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Synthesis and Characterization of Elucidating the Structure of the Heterocyclic Compounds Showing Antiamoebic Activities

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Abstract - There is a need to use certain cutting-edge 1D and 2D NMR methods due to the growing complexity of natural chemicals and their synthesized related counterparts. The primary goals of this work are to (1) explain the most important 1 H, 13C, and 15N NMR properties of three- to six-membered heterocyclic compounds, and (2) explore the use of many 1D and, more importantly, 2D NMR methods in the structural elucidation of these compounds. Element studies, UV, IR, 1H, and 13C NMR, and ESI-MS spectrum data were used to determine the structures of the compounds. Antiamoebic activity against Entamoeba histolytica was measured in vitro and compared to that of the standard antiamoebic medication, metronidazole. The IC50 values for E. histolytica were found to be lower for 10 of the 30 compounds tested for antiamoebic action (compounds 5, 6, 15, 18, 25–30). Preliminary findings suggested that the antiamoebic action was improved when the phenyl ring at position 3 of the pyrazoline ring was replaced with either 3-chloro or 3-bromo.

Keywords - Pyrimidine; sulfonamide; Entamoeba histolytica; Cytotoxicity, Heterocyclic azoles, inhibitors, SARS-CoV-2.

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INTRODUCTION

The role of heterocyclic compounds in biological activity has grown in recent years. Oxygen, nitrogen, sulfur, and other common hetero atoms form rings in heterocyclic compounds Many chemicals, including alkaloids, antibiotics, amino acids, vitamins, hemoglobin, hormones, and a great many synthetic medications and colors, rely on heterocyclic compounds, which are common in nature and in a broad range of man-made compounds. Heterocyclic compounds owe much of their biological action to the shape of their molecules. Due to their therapeutic efficacy, heterocyclic compounds, especially those with five or six members, have recently attracted the interest of the pharmaceutical industry. To a similar extent, heterocyclic molecules with nitrogen, Sulphur, and oxygen as hetero atoms are useful in the development of new pharmaceuticals. Triazole and other five-membered ring heterocyclic compounds. These could have a 1, 2, or 3-triazole structure. Furan and pyran, two examples of oxygen-containing heterocyclic compounds with five and six members, respectively. Vitamin B6 (pyridoxine), a derivative of pyridine, is crucial for amino acid metabolism and is found in all members of the vitamin B group.

Worldwide, tuberculosis is the top cause of death for young people, women, and AIDS patients. While there have been significant advances in the development of effective anti-tubercular medications, the usage of existing therapies as a single agent has led to the emergence of drug resistance The use of combination regimens helps prevent the spread of this resistance. Drug resistance will undoubtedly remain a concern in the future Therefore, novel compounds with antitubercular action are urgently needed for TB treatment. Evidence suggests that several heterocyclic compounds with five members have promising biological action. Compounds with a 1,3,4-oxadiazole nucleus are very useful in pharmaceutical research. There is evidence that these chemicals have potent anti-tubercular action. There is a pressing need for advances in environmentally friendly synthetic methods right now. Because of its usefulness, 1,3,4-oxadiazole has been the subject of several discussions in the scientific literature. When compared to multi-step conventional synthesis, which generates significant amounts of environmentally hazardous waste due to a series of complex isolation procedures involving expensive and toxic solvents after each step, organic synthesis utilizing electrochemical techniques using suitable solvent & electrolytes is fundamental to clean synthesis. In recent years, multicomponent reactions with useful features like atom economy design of reaction have emerged as an effective and

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potent tool in contemporary synthetic organic chemistry.

The study of heterocyclic compounds is crucial in the field of chemistry. Carbocyclic compounds are cyclic compounds made up entirely of carbon atoms arranged in rings. A review of the available literature indicates a vast repertoire of heterocyclic compounds. In addition to being ubiquitous in the molecules that make up living organisms, heterocyclic compounds—those with a hetero atom in a ring system—make up the bulk of many natural products and are the building blocks of nucleic acids like DNA and RNA. DNA is undeniably the most crucial macromolecule in the whole kingdom of life [29, 30]. Chlorophyll and, by extension, the oxygen carriers in plants and animals are both derivatives of huge porphyrin rings, as are nucleotides, the building blocks of human DNA.

Heterocycles are a significant class of chemicals since they account for almost half of all organic compounds. Antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, anti-microbial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents are all examples of drugs containing heterocycles. They are also an important building block in the synthesis of drugs and agricultural compounds.

