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# Synthesis of pteridines derivatives from different heterocyclic compounds

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**ABSTRACT**

*A great attention has been paid to synthesize new compounds with new sites of action. In this context, the synthesis of pterdinies derivatives has been extensively studied because of their biological importance. They are known to regulate many biological processes and their deficiency induces many disease processes. In this mini review we aim to summarize the structure and methods of pterdinies derivatives synthesis from pyrimidines, pyrazines and other different heterocyclic compounds.*

**Keywords:** Pteridines, Pyrimidines, Pyrazines, Heterocyclic compounds.

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## INTRODUCTION

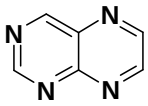
In medicinal chemistry, the chemist attempts to design and synthesize a medicine or a pharmaceutical agent, which will benefit humanity. The chemistry of heterocyclic compounds is the most important in the discovery of new drugs. Study of these compounds is of great interest both in theoretical as well as practical aspects [1] . Pteridines, pyrazino[2,3-d]pyrimidine compounds, are a group of heterocyclic compounds composed of fused pyrimidine and pyrazine rings [2]. Pteridines research has long been recognized as important for many biological processes, such as amino acid metabolism, nucleic acid synthesis, neurotransmitter synthesis, cancer, cardiovascular function, and growth and development of essentially all living organisms. Defects in synthesis, metabolism and/or nutritional availability of these compounds have been implicated as major causes of common disease processes [3], e.g. cancer, inflammatory disorders, cardiovascular disorders, neurological diseases, autoimmune processes, and birth defects [4]. In more detailed, pteridines are one of the most important heterocycles exhibiting remarkable biological activities because these compounds are constituents of the cells of the living matters [5]. For example, pteridine, is a precursor in the synthesis of dihydrofolic acid in many microorganisms. Where, pteridine and 4-Aminobenzoic acid are converted by the enzyme dihydropteroate synthetase into dihydrofolic acid in the presence of glutamate [6].

At structural level, pteridines have two major classes, ‘conjugated’ pteridines, which are characterized by relatively complex side chains, e.g. the vitamins folic acid, and ‘unconjugated’ pteridines, e.g. biopterin or neopterin bearing less complex side chains at the 6-position of the pterin [7]. Moreover, there are three main classes of naturally occurring pteridines namely, lumazines, isoalloxazine and pterins. Lumazines and isoalloxazines have oxo-substituents at the 2- and 4- positions with the difference being a phenyl ring annealed in the 6- and 7- position on the isoalloxazine. The most common class of naturally occurring pteridines are the pterins which have an amino group at the 2-position and an oxogroup at the 4-position [8].

Studies on developing new methods for new pteridines derivatives synthesis are getting increase therefore; here we aim to elucidate all available structures and methods related to pteridines.

**2 Structure and compounds of pteridines.**

Pteridine ring **1** system is a pigment and consist of pyrazine ring and pyrimidine ring. This compound was found in the wings of insects and the eyes and skin of fish, amphibbia and reptiles.

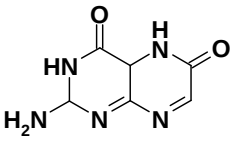


**1**

Pteridine also contains 4-hydroxy groups and two amino groups.

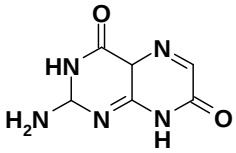
- Xanthopterin **2** is butterfly wing pigments and it found in human urine, pancreas, kidneys, liver and wasp wings

- Also isoxanthopterin **3**, leucopterin **4** and erythropterin **5** are known as butterfly wing pigments.



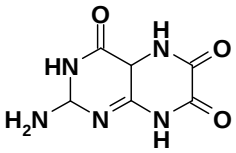
**2**

**Xanthopterin**



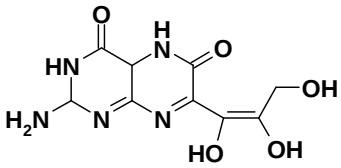
**3**

**Isoxanthopterin**



**4**

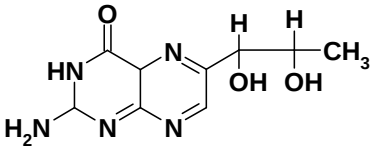
**Leucopterin**



**5**

**Erythropterin**

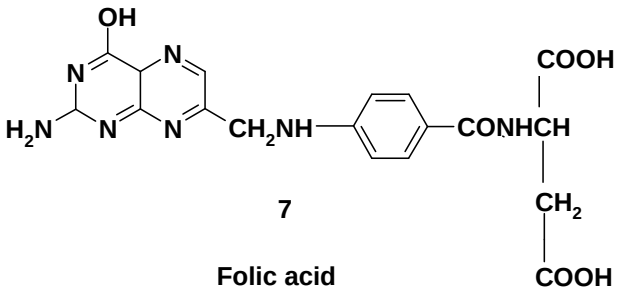
- Biopterin **6** is a widely occurring natural pterin, isolated from human urine, fruit fly, royal jelly of bees and Mediterranean flour moth.



**6**

**Biopterin**

Folic acid **7,** is one the most important compounds comprising pteridine nucleus in its molecules.



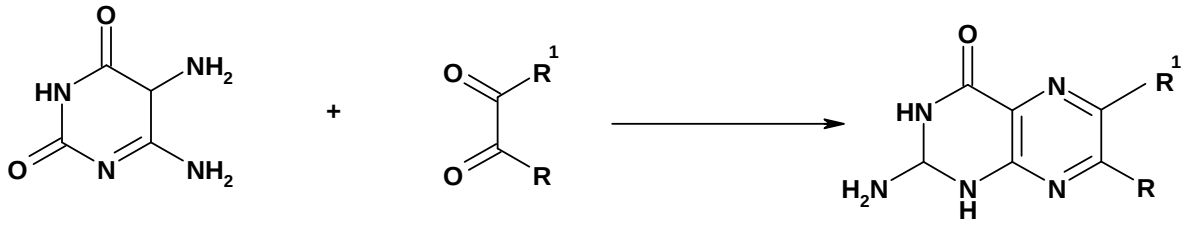

**7**

**Folic acid**

**3 Synthesis of pteridines:-**

**3. 1. From pyridines.**

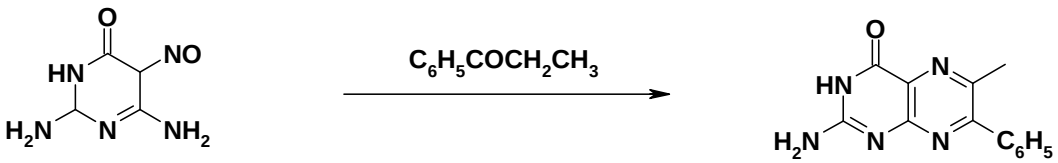
Pteridines derivatives **10** can be prepared from Pyrimidines via Isay reaction [9-15] by condensation of 4,5-diamino pyrimidine-2,6-dione **8** with dicarbonyl compounds **9** (Scheme 1).




**8** **9** **10**

**Scheme 1**

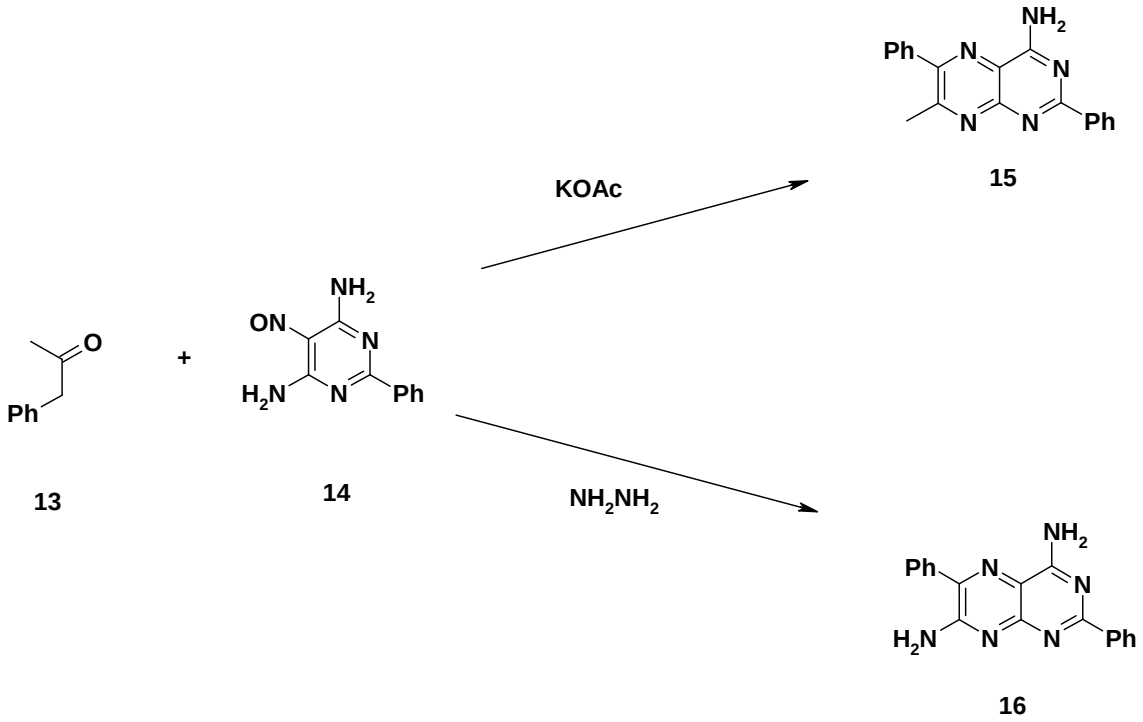
Also 2,4-di amino-5-nitroso pyrimidine-6-one **11** condensed with aldhydes and ketones to produce pteridines derivatives **12** (Scheme 2) [16,17].




**11** **12**

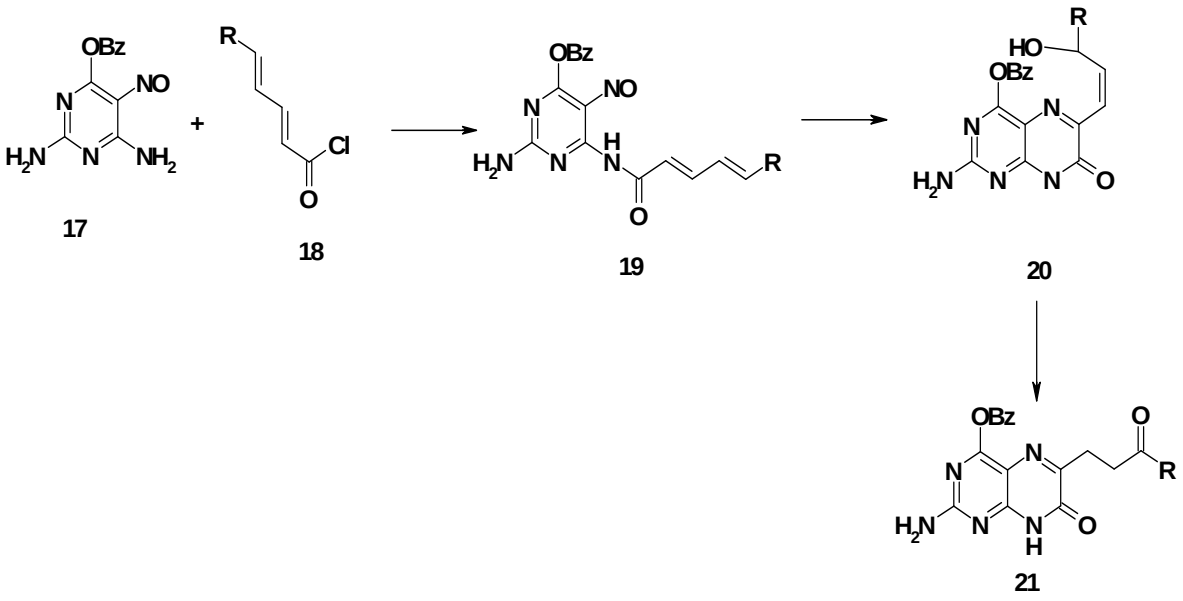
**Scheme 2**

4,6-di amino-5-nitroso-2-phenyl pyrimidine **14** with an active methylene **13** give different compounds of pteridines according to condition of reaction (Scheme 3) [18-21].



