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MINI REVIEW ON SYNTHESIS OF DIFFERENT PYRIMIDINE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY

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Abstract:
The review concerned with the synthesis of pyrimidine derivatives which have biological activity, some of method for preparation via the reaction of acrylonitrile derivatives **4a,b** with N-acetylurea led to the formation of ureido acrylonitrile derivatives **6a,b** which undergo intramolecular cyclization upon treatment with alkali to give pyrimidine derivatives **7a,b**, Also fully pyrimidine derivatives was synthesized by the reaction of benzamidine **35** which refluxed with Ethyl 3-oxo-2-(4-flourobenzylidine)-4-methylpentanoate**36** in hydrochloride and potassium acetate to give 4-(4-flurophenyl)-6-isopro-pyl-2-phenyl-5-ethoxy carbonyl-1,2-dihydro-pyrimidine **37**.

Key words: acrylonitrile derivatives, pyrimidine derivatives, Treatment, dehydration, guanidine.

Introduction:

Pyrimidine derivatives (**II**) and (**III**) [I,II]exhibit both antifungal and antibacterial activity Figure **1**and **2**.

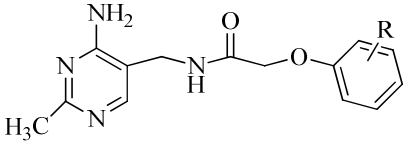


Figure 1: N-((4-amino-2-methylpyrimidin-5-yl)methyl)-2-substituted phenoxyacetamide(**I**)

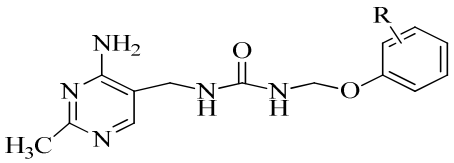


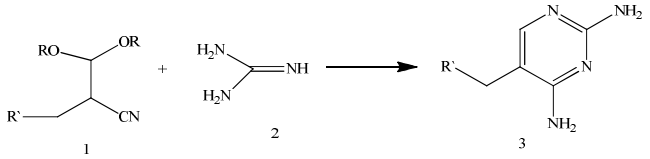
Figure 2:1-((4-amino-2-methylpyrimidin-5-yl)methyl)-3-(substituted phenoxymethyl)urea(II)

.

Pyrimidine derivatives possess pharmacological properties like medicinal drug activity [III], anti-HIV[IV], and antiprotozoal[V], analgesic[VI], anti-inflammatory[VII], antitumor[VIII], antiviral[IX], antibacterial[X], antifilarial[XI], antifungal[XII].

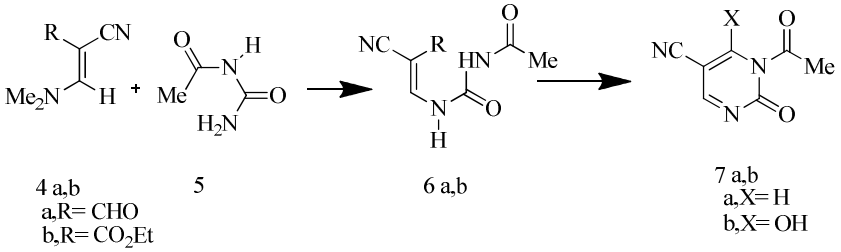
Method of preparation and biological activity:

Cyclocondensation of $R^1CH_2CH(CN)CH(OR)_2$ with guanidine gave 2,4-diaminopyrimidine derivative **3** [XIII]



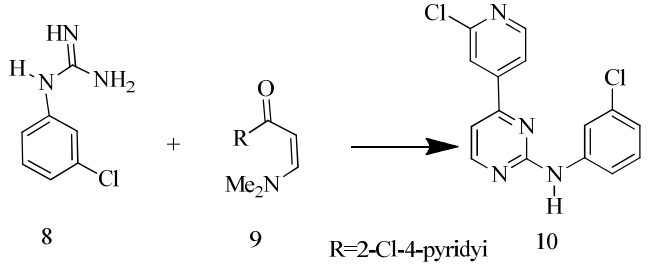
Scheme 1: Synthesis of 2,4-diaminopyrimidine derivative **3**.

Treatment of acrylonitrile derivatives **4a,b** with N-acetylurea led to the formation of ureido acrylonitrile derivatives 6a,b which undergo intramolecular cyclization upon treatment with alkali to give pyrimidine derivatives **7a,b**[XIV].



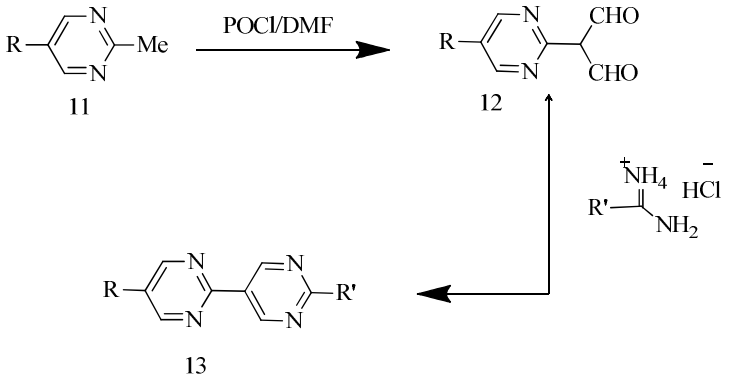
Scheme 2: Synthesis of pyrimidine derivatives **7a, b**.

Cyclocondensation of anilinoformamidine derivative with β-ketone compound **9** gave pyrimidine derivative **10** [XV].



Scheme 3: Synthesis of pyrimidine derivative **10**.

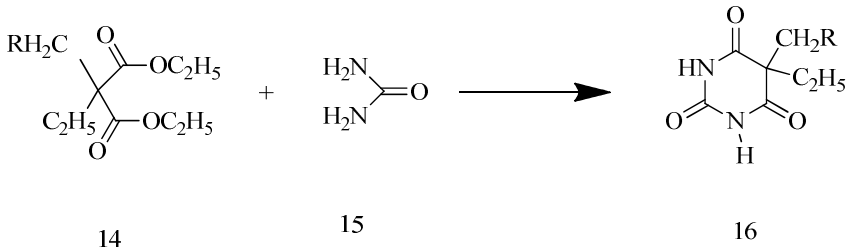
Treatment of 2-methylpyrimidine derivatives **11** with $POCl_3$/ DMF afforded diformyl derivative **12** that treated with formamidine derivative to give 2,5-bipyrimidine derivative **13** [XVI].



R= substituted phenyl R'= substituted phenyl,C_7H_5

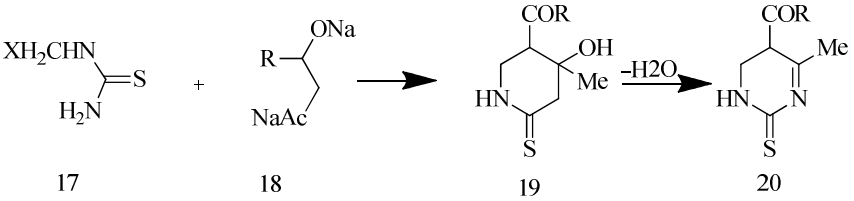
Scheme 4: Synthesis of 2, 5-bipyrimidine derivative **13**

The reaction of diethylmalonate derivative **14** with urea gave the pyrimidine derivative **16** [XVII].



