EXPERIMENTAL INVESTIGATION ON DERIVATIVES OF BENZALDEHYDE

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ABSTRACT

Using 4-[2-(5-ethylpyridin-2-yl) ethoxy] benzaldehyde as the starting material, a new sequence of chalcones, pyrimidines, and imidazolines is reported. After subjecting them to in vitro testing against 15 different ATCC strains, 8 of which were bacteria, a series of new sulfur- and nitrogen-containing ferrocene-linked heterocyclic compounds were shown to have promising antibacterial potential. By using infrared spectroscopy, proton nuclear magnetic resonance, mass spectrometry, and elemental analysis, we were able to successfully synthesis and describe several new Sulphur and nitrogen containing ferrocene linked heterocyclic compounds. Right now, the pharmacological and biological benefits of heterocyclic compounds and their derivatives are causing them to be given a lot of attention in the medical research sector. Heterocycles are abundant in nature and have gained new significance as a result of the widespread usage of the structural units they provide in many naturally occurring drugs and supplements. Those findings may serve as a foundation for the development of new chemical compounds with promising antibacterial properties on par with those of gold-standard medications.

Keywords: Nitrogen, Sulfur heterocycles (thiazine's), Antibacterial, Antifungal, Antimicrobial agents.

INTRODUCTION

Significant research efforts have been made to synthesize new heterocyclic compounds involving derivatization of naturally occurring materials such as plant alkaloids, vitamins, nucleic acids, hormones, proteins, etc., as heterocycles participate in an exceptionally significant division in modern culture and a group of diverse submissions in dissimilar fields. There is great potential for the use of heterocycles, especially those rich in heteroatoms N and S, in the pharmaceutical, agricultural, paint, and other industries. Chemical compounds based on substituted thiazine rings are classified as organic compounds with four carbon atoms and one N and S atom at different places in the rings, each of which may have six members. Furthermore, 1, 3, and 1,4 thiazine are used in the synthesis of a wide range of chemical compounds [1–15]. This article is devoted to the function of various heterocyclic thiazine ring systems in antibacterial activity. This literature research was conducted to compile information on the antibacterial properties of 1,3,4-thiazines and their derivatives. This study provides conclusive evidence that 1,3- and 1,4-thiazines need serious consideration as possible antibacterial agents. For this reason, we have chosen to conduct a comprehensive evaluation of thiazine'. Antimicrobial resistance has contributed to a worldwide alarming rise in the prevalence of microbial infection in recent decades. Antibiotic usage is widespread because microbial infections are a major challenge in modern medicine. Therefore, there is a pressing need to increase the availability of antimicrobial medicines that have broad-spectrum efficacy against the resistant pathogens. New insights into the synthesis and pharmacological effect of fused heterocycles like pyrazolines and similar heterocyclic compounds have been added to the scientific literature in recent years.

However, ferrocene and its derivatives have been the subject of considerable interest ever since they were first discovered because of their potential use in a variety of contexts, including catalysis, material sciences, biological research, and even medicine. Clinical trials of ferroquine, a ferrocene derivative of the antimalarial medication chloroquine, are now in phase II, and show the most potential for combating Plasmodium falciparum strains that have developed resistance to chloroquine. It has been shown that several ferrocene compounds have intriguing cytotoxic, anti-tumor, anti-cancer, anti-malarial, anti-fungal, and DNA-cleaving activities. Some novel ferrocene-substituted heterocyclic compounds have been described as possible medicines. In addition, these medicines are treatment-compatible since the ferrocene moiety is stable and nontoxic. Accordingly, incorporating one or more ferrocene units into a heterocyclic structure has long been

seen as an appealing technique to confer unique activity onto a molecule. Combining pharmacologically active N-heterocycles like pyrazolines and pyrazoles with a ferrocene moiety leads in a beneficial alteration in biological characteristics, generally associated with lower toxicity, as published in recent literature shows. In addition, thiazoles are included in several physiologically active molecules, such as natural products and pharmaceutical drugs, and it is well established that the combining of two or more kinds of heterocycles into a single molecule might provide a unique entity with enhanced bioactivity.

