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Triazolopyrimidine Derivatives: A Comprehensive Review of Their Synthesis, Reactivity, Biological Properties, and Molecular Docking Studies

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ABSTRACT

Triazolopyrimidines are heterocyclic compounds with a unique structure and a wide range of applications in medicinal chemistry. The versatility of the triazolopyrimidine scaffold allows for the exploration and development of compounds with diverse pharmacological properties. This literature review encompasses the period from 2014 to 2022 and offers a comprehensive and inclusive overview of the synthesis, reactivity, and biological properties studies of triazolopyrimidines. The review summarizes the various synthetic methods used to prepare triazolopyrimidines and their reactions with different reagents. It also examines their pharmacological properties, such as anti-COVID-19 and anticancer effects, and their molecular docking analysis with relevant targets. The review aims to contribute to a better understanding of the potential applications of triazolopyrimidine in the field of medicinal chemistry. This literature review from 2014 to 2022 provides a comprehensive exploration of triazolopyrimidines, highlighting their diverse applications in medicinal chemistry. The review aims to offer a thorough understanding of triazolopyrimidines' versatility, serving as a valuable resource for advancing drug development in medicinal chemistry.

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1. INTRODUCTION

Heterocycles with nitrogen, oxygen, and sulfur atoms are essential products with interesting chemical and biological properties. Nitrogen-containing heterocycles play a crucial role in organic chemistry due to their reactivities and their presence in numerous natural and synthetic molecules. Heterocyclic compounds are essential for research in organic, anticorrosion, and medicinal chemistry [1-5].

Heterocyclic compounds are widely used in drugs because they play a key role in their pharmacological effects. Over time, many new methods have been developed to make these compounds, which also help in making other complex heterocycles with important biological properties [6-12].

Nitrogenous heterocyclic compounds are especially important for biology. They are present in many drugs, antibiotics, vitamins, natural products, dyes, and agrochemicals. Among these heterocyclic systems are triazolopyrimidine and its derivatives [13-24].

Triazolopyrimidine derivatives belong to a group of aromatic heterocyclic compounds that share a crucial structural feature of a pyrimidine ring fused (condensed) to a five-membered aromatic heterocycle (triazole) at the 3- and 4-positions of the latter. This structure is also known as [1,2,4] triazolo[1,5-a] pyrimidine, and its chemical structure is illustrated in **Figure 1**.

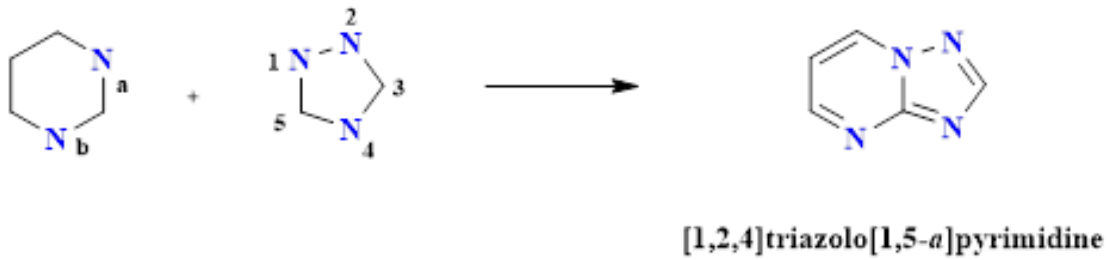

Figure 1. Structure of [1,2,4] triazolo[1,5-a] pyrimidine.

It is worth mentioning that there are eight possible isomers of triazolopyrimidine. Triazolopyrimidine has been reported to exist naturally in the forms depicted in **Figure 2** [12] of the literature. These findings highlight the importance of understanding the different isomers of triazolopyrimidine and their potential biological activities. This literature review from 2014 to 2022 provides a comprehensive exploration of triazolopyrimidines, highlighting their diverse applications in medicinal chemistry. Covering synthesis methods, reactivity, and pharmacological properties, it emphasizes their potential in combating COVID-19 and cancer through molecular docking predictions. The review aims to offer a thorough understanding of triazole pyrimidines' versatility, serving as a valuable resource for advancing drug development in medicinal chemistry.

The synthesis of triazolopyrimidine 6, was achieved by some researchers with a high yield of 93%. They used 2-(3-chlorobenzylidene) malononitrile 4, and triazolamine 5, as the starting materials.

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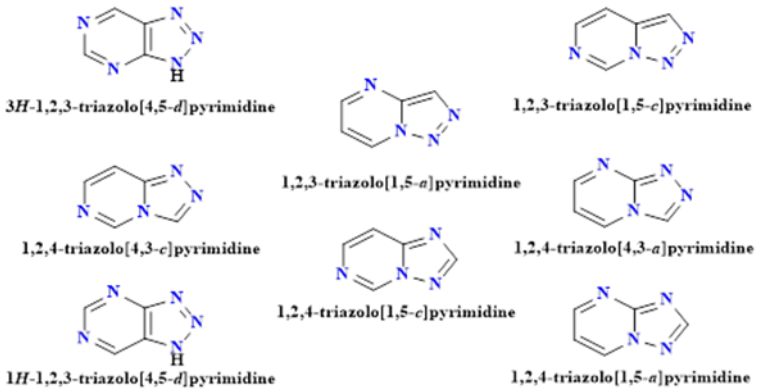

Figure 2. Different possible positional isomers of triazolopyrimidine.

2. THEORETICAL STUDY

2.1. Ligands Preparation

For the improvement and energy minimization of Triazolopyrimidine Derivatives, we employed the LigPrep module within the Maestro program version 12.8. Erlotinib, an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase pathway [25], was utilized as an anticancer control and N3 an inhibitor of the crystal structure of COVID-19 main protease [26]. The energy minimization and optimization procedures were performed using the OPLS_2005 force field, and hydrogen atoms were added, while salt and ionization were removed at pH (7 ± 2) [27].

2.2. Molecular Docking and Protein Preparation

The program operated on a Dell Model: Precision T7500. The processor is an Intel® Xeon® X5570, equivalent to a Core i7-4850HQ, with a frequency of 2.93 GHz and 48 GB of RAM. The hard disk is 2 x 400 GB (RAID 1: 400 GB SAS 15000 RPM). The graphics card is an NVIDIA Quadro FX 5800. Docking is a technique employed to compute the preferred positioning of a molecule as it binds to another molecule, forming a stable complex. In this investigation, the crystal structure of the inactive EGFR tyrosine kinase domain with erlotinib (PDB: 4HJO) at a resolution of 2.75 Å (**Figure 3**), and the crystal structure of the COVID-19 main protease in complex with an inhibitor N3 (PDB: 6LU7) at a resolution of 2.16 Å (**Figure 4**), were chosen for examination. The protein structure was sourced from the Protein Data Bank (PDB) [28], and the active site was designated as the focal point of interest. The central grid's dimensions were determined to encompass all ligand atoms, with a cubic box size of 20 Å × 20 Å × 20 Å. For protein structure preparation, the Protein Preparation Wizard from Maestro 12.8 (Schrodinger 2021-2) was employed. We visualized the protein-ligand complexes using BIOVIA Discovery Studio 2021 [29].

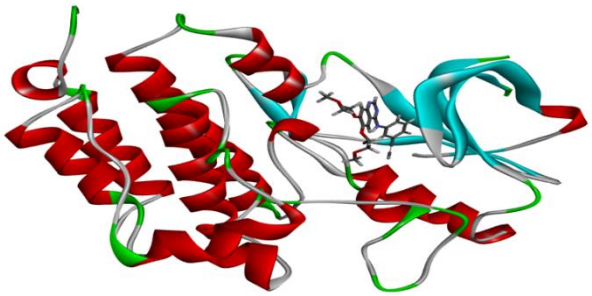

Figure 3. Crystal structure of the inactive EGFR tyrosine kinase domain with erlotinib (PDB: 4HJO).

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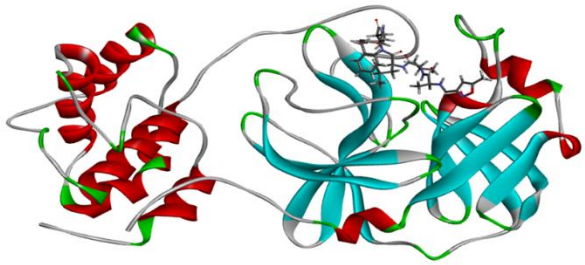

Figure 4. Crystal structure of COVID-19 main protease in complex with an inhibitor N3 (PDB: 6LU7).

2.3. Molecular Docking Analysis

Molecular docking is a term denoting the utilization of computer-based methods and algorithms for the prediction of binding interactions between a protein and a ligand molecule. This approach is essential to the discovery and development of new drugs, facilitating the identification of prospective drug candidates capable of binding to a specific protein and inducing alterations in its function [30]. The EGFR protein's active site (PDB: 4HJO) was the focus of attention for isomers of triazolopyrimidines. It was observed that all these compounds remained stable within the cavity, exhibiting notably elevated energy values, except for 1,2,4-triazolo[1,5-a] pyrimidine. The presence of negative and low docking score values suggests that the compounds engaged in robust and advantageous binding interactions **(Table 1)**. The compound displaying the highest stability is 1,2,3- triazolo [1,5-a] pyrimidine, with a docking score value of -6.968 kcal/mol. This value surpasses the control Erlotinib docking score, which is -5.744 kcal/mol. Notably, 1,2,3-triazolo [1,5-a] pyrimidine forms interactions through a conventional hydrogen bond with ASP831 and five Pi-Alkyl bonds, two with VAL702, two with LEU820 and one with CYS773. Additionally, it establishes a carbon-hydrogen bond with ASP831, and Van der Waals interactions involve residues ALA719, ARG817, ASN818, and LYS721(**Figure 5**).

Table 1. Docking score of the selected docked isomers triazolopyrimidine with the EGFR tyrosine kinase (4HJO) and the main protease of COVID-19 (6LU7) using SP docking.

Triazolopyrimidine name	Docking score (kcal/mol)	
	4HJO	6LU7
3H-1,2,3-triazolo [4,5- d] pyrimidine (a)	-4.980	-6.224
1,2,3-triazolo [4,3- c] pyrimidine (b)	-5.027	-6.356
1H-1,2,3-triazolo [4,5- d] pyrimidine (c)	-4.980	-6.224
1,2,3-triazolo [1,5- a] pyrimidine (d)	-6.968	-6.167
1,2,4-triazolo [1,5- c] pyrimidine (e)	-4.9906	-7.500
1,2,3-triazolo [1,5- c] pyrimidine (f)	-4.874	-6.020
1,2,4-triazolo [4,3- a] pyrimidine (g)	-5.021	-6.274
1,2,4-triazolo [1,5- a] pyrimidine (h)	-------	-6.685
Erlotinib (control)	-5.744	-------
N3 (control)	-------	-7.750

Molecular docking was performed to assess the docking scores of various isomers of triazolopyrimidines with the COVID-19 main protease. We designated the enzyme's binding pocket as the target receptor and evaluated the outcomes by analyzing the number of bonds formed with the amino acids at the active site. These parameters serve as indicators of the potential of these isomers to act as inhibitors of COVID-19. The compound demonstrating the highest stability is 1,2,4-triazolo[1,5-c] pyrimidine, with a docking score of -7.274 kcal/mol, a

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value near the docking score of the N3 inhibitor, which stands at -7.750 kcal/mol. Its interaction with the target includes a conventional hydrogen bond and a Pi-donor hydrogen bond with GLN189, as well as two Pi-Alkyl interactions with MET49. Moreover, it engages in two additional Pi-Pi shaped with HIS41. Furthermore, residues ARG188, TYR54, and ASP187 contribute to Van der Waals interactions (**Figure 6**). Although silico studies have shown promising results regarding the inhibitory potential of isomers triazolopyrimidine on the EGFR tyrosine kinase and the main protease of COVID-19, further investigations are required to determine their therapeutic efficacy in a clinical setting. Clinical trials involving human subjects are essential to evaluate the safety, pharmacokinetics of these compounds. Additionally, in vivo studies using animal models can provide insights into the therapeutic effectiveness and potential side effects of these compounds. Such research is pivotal for the development of effective therapies for patients.

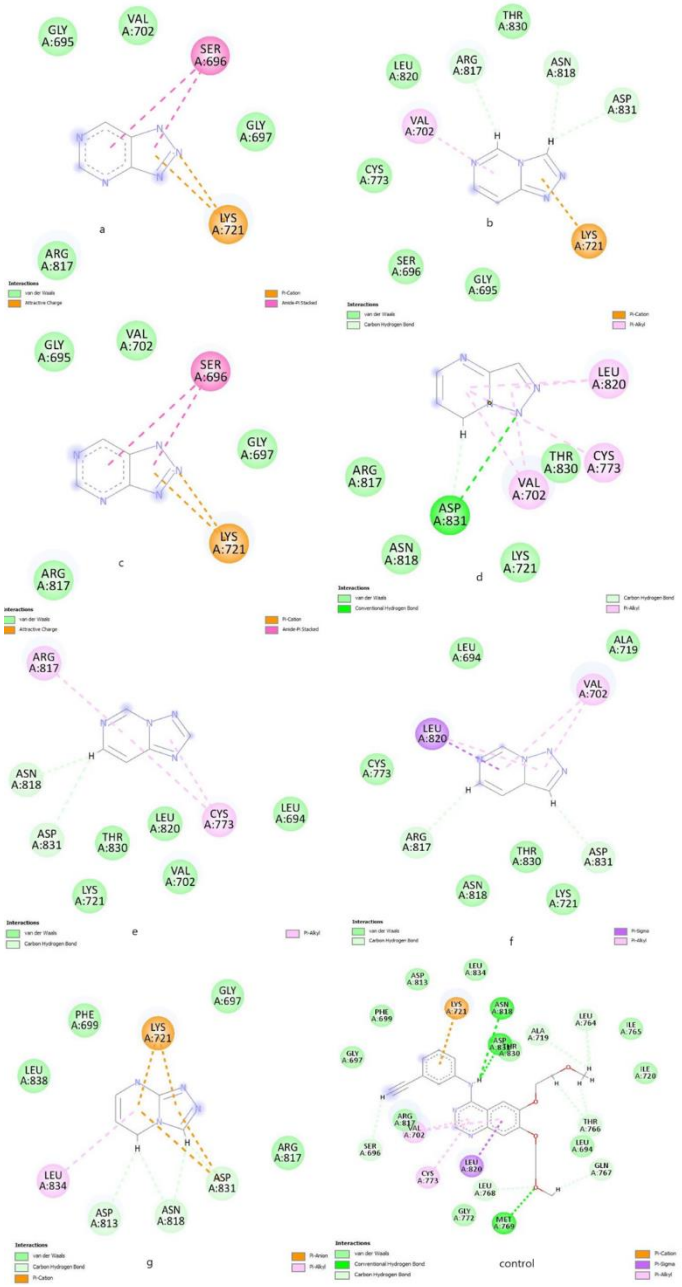

Figure 5. 2D Ligand Interactions of shapes (a-g) and Erlotinib with EGFR Tyrosine Kinase (PDB ID: 4HJO).

