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Efficient Routes to Synthesize Pyrazoline Containing 1,2,4-Triazine Moiety as Pharmacological Targets- Review Artical

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ABSTRACT: *Synthesis, chemical reactivity and biocidal effects of pyrazolines containing 1,2,4-triazine moiety are reviewed. Synthesis of these systems have been deduced from hetero annelation of hydrazine, acid hydrazide, azide, and/or aminopyrazolines with aza-reagents. The unique featersbiological significance and important applications of these constituents are also reported.*

1. Introduction

The biological and pharmacological activities of functionally 1,2,4-triazine heterocyclic systems, condensed or fused with other five membered heterocyclic moieties, have been carefully studied. These compounds are bio-isosteric with purine (pure analogues) a molecule with a wide spectrum range of biological activities [1-7].For example pyrazolo[4,3-e][1,2,4]triazine have been less studied. But, a group of naturally accruing pyrazolo[4,3-e][1,2,4]triazines are produced by the microorganisms of the *Cyanobacter Nostocspongiaelforme* [8] and genus Pseudomonas fluorescence var. *pesudoidininum* [9] (Figure 1). These natural compounds have presented slight or moderate antineoplastic and antibacterial as well as anticancer activities [10,11]. On the other hand, moderate inhibition of purine nucleoside phosphorylase by 3-methyl-5-methylthio-1H-pyrazolo[4,3-e][1,2,4]triazine (c) and 1,5,-diaryl-3-(,3,4,5-trimethoxyphenyl)-H-pyrazolo[4,3-e] [1,2,4] triazine (D) exhibited relative selected cytotoxic activity via lung carcinoma cell and T cell leukemia line CEM [12].

Based on these observations, the present work reports the synthesis of pyrazolines containing 1,2,4-triazine moiety in view of their important applications.

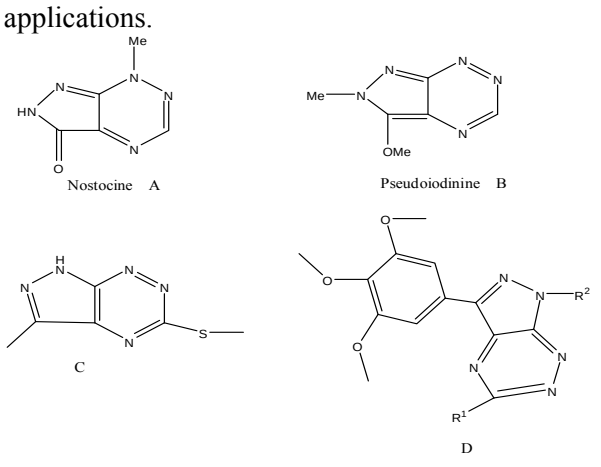
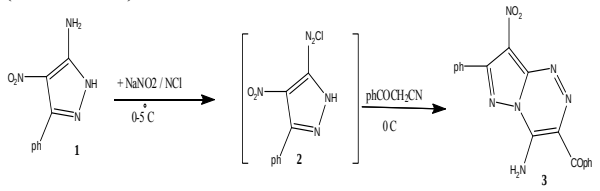


Fig.1: Some important biocidal pyrazolo[4,3-e] [1,2,4]triazines.

2. Synthesis of Pyrazolo[1,2,4]Triazine Derivatives

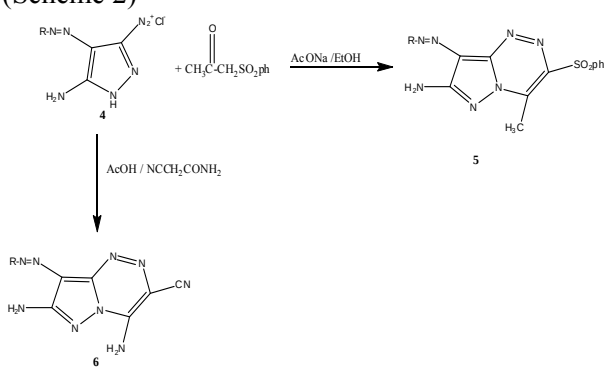
2.1. pyrazolo[1,5-c][1,2,4]triazines

Polyfunctional pyrazolo[1,5-c][1,2,4]triazine (3) was obtained from treatment of 5-amino-3-phenyl-4-nitropyrazole (1) with HCl/$NaNO_2$ followed by benzoyl methyl carbonitrile at 0-5 °C (Scheme 1)[13].



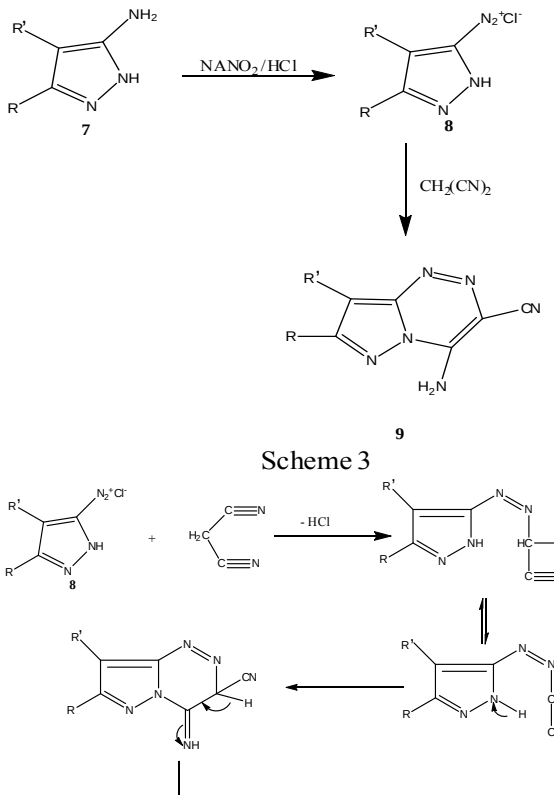
Scheme 1

Similarly,[3-amino-4-(arylazo)pyrazol-5-yl] diazoniumchloride (4) were coupled with active methylene reagents as benez-sulfonyl-acetophenone or benzene sulfonyl acetone in NaOAc/EtOH solution to give pyrazolo[1,5-c][1,2,4]triazines (5). On the other hand, the coupled compound 4 with cyanoacetamide/AcOH yielded the pyrazolo[1,5-c][1,2,4]triazines (6) (Scheme 2)[14].

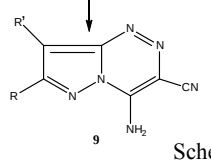


Scheme 2

Several carbonitriles bearing pyrazolotriazine (9) were obtained from reaction of 3-aminopyrazoles (7) with $NaNO_2$/HCl followed by coupling with malononitrile (Scheme 3&4) [15].



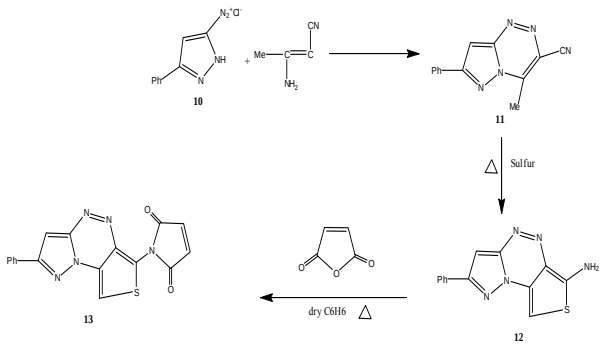
Scheme 3



Scheme 4

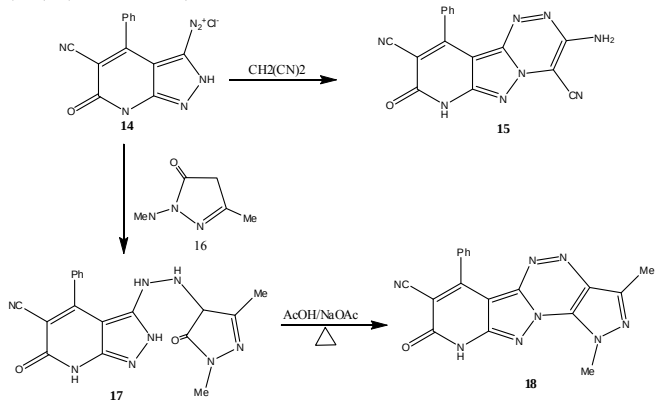
2.2. synthesis of pyrazolo[5,1-c] [1,2,4] triazine

El-Ghandour *et al* [16] synthesized a variety annulated pyrazolo[5,1-c][1,2,4]triazine (13) from coupling 3-phenylpyrazol-5-yl diazonium-chloride (10) with 2-aminocarbonitrile to give 4-phenyl-6-methyl-pyrazolo[5,1-c][1,2,4]triazine-7-carbonitrile (11). Compound (11) underwent [4+2] cycloaddition with dipolarophiles such as maleic anhydride and yielded the compound 13 (Scheme 5) [16].



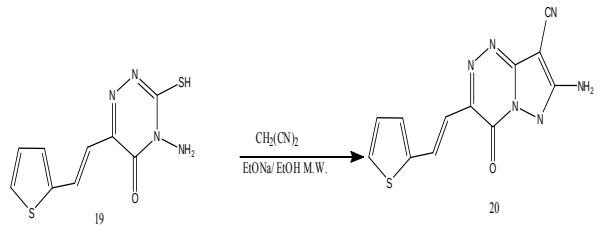
Scheme 5

Some condensed pyrazolo[5,1-c][1,2,4]triazines (15 and 18) have been prepared from treatment of 3,6-diamino-4-phenyl-pyrazolo[3,4-b]pyridine-5-carbonitile (14) with malononitrile to give 15, while on treatment with pyrazolone (16) they produce 1,2-dihetero hydrazine (17) which upon ring closure reaction by refluxing with AcOH/NaOAc afforded the pyridopyrazoltriazine (18) (Scheme 6) [17].



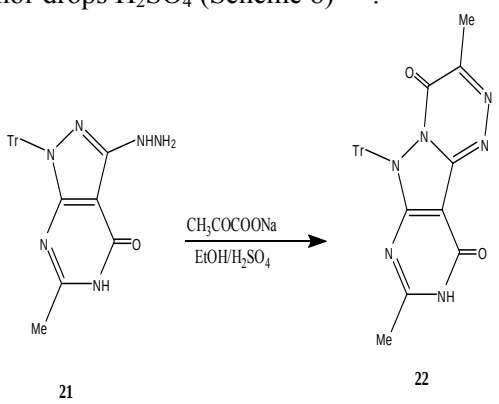
Scheme 6

A simple formation of pyrazolo[5,1-c][1,2,4]triazine-7-carbonitile (20) was deduced from treatment of 4-amino-3-mercapto-6-[2-(2-thienyl) vinyl]-1,2,4-triazin-5(4H)one (19) with malononitrile under microwave in the presence of EtONa/EtOH (Scheme 7)[1]. Compound 20 exhibited anticancer activity against different cancer cell lines.



