Synthesis, reactions and applications of pyranotriazolopyrimidines

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ABSTRACT

This review deals with synthesis, reactions and their applications of pyranotriazolopyrimidines. 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.

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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-proliferation 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-α]pyrimidine (I), 1,2,4-triazolo[1,5-c]pyrimidine (II), 1,2,4-triazolo[4,3-c]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-α]-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-c]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-α]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].

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

2. Synthesis of pyrano triazolo pyrimidine derivatives

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

Condensation of 6-methoxy-2-naphthol (I) with α-cyanocinnamionitriles (2a-f) afforded the corresponding 2-amino-4-(aryl)-7-methoxy-4H-naphtho[2,1-b]pyran-3-carbonitriles, 3a-c, ethoxymethylene derivatives (4a-c) was obtained by refluxing compounds 2-amino-4-(aryl)-7-methoxy-4H-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)-12H-naphtho [2, 1-b] pyrano-[2,3-d]pyrimidine derivatives 5a-c in good yield. Reaction of aminomino derivatives 5a-c with formic acid or triethyl ortho-formate afforded the corresponding pyrano triazolo-pyrimidine derivative 6a. Also compounds 5a-c reacted with acetyl chloride and benzoyl chloride gave the corresponding 11-methoxy-2-methylphenyl-14-(aryl)-14H-naphtho[2,1-b]-pyrano[2,3-e][1,2,4]triazolo[1,5-c]pyrimidines (6b,c), while cyclo-condensation of 5a-e with ethyl cyanacetate or diethyl oxalate afforded the corresponding 2-cyanomethyl and 2-ethoxycarbonyl derivatives 6d and 6e, respectively (Scheme 1).

While treatment of 10-amino-10,11-dihydro-11-imino-3-methoxy-12-(p-chloro/bromophenyl)-12H-naphtho [2, 1-b] pyrano-[2,3-d] pyrimidine (5b,c) with ethylichloroformate in dry benzene afforded 11-methoxy-14-(p-chloro/bromophenyl)-2-oxo-2H,3H,14H-naphtho[2,1-b]-pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines (8a,b). Reaction of compound 5b,c with Cs2/alc. KOH gave triazolo-2-thiones (8c,d), respectively, (Scheme 3).

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

Condensation of various substituted α-cyanocinnamimates 2a,c with 6-bromo-2-naphthol (10) in ethanolic piperidine afforded the corresponding 2-amino-4-(aryl)-7-bromo-4H-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 ethoxymethylene 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)-14H-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)-14H-naphtho[2,1-b]-pyrano[2,3-e][1,2,4]triazolo[1,5-c]pyrimidines (14c,d) and 2-acetoxitrile-14-(p-tolyl or p-methoxyphenyl)-14H-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 triazolo-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
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 dilydriazolopyrimidine derivative 17 and non-isolate 14i, respectively, (Scheme 5).

2.3. Synthesis from 2-naphthol [30]


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

Reaction of 2-amino 4-aryl-3-cyano-4H-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-4H-naphtho[2,1-b]pyrans 19 and 23, respectively, (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 \( \text{N-tosylamino-1-aryl-1,12-dihydro-11H-naphthopyran} \) \( [2, 3-d] \) \( \text{pyrimidine} \) (24) (Scheme 8).

In the next step, condensed the \( \text{N-tosylaminonaphthapyrano}[2,3-d] \) pyrimidines 24, with an excess of triethyl orthoformate to give 14-arylated-14H-naphtho-[2,1-d]pyrano[3,2-e][1,2,4]triazolo[1,5-d]pyrimidines \( [25a-m] \). The formation of compounds 21a and 25a-m can be explained by a sequence of events via intermediates of type \( [C] \), formed in the reaction of \( \text{N1-tosylaminonaphthapyrano}[2,3-d] \) pyrimidines 24 with triethyl orthoformate, 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 \( \text{NH} \) 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 (\( \text{N2H2} \) group) on the imidic carbon and on the cyano function to yield amidic pyranogurimidines \( [D] \). In this case hydrazides react with iminoethers 26 like hydroxyamine, primary amines [36] and tosylhydrazine [37]. The intermediate \( [D] \) can be intra-

cyclisation via elimination of water to give pyrano triazolo-

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

The condensation of substituted benzylidenemalonitile (2a), with 4-chloro-1-naphthol (30) in the ethanolic piperidine afforded naphthopyran 31. Treatment of 2-amino-6-chloro-4-(\( n \)-tolyl)-4H-naphtho[1,2-b]pyrano-3-carbonitrile (31) with triethyl orthoformate in acetic acid at reflux gave the corresponding ethoxymethylidenemino derivative 32. Compound 32 when react with hydrazine hydrate, the naphthopyrano[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).