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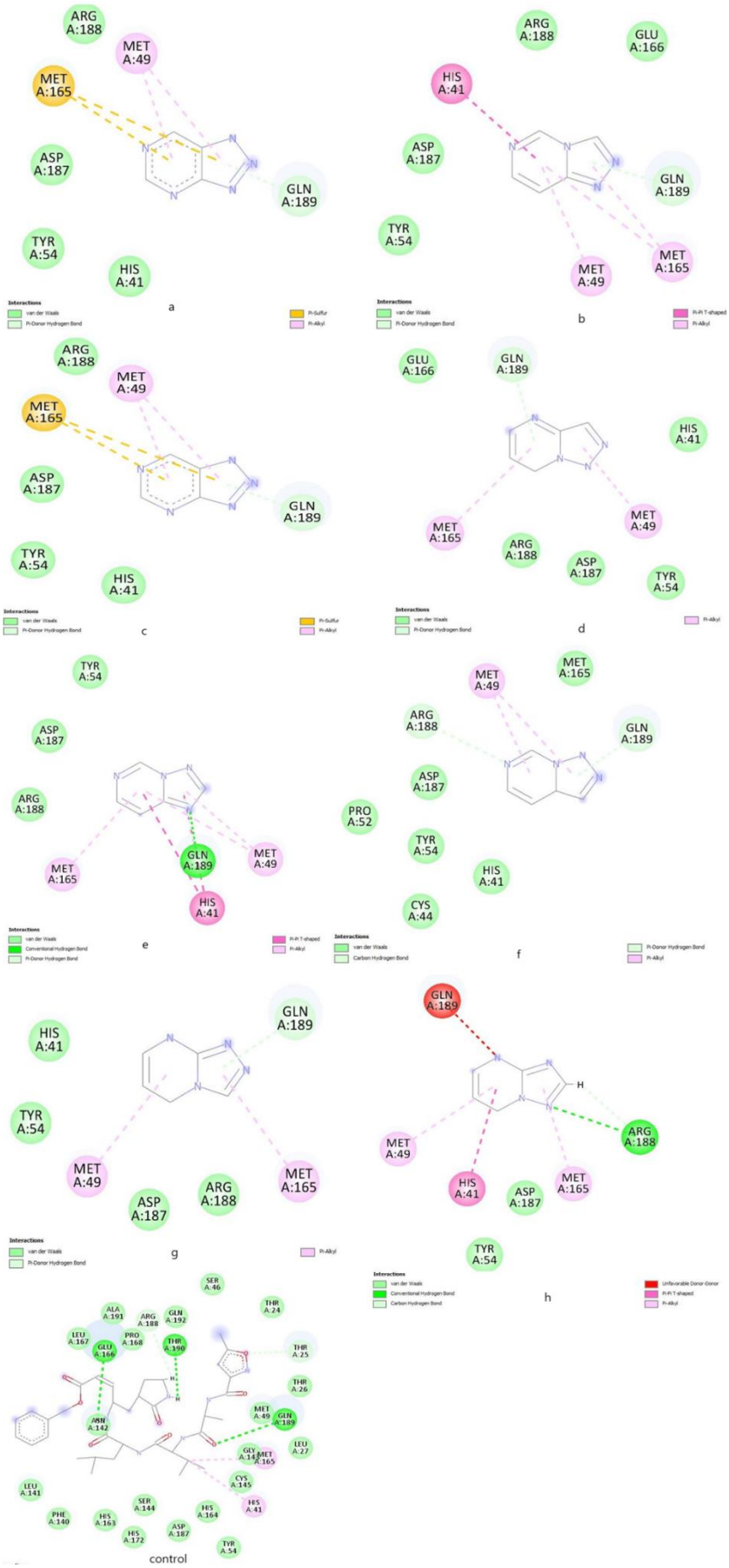

Figure 6. 2D Ligand Interactions of Shapes (α-h) and N3 with the Main Protease of COVID-19 (PDB ID: 6LU7).

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3. METHODS

This literature review encompasses the period from 2014 to 2022 and offers a comprehensive and inclusive overview of the synthesis, reactivity, and biological properties studies of triazolopyrimidines. The review summarizes the various synthetic methods used to prepare triazolopyrimidines and their reactions with different reagents.

4. RESULTS AND DISCUSSION

4.1. Synthesis Methods of Triazolopyrimidines

4.1.1. Synthesis of 1,2,4-triazolo[1,5-a] pyrimidine derivatives

Triazolopyrimidine **3** was synthesized by reacting triazolediamine **1** and ethyl 3-oxo-3-phenylpropanoate **2** in refluxing ethanol, using sodium ethanoate as a base, for 12 h. The reaction resulted in a 79% yield of the desired compound **3** (**Figure 7**) [31].

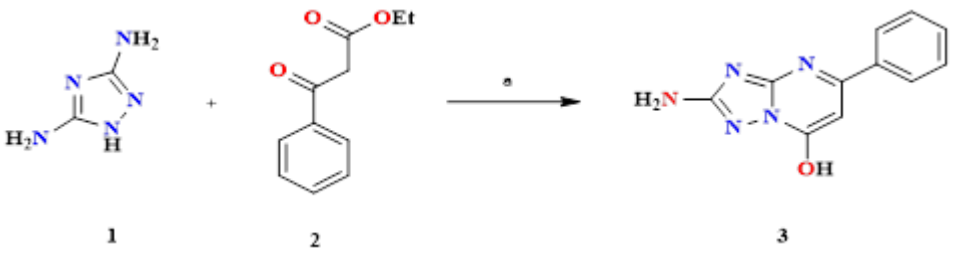

Figure 7. Reagents and conditions: *(a) EtOH, EtONa, reflux, 12 h, 79%.*

They reacted them in water as a solvent under reflux conditions. They also added 1,8-diaza bicyclo [5.4.0] under-7-ene (DBU) as a catalyst for the reaction. The reaction time was only 5 min (**Figure 8**).

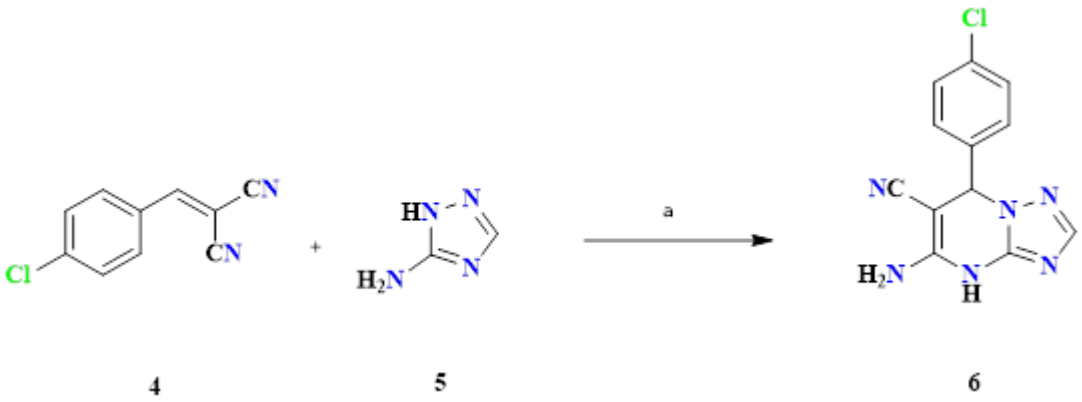

Figure 8. Reagents and conditions: *(a) H2O, DBU, reflux, 5 mn, 93 %.*

Some researchers [32] investigated the reaction of triazole amine **5**, with lithium (Z)-1,1,1-trifluoro-5,5-dimethoxy-4-oxohex-2-ene-2-olate **7**, in acetic acid as a solvent. They performed the reaction at temperatures between 30 and 35 °C and for a period of 12 h. They obtained triazolo [1,5- a] pyrimidine **8**, with a yield of 58% (**Figure 9**).

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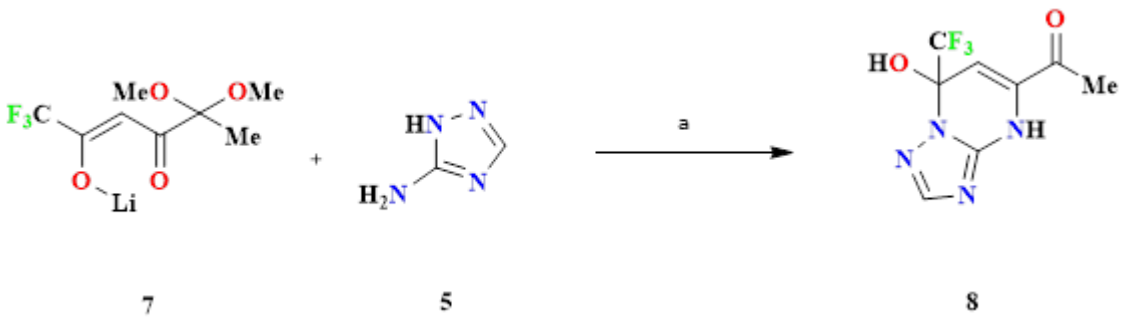

Figure 9. Reagents and conditions: *(a) AcOH, 30-35°C, 12 h, 55-58 %.*

Similarly, some researchers [33] conducted a condensation reaction between triazolamine **5** and compound **9** in pyridine at reflux conditions for a duration of 3 h. The outcome of this reaction was the synthesis of di-triazolo[1,5-a] pyrimidine derivative **10** in a yield of 80% (**Figure 10**).

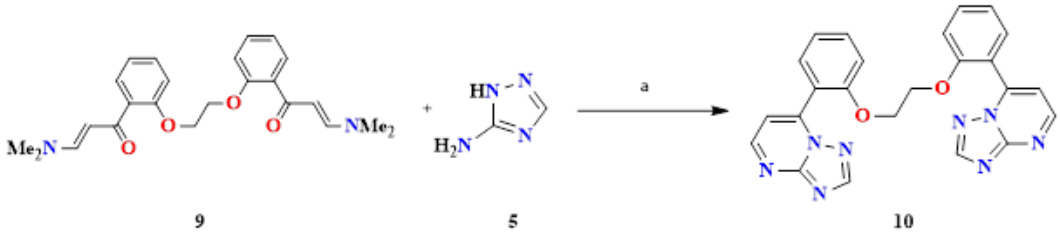

Figure 10. *Reagents and conditions: (a) Pyridine, reflux, 3 h, 80 %.*

Some researchers [34] described a novel and eco-friendly method for the synthesis of triazolo[1,5-a] pyrimidine derivatives **15** in good yields of 81-91% by a four-component condensation of amine **11**, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **14**, aldehyde **12**, and triazolamine **13**, using *p*-toluenesulfonicacid (*p*-TsOH) as a catalyst in boiling water, for 4 h (**Figure 11**).

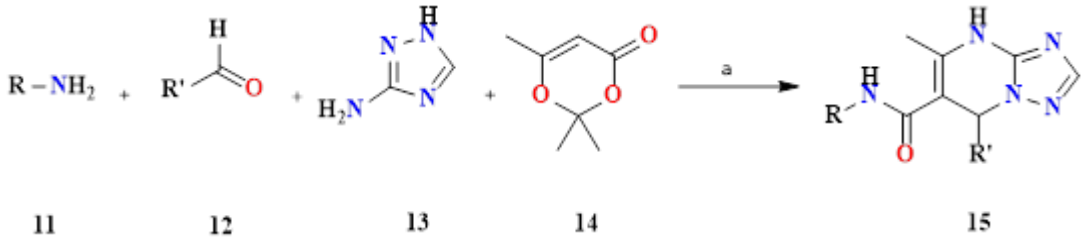

Figure 11. Reagents and conditions: (*a) p-TsOH, H_2O, reflux, 4 h, 81-91 %.*

The reaction of triazolamine **5** as a binucleophilic reagent, with ethyl malonate **16**, leads to the formation of triazolopyrimidine **17**, in 94% yield (**Figure 12**) [35]. This condensation can be carried out in ethanol at 80 °C, using sodium hydride as a base, for 2 h.

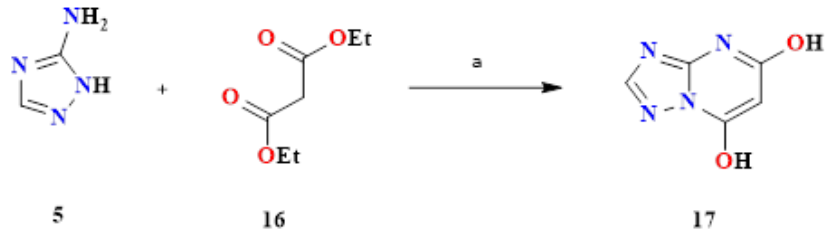

Figure 12. Reagents and conditions: *(a) DMF, NaH, 80 °C, 2 h, 94 %.*

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Some researchers [36] reported the condensation of triazolamine **18** with methyl 2-oxocyclopentane-1-carboxylate **19** in acetic acid at reflux conditions for a duration of 2-5 h. The outcome of this reaction was the formation of triazolo[1,5-a] pyrimidinone **20** (**Figure 13**).

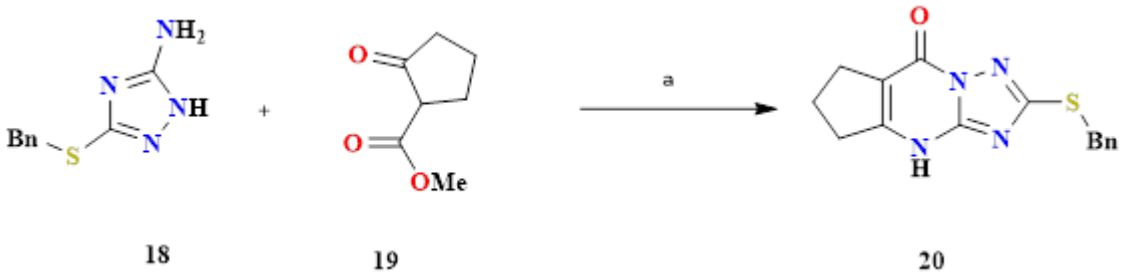

Figure 13. Reagents and conditions: (a) *AcOH, reflux, 2-5 h.*

Some researchers [37] investigated how triazolamine **21** and intermediate **22** react in a cyclocondensation process in the presence of DMF as a solvent at 160 °C. They obtained triazolo[1,5-a] pyrimidinone **23** with a high yield (**Figure 14**).

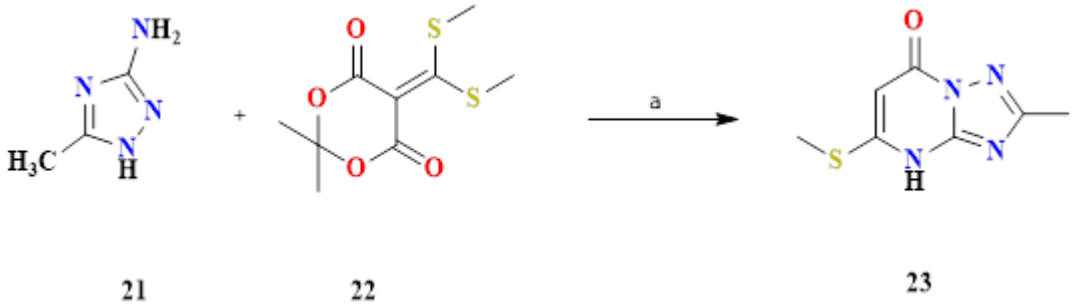

Figure 15. Reagents and conditions: *(a) DMF, 160 °C.*

Some researchers [38] studied the action of triazolamine **5** on ethyl (Z)-2-acetylbut-2-enoate **24** in *N*, *N*-dimethylformamide for 1 hour to afford ethyl triazolo[1,5-a]pyrimidine **25** in 62% yield (**Figure 16**).