Scheme 7

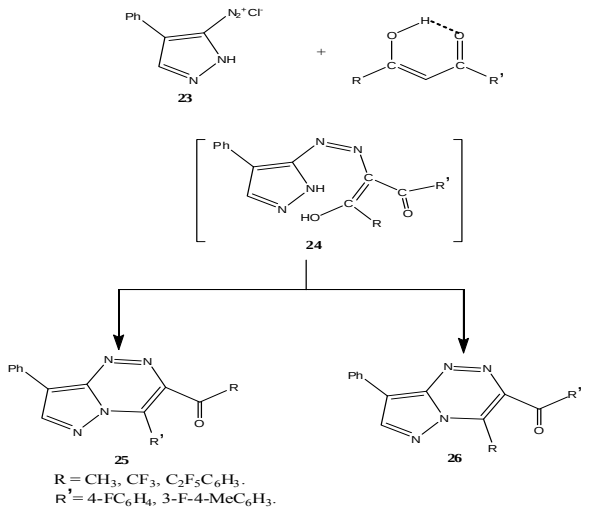
The antimicrobial agents, pyrazolo[5,1-c][1,2,4]triazine-4,10(6H,9H)-dione (22) was isolated from treatment of the 3-hydrazino-pyrazolopyrimidinone (21) with sodium pyruvate in ethanol-drops H_2SO_4 (Scheme 8) [18].



Tr : 5,6-diphenyl-1,2,4-triazin-3-yl.

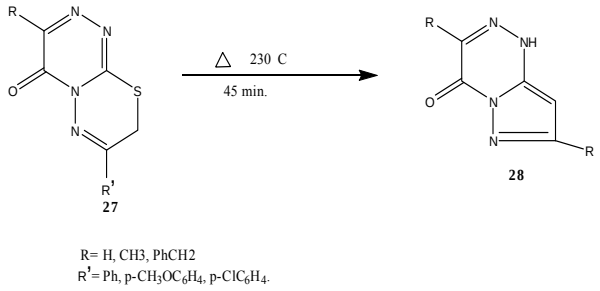
Scheme 8

Fluorinated pyrazolo[5,1-c][1,2,4]triazines (25&26) have been synthesized by the condensation of pyrazole diazonium salt (23) with 1,3-diketones in aqueous buffered solution. An intermediate 24 is obtained which on thermal cyclization in glacial AcOH gave the target 25 and 26 respectively. Compounds 25 and 26 display significant anti-inflammatory activity (Scheme 9) [19].

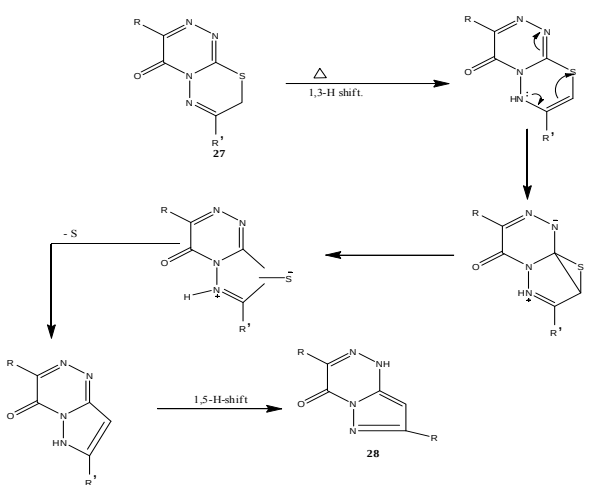


Scheme 9

Recently, Ibrahim *et al* [21] study the pyrolytic conversion of 1,2,4-triazine[3,4-b][1,3,4] thiadiazin-ones (27) into the corresponding pyrazolo[5,1-c][1,2,4]triazine-4-ones (28) via desulfurization a ring contraction [20]. Formation of 28 can be explained as showed in the Scheme 11.

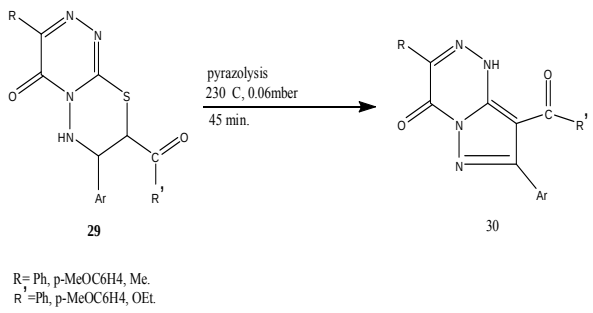


Scheme 10



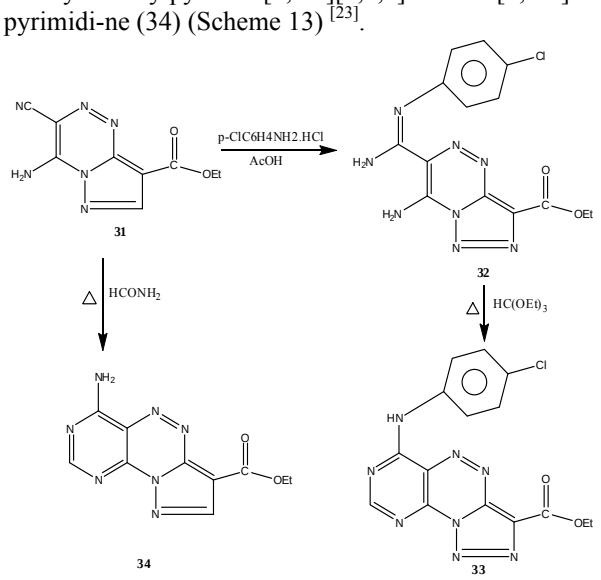
Scheme 11

Similarly, trans-8-benzoyl-3,7-diphenyl-7,8-dihydro-6H-[1,2,4]triazine [3,4-b][1,3,4]thiadiazin-4-one (29) underwent the same conditions for pyrolytic desulfurization ring contraction converted into 8-benzoyl-3,7-diphenyl-1H-pyrazolo[5,1-c][1,2,4]triazine-4-one (30) (Scheme 12) [21].



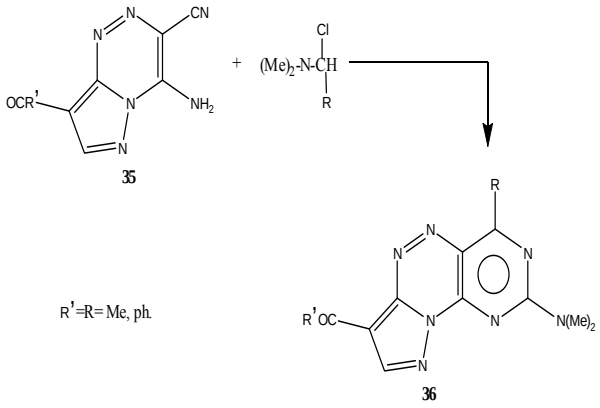
Scheme 12

Some attempts for synthesis of full fusedpyrazolo[5,1-c][1,2,4]-triazines have been reported [23,24]. Thus, reaction of 4-amino-8-ethoxycarbonylpyrazolo[5,1-c][1,2,4]triazine (31) with m-chloroaniline- hydrochloride in AcOH gave 4-amino -3-(m-chlorophenyl)-8-ethoxycarbonylpyrazolo [5,1-c][1,2,4]triazine (32) which upon refluxing with triethylorthoformate produced the pyrazolo[5,1-c][1,2,4]triazine[5,6-d]-pyrimidine (33). Ring closure reaction of 31 with formide afforded 2,4-diamino-7-ethoxycarbonylpyrazolo[5,1-c][1,2,4]triazino-[5,6-d] pyrimidi-ne (34) (Scheme 13) [23].



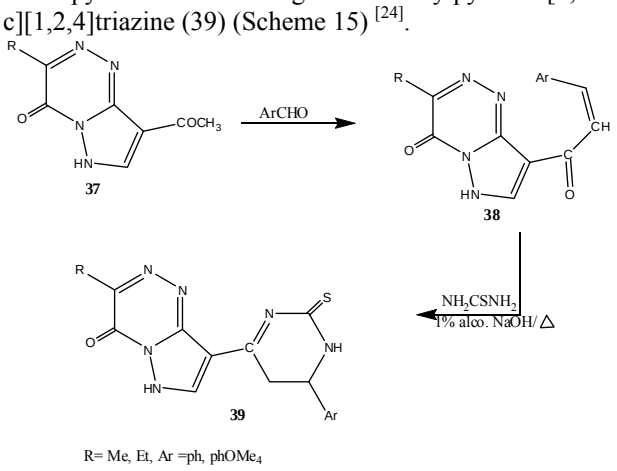
Scheme 13

On the other hand, several pyrazolo[5,1-c]pyrimido[4,5-c][1,2,4]-triazine (36) are easily obtained from reaction of N,N′-dimethyldi-chloromethylenininiumchloride with 4-amino-3-cyanopyrazolo[5,1-c]-[1,2,4]triazine-8-carboxylate (35) (Scheme 14) [23].



Scheme 14

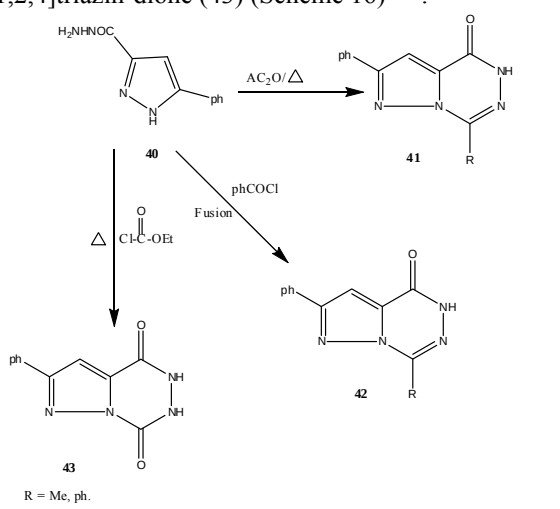
It is interesting that the reaction of acetylpyrazolo[5,1-c][1,2,4]triazine (37) with aryl aldehydes yielded the cinnamoyl derivatives 38 which on reaction with thiourea furnished the 2-thioxopyrimidine bearing a acetylpyrazolo[5,1-c][1,2,4]triazine (39) (Scheme 15) [24].



