World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2024
Volume: 3; Issue: 5
Page: 220-228

DESIGN, SYNTHESIS, AND BIOLOGICAL PROPERTIES OF NEW 1,2,4-TRIAZOLE DERIVATIVES

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Article Received: 22 July 2024 | | ***Article Revised: 13 August 2024*** | | ***Article Accepted: 04 September 2024***

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DOI: https://doi.org/10.5281/zenodo.13903664

How to cite this Article: Prytula R. L., Parchenko V. V., Bushuyeva I. V., Yerenko O. K. and Khortetska T. V. (2024). DESIGN, SYNTHESIS, AND BIOLOGICAL PROPERTIES OF NEW 1,2,4-TRIAZOLE DERIVATIVES. World Journal of Pharmaceutical Science and Research, 3(5), 220-228. https://doi.org/10.5281/zenodo.13903664

ABSTRACT

For a long time, derivatives of 1,2,4-triazole have attracted the attention of scientists worldwide. Their unique and valuable properties provide researchers with information on the practically limitless possibilities for discovering new promising molecules. The biological potential of 1,2,4-triazole derivatives is also well-known and is not limited to antifungal and antimicrobial properties. Many new types of pharmacological activity of substituted 1,2,4-triazoles have been discovered and studied by scientists over the past ten years. Regarding the general methods of synthesizing 1,2,4-triazole derivatives, they are well-known and widely used among organic chemists in the process of creating new unique molecules. The gradual, predicted introduction of different substituents into the 1,2,4-triazole derivative molecules leads to the appearance of new types of biological activity, and in some cases, this increases the activity levels already observed. Chemical modification of the compounds by altering substituents around the 1,2,4-triazole fragment fundamentally changes the type of biological activity of the new molecules. Despite the constant criticism of synthetic drugs, their role in healthcare cannot be overestimated. The ability to continuously improve synthetic molecules makes original drugs more effective and keeps them in high demand. The scientific school of Zaporizhzhia State Medical University has synthesized a significant number of 1,2,4-triazole derivatives[7–11] and developed various methods for their heterocyclization. The current scientific potential of new 1,2,4-triazole derivatives has been analyzed. The new compounds have proven to be promising biologically active agents. The wide possibilities for their application create favorable conditions for further research into new molecules based on 1,2,4-triazole.

KEYWORDS: 1,2,4-triazole, physicochemical, biological properties, synthesis, activity prediction.

INTRODUCTION

For a long time, derivatives of 1,2,4-triazole have attracted the attention of scientists worldwide. Their unique and valuable properties provide researchers with information on the practically limitless possibilities for discovering new promising molecules. The biological potential of 1,2,4-triazole derivatives is also well-known and is not limited to antifungal and antimicrobial properties. Many new types of pharmacological activity of substituted 1,2,4-triazoles have been discovered and studied by scientists over the past ten years. Regarding the general methods of synthesizing 1,2,4-triazole derivatives, they are well-known and widely used among organic chemists in the process of creating new unique molecules. The **purpose** of this work was to analyze the current scientific potential of 1,2,4-triazole derivatives and to make predictions regarding the prospects for further scientific studies.

MATERIALS AND METHODS

The formation of the 1,2,4-triazole heterocyclic system was achieved using two fragments through [3+2] heterocyclization. (3-Isothiocyanato)oxindoles reacted in asymmetric [3+2] cycloaddition with azodicarboxylates in the presence of a chiral hydroquinidine 1,4-phthalazinediyl diether catalyst.[1] The mild reaction conditions provided products with excellent yields and high enantioselectivity (up to 98%) (Fig. 1). Additionally, new quinoline/chalcone hybrids containing a 1,2,4-triazole fragment were developed and synthesized,[2] with their structure elucidated and confirmed through various spectroscopic methods (Fig. 2). The compounds demonstrated moderate to good activity against various NCI 60 cell lines in a one-dose treatment assay, with growth inhibition rates ranging from 50% to 94%.

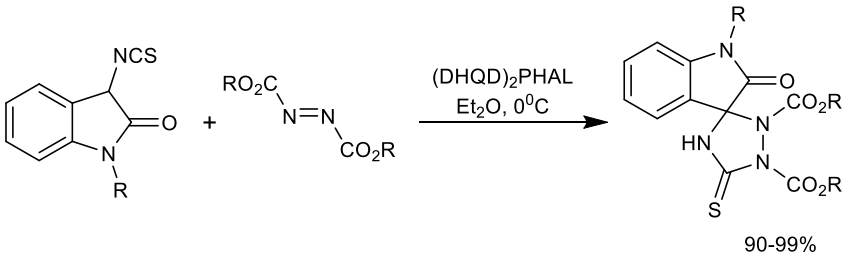


Fig. 1: Synthesis of 5-Aryl-4-Phenyl-1,2,4-Triazolidine-3-Thiones and Spiro-4-Phenyl-1,2,4-Triazolidine-3-Thiones.