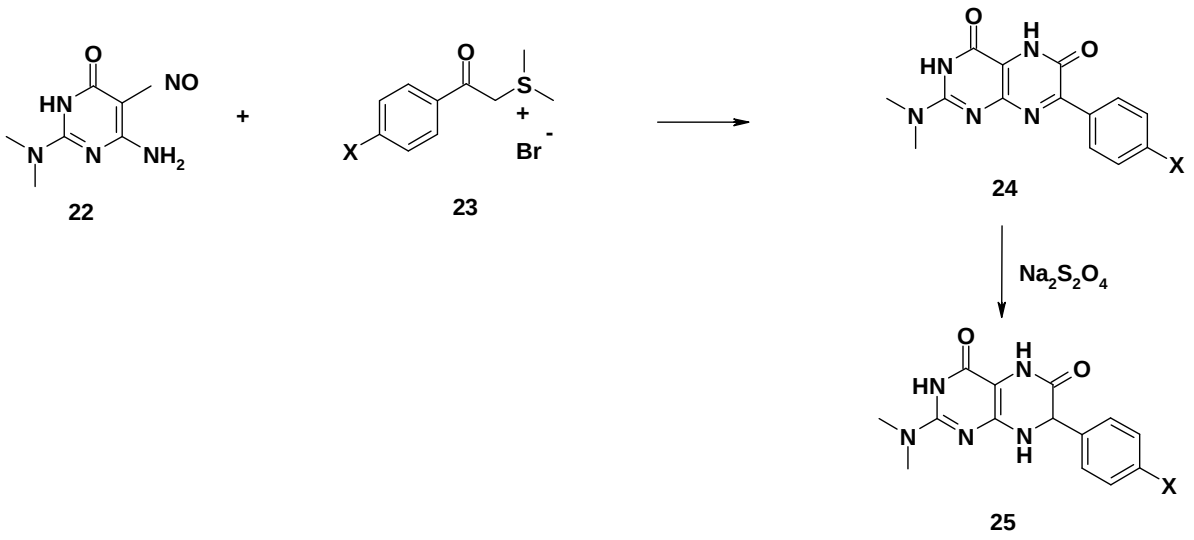

**Scheme 3**

Xu et al. was reported that Diels-Alder reaction leads to the formation of a pterin derivatives **21** (Scheme 4) [22].



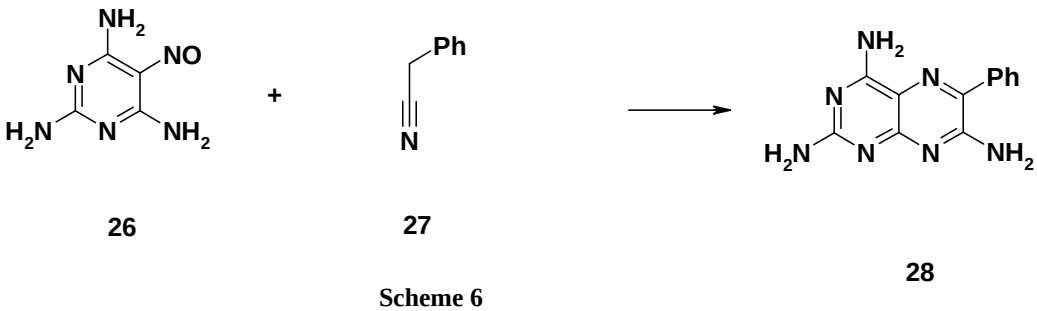

**Scheme 4**

Reaction [23] of nitrosopyrimidine **22** with dimethylphenacylsulfonium bromides **23** produced 7-aryl-2-dimethylamino-3,4,5,6-tetrahydropteridine-4,6-diones **24** which reduced by sodium dithionite to yield 7,8-dihydro derivatives **25** (Scheme 5).



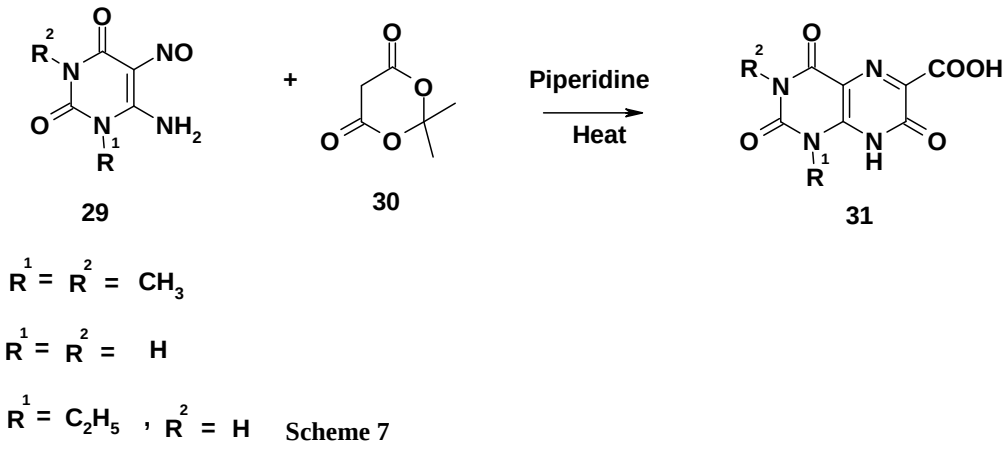

**Scheme 5**

The use of methylenenitrile **27** in the condensation with 5-nitroso-2,4,6- triamino pyrimidine **26** provided triamterene **28** (Scheme 6) [24,25].




**Scheme 6**

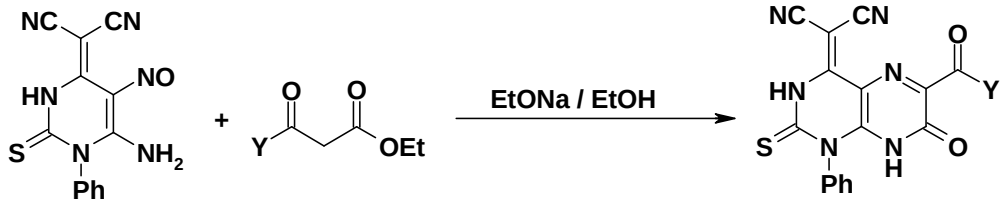
1,3-Dimethyl-2,4,7-trioxo-1,2,3,47,8 hexahydropteridine-6-carboxylic acid **31** was prepared by reaction of 6-amino-5-nitroso uracils **29** with Meldrum's acid **30** (Scheme 7) [26].




**Scheme 7**

Abdel-Latif et al [27] found that (6-Amino-5-nitroso-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene) malononitrile **32** reacts with ethylacetoacetate **33a** and diethyl malonate **33b**, in the presence of sodium ethoxide to

afford (6-Acetyl-7-oxo-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydropteridin-4-ylidene) malononitrile **34a** and Ethyl 4-dicyanomethylidene-7-oxo-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydropteridine-6-carboxylate **34b** respectively (Scheme 8).

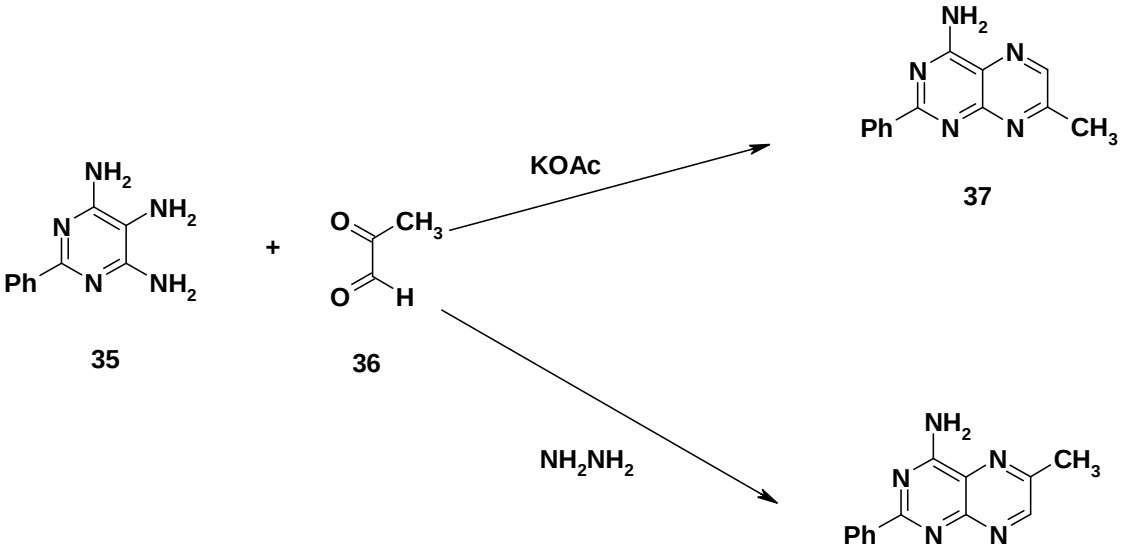



**32** **33** **34 a,b**

**Y = Me (a) , EtO (b).**

**Scheme 8**

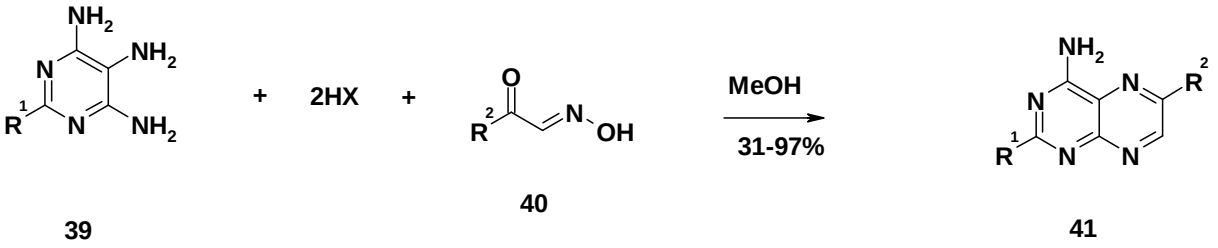
Methylglyoxal **36** with 2-phenylpyrimidine-4,5,6-triamine **35** yields 7-methyl derivative **37**, however, in the presence of hydrazine the 6-methyl derivative **38** is isolated as the only product indicating the regiospecificity of the reaction (Scheme 9) [28-30].




**35** **36** **37** **38**

**Scheme (9):-**

The regioselective, one-step synthesis of 2,6-disubstituted-4-aminopteridines **41** from 2-substituted-4,5,6-triaminopyrimidine **39**, dihydrohalides and ketoaldoximes **40** (Scheme 10) [31].




**39** **40** **41**

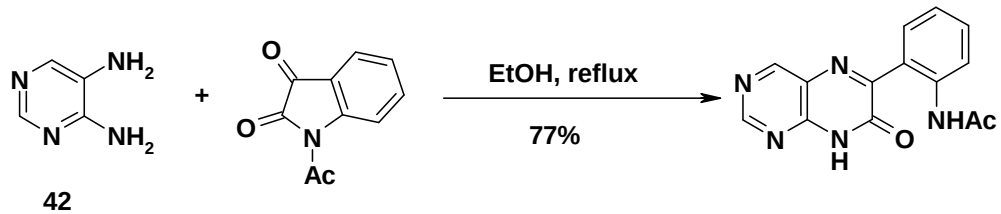
$R^1$ = H, $SCH_3$, $NH_2$, $C_6H_5$

X = Cl, Br

$R^2$ = $CH_3$, $CH_2CH_3$, $CH_2X$, $C_6H_5$, p-$CH_3$-$C_6H_4$

**Scheme 10**

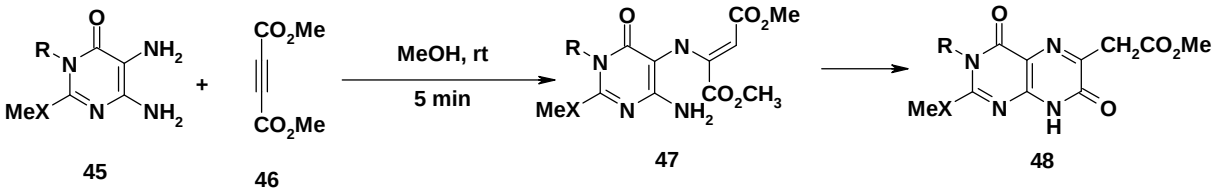
6-arylpteridin-7-one **44** can be prepared in good yield by the reaction of 4,5-diamino pyrimidine **42** with the N-acetylindolone **43** (Scheme 11) [32].




**42** **43** **44**

**Scheme 11**

5,6-Diaminopyrimidines **45** reacted with dimethyl acetylenedicarboxylate (DMAD) **46** to afford the corresponding pteridines **48** on reflux in methanol in one step through formation an intermediate **47** (Scheme 12) [33].