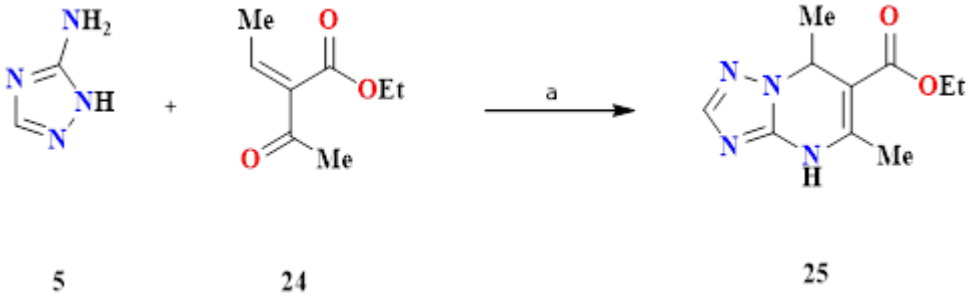

Figure 16. Reagents and conditions: *(a) DMF, 1 h, 62 %.*

4.1.2. Synthesis of 1,2,3-triazolo[4,5-d] pyrimidine derivatives

Compound **29** was prepared following the previously described methods (**Figure 17**) [39]. They refluxed compound **26** with primary amine **27** in *n*-butanol and triethylamine to obtain compound **28**. Then, they cyclized compound **28** with sodium nitrite and got triazolo[4,5-d] pyrimidine **29** with a good yield.

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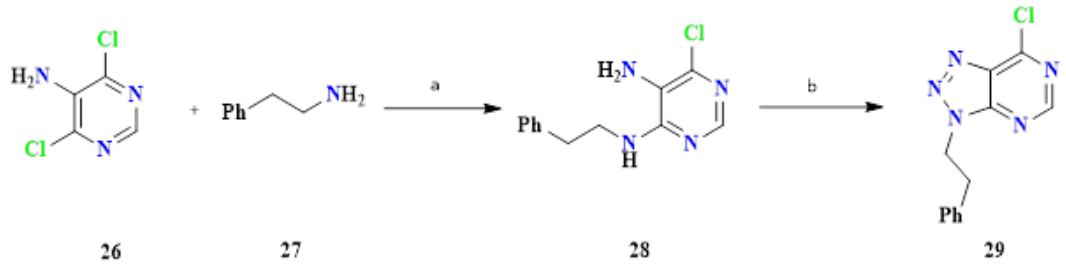

Figure 17. Reagents and conditions: *(a)TEA, n-butanol, 100 °C, 5 h; (b) NaNO2, AcOH, H2O, 0-5 °C, 1h.*

Similarly, some researchers [40] prepared the triazolopyrimidine derivative **33** in two steps according to previously reported methods (**Figure 18**). 4,6-Dichloro-2-propylpyrimidine-5-amine **30** reacted with furan-2-ylmethanamine **31**, refluxing in ethanol, for 48 h to generate compound **32.** These compounds were later subjected to cyclization reactions with sodium nitrite, resulting in the formation of triazolo[4,5-d] pyrimidine **33.**

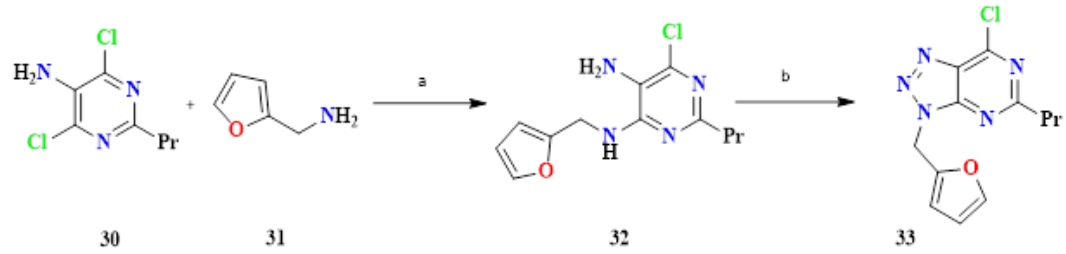

Figure 18. ***Reagents and conditions:*** *(a) EtOH, reflux, 48 h; (b) NaNO2, AcOH, H2O, 10 °C, 1h.*

4.1.3. Synthesis of 1,2,4-triazolo-[1,5-c] pyrimidine derivatives

Prepared triazolo-[1,5-c] pyrimidin-2-yl-acetonitrile **36** in 67% yield by reacting furan compound **34** with 2-cyanoacetohydrazide **35** at reflux in toluene for 22-26 h (**Figure 19**).

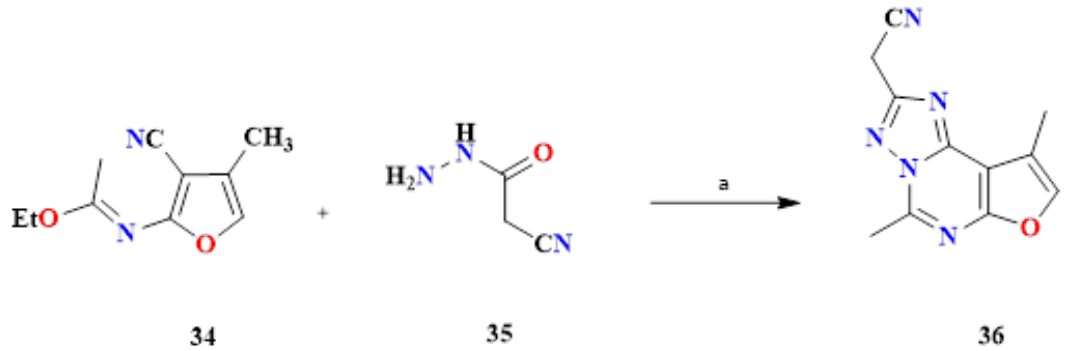

Figure 19. Reagents and conditions: (*a) TsOH (cat), toluene, reflux, 22-26 h.*

Some researchers [41] reported the action of pyrimidine derivatives **37** with semicarbazide **38**, in the presence of DBU, in THF, leading to compounds **39**, which react, subsequently, with hexamethyl disiloxane, for 2 h, to lead to compounds **40** (**Figure 20**).

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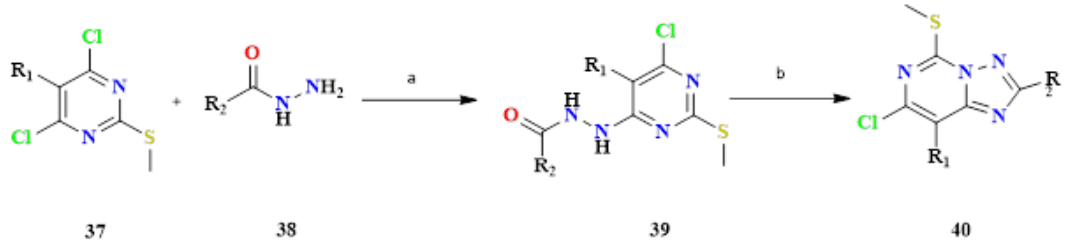

Figure 20. Reagents and conditions: *(a) DBU, THF, 5 h; (b) P_2O_5, HMDSO, xylene, 90 °C, 2h.*

Some researchers [42] reported that pyrimidinylhydrazone **41** was oxidatively cyclized by reacting with hypervalent iodide. This process yielded intermediates **42** that, when subjected to ethanol in an acidic medium, produced triazolopyrimidine derivatives **43** in a yield range of 34-86% (**Figure 21**).

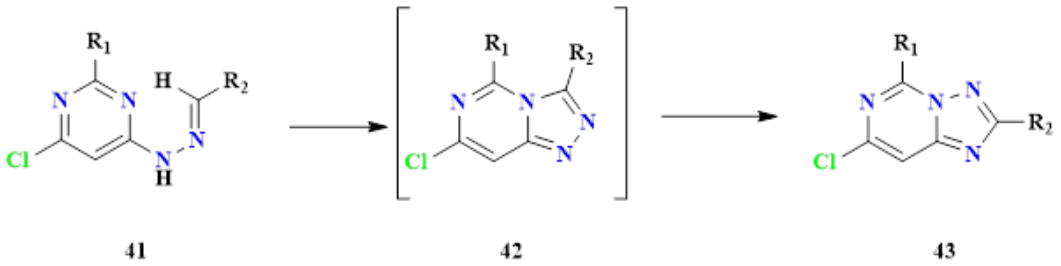

Figure 21. Reagents and conditions: (a) *hypervalent iodide, [O]; (b) EtOH, H^+, 34-86 %.*

4.1.4. Synthesis of 1,2,4-triazolo[4,3-c] pyrimidine derivatives

Some researchers [43] synthesized the triazolopyrimidine derivatives **45** by reacting compounds **44** with dibromine in acetic acid. Sodium acetate was used as a base and the reaction lasted 1 to 3 days. The reaction yields obtained ranged from 54 to 94% (**Figure 22**).

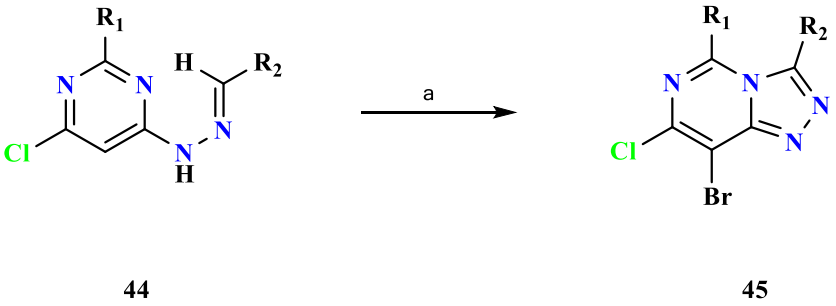

Figure 22. Reagents and conditions: *(a) Br_2, AcOH, NaOAc, 1-3 d, 54-94 %.*

The starting material for the synthesis of triazolopyrimidine **51** was pyrimidinedione 48, which was obtained by reacting methyl 3-aminthiophene-2-carboxylate **46** with urea **47** at 180 °C for 1.5 h [44]. Then, the compound **48** was reacted with phosphoryl trichloride at 110 °C for 5 h to produce 2,4-dichlorothieno[3,2-d] pyrimidine **49**. The compound **49** was reacted with hydrazine hydrate in water at 50 °C for 1 h to yield 2-chloro-4-hydrazineylthieno[3,2-d]pyrimidine **50**. The latter was reacted with triethoxymethane, at reflux for 3 h, to give compound **51** (**Figure 23**).

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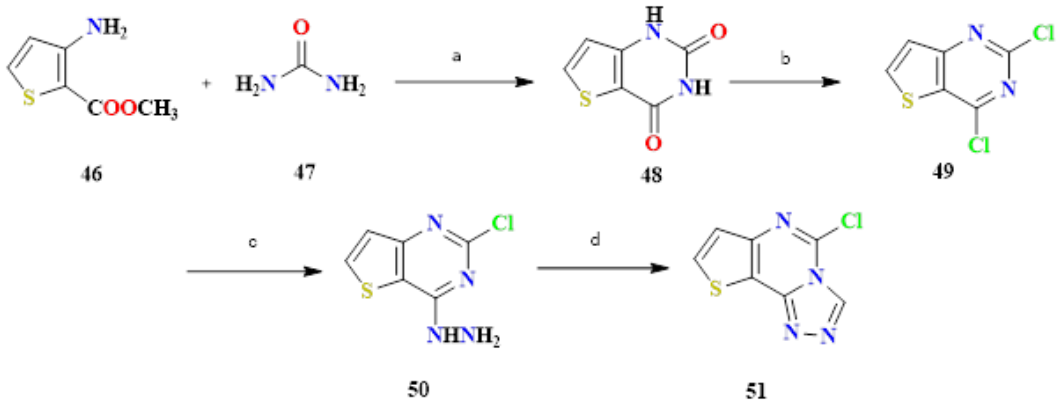

Figure 23. Reagents and conditions*: (a) 180 °C, 1,5 h; (b) $POCl_3$, 110 °C, 5 h; (c) NH_2NH_2, H_2O, 50 °C, 1 h; (d) $HC(OC_2H5)_3$, reflux, 3h.*

4.1.5. Synthesis of 1,2,3-triazolo[1,5-a] pyrimidine derivatives

Some researchers [45] utilized a multicomponent reaction that involved triazole-4-carboxamide **52**, cyclohexanone **53**, and malononitrile **54** in ethanol, using triethylamine as a base. The reaction was performed either under microwave or conventional heating and resulted in the synthesis of a triazolopyrimidine derivative **55** in a yield of 66% (**Figure 24**).

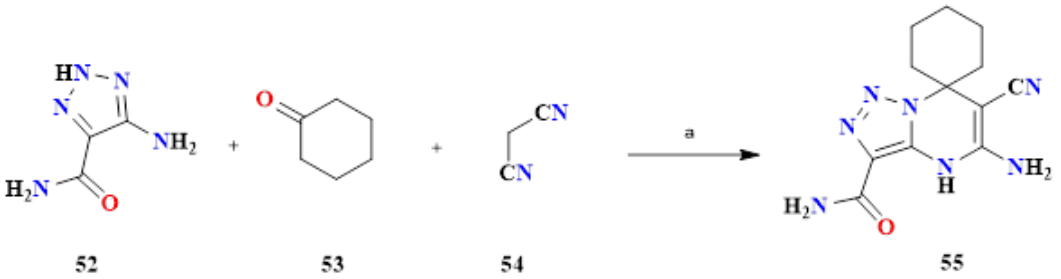

Figure 24. Reagents and conditions: *(a) TEA, EtOH, 66 %.*

Similarly, some researchers [46] investigated the reaction of compounds **56** with 2-aminoprop-1-ene-1,1,3-tricarbonitrile **57** in methanol. The reaction resulted in the synthesis of compound **58** in yields ranging from 80 to 92% (**Figure 25**).

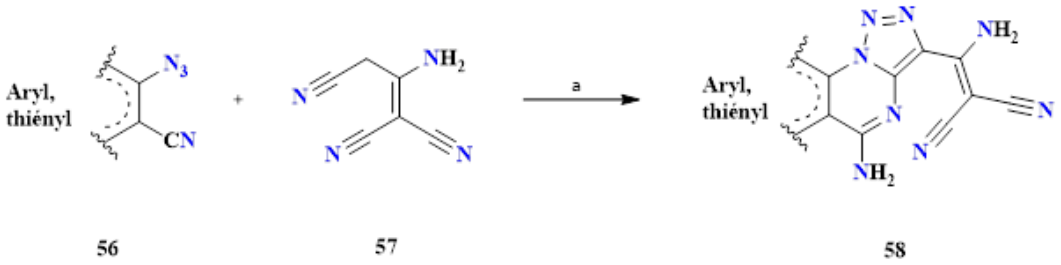

Figure 26. Reagents and conditions: (*a) MeOH, NaOMe, 80-92 %.*

4.1.6. Synthesis of 1,2,4-triazolo[4,3-a] pyrimidine derivatives

Some researchers [47] carried out the condensation of triazolamine **59** with ethyl 4,4,4-trifluorobut-2-ynoate **60** in methanol for 12 h at a temperature of 50°C. The reaction led to the synthesis of triazolopyrimidinone **61** in a yield of 72% (**Figure 27**).

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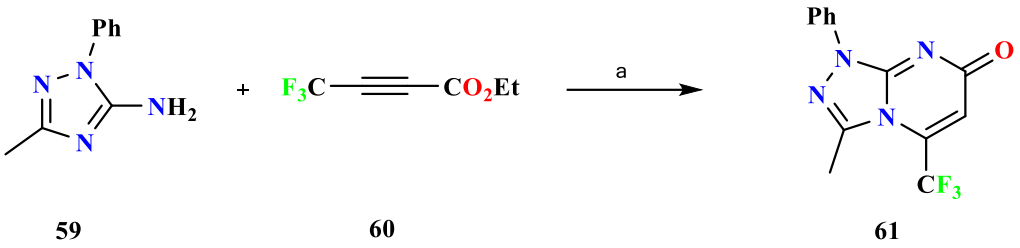

Figure 27. Reagents and conditions: *(a) MeOH, 50 °C, 12 h, 72 %.*

Likewise, some researchers [48] investigated the reaction between triazolamine 5 and ethyl 3-phenylglycidate **62** in *n*-butanol. The reaction resulted in the synthesis of triazolopyrimidinone **63** in a yield of 43% (**Figure 28**).

