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Synthesis, reactions and applications of pyranotriazolopyrimidines

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ABSTRACT

This review deals with synthesis, reactions and their applications of pyranotriazolo-pyrimidines. The main purpose of this review is present a survey of literatures on the reactivity of amino imino derivatives and carboxylic acid derivatives. Some of these reactions have been applied successfully to the synthesis of biological important compounds.

1. Introduction

Pyran derivatives have attracted a great deal of interest owing to their antimicrobial activity [1-7], inhibition of influenza, virus sialidase [8], mutagenic activity [9], activity as antiviral [10], anti-proliferaction agents [11], sex pheromones [12], antitumor [13] and anti-inflammatory agents [14].

The condensation of a ring of 1,2,4-triazole and another one of pyrimidine gives rise to the formation of bicyclic heterocycles known as 1,2,4-triazolopyrimidines. Four different possibilities exist for the relative orientation of both rings, so four different isomeric families of compounds are defined: 1,2,4-triazolo[1,5-*a*]pyrimidine (**I**), 1,2,4-triazolo[1,5-*c*]pyrimidine (**II**), 1,2,4-triazolo[4,3-*a*]pyrimidine (**III**) and 1,2,4-triazolo[4,3-*c*]pyrimidine (**V**) (Figure 1).

Among these isomeric families of compounds, 1,2,4-triazolo[1,5-*a*]-pyrimidine derivatives are thermodynamically more stable and, thus, the most studied ones [15], a few of them being commercially available. Revisions surveying the synthesis, reactivity, spectroscopic characterization and crystallographic studies of 1,2,4-triazolo[1,5-*c*]-pyrimidines [16], 1,2,4-triazolo[4,3-*a*]pyrimidines [17] and 1,2,4-triazolo [4,3-c]pyrimidines [18] have also been published.

From the standpoint of biological activity, fused heteroaromatic systems are often of much greater interest than the constituent monocyclic compounds. Recently, 1,2,4-triazolo [1,5-*a*]pyrimidines have aroused increasing attention from the chemical and biological view points, due to their diverse pharmacological activities, such as antitumor potency [19,20], inhibition of KDR kinase [21], antifungal effect [22] and macrophage activation [23].

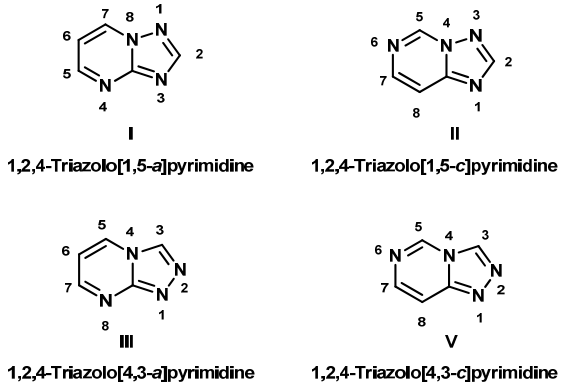

Figure 1. Structures of triazolopyrimidines.

They have proved to be promising anticancer agents with dual mechanisms of tubulin polymerization promotion [19,20] as well as anti-mycobacterial agents [24]. Some examples of

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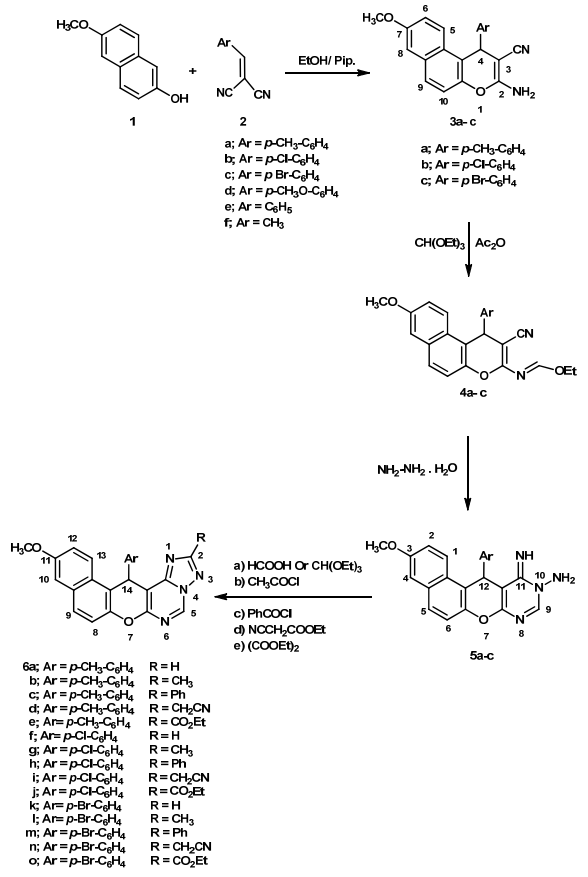
published derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine with their biological activities are as following.

2. Synthesis of pyrano triazolo pyrimidine derivatives

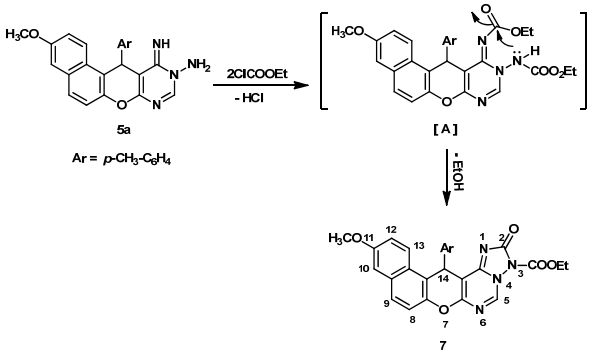
2.1. Synthesis from 6-methoxy-2-naphthol [25-27]

Condensation of 6-methoxy-2-naphthol (**1**) with α-cyanocinnamonitriles (**2a-f**) afforded the corresponding 2-amino-4-(aryl)-7-methoxy-4*H*-naphtho[2, 1-*b*]pyran-3-carbo nitriles, **3a-c**, ethoxymethylene derivatives (**4a-c**) was obtained by refluxing compounds 2-amino-4-(aryl)-7-methoxy-4*H*-naphtho[2,1-*b*]pyran-3-carbonitriles (**3a-c**) with triethyl *ortho*-formate as electrophile in the presence of acetic anhydride. Hydrazinolysis of ethoxymethylene derivatives **4a-c** in ethanol, at room temperature furnished the novel 10-amino-10,11-dihydro-11-imino-3-methoxy-12-(aryl)-12*H*-naphtho [2, 1-*b*] pyrano[2,3-*d*]pyrimidine derivatives **5a-c** in good yield. Reaction of aminoimino derivatives **5a-c** with formic acid or triethyl *ortho*-formate affords the corresponding pyrano triazolo-pyrimidine derivative **6a**. Also compounds **5a-c** reacted with acetylchloride and or benzoyl chloride gave the corresponding 11-methoxy-2-methyl/phenyl-14-(aryl)-14*H*-naphtho[2,1-*b*]-pyrano[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**6b**,**c**), while cyclo-condensation of compound **5a-c** with ethyl cyanoacetate or diethyl oxalate afforded the corresponding 2-cyanomethyl and 2-ethoxycarbonyl derivatives **6d** and **6e**, respectively (Scheme 1).



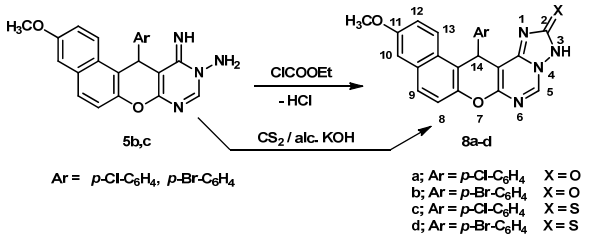
Scheme 1

Treatment of 10-amino-10,11-dihydro-11-imino-3-methoxy-12-(*p*-tolyl)-12*H*-naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidine (**5a**) with two moles of ethylchloroformate in dry benzene afforded 1:2 adduct **7**. Formation of compound **7** was assumed to proceed via *bis*(ethoxylcarbonyl) derivative [**A**] as intermediate, which cyclized into compound **7** with elimination of ethanol (Scheme 2).



Scheme 2

While treatment of 10-amino-10,11-dihydro-11-imino-3-methoxy-12-(*p*-chloro/bromophenyl)-12*H*-naphtho [2, 1-*b*] pyrano-[2,3-*d*] pyrimidine (**5b**,**c**) with ethylchloroformate in dry benzene afforded 11-methoxy-14-(*p*-chloro/bromo phenyl)-2-oxo-2*H*,3*H*,14*H*-naphtho[2,1-*b*]-pyrano[3,2-*e*][1,2,4] triazolo[1,5-*c*]pyrimidines (**8a**,**b**). Reaction of compound **5b**,**c** with CS_2/alc. KOH gave triazolo-2-thiones (**8c**,**d**), respectively, (Scheme 3).

