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BIO EVALUATION OF NITROGEN AND OXYGEN BASED HETEROCYCLES

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ABSTRACT:

In recent years, the application of green chemistry to the production of potentially bioactive heterocyclic moieties has emerged as the primary focus of study for organic chemists. This shift in emphasis can be attributed to the increased worry that people have over the state of the environment. As a consequence of this, the creation of nonhazardous synthetic procedures has garnered the particular focus of synthetic chemists as a frontier problem in the current context. Infectious microbes have been a persistent threat to human civilization ever since prehistoric times, and as a result, there have been numerous fatalities around the globe. Cancer is an awful disease that ultimately results in death and for which there is now no effective treatment, making it a danger to mankind in both the developing and the developed nations. As a consequence of this, the formulation and synthesis of new classes of chemicals as a means of protecting against various illnesses is an absolutely necessary necessity. When it comes to the production of a wide variety of medicines and agrochemicals, heterocycles are exceptional precursors, particularly for those compounds that include N- or O- moieties. When it comes to the synthesis of organic compounds, the methods used to produce heterocycles are quite important, particularly for the heterocycles that are present in natural goods.

Keywords: *nitrogen, heterocycles, oxygen*

1. INTRODUCTION

In today's world, the application of green chemistry to the production of potentially bioactive heterocyclic compounds has emerged as an important topic of research for organic chemists. This is a direct result of the growing worry that people have over the state of the environment. Green chemistry makes use of its own set of principles in order to cut down on the amount of potentially harmful compounds used and generated during the process of synthesis. The implementation of a green chemistry strategy is predicated on three guiding principles: the use of environmentally preferable solvents; the removal of potentially hazardous by-products; and the preservation of atom economy. As a consequence of this, the development of non-hazardous synthetic methods has garnered the specific attention of synthetic chemists as a frontier problem in the current context.

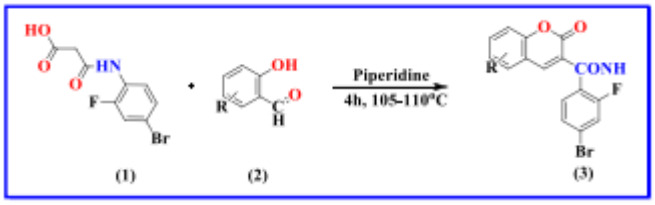
Heterocyclic compounds especially those containing nitrogen and oxygen atoms viz. coumarins, dihydropyrimidinones, imidazoles, isoxazoles, benzimidazoles, pyrazoles and triazole, etc. have been the major molecules in organic chemistry, and they are starting materials in the synthesis of various drugs related to antimalarial, antiulcer, diuretics, anthelmintic, antidepressants, anticancer, antineoplastic and antipsychotic. One of the most important classes of benzopyranes, coumarins are distinguished by the linking of benzene rings to pyrane rings. In addition to their widespread application in the production of food additives, fragrances, agrochemicals, cosmetics, and medicines, as well as optical brightening agents, dispersed fluorescent, and tunable dye lasers they are also utilised in the manufacture of insecticides. They also have a wide variety of biological properties, such as antibacterial activity, anticancer activity, and the ability to block HIV-1 protease as well as platelet aggregation [3–6]. The intriguing class of heterocyclic compounds known as dihydropyrimidinones derivatives includes molecules with a wide variety of biological actions [7-10], including antiviral, antitumor, antibacterial, and calcium channel regulating activity. Imidazole is characterised by a five-membered aromatic ring that plays a significant role in the process of drug development. The imidazole ring is found in a wide variety of naturally occurring and synthetically produced bioactive substances. Some examples include biotin, essential amino acids, histidines, histamine, fungicides, and herbicides. They also possess a wide variety of biological actions, including those that are anticancer, antifungal, antiviral, antibacterial, antitubercular, anti-parasitic, antihistaminic, antiinflammatory, anti-neuropathic, and antihypertensive. Isoxazole scaffolds are an influential class of heterocyclic compounds and display a broad spectrum of biological and pharmaceutical activities such as -adrenergic receptor antagonists, immunosuppressive, anti-inflammatory, antibacterial, HDAC inhibitors, antifungal, antitumor, antioxidant, antiprotozoal, antiviral, antituberculous, anti-HIV, analgesic, and anti-androgens (II). One of the most biologically active classes of compounds is benzimidazole and its derivatives. They possess a wide range of activities, including those of neuropeptides, YY1 receptor antagonists, potent inhibitors of TIE-2 and VEGFER-2 tyrosine kinase receptors, antitumor agents, gamma-amino butyric acid (GABA) agonists, and 5-HT3 antagonists.