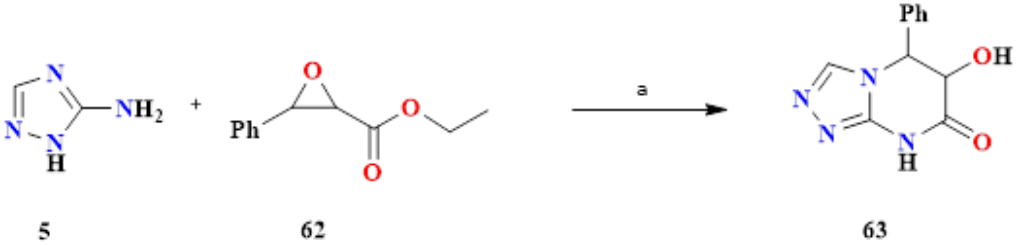

Figure 28. Reagents and conditions: *(a) n-BuOH, 43 %.*

Some researchers [49] recently proposed a multicomponent reaction catalyzed by involving benzaldehydes **64** with substitutions, triazolamine **13**, and malononitrile **54**, which were heated for 20-50 min, producing the derivatives of triazolopyrimidines **65** in yields of 86-95% (**Figure 29**).

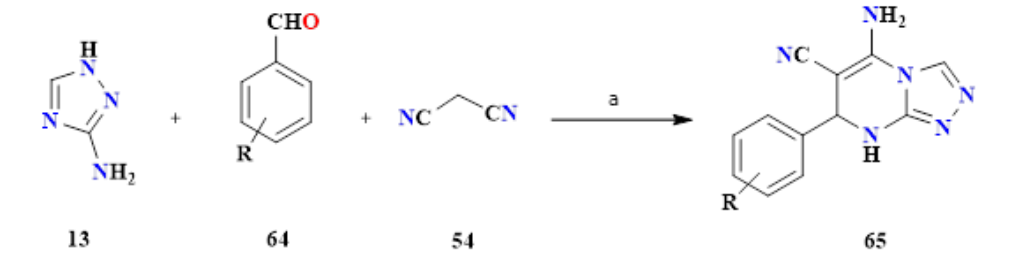

Figure 29. Reagents and conditions: *(a) cat, 90 °C, 20-50 mn, 86-95 %.*

4.1.7. Synthesis of 1,2,3-triazolo[1,5-c] pyrimidine derivatives

Some researchers [50] performed a multicomponent reaction, engaging 2*H*-azirine **68**, tosylazide **67,** and phenylacetylene **66**, using triethylamine as a base and copper iodide (CuI) as a catalyst, in toluene at room temperature. The authors obtained triazolopyrimidine **69** in high yield (**Figure 30**).

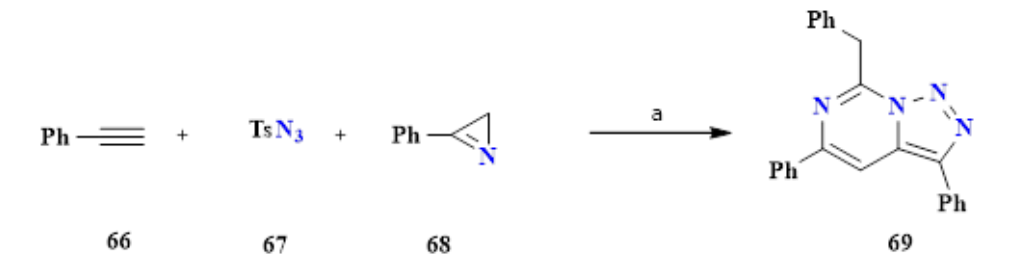

Figure 30. Reagents and conditions*: (a) CuI, TEA, PhCOOH, toluene.*

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The same authors [50] performed a multicomponent reaction, involving acetylenic compound **70**, vinyl azide**71** and tosylazide **67**, in refluxing toluene in the presence of 1,4-diazabicyclo [2.2.2] octane and copper iodide, for 1 hour, to lead to the triazolopyrimidine derivatives **72**, in good yields (**Figure 31**) [51].

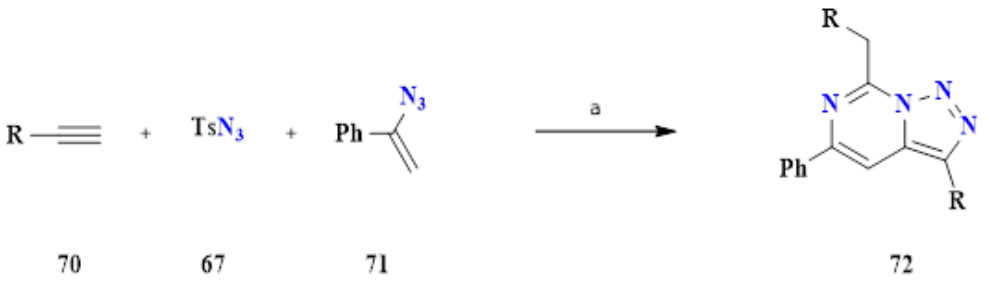

Figure 31. Reagents and conditions: *(a) DABCO, CuI, PhCOOH, toluene, reflux, 100 °C, 1 h.*

4.2. Reactions of Triazolopyrimidines

4.2.1. Halogenation

Some researchers [52] described the preparation of triazolopyrimidine **74** by chlorination of triazolo pyrimidinone **73** with phosphoryl chloride at a temperature of 90°C for 1 hour, (**Figure 32**).

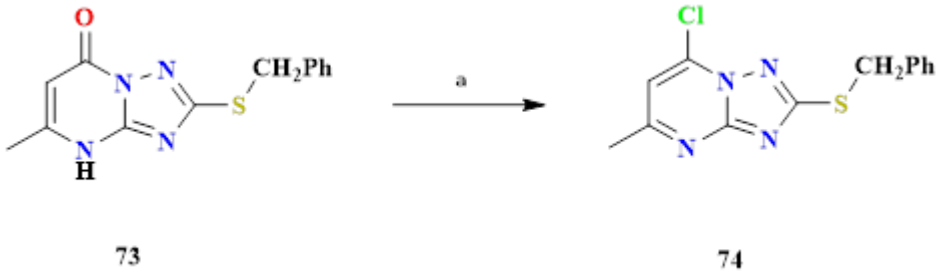

Figure 32. Reagents and conditions: (*a) $POCl_3$, 90 °C, 1 h.*

4.2.2. Alkylations and functionalization

Some researchers [53] prepared triazolopyrimidines **77** and **78** by reacting compound **75** with 3-bromoprop-1-yne **76** in the presence of potassium hydroxide in acetone. The reaction occurred at the methylene group bound to the ester group, resulting in mono or dialkylation along with hydrolysis and decarboxylation reactions. The compounds **77** and **78** were obtained in 40 and 54% yields, respectively (**Figure 33**).

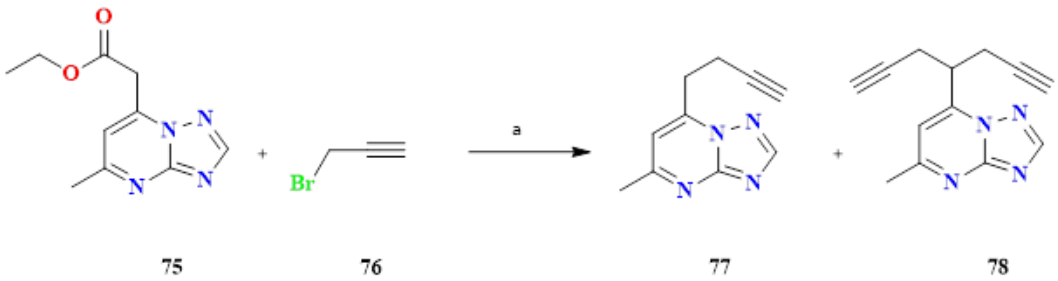

Figure 33. **Reagents and conditions**: *(a) Acetone, KOH.*

Similarly, some researchers [54] examined the alkylation reaction of triazolopyrimidine derivatives **79** with the alkylating agent **80** in dimethylformamide at reflux for 2 h in the

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presence of potassium carbonate at temperatures between35 and 40 °C to prepare the S-alkylated compounds **81** in good yields (**Figure 34**).

Figure 34. Reagents and conditions: *(a) DMF, K_2CO_3, 2 h, 35-40 %.*

Some researchers [55] investigated the condensation of ester **82** with hydrazine hydrate in ethanol at reflux for 2 h, resulting in the synthesis of compound **83** in a yield of 30%. This compound was then reacted with aromatic aldehydes in acetic acid at reflux for 2 h, resulting in the synthesis of triazolopyrimidine derivatives **84** in yields ranging from 57 to 70% (**Figure 35**).

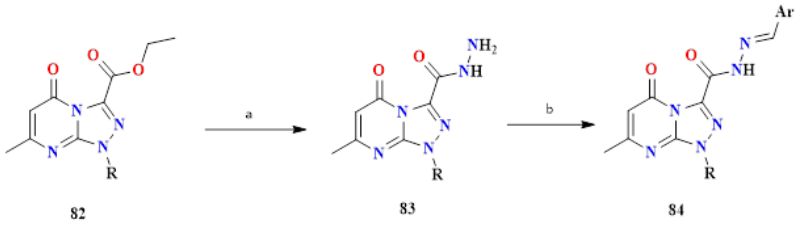

Figure 35. Reagents and conditions: *(a) NH_2NH_2, H_2O, EtOH, reflux, 2 h, 30 %; (b) ArCHO, AcOH, 110 °C, 2 h, 57-70 %.*

The alkylation reaction of triazolopyrimidine derivatives **85** with iodoethane **86** in ethanol, using potassium hydroxide as a base, to produce triazolopyrimidine derivatives **87**, which react with hydrazine hydrate in ethanol to synthesize triazolopyrimidine derivatives **88** (**Figure 36**).

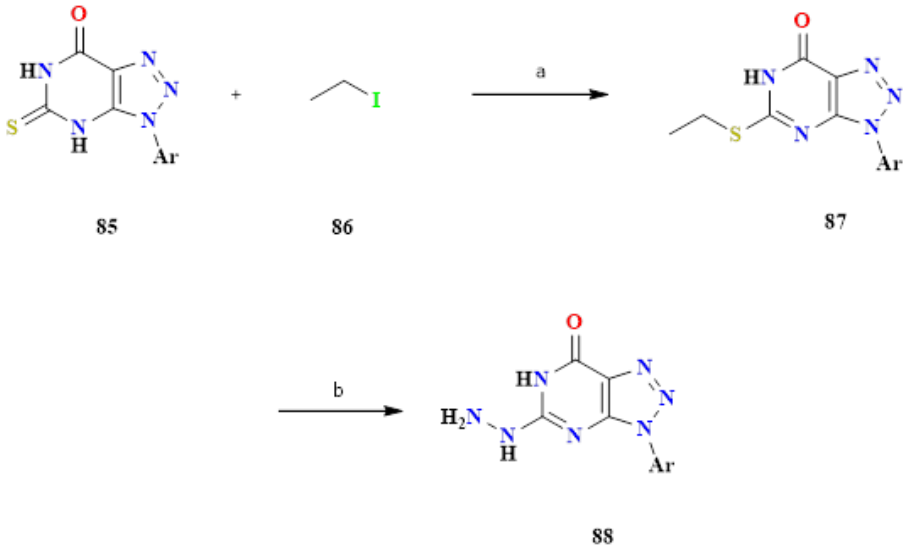

Figure 36. Reagents and conditions: *(a) EtOH, KOH; (b) NH_2NH_2, EtOH.*

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4.2.3. Nitration

Some researchers [37] examined the preparation of triazolopyrimidinone derivative **90** from triazolopyrimidine **89** in good yield. They employed nitronium borofluoride as the nitrating agent in the presence of triethylamine in acetonitrile at low temperatures (**Figure 37**).

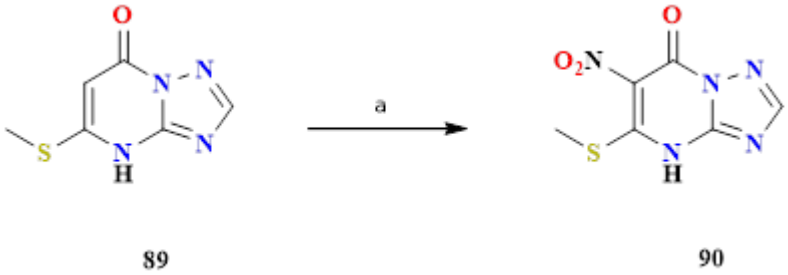

Figure 37. Reagents and conditions: *(a) BF_4NO_2, TEA, MeCN, -10-25 °C.*

Some researchers [56] described the synthesis of triazolopyrimidinone **92**, by treating triazolopyrimidinone **91** with a mixture of sulfuric and nitric acids (**Figure 38**).

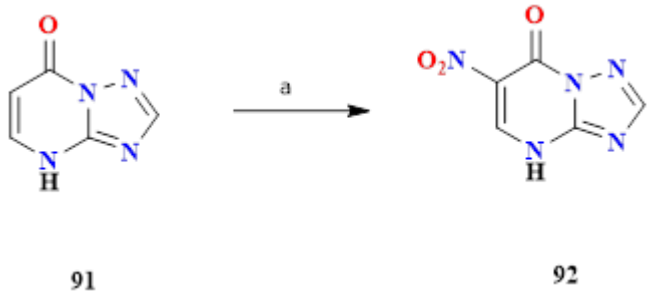

Figure 38. Reagents and conditions: *(a) HNO_3, H_2SO_4.*

4.2.4. Condensation and hetero-cyclization

Some researchers [57] researched the reaction of hydrazide **93** with isothiocyanate **94** under reflux of ethanol for 2-3 h. The solid produced was filtered, washed, and recrystallized in ethanol to obtain triazolopyrimidine **95**. The compound was then subjected to intramolecular cyclization in the presence of sodium hydroxide to yield the heterocyclic compound **96** in good yield (**Figure 38**).

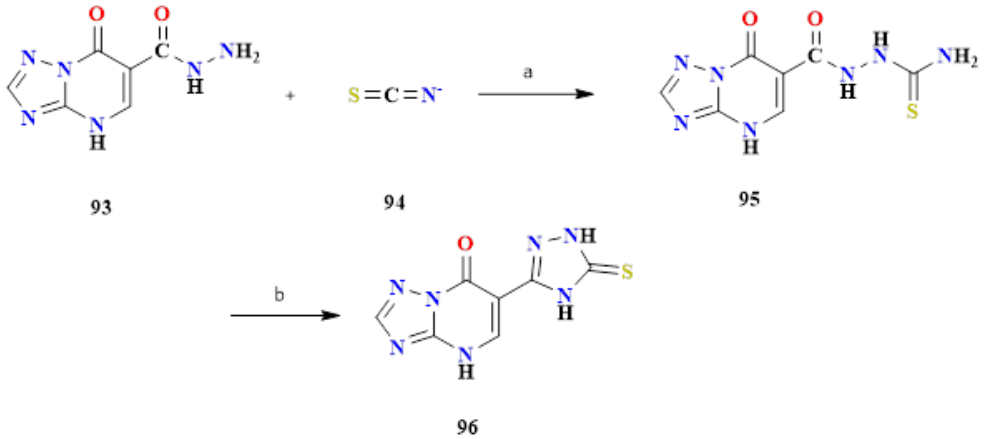

Figure 38. Reagents and conditions: *(a) EtOH, reflux, 2-3 h; (b) NaOH*

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4.2.5. Nucleophilic substitution and cyclization

Some researchers [58] investigated the preparation of triazolopyrimidinamine **99** by reacting an amine **98** with triazolopyrimidine **97** (**Figure 38**).

