Synthesis of Innovative isoxazolidines Via 1, 3 - Dipolar Cycloaddition of α -Furfural-Aryl-N-Aryl-Nitrone with Cinnamaldehyde and Its Antibacterial Activities

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***Abstract*—Cycloaddition is a significant pathway among numerous economical chemical processes due to its stereospecificity, capacity to produce complex compounds, and atom economy. The most common method for synthesizing the isoxazolidine ring system is 1,3-dipolar cycloaddition among nitrones and substituted alkenes, comprising electron-rich and electron-poor dipolarophiles. Nitrone is a prevalent dipole in the 1,3-dipolar cycloaddition process because it is persistent and does not need in vitro development. The 1,3-dipolar cycloaddition of nitrones with different dipolarophiles generates various heterocyclic rings. Because nitrones are simple derivatives of carbonyl compounds, the reaction sequence from carbonyl compounds (mostly aldehydes) to nitrone synthesis of the five-membered ring system and subsequent breakdown of the cycloadduct provides a route to new carbonyl compounds called isoxazolidines. This article focuses on nitrones that perform cycloaddition with diverse sources to produce heterocyclic rings. Using spectroscopic techniques, the structures of the generated compounds were identified.**

***Index Terms*—1,3 dipole, nitrones, 1,3 dipolar cycloaddition, dipolarophile, antibacterial activity.**

I. INTRODUCTION

Rolf Huisgen's work was significant in establishing mechanistic study and synthetic application in the 1960s. Cycloadditions are one of the most common, diverse, and beneficial types of chemical reactions. Cycloaddition is a significant pathway among numerous efficient chemical processes due to its stereospecificity, ability to produce complex compounds, and atom economy. The regio- and stereoselective synthesis of five-membered heterocycles and their ring-opened acyclic derivatives is facilitated by 1,3-dipolar cycloaddition [1]. The 1, 3-dipolar cycloaddition (1,3-DC) reaction is a powerful synthetic technique for the synthesis of a wide range of heterocycles, which are key scaffolds in many biologically active molecules [2]. Isoxazolidine is a pentatomic heterocycle with nitrogen and oxygen atoms that are adjacent. This ring is found in many compounds with substantial biological activity, and it is crucial in the synthesis of nucleotide and nucleoside analogues, which are utilised in medicinal chemistry as anticancer and antiviral medicines[3]. Nitrone cycloaddition to olefins is one of the more adaptable protocols for the synthesis of isoxazolidine, where the dipolarophiles are often alkenes[4]. Nitrones represent a long-known and thoroughly investigated class of 1,3-dipoles. Nitrone is a common dipole in the 1,3-DC process because it is stable and does not usually need in situ generation. The 1,3-DC of nitrones with various dipolarophiles produces a number of heterocyclic rings of different sizes. Natural goods, physiologically active compounds, and medications all benefit greatly from these heterocycles[5]-[10]. Because of its prospective biological activity, isoxazolidines have piqued the interest of organic chemists and biochemists among all five membered heterocyclic systems[11]-[15]. It has also been identified that isoxazolidines function as a new class of mild steel corrosion inhibitors in acidic media[16-20]. As a result, we planned to synthesise a novel nitrone and utilize that nitrone to synthesize a novel isoxazolidine as a bisheterocycle. Right here the nitrones are prepared with phenylhydroxylamine and aldehydes. Cinnamaldehyde is a flavonoid which was yellow in color has potential antimicrobial activities in nature.

As it has double bond in its structure, it acts as a dipolarophile here.

II EXPERIMENTAL

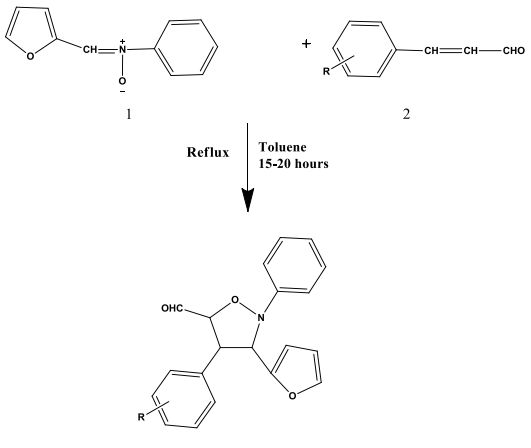
All of the chemicals were of high reagent grade and were utilised without additional purification. All melting points were measured in uncorrected open capillaries. TMS was used as an internal standard for the ^{1}HNMR and ^{13}CNMR spectra, which were recorded on a Bruker 400MHz& 100MHz in CDCl3. All chromatographic treatments were carried out on silica gel 60-120 mesh with petroleum ether-ethyl acetate as eluent. Coupling constants are reported in Hertz, and chemical shifts are indicated in parts per million (δ-scale). Other approaches, such as IR and UV- vis were captured by the Jasco spectrometer and Perkin Elmer.

