INTERNATIONAL JOURNAL OF TECHNO-ENGINEERING
IJTE

ISSN: 2057-5688

Analysis Of Bis-Mono- And DifluorophenacylAzolium Compounds

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Abstract - A brand new set of one-of-a-kind bis-mono and di-fluorophenacyl triazolium and imidazolium compounds was produced by beginning with mono and di-fluorophenacyl chloride, 1H-1,2,4-triazole, and 1H-imidazole. To generate 4-amino mono- and di-fluorophenacyl triazolium compounds, 4-amino-4H-1,2,4-triazole and mono- and ddi-fluorophenacyl chloride were employed. This is similar to what was described before. A comparative study of these compounds, with amphotericin B acting as the standard, was carried out using Aspergillus niger, Aspergillus flavus, and Penicillium chrysogenum as test organisms, respectively. The bulk of the generated azolium compounds displayed minimal to moderate activity against the selected fungus, as shown by the findings of the antifungal tests.

Keywords: Azole; synthesis, antifungal activity, triazolium chloride, imidazolium chloride

1. INTRODUCTION

The fast increase of antimicrobial resistance is causing a great deal of anxiety among both the scientific community and the general population, especially in regard to multidrug-resistant bacteria and fungi. It has been shown that immune-compromised persons are more susceptible to the detrimental effects of fungi, which has led to fungi being a major infection among the many different microorganisms.3 The growing problem of antibiotic resistance after prolonged exposure is another factor that has pushed the need of the design and development of innovative antimicrobial medications to the forefront of public health concerns. Before the 1940s, there were only a select few drugs that could be used to treat systemic fungal infections. In succeeding stages, amphotericin B developed into a cornerstone medicine for the treatment of serious infections. This was accomplished via a series of steps.

However, many decades later, during the quest for new antifungals with lesser toxicity, azoles were discovered. This discovery came about as a consequence of the search. In the early 1980s, ketoconazole was the first antifungal medicine based on imidazoles to be made available orally for the treatment of systemic fungal infections (Figure 1). As a consequence of later developments in drug discovery, however, triazole-substituted antifungal medicines have

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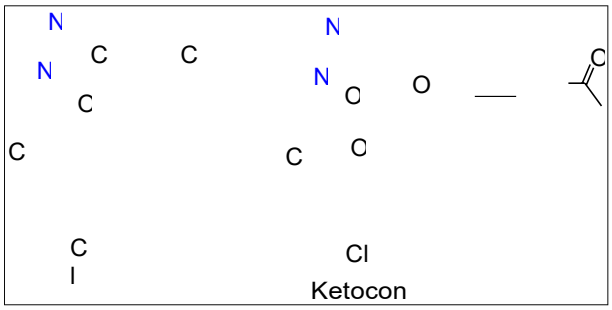
ISSN: 2057-5688

been produced as a second significant development in the treatment of fungal infections. This is a second key breakthrough in the treatment of fungal infections. It was discovered that the first-generation triazoles, fluconazole and itraconazole, had a considerably better safety profile than Amphotericin B and ketoconazole, in addition to having a broader spectrum of antifungal activity than imidazoles. These two compounds were fluconazole and itraconazole. In spite of the fact that these treatments are still widely used, a number of other analogues have been developed as a result of the problems that are associated with using them. These problems include the development of drug resistance, the possibility of hazardous drug-drug interactions, and a substandard pharmacokinetic profile. In order to circumvent these limits, second-generation triazoles including voriconazole, posaconazole, and ravuconazole have been created. It was revealed that these drugs had increased potency and effectiveness against infections that are resistant to treatment and infections that are developing, particularly those caused by Aspergillus species.