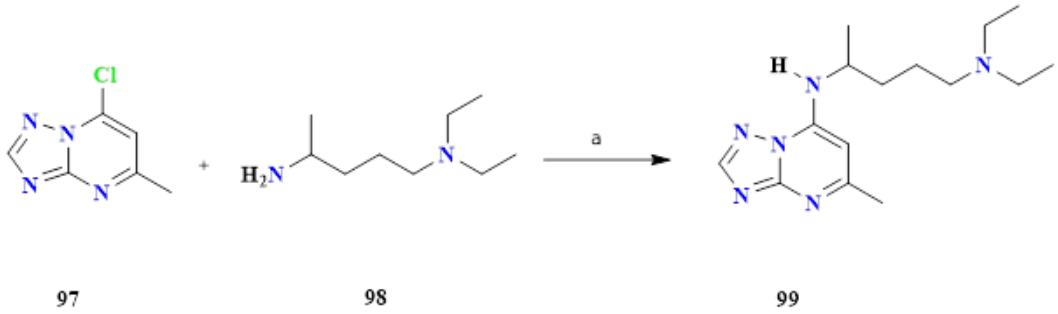

Figure 38. Reagents and conditions: *(a) EtOH, 25 °C, 43 h.*

Some researchers [59] examined the effect of substituted 2-amino-1,2,4-triazolopyrimidine **100** on 3-chloropropanoyl chloride **101** in DMF at temperatures between 0 to 5 °C for 15 min. The resulting acylamino intermediate **102** then undergoes intramolecular cyclization to yield the tricyclic compound **103** by heating at 80-90 °C for 3-5 min (**Figure 39**).

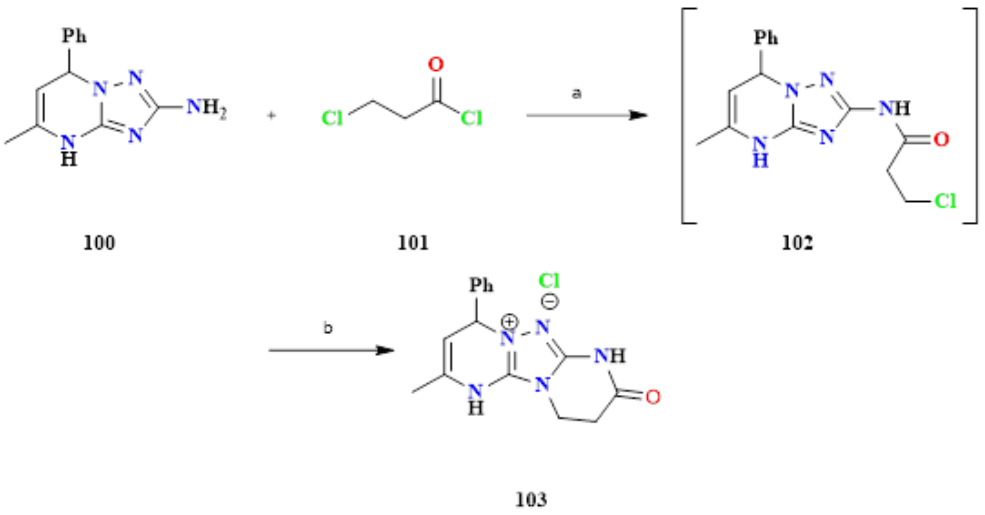

Figure 39. Reagents and conditions: *(a) DMF, 0-5 °C, 15 mn; (b) 80-90 °C, 3-5 mn.*

4.2.6. Oxidation and reduction

Some researchers [60] investigated the synthesis of triazolopyrimidinamines **105** and **106** by conducting oxidation and reduction reactions of triazolopyrimidinamine **104** derivatives, respectively (**Figure 40**).

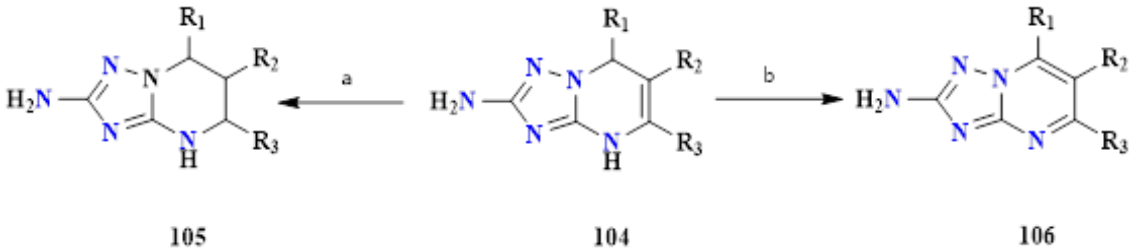

Figure 40. Reagents and conditions: *(a) $NaBH_4$; (b) [O].*

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Some researchers [38], reported the synthesis of triazolopyrimidine derivative **108** by reducing triazolopyrimidine-6-carboxylate **107** with lithium aluminum hydride in tetrahydrofuran, resulting in a 90% yield (**Figure 41**).

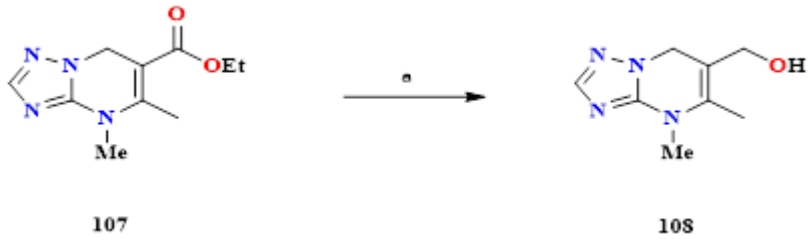

Figure 41. Reagents and conditions: *(a) LiAlH4, THF, 90 %.*

4.3. Biological Benefits of Triazolopyrimidines

4.3.1. Anti-SARS-CoV-2 activity

Natural triazolopyrimidine derivatives **109** and **110** (**Figure 42**) have demonstrated inhibitory potential against viral RdRp protein targets, including SARS-CoV-2 and SARS-CoVRdRp proteins, as well as other nonstructural proteins that are involved in virus transcription, replication, and packaging [61]. Their study hypothesis was also supported by comparative studies with Favipiravir and Remdesivir. However, further in vitro validation is required for safety and drug development reasons. This will help in developing a promising drug molecule to fight the COVID-19 pandemic.

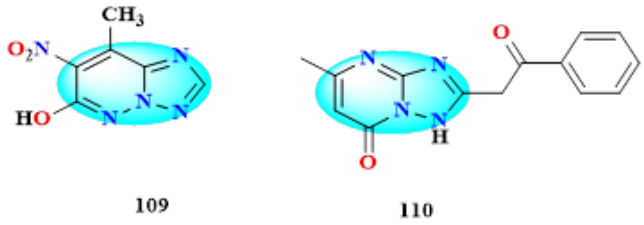

Figure 42. Structures of natural triazolopyrimidine **109** and **110**.

Some researchers [62] evaluated new triazolopyrimidine derivatives **111-113** (**Figure 43**) for their antiviral activity against the main protease (Mpro) of SARS-CoV-2 using molecular docking and molecular dynamics simulation. The study found that compounds **111-113** had higher average binding affinities of (-8.1 ± 0.33 kcal/mol, -8.0 ± 0.35 kcal/mol, and -8.2 ±0.21 kcal/mol, respectively) than the positive control Nelfinavir (-6.9 ± 0.51 kcal/mol). This implies that compounds **111-113** can bind to SARS-CoV-2 Mpro effectively and counteract the virus life cycle. These results provide a promising starting point for developing new drugs to treat COVID-19.

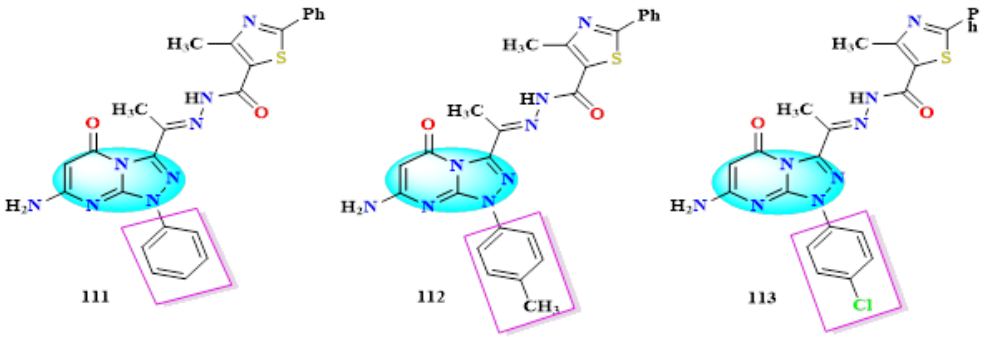

Figure 43. Structures of triazolopyrimideine derivatives **111-113**.

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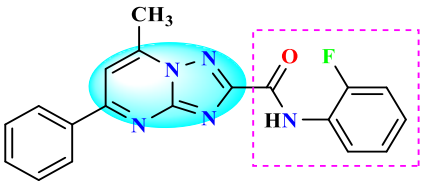
Recently, some researchers [31] synthesized triazolopyrimidine-2-carboxamide derivative **114** (**Figure 44**) and screened it for anti-COVID-19 activity. Additionally, a set of analogs available in-house was also evaluated against SARS-CoV-2. The study found that triazolopyrimidine derivative **114** had an anti-SARS-CoV2 activity with an EC_{50} value of 34.47 mM and did not harm Vero E6 cells. This effect might be related to how the compound blocks the protein-protein interaction (PPI), which is supported by its interference with the polymerase acidic protein-basic protein 1 (PA-PB1) heterodimerization (CI_{50} ¼ 17.5 mM).



114

Figure 44. Structure of product **114**.

Novel triazolopyrimidine derivatives **115** and **116** (**Figure 45**) were examined for their antiviral potential against SARS-CoV-2 [63]. The study found that these derivatives showed good suitability in the active site of COVID-19 3CL protease, suggesting the possibility that they act as antiviral agents against SARS-CoV-2.

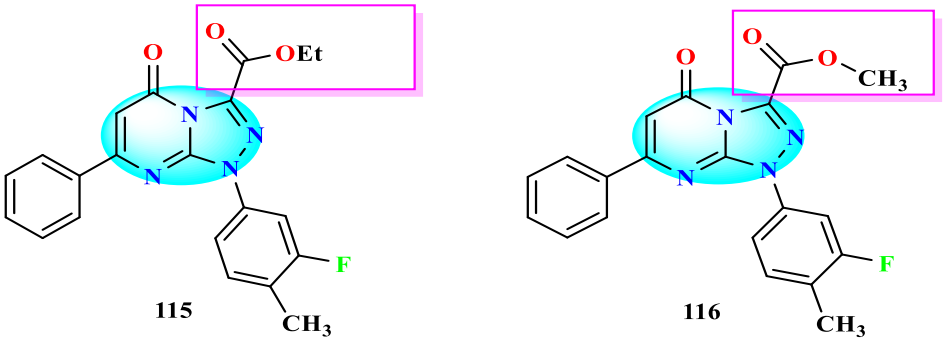


Figure 45. Structures of **115** and **116**.

4.3.2. Anti-inflammatory activity

Novel receptor agonists of triazolopyrimidine derivatives **117-120** have been identified as potential treatments for inflammatory kidney disease [64]. The study used high-throughput screening to identify novel CB2 receptor agonists and small heterocyclic molecules. The study revealed a novel triazolopyrimidine derivative that is highly potent and selective (relative to CB1) as a CB2 receptor agonist. Further analysis of the structure-activity relationship (SAR) of the derivatives revealed that adding a benzyl tetrazole at the 3-position of the triazolopyrimidine ring enhances the activity. Likewise, the 3-pyrrolidine substituent at position 7 of the bicyclic system made the compound more potent (**Figure 46**).

Compound **121** exhibited promising anti-inflammatory activity based on *in vitro* selection indicators [65]. It was found to be higher than or nearly equivalent to reference drugs against COX-2. To further evaluate its anti-inflammatory activity, the study used a claw edema protocol induced by formalin as a model of acute inflammation [66], and the granulation protocol induced by granuloma as a model of chronic inflammation (**Figure 47**) [67].

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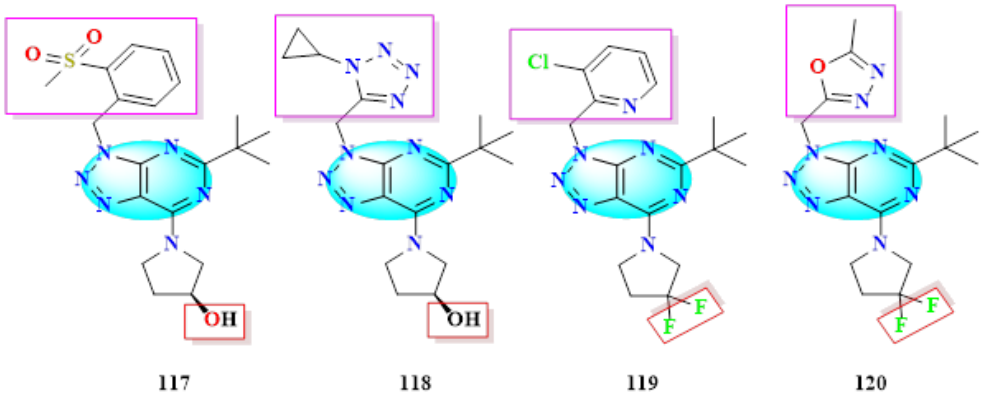

Figure 46. Structure of products **117-120**.

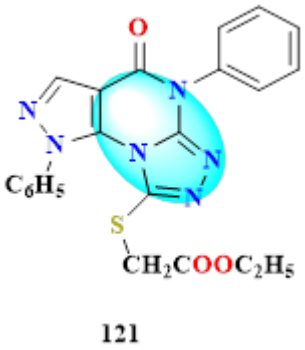

Figure 47. Structure of product **121**.

Some researchers [68] evaluated the newly synthesized compounds, for their anti-inflammatory effect on rats, using the carrageenan-induced paw edema method and indomethacin as the reference drug [69]. The study found that the new compounds had various levels of anti-inflammatory activity in rats, with compounds **122-124** being the most effective (**Figure 48**) [70].

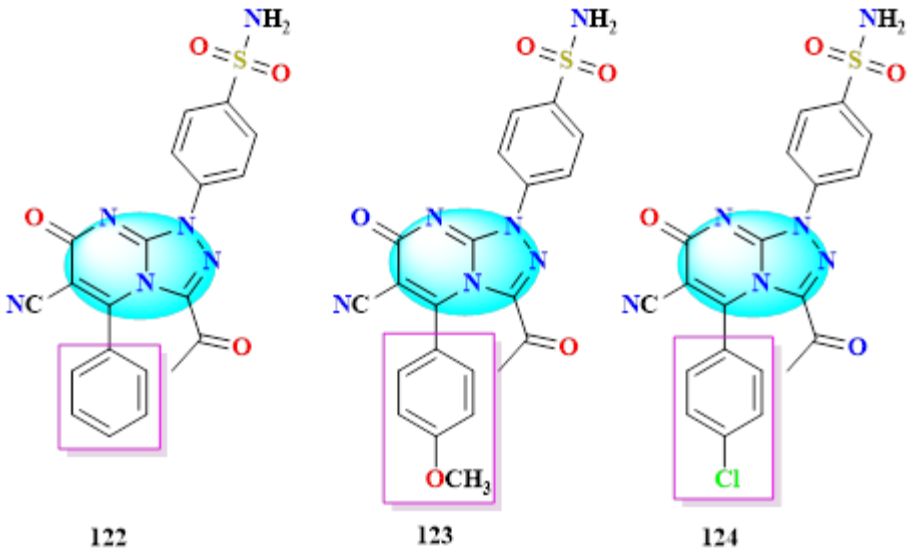

Figure 48. Structures of products **122-124**.