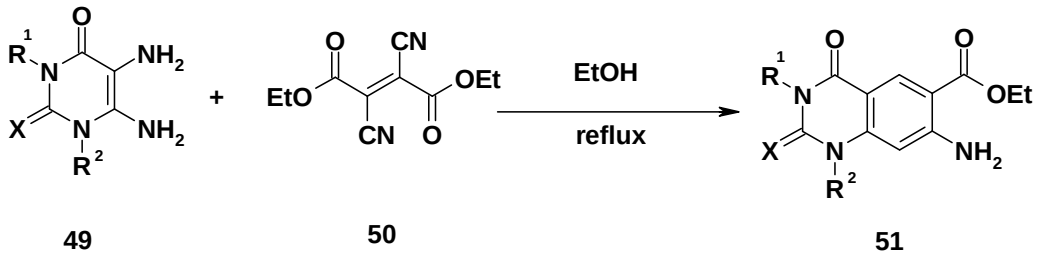

**45** **46** **47** **48**

R = H , Me

X = O , S

**Scheme 12**

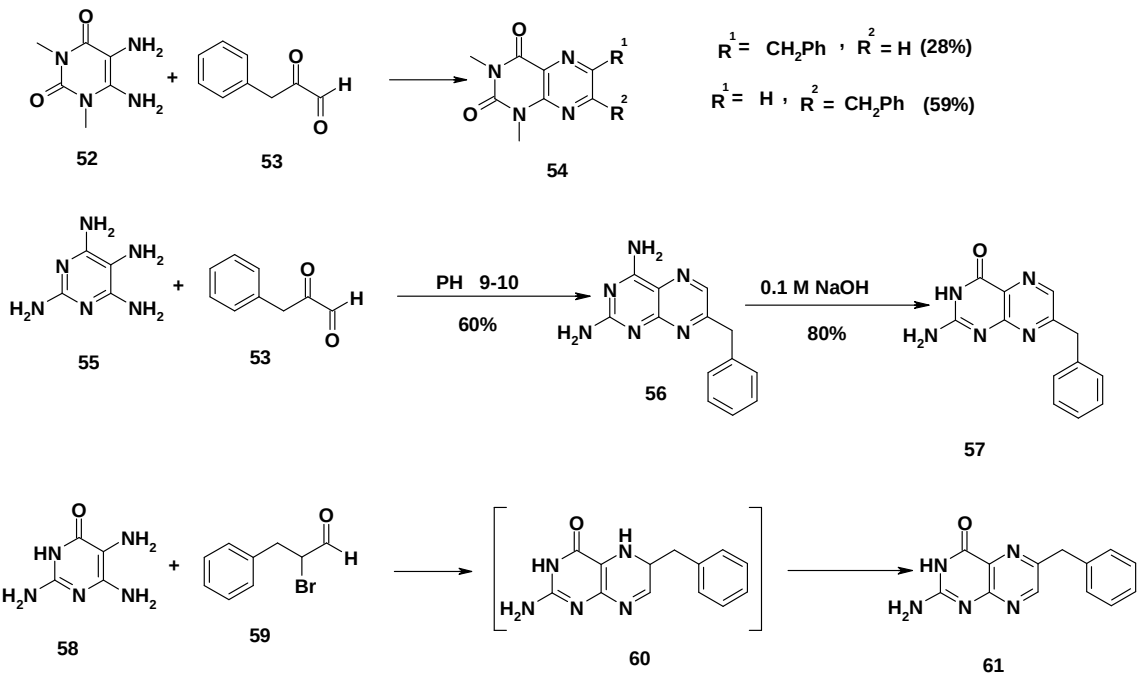
Ethyl 7-aminopteridine-6-carboxylates **51** can be synthesized by treatment of 1, 3-dialkyl-5,6-diaminouracils **49** by unsaturated carbonyl compounds such as diethyl (E)-2,3-dicyanobutenedioate **50** (Scheme 13) [34].




**49** **50** **51**

**Scheme 13**

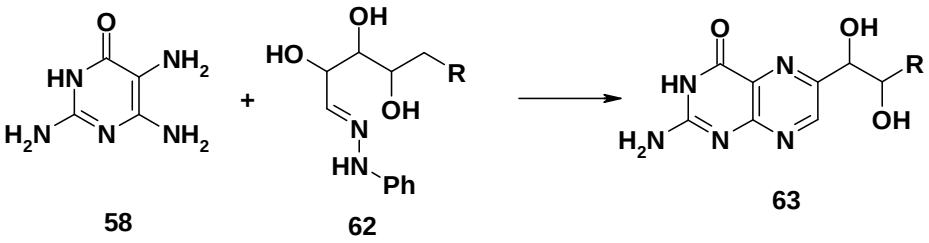
The reaction of 4,5-diamino-1,3-dimethyluracil **52** with benzylglyoxal **53** gave a mixture of pteridines, which were separated by column chromatography. However, when 2,4,5,6-tetraaminopyrimidine **55** reacted with benzylglyoxal **53** at pH 9–10, only the 7-benzyl pteridine **56** was obtained, which on hydrolysis afforded thecorresponding 4-oxopteridine **57**. On the other hand, if the reaction was carried out at a pH below 8, a mixture of 6- and 7-benzylpteridines formed. In yet another method for introducing differentiated reactivity at carbon, the 6-benzylpteridine **61** was obtained selectively by the reaction of 2, 4, 5-triaminopyrimidin-5(1H)-one **58** with 2-bromo-3-phenylpropanal **59** (Scheme 14) [35].




**52** **53** **54** **55** **53** **56** **57** **58** **59** **60** **61**

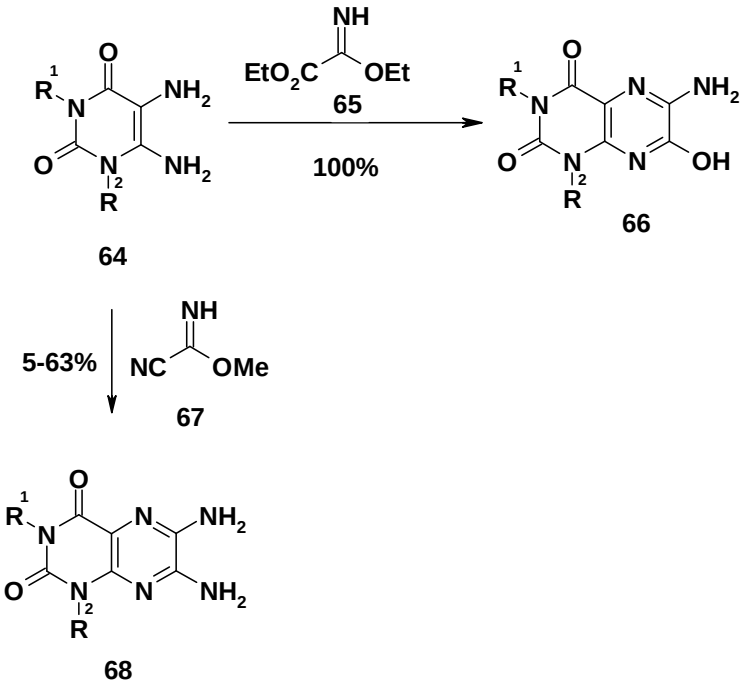
**Scheme 14**

Condensation of 2,5,6 tri aminopyrimidine-4-(3H)-one **58** with the phenyl hydrazon derivative of a sugar **62** leads to the 6 substituted 2-aminopteridin-4(3H)-one **63** (Scheme 15) [36].



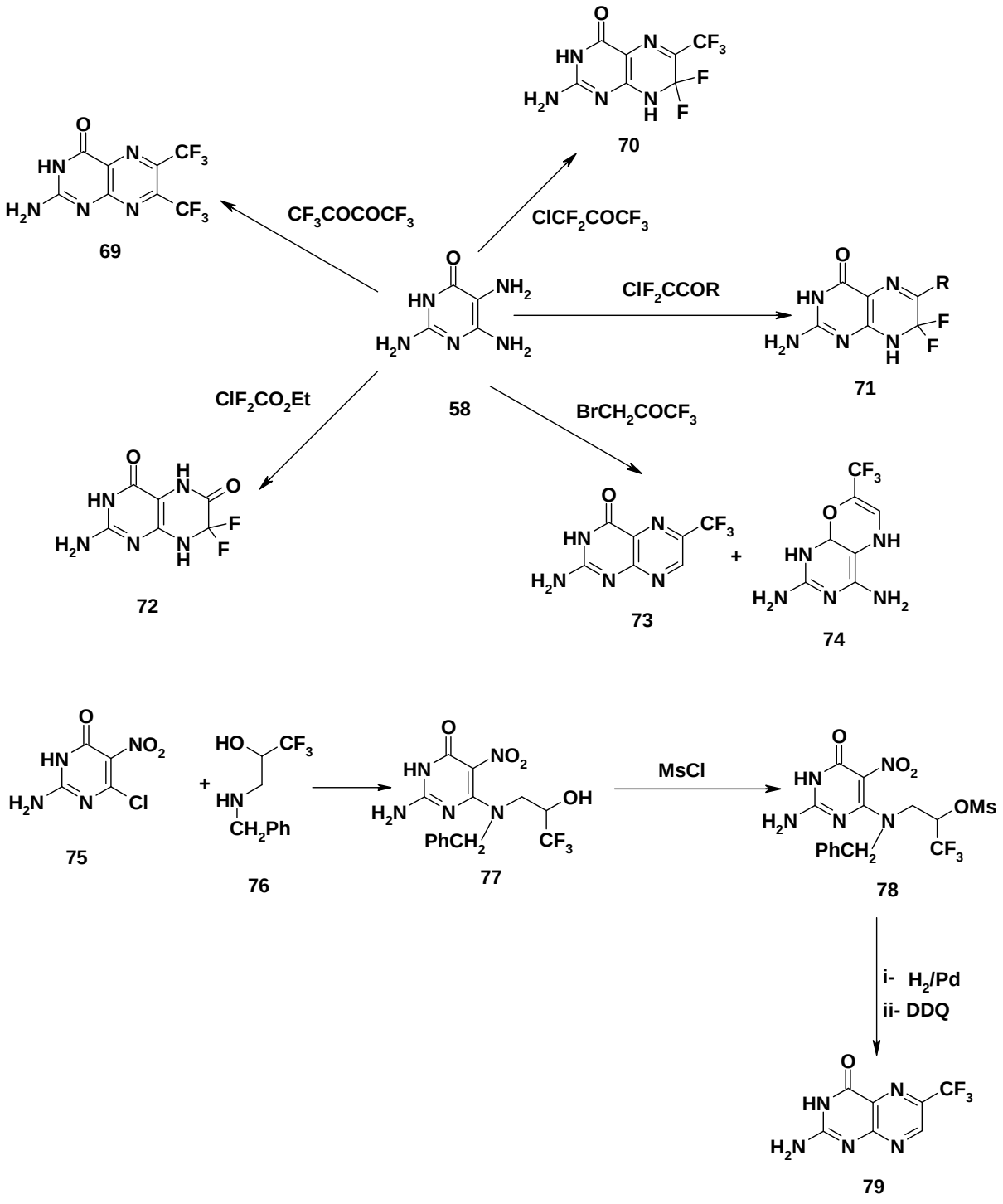
**Scheme 15**

5, 6-diaminouracils derivatives **64** can be reacted with Ethoxy-imino-acetic acid ethyl ester **65** and 2-Nitrilo-acetamidic acid methyl ester **67** to yield 6-amino,7-hydroxy-tetrahydropteridine-2,4-dione **66** derivatives and 6,7-diaminolumazines **68** respectively ( Scheme 16) [37,38].