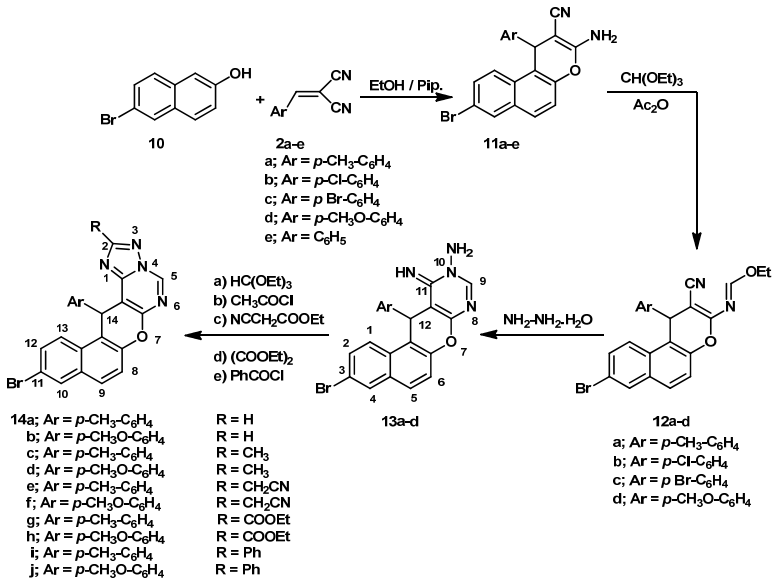


Scheme 3

2.2. Synthesis from 6-bromo-2-naphthol [28,29]

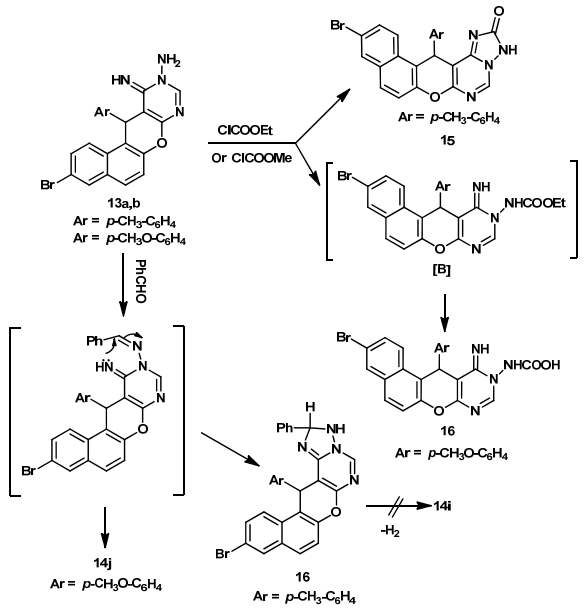
Condensation of various substituted α-cyanocinnamo nitriles **2a**,**c** with 6-bromo-2-naphthol (**10**) in ethanolic piperidine afforded the corresponding 2-amino-4-(aryl)-7-bromo-4*H*-naphtho[2,1-*b*]pyran-3-carbonitriles (**11a-e**). Treatment of compounds **11a-d** with triethyl *ortho*-formate in acetic anhydride at reflux gave the corresponding ethoxylmethylen amino derivatives **12a-d**. Hydrazinolysis of compounds **12a-d** in ethanol at room temperature afforded the imino derivatives **13a-d**. Interaction of compounds **13a,b** with triethyl ortho-formate afforded 11-bromo-14-(*p*-tolyl or *p*-methoxyphenyl)-14*H*-naphtho[1`,2`:5,6]pyrano[3,2-*e*][1,2,4]triazolo[2,3-*c*]pyrimidines (**14a**,**b**), respectively, (Scheme 4).

Reaction of compounds **13a**,**b** with acetyl chloride and ethyl cyano acetate at reflux the corresponding 2-methyl-14-(*p*-tolyl or *p*-methoxyphenyl)-14*H*-naphtho-[2,1-*b*]pyrano[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**14c**,**d**) and 2-acetonitrile-14- (*p*-tolyl or *p*-methoxyphenyl)-14*H*-naphtho[2,1-*b*] pyrano-[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**14e**,**f**), respectively, were formed. Reaction of compounds **13a**,**b** with diethyl oxalate and benzoyl chloride at reflux afforded the corresponding 2-ethoxycarbonyl **14g**,**h** and 2-phenyl **14i**,**j** derivatives. Reaction of compound **13a** with methyl or ethyl chloroformate (1 mole) in dry benzene afforded the 1:1 adduct triazol-2-one **15**, Instead of the anticipated formation of the triazolo pyrimidine derivative **15** the reaction of compound **13d** with methyl or ethyl chloroformate in dry benzene afforded **16**, through nucleophilic displacement followed by spontaneous



Scheme 4

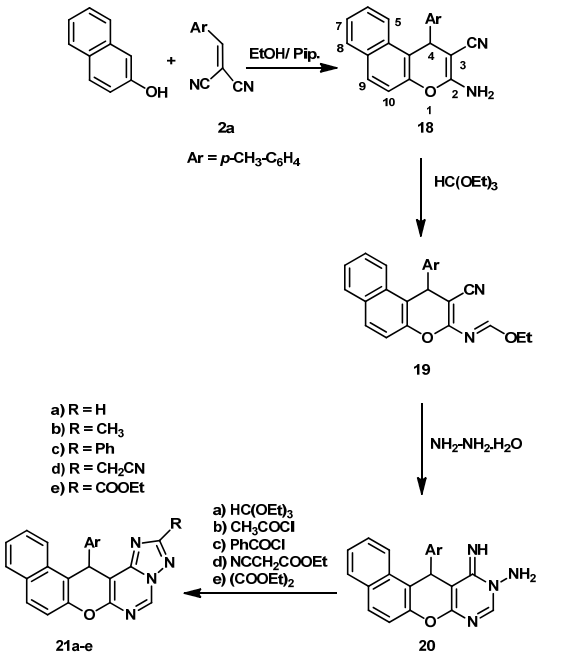
hydrolysis of the ester intermediate [**B**] into the corresponding carbamic acid derivative **16**. Interaction of compound **13a**,**d** with benzaldehydes in dioxane/piperidine afforded **14j** and dihydrotriazolopyrimidine derivative **17** and non-isolable **14i**, respectively, (Scheme 5).



Scheme 5

2.3. Synthesis from 2-naphthol [30]

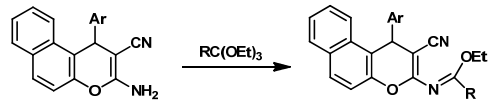
Condensation of α-cyanocinnamonitrile **2a**, with 2-naphthol in ethanolic piperidine afforded 2-amino-4-(*p*-tolyl)-4*H*-naphtho[2,1-*b*]-pyran-3-carbonitrile (**18**). Treatment of compound **18** with triethyl *ortho*-formate in acetic anhydride at reflux gave the corresponding ethoxylmethylenamino derivative **19**. Hydrazinolysis of compound **19** in ethanol at room temperature afforded the imino derivative **20**. Interaction of compound **20** with triethyl *ortho*-formate, acetyl chloride, benzoyl chloride, ethyl cyanoacetate, diethyl oxalate afforded the corresponding triazolopyrimidine derivatives **21a-e** (Scheme 6).



Scheme 6

2.4. Synthesis from naphtho[2,1-b]pyrans [31]

Reaction of 2-amino 4-aryl-3-cyano-4*H*-naphtho[2,1-*b*]pyrans **18** and **22** with triethyl *ortho*-formate, triethyl *ortho*-acetate or triethyl *ortho*-propionate in 1,4-dioxane, in presence amount of acetic acid under reflux to give 2-[(ethoxy alkylidene)amino-4-aryl-3-cyano-4*H*-naphtho-[2,1-*b*]pyrans **19** and **23**, respectively, (Scheme 7).

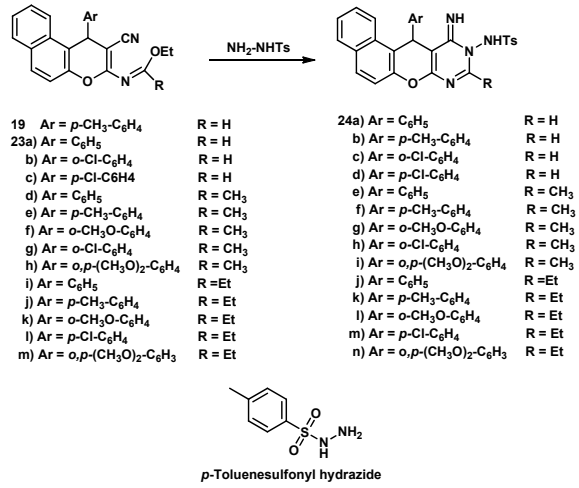


18 Ar = *p*-CH_3-C_6H_4
22a) Ar = C_6H_5
b) Ar = *o*-Cl-C_6H_4
c) Ar = *m,p*-Cl_2-C_6H_3
d) Ar = *p*-Cl-C_6H_4
e) Ar = *o*-CH_3O-C_6H_4
f) Ar = *o,p*-$(CH_3O)_2$-C_6H_3

19 Ar = *p*-CH_3-C_6H_4	R = H
23a) Ar = C_6H_5	R = H
b) Ar = *o*-Cl-C_6H_4	R = H
c) Ar = *p*-Cl-C_6H_4	R = H
d) Ar = C_6H_5	R = CH_3
e) Ar = *p*-CH_3-C_6H_4	R = CH_3
f) Ar = *o*-CH_3O-C_6H_4	R = CH_3
g) Ar = *o*-Cl-C_6H_4	R = CH_3
h) Ar = *o,p*-$(CH_3O)_2$-C_6H_3	R = CH_3
ij) Ar = C_6H_5	R =Et
j) Ar = *p*-CH_3-C_6H_4	R = Et
k) Ar = *o*-CH_3O-C_6H_4	R = Et
l) Ar = *p*-Cl-C_6H_4	R = Et
m) Ar = *o,p*-$(CH_3O)_2$-C_6H_3	R = Et

Scheme 7

The reaction of these imidates **19** and **23**, with tosyl hydrazine, in toluene at reflux and few drops of acetic acid, afforded the desired key intermediate *N*1-tosylamino-11-aryl-1,12-dihydro-11*H*-naphthopyrano-[2, 3-*d*]pyrimidine (**24**) (Scheme 8).



