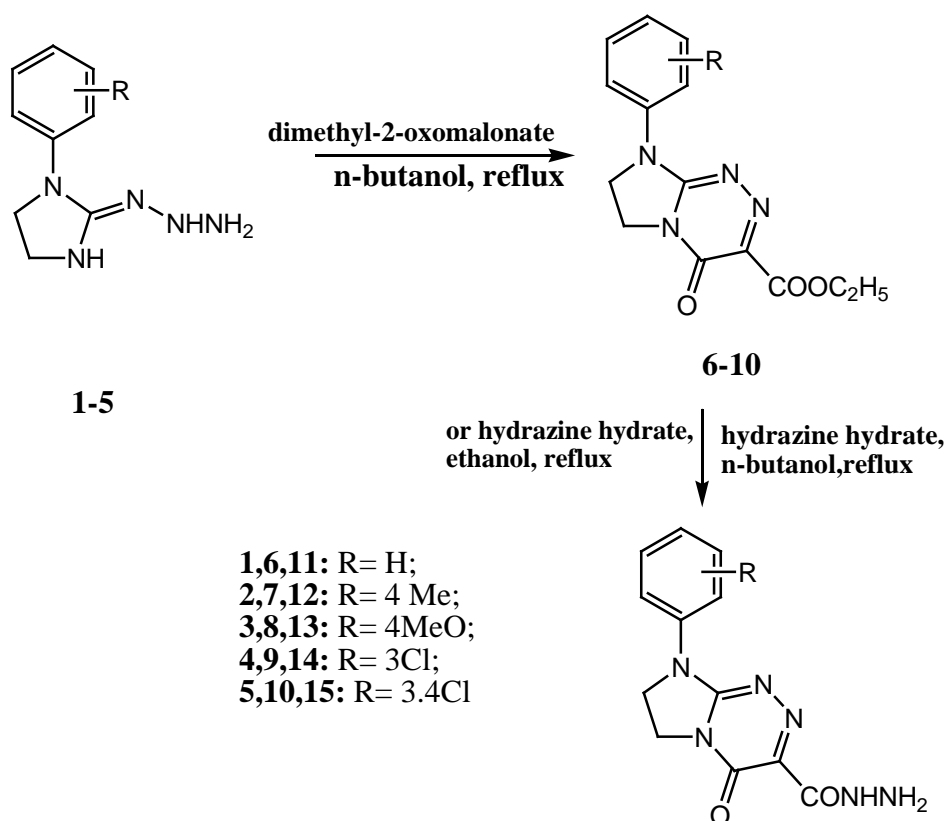


[Figure-1]

1,2,4-Triazine derivatives have been reported to possess a broad spectrum of biological activities including antifungal, anti-HIV, anticancer, antiinflammatory, analgesic antihypertensive, cardiogenic, neuroleptic, nootropic, antihistaminergic, tuberculostatic, antiviral, anti-protozoal, estrogen receptor modulators, antimalarial, cyclin-dependent kinase inhibitors, antimicrobial, antiparasitic, activities.<sup>1-21</sup>

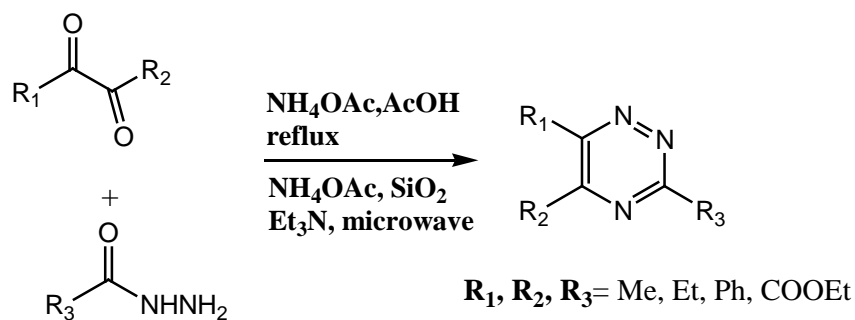
## 2. Synthesis and Biological activity:

K Sztanke et al.<sup>22</sup> reported the synthesis, structure elucidation and identification of antitumoural properties of novel fused 1,2,4-triazine aryl derivatives [Figure-2].



**Figure-2**

Z Zhao et al.<sup>23</sup> reported the new scope of 1,2,4-triazine synthesis by the application of microwave technology [Figure-3.1] & [Figure-3.2].



**Figure-3.1**

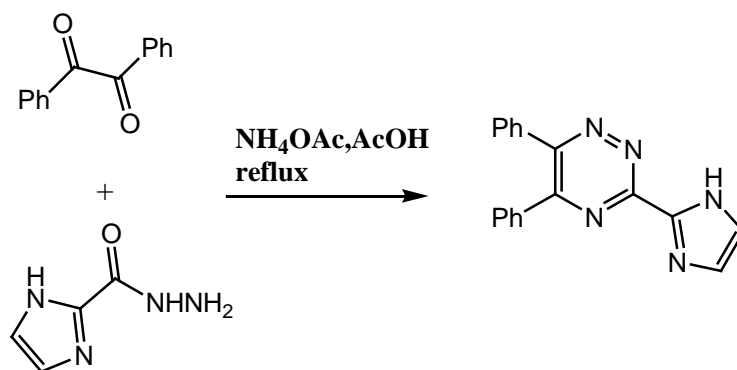


Figure-3.2

L Gupta et al.<sup>24</sup> reported the synthesis and biological evaluation of new [1,2,4] triazino [5,6-b]indol-3-ylthio-1,3,5-triazines and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines against *Leishmania donovani* [Figure-4].

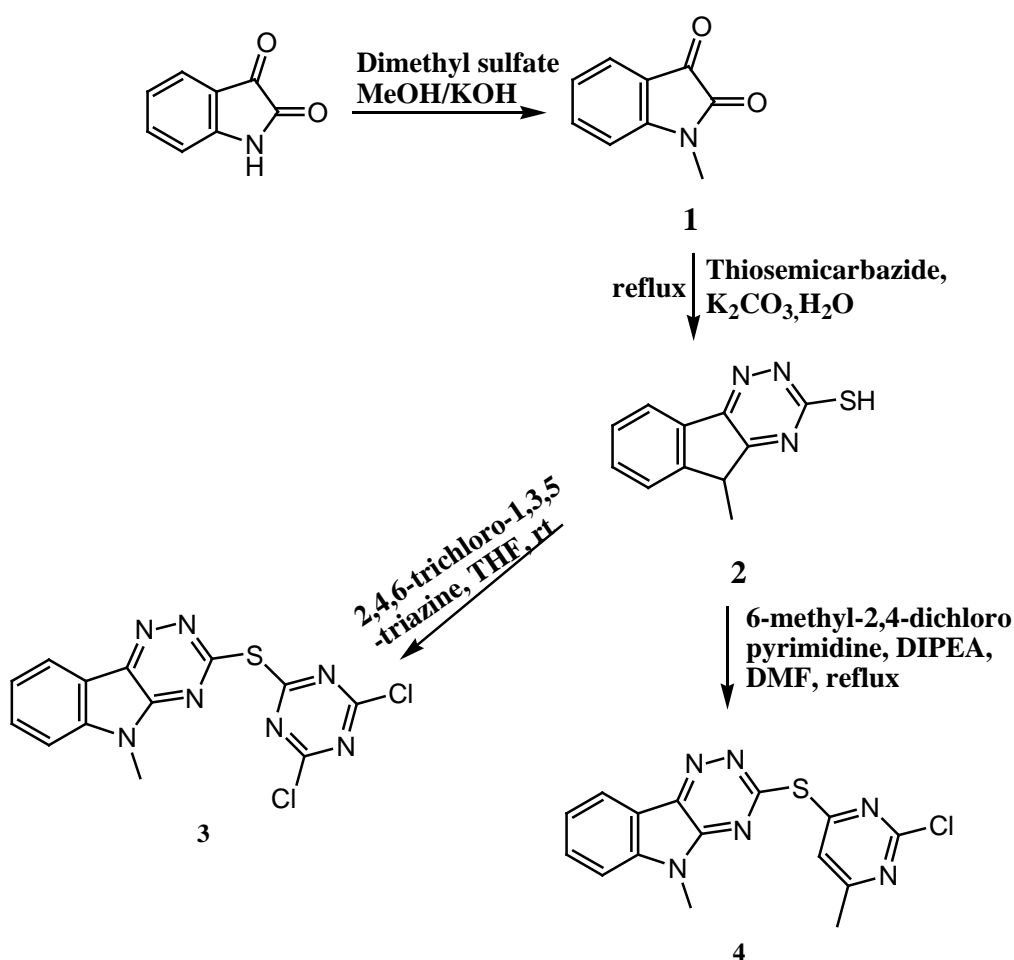
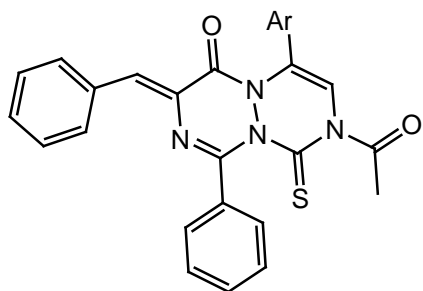
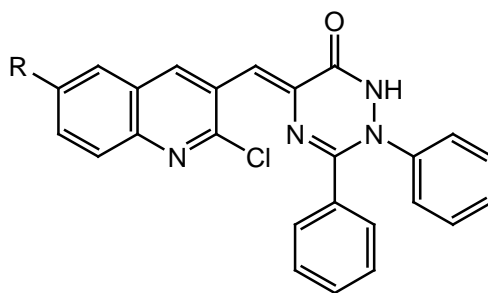