In light of these findings, and as part of our continuing effort to synthesize physiologically active heterocycles, we describe herein several new 5-ferrocenyl-3-substituted aryls-4,5-dihydro-1H-pyrazol-1-carbothioamides (1-6) and their cyclized derivatives. A group of compounds known as 2-(5-ferrocenyl-3-aryl-4,5-dihydro-1H-pyrazol-1-yl)-4-(4-substituted-aryl) thiazoles (7-12) has shown promise as a potential lead in the design of effective antibacterial drugs. Infectious diseases have been more common over the last several decades, and antimicrobial resistance is a major factor in this disturbing trend. Due to their effectiveness, antibiotics are widely used to treat microbial infections, which provide a significant problem for contemporary medicine. Because of this, there is an urgent need to enhance access to antimicrobial treatments that are effective against the resistant infections in a wide variety of different settings. Fused heterocycles, such as pyrazolines and related heterocyclic compounds, have received new attention in recent years as researchers have gained more understanding of their production and pharmacological action.

However, since its discovery, ferrocene and its derivatives have garnered considerable interest owing to their potential use in a variety of fields, including catalysis, material science, biological research, and even medicine. The antimalarial medicine chloroquine's ferrocene derivative, ferroquine, is showing the most promise in phase II clinical trials for combating Plasmodium falciparum strains that are resistant to chloroquine. There is a wide variety of ferrocene compounds that have intriguing cytotoxic, anti-tumor, anti-cancer, anti-malarial, anti-fungal, and DNA-cleaving activities. Recently, a number of ferrocene-substituted heterocyclic compounds have been described as having therapeutic potential (Huang et al., 2014; Arancini et al., 2014; Harry et al., 2014; Yu et al., 2007; Zora and Go men, 2007; Zora and Velia lug, 2008; Fabian et al., 2007; Mochida et al. The fact that the ferrocene group is stable and nontoxic makes these medications useful in combination with other therapies. Accordingly, incorporating one or more ferrocene units into a heterocyclic structure has long been seen as an appealing technique to confer unique activity onto a molecule. It has been shown in recent studies and publications that combining pharmacologically active Heterocycles like pyrazolines and pyrazoles with a ferrocene moiety leads in a favorable alteration in biological characteristics, generally related with lower toxicity. In addition, thiazoles are present in a wide variety of natural items and pharmaceuticals with biological effects (Kashyap et al., 2012; Eicher and Hauptmann, 2003; Siddiqui et al., 2011) it is known that combining several heterocycles into a single molecule might produce a new entity with enhanced bioactivities, and this is likely to be the case in many cases

LITERATURE REVIEW

MAHMOUD S. TOLBA (2021) There is no denying the biological significance of heterocyclic compounds in the fight against microbes and their impact on human existence. Following the synthesis of the difunctionalized product 5-amino-4-phenyl-2-(p-tolycaine) pyrimidine-6-carbonitrile, a series of new hybrid compounds of thienopyridine with triazine and pyrimidine scaffolds were fabricated (1). In addition, the chloro-triazine compound 2 was obtained through diazotization of compound 1 with sodium nitrite in an acidic medium, and compounds 3a–5c were obtained via nucleophilic replacement of the chlorine atom with various nucleophiles. Compound 7 was synthesized by reacting compound 1 with ethyl chloroacetate, which then underwent alkylation with ethyl chloride to form the dithiane derivative 6. Compound 8 was synthesized by reacting compound 1 with phenyl isothiocyanate, which resulted in 4-imino-3,9-diphenyl-7-(p-tolycaine)-3,4-hydroxyimide [4',5':4,5 Elements and spectra were used to characterize all produced compounds (IR, 1H NMR, 13C NMR, Mass spectroscopy). The antibacterial activity of the produced compounds was also evaluated against a variety of bacterial and fungal strains, with findings indicating excellent to moderate activity with the vast majority of the tested organisms.