19 Ar = *p*-CH_3-C_6H_4	R = H
23a) Ar = C_6H_5	R = H
b) Ar = *o*-Cl-C_6H_4	R = H
c) Ar = *p*-Cl-C6H4	R = H
d) Ar = C_6H_5	R = CH_3
e) Ar = *p*-CH_3-C_6H_4	R = CH_3
f) Ar = *o*-CH_3O-C_6H_4	R = CH_3
g) Ar = *o*-Cl-C_6H_4	R = CH_3
h) Ar = *o,p*-$(CH_3O)_2$-C_6H_4	R = CH_3
i) Ar = C_6H_5	R =Et
j) Ar = *p*-CH_3-C_6H_4	R = Et
k) Ar = *o*-CH_3O-C_6H_4	R = Et
l) Ar = *p*-Cl-C_6H_4	R = Et
m) Ar = *o,p*-$(CH_3O)_2$-C_6H_3	R = Et

24a) Ar = C_6H_5	R = H
b) Ar = *p*-CH_3-C_6H_4	R = H
c) Ar = *o*-Cl-C_6H_4	R = H
d) Ar = *p*-Cl-C_6H_4	R = H
e) Ar = C_6H_5	R = CH_3
f) Ar = *p*-CH_3-C_6H_4	R = CH_3
g) Ar = *o*-CH_3O-C_6H_4	R = CH_3
h) Ar = *o*-Cl-C_6H_4	R = CH_3
i) Ar = *o,p*-$(CH_3O)_2$-C_6H_4	R = CH_3
j) Ar = C_6H_5	R =Et
k) Ar = *p*-CH_3-C_6H_4	R = Et
l) Ar = *o*-CH_3O-C_6H_4	R = Et
m) Ar = *p*-Cl-C_6H_4	R = Et
n) Ar = *o,p*-$(CH_3O)_2$-C_6H_3	R = Et

p-Toluenesulfonyl hydrazide

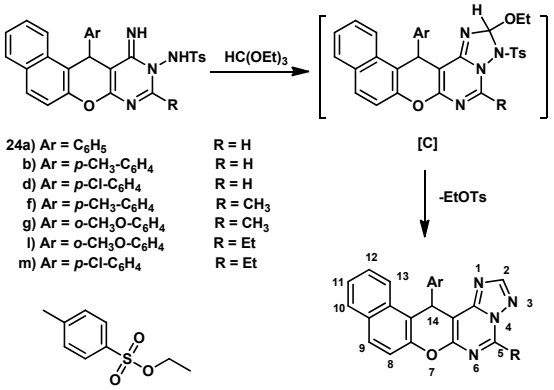
Scheme 8

In the next step, condensed the *N*1-tosylaminonaphtha pyrano[2,3-*d*]pyrimidines **24**, with an excess of triethyl *ortho*-formate to give 14-aryl-14*H*-naphtho[2,1-*b*]pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]yrimidines (**25a-m**). The formation of compounds **21a** and **25a-m** can be explained by asequence of events via intermediates of type [**C**], formed in the reaction of *N*1-tosylaminonaphthopyrano[2,3-*d*]pyrimidines **24** with triethyl *ortho*-formate, followed by spontaneous ethyl 4-methyl benzenesulfonate elimination (Scheme 9).

2.5. Synthesis from imino ethers [32]

Imino ethers are known to react with compounds containing -NH_2 moiety such as hydrazides [33-35]. In fact imino ethers (**26**) possess two reactive sites, a cyano group and an imidic carbon. These groups render them susceptible to react with hydrazides under toluene reflux in the presence of few drops of acetic acid to give new compounds. As shown in (Scheme 10) two plausible pathways and different products could be expected.

i) Successive two nucleophilic additions of (-NH_2 group) on the imidic carbon and on the cyano function to yield amido pyranopyrimidines [**D**]. In this case hydrazides react with iminoethers **26** like hydroxylamine, primary amines [36] and tosylhydrazine [37]. The intermediate [**D**] can be intra-cyclisation via elimination of water to give pyrano triazolo-pyrimidine, **27**.



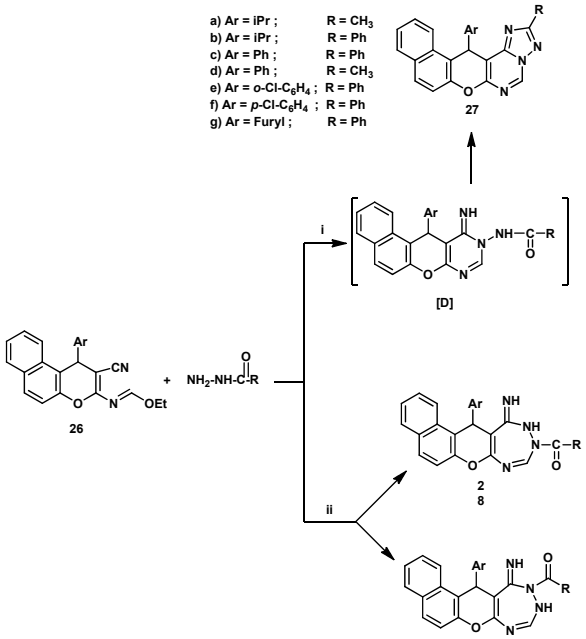
24a) Ar = C_6H_5 R = H
b) Ar = *p*-CH_3-C_6H_4 R = H
d) Ar = *p*-Cl-C_6H_4 R = H
f) Ar = *p*-CH_3-C_6H_4 R = CH_3
g) Ar = *o*-CH_3O-C_6H_4 R = CH_3
l) Ar = *o*-CH_3O-C_6H_4 R = Et
m) Ar = *p*-Cl-C_6H_4 R = Et

Ethyl 4-methyl benzenesulfonate

21a) Ar = *p*-CH_3-C_6H_4 R = H
25a) Ar = C_6H_5 R = H
d) Ar = *p*-Cl-C_6H_4 R = H
f) Ar = *p*-CH_3-C_6H_4 R = CH_3
g) Ar = *o*-CH_3O-C_6H_4 R = CH_3
l) Ar = *o*-CH_3O-C_6H_4 R = Et
m) Ar = *p*-Cl-C_6H_4 R = Et

Scheme 9

ii) Successive two nucleophilic additions of two nitrogen atoms of NH_2-NH moiety on the reactive sites of iminoethers **26** to yield pyranotriazepines **28** or their isomers **29**.



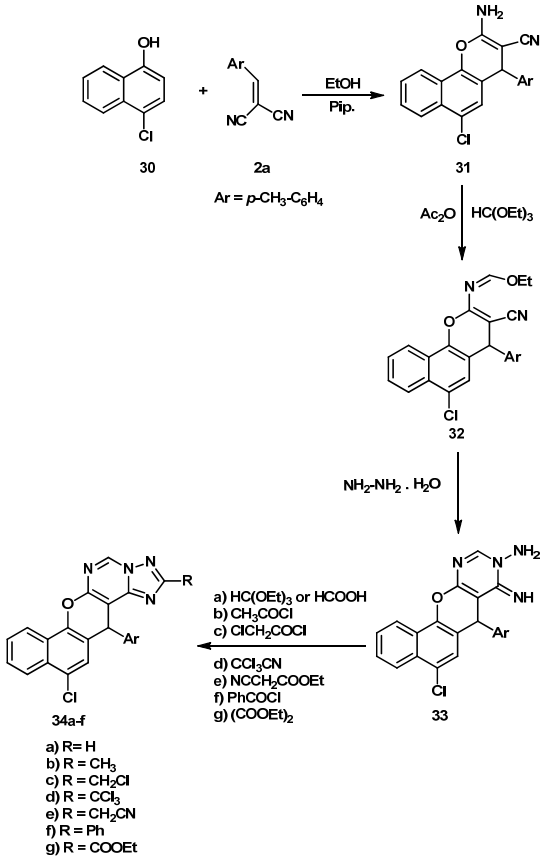
a) Ar = iPr ; R = CH_3
b) Ar = iPr ; R = Ph
c) Ar = Ph ; R = Ph
d) Ar = Ph ; R = CH_3
e) Ar = *o*-Cl-C_6H_4 ; R = Ph
f) Ar = *p*-Cl-C_6H_4 ; R = Ph
g) Ar = Furyl ; R = Ph

Scheme 10

2.6. Synthesis from 4-chloro-1-naphthol [38]

The condensation of substituted benzylidenmalonitile (**2a**), with 4-chloro-1-naphthol (**30**) in the ethanolic piperidine afforded naphthopyran **31**. Treatment of 2-amino-6-chloro-4-(*p*-tolyl)-4*H*-naphtho[1,2-*b*]pyran-3-carbonitrile (**31**) with triethyl *ortho*-formate in acetic acid at reflux gave the corresponding ethoxymethylideneamino derivative **32**. Compound **32** when react with hydrazine hydrate, the naphtho[2`:1`:5,6]pyrano[2,3-*d*]pyrimidine derivative **33** was obtained, (Scheme 11). Interaction of compound **33** with triethyl orthoformate or formic acid afforded the naphtha

[2`,1`:5,6]pyrano[3,2-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidine derivative **34a**, while with acetic acid or acetyl chloride the respective 2-methyl derivative **34b** was obtained. Reaction of compound **33** with chloroacetyl chloride and trichloroaceto nitrile at reflux yielding the corresponding 2-chloromethyl **34c** and 2-trichloromethyl **34d** derivative, respectively, while with ethyl cyanoacetate and benzoyl chloride afforded 2-cyano methyl **34e** and 2-phenyl **34f** derivative was obtained. Treatment of compound **33** with diethyl oxalate in ethanol at reflux yielded the 2-ethoxycarbonyl derivative **34g**, respectively, (Scheme 11).



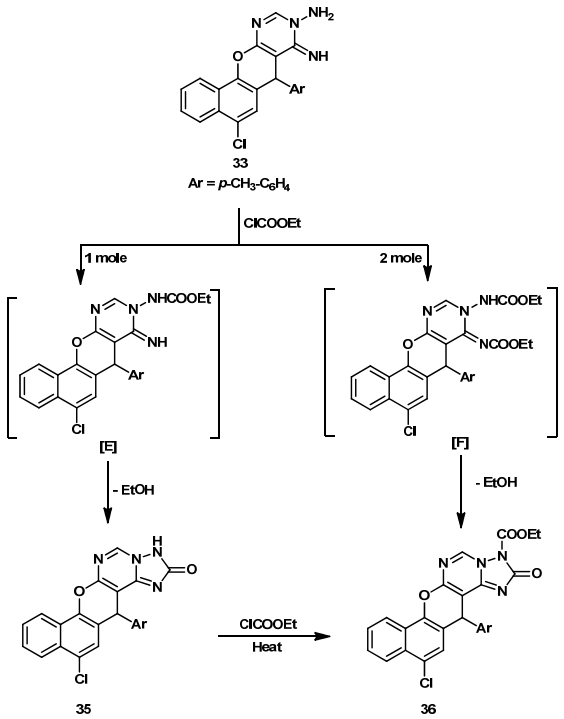
Scheme 11

Treatment of compound **33** with ethyl chloroformate (1 mole) in dry benzene afforded a 1:1 adduct **35**, while heating of compound **33** with ethyl chloroformate (2 moles) under reflux for 3 h yielded a 1:2 adduct, **36**.