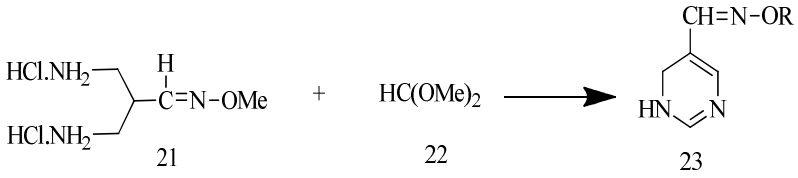
Scheme 5: Synthesis of pyrimidine derivatives **16**.

Heterocyclization of thiourea derivative **17** with the enolate of 1,3-dicarbonyl derivative **18** afforded hydroxyhexahydropyrimidinthiones **19**, which upon dehydration afforded tetrahydropyrimidinthiones **20** [XVIII].



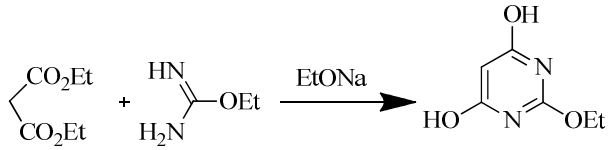
Scheme 6: Synthesis of tetrahydropyrimidinthiones **20**.

Treatment of 3-amino-2-(methylamino)propionaldehyde-O-methyl-oxime2HCl **21** with trimethyl orthoformate **22** gave Z and E-1,2,5,6-tetrahydro-5-pyrimidinecarboxaldehyde-O-methyloxi-me **23** [XIX].



Scheme 7: Synthesis of Z and E-1,2,5,6-tetrahydro-5-pyrimidinecarboxaldehyde-O-methyloxime **23.**

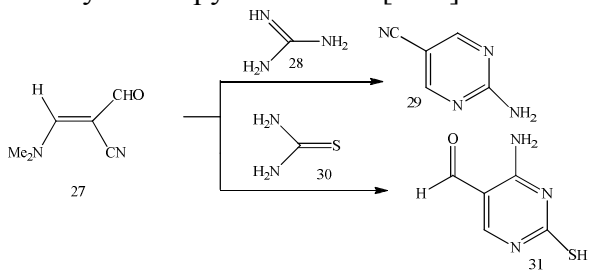
Condensation of the O-ethylthiourea **25** with diethylmalonate **24** gave the pyrimidine derivative **26** [XX].



24 25 26

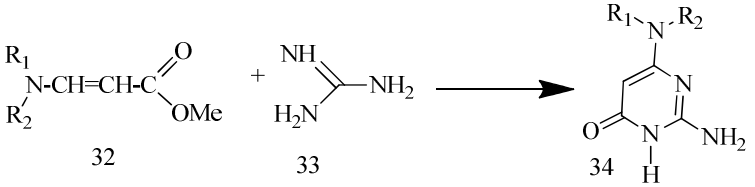
Scheme 8: Synthesis of pyrimidine derivative **26**.

Reaction of acrylonitrile derivative **27** with guanidine **28** and thiourea **30** led to 2-amino-5-cyanopyrimidine **29** and 2-formyl-2-thiopyrimidine **31** [XXI].



Scheme 9: Synthesis of 2-amino-5-cyanopyrimidine **29** and 2-formyl-2-thiopyrimidine **31**.

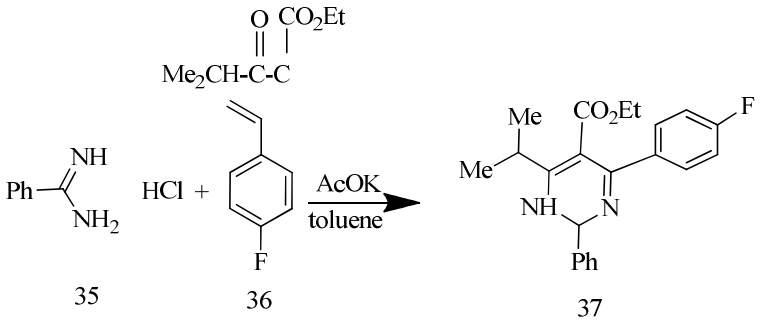
Cyclocondensation of acrylate derivative **32** with guanidine **33** gave pyrimidine derivative **34** [XXII].



32 33 34

Scheme 10: Synthesis of pyrimidine derivative **34**.

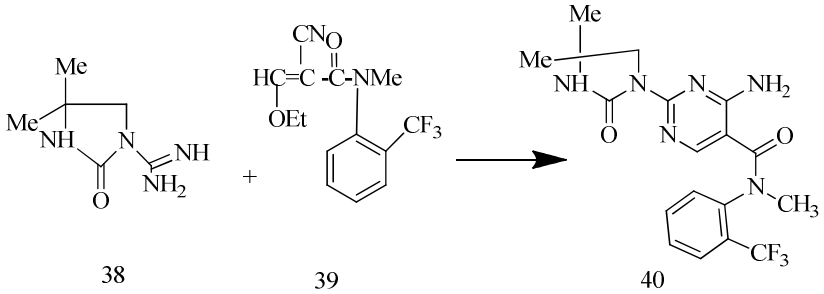
Benzamidine **35** was refluxed with Ethyl 3-oxo-2-(4-flourobenzylidine)-4-methylpentanoate**36** in hydrochloride and potassium acetate to give 4-(4-flurophenyl)-6-isopro-pyl-2-phenyl-5-ethoxy carbonyl-1,2-dihydro-pyrimidine **37** [XXIII].



35 36 37

Scheme 11: Synthesis of 4-(4-flurophenyl)-6-isopro-pyl-2-phenyl-5-ethoxy carbonyl-1,2-dihydro-pyrimidine **37**.

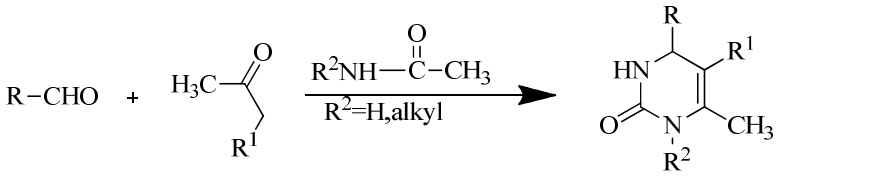
Cyclocondensation of amidino-oxoimidazolidine derivative **38** with acrylamide derivative **39** gave 4-amino-pyrimidine derivative **40** [XXIV].



38 39 40

Scheme 12: Synthesis of 4-amino-pyrimidine derivative **40**.

Reaction of aldehyde **41** with ketomethylene derivatives **42** and urea or N-alkylurea in presence of HCl afforded 2-oxopyrimidine derivatives **43a, b** [XXV].

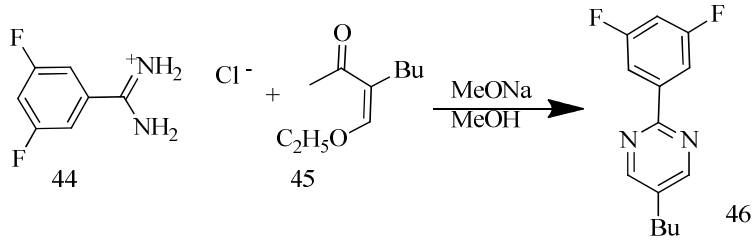


41 42 43 a,b

a,R= alkyl R^1= NO_2 b,R = Ph R^1 = acetyl

Scheme 13: Synthesis of 2-oxopyrimidine derivatives **43a, b**.