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(ethoxycarbonyl) 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-4H-chromene-3-carbonitrile (37) using methyl or ethyl iodide afforded 2-amino-4-(4-chlorophenyl)-7-methoxy-4H-chromene-3-carbonitrile (38a), and 2-amino-4-(4-chlorophenyl)-7-ethoxy-4H-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 triazole derivatives 45a-d (Scheme 13).

Scheme 11

Scheme 12

Scheme 13
Compounds triazole-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).

2.8. Chromeno pyrimidine [40]

The condensation between iminoether 47 and hydrazine hydrate in ethanol at room temperature afforded the pyrimidines 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).

Interaction between the aminopyrimidine 48 and benzyldiene-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).

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

This synthesis involves Michael cycloaddition reaction of the readily available 4-hydroxy coumarin (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)-4H5H-pyran-3,2-c[1]benzopyran-5-ones (58a-c). Treatment of 2-amino-4-(p-tolyl/p-chlorophenyl or methyl)-3-cyano-4H5H-pyran-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 amin-o-4H5H-pyran-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-6H,7H[1]benzopyranol-3', 4':5,6'-pyran[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]pyrimidinones 61a-c while with acetyl chloride or chloroacety1 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).
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 CS₂/alc.KOH to give 14-methyl-2,3-dihydro-13-oxo-2\(\text{H}\)14\(\text{H}\)-[1]benzo pyrano-[3', 4':5, 6']-pyrano[3, 2-\(\text{H}\)]pyrazole-6-carbonitrile \(\text{H}\) -, which could be assigned the structure of ethyl methanimidate derivative \(\text{H}\) (Scheme 19).

When compound 60b was treated with methyl chloroformate 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-2-thione \(\text{H}\) 67 via elimination of methanol from compound \(\text{H}\) 64

2.10. Synthesis from \(\alpha\)-tetralone \([45]\)

Synthesis of 2-amino3-cyano-5,6-dihydro-spiro[benzo(h) chromene-4(\(\text{H}\)\)]3(3\(\text{H}\))indol]-2'-\(\text{H}\)-one \(\text{H}\) 73, was performed by treating a mixture of \(\alpha\)-tetralone \(\text{H}\) with 1\(\text{H}\)-indole-2,3-dione \(\text{H}\) 71 and malononitrile \(\text{H}\) 72 as a ternary mixture. Heating under reflux \(\text{H}\) with triethyl orthoformate gave the corresponding ethyl methanimidate derivative \(\text{H}\). Hydrazine hydrate with compound \(\text{H}\) 74 gave the corresponding amino imino derivatives \(\text{H}\). Refluxing of imino derivative \(\text{H}\) with formic or acetic acid gives the corresponding pyranotriazolopyrimidine derivatives \(\text{H}\). Refluxing of compound \(\text{H}\) with ethyl cyanoacetate in dioctane affords the pyranotriazolopyrimidine derivative \(\text{H}\) \(\text{H}\) (Scheme 22).

2.11. Synthesis from 3-methyl-pyranopyrazole derivative \([46]\)

6-Amino-2, 4-dihydro-3-methyl-4-(\(p\)-nitrophenyl)pyrano[2,3-\(c\)]pyrazole-5-carbonitrile \(\text{H}\) [47,48], as the key compound for this study and for further synthesis of other fused heterocyclic compounds, was heated at reflux temperature with an equimolar amount of triethyl orthoformate in the presence of acetic anhydride to give a major product which could be assigned the structure of ethyl N-[2-acetyl-3-cyano-3-methyl-4-(\(p\)-nitrophenyl)-2,4-dihydropyrano[2,3-\(c\)]pyrazol-6-yl]ethanimidate \(\text{H}\).
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-tetrahydropyrano[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-dihydropyrazo [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-pyrazolo[4',3':5,6]-pyrano[3,2-e][1,2,4]triazolo[1,5-c] pyrimidine (81), respectively, (Scheme 23).