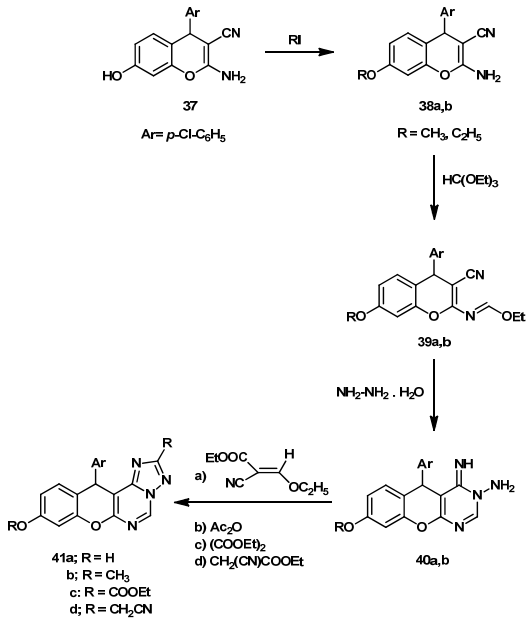
The formation of compound **35** is assumed to proceed via interaction of compound **33** with ethyl chloroformate with elimination of HCl to yield [**E**] ,which then cyclizes into compound **35** with elimination of ethanol. However, compound **36** is assumed to be obtained via formation of a *bis*(ethoxy carbonyl) derivative [**F**], which cyclizes into compound **36** with elimination of ethanol (Scheme 12).

2.7. Synthesis from 4H-chromene derivatives [39]

Alkylation of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4*H*-chromene-3- carbonitrile (**37**) using methyl or ethyl iodide afford 2-amino-4-(4-chlorophenyl)-7-methoxy-4*H*-chromene-3-carbonitrile (**38a**), and 2-amino-4-(4-chlorophenyl)-7-ethoxy-4*H*-chromene-3-carbonitrile (**38b**). Compounds **38a** and **38b** were reacted with triethyl orthoformate to give formimidate, **39a** and **39b** Interaction of compound **39a** and **39b** with equimolar amount of hydrazine hydrate in absolute ethanol at ambient temperature gave the key intermediates pyranopyrimidine derivatives **40a**,**b** Reaction of compound **40a**,**b** with triethyl orthoformate or ethyl ethoxymethylene cyanoacetate afforded pyranotriazolopyrimidines, **41a**,**b** While treatment of compounds **40a**,**b** with acetic anhydride or acetoacetone gave the corresponding pyranotriazolo pyrimidines **42a**,**b** and reaction of compounds **40a**,**b** with diethyl oxalate gave the corresponding pyrano triazolo pyrimidines **43a**,**b**. Treating compounds **40a**,**b** with equimolar amount of chloro acid chloride derivatives in dioxane containing catalytic amount of triethylamine afford triazolo derivatives **45a-d** (Scheme 13).

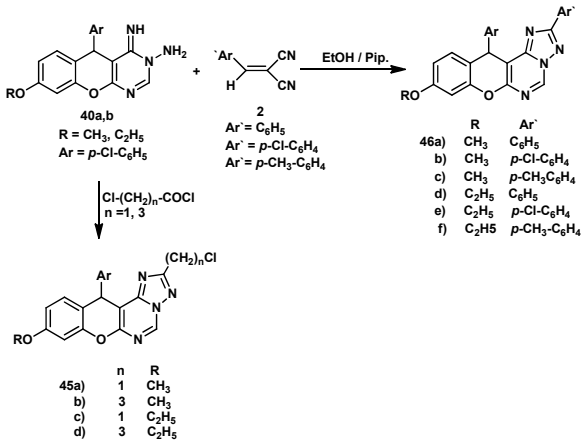


Scheme 12



Scheme 13

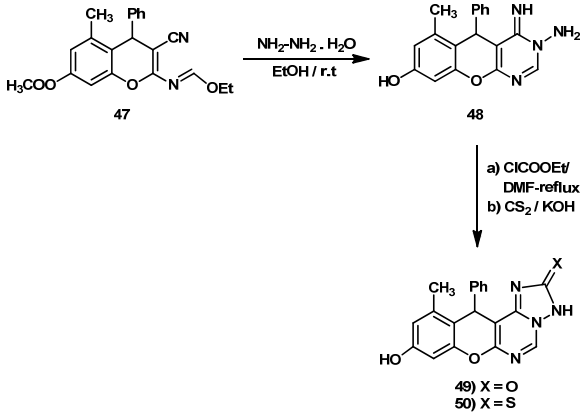
Compounds triazolo-pyrimidines **46a-f** were prepared from the interaction of the key intermediates **40a**,**b** with different arylidene malononitriles **2** in the presence of piperidine under reflux in absolute ethanol (Scheme 14).



Scheme 14

2.8. Chromeno pyrimidine [40]

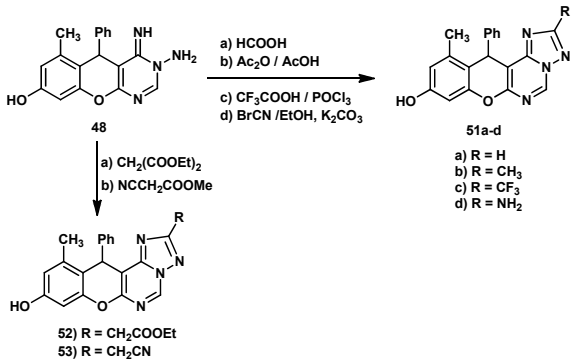
The condensation between iminoether **47** and hydrazine hydrate in ethanol at room temperature afforded the pyimidines **48** in 61% yield. The synthesis of triazol-2-one derivative **49** could be accomplished through the interaction of the aminopyrimidine **48** and ethyl chloroformate, in anhydrous DMF at reflux temperature for 1 h and resulted in 69% yield. Treatment of compound **48** with carbon disulfide in an alcoholic solution of potassium hydroxide at reflux gave the triazol-2-thione, **50** (Scheme 15).



Scheme 15

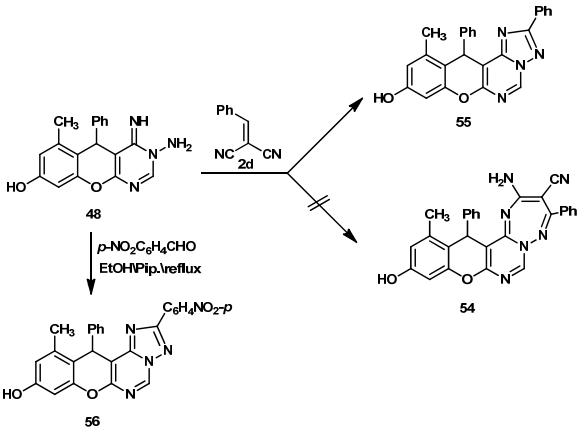
The condensation between the aminopyrimidine **48** and different carboxylic acid such as formic acid, acetic anhydride and trifluroacetic acid under reflux temperature readily, after aqueous workup, furnished the expected triazole products **51a-c**.

While compound **48** react with cyanogen bromide in absolute ethanol containing anhydrous potassium carbonate under reflux afforded 2-amino-triazolo[1,5-c]pyrimidin-9-ol, **51d**. Reaction between compound **48** and diethyl malonate was conducted in DMF under reflux conditions; elimination of water and ethanol occurred and gave the acetate derivatives **52**, while condensation of compound **48** with methylcyano acetate in refluxing ethanol resulted in formation of the acetonitrile derivative **53** (Scheme 16).



Scheme 16

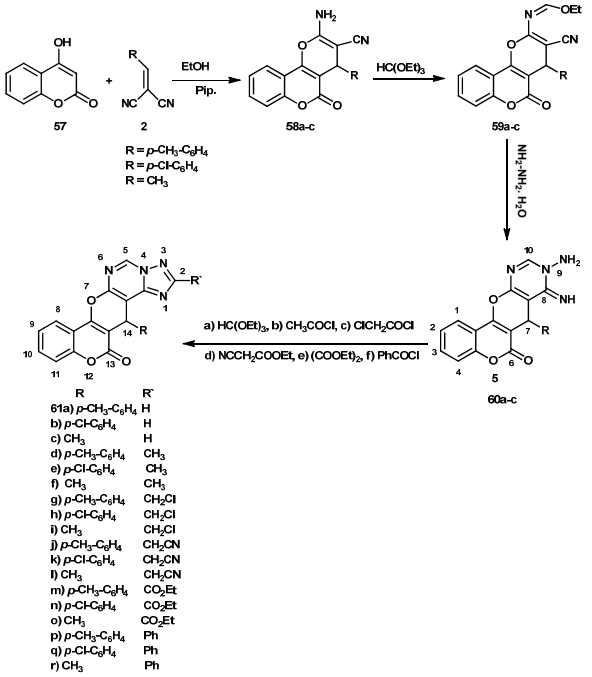
Interaction between the aminopyrimidine **48** and benzylidene-malononitrile **2d** in a basic medium was expected to give compound **54**, but instead led interestingly to compound **55** which formed when the reactants were mixed together with few drops of acetone and left at room temperature for 30 min. The condensation between aminopyrimidine compound **48** and *p*-nitrobenzaldehyde in ethanolic piperidine at reflux temperature, furnish the triazolopyrimidine **56** (Scheme 17).



