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BIO EVALUATION OF NITROGEN AND OXYGEN BASED HETEROCYCLES

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Abstract:

Heterocycles based on nitrogen and oxygen are key structural motifs that may be found in a wide variety of physiologically active chemicals. With a particular emphasis on the heterocycles' varied pharmacological activity and therapeutic potential, the purpose of this review is to investigate the bioevaluation of heterocycles of this kind. A broad variety of biological activities, including antimicrobial, anticancer, anti-inflammatory, and antiviral capabilities, are exhibited by heterocycles that contain nitrogen. These heterocycles include pyridines, pyrimidines, purines, imidazoles, and pyrroles. Furans, thiophenes, and coumarins are examples of heterocycles that contain oxygen and possess substantial pharmacological actions. These activities include antioxidant, anticoagulant, and antibacterial properties. When it comes to rational medication design and development, having a solid understanding of the structure-activity interactions of these heterocycles is absolutely necessary. It is also mentioned that the molecular processes that are responsible for their pharmacological actions are explored, which sheds insight on the potential of these substances as therapeutic agents. In addition, current developments in synthetic techniques for the creation of heterocycles based on nitrogen and oxygen are discussed, which makes it easier to access these heterocycles for the purpose of biological assessment. Taking everything into consideration, this review highlights the significance of nitrogen and oxygen-based heterocycles in the process of drug discovery and development, highlighting the potential role that these heterocycles play in tackling a variety of therapeutic issues.

keywords: *Nitrogen, Oxygen, Heterocycles*

Introduction

The topic of heterocyclic molecules is a prominent one in the field of organic chemistry, where they are the subject of study. Organic chemists have shown interest in this topic for a variety of reasons, and one of those reasons is because it is rather interesting. These factors include the widespread presence of heterocyclic compounds in nature, such as alkaloids,

vitamins, pigments, and a wide range of constituents found in plant and animal cells; the essential role that these compounds play in biological processes; the availability of these compounds from agricultural wastes; and the commercial value of these compounds as solvents, dyes, and pharmaceuticals. Chemical chemists that specialize in organic chemistry are the ones who are responsible for the design and manufacturing of novel heterocycles. These heterocycles are subsequently employed in the industrial production of agrochemicals and medicines, both of which play important roles in the existence of humans. According to some estimates, heterocycles can be found in more than half of the compounds that exist naturally, as well as in a large number of medications. The heterocycles that include nitrogen and oxygen are by far the most prevalent in terms of the frequency with which they occur. Through the utilization of 1,3-dipolar cycloadditions and multicomponent processes, the major focus of this thesis is on the synthesis of heterocyclic compounds that are based on nitrogen and oxygen through the application of these techniques.

NITROGEN CONTAINING HETEROCYCLES

It has been demonstrated that nitrogen-based heterocycles have been involved in the process of DNA synthesis ever since the beginning of life. Additionally, these heterocycles are considered to be of significant importance in a wide range of biological systems. Derivatives of aromatic nitrogen heterocycles are responsible for the formation of four different nucleic acid bases. Bases such as adenine, guanine, cytosine, and thymine are included in this category. A heterocyclic imidazole ring is a component of the chemical structure of histidine, which is regarded as one of the amino acids that are thought to be crucial for human survival. The structure of tryptophan, the second necessary amino acid, as well as a large number of naturally occurring alkaloids, all originate from indose. In addition, indose is the source of a huge number of alkaloids. Please have a look at the following list of examples of bioactive nitrogen heterocycles for your consideration.