General procedure

Cycloaddition reaction of α-Furfural aryl-N-aryl nitrone with Cinnamaldehyde

3-(furan-2-yl)-2,4-diphenylisoxazolidine-5-carbaldehyde (3a)

A mixture of α-Furfural aryl-N-aryl nitrone (1) and Cinnamaldehyde (2) was refluxed in toluene (50ml) for the time period specified in Scheme I. After completion of the reaction (as indicated by TLC), the solvent was removed under reduced pressure and the product (3) was recrystallised from petroleum ether. (Scheme I).



Scheme I

III RESULTS AND DISCUSSION

Recent literatures have considered carefully the synthesis of isoxazolidines by 1,3 dipolar cycloaddition processes, as well as the characterization of their spectral and structural properties[21]-[23]. Similar to previous studies, it is proposed to synthesize bisheterocycles containing at least one isoxazolidine unit. It has known that a series of keto-linked bisheterocycles has been synthesized[24]. However, a thorough review of the literature indicated that there is no record on the cycloaddition of α-Furfural aryl-N-aryl nitrone [25] with Cinnamaldehyde. This new dipolarophile cinnamaldehyde (2) is a fascinating dipolarophile because it have potentially activated double bond along with the aldehyde functional group and can lead to the formation of adducts with sufficient quantities of the 1,3 dipoles namely α-Furfural aryl-N-aryl nitrone(1) which has already a heterocyclic moiety. So, the dipole of choice for the current investigation is α-Furfural-aryl-N-aryl nitrone(1). Thus, there is more scope for additional new products in addition to normally expected region and stereo isomers. For 15-20 hours, an equimolar combination of α-Furfural-aryl-N-aryl nitrone [26] and Cinnamaldehyde was refluxed in toluene. After further investigation, it was discovered that only the product predominate the reaction mixture, as evidenced by TLC, and the product was separated using column chromatography.

The product isolated was identified as 3-(furan-2-yl)-2,4-diphenylisoxazolidine-5-carbaldehyde (3). From the recent literature[28], a strong indication of the regio and stereoselectivities involved in the reaction have no other additional regio and stereoisomer resulting from the addition and it clearly shows that the absence of another mole of the 1,3 dipole reacting with one of the double bonds. Obviously, now the cycloadduct formed (3) has one more potential activated double bond. So, it has been planned to do a experiment with 1:2 dipolarophile and dipole for further investigation to check the further addition on the compound. But, only one product, 3-(furan-2-yl)-2,4-diphenylisoxazolidine-5-carbaldehyde (**3**), was obtained from the reaction mixture when the process was performed.

Finally, we choose to investigate the cycloaddition reaction of C-aryl-N-aryl nitrone (1) as our initial model which reacts with the dipolarophile of cinnamaldehyde (**2**). The systematic structure analysis for the product 3 to arrive at the exact region and stereochemistry was carried out using ^{1}HNMR and ^{13}CNMR.

The ^{1}H NMR spectrum shows the signal at δ 4.05 (1H, dd, *J* = 8.1, 6.9 Hz), 5.04-5.20 (2H, 5.10 (d, *J* = 8.1 Hz), 5.13 (dd, *J* = 6.9, 3.8 Hz)) which confirms the formation of novel isoxazolidine. And its miles feasible to attain the same product by means of microwave irradiation that is a simple and price green approach to produce new heterocycles.

Strong evidence exists that the C-aryl and N-aryl groups in nitrones generated from aromatic aldehydes are arranged in a trans relationship. This uses a comparison of the UV spectra of structures with fixed cis and trans geometry as its main premise. The UV absorption at 232 nm confirms the isoxazolidine ring (Fig. 1) In FT-IR spectrum (Fig. 2) the disappearance of C=C(olefine) band at 1592.91cm^{-1} and C=N (nitrone) band disappearance at 1670.05cm^{-1} which results the formation of isoxazolidine ring system.