Figure-4

J A Hassanen et al.<sup>25</sup> reported the synthesis, biological activity and mass spectral investigation of 1,2,4- triazino-[2,1-a]-1,2,4-triazine derivatives [Figure-5]. B S Dawane et al.<sup>26</sup> have synthesized 1,2,4-triazine derivatives containing quinoline nucleus [Figure-6] and evaluated *in vitro* antimicrobial activity.

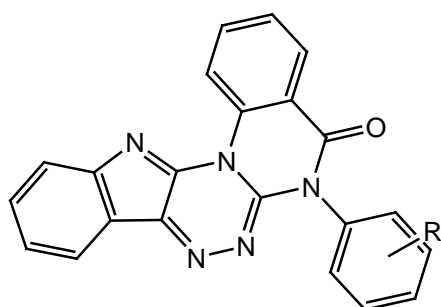


**Figure-5**

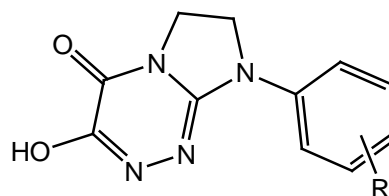


**Figure-6**

S K Pandey et al.<sup>27</sup> reported the antimicrobial studies of some novel quinazolinones derivatives fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings [Figure-7]. K Sztanke et al.<sup>28</sup> have synthesized 8-aryl-3,4-dioxo-2*H*,8*H*-6,7-dihydroimidazo[2,1-*c*] [1,2,4]triazines [Figure-8] and tested them for pharmacological activity.

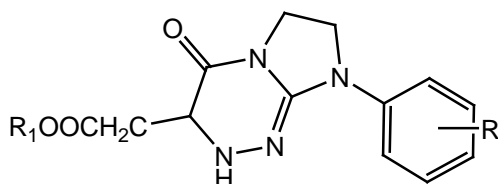


**Figure-7**

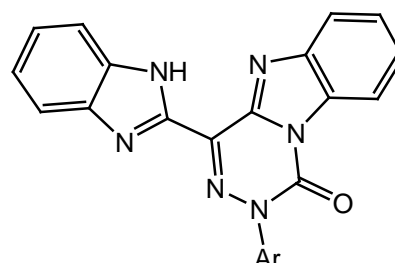


**Figure-8**

K Sztanke et al.<sup>29</sup> reported the synthesis, crystal structure and anticancer activity of novel derivatives of ethyl 1-(4-oxo-8-aryl-4,6,7,8-tetrahydroimidazo[2,1-*c*][1,2,4]triazin-3-yl)formate [Figure-9]. J Styskala et al.<sup>30</sup> have synthesized a new series of 2-aryl-4-(benzimidazol-2-yl)-1,2-dihydro[1,2,4]triazino-[4,5-*a*]benzimidazol-1-one derivatives [Figure-10] with preferential cytotoxicity against carcinoma cell lines.

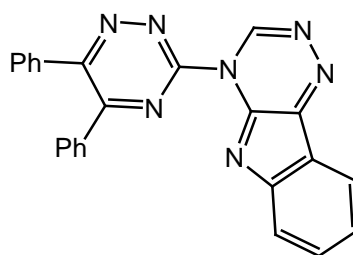
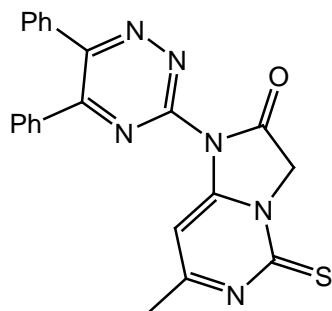


**Figure-9**



**Figure-10**

W R Abdel-Monem et al.<sup>31</sup> have synthesized and screened antimicrobial activity of some new nitrogen heterocyclic systems bearing 1,2,4-triazine moiety [Figure-11].



**Figure-11**

P Barraja et al.<sup>32</sup> reported the synthesis and antiproliferative activity of [1,2,4]triazino[4,3-*a*]indoles [Figure-12]. P Diana et al.<sup>33</sup> have synthesized some novel pyrrolo[2,1-*c*][1,2,4]triazines [Figure-13] from 2-diazopyrroles and evaluated their antiproliferative activity.

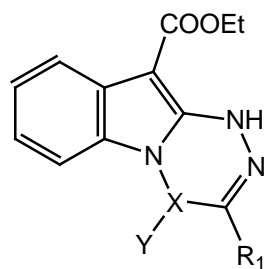


Figure-12

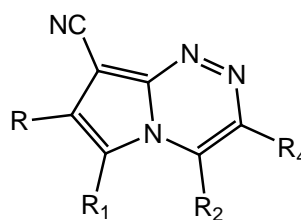


Figure-13

K Sztanke et al.<sup>34</sup> reported the synthesis, crystal structure and antiproliferative activity of novel derivatives of methyl and ethyl 2-(4-oxo-8-aryl-2*H*-3,4,6,7-tetrahydroimidazo[2,1-*c*][1,2,4]triazin-3-yl)acetates [Figure-14] from biologically active 1-aryl-2-hydrazinoimidazolines. T T Gucky et al.<sup>35</sup> have synthesized and tested cytotoxic activity of some 3,7-diaryl-5-(3,4,5-trimethoxyphenyl)pyrazolo[4,3-*e*][1,2,4]triazines [Figure-15].