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).

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. In the case of involving the condensation of compound 84 with cyanogens bromide and S-methyl isothiourea sulfate, the intermediate formed might bear a cyanamino [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).
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].

The activity of compound 84 towards active methylene compounds, such as ethyl cyanocacetate was studied, to give 9,12-dihydro-3-hydroxyl-11-methyl-8-phenyl-12-(p-chlorophenyl)-2H-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).

Compound 84, when reacted with β-cyanoacinnammonitrile derivatives, namely p-tolylmalononitrile 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-tolualdehyde and p-anisaldehyde, respectively, [Scheme 28].

2.13. Synthesis from spirooxindolopyran [59]

The reaction of spirooxindolopyran 95 with an excess of orthofomeric 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-benzo]pyrano[3, 2-e][1, 2, 4]triazolo [1,5-c]pyrimidine-2,3'-[3H]indole] (97), respectively, [Scheme 29].


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).
The reaction of (E)-2-(4-chlorostyryl)-8-hydroxyquinoline (99) with α-cyano-p-chloro-cinnamoneitrile (2b) in ethanolic piperidine under reflux afforded (E)-2-amino-4-(4-chlorophenyl)-9-(4-chlorostyryl)-4H-pyran0[3,2-h]-quino line-3-carbonitrile (100). Compound 100 was subjected for further reactions to produce fused heterotetraycyclic 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 4-(4-chloro/bromophenyl)-7-(diethylamino)-coumarin-3-carbonitrile (105a-c). The aminoimino derivatives 3-amino-5-(4-chloro/bromo phenyl)-8-(diethylamino)-2-ethoxymethyleneamino-4H-pyrano[3,2-c]quinoline (102) with triethyl orthoformate, acetic anhydride afforded 2-oxo-triazolopyrimidine derivatives 106a in ethanol at room temperature afforded.

The imino compound 102 proved to be a useful intermediate for the synthesis of a variety of 2-substituted-14H-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-chlorostyryl)-2-cyanomethyl-14H-pyrimido[4', 5': 6, 5]pyrano[3, 2-h]-[1,2,4]triazolo[1,5-c]quinoline (103a) and ethyl 14-(4-chlorophenyl)-9-(4-chlorostyryl)-14H-pyrimido[4', 5': 6, 5]pyrano[3, 2-h][1,2,4]triazolo[1,5-c]quino line-2-carboxylate (103b), respectively. Aromatic condensation of 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-cyanocinnamoneitriles (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 orthoformate in acetic anhydride at reflux gave the corresponding 4-(4-chloro/bromophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4H-chromene-3-carbonitrile (106a,b). Hydrazinolysis of compound 106a in ethanol at room temperature afforded.

The aminoimino derivatives 3-amino-5-(4-chloro/bromophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5H-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, malononitrile and 5,5-dimethyl-1,3-cyclohexanedione (111) in ethanol and piperidine afforded 4H-chromeno-3-carbonitrile (112). Treatment of compound 112 with triethyl orthoformate in acetic anhydride at reflux gave the corresponding ethoxy methyleneamino-4H-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 triazolopyrimidine derivatives 115 (Scheme 32).
3. Reactions of pyranotriazolopyrimidines with

3.1. Phenolic aldehydes [25,56]


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 phosphonate 121, in good yield was carried out via Michaelis-Arbuzov rearrangement (Arbusov reaction) of naphthopyrano triazolopyrimidines chloride 120 with trialkyl phosphate (Scheme 34).
nerve 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 chromotriazolopyrimidines (108-110) (Scheme 35).

4.2. Antitumor activities

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

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
4.3. Anti-genotoxic activities

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

Scheme 37

4.4. Cytotoxicity activities

Chromenotriazolopyrimidines (108-110) have cytotoxicity 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 aminomino pyranopyrimidines and appropriate carboxylic acid derivatives (Scheme 40). Reaction of 2-acetonitrile pyrano triazolo pyrimidines with phenolic aldehydes afforded coumarin derivatives. Also reaction of 2-chloromethyl-naphthopyranotriazolopyrimidines with trialkyl phosphite afforded naphthopyranotriazolopyrimidine dialky phosphonates. Pyranotriazolopyrimidine derivatives have been reported to furnish interesting biological properties (Figure 2).

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