Recently, the environmentally friendly synthesis of heterocyclic compounds like these has been acquiring more and more relevance. Therefore, in this review paper, we discuss the environmentally friendly synthesis of these heterocyclic compounds as well as their biological activities. This is because these heterocyclic compounds are more prevalent as subunits in a variety of pharmaceutical and agrochemical goods owing to their fascinating capabilities. This worry is a direct result of the important role that heterocycles play in the design and development of current drugs, as well as the utilisation of heterocycles in the scaffold-hopping method. We have high hopes that this study will pave the way for future generations of organic chemists to create heterocycles that include nitrogen and oxygen that are both innovative and highly effective. In today's world, chemistry research is increasingly focusing on environmentally friendly practises; as a result, the primary focus of

this article is to outline environmentally responsible methods for preparing a variety of heterocycles. We believe that this article inspires organic chemists to create innovative heterocyclic compounds in an environmentally responsible manner, which is one of the ways they may help save the environment. This review article includes the literature review on biologically active nitrogen and oxygen-containing heterocycles from 1995 to 2020. It focuses on the period between those two years.

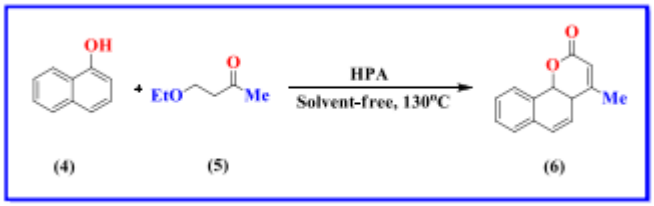
GREEN SYNTHETIC METHODS FOR THE PREPARATION OF SUBSTITUTED COUMARINS

Khan et al. described an environmentally friendly technique for the synthesis of new substituted chromene-3-carboxamide derivatives (3) by conducting a condensation reaction between substituted salicylaldehyde (2) and N- (Substituted) phenyl malonic acid (1) in the presence of a basic catalyst known as piperidine (Scheme 1) [40]. This reaction was carried out in the presence of a basic catalyst.



Scheme 1. Synthesis of Chromene-3-carboxamide Derivatives With Substituted Chromenes

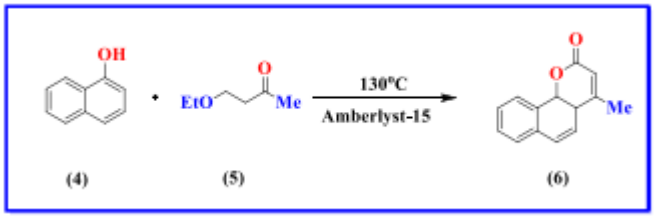
Synthesis of 4-methylnaphtho-(1,2-b)-pyran-2-one (6) from the condensation reaction between -naphthol (4) and -ketoester (5) in the presence of an environmentally friendly and reuseable catalyst known as sodium30-tungsto pentaphosphate in a solvent-free medium and under thermal conditions was reported by Heravi and his coworkers (Scheme 2).



