



An exhaustive compilation on chemistry of triazolopyrimidine: A journey through decades

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ABSTRACT

The triazolopyrimidine scaffold represents one of the privileged structure in chemistry, and there has been an increase in number of studies utilizing this scaffold and its derivatives. Optimization of synthetic protocols such as aza-Wittig reaction, [3 + 2] cycloaddition reaction along with previous methods including condensation with 1,3-dicarbonyl substrates and oxidation of aminopyrimidine Schiff bases have been performed to obtain desired triazolopyrimidines. The triazolopyrimidine ring has been extensively used as a template in medicinal chemistry for its diverse pharmacological properties. Several medicinally active molecules possessing triazolopyrimidine scaffold, either fused or coupled with other heterocycles, have been reported in the literature, highlighting the significance of this nucleus. Interestingly, the unique triazolopyrimidine scaffold also exhibits an impressive potential as a ligand for the synthesis of several metal complexes with significant biological potential. Literature provides enough evidence of exhaustive exploration of this scaffold as a ligand for the chelates of platinum, ruthenium and other metals. This review aims to be a comprehensive and general summary of the different triazolopyrimidine syntheses, their use as ligands for the synthesis and development of metal complexes as medicinal agents and their main biological activities.

1. Introduction

Heterocyclic compounds such as five- and six membered nitrogen containing aryl systems have had a considerable development due to disclosure of their varied effects in diverse domains of chemistry [1–3]. Triazolopyrimidine, a fused biaryl scaffold comprising of triazole and pyrimidine, forms one such heterocycle which is very attractive moiety from both theoretical and synthetic point of view. Such fused nitrogen heterocycles have been a center of attention for several decades now. Triazole, three nitrogen-containing five-membered aromatic ring system, fused with a pyrimidine, two nitrogen-containing six-membered aromatic ring system, form this class of fused heterocycles. On the basis of structural arrangement, 8 different isomers of triazolopyrimidine may exist in nature, as given in the literature (Fig. 1) [4–8].

This scaffold can be synthesized through well-known Biginelli reaction, providing access to a large diversity of derivatives. Other efficient multi-component strategies have also been proposed to enlarge the variety of triazolopyrimidine derivatives that could not be obtained by this classical method [9]. Since this moiety is rarely found in natural products, it represents an important synthetic intermediate.

Accordingly, several groups of investigators have developed mild conditions to improve the synthesis of a large variety of triazolopyrimidine derivatives. Triazolopyrimidine has been an important scaffold in drug discovery, mimicking a wide range of natural building blocks and being found to exhibit interesting diverse biological activities. The derivatives of the triazolopyrimidine ring system have been reported to possess medicinal attributes such as antitumor [10], antibacterial agents [11], etc. The objective of the present review is to summarize and discuss different synthetic routes of the triazolopyrimidines, as well as the significance of this moiety in developing other medicinal agents, and the potential applications of this structure as a ligand in different metal complexes.

2. Synthetic strategies for triazolopyrimidines

2.1. Annulation of triazole ring to 1,2-diaminopyrimidine

One of the earliest reports for the synthesis of the triazolopyrimidine nucleus was published in 1945. Roblin et al. synthesized triazolo[d]pyrimidine (Scheme 1) based analogs of adenine, guanine, xanthine,

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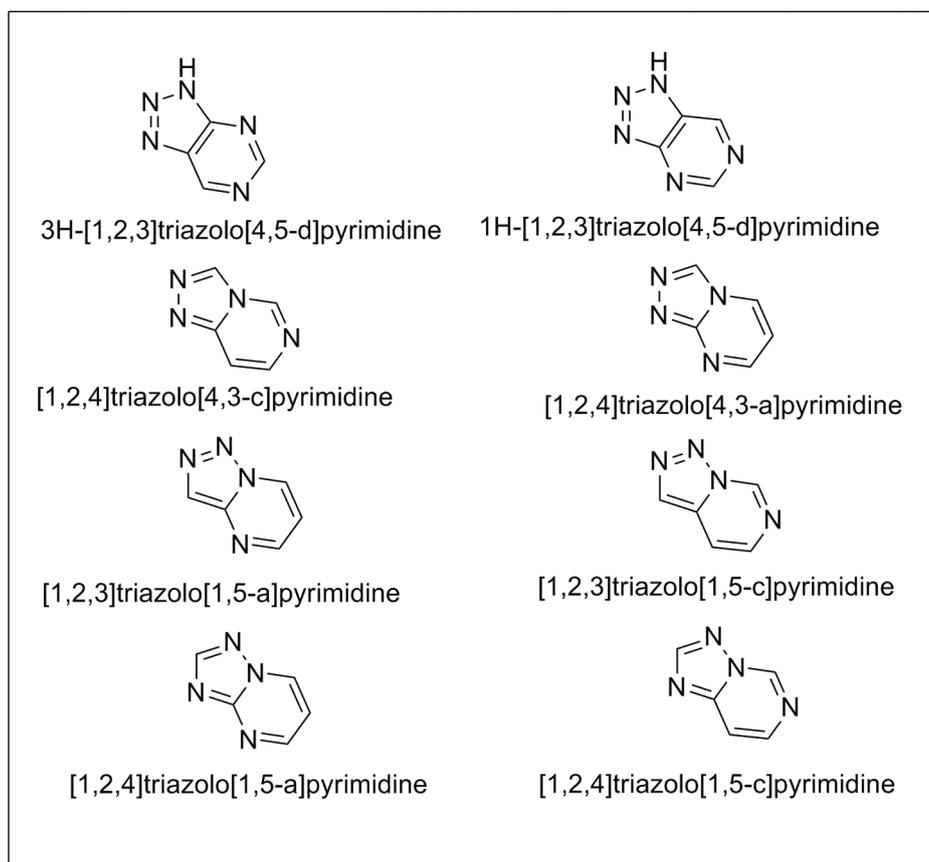
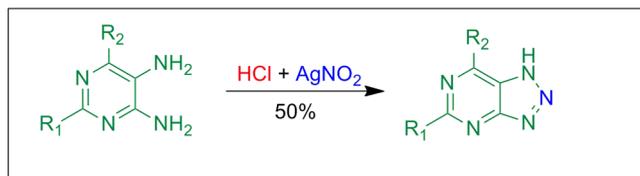
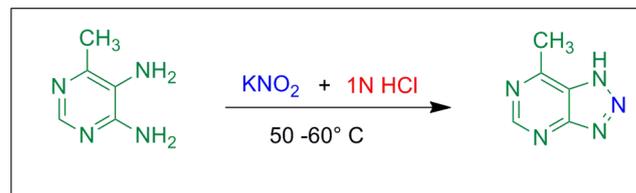


Fig. 1. Different possible positional isomers of triazolopyrimidine.



Scheme 1. Synthesis of triazolo[d]pyrimidine based analogs of adenine, guanine, xanthine, and hypoxanthine.



Scheme 3. Synthesis of 7-methyl-v-triazolo[d]pyrimidine from 4,5-diamino-6-methyl-pyrimidine.

and hypoxanthine from 4,5-diaminopyrimidines [12].

In 1946, English et al. patented the synthetic protocol for the synthesis of triazolo[d]pyrimidine derivatives from various 4,5-diaminopyrimidines (Scheme 2) [13]. A similar method was explored by Dille K.L. and Christensen B.E., in 1954. They prepared triazolo[d]pyrimidine derivatives from 2,6-dichloro-4-amino-5-nitropyrimidine. This preparation involved catalytic hydrogenation of N–O bond of substituted pyrimidines, using Raney nickel in methanol. These intermediates were further converted to their corresponding triazolo[d]pyrimidines [14]. In 1950, Benson et al. synthesized 7-methyl-v-



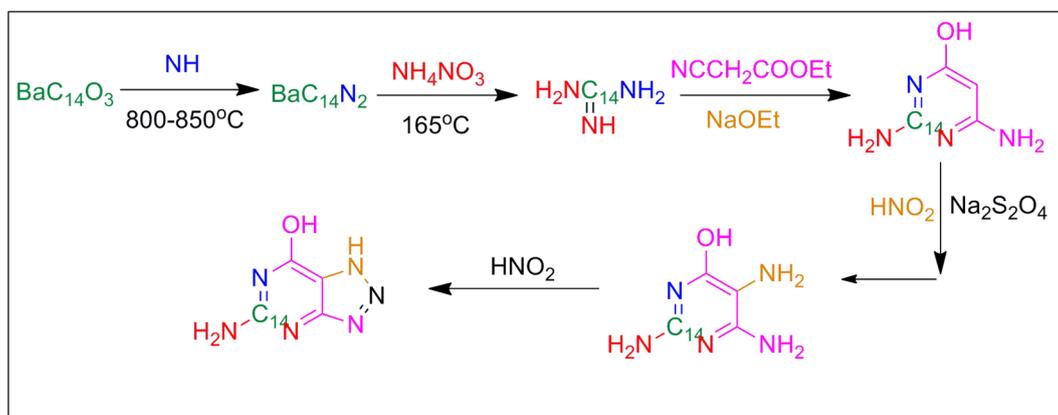
Scheme 2. Preparation of triazolo[d]pyrimidine derivatives from various 4,5-diamino pyrimidines.

triazolo[d]pyrimidine from 4,5-diamino-6-methyl-pyrimidine with potassium nitrite and 1N hydrochloride solution (Scheme 3) [15]. In the same year, Bennett et al. synthesized 8-azaguanine-2-C by modifications in the previously reported scheme as displayed in Scheme 4 [16]. Then again in 1952, Bennett Edward L. described the methods (Scheme 5) for the isotopic synthesis of 8-azaadenine-4,6-C and 8-azaguanine-4-C [17].

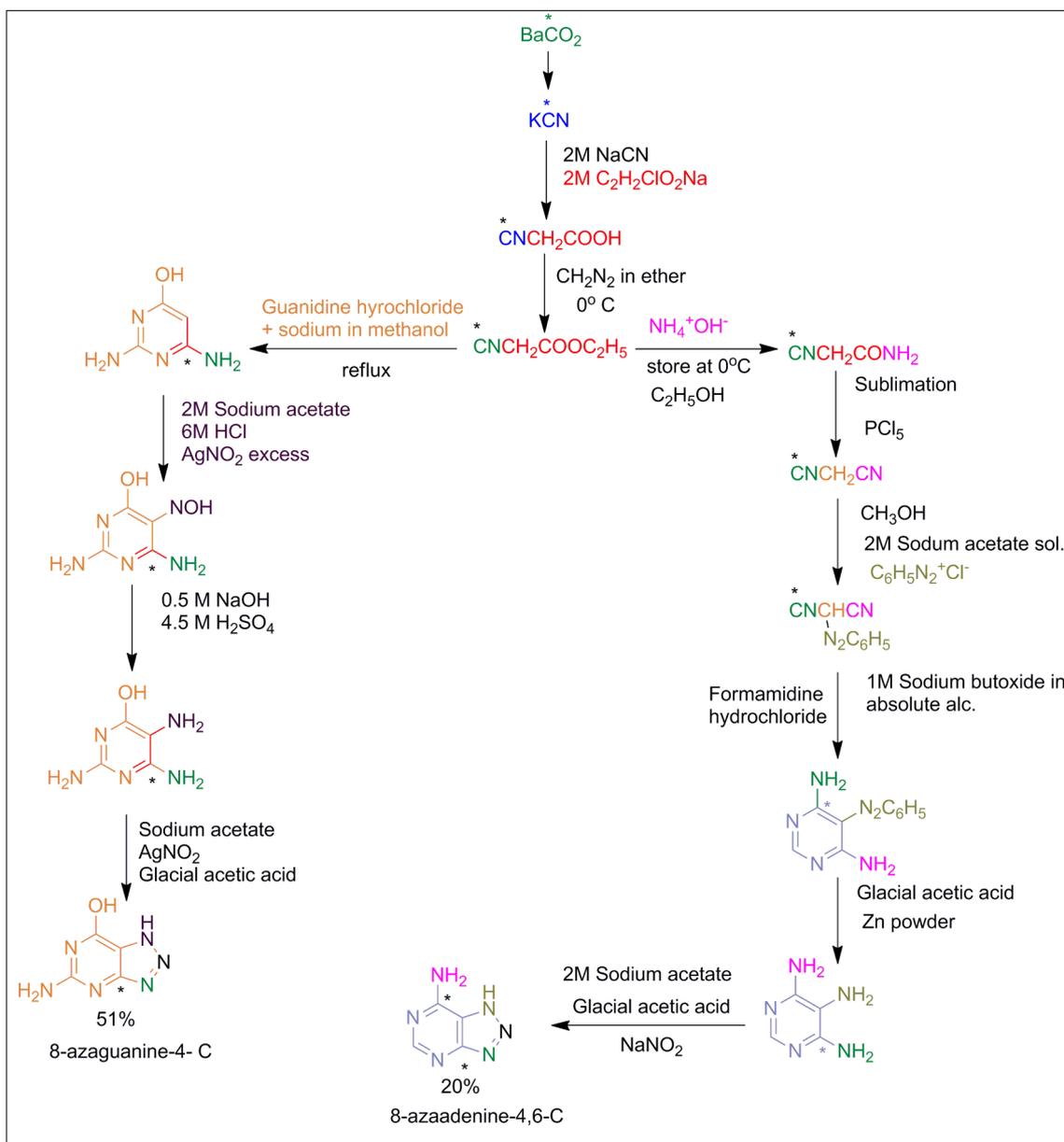
In 1961, Shealy et al. treated 4,5-diaminopyrimidines with sodium nitrite in the presence of aqueous acetic acid to afford a good yield of 3-alkyl-7-chloro-3H-v-triazolo [4,5-d]-pyrimidines (Scheme 6). The nucleophilic reagent displaced 7-chloro substituent and in the alkaline solution, the 7-chloro derivatives were converted into 5-amino-3-alkyl-3H-v-triazolo [4,5-d]-pyrimidine-7(6H)-ones [4].

Next year, the same group prepared 5-amino-7-chloro-v-triazolo [4,5-d] pyrimidine by treatment of 2,4,5-triamino-6-chloropyrimidine with isoamyl nitrite. 7-chloro-v-triazolo[4,5-d]pyrimidines (Scheme 7) had been previously obtained in dioxane solution by the same method [18].

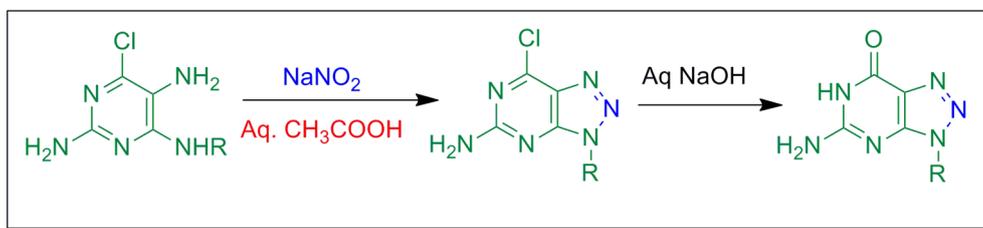
In 1978, Christophe et al. reported the synthesis of v-triazolo[4,5-d] pyrimidine [19]. The synthesis was initiated by nitration of 2-*t*-butyl-4-hydroxypyrimidine, followed by conversion of the 5-nitro derivative to



Scheme 4. Synthesis of 8-azaguanine-2-C.



Scheme 5. Methods for the isotopic synthesis of 8-azaadenine-4,6-C and 8-azaguanine-4-C.



Scheme 6. Synthesis of 5-amino-3-alkyl-3H-v-triazolo [4,5-d]-pyrimidine-7(6H)-ones.

2-*t*-butyl-4-chloro-5-nitropyrimidine (Scheme 8). The chloro compound was treated with ammonia solution to give 4-amino-2-*t*-butyl-5-nitropyrimidine, which was converted to 4,5-diamino-2-*t*-butylpyrimidine via reduction of the nitro group. The di-amino derivative was then reacted with nitrous acid to afford 5-*t*-butyl-*v*-triazolo [4,5-*d*] pyrimidine. The triazolopyrimidine was further treated with *o*-mesitylsulfonylhydroxylamine (MSH) to yield desired 1- or 3-amino-5-*t*-butyl-*v*-triazolo [4,5-*d*] pyrimidine.

In 1984, Asenjo and co-workers synthesized a series of 3-glycosyl-*vic*-triazolo-[4,5-*d*] pyrimidine and their *O*-acetyl derivatives (Scheme 9). To synthesize one of the proposed derivatives, an equimolar amount of NaNO₂ and acetic acid were added to an aqueous solution of 5-amino-4-β-D-glycosyl amino pyrimidines. Later, the reaction mixture was stirred for 15 mins to obtain the desired compound 3-glycosyl-*vic*-triazolo-(4,5-*d*) pyrimidine [20].

In 1984, Shishoo and co-workers synthesized 5-(2-arylvinyl) triazolothieno[3,2-*e*] pyrimidine, by the cyclization of (*E*)-4-hydrazinyl-2-styryl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine with orthoesters (Scheme 10). The triazole underwent isomerization to form 5-(2-arylvinyl) triazolothieno[3,2-*e*]pyrimidine in the presence of a catalytic amount of sodium ethoxide in ethanol [21].

The aryl-substituted heterocyclic compounds can be afforded through the Suzuki reaction (Scheme 11). The heteroaromatic derivatives of triazolopyrimidines have been synthesized using this well-known coupling reaction. The 4,6-dichloro-2-methyl-5-nitropyrimidine on treatment with *o*-(trifluoromethyl) phenylboronic acid yield chlorides of triazolopyrimidines which in turn on reaction with 2-bromo-4,6-dimethoxyaniline and further reflux with acetic acid and iron produce an intermediate which subsequently gives desired compound in good yield [22].

In 2016, Fizer and Slivka discussed previously reported procedure for the annulation of triazoles on 1,2-diaminopyrimidine to yield triazolopyrimidines (Scheme 12). They disclosed that condensation of diamino-substituted pyrimidinones with orthoesters or chloroanhydrides lead to the synthesis of desired [1,2,4] triazolo[1,5-*a*]pyrimidines [23].

2.2. Oxidative ring closure

In 1950, Benson et al. synthesized 2-aryl-5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine derivatives by reacting 2,6-diaminopyridin-4-ol with substituted benzenediazonium chlorides (Scheme 13) in order to synthesize *o*-amino azo intermediate which further gets oxidized in the presence of copper sulfate and pyridine-water mixture results in oxidative ring closure [24].

Another attempt was made by Westerlund and associates to prepare

this heterocyclic ring system via aryl azide, which further condensed with ethyl cyanoacetate to form 3-carboxy derivative, followed by intramolecular cyclization. As a resultant of this cyclization, the formation of a heterocyclic ring takes place (Scheme 14) [25].

Condensation of hydrazides with aminopyrimidine Schiff bases under mild oxidation with iron (III) chloride lead to the formation of [1,2,4] triazolo[1,5-*a*]pyrimidine system (Scheme 15). This reaction occurred at room temperature by simply mixing reagents in the mortar followed by water extraction and recrystallization [26]. Similarly, other oxidizing agents can be used to cyclize *N*-(2-pyrimido) amidines and guanidyl pyrimidines into the target system under different conditions [27].

2.3. Condensation with 1,3-dicarbonyl substrates

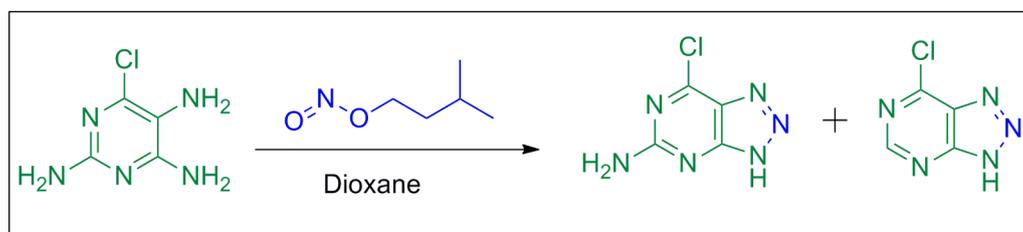
Condensation reaction is a class of organic addition reaction, in which two unique, reactive functional groups are utilized, one on each of the reactive entities; these reactive groups are designed such that they react with one another, but not react with any of other functionalities present in either entity, thus giving a single end product [28]. In 1958, Acker D.S. and Castle J.E. reported the synthesis of 7-hydroxy-5-methyl-*v*-triazolo[*d*]pyrimidine via the condensation of ethyl acetamido cyanoacetate with acetamide through intermediate formation (Scheme 16). The reaction was influenced by several factors, such as reflux with hydrochloric acid and treatment with sodium nitrite [29].

In 1961, Makisumi carried out condensation of 5-amino-*s*-triazole with ethyl malonate, ethyl cyanoacetate and methyl ethoxycarbonyl dithioacetate in the presence of sodium ethoxide in ethanol. After completion of condensation, the products were isolated as following: 5,7-dihydroxy-*s*-triazolo[2,3-*a*]pyrimidine, 5-hydroxy-7-amino-*s*-triazolo[2,3-*a*]pyrimidine and 5-hydroxy-7-mercapto-*s*-triazolo[2,3-*a*]pyrimidine, respectively (Scheme 17) [5].

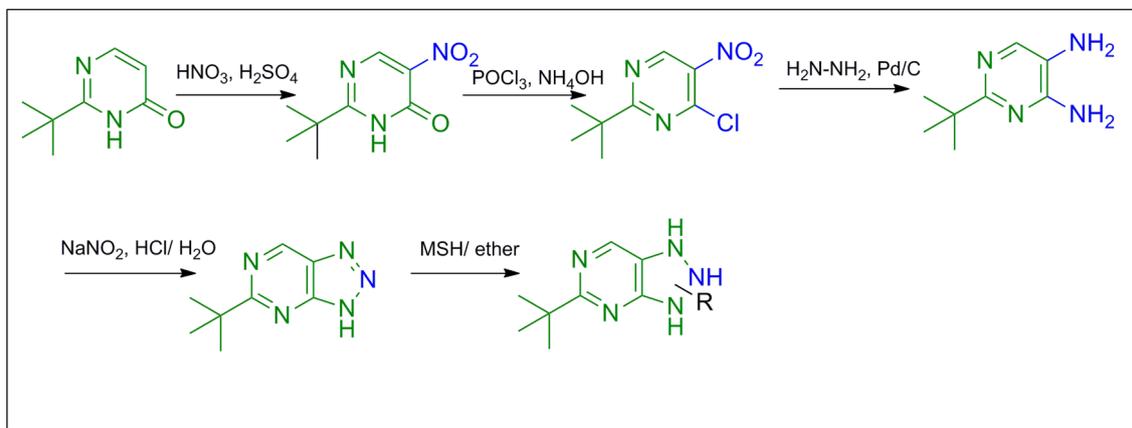
In the year 1969, Sutherland carried out condensation of 5-amino-1H-1, 2,3-triazole with acetyl acetone or ethyl acetoacetate in the presence of piperidine (Scheme 18), the derivative 5,7-dimethyl-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidine was obtained [30].

In 1971, Sutherland et al. reported the synthesis and scission of triazolo[3,4-*a*]pyrimidine [31]. The synthesis of *v*-Triazolo[3,4-*a*]pyrimidine was carried out by condensation of 4-substituted-5-amino-1H-1,2,3-triazole and acetylacetone in the presence of ethanol (Scheme 19). The acid catalyzed scission of triazole ring from triazolopyrimidine intermediates was performed to produce acetoxybenzyl pyrimidine derivatives.

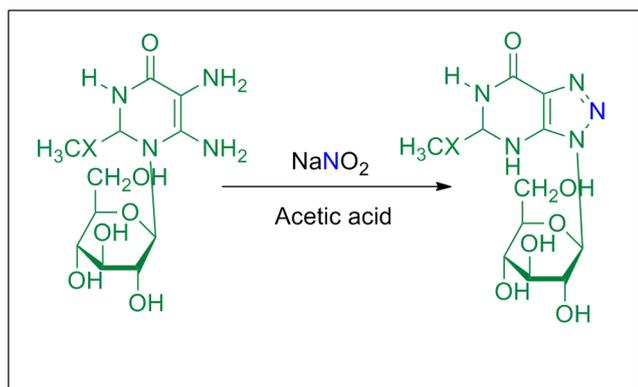
In 1974, Woodruff et al. reported the synthesis of substituted pyrazolidine-3,5-diones along with a few *s*-triazolo[1,5-*a*]pyrimidine



Scheme 7. Synthesis of 5-amino-7-chloro-*v*-triazolo [4,5-*d*] pyrimidine.



Scheme 8. Synthesis of 5-*t*-butyl-*v*-triazolo [4,5-*d*] pyrimidine.



Scheme 9. Synthesis of 3-glycosyl-*vic*-triazolo-[4,5-*d*] pyrimidine and their O-acetyl derivatives.

derivatives as by-products (Scheme 20) [32]. They carried out the synthesis of *s*-triazolo[1,5-*a*]pyrimidine derivatives by condensation of either 3-phenyl-5-phenylhydrazino-1,2,4-triazole or 3-phenyl-1,2,4-triazol-5-ylhydrazones or acylhydrazinotriazoles with diethyl malonyl chloride.

In 1979, Bajwa et al. reported condensation reaction in order to synthesize *s*-triazolo[1,5-*a*]pyrimidine derivatives (Scheme 21) [33]. The condensation reaction was carried out between 4,4-dimethoxybutan-2-one and subsequent aminotriazoles to yield two products, one triazolopyrimidine derivative and another self-condensation product,

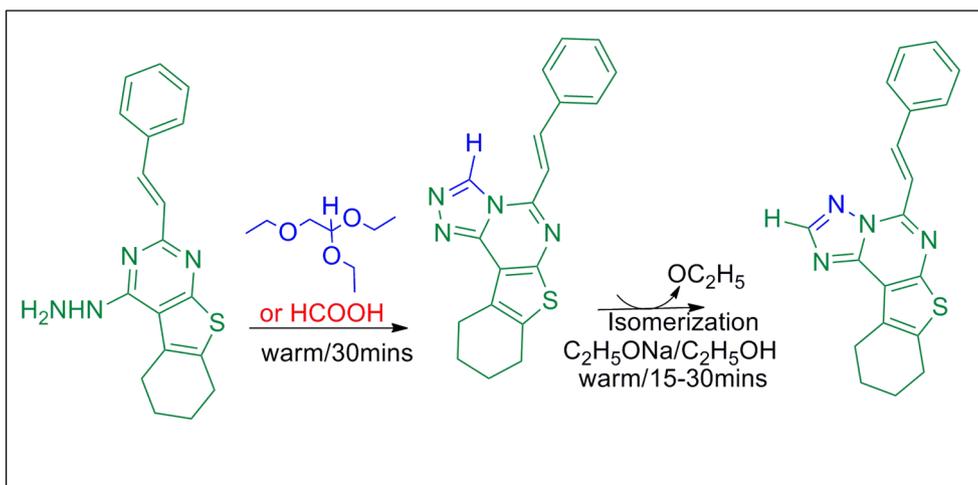
1,3,5-triacetylbenzene.

In the same year, Glennon et al. synthesized derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine-5,7-dione, a mesoionic xanthine ring system by a condensation reaction between appropriate bis-(2,4,6-trichlorophenyl) malonates (20) and free base 1,2,4-triazole (21) (Scheme 22). Among all synthesized derivatives, anhydrous 3,4-dimethyl-6-*n*-propyl-5-hydroxy-7-oxo-1,2,4-triazolo[1,5-*a*]pyrimidinium hydroxide, was most potent AMP phosphodiesterase inhibitor [34].

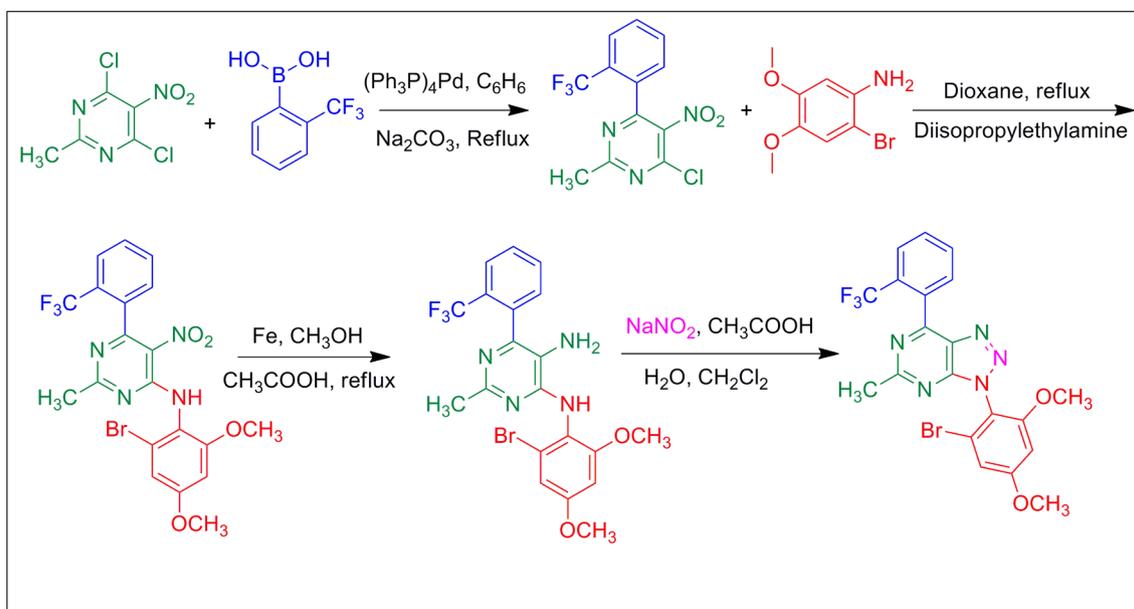
In 1980, Sato et al. reported the synthesis of 1,2,4-triazolo pyrimidines fused to various heterocyclic rings (Scheme 23). Initially, substituted 3-amino-1,2,4-triazoles and α -acetyl- γ -butyrolactones undergo condensation reaction in the presence of boron trifluoride to form an intermediate, followed by ring cyclization in a basic medium to form a heterocyclic ring system of interest [35].

Novinson and coworkers in 1982 synthesized series of novel 2-(alkylthio)-5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines as inhibitors of cAMP phosphodiesterase from varied tissues (Scheme 24). The proposed derivatives were prepared from various 3-amino-1,2,4-triazole intermediates that later underwent ring closure reaction [36]. For the synthesis of triazolopyrimidine derivative, a mixture of 3-amino-5-(benzylthio)-*s*-triazole, nonane-4,6-dione and acetic acid were refluxed for 4hrs, to obtain desired compounds [36].

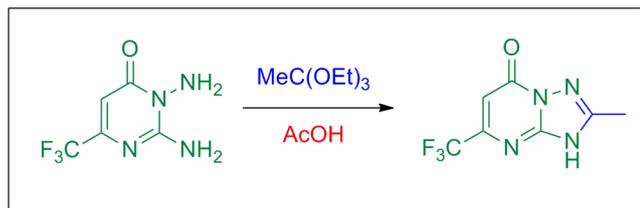
Chen et al. reported a new method for catalyzed synthesis of triazolopyrimidine derivatives that involves the alkylamine reaction with dialkyl cyanodithioiminocarbonate and was catalyzed by quaternary ammonium salts at room temperature to yield 3-alkylamine-5-amino-1,2,4-triazole. Later, this compound was subjected to imidization



Scheme 10. Synthesis of 5-(2-arylvinyl)triazolothieno[3,2-*e*]pyrimidine.



Scheme 11. Synthesis of triazolopyrimidines derivatives using Suzuki reaction.



Scheme 12. Synthesis of [1,2,4]triazolo[1,5-a]pyrimidines.

reaction followed by reaction with an α,β -unsaturated acid derivative, and then was hydrolyzed to obtain triazolopyrimidine derivative as shown in Scheme 25. This novel catalytic method employed for the synthesis of triazolopyrimidine derivatives can be carried out under inexpensive and mild conditions and, is safe and environmentally friendly [37].

Another method, which involves the reaction of 3-amino-1,2,4-triazole with equimolar arylidene derivatives of dehydroacetic acid and 5-acetyl barbituric acids in the presence of *n*-butanol or acetic acid has also been reported for the synthesis of triazolopyrimidine derivatives as shown in Scheme 26 [38].

Zhai et al, in 2008, reported synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine-7-amines (Scheme 27). They disclosed that condensation of 5-amino-1,2,4-triazoles with 3-oxo esters or thioamides leads to the formation of triazolopyrimidines. Reaction with ethyl acetoacetate selectively yields 7-oxo derivative, but in the case of thioamides, the reaction is not selective [39].

In 2016, Kumar et al. treated 3-amino triazole with ethyl acetoacetate in acetic acid at 110 °C, to afford desired triazolopyrimidine (Scheme 28). The reaction occurred in a single step, initiated by the attack of lone pair of electrons of the amino group on the carbonyl

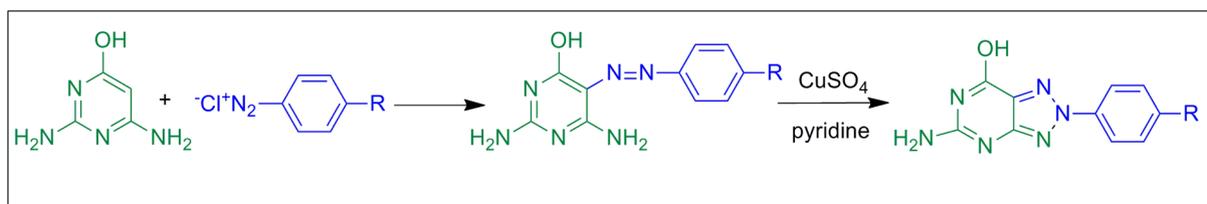
carbon of ethyl acetoacetate, followed by subsequent cyclization and dehydration. This reaction requires high temperature for the formation of desired compounds [40,41]. A similar procedure was again reported by Jameel et al. in 2017 for the synthesis of triazolopyrimidine [42]. In 2017, Hassan et al. reported the utilization of the same procedure for the synthesis of triazolopyrimidines. They, however, substituted ethyl acetoacetate before treating with amino triazole, to diversify the obtained triazolopyrimidine [43].