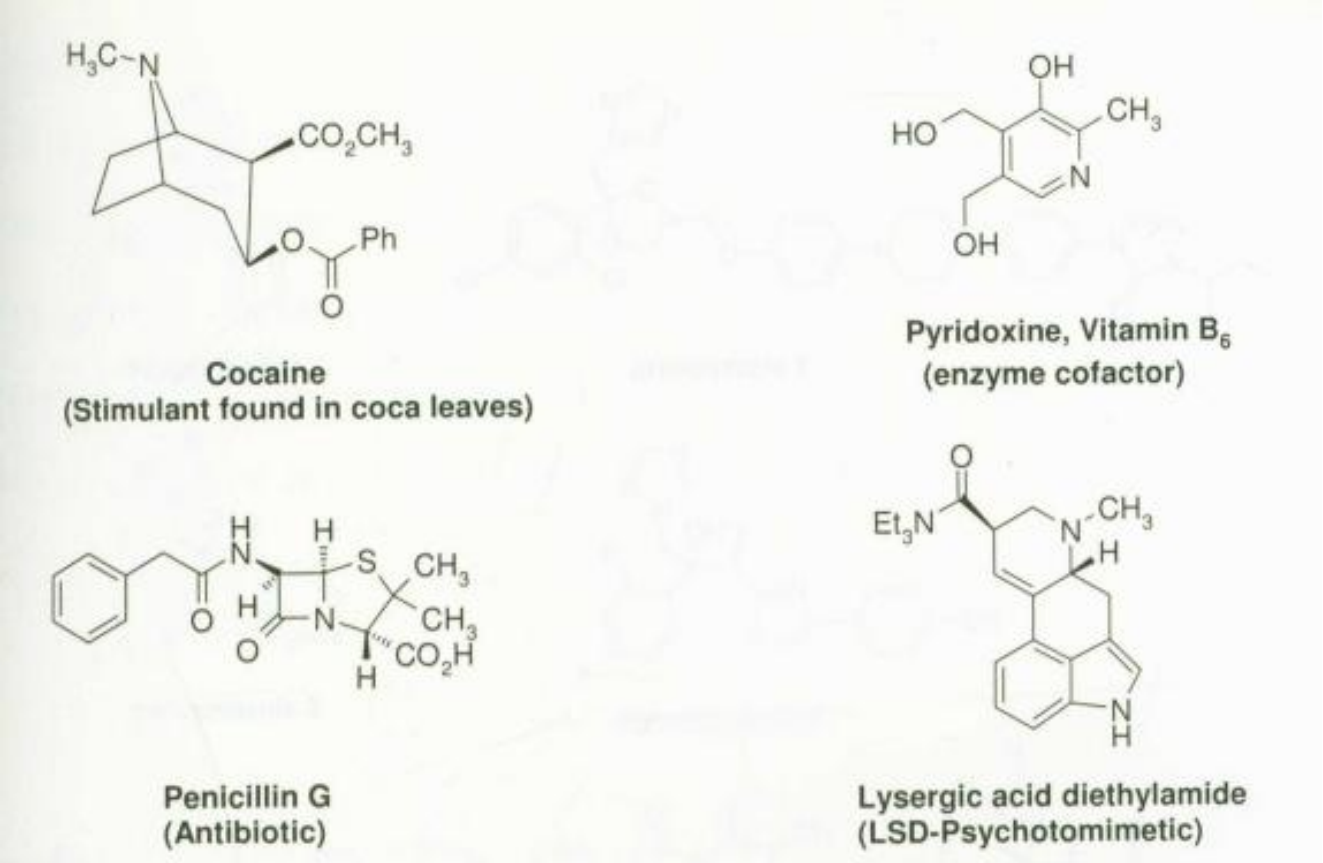


Figure 1.1:

TRIAZOLES

There is a broad variety of pharmacological effects that have been associated with 1,2,4-triazoles. These effects include those that are analgesic, antiasthmatic, diuretic, antihypertensive, anticholinergic, antibacterial, antifungal, and anti-inflammatory. Fluconazole (1) is the antifungal medicine of choice for the treatment of infections caused by Candida albicans and Cryptococcus neoformans. This is due to the fact that fluconazole possesses a potent antifungal effect, an acceptable safety profile, and favorable pharmacokinetic properties. II. Itraconazole possesses an antifungal spectrum that is better and more complete than other antifungal agents. A number of recently developed triazole medications, including voriconazole (3), posaconazole (4), ravuconazole (5), and albaconazole (6), are now being evaluated in clinical trials to determine whether or not they are effective against Aspergillus.