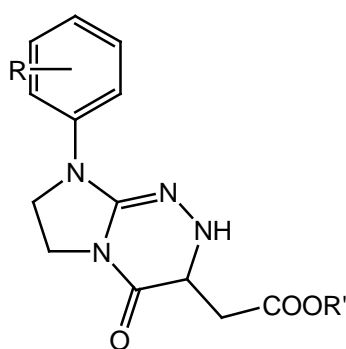


Figure-14

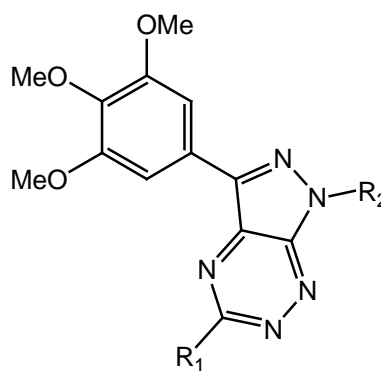


Figure-15

H Irannejad et al.<sup>36</sup> reported the synthesis and *in vitro* evaluation of novel 1,2,4-triazine derivatives as neuroprotective agents [Figure-16].

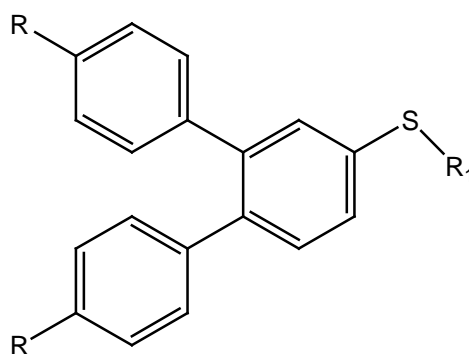
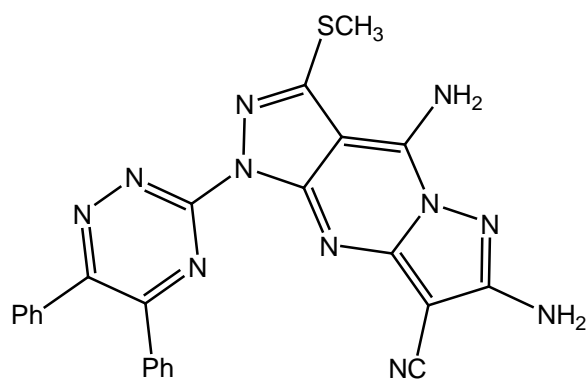


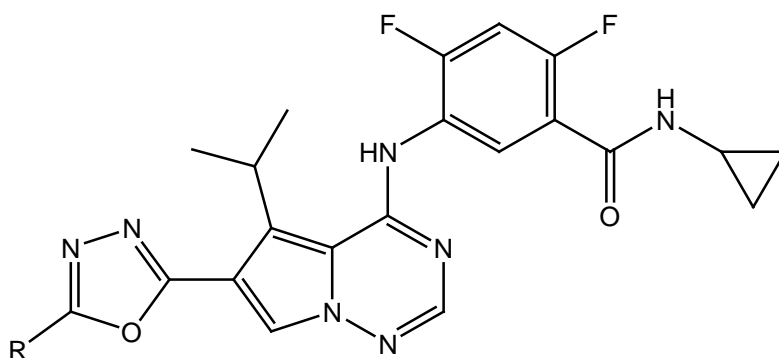
Figure-16

T El S Ali et al.<sup>37</sup> reported the synthesis of some novel pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine derivatives bearing 5,6-diphenyl-1,2,4-triazine moiety as potential antimicrobial agents [Figure-17].



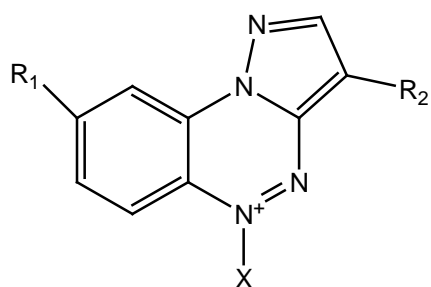
**Figure-17**

Z Cai et al.<sup>38</sup> have reported the synthesis, SAR and evaluation of 4-[2,4-difluoro-5(cyclopropylcarbamoyl)phenylamino]pyrrolo[2,1-f][1,2,4]triazine-based VEGFR-2 kinase inhibitors [**Figure-18**].

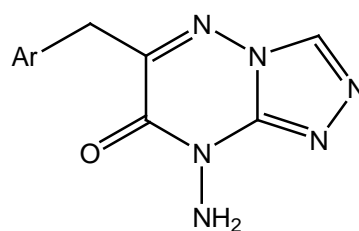


**Figure-18**

G Ciciani et al.<sup>39</sup> have reported the synthesis of new pyrazolo[5,1-c][1,2,4] benzotriazines, pyrazolo[5,1-c]pyrido[4,3-e][1,2,4] triazines and their open analogues as cytotoxic agents in normoxic and hypoxic conditions. A M EL Massry et al.<sup>40</sup> reported the synthesis and structure elucidation of novel fused 1,2,4-triazine derivatives as potent inhibitors targeting CYP1A1 activity [**Figure-19**]and [**Figure-20**].

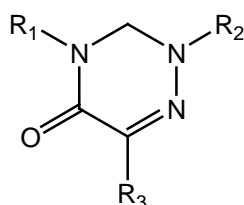


**Figure-19**



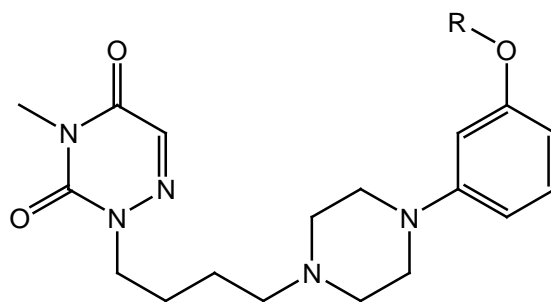
**Figure-20**

F Krauth et al.<sup>41</sup> reported the synthesis and characterization of novel 1,2,4-triazine derivatives with antiproliferative activity [**Figure-21**].



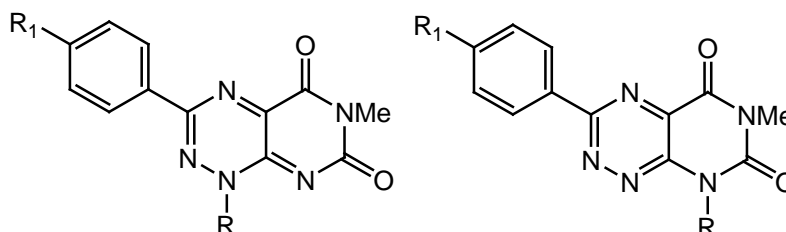
**Figure-21**

J. Prabhakaran et al.<sup>42</sup> reported the synthesis, in vitro and in vivo evaluation of [O-methyl-11C] 2-{4-[4-(3-methoxyphenyl)piperazin-1-yl]-butyl}-4-methyl-2H-[1,2,4]-triazine-3,5-dione: A novel agonist 5-HT<sub>1A</sub> receptor PET ligand [Figure-22].