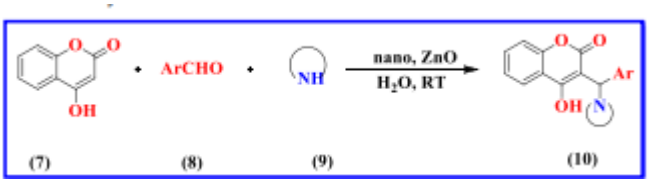
Scheme 2. Construction of 4-methylnaphtho(1,2-b)pyran-2-one compound

The Pechmann condensation reaction of naphthol (4) and -ketoester (5) was used by Hussien and his colleagues to synthesise coumarin derivatives (6). This reaction was carried out with Amberlyst-15 as an environmentally friendly and highly effective catalyst. In order to standardise the reaction conditions, a combination of ethylacetoacetate and -naphthol was employed as a model substrate. This mixture was then used to investigate the reaction circumstances, including temperature, amount of time needed to complete the reaction, solvent molar ratio of catalyst, and the different types of catalysts. They discovered that the

model reaction worked best when it was carried out in the presence of Amberlyst-15 at 110 degrees Celsius for one hundred fifty minutes in the absence of any solvents. This produced an excellent yield of (6), which was equal to 85 percent. Ghosh and Das reported a green, efficient, and simple method for the synthesis of substituted benzyl amino coumarin derivatives (10) by the reaction of 4-Hydroxycoumarin (7), cyclic secondary amine (9) and substituted aldehydes (8) in aqueous media in the presence of nano crystalline ZnO at room temperature (Scheme 4). This reaction was carried out in the presence of nano crystalline ZnO. In the beginning, m-nitrobenzaldehyde, 4-Hydroxycoumarin, and pi-peridine were used as reactants for the model reaction that was performed to synthesise benzyl amino coumarin derivatives while zinc oxide was present in a quantity that was sufficient to function as a catalytic agent. They carried out the reaction in the presence of polar and nonpolar solvents such as DMSO, ethanol, methanol, toluene, tetrahydrofuran, and acetonitrile in order to optimise the circumstances under which the reaction took place. They discovered that polar protic solvents provided a greater yield than other solvents, and they found that nano-Zno exhibited outstanding catalytic activity in a media consisting of water. The researchers proceeded to investigate the same model process in an aqueous medium at room temperature while using a variety of catalysts, including nanoaluminium oxide, L-proline, alum zeolites, tetrabutylammonium bromide, and commercial zinc oxide. They discovered that the intended product (10) could be achieved in 93% of cases when ZnO was present in the reaction within 15 minutes.



Scheme 3. Synthesis of coumarin derivatives



Scheme 4. Synthesis of benzyl amino coumarin derivatives catalysed by nanocrystalline ZnO at room temperature

Four-Membered Ring Heterocycles

The nitrogen-containing four-membered ring heterocycles have demonstrated their biological significance in medicinal chemistry, which has further elevated the significance of the nitrogen-containing four-membered ring heterocycles in biology.

β-Lactams

The four-membered cyclic amide ring system of -lactams has emerged as the scaffold of choice in the creation of many antibiotics, and it is also a valuable building block in chemical synthesis. This system is one of the heterocyclic compounds. It is widely acknowledged that it plays a critical role in the bioactivity profile of antibiotics. Incorporating the structure of a beta-lactam as a crucial scaffold or utilising it as an important building block for the synthesis of a variety of bioactive heterocycles allows for the synthesis of a number of conjugates that have a wide variety of pharmacological uses. These conjugates can be synthesised. There are additional therapeutic uses for beta-lactams besides antibiotics; for instance, clavulanic acids are beta-lactamase inhibitors, and ezetimibe is a cholesterol absorption inhibitor (Figure 2). These many uses have brought attention to the continued development of the -lactam ring, and as a result, numerous different methods have been developed to synthesise four-membered ring -lactams. The development of bacterial resistance to known -lactam antibiotics has served as a driving force behind the research that is now being conducted in this field.