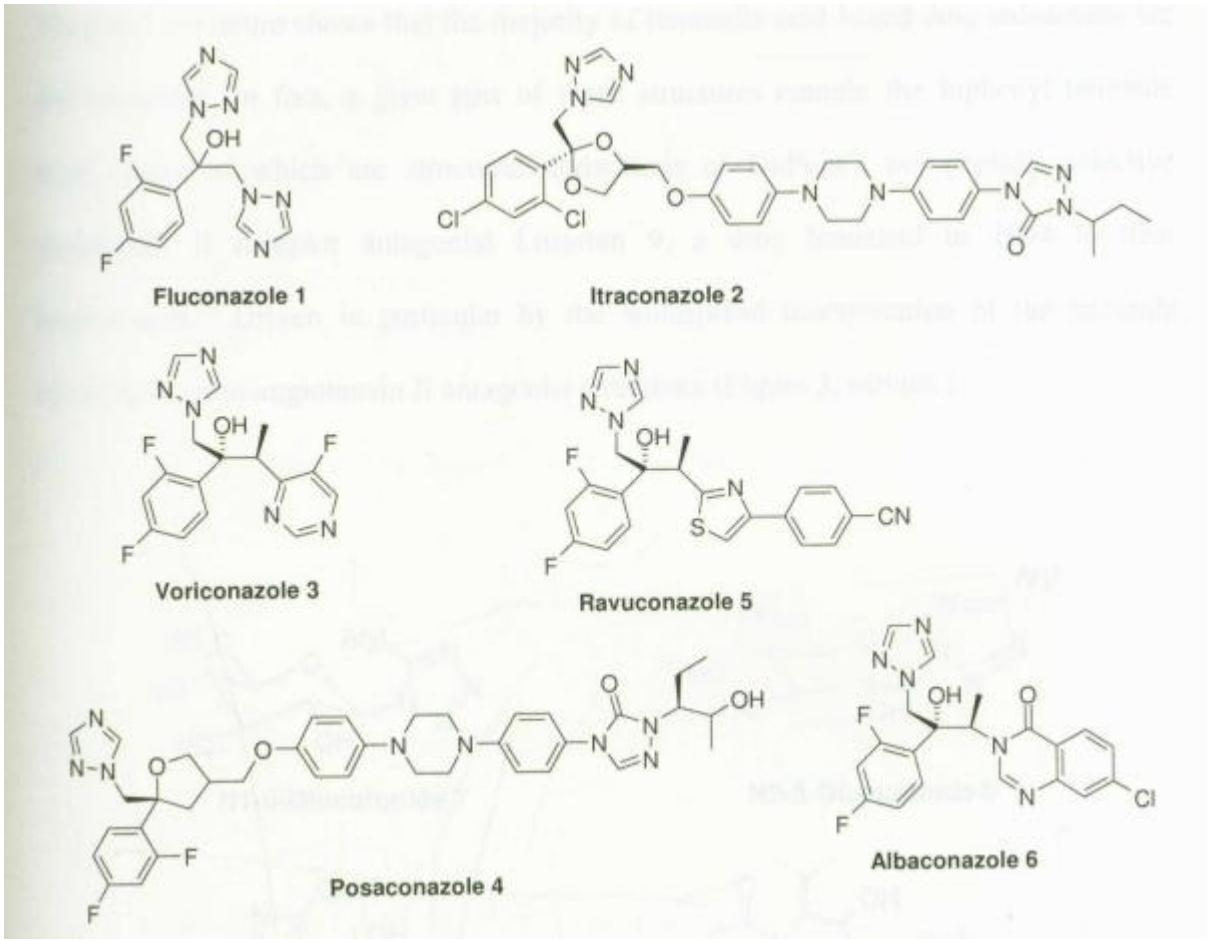


Figure 1.2

TETRAZOLES

Tetrazoles are a class of heterocycles that are now attracting a substantial amount of interest owing to the enormous number of applications that they may be utilized for. 5-substituted-/H-tetrazoles have gained popularity in recent years as an isosteric alternative for the carboxylic acid moiety in a range of applications. This trend has been seen in a number of different contexts. Tetrazoles are frequently used as metabolically stable surrogates for carboxylic acids. This is mostly due to the fact that their pharmacokinetic profile is generally more favorable. Tetrazoles provide a more beneficial mode of action, which is the reason for this reason.

Through the examination of the urine streams of a large number of animals that had been orally dosed with a chromone-derived tetrazole, Nohara was able to find the very first tetrazole NI glucuronide 7 that had ever been identified. A ten Recent discoveries have also shown that an aliphatic medication candidate contains the N2-glucuronide 8 structure. This information was made public.

In the patent literature, it is said that aryl tetrazoles constitute the great majority of the pharmacological compounds that are derived from tetrazolic acid. A sizeable proportion of these compounds include the biphenyl tetrazole motif in their structure. Losartan 9 is a non-peptidic selective angiotensin II receptor antagonist that is made by DuPont. Many of these

structures are structural derivations of Losartan 9. In 1994, the medicine known as losartan 9 was originally brought to the market as a treatment for elevated blood pressure. In recent years, sartans have seen a rise in popularity, which may be attributed, in particular, to the widespread incorporation of the tetrazole functionality into angiotensin II antagonist structures (Figure1.3, sartans).