2.4. Intramolecular cyclo-condensation reaction

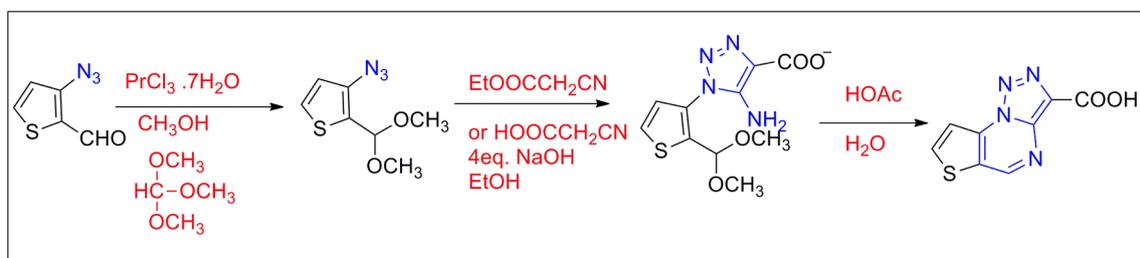
In 1962, Miller et al. reported the synthesis of *s*-triazolo-[2,3-*c*]pyrimidine derivatives via intramolecular cyclization of pyrimidylsemicarbazide derivatives (Scheme 29). This reaction can be carried out with dehydrating agents such as phosphorus oxychloride or phosphorus pentoxide in the presence of a suitable solvent and can be accelerated by applying heat [6].

In 1971, Sutherland et al. reported synthesis of *v*-triazolo[4,5-*d*]pyrimidine via rearrangement of acyl derivatives of 5-amino-1-phenyl-1,2,3-triazole-4-carboxamide [44]. The synthesis was carried out by the treatment of acylaminotriazoles with aqueous ethanolic alkali to yield subsequent triazolopyrimidine. Next year, Albert and colleagues reported the synthesis of 2-benzyl-*v*-triazolo[4,5-*d*]pyrimidine [45] using the similar synthetic procedure with additional benzyl group at the 2nd position of 4-formamido-1,2,3-triazole-5-carboxamide (Scheme 30).

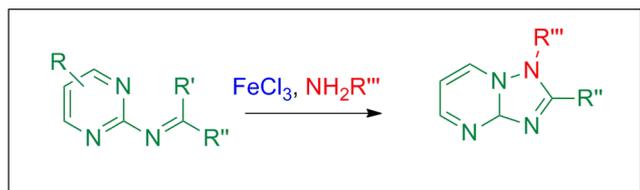
In 1978, Hayatsu et al. reported synthesis of 3-methyl-5-oxo-5,6-dihydro-*s*-triazolo[4,3-*c*]pyrimidine (Scheme 31) [46]. The reaction was carried out by the treatment of 4-aminocytosine with 0.05M ethylacetamide under neutral conditions to obtain amidrazone derivative. The ring closure in this derivative was induced by acidifying the mixture to pH 4.



Scheme 13. Synthesis of 2-Aryl-5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine derivatives.



Scheme 14. Synthesis of carboxylic acid derivatives of triazolopyrimidine.



Scheme 15. Oxidation of aminopyrimidine Schiff bases for the synthesis of triazolopyrimidine derivatives.

Albert et al. in 1980, synthesized 1,6-dihydro-8-methyl-8-azapurin-2-one by ring closure of 4-amino-5-ethoxycarbonyl-aminomethyl-1-methyl-1,2,3-triazole (Scheme 32), and the reaction was carried out in the presence of butanolic sodium butoxide. The resultant compound possesses strong covalent hydrating tendencies to form secondary alcohols [47].

In 1985, the synthesis of poly[benz(di(*syn*-triazolopyrimidines))] (PBDTPs) was reported by modified reductive poly heterocyclization (Scheme 33). For the synthesis of PBDTPs, 4,6-dinitro isophthalic acid dichloride and bis-amidrazones of dicarboxylic acids were used as reactants, followed by polymer-analog conversions of the nitro-substituted heterochain polymer. The synthesis of PBDTPs is a complex reaction, which is carried out in two stages: firstly, catalytic dehydrogenation in the presence of triethylamine at 160–180 °C, followed by reductive polyheterocyclization using a mixture of iron and hydrochloric acid to give desired product [48].

In the year 1987, Kokel and associates reported mild “one pot” synthesis of 3-aryl-(and 3-alkyl)-4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-*d*]pyrimidine via transfer of diazo group (Scheme 34). A mixture of azidophosgeniminium chloride, 1,3-dimethyl-4-aminouracil, and dry dichloromethane was refluxed for 2–3 h [49].

In 1988, Dlugosz synthesized novel triazolopyrimido-pyrimidine-5,8-dione by treating hydrazinopyrimidine with aqueous-ethanolic formaldehyde in heat conditions, followed by cyclization in the presence of pyridine to yield triazolopyrimidopyrimidine derivative (Scheme 35) [50].

Guillot et al. in the year 1990 synthesized some 3-amino substituted triazolo-[4,3-*c*]-pyrimidines via reaction of 4-hydrazinopyrimidines with iminium chloride and *N*-aryl phosgenimines. This regioselective cyclization reaction afforded 3-dimethylaminotriazolo-[4,3-*c*]-pyrimidine in good yield (Scheme 36) [51].

In 2001, Oganisyan et al. also carried out the synthesis of

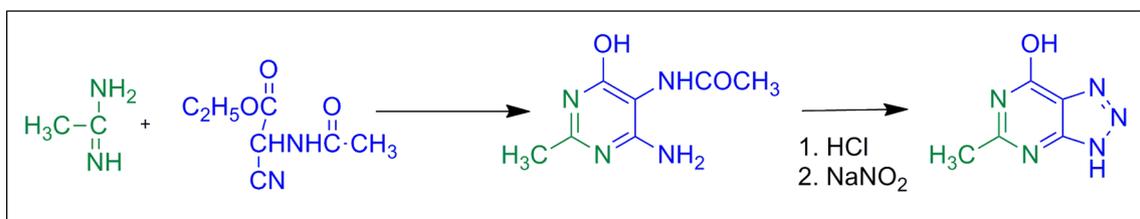
triazolopyrimidine derivatives from thienopyrimidine derivative. The fused thienopyrimidine was first treated with methyl iodide (MeI) in the presence of potassium hydroxide (KOH) to yield the corresponding 2,4-dimethyl substituted thienopyrimidine, which was later condensed with hydrazine hydrate that resulted in the formation of 4-hydrazino-2-methylthiothienopyrimidine. It was observed that the hydrazine group was selectively substituted at the 4th position of the pyrimidine ring. Later hydrazine substituted derivative was cyclized to triazol[4,3-*c*]pyrimidine in the presence of formic acid as shown in Scheme 37[52].

In 2011, Khera et al. reported the synthesis of triazolopyrimidines using 2-chloro pyrimidine as an initial substrate (Scheme 38). In this multistep scheme, after replacing chloro with hydrazide at the 2nd position, they treated this substituted pyrimidine with substituted benzaldehyde to form Schiff base with the free NH₂ of hydrazide. In the final step, the Schiff base of pyrimidine was treated with iodobenzene diacetate in DCM in order to get the desired triazolopyrimidines [11]. In 2015, Vilapara et al. optimized similar synthetic procedure to develop a one-pot sequential approach for the construction of highly functionalized triazolo[4,3-*c*]pyrimidine library [53]. Similar synthetic procedure was reported by Kamal et al. in 2017 for the synthesis of triazolopyrimidine derivatives [54].

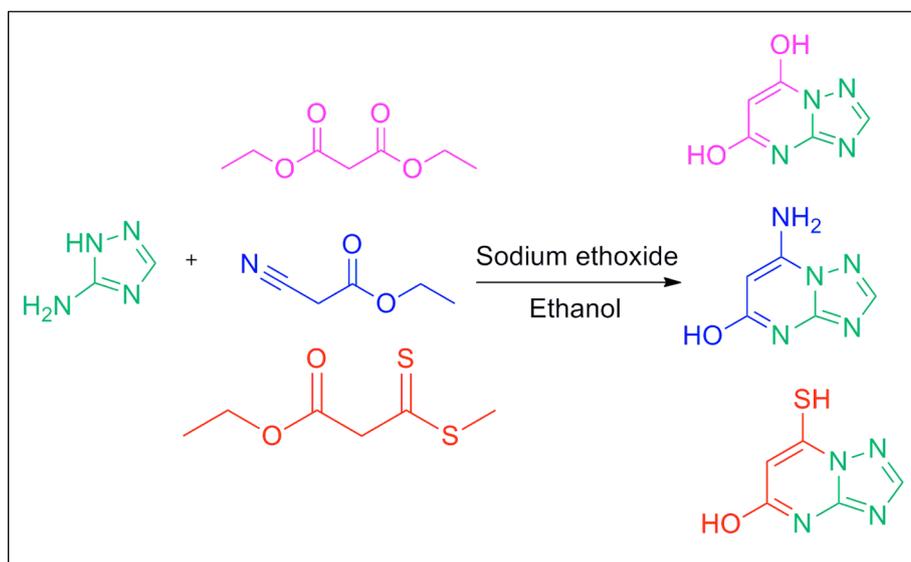
In 2015, Romdhane et al. reported the construction of the triazolopyrimidine skeleton via intramolecular cyclocondensation reaction (Scheme 39). The intermediates they explored possessed two reactive sites, i.e., a cyano group and an imidic carbon, which were treated with appropriate acid hydrazide under ethanol reflux to give desired fused triazolopyrimidines. Plausible pathway involved two successive nucleophilic additions of –NH₂ group on the imidic carbon and on the cyano function followed by dehydrocyclization to give triazolopyrimidines [1]. The similar synthetic strategy was utilized previously by Whang and Song in 2013, for the synthesis of thienotriazolopyrimidine derivatives containing triazolothiadiazole moiety [55].

2.5. Cyclization reaction

Cyclization is basically a ring forming reaction that is not only applicable to a particular heterocycle but also to other range of structures [56]. In 1963, Temple et al. carried out the synthesis of 7-chloro-8-ethoxymethylene-amino-*s*-triazolo[4,3-*c*]pyrimidine. The 5-amino-4-chloro-6-hydrazinopyrimidine was treated with an excess of diethoxymethyl acetate at room temperature to obtain the desired product (Scheme 40) [7].



Scheme 16. Synthesis of 7-hydroxy-5-methyl-*v*-triazolo[*d*]pyrimidine via the condensation of ethyl acetamido cyanoacetate with acetamide.



Scheme 17. Condensation of 5-amino-s-triazole with ethyl malonate, ethyl cyanoacetate, and methyl ethoxycarbonyldithioacetate.

In 1965, Broadbent et al. prepared mercapto-s-triazolopyrimidines from 4-hydrazinopyrimidines and carbon disulfide (Scheme 41). They carried out the reaction of 4-hydrazino-6-methyl-2-*n*-propylpyrimidine or 2-mercapto-5-*n*-propyl-6-trifluoromethylpyrimidine with carbon disulfide and *n*-butanol, to obtain the corresponding triazolopyrimidine derivatives [57].

In 1966, Bee et al. synthesized 3-amino-s-triazolo [4,3-*a*] pyrimidine derivatives from hydrazinopyrimidine derivatives and cyanogen chloride reaction under mild conditions at low temperature (Scheme 42). The [4,3-*a*] derivatives are able to isomerize under suitable conditions to the corresponding 2-amino-s-triazolo-[2,3-*a*]pyrimidine derivatives [58].

In 1966, Paudler et al. synthesized triazolo [4,3-*a*] and [1,5-*a*] pyrimidine by two routes, starting with a) 3-amino-1,2,4-triazole and (b) 2-hydrazinopyrimidine (Scheme 43). The compounds [1,2,4] triazolo [4,3-*a*] pyrimidine or [1,2,4] triazolo [1,5-*a*] pyrimidine or both of these were obtained [8].

In 1967 Spickett et al. carried out cyclization of 2-hydrazinopyrimidines with ethyl imidate hydrochloride and prepared 3-methyl-5-hydroxy-s-triazolo[4,3-*a*]pyrimidine via intermediate hydrazide (Scheme 44). However, the isomer 2-methyl-s-triazolo[1,5-*a*]pyrimidine was also obtained [59].

In 1977, Brown et al. reported the synthesis of s-triazolo[4,3-*a*] pyrimidines and their rearrangement to s-triazolo[1,5-*a*]pyrimidines (Scheme 45) [60]. The synthesis was carried out by the treatment of 2-hydrazino pyrimidine with appropriate acylating agents such as triethyl orthoformate, triethyl orthoacetate, triethyl orthobenzoate, benzaldehyde, 4-nitrobenzaldehyde, 4-chloro benzaldehyde and cinnamaldehyde, under reflux to produce s-triazolo[4,3-*a*]pyrimidine derivatives. These s-triazolo[4,3-*a*]pyrimidines were rearranged to s-triazolo[1,5-*a*]pyrimidines under acidic conditions.

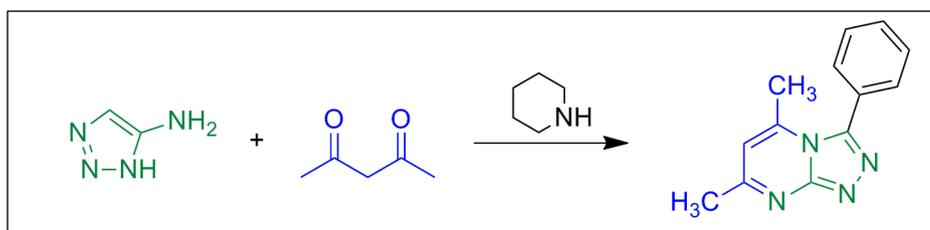
In 1978, Brown et al. reported the synthesis of s-triazolo[4,3-*c*] pyrimidines and their isomers s-triazolo[1,5-*c*]pyrimidines derivatives

(Scheme 46) [61]. The synthesis was carried out by reaction between pyrimidin-4-ylhydrazines and simple orthoesters to produce *N*-ethoxyalkylidene-*N'*-pyrimidinylhydrazines as an intermediate which either directly led to s-triazolo[4,3-*c*]pyrimidines or was further stirred in DMF for 3 h to produce the s-triazolo[4,3-*c*]pyrimidines. The s-triazolo [1,5-*c*]pyrimidine isomers were either produced directly by fusion of intermediate or by treatment of their s-triazolo[4,3-*c*]pyrimidines isomer with hot glacial acetic acid.

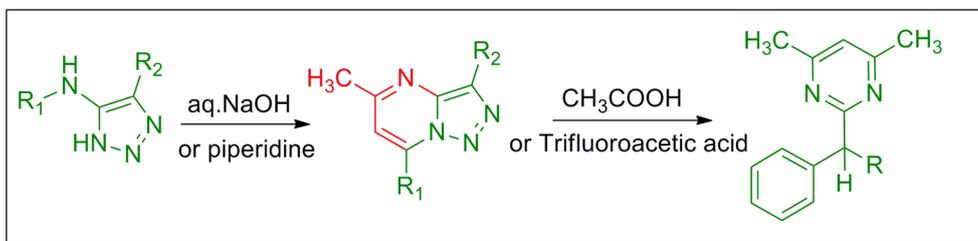
Brown and coworkers reported bis-s-triazolo[1,5-*a*:1',5'-*c*]pyrimidine and some simple derivatives, using uracil as a starting reactant, which was further converted to 4-thiouracil (86% yield) with the help of phosphorous pentasulfide in anhydrous pyridine, then to 4-hydrazino-6-pyrimidin-2(1H)-one (67% yield) by refluxing the mixture of 4-thiouracil (yield 86%), hydrazine hydrate and ethanol for 1hr (Scheme 47). The obtained compound then underwent cyclization in boiling formic acid to an intermediate triazolo[4,3-*c*]pyrimidinone (48) [62].

In 1981, Yamazaki et al. reported for the first time one step synthesis of the bicyclic pyrimidines from an open-chain, flexible molecule (Scheme 48). The cyclization of starting compound at N-4 by the reaction with ethoxymethylenemalononitrile that might initially forms an intermediate that later undergoes intramolecular cycloaddition of the 6-imino group to azomethine double bond at the 1st position. Later, the formed intermediate in DMSO undergoes oxidation in an open vessel at an ambient temperature to yield desired molecules [63].

Vas'kevich and his research group reported heterocyclization of thiosemicarbazides derivatives of pyrimidines reacted with methyl iodide with boiling methanol in the presence of sodium acetate accompanied by Dimroth rearrangement yielding amino derivatives of triazolopyrimidines as shown in Scheme 49 [64]. Initially the alkylation of sulfur atom with the formation of S-methyl derivative **A** which undergoes intramolecular cyclization to yield final compound **B**.



Scheme 18. Condensation of 5-amino-1H-1, 2,3-triazole with acetyl acetone or ethyl acetoacetate.



Scheme 19. Synthesis and scission of *v*-Triazolo[3,4a]pyrimidine.

2.6. Photochemical synthesis

In 1974, Maki et al. reported the photochemical synthesis of condensed *N*-triazoles including triazolo [4,5-*d*] pyrimidinedione-1-oxide [65]. 3,4,6-trimethyl-5,7-(4*H*,6*H*)-triazolo(4,5-*d*) pyrimidinedione-1-oxide was synthesized by either photolysis of 1,3-dimethyl-5-nitro-6-benzylidenemethyl hydrazinouracil or irradiation of 1,3-dimethyl-5-nitro-6-acetophenylidene methyl hydrazinouracil (Scheme 50).

2.7. Cycloaddition reaction

According to literature, 1,2,4-triazole ring fused to a pyrazolopyrimidine were well reported and described till 1979, but none of the reports had mentioned *v*-triazole fused pyrazolopyrimidine ring system. In an attempt to obtain this new fused ring system, Khan et al. in 1980, reacted 5-azido-4-cyano-1-phenylpyrazole to benzyl cyanide using sodium methoxide under thermal conditions. The spectral analysis confirmed the fused ring system obtained as 5-amino-3,8-diphenyl-8*H*-pyrazolo[4,3-*e*]-*v*-triazolo[1,5-*a*]-pyrimidine (yield 69%) (Scheme 51) [66].

Michael in 1981, employed intramolecular 1,3-dipolar cycloaddition reaction to synthesize novel β -lactams fused triazolo[3,4-*c*]pyrimidine (Scheme 52). Initially, lactam was refluxed under argon in dry toluene for 8 hrs which resulted in the formation of triazolocepham (86%yield) by means of smooth intramolecular cycloaddition [67].

In 1985, Biagi et al. prepared 2,9-disubstituted azapurin-6-ones via ring closure using one pot synthesis strategy (Scheme 53). The desired compound was obtained by adding benzyl azide to an ethanolic solution of cyanoacetamide salt, firstly to obtain 4-amino-3-benzyltriazole-5-carboxamide, and finally, the target compound was isolated in a good yield [68].

In 2014, Sadler et al. utilized [3 + 2] cycloaddition as a facile route to synthesize triazolopyrimidines. Using continuous-flow microreactor technology, they prepared organic azides in situ and reacted with cyanoacetamide to produce a variety of substituted 1,2,3-triazoles (Scheme 54). Further, they functionalized benzyl-substituted triazole

into the core structure of triazolopyrimidines [69].

2.8. Thermal decomposition reactions

Thermal decomposition was another strategy reported in the literature to obtain triazolopyrimidine scaffold. Thermal energy is employed as a source of energy to facilitate the breaking of chemical bonds in compounds undergoing thermal decomposition. In 1981, Nishigaki and companions proposed the formation of *v*-triazolo[4,5-*d*]pyrimidine derivatives (10% yield) by thermolysis of uracil derivative at 200 °C for about 3 h (Scheme 55) [70].

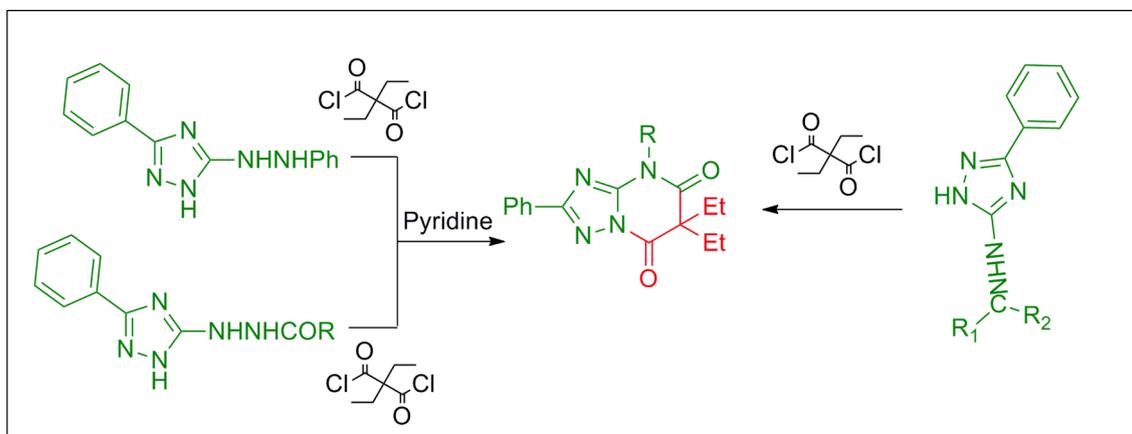
In 1988, Kamala et al. synthesized 2-aryl [1,2,4] triazolo[1,5-*a*] pyrimidine via pyrolysis in order to obtain the desired molecule. Pyrolysis resulted in thermal decomposition of substituted tetrazole, when refluxed for 3hrs in decalin, following the pyrolysis, nitrene intermediate undergoes cyclization to give final product (Scheme 56) [71].

2.9. Electrophilic cyclization of allyl-substituted aminotriazoles

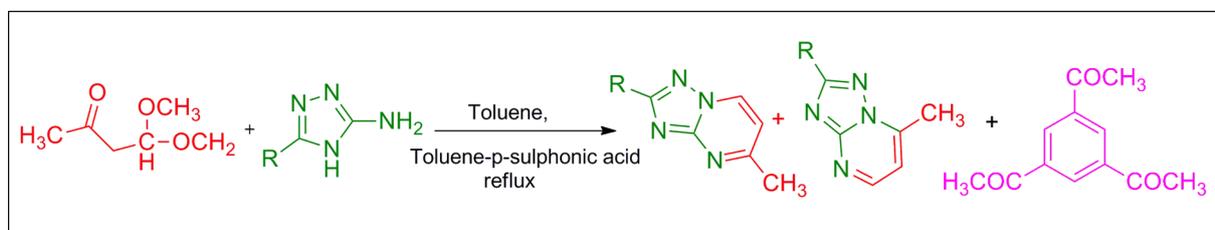
In 1987, Molina et al. proposed electrocyclic ring closure reaction to prepare fused pyrimidine i.e. 1,2,3-triazolo[4,5-*d*]pyrimidine derivatives (Scheme 57). To achieve the final compound, they stirred a mixture of iminophosphorane and aromatic isocyanates in dichloromethane at room temperature [72].

Petrich et al., in 1994, reported some monosubstituted (5, 6 and 7-substituted) triazolo [1,5-*a*] pyrimidines by reacting vinyl iminium salt with 3-amino-1,2,4-triazole analogs. The 6-substituted triazolopyrimidines were obtained if symmetrical vinamidinium is used under basic conditions [73]. Similarly, 5 and 7 substituted derivatives can be synthesized in the presence of unsymmetrical vinamidinium salt. The yield of both isomers is temperature dependent thus, only 7-substituted product is obtained at a lower temperature and both isomers (5,7-substituted) in low yield are obtained at a higher temperature (Scheme 58) [74].

In year 1994, Nicolai et al. synthesized some [1,2,4]-triazolo[1,5-*c*]



Scheme 20. Synthesis of *s*-triazolo[1,5*a*]pyrimidine derivatives.



Scheme 21. Synthesis of s-triazolo[1,5-a]pyrimidine derivatives.

pyrimidine and 1,2,4-triazolo[4,3-c]-pyrimidine derivatives. Key intermediate 4-hydrazinopyrimidine is required for the synthesis of these derivatives which in turn was obtained by alkylation of β -ketoester with different benzyl bromides and diisopropylethylamine using THF as a solvent and lithium chloride as a catalyst. The resulting product was then further cyclised in the presence of amidine hydrochlorides and NaOMe, and further chlorinated using POCl_3 . The product obtained at this step on treatment with hydrazine hydrate in EtOH gave 4-hydrazino derivatives of triazolopyrimidines. This intermediate eventually afforded different 1,2,4-triazolo[4,3-c]-pyrimidines (Scheme 59). The mixture of 1,2,4-triazolo[4,3-c]-pyrimidine and 1,2,4-triazolo[1,5-c]-pyrimidine can be obtained by reacting intermediate 4-hydrazinopyrimidine in a different way as depicted in Scheme 60.

Okamura et al., carried out condensation of iminoester with acyl hydrazine to yield fused triazolopyrimidine derivatives in the presence of 1% of camphor sulfonic acid (CSA) in dimethylformamide (DMF) at room temperature (Scheme 61) [75].

In 2013, Fizer et al. reported new method for the synthesis of 3,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-2(1H)-thione (Scheme 62). Their study disclosed the mechanism of electrophilic heterocyclization of allyl amino substituted triazole which leads to the annulation of the partially hydrogenated pyrimidine ring. This synthesis was carried out via bromine-assisted direct electrophilic cyclization at room temperature in acetic acid or acetonitrile medium with good yield [76].

2.10. Condensation with vinyl ketones and allyl derivatives

Konkel and Vince in 1996, reported the palladium-catalyzed coupling of 7-amino-1,2,3-triazolo[4,5-d]pyrimidine using allylic carbonates and phosphates. The mixture of 2 and 3 substituted triazolopyrimidines so obtained was purified and separated using column chromatography. The 3-allyl-1,2,3-triazolo[4,5-d]-pyrimidines can be synthesized as depicted in Scheme 63. The 5-amino-1,2,3-triazolo[4,5-d]pyrimidin-7-ones can also afford their allylic derivatives (Scheme 64).

Krasovsky et al. synthesized fluorine-containing triazolopyrimidine derivatives by carrying out one-pot synthesis with varying reaction conditions as described in Scheme 65(i-iii). They carried out the cyclocondensation of substituted β -trifluoroacetylvinylsulfones by reacting them with different 3-amino-1,2,4-triazoles and 5-aminotriazole in acetic acid to obtain a mixture of CF_3 substituted at the 5th and 7th position of pyrimidine ring as triazolopyrimidine isomers

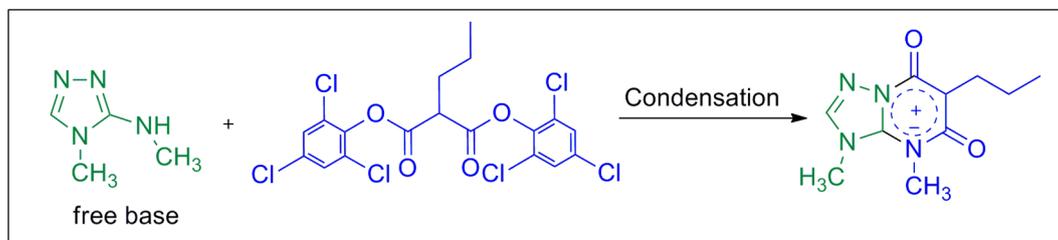
(Scheme 65i). However, when the similar reaction was carried out with 3-amino-1,2,4-triazole in the presence of acetonitrile at room temperature, it leads to the formation of a 5- CF_3 isomer of tetrahydro-triazolopyrimidine which was aromatized by refluxing in the presence of acetic acid to obtain 5- CF_3 substituted triazolopyrimidine as one regioisomer quantitatively (Scheme 65ii). On carrying out the heterocyclization of sulfones with 3-amino-1H-1,2,4-triazole-5-carboxylic acid in acetic acid under reflux, a mixture of triazolopyrimidine derivatives was obtained in a good yield. To avoid the decarboxylation of 3-amino-1H-1,2,4-triazole-5-carboxylic acid and precede the step of heterocyclization, the substituted sulfones were firstly treated with corresponding esters of triazolopyrimidine-2-carboxylic acid which were further hydrolyzed to yield triazolopyrimidine-2-carboxylic acid in the presence of lithium hydroxide (LiOH) in methanol (MeOH) (Scheme 65iii) [77].

Ahmed et al., in 2014, reported the synthesis of [1,2,4]triazolo[1,5-a]pyrimidine derivatives (Scheme 66). They reported that the reaction of aminotriazole with β -ketovinyl ethers or β -ketoenamines also give highly substituted model heterocycle in moderate and excellent yields. The yield in this cyclocondensation reaction can be slightly improved by using ultrasound irradiation [78].

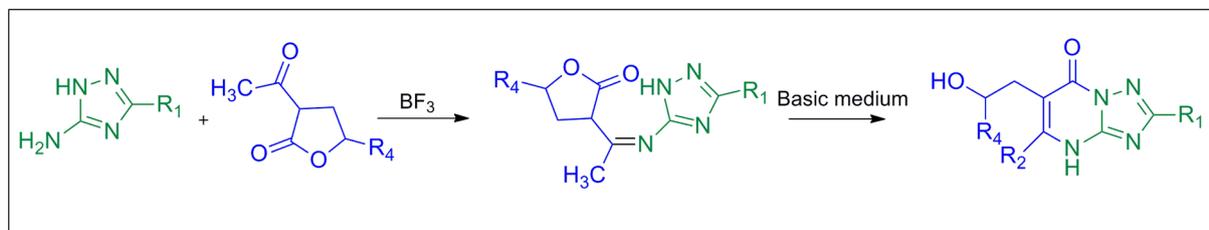
2.11. Three component one-pot reaction (Biginelli reaction)

In 2010, Karimi et al. reported three-component synthesis of some 2-amino-5-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitriles. Their study concerned one-pot synthesis of 2-amino-[1,2,4]triazolopyrimidine compounds using aromatic aldehydes, ethyl cyanoacetate, and 3,5-diamino-1,2,4-triazole. The target products were synthesized by a three-component condensation procedure as shown in Scheme 67. The formation of products was reported to take place via an initial addition of the more nucleophilic endocyclic nitrogen in 3,5-diamino-1,2,4-triazole to the intermediate with subsequent intramolecular cyclization and aromatization to give the final products [79].

In 2014, Astakhov et al. optimized this reaction to selectively yield 3-alkylamino-1-phenyl[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-ones by the condensation of 3-alkylamino-5-amino-1-phenyl[1,2,4]triazoles with β -keto esters or diethyl ethoxymethylenemalonate [80]. In 2015, Wang et al. utilized three-component Biginelli-like heterocyclization reaction to afford the rapid and efficient synthesis of a focused library of triazolopyrimidine derivatives, using commercially available reagents [81]. They added equal amounts of these derivatives in DMF and heated for roughly 15–20 min (with a temperature of 130–160 °C),



Scheme 22. Synthesis of 1,2,4-triazolo[1,5-a]pyrimidine-5,7-dione derivatives.



Scheme 23. Synthesis of 1,2,4-triazolo pyrimidines.

which yielded the desired compounds after the workup (Scheme 68) [82].

2.12. Tandem Aza-Wittig reaction

In 2012, Wang et al. reported a new efficient synthesis of 5,6-disubstituted-3-phenyl-1,2,3-triazolo[4,5-d]pyrimidin-7-ones via a tandem aza-Wittig reaction (Scheme 69). Initially, they obtained iminophosphorane derivative by treating ethyl 5-amino-1-phenyl-1H-1,2,3-triazole-4-carboxylate with triphenylphosphine, hexachloroethane, and triethylamine. Iminophosphorane derivative was then reacted with aryl isocyanate to give carbodiimides. The direct reaction of carbodiimides with substituted thiophenols resulted in desired triazolopyrimidines in good yields under the condition of heating for 2–3 h in the presence of a catalytic amount of K_2CO_3 [83].

2.13. One-pot four-component reaction

In 2015, Shaabani et al. reported an efficient and green four-component procedure for the synthesis of a new class of [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide derivatives via a condensation reaction between an amine, 2,2,6-trimethyl-4H-1,3-dioxin-4-one, an aldehyde, and 3-amino-1,2,4-triazole, in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH·H₂O) as a catalyst in water (Scheme 70) [84].

3. Reaction of triazolopyrimidines

3.1. Halogenation

In 1961 Makisumi Y. carried out the halogenation of *s*-triazolo pyrimidine derivatives, to synthesize 6-halo-*s*-triazolo pyrimidines (scheme 71). These were obtained by halogenation of *s*-triazolo pyrimidine and its 5-methyl derivative with chlorine or bromine (X_2) in glacial acetic acid at room temperature to corresponding mono-halogenated products. In the case of *s*-triazolo pyrimidine and its 5-methyl derivative, their 6th position undergoes electrophilic substitution due to $-M$ effect of the ring nitrogen present at the 8-position [85].

3.2. Electrophilic substitution

In 1961 Makisumi Y. carried out the coupling of 5-hydroxy-7-amino

& 5, 7 dihydroxy derivatives of triazolo pyrimidine with *p*-diazobenzenesulfonic acid or benzene diazonium salt in various media (Scheme 72). The electrophilic substitution reaction occurred and 6-phenylazo derivatives were produced. These derivatives were tested for antimetabolic and antitumor activity [86].