Imidazolebasedantifungalagents



SecondenervationTriazolebasedantifungalagents

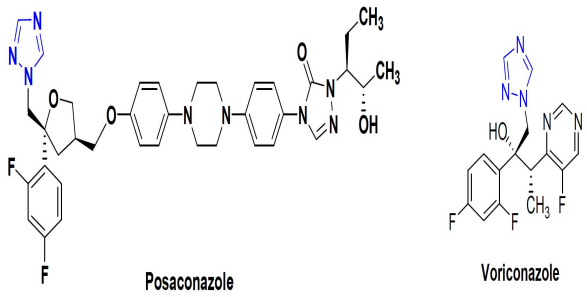


Figure1: Imidazoleandtriazole based antifungal Agents

The N-substituted azoles and their derivatives are considered to be an important class of aromatic heterocyclic compounds. These compounds have a wide range of applications in the biological world, including serving as active components in conazoles of the first and second generation, which are used to treat fungal infections. These chemicals exert their antifungal effects by inhibiting the biosynthesis of ergosterol, which is the primary steroid found in the fungal membrane.

It has been shown, by the use of structural modification, that azole compounds also contain actions such as those of an antibacterial, anticonvulsant, anticancer, anti-inflammatory, antimalarial, anti-neoplastic, insecticidal, and herbicidal nature. These abilities have been demonstrated. A wide number of fields may make use of azolium salts because of the peculiar behavior they exhibit, similar to that of azoles. Because of their polyfluoroalkylated and perfluoroalkylated 1,2,4-triazolium compounds' low melting points (100 degrees Celsius), thermal stability at

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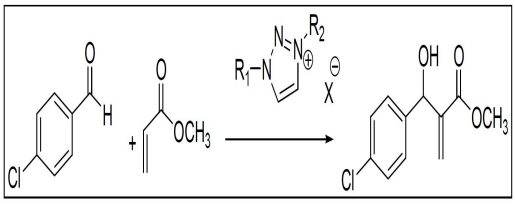
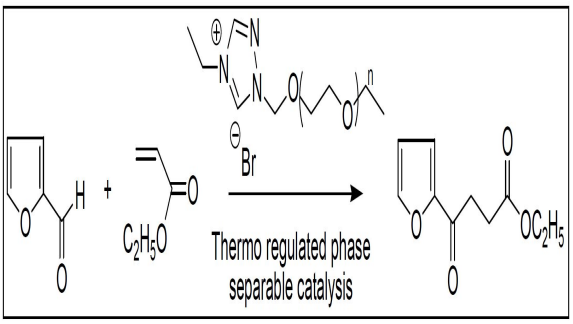
IJTE
ISSN: 2057-5688

higher temperatures, low vapour pressure, and highly polar (non-coordinating) nature, they are drawn to the fields of catalysis, lubrication, reaction media, and material science. The Umpolung reaction, redox catalysis, transesterification, polymerization, and ring opening reactions are all facilitated by the use of [BMIM]PF6, which belongs to the other family of azolium salts known as ionic liquids (ILs). [BMIM]PF6 is an efficient nucleophilic catalyst. Some of them are employed in the Baylis-Hillman reaction (Scheme 1) and the Stetter reaction (Scheme 2) due to features such as strong electrical conductivity, high dielectric constant, thermal and chemical stabilities. Gree and his colleagues have made a discovery about a number of the imidazolium compounds that may function as room temperature ionic liquids (RTILs) in Stetter reactions. These ILs are often defined as thermally stable salts that include a substantial organic cation and a diverse collection of anions. Most of the time, they are made up of liquids or compounds that have low melting points and low vapour pressures.



Scheme 1 Baylis-Hillman reaction of *p*-chlorobenzaldehyde and methylacrylatein1,2,3-triazoliumionicliquids



Scheme2Stetterreactionoffurfuralwithethylacrylate

Previous studies have shown that the presence of a positive charge on the nitrogen atom in triazolium compounds has a considerable impact on the molecule's capacity to dissolve in water and pass across membranes, leading to an increase in the biofeasibility of the chemical. These quaternary ammonium salts interact with the cytoplasmic membranes of bacteria to stop the eventual degradation of the memberane's permeability features.

Substituent fluorine has a substantial impact on the way a molecule functions in a biological setting as a result of its unique properties, which include its tiny size, high electro negativity, and poor polarizability of the C-F bond. In addition, the disciplines of health, agriculture, material science, and fluorine chemistry have all shown a great deal of interest in fluorine-containing triazole compounds.

