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DESIGNING, SYNTHESIZING, AND CHARACTERIZING 1, 3-THIAZINE DERIVATIVES AND THEIR ANTIMICROBIAL SCREENING

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Abstract
The manufacture of 1,3-thiazine derivatives was done through the utilisation of one-pot three-component (1P-3C) isoniazid (INH) condensations, and 3-mercaptopropionic acid, and a number of aryl/heteroaryl aldehydes in the existence of ethylene difluoride. This reaction was carried out in order to get the desired results. The synthesis of 1,4-thiazines derivatives was carried out in the existence of the green catalyst (L) proline. This was accomplished by employing a domino sequence that was carried out in a single pot. In terms of its ability to suppress MTB, the chemical 17- N-(2-(4-(benzyloxy) phenyl-4-oxo-1, 3-thiazinan-3-yl) isonicotinamide was found to be three times more effective than INH. The fact that it had a minimum inhibitory concentration (MIC) of 0.12 M was an additional factor that contributed to its effectiveness.
Keywords:*1, 3-thiazine, 1, 4-thiazine, Antimicrobial activity, MTB, TLC.*

Introduction

There is an inextricable connection between compounds that contain heterocyclic rings and the bulk of the key metabolic activities that are necessary for life [1]. If one were to choose a stage in a biological process at random, there is a very high possibility that one of the reactants or products would be a heterocyclic compound [2,3]. This is because heterocyclic compounds are characterized. This is due to the fact that heterocyclic chemicals are found in biological systems in quite high quantities [4]. The presence of heterocyclic rings in the product of the reaction in question is a near-certainty due to the fact that enzymes are responsible for the catalysis of all biological reactions, and there are twenty amino acids in enzymes, all of which include heterocyclic rings [5]. Even if this is not the case, the presence of heterocyclic rings in the product of the reaction in question is a probable occurrence.

In the past ten years, a consistent rise occurred in the count of people who contracted tuberculosis (TB), and this growth can be ascribed to a comparable rise in the number of people who have contracted human immunodeficiency virus (HIV) [1±3]. The correlation between tuberculosis and HIV infections is very strong,and in certain instances, over two-thirds of the individuals who have been diagnosed with tuberculosis are also known to be HIV-1 seropositive [1±4] [6]. In addition, a multitude of research have demonstrated that tuberculosis (TB) is a factor that contributes to HIV infection'sprogression [1±5]. The resurgence of tuberculosis infection is made even more complex by the rise in the count of cases resistant to the standard approaches to treating tuberculosis with drugs. The ever-increasing prevalence of tuberculosis that is resistant to many drugs not only poses challenges for the treatment process, but it also causes the prices to skyrocket. Therefore, the development of new medications is essential to address the challenges now being faced within therapy [7].

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Methodology

Without any additional purification, all of the chemicals and solvents that are accessible for commercial use were utilized. Using alumina-backed silica gel 40 F254 plates manufactured by Merck in Darmstadt, in Germany, TLC experiments were carried out respectively. In order to illuminate the plates, molybdenum acid and ultraviolet light (254 nm) were used. Using the Buchi B-540, melting points were calculated, and these results have not been rectified. An automated Flash EA 1112 Series CHN Analyzer (Thermo) was utilized all during the process of conducting elemental analyses. An Bruker AM- 300 (300.12 MHz and 75.12 MHz) from BrukerBioSpin Corp. in Germany was used to record all of the 1H and 13C NMR spectra. Agilent Technology's LCMS ñ100B series was utilized to examine the molecular weights of substances that were not previously recognized.

Chemistry

The synthesis of a total of 32 molecules was carried out. In accordance with the diagram in Scheme 1, the synthesis of the compounds of interest was successfully completed.

The characterization of chemicals

Through the use of TLC and elemental analysis, the purity of compounds 1–32 was thoroughly examined. There was complete concordance between the hypothesized structures with the analytical along with spectral data (1H NMR, and 13C NMR, along with mass spectra (MS)) of all of the compounds that were synthesized. The lipophilicity of the derivatives that were synthesized, as well as the characteristics of the parent molecule, INH, arearticulatedper the logP values that they have . The ChemBioDraw Ultra 11.0 program was utilized in order to achieve the computation of these values utilizing a standard technique known as calculated logP (ClogP).