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4.3.3. Anticancer activity

Some researchers [71] developed triazolopyrimidine derivatives, such as compound **125** (Figure 9), which have shown significant efficacy against various plant diseases. The pharmaceutical company Wyeth tested these derivatives as potential chemotherapeutic agents. During the process, a triazolopyrimidine derivative known as cevipabulin **126** (Figure 10) was identified as having potent antitumor effect both *in vitro* and *in vivo*. However, further studies on SAR and mode of action with related triazolopyrimidine congeners revealed that even the compounds without the alkoxy side chain in the para position of the phenyl ring, such as fluorinated **127** (**Figure 49**), had good activity.

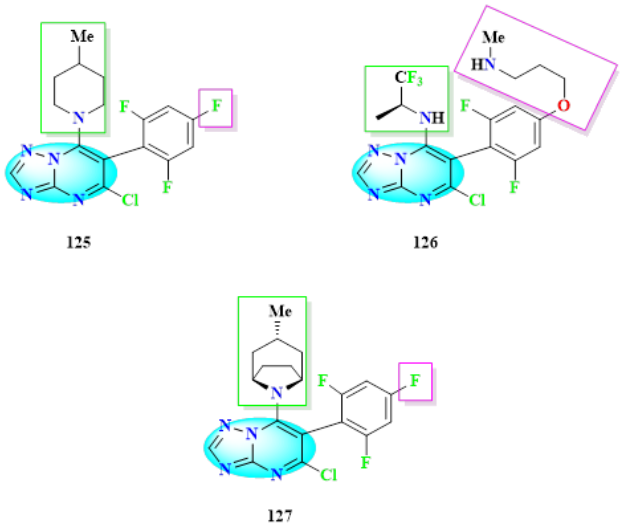

Figure 49. Structures of products tested **125-127**.

It delves into the evaluation of a fascinating compound, referred to as **128** (depicted in **Figure 50**), for its potential as an anticancer agent [72]. This research sheds light on the exploration of novel compounds and their therapeutic applications in the field of oncology. The study reported the synthesis of derivative **128**, which demonstrated strong antiproliferative effect against MGC-803, a human gastric carcinoma cell line. Compound **128** inhibited MGC-803, with an IC_{50} of 0.96 µM and was about 38 times more selective than GES-1, a normal gastric mucosa cell line. The study also showed that compound 128 blocked the colony formation and migration of MGC-803 and stopped their growth by causing G0/G1 phase arrest. Additionally, compound **128** triggered cell death by activating both the mitochondria-dependent and the death receptor-dependent pathways. The study revealed that compound **128** increased the level of reactive oxygen species (ROS) to induce cell death. Additionally, this compound was safe in vivo according to acute toxicity tests. Therefore, compound 128 could be a lead for developing [1,2,4] triazolo[1,5-a] pyrimidine-based antitumor drugs.

Some researchers [73] indeed shed light on the anticancer potential of the novel compound **129** (**Figure 51**). Their study revealed that compound **129** exhibited remarkable selectivity towards PC3, a human prostatic carcinoma cell line, surpassing its activity against other cancer cell lines such as MGC-803, EC9706, SMMC-7721, and PC9. Notably, compound **129** also demonstrated good selectivity to normal cell lines, including Het-1A, GES-1, and L02.

Further studies conducted by Xu and colleagues delved into the mechanisms responsible for the anticancer effects of compound **129**. It was observed that **129** significantly hindered the formation of PC3 cell colonies, indicating its potential to impede the growth of cancer

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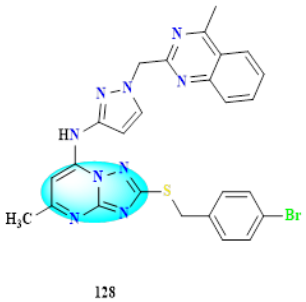
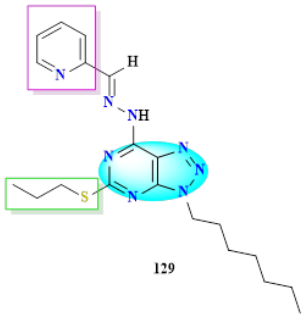
cells. Moreover, compound **129** was found to increase the cellular content of ROS, which are known to induce cellular stress and promote apoptosis. Additionally, the compound exhibited the ability to suppress the expression of EGFR, a protein associated with the proliferation and survival of cancer cells. Encouragingly, compound 129 also induced apoptosis, a crucial process in eliminating cancer cells.



128

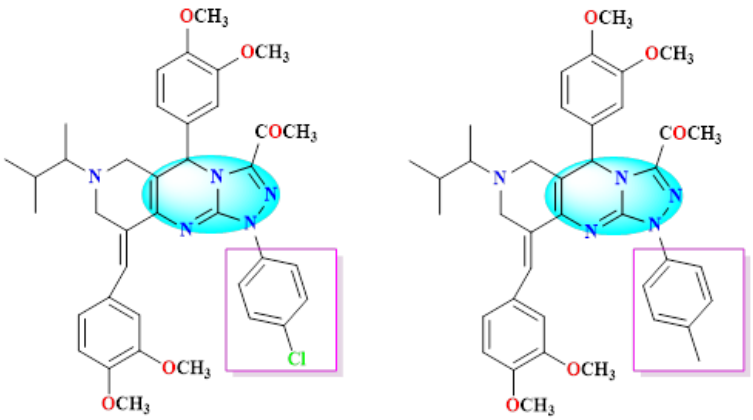
Figure 50. Structure of product **128**.



129

Figure 51. Structure of product **129**.

Some researchers [74] demonstrated the potential of triazolopyrimidine derivatives as anticancer agents. The study involved the synthesis of several new condensed heterocyclic compounds, including products **130** and **131** (**Figure 52**), which exhibited high anti-tumor activity. These compounds were evaluated for their anticancer efficacy against three human tumor cell lines, including PC3, HCT116, HepG2, and MCF7. The study revealed that compounds **130** and **131** demonstrated considerable potency against the tumor cell lines.



130 131

Figure 52. Structures of products **130** and **131**.

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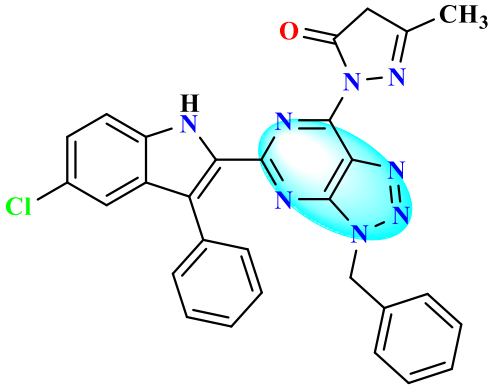
4.3.4. Antimicrobial activity

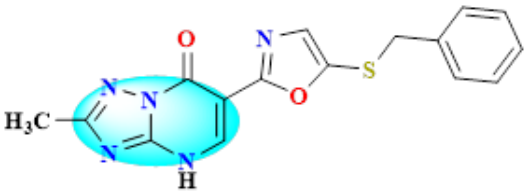
The potential antimicrobial activity of new indole analogs containing the triazolopyrimidine **132** (depicted in **Figure 53**) was evaluated [75]. The researchers found that the presence of chloro and methoxy substitutions in these hybrids significantly increased their antimicrobial and antioxidant activities compared to compounds without any substitution. Moreover, the inclusion of the triazolopyrimidine **132** moiety generally increased the overall effect of the derivatives. The study also revealed that the indole unit was crucial to the antimicrobial potency of these hybrids. These findings shed light on the SAR and suggest that the presence of specific substituents and the triazolopyrimidine **132** scaffold contribute to the enhanced antimicrobial properties of these compounds.



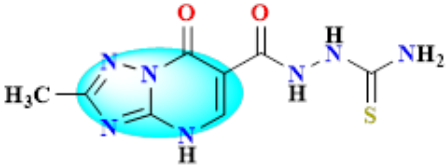
132

Figure 53. Structure of product **132**.

The antimicrobial potential of novel triazolopyrimidine derivatives **133** and **134** (**Figure 54**) was evaluated [76]. The compounds underwent testing against a range of bacterial and fungal strains to assess their antimicrobial activity, as well as to evaluate their safety and potential for causing hemolysis. Subsequently, the most active derivatives were further evaluated to determine their mode of action as inhibitors of DNA Gyrase [77].



133



134

Figure 54. Structures of products **133** and **134**.

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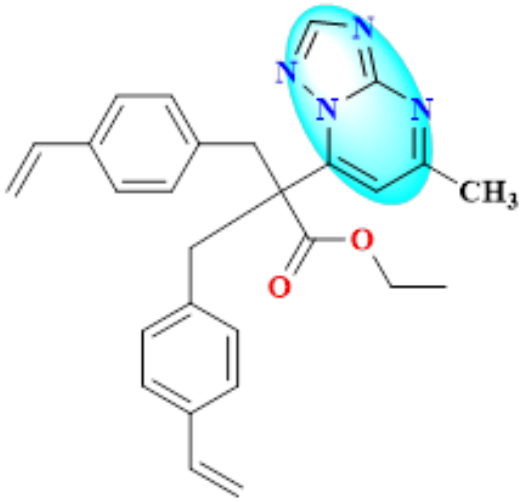
Some researchers [78] have tested a new triazolopyrimidine **135** (**Figure 55**), as a possible antimicrobial agent. They have evaluated its activity against Gram-negative bacterial strains, like *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, which are common causes of infections in humans and animals. They have found that compound **135** has superior antibacterial activity compared to the reference [79-80], which are standard drugs used to treat these infections.

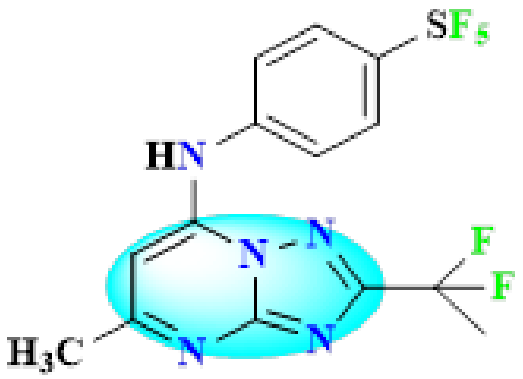


135

Figure 55. Structure of product **135**.

4.3.5. Anti-malarial activity

Some researchers [81] developed dihydroorotate dehydrogenase inhibitors based on triazolopyrimidine to enhance their drug properties. They utilized SF-aniline derivatives$_5$ to identify molecules that have better species selectivity, improved drug properties. Furthermore, the researchers dedicated their efforts to ensuring sustained efficacy and favorable pharmacokinetic profiles while aiming to maintain a similar product profile. Remarkably, their study yielded significant advancements in both the physical and chemical properties of triazolopyrimidinamine **136** (**Figure 56**)



136

Figure 56. Structure of product **136**.

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4.3.6. Antifungal activity

Some researchers [82] evaluated new triazolopyrimidine derivatives **137-141** (**Figure 57**) as potential antifungal agents. These compounds have been used to protect crops with high efficacy worldwide and are noteworthy for their low toxicity towards animals. Additionally, a potential target for antifungal drugs has been identified in the inhibition of acetohydroxy acid synthase by herbicides, which involves a complex process with two mechanisms at play.

The antifungal properties of recently discovered triazolopyrimidine derivatives **142** and **143** were investigated [83]. The structures of these compounds are depicted in **Figure 58**. The study focused on their efficacy against two fungal strains, *Rhizoctonia solani* and *Trichoderma sp*. The results revealed that compound **142** exhibited higher effectiveness against *R. solani* compared to a concentration of 100 ppm. On the other hand, compound **143** demonstrated superior antifungal activity against Trichoderma sp. when compared to the same concentration of 100 ppm.

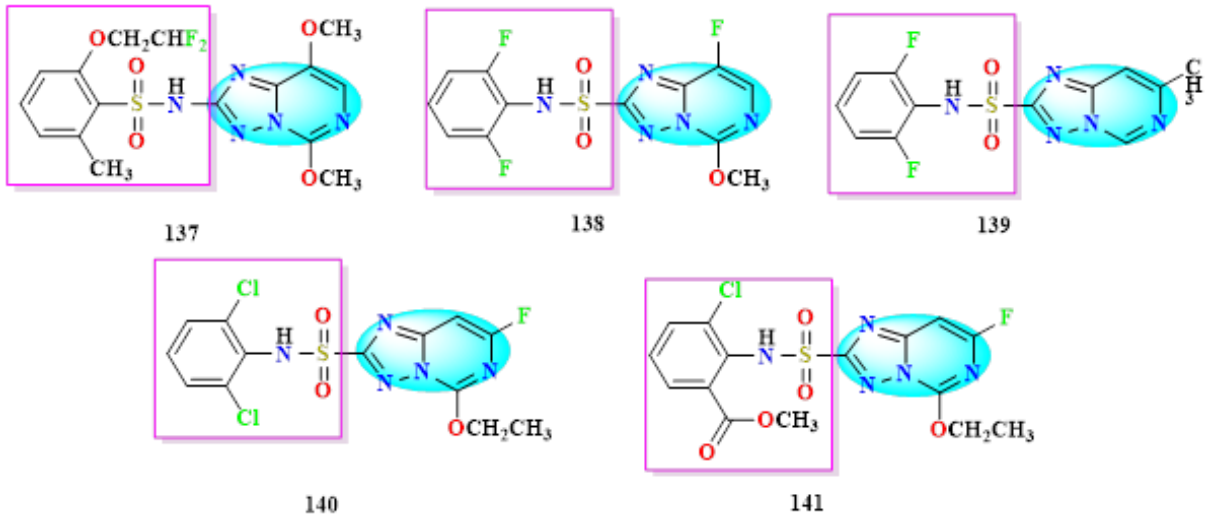

Figure 57. Structures of products **137-141**.

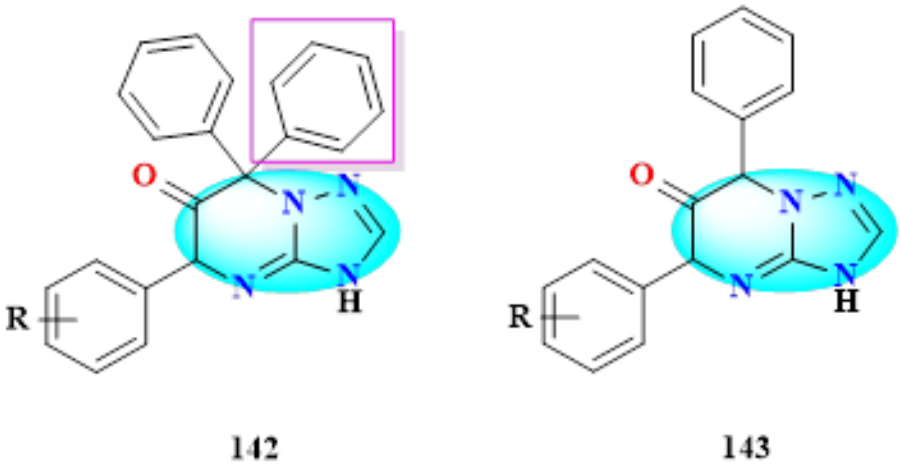

Figure 58. Structures of products **142** and **143**.