3.3. Condensation

In 1961 Makisumi Y. treated the monomethyl derivatives of *s*-triazolo[2,3-*a*]pyrimidine with 1.2 mol of benzaldehyde in the presence of zinc chloride at 160–170 °C which produced 5- and 7-styryl derivatives (Scheme 73).

Similarly, the dimethyl derivatives of triazolopyrimidine were treated with 2.5–3 mol of benzaldehyde at 190–195 °C, only one of the derivatives was converted into 5,7-distyryl derivative, while the remaining two were converted into monostyryl derivative (Scheme 74) [87].

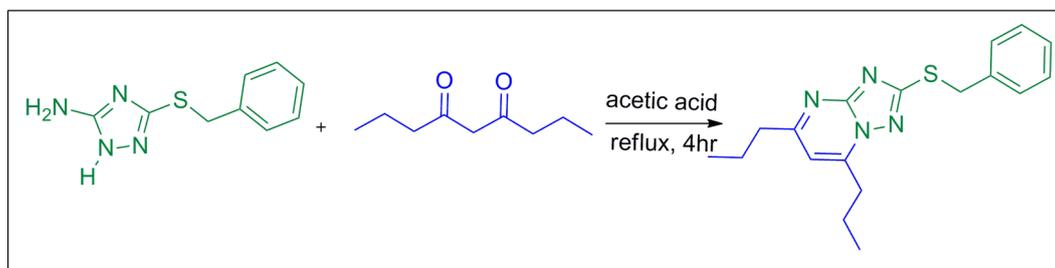
3.4. Nitration

In 1961 Makisumi Y. treated 7-hydroxy, 5-methyl-7-hydroxy, 5-hydroxy-7-amino, and 5, 7 dihydroxy derivatives of *s*-triazolo[2,3-*a*]pyrimidine with a mixture of fuming nitric acid and concentrated sulphuric acid or glacial acetic acid at low temperature yielding mono nitro derivatives. They were dissolved in the solution of sodium hydrogen carbonate and converted into corresponding 6-amino derivatives by catalytic reduction (Scheme 75) [88].

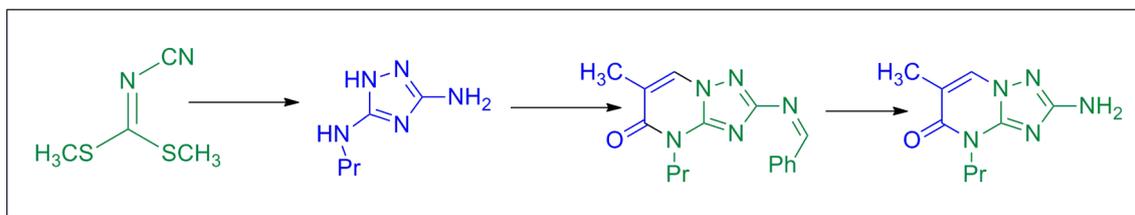
3.5. Nucleophilic substitution

Bahner and Co-workers in 1953 reported the synthesis of sulfur-containing triazolopyrimidines by refluxing 7-hydroxy-1-*v*-triazolo[*d*]pyrimidine with phosphorus pentasulfide under reflux (Scheme 76). The product may exist in both oxidized and reduced form. The hot solution was filtered, dissolved into potassium hydrosulphide and acidified with acetic acid. The crystals of sulfur derivatives were obtained by treatment with activated charcoal and methanol, respectively [89].

In 1961 Makisumi Y. carried out the reaction of 5-hydroxy-6-bromo-7-amino-*s*-triazolo [2,3-*a*] pyrimidine and 5,7-dihydroxy-6-bromo-*s*-triazolo [2,3-*a*]pyrimidine with substituted amines, butylamine, and cyclohexylamine as primary amines and piperidine and morpholine as



Scheme 24. Synthesis of novel 2-(alkylthio)-5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines.



Scheme 25.

secondary amines (Scheme 77). The reaction was carried out at the boiling temperature of the amines. The compounds reacted with secondary amines and were converted into corresponding 6-piperidino and 6-morpholino derivatives, but reaction with the primary amines was unsuccessful [90].

In 1963, Makisumi et al. carried out the reaction of 5-methyl-7-chloro-s-triazolo [1,5-a] pyrimidine with sodium methoxide at below room temperature, resulting in the formation of 5-methyl-7-methoxy-s-triazolo [1,5-a] pyrimidine (Scheme 78). It was examined that the alkyl group of this product undergoes rearrangement to the ring nitrogen at 3- and 4-position [91].

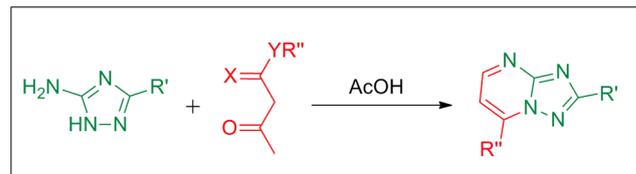
3.6. Acylation

In 1961, Nathan et al. reported derivatives of 2-(4-arylamino-phenyl)-5,7-dihydroxy-2H-v-triazolo[d]pyrimidine. These derivatives were prepared by heating 2-(4-aminophenyl)-5,7-dihydroxy-2H-v-triazolo[d]pyrimidine and pyridine (Scheme 79). Then to the resulted solution, they added variedly substituted benzoyl chlorides to obtain the desired derivatives [92].

3.7. Rearrangement

In 1963, Makisumi Y. investigated thermal rearrangement of 7-allyloxy-5,6-dimethyl-s-triazolo [1,5-a] pyrimidine having a substituent at the ortho position of the allyloxy group, into 5-(3-butenyl)-6-methyl-s-triazolo [1,5-a] pyrimidine-7-ol (Scheme 80). The reaction was carried out by heating it at 180 °C for 1 h without solvent. The reaction mixture was dissolved in chloroform and the insoluble crystals were obtained. It was observed that the product is formed by the migration of the allyl group to one of the methyl group at the 5- or 6-position [93].

In 1963, Makisumi Y. carried out transesterification of alkoxy-s-triazolo [1,5-a] pyrimidines. The 5-chloro, and 7-chloro-s-triazolo pyrimidine (a and b) were converted into corresponding 5-methoxy-(1a), 5-ethoxy-(1b), 7-methoxy-, and 7-ethoxy-(2b)- s-triazolo [1,5-a]-pyrimidines in the presence of an equimolar amount of sodium alkoxide at room temperature (Scheme 81). When 5,7-dichloro-s-triazolo [1,5-a] pyrimidine was treated with two moles of sodium alkoxide, 5,7-dimethoxy and 5,7-diethoxy derivatives were obtained. But when they used an equimolar amount of sodium alkoxide, 5-chloro-7-methoxy,



Scheme 27. Condensation reaction of 3-oxocarboxylic acid derivative for the synthesis of triazolopyrimidine.

and 5-chloro-7-ethoxy derivatives were obtained [94].

3.8. Alkylation

In the year 1963, Makisumi Y. carried out alkylation of 5-methyl-s-triazolo-[1,5-a] pyrimidine-7-ol with ethyl iodide, two ethylated products 4-ethyl-5-methyl-s-triazolo [1,5-a] pyrimidine-7(4H)-one and 3-ethyl-5-methyl-s-triazolo [1,5-a] pyrimidine-7(3H)-one were obtained (Scheme 82). When ethyl iodide was replaced with methyl iodide then the two dimethyl derivatives were obtained [95].

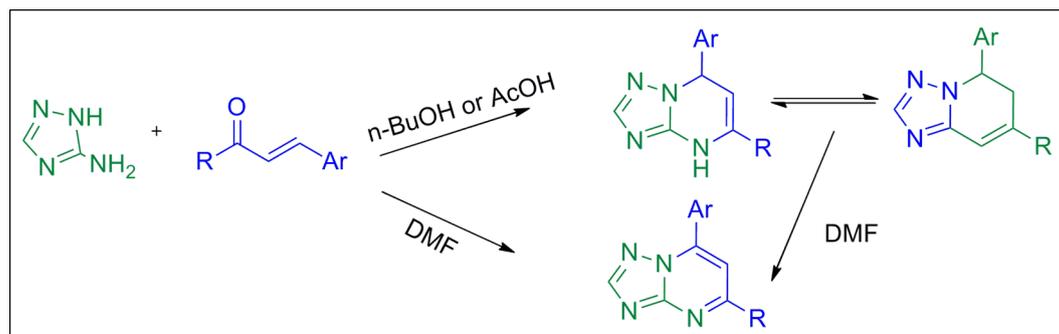
4. Triazolopyrimidines as hybrids

4.1. Coupled with other heterocycles

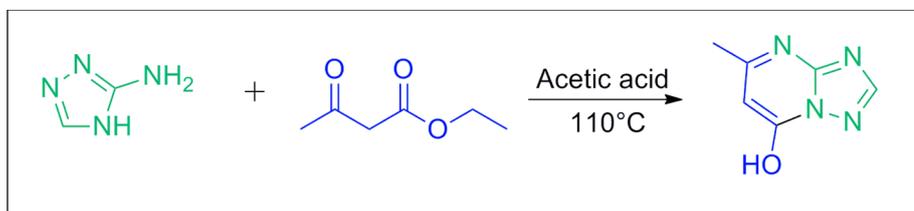
Synthetic chemists attempted to couple various heterocyclic fragments with triazolopyrimidines to obtain its different derivatives. In 1972, Albert et al. reported synthesis of 7-substituted 6,7-dihydro-v-triazolo[4,5-d]pyrimidines [96]. The reaction was carried out by condensation of v-triazolo[4,5-d]pyrimidines with appropriate nucleophilic agents such as potassium hydrogen sulfite, methanol, benzenethiol, barbituric acids, etc to yield condensation products i.e., 7-substituted 6,7-dihydro derivatives of triazolopyrimidines (Scheme 83).

This approach was used by Novikova et al. in 1981 to obtain an anti-tumor agent by coupling morpholine ring to triazolopyrimidine (Scheme 84). The morpholine coupled triazolopyrimidine was obtained by refluxing the mixture of substituted triazolopyrimidine with morpholine for 5 hr in butanol [97].

In 1986, Rusinov et al. coupled indole ring to the desired ring system to obtain indolyl derivatives of triazolo[1,5-a]pyrimidine



Scheme 26. Synthesis of aryl substituted triazolopyrimidines.



Scheme 28. Cyclization reaction for single step synthesis of triazolopyrimidine.

(Scheme 85). The nitro-substituted triazolopyrimidine was made to react with indole fragment using butanol as a solvent in heating conditions. The nitro group as a substituent at position 6th on the desired ring system activated the ring system and made it susceptible to nucleophilic attack [98].

In 1984, Tominaga et al. attempted to couple heterocyclic amines like morpholine or *N*-methylpiperazine to triazolo[1,5-*a*]pyrimidine to form desired derivatives (Scheme 86). The mixture of triazolo[1,5-*a*]pyrimidine and morpholine/*N*-methylpiperazine was heated at 120 °C for 2hrs, then cooled to obtain desired compounds [99].

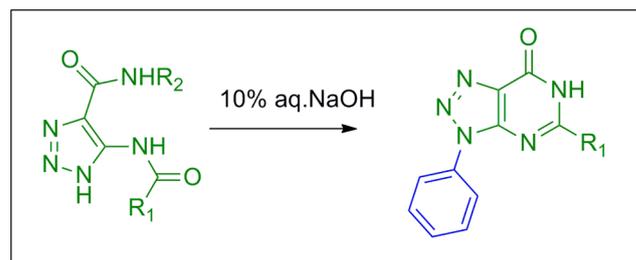
In 1989, Kazimierczuk et al. carried out stereoselective glycosylation of the anion of 7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine in the presence of DMF/ K_2CO_3 and tris[2-(2-methoxy ethoxy) ethyl]amine (TDA-1) that yielded 7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-2'-deoxyribofuranosides (Scheme 87). The desired N^2 2'-deoxy- β -*D*-ribofuranosides (11% yield) and α -*D*-anomer (12% yield) were obtained [100].

In 2000, Kofman and Kartseva, reported the halogen replacement in 7-chloro-1,2,4-triazolo[1,5-*a*]pyrimidine with various nucleophilic agents, particularly *N*-nucleophiles. Different derivatives of azolyl derivatives were synthesized by carrying out the heating of 7-chloro-1,2,4-triazolo[1,5-*a*]pyrimidine with five-membered NH heterocycles in the presence of aprotic solvents (Scheme 88) [101].

In another study, microwave-assisted organic synthesis of carboxamides derivatives of triazolopyrimidines was reported as shown in Scheme 89. The microwave irradiation assisted three component condensation was carried out, for 5 mins at 120 °C of thione derivatives of triazole with aromatic aldehydes and acetoacetamides that yielded dihydrotriazolopyrimidines. The synthesized dihydrotriazolopyrimidines were then subjected to selective reduction with sodium borohydride using 2-propanol as a solvent to yield carboxamide derivatives of triazolopyrimidine [102].

In 2015, Romdhane et al. explored the 3rd position of [1,2,4]triazolo[1,5-*c*]pyrimidine (Scheme 90). They initially synthesized triazolopyrimidine scaffolds with alkyl nitrile substitution at 3rd position and further coupled 2-hydroxy benzaldehyde nucleus in the presence of piperidine, followed by treatment with HCl to yield coumarin coupled triazolopyrimidines [11].

In 2016, Kumar et al. explored the 7th position of [1,2,4]triazolo[1,5-*a*]pyrimidine (Scheme 91). They initially synthesized [1,2,4]triazolo[1,5-*a*]pyrimidine scaffold with hydroxy substitution at 7th position. They substituted hydroxy group with chloro using $POCl_3$, followed by coupling with piperazine using K_2CO_3 in dioxane. Finally, chloro substituted quinolone was treated with piperidine substituted [1,2,4]



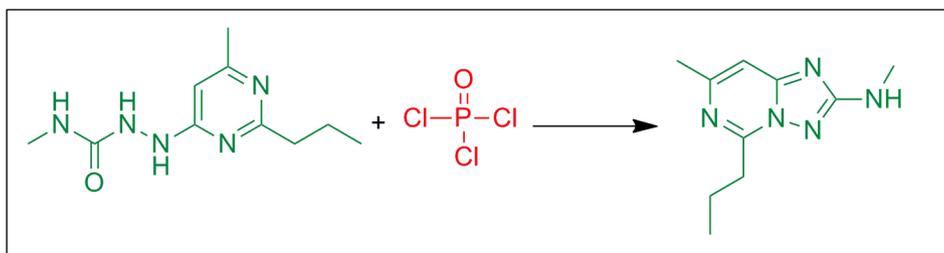
Scheme 30. Synthesis of 2-benzyl-v-triazolo[4,5-*d*]pyrimidine.

triazolo[1,5-*a*]pyrimidine to obtain the desired quinolone coupled triazolopyrimidines [40]. In 2018, they utilized a similar approach to synthesize pyrimidine coupled triazolopyrimidines [41]. Similar synthetic procedure was again employed by Jameel et al. in 2017, to synthesize triazine coupled triazolopyrimidines [42].

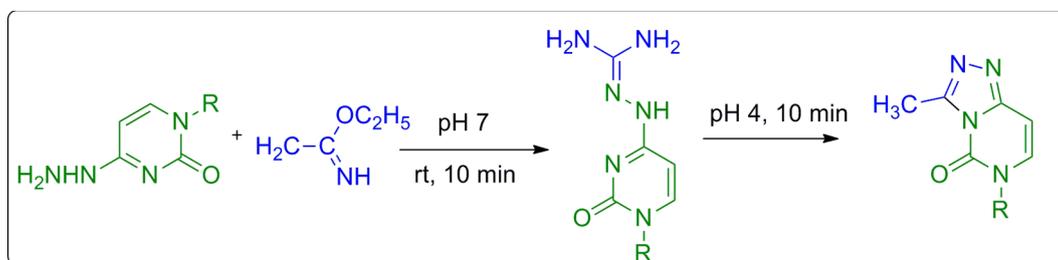
In 2011, Khera et al. reported the synthesis of oxazolidinone coupled triazolopyrimidines (Scheme 92). They initially synthesized 3-nitro aryl substituted [1,2,4]triazolo[4,3-*a*]pyrimidine. They further reduced the nitro group on the aryl ring to an amine using stannous chloride. In the next step, they treated the substituted triazolopyrimidine with benzyl chloroformate in the presence of aqueous sodium bicarbonate. Finally, the ester side chain in the obtained product was cyclized to yield oxazolidinone ring using butyl lithium and (*R*)-glycidyl butyrate in THF [11].

In 2014, Patil et al. reported the synthesis of triazolopyrimidine coupled with acylsulfonamides (Scheme 93). They initially synthesized triazolopyrimidine carboxylic acid by condensing ethyl 5-amino-4*H*-1,2,4-triazole-3-carboxylate with acetylacetone. Further, the series of triazolopyrimidine coupled acylsulfonamides were synthesized in a convergent fashion by coupling sulfonamides and triazolopyrimidine carboxylic acid using EDCl as coupling reagent (Scheme 1) [103].

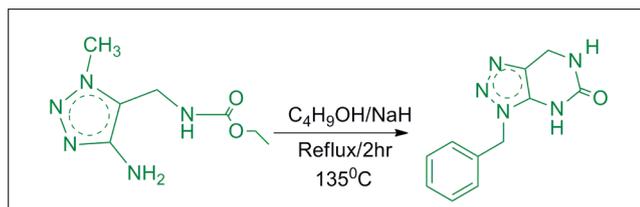
In 2010, El-Sayed et al. reported the synthesis of oxadiazolyl coupled triazolo[4,5-*d*]pyrimidine derivatives (Scheme 94). They initiated the scheme with the reaction of 1-naphthonitrile with hydroxylamine hydrochloride in the presence of 8-hydroxyquinoline to afford *N*'-hydroxy-1-naphthimidamide. Subsequently, the oxime derivative was treated with chloroacetyl chloride in acetone to obtain 1,2,4-oxadiazole derivative. Further, the substituted 1,2,4-oxadiazole derivative was converted to the corresponding azide derivative by treatment with sodium azide in DMF. In the next step, substituted oxadiazolyl 1,2,3-triazole derivative was obtained by the reaction of azide with cyanoacetamide in the presence of sodium ethoxide at reflux temperature.



Scheme 29. Synthesis of *s*-triazolo-[2,3-*c*] pyrimidine derivatives via intramolecular cyclization of pyrimidylsemicarbazide derivatives.



Scheme 31. Synthesis of 3-methyl-5-oxo-5,6-dihydro-s-triazolo[4,3-c]pyrimidine.



Scheme 32. Synthesis of 1,6-Dihydro-8-methyl-8-azapurin-2-one.

Finally, the desired derivatives were afforded by treating obtained oxiazazolyl-triazole derivatives with ethyl benzoate in ethanol at reflux [104].

In 2015, Bhatt et al. reported the synthesis of pyrazole coupled triazolo[1,5-*a*]pyrimidine hybrid (Scheme 95). To afford the desired hybrids, they utilized a three-component reaction. A mixture of the substituted pyrazolo carbaldehyde, aminoazole, and appropriate acetacetanilides was refluxed in DMF. The reaction mixture was allowed to stand overnight and then filtered to yield the desired pyrazolo-triazolopyrimidine hybrids [105].

In 2017, Saundane et al. reported the synthesis of some novel indole coupled triazolopyrimidine moiety (Scheme 96). They treated 5-amino-1-benzyl-1*H*-1,2,3-triazole-4-carboxamide in a solution of anhydrous ethyl alcohol with substituted ethyl-5-substituted-3-phenylindol-2-carboxylates and refluxed for 40 h. Further, the excess solvent was

removed under reduced pressure and the residue was decomposed in crushed ice followed by neutralization with acetic acid to yield the desired product [106].

4.2. Fused with other heterocycles

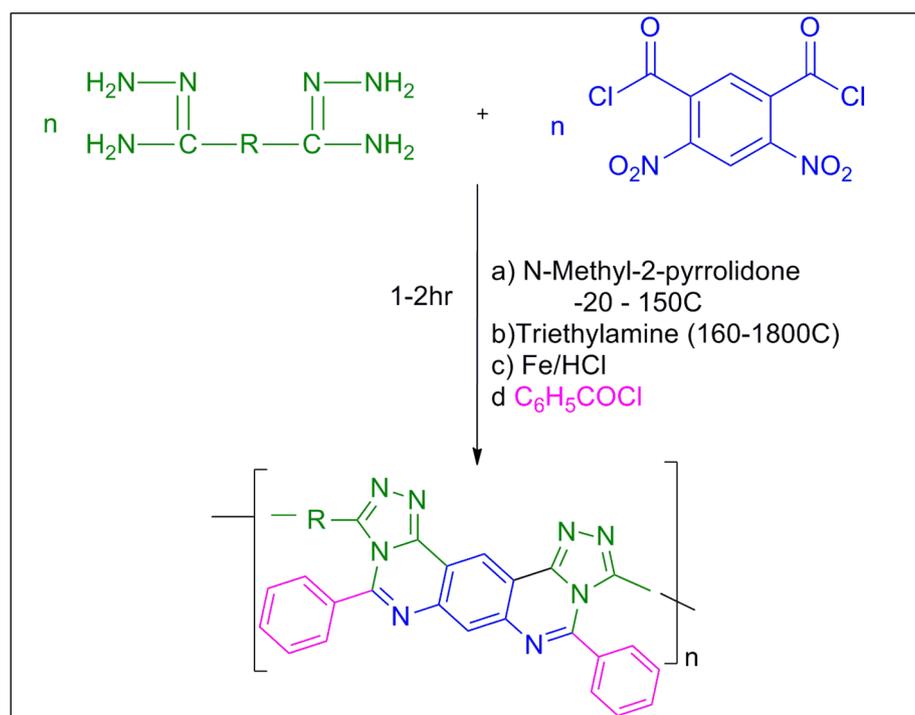
In year 1977, Sugimoto et al. reported synthesis of imidazo[1,2-*c*] [1,2,3]triazolo[4,5-*e*]pyrimidines (Scheme 97) [107]. The reaction was carried by treatment of appropriate 7-amino-triazolopyrimidine derivative with chloroacetaldehyde to obtain fluorescent imidazo[1,2-*c*] [1,2,3]triazolo[4,5-*e*]pyrimidines. These compounds on treatment with HCl gave ring-opened, imidazolyl-triazole derivatives.

In 1979, Brown et al. reported the synthesis of bis-s-triazolo[4,3-*a*:4',3'-*c*] pyrimidines and related ring systems via acylative cyclization (Scheme 98) [108]. The synthesis was carried out by treatment of suitable s-triazolo[4,3-*c*]pyrimidin-5-ylhydrazine or s-triazolo[1,5-*c*]pyrimidin-5-ylhydrazine with appropriate orthoester to produce required bistriazolopyrimidine ring system.

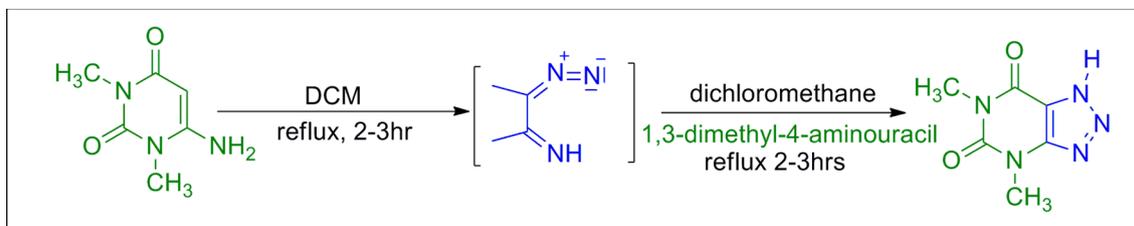
In 1980, Sato and associates fused various heterocycles i.e. pyrrole, thiophene, pyran, pyridine, and pyridazine to 1,2,4-triazolo[1,5-*a*] pyrimidines (Scheme 99) [35].

In 1984, Tominaga et al. prepared indene ring fused to triazolopyrimidine by condensation of 3-amino-1*H*-s-triazole with 2-bis(methylthio)methylene-1,3-indandione (Scheme 100) [99].

In 1987, Hori et al. reported an unexpected double 1,3-dipolar



Scheme 33. Synthesis of Poly[benz(di(syn-triazolopyrimidines))] (PBDTPs) through modified reductive polyheterocyclization.



Scheme 34. Mild "one pot" synthesis of 3-Aryl-(and 3-alkyl)-4,6-dimethyl-5,7-dioxo-1,2,3-triazolo[4,5-d]pyrimidine.

cycloaddition of [1,2,4]triazole[1,5-*a*]pyrimidine *N*-ylide using activated acetylenes and alkenes (Scheme 101) [109].

Nasser in 2000 reported the single step synthesis of various furo [3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines derivatives by refluxing simple bifunctional reagents like carbon disulfide, cyanogen bromide, ethyl cyanoacetate, diethyl oxalate and triethyl orthoformate with 5,6-di-(2-furyl)-3*H*-4*H*-4-imino-2-methylfuro[2,3-*d*]pyrimidine-3-amine using ethanol as solvent (Scheme 102) [110].

Hassan et al. reported the synthesis of various triazolopyrimidine derivatives by carrying out reflux of benzopyrano-[3',4':5,6]pyrano-[3,2-*d*]pyrimidine-6-on derivative with equimolar acid chlorides for 3 hours in the presence of dry benzene (Scheme 103) [111].

In the same year, Biagi and co-workers reported the preparation of derivatives of triazolopyrimidines by refluxing the mixture of 7-chlorotriazolopyrimidine with hydrazide in the presence of triethylamine (TEA) and using ethanol as solvent. In this reaction, nucleophilic attack of hydrazide group occurs on the 7th position of triazolopyrimidine ring having chloro substitution. The resultant hydrazido substituted triazolopyrimidine compounds was then cyclized to 1,2,4-triazolopyrimidine ring by heating the mixture at approximately 230 °C under reflux for 2 h as described in Scheme 104 [112].

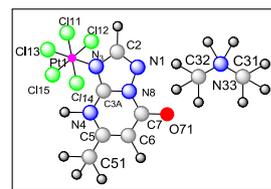
In 2017, Hassan et al. reported the synthesis of pyrazolo fused triazolopyrimidine derivatives (Scheme 105). They initially synthesized 6-carboxylate derivatives of tirazolopyrimidine with hydroxyl substitution at 7th position. They treated this derivative of triazolopyrimidine with POCl₃, to replace the -OH group with a chloro group. In the next step, they treated the chloro derivative with hydrazine hydrate to obtain desired pyrazole fused triazolopyrimidines [43].

In 2012, Huang et al. reported the synthesis of novel steroidal [17,16-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines (Scheme 106). In the single step scheme, they treated 16-arylidene-17-ketosteroid, in *n*-BuOH with the solution of 3-amino-1,2,4-triazole and tertiary potassium butoxide. The resulting mixture was refluxed for 30 h to obtain the desired steroid fused triazolopyrimidines [113].

5. Role as a chelating agent

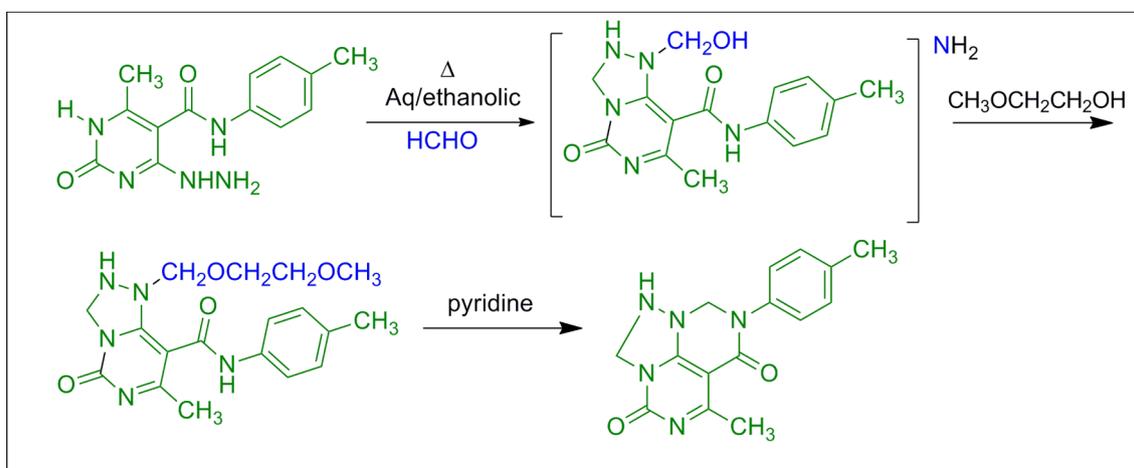
5.1. Platinum complexes

Lakomsa et al. in 2011, reported novel platinum (IV) coordination compounds with 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one (HmtpO) (1). They prepared two complexes i.e., *cis*-*trans*-[PtCl₂(OH)₂(NH₃)(HmtpO)] and *cis*-*trans*-[PtCl₅(HmtpO)] [(CH₃)₂NH₂], and structurally characterized them by spectroscopic methods such 1H, IR and X-ray crystallography. Their results established that the local geometry around the platinum (IV) center approximates a typical octahedral arrangement with nitrogen atom N₃ of the triazolopyrimidone and three chloride atoms in equatorial positions. The remaining two axial positions were occupied by two chlorides. They further evaluated the complexes for their antitumor properties via an *in-vitro* anti-proliferative activity against HL-60 and HCV29T cell lines. The *in-vitro* study concluded that *cis*-*trans*-[PtCl₂(OH)₂(NH₃)(HmtpO)] exhibits higher cytotoxic activity against HL-60 (IC₅₀ = 6.4 μM) than cisplatin [114].

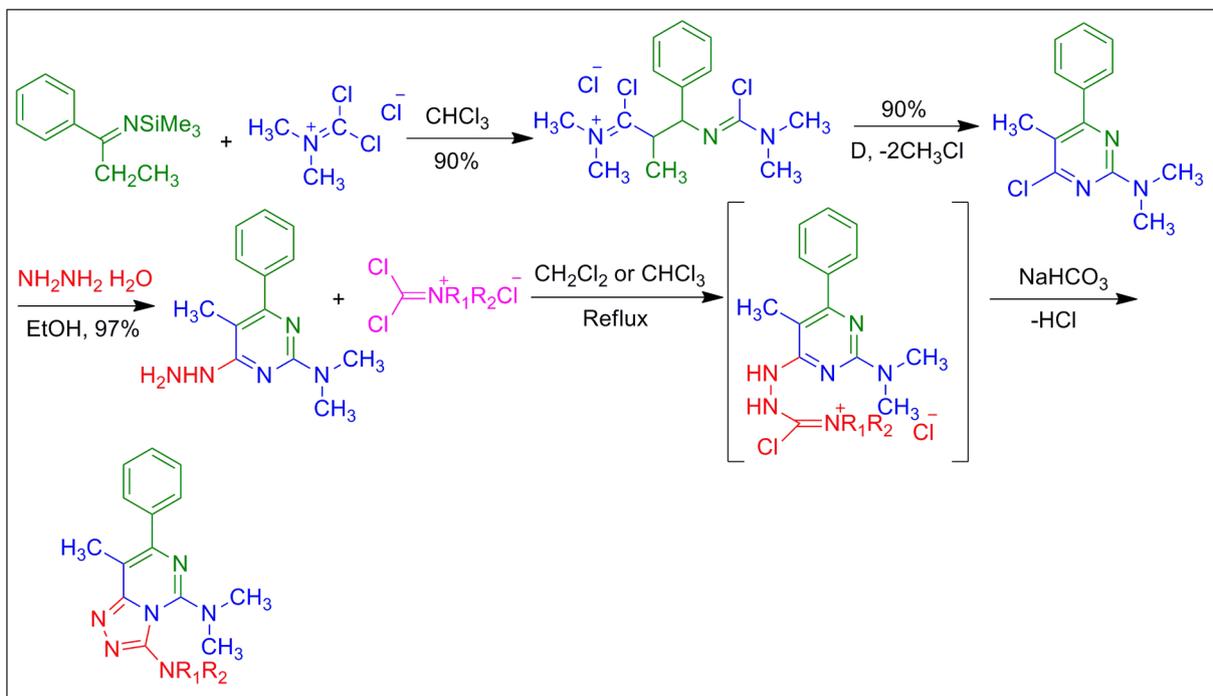


(1)

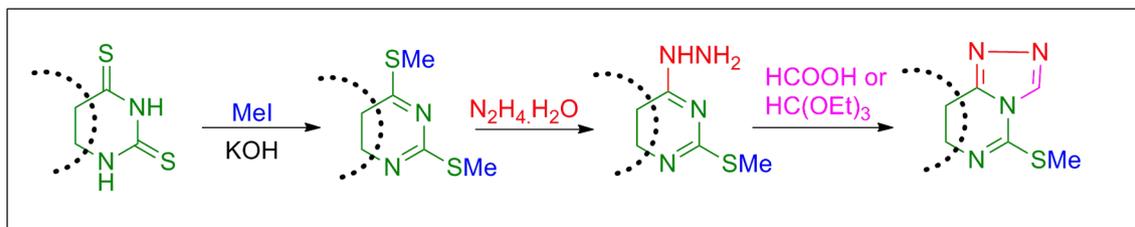
In 2012, Lakomska et al. disclosed the characterization and *in-vitro* cytotoxic activity of Platinum (II) complexes with 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines. The NMR data showed the presence of single resonance signals suggesting monodentate structures of the synthesized coordination compounds. The Pt signals of the complexes



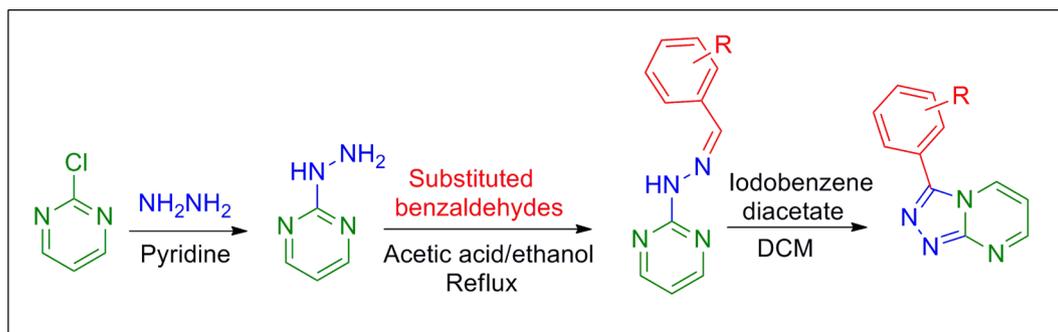
Scheme 35. Synthesis of novel triazolopyrimido-pyrimidine derivative.