LITERATURE REVIEW

Saba Tariq, (2018) To find new ant amoebic scaffolds that are more effective than metronidazole (IC50 = 1.80 M) against the HM1: IMSS strain of E. histolytica, quinazolin-4(3H)-one Schiff base conjugates were produced and tested. Thirteen compounds (S2-S14) were tested for their ability to suppress the growth of HeLa cells, a cervical cancer cell line. Of these, six compounds (S2, S3, S4, S5, S6, and S11) were shown to be more effective inhibitors than metronidazole. Studying the crystal structure of the intermediate compound S1 validated its structure.

Shahad A. Jarallah, et.al (2019) New 2-methylquinazolin-4(3H)-ones were synthesized with improved yields, and their potential antibacterial properties were investigated. These compounds include biphenyl derivatives (A1-A12). The spectrum data [FTIR, 1H-NMR] and physical characteristics of the produced compounds were used to verify their structures. The agar well diffusion technique was used to determine their antibacterial1 efficacy. Some of these compounds were shown to have superior antibacterial properties than those of conventional antibiotics.

Lotfi M. Aroua, et.al (2023) Schiff base ligand (H2L) (1) is produced by condensing (1H-benzimidazole-2-yl) methenamine with 2-hydroxy naphthaldehyde. Metal salts (ZnCl2, CrCl36H2O, and MnCl24H2O) were subsequently reacted with this to yield the matching metal complexes. Results from tests of biological activity show that the metal complexes are effective against Escherichia coli and Bacillus subtilis but only moderately effective against Aspergillus niger. Mn (II) complex was found to be the most potent cytotoxic agent against human cell lines of colorectal adenocarcinoma HCT 116, hepatocellular carcinoma HepG2, and breast adenocarcinoma MCF-7 in an in vitro study, with IC50 values of 0.7, 1.1, and 6.7 g, respectively. This allowed the Mn (II) complex and ligand to be docked within ERK2's energetic region, where they displayed binding-favorable energy. Biological experiments on mosquito larvae reveal that Cr (III) and Mn (II) complexes are highly toxic to Aedes aegypti larvae, with LC50 values of 3.458 and 4.764 ppm, respectively.

Abdelhamid, et.al (2019). The biological actions of pyrazolines vary. The study of the chemistry of hydrazonoyl halides has recently seen a resurgence in popularity. One of the most frequent heterocyclic pharmacophores with diverse biological functions is 1,3,4-thiadiazole.Two, five-furan-2-yl, three-p-tolyl ethyl2-(5-(furan-2-yl)-3-(p-tolyl)-4-methyl-thiazole-5-carboxylate, -4,5-dihydro-1H-pyrazol-1-yl-4,5-dihydro-1H-pyrazol-1-yl)combination of thiazol-4(5H)-one and 1-(2-(5-(furan-2-yl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-4-methylthiazol-5-yl)5-(furan-2-yl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide was reacted with several halogenated chemicals to produce ethan-1-one. Derivatives of thiazole, 1,3,4-thiadiazole, and pyrano[2,3-d] thiazole were also produced. Element analysis, spectrum data, and, where feasible, alternate synthetic pathways were used to determine the structures of the newly synthesized compounds. Antimicrobial activity was also tested for in the newly synthesized compounds against a wide range of bacteria.Using hydrazonoyl halides as precursors, a new series of novel functionalized 1,3,4-thiadiazoles, 1,3-thiazoles, and pyrazoline-containing moieties were synthesized and tested for in vitro antibacterial and antifungal activity. Results from testing these compounds' antibacterial efficacy were encouraging, and several derivatives showed activity levels comparable to the cited references.

V. Asha Kumar et.al (2018) Four novel 2,4-dihydroxybenzaldehyde-4-phenyl-3-thiosemicarbazone (DHBPTSC) complexes are described here: [Pd(II)], [Ni(II)dppm], [Cu(II)bipy), and [Cu(II)phen]. IR, 1H NMR, Mass, electronic, EPR, and elemental studies were used to confirm the DHBPTSC (ligand) and complexes. Coordination of sulfur and nitrogen in the azomethine form with the central metal ion is suggested by the FT-IR spectrum data. Absorbance EPR spectra were seen for complexes of Cu (II)bipy and Cu(II)phen with g values of g = 2.126 and g = 2.108, respectively. Both complexes have g values that are consistent with the proposal that their molecules have an extended tetragonal shape. Antibacterial, antifungal, and antioxidant properties of these compounds were also investigated.

