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Exploring the Therapeutic Potential of Imidazothiadiazole Derivatives: A Comprehensive Review with Structures

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Abstract

Thiadiazole heterocycles are best known to offer a variety of biological activities as therapeutic sensitive agents in medicinal chemistry. Thiadiazole nucleus can be found in certain bacteria thiazolyl peptide antibiotics. In this review we have discussed the applications of imidazothiadiazoles in different fields. Based on concerns related to imidazothiadiazoles, their structural features, anticonvulsant activities, bactericidal, antifungal, antimycobacterial, anticancer, anti-inflammatory, antihypertensive, and anti-HIV properties, and the molecular targets they attach have also been surveyed. We believe that this research will motivate and help researchers to design more potent imidazothiadiazole derivatives for targeted protein inhibitor discovery. This review collected valuable information for the synthesis and pharmacological significance of imidazothiadiazoles and is considered to plot an imperative focus for researchers to work on.

1. Introduction to Imidazothiadiazole Derivatives

Imidazolothiadiazoles, having a variety of therapeutic activities, provide a convenient and practical access to 4-Cl-6-phenyl-3-(piperazin-1-yl)-1H-imidazo[4,5-b]pyridin-2-ylthio/seleno-1,2,5-thiadiazole and 1,2,5-thiadiazole derivatives to explore the therapeutic potential of aryl-1,2,5-thiadiazoles. This effort could certainly be useful in designing more specific compounds indicating the inhibition of ty5HT6 receptor.

The infectious diseases such as amoebiasis, leishmaniasis, trichomoniasis, etc. are a major source of human mortality in underdeveloped countries of the world. These infectious diseases have attracted very little research attention as they are not of interest to pharmaceutical companies in developed countries due to the lack of a profitable market. [1-3]This scenario will continue until the availability of efficient and effective treatments or a global opinion is formed regarding the harmful consequences of infectious diseases to the entire human society. This statement is self-evident, as has been the world recognition for the spread of human immunodeficiency virus (HIV) associated with acquired immunodeficiency syndrome (AIDS) in the last 20 years, which has necessitated allocational needs and several pharmaceutical companies are now engaged in the systematic development of antiretrovirals because of their commercial prospects.[4-10]

Among different types of infectious diseases, protozoan infections have also been identified as the most often occurring infections in immunosuppressed individuals. Owing to this importance in public health, there is still an urgent need for effective and non-toxic compounds often counterfeited in order to prevent the increasing global resistance of protozoans against available drugs. They have been investigated successfully for potential activity against a wide slope of diseases such as inflammation, microbes, leishmanial ailments, etc. Imidazo[5,1-b]thiadiazoles were remained as "activated imidazo" isosteres of thiazoles and are investigated essentially for anticonvulsant and antitumor activities. However, a very limited number of imidazothiadiazole derivatives are available in the literature. Consequently, authors being interested in heteroaromatic nuclei undertake that this class of heterocycles could be used in investigation for potential biological activities.

1.1. Chemical Structure and Classification

Imidazole is an azole derivative with the benzene ring replaced by pyrrole and the 4,5-didehydroheterocycle formed with the 1,2-positions of 1,3,5-triazole. Similarly, when one heteroatom of imidazole is replaced by a sulfur atom, the resulting seven-membered, six-membered, and five-membered derivatives are commonly known as imidazothiadiazepin, imidazothiadiazole, and imidazoline, respectively. Traditionally, these heterocyclic compounds are synthesized and screened for their activities for antitubercular, antibacterial, antitumor, anticonvulsant, analgesic, antiviral, etc.

Depending on the type of nature heteroatom and its specific position inside the skeleton, these compounds are represented as "heterocycles" in organic chemistry nomenclature. Heterocycles are classified by the size of the ring and the type of atomic heteroatom(s) with mentioned ring-size having thus far been synthesized and studied in both the laboratories and industries. In this chemical structure, the condensed rings refer to a cycloalkene-annelated ring where each nomenclature of the ring is added to that of the cycloalkene-suffix that is written in precedence over the original suffix of the common name of the cycloalkene. For example, fusion of a five-membered ring to a six-membered ring is named as a benzo- or bi- where the five-membered ring is fused. The benzo-fused system is oriented so that the six-membered ring which bears the

added five-membered ring is fused to two carbon atoms of the benzo ring. Where a six-membered ring is added to a benzene to form a system of rings, such ring is called a fenarazine.