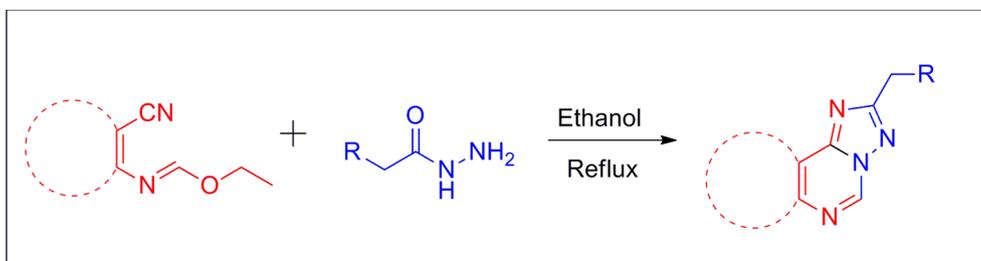
Scheme 36. Synthesis of 3-amino substituted triazolo-[4,3-c]-pyrimidines.



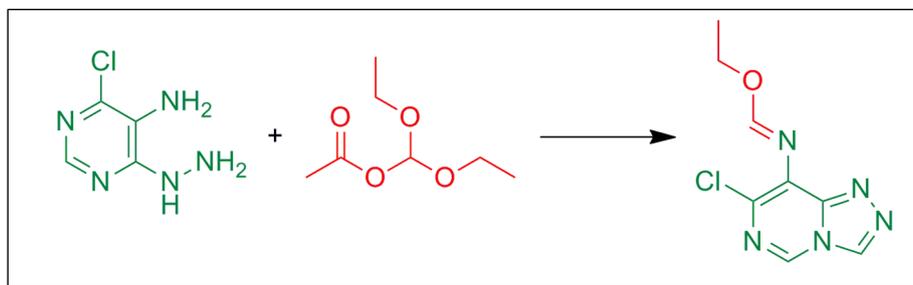
Scheme 37. Synthesis of triazolopyrimidine derivatives from thienopyrimidine derivative.



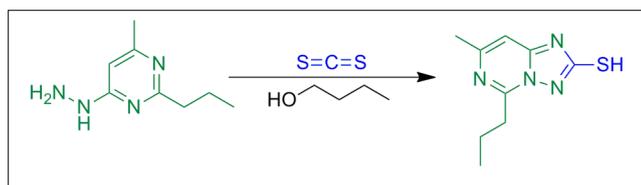
Scheme 38. Cyclization of hydrazide Schiff base for the synthesis of triazolopyrimidine.



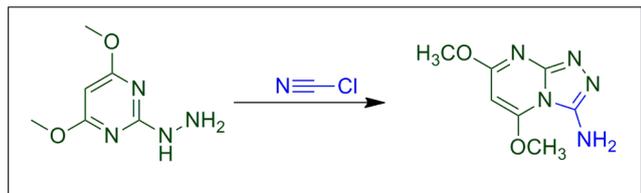
Scheme 39. Intramolecular cyclocondensation for single step synthesis of triazolopyrimidine.



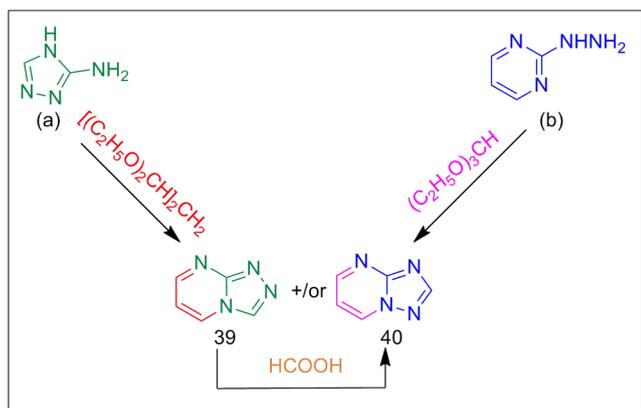
Scheme 40. Synthesis of 7-chloro-8-ethoxymethylene-amino-s-triazolo[4,3-c]pyrimidine.



Scheme 41. Synthesis of mercapto-s-triazolopyrimidines from 4-hydrazinopyrimidines.



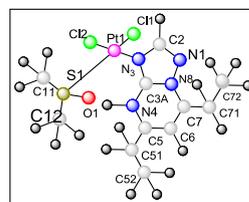
Scheme 42. Synthesis of 3-amino-s-triazolo [4,3-a] pyrimidine derivatives.



Scheme 43. Synthesis of triazolo [4,3-a] and [1,5-a] pyrimidine by two routes.

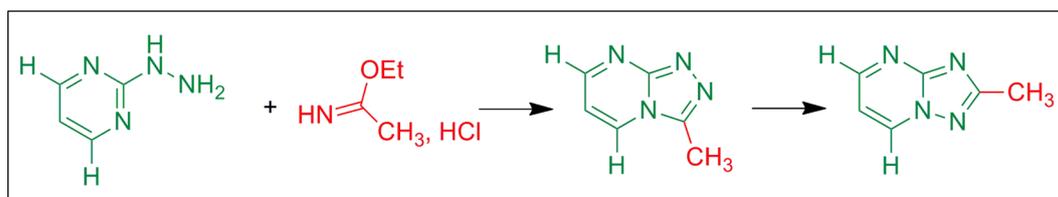
shifted toward higher fields in comparison with K_2PtCl_4 pointing towards trans complexes as trans are detected at higher field than cis. Finally, they evaluated the cytotoxic potential of the complexes against two tumor cell lines: A549 and T47D. They found that the replacement of the NH_3 molecule with bulkier 5,7-diphenyl-1,2,4-triazolo[1,5-a]

pyrimidine significantly increased the IC_{50} values. They also concluded that the choice of leaving groups plays a major role in affecting the cytotoxic activity of the platinum (II) complexes with 5,7-diphenyl-1,2,4-triazolo[1,5-a]pyrimidine [115]. In 2016, Lakomsa et al. reported the synthesis and in vitro cytotoxicity of three structurally different mononuclear dichlorido platinum (II) complexes containing 5,7-diethyl-1,2,4-triazolo[1,5-a]pyrimidine (2). They determined the structure of cis-[PtCl₂(detp)(dmsu)] using the single-crystal X-ray diffraction technique. The molecular structure of the complex exhibited a square planar geometry surrounding the Pt (II) ion with a unique placement of two chloride ligands in the cis position, in the presence of a DMSO molecule in the coordination sphere. In addition to the X-ray diffraction technique, NMR data obtained in solution unambiguously confirmed the square planar geometry of Pt(II) with monodentate N3-bonded triazolopyrimidine (detp), a monodentate second ligand (DMSO or detp) and two chloride ligands in the cis geometry. Further, they evaluated the obtained complex for their cytotoxicity activity using human carcinoma cell lines, T47D, A549 and LoVo, and a normal healthy cell line BALB/3T3. The results of the *in-vitro* study indicated that cis-[PtCl₂(detp)₂] possesses similar cytotoxicity and sevenfold lower toxicity than cisplatin against T47D [116].

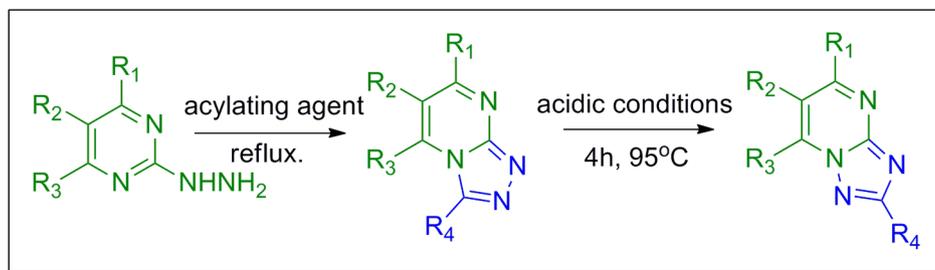


(2)

In 2018, Jakubowski et al. reported the synthesis, structural and biological studies of dicarboxylato platinum (II) complexes containing dimethyl sulfoxide and triazolopyrimidine as potential anticancer agents in a solution. They synthesized and characterized four dicarboxylato platinum (II) complexes of the general formula [Pt(R(COO)₂)(DMSO)(N-donor)], where: R(COO)₂ were cyclobutane-1,1-dicarboxylato or malonato, dimethyl sulfoxide, and N-donor were 5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (dntp) or 5,7-diphenyl-1,2,4-triazolo[1,5-a]pyrimidine (dptp) and structurally characterized them with the use of multinuclear magnetic resonance (¹H, ¹³C, ¹⁵N, ¹⁹⁵Pt). The NMR parameters unambiguously disclosed that complex possess



Scheme 44. Cyclization of 2-hydrazinopyrimidines with ethyl imidate hydrochloride.

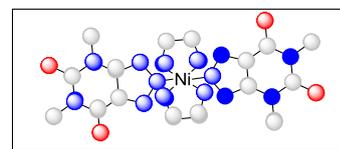


Scheme 45. Synthesis of s-triazolo[1,5a]pyrimidines.

square-planar geometry of Pt (II) in a solution with monodentate N (3)-bonded 5,7-disubstituted-1,2,4-triazolo[1,5-a]pyrimidine, S-bonded dimethyl sulfoxide, and O, O-chelating dicarboxylate. Further in-vitro cytotoxic activity disclosed that synthesized platinum (II) complexes exhibit higher susceptibility to hydrolysis with lower toxicity and affinity to glutathione in comparison with cisplatin and carboplatin. Additionally, it is noticed that two lipophilic platinum (II) complexes, [Pt(mal)(DMSO)(dptp)] and [Pt(CBDC)(DMSO)(dptp)] display the most gratifying in vitro antiproliferative activity [117].

5.2. Nickel complexes

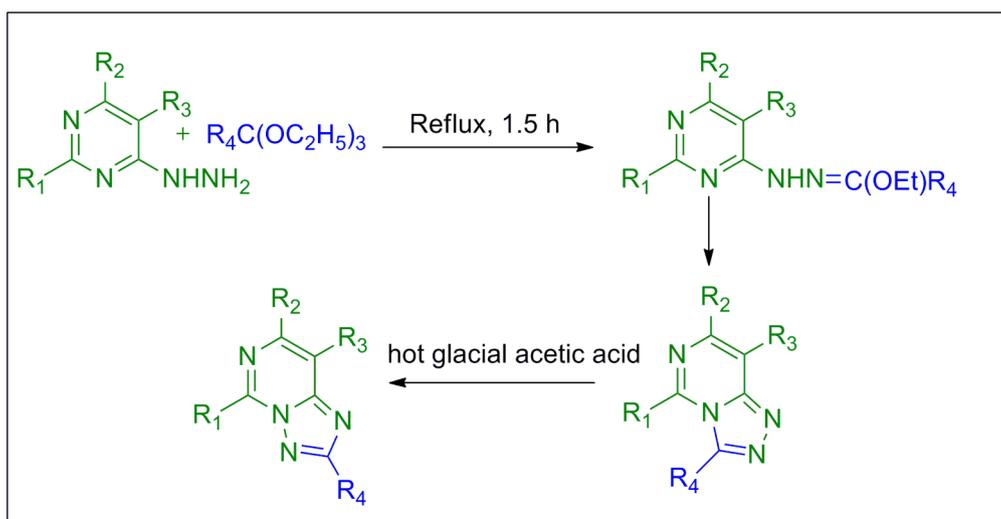
In 2012, Ramírez-Macías et al. reported in vitro anti-leishmanial evaluation of nickel complexes (3) with a triazolopyrimidine derivative against *L. infantum* and *L. braziliensis*. Further, they studied complexes of seven ternary nickel (II) complexes with a triazolopyrimidine derivative and different aliphatic or aromatic amines as auxiliary ligands for their anti-proliferative activity *in vitro* against promastigote and amastigote forms of *L. infantum* and *L. braziliensis*. They disclosed that complexes were not toxic for the host cells and two of them were effective at lower concentrations than the reference drug against leishmaniasis. In general, complexes reduced the *in vitro* growth rate of *Leishmania* spp, its capacity to infect cells and multiplication of the amastigotes. Their study revealed that the potential mechanism, at the level of organelles membranes, involved either direct action on the microtubules or their disorganization, leading to vacuolization, degradation and ultimately cell death [118].



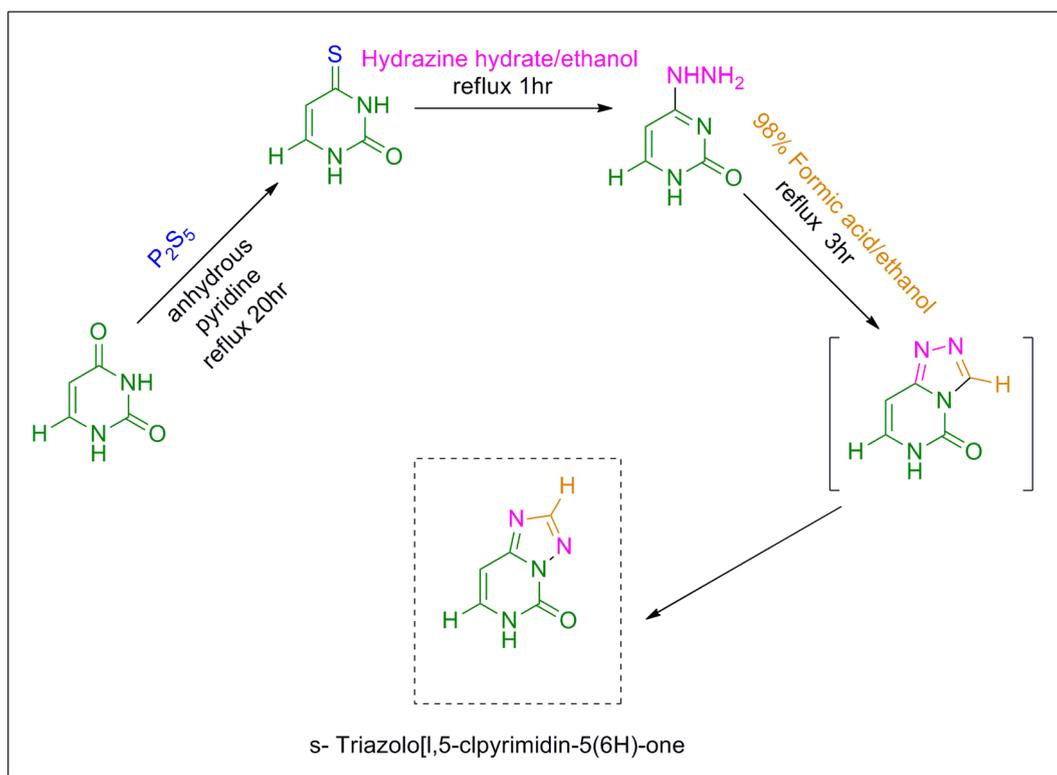
(3)

5.3. Copper complexes

In 2011, Caballero et al. reported the in vitro and in vivo evaluation of anti-parasital activity against *Trypanosoma cruzi* of novel 5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7(4H)-one-based copper complexes 4. They performed conventional reactions of the versatile multidentate ligand 5-methyl-1,2,4-triazolo[1,5-a] pyrimidin-7(4H)-one (HmtpO) with Cu (II) perchlorate salts leading to novel mononuclear complex, [Cu(HmtpO)₂(H₂O)₃](ClO₄)₂·H₂O and bi-dimensional complex, ([Cu(HmtpO)₂(H₂O)₂](ClO₄)₂·2HmtpO)_n. The mononuclear, Cu (HmtpO)₂(H₂O)₃](ClO₄)₂·H₂O complex having two HmtpO show N3-monodentate and N1, O71-bidentate modes. The bi-dimensional polymer is a sandwich-type complex which consists of alternating cationic square-grid layers of [Cu(HmtpO)₂(H₂O)₂]₂⁺, perchlorate anions and purely organic layers formed by non-coordinated HmtpO molecules. Further, the biological evaluation revealed that the complexes were very active *in vitro* against both extra and intracellular forms of *T. cruzi* and were effective at concentrations similar to those of the commonly used drug (benznidazole) but are much less toxic for the host cells [119]. In 2011, Ramírez-Macías reported an evaluation of some complexes against *Leishmania* spp. They found that these copper complexes were most active against *L. infantum* (IC₅₀ 20.0 and 24.4 mM, respectively). Additionally, these compounds were not toxic

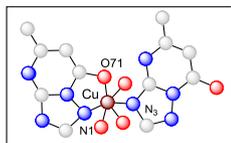


Scheme 46. Synthesis of s-triazolo[4,3-c]pyrimidines and their isomers.



Scheme 47. Synthesis of bis-s-triazolo[1,5- α :1',5'-c]pyrimidine and its derivatives.

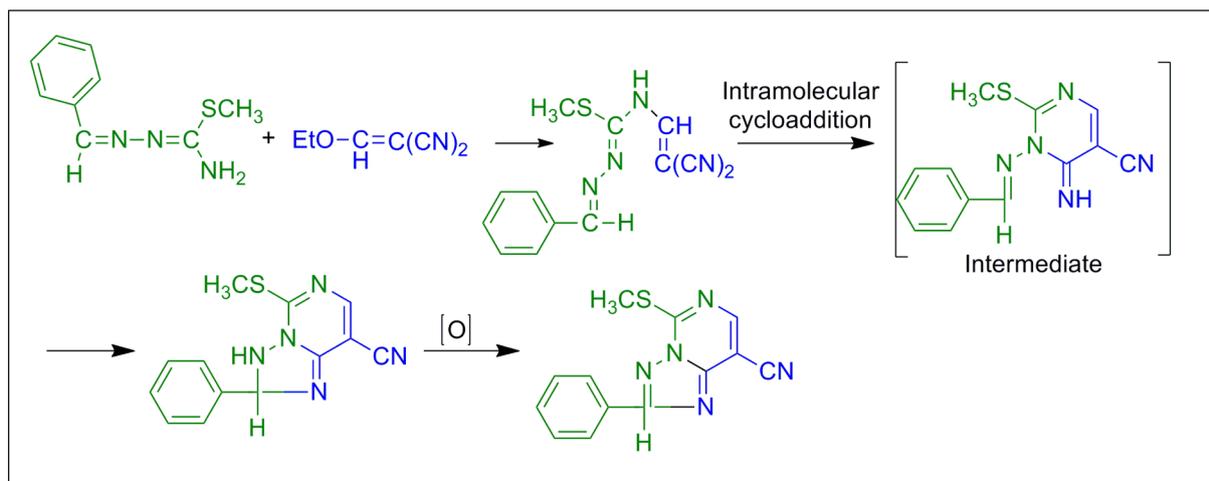
towards J774.2 macrophages. They also decreased infection capacity and severely reduced the multiplication of intracellular amastigotes. Mechanistically, these complexes were found to disrupt the energy metabolism of the parasites at the level of the NAD⁺/NADH balance and the organelle membranes, causing their degradation and cell death [120].



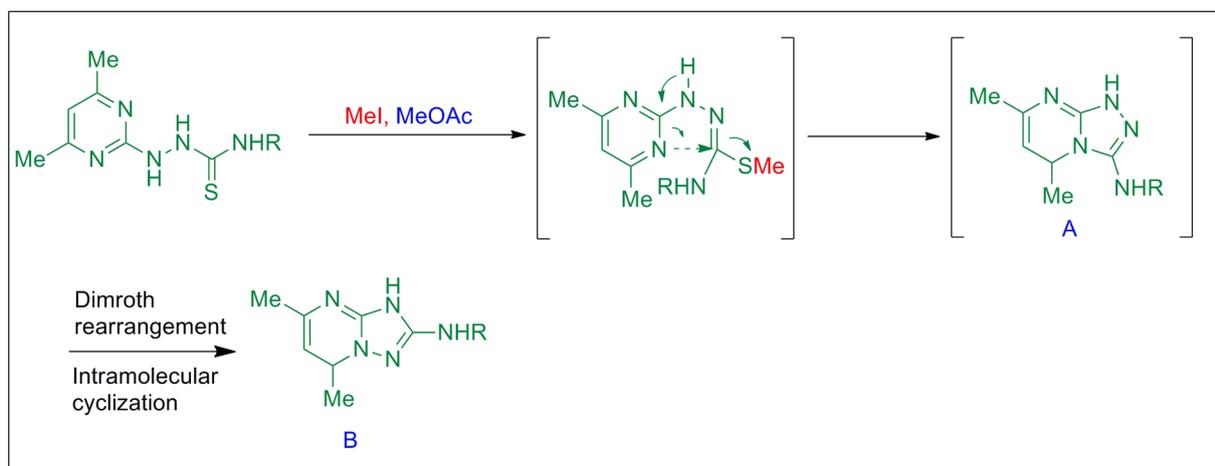
(4)

5.4. Ruthenium complexes

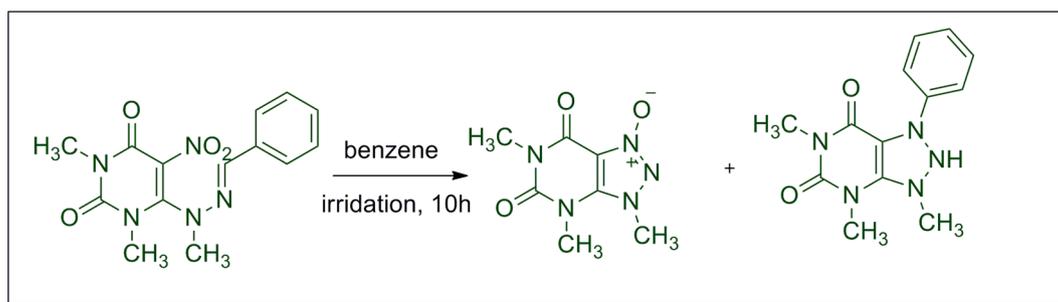
In 2012, Lakomska et al. performed the synthesis, characterization and antitumor evaluation of two highly cytotoxic ruthenium(III) complexes with bulky triazolopyrimidine ligand **5**. They reported two ruthenium(III) complexes composed of 5,7-ditertbutyl-1,2,4-triazolo[1,5- α]pyrimidine (dbtp) ligands. The crystal structures of trans-[RuCl₃(H₂O)(dbtp)₂] and mer-[RuCl₃(dbtp)₃].0.815OCMe₂ showed slightly distorted octahedral geometries with two and three monodentate dbtp ligands bound in a head-to-head orientation, respectively. In both complexes, the heterocyclic dbtp ligands were bound to the ruthenium (III) ion through the N3 nitrogen atom. Further anti-tumor evaluation of both ruthenium (III) compounds against two human cell lines, A549 and T47D showed excellent cytotoxicity with IC₅₀ values in the range of 0.02–2.4 μ M against both cancer cell lines. In addition, the



Scheme 48. Synthesis of one step synthesis of the bicyclic pyrimidines from an open-chain, flexible molecule.

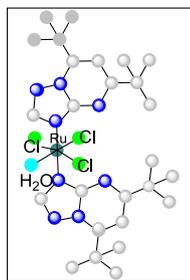


Scheme 49. Heterocyclization of thiosemicarbazides derivatives of pyrimidines to yield amino derivatives of triazolopyrimidines.



Scheme 50. Synthesis of triazolo [4,5-d] pyrimidinedione-1-oxide.

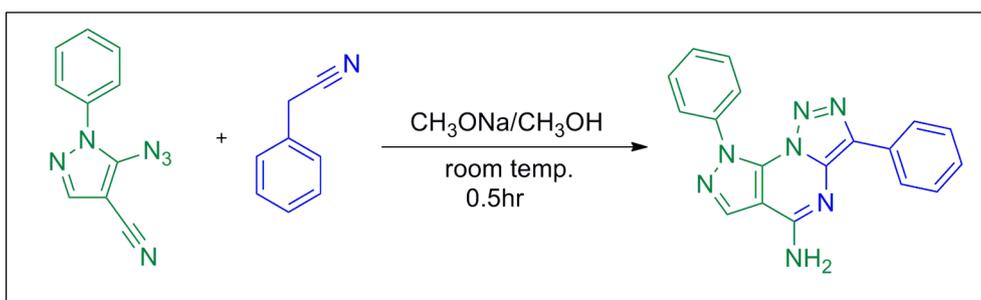
in vitro cytotoxic values of the ruthenium (III) compounds were higher against T47D than the clinically used antitumor drug cisplatin [121].



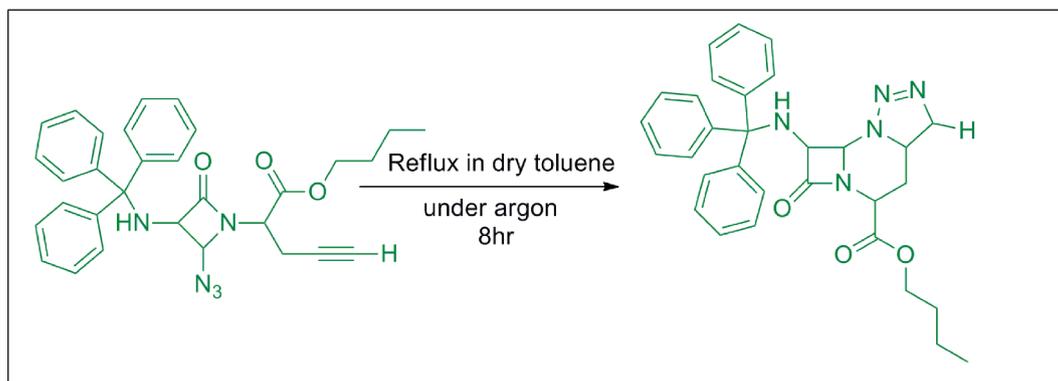
(5)

In 2014, Lakomska et al. reported the synthesis and characterization of the dimeric ruthenium-triazolopyrimidine complex (6). Their study disclosed the crystal structure of homodinuclear $[\text{Ru}_2\text{Cl}_4(\text{tp})(\text{DMSO})_4]$ complex molecules with two water molecules with partial occupancies

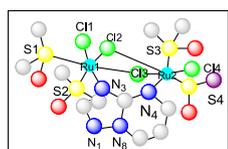
of 50%. Interestingly they claimed that two Ru (II) ions had different ligand positions relative to the central Ru_2Cl_2 ring that defined the equatorial plane. For Ru1, the two remaining equatorial positions were occupied by DMSO, while the chloride and N atom of triazolopyrimidine are in the axial positions. In the Ru2 sphere, the DMSO is in equatorial while the N4 of triazolopyrimidine are axial. In the complex molecule, the deformed octahedral coordination sphere of each Ru (II) is formed by three Cl ligands and two DMSO ligands coordinated with one sulfur atom and one nitrogen atom from the bridging triazolopyrimidine ligand. Two Ru (II) ions were bridged with the chlorine ligand pair. The bond distances of the two Ru ions were found to be slightly different. Additionally, they also performed the *in-vitro* anti-proliferative activity of the complex against two tumor cell lines and normal mice fibroblast cell line, BALB/3T3. However, the synthesized diruthenium(II) complex was not found to be active in the concentration range of 0.1–100 $\mu\text{g}/\text{mL}$ [122].



Scheme 51. Synthesis of 5-amino-3,8-diphenyl-8H-pyrazolo[4,3-e]-v-triazolo[1,5-a]-pyrimidine.



Scheme 52. Intramolecular 1,3-dipolar cycloaddition reaction to synthesize novel β -lactams fused triazolo [3,4-c] pyrimidine.



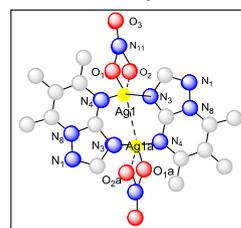
(6)

In 2018, Fandzloch et al. developed and studied mode of action of dimethylsulfoxide ruthenium (III) complex with bulky triazolopyrimidine derivative as a new anticancer drug. They reported that the crystal structure of the Ru(III) complex showed slightly distorted octahedral geometry with unique cis positioned monodentate dbtp ligands bound to the ruthenium(III) ion through the N3 nitrogen atom. Finally, they performed in vitro toxicity assay which proved that slightly lipophilic mer, cis-[RuCl₃(dbtp)₂(DMSO)] (logP = 0.80) was 5-fold less toxic against non-tumorigenic human epithelial cell line (MCF-10A) and normal murine embryonic fibroblast cells (BALB/3T3) than cisplatin. Preliminary studies performed by them towards understanding the mode of action suggested that activation by reduction, electrostatic interactions of the mer, cis-[RuCl₃(dbtp)₂(DMSO)] with CT-DNA and selective delivery to cells by apotransferrin might be relevant for the biological properties of the complex [123].

5.5. Silver complexes

In 2011, Bavelaar et al. reported the synthesis, characterization, single-crystal structure analysis and cytostatic activity of a dinuclear silver compound with 5,6,7-trimethyl-[1,2,4]triazolo[1,5-a]pyrimidine with a short Ag–Ag bond (7). Their study disclosed that the silver ions in the complex were linearly coordinated with two N-atoms of two ligands, generating the dinuclear structure. The Ag–Ag distance was found to be 3.109 Å, which is relatively short but is considered as too long for M–M bonding. Interestingly the Ag (I) coordination in the complex was completed by weakly coordinated, asymmetric bidentate nitrate anions. They further evaluated the anti-cancer potential of the complex using A2780 and A2780R cell lines. The results suggested a

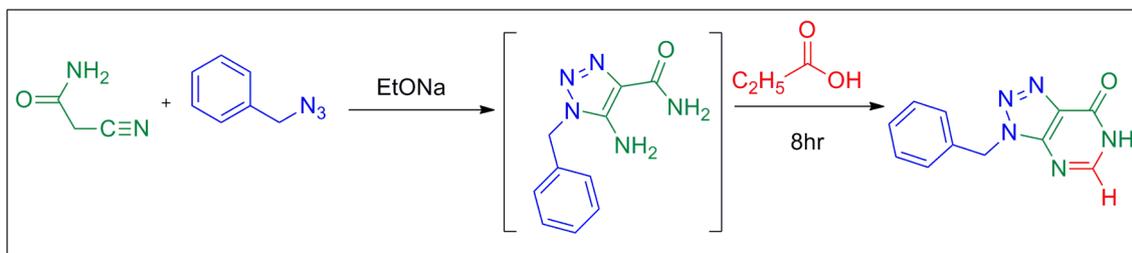
silver complex to be a promising candidate, as the activity was better than that of cisplatin. However, subsequent tests in a panel of tumor cell lines indicated only moderate activity in the EVSA-T cell line [124].



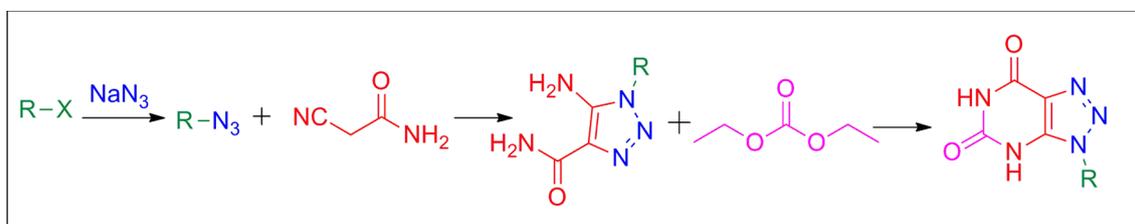
(7)

5.6. Zinc complexes

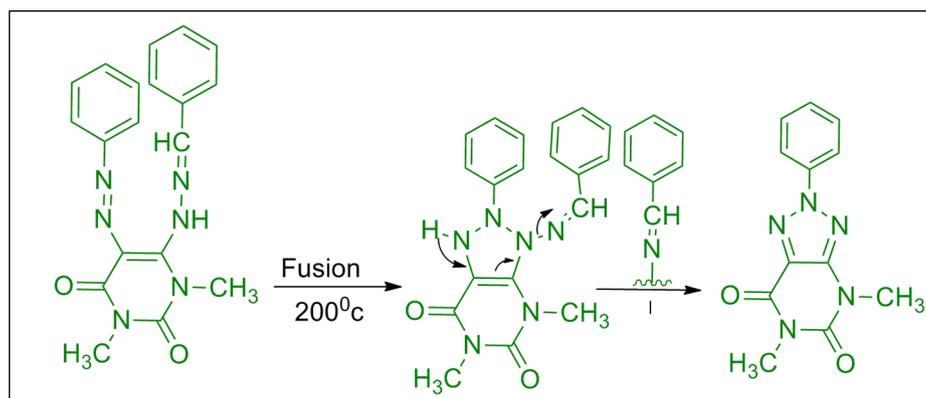
In 2011, Maldonado et al. disclosed one-dimensional zinc (II) polymers with 4,6-dimethyl-1,2,3-triazolo[4,5-d] pyrimidin-5,7-dionato (8) built by bipyridyl-based ligands acting as spacers both in the first and in the second sphere. They utilized three spacers namely, 1,2-bis(4-pyridyl)ethane (bpe), 1,3-bis(4-pyridyl)propane (bpp) and trans-1,2-bis(4-pyridyl)ethene (bpethe) with hexaquaquazinc(II) salt of 4,6-dimethyl-1,2,3-triazolo[4,5-d]pyrimidin-5,7-dionato (Hdmax) to form three different complexes. The crystal structure of complexes containing bpe and bpethe was found to be one-dimensional polymers with a zigzag (bpe) or linear (bpethe) disposition of the metal atoms, as suggested by X-ray diffraction. The triazolopyrimidinato anion, in both the cases, monodentately coordinated through the N atom furthest from the pyrimidine ring whereas the bipyridyl ligands bridge through their N atoms consecutive metal atoms in the polymer. For the bpethe compound, an additional non-coordinated molecule of the spacer per Zn atom was also present, accepting H-bonds from coordinated water molecules and linking in this way the one-dimensional chains into a two-dimensional superstructure [125].