Scheme 15

2.3. Synthesis of pyrazolo[1,5-d][1,2,4]triazines

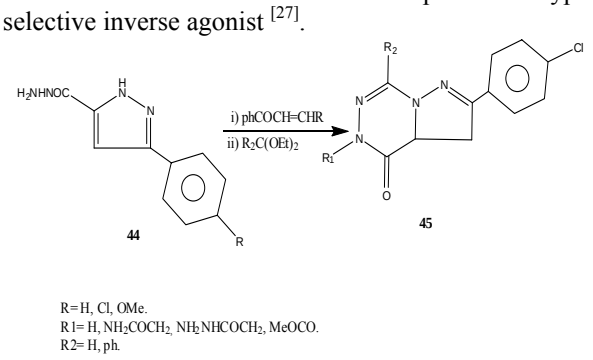
The pyrazolo[1,5-d][1,2,4]triazines (41-43) have been synthesized via the reaction of 3-phenyl-5-pyrazole-carboxylic acid hydrazide 40 with Ac_2O afforded the pyrazolo[1,5-d][1,2,4]triazinone (41), while fusion of 40 with benzoyl chloride produced the pyrazolotriazine (42). Also, cyclization of 40 with ethyl chloroformate yielded the pyrazolo[1,5-d][1,2,4]triazin-dione (43) (Scheme 16) [25].



Scheme 16

Some pyrazolo triazines 45 were prepared from carboxylic acid hydrazide 44 via the reaction with the appropriate ethyl aroyl acrylates followed by condensation with $R_2C(OEt)_3$. Compound 45 showed a good anti convulsant activity (Scheme 17) [26].

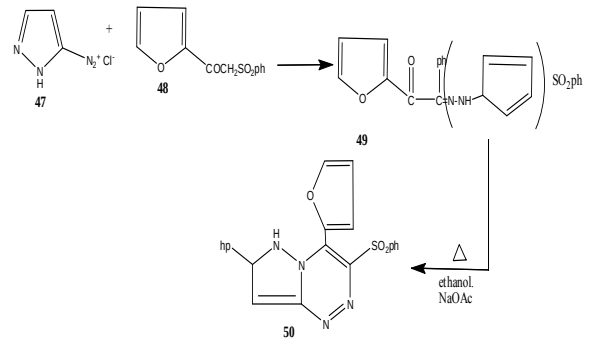
Similarly, 3-tert-butyl-7-(5-methylisoxazol-3-yl)-2-(1-methyl-1H-1,2,4-trizol-5-yl methoxy)-pyrazolo[1,5-d][1,2,4]triazine (46) was obta-ined as in vitro and in vivo of GABAA receptor α-subtype-selective inverse agonist [27].



Scheme 17

2.4. Synthesis of pyrazolo[3,2-c][1,2,4]triazines

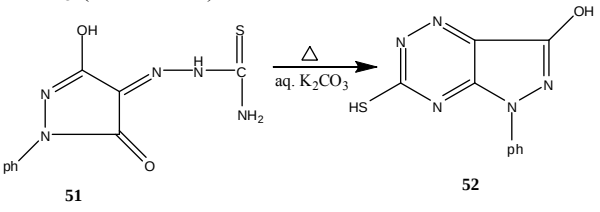
Abdel-Hamid *et al* [28] reported the synthesis of several pyrazolo[3,2-c][1,2,4]triazines (50) starting from coupling the diazonium salt 47 with ketosulfones 48 in ethanol in the presence of AcONa at 0 ^{O}C to afford the hydrazine 49. Cyclocondensation of 49 by warming with ethanolic sodium acetate yielded the target 50 (Scheme 18)[28].



Scheme 18

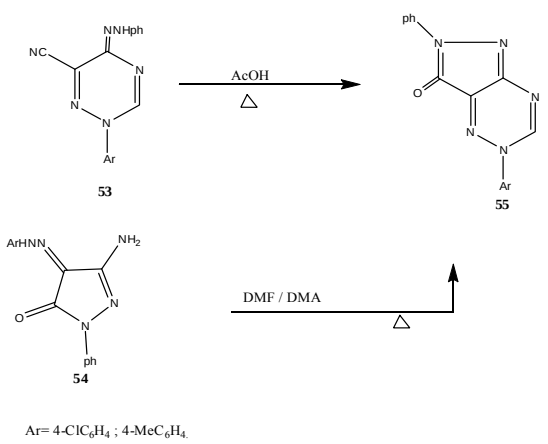
2.5. Synthesis of pyrazolo[3,4-e][1,2,4]triazine

1-Phenyl-3-hydroxy-6-mercapto-pyrazolo[3,2-c][1,2,4]triazine (52) was prepared by cyclization of pyrazolone 51 with refluxing aqueous K_2CO_3 (Scheme 19) [29].



Scheme 19

A simple route to the synthesis of pyrazolo[3,4-e][1,2,4]triazine(55) was deduced from refluxing 2-aryl-5-phenyl-hydrazono-2,3-dihydro[1,2,4] triazine-6-carbonitriles(53) with glacial acetic acid and/or refluxing 3-amino-4-phenylhydrazono-1-phenyl-2-pyrazolin-5-ones(54) with DMFDMA (Scheme 20) [30].



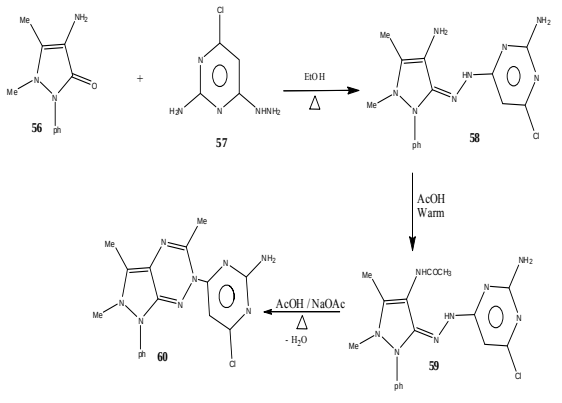
Ar= 4-ClC_6H_4 ; 4-MeC_6H_4.

Scheme 20

2.6. synthesis of pyrazolo[4,3-e][1,2,4]triazines

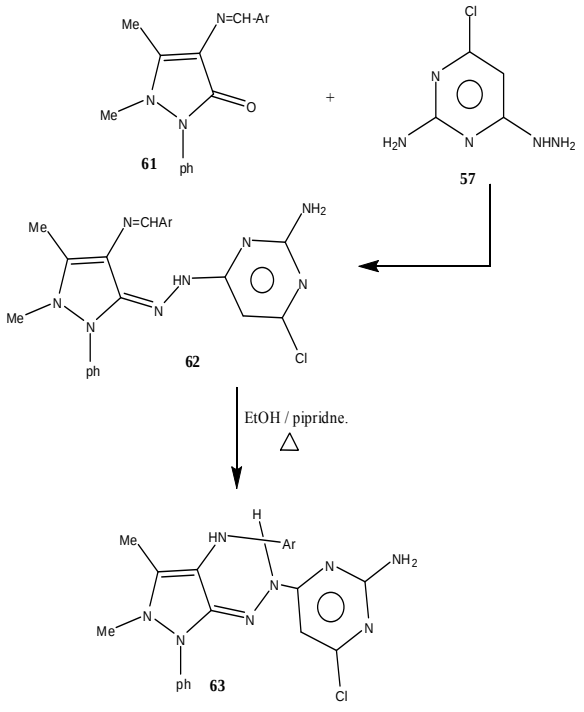
Condensed pyrazolo[4,3-e][1,2,4]triazines starting from 4-aminopyrine were reported by Seada *et al* [31].

Thus condensation of 4-aminoantipyrine 56 with 2-amino-4-hydrazino-6-chloropyrimidine 57 in absolute ethanol produced the hydrazine 58. Ring closure reaction of 58 via refluxing with AcOH yielded the pyrazolo[4,3-e][1,2,4]triazines (60) (scheme 21). On the other hand, condensation of 57 with arylidene 61 under the same condition afforded the hydrazone 62, which on refluxing with ethanol-pipridine led to the direct formation of 2-[2'-amino-6-chloropyrimdin-4'-yl]-3-aryl-3,4-dihydro-7-phenyl-5-6-dimethylpyrazolo [4,3-e][1,2,4]triazines(63) (Scheme 22)[31].



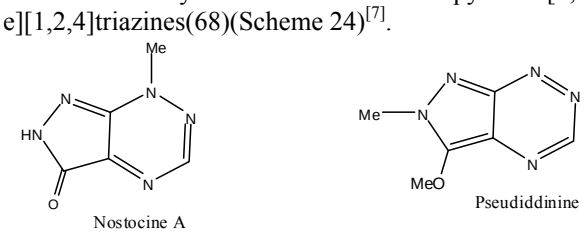
Scheme 21

Modified purine nucleoside and their analogues such as pyrazolo[4,3-e][1,2,4]triazines have found numerous applications in biological and pharmacological evaluations [32-34]. The isomeric pyrazolopyrimidines and triazolopyrimidines (8-azapurines) exhibit favorable spectroscopic and biochemical activities and have potential for use in cancer chemotherapy field [34-37]. It has been found that a class of natural occurring purine atnalogues produced by pseudomonas fluoresces var. pseudoiodininumand Nostocspongiaeformesuch as pseudoiodinine and nostocine A (Scheme 23) which display more interesting spectral characteristics [38,39].



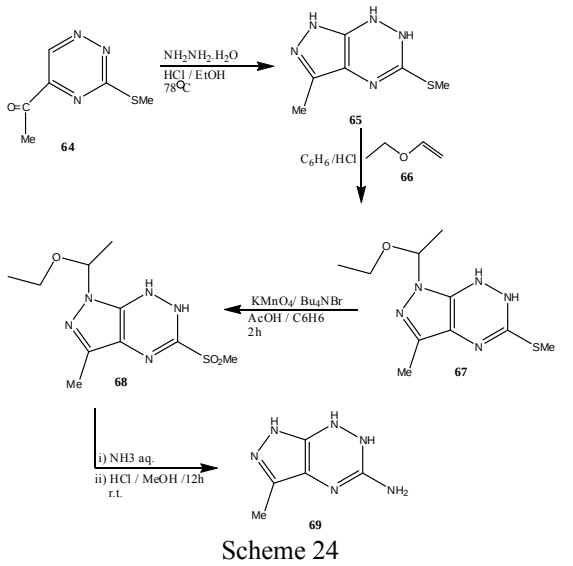
Scheme 22

Based on these observations, Mojzych *et al* [7] synthesized N-un substituted/substituted pyrazolo[4,3-e][1,2,4]triazines starting from reaction of 3-methylthia-5-acetyl-[1,2,4]triazine (65) with hydrazine hydrate to give N-unsubstituted pyrazolo[4,3-e][1,2,4]triazines (65). Treatment of 65 with unsubstituted aliphatic ether (66) in dry benzene-HCl afforded the N-substituted pyrazolo[4,3-e][1,2,4]triazines(67). Oxidation followed by amination of 67 yielded the unsubstituted pyrazolo[4,3-e][1,2,4]triazines(68)(Scheme 24)[7].