Scheme 17

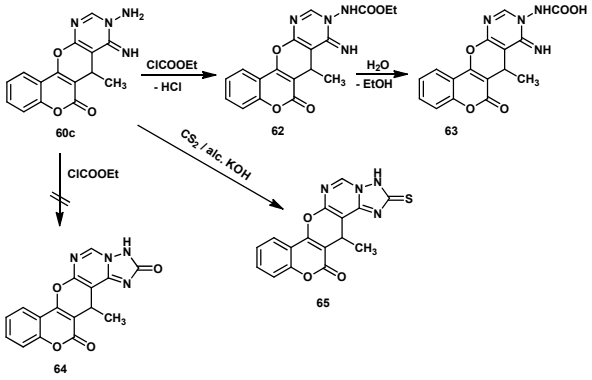
2.9. Synthesis from 4-hydroxy coumarin [41-44]

This synthesis involves Michael cycloaddition reaction of the readily available 4-hydroxycoumarin (**57**) with α-cyano crotononitrile (**2a**,**b** and **e**) in ethanolic piperidine to afforded 2-amino-3-cyano-4-(*p*-tolyl/*p*-chlorophenyl or methyl)-4*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-5-ones (**58a-c**). Treatment of 2-amino-4-(*p*-tolyl/*p*-chlorophenyl or methyl)-3-cyano-4*H*,5*H*-pyrano[3,2-c][1]benzopyran-5-ones (**58a-c**) with triethyl *ortho*-formate in acetic anhydride at reflux afforded 4-(*p*-tolyl/*p*-chlorophenyl or methyl)-3cyano-2-ethoxymethylene amino-4*H*,5*H*-pyrano[3,2-*c*][1]benzo-pyran-5-ones (**59a-c**). Hydrazinolysis of the compound **59** in ethanol at room temperature yielded 9-amino-7-(*p*-tolyl/*p*-chlorophenyl or methyl)-8 ,9-dihydro-8-imino-6*H*, 7*H*-[1]benzopyrano[-3`, 4`: 5,6]-pyrano[2,3-*d*]pyrimidine-6-ones (**60a-c**) (Scheme 18). Refluxing compound **60a-c** with triethyl orthoformate afforded the [1,2,4]triazolo[1,5-*c*]pyrimidines, **61a-c**, while with acetyl chloride or chloroacetyl chloride compounds **61d-f** and **61g-i** were formed, respectively. Reaction of compound **60a-c** with ethyl cyanoacetate and diethyl oxalate afforded the hetero cycles **61j-l** and **61m-o**, respectively, while with benzoyl chloride the 2-phenyl derivatives **61p-r** was obtained (Scheme 18).



Scheme 18

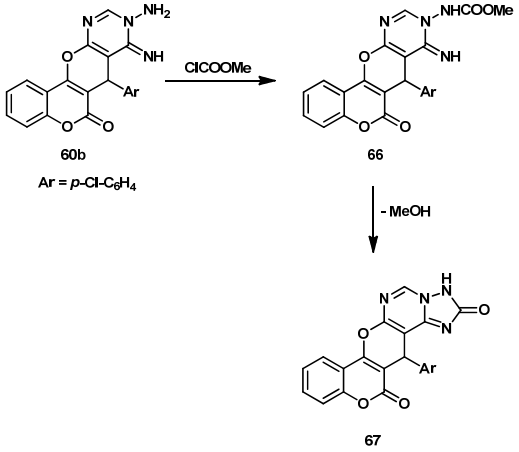
The reaction of compound **60c** with ethyl chloroformate, through nucleophilic displacement followed by spontaneous hydrolysis of the ester intermediate **62**, led to the corresponding carbamic acid derivative **63**, instead of compound **64**. While compound **60c** was reacted with alcoholic CS_2/alc.KOH to give 14-methyl-2,3-dihydro-13-oxo-2*H*,13*H*,14*H*-[1]benzo pyrano-[3`, 4`:5, 6]-pyrano[3, 2-*e*][1,2,4]triazolo [1,5-*c*]-pyrimidine-2-thione (**65**), respectively, (Scheme 19).



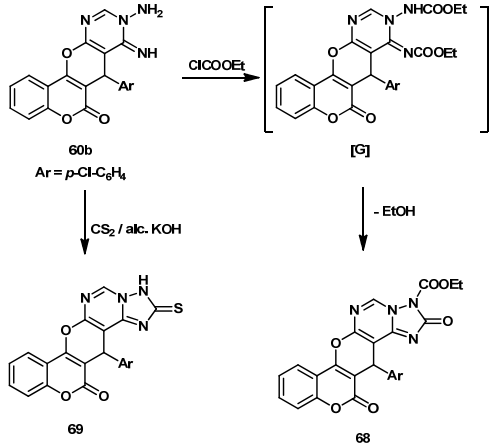
Scheme 19

When compound **60b** was treated with methyl chloro formate for 30 min, the methoxycarbonyl derivative **66** was formed, while heating of compound **60b** with methyl chloroformate under reflux for 6 h afforded [1,2,4]triazolo[1,5-*c*]pyrimidine **67** via elimination of methanol from compound **67** (Scheme 20).

When compound **60b** was treated with ethyl chloroformate (2 moles) an intermediate *bis*(ethoxycarbonyl) derivative [**G**] was formed, which eliminated ethanol to furnish the ester **68**. Treatment of compound **64** with carbon disulfide in alcoholic potassium hydroxide solution gave the 2-thione derivative **69** (Scheme 21).



Scheme 20



Scheme 21

2.10. Synthesis from α-tetralone [45]

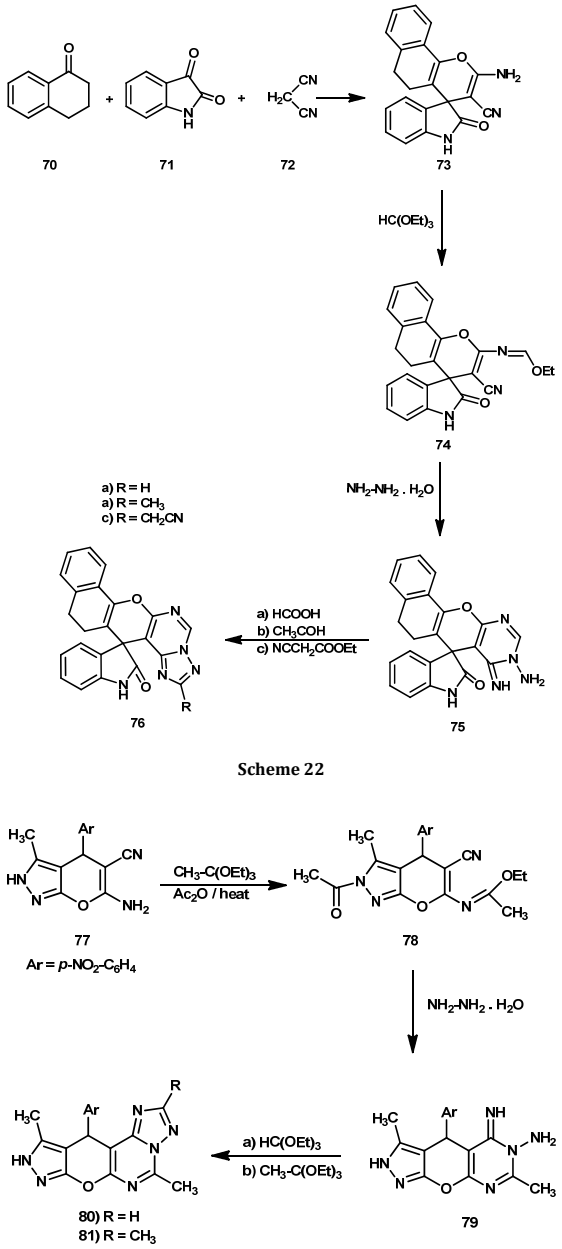
Synthesis of 2-amino3-cyano-5,6-dihydro-spiro[benzo(*h*) chromene-4(4*H*),3`(3*H*)indol]-2`-[1*H*]-one (**73**), was performed by treating of a mixture of α-tetralone (**70**) with 1*H*-indole-2,3-dione (**71**) and malononitrile (**72**) as a ternary mixture. Heating under reflux **73** with triethyl orthoformate gave the corresponding ethyl methanimidate derivative **74**. Hydrazine hydrate with compound **74** gave the corresponding amino imino derivatives **75**. Refluxing of imino derivative **75** with formic or acetic acid gives the corresponding pyranotriazolo pyrimidine derivatives **76a**,**b**.

Refluxing of compound **75** with ethyl cyanoacetate in dioxane affords the pyranotriazolopyrimidine derivative **76c** (Scheme 22).

2.11. Synthesis form 3-methyl-pyranopyrazole derivative [46]

6-Amino-2, 4-dihydro-3-methyl-4-(*p*-nitrophenyl)pyrano [2,3-*c*]pyrazole-5-carbonitrile (**77**) [47,48], as the key compound for this study and for further syntheses of other fused heterocyclic compounds, was heated at reflux temperature with an equimolar amount of triethyl orthoacetate in the presence of acetic anhydride to give a major product which could be assigned the structure of ethyl *N*-[2-acetyl-5-cyano-3-methyl-4-(*p*-nitrophenyl)-2,4-dihydropyrano[2,3-*c*] pyrazol-6-yl]ethanimidate (**78**).

When a solution of compound **78**, in dry benzene, was stirred with hydrazine hydrate, it afforded 6-amino-3,7-dimethyl-5-imino-4-(*p*-nitrophenyl)2,4,5, 6-tetrahydropyrazolo [4`,3`:5,6]pyrano[2,3-*d*]pyrimidine (**79**). When compound **79** was refluxed with triethyl orthoformate, it gave 5,10-dimethyl-11-(*p*-nitrophenyl)-9,11-dihydropyrazolo [4`,3`:5,6]pyrano[3, 2-e][1,2,4]triazolo[1,5-c] pyrimidine (**80**). Heating of compound **79** with triethyl orthoacetate at reflux temperature, gave 2,5,10-trimethyl-11-(*p*-nitrophenyl)-9,11-dihydro-pyra zolo[4`,3`:5,6]-pyrano[3,2e][1,2,4]triazolo-[1,5-*c*] pyrimidine (**81**), respectively, (Scheme 23).