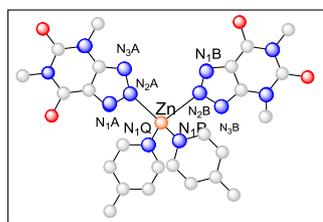
Scheme 53. Synthesis of 2,9-disubstituted Azapurin-6-ones using one pot synthesis strategy.



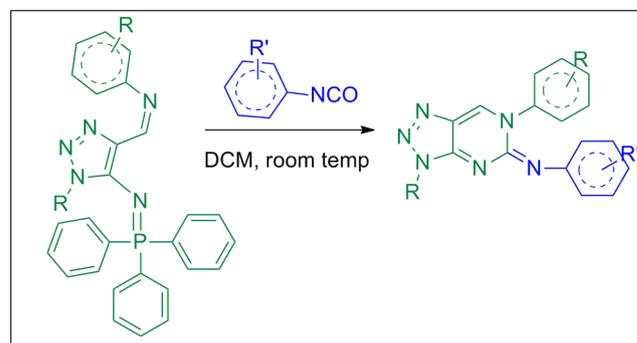
Scheme 54. [3 + 2] Cycloaddition reaction for the synthesis of triazolopyrimidine.



Scheme 55. Formation of v-triazolo[4,5-d]pyrimidine derivative by thermolysis.



(8)



Scheme 57. Electrocyclic ring closure reaction to prepare 1,2,3-triazolo[4,5-d]pyrimidine derivatives.

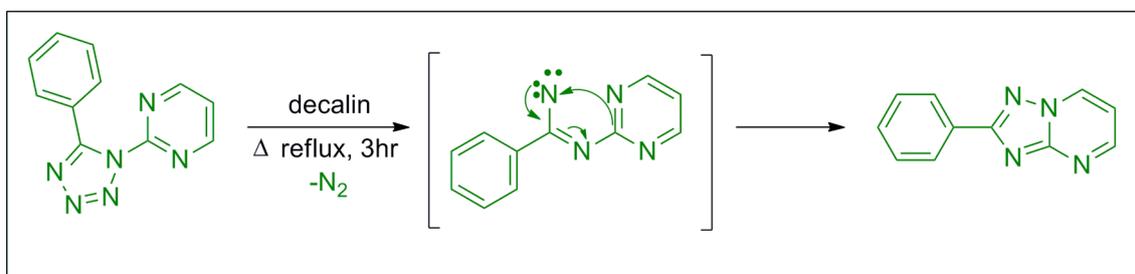
6. Medicinal attributes

6.1. CNS agents

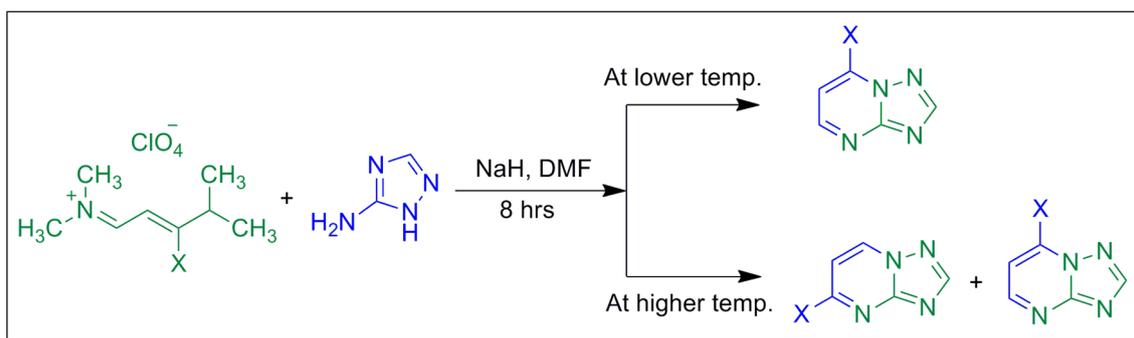
The adenosine A_{2a} receptors belong to a family of seven transmembrane G-protein-coupled receptors (GPCRs) and comprise of four subtypes (A_1 , A_{2a} , A_{2b} , and A_3). The A_{2a} receptors are located in the basal ganglia and within the striatum; they are selectively located on the GABA/enkephalin-containing neurons bearing the dopamine D2 receptors. The A_{2a} receptors, therefore, have the ability to modulate motor functions as they are capable of indirectly regulating the striatal output activity. In rats, intracerebroventricular injection with a selective adenosine A_{2a} agonist induces catalepsy, a motor disability that is similar to that exhibited by patients with Parkinson's disease. Vu et al.

reported the series of triazolopyrimidine derivatives as the selective adenosine A_{2a} receptor antagonists (Fig. 2) [126].

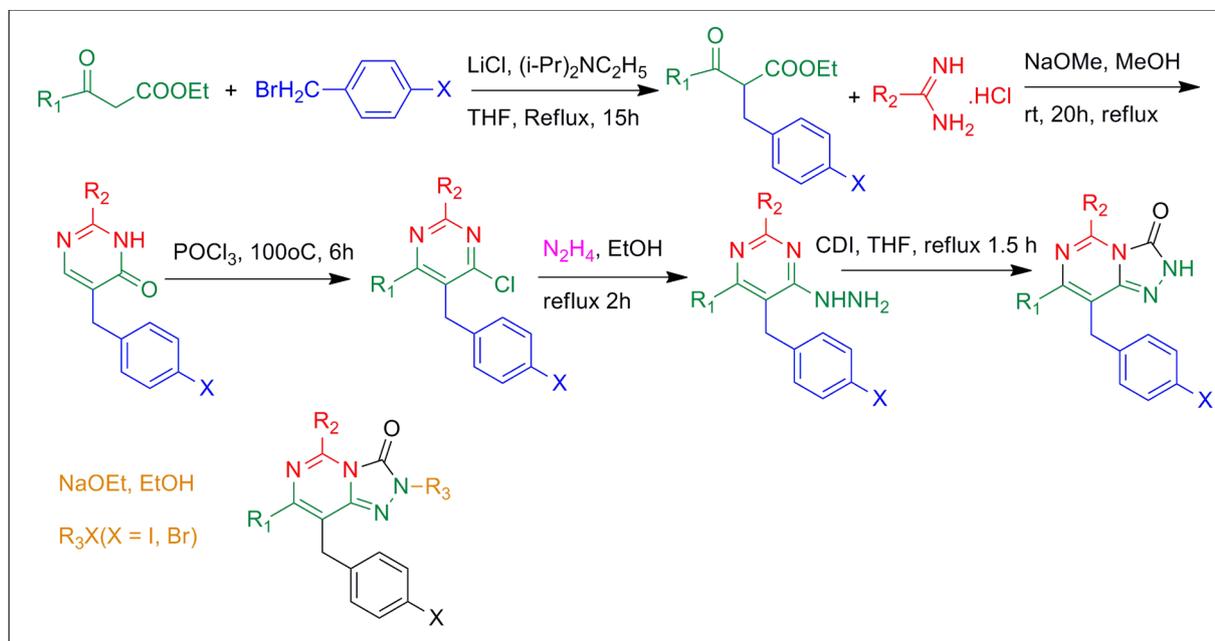
In 2015, Romdhane et al. reported anti-acetylcholinesterase activity of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine derivatives (Fig. 3). They disclosed that all the tested derivatives were having significant acetylcholinesterase inhibition. Mechanistically, they claimed that phosphonate derivatives make covalent adduct with serine in the catalytic domain of acetylcholinesterase enzyme. Out of all, the derivatives with methylated phosphonate substitution at the 3rd position of the



Scheme 56. Synthesis of 2-aryl[1,2,4]triazolo[1,5-a]pyrimidine via pyrolysis.



Scheme 58. Synthesis of monosubstituted triazolo [1,5-*a*] pyrimidines by reacting vinyl iminium salt.



Scheme 59. 4-hydrazinopyrimidine mediated synthesis of different 1,2,4-triazolo[4,3-*c*]-pyrimidines.

triazole nucleus were more active than their ethylated analogues. They established that upon increasing the carbon chain at 3rd position, anti-acetylcholinesterase activity decrease for phosphonate derivatives of triazolopyrimidines. Similarly, for derivatives with coumarin nucleus coupled at 3rd position, they concluded that coumarin nucleus forms an additional π - π interaction with some active residues of AChE resulting more stability of the formed ligand which prevents hydrolysis of ACh [1].

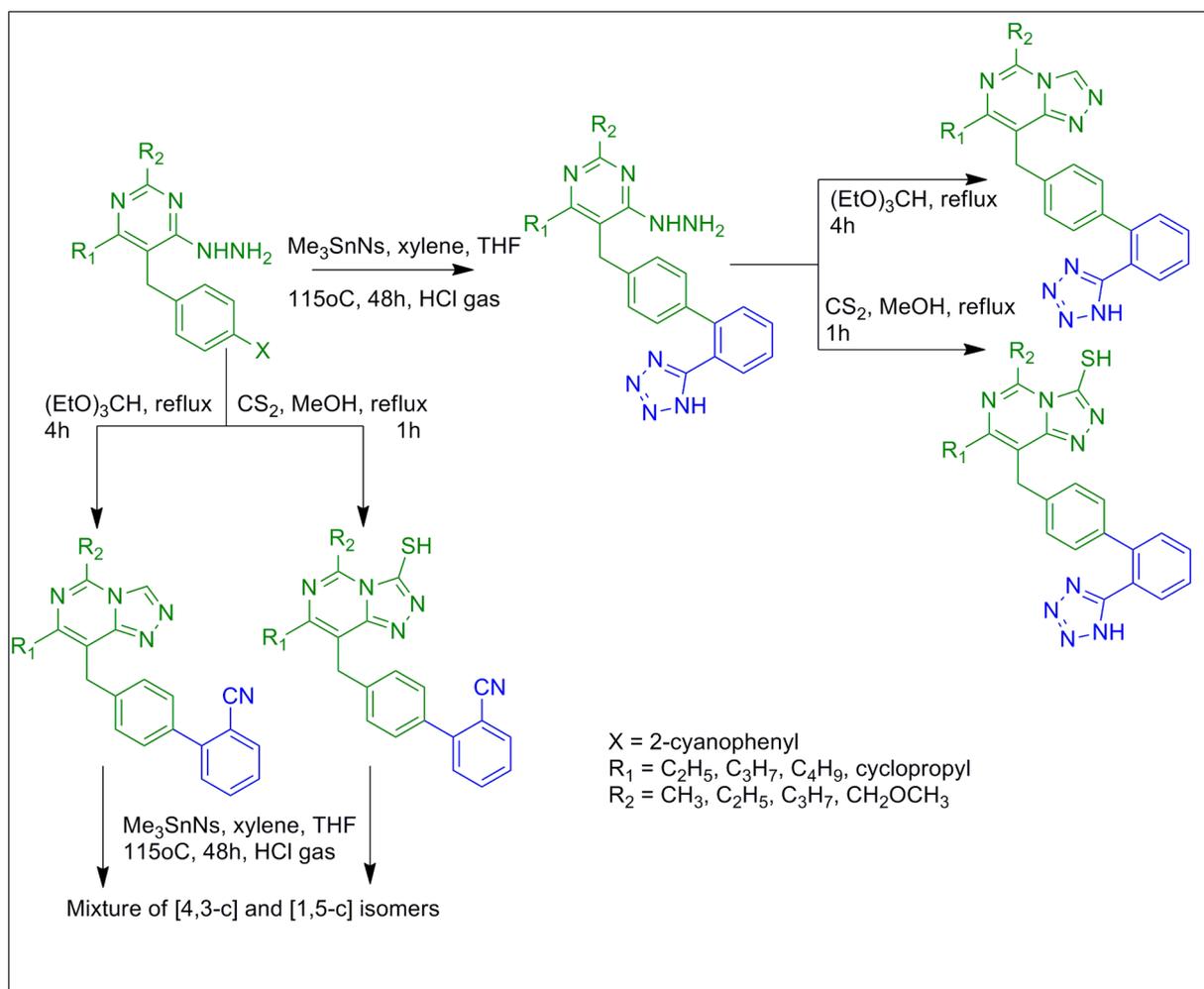
In 2016, Kumar et al. reported AChE inhibitory activity of a series of triazolo pyrimidine derivatives. They found that compounds with substituted quinolone coupled via piperazine ring at the 7th position of triazolopyrimidine effectively inhibited both ChEs (AChE and BuChE) in the sub-micromolar range *in vitro* (Fig. 4). Their study disclosed that the triazolopyrimidine nucleus in the synthesized compounds form π - π interactions with the residues in the peripheral anionic site of AChE, while the quinoline nucleus interacts with the catalytic active site of AChE. Overall, the substitution of quinoline ring by fluoro group and presence of triazolo pyrimidine moiety imparts strong AChE inhibition [40]. They performed similar kind of study again in 2018, keeping triazolopyrimidine but replacing quinoline with a pyrimidine, however no significant improvement in activity was observed [41]. In 2017, Jameel et al. reported a similar kind of study where they evaluated AChE inhibitory potential of triazolopyrimidine coupled with substituted triazine via piperazine ring. They concluded that triazolopyrimidines coupled with triazine show better AChE inhibitory potential

and overall improved *in-vitro* results in Alzheimer's disease [42].

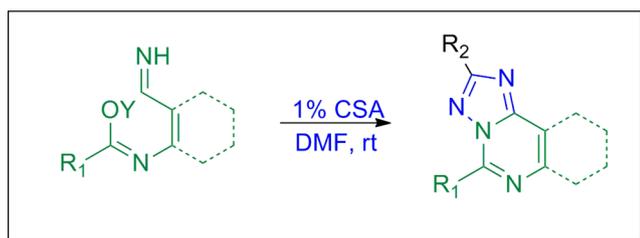
6.2. Histaminic activity

In 1975, Wan et al. examined and reported the effects of dibutyryl cyclic AMP in the presence and absence of metiamide, a histamine antagonist and 2-amino-6-methyl-5-oxo-4-propyl-4,5-dihydro-*s*-triazolo (1,5-*a*) pyrimidine (ICI 63197) on acid secretion responses to histamine and pentagastrin [127]. *In-vitro* studies carried out on isolated whole mouse stomach showed that db cyclic AMP regularly stimulated the acid secretion and there was no significant difference in acid secretion response to db cyclic AMP in presence or absence of metiamide. Moreover, unlike db cyclic AMP, histamine and pentagastrin could not stimulate acid secretion. However, there was significant an increase in acid secretion by histamine and pentagastrin in the presence of phosphodiesterase inhibitor, ICI 63197. Thus, it was hypothesized that triazolopyrimidine (phosphodiesterase inhibitor) enhanced the level of cyclic AMP which in turn stimulated the acid secretion in the presence of histamine and pentagastrin. It was also concluded that triazolopyrimidine was more effective than classical methylxanthine phosphodiesterase inhibitors i.e., theophylline and caffeine.

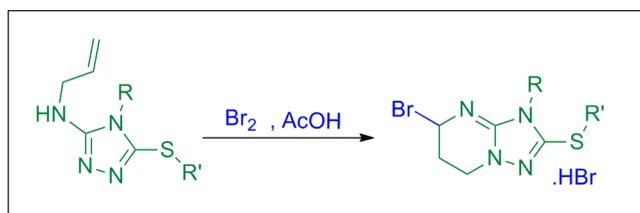
A similar study was reported by Nahorski et al. in 1975 [128]. They studied the ability of potent phosphodiesterase inhibitors i.e., 4-(3-butoxy-4-methoxy)-2-imidazolidinone (Ro 20-1724) and 2-amino-6-methyl-5-oxo-4-*n*-propyl-4,5-dihydro-*s*-triazolo(1,5-*a*) pyrimidine (ICI 63



Scheme 60. 4-hydrazinopyrimidine mediated synthesis of mixture of 1,2,4-triazolo[4,3-c]-pyrimidine and 1,2,4-triazolo[1,5-c]-pyrimidine.



Scheme 61. Synthesis of triazolopyrimidine derivatives carried out by condensation of iminoester.



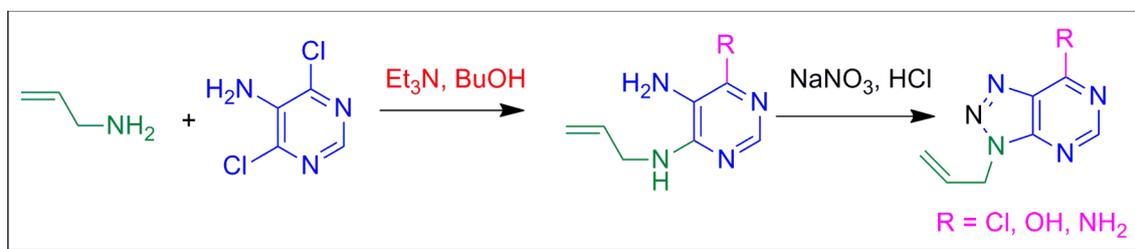
Scheme 62. Electrophilic cyclization of allyl-substituted aminotriazoles for the synthesis of triazolopyrimidine.

197) to stimulate cerebral cyclic AMP by biogenic amines. The tests were performed both in vivo and in vitro. In vitro results showed that dopamine and histamine were unable to stimulate cyclic AMP production in mouse forebrain slices until they were in presence of 200 μM

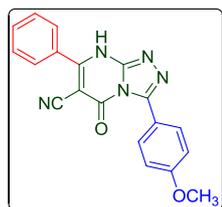
Ro 20-1724 and ICI 63197. Prostaglandin E1 and 5-hydroxytryptamine at concentrations up to 100 μM did not produce cyclic AMP in the presence or absence of phosphodiesterase inhibitors. Similar results were attained after in vivo tests and it was concluded that both dialkyl imidazolidinone and triazolopyrimidine were able to enhance the level of cyclic AMP-induced by biogenic amines.

6.3. Anti-microbial

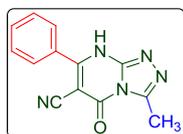
In 1945, Roblin and co-workers reported that 8-azaguanine (5-amino-7-hydroxy-1- ν -triazolo[*d*]pyrimidine) was found to be most potent purine inhibitor in *E. coli* and *S. aureus* and produced a synergistic effect when given in combination with sulfonamides [12]. In 1952, Arnow et al. tested the inhibitory activity of triazolopyrimidine analogs against the growth of *S. subtilis*. The powerful inhibition was obtained with the 8-azaguanine. Interestingly, the inhibition was reversed by guanine and it was confirmed from the study that alga showed similar behavior towards 8-azaguanine as that of a variety of animal and plant system shown when the compound was tested on them [129]. In 1988, Khalil et al. explored thiazolo[3,2-*a*]-triazolo[4,3-*a*]-pyrimidine as microbicidal agents. The study disclosed that compound 9 possessed enhanced bacteriocidal activity against *P. aeruginosa* due to OCH_3 substitution on the phenyl ring. While fungicidal activity was observed in compound 10 against *A. flavus*, was favored by phenyl substitution [130].



Scheme 63. Palladium-catalyzed synthesis of 3-allyl-1,2,3-triazolo[4,5-d]-pyrimidines.



(9)



(10)

In the year 1990, Shimizu et al. reported some intermediates of triazolopyrimidine by combining it with β -lactam antibiotics (novel cephalosporin series), in an effort to overcome the problem of resistance against beta-lactam antibiotics (Fig. 5). These molecules were found to possess essential medicinal composition for bacterial disease [131].

Pees et al. in 1998 filed a patent claiming the fungicidal activity of certain triazolopyrimidine derivatives (Fig. 6). These compounds were found effective against ascomycete class fungus namely *A. solani*, *V. inaequalis* and *B. cinerea*. Further, it was also reported that the heterocyclic and cycloalkyl analogs of series 1 also display good fungicidal activity [132]. The dihalo derivatives of triazolopyrimidines (series 2) were also reported with fungicidal activity [133].

After one year, the same research group again filed a patent claiming the fungicidal activity of trifluoromethylalkylamino derivatives of triazolopyrimidines. It was reported that the presence of alkyl and substituted alkyl groups at R_1 and R_2 provide selective fungicidal activity. Also, adding halogen group at R_3 - R_8 and alkyl groups at R_4 - R_8 provide potential to combat fungus at a locus in various crops (Fig. 7) [134].

Later on, they claimed that incorporating chloro or fluoro group at R_4 , R_6 , and R_8 shows selective fungicidal activity, particularly against rice blast disease. In this case, R_1 and R_2 represented the substituted alkyl, alkenyl, alkynyl, alkadienyl, haloalkyl, aryl, heteroaryl, cycloalkyl, bicycloalkyl or heterocyclyl groups. The resulted trichlorophenyl-triazolopyrimidines display good fungicidal activity

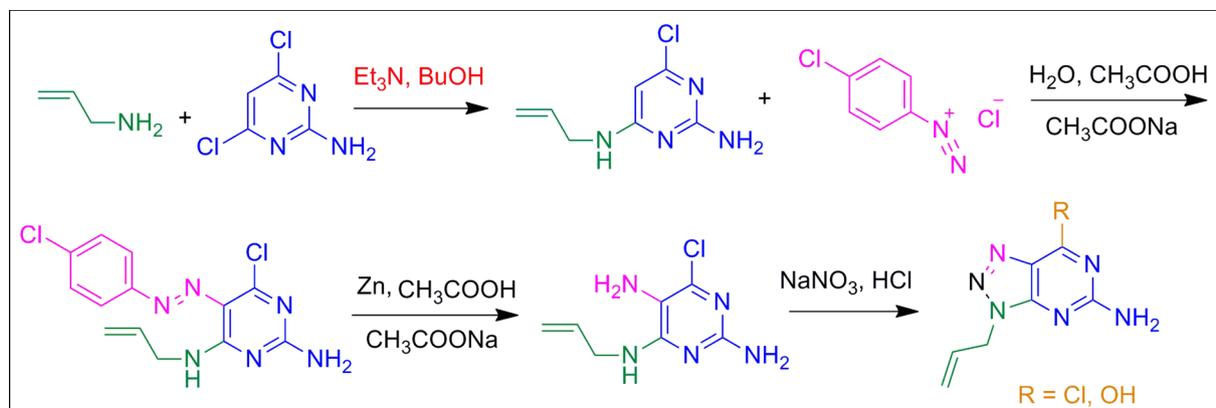
[135,136]. Additionally, alkylation at the 5th position of triazolopyrimidine scaffold provided a novel series of antifungal compounds with excellent fungicidal activity reported in various crops [137].

Hassan et al. screened a series of 4-hydroxy coumarin derivatives as antifungal and antibacterial agents. The biological data revealed that compounds substituted with triazolopyrimidine derivatives were found to be most active against *S. aureus*, *B. cereus*, *S. marcescens*, and *P. mirabilis* compared to reference drug ampicillin (Fig. 8).

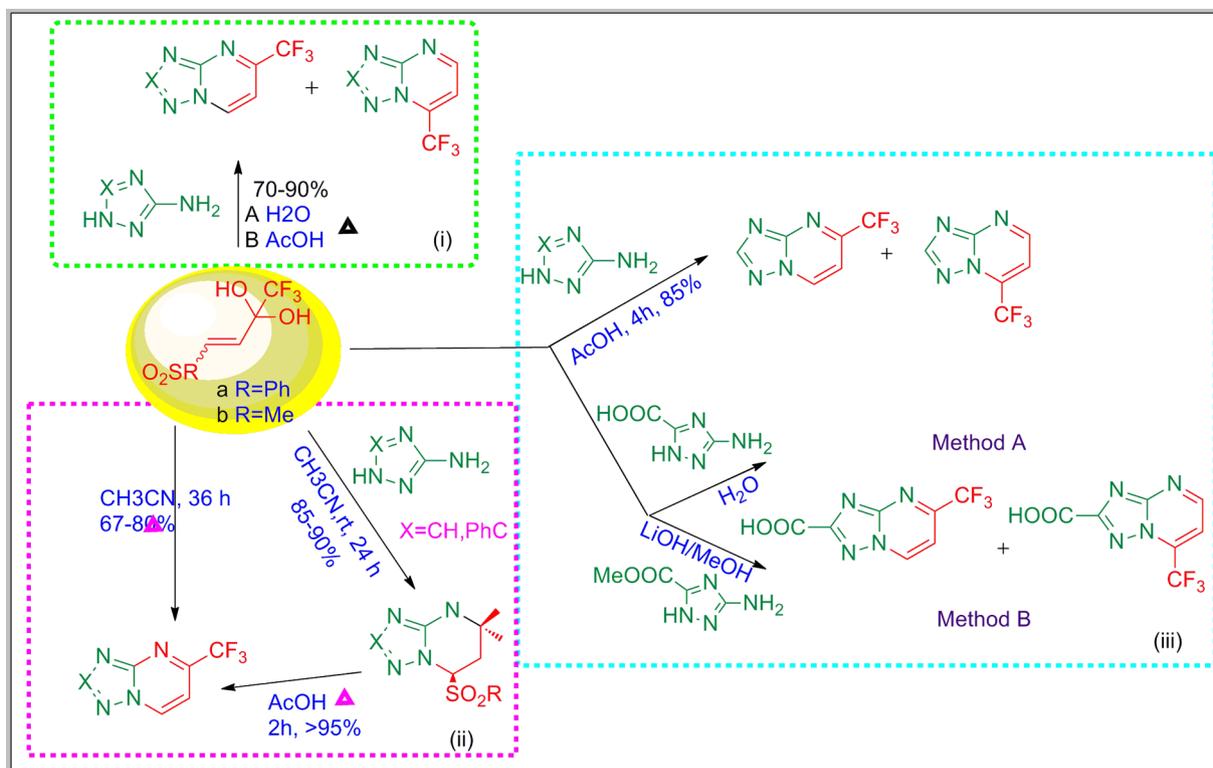
In 2010, El-Sayed et al. reported the synthesis of novel 1,2,3-triazolopyrimidine derivatives, their glycoside and acyclic nucleoside analogs as anti-microbial agents (Fig. 9). Their structure-activity relationship indicated that substitution at N-1 in the pyrimidine ring in the 1,2,3-triazolyl moiety resulted in an increase in the antimicrobial activity with respect to the three microorganisms. Moreover, substitution at N-1 with long oxygenated alkyl chain with terminal free hydroxyl group resulted in a significant increase in the activity against *P. aeruginosa* [104].

In 2011, Khera et al. evaluated oxazolidinone coupled triazolopyrimidines as anti-microbial agents (Fig. 10). They disclosed that triazolopyrimidines with substituted oxazolidinone coupled at the 3rd position via a phenyl ring show significant anti-microbial potential. Interestingly the derivatives reported by them were inactive against *E. coli*. They found that modifications on the oxazolidinone nucleus improved the anti-microbial potential of the compounds, according to the variation in the electron density in the region, against gram-positive pathogens [11].

In 2012, Abdel-Azeim reported anti-microbial potential of pyrido fused triazolopyrimidine derivatives. Their study disclosed that all pyrido fused triazolopyrimidine compounds were capable of inhibition against Gram-positive bacteria, *B. Subtilis*. Additionally, few of the derivatives also showed a significant effect against Gram-negative bacteria, *E. coli*. Interestingly, one derivative also showed intermediate inhibition against yeast and fungi [138]. Luo et al. in 2013, reported a novel class of 1,3,4-thiadiazole coupled 1,2,4-triazolo[1,5-a]pyrimidine derivatives as anti-microbial agents (Fig. 11). Their study disclosed that the presence of fluoro substituent in the molecule increases the anti-microbial efficiency of corresponding compounds. Also, substituents on



Scheme 64. Synthesis of allylic derivatives of 5-amino-1,2,3-triazolo[4,5-d]pyrimidin-7-ones.



Scheme 65. One-pot synthesis of fluorine-containing triazolopyrimidine derivatives.

ortho- and para-position can improve the antimicrobial activity of the compounds. Interestingly 1,3,4-thiadiazole coupled 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives exhibited better inhibitory activity against Gram-negative bacteria than Gram-positive bacteria [139].

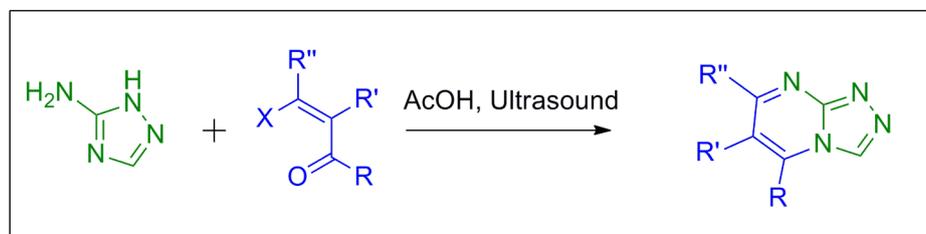
In 2014, Patil et al. reported the synthesis of triazolopyrimidine acylsulfonamides as novel acetoxyacid synthase (AHAS) inhibitors having anti-mycobacterial activity (Fig. 12). They demonstrated that the molecules exhibited potent Mtb AHAS inhibition as well as Mtb MIC via the expected mechanism of action. The SAR study disclosed that the inhibition could be ascribed to the electronic nature as well as the size of ortho substitution of the phenyl ring. The moderate activity of the methoxy and methyl groups reinforces the fact that both electronics, as well as the steric factor, plays an important role in AHAS inhibition [103].

In 2015, Wang et al. reported multiple derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidines and evaluated them for narrow spectrum anti-microbial activity (Fig. 13). The study initiated from an in-silico screening against a penicillin-binding protein (PBP), which is an essential enzyme for peptidoglycan biosynthesis, leading to the identification of triazolopyrimidine scaffold. They further explored the various positions of the scaffold for their *E. faecium* inhibitory. Their study disclosed that dimethyl amino-substituted aryl ring at the 7th position of triazolopyrimidine showed good inhibitory activity. Similarly, they substituted different heterocycles and aryl rings at the 2nd position of

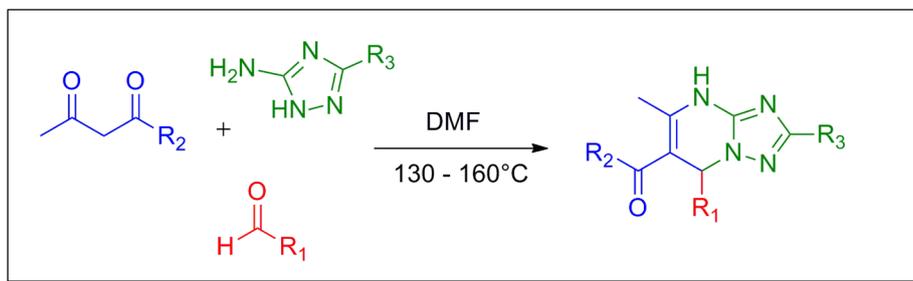
triazolopyrimidine and found that the thiobenzyl substituted compound display best activity [81].

Bhatt et al., in 2015, evaluated pyrazole coupled triazolo[1,5-*a*]pyrimidine hybrids as anti-tubercular agents. Their study disclosed that the substitution of halogens on the aryl ring of pyrazole demonstrated improved activity. Interestingly, fluorine substituted compounds were found to be most potent due to their high electronegativity and hydrophobicity. The substitutional changes at the para position of the pyridyl ring of the carboxamide arm also influence the activity pattern. The presence of -Br group greatly increases the potency of the compounds as compared to methyl substituted and unsubstituted pyridyl ring. The results of this study established pyrazolo coupled triazolopyrimidine hybrids as lead molecules for anti-TB drug discovery process [105].

In 2017, Saundane et al reported the evaluation of some novel indole analogs containing triazolopyrimidine moiety as anti-microbial agents (Fig. 14). Their study disclosed that the antimicrobial and antioxidant activities of the hybrids could be due to the presence of chloro and methoxy substitutions. Evidently, the presence of these substitutions enhanced the activity in contrast to the compounds devoid of any substitution. Additionally, the triazolopyrimidine scaffold generally augments the activity. Furthermore, the indole moiety was found to be essential for anti-microbial activity [106].



Scheme 66. Condensation of aminotriazole with vinyl keto Snes for the synthesis of triazolopyrimidine.



Scheme 67. Three component one synthesis of 2-amino-5-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitriles.