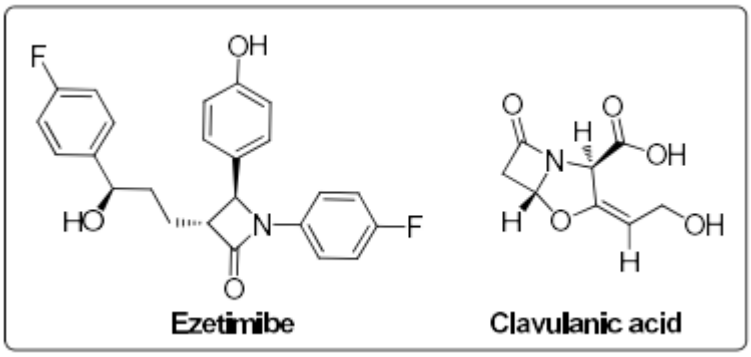


Figure 2. β-Lactam clinical drugs.

(1) Chromene-tagged beta-lactam molecular hybrids were created, and then these molecules were tested to see whether or not they have anti-inflammatory or anti-cancer properties. The RAW 264.7 murine macrophage assay was utilised by the scientists in order to investigate the anti-inflammatory properties exhibited by the -lactam hybrids. Additionally, the authors assessed the potential of the compounds to inhibit the pro-inflammatory cascade, which resulted in NO generation in mouse macrophages. Compound 1a, which has a para-methylphenyl moiety at N1 and a para-chlorophenyl moiety at the C4 position of the -lactam ring, exhibited the most M and IC50-cell viability = 123.47 significant activity among the established compounds, along with a 19.8 anti-inflammatory ratio (IC50-NO release = 6.24 M) (Figure 3). On the other hand, 4-chlorophenyl at the N1 position and 3-nitrophenyl at the C4 position of the M-lactam ring hybrid (1b) demonstrated the potential anticancer activity against the SW1116 colon cancer cell line with an IC50 value of 7.29 M).(compared to the standard methotrexate (IC50 = 2.49 Structure-activity relationship (SAR) studies revealed that p-methoxy, p-tolyl, and a p-chlorophenyl ring on the N1 of the -

lactam ring provided enhanced anticancer activity against the colon cancer (SW1116) cell line. On the other hand, a lower activity was observed against the HepG2 cell line for all the tested compounds. The in vitro anti-inflammatory action was significantly diminished when a p-nitrophenyl group was substituted for the p-chlorophenyl group that was originally located at the C-4 position of the lactam ring. Docking tests have shown that there is only a weak - contact between the lactam ring and the enzyme active sites. This may be the cause of the activity decrease that has been observed. The lipophilic activity of the active molecule was much higher than that of the derivatives. As a result, the molecule engages in more robust interactions with hydrophobic amino acids, which can be attributed to the enhanced anti-inflammatory properties of the substance.