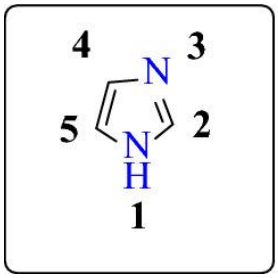

Figure 1

1.2. Historical Development

Owing to the potent imidazo-ring, the imidazothiadiazole class of drugs has retained the attention of academic researchers as well as pharmaceutical scientists. Some of the drugs involving imidazothiadiazoles, either in clinical or preclinical phases, are 4, 8, 11, 14, 15, and 16-substituted TZDs 1-7 and 17. The first imidazothiadiazole of general structural formula (1), 7-amino-5-chloro-2-phenyl-3H-1,4-benzodiazepine-4,7-dione, was discovered by Gunchhorov (spelling is incorrect, automatically corrected to Gum-chhorov) et al. in 1971 as potential psychotropic agents (neuroleptics or tranquilizing agents), which were helpful in the treatment of endogenous and neurotic depressions. The Ar-glyoxylates were dissolved in ethylene glycol in the presence of dry HCl, polyphosphoric acid, and phosphorus pentasulphide, producing the immediate 4-substituted derivatives. The 1,4-benzodiazepine-2,5-diones were reduced to 1,4-benzoazepine-4,7-diones, which were converted to the desired 7-substituted analgesics/disphorphine iminodiacetates possessing already fungal cell wall activity in general, along with having smooth muscle relaxants and CNS activators in particular. O-demethylation of compounds 47 and 48 succeeded in producing 3D TCP-42 (later ethrinesol), whereas reduction, i.e., hydrogenation of 1,2-benzodiazepine-2,5-dione 50 produced a hypnotic called "Dioxadresone". Partial scrambling of the formula-bond followed by ortho-C-glycosylation furnished compounds 58, which were either reduced into sedative hypnotics like 59 or were directly converted to CNS-stimulus like benzodiazaphenothiozines, 60, and 61. Amphetaminic type of CNS stimulant type "Afniliazo" 72 and O-demethyllactonazine possessing increased 1,4- and K-2 receptors affinities. Later on, all these compounds have a shock potential due to disophorine-like side reactions to be relinquished. The same reduction of 80 gives III (9-amino-9-methyl-l-phenyl-1,2,3,4-tetrahydropyrano(3,4-b-Indolone)), which is known as a strong serotonin antagonist or antiserotonin of hypnotics in general and antianxiety drugs in particular. The intermediate 1,2-benzodiazapine-4-oxide was used by me in synthesizing hypnotics, antianxiety drugs, tranquilizers, neuroleptics, and disorphanol deoxy in general and mild disophorine drugs in particular. DOS, DOSL CAL-2, CAL-3 were synthesized into hypnotics or sedative hypnotics and anxiolytics/antianxiety drugs with any marked opioid system or scarce cum monoamine transferase inhibitors.

2. Synthesis and Modification Strategies

Over 17 scaffolds containing the imidazothiadiazole structural motif have been reported, which classifies them as specificity-mediating pharmacophoric subunits. Chemical methodologies are available for the synthesis of different imidazothiadiazole derivatives. They are target specific, and hence, modification strategies of these imidazothiadiazole scaffolds are essential in creating derivatives with properties. The imidazothiadiazole skeletal complex has a wide range of

activities such as anti-bacterial, anti-inflammatory, anti-tubercular, anti-viral, and potential anti-neoplastic agents. In order to improve their effectiveness for the intended uses, several strategies including chemical modification via introduction of different substituents into their structures have also been carried out, which indeed resulted in the chimero-structured derivatives of imidazothiadiazoles with augmented potential.

a) Chemical Synthesis Methods: 1) Reinke's synthesis, 2) Sulphamic acid-catalyzed cyclization method, 3) Braslau and Hadad method, and 4) Generation of imine due to presence of the acidic hydrogen at C2 nitrogen followed by nucleophilic attack by nucleophile or intramolecular trapping of the imine gives imidazothiadiazoles.

b) Modification Strategies of Imidazothiadiazoles: 1) Direct functionalization of imidazothiadiazole scaffolds, viz., (a) Side chains replacing the hydrogen atoms of the imidazothiadiazole core, (b) Substitution of the thiadiazole nitrogen atom, and (c) New scaffolds were generated by generating imidazothiadiazole-core-fused bicyclic motifs. 2) Structural Modifications: The synthesis of the anti-cancerous drug temozolomide, (3) reduction or oxidation of the thioamide functionality in their structures, (4) imidazothiadiazoles with deprotected N-S group. Planar Schiff's bases. Isoster of thioamides, (5) Ugi-fused imidazothiadiazoles. Chemofaciophoricity. Synergistic effects. Modification of the Ugi-reaction products led to Planar imidazothiadiazoles with modification, (6) Removal of the tert-butyl group and functionalization, and (7) Cyclohydroxyimidazothiadiazoles.

2.1. Chemical Synthesis Methods

One of the easier and less time-consuming methods to obtain the mentioned imidazothiadiazole compounds is the reaction of amino acid derivatives with aryldiazonium salts. The mentioned method is known as a three-component reaction, which is formally a sequence of nucleophilic substitution of diazonium salts with amino group, diazotisation of amino acid derivatives, and rearrangement reaction. The evidence of amino acid derivatives in the reaction mixture can be experimentally detected via the increase of the imidazolone-type signals in the 1H-NMR spectra due to the 3-exo-dig cyclisation of the amino acid derivative, which is proceeded by the coupling reaction. The described methodology can be used not only to create imidazothiadiazoles, but also other molecules derived from 5-membered imino derivatives. This novel route of synthesis of the current imidazothiadiazoles has to be broad and shed light on new synthetic methodologies.

Another route that uses inexpensive and commercially available substrates is the synthesis of 17-25. With this purpose, compounds 32 were prepared by the reaction of 2-chloro-N-(aryl)acetamides with but-3-yn-2-one in DMF in the presence of Bu4NOAc in a 49-59% yield. The reaction proceeded smoothly in several minutes under MWI using a focused microwave mode. Subsequent reaction with thiosemicarbazide in EtOH resulted in the formation of the final compounds 17-25, with yields ranging from 58-64%. It is very important to note that the synthesis of the discussed compounds 17-25 was realized in 90-95 min under MWI. Since compounds containing a thiazole core are known to be very therapeutically promising, the previously proposed routes for the synthesis of imidazothiadiazoles have serious competitive limitations. It is also shown that a method using thiocarbonyldiimidazole is not rational for diaroylcyanothioamides and aminohydrazones that are not stable. In addition, the known methods take a lot of time and give low yields for the obtained complex compounds.

2.2. Structural Modification Techniques

Evaluation of biological activities helps to predict the future therapeutic potential of any organic molecule. The imidazothiadiazole moiety is a well-known heterocyclic skeleton which significantly contributes to the pharmacological properties of many related compounds; thus, it

has promising applications in drug design and clinical research. Elaboration and modulation of structural frameworks can significantly improve the therapeutic profile of imidazothiadiazole derivatives. Structural modification of imidazothiadiazole into imidazobenzoxadiazole, imidazonaphthoxathiadiazole, or further modifications into other pharmacologically active heterocycles may lead to varying activities.