6.4. Anti-cancer

Initially, in 1949, it was reported that guanine analogs cause definite inhibition of growth in mice of a transplantable mammary adenocarcinoma EO771. It also inhibited the growth of *T. gelii* and various cancer tissues which relate to guanine metabolism, as interpreted by Kidder et al. This work was later extended by Stock et al., testing the anticancer activity of triazolopyrimidine against the Sarcoma. Interestingly, inhibition was observed with 8-azaguanine and 4 other triazolopyrimidines at tolerated doses [140]. In 1950, Gellhorn et al. observed the pharmacological action of guanine analog 5-amino-7-Hydroxy-1H-v-triazolo (d) pyrimidine on a wide variety of sarcoma and leukemia's, with an exception to lymphatic leukemia. It was also concluded that the chemical pattern of all neoplastic cells is not homogenous; in itself, triazolopyrimidine fails to suppress various tumors [141]. Bennett and co-workers studied that in 8-azaguanine-2-C¹⁴, very little isotopic carbon is oxidized to carbon dioxide and exhaled but most of them are excreted in urine. The compound was preferentially accumulated and possesses little activity against Eo771 adenocarcinoma as compared to 8-azaguanine [16]. In 1950 Shapiro et al. reported that 5-amino-7-hydroxy-1H-v-triazolo[d]pyrimidine (8-azaguanine) decreases the mitotic rate of tumor cells in Brown-Pearce carcinoma [142]. Later, Kidder et al. gave evidence on the previously reported activity of 8-azaguanine. They showed that the compound is active against adenocarcinoma, lymphoma, and leukemia [143]. In 1952, Hirschberg et al. reported that 8-azaxanthine, enzymatic product of 8-azaguanine exhibited no carcinostatic activity in tumor-bearing tissue homogenates of different tumors while they showed rapid inactivation of major portions of injected 8-azaguanine in normal tissue homogenates (Fig. 15). Although deaminase activity of 8-azaguanine was high in three azaguanine resistance tumors and low or negligible in four azaguanine susceptible tumors [144].

In 1958, Hideo and Yasuo synthesized a variety of 5-substituted 7-methyl-s-triazolo(4,3-a)- and -tetrazole (1,5-a) pyrimidines, a derivative of triazolo and tetrazolo pyrimidine. Nucleophilic substitution of the corresponding chloro compound was involved in a variety of pyrimidine. The synthesized molecules were then screened for anticancer activity [145]. In 1960, Yoshida et al. concluded that the compounds containing triazolopyrimidine nuclei including 8-azaguanine and its

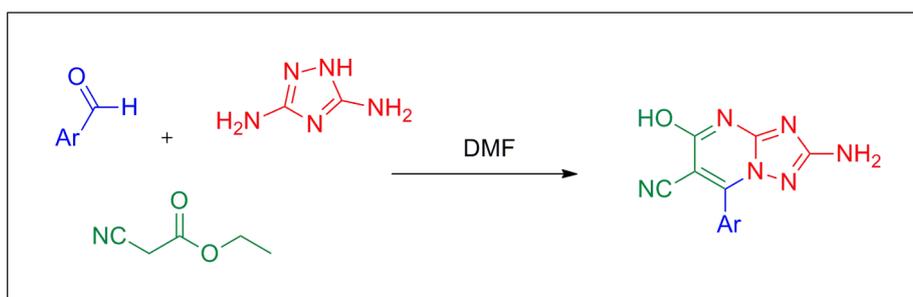
four related molecules have high potency against the deformation of chromosomes and alter mitotic rate in Yoshida sarcoma cells [146]. In 1982, Novikova et al. synthesized varied 5,7- substituted s-triazolo[1,5-a]pyrimidine and tested the synthesized molecules on transplanted tumors in mice [97]. In 2017, Kamal et al. reported triazolopyrimidine-pyrazole hybrids as potent apoptosis inducers (Fig. 16). Their investigation revealed that newly reported hybrids were having significant potential to induce apoptotic cell death in testicular germ cells of goat *Capra hircus*. Among all, compounds with bulky phenyl and naphthyl substitutions were found to be most cytotoxic to induce apoptotic cell death [54].

In 2017, Hassan et al. reported the anti-cancer potential of fused triazolopyrimidine derivatives (Fig. 17). They evaluated the synthesized derivatives for their anti-tumor activity by evaluating their ability to interact with the DNA. Their study disclosed that the morpholine ring containing molecules showed better activity than *N*-methyl piperazine derivatives. The phenyl azo group proved to enhance in vitro activity especially when attached to an electron-withdrawing group at the para position [43].

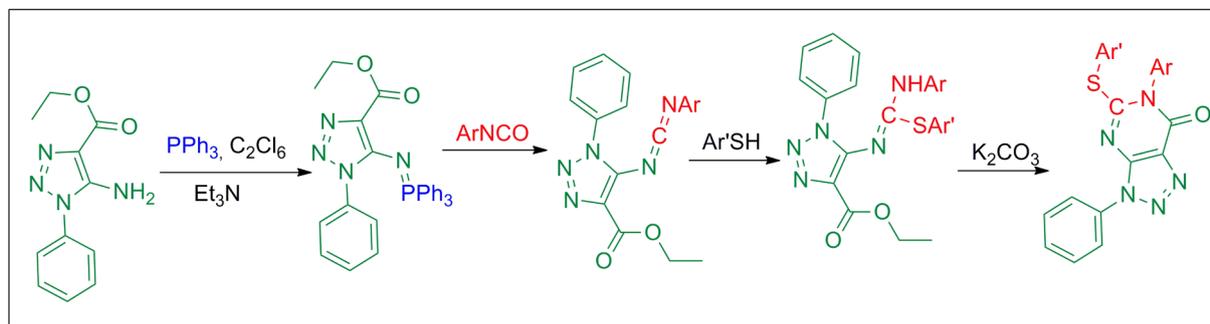
In 2012, Huang et al. reported novel 7'-aryl-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidines derivatives (Fig. 18). They evaluated all the synthesized compounds for their in-vitro anticancer activity against PC-3, MCF-7, and EC9706 cell lines. The preliminary results exhibited that the substituents on the phenyl ring remarkably influenced the cytotoxicity [113].

In 2018, Oukoloff et al. reported photoactivatable derivatives of [1,2,4]triazolo[1,5-a]pyrimidines as microtubule active agents (Fig. 19). Their study disclosed that incorporation of photoactivatable diazirine rings in the C-7 substituent of [1,2,4]- triazolo[1,5-a]pyrimidines can result in derivatives that retain significant biological activity. Additionally, they reported that depending on an appropriate alkoxy side chain, the mode of action of these compounds can be switched from microtubule stabilizing agents to microtubule-disrupting compounds that cause a reduction in tubulin levels [147].

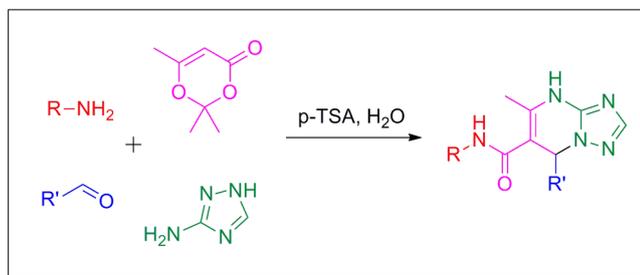
In another study, Wang et al. developed some potent and selective triazolo[1,5-a]pyrimidine inhibitors targeting DCN1-UBC12 protein-protein interactions. The triazolo[1,5-a]pyrimidine core was explored with varied as described in Fig. 20. The methyl group i.e. less steric group at R₁ is preferred over other bulky groups for the desired activity.



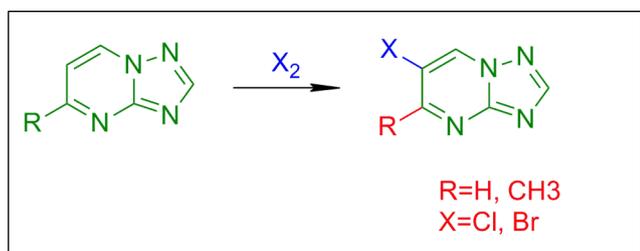
Scheme 68. Three component one-pot synthesis of triazolopyrimidine.



Scheme 69. Tandem Aza-Wittig reaction for the synthesis of triazolopyrimidine.



Scheme 70. Four component one synthesis of triazolopyrimidine.



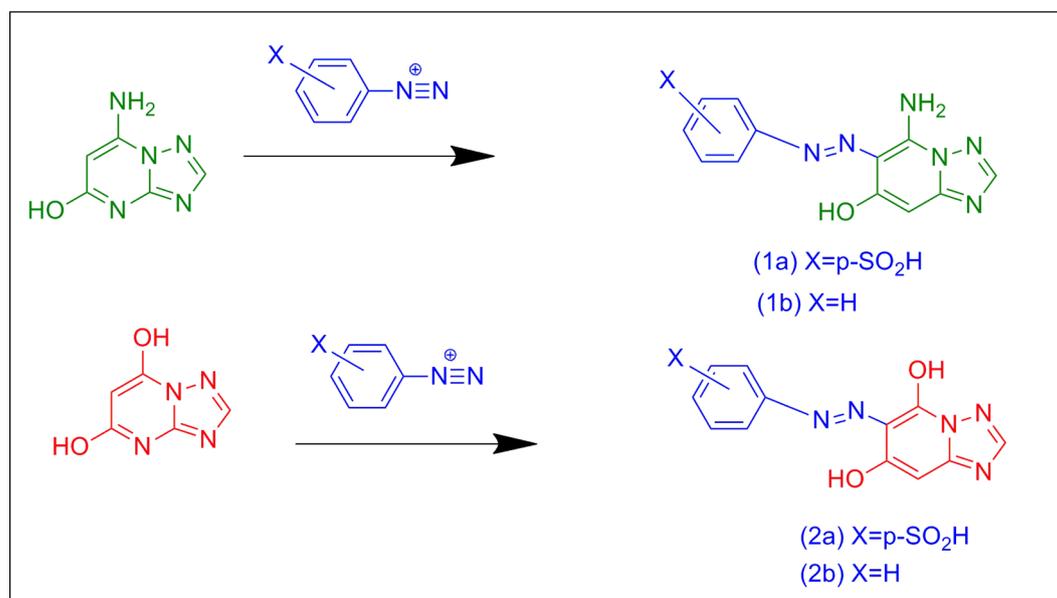
Scheme 71. Halogenation reaction on the triazolopyrimidine nucleus.

At R_2 position, the introduction of 2- and 3-substituted phenyl ring was found to be less potent because of steric hindrance, while 4-substituted phenyl ring was found to be most potent against DCN1. The

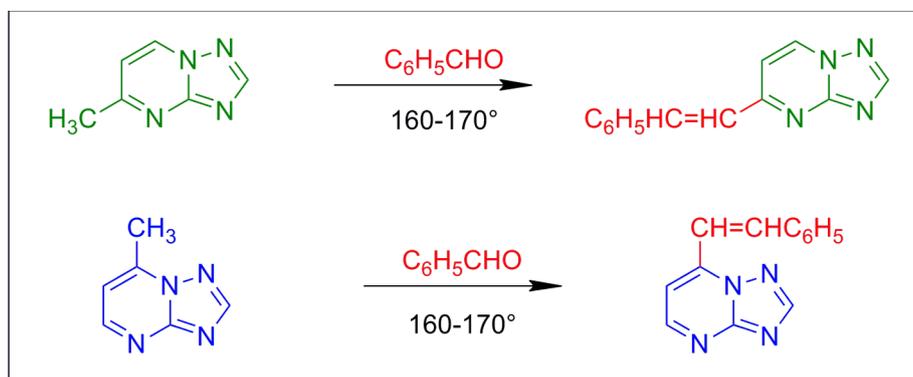
hydrophobic group at the R_3 position could lead to the loss of the activity by destabilizing the complex. The N,N -dimethyl group at R_4 occupied the hydrophobic pocket thereby increased binding affinity and biochemical potency against DCN1. Among all compounds, the compound with substitutions shown in Fig. 20 efficiently inactivated the DCN1–UBC12 interaction in a reversible manner with an IC_{50} value of 11 nM and showed specific selectivity over CDK, BTK, and EGFR kinases. This compound may serve as a novel potent DCN1 inhibitor which can target the interaction of DCN1 with UBC12 and is a smart approach against various types of cancer, in which Cul3/1 was dysregulated [148].

6.5. Anti-inflammatory

In 1983, Chipkin and associates found 4,7-dimethyl-2-(4-pyridinyl)-1,2,4-triazolo[1,5-*a*]pyrimidin-5(4H)-one as potent analgesic and anti-inflammatory agent. Activity results revealed that ED_{50} was found to be 34 mg/kg po with mouse acetic acid writhing test. While, ED_{7sec} was found to be 12.3 mg/kg po, determined with a yeast-paw test at 30mins post-treatment [149]. In 2015, Nettekoven et al. reported novel triazolopyrimidine-derived cannabinoid receptor 2 agonists as a potential treatment for inflammatory kidney diseases. They initially utilized high-throughput screening to identify new heterocyclic small-molecule CB2 receptor agonists. Followed by lead optimization, a novel, highly potent and selective (over CB1) triazolopyrimidine derivatives were developed as CB2 receptor agonists. SAR of the compounds disclosed that a benzylic tetrazole at the 3-position of triazolopyrimidine



Scheme 72. Electrophilic substitution reaction on substituted triazolopyrimidine scaffold.

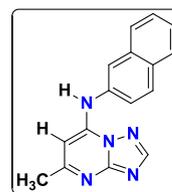


Scheme 73. Monomethyl condensation derivatives of s-triazolo [2,3-a] pyrimidine.

improves activity. Similarly, the 3-pyrrolidine substituent at the 7-position of the scaffold also enhances the potency of the compounds (Fig. 21) [150].

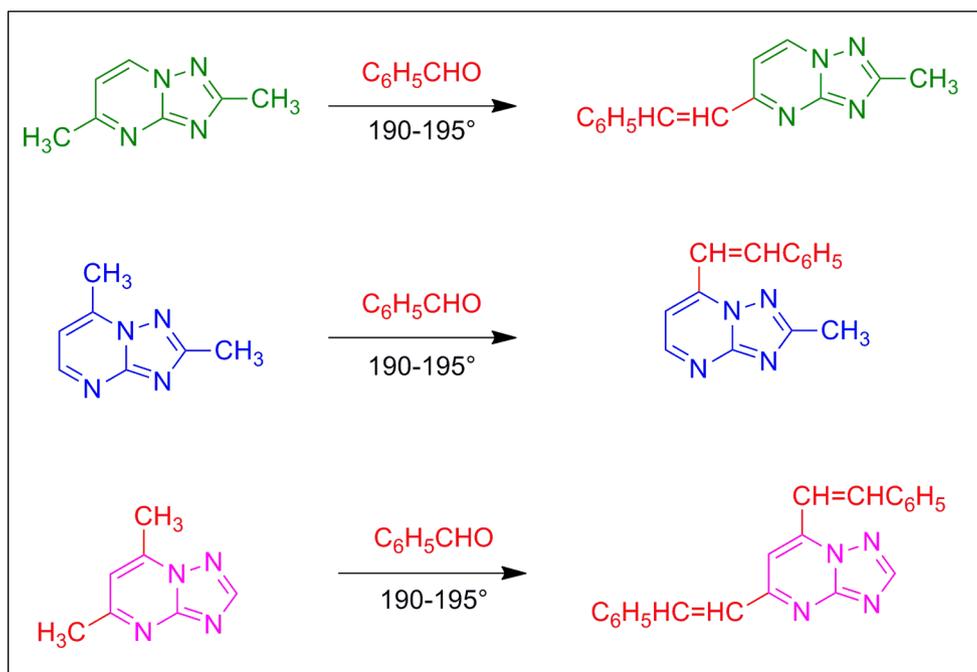
6.6. Anti-malarial

Phillips et al., in 2008 identified highly potent triazolopyrimidine-based *P. falciparum* dihydroorotate dehydrogenase (PfDHODH) inhibitor with activity in nano molar (i.e. $EC_{50} = 79$ nM), using high throughput screening. The identified inhibitor (**11**) was highly selective towards PfDHODH of the malaria parasite, which is > 5000-fold over the human enzyme. Additionally, **11** could be considered as a druglike (as per the Lipinski's rule of five) simple molecule with the inexpensive synthetic procedure. The data of the study supported compound **11** as a promising candidate for the lead optimization program in developing a novel antimalarial drug against the PfDHODH [151].

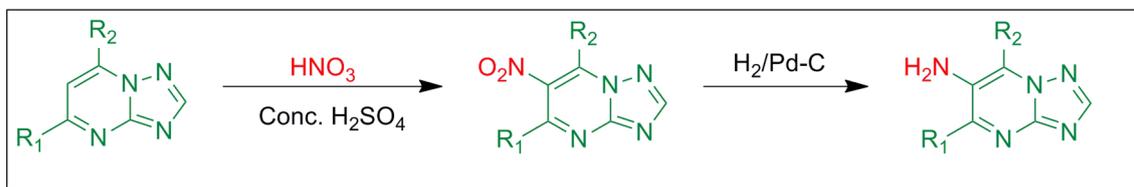


(11)

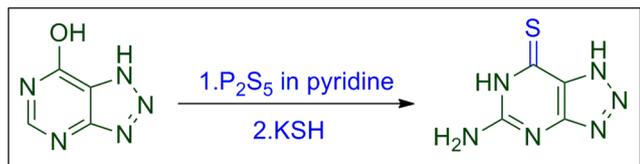
Another attempt was made by Gujjar et al. in 2008, to explore triazolopyrimidine scaffold and develop metabolically stable PfDHODH inhibitors. It was the first study to report that triazolopyrimidine based inhibitors can inhibit the growth of malaria parasites in animals. This study provided strong validation of PfDHODH as a new target. *The in-vitro* study revealed that triazolopyrimidine containing naphthyl moiety with a substituted phenyl containing trifluoromethyl at the para position was essential to be metabolically stable in liver microsomes and could successfully manage to maintain high plasma concentration in mice. Among this series, **12** was found to be most potent with $IC_{50} = 0.28 \pm 0.02$ μ M against *P. falciparum* species and 0.38 ± 0.02 μ M against *P. berghei*. The same molecule exhibited $EC_{50} = 0.34 \pm 0.04$ μ M against Pf 3D7 cells [152].



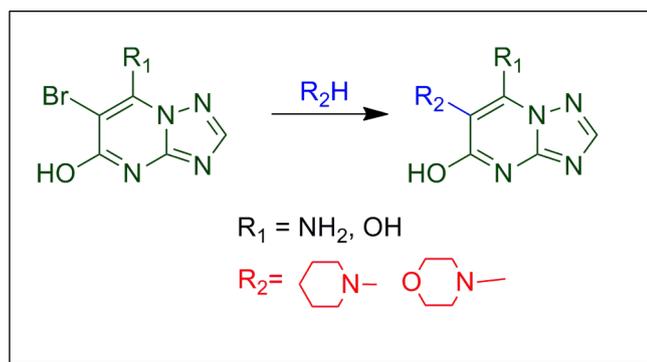
Scheme 74. Dimethyl condensation derivatives of s-triazolo[2,3-a]pyrimidine.



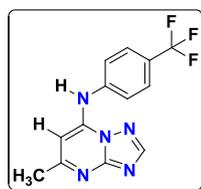
Scheme 75. Nitration followed by reduction of derivatives of s-triazolo [2,3a] pyrimidine.



Scheme 76. Synthesis of sulfur-containing triazolopyrimidines via nucleophilic substitution.



Scheme 77. Synthesis of amine derivatives of triazolo [2,3-a] pyrimidine via nucleophilic substitution.

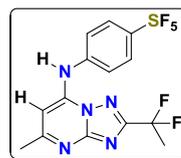


(12)

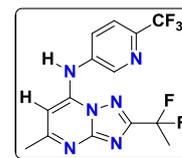
In 2011, Coteron et al. reported structure-guided development of triazolopyrimidine derivatives as dihydroorotate dehydrogenase inhibitors for the management of malaria (Fig. 22). Their study disclosed that significant inhibitory activity against dihydroorotate dehydrogenase was obtained via compounds that possessed an unbranched haloalkyl group at second carbon of triazole nucleus, including $-\text{CF}_2\text{CH}_3$, $-\text{CF}_2\text{CH}_2\text{CH}_3$, or $-\text{CF}_3$, and unbranched alkyl sulfur or oxygen-containing group like $-\text{SCH}_3$, or $-\text{SO}_2\text{CH}_3$. Out of these

compounds, compounds with 4- CF_3 -aniline and 4- SF_5 -aniline substitution at the pyrimidine ring demonstrated the best potency against the parasite in whole cell assays with EC_{50} values were below 20 nM against *P. falciparum* [153].

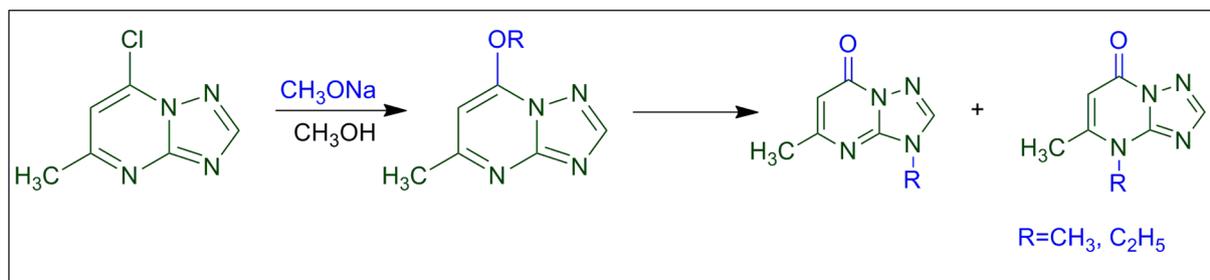
In 2014, Deng et al. evaluated the effect of alteration in fluorine substitution on the triazolopyrimidine derivatives, on their dihydroorotate dehydrogenase inhibitory potential. Their study disclosed that triazolopyrimidine derivatives with the fluoro-substituted alkyl groups were significantly more potent than the analogous non-fluorinated alkyl groups (ethyl or methyl). Fluorine substituents alter potency through influencing the electronics of the triazolopyrimidine ring or by providing better hydrophobic interactions in the binding pocket. They reported that the addition of meta fluorines to compounds with para- CF_3 aniline further improve plasma exposure and provide a modest boost in potency toward dihydroorotate dehydrogenase [154]. Similarly, in 2016, Phillips et al. further explored the triazolopyrimidine-based dihydroorotate dehydrogenase inhibitors to improve their drug-like properties. They utilized the previously reported derivatives with SF_5 -aniline ring and modified them with a series of CF_3 -pyridinyl leading to the identification of molecules with improved drug-like properties and better species selectivity while maintaining efficacy and pharmacokinetic properties to support a similar product profile. The study successfully improved the physical and chemical properties of **13**, which is already under clinical development by simply replacing the SF_5 -aniline moiety of **13** with a series of CF_3 -pyridinyls, while maintained the triazolopyrimidine core. The solubility, *in-vivo* pharmacokinetic and pharmacologic properties improved favorably with a slight modification in the existing drug candidate **13**. As a resultant of this replacement compound **14** was obtained and the whole data of this study supported its advancement towards preclinical trial as a potential drug candidate for the treatment of malaria. Compound **14** manifested 2-fold higher IC_{50} against *P. vivax* DHODH i.e. 0.094 μM . The IC_{50} against PfDHODH was found to be 0.053 μM . The developed compound **14** does not significantly inhibit human, rabbit, monkey or minipig DHODH ($\text{IC}_{50} > 100 \mu\text{M}$), making it a selective drug candidate towards DHODH malarial parasite [155].



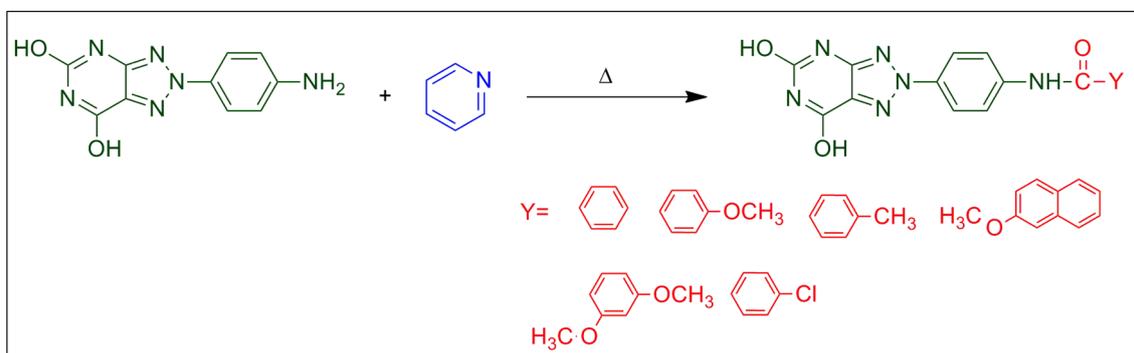
(13)



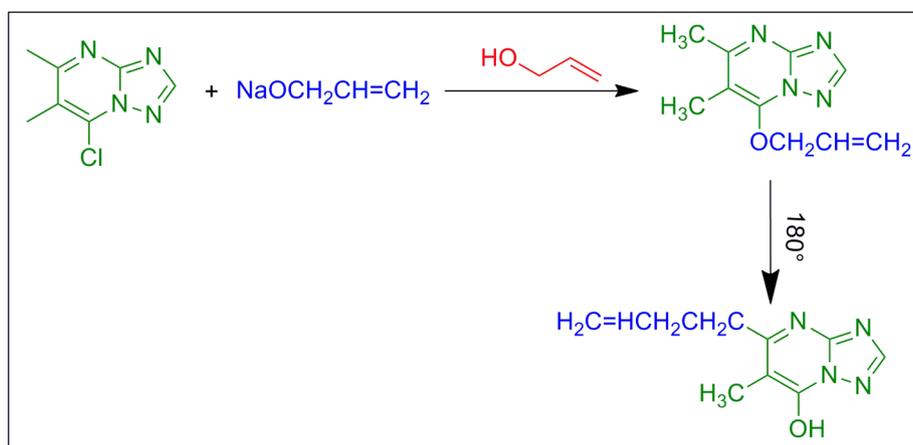
(14)



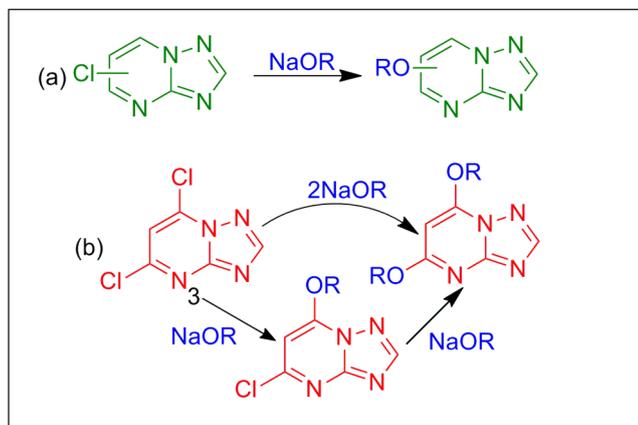
Scheme 78. Nucleophilic substitution of 5-methyl-7-chloro-s-triazolo [1,5-a] pyrimidine.



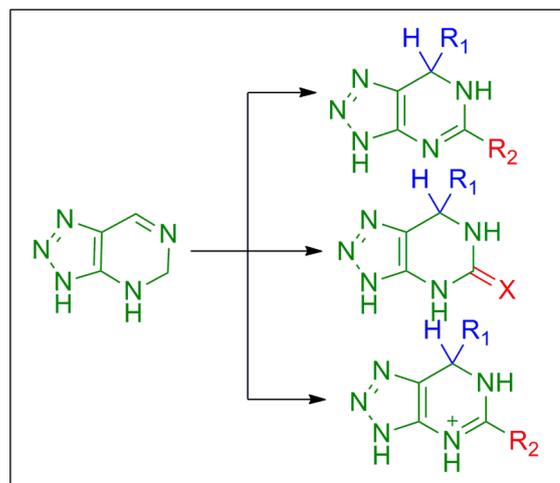
Scheme 79. Synthesis of acyl derivatives of triazolo [2,3-a]-pyrimidine.



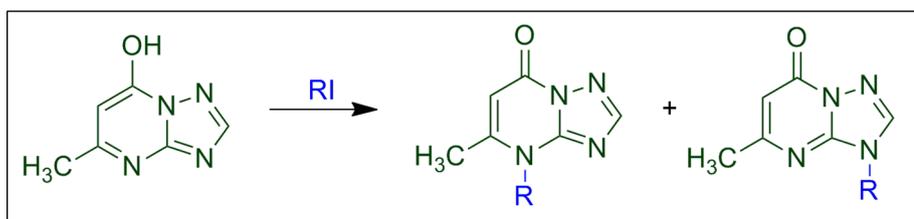
Scheme 80. Thermal rearrangement of 7-allyloxy-5,6-dimethyl-s-triazol [1,5-a] pyrimidine.



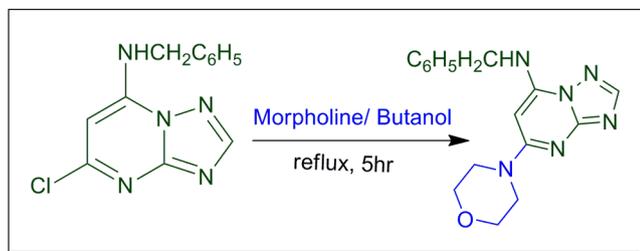
Scheme 81. Transesterification of alkoxy-s-triazolo [1,5-a] pyrimidines.



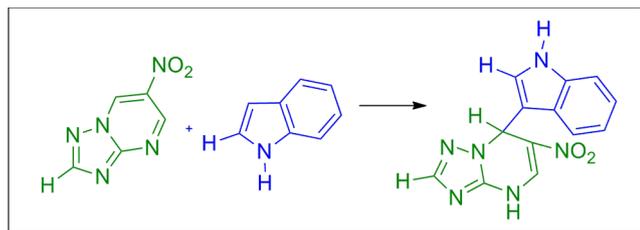
Scheme 83. Synthesis of 7-substituted 6,7-dihydro-v-triazolo[4,5-d]pyrimidines.



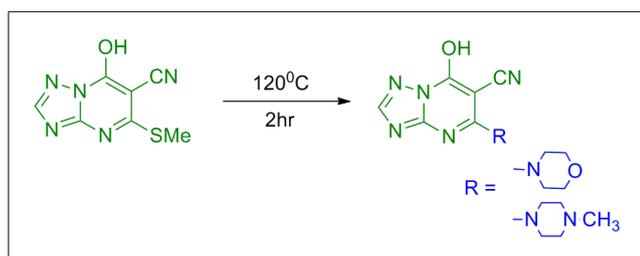
Scheme 82. Alkylation of 5-methyl-s-triazolo-[1,5-a] pyrimidine-7-ol.



Scheme 84. Coupling of morpholine ring with triazolopyrimidine.



Scheme 85. Coupling of indole ring with triazolo[1,5-a]pyrimidine.

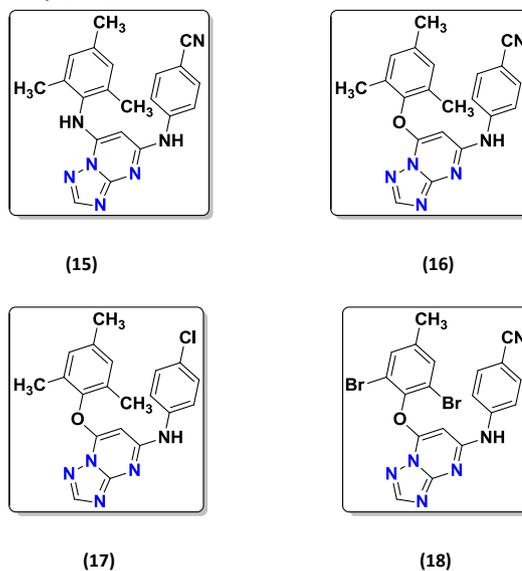


Scheme 86. Synthesis of heterocyclic amines coupled triazolo[1,5-a] pyrimidine.