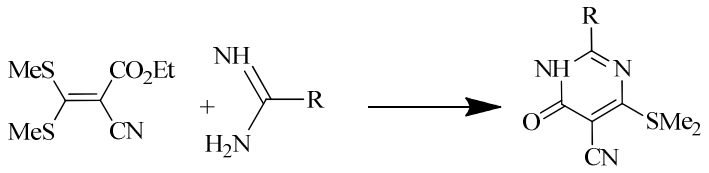
Treatment of benzamidine derivative **44** with acrolein derivative **45** under basic condition in methanol gave pyrimidine derivative **46** [XXVI].



44 45 46

Scheme 14 : Synthesis of pyrimidine derivative **46**.

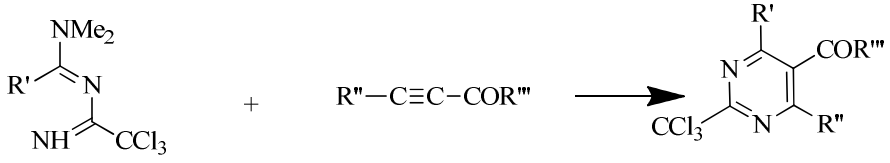
Reaction of acrylate derivative **47** with formamidine derivative **48** yielded the cyanopyrimidine derivative **49** [XXVII].



47 48 49

Scheme 15 : Synthesis of cyanopyrimidine derivative **49**.

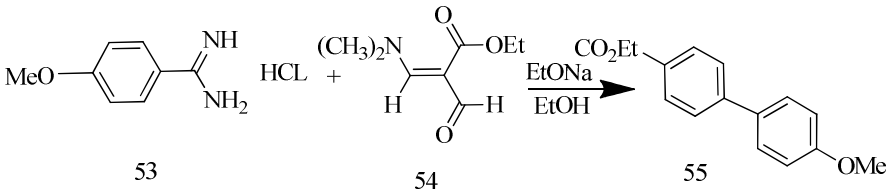
Cycloaddition between diazadiene **50** and alkynes derivatives **51** afforded fully pyrimidine derivative**52** [XXVIII].



50 51 52

Scheme 16 : Synthesis of fully pyrimidine derivative**52**.

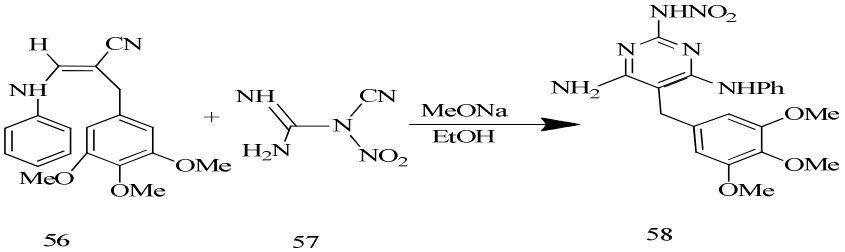
Cyclocondensation of p-methoxybenzamidine **53** HCl with 2-methoxycarbonyl-3-dimethylaminoacrolin **54** in presence of EtONa in refluxing EtOH afforded the 2-p-anisyl pyrimidine **55** [XXIX].



53 54 55

Scheme 17 : Synthesis of 2-p-anisyl pyrimidine **55**.

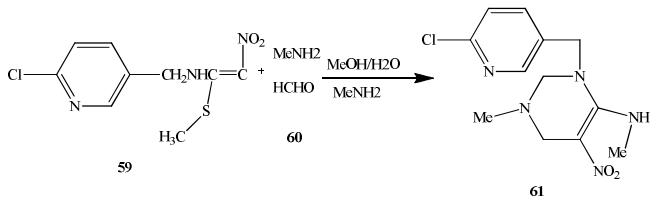
Reaction of acrylonitrile derivative **56** with nitro-guanidine **57** gave (3,4,5-trimethoxy benzyl) pyrimidine **58** [XXX].



56 57 58

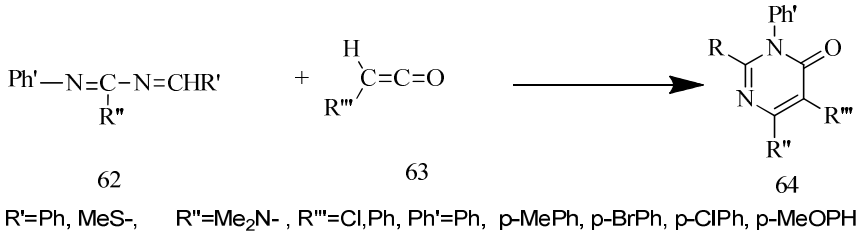
Scheme 18 : Synthesis of (3,4,5-trimethoxy benzyl) pyrimidine **58**.

Cyclocondensation of nitroethylene derivative **59** with methylamine and formaldehyde **60** and heating the product with methylamine gave pyrimidine derivative **61** [XXXI].



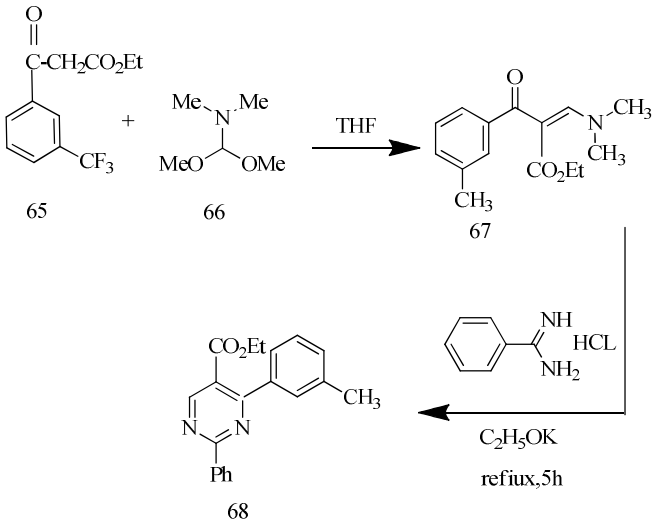
Scheme 19 : Synthesis of pyrimidine derivative **61**.

Reaction of 1 [59] derivative **62** keten derivative **63** afforded pyrimidine derivatives **64** [XXXII].



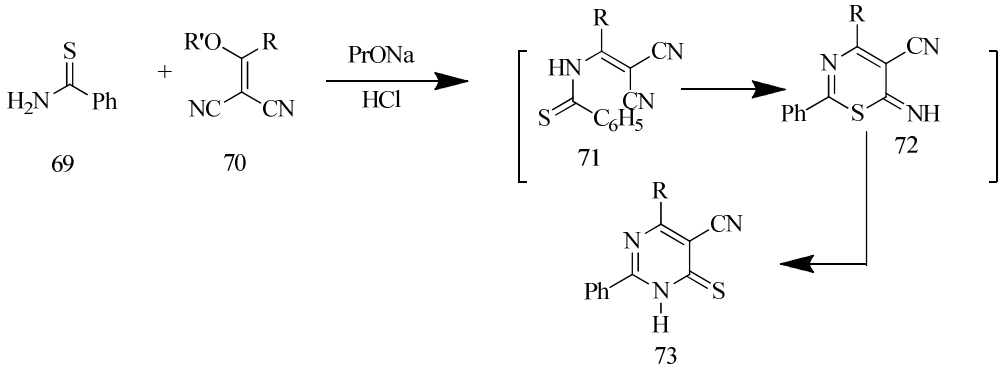
Scheme 20 : Synthesis of pyrimidine derivative **64**.