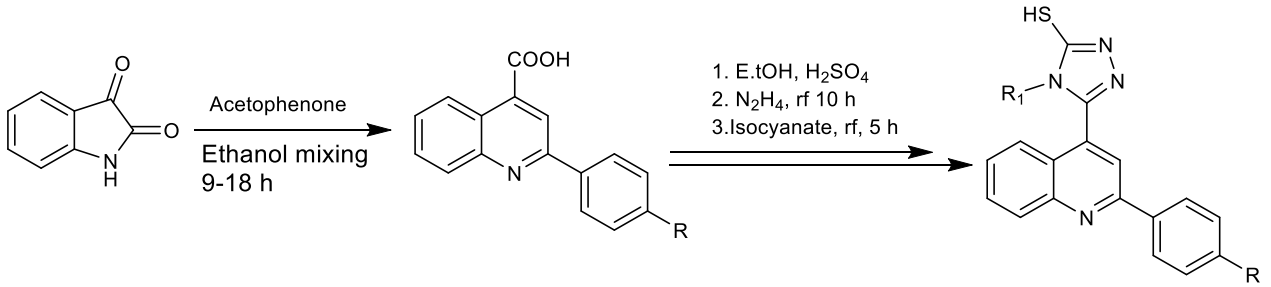


Fig. 2: Synthesis of New 5-(2-Phenylquinolin-4-yl)-4H-1,2,4-Triazole-3-Thiols.

RESULTS AND DISCUSSION

Triazoles and their heterocyclic analogs represent compounds that contain a certain number of nitrogen atoms, displaying the properties of typical pharmacophores. Their derivatives are easily synthesized and can be converted into various biologically active molecules. Chemical modeling of 1,2,4-triazole derivatives allows the targeted acquisition of compounds with specific biological properties, taking into account the toxicity profiles of new molecules. The

gradual, predicted introduction of different substituents into the 1,2,4-triazole derivative molecules leads to the appearance of new types of biological activity, and in some cases, this increases the activity levels already observed. Chemical modification of the compounds by altering substituents around the 1,2,4-triazole fragment fundamentally changes the type of biological activity of the new molecules. In this study[3], the authors synthesized a series of new N-alkyl/arylalkyl/aryl derivatives of 2-(4-phenyl-5-(1-phenylcarbamoyl)piperidine-4H-1,2,4-triazole-3-ylthio)acetamide (Fig. 3). The synthesized compounds were tested for their inhibitory potential against the enzyme 15-lipoxygenase. The simple precursor ethylpiperidine-4-carboxylate was successively converted into phenylcarbamoyl derivative, hydrazide, semicarbazide, and N-phenyl 5-(1-phenylcarbamoyl)piperidine-1,2,4-triazole, followed by further multi-step synthesis with electrophiles to obtain the final hybrid products. This work demonstrates the synthetic approach's potential to create compounds that inhibit lipoxygenase, serving as model compounds.