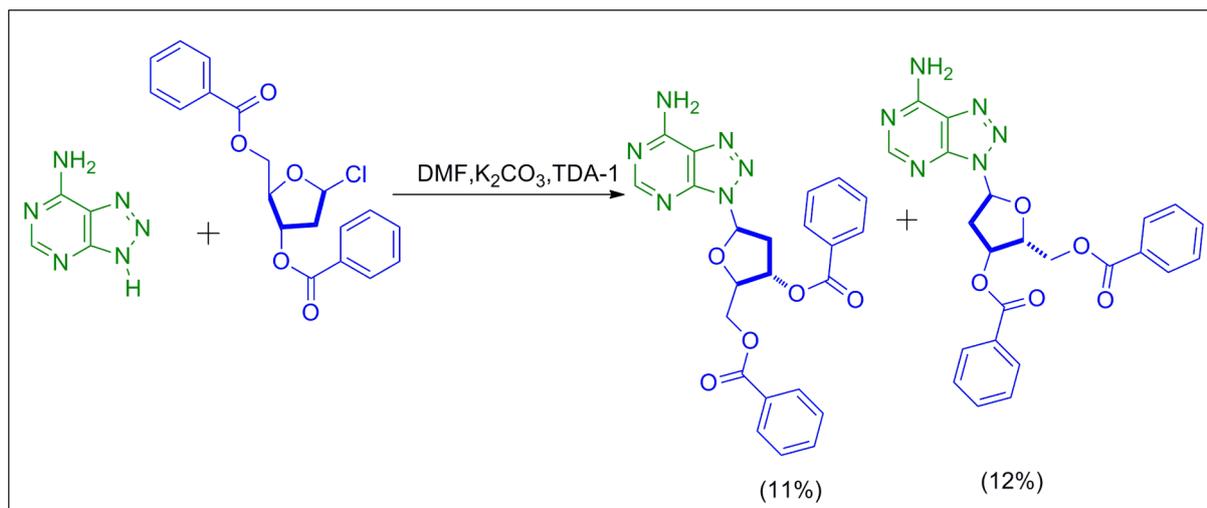
6.7. Anti-viral

In 1953, Matthews R.E.F evaluated the ability of purine derivatives against antiviral potential in plants. Among all, guanine analog 5-amino-7-hydroxy-1- ν -triazolo[d]pyrimidine (guanazolo) in solution in 0.1% sodium bicarbonate effectively reduces the size and number of lesions and inhibited the systemic spread of lucerne mosaic virus. The guanazolo activity was reversed by guanine, adenine and maybe by

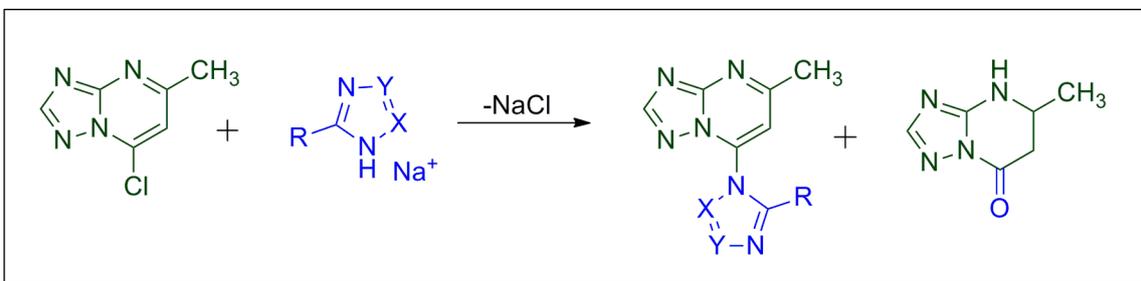
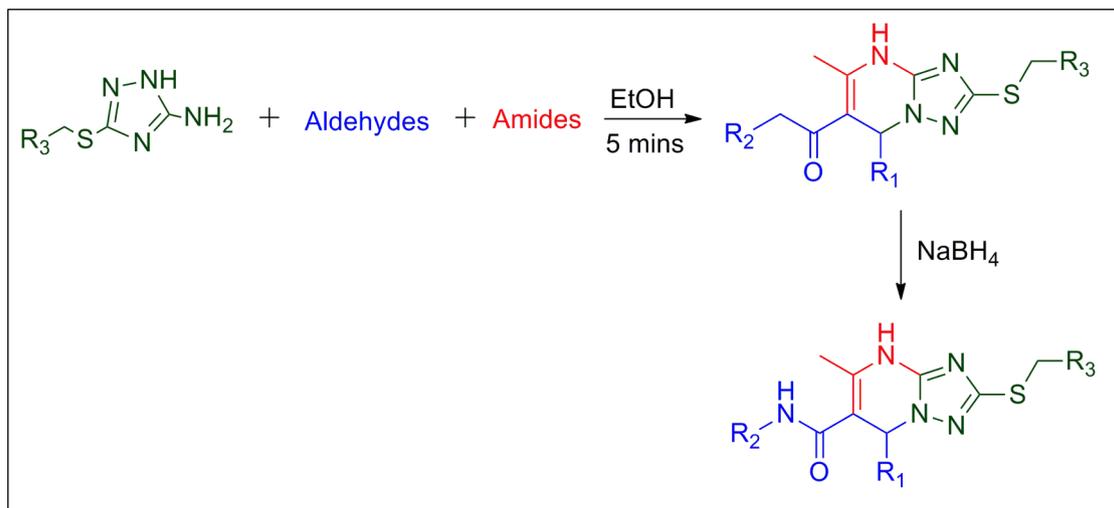
hypoxanthine. The triazolo analog of adenine possess slight antiviral activity but damaged the plant via necrosis. Moreover, hypoxanthine preparation was more effective than adenine in annulling the activity of guanazolo [156]. Slusarchyk et al. in 1992 reported some bis (hydroxymethyl) cyclobutyl triazolopyrimidines which are effective in the treatment of viral infection in animals, human and avian species [157]. In 2014, Wang et al. studied the crystal structure of human immunodeficiency virus type-1 reverse transcriptase (HIV-1 RT) in complex with diarylpyrimidines (DAPYs). On the basis of their observation, they designed and synthesized some derivatives of [1,2,4] triazolo [1,5- a] pyrimidine. The synthesized derivatives were evaluated for their anti-HIV activities in MT-4 cells and compound 15 showed the best inhibitory activity against wild-type and K103N/Y181C double resistant mutant strain of HIV-1, and the activity was found to be better than or similar to nevirapine (NVP) and delavirdine (DLV). Furthermore, compounds 16–18 also showed significant inhibitory activity, which supported the hypothesis that this type of bridgehead nitrogen heterocycles can be further developed and optimized to get non-nucleoside reverse-transcriptase inhibitors (NNRTIs) with improved antiviral activity [158].



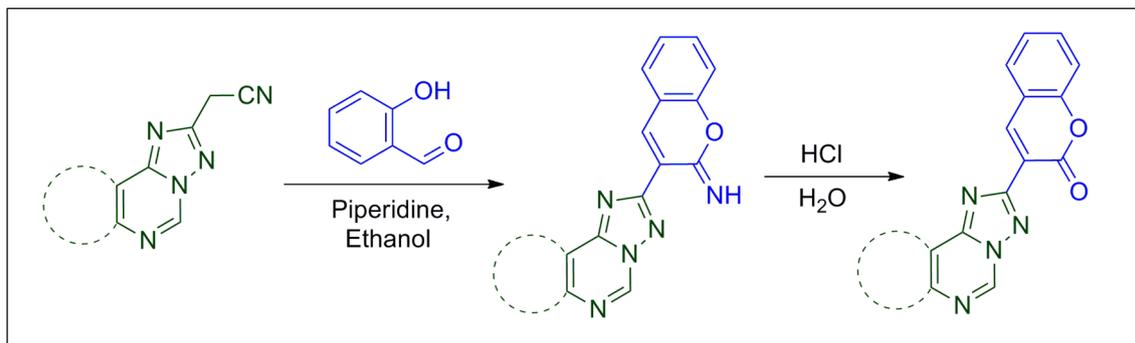
In 2015, Huang et al. designed and synthesized some [1,2,4] triazolo [1,5- a] pyrimidine derivatives having piperidine-linkage based novel NNRTIs and evaluated them for their antiviral inhibitory activity



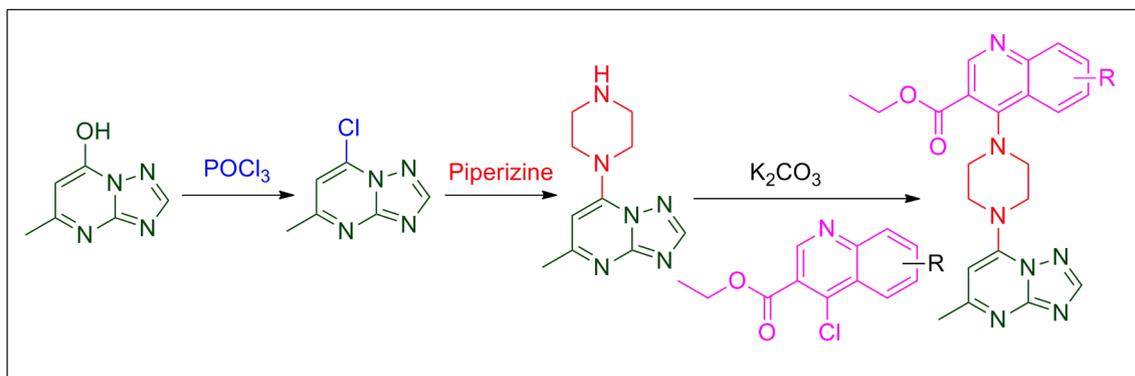
Scheme 87. Synthesis of stereoselective glycosylated 1,2,3-triazolo[4,5-d]pyrimidine.

Scheme 88. Synthesis of *N*-substituted triazolo[1,5-*a*]pyrimidines.

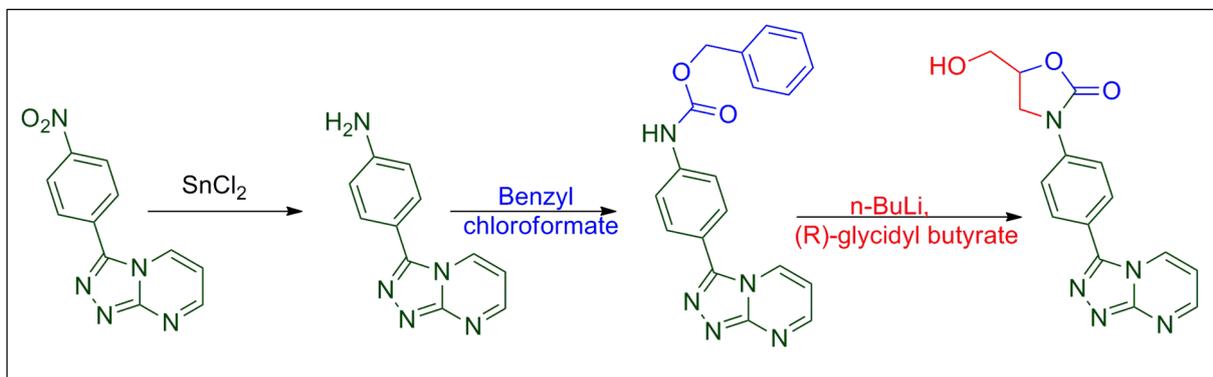
Scheme 89. Synthesis of carboxamides derivatives of triazolopyrimidines.



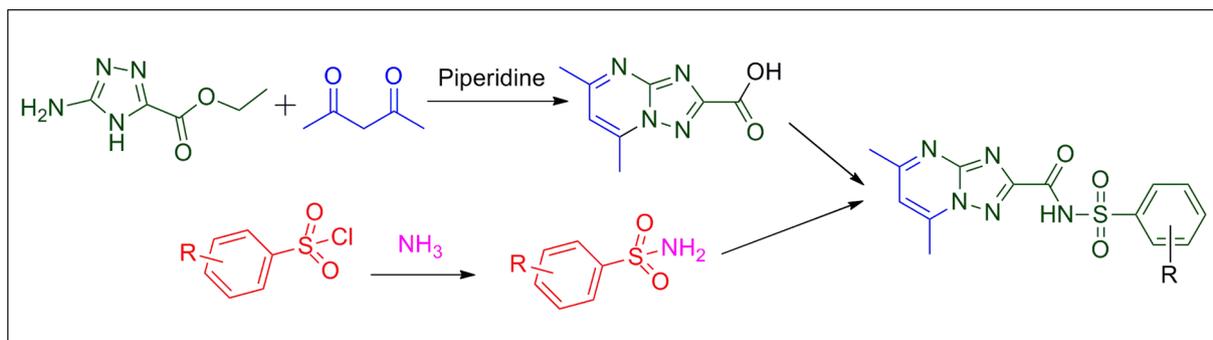
Scheme 90. Synthesis of coumarin coupled triazolopyrimidine derivatives.



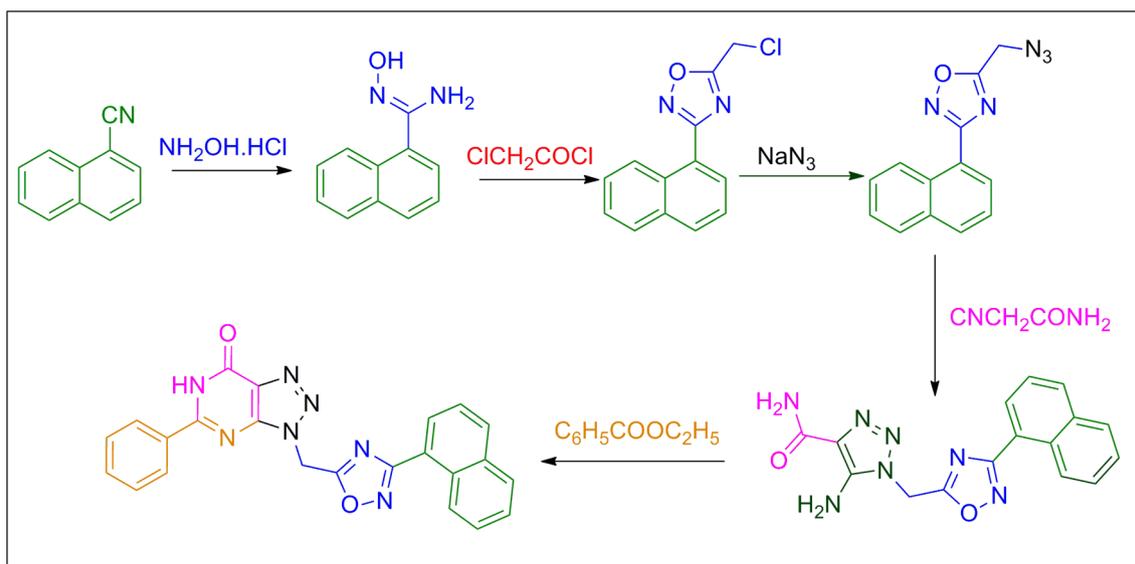
Scheme 91. Synthesis of quinoline coupled triazolopyrimidine derivatives.



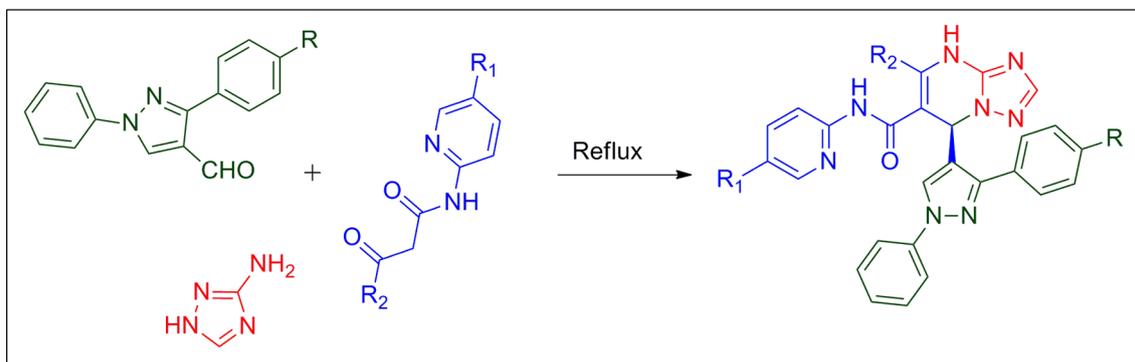
Scheme 92. Synthesis of oxazolidinone coupled triazolopyrimidine derivatives.



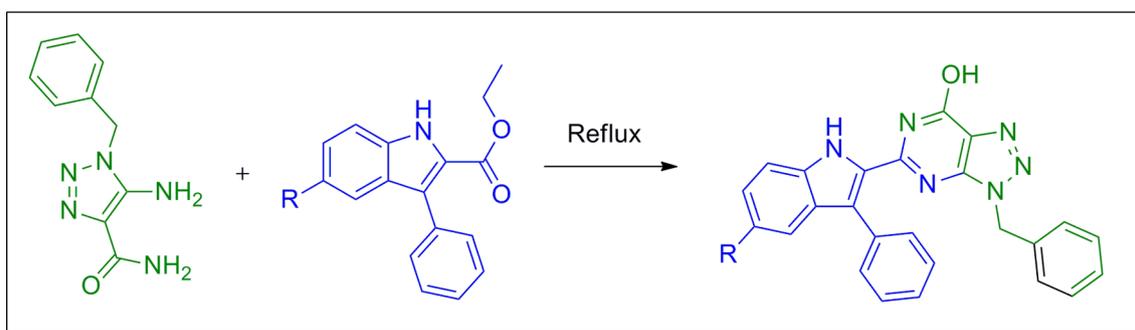
Scheme 93. Synthesis of sulphonamide coupled triazolopyrimidine derivatives.



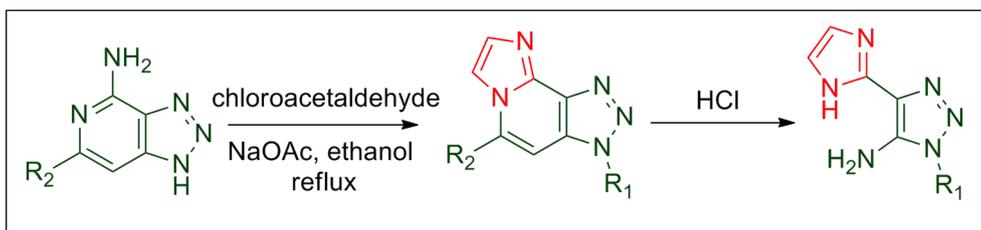
Scheme 94. Synthesis of oxadiazolyl coupled triazolopyrimidine derivatives.



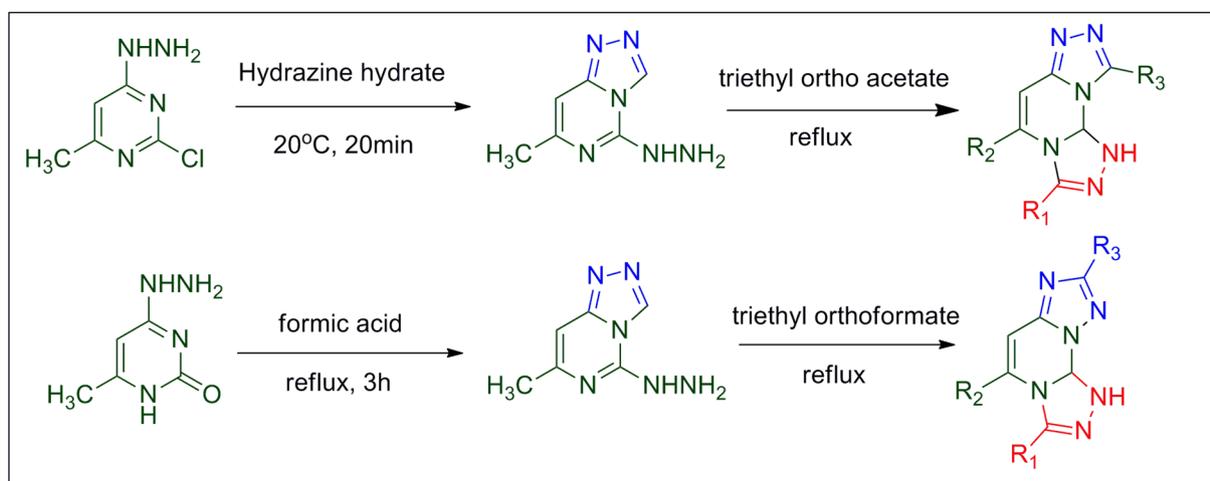
Scheme 95. Synthesis of pyrazolo coupled triazolopyrimidine derivatives.



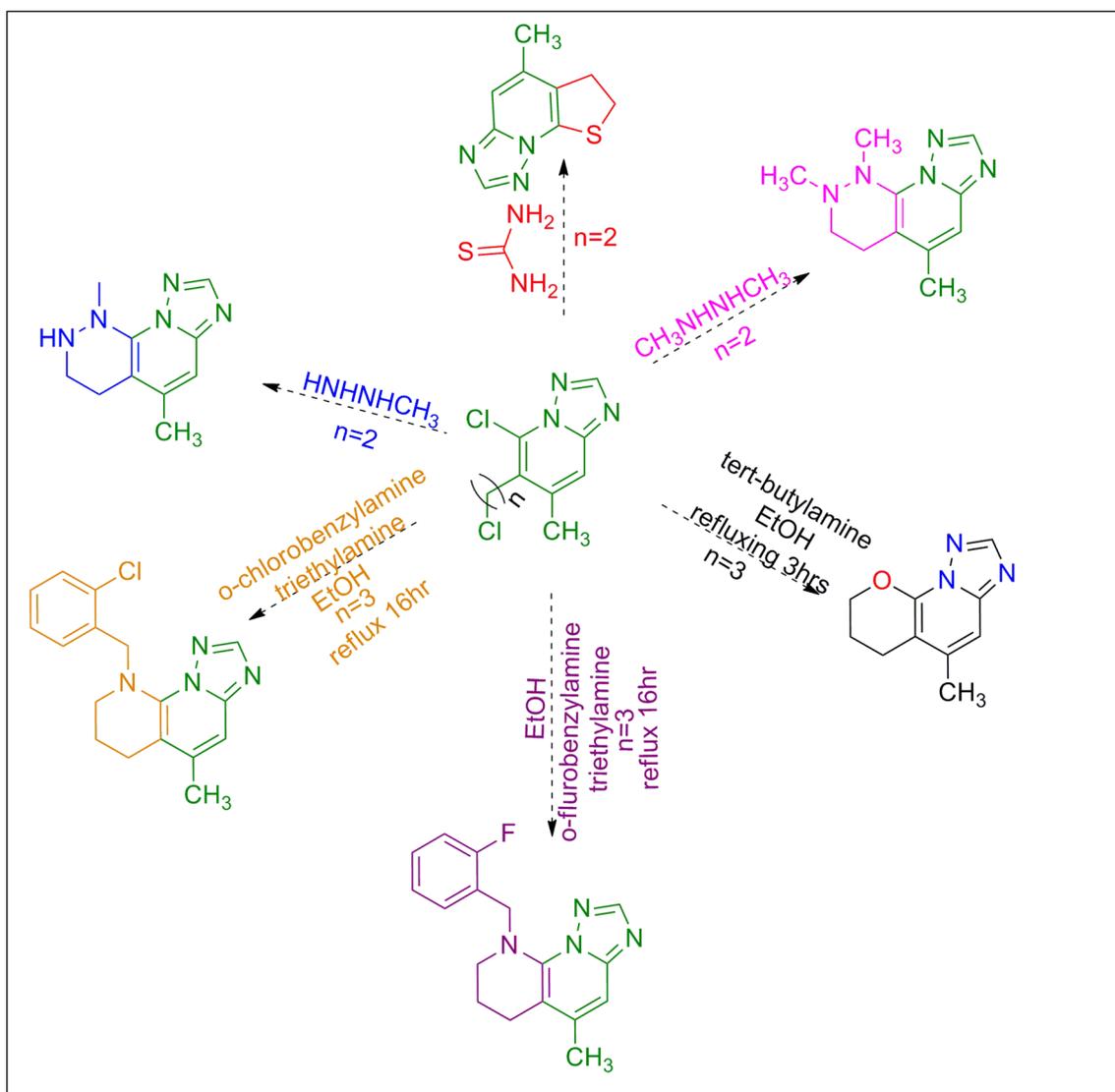
Scheme 96. Synthesis of indole coupled triazolopyrimidine derivatives.



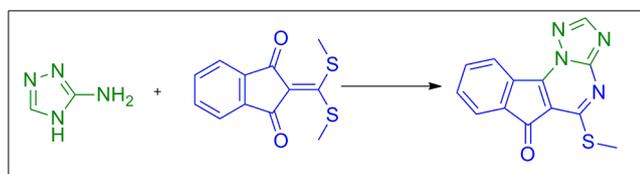
Scheme 97. Synthesis and ring opening reaction of imidazo[1,2-c][1,2,3]triazolo[4,5-e]pyrimidines.



Scheme 98. Synthesis of bis-s-triazolo[4,3-a:4',3'-c] pyrimidine derivatives by acylative cyclization.

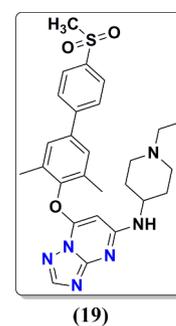


Scheme 99. Synthesis of various heterocycles fused 1,2,4-triazolo[1,5-a]pyrimidines.

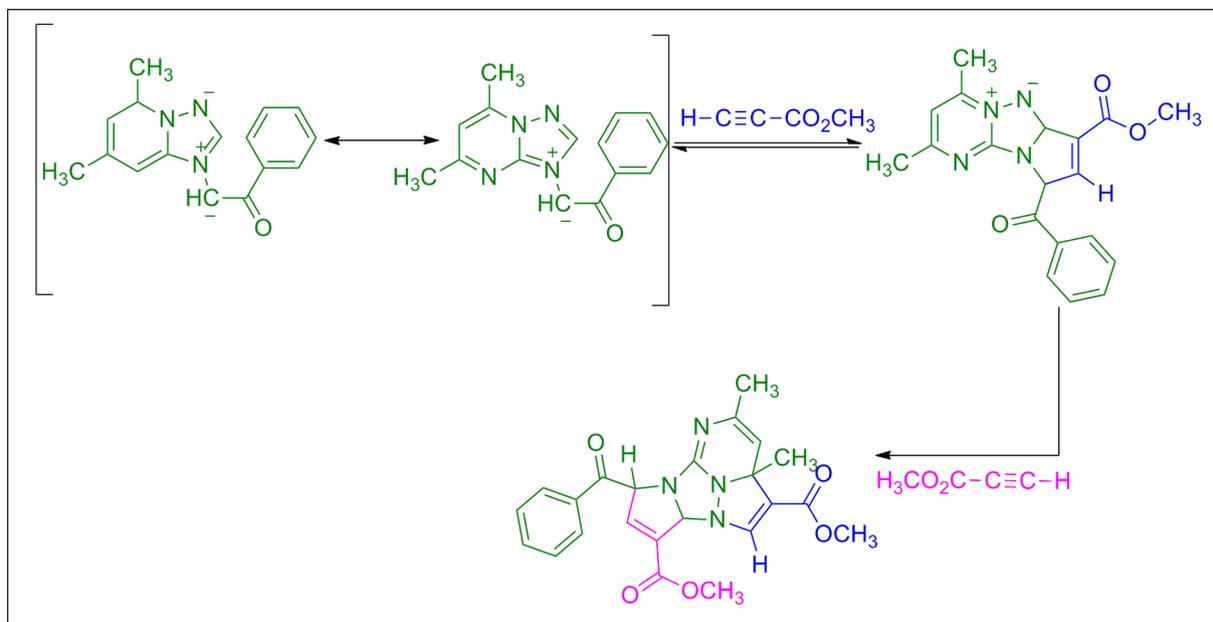


Scheme 100. Synthesis of indene ring fused to triazolopyrimidine.

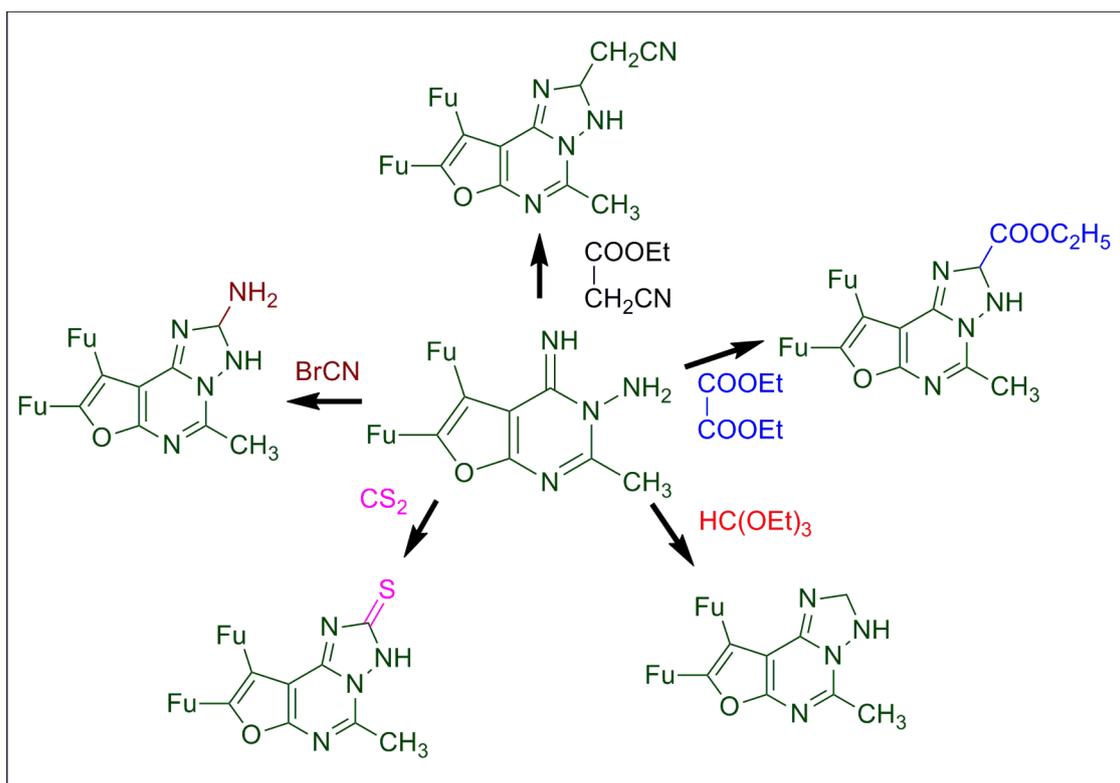
in MT-4 cell cultures. Among the synthesized compounds, **19** was found to be most potent against the wild-type HIV-1, double mutant HIV-1 strain (K103N and Y181C), and the inhibitory activity was found to be more than the reference compounds NVP, DLV [159].



In 2015, Massari et al. reported triazolopyrimidine based small molecule heterocycles as anti-influenza agents (Fig. 23). They evaluated all the derivatives for their ability to inhibit the physical interaction between PA and PB1 subunits. Their study disclosed that shifting of the methoxy group from para to meta and ortho positions on the phenyl ring of the dihydrotriazolopyrimidine core decreased the PA–PB1 interaction inhibitory activity. Interestingly for various para-substituted derivatives, a compound with *p*-propoxy substitution translated its PA–PB1 interaction inhibition ability into anti-flu activity in cellular context. On the other hand, few compounds with a bulky substituent at the C-2 position did inhibit the viral growth but did not



Scheme 101. Double 1,3-dipolar cycloaddition of [1,2,4]triazole[1,5-a]pyrimidine.

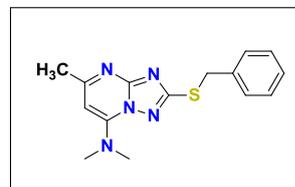


Scheme 102. Single step synthesis of various Furo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines derivatives.

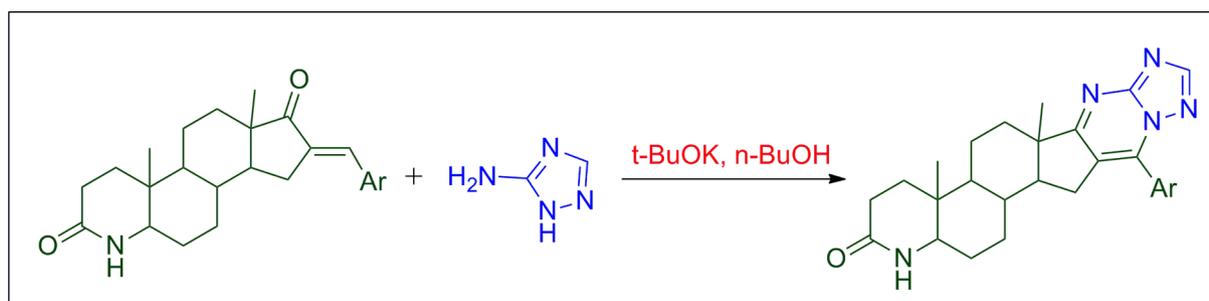
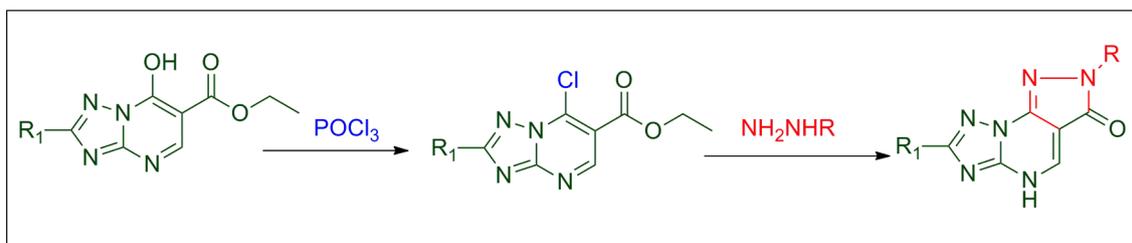
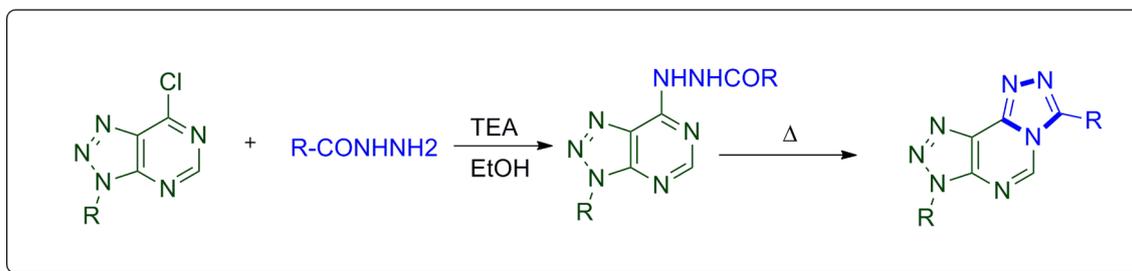
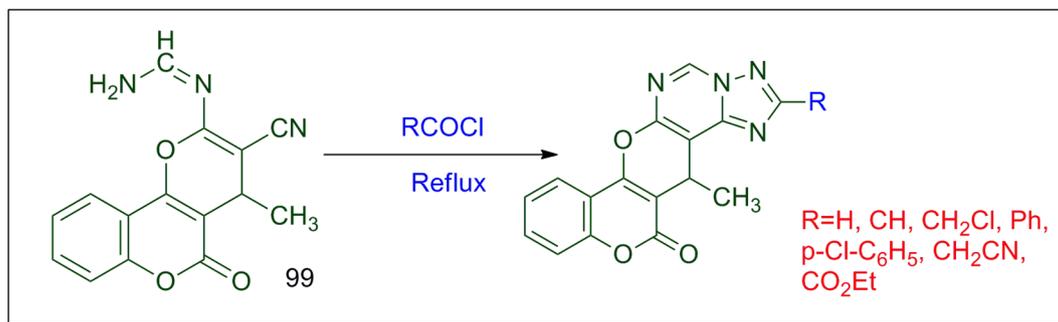
interfere with the PA–PB1 complex formation [160].