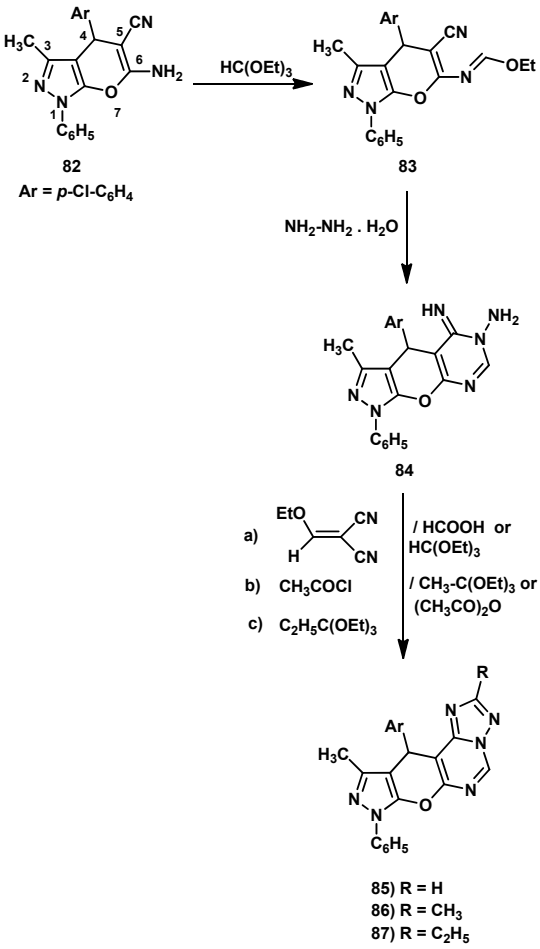
Scheme 22

Scheme 23

2.12. Synthesis from 1-phenyl-3-methyl-pyranopyrazole derivative [49]

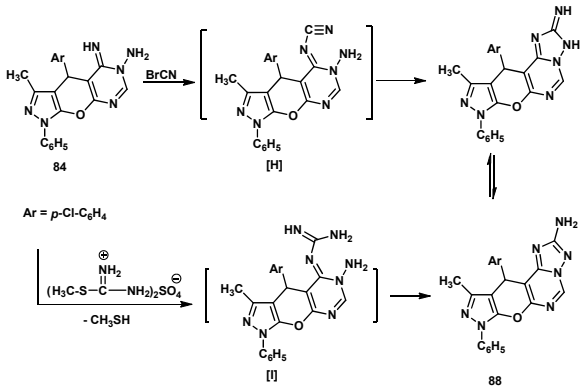
Reaction of 6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-methyl-1-phenyl-pyrano[2,3-*c*]pyrazole-5-carbonitrile (**82**) with triethyl *ortho*-formate in acetic anhydride afforded methanimidate derivative (**83**), hydrazinolysis of compound **83** in methanol at room temperature afforded 1-phenyl-4-(*p*-chlorophenyl)pyrazolo[4`,3`:5,6]pyrano[2,3,-d]pyrimidine (**84**). Compound **84**, considered as a key intermediate to prepare fused heterocycles as triazolo[1,5-*c*]pyrimidines which may possess pharmacological properties.

The cyclo-condensation of compound **84** with the appropriate carboxylic acid derivatives was performed by heating with an excess of neat formic acid, triethyl orthoformate or ethoxymethylene malononitrile afforded 8,11-dihydro-10-methyl-8-phenyl-11-(p-chlorophenyl)[4`,3`:5,6] pyrano-[3, 2-*e*][1, 2, 4]triazolo[1, 5-*c*]pyrimidine (**85**). When triethyl orthoacetate was used in the above cyclocondensation 3,10-dimethyl-8,11-dihydro-8-phenyl-11-(p-chlorophenyl) [4`,3`:5,6]-pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**86**) was produced. Compound **86** was also produced via the reaction of compound **84** with acetic anhydride as carboxylic acid anhydride and acetyl chloride as acid chloride. Moreover, the interaction of triethyl orthopropionate with compound **84** afforded 3-ethyl-8,11-dihydro-10-methyl-8-phenyl-11-(*p*-chlorophenyl)-[4`,3`:5,6]pyrano[3,2-e][1,2,4]triazolo[1, 5-c] pyrimidine (**87**), respectively, (Scheme 24).



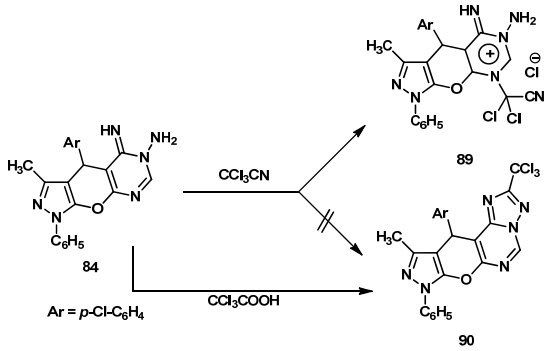
Scheme 24

In the case of involving the condensation of compound **84** with cyanogens bromide and S-methyl isothiourea sulfate, the intermediate formed might bear a cyanimino [**H**] or guanidine function [**I**]. These intermediates [**H** and **I**] were cyclized in an alkaline medium to give the target molecule **88** as expected (Scheme 25).



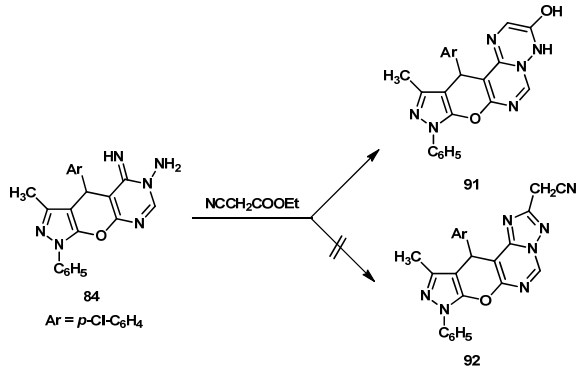
Scheme 25

The formation of 2-trichloromethyl 10-methyl-8,11-dihydro-8-phenyl-11-(*p*-chlorophenyl)-[4`, 3`:5, 6]pyrano[3, 2-*e*][1,2,4]triazolo[1,5-c]- pyrimidine (**90**) via the interaction of compound **84** with trichloroacetic acid in the presence of phosphoryl chloride under reflux, or trichloro-acetonitrile in absence of solvent under reflux was unsuccessful. But The pyrimidinium salt **89** only isolable product (Scheme 26).



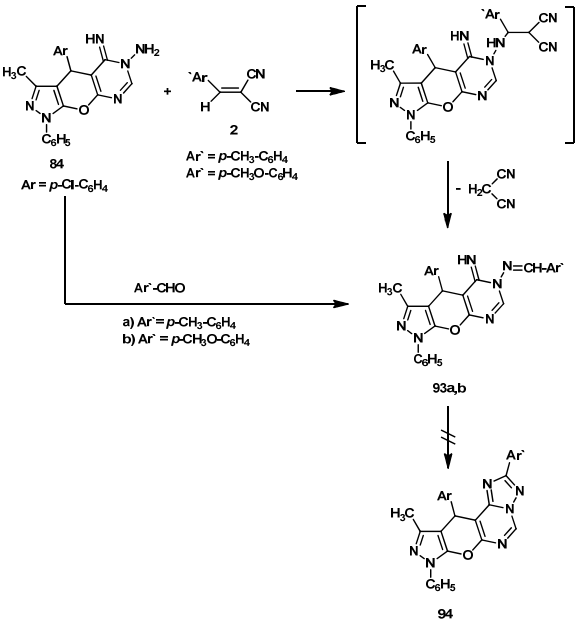
Scheme 26

The activity of compound **84** towards active methylene compounds, such as ethyl cyanoacetate was studied, to give 9,12-dihydro-3-hydroxyl-11-methyl-8-phenyl-12-(*p*-chloro phenyl)-2*H*-pyrazolo[4`,3`:5,6]pyrano-[2`,3`:5,6]pyrimido[1,6-*b*][1,2,4]triazine (**91**), but non-isolable triazolopyrimidine **92** (Scheme 27).



Scheme 27

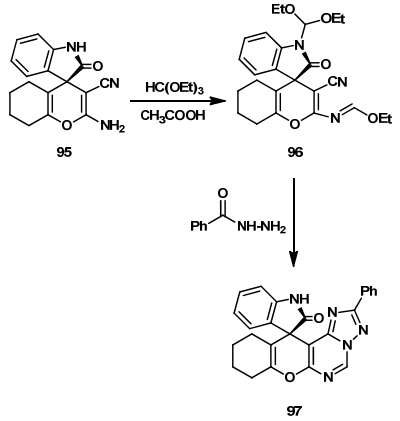
Compound **84**, when reacted with *β*-cyanocinnamonitrile derivatives, namly *p*-toylmalononitrile and *p*-anisylmalono nitrile respectively, in dioxane under reflux and in the presence of a catalytic amount of piperidine failed to afford pyrano triazolopyrimidine derivatives **94** and pyranopyrimidine derivatives **93a**,**b**, were isolable products, via the formation of 1:1 adduct followed by the loss of malononitrile. Also the same product **93a**,**b** was isolate from the reaction of compound **84** with *p*-tolulaldehyde and *p*-anisaldehyde, respectively, (Scheme 28).



Scheme 28

2.13. Synthesis from spirooxindolopyran [50]

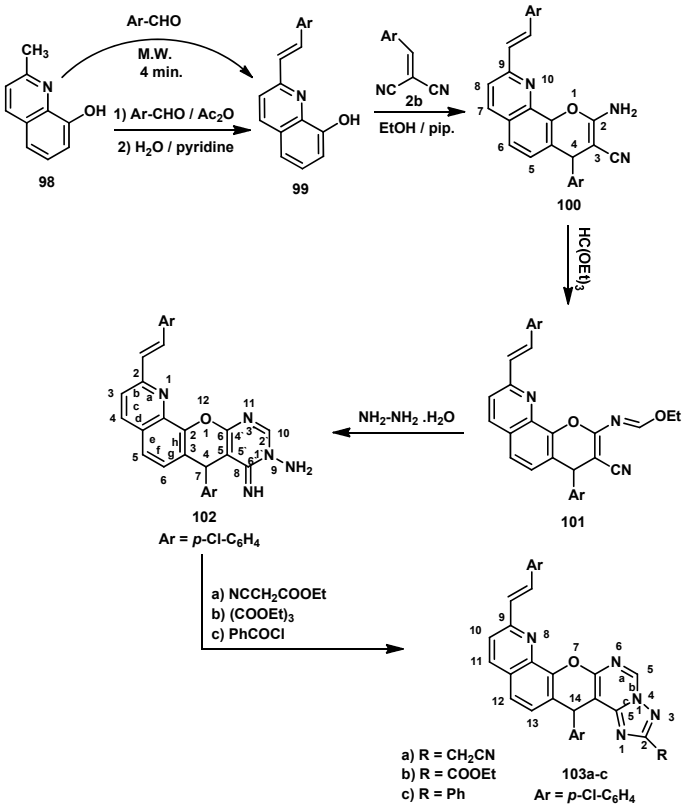
The reaction of spirooxindolopyran **95** with an excess of orthoformic ester leads to the ethoxymethyleneaminonitrile **96**, which enters into cascade heterocyclization with benzo hydrazide and subsequent closure of the pyrimidine and triazole rings, leading to a high yield of 2'-oxo-2-phenyl-1', 2', 5, 6, 7, 8-hexahydrospiro[1-benzopyrano[3, 2-*e*][1, 2, 4]triazolo [1,5-*c*]pyrimidine-2,3'-[3*H*]indole] (**97**), respectively, (Scheme 29).



