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Synthesize Characterize and Biological Evaluation of Imidazole Derivatives

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I. INTRODUCTION

Imidazole was first found in the 1840s, and since then, there has been an explosion of research and development on compounds that are based on imidazole. This is due to the fact that imidazole has a wide variety of applications, including pharmaceutical drugs, agrochemicals, ligands, and synthetic acceptors, catalysts, and so on. Compounds based on the imidazole ring hold a unique position within the realm of therapeutic medications. Numerous imidazole derivatives are currently playing an important part in the treatment of a wide range of illnesses, and researchers are actively pursuing the development of new imidazole derivatives that have potential medical uses. Because of its unique structural characteristics, the imidazole ring is able to interact with a wide variety of enzymes and receptors in biotic organisms. These interactions can take place via ion-dipole, hydrogen bonds, – stacking, coordination, cation–, van der Waals forces, and other mechanisms. The presence of an imidazole ring in several essential biological components, such as deoxyribonucleic acid (DNA), histamine, vitamin B12, and haemoglobin, is thought to be the driving force behind the diverse array of biological activities exhibited by imidazole derivatives. Because it is an isostere of many different types of physiologically active compounds, such as triazole, oxazole, pyrazole, thiazole, tetrazole, and amides, it is commonly utilised in the design and synthesis of these types of molecules.

Imidazoles are a class of heterocyclic aromatic organic compounds. Natural products, including alkaloids, feature an imidazole ring. The fundamental structure of imidazole is represented by the chemical formula C3H4N2, as illustrated in Figure 1. Imidazoles are a class of organic compounds that are alternatively referred to as diazoles, characterized by the presence of two nitrogen atoms that are not adjacent to each other. The presence of a ring system can be observed in various biological building blocks, including but not limited to histidine, related histamine hormones, nucleic acid, and biotin, as depicted in Figure 2. Imidazole exhibits amphoteric behavior, functioning as both a base and a weak acid. This is exemplified in nitroimidazole. The compound exists in two tautomeric forms, wherein a hydrogen atom oscillates between the two nitrogens [1-5].

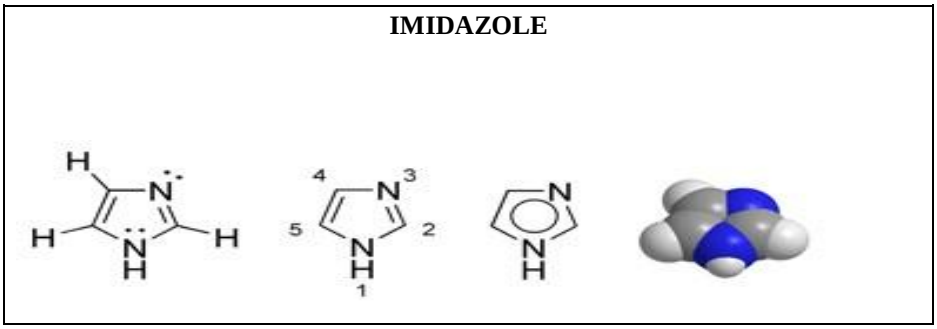

Figure 1:Structure of imidazole

Imidazole derivatives have gained significant importance in the medical field. Researchers have focused on designing novel imidazole derivatives with distinct structures and biological activities, as well as developing new methods of synthesis. These derivatives have also played a crucial role in the identification, development, and understanding of their molecular mechanisms of action [6-10].

II. STATEMENT OF PROBLEM

The development of resistance in patients to currently available treatments is increasingly becoming a significant issue on a global scale. One of the most important priorities for research in the current climate is figuring out how to come up with novel chemical combinations that can overcome the resistance that has developed. Compounds that contain a thiadiazole nucleus exhibit a diverse range of pharmacological activities,

including those that are anti-microbial, anti-tubercular, anti-leishmanial, anti-inflammatory, analgesic, CNS depressant, anti-convulsant, anti-cancer, anti-oxidant, anti-diabetic, molluscicidal, anti-hypertensive, diuretic, and analges In the pharmaceutical and agrochemical industries, 1,3,4-thiadiazole compounds have shown to possess a diverse range of biological characteristics. A new acylated 5-thio—D-glucopyranosylimino-disubstituted 1,3,4-thiadiazole that was prepared by cycloaddition of the glycosylisothiocyanate with reactive intermediates such as 1-aza-2- azoniaallenehexachloroantimonates is being tested in vitro for its antiviral activity against HIV-1, HIV-2, and human cytomegalovirus (HMCV). Within the realm of plant protection technologies, there has been an increased emphasis placed on research to identify more effective pesticides with which to deal with newly emerging issues.