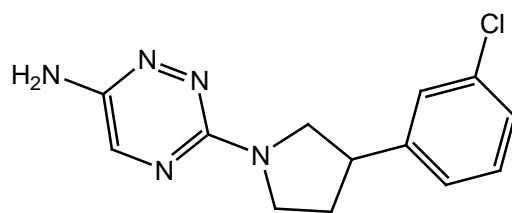
**Figure-22**

Nearly all colorectal cancers (crCs) and varied subsets of other cancers have somatic mutations leading to  $\beta$ -catenin stabilization and increased  $\beta$ -catenin/TCF transcriptional activity. Inhibition of stabilized  $\beta$ -catenin in CRC cell lines arrests their growth and highlights the potential of this mechanism for novel cancer therapeutics. We have pursued efforts to develop small molecules that inhibit  $\beta$ -catenin/TCF transcriptional activity. We used xanthothricin, a known  $\beta$ -catenin/TCF antagonist of microbial origin, as a lead compound to synthesize related analogues with drug-like features such as low molecular weight and good metabolic stability. J. Zeller et al.<sup>43</sup> studied a panel of six candidate Wnt/  $\beta$ -catenin/Tcf-regulated genes and found that two of them (Axin2, Lgr5) were reproducibly activated (9–10 fold) in rat intestinal epithelial cells (IEC-6) following  $\beta$ -catenin stabilization by Wnt-3a ligand treatment. Two previously reported  $\beta$ -catenin/TCF antagonists (calphostin C, xanthothricin) and XAV939 (tankyrase antagonist) inhibited Wnt-activated genes in a dose-dependent fashion. The author found that four compounds were also potently inhibited Wnt-mediated activation in the panel of target genes. They also investigated the mechanism of action for one of the SERIES and demonstrated these novel small molecules inhibit  $\beta$ -catenin transcriptional activity by degrading  $\beta$ -catenin via a proteasome-dependent, but GSK3  $\beta$ -, APC-, AXIN2- and bTrCP-independent, pathway. The data indicate the compounds act at the level of  $\beta$ -catenin to inhibit Wnt/  $\beta$ -catenin/TCF function and highlight a robust strategy for assessing the activity of  $\beta$ -catenin/TCF antagonists [Figure-23].



**Figure-23**

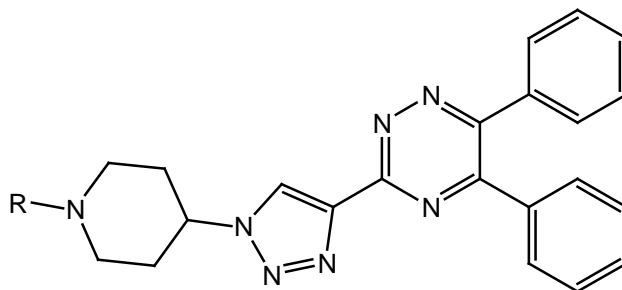
Inorganic pyrophosphatases are potential targets for the development of novel antibacterial agents. W. Lv et al.<sup>44</sup> reported a pyrophosphatase-coupled high-throughput screening assay intended to detect o-succinyl benzoic acid coenzyme A (OSB CoA) synthetase inhibitors led to the unexpected discovery of a new series of novel inorganic pyrophosphatase inhibitors. Lead optimization studies resulted in a series of 3-(3-aryl-pyrrolidin-1-yl)-5-aryl-1,2,4-triazine derivatives that were prepared by an efficient synthetic pathway. One of the tetracyclic triazine analogues 3-(3-(3-chlorophenyl)pyrrolidin-1-yl)-1,2,4-triazin-6-amine displayed promising antibiotic activity against a wide variety of drug-resistant *Staphylococcus aureus* strains, as well as activity versus *Mycobacterium tuberculosis* and *Bacillus anthracis*, at a concentration that was not cytotoxic to mammalian cells [Figure-24].



**3-(3-(3-chlorophenyl)pyrrolidin-1-yl)-1,2,4-triazin-6-amine**

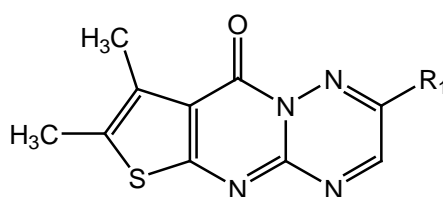
**Figure-24**

J. N. Sangshetti et al.<sup>45</sup> reported an improved protocol for the synthesis of a novel series of 1,2,4-triazines possessing 1,2,3-triazole and piperidine ring using 1-(1-substituted piperidin-4-yl)-1H-1,2,3-triazole-4-carbohydrazide, benzil, ammonium acetate and  $ZrOCl_2 \cdot 8H_2O$  as a catalyst in ethanol–water has been presented. The yields obtained are in the range of 87–94%. All the synthesized compounds were screened for in vitro antifungal activity. The antifungal activity was evaluated against different fungal strains such as *Candida albicans* (NCIM3471), *Fusarium oxysporum* (NCIM1332) *Aspergillus flavus* (NCIM539) *Aspergillus niger* (NCIM1196), *Cryptococcus neoformans* (NCIM576) [Figure-25].



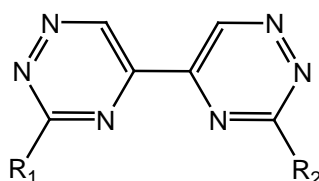
**Figure-25**

H. M. Ashour et al.<sup>46</sup> have synthesized a new series of thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidines and thieno[2,3-d][1,2,4]triazolo[1,5-a] pyrimidines. The newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activity using diclofenac Na as a reference standard. Additionally, the ulcerogenic effects and acute toxicity (ALD50) values of the active compounds were also determined. In general, the thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidine derivatives exhibited better biological activities than the thieno[2,3:4,5]pyrimido[1,2-b][1,2,4]triazines [Figure-26].



**Figure-26**

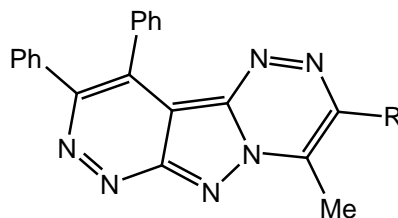
K. Ban et al.<sup>47</sup> reported the discovery of 3-alkylthio-1,2,4-triazine dimers that are potently toxic to *Plasmodium falciparum*, with single digit nanomolar activity, and up to several thousand-fold lower toxicity to mammalian cells. They are equipotent against chloroquine-resistant strains of *P. falciparum* [Figure-27].



**Figure-27**

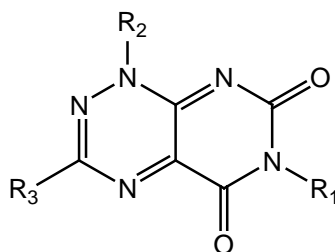


A. Deeb et al.<sup>48</sup> reported. The synthesis of 3-Aminopyrazolo[3,4-d]pyridazine which was diazotized and coupled with active methylene reagents to afford the tricyclic pyridazino[3,4':3,4]pyrazolo[5,1-c]-1,2,4-triazines with substituents such as methyl, phenyl, ethoxycarbonyl, acetyl or benzoyl, depending on the methylene reagent used. The in vitro antimicrobial activities for some of the synthesized compounds were evaluated against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* and *Candida albicans* were determined [Figure-28].



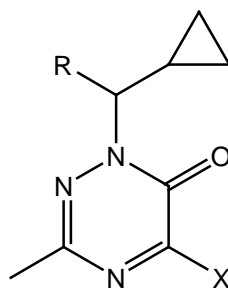
**Figure-28**

Y. Zhou et al.<sup>49</sup> reported that pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione derivatives were investigated as novel small molecule amplifiers of heat shock factor-1 transcriptional activity. Lead optimization led to the discovery of compound, which displayed potent HSF1 activity under mild heat stress ( $EC_{50} = 2.5 \mu\text{M}$ ) and significant cytoprotection in both rotenone ( $EC_{50} = 0.23 \mu\text{M}$ ) and oxygen-glucose deprivation cell toxicity models (80% protection at  $2.5 \mu\text{M}$ ) [Figure-29].