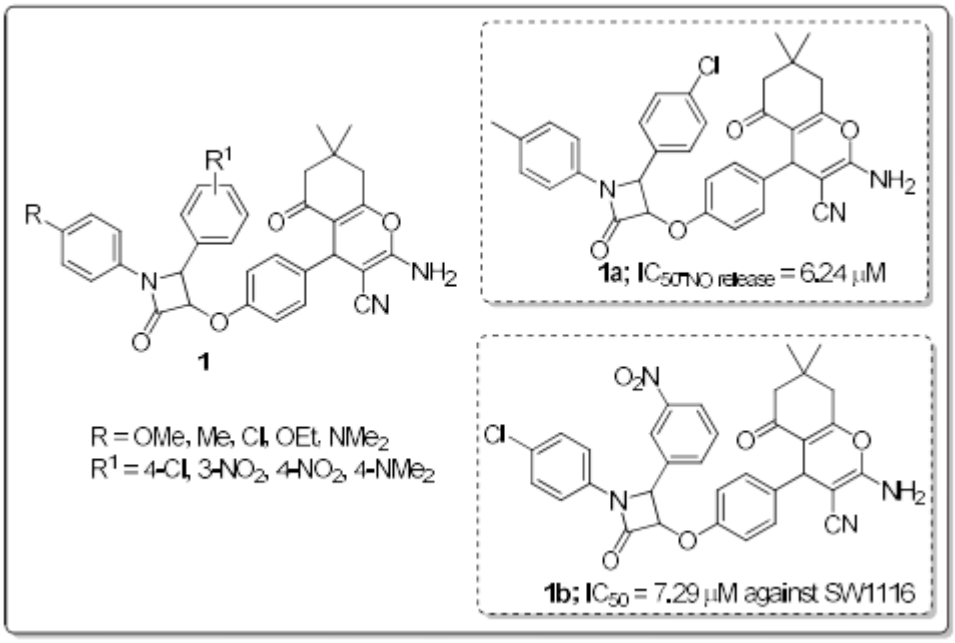


Figure 3. Activity against inflammation (compound 1a) and cancer (compound 1b) exhibited by the chromeno--lactam hybrids with the highest level of activity.

A number of different beta-lactam analogues 2 were synthesised, and then those analogues were tested for their ability to inhibit the proliferation of human cancer cell lines derived from the colon (HT-29) and breast (MCF-7) [51]. Compound 2a, which had a hydroxyl group connected to the beta-lactam's third position and a fluorophenyl conjugate, exhibited remarkable antiproliferative action with IC50 values of 0.022 lines against HT-29 cells, MCF-7 cells, and 0.003 against MCF-7 cells (Figure 4). When an atom of fluorine was substituted for the chloro, bromo, or iodo substituents in the following order: Br > Cl > I, the substance's efficacy against the colon HT-29 cell line was found to be significantly diminished. A compound's pharmacological and physicochemical characteristics, such as its metabolic stability, lipophilicity, and ligand binding, may be improved by the incorporation of fluorine. The active chemical, 2a, substantially blocked the colchicine site of tubulin and caused mitotic arrest (G2/M phase) at a micromolar dosage in colon cancer cell lines as well as

breast cancer cell lines. Within the bottom subpocket that is delimited by Valb318 and Cysb241, the 3,4,5-trimethoxyphenyl group has the potential to create van der Waals interactions that are favourable. The HBA connection with Lysb352 is made easier by the overlap of the fluorine atom onto the carbonyl oxygen atom of DAMA-colchicine, and a HDB interaction with Lys254 can be formed by the hydroxyl group on the -lactam ring. The results of the molecular modelling investigation allow for the conclusion to be drawn that the active chemical interacts with tubulin at the same place as colchicine and utilises binding mechanisms that are quite similar to one another. When it comes to the development of tubulin-targeting medicines for the treatment of colon and breast cancers, the beta-lactam derivatives are now among the most promising choices.

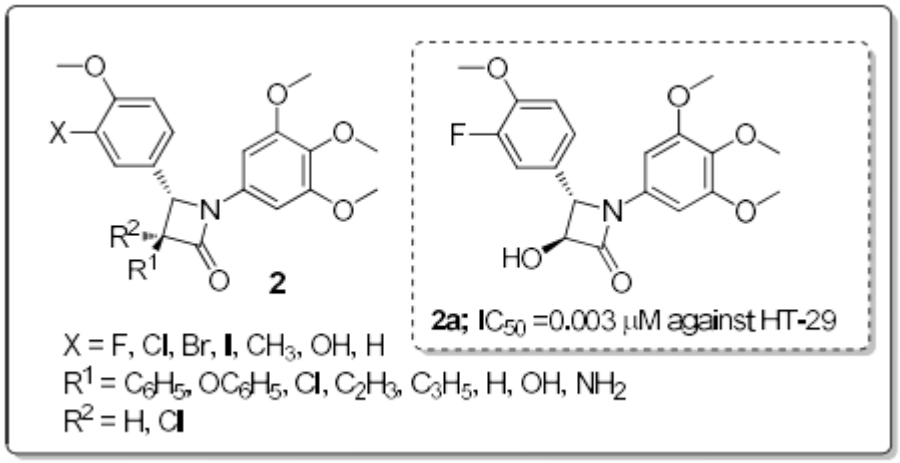


Figure 4. Antiproliferative activity of most potent β-lactam derivative 2a.