Ethyl (3-triflouromethylbenzoyl) acetate **65** was refluxed with N,N-dimethylformamid acetal **66** in tetrhydrofuran to give the 1-(3-triflouro-methylbenzoyl)-1-ethoxy-carbonyl-2-(N,N-dimet-h-ylamino) ethene **67** which was refluxed with benzamidine HCl in the presence of potassium ethoxide and gave 2-phenyl-4-(3-triflouromethylphenyl)-5-ethoxy-carbonylpyrimidine **68** [XXXIII].



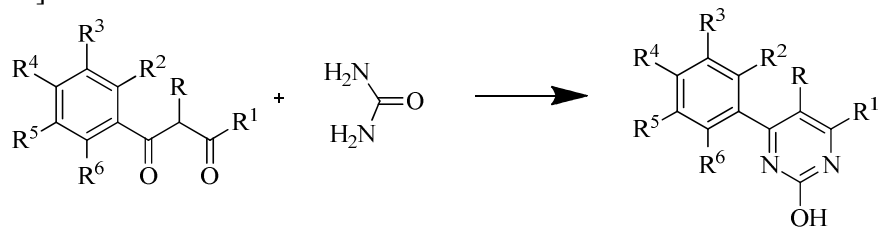
Scheme 21 : Synthesis 2-phenyl-4-(3-triflouromethylphenyl)-5-ethoxy-carbonylpyrimidine **68**.

The reaction of thiobenzamide with 3-alkoxy-3-aryl(or alkyl)-2-cyanoacrylo-nitriles **71** and sodium isopropoxide in 2-propanol afforded 4-thioxo-3,4-dihydro-pyrimidine derivatives **73** [XXXIV] through formation of the 3-aryl(or alkyl)-2-cyano-3-thiobenzamide acrylonitriles **72**.



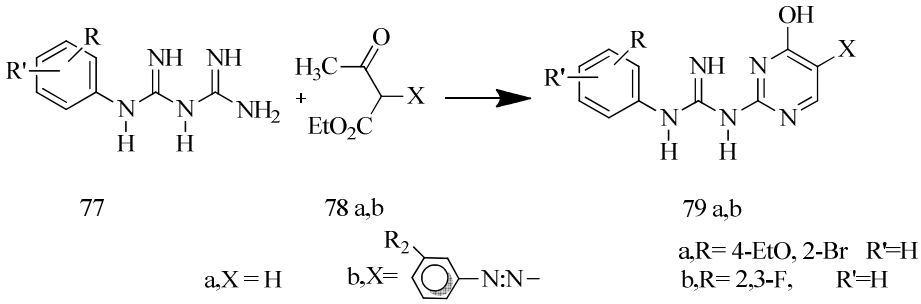
Scheme 22 : Synthesis of 4-thioxo-3,4-dihydro-Pyrimidine derivatives **73**.

Cyclocondensation of 1,3-dicarbonyl derivatives **74** with urea **75** gave pyrimidines **76** [XXXV,XXXVI].



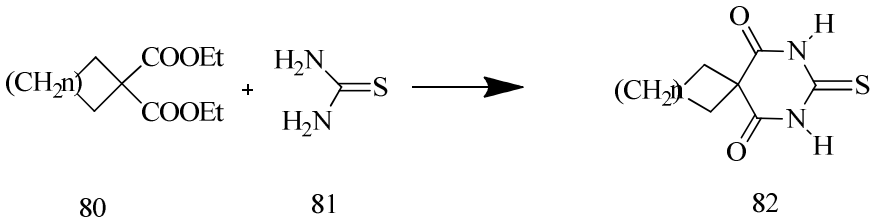
Scheme 23 : Synthesis of pyrimidines **76**.

Cyclization of N-arylbiguanidines **77** with ethyl acetoacetate derivative **78a, b** yielded pyrimidine derivatives **79a, b** [XXXVII,XXXVIII].



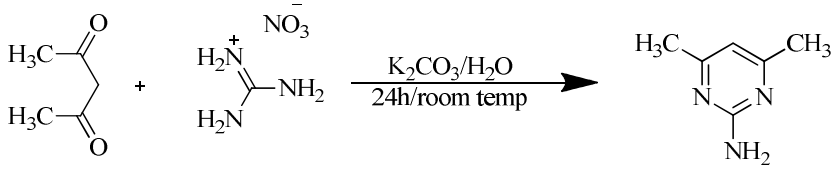
Scheme 24 : Synthesis of pyrimidines derivatives **79a, b**.

Reaction of 1,1-cycloalkanedicarboxylic acid diethyl esters **80** with thiourea gave barbituric acid derivative **82** [XXXIX].



Scheme 25 : Synthesis of barbituric acid derivative **82**.

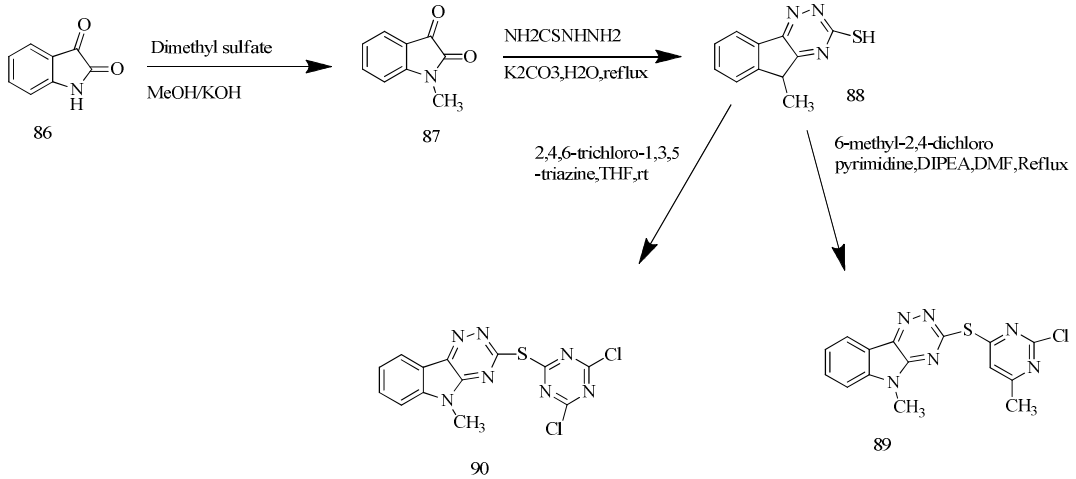
Treatment of guanidine nitrate **84** with acetylacetone **83** in the presence of potassium carbonate gave 2-amino-4,6-dimethylpyrimidine **85** [XL].



83 84 85

Scheme 26 : Synthesis of 2-amino-4,6-dimethylpyrimidine **85**.

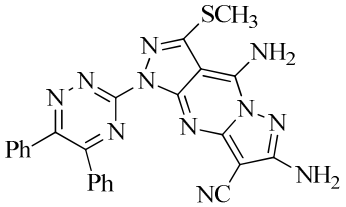
The synthesis and biological evaluation of new [1,2,4] triazino [5,6-b]indol-3-ylthio-1,3,5-triazines **89** and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines **90** against *Leishmania donovani* were reported [XLI].