2. PRESENTWORK

In light of the information presented above, we have manufactured salts of imidazolium, difluorophenacyl triazolium, and bis-mono and difluorophenacyl triazolium. In the present work, we

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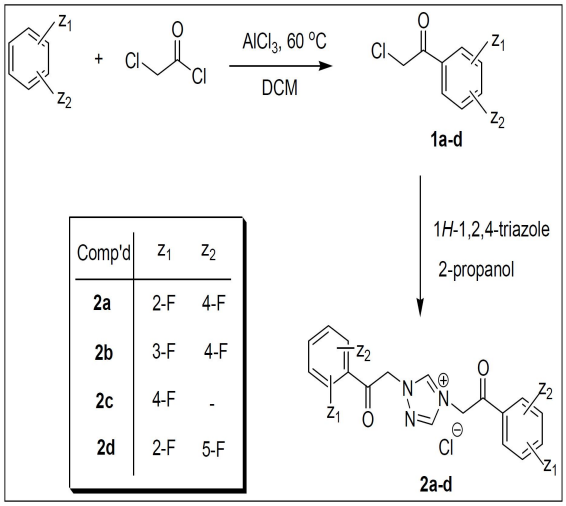
describe the antifungal activity of these salts against popular medications such as amphotericin B as well as fungi such as Penicillium chrysogenum, Aspergillus niger, and Aspergillus flavus.

3. RESULTSANDDISCUSSION

targeted compounds were readily synthesized from the intermediates 1a-dand3a.Theseintermediateswerepre paredbyfollowingtheknownprocedu resdescribedbyUpadhayay*et al*.



Comp'd	z_1	z_2
2a	2-F	4-F
2b	3-F	4-F
2c	4-F	-
2d	2-F	5-F

Scheme3Synthesisofcompound2a-d

Compounds 2a through d were produced as a result of a reaction between an excessive amount of mono- and difluorophenacyl chloride and 1H-1,2,4-triazole in 2-propanol (Scheme 3). The yield indicated that a higher temperature is necessary for the manufacture of quaternary ammonium salt, as evidenced by the fact that it is needed. As a result, we came to the conclusion that it would be best to prepare these target compounds at a higher temperature (80 degrees Celsius).

The information obtained from its spectrum served as confirmation for compound 2a-d. In the mass spectrum of the compound 2a-d, there was a peak at m/z [M-Cl]+ 378.0674, 378.0649, 378.0894, and 342.105, which suggests the synthesis of triazolium salt. In the 1H NMR spectra, there is visible evidence of a singlet integrating for two protons of the -CH2 group at coordinates 6.11-6.36 and 6.27-6.52. At 9.27-9.39 and 10.11-10.31, there is evidence of a singlet integration involving two aromatic protons originating from the triazole ring. In addition, by making use of 1H NMR, compounds 2a through 2d were successfully isolated from the aromatic ring that included fluorine atoms in a number of different positions.This result was corroborated by the multiplets 7.34–7.42 found in compound 2a, which integrated for two aromatic protons in the meta position (C3), 7.57–7.64 found in compound 2a, which integrated for two aromatic protons in the meta position (C5), and 8.08–8.14 found in compound 2a, which integrated for two protons in the ortho position. Corroboration of the structure of the compound was accomplished by using the multiplet at 7.75–7.78 integrating for two aromatic protons in the meta position, a multiplet at 8.00–8.02 integrating for two protons in the ortho position (C2), and a multiplet at 8.17-8.23 integrating for two aromatic protons in the ortho position (C6), all of which are for compound 2b. Both the broad singlet at 8.20, which integrates four aromatic protons in the ortho position, and the wide singlet between 7.49 and 7.55, which integrates four aromatic protons in the meta position, provided evidence that compound 2c exists. Validation of compound 2d was provided by the multiplet at 7.59–7.82, which integrated for six aromatic protons in ortho, meta, and para positions.