Praveen K. Sharma et.al (2017) As a result of their unique features, heterocycles containing nitrogen and Sulphur have applications in a wide range of industries, including the pharmaceutical, chemical, paint, packaging, and textile sectors. Their importance increases when used in things like dyes, paint, agrochemicals, medicines, and so on. Nitrogen-sulfur heterocycles have been the subject of intense study in

recent years owing to their remarkable bioactive activity, which has piqued the curiosity of chemists on several occasions. This report summarizes a chemist's efforts to identify promising novel heterocyclic compounds with potential medical applications. Nitrogen-sulfur heterocycles, such as thiazole, thiazine, pyrimidine, morpholine, and piperazine heterosystems, benzothiazines, pyrazole-benzothiazines, morpholine-benzothiazines, piperazine-benzothiazoles, and pyrimidine-benzothiazoles, are of particular interest as potential therapeutics due to their distinctive structural features. Nitrogen Sulphur containing heterocycles have been used as a starting point for the development of improved features in drug design and synthesis because of their new method of action, wide range of activity, reduced toxicity towards mammalian cells, and favorable profiles in humans. The overarching goal of this review is to discuss the significance of novel biodynamic structurally diverse heterocycles of potential therapeutic interest, such as pyrimidine, morpholine, piperazine, pyrazole, benzothiazoles, pyrimidine thiazoles, 4H-1,4-benzothiazines, pyrazolyl-benzothiazines, morpholinyl-benzothiazines, and piperazinyl-Benz

Assailant Yasser Fakir Mustafa (2018) The medicinal chemistry field relies heavily on heterocyclic nuclei as a starting point for the design of a wide range of therapeutic medicines, including broad-spectrum antibacterial. A bicyclic, twelve-membered heterocyclic nucleus, generated from coumarin, was easily produced in an endeavor to create novel antibacterial drugs. Spectroscopic monitoring of the rate of ring closure for this nucleus (named coumadin) and two of its derivatives revealed that the rate followed zero order kinetics. Infrared (IR), nuclear magnetic resonance (NMR), and carbon-13 nuclear magnetic resonance (NMR) spectroscopy were used to determine the chemical structures of the produced products. Agar dilution assays were used to determine the in vitro antibacterial activity of coumarins against a panel of standard aerobic and anaerobic bacterial strains, with ciprofloxacin and metronidazole serving as positive controls, respectively; the results showed that coumadin I exhibited excellent broad spectrum antibacterial activity against the tested bacterial strains, with percentages of growth inhibition approximating those of the positive controls.

RESEARCH AND METHODOLOGY

Companies like Ranke India Ltd. and Fisher Scientific Ltd. The melting points were calculated using the open tube capillary technique with no corrections. Thin layer chromatography (TLC) plates (silica gel G) in a toluene: ethyl acetate solvent mixture was used to analyses the compounds' purity (75:25). Iodine vapors and ultraviolet light were used to detect the spots. Perkin-Elmer 1720 FT-IR spectra were collected for this study (KBr pellets). Using TMS as the internal standard in CDCl3, the 1H and 13C-NMR spectra were acquired on a Bruker Advance II 400 spectrometer. The freshly synthesized compounds were elementally analyzed using a Carlo Reba 1108 analyzer.

All of the fungal and bacterial strains used in this study were obtained from the Faculty of Medicine, Annamalai University, Annamalai Nagar, 60802, Tamil Nadu, India (Aspergillus flavus, Aspergillus Niger, Mucor, Rhizopus, and Microspore gypsum) and Salmonella typhi, Klebsiella pneumoniae, Escherichia coli, Pseudomonad Efficacy against bacteria and yeasts in laboratory dishes The MIC is determined by a two-fold serial dilution technique, with results expressed in micrograms per milliliter (g/mL) (22). A 1 mg mL-1 stock solution of each of the test chemicals 17–24 is prepared by dissolving them in dimethyl sulfoxide (DMSO). Prepared in NB from 24-hour old bacterial cultures on nutritional agar (Hi-media, Mumbai) at 37 1 °C, seeded broth (broth containing microbial spores) is suspended in SDB from 1–7-day old Samourai agar (Hi-media, Mumbai) slant cultures. Using the plating method, the cuff of the seeded broth is calculated and adjusted to be between 104 and 105 cfu/mL. Antibacterial inoculums were at 105 cfu/mL, while fungal inoculums ranged from 1.1 to 1.5 x 102 cuff/mL. pH 7.4 0.2 is used for bacterial (NB) testing, whereas pH 5.6 is used for fungal growth (SDB). As a starting point for the first dilution, 0.4 mL of the test chemical solution was added to 1.6 mL of seeded broth. One milliliter of this was diluted with another milliliter of seeded broth to provide the second dilution, and so on, for a total of six dilutions. As a baseline, we maintained a set of test tubes with only seeded broth. The tubes were kept at 37 1°C for bacteria and 28 1°C for fungus in BOD incubators. After 24 hours (for bacteria) or 72-96 hours (for fungus) of incubation, the minimum inhibitory concentrations (MICs) are recorded visually. For bacterial investigations, the gold standard is ciprofloxacin, whereas for fungal studies, the gold standard is fluconazole.