As potential antibacterial and antifungal drugs, a number of -lactam-anthraquinone hybrids 3 were synthesised in a laboratory setting. The most strong antibacterial action was demonstrated by the thio-methyl substituent at C-3 and the 3,4,5-trimethoxy phenyl group at the C-4 position of the beta-lactam ring scaffold (compound 3a) against the Staphylococcus aureus bacterial strain (MIC = 0.25 g/mL) (Figure 5). Both the standard ciprofloxacin (MIC = 0.5 g/mL) and the reference ciclopirox olamine (MIC = 4) exhibited the same level of antifungal activity (MIC = 4 g/mL) against the Candida albicans strain. Comparatively, the MIC for the standard ciprofloxacin was 0.5 g/mL. It was discovered that anthraquinone--lactam derivatives, which had a 2-naphtho group at the C-3 position, and 4-chloro and 4-methoxyphenyl groups at C-4 of the -lactam ring, displayed decreased activity. This lower activity can be due to steric hindrance, which weakens the intermolecular contacts. Furthermore, the active hybrid was evaluated by molecular docking studies and the carbonyl groups of the anthraquinone moiety and the β-lactam ring had three hydrogen bonding interactions with Lys273, Asp295 and Val277 residuces, while the MeS group interacted with the active site of Tyr272 and the 3,4,5-tri methoxyphenyl group exerted hydrophobic interactions with His293, Lys289, Gln292 and Lys319 residues of a penicillin-binding protein (PBP).

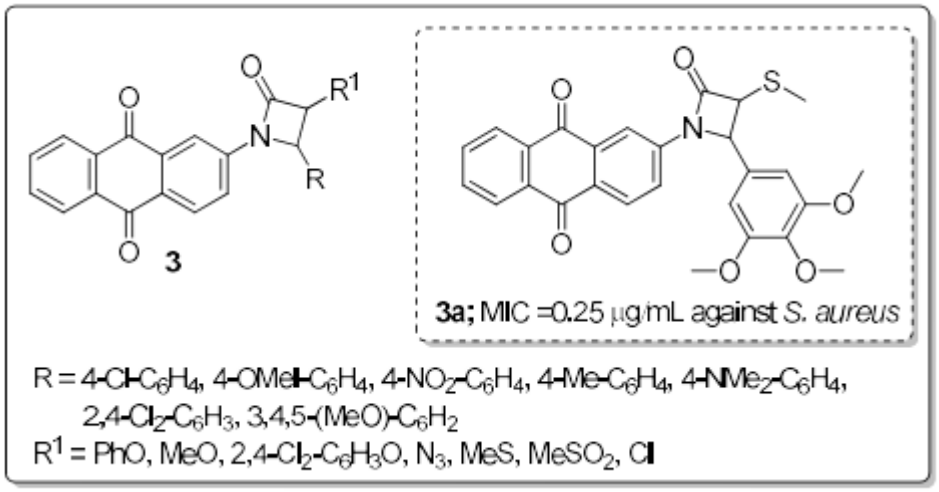


Figure 5. Most potent antibacterial β-lactam-anthraquinone hybrid 3a.

Synthesised beta-lactams and their derivatives were tested for their ability to inhibit the growth of Mycobacterium tuberculosis (M.tb) and Moraxella catarrhalis (M.cat) [53]. Among them, the most effective ones were the metaCF3 of the phenylthiol ring and the achiral carbamyl group at the lactam nitrogen (Figure 6). In contrast, a decreasing activity was discovered with para-CF3, fluorine (para-, meta-, and ortho-), and difluoro groups replaced on the phenylthiol ring analogues. The MIC for M.tb was reported to be 25. In addition, the incorporation of the achiral carbamyl group resulted in an increase in anti-Mtb activity in comparison to the derivative that lacked any substitutions. It is possible that nonspecific binding of the various drugs to hydrophobic medium components is to blame for the absence of a significant difference in the level of action against M.cat and M.tb. The active chemical shown good effectiveness against Mtb strains that did not replicate and were resistant to many drugs.