III. RESEARCH OBJECTIVES

1. Study on Chemical synthesis, characterization of 4,6-substituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives, and their potency in inhibiting cancer tumour cell invasion and potentiating the apoptotic by abrogating NF-B activationeffect of TNF cascade were performed.
2. Study on Chemical synthesis and characterisation of 2-(2-butyl-4- chloro-5-formyl-1H-imidazole-1-yl)-Nphenylacetamide derivatives, as well as determination of their ability to inhibit cell proliferation and induce apoptosis in human cervical cancer cell lines for testing purposes.
3. Study on Chemical synthesis, characterisation of substituted 1,2,4-triazole-3-thiol derivatives, and their potential as dual Akt / mTOR inhibitors. These inhibitors decrease Akt / mTOR pathways in hepatocellular carcinoma, which slows growth and promotes apoptosis.
4. Study on Chemical synthesis, characterization of 4,6-substituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives, and their potency in inhibiting cancer tumour cell invasion and potentiating the apoptotic by abrogating NF-B activationeffect of TNF cascade were performed.
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6. Study on Chemical synthesis, characterisation of substituted 1,2,4-triazole-3-thiol derivatives, and their potential as dual Akt / mTOR inhibitors. These inhibitors decrease Akt / mTOR pathways in hepatocellular carcinoma, which slows growth and promotes apoptosis.

IV. RESEARCH METHODOLOGY

In the following, a synopsis of the synthesis of a series of 4, 6-substituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives is shown. 3(a-m) via the reaction of amino thiol with a variety of aromatic carboxylic acid while phosphorous oxychloride was present, and then structurally characterising the resulting compound. One of these, the 5-(3-(2,3-dichlorophenyl)-[1,2,4]triazolo[3,4-b] compound, is particularly intriguing. [1,3,4]thiadiazol-6-yl)-2- fluorobenzonitrile (3f) greatly amplified the apoptotic impact of TNF and prevented cellular migration as well as invasion in cervical cancer cells by decreasing NF-B activation. These effects were achieved by inhibiting NF-B activity. In particular, 3f inhibited the time-dependent phosphorylation of upstream IB kinase, which resulted in the inhibition of p65 activation and nuclear translocation in tumour cells.

The impact of 2-(2-butyl-4-chloro-5-formyl-1H-imidazole-1-yl)-N-phenylacetamide derivatives on the inhibition of growth 5(a-j) on human cervical cancer cell lines, the MTT assay was performed, and interestingly, one of the tested compounds, 5d, inhibited cell proliferation in a concentration-dependent manner in both the Caski and SiHa cell lines in comparison to the normal HaCaT cell. This was observed in both of the Caski and SiHa cell lines. The IC50 value of 5d against SiHA was 31 nM, whereas the value against Caski was 35 nM, and the value against HaCat was 50 nM. The other substances that were examined did not demonstrate any meaningful effects. 5d caused apoptosis in human cervical cancer cell lines in a manner that was dependent on both concentration and time. Caski, SiHa, and HaCaT cells were given 10 M concentrations of 5d for a period of 24 to 72 hours. In a concentration and time dependent manner, it was discovered that 5d treated Caski and SiHa cells caused a considerable rise in the number of cells in the sub-G1 phase. On the other hand, the impact is negligible on immortalisedHaCaT cells.

A novel series of 4-amino-substituted-4H-1,2,4-triazole-3-thiol derivatives 7(a-j) was synthesised and their structural characterisation was described in this paper. It was determined whether or not these chemicals had an anticancer impact. It is interesting to note that one of the derivatives, 4-(4-fluoro-3-nitrobenzylideneamino)-5-(2, 3-dichlorophenyl)-4H-1,2,4-triazole-3-thiol (7i), has the ability to inhibit activation of both Akt and mTOR kinases in human liver cancer cells, in addition to suppressing proliferation and inducing apoptosis. In tumour cells, we discovered that 7i was able to block the activation of a signalling cascade involving PI3K/Akt/mTOR.