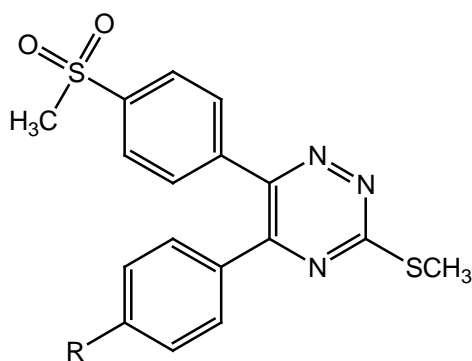
**Figure-29**

W. D. Schmitz et al.<sup>50</sup> reported a series of 5-aryl-amino-1,2,4-triazin-6(1H)-ones was synthesized and evaluated as antagonists at the corticotropin releasing factor receptor. Formation of CYP-mediated oxidative reactive metabolites previously observed in a related N3-phenylpyrazinone structure was minimized by incorporation of the additional ring nitrogen found in the triazinones [Figure-30].



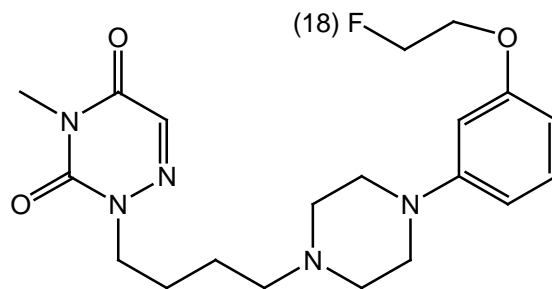
**Figure-30**

H. Irannejad et al.<sup>51</sup> reported that a series of 5-Aryl-6-(4-methylsulfonyl)-3-(methylthio)-1,2,4-triazine derivatives were synthesized and their COX-1/COX-2 inhibitory activity as well as in vivo anti-inflammatory and analgesic effects were evaluated. All of compounds showed strong inhibition of COX-2 with  $IC_{50}$  values in the range of  $0.1-0.2 \mu\text{M}$  and in most cases had stronger anti-inflammatory and analgesic effects than indomethacin at doses 3 and 6 mg/kg. Among them, 5-(4-chlorophenyl)-6-(4-(methylsulfonyl) phenyl)-3-(methylthio)-1,2,4-triazine was the most potent and selective COX-2 compound; its selectivity index of 395 was comparable to celecoxib ( $SI = 405$ ). Evaluation of anti-inflammatory and analgesic effects showed its higher potency than indomethacin and hence could be considered as a promising lead candidate for further drug development. Furthermore, the affinity data of these compounds were rationalized through enzyme docking simulation and 3D-QSAR study by k-Nearest Neighbour Molecular Field Analysis [Figure-31].



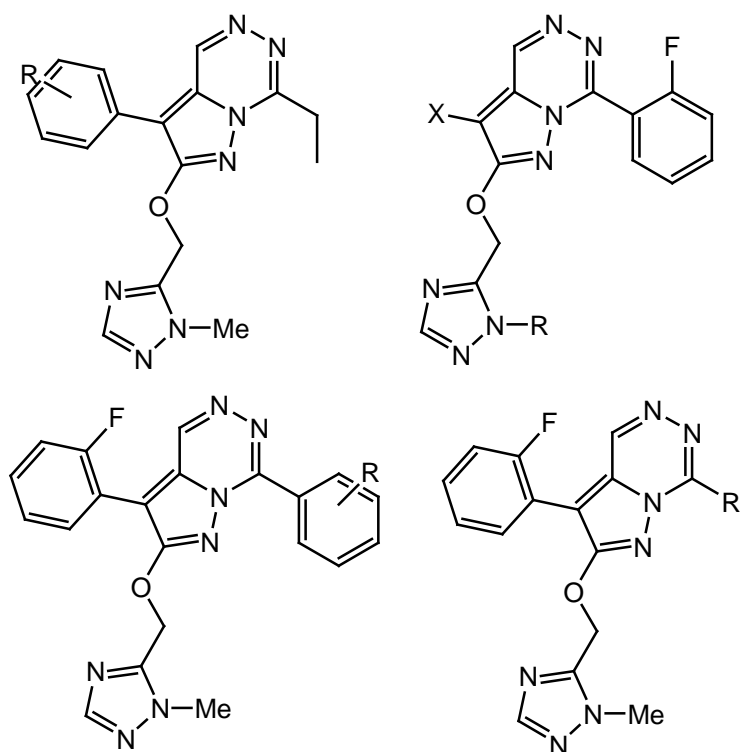
**Figure-31**

The 5-HT<sub>1A</sub>R partial agonist PET radiotracer, [<sup>11</sup>C]CUMI-101, has advantages over an antagonist radiotracer as it binds preferentially to the high affinity state of the receptor and thereby provides more functionally meaningful information. The major drawback of C-11 tracers is the lack of cyclotron facility in many health care centers thereby limiting widespread clinical or research use. V. J. Majo et al.<sup>52</sup> identified the fluoroethyl derivative, 2-(4-(4-(2-(2-fluoroethoxy)phenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2H,4H)dione (FECUMI-101) ( $K_i = 0.1$  nM;  $E_{max} = 77\%$ ;  $EC_{50} = 0.65$  nM) as a partial agonist 5-HT<sub>1A</sub>R ligand of the parent ligand CUMI-101. FECUMI-101 is radiolabeled with F-18 by O-fluoroethylation of the corresponding desmethyl analogue with [<sup>18</sup>F]fluoroethyltosylate in DMSO in the presence of 1.6 equiv of K<sub>2</sub>CO<sub>3</sub> in 45 ± 5% yield (EOS). PET shows [<sup>18</sup>F]FECUMI-101 binds specifically to 5-HT<sub>1A</sub>R enriched brain regions of baboon. The specificity of [<sup>18</sup>F]FECUMI-101 binding to 5-HT<sub>1A</sub>R was confirmed by challenge studies with the known 5-HT<sub>1A</sub>R ligand WAY100635. These findings indicate that [<sup>18</sup>F]FECUMI-101 can be a viable agonist ligand for the in vivo quantification of high affinity 5-HT<sub>1A</sub>R with PET.



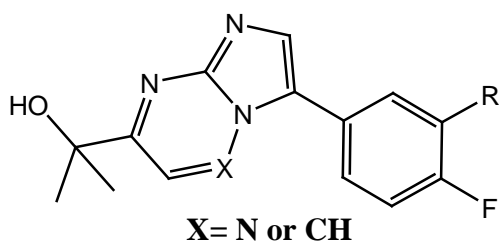
**Figure-31**

R. W. Carling et al.<sup>53</sup> devised a novel synthetic routes have been for the preparation of previously inaccessible 2,3,7-trisubstituted pyrazolo-[1,5-d][1,2,4]triazines. These compounds are high affinity ligands for the GABAA benzodiazepine binding site and some analogues show functional selectivity for agonism at  $\alpha 3$ -containing receptors over  $\alpha 1$ -containing receptors with the lead compound.



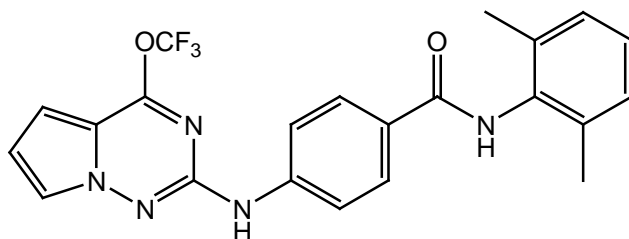
**Figure-31**

A. S. R. Jennings et al.<sup>54</sup> reported the Imidazo[1,2-*b*][1,2,4]triazines as  $\alpha 2/\alpha 3$  subtype selective GABAA agonists for the treatment of anxiety [Figure-32].