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SYNTHESIS OF AZOLE-BASED HETEROCYCLIC COMPOUNDS

Schematically shown in Scheme 1, 3-(2,3-dihydrobenzo[d]thiazol-2-yl)-4H-chromen-4-one (SVS1) was prepared by refluxing 4-oxo-4H-chromene-3-carbaldehyde and 2-aminothiophenol in C2H5OH for 4 hours. 5-(1H-indol-3-yl)From (E)-2-((1H-indol-3-yl)methylene, 4-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (SVS2) was synthesized.the reaction of -N-methylhydrazine-1-carbothioamide [[34], [35], [36],47] with methanol and anhydrous FeCl3 under reflux for 6 hours, as shown in Scheme 2. The temperature range for this reaction is 60-65 °C. Although cyclization reactions of this sort are seldom documented in the literature, they may prove to be essential in the creation of novel bioactive heterocyclic medicines. Spectroscopic analysis employing UV-Visible, FT-IR, and NMR spectra provided full characterization of both substances. Single crystal X-ray diffraction and density functional theory calculations both corroborated the three-dimensional structures of SVS1 and SVS2. Unlike SVS2, which was only soluble in DMF and DMSO, SVS1 was soluble in a wide variety of organic solvents, including CH2Cl2, CHCl3, DMF, DMSO, etc.

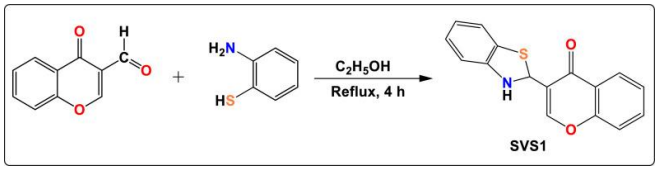

Figure 1 Synthetic route for chromone-based thiazole compound (SVS1).

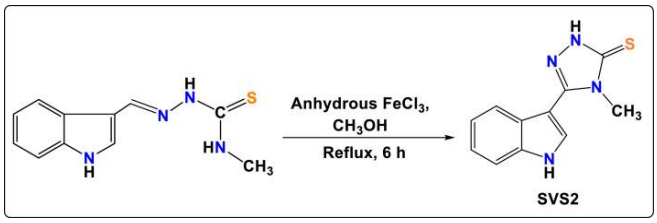

Figure 2 Synthetic route for indole-based triazole compound (SVS2).

Molecular docking with SARS-CoV-2 Mpro and ACE-2, and molecular dynamics simulation

The enclosed, RNA-positive, single-stranded RNA of coronaviruses makes them unique. Both structural and non-structural proteins are present in SARS-CoV-2. Spike glycoprotein (S) is one of the body's most crucial structural proteins. Spike glycoprotein (S) connects with the host receptor and angiotensin-converting enzyme-2 (ACE-2) for SARS-CoV entrance into the host cell [31,32]. Other than structural proteins, the viral replication requires non-structural proteins such as papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro or Mpro). There are three subunits that make up the primary protease of SARS-CoV-2. At the junction of domains I and II, a distinctive Cys-His dyad forms the protein's active site. Important for protein dimerization is the connection between domains II and III, which is provided by a linker.

One of the most crucial pathophysiological processes that allows a virus to enter a host through the ACE-2 receptor is the activation of a viral spike protein. Iron entrance into cells is regulated by hepacidin, which interacts with ferroportin. In severe instances of SARS-CoV-2 infection, a malfunction in iron metabolism causes ferroptosis. Dysfunction in iron metabolism is a key contributor to organ failure in several organ systems [56]. Thus, a lack of oxygen in the blood causes lung illness. Factors like (a) an ACE-2 receptor blocker or an inhibitor of SARS-CoV-2 main protease (Mpro) [57], (b) an iron chelating agent to conjugate with the excess iron resulting from its dysmetabolism, and (c) anti-inflammatory drugs as phosphodiesterase-4 inhibitors for the treatment of lung inflammation and necrosis [32,34] have been shown to be effective protocols for the treatment of COVID-19 disease.