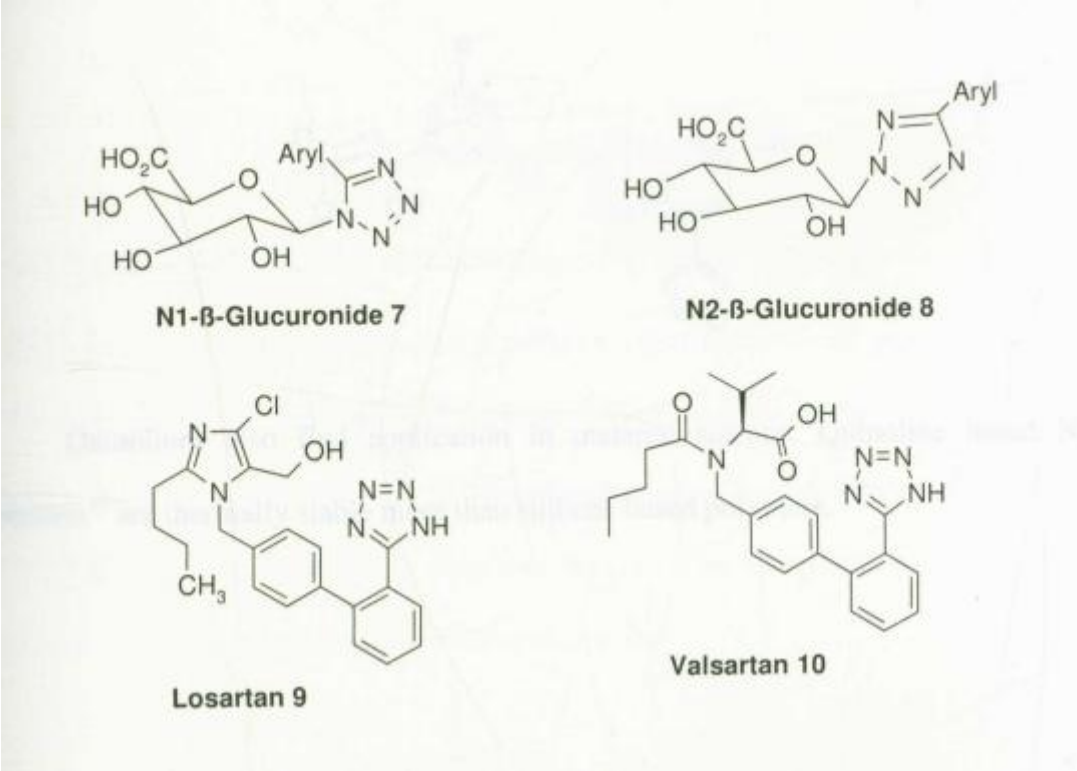


Figure 1.3: sartans

FEATURES OF HETEROCYCLIC COMPOUNDS

- Heterocycles that have five or six members and contain heteroatoms of nitrogen (N), oxygen (O), or sulfur (S) are the most prevalent types of heterocycles. Pyridine, pyrrole, furan, and thiophene are examples of simple heterocyclic compounds that are known to exist.
- Pyrrole, furan, and thiophene molecules each possess five-membered rings, which are formed of four carbon atoms and one atom of nitrogen, oxygen, or sulfur.
- Pyridine molecules contain a ring that is composed of six atoms, five of which are carbon atoms and one of which is nitrogen.An oxygen-containing heterocycle is referred to as furan. Both pyridine and pyrrole are examples of nitrogen heterocycles, meaning that their molecules contain carbon atoms in addition to nitrogen atoms in the outer rings.
- Comparing heterocyclic compounds with regular organic compounds that do not include heteroatoms is the most effective way to gain an understanding of the physical and chemical features of heterocyclic compounds.
- In organic chemistry, heterocyclic molecules make up 65 percent of the total, and heterocyclic chemistry is concerned with those chemicals.

- Certain natural products, such as antibiotics like penicillin and cephalosporin, as well as alkaloids like morphine and reserpine, are examples of natural products.

Biological importance of Heterocyclic Compounds

There is a substantial category of molecules that are referred to as heterocycles. These heterocycles are responsible for more than half of all organic compounds that are currently known. There are many different types of heterocycles, including antitumor, anthelmintic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents. These heterocycles can be found in a wide variety of pharmaceuticals, the majority of vitamins, and a large number of natural products, biomolecules, and biologically active compounds.Among the naturally occurring heterocyclic compounds that display a wide range of biological activity, the alkaloids form a large minority. The majority of alkaloids include atoms of nitrogen that are considered to be basic. Ergotamine, an alkaloid that is derived from indole, has been demonstrated to possess antimigraine effects. Cinchonine, which belongs to the quinolone class of alkaloids, has been demonstrated to possess antimalarial effects when tested. It has been discovered that a great number of heterocyclic compounds play a significant part in the activities that take place in living organisms. There are a number of heterocyclic compounds that are included in the important components of a diet. These include thiamine (Vitamin B1), riboflavin (Vitamin B2), nicotinamide (Vitamin B3), pyridoxal (Vitamin B6), and ascorbic acid (Vitamin C). Furthermore, tryptophan and histidine, both of which are frequently regarded as essential amino acids, are examples of heterocycles. Furthermore, it has been shown that critical structural units of synthetic pharmaceuticals and agrochemicals include them on several times.