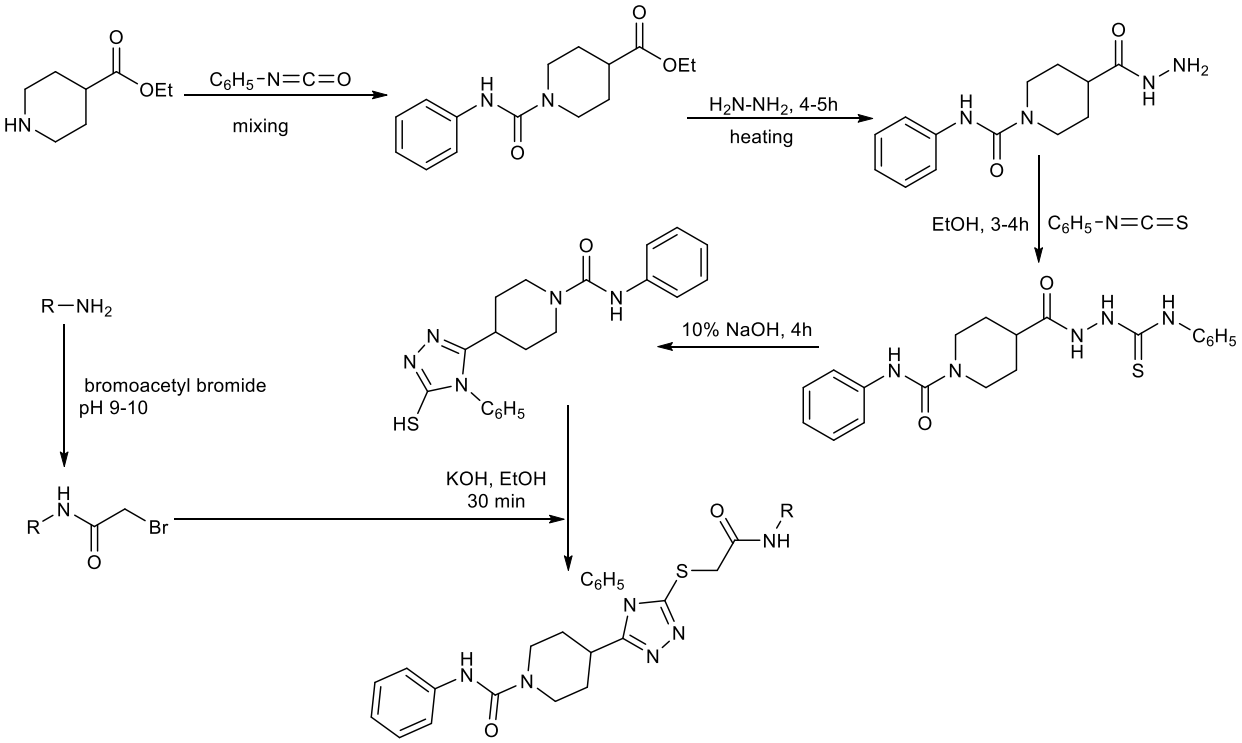


Fig. 3: Synthesis of New Derivatives of 2-(4-Phenyl-5-(1-Phenylcarbamoyl)Piperidine-4H-1,2,4-Triazole-3-ylthio) acetamide.

In the study[4], a series of eleven bis-heterocyclic compounds with an indole derivative (Fig. 4), containing a 1,2,4-triazole fragment, was synthesized and their in vitro inhibitory activity against α-amylase and α-glucosidase was evaluated. The addition of a 2,5-dimethoxy substituent (2,5-dimethoxybenzaldehyde) or a hydroxymethoxy substituent (6-methoxy-2-naphthol aldehyde) in the ortho- and meta-positions showed significant inhibition of α-amylase and α-glucosidase. Additionally, a new series of S-benzo[4,5]thiazolo[2,3-c][1,2,4]triazoles (Fig. 5) was synthesized.[5] The structure-activity relationship of the compounds indicated favorable cytotoxic results due to the opening of the cyclic amine and substitution with an aminothiazole fragment.

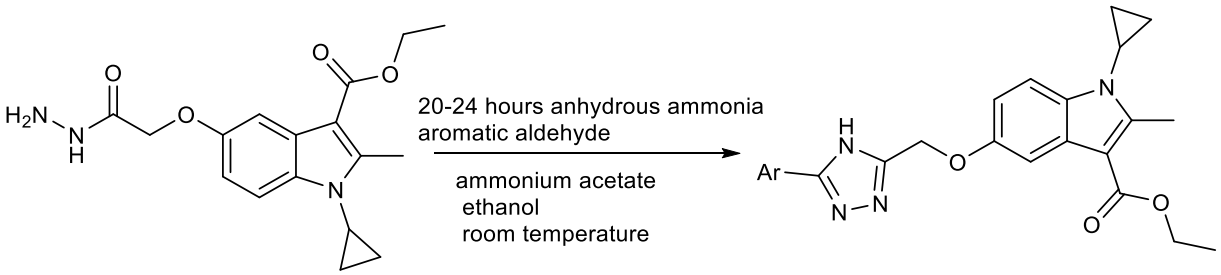


Fig. 4: Synthesis of New Indole Derivatives Containing a 1,2,4-Triazole Fragment.