Scheme 29

2.14. Synthesis from 8-hydroxy-2-methylquinoline [51,52]

Condensation of 8-hydroxy-2-methylquinoline (**98**) with *p*-chloro-benzaldehyde in acetic anhydride under reflux or microwave irradiation afforded (*E*)-2-(4-chlorostyryl)-8-hydroxyquinoline (**99**).



Scheme 30

The reaction of (*E*)-2-(4-chlorostyryl)-8-hydroxyquinoline (**99**) with *α*-cyano-*p*-chloro-cinnamonitrile (**2b**) in ethanolic piperidine under reflux afforded (*E*)-2-amino-4-(4-chlorophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]-quino line-3-carbonitrile (**100**). Compound **100** was subjected for further reactions to produce fused heterotetracyclic or hetero pentacyclic systems incorporating pyrimidine or pyrimido [1,2,4]triazolo nuclei in addition to pyranoquinoline moiety. Treatment of compound **100** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding (*E*)-2-ethoxy methyleneamino-4-(4-chlorophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**101**), while reaction with hydrazine hydrate gave the cyclic addition product (*E*)-9-amino-7-(4-chlorophenyl)-2-(4-chlorostyryl)-8-imino-8,9-di hydro-7*H*-pyrimido[4',5': 6,5]pyrano[3,2-*h*]quinoline (**102**) (Scheme 30).

The imino compound 102 proved to be a useful intermediate for the synthesis of a variety of 2-substituted-14*H*-pyrimido[4', 5' : 6, 5]pyrano-[3, 2-*h*][1, 2, 4]triazolo[1, 5-*c*]quinoline derivatives. Thus, treatment of compound **102** with ethyl cyanoacetate and with diethyl oxalate in refluxing absolute ethanol afforded 14-(4-chlorophenyl)-9-(4-chloro tyryl)-2-cyanomethyl-14*H*-pyrimido[4', 5':6, 5]pyrano[3, 2-*h*]-[1,2,4]triazolo[1,5-*c*]quinoline (**103a**) and ethyl 14-(4-chloro phenyl)-9-(4-chlorotyryl)-14*H*-pyrimido[4', 5':6, 5]pyrano[3, 2-*h*][1,2,4]triazolo[1,5-*c*]-quinoline-2-carboxylate (**103b**), respectively. Arylation of compound **102** with benzoyl chloride in refluxing dry benzene proceeded readily to give the 2-phenyl derivative **103c**, respectively, (Scheme 30).

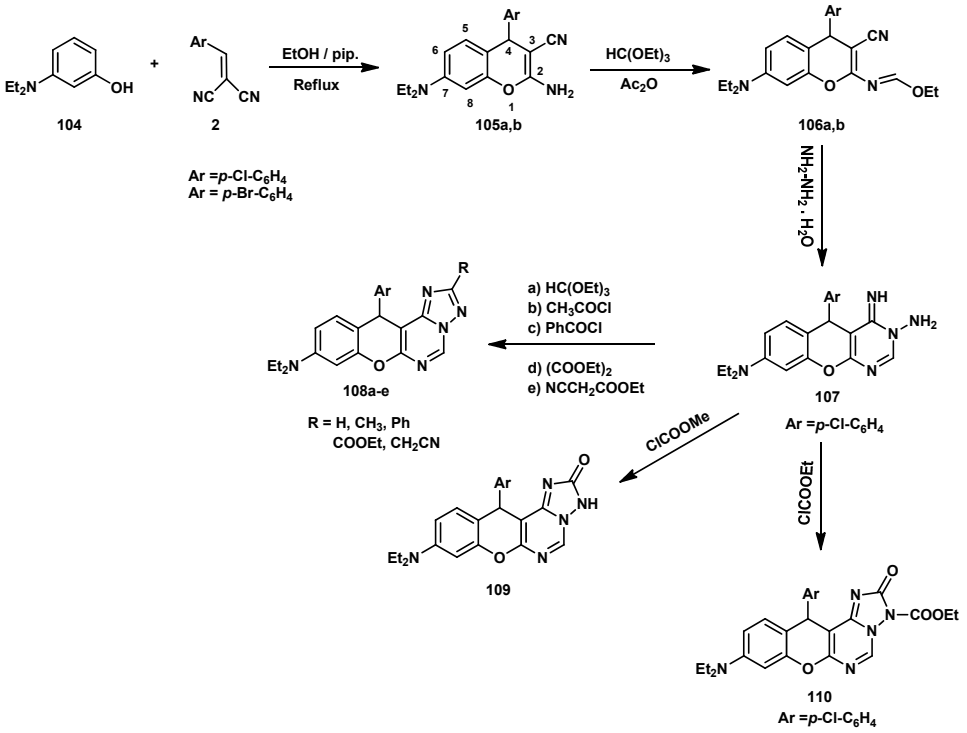
2.15. Synthesis from 3-N,N-diethylaminophenol [53,54]

Treatment of 3-*N*,*N*-diethylaminophenol (**104**) with various substituted α-cyanocinnamonitriles (**2b**,**c**) in ethanol and piperidine afforded 2-amino 4-(4-chloro/bromophenyl)-7-(diethylamino)-coumarin-3-carbonitrile (**105a**,**b**). Treatment of **105a**,**b** with triethyl *ortho*-formate in acetic anhydride at reflux gave the corresponding 4-(4-chloro/bromophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4*H*-chromene-3-carbonitrile (**106a**,**b**). Hydrazinolysis of compound **106a** in ethanol at room temperature afforded.

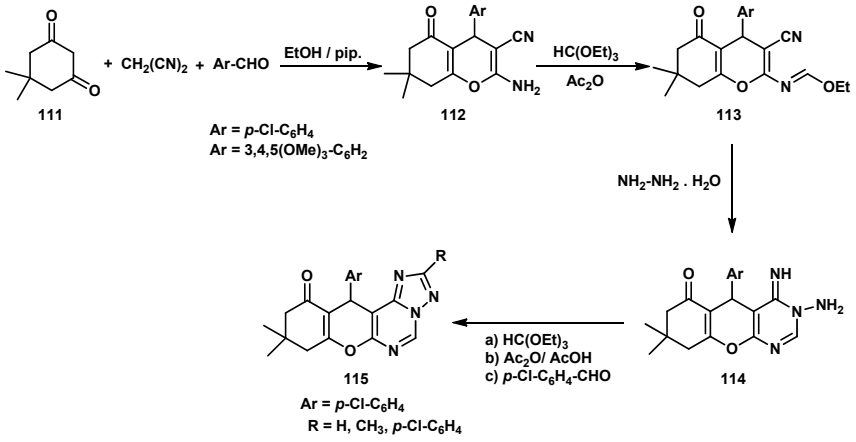
The aminoimino derivatives 3-amino-5-(4-chloro/bromo phenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5*H*-chromeno [2,3-*d*]pyrimidine (**107**). Reactions of compound **107** with carboxylic acid derivatives afforded triazolopyrimidine derivatives 108. When compound 107 was treated with methyl chloroformate afforded 2-oxo-triazolopyrimidine **109** via elimination of methanol. While treatment compound **107** with ethyl chloroformate an eliminated ethanol to furnish the ester **110** (Scheme 31).

2.16. Synthesis from 5, 5-dimethyl-1,3-cyclohexanedione [55]

One pot multicomponent, condensation reaction of *p*-chlorobenzaldehyde or 3,4,5 trimethoxy benzaldehyde, malono nitrile and 5,5-dimethyl-1,3-cyclohexanedione (**111**) in ethanol and piperidine afforded 4*H*-chromeno-3-carbonitrile (**112**). Treatment of compound **112** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding ethoxy methyleneamino-4*H*-chromene-3-carbonitrile, **113**. Hydrazinolysis of compound **113** in ethanol at room temperature afforded the aminoimino derivatives **114**. Reactions of compound **114** with triethyl orthoformate, acetic anhydride, and *p*-chlorobenzaldehyde in pyridine afforded triazolo-pyrimidine derivatives **115** (Scheme 32).