Antimalarial Activity:

One of the most dangerous diseases in the world, malaria is caused by parasites that are transmitted to humans through the bites of Anopheles mosquitoes that are afflicted with the disease. Malaria affects a significant portion of the globe's world population.The infectious illness known as malaria is still very much present throughout the world. In a given year, there are around 300 to 500 million clinical cases of malaria. Malaria is diagnosed and treated with antimalarial medication.Additionally, there are antimalarial medications that belong to the heterocyclic group that have a higher level of action in the treatment of malaria.Cinchonine, Quinine, Chloroquine, and Primaquine are all examples of alkaloid compounds that exhibit antibacterial activity or properties. It is well known that quinones and chloroquines have a higher activity in treating malaria, while also having a lesser toxicity..

RESEARCH METHODOLOGY

A significant number of the anticancer medications that are now on the market are incapable of distinguishing between normal and neoplastic cells, nor are they able to overpower primary or secondary resistance mechanisms that have developed in tumor cells. As a result, there is an urgent requirement for the development of novel anticancer medicines that possess

high efficacy, lower toxicity in cells that are not malignant, and distinct sites of action. Interfering with a single biological molecule or pathway has shown to be an effective method of treating tumors at the present time. On the other hand, there is a widespread opinion that medications that modulate more than one target or several sites on a single target as opposed to treatments that only target a single target might potentially have a higher level of effectiveness.

As a result, it is possible to modulate several targets or many sites on a single target at the same time. This may be accomplished by combining multiple medications that target different targets or by using a single chemical entity that has the ability to modulate multiple sites on a specific target. As a consequence of this, there is a growing interest in the identification of hybrids that simultaneously target many biological targets for the treatment of tumors. Keeping in mind the limits of compounds that only modulate one target, these hybrids have the potential to offer new dimensions to molecules that modulate more than one target site. As a result, they have the potential to be incredibly useful for the society that is now working very hard to combat this terrible illness.

In the realm of anticancer medicines, tubulin is considered to be among the most advantageous and strategic molecular targets. It is possible to impede the dynamic process of microtubule construction and disassembly by employing a variety of chemicals that bind to specific locations within the β-tubulin subunit. These chemicals cause cells to stop in the process of mitosis by interfering with the activity of microtubules, which ultimately results in cell death by a combination of apoptosis and necrosis.