The heterocyclic compounds SVS1 and SVS2 were produced and molecular docking was used to test their effectiveness against the SARS-CoV-2 major protease (Mpro) enzyme and the human ACE-2 receptor. Some pharmaceuticals on the market have structural similarities with our molecules due to the presence of thiazole, 1,3,4-oxadiazole, and heterocyclic moieties. The primary protease (Mpro) of coronaviruses is a key focus of research [58,59], and ACE-2 is essential for SARS-CoV entry into host cells. Antiviral medication research [36,37] has identified ACE-2 as a potential target for treating SARS-CoV-2. Chain A represents the angiotensin-converting enzyme-2, and chain E is the spike receptor binding domain, in the crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE-2 (PDB ID: 6M0J). In this docking analysis, we focused only on chain A of 6M0J (ACE-2). The molecular targets SARS-CoV-2 main protease and human ACE-2 were successfully docked with by both drugs. displays the docking energies of SVS1, SVS2, remdesivir, chloroquine, hydroxychloroquine, and human ACE-2 with SARS-CoV-2 Mpro and human ACE-2. The compounds' interactions with the active site of SARS-CoV-2 major protease and human ACE-2 In contrast to remdesivir (SARS-CoV-2), chloroquine (CQ), and hydroxychloroquine (HCQ), the docking findings for SVS1 and SVS2 indicated that they had preserved similar contacts in the active region of the enzymes.

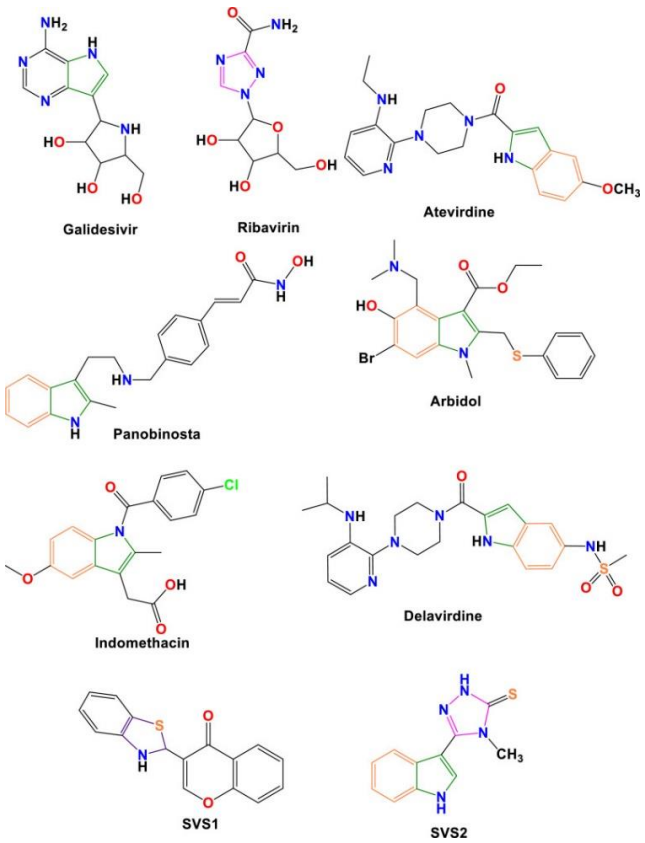

Figure 3 Commercially available drugs containing thiazole-based heterocyclic moiety and structures of heterocyclic compounds (SVS1 and SVS2) used in this work.

ANTI-AMOEBIC ACTIVITY

Using the HMI:1 MSS strain of E.histolytica, the in vitro activity of all pyrimidine and sulfonamide compounds was compared with that of the gold standard Anti-amoebic medication, metronidazole. In our study, the 50% inhibitory concentration of metronidazole was 1.82 microM. IC50 values ranged from 2.00 to 7.00 M for pyrimidines and 0.38 to 11.02 M for sulfonamide compounds. Among the compounds tested, those with a chloro group in one phenyl ring (compounds 3, 4, 8, 9, and 10) were the most active (IC50= 0.07 - 1.70 M). Chloro group at meta position compounds showed no action against E.histolytica. In addition, compounds with dichloro groups in the ortho and para positions were shown to be particularly active. It's likely because the chloro group in the phenyl ring acts as an electron-withdrawing molecule, which boosts the compounds' activity. There is something more there that makes the chemicals more effective. Compounds with a methyl group in either the phenyl or phenylthio ring were particularly active. The compounds' activity was boosted by the presence of a meta-positioned methyl group. SAR shows that the compounds' activity was improved by the presence of chloro groups in the ortho and para positions on the phenyl ring, and by a methyl group in the meta position. This should occur because the methyl group releases electrons while the chloro group pulls them in. Ortho and para have a greater tendency to pull electrons in, whereas the Meta position has a greater tendency to release electrons.