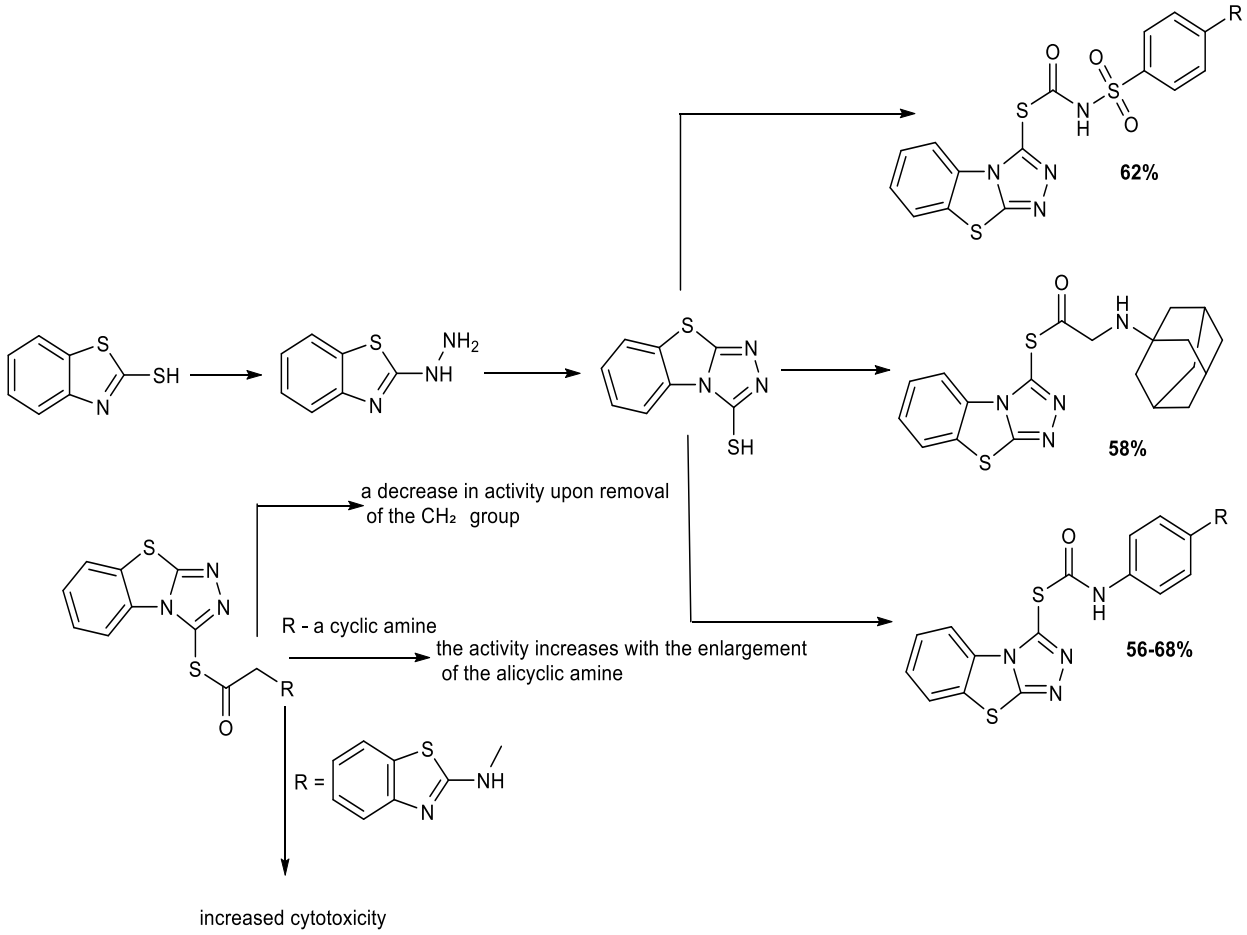


Fig. 5: Synthesis of New S-benzo[4,5]thiazolo[2,3-c][1,2,4]triazoles.

In the study[6], the synthesis of a series of new 1,2,4-triazole-3-yl-thioacetamides and 5-pyrazin-2-yl-3H-[1,3,4]oxadiazole-2-thiones (Fig. 6) was described. The synthesized compounds were evaluated using α-difluoromethylornithine (DFMO) as a reference drug for their *in vitro* antitrypanosomal activity against T*rypanosoma brucei*. The results showed that the compounds were more potent than the control DFMO.