Procedure for the synthesis of 4-[2-(5-ethylpyridin-2-yl) ethoxy] benzaldehyde (3):

The literature-described synthesis of 4-[2-(5-ethylpyridin-2-yl) ethoxy] benzaldehyde (3) was followed. The disclosed procedure was used to synthesis and characterize chalcones and pyrimidines.

General Process of oxazol-5(*4H*)-one (Erlenmeyer azlactone synthesis) (C):

For 15 minutes, p-fluor benzaldehyde, hippuric acid, and potassium acetate were refluxed with stirring in acetic anhydride (0.83 mol) while the reaction was monitored by thin-layer chromatography (TLC) (3:1 isohexane-ethyl acetate as eluent). Following the addition of solid potassium carbonate, the liquid was cooled and neutralized. The solid product was filtered, dried, and crystallized to remove impurities. It has been demonstrated in how to synthesize it in.

DATA ANALYSIS

We used the broth microdilution technique, as reported by Rattan [26], to determine the MICs of our produced compounds. As a reference standard, ampicillin was used to test for antibacterial activity against four different bacteria: two gram-positive (Staphylococcus aureus MTCC 96 and Streptococcus pyogenic MTCC 443) and two gram-negative (Escherichia coli MTCC 442 and Pseudomonas aeruginosa MTCC 2488). Candida albicans MTCC 226, Aspergillus Niger MTCC 282, and Aspergillus clavate MTCC 1323 were utilized to test for antifungal activity, while Griseofulvin was employed as a reference antifungal. MTCC samples were obtained from the Institute of Microbial Technology in Chandigarh, India. Table 1 displays the 4a-o, 5a-o, and 6a-o MBCs, which are the lowest concentrations at which bacteria will no longer multiply. Based on the results of the screening, it was determined that the majority of the compounds had better antibacterial activity (MBC, 50-250 g/ml) against S. aureus; chalcones 4b, 4f, and 4h with the 4-OCH3, 4-CH3, and 4-F group showed MBC value in the range between 62.5-100 g/ml against E. coli; 4h at 100 g/ml against P. aeruginosa All four bacterial species were less affected by the remaining chalcones. The pyrimidines 5b and 5i, which included 4-OCH3 and 2,4-F, were the most active at 62.5 g/ml against E. coli; pyrimidine 5h, which had 4-F, was effective at 100 g/ml against S. aureus and S. pyogenes; pyrimidine 5i, which contained 2,4-F, was effective at 150 g/ml against S. aureus; and Less action against all four bacterial species was seen for the remaining pyrimidines compared to ampicillin.

The bactericidal activity of the imidazolines 6a, 6d, 6f, 6h, 6i, 6k, 6n, and 6o containing 2,4-Cl, 5-F, 4-OH, 4-CH3, 4-F, 2,4-F, 4-Br, 3,4-Cl, 3-F, and 3,4-F groups against S. aureus was equivalent to that of ampicillin at concentrations of 200-250 g/ml Table 2 displays the minimum concentrations needed to kill fungus. The majority of these compounds showed potent antifungal activity against C. albicans, with MICs ranging from 100 to 500 g/ml. In chalcones, 2,4-Cl, 4-OH, phenyl, 4-F, 3-OCH3, and 3-F at 200-500 g/ml; 3,4-F at 200 g/ml against C. albicans; the other pyrimidines are less potent against A. Niger and A. clavate compared to Griseofulvin. With Griseofulvin and nystatin, imidazolines 6c with 2,4-Cl showed increased activity at 100 g/ml against C. albicans, A. Niger, and A. clavate; 6e and 6h with 2,6-Cl, 5-F, and 4-F showed more activity at 250 g/ml against C. albicans; and other imidazolines exhibit moderate activity against C. The fungal pathogens Aspergillus Niger and Aspergillus clavate are more resistant to the remaining imidazolines. All substances are equivalent to S. aureus and C. albicans in terms of total microbiological analysis. Methoxy, methyl, hydroxy, and fluor substituted chalcones; methoxy, difluoro, and choro substituted pyrimidines