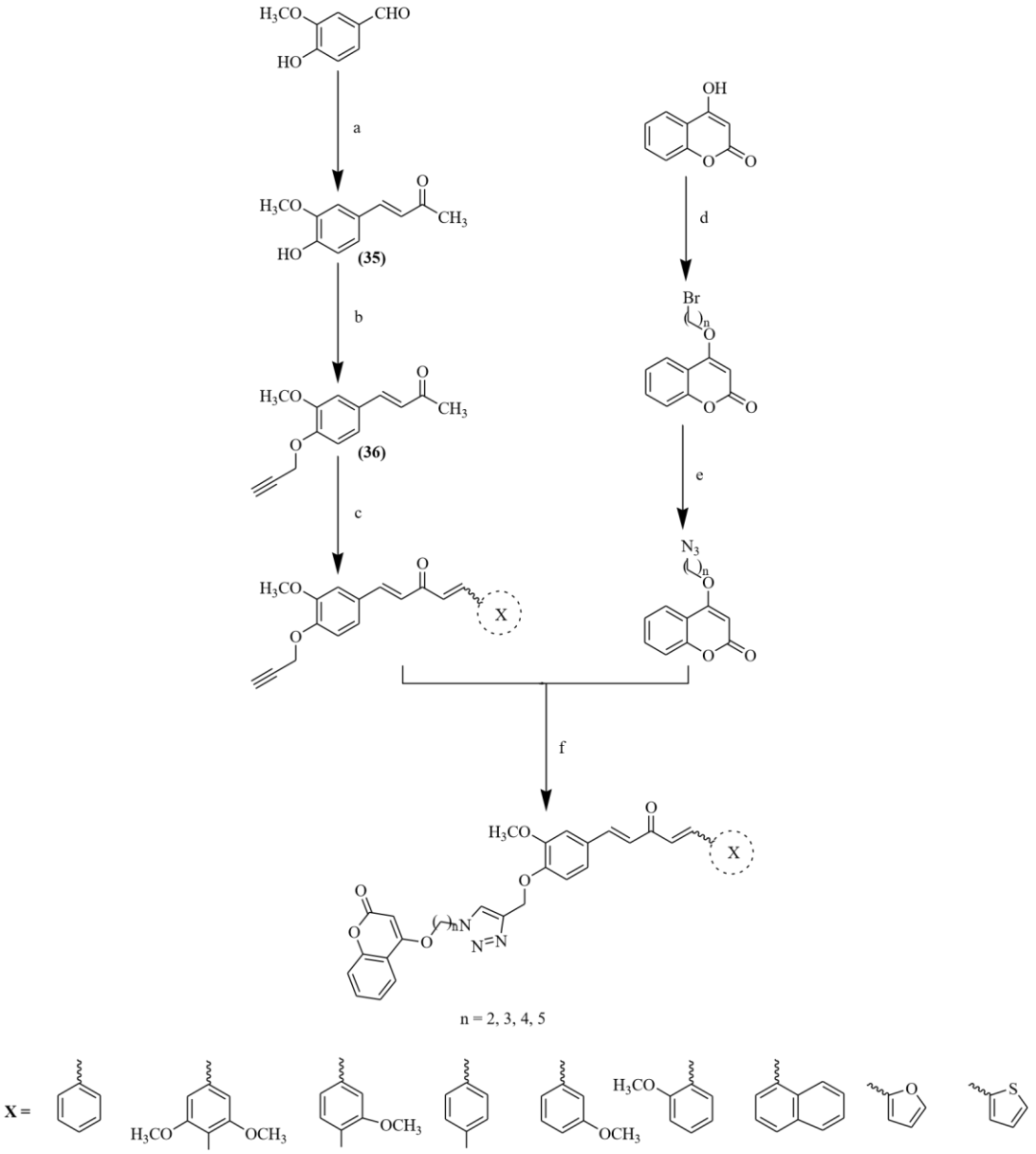
RESULT AND DISCUSSION

CHEMISTRY

Vanillin was the starting point for the series of reactions (Scheme 1) that were used to synthesis target hybrids. These reactions began with vanillin being treated with acetone in the presence of 40% potassium hydroxide at ambient temperature. The substance that was required, vinyldenacetone (35), was consequently produced. In order to obtain the desired product, which is known as propargylatedvinyldenacetone (36), intermediate 35 was subjected to a treatment that involved the use of propargyl bromide in DMF as a solvent accompanied by the presence of K2CO3 at room temperature. The target result, which was propargylated C5-curcuminoid analogues, was obtained by further treating compound 36 with a variety of substituted aldehydes in methanol as a solvent and in the presence of 5% sodium hydroxide at room temperature. Each of these treatments was carried out at room temperature.

The desired product, 4-(2-bromoalkoxy)-2H-chromen-2-one, was obtained by sequentially treating 4-hydroxy coumarin with a variety of 1,2-dibromoalkanes in the presence of K2CO3 in DMF as a solvent at room temperature. This was followed by a reaction with NaN3 in DMF as a solvent at room temperature, which resulted in the production of 4-(2-azidoalkoxy)-2Hchromen-2-one.
These 4-(2-azidoalkoxy)-2H-chromen-2-ones were subjected to a treatment with

propargylated C5curcuminoid analogues in the presence of copper sulfate and sodium ascorbate, with DMF serving as the solvent. The treatment was carried out at room temperature in order to get the triazole linked C5curcuminoid-coumarin hybrids that were necessary.



Scheme 1 Making triazole-linked C5-curcuminoid-coumarin hybrids. Conditions and agents: (a) Stir, reflux for 2 hours in an acetone and 40% potassium hydroxide solution; (b) Stir, reflux for 2 hours in a potassium bicarbonate and dimethylformamide (DMF) solution; (c) Stir, reflux for 2 hours in a mixture of aldehydes and 5% sodium hydroxide in methoxyethanol; (d) Stir, reflux for 2 hours in a potassium bicarbonate and dimethylformamide solution; (e) Stir, reflux for 1 hour in a solution of sodium bicarbonate and dimethylformamide (DMF); (f) Stir, reflux for 15 minutes in a DMF solution.