N-(4-ozo-2-phenyl-1, 3-thiazinan-3-yl)isonicotinamide (1) is a white solidwith a molecular weight ranging from 14 to 148. It has a yield of 87%. The analytical calculation for C1±H15N3O2S is as follows: C, ±1.32; H, 4.8. Found: carbon, α0.93; hydrogen, 4.87; nitrogen, 13.79. 1H nuclear magnetic resonance (300 MHz, CDCl3): 2.78–2.9α (m, and 4H, and CH2CH2), 5.73 (s, 1H, CH), and 7.09-7.23 (phenyl's m, and 5H, and ArH), and 7.72–8.81 (pyridyl's m, and 4H, and ArH), and 8.19 (s, IH, NH). 13C nuclear magnetic resonance (NMR) spectra (75MHz, CDCl3): 170.9, 1α3.8, 149.8, 140.2, 138.α, 128.7, 127.9, 12α.3, 122.9, α3.7, 38.α, 31.9. Mass spectrometry (MS) m/z: 313.09 [M+].

N-(4-ozo-2-o-tolyl-1, 3-thiazinan-3-yl) isonicotinamide II: Stable and white;For C17H17N3O2S, the M.P. ranges from 111 to 113, and the yield is 83%. C, б2.3б; H, 5.23; N, 12.83 Found: C, б2.5б; H, 5.0б; N, 12.б1. 1H NMR (300 MHz and CDCl3): 2.31(s, and 3H, and CH3), 2.74–2.94 (m, and 4H, and CH2CH2), 5.79 (s, 1H, CH), б.99-7.11 (phenyl's m, and 4H, and ArH), and 7.79 - 8.91(pyridyl's m, and 4H, and ArH), and 8.31 (s, IH, NH). Using CDCl3 at a frequency of 75MHz, the following 13C NMR spectra were obtained: 171, 1α3.9, 149.7, 140.3, 139, 13α.α, 128.9, 12α.9, 125.1, 122.8, 57.4, 38.2, 31.8, 18.3.The MS mass-to-charge ratio is 327.10 [M+].

Antimicrobial analysis of compounds

Each and every substance was examined to see whether or not it possessed antimycobacterial activity in vitro against log-phase colonies of M. For the purpose of determining the minimum inhibitory concentration (MIC) in triplicate.

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Result and discussion

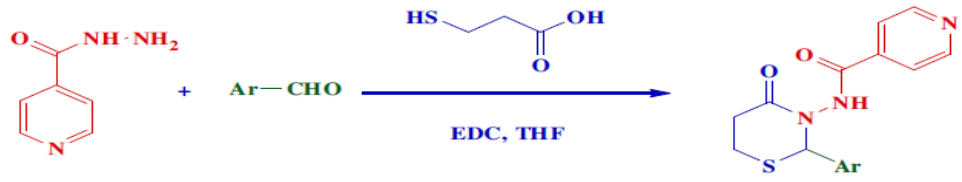
All the synthesized 1, 3 thiazine derivative mentioned below along with their structure.

Antimicrobial testing of compounds

The antimycobacterial action observed in vitro

Each compounds that were examined indicated potential in vitro action against MTB, and their minimum inhibitory concentrations (MICs) ranged from 0.57-98.90 M. A total of 52 compounds were examined. Four compounds, specifically 4, 7, 1o, and 4o, were able to inhibit MTB at concentrations lower than 5 M. These compounds were able to inhibit MTB. An example of a compound is compound 7, which is made up of ethyl 4-(4-toluoyl)-α-(4-chlorobenzoyl) - 3, 5-di (4-nitrophenyl).The molecule known as -1, 1-dioxo-1, 4-thiazinane-2-carboxylate was proven as the most effective chemical in vitro, having a minimum inhibitory concentration -0.57 µM vs the log-phase MTB culture. When bulky groups such as benzyloxy are introduced onto the phenyl ring, the action is increased by 39-92 times, and the MIC is under 1 M. The increased action could be attributed to the hydrophobicity of the compounds 15-17, since their ClogP values were 4.25, whereas the conventional compound 1 had a ClogP value of 2.5±. By introducing electron-withdrawing groups such as nitro, and halogen, along withtriflouromethyl, the potency of the compound is increased, and the minimum inhibitory concentration (MIC) ranges from 0.13 to 2.12 M. The activity order across the groups that extract electrons is as follows: CF3 > Br > F > Cl > NO2. The molecule becomes less active when the phenyl ring is replaced with a furan ring; however, the addition of a nitro group to the furan ring causes the drug to become ten times more active, with a minimum inhibitory concentration of 4.48 M.