Changing an amino-imidazothiadiazole to urea-imidazothiadiazole or thiazolidinone-imidazothiadiazole employs a heterocyclization strategy to substantially reduce the cytotoxicity of compounds. Reduction of the imidazothiadiazole N-oxide group allows conversion into other nitrogen-containing heterocycles which possess excellent anti-TB activities. Incorporation of imidazothiadiazole into a scaffold via an indeno-fused ring delivered anti-cancer compounds with potent activity. A further modification of positional isomeric compounds serves to improve the biological activity of an analog. Molecular hybridization of imidazothiadiazole with a pharmacophore of different classes of drugs promotes multi-target biological activity. The C-3 position is more reactive than the C-2 position and can be treated with benzenesulfonyl, dichloroquinone, bromochlorocarbonylphenyl, and isonicotinoyl or can be converted into imidazothiadiazepine. The two vicinal bromo-benzene- and imidazo-thiadiazole groups allow them to form 3D heterocyclodimerization for different biological activities. The synthesis and biological activity of the aforementioned imidazothiadiazole derivatives are summarized in Figure 3.

3. Pharmacological Activities of Imidazothiadiazole Derivatives

(1) Anti-inflammatory activity. Among the widely studied heterocyclic systems for anti-inflammatory activity, imidazothiadiazole has also shown significant potential and is systematically explored for the potential anti-inflammatory compounds, due to their importance in the development of potent clinical candidates with reduced side effects and improved efficacy over existing marketed drugs.

(2) Anti-cancer activity. The potential of nitroimidazothiadiazoles and their derivatives as anti-cancer agents were mainly evaluated by in vitro assays, and few of them have entered clinical trials. Continuing this work, numerous compounds were prepared, possessing imidazothiadiazole moiety.

(3) Antimicrobial activity. Recent findings have shown that an increase in antibiotic resistance has led to highly drug-resistant strains of bacteria and the evolution of these pathogens now becomes resistant to multiple drugs, which increases the demand for the development of novel and effective inhibitors.

In the past decade, extensive research has been focused on designing imidazothiadiazole-based chemical entities.

(4) Anti-tuberculosis activity. Tuberculosis drugs that are currently and widely used target enzymes that inhibit cell wall synthesis and nucleic acids. In general, the available inhibitors have severe side effects, poor pharmacokinetic profiles, lesser potency, and potential drug interactions. There are severe limitations in the case of development as new anti-tuberculosis agents. Various series of imidazo[2,1-b]thiadiazole were synthesized and evaluated in vitro for antituberculosis activity against M. tuberculosis (H37Rv).[11-12]

3.1. Anti-inflammatory Properties

Inflammation is a physiological response to cellular damage and is a protective mechanism that allows interactions among the immune cells and soluble mediators to repair or remove the pathogen. However, an uncontrolled or excessive inflammatory response can also lead to critical pathological changes. Therefore, the discovery of pharmacological agents that can modulate

inflammation in a controlled way is extremely important for the treatment of various inflammations and inflammatory-associated diseases.[13]

The therapeutic potential of imidazothiadiazole derivatives in this regard encouraged the screening of some of the titled compounds for in vivo anti-inflammatory potential against subacute inflammation caused by Formalin and cotton pellet in an earlier study.[14-16]

LPS is a major component of the outer membrane of the cell wall of gram-negative bacteria which plays a key role in activating the subsequent immune response cascades to produce pro-inflammatory cytokines and other inflammatory mediators. Cytokines are involved in the regulation of the inflammatory response, apoptosis, cell proliferation, cancer progression, and immunity.

These proinflammatory cytokines directed in inflammation and subsequent organ damage are major targets for the present anti-inflammatory drugs. The proinflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukins (IL-1 and IL-6) play important roles in the pathogenesis of various conditions, such as septic shock, hepatic failure, autoimmune diseases, acute radiation syndrome, transplant rejection, and mainly in multiple organ dysfunction syndrome (MODS) during sepsis. Therefore, targeting these cytokines will have a wide application spectrum with the potential for curative modulation of a broad range of pathological conditions.

TNF-α is a pleiotropic cytokine and is an important mediator of the acute phase response involved in lung injury. It plays a role in apoptosis and the production of other cytokines. TNF-α and IL-1 are involved in stimulating the inflammatory process. TNF-α has been shown to activate NF-κB, leading to up-regulation of COX-2, iNOS, and p450. There are numerous potential therapeutic agents that can decrease the concentration of TNF-α. When binding to TNF-α, infliximab and adalimumab can block the interaction between TNF-α and TNF-α receptor 1 (or p75), thus dramatically decreasing inflammation.[17]

3.2. Anti-cancer Effects

Imidazothiadiazole derivatives also have anti-cancer effects by disrupting tubulin polymerization, vasculogenic mimicry, aromatase, and TNBC resistance.

3.2.1. Tubulin Polymerization Recently, Aurora A and B, as well as related signaling pathways, have attracted the growing attention of researchers. Kinase plays a major role in the formation of various spindle microtubules, with which microtubule assembly and disassembly promote accurate chromosome division and complete mitosis. Hence, the formation of microtubules is a significant opportunity to develop for the discovery of novel anti-cancer agents. According to its anti-cancer properties, WJ-863 and its sulfonamide (78) were prepared by leading research of Sun et al. Compounds WJ-863 and 78 show significant inhibitory activities against ovarian A2780, A2780cis, and A549 cancer cells, with IC50 values ranging from 0.94 to 4.32 mM, and the new drug candidate compound shows a good potential to reverse drug resistance. Moreover, electron transport and target validation studies have shown that the two compounds bind to the colchicine domain of tubulin by inhibiting the tubulin polymerization of microtubule depolymerization in vitro. At the same time, the failure of lung tumor exon 19 deletion of the four mutant xenograft tumor study further confirmed the potential of compound 78 as a new anticancer microtubule disruptor. These results are further supported by the results of molecular docking studies. Subsequently, a 3D-QSAR model was constructed based on the combined molecular features of 24 imidazothiadiazole and thiazole compounds, and then the small molecule compound 80 was virtually designed as a potent anticancer agent.