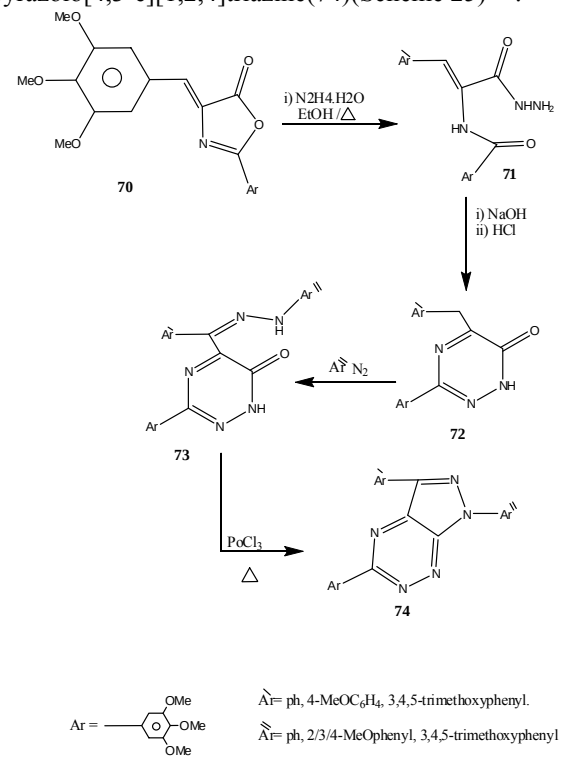
Scheme 23

The compounds 65-69 exhibit interesting spectral behavior and also interact with enzymes like xanthine oxidase bacterial purine nucleosidephosphorylase with K1 value in the 10-3-10-5 M range [7].



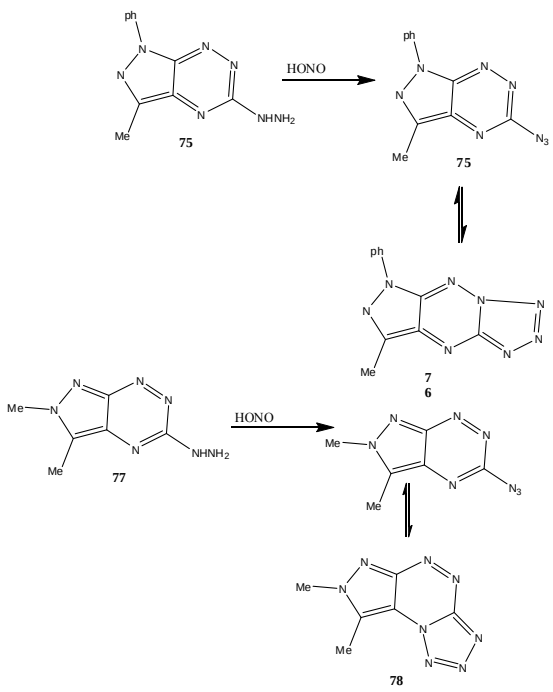
Scheme 24

Synthesis and cytotoxic agent 3,5,7-triaryl-pyrazolo[4,3-e] [1,2,4]triazine(74) has been obtained from treatment of 5-oxazolone (70) with hydrazine hydrate followed by a ring closure reaction to give 1,2,4-triazin-5-ones(75). Addition reaction between 72 and diazonium salt produced the hydrazone 73. Finally, warming of compound 73 with $POCl_3$ led to the direct formation of 3,7-diaryl-5-(3,4,5-trimethyl-oxyphenyl) pyrazolo[4,3-e][1,2,4]triazine(74)(Scheme 25)[40].

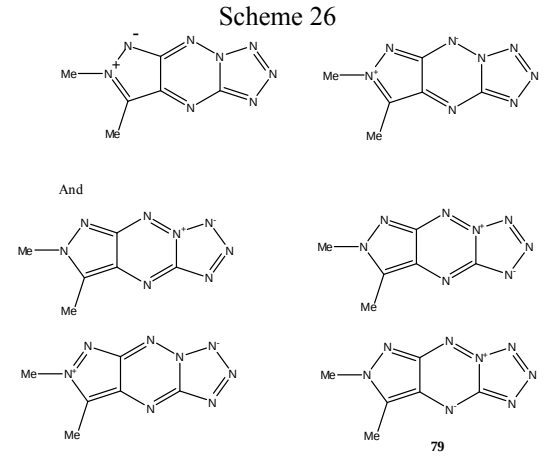


Scheme 25

Annulated 1,2,4-triazine derivatives are present as important core structurally in many biologically active compounds, in the form naturally occurring and synthetic compounds [41-44]. Recently, Karezmarzyk *et al* [45] reported the synthesis of mesomericbetaine 6,7-dimethyl-2H-pyrazolo[4,3-e]tetrazolo[4,5-][1,2,4]triazines (76&78) from treatment of 3-hydrazo-pyrazolo[4,3-b][1,2,4]triazines (75&77) with nitrous acid oxidation (Scheme 26)[45]. The study of the structures of these systems showed that the negative charge concentrates at nitrogen atoms of pyrazolo, 1,2,4-triazole moieties, while the positive charge only concentrates on the nitrogen atoms of 1,2,4-triazine moiety (Scheme 27)[45].



Scheme 26



Scheme 27

3. Synthesis of pyrazolyl-1,2,4-triazines

1,2,4-triazines have attracted the attention of chemists, due to their biological and pharmacological properties[46-52], and their uses as anti HIV and anticancer agents[53-55]. In addition, phospho-1,2,4-triazine derivatives are used as milluscicidal agents[56] as well as the formation of metal complexes with toxic metals[57-60]. On the other hand, polyfunctional 1,2,4-triazine derivatives are used as starting materials for the synthesis of a great variety of pyrazolines pyridines, pyrimidines and other heterocyclic nitrogen systems[61-63]. Recently pyrazoline derivatives have been exploited as herbicides, acricides and insecticides[64-65].

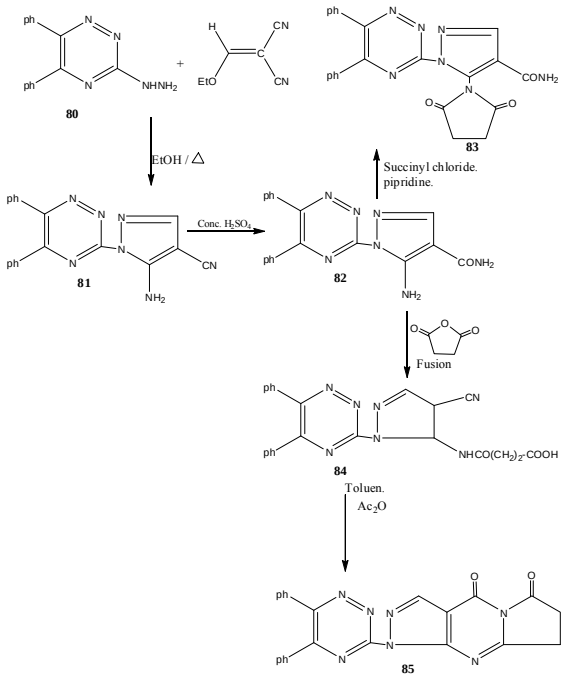
In addition, functional pyrazolines exhibit a wide range of pharmacological and biological properties[66-69], and the formation of metal complexes[70-73]. Thus, molecular modification of pyrazole ring by introducing 1,2,4-triazine moieties might be expected to exhibit the potential pharmacological and biological activities. Depending on these observations it is necessary to develop a respective synthetic approach and chemical study in view of their applications.

3.1 synthesis of 3-(pyrazol-1-yl)-1,2,4-triazines

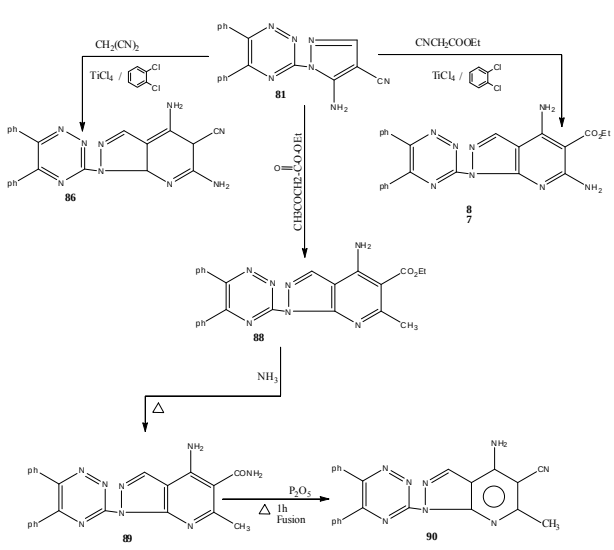
The antifungal agents 3-pyrazolyl-1,2,4-triazines derivatives (81-86) have been obtained from treatment of 5,6-diphenyl-3-hydrazino-1,2,4-triazine (80) with ethoxy methylene malononitrile followed by acidic hydrolysis and heterocyclization with α-oxo-compounds (Scheme 28)[74].

On the other hand, reaction of compound 81 with active methylene reagents produced the pyrazolopyridine derivatives (86-90) (Scheme 29) [74].

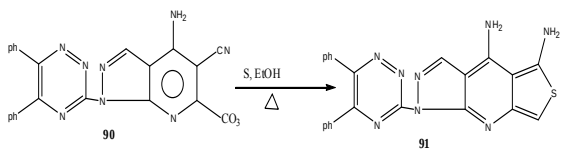
It is interesting to not that refluxing compound 90 with sulfur element in the presence of EtOH-piperidine afforded 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1H-pyrazolo[3,4-b]thieno[3,4-e]pyridine-4,5-diamine (91) (Scheme 30)[74].