86 87 88 89 90

Scheme 27 : Synthesis of new [1,2,4] triazino [5,6-b]indol-3-ylthio-1,3,5-triazines **89** and [1,2,4]triazino[5,6-b]indol-3-ylthio-pyrimidines **90**.

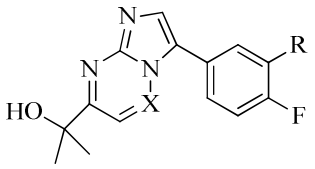
The synthesis of some novel pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives **91** bearing 5,6-diphenyl-1,2,4-triazine moiety which exhipt potential antimicrobial agents were reported [XLII].



91

Figure 3 : novel pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives **91** bearing 5,6-diphenyl-1,2,4-triazine moiety.

The Imidazo[1,2-*b*][1,2,4]triazines **92** as a2/a3 subtype selective GABAA agonists for the treatment of anxiety were reported [XLIII].

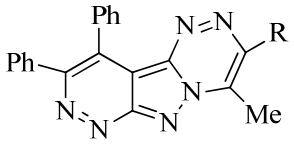


X=N or CH

92

Figure 4: Imidazo[1,2-*b*][1,2,4]triazines **92**.

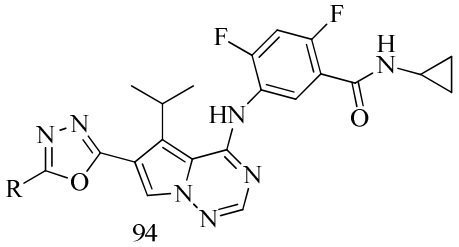
Diazotization of 3-Aminopyrazolo[3,4-d]pyridazine which was coupled with active methylene reagents to give the tricyclic pyridazino[3',4':3,4]pyrazolo[5,1-c]-1,2,4-triazines **93** with substituents such as methyl, phenyl, ethoxycarbonyl, acetyl or benzoyl, depending on the methylene reagent used. some of the synthesized compounds were evaluated against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus and Candida albicans were determined and reported [XLIV].



93

Figure 5: Tricyclic pyridazino[3',4':3,4]pyrazolo[5,1-c]-1,2,4-triazines **93**.

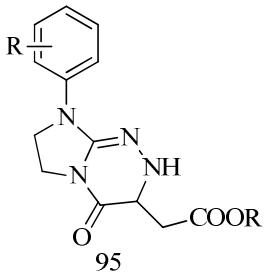
The synthesis, SAR and evaluation of 4-[2,4-difluoro-5(cyclopropylcarbamoyl)phenylamino]pyrrolo[2,1-f][1,2,4]triazine **94** -based VEGFR-2 kinase inhibitors were reported [XLV].



94

Figure 6: 4-[2,4-difluoro-5(cyclopropylcarbamoyl)phenylamino]pyrrolo[2,1-f][1,2,4]triazine **94**.

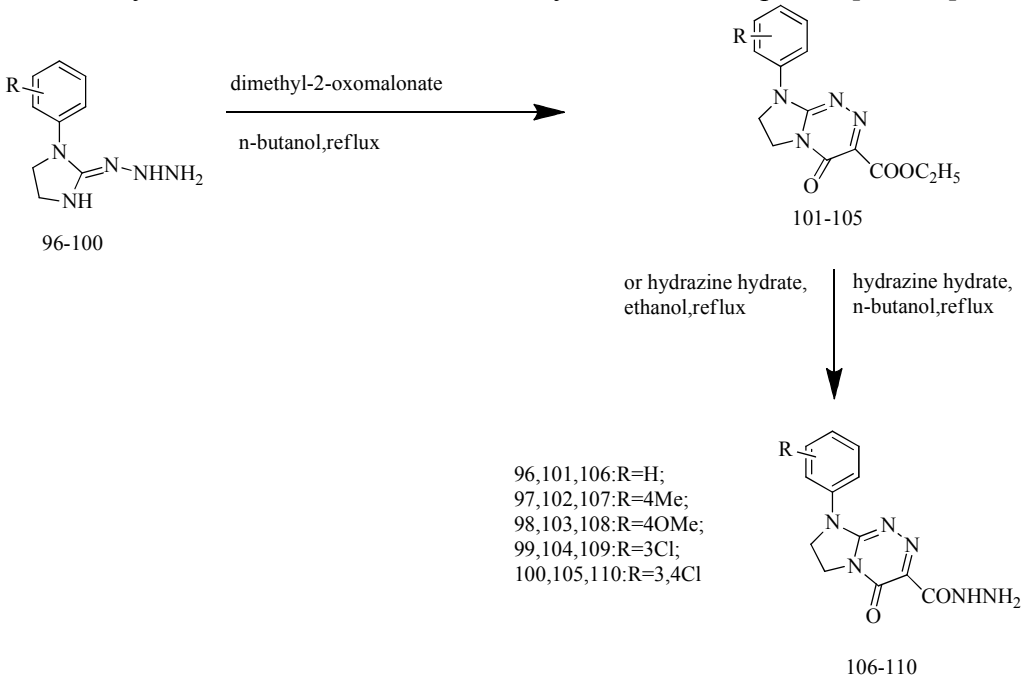
The synthesis, crystal structure and antproiferative activity of novel derivatives of methyl and ethyl 2-(4-oxo-8-aryl-2*H*-3,4,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazin-3-yl)acetates **95** were reported [XLVI].



95

Figure 7: novel derivatives of methyl and ethyl 2-(4-oxo-8-aryl-2*H*-3,4,6,7-tetrahydro imidazo [2,1-c][1,2,4]triazin-3-yl)acetates **95**.

The structure elucidation and identification of antitumoural properties of novel fused 1, 2, 4-triazine aryl derivatives**106-110** and their synthesis were reported [XLVII].