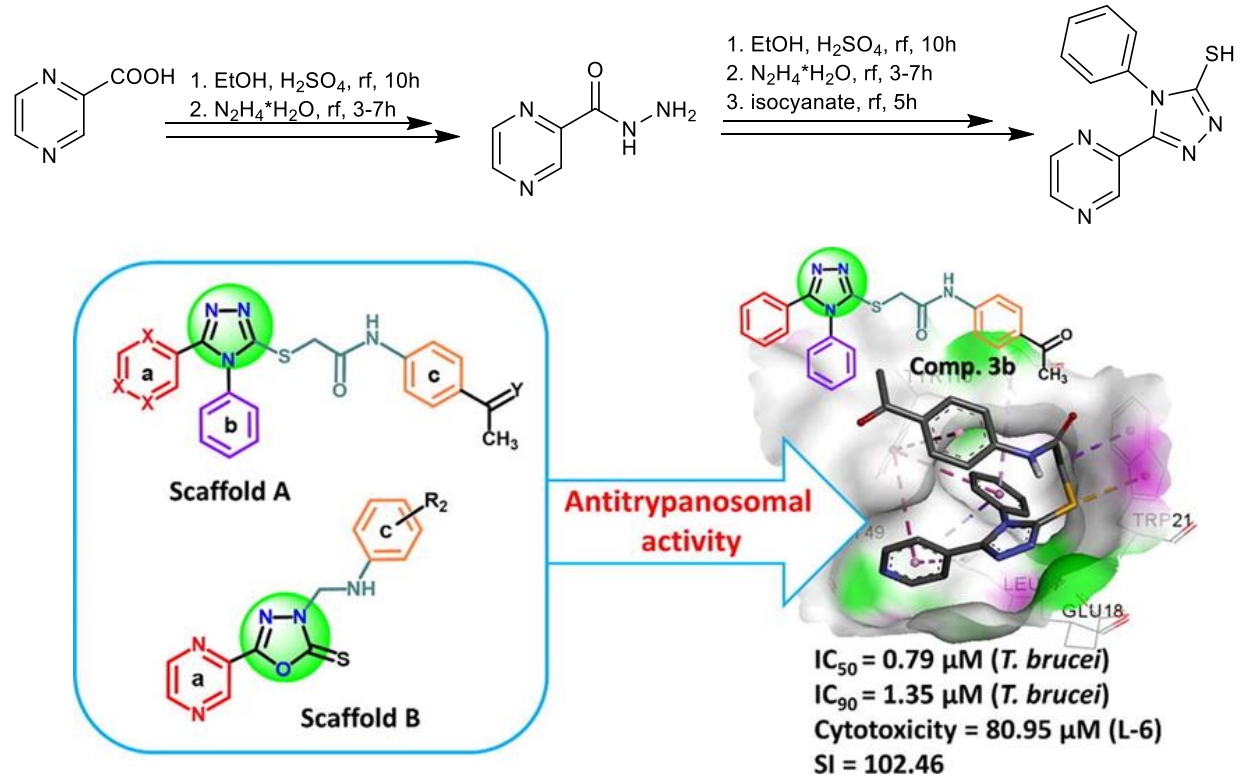
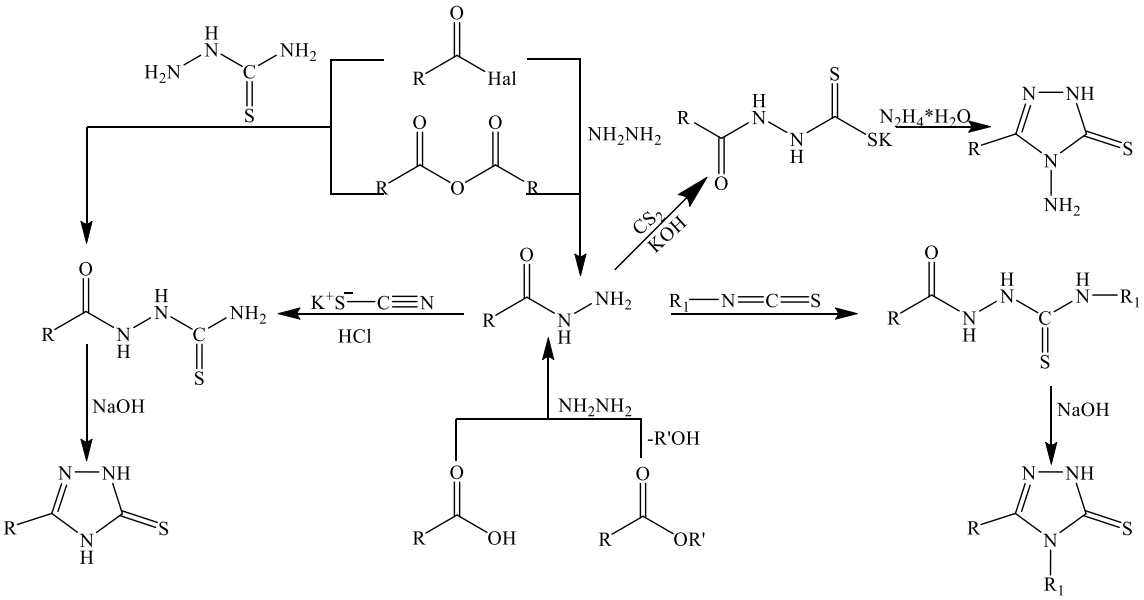