Scheme 28



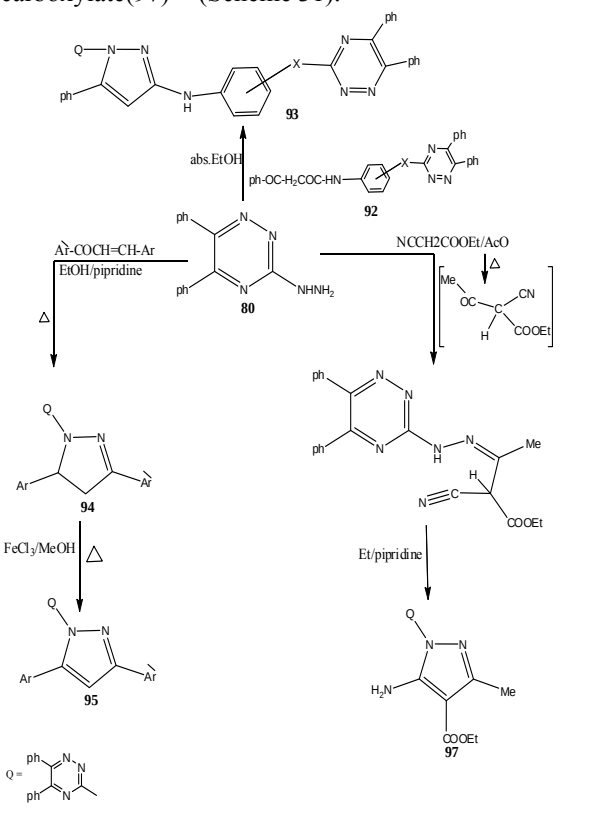
Scheme 29



Scheme 30

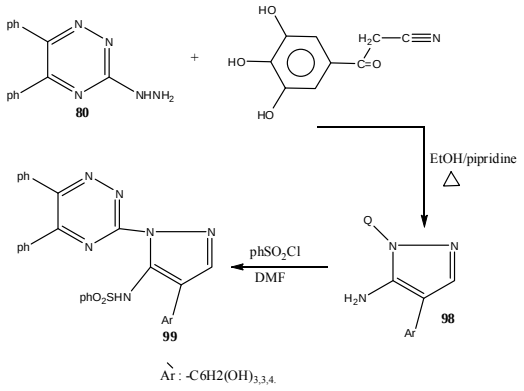
Abdel-Rahman *et al* [75-80] synthesized various unsymmetrical substituted pyrazolines bearing 1,2,4-triazin-3-yl as biocidal agents.

Thus, antimicrobial agents 93-97 substituted pyrazolyl-1,2,4-triazines were obtained from cyclocondensation of 3-hydrazino-1,2,4-triazine(80) with benzoyl acetanilide in boiling EtOH to give 1,3,5-trisubstitued pyrazole (93), while cyclocondensation of 80 with chalcones in refluxing ethanol-pipridine yielded the dihydropyrazole(94). Oxidative reaction of 94 via warming with $FeCl_3$-MeOH produced the pyrazole derivatives (95). Also, treatment of compound 80 with acetyl-ethyl cyano acetic acid afforded the hydrazone 96, which on cycloaddition by refluxing with ethanol-pipridine furnished ethyl 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-3-methyl-5-iminopyrazol-4-carboxylate(97)[75](Scheme 31).



Scheme 31

The antimicrobial agents 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-(3,3′,4-trihydroxyphenyl)-5-bezenesulfonamide-pyrazole(99) was obtained from heterocyclization of 3-hydrazino-1,2,4-triazine 80 with α-cyanoacetophenone in boiling ethanol-pipridine followed by treated with benzene sulfonyl chloride in warming DMF (Scheme 32)[76].

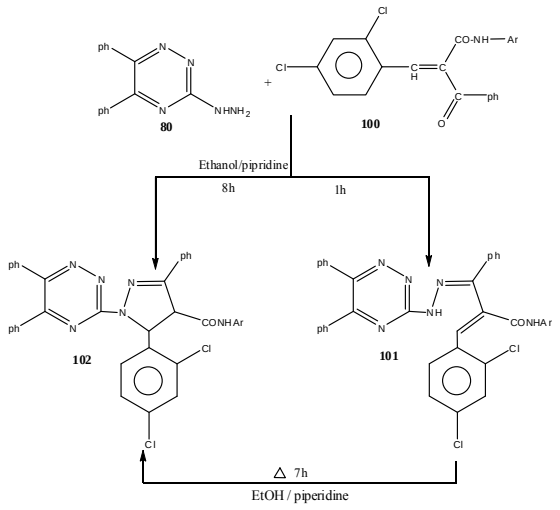


Scheme 32

It is interesting to show that thermal treatment of compound 80 with anilido-α,β-unsaturated ketones (100) in the presence of ethanol-pipridine for 1h yielded the monohydrazones 101. Refluxing 101 under the same conditions for 7h, produced 4,5-dihydro-1,3,4,5-tetrasubstituted pyrazoles (102) (Scheme 33)[76].

In addition, condensation of compound 80 with benezoly acetic acid hydrazide (102) in refluxing absolute ethanol produced the monohydrzones 103 which upon ring closure reaction via boiling with glacial acid yielded the 1,3,5-trisubstituted pyrazoles (104).

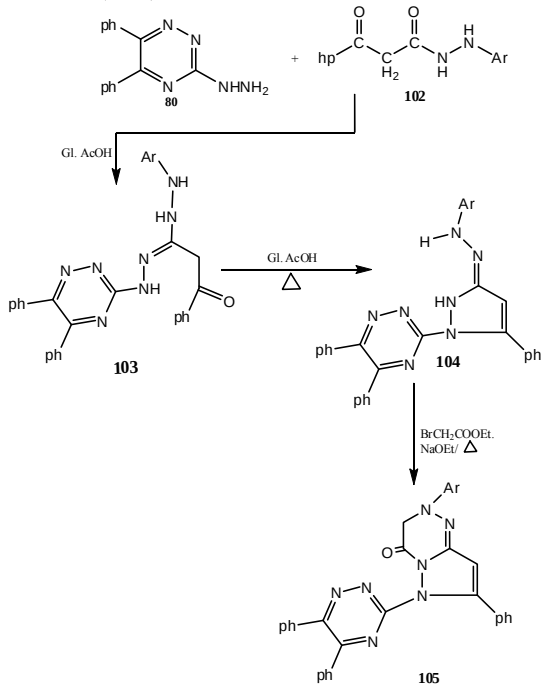
Full heterocyclization of 104 by refluxing with ethyl bromoacetate furnished 1-aryl-[1,2,4]triazin[4,3-b]pyrazolin-5-one derivatives (105) (Scheme 34)[76].



Ar, a = 3-hydroxy-4-nitrophenyl.
b = 2,4-dichlorophenyl.
c = 3--chlorophenyl.
d = 4-nitrophenyl.

Scheme 33

Substituted Pyrazoline bearing and/or containing other pyrazole moiety have been obtained form cyclocondensation of 3-hydrazino-1,2,4-triazine 80 with 1,3-bicarbonyl reagent in refluxing ethanol to give 1,3,5-trisubstituted pyrazoles (107),



Scheme 34

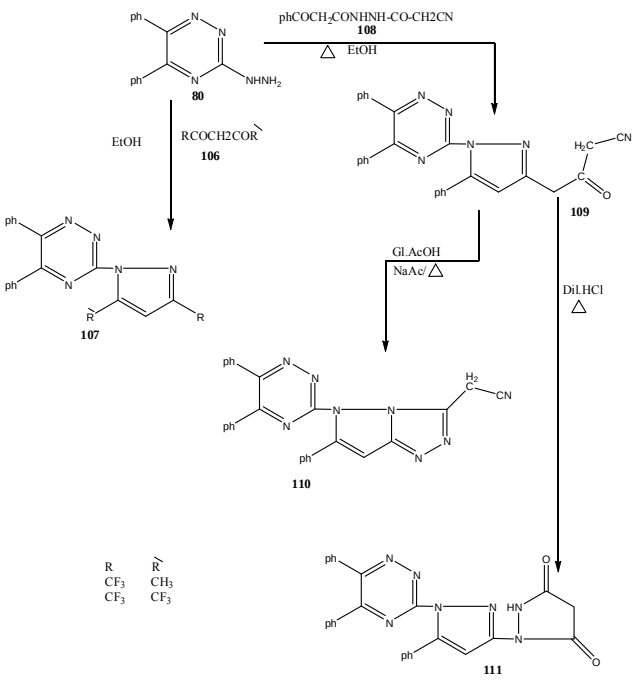
1-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-phenyl-3-(tetrahydro-3,5-dioxo-pyrazol-1-yl)pyrazole (111) (Schmem 35)[76].

Some more pyrazolone bearing 1,2,4-triazines have been obtained by Abel-Rahman *et al* [77-79]. Thus, treatment of 3-hydrazino-1,2,4-triazine 80 with ethyl cyanoacetate in the presence of sodium ethoxide underwent acylation predominantly at the unsubstituted nitrogen of the hydrazine moiety giving N1-cyanoacetyl hydrazine . Acidic hydrolysis by refluxing with dilute HCl afforded 1-(5,6-diphenyl-1,2,4-triazin-3-yl)pyrazolidine-3,5-dione (113) (Scheme 36)[77].

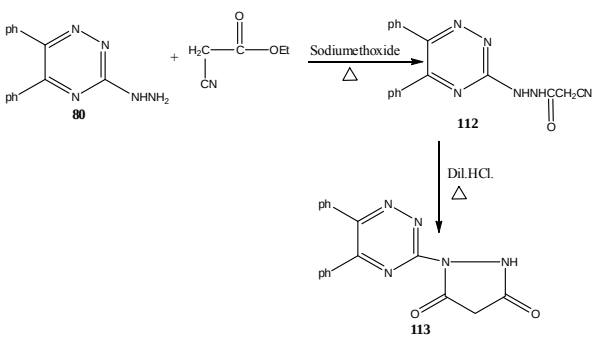
Also, cycloaddition of compound 80 with ethylaceto in refluxing absolute ethanol yielded 3-methyl-1-(5,6-dipgenyl-1,2,4-triazin-yl)-2-pyrazolin-5-one (114) directly [77] (Scheme 37).