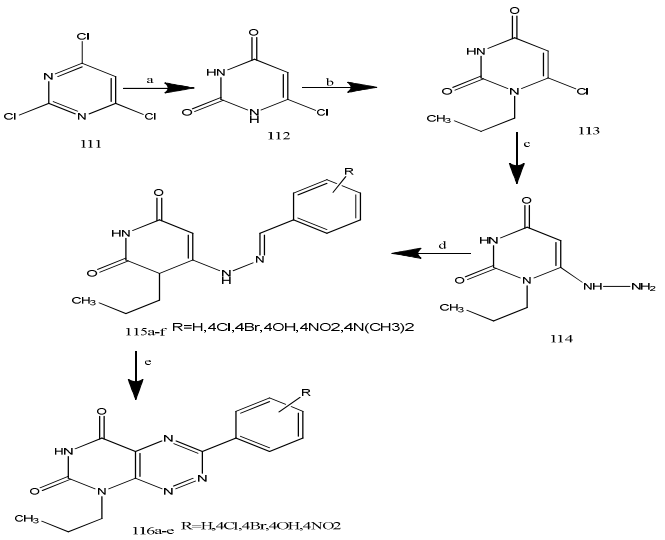
96-100

101-105

106-110

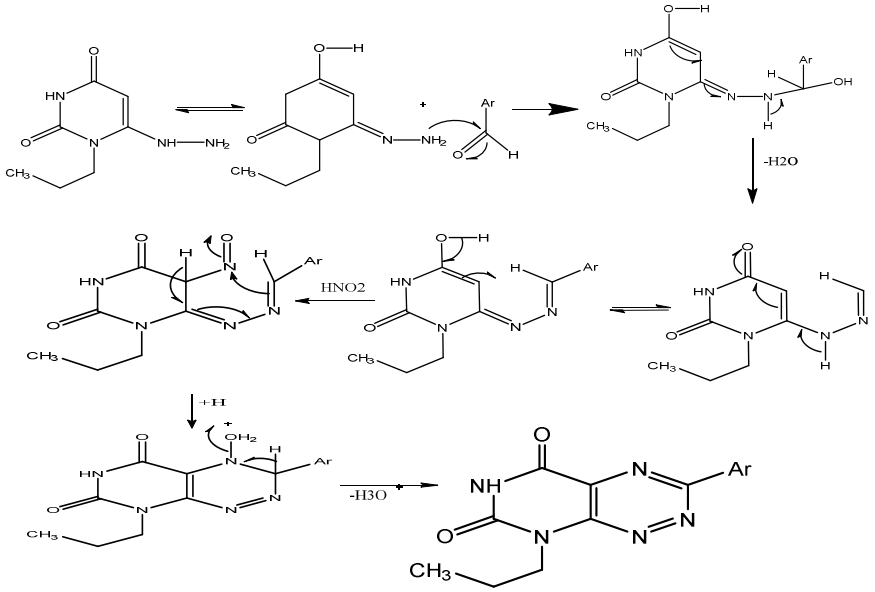
Scheme 28: Synthesis of novel fused 1,2,4-triazine aryl derivatives **106-110**.

Treatment of **114** and substituted aromatic aldehydes in presence of ethanol at room temperaturefor 1h. Give hydrazones **115a**–**fa**goodyield [XLVIII].
Nitrosation of compounds **115a-e** with nitrous acid prepared in situ afford the corresponding Pyrimidotriazines **116a–e**.



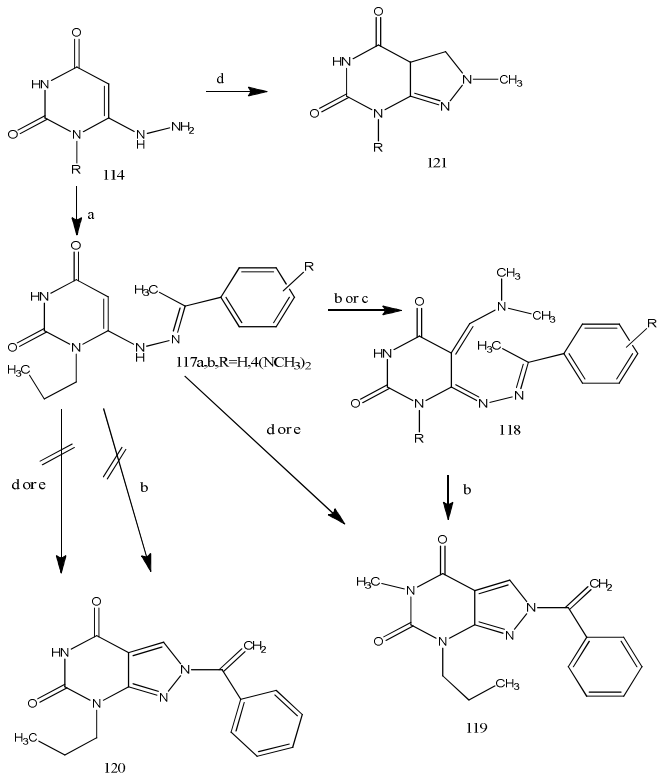
Scheme 29: Reaction of 6-hydrazinyluracil with different aromatic aldehydes and formation of pyrimidotriazines **116a-c**. a = NaOH/H_2O/Reflux; b = PrI/K_2CO_3 /DMSO ; c = $NH_2NH_2.H_2O$/rt; d = ArCHO/EtOH/rt; e = $NaNO_2$/AcOH/Reflux

The inseparable 5-nitroso-derivativesUndergoes cyclization via the nucleophilic attack of the electron rich α-carbon of the hydrazones on the nitroso group to form hydroxylamine intermediates, which are converted into the target pyrimidotriazines **116a–e** by protonation of the N-hydroxyl group followed by the elimination of H3O+ (**Scheme 30**).



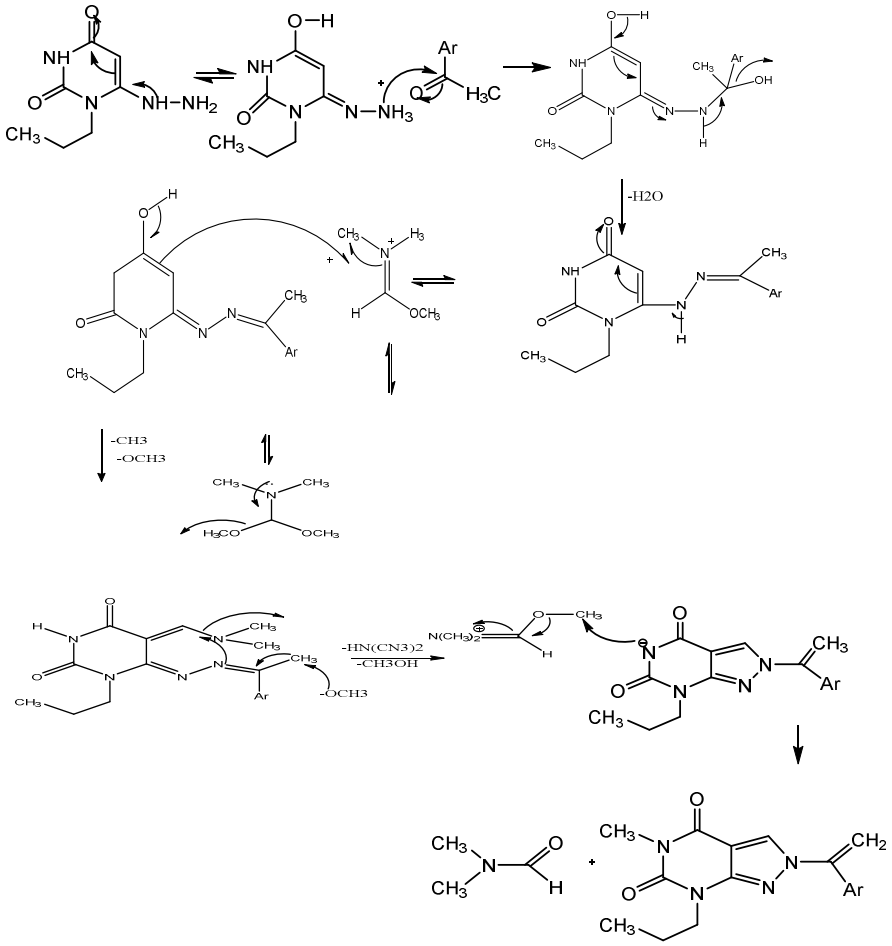
Scheme 30: The plausible reaction mechanism formation of compounds **115a**–**f** and **116a**–**e**.
Condensation of compound **114** with different acetophenones under stirring for 3-4h at room temperature **(Scheme 31).**

Compound **119** was synthesized via reaction of **117a** with DMF-DMA under reflux for 12 h or DMF-DMA in presence of DMF as a solvent for 1 h (**Scheme 31**).