Fig. 6: Synthesis of New 5-Pyrazin-2-yl-3H-[1,3,4]oxadiazole-2-thiones.

Despite the constant criticism of synthetic drugs, their role in healthcare cannot be overestimated. The ability to continuously improve synthetic molecules makes original drugs more effective and keeps them in high demand. Moreover, synthetic organic compounds are not only used as drug substances, but they are also known to be effective fungicides, herbicides, plant growth regulators, anti-corrosion agents, plasticizers for plastics, fuel additives, and more. An indisputable fact today is the high attractiveness of 1,2,4-triazole derivatives. These compounds are at the center of attention for researchers in various fields due to the unique properties of this heterocycle. For a long time, they have served as a "foundation" for the search for new biologically active substances, exhibiting a wide range of properties while having low toxicity.

The scientific school of Zaporizhzhia State Medical University has synthesized a significant number of 1,2,4-triazole derivatives[7–11] and developed various methods for their heterocyclization (Fig. 7). The obtained derivatives contain the most active pharmacophore groups, such as adamantane residues, fluoro- and bromophenyl substituents, and residues of 5-bromo-furan, thiophene, pyridine, and others. The synthesis is mainly considered as classical [3+2] heterocyclization, resulting in a broad range of compounds. In addition, there are works featuring quite original modifications of methods, using $POCl_3$, catalysts, and other techniques.



R = Me, Ph, 2-F-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4, 2-Br-C_6H_4, 4-(t-Bu)-C_6H_4, Ad, 5-bromofuranyl-2, 2-Py, 3-Py, 4-Py, thienyl-2;
R_1 = Me, Et, Ph, 2-Br-C_6H_4, 2-Me-C_6H_4, 2-MeO-C_6H_4

Fig. 7: Synthesis of New 1,2,4-Triazole-3-Thiones with Various Substituents.

A small collection of 12 distinct 3-mercapto-1,2,4-triazoles derived from ursolic acid has been identified (Fig. 8). Hydrazides derived from ursolic acid were identified as useful precursors for the developed synthesis. However, the hydrazide of ursolic acid was not feasible for producing structurally related 3-mercapto-1,2,4-triazoles due to the steric hindrance of the triterpenoid. Ether- and amide-bound hydrazides, formed from ethoxycarbonylmethyl-ursolate and the amide of ursolic acid with methyl β-alaninate, served as key starting materials for distantly related mercapto- and aminoazoles. New hybrid heterocycles with amino- and mercapto-substituents show great potential for further derivatization and are promising precursors for the synthesis of triterpenoid analogs with chemopreventive and cytotoxic properties.