Addition of cyano acetic acid to compound 80 gave 2-(hydrazine)-2-iminopropinic acid (115) which underwent basic cyclization using aqueous sodium hydroxide to produced 1-(5,6-diphenyl-

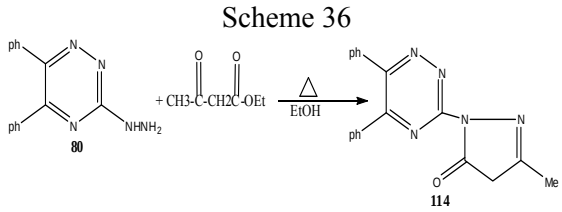
1,2,4-triazin-3-yl)-3-imino-2H-pyrazolin-5-one (116) as antimicrobial agents (Scheme 38)[78].



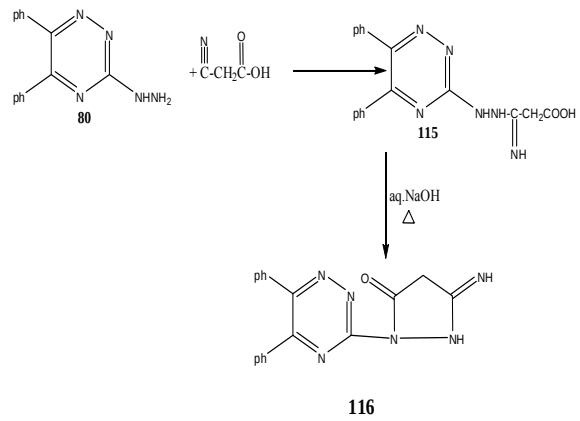
Scheme 35



Scheme 36

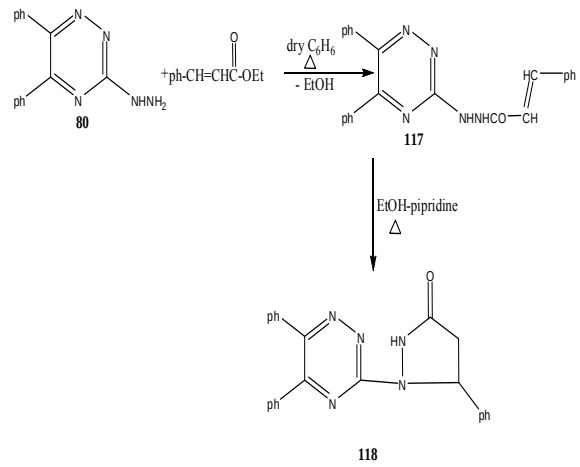


Scheme 37



Scheme 38

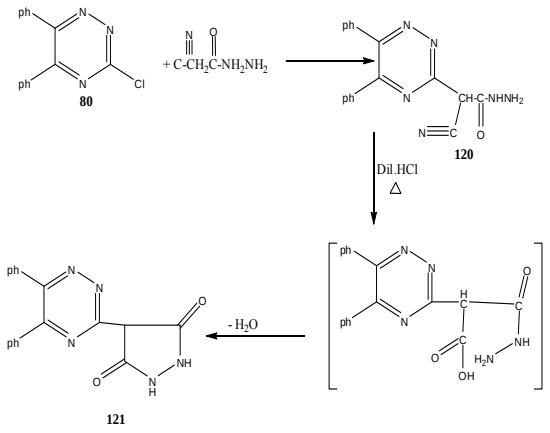
Reaction of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (80) with ethyl cinnamate in dry benzene gave the N1-acyl derivatives 117, which upon cycloaddition by refluxing with ethanol-piptridine yielded tetrahdrop-yazolone 118 (Scheme 39)[78].



Scheme 39

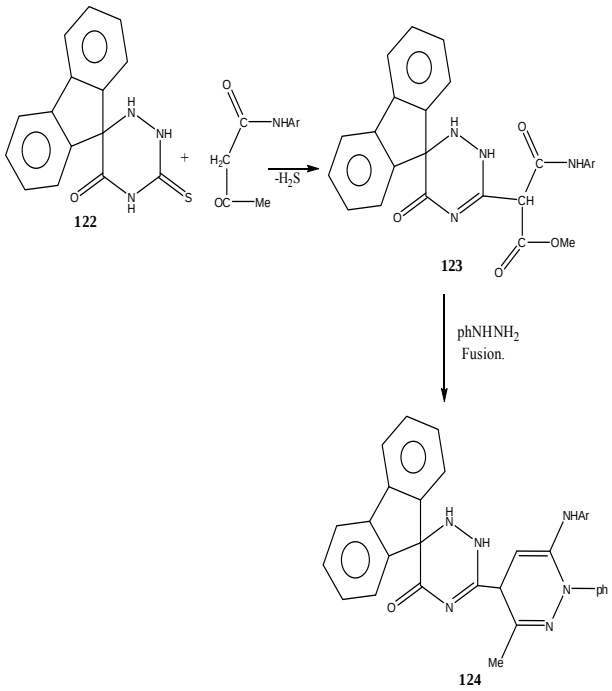
3.2 Synthesis of 3-pyrazol-4-yl-1,2,4-triazine

Pyrazoline bearing 1,2,4-triazine moiety at carbon atom was obtained by Abel-Rahman *et al*[79]. Thus, the interaction between 3-chloro-5,6-diphenyl-1,2,4-triazine (119) and cyanoacetic acid hydrazide in refluxing dry pyridine afforded the acid hydrazide derivatives 120. Acidic hydrolysis of 120 by refluxing with diluted HCl afforded 4-(5,6-diphenyl-1,2,4-triazin-3-yl)pyrazol-3,5(2H,4H)dione (121) (Scheme 40)[79].



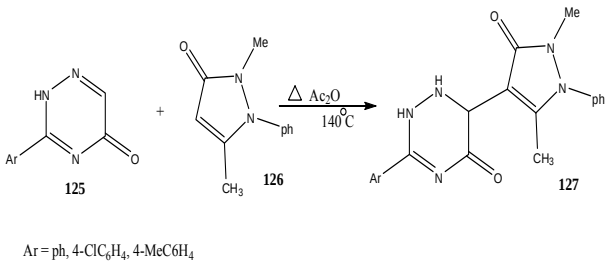
Scheme 40

Similarly, the reaction between 3-thioxo-1,2,4-triazin-5-one derivatives (122) with acetylacetamides produced the malonamide 123. Refluxing 123 with phenylhydrazine via fusion at 150 ^{O}C yielded 3-methyl-1-phenyl-5-substitutedamino-4-[1′,6′-dihydro-6′-spiro(9-flurene)-5′-(4H)-oxo-1,2,4-triazin-3′-yl]pyrazole (124) (Scheme 41)[80]. Compound 124 exhibited anti HIV and anticancer activities [80].



Scheme 41

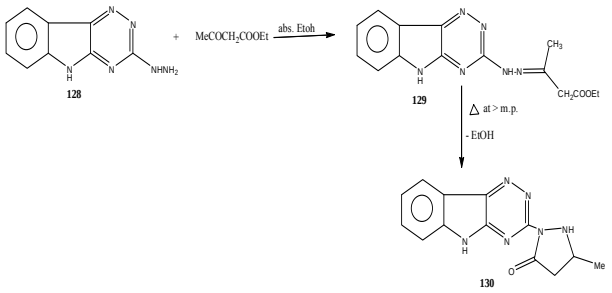
Finally, refluxing 1,2,4-triazin-5-one derivatives (125) with 1,3-dimethyl-2-phenylpyrazol-5-one (126) in the presence of acetic acid anhydride furnished 1-acetyl-3-aryl-6-(1-phenyl-2-methyl-3-oxo-5-meth- -ylpyrazol-4-yl)-tetrahydro-1,2,4-triazin-5-one (127) (Scheme 42) [81].



Scheme 42

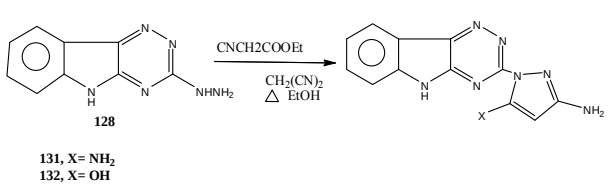
3.3 Synthesis 3-(pyrazol-5-yl)-1,2,4-triazines

Pyrazolone bearing 1,2,4-triazino-indole moiety 130 was obtained from the reaction of 3-hydrazino-1,2,4-triazinoindol 128 with ethyl acetoacetate to give the hydrazone 129. Heating 129 above its melting point yielded 1-(1,2,4-triazinoindol-3-yl)-2H-3methyl-4,5-dihydropyrazol-5-one(130) (Scheme 43) [82].



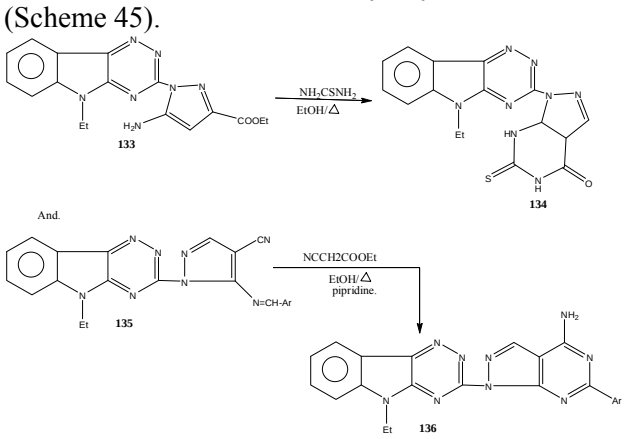
Scheme43

Also, refluxing 3-hydrazino-1,2,4-triazino-[5,6-b]indole (128) with malononitrile on absolute ethanol yielded 3-(3′-5′-diamino-1H-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole (131) while cycloaddition of 128 with ethyl cyanoacetate under the same condition afforded 1-substitued-3-methyl-5-hydroxypyrazole (132) (Scheme 44) [23].



Scheme 44

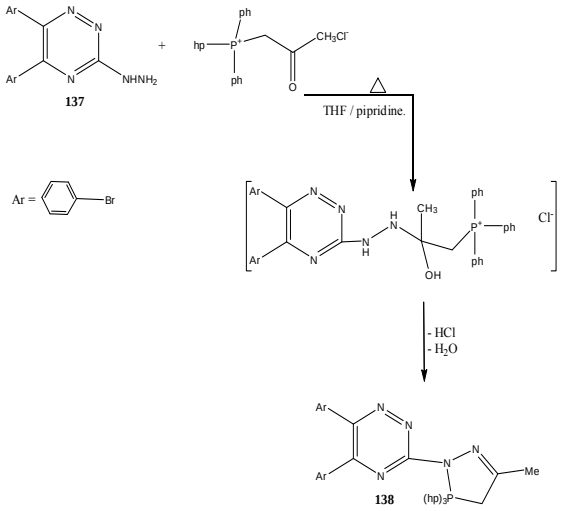
On the other hand, the reaction of ethyl 5-amino pyrazol-4-carboxylate derivatives (133) with thiourea in boiling ethanol furnished pyrazolo[3,4-d]pyrimidinthione 134 [89]. While pyrazolo[3,4-d]pyrimidine 136 was isolated from the reaction of 135 with ethyl cyaniacetate [85] (Scheme 45).