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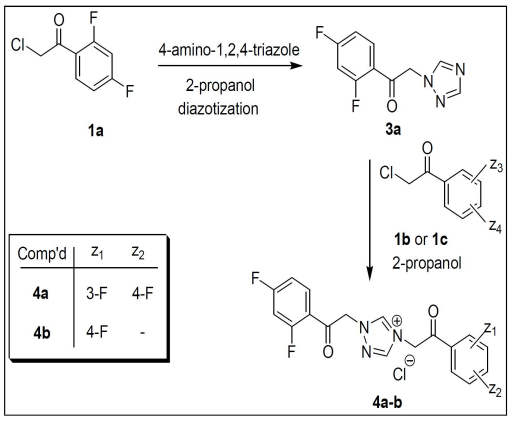
Schmidt-Gordon and Boatz offered an explanation, based on theory, for the possibility of alkylation at the N2 position. It was believed that the 1,2-disubstituted triazolium compounds contained more energy than the 1,4-disubstituted triazolium compounds. As a result, the 1,2-disubstituted triazolium compounds were less beneficial. Because of their symmetry, it is believed that 1,2-disubstituted triazolium compounds only emit a single signal in 1H NMR. This signal is supposed to correspond to the protons that are located at the C3 and C5 positions of the triazole ring. On the other hand, there were two signs that pointed to the formation of 1,4-disubstituted molecules. The C3 and C5 chemical shift values of these protons, which were found in compounds 2a–d, corresponded with those found in triazolium compounds that had been 1,4-disubstituted. The positive charge that was located at the N4 position was the reason of the distinct chemical shift values that were seen for the two methylene protons, and this was further supported by the information that was provided by Pirotte et al.

In order to investigate the positional influence of fluorine atom towards the targeted fungus, we generated the azolium compounds 4a-b by reacting 3a with 1b-c, each of which contains a different substituted fluorine atom in an equimolar ratio (Scheme 4). These compounds were created by reacting 3a with 1b-c.



Scheme4Synthesisofcompound4a-b

The results of its spectral measurements confirmed the presence of component 4a-b. It is possible to make out the peak in the mass spectrum of compound 4a-b's at m/z [M-Cl]+ 378.0894 and 360.0986, which indicates the formation of triazolium salt. In the 1H NMR spectrum, it is possible to make out a singlet at 6.26–6.32 that integrates for four -CH2 protons. Additionally, it is possible to make out singlets at 9.27–9.34 and 10.10–10.20 that integrate for two aromatic protons from the triazole ring.

The compound 4a was recognized by its multiplet at 7.37, which integrated for one proton at the meta position (C3; 2,4-disubstituted ring), its multiplet at 7.61–7.80, which integrated for one aromatic proton at the meta position (C5; 2,4–disubstituted ring), its multiplet at 7.76–80, which integrated for one proton at the meta position (C5; 3,4–disubstituted Compound 4b was confirmed by the multiplet at 7.35-7.66, which integrated for four aromatic protons at meta positions (C3, C5 of 2,4-disubstituted and 4-monosubstituted rings), as well as the multiplet at 8.11-8.21, which integrated for three protons: two from the 4-monosubstituted ring at ortho position and one proton from the ortho

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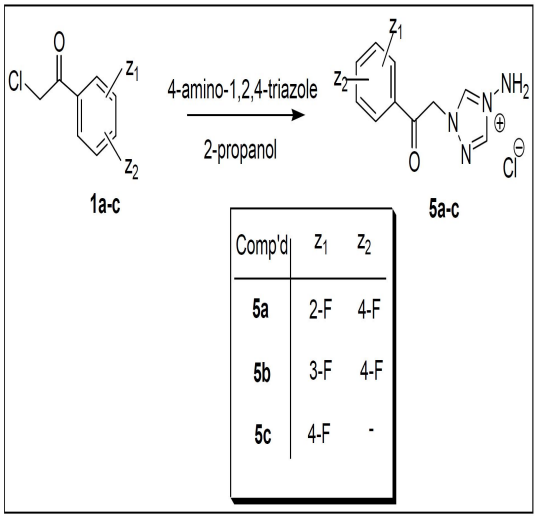
position of the 2,4-disubstituted ring.