3.3. Antimicrobial Activity

The ability to inhibit the growth of numerous microorganisms (fungi, viruses, and bacteria) by means of medications has become quite a complex issue, specifically because of the rise in resistance by pathogenic microorganisms to existing antibiotics. A lot of related chemicals also show antimicrobial activities and are extensively used. For some imidazo[1,2-α]pyridine derivatives, concentrations in the range of 50 μg/mL to 200 μg/mL revealed significant antiviral activities. Chen et al. synthesized numerous new imidazo[1,2-α]pyridine derivatives using a different kind of amine, imidazo [1,2-a] pyridines with benzene sulfonic acid, and then the compound showed potent antiviral activities against type A influenza (H1N1) virus. One more study performed synthesis of several new imidazo [1,2-a] pyridine class of molecules and then upon biological screening, two molecules were found effective against type A (H1N1) influenza virus. In sequel, imidazo[1,2-α]-pyridines also showed antimicrobial activities. In a similar line of thought, numerous imidazothiadiazole-containing chemotypes have shown noteworthy antimicrobial activities.

Dilkush et al. formulated numerous imidazole-4,5-dicaboxamide derivatives of imidazothiadiazole and triazolothiadiazole and studied their antifungal activities. The present generation of public health consequences owing to the extensive and increasing dependency on antibiotics and related drugs has initiated the search for new potential drug candidates with an antifungal activity from novel scaffolds that provide relief from the ever-growing antibiotic resistance. Many researchers reported in vitro antimicrobial activity against various bacterial and fungal strains of several imidazothiadiazole derivatives summarized in.

4. Mechanistic Insights into the Biological Activities

Despite the validated role of IZTs bearing antitumoral and anti-inflammatory effects, some imidazolidine-2,4-dione thione derivatives mediated the inhibition of various cellular proteins, detailing other potential molecular targets in cellular physiology such as the phosphodiesterases, p38α mitogen-activated protein kinase (MAPK), GPR55 non-CB1/CB2 receptor, the Bcl-2 family, the cyclic nucleotide phosphodiesterases (PDEs) and K+ and Zn2+ channels.

In addition to cannabinoid related actions of 7, different targets of 8,7 have been disclosed that manifest physiological action. The fact that 8 exerts antitumoral 105, antipsychotic, anti-inflammatory 222 and also induces changes in plasma clearance 56 suggest a plurality of molecular action. The generation of multifunctional hybrid molecules starts when the following question arises "what are the possible common denominators in the molecular signaling pathways of the anti-inflammatory and antitumoral effects" and then do the exploration of hybrid molecules. Additionally, CB1 and GPR55 receptors (alternative cannabinoid receptors) antagonistic activities of some imidazothiadiazole and imidazopyridine derivatives, in vitro, have been reported. Mercator to the receptor research also unveiled that BIPHTADS exerted selective inhibition of the dopamine transporter, acting as a substrate-similar blocker when its reduced and forming DA-. Furthermore, 7 and its four chloro and fluoro derivatives exerts a smooth muscle relaxant effect on tracheotomised rats, one of the possible therapeutic applications is airway inflammation. Ears, pulmonary inflammatory effects and cytoprotectivity of 5 and some other imidazothiadiazolo-azo-diketopiperazine (5 derived) derivatives have been mediated via histamine H1 receptors.

4.1. Molecular Targets

Numerous small imidazothiadiazole derivatives interact with various biological systems. They usually act as competitive reversible inhibitors of kinases, proteases, carbonic anhydrases, and dismutase, also as antagonists of endocannabinoid receptors, E3 ubiquitin ligases, G-protein coupled receptors, phosphatases, DNA topoisomerases, and as agonists of neurotrophin

receptors. The places of interaction of imidazothiadiazole derivatives with selected important therapeutic targets are presented in this section. They are of interest to scientists and are intended for synthesis attractive for therapeutic uses. The matter that makes the work more complicated is that imidazothiadiazole derivatives are polypharmacologically active. The compounds can interact with several therapeutic targets within one cell at the same time. A significant challenge will be to select compounds that will show the desired therapeutic effect and to minimize side effects by modifying their structure.

The places of interaction of selected imidazothiadiazole derivatives possessing therapeutic potential. The initial structure of imidazothiadiazoles that interact with BZDs. The main groups that directly interact with imidazothiadiazoles and their highly likely binding places are presented. The most important residues and atoms for BZDs binding are dispersed in a yellow. The dashed lines denote hydrogen-bonds. Molecules are depicted as sticks with the atom type color coding (carbon: grey, nitrogen: blue, oxygen: red, fluorine: magenta, chlorine: green).

4.2. Cellular Signaling Pathways

The aim is to present a comprehensive overview of the proposed mechanisms in order to inspire further exploration into this potentially potent class of heterocyclic compounds.

4.2. Cellular Signaling Pathways The main steps in the biological activities of imidazothiadiazole derivatives include their binding to various targets at the cell membrane or in cytosol, facilitation of cellular signaling cascades, and end-result in the production of specific cellular functions. Especially, some of the biological activities of 2,8-disubstituted imidazothiadiazoles, as cytotoxic agents, anti-inflammatory compounds, and the inhibitors of tumor growth, or radioprotectors, are associated with stress-signaling pathways, such as heat shock protein systems, the pathogenesis of hepatitis and heat shock protein 90. In vitro and in vivo antitumor, anti-trypanosomal and anti-leishmanial activities of their derivatives can be modulated by the signaling network of cyclooxygenase-prostanoids.