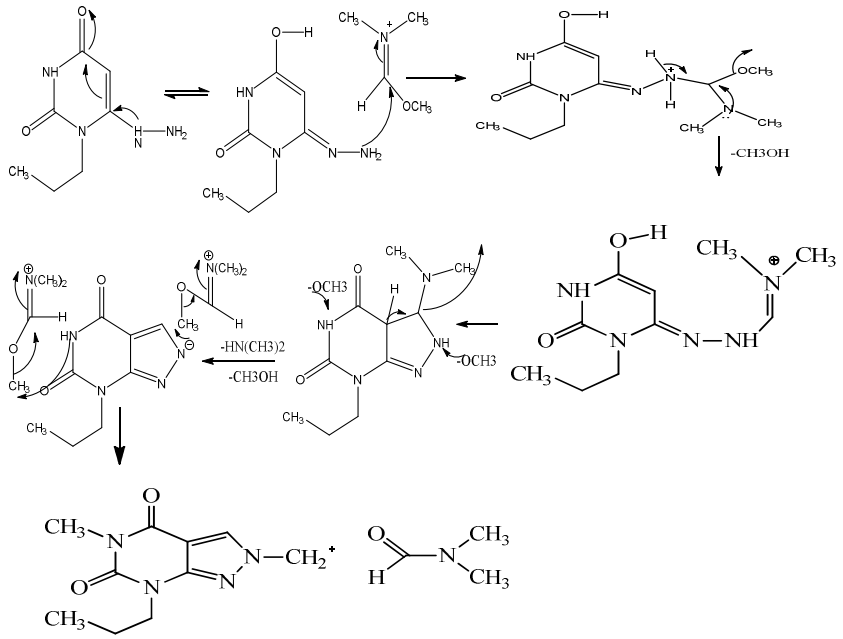
Scheme 31: Synthesis of pyrazolopyrimidines. a = EtOH/rt; b = DMF-DMA/Reflux/1 h; c = DMF-DMA/DMF/Reflux/15 min; d = DMF-DMA/DMF/Reflux/1 h; e = DMF-DMA/Reflux/12h

The plausible mechanism is proved by isolation of the intermediate **118 (scheme 32)**.



Scheme 32: The plausible reaction mechanism formation of compounds **117a**, **b** and the intermediate **118** and **119.**

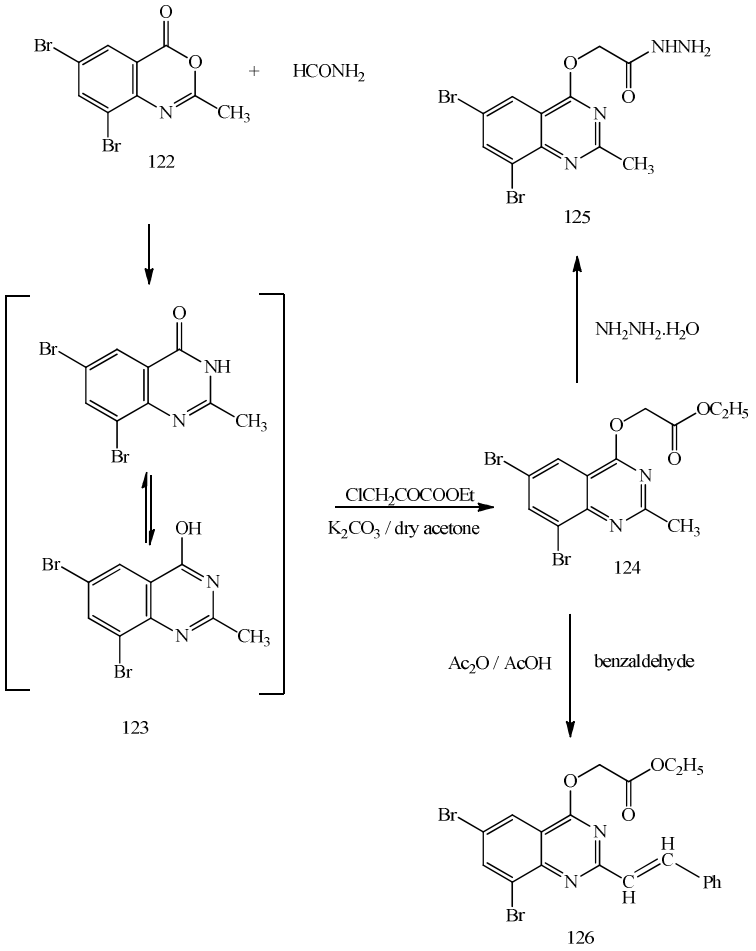
Compound **121** was synthesized by reaction of **114** withDMF-DMA and DMF as solvent
The reaction proceed under reflux for 1 h(**Scheme 31**)
The mechanism of formation of compound **121** shown in (Scheme **33**).



Scheme 33: The plausible reaction mechanism formation of compound **121**.

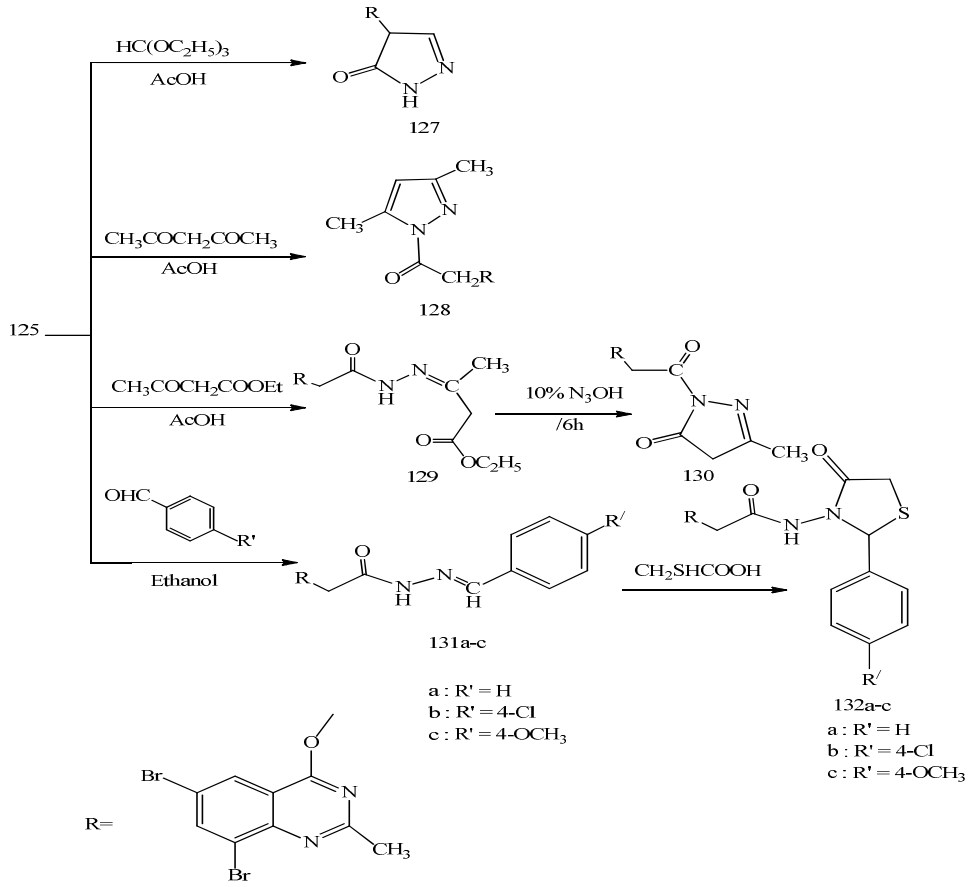
The newly synthesized compounds of substituted benzaldehyde-pyrimidin-4-yl)hydrazones (**115a**–**f**), pyrimido[5,4-*e*][1,2,4]triazines **116a**–**e**, arylethylidenehydrazinylpyrimidines **117a**, **b** and pyrazolopyrimidines **119**,**121** exhibitedanticancer activity[XLVIII].