TABLE 1: ANTIBACTERIAL ACTIVITY OF COMPOUND 4A-O, 5A-O AND 6A-O

Compounds R		Minimal bactericidal concentration mg./ml			
		Gram negative		Gram positive	
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenic*
4b	4-OCH_3	100	150	250	250

4d	4-OH	150	200	250	250
4f	4-CH_3	100	150	100	250
4h	4-F	62.5	100	150	150
4n	3-F	250	500	250	500
5b	4-OCH_3	62.5	150	250	250
5c	2,4-Cl	500	500	250	500
5f	4-CH_3	200	200	250	250
5h	4-F	250	250	100	100
5i	2,4-F	62.5	150	150	200
5j	4-Br	250	250	200	200
5k	3,4-Cl	250	250	250	250
5l	4-Cl	250	100	150	250
5n	3-F	500	500	250	250
6a	2,4-Cl,5-F	500	500	250	250
6d	4-OH	500	500	250	500
6f	4-CH_3	125	200	250	250
6h	4-F	150	250	250	250
6i	2,4-F	500	500	250	250
6j	4-Br	100	150	250	250
6k	3,4-Cl	500	500	200	200
6n	3-F	500	250	250	200
6o	3,4-F	500	500	250	500
Ampicillin		100	100	250	100

TABLE 2: ANTIFUNGAL ACTIVITY OF COMPOUND 4A-O, 5A-O AND 6A-O

Compounds	R	Minimal fungicidal concentration mg./ml		
		C. albicans	*A. Niger*	*A. clavate*
4c	2,4-Cl	500	500	1000
4d	4-OH	500	500	1000
4g	Phenyl	200	500	500

4h	4-F	250	>1000	>1000
4m	3-OCH_3	500	500	500
4n	3-F	500	1000	1000
5a	2,4-Cl,5-F	500	500	1000
5b	4-OCH_3	500	>1000	>1000
5c	2,4-Cl	500	>1000	>1000
5d	4-OH	500	500	1000
5e	2,6-Cl,5-F	500	500	500
5f	4-CH_3	500	500	500
5g	Phenyl	500	500	500
5h	4-F	500	250	250
5i	2,4-F	500	1000	1000
5l	4-Cl	500	500	500
5n	3-F	500	1000	1000
5o	3,4-F	200	200	200
6c	2,4-Cl	100	100	100
6e	2,6-Cl,5-F	250	>1000	>1000
6f	4-CH_3	500	1000	1000
6h	4-F	250	1000	1000
6j	4-Br	500	1000	1000
6k	3,4-Cl	500	1000	1000
6m	3-OCH_3	500	500	500
6n	3-F	500	250	500
Nystatin		100	100	100
Griseofulvin		500	100	100

Groups composed of choro, dichlorvos, fluor, and difluoro substituents and imidazolines are more effective against S. aureus and C. albicans. Similarities exist between imidazoline 6c 2,4-Cl and nystatin and Griseofulvin.

CONCLUSION

According to the research, thiazines are the most important group of heterocyclic chemicals, and their effects are particularly taxing on illnesses caused by microorganisms. The thiazine moiety has attracted a great deal of interest from biochemists and medicinal chemists, and this review of thiazine-based heterocycles has shown that it has the potential to be an essential molecule in the creation of new biologically active

pharmaceutical molecules. Using spectroscopic techniques including IR, 1 H NMR, 13C NMR, Mass spectrometry, and elemental analyses, we synthesized and thoroughly characterized several new Sulphur and nitrogen containing ferrocene linked heterocyclic compounds. Rattan's broth microdilution technique was used to test the microbiological inactivation concentrations (MICs) of synthetic substances. The synthesis and characterization of the physical and analytical data for a series of new (2E)-ethyl-2-(2-(2,4-dinitrophenyl) hydrazone)-4-(naphthalene- 2-yl)-6-arylcyclohex-3-enecarboxylates 17-24 is shown in crisp.

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