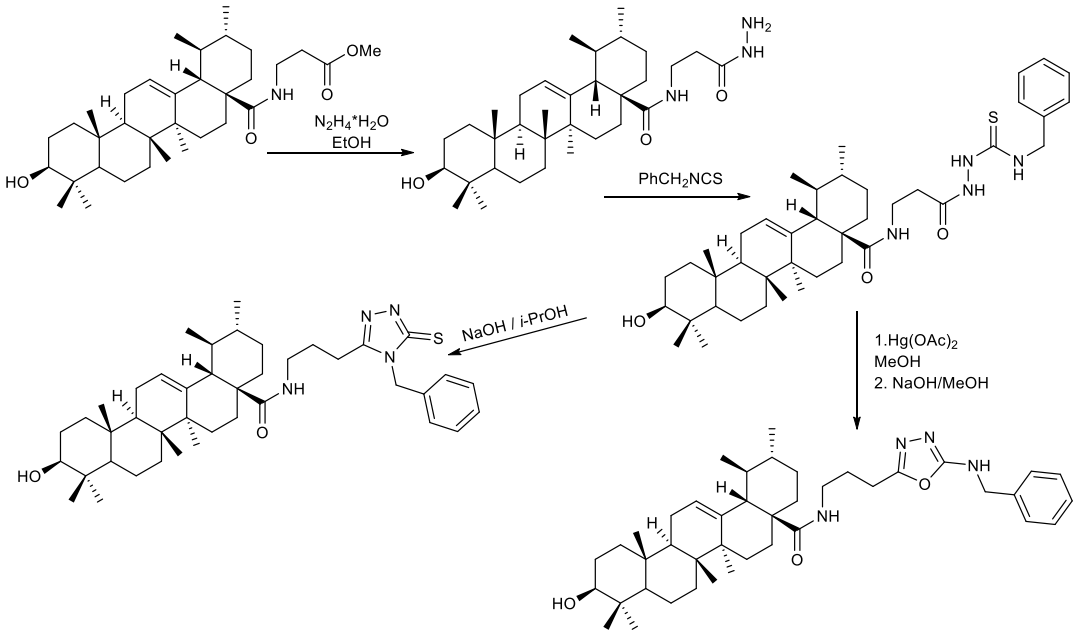


Fig. 8: Synthesis of New 3-Mercapto-1,2,4-Triazole Derivatives.

A series of 1,2,4-triazole-norfloxacin hybrids was developed, synthesized, and evaluated for antibacterial activity in vitro against common pathogens (Fig. 9). Representative compounds from each stage of synthesis were further characterized using X-ray crystallography.[13]

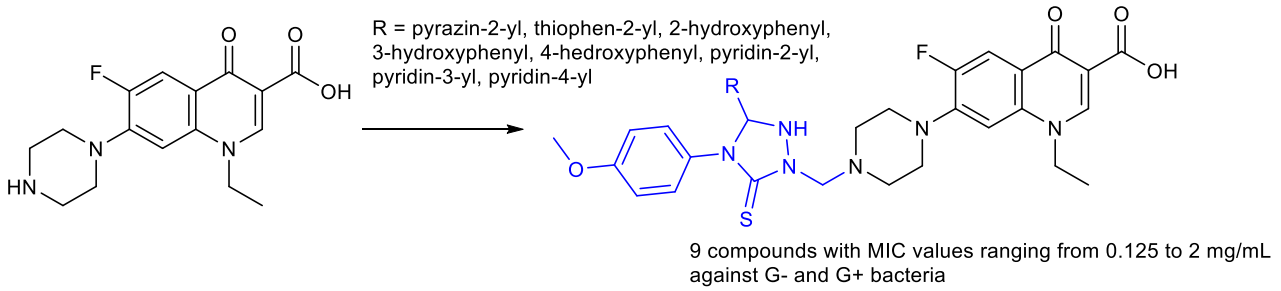


Fig. 9: Synthesis of New 1,2,4-Triazole-Norfloxacin Hybrids.

Formation of the 1,2,4-triazole heterocyclic system using a single fragment with subsequent heterocyclization. The authors developed the synthesis[14] of compounds based on the 1,2,4-triazole-3-thione framework, which is originally linked to the dizinc catalytic site of VIM, showing promising potential for the development of broad-spectrum inhibitors. A series of compounds was synthesized and characterized, featuring variously functionalized alkyl chains at the 4-position of the heterocycle. The presence of a carboxyl group at the end of the alkyl chain provides potent inhibitors of VIM-type enzymes, with Ki values ranging from micromolar to sub-micromolar, indicating that the alkyl chain should be at least as long as a propyl chain (Fig. 10).