Treatment of 6,8-Dibromo-2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one **122** with form amide afford the corresponding 6,8-dibromo-2-methylquinazolin-4(3*H*)one **123**[XLIX]. On the other hand treatment of **123** with ethyl chloroacetate in presence of potassium carbonate and dry acetone produce ethyl 2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetate **124**. Reaction of compound **124** with hydrazine hydrate afford 2-(6,8-dibromo -2-methylquinazolin-4-yloxy) acetohydrazide **125**,compound **125**wasconsidered as key material for synthesis of quinazoline derivatives (**Scheme 34**)



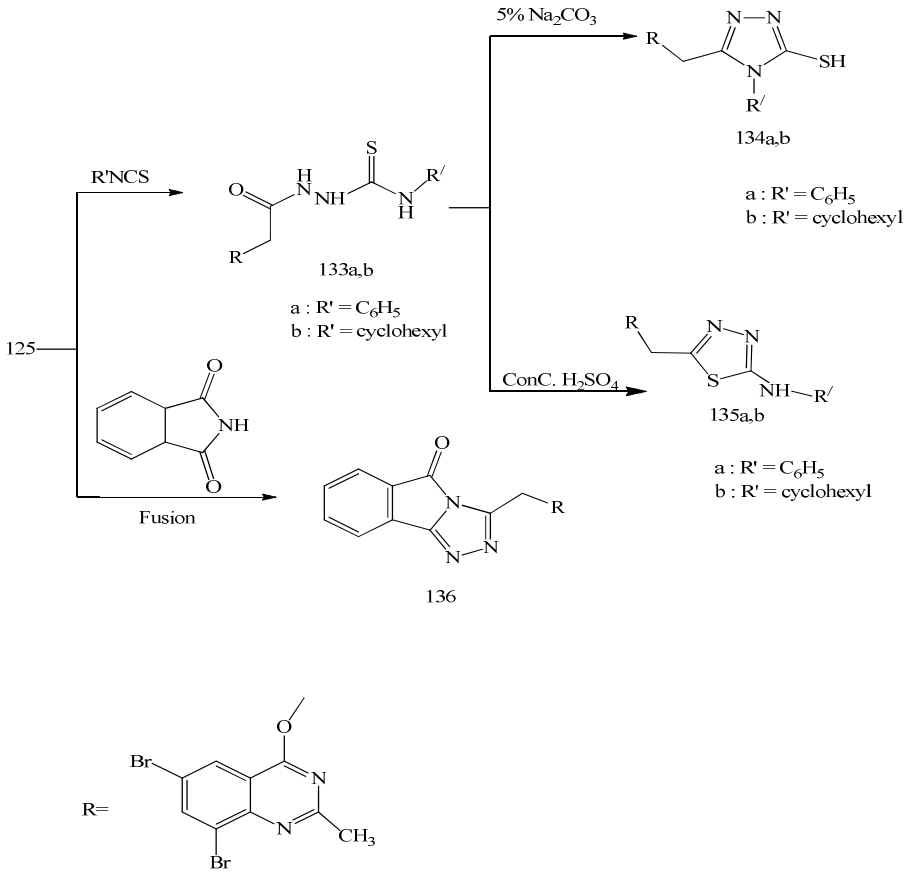
Scheme 34:Synthesis and reactions of ethyl 2-(6,8-dibromo-2-methylquinazolin-4-yloxy)-acetate **124**.

Reaction of2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetohydrazide **125 and** triethyl orthoformate and/or acetyl-acetone, give the corresponding of pyrazolone **127** and pyrazole derivatives **128**, respectively , **Scheme 35**.



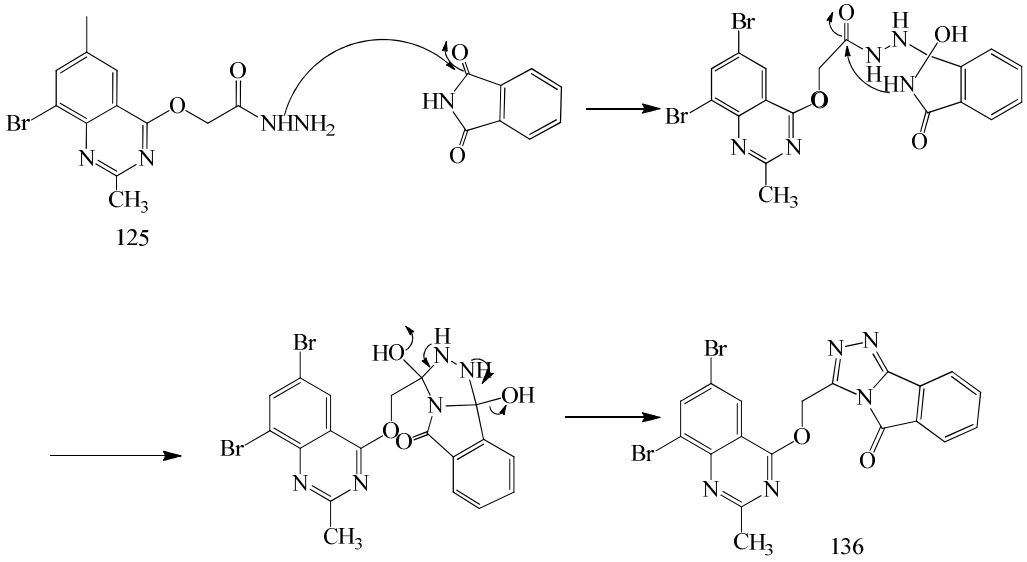
Scheme 35:Reactions of 2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetohydrazide**125**.

Treatment of compound **125** and phenyl and/or cyclohexyl isothiocyanate afford Hydrazine ecarbothioamide derivatives **133a,b**,adding Na_2CO_3solution(5%) to **133a,b** give **134a,b**
Also treatment of **133a, b** withconc.H_2SO_4 produces **135a, b (Scheme 36).**
Reaction of hydrazide **125** and phthalimide under fusion gave 3-[(6, 8-dibromo2-methylquinazolin-4-yloxy) methyl]-5*H* [1, 2, 4] triazolo[3,4-*a*]isoindol-5-one **136 (Scheme 36).**



Scheme 36: Further reactions of 2-(6, 8-dibromo-2-methylquinazolin-4-yloxy)acetohydrazide **125**.

The plausible mechanism for formation of compound **136** is showed in **Scheme 37.**



Scheme37: The mechanism of formation of compound **136**.
Some new synthesized compounds possess Analgesic activities [XLIX]

Conclusion :

This review concerned with the synthesis of some novel pyrazolo[3,4-b]pyridine and pyrazolo[3,4-d]pyrimidine derivatives **91** bearing 5,6-diphenyl-1,2,4-triazine moiety which exhibit potential antimicrobial agents and also
diazotization of 3-Aminopyrazolo[3,4-d]pyridazine which was coupled with active methylene reagents to give the tricyclic pyridazino[3',4':3,4]pyrazolo[5,1-c]-1,2,4-triazines **93** with substituents such as methyl, phenyl, ethoxycarbonyl, acetyl or benzoyl, depending on the methylene reagent used. Some of the synthesized compounds were evaluated against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus and Candida albicans were determined

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