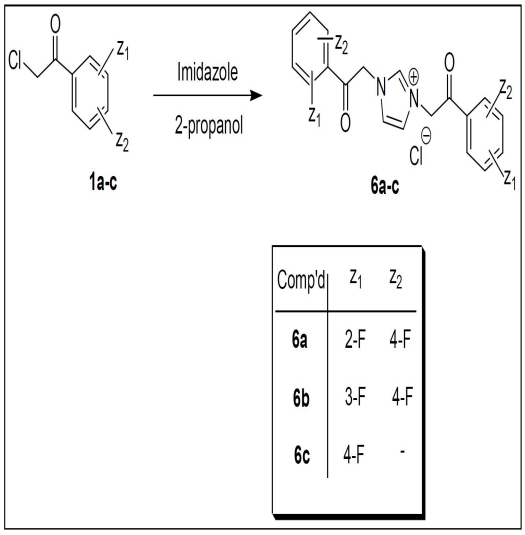
Comp'd	z_1	z_2
5a	2-F	4-F
5b	3-F	4-F
5c	4-F	-

Scheme5Synthesisofcompound5a-c

In addition, we produced the 5a-c family of triazolium compounds by combining 4-amino-4H-1,2,4-triazole, bis-mono, and difluorophenacyl chloride (Scheme 3.5). The information obtained from its spectrum served as confirmation for compound 5a-c. According to the mass spectra of compound 5a-c, which displayed a peak at m/z [M-Cl]+ 239.0749, 239.0747, and 221.0844, the triazolium salt was successfully produced. In the 1H NMR spectrum, there is a broad singlet at 7.34-7.44 that corresponds to -NH2 proton integration, singlets at 9.34-9.36 and 10.28-10.39 that integrate for one proton each from the triazole ring, and a singlet at 6.14-6.36 that integrates for two proton integrations of the -CH2 group.

The multiplet that integrated for the single aromatic proton in the meta position (C5) at 7.35-7.39, the multiplet that integrated for the single aromatic proton in the meta position (C2) at 7.57-7.62, and the multiplet that integrated for the single aromatic proton in the ortho position at 8.08-8.10 all supported the existence of compound 5a. Confirmation was provided by the multiplets of compound 5b at 7.72–7.77, which integrated for one proton in ortho position (C2), 7.98–8.01, which integrated for one proton in meta position, and 8.16–20, which integrated for one proton in ortho position (C6) respectively. Verification of compound 5c was accomplished by looking at its multiplet at 7.47–7.50, which integrated for two aromatic protons in the meta position, as well as a multiplet at 8.1–8.18, which integrated for two protons in the ortho position.

In light of the assertion that both triazole and imidazole compounds may have uses in biological settings, we have also developed compounds based on the imidazolium molecule in addition to those based on the triazolium molecule. After reacting the imidazole with an excess of bis-mono and difluorophenacyl chloride in 2-propanol, the imidazolium compounds 6a–c were produced (Scheme 6).



Comp'd	z_1	z_2
6a	2-F	4-F
6b	3-F	4-F
6c	4-F	-

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Scheme6Synthesisofcompound6a-c

The results of its spectral measurements supported the validity of compound 6a-c. In the mass spectrum of compound 6a-c, there is a peak that implies the synthesis of imidazolium salt. This peak can be seen at m/z [M-Cl]+ 377.0910, 377.0910, and 341.1106. It can be seen in the 1H NMR spectrum that there are four protons in a singlet at 6.00–6.14, two protons in each -CH2 group adjacent to the carbonyl carbon, two aromatic protons in an imidazole ring in a singlet at 7.76–8.00, and one aromatic protons in an imidazole ring in a singlet at 9.09–9.11 in the spectrum. In addition, a differentiating characteristic was provided by the aromatic ring of each of the compounds 6a–c. Each of these rings included a fluorine atom in a different position, thus they were easily distinguished from one another.