V. RESULT AND FINDINGS

The content describes a study on molecular docking and QSAR analysis of imidazole derivatives. The study focuses on evaluating the efficacy of Cdc2 like kinase (CLK1) inhibition in inducing autophagy, a cellular process that involves the selective removal of damaged organelles and proteins. CLK1 inhibitors are being explored for the treatment of autophagy-related diseases such as cancer, diabetes, neurodegenerative diseases, and organ injury.

In the molecular docking studies, the researchers utilized the Schrodinger software with the GLIDE XP protocol, known for its high accuracy in docking and enrichment across various receptor types. The ligands were prepared and minimized using Ligprep, while the protein was prepared and minimized using the Preparation wizard from the Protein Data Bank (PDB). The active site of the protein was identified based on hydrogen bonding interactions. Grid formation was performed using AutoDock, and docking studies were conducted on 15 compounds. The docking scores were based on hydrogen-bonded residue and hydrophobic interactions.

The results of the docking study showed that ligand P2 exhibited the highest binding score with CLK1 protein, followed by P1, P3, and P5. Ligand P2 formed a hydrogen bond with LEU 244, indicating a favorable binding affinity. Based on these findings, ligand P2 was identified as a potential candidate for further development of novel anticancer agents.

The study also involved QSAR analysis, which establishes a mathematical model correlating the biological activity of a compound with its physicochemical properties. A multiple linear regression-based QSAR tool was used to generate QSAR equations and calculate correlation coefficients, standard deviation, and variance ratios. The quality of the QSAR equation was assessed using various parameters such as r2, r2adj, Q2, and RMSE. Outliers were identified based on the discrepancy between observed and calculated activities.

The QSAR analysis identified a correlation between the activities of the compounds and physicochemical, electronic, and steric parameters. The final QSAR equation included lipophilic parameter ClogP and steric parameter MR. Lipophilicity was found to facilitate the penetration of the molecule across the cell membrane, while bulkier groups were involved in steric interactions. The QSAR model provided insights for the design of new substituents with high ClogP values.

In addition to the docking and QSAR studies, the content briefly mentions the synthetic procedure of preparing imidazole derivatives. It also describes preliminary studies conducted on the reactants and products, including determination of melting point ranges, thin-layer chromatography analysis, and solubility studies.

The study explored the potential of CLK1 inhibition in inducing autophagy and identified ligand P2 as a promising candidate for further development. The QSAR analysis provided insights into the relationship between compound activities and physicochemical properties. The content also briefly mentioned the synthetic procedure and preliminary studies conducted on the synthesized compounds.

VI. CONCLUSION

In this study, a set of imidazole derivatives (SP1-SP11) was synthesized using ZnOnanorods as catalysts. A one-pot synthesis approach was employed to increase the percent yield of the compounds. Docking studies were performed to understand the drug-receptor interaction of the synthesized compounds. Molecular docking using Glide XP was conducted against CLK1, a drug-target protein. Four derivatives showed a strong affinity towards CLK1, with SP1 exhibiting the highest activity and affinity. CLK1 isoforms are involved in mRNA splicing.

Quantitative Structure-Activity Relationship (QSAR) analysis was performed on the chemical compounds. QSAR involved using suitable descriptors to establish an optimal equation to determine the lipophilicity (ClogP) of the compounds. Lipophilicity affects a compound's ability to penetrate and be absorbed as a drug. Compound SP1 showed higher lipophilicity due to its relatively small chlorine substituent. A validated 2D-QSAR model predicted the potency and penetration of compounds with small sizes. The synthesized compounds were analyzed using spectral techniques such as 1H, C13 NMR, and mass spectroscopy.

The antimicrobial properties of the compounds were evaluated against Bacillus subtilis (Gram-positive) and Escherichia coli (Gram-negative) bacteria. Compound SP1 demonstrated activity against both types of bacteria at varying concentrations and was compared to the standard reference amoxicillin.

The anticancer activity of the compounds was determined using the MTT assay method. The percent viability of the compounds was calculated, and the LC50 value was computed to determine cytotoxicity. Compound SP1 showed an LC50 value of 10.0105 µg/ml. Based on the results, the synthesized compounds exhibited antibacterial and anticancer properties.

In summary, the study synthesized imidazole derivatives using ZnOnanorods, performed docking studies to understand their drug-receptor interaction, and conducted QSAR analysis to determine their lipophilicity. The compounds showed antimicrobial activity against Gram-positive and Gram-negative bacteria

and demonstrated anticancer properties.

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