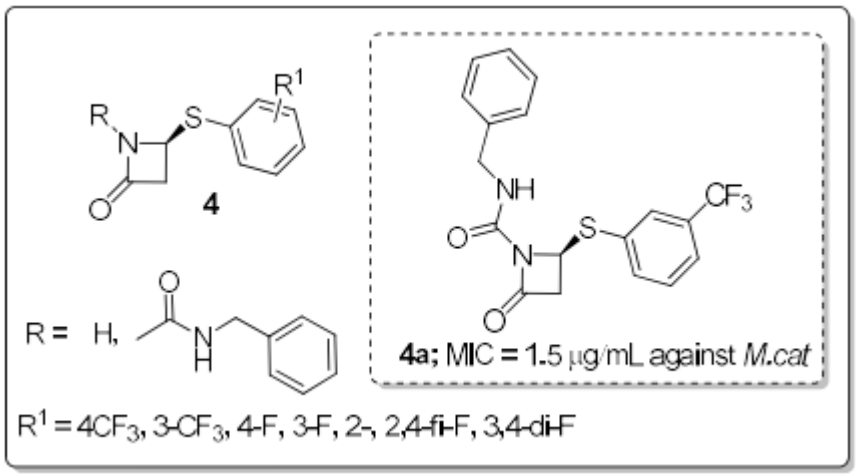


Figure 6. The antimicrobial activity of the most potent β-lactam analog 4a.

Five-Membered Ring Heterocycles

The heterocyclic motifs with five members are referred to as 1,2,3-triazoles, imidazoles, pyrazoles, oxadiazoles, oxazoles, isoxazoles, and thiazoles. Which are essential pharmocophores in medicinal chemistry because to the wide range of biological actions that they exhibit.

1,2,3-Triazoles

The 1,2,3-triazole moiety is the primary pharmacophore system among nitrogen-based compounds. Additionally, the 1,2,3-triazole moiety is a privileged building block that has been utilised in the development of a variety of novel biological targets. These five-membered heterocyclic motifs with three nitrogen heteroatoms may be easily synthesised using 'click' chemistry, which is to say, by copper-catalyzed azide-alkyne cycloaddition [Cu-AAC] processes. Click chemistry refers to a type of chemistry that involves the use of a trigger to initiate a chemical reaction. In general, the 'linker' feature of 1,2,3-triazoles is resistant to hydrolysis in acidic or basic environments, as well as breakdown through metabolic processes. These compounds have the potential to interact with a wide variety of biological targets via hydrogen bonding, noncovalent and van der Waals interactions, and dipole-dipole bonding. In addition, triazoles are neither strongly acidic nor strongly basic; yet, they are more reactive towards reducing agents. In addition, the 1,2,3-triazole-based chemical known as carboxyamidotriazole has been tested and found to be effective in clinical trials for the treatment of cancer (Figure 7) [54–56]. Additionally, the triazole unit's strong dipole qualities boosted its relevance in the field of medicinal chemistry, since it attaches to the biological target with a high affinity. This is due to the fact that the triazole unit has strong dipole properties.

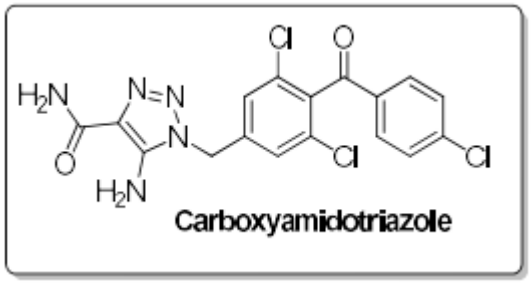


Figure 7. A 1,2,3-triazole-containing clinical drug.