Synthesis of N (Aryl-4-oxo-1, 3-thiazinan-3yl) isonicotinamide:



Scheme 4.1.1. Formation of [1, 3]-thiazines

Scheme 1: 1,3 thiazine formation

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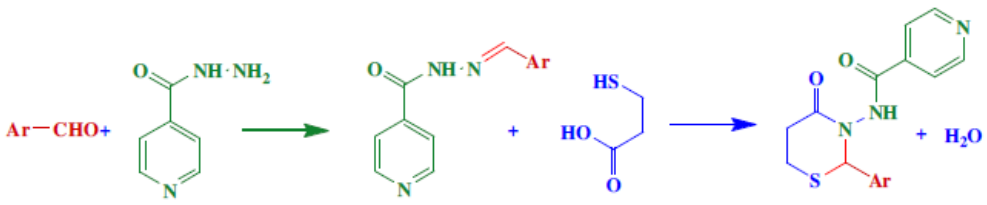

Scheme 2: Mechanism of formation of 1,3 thiazine

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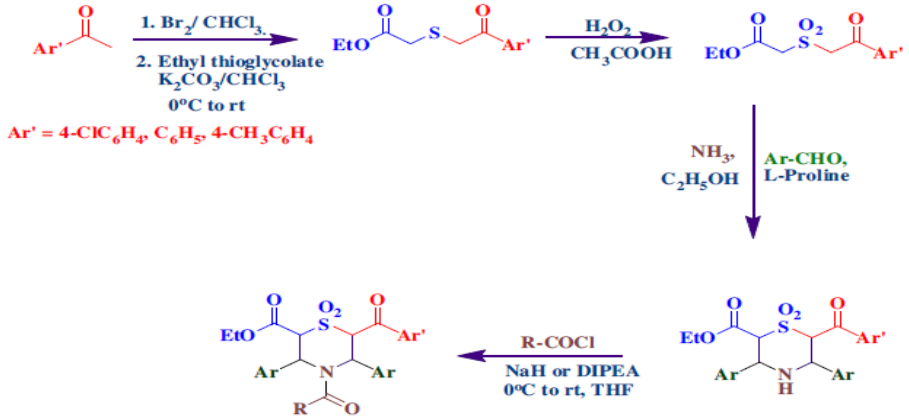
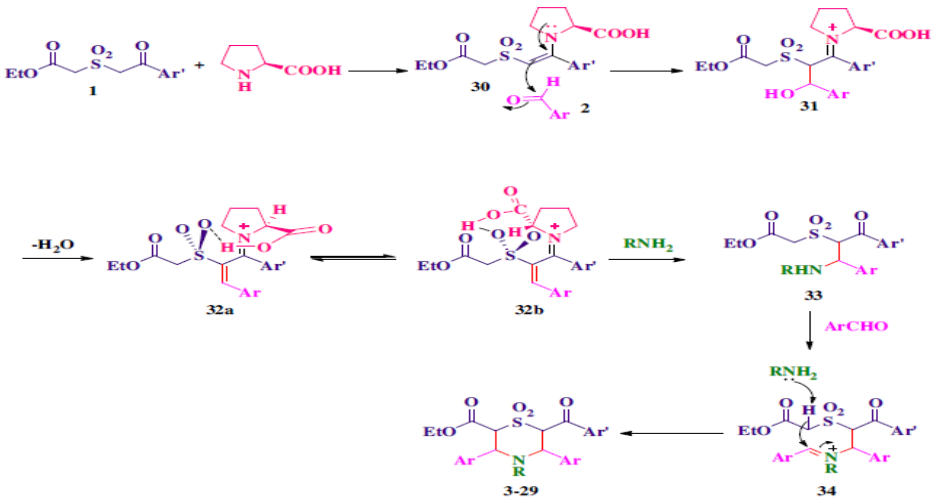


Scheme 3: 1,4thiazine formation



Scheme 4: mechanism for 1,4thiazine formation

Conclusion

In this study synthesis of 1,3-thiazine derivatives was done through the utilization of 1P-3C and checked for their antimicrobial action also. The spectral and analytical data of all of the compounds that were synthesised, counting 1H NMRalong with13C NMR, along withMS, were in total agreement with the structures that were postulated. It found that compound 17, which does not include any substituents on the phenyl rings, exhibited a minimum inhibitory concentration (MIC) of 9.9 µM and is used as the benchmark for comparing drug efficacy. In the phenyl ring 2-13, the introduction of smaller electron donating groups does not significantly modify the activity; the minimum inhibitory concentration (MIC) ranges from 4.54 to 18.98 µ M. One of these groups, the 4-methoxy group (7), is the only one that increases the activity twice, and the addition of the hydroxyl group has a negative impact on the activity.

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