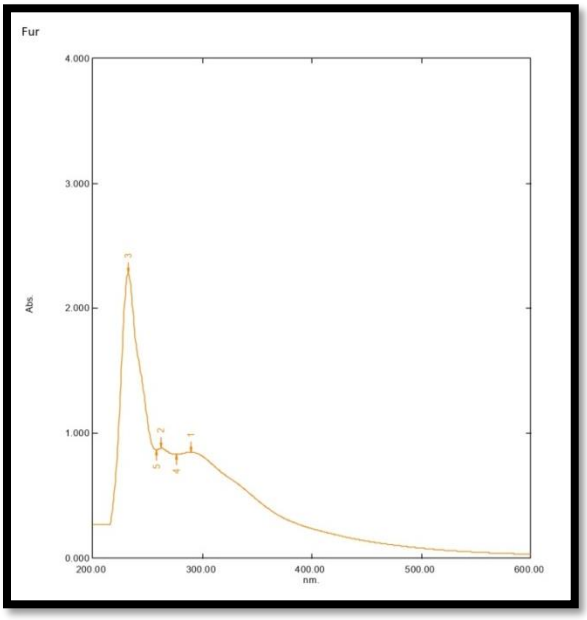


Fig. 1 UV-Visible spectra of the synthesized novel isoxazolidine 3

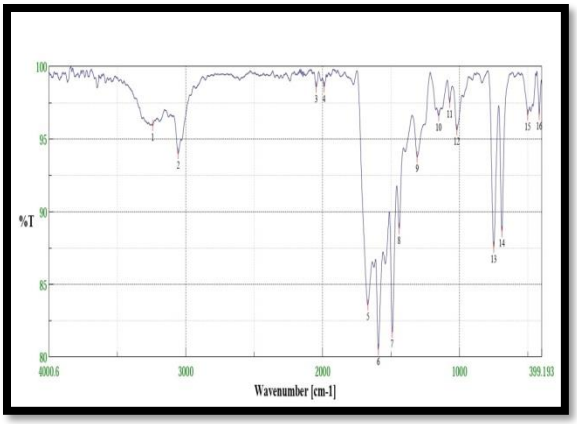


Fig. 2 FT-IR spectra of the synthesized novel isoxazolidine 3

Here the substituted cinnamaldehydes reacts with the synthesized α-Cinnamic aryl-N-aryl nitrone (1) to give various isoxazolidine systems (3a-3i). Table I

Table I Synthesis of novel isoxazolidines using different dipolarophiles 2

Compound	R	Time (h)	Yield (%)
3a	H	20	90
3b	4-Cl	18	85
3c	2-NO_2	19	87
3d	2-OH	18	86
3e	α-CH_3	20	85
3f	α-OCH_3	17	86
3g	2-Br	16	85
3h	4-OH, 3-OCH_3	18	89
3i	4-NO_2	20	90

3-(furan-2-yl)-2,4-diphenylisoxazolidine-5-carbaldehyde (3a)

^{1}H NMR: δ 4.05 (1H, dd, *J* = 8.1, 6.9 Hz), 5.04-5.20 (2H, 5.10 (d, *J* = 8.1 Hz), 5.13 (dd, *J* = 6.9, 3.8 Hz)), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.99-7.42 (12H, 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz), 7.21 (tt, *J* = 7.7, 1.6 Hz), 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.32 (tdd, *J* = 7.7, 1.9, 0.5 Hz), 7.36 (dtd, *J* = 7.6, 1.6, 0.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz)), 9.72 (1H, d, *J* = 3.8 Hz).

^{13}C NMR: δ 30.3 (1C, s), 40.7-40.8 (2C, 40.7 (s), 40.7 (s)), 56.6 (1C, s), 67.8 (1C, s), 71.3 (1C, s), 73.9 (1C, s), 115.9 (2C, s), 127.6 (2C, s), 127.8-127.8 (2C, 127.8 (s), 127.8 (s)), 128.2 (2C, s), 128.4 (2C, s), 139.2 (1C, s), 148.0 (1C, s), 201.6 (1C, s).

4-(4-chlorophenyl)-3-(furan-2-yl)-2-phenylisoxazolidine-5-carbaldehyde (3b)

^{1}H NMR: δ 4.03 (1H, dd, *J* = 8.1, 6.9 Hz), 5.04-5.18 (2H, 5.10 (dd, *J* = 6.9, 3.8 Hz), 5.12 (d, *J* = 8.1 Hz)), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.88-7.15 (6H, 6.94 (ddd, *J* = 8.2, 1.5, 0.5 Hz), 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz)), 7.24-7.51 (5H, 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz), 7.45 (ddd, *J* = 8.2, 1.4, 0.5 Hz)), 9.72 (1H, d, *J* = 3.8 Hz).

^{13}C NMR: δ 40.7 (1C, s), 64.9 (1C, s), 73.9 (1C, s), 109.2 (1C, s), 115.9 (2C, s), 127.8 (1C, s), 128.0-128.3 (4C, 128.1 (s), 128.2 (s)), 128.7 (2C, s), 129.2 (1C, s), 133.7 (1C, s), 138.4 (1C, s), 139.2 (1C, s), 143.0 (1C, s), 148.0 (1C, s), 201.6 (1C, s).