4.3.7. Antidiabetic activity

Some researchers [84] discovered new derivatives of triazolopyrimidine **144-146** (**Figure 59**), which showed antidiabetic activity. These compounds **144-146**, inhibited the enzyme *α-glucosidase*, which is involved in the digestion of carbohydrates, with IC_{50} values of 20.12 ±

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0.19 µM, 21.55 ± 0.46 µM and 24.92 ± 0.98 µM, respectively. This means that they can lower the blood glucose levels by reducing the absorption of sugars from the intestine.

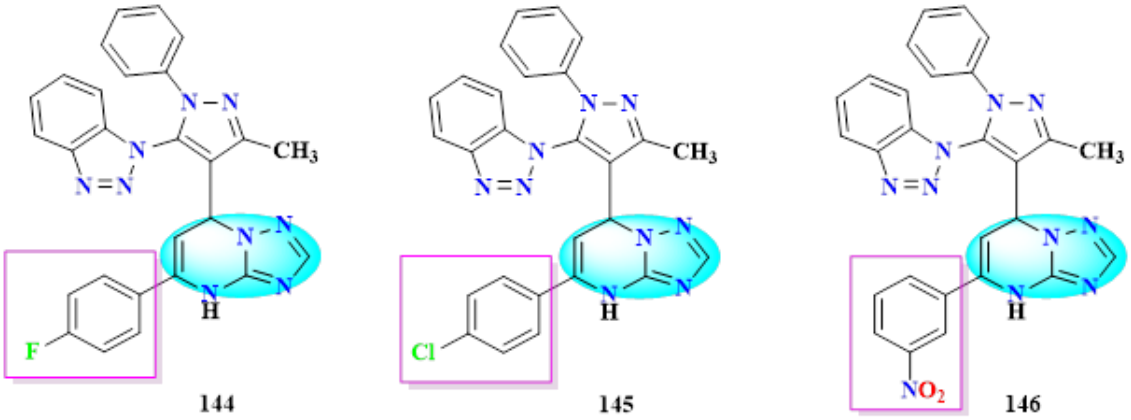

Figure 59. Structures of products **144-146**.

5. CONCLUSION

Triazolopyrimidine holds a significant position as a pivotal entity within the realms of organic, inorganic, and medicinal chemistry. Its derivatives have garnered substantial attention, and researchers have explored and improved various synthetic methods for their synthesis. New synthetic protocols have enabled the access to triazolopyrimidine derivatives that were not possible with traditional methods, resulting in a higher diversity of triazolopyrimidine-based molecules. This review covers the different synthetic methods for triazolopyrimidine derivatives and their reactivities with various reagents. It also highlights the important biological and pharmacological properties of triazolopyrimidine derivatives, which make them valuable in medicinal chemistry. Furthermore, the molecular docking study shows that the use of triazolopyrimidine isomers at the receptor's active site can help predict and optimize both anti-COVID-19 and anticancer effects. This approach allows the specific targeting of molecular interactions at the active site, which helps understand the possible mechanisms of action of these compounds against both COVID-19 and cancer. This literature review from 2014 to 2022 provides a comprehensive exploration of triazolopyrimidines, highlighting their diverse applications in medicinal chemistry. Covering synthesis methods, reactivity, and pharmacological properties, it emphasizes their potential in combating COVID-19 and cancer through molecular docking predictions. The review aims to offer a thorough understanding of triazolopyrimidines' versatility, serving as a valuable resource for advancing drug development in medicinal chemistry.

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7. AUTHORS' NOTE

The authors declare that there is no conflict of interest regarding the publication of this article. The authors confirmed that the paper was free of plagiarism.

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8. REFERENCES

[1] Cebeci, Y. U., Batur, Ö. Ö., and Boulebd, H. (2024). Design, synthesis, theoretical studies, and biological activity evaluation of new nitrogen-containing poly heterocyclic compounds as promising antimicrobial agents. *Journal of Molecular Structure, 1299*, 137115.

[2] Obaid, R. J., Mughal, E. U., Naeem, N., Al-Rooqi, M. M., Sadiq, A., Jassas, R. S., Moussa, Z., and Saleh, A. (2022). Pharmacological significance of nitrogen-containing five and six-membered heterocyclic scaffolds as potent cholinesterase inhibitors for drug discovery. *Process Biochemistry, 120*, 250-259.

[3] Elmsellem, H., Basbas, N., Chetouani, A., Aouniti, A. S., Radi, M., Messali, M., and Hammouti, B. (2014). Quantum chemical studies and corrosion inhibitive properties of mild steel by some pyridine derivatives in 1 N HCl solution. *Portugaliae Electrochimica Acta, 32*(2), 77-108.

[4] Ghazoui, A., Saddik, R., Benchat, N., Guenbour, M., Hammouti, B., Al-Deyab, S. S., and Zarrouk, A. (2012). Comparative study of pyridine and pyrimidine derivatives as corrosion inhibitors of C38 steel in molar HCl. *International Journal of Electrochemical Science, 7*(8), 7080-7097.

[5] Zarrouk, A., Hammouti, B., Al-Deyab, S. S., Salghi, R., Zarrok, H., Jama, C., and Bentiss, F. (2012). Corrosion inhibition performance of 3,5-diamino-1,2,4-triazole for protection of copper in nitric acid solution. *International Journal of Electrochemical Science, 7*(7), 5997-6011.

[6] Renyu, Q., Yuchao, L., Wishwajith, W. M., Kandegama, W., Qiong, C., and Guagfa, Y. (2018). Recent applications of triazolopyrimidine-based bioactive compounds in medicinal and agrochemical chemistry. *Mini-Reviews in Medicinal Chemistry, 18*, 781-790.

[7] Ramadan, M., Abd El-Aziz, M., Elshaier, Y. A. M. M., Youssif, B. G. M., Brown, A. B., Fathy, H. M., and Aly, A. A. (2020). Design and synthesis of new pyranoquinolinone heteroannulated to triazolopyrimidine of potential apoptotic antiproliferative activity. *Bioorganic Chemistry, 105*, 104392.

[8] Li, Y., Du, R., Nie, Y., Wang, T., Ma, Y., and Fan, Y. (2021). Design, synthesis and biological assessment of novel CDK4 inhibitor with potent anticancer activity. *Bioorganic Chemistry, 109*, 104717.

[9] Dawood, D. H., Nossier, E. S., Ali, M. M., and Mahmoud, A. E. (2020). Synthesis and molecular docking study of new pyrazole derivatives as potent anti-breast cancer agents targeting VEGFR-2 kinase. *Bioorganic Chemistry, 101*, 103916.

[10] Ettahiri, W., and Essassi, E. M. (2019). Recent advances in the development of nitrogen-containing heterocyclic compounds as anticancer agents: A review. *Moroccan Journal of Heterocyclic Chemistry, 18*, 74-102.

[11] Nemr, M. M. T., and AboulMagd, A. M. (2020). New fused pyrimidine derivatives with anticancer activity: Synthesis, topoisomerase II inhibition, apoptotic inducing activity and molecular modeling study. *Bioorganic Chemistry, 103*, 104134.

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045

[12] Singh, P. K., Choudhary, S., Kashyap, A., Verma, H., Kapil, S., Kumar, M., Arora, M., and Silakari, O. (2019). An exhaustive compilation on chemistry of triazolopyrimidine: A journey through decades. *Bioorganic Chemistry, 88*, 102919.

[13] Lahmidi, S., Sert, Y., Şen, F., El Hafi, M., Ettahiri, W., Gökce, H., Essassi, E. M., Mague, J. T., and Ucun, F. (2021). Synthesis, crystal structure, Hirshfeld surface analysis, spectral characterizations and quantum computational assessments of 1-hydroxy-3-methyl-11H-pyrido[2,1-b] quinazolin-11-one. *Journal of Molecular Structure, 1249*, 131592.

[14] Ettahiri, W., El Hafi, M., Lahmidi, S., Abad, N., Ramli, Y., El Ghayati, L., and Essassi, E. M. (2020). Pyrazolo [3, 4-d] pyrimidine derivatives: Synthesis, reactivity and biological properties. *Journal Marocain de Chimie Hétérocyclique, 19*, 1–36.

[15] Abad, N., Ramli, Y., Ettahiri, W., Ferfra, S., and Essassi, E. M. (2020). Quinoxaline derivatives: Syntheses, reactivities and biological properties. *Journal Marocain de Chimie Hétérocyclique, 19*, 1–62.

[16] Ettahiri, W., and Essassi, E. M. (2019). Benzimidazolone derivatives: Synthesis, reactivity and biological properties. *Journal Marocain de Chimie Hétérocyclique, 18*, 48–73.

[17] Bououdina, A., Ech-Chihbi, E., El-Hajjaji, F., El Ibrahimi, B., Kaya, S., and Taleb, M. (2021). Anisole derivatives as sustainable-green inhibitors for mild steel corrosion in 1 M HCl: DFT and molecular dynamic simulations approach. *Journal of Molecular Liquids, 324*, 115088.

[18] Arrousse, N., Salim, R., Abdellaoui, A., El Hajjaji, F., Hammouti, B., Mabrouk, E. H., Diño, W. A., and Taleb, M. (2021). Synthesis, characterization, and evaluation of xanthene derivative as highly effective, nontoxic corrosion inhibitor for mild steel immersed in 1 M HCl solution. *Journal of the Taiwan Institute of Chemical Engineers, 120*, 344–359.

[19] El Arrouji, S., Karrouchi, K., Berisha, A., Alaoui, K. I., Warad, I., Rais, Z., Radi, S., Taleb, M., Ansar, M., and Zarrouk, A. (2020). New pyrazole derivatives as effective corrosion inhibitors on steel-electrolyte interface in 1 M HCl: Electrochemical, surface morphological (SEM) and computational analysis. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 604*, 125325.

[20] Ech-Chihbi, E., Nahlé, A., Salim, R., Oudda, H., El Hajjaji, F., El Kalai, F., El Aatiaoui, A., and Taleb, M. (2019). An investigation into quantum chemistry and experimental evaluation of imidazopyridine derivatives as corrosion inhibitors for C-steel in acidic media. *Journal of Bio-and Tribo-Corrosion, 5*, 1–18.

[21] Rahmani, H., Alaoui, K. I., Azzouzi, M. E., Benhiba, F., El Hallaoui, A., Rais, Z., Taleb, M., Saady, A., Labriti, B., Aouniti, A., and Zarrouk, A. (2019). Corrosion assessment of mild steel in acid environment using novel triazole derivative as an anti-corrosion agent: A combined experimental and quantum chemical study. *Chemical Data Collections, 24*, 100302.

[22] Bakhouch, M., Es-Sounni, B., Nakkabi, A., and El Yazidi, M. (2021). Thioaurones: Recent advances in synthesis, reactivity, and biological activity. *Mini-Reviews in Organic Chemistry, 18*, 313–327.

[23] Chalkha, M., Bakhouch, M., Akhazzan, M., Bourass, M., Nicolas, Y., and Al Houari, G., El Yazidi, M. (2020). Design, synthesis and characterization of functionalized pyrazole

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045

derivatives bearing amide and sulfonamide moieties from aza-aurones. *Journal of Chemical Sciences, 132*, 86.

[24] Chalkha, M., El Moussaoui, A., Hadda, T. B., Berredjem, M., Bouzina, A., Almalki, F. A., Seghrouchni, H., Bakhouch, M., Saadi, M., El Ammari, L., Abdellatif, M. H., and El Yazidi, M. (2022). Crystallographic study, biological evaluation and DFT/POM/Docking analyses of pyrazole-linked amide conjugates: Identification of antimicrobial and antitumor pharmacophore sites. *Journal of Molecular Structure, 1252*, 131818.

[25] Cherriet, S., Merzouki, M., El-Fechtali, M., Loukili, E., Challioui, A., Soulaymani, A., and Ouasghir, A. (2023). In silico investigation of *Aristolochia longa* anticancer potential against the epidermal growth factor receptor (EGFR) in the tyrosine kinase domain. *Moroccan Journal of Chemistry, 11*(4), 1074–1085.

[26] Merzouki, M., Challioui, A., Bourassi, L., Abidi, R., Bouammli, B., and El Farh, L. (2023). In silico evaluation of antiviral activity of flavone derivatives and commercial drugs against SARS-CoV-2 main protease (3CLpro). *Moroccan Journal of Chemistry, 11*, 11.

[27] Diass, K., Merzouki, M., Elfazazi, K., Azzouzi, H., Challioui, A., Azzaoui, K., Hammouti, B., Touzani, R., Depeint, F., and Ayerdi Gotor, A. (2023). Essential oil of *Lavandula officinalis*: Chemical composition and antibacterial activities. *Plants, 12*, 1571.

[28] Burley, S. K., Berman, H. M., Kleywegt, G. J., Markley, J. L., Nakamura, H., and Velankar, S. (2017). Protein Data Bank (PDB): The single global macromolecular structure archive. *Protein Crystallography: Methods and Protocols*, 627–641.

[29] Faris, A., Edder, Y., and Louchachha, I. (2023). From himachalenes to trans-himachal: Unveiling bioactivity through hemisynthesis and molecular docking analysis. *Scientific Reports, 13*, 17653.

[30] Fajriyah, N. N., Mugiyanto, E., Rahmasari, K. S., Nur, A. V., Najihah, V. H., Wihadi, M. N., ... and Vo, T. H. (2023). Indonesian herbal medicine and its active compounds for anti-diabetic treatment: A systematic mini review. *Moroccan Journal of Chemistry, 11*(4), 948–964.

[31] Pismataro, M. C., Felicetti, T., and Bertagnin, C., (2021). 1,2,4-Triazolo[1,5-a]pyrimidines: Efficient one-step synthesis and functionalization as influenza polymerase PA-PB1 interaction disruptors. *European Journal of Medicinal Chemistry, 221*, 113494.

[32] Kudyakova, Y. S., Onoprienko, A. Y., Slepukhin, P. A., Burgart, Y. V., Saloutin, V. I., and Bazhin, D. N. (2019). Fluorine-containing furan-3(2H)-ones in reactions with binucleophiles: CF3 vs C2F5. *Chemistry of Heterocyclic Compounds, 55*, 517–522.

[33] Fares, I. M. Z., Mekky, A. E. M., Abdelhamid, I. A., and Elwahy, A. H. M. (2019). Bis(enaminones) as versatile precursors for novel bis([1,2,4]triazolo[1,5-a]pyrimidines). *Journal of Heterocyclic Chemistry, 56*, 1958–1965.

[34] Shaabani, A., Seyyedhamzeh, M., Ganji, N., Sangachin, M. H., and Armaghan, M. (2015). One-pot four-component synthesis of highly substituted [1,2,4]triazolo[1,5-a]pyrimidines. *Molecular Diversity, 19*, 709–715.

[35] Fizer, M., and Slivka, M. (2016). Synthesis of [1,2,4]triazolo[1,5-a]pyrimidine (microreview). *Chemistry of Heterocyclic Compounds, 52*, 155–157.

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045

[36] Li, Z. R., Wang, S., Yang, L., Yuan, X. H., Suo, F. Z., Yu, B., and Liu, H. M. (2019). Experience-based discovery (EBD) of aryl hydrazines as new scaffolds for the development of LSD1/KDM1A inhibitors. *European Journal of Medicinal Chemistry, 166*, 432–444.

[37] Lyapustin, D. N., Ulomsky, E. N., Voinkov, E. K., and Rusinov, V. L. (2019). Preparation of new 5-methylthio-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine-7-ones as structural analogues of antiviral drugs. *Actes de la conférence AIP, 2063*, 300121–300124.

[38] Kolosov, M. A., Shvets, E. H., Manuenkov, D. A., Kulyk, O. G., Mazepa, A. V., and Orlov, V. D. (2019). A synthesis of 6-functionalized 7-unsubstituted- and 7-methyl[1,2,4]azolo[1,5-a]pyrimidine derivatives. *Synthetic Communications, 49*, 611–615.