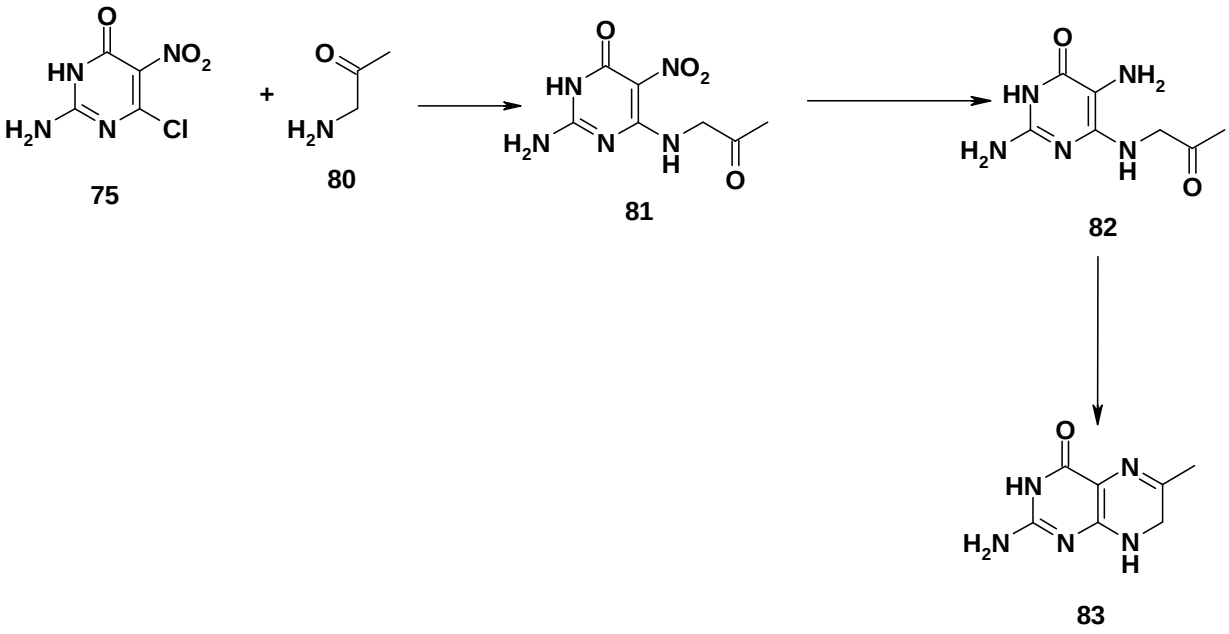
**Scheme 16**

2,4,5-Triaminopyrimidine-5(1H)-one **58** reacted with aliphatic fluorinated precursors to give different fluro pterins. In the case of bromotrifluoroacetone as the aliphatic precursor, the pyrimidooxazine was also isolated. 2-Amino-6-chloro-5-nitropyrimidin-4(3H)one **75** reacted with amino alcohol to give the 6-substituted pyrimidine **77** which on activation of the OH group with mesyl chloride and reduction of the nitro group with $H_2$/Pd gave the 6-trifluoromethylpterin **79** (Scheme 17) [39-41].



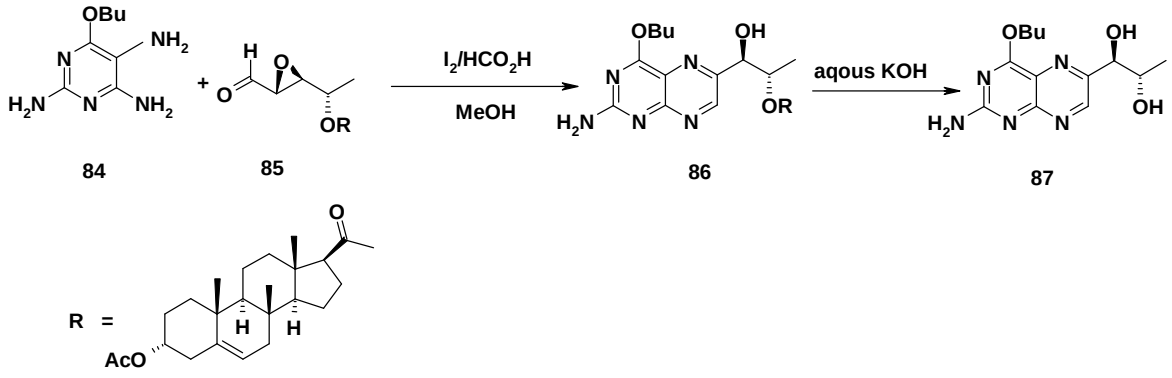

**Scheme 17**

Condensing of 6-chloro-5-nitro-pyrimidine **75** with amino carbonyl compounds **80**, in a reaction known as the Polonovski–Boon cyclization [42,43] to form dihydropterin which can be oxidized to afford fully oxidized pterin. This regiospecific reaction has been used in synthesizing functionalized tetrahydrobiopterin **83** (Scheme 18) [44,45].



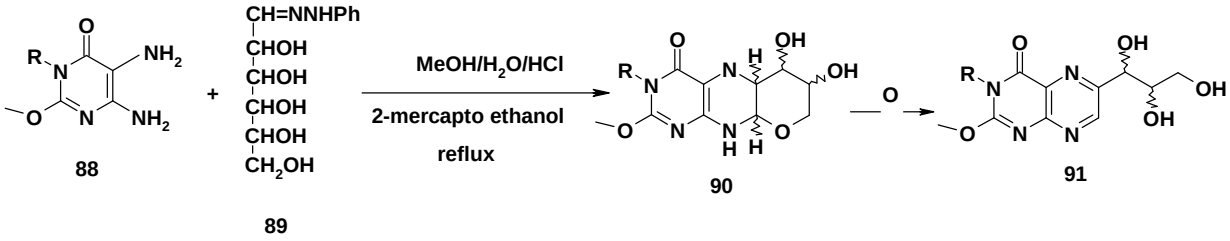

**Scheme 18**

Treatment of 2,4,5-triamino-6-butoxypyrimidine **84** by 2-formyloxiranes **85** to afforded 6-(1-hydroxyalkyl)-substituted pteridines (Biopterin) **87** (Scheme 19) [46,47].



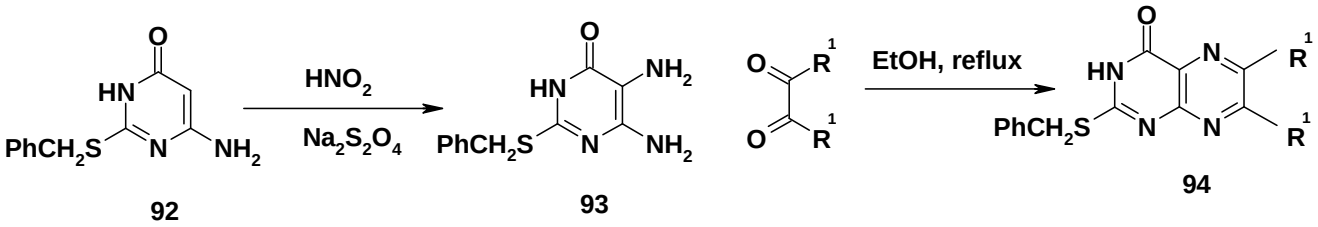

**Scheme 19**

Condensation of 5,6-diamino-2-methoxypyrimidin-4(3H)-ones **88** with protected pentose phenyl hydrazones **89** of both D- and L-series such as D-ribose, D- and L-xylose, D- and L-arabinose which yielded pyrano[3,2-g]pteridines **91** (Scheme 20) [48-53].




**Scheme 20**

6-Amino-2-(benzylsulfanyl)pyrimidin-4(3H)-one **92** was treated to give 5,6-Diamino-2-(benzylsulfanyl) pyrimidin-4(3H)-one **93** to react with biacetyl to yield 2-(Benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone **94** (Scheme 21) [54].

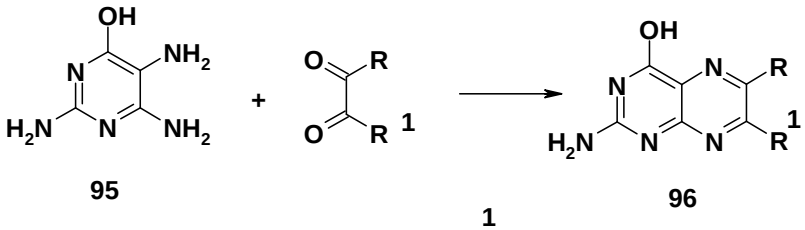



**a** $R^1$ = Me 85%

**b** $R^1$ = $CH_2Ph$ 15%

**Scheme 21**

Reaction of 2,4,5-tri amino-6-hydroxy pyrimidine **95** with glyoxal, Bi acetyl, oxalic acid and benzil afforded to 2-amino-4-hydroxy pteridine, 2-amino-4-hydroxy-6,7-di methyl pteridine, 2-amino-4,6,7-tri hydroxy pteridine and 2-amino-6,7-di phenyl peteridine respectively **96 a-d** (Scheme 22) [47,55].




**a, R = $R^1$ = H**

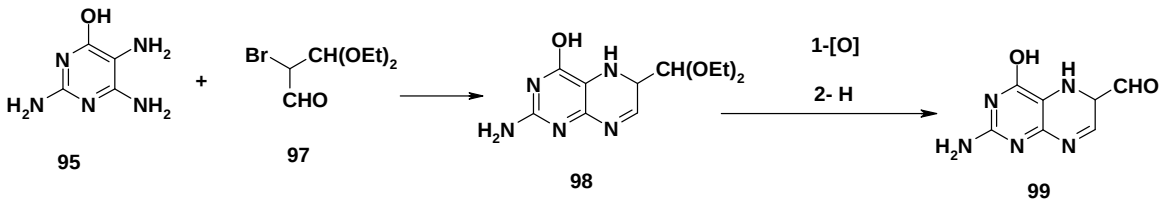
**b, R = $R^1$ = CH3**

**c, R = $R^1$ = OH**

**d, R = $R_1$ = Ph**

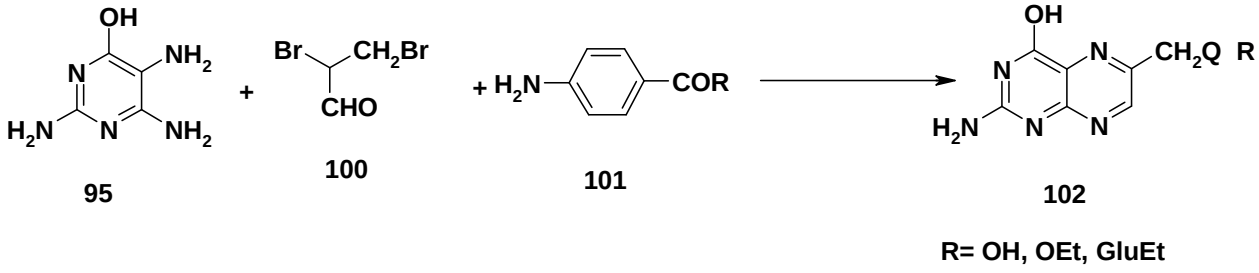
**Scheme 22**

Reaction of α-bromo-β,β-diethoxypropanal **97** with 2,4,5-triamino-6-hydroxy pyrimidin **95** which by oxidation of the resulting 5,6-dihydropterin **98** and hydrolysis of the acetal **(**Scheme 23) [56].



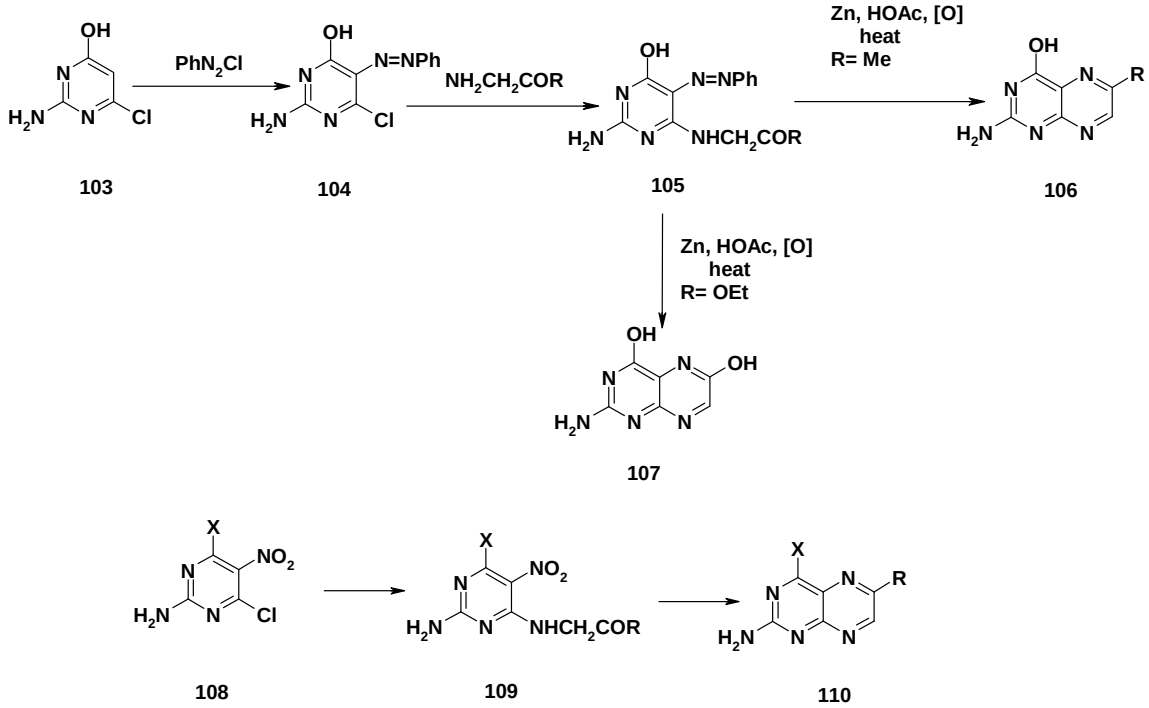

**Scheme 23**

Waller et al found that condensation of 2,4,5-triamino-6-hydoxypyrimidine **95** and 2,3 - Dibromopropionaldehyde **100** and p-aminobenzoylglutamic acid **101** were afforded Ptereidines derivatives **102** (Scheme 24) [57].