Multiplets of the compound 6a were measured at 7.35-7.39, 7.60-7.61, and 8.10-8.12, and these measurements integrated for two aromatic protons in meta position (between two fluorine atoms), two protons in ortho position, and two protons in meta position, respectively. This allowed the compound to be identified. The presence of compound 6b was shown by integrating the multiplet at 7.73-7.78 for four aromatic protons at ortho (C2) and meta positions, as well as integrating the multiplet at 8.15-8.19 for two protons at the ortho (C6) position. Both of these integrations were performed simultaneously. Both a multiplet that integrated for four aromatic protons in the meta position at 7.48–7.52 and a multiplet that integrated for four additional aromatic protons in the ortho position at 8.1–8.18 validated compound 6c.

4. BIOLOGICAL ACTIVITY

In vitro tests were performed on the synthesized compounds 2a-d, 4a-b, 5a-c, and 6a-c to determine whether or not they have antifungal activity against the fungi Aspergillus niger, Aspergillus flavus, and Penicillium chrysogenum. The minimum inhibitory concentration (MIC) was determined with the use of the agar diffusion method at concentrations of 0.065, 0.125, 0.25, 0.5, 1.0, and 2.0 mg/mL. The stock solutions were prepared using methanol as the solvent. For the growth of fungi, we made use of Czapek-Dox agar. After being injected in broth medium, the stock culture was allowed to grow for another 48 hours at a temperature of 27 degrees Celsius. After the agar medium was prepared, the wells that are found in those plates were subsequently constructed. Before being injected, an identical amount of culture that had been grown for 48 hours (104 CFUs/100 L) was spread throughout each plate. After waiting for twenty minutes, different chemical concentrations were added to the wells, while amphotericin B was put into the wells that served as controls. The minimal inhibitory concentration (MIC) values were determined by determining the lowest antifungal agent concentration at which no fungal growth took place. Table 1 offers an overview of the minimum inhibitory concentration (MIC) values for a number of different fungi in comparison to the commonly used amphotericin B.

The in vitro antifungal activity of the compounds is outlined in Table 1, which presents the results of tests conducted using the agar well diffusion method.

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Compound	Diameter of inhibition zone in mm (MIC in mg/mL)		
	Penicillium chrysogenum	*Aspergillus niger*	*Aspergillus flavus*
2a	5 (1.0)	--	--
2b	--	--	8 (0.5)
2c	--	--	5 (1.0)
2d	5 (0.5)	3 (2.0)	--
4a	3 (2.0)	--	--
4b	--	2 (2.0)	--
5a	4 (2.0)	--	--
5b	--	--	--
5c	--	2 (2.0)	--
6a	3(1.0)	--	--
6b	--	--	8 (2.0)
6c	--	--	4 (1.0)
Amphotericin B	5 (0.4)	7 (0.1)	10 (0.4)

-- No activity

The results of the in vitro antifungal activity test demonstrated that all of the compounds, with the exception of compound 5b, were successful in inhibiting the growth of fungus. The majority of these compounds showed in vitro antifungal activity against the fungi that were investigated, and their minimum inhibitory concentration (MIC) values were rather low, ranging from 0.5 to 1.0 mg/mL. The compounds that were the most efficient against Penicillium chrysogenum had MIC values between 0.5 and 1.0 mg/mL; nevertheless, these compounds were less potent than Amphotericin B, which had a MIC value of 0.4 mg/mL. When tested against Aspergillus flavus, the minimum inhibitory concentration (MIC) values for compound 2b, 2c, 6b, and 6c range from 0.5 to 2.0 mg/mL. Aspergillus niger is immune to the effects of the chemicals that are derived from imidazolium. According to the findings of the experiment, the compounds containing 4-amino triazolium exhibited the least amount of action against the fungus that was being studied when compared to the other chemicals.

5. CONCLUSION

In conclusion, the synthesized azolium compounds 2a-d, 4a-b, 5a, 5c, and 6a-c have shown significant in vitro antifungal activity against P. chrysogenum, A. niger, and A. Flavus. This is the case regardless of the fluorine atom in the aromatic ring that has been replaced with fluorine. Because the antifungal activity of some of these compounds was only moderate, it is possible that those compounds may be further changed by using a different substitution that comprised a variety of anions in order to produce more potent antifungal effects. Since some of these compounds had only moderate antifungal activity, it is possible to further modify them by making a new substitution that contains diverse anions. This would allow for the antifungal activities of these compounds to be improved.

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