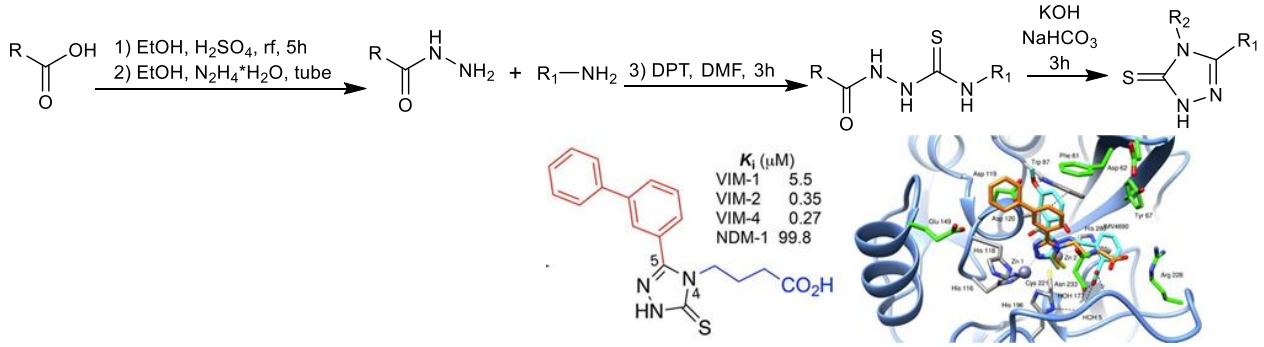


Fig. 10: Synthesis of New 1,2,4-Triazole-3-Thiones with Various Substituents.

New indolyl-1,2,4-triazole hybrids were developed and synthesized as VEGFR-2 kinase inhibitors with potential anti-kidney cancer activity. The results of the in vitro kinase assay showed that all target compounds exhibited submicromolar inhibition of the VEGFR-2 kinase enzyme. For the synthesis of the target indolyl-1,2,4-triazole hybrids, amino-thione derivative 3 was synthesized through two reaction stages, as illustrated in (Fig. 11).[15]

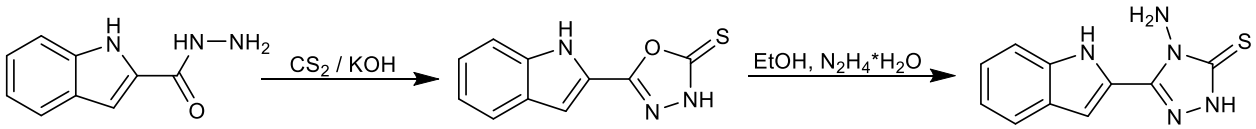


Fig. 11: Synthesis of New 1,2,4-Triazole-3-Thiones with Various Substituents.

New N-4-piperazinylciprofloxacin-1,2,4-triazole hybrids were obtained and characterized (Fig. 12).[16] In vitro antimycobacterial activity demonstrated that the compound exhibited promising antimycobacterial activity against *Mycobacterium smegmatis* compared to the reference drug isoniazid (INH).

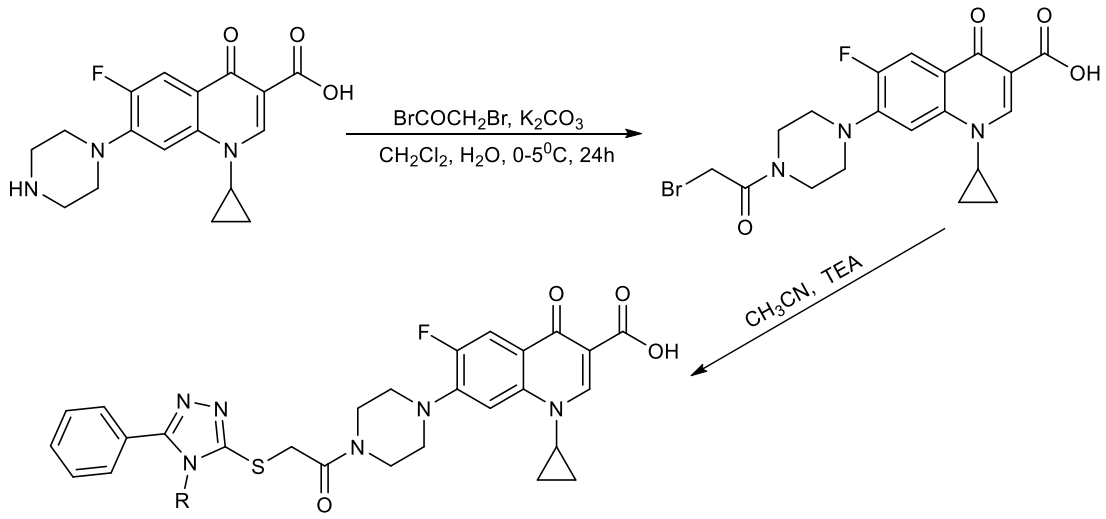


Fig. 12: Synthesis of New N-4-Piperazinylciprofloxacin-1,2,4-Triazoles.

CONCLUSION

The current scientific potential of new 1,2,4-triazole derivatives has been analyzed. The new compounds have proven to be promising biologically active agents. The wide possibilities for their application create favorable conditions for further research into new molecules based on 1,2,4-triazole.

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