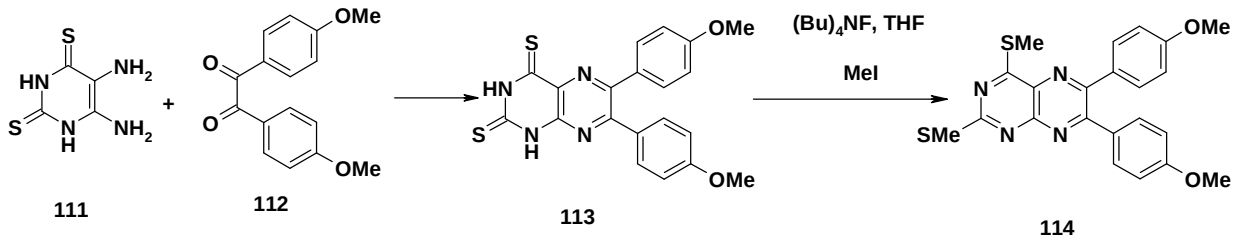

**Scheme 24**

Condensation of 5-arylazo-4-chloropyrimidines **104** with α-aminoketones or esters, followed by reduction (usually with Zn/HOAc) and thermal cyclization. The phenylazo moiety serves both as a precursor of the 5-amino group. This also prepared from 5-nitro-4-chloropyrimidines **108** (Scheme 25) [58].



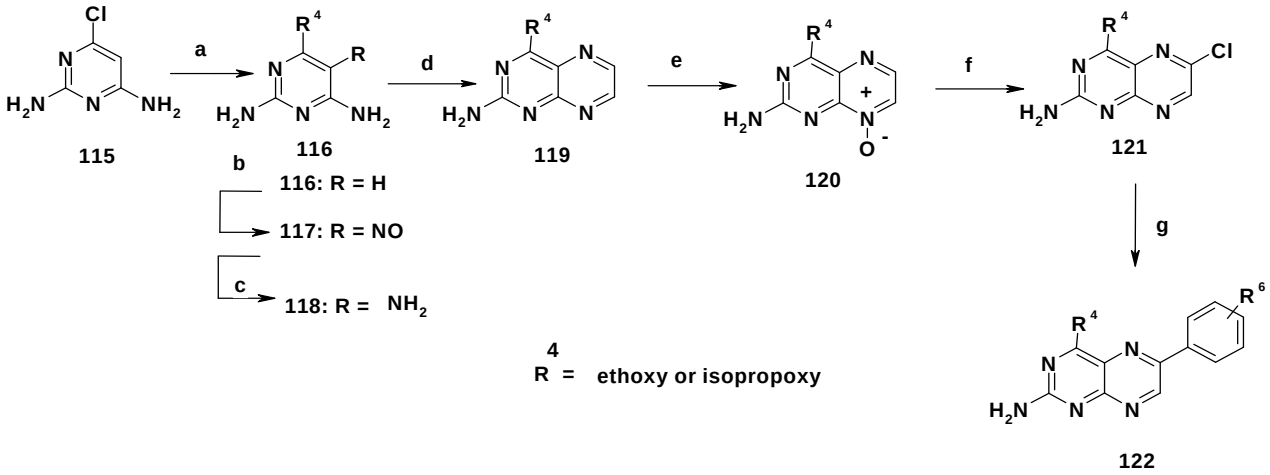

**Scheme 25**

Condensation between 4,5-diamino-2,6-dimercaptopyrimidine **111** and p-dimethoxybenzil **112** to afforded 6,7-Bis-(p-methoxyphenyl)-2,4-(1H,3H)-pteridinedithione **113** which by S-Methylation tetrabutylammonium fluoride (TBAF), as base, and an excess of methyl iodide, as alkylating agent, afforded dimethyl derivatives **114** (Scheme 26) [59].




**Scheme 26**

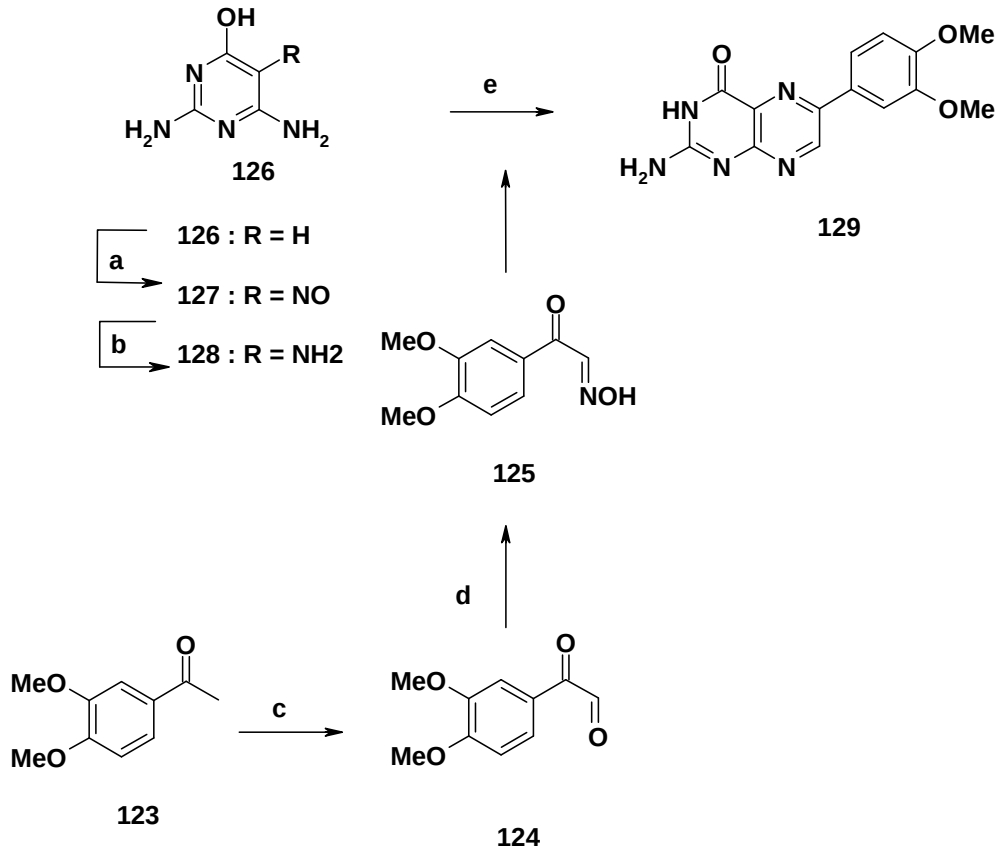
De Jonghe et al [60] found that, 5,6-diamino-pyrimidine derivatives were prepared by action of sodium ethoxide or sodium isopropoxide on 2,6-diamino-4-chloro-pyrimidine **115**, to introduce an alkoxy substituent. Nitrosation of the pyrimidine ring, followed by reduction of the nitroso group (using sodium dithionite in water), the product was reacted with glyoxal, affording 2-amino-4-alkoxy-pteridine [61] Oxidation of product in trifluoroacetic acid with 30% $H_2O_2$ afforded the N-(8)-oxide derivative. The chlorine was introduced using acetyl chloride and trifluoroacetic acid, yielding 2-amino-4-alkoxy-6-chloro-pteridine **122** (Scheme 27) [62].




**Scheme 27**

Reagents and conditions: (a) R4H, Na, 160 _C, 6 h, 72%; (b) NaNO2, CH3COOH, H2O, 80 _C, 68%; (c) Na2S2O4, H2O, 60 _C, 61%; (d) glyoxal, ethanol or isopropanol, reflux, 4 h, 62%; (e) TFA, H2O2, 4 _C, 2 d, 32%; (f) AcCl, TFA, _40–0 _C, 72%; (g) ArB(OH)2, Na2CO3, Pd(PPh3)4, dioxane, reflux, 4 h, 20–70%.

Introduction of a nitroso group at position 5 of 2,6-diamino-4-hydroxy-pyrimidine **126** and its subsequent reduction yielded the 5,6-diamino-pyrimidine derivative **128**. The 6-(3,4-dimethoxyphenyl)-pteridine **129** was constructed by condensation reaction between pyrimidine and a-ketoaldoxime (which was prepared from the corresponding acetophenone derivative by oxidation with SeO2, followed by displacement reaction (Scheme 28) [60].

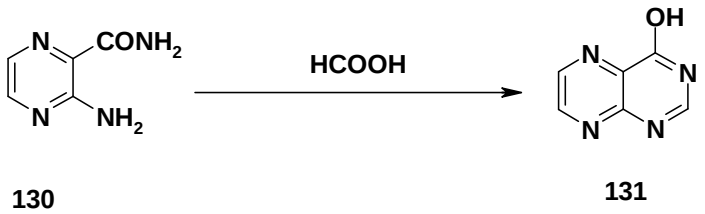



**Scheme 28**

Reagents and conditions: (a) NaNO2, CH3COOH, H2O, 97%; (b) Na2S2O4, H2O, rt, 83%; (c) SeO2, dioxane, H2O, 50 _C; (d) acetonoxime, CH3OH, H2O, 50 _C, 2 h, 71% (over 2 steps); (e) 15, CH3OH, reflux, 3 h, 85.

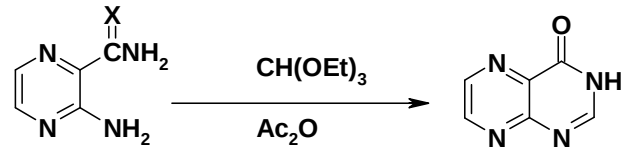
**3.2. From Pyrazines.**

4-hydroxy pteridine [63] **131** can be prepared by the condensation of 3-amino pyrazine-4-carboxamide **130** with formic acid (Scheme 29).




**Scheme 29**

Cyclisation of 3-aminopyrazine-2-carboxamide **132** or its thio-analogue with triethyl orthoformate in acetic anhydride gave pteridin-4-one or-4-thione **133**, respectively (Scheme 30) [64].



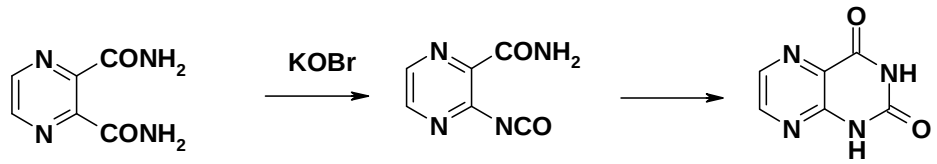

**132**

**X = O , S**

**133**

**Scheme 30**

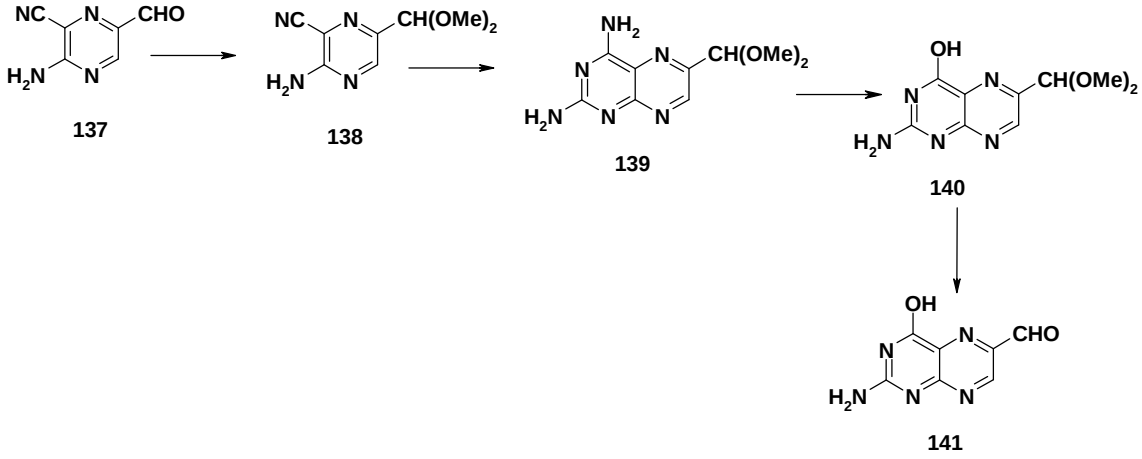
Gabriel et al [65] found that pyrazine-2,3-dicarboxamide **134** by Hofmann reaction into lumazine (pteridine-2,4-dione) **136** (Scheme 31).