Scheme 31



Scheme 32

3. Reactions of pyranotriazolopyrimidines with

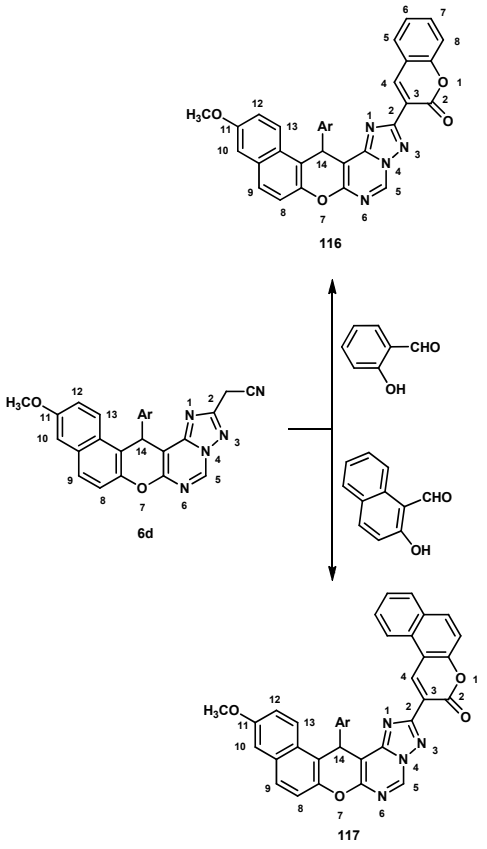
3.1. Phenolic aldehydes [25,56]

Reaction of 11-methoxy-14-(*p*-tolyl)-14*H*-naphtho[2,1-*b*]pyrano[3,2-*e*][1, 2, 3]triazol[1,5-*c*]pyrimidine-2-ethanenitrile (**6d**) with phenolic aldehydes such as salicylaldehyde and or 2-hydroxy-1-naphthaldehyde in dioxane refluxed for 3 h, afforded the corresponding 2-(coumarin-3-yl)-11-methoy-14-(*p*-tolyl)-14*H*-naphtho[2,1-*b*]pyrano[3, 2-*e*][1,2,4]triazolo-[1, 5-*c*]pyrimidine (**116**) and 2-(benzo-5:6-coumarin-3-yl)-11-methoy-14-(*p*-tolyl)-14*H*-naphtho[2, 1-*b*]pyrano[3, 2-*e*][1, 2, 4] triazolo[1,5-*c*]pyrimidine (**117**), respectively (Scheme 33).

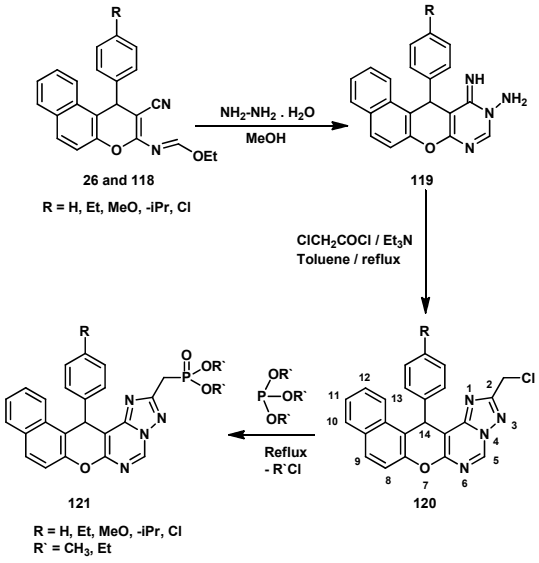
3.2. Trialkyl phosphite [57]

Synthesis a series of α-functionalized imino ethers **26** and **118** have subjected them to reaction with aqueous solution of hydrazine in methanol at 0 °C to give the naphthopyrano triazolopyrimidines **119**. The key intermediate, 2-chloro methyl-naphthopyranotriazolopyrimidines **120**, was prepared according to the literature procedure[31], through a cyclization reaction of binucleophiles **119** using chloroacetyl chloride.

The formation of naphthopyranotriazolopyrimidines phosphornate **121**, in good yield was carried out via Michaelis-Arbuzov rearrangement (Arbusov reaction) of naphthopyrano triazolopyrimidines chloride **120** with trialkyl phosphate (Scheme 34).



Scheme 33



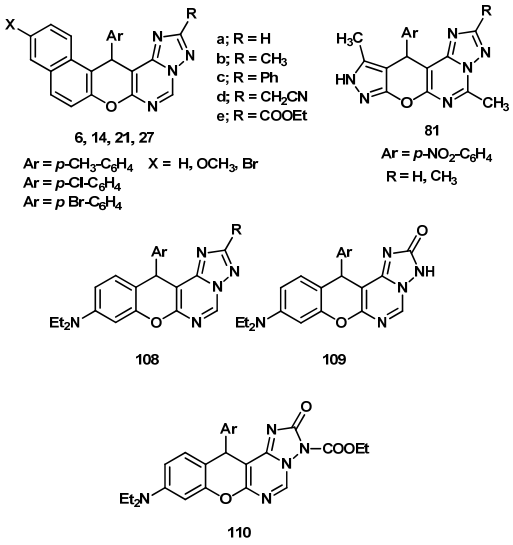
Scheme 34

4. Applications of pyrano triazolo pyrimidines

The chemistry of pyran and fused pyran derivatives has attracted many researchers due to their biological activities and their potential applications as pharmacological agents. Several derivatives of the pyran exhibit antimicrobial activity [29,53,58], growth stimulating effects [59], antifungal and plant growth regulation effects [60], antitumor activity [61], central nervous system (CNS) activity [62] and hypotensive effect [63]. Moreover pyran derivatives are well known for antihistaminic activity [64], platelet anti-aggregating activity and local anaesthetic activity [65-67], antiallergenic effect [68], antidepressant effect [69] and as anti-proliferation agents [70,71]

4.1. Potent antibacterial activities

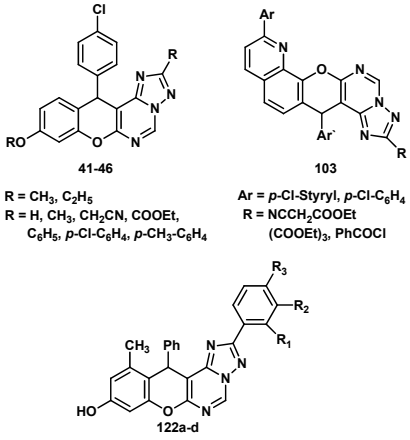
Potent antibacterial activities [25-27,30,32,46,53,54] were found naphthopyranotriazolopyrimidine derivatives (**6**,**14**,**21** and **27**), pyrazolopyranotriazolopyrimidines (**81**) and chrome notriazolopyrimidines (**108-110**) (Scheme 35).



Scheme 35

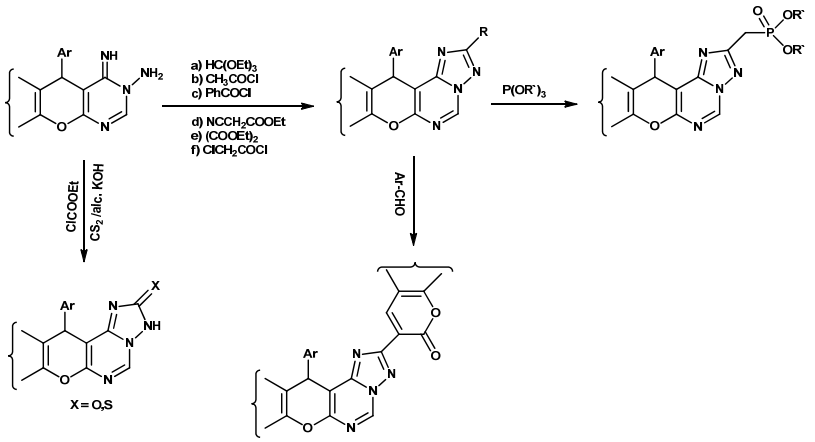
4.2. Antitumor activities

Chromenotriazolopyrimidines (**41-46**) and pyrimido pyranotriazolo-quinolines (**103**, **122**) have antitumor (Scheme 36) [39,51,52,72].



122a-d	R_1	R_2	R_3
a	H	H	Cl
b	Cl	H	H
c	Cl	H	Cl
d	H	NO_2	H

Scheme 36



Scheme 40

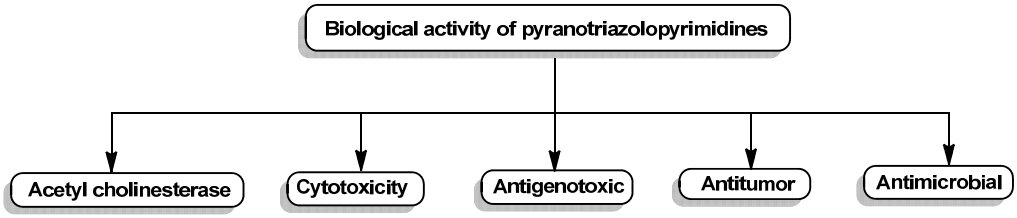
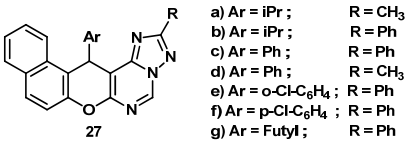


Figure 2. Biological activity of pyranotriazolopyrimidines.

4.3. Anti-genotoxic activities

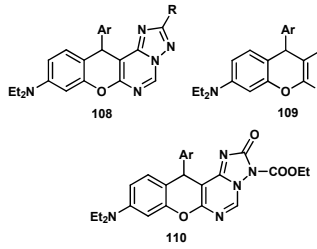
Naphthopyranotriazolopyrimidine derivatives (**27a-g**) have anti-genotoxic activity (Scheme 37) [32].



Scheme 37

4.4. Cytoxicity activities

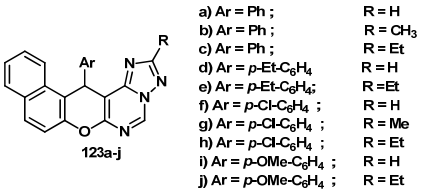
Chromenotriazolopyrimidines (**108-110**) have cytoxicity activities (Scheme 38) [54].



Scheme 38

4.5. Acetyl cholinesterase inhibition

Naphthopyranotriazolopyrimidine derivatives (**123**) have acetyl cholinesterase, also known as AChE or acetylhydrolase inhibition (Scheme 39) [73].



Scheme 39

5. Conclusions

The present review has outlined the synthesis of pyranotriazolo-pyrimidine derivatives by using key intermediate aminoimino pyranopyrimidines and appropriate carboxylic acid derivatives (Scheme 40). Reaction of 2-aceto nitrile pyrano triazolo pyrimidines with phenolic aldehydes afforded coumarin derivatives. Also reaction of 2-chloromethyl-naphthopyranotriazolopyrimidines with trialkyl phosphite afforded naphthopyranotriazolopyrimidine dialkyl phosphonates. Pyranotriazolopyrimidine derivatives have been reported to furnish interesting biological properties (Figure 2).

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