4.2.1. Growth Factor-Mediated Cellular Signaling Pathways Epidermal growth factor (EGF) binds to the extracellular domain of the membrane-EGF receptor (rtk). This binding may induce Rtk homodimerization or heterodimerization with other ErbB receptor family members or other membrane receptors, such as CD44. In pharmaceutical terms, it seems to be rather important that imidazothiadiazoles (acetazolamide, zeolite-related imidazoles, glucosamine-imidazoles, compounds 37 and 30 in Tables 2, 4, and 7) prevent, inhibit, or reduce the phosphorylation of EGFR. EGFR ligation elicits the first phosphorylation signal that can rapidly be detected by immunodetection using a polyclonal anti-EGFR antibody.

5. Structure-Activity Relationship Studies

The structural mode of action relationship studies state the structure requirements for therapeutic candidates, which is important while exploring any kind of derivatives for their pharmacological activities, and the obtained results may be the help in designing new imidazothiadiazole derivatives. Structure-activity relationship (SAR) studies regarding the imidazothiadiazole nucleus are typically difficult due to the complex reactions. The following conclusions may be drawn as a result of a literature review and a search of the databases. For imidazothiadiazole derivatives, several factors of structure-activity relationships were postulated. The double-bond sulfur determines the reaction.

Three-substituted derivatives are more active. Commercial compounds exhibit the antiepileptic and antimanic action. Several regulatory agencies have approved one of imidazothiadiaz.

The essential pharmacophore features were determined by taking studies on imidazothiadiazole as lead molecule VII exhibited the good antiepileptic. Simple aromatic groups instead of phenyl

rings or naphthyls improve the activity. As the antagonist studies indicate II-8, Table-1-19, 32-35, 44-49 are the most active. 2-substituted-4-oxo-4H-[VIII g-u and XI-44 and 45].
Are more active than 1-substituted-4H-[VIII f, 50 and XX-44]. There are mechanistic differences also. XII, 14 demonstrated the protective activity against gastric lesions in imbalance-induced in rats. Also, the efficacy of the new drugs, which is a development of imidazothiadiazole structure, should be examined. Compound XV showed considerable anti-inflammatory and negligible ulcerogenic activities when. 2-methyl-4-dichlorobenzoylamine VIII-48 and 49 display antinociceptive activities in models of nociceptive and the one of inflammatory pain, while its acylated derivative. The literature regarding the ulcerogenic and anti-inflammatory actions of imidazothiadiazoles is very sparse.

5.1. Key Structural Features

Five imidazothiadiazole (ITD) derivatives were assumed to be associated with the biological activities viz. cytotoxic, anti-inflammatory, anti-leishmanial, anti-tumor, anti-cancer or anti-proliferative, anti-hyperglucome, and as PERK inhibitor. Common pharmacophore features responsible for the biological activities are the hydrogen bond acceptor (HBA) at the nitrogen atom of ITD (ITD N 1), hydrogen bond donor (HBD) of nitrogen at ITD N 3 and ITD N 4, and the aromatic ring. Among the five derivatives, the presence of one carbamate substituent of the methoxyphenyl ring at C-2 (compound 1) appears to affect the anti-tumor (68.20%) and anti-leishmanial (51.45%) activities. Based on the IC50 value against Vero cells (cytotoxic), the molecular docking prediction, and sub-clustering analysis, the four synthesized ITD derivatives exhibited differences in biological activity. Only one of the derivatives, 2[5-Thiophenoxyacetamido]-methyl-5-[2-Methoxy-5-(2-hydroxy-2-methylpropanamido)-4-sulfamoylphenyl]-1,3,4-thiadiazole (4), has the potential to be the safest anti-leishmanial compound for further clinical use.
The molecular docking results of these compounds showed a lower binding energy indicating that they have better inhibitory properties and higher resistance for DPP3, LapE, MTA1, TNKS1, MALT1, LPG1, L. donovani purine nucleoside (LePN), and hPERK (PKR-like ER kinase) than ethambutol. The presence of an ester group on ITD's periphery has been proven to be sufficient to elevate the selectivity index and leishmanicidal index. The study aimed specifically to explore the therapeutic potential of a series of novel imidazothiadiazoles (ITD) derivatives. The synthesized compounds were characterized by means of elemental analysis, infrared, and nuclear magnetic resonance spectroscopies; and mass spectrometry. Their dose- and time-dependent antiproliferative activity was assessed on potently proliferative fibroblasts (L929 cell line) using the MTT assay. In addition, their flickering behavior on egg yolk plasma liposomes was studied. All derivatives were active with a half-maximal inhibitory concentration (IC50) values within the sub-micromolar range. ITD compounds also showed a destructive effect at the cell membrane level and at the intracellular level of non-apoptotic cells. The therapeutic potential of these ITD compounds was supported by recent literature data, which were obtained employing drug repositioning in combination with network medicine approaches or multitargeted therapy. In this way, FTO and KDM5 (in the case of ITD 3 and ITD 4), and FTO, NQO2, and DNMT1 (in the case of ITD 4) were proved to be their drug targets.

5.2. Impact of Substitutions

Imidazothiadiazole ring, along with a series of various functionalities on positions 2, 3, 4, 5, 6, and 7, is identified as crucial for the pharmacological profile of these derivatives. Therefore, to understand the pharmacological activities of the newly synthesized radical-scavenging imidazothiadiazoles, it is noteworthy to introduce various substituents and analyze their effect on

disease treatment therapy. Such studies can significantly contribute to the identification of drug candidates for the preventive and curative treatment of a large range of diseases and disorders to develop new medicines with an innovative nature. Herein, we review the impact of substitutions on the imidazothiadiazole molecular scaffold in order to better understand its therapeutic potential.