In order to shed light on the structures of all of the compounds that were synthesized, 1H NMR, 13C NMR, and Elemental Analysis were utilized. The spectral measurements were consistent with the structures that were speculated to exist. All of the data pertaining to the

characterisation is included in Appendix-1. Page number 203 " Only those C5-curcuminoids that had previously demonstrated significant cytotoxicity when linked to isatin via triazole have been synthesized and tethered to coumarin through triazole. This is in light of our recent report on triazole linked mono carbonyl curcumin-isatin bifunctional hybrids that have the potential to inhibit the activity of tubulin. Additionally, out of the eight cell lines that were used in the previous study, only four of them, namely THP-1, COLO-205, HCT-116, and PC-3, were utilized for the purpose of conducting biological research. These four cell lines were the only ones that were sensitive to triazole connected mono carbonyl curcumin-isatin bi-functional hybrid structures.

BIOASSAY

In vitro cytotoxicity tests were performed on all of the synthetic compounds using sulforhodamine B19 [92,93]. The synthetic compounds were tested against four human cancer cell lines: THP-1, COLO-205, HCT-116, and PC-3. In the presence of the test substance, the cells were allowed to multiply for a period of forty-eight hours. All of the hybrids that were generated were tested against the cell lines at a concentration of 50 µM. The hybrids that showed a percentage inhibition against at least one cell line that was larger than 70 percent; these hybrids were solely examined at different doses, and the IC50 values were computed In contrast to what was stated in our earlier article [81], it was discovered that out of the four cancer cell lines, THP-1, COLO-205, and HCT-116 were sensitive to the hybrids that were created, however PC-3 was shown to be resistant to the hybrids. The most surprise finding was that, out of the three susceptible cell lines, the THP-1 cancer cell line, rather than the HCT-116 cell line, which was the most sensitive to triazole connected mono carbonyl curcumin-isatin bi-functional hybrids, was the most sensitive to these hybrids. The compounds 40, 41, and 45 exhibited noteworthy cytotoxicity, as seen by their IC50 values, which varied from 0.82-4.68 µM, 2.34-6.78 µM, and 4.48-9.95 µM, respectively, when tested against the THP-1, HCT-116, and COLO-205 cell lines. The hybrid 40, which included a trimethoxy phenyl ring as Ring X and had an IC50 value of 0.82 µM, was almost three times more effective than the hybrid 41, which also contained a trimethoxy phenyl ring as Ring X and had an IC50 value of 2.34 µM. The latter hybrid was the second most powerful hybrid against the THP-1 cell line. With regard to these hybrids that were created, the cytotoxicity data that were presented demonstrated an intriguing structure-activity link (Fig. 1.4): (i) methoxy substituted phenyl ring as Ring X remarkably enhances the cytotoxic potential (compare 39 with 40 to 44); (ii) placement of a heteroaryl ring such as furan and thiophene in place of the unsubstituted phenyl ring as Ring X improved the activity profile (compare 39 with 46 and 47); (iii) an enhanced effect was observed with the increased number of methoxy substituents on phenyl ring as Ring X such as trimethoxy phenyl > dimethoxy phenyl > monomethoxy phenyl (compare 40 and 41 with 42, 43 and 44); (iv) placement of naphthyl ring as Ring X behaved as a surrogate for dimethoxy substituted phenyl ring (compare 41 with 45); (v) cytotoxicity of hybrids with monomethoxy substituted phenyl ring as Ring X was found similar to the heteroaryl ring substituted hybrids (compare 42, 43 and 44 As a result, the following is the classification of the overall preference order of Ring X: trimethoxy phenyl is superior to dimethoxy phenyl, naphthyl is superior to monomethoxy phenyl, furan is superior to thiophene, and phenyl is the highest.

Furthermore, the length of the carbon-bridge that connects the triazole ring with the coumarin moiety has a significant impact on the activity. There is a considerable reduction in cytotoxicity that occurs as the chain length of the carbon-bridge is increased. As a result of the findings presented above, it has become abundantly evident that the trimethoxy substitution is essential for the anticancer potential. This is also the case with the powerful medication combretastatin, which also has a trimethoxy ring in its molecular skeleton. Docking studies provide evidence that the longer molecules (n > 3) do not have a good anticancer potential. This is the reason why the longer molecules are not favorable.