Phenothiazine conjugates 5 and 6 were created using a 1,2,3-triazole linker, and the conjugates were evaluated for anti-tubercular activity against the H37Rv strain of Mycobacterium TB. All of the compounds had reasonably strong anti-tubercular activity in vitro, as shown by the compound 5a with a 4-nitro group, which revealed considerable anti-tubercular activity with a MIC M against M.tb H37Rv (Figure 8). All of the compounds were able to inhibit the growth of M.tb. Compound 5a exhibited non-toxic properties against VERO cell lines, displaying a value of 2.44. The derivatives of isonicotinohydrazide and nicotinohydrazide at a concentration of 6 M against M. tuberculosis H37Rv. A SAR analysis

found that substituted phenyl rings, rather than the isonicotinohydrazide/nicotinohydrazide, resulted in very powerful activity. This highly potent activity was reliant on the electronic impact that the substituents had on the phenyl ring. The MIC values for this study ranged from 2.61-2.94. Both the Inh A and Cyp121 enzymes were able to accommodate the active molecule without any problems. Compound 5a showed clear evidence of hydrogen bonding creation as well as pi-pi interactions with the hydrophobic residue Tyr158 found in the Inh A enzyme. The most powerful molecule had permeability and aqueous solubility values that were much greater than those of the corresponding analogues. In addition to that, the pharmacokinetic characteristics indicated that the chemical had an excellent bioavailability when taken orally. The powerful molecule represented an innovative hybrid that may be used in the research and development of future anti-tubercular drugs.

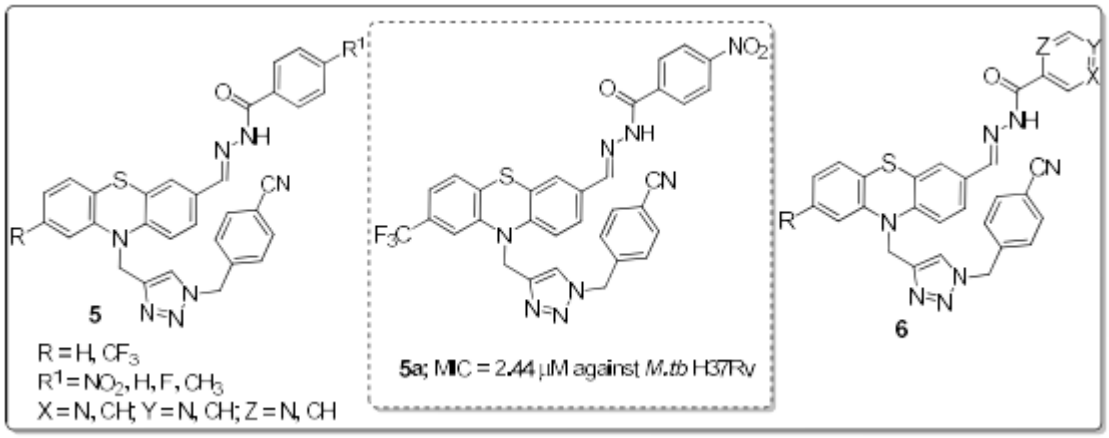


Figure 8. The phenothiazine-1,2,3-triazole conjugate 5a had the most substantial antitubercular efficacy.

CONCLUSION

This review article provides a comprehensive look at the numerous environmentally friendly techniques of producing heterocycles that include nitrogen and oxygen, such as coumarins, dihydropyrimidinones, imidazoles, isoxazoles, and benzimidazoles, as well as their varied biological functions. These techniques have a number of advantages, such as clean reaction profiles, the absence of side reactions, the reduction of waste to a minimum, the optimisation of experimental processes, high atom economy, and cost-effectiveness. With the help of this study, we want to uncover potential future avenues for the production of more effective and specific analogues of molecules containing nitrogen and oxygen that may be used to target the biological system. The information presented in this review can also stimulate organic chemists to develop innovative compounds in order to find a great deal more physiologically active heterocycles for the benefit of humankind. This information is displayed throughout the study.

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