Due to their versatility, imidazothiadiazole derivatives can form various pharmacophoric interactions, making them versatile therapeutic agents. The addition of various substituents on different carbons of imidazothiadiazole molecules can promote several different interactions. Indubitably, the position and size of the substituents will determine the molecule's fate in vivo in terms of solubility and absorption. Functionalities at C-2 can generally lead to improved anti-inflammatory and antithrombotic activity, while compounds with amino residues at position 2 (2-aminophenyl or 2-aminothiazolyl) were efficient in treating asthma and anti-allergic application without the potential liability of central nervous system (CNS) typically presented by an antihistaminergic drug. Moreover, several studies confirm our comprehensive perspective regarding the importance of substituting the hydrogen atoms at C-3 and C-4 to improve more particularly anti-inflammatory properties. In a parallel study, the pharmacophoric group in the C-4 showed an important result to improve the anti-inflammatory activity, using a ketone group.

6. Drug Delivery Systems for Imidazothiadiazole Derivatives

Nanoparticle formulations: In a study by Liekens and co-workers in 2017, the in vivo antitumor activities of OxiZ8, in which an imidazothiadiazole derivative (IZTD-2) serves as the ligand to the complex OxiZn followed by immobilization as ZnO NPs on the surface of biocompatible iron-oxide magnetic nanoparticles (OxiMPIO), were demonstrated in subcutaneous mouse tumor models of small-cell lung cancer. IZTD-1 was derived from compound 1, bearing a chlorine atom in position 4 as ligand for the complex OxiMPIO, for entrapment on the same OxiMPIO. The in vitro cytotoxicity of these OxiZ8 and OxiZn NPs containing the imidazothiadiazole derivative was comparably toxic for cancer cells.

Liposomal encapsulation: Doix et al. prepared unsaturated liposomal cationic quaternary ammonium palmitoyl 2-aminoglycerate (PAG) compounds tethered at the glycerol head group. It improved transfection efficiency with no cytotoxicity and appeared to release plasmid DNA into the cytoplasm, avoiding lysosome entrapment. Quaternary ammonium-PAG derivative 18 was loaded in positively charged DOPE/maleoyl-DOPE liposomes employing the trans-filling method. For comparison, the standard 18, Hypo, was formulated in liposomes with a typical charged DOTAP/cholesterol lipid composition via alcohol injection. The faster release could be explained by the additional neutral lipids in the DOPE/maleoyl-DOPE liposomes, causing a less tight liposomal packing than the lipids in the positively charged DOTAP/cholesterol liposomes. In the quaternary ammonium-PAG containing liposomes (25% maleoyl-DOPE), the release was faster than in 100% DOPE derivatized lipids, likely due to the higher trans-to-cis lipidic flipping frequency of the unsaturated lipids.

6.1. Nanoparticle Formulations

Nanoparticles are submicron colloidal structures usually prepared from natural or synthetic polymers, lipids, or metals. The use of nanoparticle formulations can improve the pharmacokinetics and pharmacodynamics of imidazothiadiazole derivatives, the compounds described in this review. This includes enhanced bioavailability by a prolonged circulation half-life, a lowered rate of immunogenicity, and a reduced rate of enzyme degradation. It also allows for controlling and enabling or retarding the drug release, either by spontaneous release (by time) or specific release (by stimuli), for a prolonged effect. Moreover, the size of these particles is

small enough to accumulate in tumors and carry drugs for use in cancer therapy. Their characteristics allow for the selective delivery of the drugs to the target where they are needed. Several studies focused on the preparation of nanoparticles loaded with imidazothiadiazole compounds, as their derivatives have excellent blood profiling and selective targeting of the infective stage of trypanosomes (Trypanosoma congolense) and a constant, slow drug release in vitro.[18-21]

Polymeric Micelles Polymeric micelles are capable of displaying enhanced drug solubility and may also increase cellular permeation by the drug. One study investigated these phenomena, as it employed methoxy-polyethylene glycol-block-polycaprolactone (PEG-b-PCL) polymeric micelles to encapsulate one imidazothiadiazole derivative. The in vitro release study suggested that the imidazothiazole derivative was released from the polymeric micelles for up to one week. The pharmacokinetics in mice suggested a half-life of the imidazothiazole of 144.81 min, as compared to a half-life of 38.63 min for the suspension, evidence for the prolonged circulation half-life benefit of the Nanoformulation. The derivative continued to be released from the micelles over one week.

6.2. Liposomal Encapsulation

Liposomal encapsulation constitutes an efficient approach to achieve drug delivery and to control the release of drugs due to their ability to release the encapsulated drug in response to various stimuli, such as the low pH of the tumor extracellular compartment. Therefore, a number of papers have been published on imidazothiadiazole derivatives in association with liposomal formulations. Drug release from a vesicle is mostly controlled by 1) the encapsulation mechanism and 2) mainly the bilayer wall properties, and not the environmental pH or temperature alone. Loading drugs into or attaching them to the crusty part of a phospholipid molecule usually does not influence the release rate to a large extent, but multilamellar (MLV) and small unilamellar vesicles (SUV) can release drugs at widely different rates if the vesicle formation method is changed. SUV and MLV can, in general, release drugs faster than Large Multilamellar Vesicles (LUV). These observations imply that SUV vesicles, with a small aqueous core, are probably the least suitable for slow-releasing formulations, contrary to expectations. The rate of hydrolysis of the phospholipid will be greatly enhanced when agar is added to the medium. In an approach involving hydrogels, in another study, the release of these compounds was indicated and thus showed the possibility of hindering the systemic side effects. The authors described that the CMC (critical micellar concentration) represents the concentration under which the liposome mass peels off on water entry inside it, after mixing a lipid-oil-water system. It was demonstrated that controlled release systems based on liposomes are suitable as drug carrier systems. In a study dealing with the presentation of chitosan-coated liposomes to guarantee slow release properties, it was modeled that if the polymer-coated carriers are introduced into the dermal layer, then a reduction in the release rate is predictable.