Scheme 45

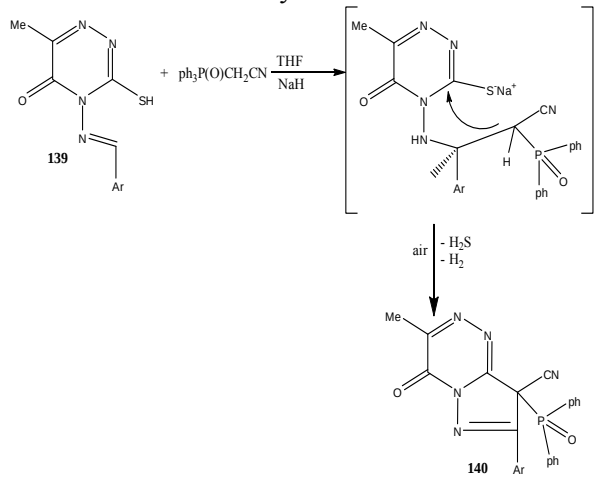
4. Synthesis of phosphorus containing pyrazolyl-1,2,4-triazines

It is known that phosphorus containing heterocyclic compounds have very interesting biological activity [86]. The synthesis of several phospho- substituted 1,2,4-triazines, triazinylphosphoramidetes [87,88] and series of stable phosphorus compounds incorporating 1,2,4-triazine moiety are known as accessible intermediates for preparing new 1,2,4-triazine derivatives with their therapeutically potencies have been reported [89,90]. Thus, 6,7-bis(4-bromophenyl)-2,3-dihydro-3,3,3-triphenyl-3-λ5-1,2,4,3-triazaphospho-lino[4,5-b][1,2,4-triazine (138) was isolated from stirring 3-hydrazino-5,6-diaryl-1,2,4-triazine (137) with dibromotriphenylphos- phorane in THF containing drops of pipridine at room temperature for 24h (Scheme 46) [56].Compound 138 exhibited a molluscicidal activity against Biomphalaria Alexandrina Snails (the intermediate host of Schistosomamansoni) [56].



Scheme 46

It is interesting that when compound 139 was heated under refluxing with diphenylphosphoryl acetonitrile for 12h in THF and presence of NaH as a catalyst, produced 7-(4-chlorophenyl-8-(diphenylphosphoryl)-3-methyl-4-oxo-4,8-dihydropyrazolo[5,1-c][1,2,4]triazine-carbonitrile(140) (Scheme 47) [18]. Compound 140 had antibacterial activity.



Scheme 47

5. Applications and Importance

Most of pyrazolo-1,2,4-triazine derivatives and pyrazolyl-1,2,4-triazine compounds have exhibited a wide spectrum of pharmacological and biological properties.

Thus, 3,7- and 8-substituted pyrazolo[5,1-c] [1,2,4]benezotriazine-5-oxides (141) have been synthesized and used as benzodiazepine receptor

ligands [91].Also, 2-aryl-4-oxopyrazolo[1,5-d][1,2,4]triazines (142) have shown analgesic, anti-inflammatory and antipyretic activities [92].In addition, dihydropyrazolo-1,2,4-triazines 143 showed anticonvulsant activity [26].Many pyrazolo[1,5-c][1,2,4]triazines are used as antitumor agents, especially anti Leukemia [93].

6.Conclusion

Nitrogen heterocyclic compounds play important role in biochemical processes, because the side groups of the most typical and essential constituents of living cells, DNA and RNA are based on aromatic heterocyclic nitrogen systems [94]. Among these pyrazolo[4,3-e][1,2,4]triazines accur the purine analogues. The importance of pyrazolo triazines and pyrazolyl triazines was shown by their biological activities and unique structure that led to several applications in different areas of pharmacological and agrochemical research and more recently in material sciences [95].

The number of potentially very versatile pyrazolo-1,2,4-triazine building block that may be accessed by direct nucleophilic attack of functional pyrazoles and /or cycloaddition or cyclocondensation of hydrazineo triazines to produce pyrazolyl-triazines.

Extending the numbers of functional pyrazole containing 1,2,4-triazine moiety systems available to discovery chemists whilst microreactor techniques show great promise as efficient and effective reactor devices for both medicinal and pharmacological industries.

7.. REFERNCES

[1]**Saad H.A. , Youssef M.M. ,Mosselhi M.A.** ; *molecules*, ,**16**,4937-4957. (2011)

[2]**Gucky T., Reznickova E., Dzubak P., Monatsh Chem., 141**, 709-714 (2010)

[3]**Atack J.R., Maubach K.A., Wafford K.A., Oconnor D., Rodrigues A.D., Evans D.C., Tattersall F.D., Petty K.J.;** *J. pharmacology& Experimental Therapeutics*, **331**(2), 470-484 (2009).

[4]**Gucky T., Frysova I., Slouka J., Hajduch M., Dzubak P.; Eur.J.** *Medicinal Chem*.,44,891-900 (2009).

[5]**El-sayed A.T.,** *Eur.J. Medicinal Chem*.,**44**,4385-4392 (2009).

[6]**Karczmarzyk Z.,Mojzych M., Rykowski A**.; *J.Moleocular Structure*,**829**,22-28 (2007).

[7]Mojzych M., Rykowski A.,Wierzchowski J.; molecules, 2005,10,198-1306.

[8]**Hirata K., Nakagami H., Takashina J., Mahmud T., Kobayashi M., In Y., Ishida T., Miyamoto K.;** *Heterocycles*, **43**, 1513-1519 (1996)

[9]**Smirnov V.V., Kiprianova E.A.,Garagulya A.D., Esipov S.E., Dovjenko S.A**.; *Microbial Lett.,* **53**, 357-361 (1997)

[10]**Parker W.B.,Secrist J.A.,3rd,Waud W.R**., *Curr.Op.Invest. Drugs*, 5,592-596 (2004)

[11]**Sugiyama T.,Schweinberger E., Kazimierczuk Z., Ramzaeva N., Rosemyer H.,Seela E**.; *Chem.,Eur.J.;* 6,369-378 (2000).

[12]**Wierzchowski J., wielgus K.B., Shugar D**.; *Biochem.Biophys. Acta*, 1290,9-17(1996).

[13]**Ibrahim M.K.A., Ramiz M.M., El-Ghandour AH.H.;***J. Chem. Soc. Pak*. 1989, 11(4),291; *Chem. Abstr.*,113,191303k (1990)

[14] **Ibrahim M.K.A.;** *Pak. J. Sci. Ind. Res*.,32(5),301; *Chem. Abstr. 1990,**113**, 198390b (*1989).

[15]EI-**Nagdi M.H., Sadek K.M., Galil F.MA, Hassan S.M.E**; *Arch Pharm.(WeinheimGer.);*1988,321(12),851;Chem.Abstr.,**110**, 114805m (1989)

[16]**EI-Ghandour A.H.H., Zohdi H.F., Afeely H.Y., Ibrahim M.KA**, *Phosphorus, Sulfur and Silicon* **70**(3-4), 297(1992).

[17]**EI-Mobayed M., Elssawy A, EI-Bahnasawi A.A, Atef M.;***Gazz. Ital.* 1991, 121(4),209; Chem. Abstr., **115**, 71551j(1991).

[18]**Ali T.E**.; *Eur. J. Med. Chem*., **44**, 4385-4392(2009).

[19]**Josih K.C., Pathak V.N., Gary U.;***J.IndianChem.Soci*;60,1074-1074(1983).

[20]**Ibrahim Y.A.,Al-Awadi N.A.**, **John Elizabeth**; *Tetrahedron*, **64**,10365-10374(2008).

[21]**Al-Etaibi A., John Elizabeth, Ibrahim M.R, Al-Awadi N.,Ibrahim Y.A.;***Tetrahedron*, **67**,6259-6274(2011)

[22]**Yoshihisa K., Yumiko K., Hosik R.F., Megumi K., Marioki Y., Atsushi T.k**; *J. Heterocycl. Chem*., 26,853 ; Chem. Abstr. 1990,112, 98491q.z(1989).

[23]**Quintela L., Moreiva M.J., Peinador C.;** *Tetrahedron*., **52**(8),3037; Chem. Abstr. 1995,124, 289464r. (1996)

[24]**Ghozlan S.A.S., Ibrahim L.I.;** *J. Chem. Soc. Pak*.,**12**(2), 134; Chem. Abstr. 1991, 114, 42743x.(1990)

[25]**Shaaban M.A., Abdou N.A., EI-Meligie S., Taber A**.; *Bull. Fac. Pharm.* **28**(3), 19; Chem. Abstr. 1991,115, 71547n(1999)

[26]**Coudert P., Mavel S., Couquelet J., Tvonche P., Rubat C. , Bastide J.;** *J. Heterocycl. Chem*.,28(3),769 (1991)

[27]**Atack J.R., Maubach K.A., Wafford K.A., Oconnor D., Rodrigues A.D., Evans D.C., Tattersall F.D., Petty K.J**.; *Pharmacological and Experimental therapeutics*, **331**(2),470-484(2009)

[28]**Abdel-Hamid A.O., Attaby FA, Khalifa FA, Ghabrial S.S.,** *Arch. Pharmacol. Res.*, **15**(1), 14 ; Chem. Abstr. 1993, 118, 6950m (1992)