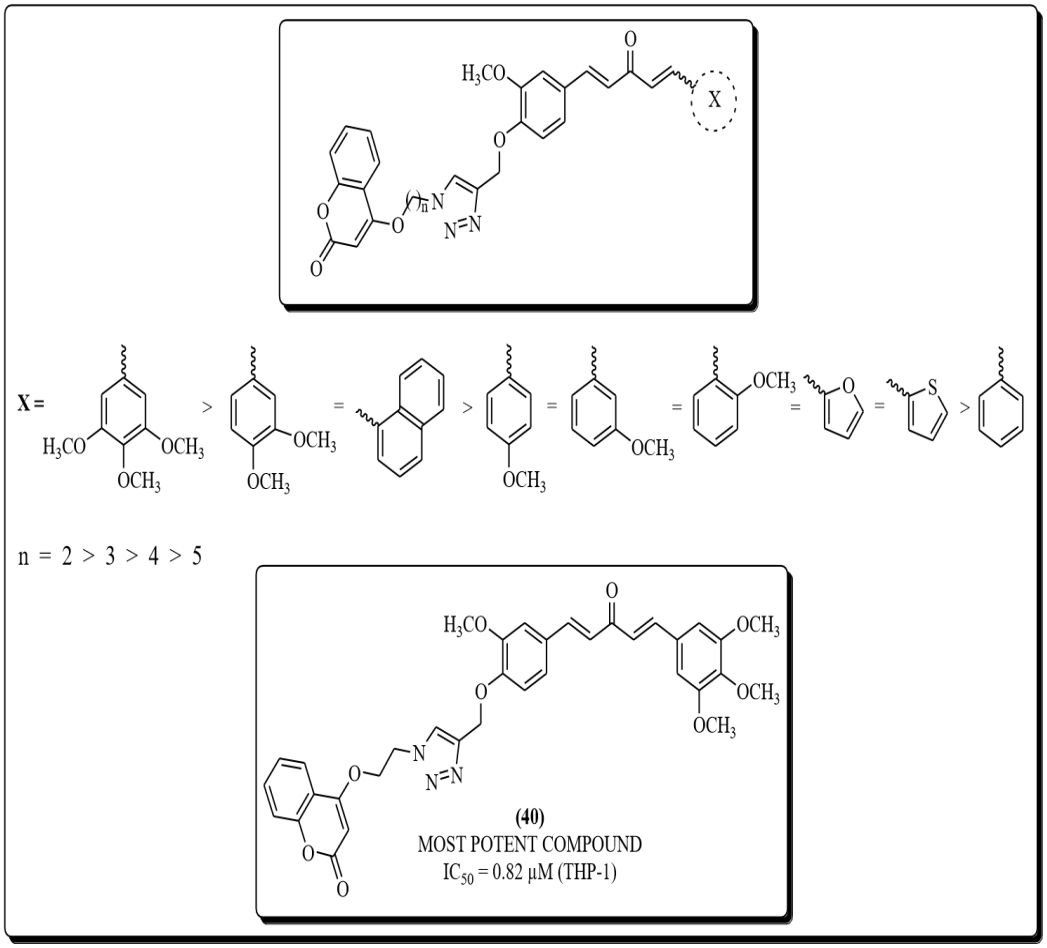


Fig. 1.4 Association between structure and activity

A cytoskeleton tubulin polymerization test kit was utilized in order to analyze the inhibitory effects of the most active compounds within the series. This evaluation was carried out in accordance with the assay that was described. The compound 40, which is the most potent hybrid, exhibited the most strong antitubulin activity, with an IC50 value of 1.55 µM. This compound also possessed a trimethoxy phenyl ring, which is referred to as Ring X. Additionally, compound 41 demonstrated a noteworthy and substantial suppression of tubulin polymerization, as seen by its IC50 value of 2.88 µM. It was discovered that the hybrid molecule 45, which possesses a naphthyl ring (Ring X), possesses a mild inhibitory potential for the polymerization of tubulin. The results of the in vitro tubulin polymerization experiment clearly suggest that both 40 and 41 exert their cytotoxic effects through tubulin inhibition.

CONCLUSION

The current investigation involved the design, synthesis, and evaluation of new antitubulin bi-functional C5-curcuminoid-coumarin hybrids. These hybrids were tested for their ability to induce cytotoxicity against a variety of human cancer cell lines. Tuberculin inhibitory potential of the most effective compound 40 (with trimethoxy phenyl ring as ring X and n = 2) was validated by in vitro tubulin test, which clearly suggests that 40 exerts its cytotoxic action through tubulin inhibition. For example, the trimethoxy phenyl ring was present in compound 40. In addition, docking studies helped to simplify the process of tubulin inhibition by compound 40, which is an important factor to highlight. In the current investigation, a molecular hybridization approach is utilized for the purpose of designing benzoflavones as hybrids of naphthopyrans and flavones, which are two kinds of xanthine oxidase inhibitors that have been presented in previous research. The hybrids that were created have been produced and tested for the first time to see whether or not they suppress xanthine oxidase levels.

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