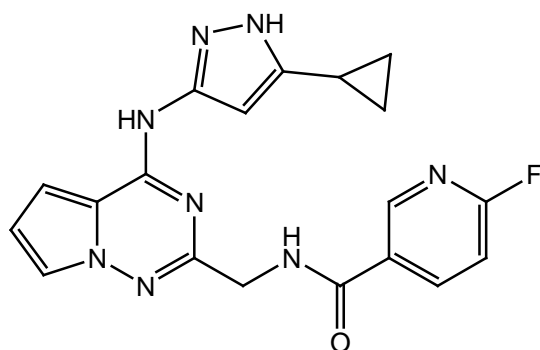
**Figure-32**

M. Xin et al.<sup>55</sup> reported the design, synthesis, and evaluation of pyrrolo[2,1-*f*][1,2,4]triazine derivatives as novel hedgehog signaling pathway inhibitors [Figure-33].



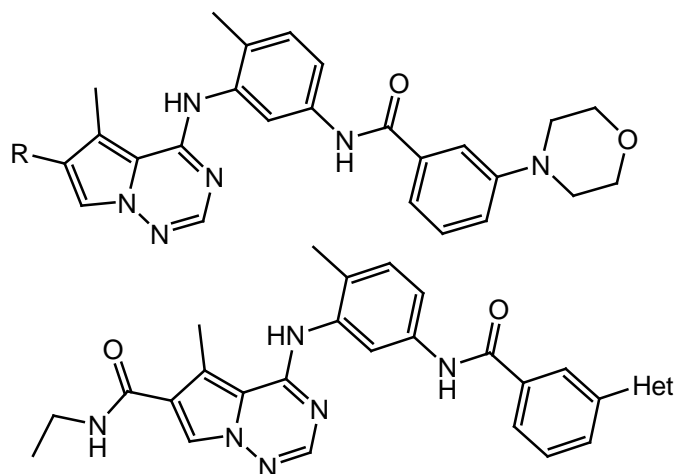
**Figure-33**

A. J. Sampognaro et al.<sup>56</sup> reported the proline isosteres in a series of 2,4-disubstituted pyrrolo[1,2-*f*][1,2,4]triazine inhibitors of IGF-1R kinase and IR kinase [Figure-34].



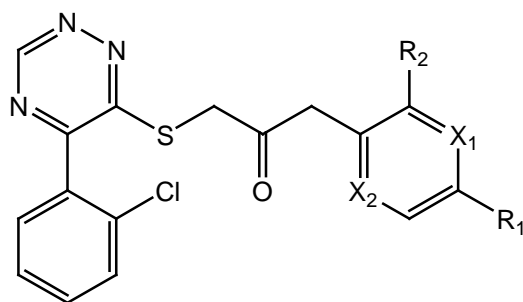
**Figure-34**

S. T. Wroblewski et al.<sup>57</sup> reported a novel series of compounds based on the pyrrolo[2,1-f][1,2,4]triazine ring system have been identified as potent p38 $\alpha$  MAP kinase inhibitors. The synthesis, structure–activity relationships (SAR), and in vivo activity of selected analogs from this class of inhibitors are reported. Additional studies based on X-ray co-crystallography have revealed that one of the potent inhibitors from this series binds to the DFG-out conformation of the p38 $\alpha$  enzyme [Figure-35].



**Figure-35**

P. Zhan et al.<sup>58</sup> reported the structure-based bioisosterism design, synthesis and biological evaluation of novel 1,2,4-triazin-6-ylthioacetamides as potent HIV-1 NNRTIs [Figure-36].



**Figure-36**

### 3. Conclusion:

The biological potential of 1,2,4-triazine derivatives is cleared from the literature and clinically used drugs. The literature revealed that 1,2,4-triazine derivatives possess diverse biological potential, easy synthetic routes for the synthesis and attracted researchers for development of new chemotherapeutic agents and it also revealed the importance of the nucleus.