The impacts of these two variables were muted in pyrimidine compounds but pronounced in sulfonamides. This might be because sulfonamide molecules include an NH-SO2 link. This should be the primary motivation for improving the chemicals' efficacy. The data was analyzed statistically using analysis of variance. T-test was used to examine validity of null hypothesis. The metronidazole IC50 value was compared to that of the most effective drugs, and the significance of the difference was determined using a t-test. The estimated values of t were determined to be greater than the table value of t at the 5% level, suggesting that there was a statistically significant effect of the therapy on the character.

Cytotoxicity of active pyrimidine compounds and their in vitro activity against Escherichia coli are listed. Compounds IC50 values (nM)a SDb S.No R i = 6.00 0.01 ii = 2.00 0.03 iii = 3.15 0.03 for antiamoebic activity Pages 1-8 of Volume 2, Issue 6 of the June 2015 issue of the SK International Journal of Multidisciplinary Research Hub, authored by Dr. Deepa et al. All Rights Reserved, SK Publisher, 2015. Online ISSN: 2394-3122 Cl7.00 0.01 V Cl5.00 0.04 V CH34.47 0.02 (MNZ) 1.80 0.02 VII Cl7.00 0.05 The cytotoxicity of active sulfonamide compounds and their in vitro activity against Escherichia coli are listed.

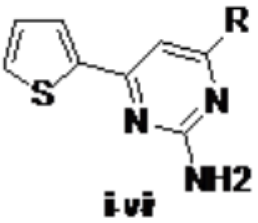

Table 1: In vitro activity sulfonamide compounds against E.histolytica, and the cytotoxicity of active compounds

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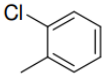
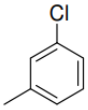
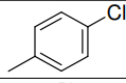
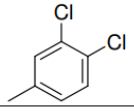
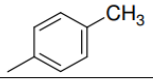
Compounds		Antiamoebic IC_{50} (μM)[a]	S.D.[b]
S.No	R		
i.		6.00	0.01
ii.		2.00	0.03
iii.		3.15	0.03
iv.		7.00	0.01
v.		5.00	0.04
vi.		4.47	0.02
(MNZ)		1.80	0.02

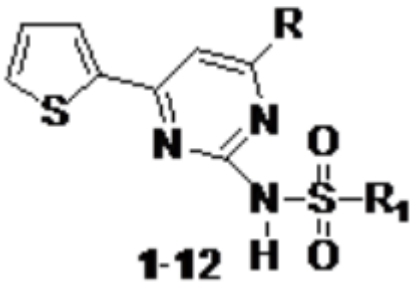


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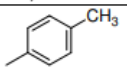
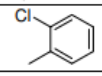
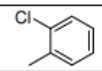
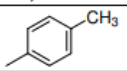
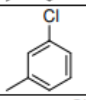
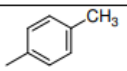
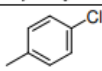
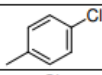
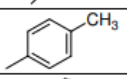
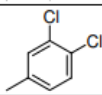
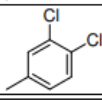
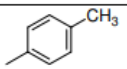
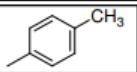
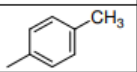
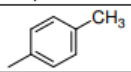
Table 2: Sulfonamide compounds that are active against Escherichia coli in vitro also have cytotoxic effects, as shown below.

Compounds			Antiamoebic	
S.No	R	R_1	IC_{50} (μM)[a]	S.D.[b]
1.			0.07	0.08
2.			2.35	0.01
3.			0.011	0.01
4.			1.76	0.03
5.			4.11	0.06
6.			5.50	0.01
7.			6.78	0.03
8.			1.30	0.05
9.			1.20	0.02
10.			1.00	0.07
11.			3.31	0.04
12.			2.71	0.02
(MNZ)			1.80	0.02

CONCLUSION

The precursor of SVS1 was synthesized from 2-aminothiophenol and 4-oxo-4H-chromene-3-carbaldehyde. With the help of anhydrous FeCl3, SVS2 was synthesized from (E)2-((1H-indol-3-yl) methylene)-N-methylhydrazine-1-carbothioamide.
Both SVS1 and SVS2 were heterocyclic compounds, however SVS2 was a triazole with indole while SVS1 was a thiazole with chromone. We have also looked at how these novel sulphonamide derivatives fare against amoebas. The biological activities of the compounds were shown to be superior to those of the gold-standard antibiotic metronidazole.

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