**134** **135** **136**

**Scheme 31**

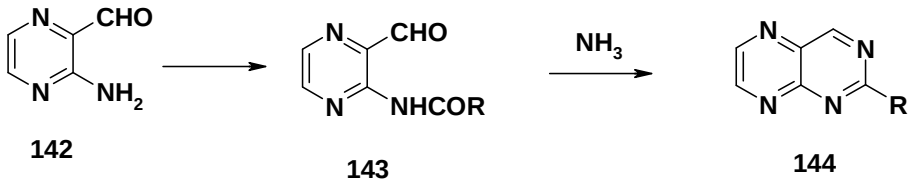
2-amino-3-cyanopyrazine-5-carbaldehyde **137** was converted to dimethylacetal **138** which was cyclized to 2,4-diamino-5-formyl pteridinemethylacetal **139** with guanidine gave the dimethylacetal of 6-formylpterin **140**, which was converted to 6-Formylpterin **141** with formic or trifluoroacetic acid (Scheme 32) [66].




**137** **138** **139** **140** **141**

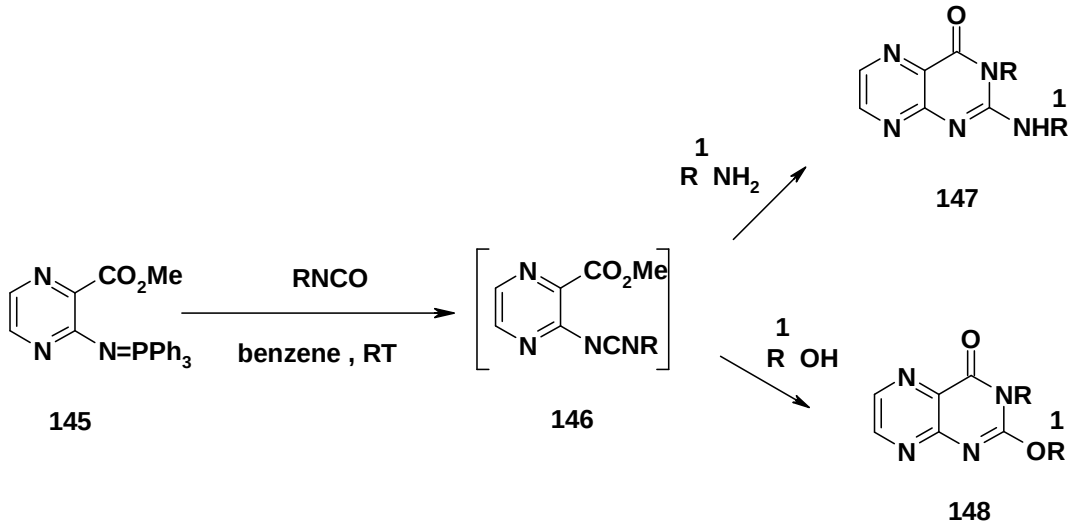
**Scheme 32**

4-Unsubstituted pteridines **144** have been prepared by a modification of this route using pyrazinecarbaldehydes **142** as starting materials (Scheme 33) [67].



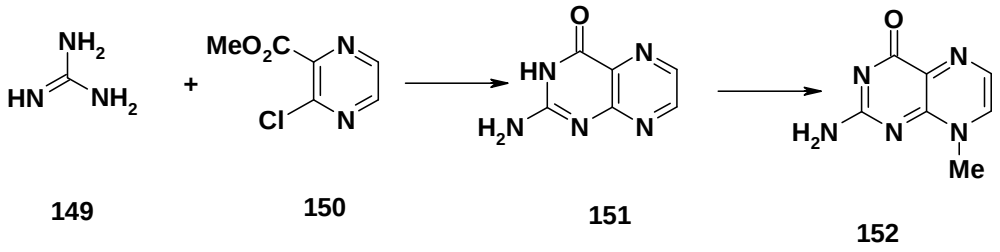

**Scheme 33**

Methyl-3-(triphenylphosphoranylideneamino)pyrazine-2-carboxylate **145** used to obtain different pteridines by reaction with isocyanates followed by adding alcohols or amines (Scheme 34) [68,69].



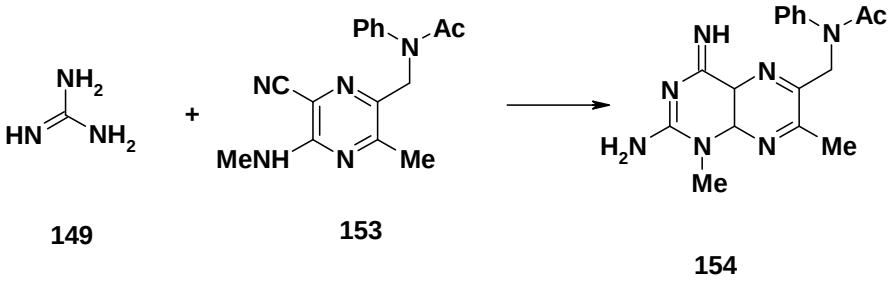

**Scheme 34**

Methyl 3-chloropyrazine-2-carboxylate **150** and guanidine **149** were reacted to yield 2-aminopteridin-4-one **151**. The product is best purified via the sodium salt; Methylation of pterin gives the unexpected N-methylated product **152** (Scheme 35) [70,71].




**Scheme 35**

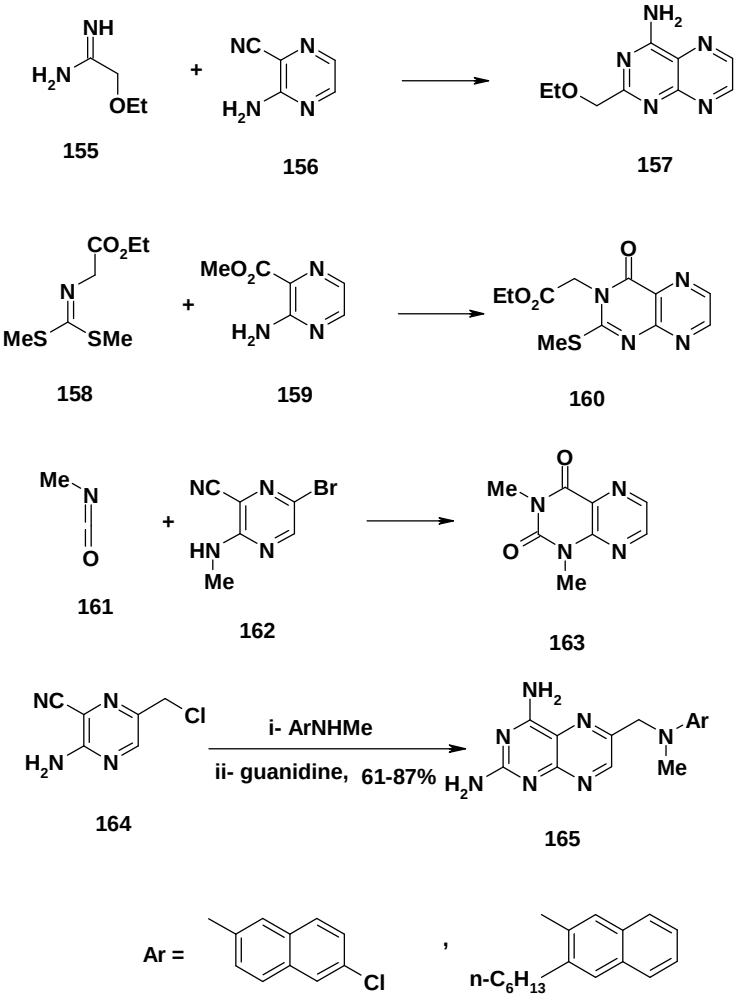
Guanidine **149** was reacted again with Pyrazine derivatives **153** to afford new 4-imino pteridine derivatives**154** (Scheme 36) [72].




149 153 154

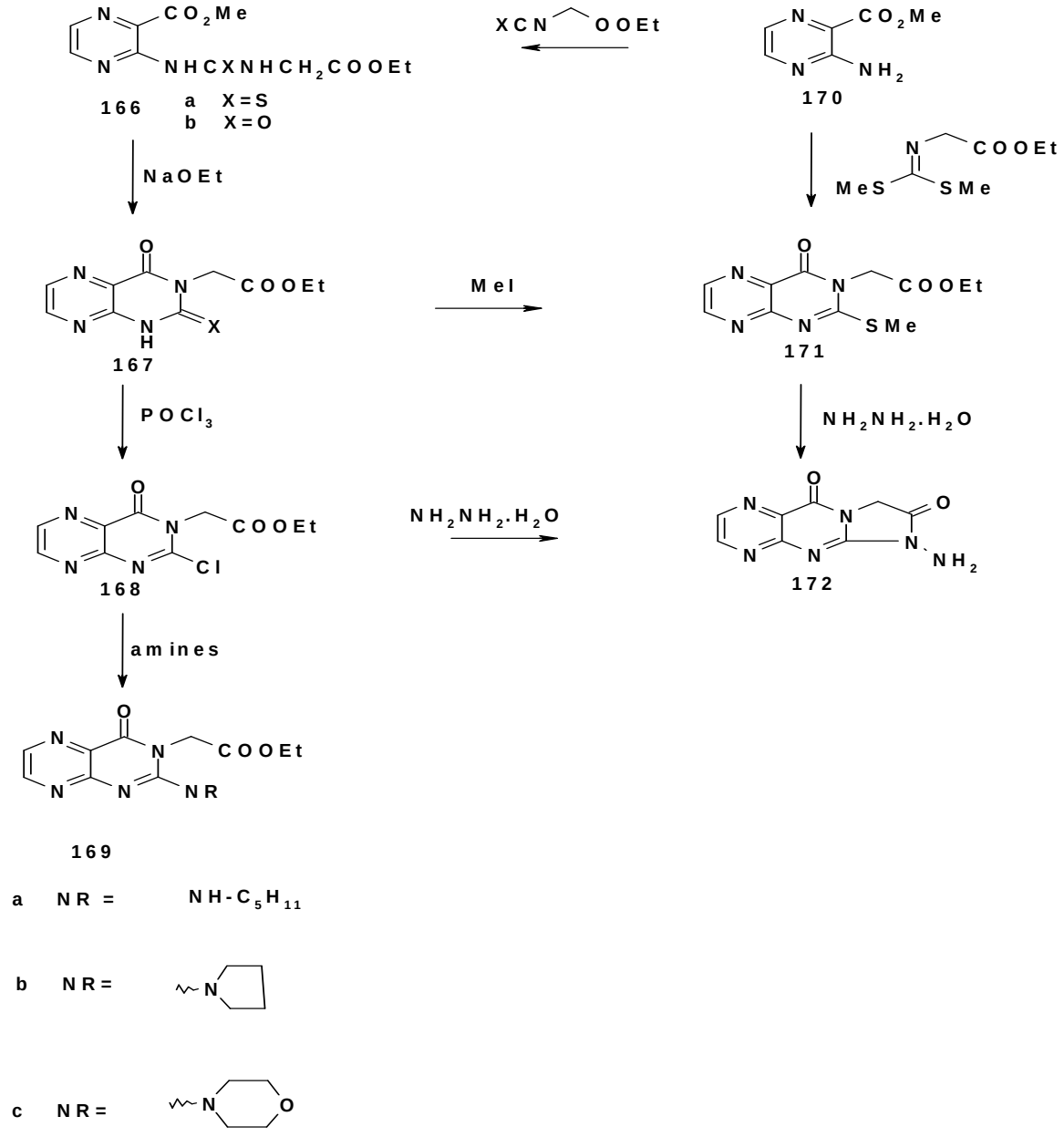
**Scheme 36**

Substituted amidines have been found to react in good yield to give 6,7-unsubstituted pteridines from the corresponding pyrazine. Similarly, methyl-2-aminopyrazine-3-carboxylate **159** condensed, with the bis(dithioimidate) **158** giving access to an unusual N-3-substituted 2-methylthiopteridine-4-one **160**. Also 1,3-dimethyllumazine system **163** can be prepared from methyl isocyanate **161** and a 5-aminomethyl-6-cyanopyrazine **162**.The 5-chloromethylpyrazine **164** was reacted firstly with substituted aromatic amines and then with guanidine to form the compounds for evaluation (Scheme 37) [73].