6.8. Cardiovascular agents

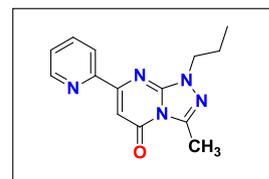
In 1981, Novinson and associates described a series of 2-(alkylthio)-5,7-disubstituted-1,2,4-triazolo[1,5-a]pyrimidines as selective inhibitors of cAMP phosphodiesterase. The study revealed that compound **20** was 6.3 times more potent than theophylline in inhibiting cAMP-phosphodiesterase from rabbit heart. Moreover, cardiac output was enhanced (69%), when administered intravenously [36].



(20)



In 1984, a study carried out by Barthelemy et al. disclosed the preparation of triazolo-pyrimidine derivatives and their therapeutic use as cardiotonics. The proposed derivatives demonstrated low toxicity with good tolerance and also showed a positive inotropic effect. Among all derivatives, compound **21** was found to most active as it manifested 145% of the tension at 10^{-3} M/L dosage [161].



(21)

In 1985, Witkowski et al. invention disclosed derivatives of 2-(pyridinyl)-1,2,4-triazolo[1,5-a]pyrimidines as effective compounds for the treatment of congestive heart failure. The compounds were evaluated for their potential to improve cardiac contractility by carrying out

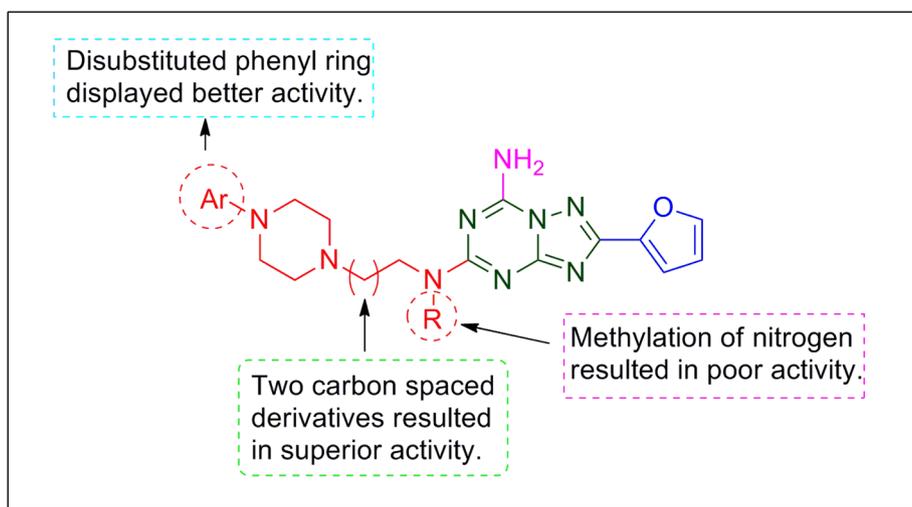


Fig. 2. SAR profiling of triazolopyrimidine derivative as selective adenosine A_{2a} receptor antagonists.

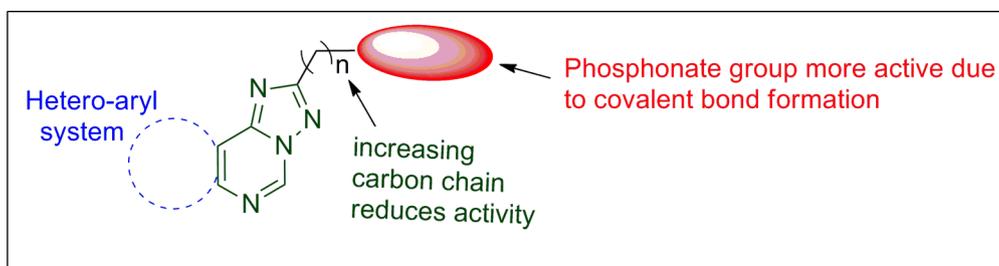


Fig. 3. SAR analysis of 1,2,4-triazolo[1,5-c]pyrimidine derivatives as anti acetylcholinesterase inhibitors.

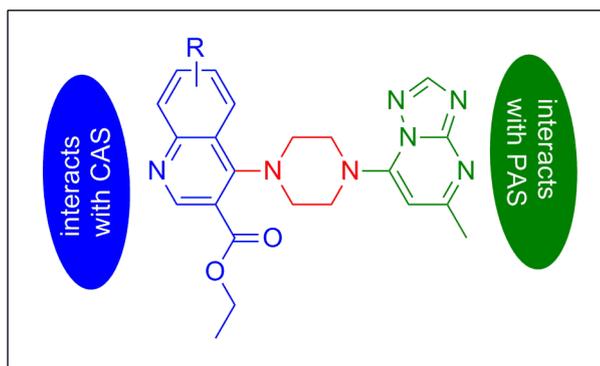


Fig. 4. Structural analysis of 1,2,4-triazolo[1,5-a]pyrimidine derivatives as anti-acetylcholinesterase inhibitors.

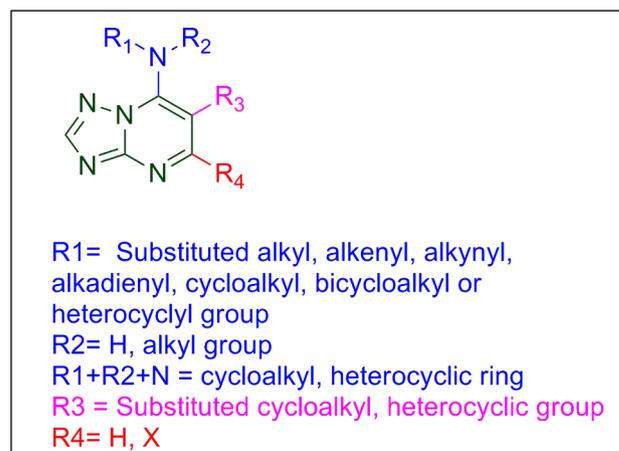


Fig. 6. Cycloalkyl analogues of triazolo[1,5-a]pyrimidine derivatives as fungicidal.

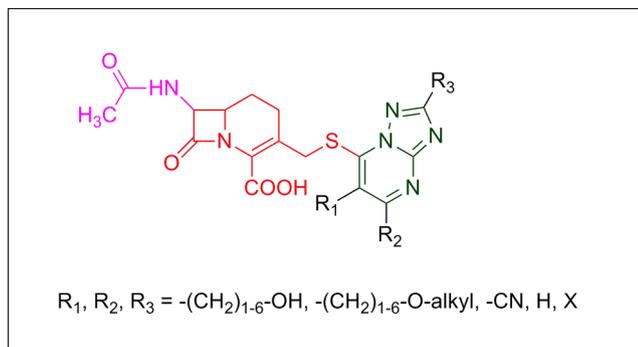


Fig. 5. Triazolo[1,5-a]pyrimidine derivatives coupled with β -lactam antibiotics.

in-vitro and in-vivo studies. In-vitro studies revealed that all the synthesized derivatives improved cardiac contractility at a concentration ranging from 32 $\mu\text{g}/\text{ml}$ to 1000 $\mu\text{g}/\text{ml}$. While the in-vivo test improved cardiac contractility at the dosage levels of 3.2 mg/ml to 10 mg/ml of the body weight of open-chest barbituates-anesthetized dogs [162]. In 1985, Wagner and associates disclosed the antihypertensive activity possessed by novel class of 6-substituted 5-phenyltetrazolo-[1,5-a][1,2,4]-triazole-[1,5-c]-pyrimidines. Among all, **22** exhibited 303% of hydrochlorothiazide activity, indicating its ability to function as an antihypertensive agent. Additionally, it possessed the ability to increase urine output, thus a lead compound to treat hypertension [163].

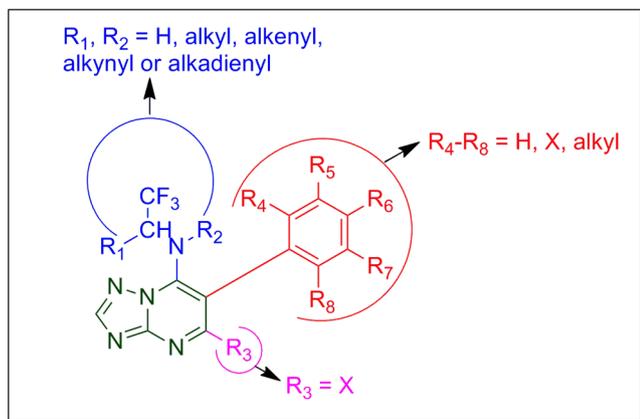
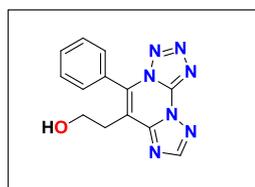


Fig. 7. Trifluoromethylalkylamino derivatives of triazolopyrimidine derivatives as fungicidal.



(22)

Nicolai et al. in 1994 reported some orally active bicyclic triazolopyrimidines having angiotensin II receptor antagonist activity. Two series (1,2,4-triazolo-[4,3-c]-pyrimidine and [1,2,4]-triazolo-[5-c]-pyrimidine derivatives) were evaluated for their antihypertensive activity using renal artery-ligated rat model. Compound (1) was found to be most potent antihypertensive molecule with higher selectivity for AT1 (K_i AT1 = 24 nM; K_i AT2 = 79 200 nM) and is currently in phase II of clinical trials. The SAR data for both series suggest that tetrazol-5-yl group is required for best oral activity and substitution at R_1 with cyclopropyl group decrease activity while propyl group enhances the activity. Introduction of hydrogen at R_2 diminish the activity thus, an alkyl chain is required for antihypertensive activity (Fig. 24).

6.9. Adenosine receptor antagonists

The in vitro pharmacological profile of 5-amino-8-(4-fluorobenzyl)-2-(2-furyl)-pyrazolo [4,3-e]-1,2,4-triazolo[5-c]pyrimidine (23) has been established for A2 adenosine receptor antagonistic activity. A binding study on bovine brain suggests its high potency (K_i = 0.074 nM) with a selectivity index of 27.6 over A1 adenosine receptor. On the other hand, in biological assays such as 5'-N-ethyl carboxamidoadenosine (NECA)-induced vasodilation in the bovine coronary artery and NECA-induced platelet aggregation in rabbit

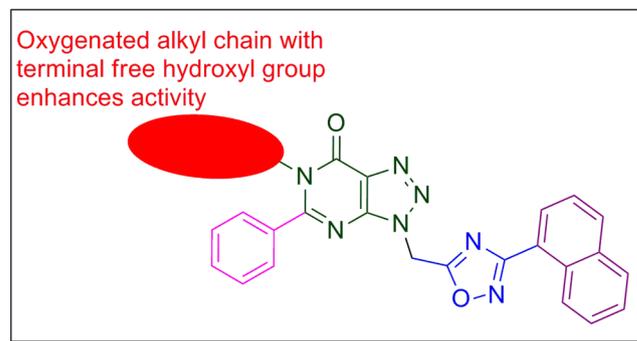


Fig. 9. SAR analysis of 1,2,3-triazolopyrimidine derivatives as anti-microbial agents.

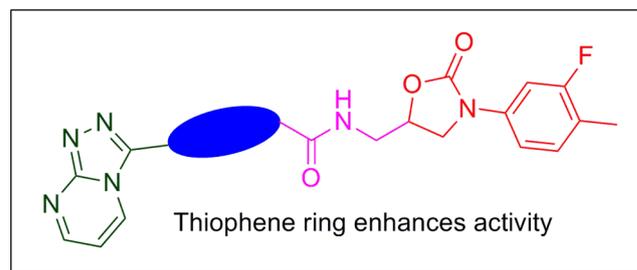
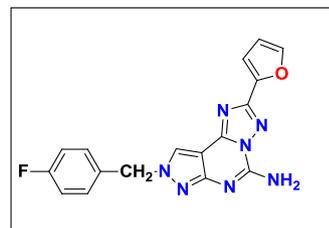


Fig. 10. SAR analysis of 1,2,4-triazolo[4,3-a]pyrimidine derivatives as anti-microbial agents.

antagonized the A2 adenosine receptor with affinity pA_2 = 7.98 and pA_2 = 8.20 respectively. It inhibits the adenylate cyclase which has a stimulatory effect on A2 [164].



(23)

Further, Baradli et al. in 1999 carried out a quantitative structure-activity relationship using comparative molecular field analysis (CoMFA) for some selective A2 receptor antagonists. CoMFA model was generated using 34 diverse triazolopyrimidine derivatives. It is reported that the developed model effectively predict novel molecules and found to have a good correlation between experimental and predicted activities (q^2 = 0.840, r^2 = 0.970). As per 3D-QSAR results, compound 24 emerged as the most potent triazolopyrimidine derivative (K_i = 4 nM).

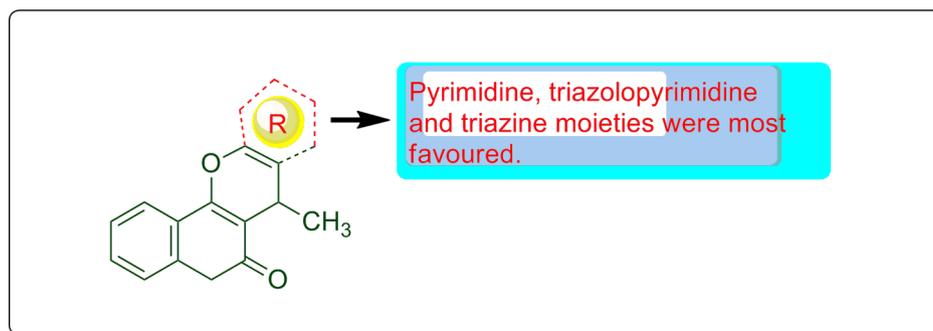


Fig. 8. Triazolopyrimidine-coumarin derivatives as antifungal and antibacterial agents.

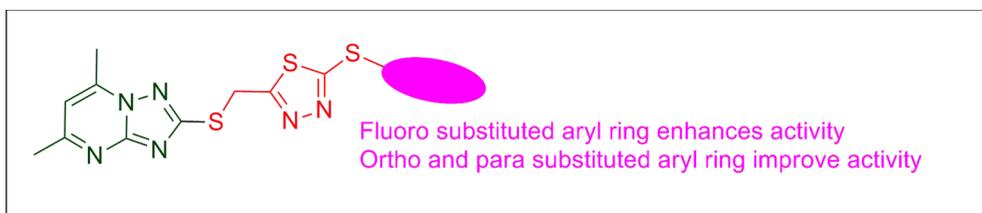


Fig. 11. SAR analysis of 1,3,4-thiadiazole coupled 1,2,4-triazolo[1,5-a]pyrimidine derivatives as anti-microbial agents.

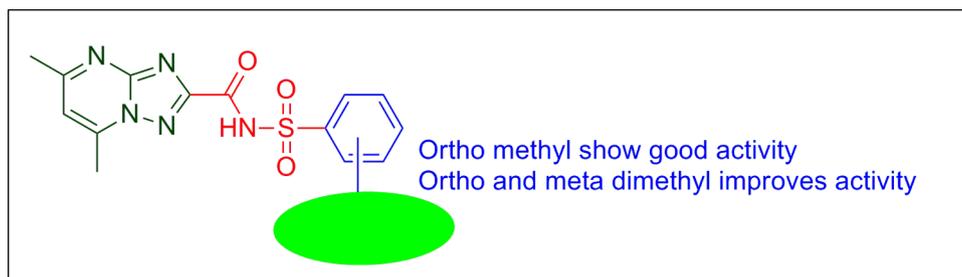


Fig. 12. SAR analysis of triazolopyrimidine acylsulfonamides derivatives AHAS inhibitors.

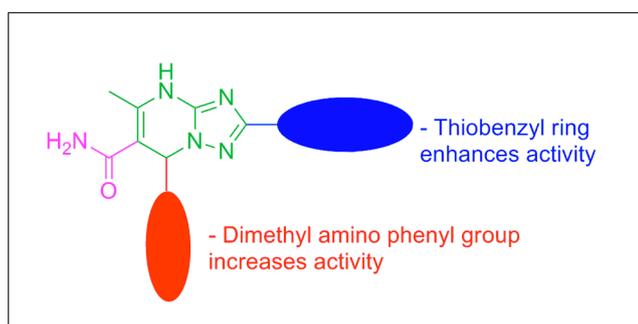


Fig. 13. SAR analysis of 1,2,4-triazolo[1,5-a]pyrimidine derivatives as anti-microbial agents.

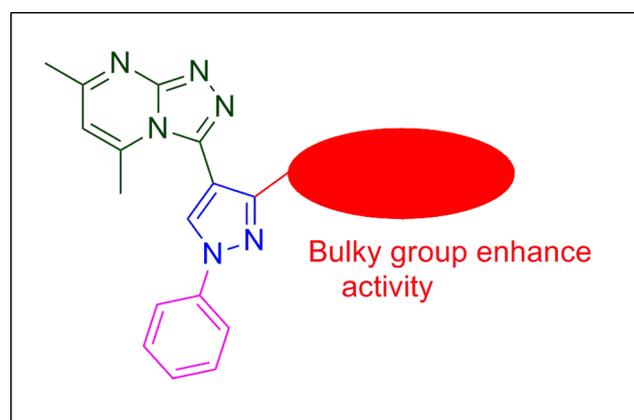


Fig. 16. Structural requirement to development apoptosis inducing triazolopyrimidine derivatives.

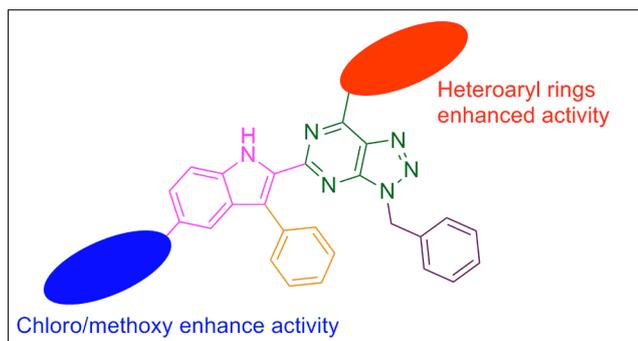


Fig. 14. SAR analysis of indole coupled triazolopyrimidine derivatives as anti-microbial agents.

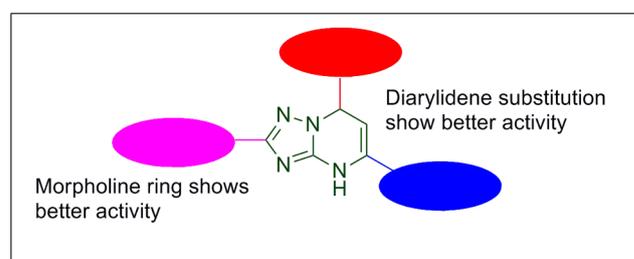


Fig. 17. SAR analysis of fused triazolopyrimidine derivatives as anti-cancer agents.

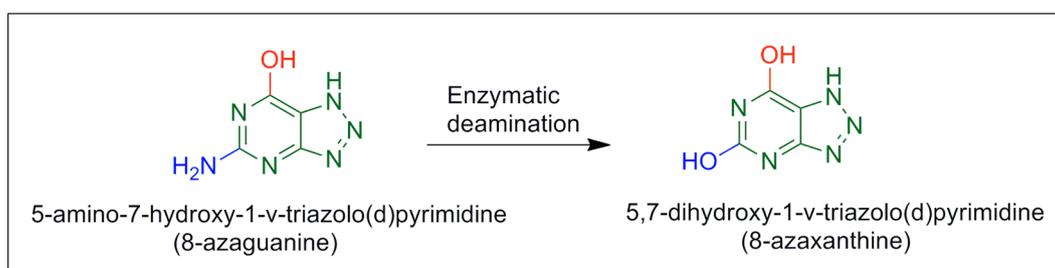


Fig. 15. Enzymatic deamination of 8-azaguanine.

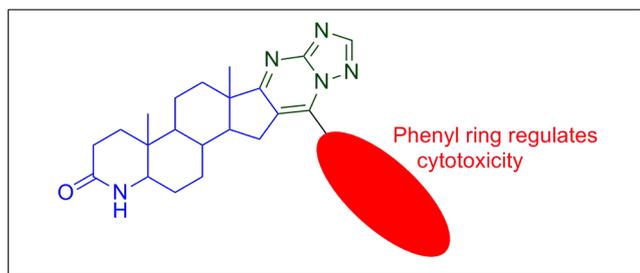


Fig. 18. SAR analysis of triazolopyrimidine derivatives as cytotoxic agents.

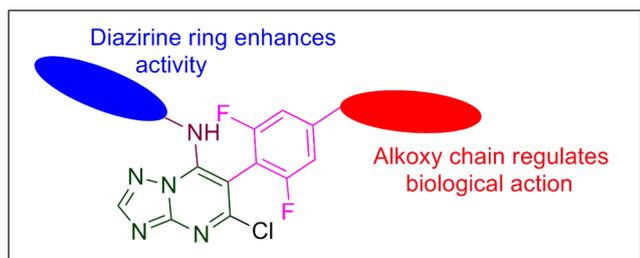
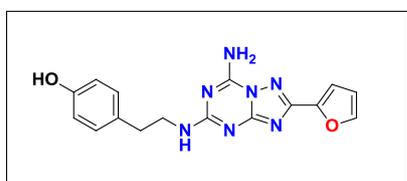


Fig. 19. SAR analysis of triazolopyrimidine derivatives as microtubule active agents.

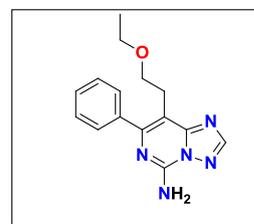
The study led to the conclusion that the molecules with triazolopyrimidine scaffold are most effective A2 inhibitors with high selectivity over A1 [165].



(24)

6.10. Diuretics

Wagner study disclosed diuretic property possessed by 8-substituted-7-phenyl-1,2,4-triazolo[4,3-c]/[2,3-c]pyrimidines-5-amines and amides. Astonishingly, compound 25 was found to be 2.7 times potent than well-established diuretic drug hydrochlorothiazide [166].



(25)

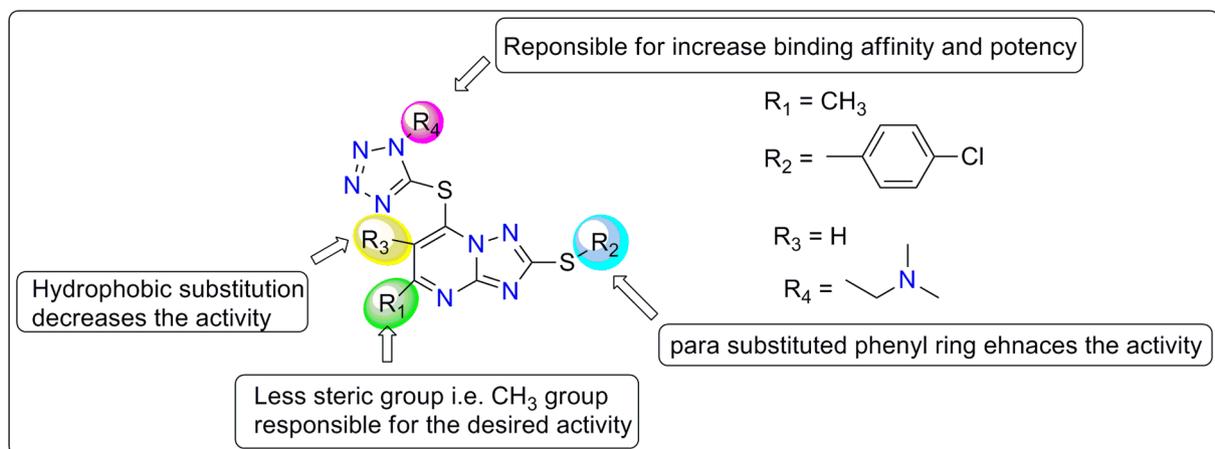


Fig. 20. The structural features required for the remarkable activity against DCN1.

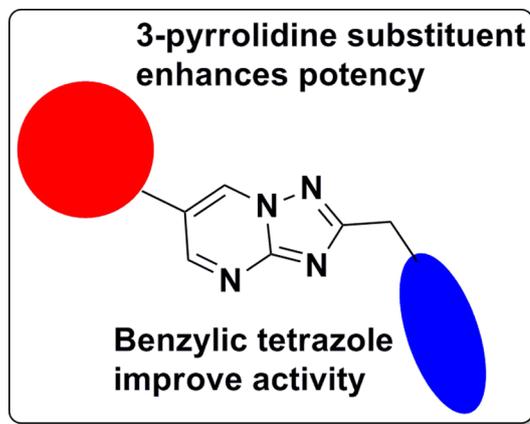


Fig. 21. SAR analysis of triazolopyrimidine derivatives as anti-inflammatory agents.

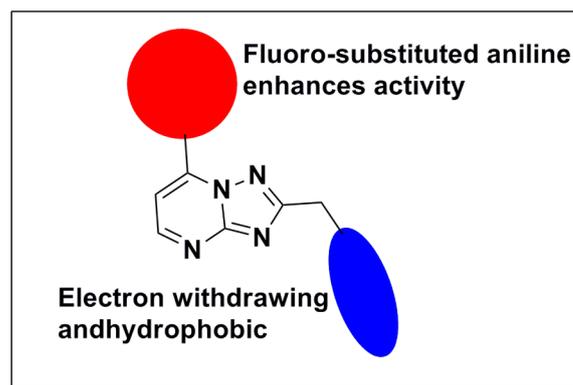


Fig. 22. SAR analysis of triazolopyrimidine derivatives as anti-malarial agents.

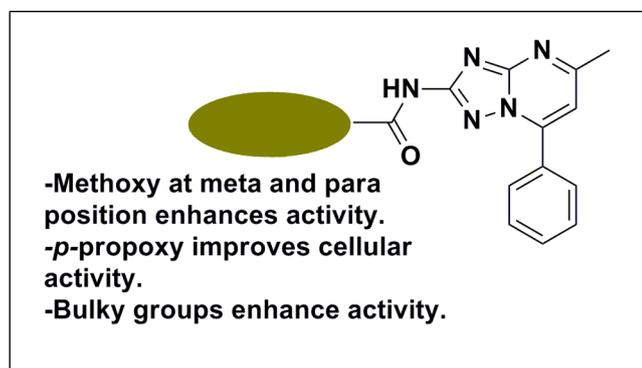
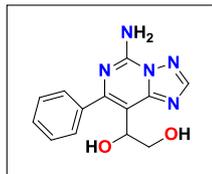


Fig. 23. SAR analysis of triazolopyrimidine derivatives as anti-influenza agents.

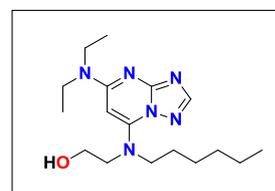
Burton et al. in 1989, discovered a novel diol metabolite of 7-phenyl-1,2,4-triazolo[2,3-*c*] pyrimidines-5-amines as a lead compound with the diuretic property. Among all the diol metabolite of triazolopyrimidine, compound **26** was found to be one of the most potent diuretics with no cardiotoxicity. This indicates the application of **26** as a potential diuretic and useful candidate in the treatment of congestive heart failure [167].



(26)

6.11. Platelet aggregation inhibition

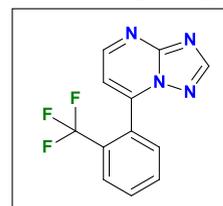
In 1987, Block et al. evaluated trapidil and 5,7-disubstituted s-triazolo (1,5-*a*) pyrimidine derivatives against platelet aggregation. Among all, compound **27** was found to be the most potent inhibitor of platelet thromboxane A₂ biosynthesis. It exhibited excellent IC₅₀ value of 55 μmol/l against the TXB₂ biosynthesis i.e. it suppressed the formation of TXB₂ by 95.3%, thus making it active under *in vitro* conditions [168].



(27)

6.12. Anxiolytic agents

Initially, Dusza et al. performed diazepam binding assay and measured the degree of protection from convulsions resulting from pentylenetetrazole. The results revealed that compound **28** was very potent molecule with favorable results (inhibit binding ≥ 20%) and higher protection from convulsions resulting from pentylenetetrazole [169].



(28)

Hardy et al. in 1981 invented the anxiolytic property of the fused heterocyclic nucleus by exploring its 5th, 7th and 8th position with varied substituents. 1,2,4-triazolo [4,5-*c*]pyrimidine scaffold with different substituents, was found to be highly active. These varied substituted compounds were found to be highly useful for the quality treatment of anxiety when administered in an amount ranging from 0.5 mg. to about 50 mg/kg of body weight per day [170]. In 1984, Dusza et al. disclosed anxiolytic property of 7-heteroaryl[1,2,4]-triazolo [1,5-*a*]pyrimidines, using an animal model and measuring their potential to protect from convulsions resulting from the administration of pentylenetetrazole. The presence of 3-pyridyl, 3-thienyl, 3-pyridinyl or 2-thienyl as substituents at position 7th and methyl/ethyl substitution at position 2nd of [1,2,4]triazolo[1,5-*a*]pyrimidine was found to be favorable for anxiolytic property [171].

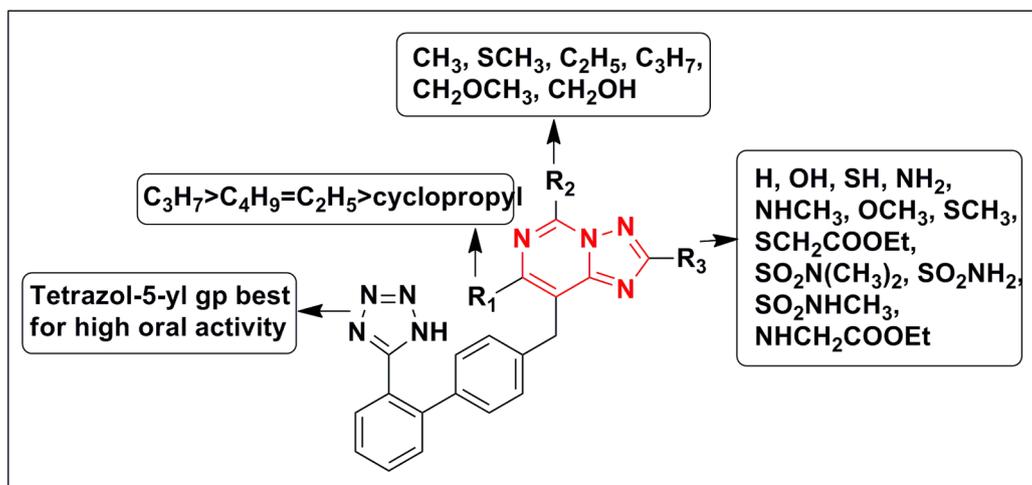
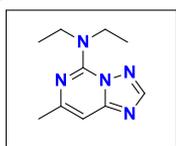


Fig. 24. SAR profile of bicyclic triazolopyrimidines having angiotensin II receptor antagonist activity.

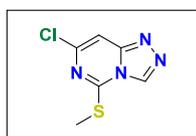
6.13. Bronchodilator

In 1973, Davies reported the anti-bronchoconstrictor activity of two phosphodiesterase inhibitors i.e, a triazolopyrimidine (ICI63197) and a triazolopyrazine. The activity of the compounds was evaluated by the protection of guinea pigs from bronchospasm induced by a lethal dose of histamine. Both the compounds were found to be active and it was hypothesized that relief from histamine-induced bronchospasm was directly proportional to the amount of available cyclic AMP [172]. Based on the results of the above study, Giles et al in 1974 hypothesized the use of phosphodiesterase inhibitors (ICI63197) in the treatment of asthma [173]. In 1985, Wade studied bronchodilator property of substituted triazolo[1,5-*a*]pyrimidines by measuring the effect of these derivatives on isolated tracheal spirals, a well-established in-vitro test method. The study revealed that compound **29** is the most potent molecule, active at < 5 µg/ml concentration [174].



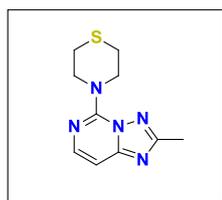
(29)

In the same year, another report published by Wade, reported 5-methylthio-7-chloro-1,2,4-triazolo[4,3-*c*]pyrimidine (**30**), as another derivative, active at concentrations of 10 µg/ml or lower. It was further evaluated for its bronchodilating and mucolytics activity, in-vitro [175].



(30)

Subsequently, Wade explored the same ring system to identify more active bronchodilator. The study disclosed that 1,2,4-triazolo[1,5-*c*]pyrimidines substituted at the 5 or 7 positions through a nitrogen atom (part of the heterocyclic ring) are lead molecules to act as potential bronchodilators. Compound **31** possessed higher potency in protecting against a histamine-induced contraction of isolated guinea pig tracheal tissue and was found to be active [176].



(31)

7. Conclusion

Since long exhaustive work has been carried out on the triazolopyrimidine scaffold, it has been an important entity in the field of organic, inorganic and medicinal chemistry. The exploration of this scaffold has risen significantly since the optimization of different synthetic methodologies and development of crystallization approaches. Several novel protocols have been recently reported to access triazolopyrimidine derivatives that could not be obtained through conventional synthetic procedures, enlarging the diversity of

triazolopyrimidine-based molecules. The transformation of the triazolopyrimidine via a coupling or fusing with other heterocycles into desirable derivatives has been deeply investigated and have been reported to possess a wide spectrum of a pharmacological profile. On the other hand, the unique triazolopyrimidine skeleton makes this structure a scaffold of choice for the synthesis and development of metal complexes with remarkable bioactivities. The number of reports describing triazolopyrimidine-containing active compounds highlights the potential of this scaffold to yield potent drug-like candidates in the field of medicinal chemistry.

Conflict of interest

Declared none.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bioorg.2019.102919>.

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