[29]**Lu-Yan., Cui-Xiufang, Pang-Jibai, Cai-Mengsheng.,** *Huaxve - Tongbao*, **11**,30; Chem. Abstr. 1991, 116, 214463r(1991)
[30]**Al-Mater H.M.,Khalil K.D.,Al-Dorri D.M., Elnagdi M.H**.; *molecules* , **15**,3302-3310(2010)
[31]**Seada M., Abdel-Rahman R.M., Hanafy F**.;*J. Indian Chem.Soc.*, **69**,882(1992)
[32]**Montgomery J.A.**; *Med. Rec.,Rev*,**2**,271-308(1982)
[33]**Plunkett W., Saunders P.P.;** *Pharmacol.Therpeut*., **49**,239-286(1991)
[34]**Parker W.B., Secrist J.A.**, *3rd; Wand W.R.; Curr.Op. Invest. Drugs*, **5**,592-596(2004)
[35]**Albert A.A.,** *Adv. Heterocycl. Chem*.,**39**,117-178(1986)
[36]**Wierzchowski J., Wielgus K.B., Shugar D**.; *Biochim. Biophys.Acta*, **1290**, 9-17 (1996)
[37]**Sugiyama T., Schweinberger E., Kazimierczu K., Ramzaeva N., Rosemeyer H., Seela F**.; *Chem. Eur. J*., **6,**369-378(2000)
[38]**Smirnov V.V., Kiprianova E.A., Garagulya A.D., Esipov S. E., Dovjenko S.A.;** *Microbial. Lett*.,**53**,357-361(1997)
[39]**Hirata K., Nakagami H., Takashina J., Mahmud T., Kobayashi M., In.Y.,Ishida T., Miyamoto K.;** *Heterocycles*, 43,1513-1519 (1996)
[40]**Gucky T., Frysova I., Slouka J., Hajduch M., Dzubak P**.; *Eru.J.Med.Chem*. ,**44**,891-900(2009)
[41]**Part 36 in 1,2,4-triazines in organic synthesis, For part 35 see Lipinska T.,** *Tetrahedron*, **62**,5736(2006).
[42]**El-Ashry E.S.H., Rashed N., Taha M., Ramdan E**., *Adv. Heterocycl.Chem.*,**59**,39;61,207(1994).
[43]**Mojzych M., Rykowshi A.**, *Heterocycles*, **63**,1829(2004)
[44]**Mojzych M., Karczmarzyk Z., Rykowshi A.,** *J.Chem.Crystallogr*, **35**,151(2005)
[45]**Karczmarzyk Z., Mojzych M., ., Rykowshi A.,** *J. Molecular structures*,**829**,22-28(2007)
[46]**Abdel-Rahman R.M., Morsy J.M., Allimony H.A., AbdEl-Monem W.R.;** *Boll.Chem.Farmaceutico*, **138**(4),176-185(1999).
[47]**Abdel-Monem W.R, Abdel-Rahman R.M;** *International J. Chem*., **16**(1), 1-14(2006)
[48]**Ibrahim M.A., Abdel-Rahman R.M., Abdel-Halim A.M., Ibarhim S.S., Allimony H.A**.; *ARKIVOC*, **xiv**,202-215(2008)
[49]**Ibrahim M.A., Abdel-Rahman R.M., Abdel-Halim A.M., Ibarhim S.S., Allimony H.A**.; *J.Barz.Chem.Soc*., **20**(7) 1275-1286(2009).
[50]*Abdel-Rahman R.M., Pharmazie*, **56**(4)275-286(2001).
[51]**Abdel-Rahman R.M.,** *Pharmazie*, **56**(3)195-204(2001).
[52]**Abdel-Rahman R.M**., *Pharmazie* , **56**(1)18-22(2001)
[53]**Abdel-Rahman R.M.,** *Pharmaco*,**46**(2) 379-389(1991)
[54]**Abdel-Rahman R.M**., *Pharmaco* ,**47**(3) 319-326(1992)
[55]**El-Gendy, Z.; Morsy, J. M.; Allimony, H. A; Abdel-Monem Ali, W. R.; Abdel-Rahman, R. M.**, *Phosphorus, Sulfur Silicon Relat. Elem*., **178**(9), 2055-2071(2003)
[56]**Ali T.E. Adel-Raman R.M.,Hanaly F.I., El- Edfawey S.M.,***Phosphorus, sulfur and Silicon*, **183**,2565-2577(2008)
[57]**RamadanA.T., Abdel- Rahman R.M., Seada M.H**.; *Asian J.Chem.,* **4**(3) 569 -578(1992)
[58]**Ramdan A.T., Abdel- Rahman R.M., El-Behairy M.A., Ismail A.I., Mahmoud M.M.;***Thermochim Acta*, **222**, 291-303(1993)
[59]**Ramadan A.T., Abdel- Rahman R.M., Seada M.H.;** *Asian J.Chem- Soc*., **1**(3) 186(1992).
[60]**Ghassemzadeh, M., AghayanM.M.,Neumüller B.**, *Inorg. Chim. Acta.*, **358**, 2057-2065(2005).
[61]**Abdel-Rahman R. M.,** *Trends Heterocycl. Chem.;* **6** , 126- 133(1999).
[62]**Abdel-RahmanR. M**.; Trends Heterocycl. Chem.,**8**, 187-194(2002).
[63]**Abdel- Rahman R.M., Makki M.T, Ali T.E., Ibrahim M.A**.; *Current Org. Synthesis*, **10**,136-160(2013).
[64]**Ursula D., Marcela B. Brigitte S**.;*Phosphorus,Sulfur and Silicon*,**146**,85(1999).
[65]**Lizai-Guo, Huang R-Q., li H.y., Tianjin P.R.C**.;*Phosphrus, Sulfuer and Silicon;* **147**,455(1999).
[66]**Wang, J., Soundarajan, N., Liu N., Zimmermann, K., Naidu B. N**.; *Tetrahedron Lett*, **46**, 907–910(2005).
[67]**Carling R.W., Russell M.G., Moore K.W., Mitchinson A., Guiblin A., Smith A., Wafford K.A., Marshall G., Atack J.R., Street L. J**.;*Bioorg& Med. Chem. Lett*., **16**(13),3550-3554(2006).
[68]**Sharon A., Pratap R., Tiwari P., Srivastava A., Maulik P.R., Ram V.J.**, *Bioorg& Med. Chem.Lett*, **15**,2115-2117(2005).
[69]**Ciciani G., Coronnelo M., Guerrini G., Selleri S., Cantore M., Failli P., Mini E., Costanzo A**.;*Bioorg& Med. Chem*., **16**,9409-9419(2008).
[70]**Cingolani A., Marchetti E.F., Pettinari C., Pettinari R., Skelton B.W., White A.H**.; *Inorg. Chem*., **329**,100-112(2002).
[71]**Khalil, A., Hassan, M.A., Mohamed, M.M., Elsayed, A.M**., *Dyes and Pigments*, **66**, 241-245(2005).
[72]**CerchiaroG.,Ferreira A.M.C., Teixeira A.B., Magalhaes H.M., Cunha A.C., Ferreira V.F., Santos L.S., Eberlin M.N., Skakle J.M.S., Wardell S.M.V, Wardell J.L.;** *Polyhedron*, 25,2055-2064(2006).
[73]**Ramakanth P.A.P., Meshram J.,** *J. Coodination Chem*., **63**(2) 323-329(2010).
[74]**Harb A.F.A., Abbas H.H., Mostafa F.H**.; *Chem.Papers*; **59**(3) 187-197(2005).
[75]**Abdel-Rahman R.M., Seada M., Fawzy M.M.,** *Pak. J. Sci. Ind. Res.* **34**(12), 465-468(1991).
[76]**Abdel-Rahman R.M.;** *Indian J. Chem*., **27B**, 548-553(1988).
[77]**Zaher HA, Abdel-Rahman R.M., Abdel-Halim AM.**, *Indian J. Chem.*, **26B**,110-115(1987).
[78]**Abdel-Rahman R.M.** ,*Pak. J. Sci. Ind. Res.,* **32**(4), 240-245(1989).
[79]**Abdel-Rahman R.M.**, *Indian J. Chem*., **25B**, 815-819(1986).
[80]**Abdel-Rahman R.M., Seada M., Fawzy M.M., El-Baz I**.; *Pharmazie*, **49**(10) 729-733(1994).
[81]**Valdimir L., RusinovS., Grigori V.Z., Tatjanal P., Oleg N.C., Hans N.;** *J. Heterocycl.Chem*.,**34**,1013; Chem.Abstr.1997,127, 176407t \(1997).

[82]**Krishna C., Johi A.D., Sunita B.,** *J.Heterocycl.Chem*.,**26**,545 (1989).
[83]**Abdel-Latiff F., Shaker R.M., Mabgoub S.A., Bader M.Z.;** *J.Heterocycl.Chem*.,**26**,769(1989).
[84]**Younes M.I., Abbas H.H., Metwally S.A.M.;** *Pharmazie,* 46(2), 98; Chem.Abstr. 1991,115,29256s(1991).
[85]**Younes M.I., Abbas H.H., Metwally S.A.M.;** *J.Chin.Chem.Soc., Taipei*,**37**(6),611; Chem.Abstr.1990,112,10819b(1990).
[86]**Wan L., Alkorta I., Elguero J., Sum J., Zheng W**.; *Tetrahedron*, 63,9129(2007).
[87]**Wang Z., Verkade J.G.;** *Tetrahedron Lett*.,**39**,9331(1998).
[88]**Abdel-Rahman R.M., Ibrahim M.A., El-SayedT.Ali;** *Eur.J.Chem*., **1(**4),388,396(2010).
[89]**Wanoff H., Tzanova M.,** *Arkivoc*, 98(2003).
[90]**Pirat J., Monbrun J., Virieux D., Cristau H.J**.; *Tetrahedron*, **61**,7029(2005).
[91]**Costanzo A., Guernni G., Bruni F., Sellri S**.; *J,Heterocycl.Chem*.(1994),**31**(6),1369;Chem.Abstr.,**122**,160610q (1995).
[92]**Movel S., Rubat C., Couetert P., Privat A.M., Couquelet J., Tonche P., Bastide P.**; *Arzneim-Forsch*, 1993,**43**(4) 464;Chem.Abstr.,**119**,85406k(1993).
[93]**Kawai Y., Yamazki H., Tanaka H., Oku T**.; *Pet.Int.Appl.Wo* 9419,350(CICO 7D 487-104)1Sept.,G.B.Appl.9313,993,26(1994).
[94]**Valverde M.G., Torroba T., Molecules**, **10**,318-320(2005).
[95]*Torroba T.; J. Prakt.Chem.,* ,**341**,99-113(1999).

طرق فعالة لتحضير بيرازولين يحتوي على جزء 1،2،4–ترايازين كأهداف دوائية

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الخلاصة :

تتم استعراض ومراجعة تحضير ، الفعالية الكيميائية والتأثير البيولوجي للبيروزولين المحتوي على جزء 1،2،4– ترايازين . تحضير هذه الأنظمة تم من خلال annelation غير المتجانسة لل هيدرازين ، حمض هيدرازيد و / أو امينو بيرازولين مع عوامل ازا.

تم الأشارة في المقالة الى المميزات البيولوجية الفريدة والتطبيقات الهامة لهذة المكونات .