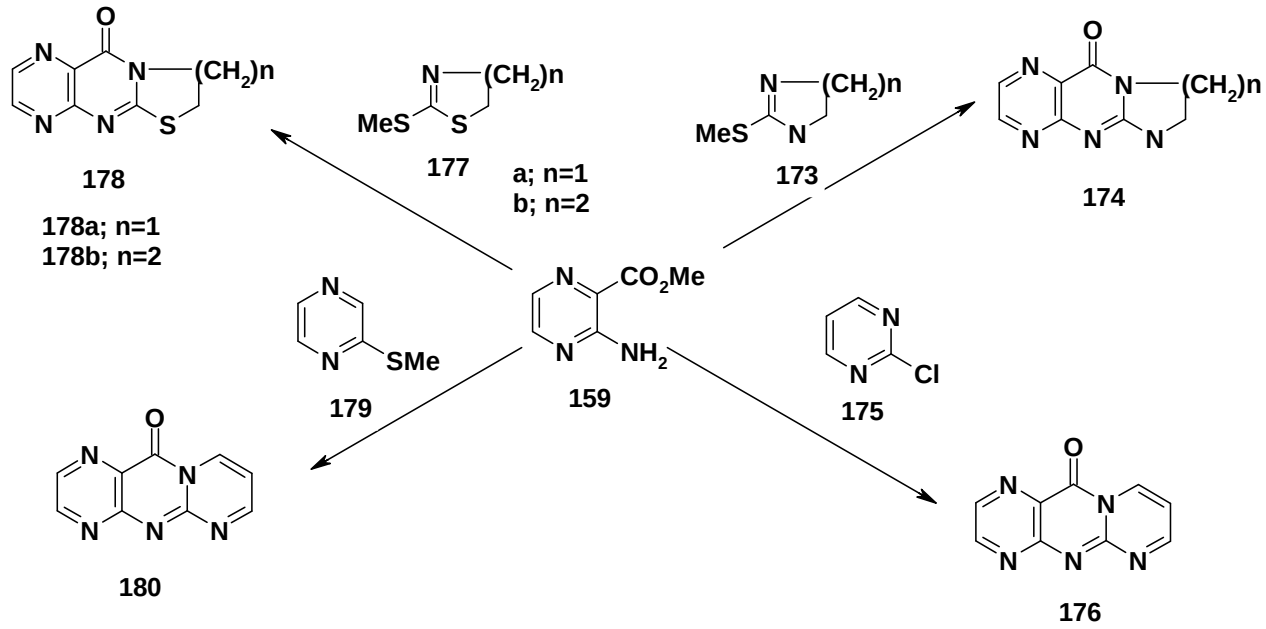

**Scheme 37**

2-aminopyrazine also reacted with isothiocyanates, isocyanates, or dithioketals to afford the corresponding pteridines. For example, with ethyl isothiocyanatoacetate, and ethyl isocyanatoacetate, the corresponding thioureidopyrazine and urethane derivatives, respectively, were obtained, which, on cyclization in the presence of sodium ethoxide, gave 2-thio and oxo-N-3-protected pteridines in good yields. on reaction with methyl iodide, afforded a 2-methylthiopteridine **171** was also obtained directly from by the condensation with ethyl N-[bis(methylthio)methylene]glycinate also reacted with phosphorusoxychloride to give a 2-chloro derivative **168**, which was reacted with pyrrolidine, giving 2-pyrrolodinyl pteridine-4-one derivatives **169**. Hydrazine hydrate reacted with 2-methylthioderivatives to give N-aminolactam derivatives **172** (Scheme 38) [74].



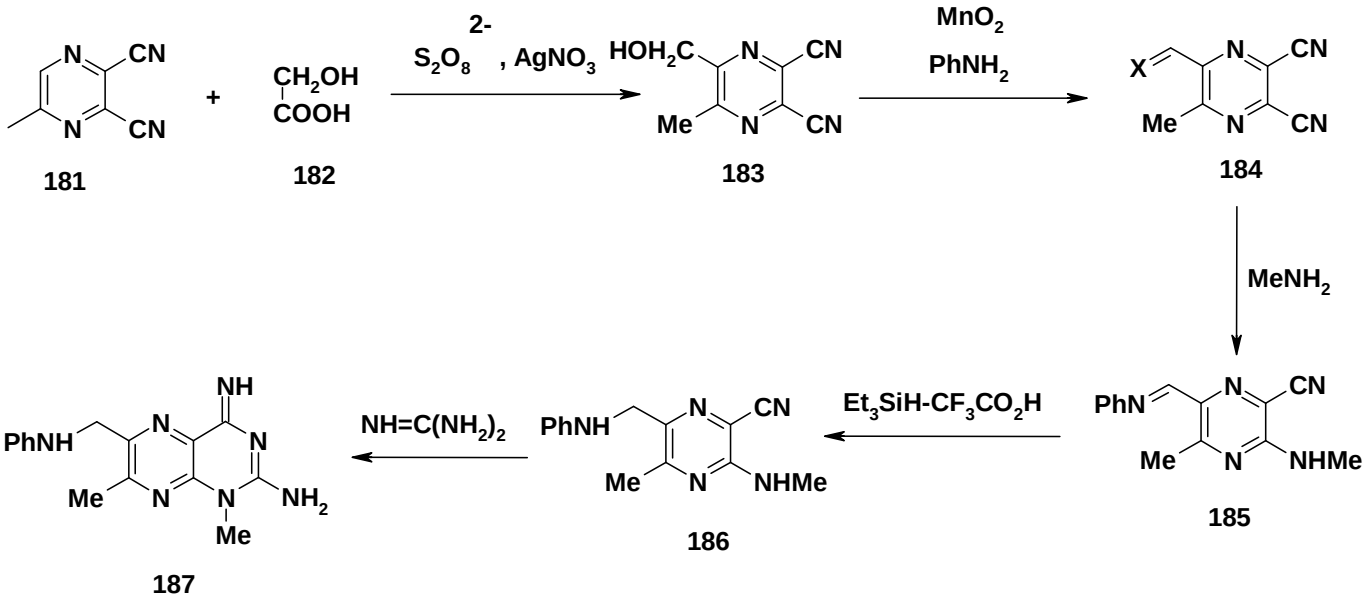

**Scheme 38**

series of imino thioacetals [74] 2-(methylthio)-2-thiazoline **177a** ,5,6-dihydro-2-(methylthio)-4H-1,3-thiazine **177b,** 2-(methylthio)-2-imidazoline **173**, 2-(methylthio)-1,4,5,6-tetrahydropyrimidine **175** and 2-(methylthio)-2-pyrazine **179** ,reacted readily with 2 aminopyrazine **159** to give the desired tricyclic fusion products, thiazolo[2,3-b]pteridine derivative **178a**, thiazino[2,3-b]pteridine derivative**178b** [75,76] , imidazo[2,1-b]pteridine derivative **174**, pyrimido[2,1-b]pteridine derivative **176** and pyrazino[2,1-b]pteridine derivative **180** respectively by one-step reaction (Scheme 39).



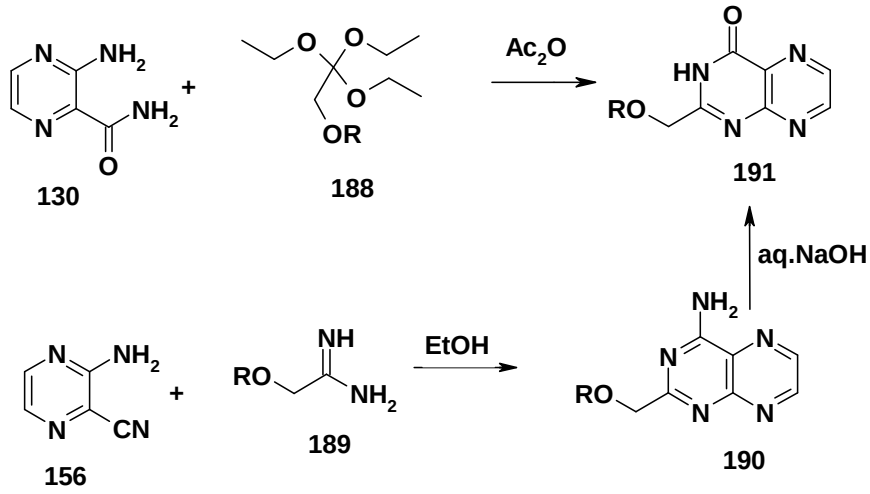

**Scheme 39**

6-anilinomethylpteridine derivatives **187** were prepared by the reaction of glycolic acid **182** with 5-metyl Pyrazine-2,3-dicarbonitrile **181** (Scheme 40)[72].



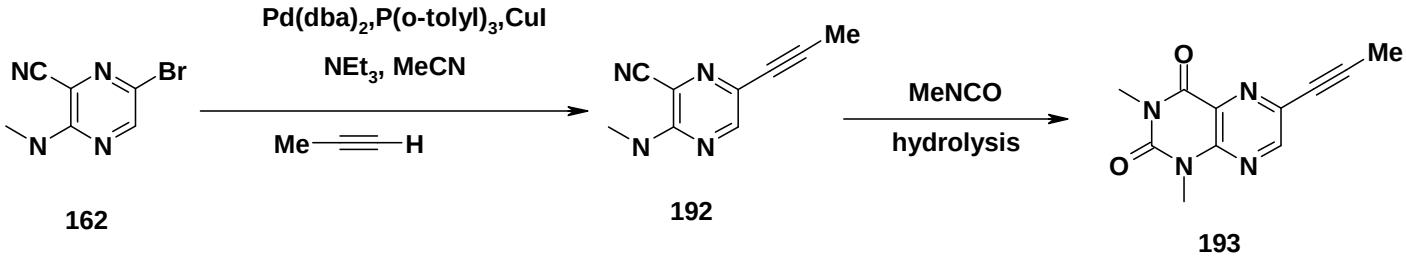

**Scheme 40**

The synthesis of 2-alkoxymethylpteridines has been achieved by the reaction of 3-aminopyrazine-2-carboxamide **130** with orthoesters **188** to give 2-alkoxymethylpteridine derivatives **191**, which was synthesized by condensing 3-aminopyrazine-2-carbonitrile **156** with the acetoxyamidine **189** followed by the base hydrolysis (Scheme 41) [77].



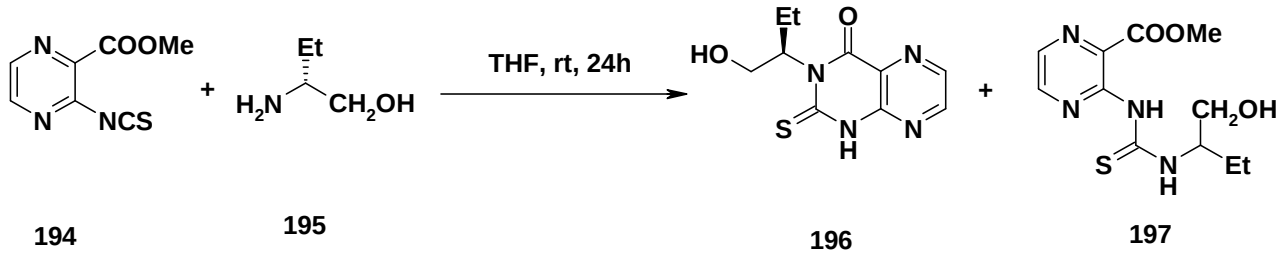

**Scheme 41**

6-bromo-3-methyl amino Pyrazine-2-carbonitrile **162** underwent cross-coupling with propyne in the presence of bis(dibenzylidineacetone) palladium(0), tri-o-tolylphosphine, and copper (I) iodide to provide The pyrazines which was cyclized with methyl isocyanate to give corresponding pteridines **193** (Scheme 42) [78].