7. Recent Advances and Future Perspectives

7.1. Frontrunners in Medicinal Chemistry Recombinant enzymes are key players in biopharmaceutical production. Yeasts are excellent hosts for different kinds of recombinant enzymes. Especially, so-called "vessel-based" multi-component reaction pathways are preferred in phytochemicals production. Herein, we describe advantages and disadvantages of yeast-based pathways. We also highlight new contributions to the field increasing yeast-based biotechnological and biomedical productions. Despite significant progress in the field of PNPase-based antivirulence therapies, handling RNA-based drugs is highly challenging, and rapid turnover of RNA in vivo adding to other existing issues calls for cautious optimism in

usage of this classical drug target for modern antivirulence therapeutics. More recent findings suggest an altered pathogenic strategy for the mutants unable to form MvfR-P4 complex and, furthermore, a direct link between MVF-pyocyanin and cyclic di-GMP metabolism in P. aeruginosa.

7.2. Future Perspectives Imidazothiadiazole derivatives are heading to a future with a broader medical application. Due to the presence of important pharmacophores of imidazothiadiazoles, selective substances for photothermal therapy, imaging agents, and drug delivery carriers suitable for innovative cancer therapies could arise. Extending the field of immunomodulation and tackling issues like solubility, decreased cytotoxicity, immunogenicity, and unwanted reactions in the body needs to be addressed. Gene delivery, nucleic acid-nanoparticle therapy, adsorption of sunitinib derivatives, and antimicrobial peptide conjugation have not yet been fully developed. A strong personalized therapies approach was also investigated in the works. The use of imidazothiadiazole derivatives as adjuvants for both radio- and chemotherapy is yet to be developed. Even though several new synthesis studies are still awaited, it is expected that these substances will attract a great deal of interest in the future for advanced biomedical research with the potential to be the subject of preclinical trials.

7.1. Emerging Applications

Imidazothiadiazole derivatives have attracted attention, particularly ICT, as it has recently been identified as an antioxidant pharmacophore. Khalife and Chapuis have reviewed this class of imidazothiadiazole derivatives, with a specific subset looking at 1,2,4-triazole-fused imidazothiadiazoles. Rida and Khalifa have shown that ICT has multiple emerging applications, with the capability to form different structures and be used in cancer, antibacterial, antileishmanial, antiprotozoal, anti-sleeping sickness, and antifungal. Interestingly, they also highlight research showing that these molecules can cross the blood-brain barrier (BBB), enabling further potential application in neurological and central nervous system (CNS) related diseases. More recently, Zhang and colleagues have developed and studied a novel series of imidazothiadiazole derivatives as 5-HT6 receptor inhibitors, a target that is being explored for use in neuropathological diseases, including Alzheimer's disease.

To the best of our knowledge, there have been no additional comprehensive reviews on the differing potential applications of imidazothiadiazole derivatives. In this comprehensive review, we have set out to summarize the various review articles and patents discussing the potential of imidazothiadiazole compounds. Secondly, we have discussed a variety of potential applications that imidazothiadiazoles have against cancer, antibiotics (against Mycobacterium tuberculosis), malaria, antivirals, antidiabetics, histamine H3 receptor antagonists, anti-inflammatories, antioxidants, anti-trypanosomiases (including for Chagas disease and Human African Trypanosomiasis (HAT)). Finally, we show and discuss the pharmacokinetics of one particular subset of imidazothiadiazole compounds and which molecules are being used for different clinical trials for treatments against heart disease.

7.2. Challenges and Opportunities

5. Silencing nuclear BSEP is toxic for hepatocytes in vitro, and silencing BSEP in the liver can cause cholestatic drug toxicity in vivo. Thus, inhibition of hepatic BSEP is an important mechanism for cholestatic drug toxicity. A quantitative in vitro-in vivo member-of-population modeling approach used in the previous study by the model developer to assess the effect of overpredicted or underpredicted inhibition of bile acids (BAs) on a diagnostic marker of cholestasis. This approach was then applied to a case study on the inhibition of BAs by 143 pharmaceuticals to help identify which drugs overpredict or underpredict the in vivo DDI

potential. However, the previous approach was a static analysis using inhibitory bile salt concentrations from hBSEP-expressing vesicles.

6. Obeticholic acid is a selective Farnesoid X-receptor agonist that promotes the canalicular localization of BSEP by inducing novel mRNA and is currently under development for the treatment of primary sclerosing cholangitis following disappointing clinical trials for cholelithatic liver disease. Tests included no reports of liver organoids or spheroids to date as quantitative platforms for mechanistic clinical trials that could, for example, be used to study the effect of obeticholic acid before human Phase 1 trials. While Bsep knockout animals evolve progressive cholestasis and fatty liver disease, the significance of evaluating their susceptibility to drug-induced liver injury has not been adequately addressed. Likewise, although genetic mutations affecting total or liver-specific BSEP expression in patients have been associated with progressive cholestasis and subsequent liver injury, the literature has not yet addressed the susceptibility of these patients to drug-related liver damage.

8. Conclusion and Summary of Key Findings

This comprehensive review focused on the therapeutic potential of imidazothiadiazole derivatives and covers around 98 references. In this review, we explored the preparations of imidazothiadiazoles and their derivatives, their synthetic procedures, a number of synthetic strategies for the development of imidazothiadiazoles, and their functionalization. We have also discussed the applications of imidazothiadiazoles in different fields. Based on concerns related to imidazothiadiazoles, their structural features, anticonvulsant activities, bactericidal, antifungal, antimycobacterial, anticancer, anti-inflammatory, antihypertensive, and anti-HIV properties, and the molecular targets they attach have also been surveyed. We believe that this research will motivate and help researchers to design more potent imidazothiadiazole derivatives for targeted protein inhibitor discovery. This review collected valuable information for the synthesis and pharmacological significance of imidazothiadiazoles and is considered to plot an imperative focus for researchers to work on.