#### 4. References:

- [1] H Schroeder, C Grundmann; Triazines. XIV. The Extension of the Pinner Synthesis of Monohydroxy-s-triazines to the Aliphatic Series. 2,4-Dimethyl-s-triazine-1-3: *J. Am. Chem. Soc.* 78, 2447–2451 (1956).
- [2] M Kidwai, Y Goel, R Kumor; Microwave assisted synthesis and antifungal activity of 1,2,4-triazine, 1,2,4-triazole, tetrazole and pyrazoles derivatives: *Indian J. chem.* 37b, 174 (1998).
- [3] B S Holla, R Gonsalves, S Rao, S Henoy, H N Gopalkrishna; Synthesis of some new biologically active bis-(thiadiazolotriazines) and bis-(thiadiazolotriazinyl) alkanes: *Farmaco* 56, 899 (2001).
- [4] R M Abdel-Rahman, J M Morsy, F Hanafy, H A Amene; Synthesis of heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety as anti-HIV and anticancer drugs: Part I. *Pharmazie* 54, 347(1999).
- [5] M W Partridge, M F G J Stevens; Pyrazolo-as-triazines: Part I. *Chem. Soc.* 1127 (1966).
- [6] E I Abd, ZK Samii; Synthesis and anti-inflammatory activity of some novel 1,3,4-oxadiazole derivatives: *J. Chem. Technol, Biotechnol.* 53, 143 (1992).
- [7] M P Hay, F B Prujin, S A Gamage, H D Liyanage, W R Wilson; Targeted 1,2,4-Benzotriazine 1,4-Dioxides: Potent Analogues of the Hypoxia-Selective Cytotoxin Tirapazamine: *J. Med. Chem.* 47, 475 (2004).
- [8] W P Heilman, R D Heilman, J A Scozzie, R J Wayner, J M Gullo, Z S Riyan; Synthesis and antihypertensive activity of novel 3-hydrazino-5-phenyl-1,2,4-triazines: *J. Med. Chem.* 22, 671 (1979).
- [9] I Kosary, E Kosztreiner, G Rabloczky, M Kurhy; *Eur. J. Med. Chem.* 24, 97–105 (1989).
- [10] A Baliani, G J Bueno, M L Stewart, V Yardley, R Brun, M P Barrett, I H Gilbert; Design and synthesis of a series of melamine-based nitroheterocycles with activity against Trypanosomatid parasites: *J. Med. Chem.* 48, 5570–5579 (2005).
- [11] B R Henke, T G Consler, N Go, R L Hale, D R Hohman, S A Jones, A T Lu, L B Moore, J T Moore, L A Orband-Miller, R G Robinett, J Shearin, P K Spearing, E L Stewart, P S Turnbull, S L Weaver, S P Williams, G B Wisely, M H Lambert; A new series of estrogen receptor modulators that display selectivity for estrogen receptor beta: *J. Med. Chem.* 45, 5492–5505 (2002).
- [12] N P Jensen, A L Ager, R A Bliss, C J Canfield, B M Kotecka, K H Rieckmann, J. Terpinski, D P Jacobus; Phenoxypropoxybiguanides, prodrugs of DHFR-inhibiting diaminotriazine antimalarials: *J. Med. Chem.* 44, 3925–3931 (2001).
- [13] A Agarwal, K Srivastava, S K Puri, P M S Chauhan; Syntheses of 2,4,6-trisubstituted triazines as antimalarial agents: *Bioorg. Med. Chem. Lett.* 15, 531–533 (2005).
- [14] G-H Kuo, A DeAngelis, S Emanuel, A Wang, Y Zhang, P J Connolly, X Chen, R H Gruninger, C Rugg, A F Pesquera, S A Middleton, L Jolliffe, W V Murray; *J. Med. Chem.* 48, 4535–4546 (2005).
- [15] K Srinivas, U Srinivas, K Harakishore, V Jayathirha Rao, K Bhanuprakash, U S N Murthy, Synthesis and antibacterial activity of various substituted s-triazines. *Bioorg. Med. Chem. Lett.* 15, 1121–1123 (2005).
- [16] G A McKay, R Reddy, F Arhin, A Belley, D Lehoux, G Moeck, I Sarmiento, T R Parr, P Gros, J Pelletier, A R Far; Triaminotriazine DNA helicase inhibitors with antibacterial activity: *Bioorg. Med. Chem. Lett.* 16, 891–896 (2005).
- [17] A Ghaib, S Menager, P Verite, O Lafont; Synthesis of variously 9,9-dialkylated octahydropyrimido [3,4-a]-s-triazines with potential antifungal activity: *IL Farmaco* 57, 109–116 (2002).
- [18] T Lubbers, P Angehrn, H Gmunder, S Herzig, J Kulhanek; Design, synthesis, and structure-activity relationship studies of ATP analogues as DNA gyrase inhibitors: *Bioorg. Med. Chem. Lett.* 10, 821–826 (2000).
- [19] S Lebreton, N Newcombe, M. Bradle; Antibacterial single-bead screening: *Tetrahedron*; 59, 10213–10222 (2003).
- [20] V.V. Malwad, J.M. Shirodkar; Synthesis and Antibacterial Activity of New Tetrazole Derivatives: *Ind. J. Chem.* 42B, 621–626 (2003).
- [21] JG Erickson; Chapter II. The 1,2,4-Triazines. *Chem Heterocycl. Comp*; 10, 44 (1956).
- [22] K Sztanke, K Pasternak, J Rzymowska, M Sztanke, M K Szerszen; Synthesis, structure elucidation and identification of antitumoural properties of novel fused 1,2,4-triazine aryl derivatives: *Eur. J. Med. Chem.* 43, 1085-1094 (2008).
- [23] Z Zhao, W H Leister, K A Strauss, D D Wisnoski and C W Lindsley; *Tetrahedron Lett.* 44, 1123–1127 (2003).
- [24] L Gupta, N Sunduru, A Verma, S Srivastava, S Gupta, N Goyal, P M S Chauhan; Synthesis and biological evaluation of new [1,2,4]triazino[5,6-b]indol-3-ylthio-1,3,5-triazines and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines against *Leishmania donovani*: *Eur. J. Med. Chem.* 45, 2359-2365 (2010).
- [25] J A Hassanen, H KH Ashour and SH A Zkaria; Synthesis, Biological Activity and Mass Spectra Investigation of 1,2,4- Triazino- [2,1-a]-1,2,4- triazine Derivatives: *Der Pharma Chemica* 4(5), 2091-2106 (2012).
- [26] B S. Dawane, S N. Kadam, B M. Shaikh; An efficient synthesis of 1, 2, 4-triazine derivatives and in vitro antimicrobial activity: *Der Pharmacia Lett.* 2(4), 126-131 (2010).
- [27] S K Pandey, A Singh, A Singh, Nizamuddin; Antimicrobial studies of some novel quinazolinones fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings: *Eur. J. Med. Chem.* 44, 1188-1197 (2009).
- [28] K Sztanke, S Fidecka, EKVDzierska, Z Karczmarzyk, K Pihlaja, D Matosiuk; Antinociceptive activity of new imidazolidine carbonyl derivatives: Part 4. Synthesis and pharmacological activity of 8-aryl-3,4-dioxo-2H,8H-6,7-dihydroimidazo[2,1-c][1,2,4]triazines: *Eur. J. Med. Chem.* 40, 127–134 (2005).
- [29] K Sztanke, J Rzymowska, M Niemczyk, I Dybała, A E. Koziol; Synthesis, crystal structure and anticancer activity of novel derivatives of ethyl 1-(4-oxo-8-aryl-4,6,7,8-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)formate: *Eur. J. Med. Chem.* 41, 539–547 (2006).
- [30] J Styskala, L Styskalova, J Slouka, M Hajduch; Synthesis of 2-aryl-4-(benzimidazol-2-yl)-1,2-dihydro[1,2,4]triazino-[4,5-a]benzimidazol-1-one derivatives with preferential cytotoxicity against carcinoma cell lines: *Eur. J. Med. Chem.* 43, 449-455 (2008).
- [31] W R. Abdel-Monem; Synthesis and Antimicrobial Activity of Some New Nitrogen
- [32] Heterocyclic Systems Bearing 1, 2, 4-Tiazine Moiety: *Global Journal of Science Frontier Research Chemistry* 12 (5), (2012).
- [33] P Barraja, P Diana, A Lauria, A Montalbano, A M Almerico, G Dattolo and G Cirrincione; Synthesis and Antiproliferative Activity of [1,2,4]Triazino[4,3-a]indoles: *Anticancer Research.* 24, 3775-3780 (2004).
- [34] P Diana, P Barraja, A Lauria, A Montalbano, A M Almerico, G Dattolo, G Cirrincione; Pyrrolo[2,1-c][1,2,4]triazines from 2-Diazopyroles: Synthesis and Antiproliferative Activity: *Eur. J. Med. Chem.* 37, 267–272 (2002).
- [35] K Sztanke, J Rzymowska, M Niemczyk, I Dybała, A E. Koziol; Novel derivatives of methyl and ethyl 2-(4-oxo-8-aryl-2H-3,4,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)acetates from biologically active 1-aryl-2-hydrazinoimidazolines: Synthesis, crystal structure and antiproliferative activity: *Eur. J. Med. Chem.* 41 1373-1384 (2006).
- [36] T Gucky, I Frysova, J Slouka, M Hajduch, P Dzubak; Cyclocondensation reaction of heterocyclic carbonyl compounds, Part XIII: Synthesis and cytotoxic activity of some 3,7-diaryl-5-(3,4,5-trimethoxyphenyl)pyrazolo[4,3-e][1,2,4]triazines: *Eur. J. Med. Chem.* 44, 891-900 (2009).
- [37] H Irannejad, M Amini, F Khodaghali, N Ansari, S K Tusi, M Sharifzadeh, A Shafiee; Synthesis and in vitro evaluation of novel 1, 2, 4-triazine derivatives as neuroprotective agents: *Bioorg Med. Chem.* 18, 4224–4230 (2010).
- [38] T. El. S Ali; Synthesis of some novel pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives bearing 5,6-diphenyl-1,2,4-triazine moiety as potential antimicrobial agents: *Eur. J. Med. Chem.* 44, 4385–4392 (2009).