[39] Elkamhawy, A., Al-Sanea, M. M., Song, C., Sim, T., and Roh, E. J. (2015). Design and synthesis of new [1,2,3]triazolo[4,5-d]pyrimidine derivatives as potential antiproliferative agents. *Korean Chemical Society, 36*, 1863–1873.

[40] Li, Z. H., Yang, D. X., Geng, P. F., Zhang, J., Wei, H. M., Hu, B., Guo, Q., Zhang, X. H., Guo, W. G., Zhao, B., Yu, B., Ma, L. Y., and Liu, H. M. (2016). Design, synthesis and biological evaluation of [1,2,3]triazolo[4,5-d]pyrimidine derivatives possessing a hydrazone moiety as antiproliferative agents. *European Journal of Medicinal Chemistry, 124*, 967–980.

[41] Redenti, S., Ciancetta, A., Pastorin, G., Cacciari, B., Moro, S., Spalluto, G., and Federico, S. (2016). Pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines and structurally simplified analogs: Chemistry and SAR profile as adenosine receptor antagonists. *Current Topics in Medicinal Chemistry, 16*, 3224–3257.

[42] Wang, C., Tang, C., Fang, X., Li, Z., and Wang, Q. (2015). Synthesis of unprecedented benzofused [1,2,4]-triazoloquinazolines via benzyne Diels–Alder reaction with 7-vinyl-[1,2,4]triazolo[1,5-c]pyrimidines as dienes. *Synlett, 26*, 931–936.

[43] Tang, C., Wang, C., Li, Z., and Wang, Q. (2014). Synthesis of 8-bromo-7-chloro[1,2,4]triazolo[4,3-c]pyrimidines, their ring rearrangement to [1,5-c] analogues, and further diversification. *Synthesis, 46*, 2734–2746.

[44] Wang, S. B., Piao, G. C., Zhang, H. J., and Qua, Z. S. (2015). Synthesis of 5-alkoxythieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine derivatives and evaluation of their anticonvulsant activities. *Molecules, 20*, 6827–6843.

[45] Gladkov, E. S., Sirko, S. M., Musatov, V. I., Shishkina, S. V., Tkachenko, I. G., and Komykhov, S. A. (2018). New spiro derivative of dihydro-1,2,3-triazolo[1,5-a]pyrimidine as a product of multicomponent reaction. *Chemistry of Heterocyclic Compounds, 54*, 1139–1144.

[46] Knyazev, A. A., Slepukhin, P. A., Tolkunov, S. V., Tyurin, V. I., and Komarov, V. Y. (2018). Investigation of the transformation of 3-ethoxycarbonyl-5-methyl-2,3-dihydro-1H-1,2,4-triazolo[4,3-a]pyrimidine under the action of strong nucleophiles. *Russian Journal of Organic Chemistry, 54*, 1190–1196.

[47] Pericherla, K., Barua, A., and Ranu, B. C. (2018). Microwave-assisted one-pot three-component synthesis of novel [1,2,4]triazolo[1,5-a]pyrimidines under transition-metal-free conditions. *Tetrahedron Letters, 59*, 2326–2329.

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045

[48] Shafiee, M., Nasr-Esfahani, M., Mousavi, F., and Baghery, S. (2018). Synthesis and biological evaluation of new 1,2,4-triazolo[1,5-a]pyrimidine derivatives as potential antimicrobial agents. *Bioorganic and Medicinal Chemistry Letters, 28*, 2549–2554.

[49] Singh, G. S., Desta, Z. Y., and Alnamer, Y. (2018). Advances in the synthesis and medicinal applications of triazolopyrimidines. *European Journal of Medicinal Chemistry, 158*, 543–570.

[50] Vassilev, G. N., Todorov, I. T., Ivanov, D. G., and Doytchinova, I. A. (2019). Synthesis and QSAR modeling of triazolo[1,5-a]pyrimidine derivatives as potential A2A adenosine receptor antagonists. *Journal of Molecular Graphics and Modelling, 89*, 21–30.

[51] Xia, L., Zhang, Y., Wang, Y., and Zhao, H. (2019). Design, synthesis, and antitumor evaluation of novel 1,2,4-triazolo[4,3-a]pyrimidine derivatives. *Bioorganic and Medicinal Chemistry, 27*, 1125–1134.

[52] Zhang, C., Zhang, Z., Liu, H., and Li, J. (2019). Synthesis and biological evaluation of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives as potential antiviral agents. *European Journal of Pharmaceutical Sciences, 134*, 30–38.

[53] Lhamidi, S., Anouar, E. H., El Hafi, M., Boulhaoua, M., Ejjoumamany, A., El Jemli, M., Essassi, E. M., and Magu, J. T. (2019). Synthesis, X-ray, spectroscopic characterization, DFT and antioxidant activity of 1,2,4-triazolo[1,5-a]pyrimidine derivatives. *Journal of Molecular Structure, 1177*, 131-142.

[54] Sirakanyan, S. N., Hakobyan, E. K., and Hovakimyan, A. A. (2019). Synthesis of new sulfur-substituted pentacyclic 1,2,4-triazolopyrimidine derivatives. *Russian Journal of Organic Chemistry, 55*, 308-313.

[55] Said, M. A., Eldehna, W. M., Nocentini, A., Bonardi, A., Fahim, S. H., Bua, S., Soliman, D. H., Abdel-Aziz, H. A., Gratteri, P., Abou-Seri, S. M., and Supuran, C. T. (2019). Synthesis, biological and molecular dynamics investigations with a series of triazolopyrimidine/triazole-based benzenesulfonamides as novel carbonic anhydrase inhibitors. *Journal Européen de Chimie Médicinale, 185*, 111843.

[56] Savateev, K. V., Ulomsky, E. N., Fedotov, V. V., Rusinov, V. L., Sivak, K. V., Lyubishin, M. M., Kuzmich, N. N., and Aleksandrov, A. G. (2017). 6-Nitrotriazolo[1,5-a]pyrimidines as promising structures for pharmacotherapy of septic conditions. *Russian Journal of Bioorganic Chemistry, 43*, 402-410.

[57] Abd El-Aleam, R. H., George, R. F., Lee, K. J., Keeton, A. B., Piazza, G. A., Kamel, A. A., El-Daly, M. E., Hassan, G. S., and Abdel-Rahman, H. M. (2019). Design and synthesis of 1,2,4-triazolo[1,5-a]pyrimidine derivatives as PDE 4B inhibitors endowed with bronchodilator activity. *Archiv der Pharmazie - Chemistry in Life Sciences, 352*(1), 1-11.

[58] Pinheiro, L. C. S., Feitosa, L. M., Gandi, M. O., Silveira, F. F., and Boechat, N. (2019). The development of novel compounds against malaria: Quinolines, triazolpyridines, pyrazolopyridines, and pyrazolopyrimidines. *Molecules, 24*(1), 1-24.

[59] Chernyshev, V. M., Pyatakov, D. A., Sokolov, A. N., Astakhov, A. V., Gladkov, E. S., Shishkina, S. V., and Shishkin, O. V. (2014). Partially hydrogenated 2-amino[1,2,4]triazolo[1,5-a]pyrimidines as synthons for the preparation of

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045

polycondensed heterocycles: Reaction with chlorocarboxylic acid chlorides. *Tetrahedron, 70*, 684-701.

[60] Astakhov, A. V., Sokolov, A. N., Pyatakov, D. A., Shishkina, S. V., Shishkin, O. V., and Chernyshev, V. M. (2015). Reactivity of 2-amino[1,2,4]triazolo[1,5-a]pyrimidines with various saturation of the pyrimidine ring towards electrophiles. *Chemistry of Heterocyclic Compounds, 51*, 1039-1047.

[61] Karthic, A., Kesarwani, V., Singh, R. K., Yadav, P. K., Chaturvedi, N., Chauhan, P., Yadav, B. S., and Kushwaha, S. K. (2022). Computational analysis reveals monomethylated triazolopyrimidine as a novel inhibitor of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp). *Molecules, 27*, 801.

[62] Abu-Melha, S., Edrees, M. M., Riyadh, S. M., Abdelaziz, M. R., Elfiky, A. A., and Gomha, S. M. (2020). Clean grinding technique: A facile synthesis and in silico antiviral activity of hydrazones, pyrazoles, and pyrazines bearing thiazole moiety against SARS-CoV-2 main protease (Mpro). *Molecules, 25*, 4565.

[63] Muhammad, Z. A., Farghaly, T. A., Althagafi, I., Al-Hussain, S. A., Zaki, M. E., and Harras, M. F. (2021). Synthesis of antimicrobial azoloazines and molecular docking for inhibiting COVID-19. *Journal of Heterocyclic Chemistry, 58*, 1286-1301.

[64] Nettekoven, M., Adam, J. M., Bendels, S., Bissantz, C., Fingerle, J., Grether, U., Grüner, S., Guba, W., Kimbara, A., and Ottaviani, G. (2016). Novel triazolopyrimidine-derived cannabinoid receptor 2 agonists as potential treatment for inflammatory kidney diseases. *ChemMedChem, 11*, 179-189.

[65] Tageldin, G. N., Ibrahim, T. M., Fahmy, S. M., Ashour, H. M., Khalil, M. A., Nassra, R. A., and Labouta, I. M. (2019). Design, synthesis and evaluation of some pyrazolo[3,4-d]pyrimidines as anti-inflammatory agents. *Bioorganic Chemistry, 90*, 102844.

[66] Subramanium, P. (2015). Evaluation of anti-inflammatory and analgesic activities of methanolic leaf extract of the endangered tree species *Hildegardia populifolia* (Roxb.) Schott and Endl. *International Journal of Green Pharmacy, 9*, 125-130.

[67] Tageldin, G. N., Fahmy, S. M., Ashour, H. M., Khalil, M. A., Nassra, R. A., and Labouta, I. M. (2018). Design, synthesis and evaluation of some pyrazolo[3,4-d]pyrimidines as anti-inflammatory agents. *Bioorganic Chemistry, 78*, 358-371.

[68] Abdel Hafez, N. A., Ali, K. A., Ibrahim, A. A., Elnaggar, D. H., and Sleem, A. A. (2018). Design, synthesis, and in-vivo anti-inflammatory activity of new celecoxib analogues as NSAID. *Mini Reviews in Medicinal Chemistry, 18*, 1398-1408.

[69] Abdel-Aziz, H. A., Eldehna, W. M., Fares, M., Elsaman, T., AbdelAziz, M. M., and Soliman, D. H. (2015). Synthesis, in vitro and in silico studies of some novel 5-nitrofuran-2-yl hydrazones as antimicrobial and antitubercular agents. *Biological and Pharmaceutical Bulletin, 38*, 1617-1630.

[70] Deb, P. K., Kaur, R., Chandrasekaran, B., Bala, M., Gill, D., Kaki, V. R., Akkinepalli, R. R., and Mylavaram, R. (2014). Synthesis, anti-inflammatory evaluation, and docking studies of some new thiazole derivatives. *Medicinal Chemistry Research, 23*, 2780-2792.

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045

[71] Oukoloff, K., Lucero, B., Francisco, K. R., Brunden, K. R., and Ballatore, C. (2019). 1, 2, 4-Triazolo [1, 5-a] pyrimidines in drug design. *European Journal of Medicinal Chemistry, 165*, 332-346.

[72] Huo, J. L., Wang, S., Yuan, X. H., Yu, B., Zhao, W., and Liu, H. M. (2020). Discovery of [1, 2, 4] triazolo [1, 5-a] pyrimidines derivatives as potential anticancer agents. *European Journal of Medicinal Chemistry, 211*, 113108.

[73] Xu, C., Zhou, W., Dong, G., Qiao, H., Peng, J., Jia, P., Li, Y., Liu, H., Sun, K., and Zhao, W. (2020). Novel [1, 2, 3] triazolo [4, 5-d] pyrimidine derivatives containing hydrazone fragment as potent and selective anticancer agents. *Bioorganic Chemistry, 105*, 104424.

[74] El-Hag, F. A. A., Abdel-Hafez, N. A., Abbas, E. M. H., El-Manawaty, M. A., and El-Rashedy, A. A. (2019). Synthesis and antitumor activity of some new fused heterocyclic compounds. *Russian Journal of General Chemistry, 89*, 128-137.

[75] Saundane, A. R., Halu, A., and Kirankumar, N. (2017). Synthesis and biological evaluation of some novel indole analogues containing triazolopyrimidine moiety. *Monatshefte für Chemie - Chemical Monthly, 148*, 1497-1511.

[76] Abd El-Aleam, R. H., George, R. F., Hassan, G. S., and Abdel-Rahman, H. M. (2020). Synthesis and biological evaluation of some novel indole analogues containing triazolopyrimidine moiety. *Bioorganic Chemistry, 94*, 103411.

[77] Al-Harthy, T., Zoghaib, W. M., Stoll, R., and Abdel-Jalil, R. (2018). Design, synthesis, and antimicrobial evaluation of novel 2-arylbenzothiazole analogs bearing fluorine and piperazine moieties. *Monatshefte für Chemie, 149*, 645-651.

[78] Lahmidi, S., Anouar, E. H., El Hamdaoui, L., Ouzidane, Y., Kaur, M., Jasinski, J. P., Sebbar, N. K., Essassi, E. M., and El Moussaouiti, M. (2019). Synthesis, crystal structure, spectroscopic characterization, Hirshfeld surface analysis, DFT calculations, and antibacterial activity of ethyl 2-(4-vinylbenzyl)-2-(5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)-3-(4-vinylphenyl)propanoate. *Journal of Molecular Structure, 1191*, 66-75.

[79] Gami, S. P., Vilapara, K. V., Khunt, H. R., Babariya, J. S., and Naliyapara, Y. T. (2014). Synthesis and antimicrobial activities of some pyrazoline derivatives. *International Letters of Chemistry, Physics and Astronomy, 11*, 127-134.

[80] Mabkhoot, Y. N., Alatibi, F., El-Sayed, N. N. E., Kheder, N. A., and Al-Showman, S. S. (2016). Synthesis and structure-activity relationship of some new thiophene-based heterocycles as potential antimicrobial agents. *Molecules, 21*, 1036-1036.

[81] Phillips, M. A., White, K. L., Kokkonda, S., Deng, X., White, J., El Mazouni, F., Marsh, K., Manjalanagara, K. D. R., and Rudra, K. R. (2016). Triazolopyrimidine-based dihydroorotate dehydrogenase inhibitors with potent and selective activity against the malaria parasite *Plasmodium falciparum*. *ACS Infectious Diseases, 2*, 945-957.

[82] Low, Y. S., Garcia, M. D., Lonhienne, T., Fraser, J. A., Schenk, G., and Guddat, L. W. (2021). Triazolopyrimidine herbicides are potent inhibitors of *Aspergillus fumigatus* acetohydroxyacid synthase and potential antifungal drug leads. *Scientific Reports, 11*, 21055.

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045

[83] Borthakur, S. K., Borthakur, S., Goswami, D., Boruah, P., and Kalita, P. K. (2016). Synthesis and antifungal activities of some new 5,7-disubstituted [1,2,4]triazolo[1,5-a]pyrimidin-6-one derivatives. *Journal of Heterocyclic Chemistry, 53*, 2079-2083.

[84] Pogaku, V., Krishnan, R., and Basavoju, S. (2021). Synthesis and antifungal activities of some new 5,7-disubstituted [1,2,4]triazolo[1,5-a]pyrimidin-6-one derivatives. *Research on Chemical Intermediates, 47*, 551-571.

DOI: https://doi.org/10.17509/ijost.v10i1.80301
p- ISSN 2528-1410 e- ISSN 2527-8045