**Scheme 42**

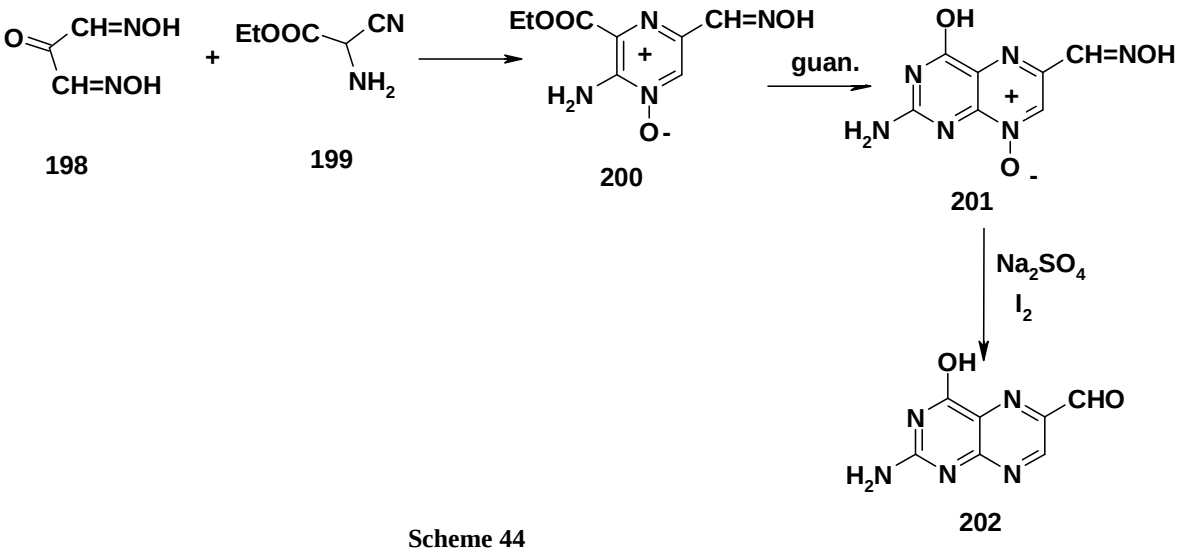
Methyl-3-isothiocyanatopyrazine-2-carboxylate **194** reacted with (R)-(_)-2-amino-1-butanol **195** in the absence of base, which provided the pteridine derivative **196** and uncyclized pyrazine derivative **197** in similar amounts (Scheme 43) [79].



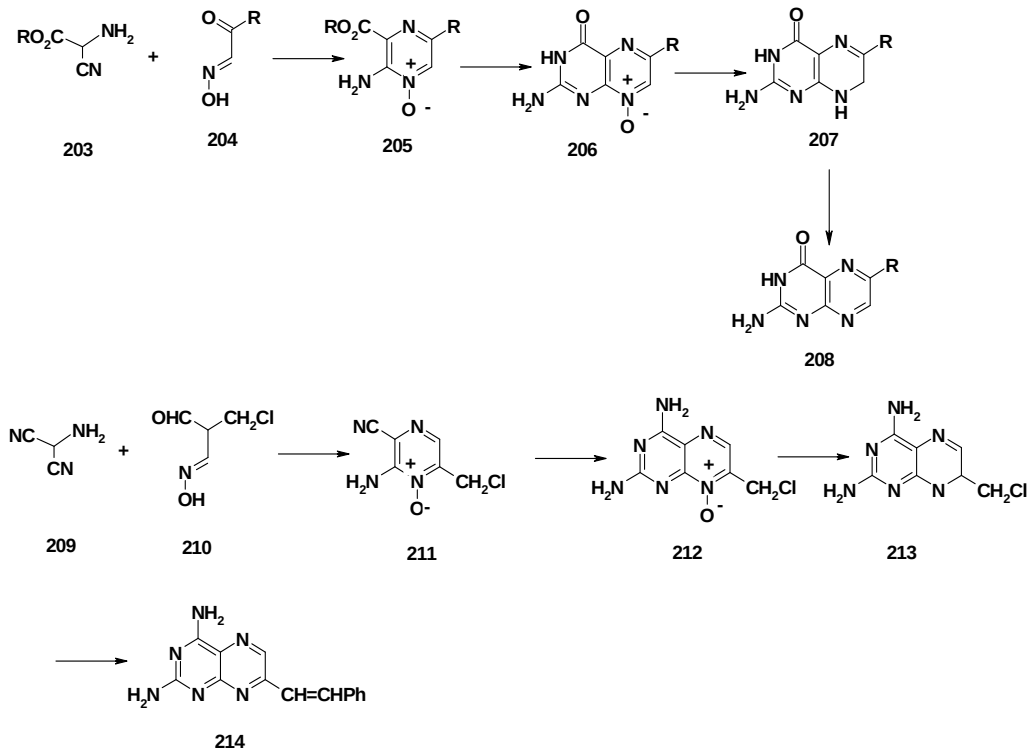

**Scheme 43**

**3.3. From different Heterocyclic compounds.**

Condensation of ethyl α-aminocyanoacetate **199** with diisonitrosoacetone **198** to give ethyl 2-amino-5-oximinomethylpyrazine-3-carboxylate1-oxide **200**, which was cyclized with guanidine to pterin-6-carboxaldehyde oxime 8-oxide **201** direct hydrolysis of the oxime was not possible, but conversion to was achieved by reduction with sodium sulphite which gave 6-aminomethylpterin **202** followed by oxidation with iodine (Scheme 44) [80].

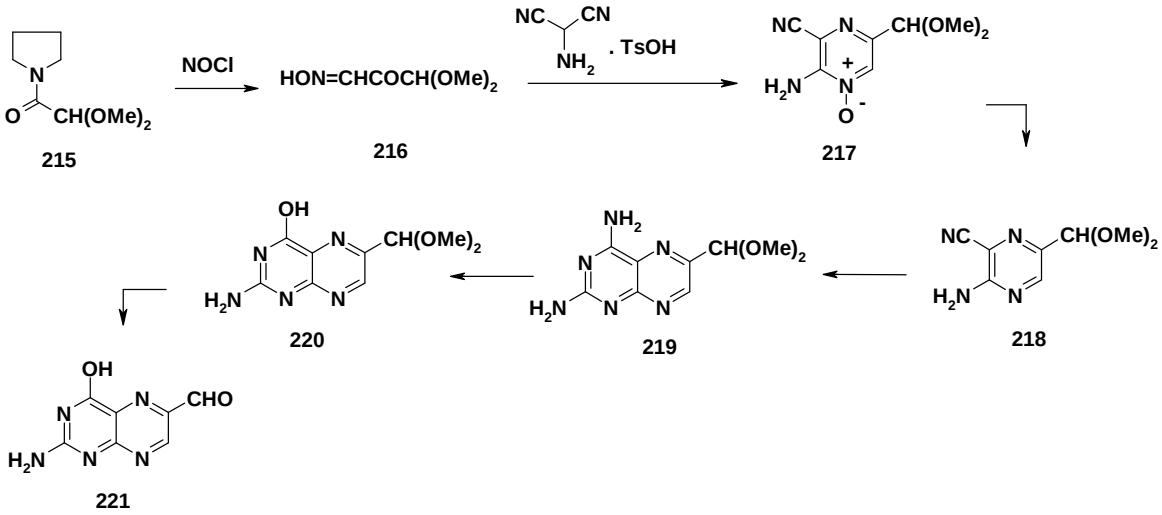



**Scheme 44**



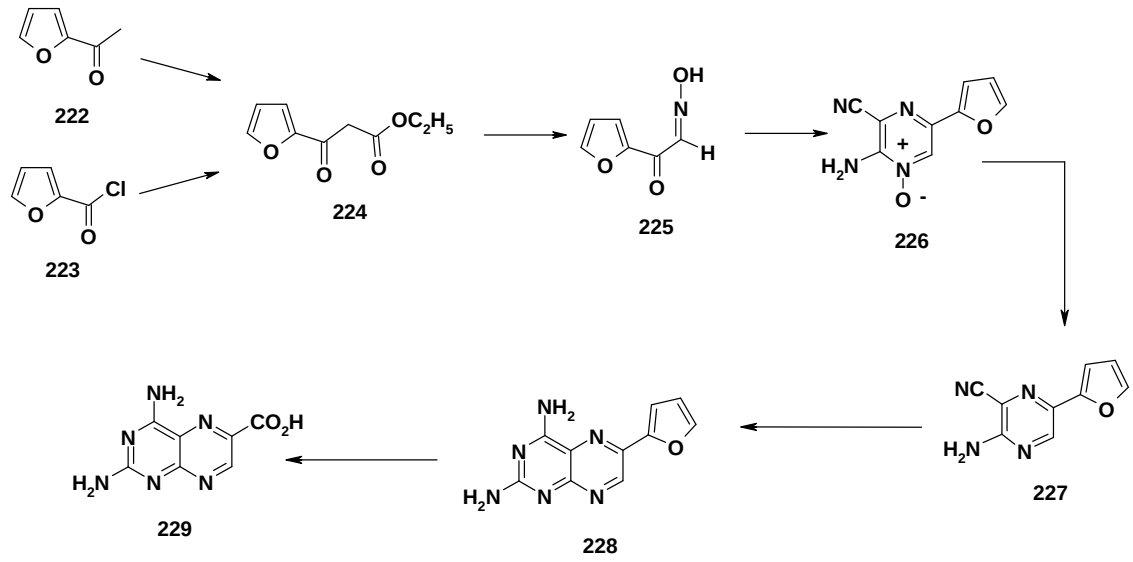

**Scheme 45**

Reaction of 3,3-dimethoxy- 1-pyrrolidinopropene **215** with nitrosyl chloride and addition of aminomalononitrile tosylate to the resulting oxime gave 2-amino-3-cyano-5-(dimethoxymethy1)pyrazine-1-oxide **217** which was deoxygenated to dimethylaceta with trimethyl phosphate then produce 6-aminomethylpterin **221** (Scheme 46) [85].




**Scheme 46**

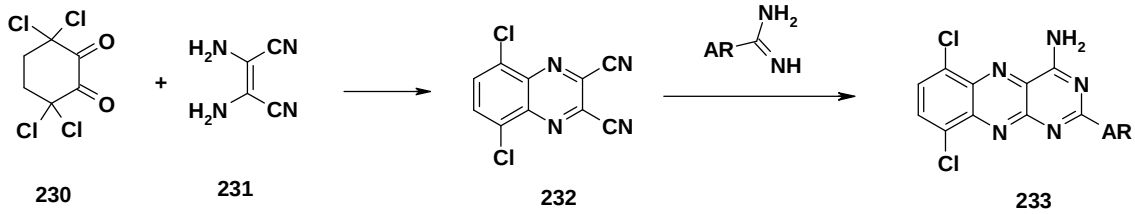
2,4-Diaminopteridine-6-carboxlic acid **229** was prepared by base catalyzed condensation of 2-acetyl furan **222** and 2-furoyl chloride **223** to yield β-keto ester which by hydrolysis in KOH aqueous furnished the β-carboxlic acids which was treated with sodium nitrite and acidified leading to oximinoketone, Condensation of oximinoketone with malanonitrile tosylate in 2-propanol was gave the Pyrazine-N-oxide **226**. The latter was deoxygenated giving aminocyanopyrazine **227** which cyclized readily with guanidine to give 2,4-diaminopeteridines **228** then oxidation to yield 2,4-diaminopeteridine-6-carboxlic acid **229** (Scheme 47) [86].




**Scheme 47**

5,8-dichloro-2,3-dicyanoquinoxaline **233** was prepared by reaction of 3,3,6,6- tetrachloro-1,2-cyclohexanedione **230** with diaminomaleonitrile **231** followed by treatment with pyridine then treated with an equimolar amount of

benzamidine in the presence of triethylamine to produce 4-amino-2-aryl-6,9-dichlorobenzo[g]pteridine **233** (Scheme 48) [87].




**230** **231** **232** **233**

**Scheme 48**

## CONCLUSION

Taken together, we have described some recent advances in the synthesis of pteridines derivatives from heterocyclic compounds. This review showed the significant development in pteridines synthetic methods, however, these derivatives are now being more popular because of its efficiency, and many new methods will probably be developed.

**Acknowledgment**
The authors are gratefully indebted to Dr. Emadeldin M. Kamel, Chemistry department, Faculty of science, Beni Suef University for his help.

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