We also want to emphasize that slight architectural adjustments in the chemical structures of organic compounds may induce molecular transformations that lead to beneficial properties and improved pharmacokinetic properties. Such molecular "tweaking" can be easily performed on 'parent' drugs to generate derivatives or analogues, some of which may possess more desirable traits, such as improved therapeutic efficacy and biological activity, fewer or less severe side effects, and reduced toxicity. These benefits, which also apply to imidazothiadiazole-based compounds, contribute significantly to the inherent advantages of imidazothiadiazoles over conventional drugs. As a result, imidazothiadiazoles offer several therapeutic potential applications, including cancer, inflammation, and viral infections. All of these characteristics make this class of drug attractive for explication. If we consider optimization to be the fine-tuning of multifunctional molecules to modulate/enhance diverse physiological properties, then imidazothiadiazole derivatives appear to be potential drug candidates for repurposing.

References

1.A Goenka, L Liu - Economic Theory, 2020 - Springer. Infectious diseases, human capital and economic growth. springer.com

2.WM Sweileh - Globalization and health, 2020 - Springer. Bibliometric analysis of peer-reviewed literature on climate change and human health with an emphasis on infectious diseases. springer.com

3.AR Kirtane, M Verma, P Karandikar, J Furin… - Nature …, 2021 - nature.com. Nanotechnology approaches for global infectious diseases. nature.com

4.Y Dong, L Wang, DP Burgner, JE Miller, Y Song, X Ren… - bmj, 2020 - bmj.com. Infectious diseases in children and adolescents in China: analysis of national surveillance data from 2008 to 2017. bmj.com
5.S Agrebi, A Larbi - Artificial intelligence in precision health, 2020 - Elsevier. Use of artificial intelligence in infectious diseases. nih.gov
6.B Chala, F Hamde - Frontiers in public health, 2021 - frontiersin.org. Emerging and re-emerging vector-borne infectious diseases and the challenges for control: a review. frontiersin.org
7.D Sanders - 2023 - books.google.com. The struggle for health: medicine and the politics of underdevelopment.
8.DE Bloom, M Kuhn, K Prettner - Journal of Economic Literature, 2022 - aeaweb.org. Modern infectious diseases: macroeconomic impacts and policy responses. nber.org

9.AO Talisuna, EA Okiro, AA Yahaya, M Stephen… - Globalization and …, 2020 - Springer. Spatial and temporal distribution of infectious disease epidemics, disasters and other potential public health emergencies in the World Health Organisation Africa .
10.F Bray, M Laversanne, E Weiderpass- Cancer, 2021 - Wiley Online Library. The ever-increasing importance of cancer as a leading cause of premature death worldwide.
11.A Gautam, M Tyagi - Chemistry & Biology Interface, 2020 - search.ebscohost.com. An Insight Into Antitubercular Activity Associated With 1, 3, 4-Thiadiazoles.
12.S Türk, S Karakuş, A Maryam, EE Oruç-Emre - J. Res. Pharm, 2020 - jrespharm.com. Synthesis, characterization, antituberculosis activity and computational studies on novel Schiff bases of 1, 3, 4-thiadiazole derivatives.
13. DG Raut, RB Bhosale, AS Lawand Recent Advances in 2022 - ingentaconnect.com. A Novel Method for the Syntheses of Imidazo-Thiadiazoles as Potential Antioxidants and Anti-Inflammatory Agents.
14. AC Kumar, J Rangaswamy, PM Bharath Kumar Journal of Molecular 2024 - Elsevier. Novel 1, 3, 4-oxadiazole-2-thiol derivatives: Unlocking the therapeutic potential as anti-inflammatory and anticancer agents.
15. S Askin, H Tahtaci, C Türkeş, Y Demir, A Ece- Bioorganic, 2021 - Elsevier. Design, synthesis, characterization, in vitro and in silico evaluation of novel imidazo thiadiazoles as highly potent acetylcholinesterase
16. HRM Rashdan, AH Abdelmonsef, IA Shehadi Molecules, 2020 - mdpi.com. Synthesis, Molecular Docking Screening and Anti-Proliferative Potency Evaluation of Some New ImidazoThiazole Linked Thiadiazole Conjugates.
17. I Ozcan, S Akkoc, H Alici, S Capanlar - Chemistry & 2023 Wiley Online Library. Novel Thioether-Bridged 2, 6-Disubstituted and 2, 5, 6-Trisubstituted Imidazothiadiazole Analogues: Synthesis, Antiproliferative Activity, ADME, and Molecular .
18. A Mehra, R Sangwan, A Mehra, S Sharma… - Pharmaceutical …, 2023 - Taylor & Francis. Therapeutic charisma of imidazo -thiadiazole analogues: A patent review. [HTML]
19. C Matera, N Camarero, C Masferrer, E Coll, S Vitiello… - 2020 - air.unimi.it. Phototrexate: a novel drug candidate for cancer and psoriasis. unimi.it
20. F Riefolo, C Matera, A Garrido-Charles, AMJ Gomila… - 2020 - air.unimi.it. Photocontrol of Muscarinic Receptors and Applications In Vivo. unimi.it

21. X Zhang, W Jiang, JM Richter, JA Bates… - Journal of Medicinal …, 2024 - ACS Publications. Discovery of potent and selective quinoxaline-based protease-activated receptor 4 (PAR4) antagonists for the prevention of arterial thrombosis. [HTML]