- [39] Z Cai, D Wei, R M Borzilleri, L Qian, A Kamath, S Mortillo, B Wautlet, B J Henley, R Jeyaseelan, S J Tokarski, J T Hunt, R S Bhide, J Fagnoli and L J Lombardo; Synthesis, SAR, and Evaluation of 4-[2,4-Difluoro-5-(cyclopropylcarbonyl)phenylamino]pyrrolo[2,1-f][1,2,4]triazine-based VEGFR-2 kinase inhibitors. *Bioorg. Med. Chem. Lett.* 18, 1354–1358 (2008).
- [40] G Ciciani, Ma Coronello, G Guerrini, S Selleri, M Cantore, P Failli, E Mini, A Costanzo; Synthesis of new pyrazolo[5,1-c][1,2,4]benzotriazines, pyrazolo[5,1-c]pyrido[4,3-e][1,2,4] triazines and their open analogues as cytotoxic agents in normoxic and hypoxic conditions: *Bioorg. Med. Chem.* 16, 9409–9419 (2008).
- [41] A M EL Massry, A M Asal, S N Khattab, N S Haiba, H A. Awney, M Helmy, V Langer, A Amer; Synthesis and structure elucidation of novel fused 1,2,4-triazine derivatives as potent inhibitors targeting CYP1A1 activity; *Bioorg. Med. Chem.* 20, (2012) 2624–2637 (2012).
- [42] F Krauth, H M Dahse, H H Ruttinger, P Froberg, Synthesis and characterization of novel 1,2,4-triazine derivatives with antiproliferative activity: *Bioorg. Med. Chem.* 18, 1816–1821 (2010).
- [43] J. Prabhakaran, R. V. Parsey, V. J. Majo, S-C. Hsiung, M S. Milak, H Tamir, N. R. Simpson, R. L. V. Heertum, J. J. Manna and J. S. D. Kumara; Synthesis, in vitro and in vivo evaluation of [O-methyl-11C] 2-[4-[4-(3-methoxyphenyl)piperazin-1-yl]butyl]-4-methyl-2H-[1,2,4]-triazine-3,5-dione: A novel agonist 5-HT1A receptor PET ligand: *Bioorg. Med. Chem. Lett.* 16, 2101–2104 (2006).
- [44] J. Zeller, A. J. Turbiak, I. A. Powelson, S. Lee, D. Sun, H. D. H. Showalter, E. R. Fearon; Investigation of 3-aryl-pyrimido[5,4-e][1,2,4]triazine-5,7-diones as small molecule antagonists of  $\beta$ -catenin/TCF transcription: *Bioorg. Med. Chem. Lett.* 23 5814–5820 (2013).
- [45] W. Lv, B. Banerjee, K. L. Molland, M. N. Seleem, A. Ghafour, M. I. Hamed, B. Wan, S. G. Franzblau, A. D. Mesecar, M. Cushman; Synthesis of 3-(3-aryl-pyrrolidin-1-yl)-5-aryl-1,2,4-triazines that have antibacterial activity and also inhibit inorganic pyrophosphatase: *Bioorg. Med. Chem.* 22 (2014) 406–418.
- [46] J. N. Sangshetti, D. B. Shinde; One pot synthesis and SAR of some novel 3-substituted 5,6-diphenyl-1,2,4-triazines as antifungal agents: *Bioorg. Med. Chem. Lett.* 20, 742–745 (2010).
- [47] H. M. Ashour, O. G. Shaaban, O. H. Rizk, I. M. El-Ashmawy; Synthesis and biological evaluation of thieno [2,3':4,5]pyrimido[1,2-b][1,2,4]triazines and thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidines as anti-inflammatory and analgesic agents: *Eur. J. Med. Chem.* 62, 341-351(2013).
- [48] K. Ban, S. Duffy, Y. Khakham, V. M. Avery, A. Hughes, O. Montagnat, K. Katneni, E. Ryan, J. B. Baell; 3-Alkylthio-1,2,4-triazine dimers with potent antimalarial activity: *Bioorg. Med. Chem. Lett.* 20, 6024–6029 (2010).
- [49] A. Deeb, F. El-Mariah and M. Hosny; Pyridazine derivatives and related compounds. Part 13: Synthesis and antimicrobial activity of some pyridazino[3,4':3,4]pyrazolo[5,1-c]-1,2,4-triazines: *Bioorg. Med. Chem. Lett.* 14, 5013–5017 (2004).
- [50] Y. Zhou, L. Wei, T. P. Brady, P. S. Murali Mohan Reddy, T. Nguyen, J. Chen, Q. Au, S. Yoon, G. Yip, B. Zhang, J. R. Barber, S. Chung Ng; Pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione derivatives as novel small molecule chaperone amplifiers: *Bioorg. Med. Chem. Lett.* 19, 4303–4307 (2009).
- [51] W. D. Schmitz, A. B. Brenner, J. J. Bronson, J. L. Ditta, C. R. Griffin, Y-W. Li, N. J. Lodge, T. F. Molski, R. E. Olson, X. Zhuo, J. E. Macor; 5-Arylamino-1,2,4-triazin-6(1H)-one CRF1 receptor antagonists: *Bioorg. Med. Chem. Lett.* 20, 3579–3583 (2010).
- [52] H. Irannejad, A. Kebriaieezadeh, A. Zarghi, F. Montazer-Sadegh, A. Shafiee, A. Assadieskandar, M. Amini; Synthesis, docking simulation, biological evaluations and 3D-QSAR study of 5-Aryl-6-(4-methylsulfonyl)-3-(methylthio)-1,2,4-triazine as selective cyclooxygenase-2 inhibitors: *Bioorg. Med. Chem.* 22, 865–873 (2014).
- [53] V. J. Majo, M. S. Milak, J. Prabhakaran, P. Mali, L. Savenkova, N. R. Simpson, J. J. Mann, R. V. Parsey, J. S. Dileep Kumar; Synthesis and in vivo evaluation of [18F]2-(4-(4-(2-(2-fluoroethoxy) phenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2H,4H)-dione ([18F]FECUMI-101) as an imaging probe for 5-HT1A receptor agonist in nonhuman primates: *Bioorg. Med. Chem.* 21, 5598–5604 (2013).
- [54] R. W. Carling, M. G. N. Russell, K. W. Moore, A. Mitchinson, A. Guiblin, A. Smith, K. A. Wafford, G. Marshall, J. R. Atack and L. J. Street; 2,3,7-Trisubstituted pyrazolo[1,5-d][1,2,4]triazines: Functionally selective GABAA  $\alpha$  3-subtype agonists: *Bioorg. Med. Chem. Lett.* 16, 3550–3554 (2006).
- [55] A. S. R. Jennings, R. T. Lewis, M. G. N. Russell, D. J. Hallett, L. J. Street, J. L. Castro, J. R. Atack, S. M. Cook, R. Lincoln, J. Stanley, A. J. Smith, D. S. Reynolds, B. Sohal, A. Pike, G. R. Marshall, K. A. Wafford, W. F. A. S. and S. J. Tye; Imidazo[1,2-b][1,2,4]triazines as  $\alpha$ 2/ $\alpha$ 3 subtype selective GABAA agonists for the treatment of anxiety: *Bioorg. Med. Chem. Lett.* 16, 1477–1480 (2006).
- [56] M. Xin, L. Zhang, F. Tang, C. Tu, J. Wen, X. Zhao, Z. Liu, L. Cheng, H. Shen; Design, synthesis, and evaluation of pyrrolo[2,1-f][1,2,4]triazine derivatives as novel hedgehog signaling pathway inhibitors: *Bioorg. Med. Chem.* 22, 1429–1440 (2014).
- [57] A. J. Sampognaro, M. D. Wittman, J. M. Carboni, C. Chang, A. F. Greer, W. W. Hurlburt, J. S. Sack, D. M. Vyas; Proline isosteres in a series of 2,4-disubstituted pyrrolo[1,2-f][1,2,4]triazine inhibitors of IGF-1R kinase and IR kinase: *Bioorg. Med. Chem. Lett.* 20, 5027–5030 (2010).
- [58] S. T. Wroblewski, S. Lin, J. Hynes, Jr. Hong Wu, S. Pitt, D. Ren Shen, R. Zhang, K. M. Gillooly, D. J. Shuster, K. W. McIntyre, A. M. Doweiko, K. F. Kish, J. A. Tredup, G. J. Duke, J. S. Sack, M. McKinnon, J. Dodd, J. C. Barrish, G. L. Schievenb and K. Leftheris; Synthesis and SAR of new pyrrolo[2,1-f][1,2,4]triazines as potent p38a MAP kinase inhibitors: *Bioorg. Med. Chem. Lett.* 18, 2739–2744 (2008).
- [59] P. Zhan, X. Li, Z. Li, X. Chen, Y. Tian, W. Chen, X. Liu, C. Pannecouque, E. De Clercq; Structure-based bioisosterism design, synthesis and biological evaluation of novel 1,2,4-triazin-6-ylthioacetamides as potent HIV-1 NNRTIs: *Bioorg. Med. Chem. Lett.* 22, 7155–7162 (2012).