3-(furan-2-yl)-4-(2-nitrophenyl)-2-phenylisoxazolidine-5-carbaldehyde (3c)

^{1}H NMR: δ 4.16 (1H, dd, *J* = 8.1, 6.9 Hz), 4.92-5.14 (2H, 4.98 (d, *J* = 8.1 Hz), 5.08 (dd, *J* = 6.9, 3.8 Hz)), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.99-7.19 (5H, 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz), 7.13 (ddd, *J* = 8.2, 1.4, 0.5 Hz)), 7.21-7.45 (6H, 7.28 (ddd, *J* = 8.1, 1.5, 0.5 Hz), 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.37 (ddd, *J* = 8.2, 7.4, 1.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz), 7.38 (ddd, *J* = 8.1, 7.4, 1.4 Hz)), 9.73 (1H, d, *J* = 3.8 Hz).

^{13}C NMR: δ 40.7 (1C, s), 64.9 (1C, s), 73.9 (1C, s), 109.2 (1C, s), 114.8 (1C, s), 115.9 (2C, s), 124.1 (1C, s), 127.3 (1C, s), 127.8 (1C, s), 128.2 (2C, s), 128.4 (1C, s), 129.2 (1C, s), 129.4 (1C, s), 138.4 (1C, s), 143.0 (1C, s), 148.0 (1C, s), 154.1 (1C, s), 201.6 (1C, s).

3-(furan-2-yl)-4-(2-hydroxyphenyl)-2-phenylisoxazolidine-5-carbaldehyde (3d)

^{1}H NMR: δ 4.09 (1H, dd, *J* = 8.1, 6.9 Hz), 4.92-5.09 (2H, 4.98 (d, *J* = 8.1 Hz), 5.03 (dd, *J* = 6.9, 3.8 Hz)), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.64 (1H, ddd, *J* = 8.3, 1.2, 0.5 Hz), 6.92 (1H, ddd, *J* = 8.0, 7.5, 1.2 Hz), 6.99-7.41 (9H, 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz), 7.17 (ddd, *J* = 8.0, 1.3, 0.5 Hz), 7.24 (ddd, *J* = 8.3, 7.5, 1.3 Hz), 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz)), 9.72 (1H, d, *J* = 3.8 Hz).

^{13}C NMR: δ 40.7 (1C, s), 64.9 (1C, s), 73.9 (1C, s), 109.2 (1C, s), 115.9 (2C, s), 116.8 (1C, s), 124.1 (1C, s), 127.3 (1C, s), 127.8 (1C, s), 128.2 (2C, s), 128.4 (1C, s), 129.2 (1C, s), 129.4 (1C, s), 138.4 (1C, s), 143.0 (1C, s), 148.0 (1C, s), 155.9 (1C, s), 201.6 (1C, s).

3-(furan-2-yl)-5-methyl-2,4-diphenylisoxazolidine-5-carbaldehyde (3e)

^{1}H NMR: δ 1.51 (3H, s), 4.12 (1H, d, *J* = 7.0 Hz), 5.36 (1H, d, *J* = 7.0 Hz), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.99-7.43 (12H, 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz), 7.21 (tt, *J* = 7.7, 1.6 Hz), 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.36 (tdd, *J* = 7.7, 1.9, 0.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz), 7.37 (dtd, *J* = 7.6, 1.6, 0.5 Hz)), 9.71 (1H, s).

^{13}C NMR: δ 27.6 (1C, s), 40.7 (1C, s), 64.9 (1C, s), 79.7 (1C, s), 109.2 (1C, s), 115.9 (2C, s), 127.6 (2C, s), 127.8-127.8 (2C, 127.8 (s), 127.8 (s)), 128.2 (2C, s), 128.4 (2C, s), 129.2 (1C, s), 138.4 (1C, s), 139.2 (1C, s), 143.0 (1C, s), 148.0 (1C, s), 202.2 (1C, s).

3-(furan-2-yl)-4-(2-methoxyphenyl)-2-phenylisoxazolidine-5-carbaldehyde (3f)

^{1}H NMR: δ 3.80 (3H, s), 4.11 (1H, dd, *J* = 8.1, 6.9 Hz), 4.96 (1H, d, *J* = 8.1 Hz), 5.10 (1H, dd, *J* = 6.9, 3.8 Hz), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.83-7.15 (6H, 6.90 (ddd, *J* = 8.0, 7.5, 1.3 Hz), 7.02 (ddd, *J* = 8.3, 1.3, 0.5 Hz), 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz)), 7.15-7.41 (5H, 7.22 (ddd, *J* = 8.0, 1.3, 0.5 Hz), 7.23 (ddd, *J* = 8.3, 7.5, 1.3 Hz), 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz)), 9.72 (1H, d, *J* = 3.8 Hz).

^{13}C NMR: δ 40.7 (1C, s), 56.0 (1C, s), 64.9 (1C, s), 73.9 (1C, s), 109.2 (1C, s), 115.8 (1C, s), 115.9 (2C, s), 124.1 (1C, s), 127.3 (1C, s), 127.8 (1C, s), 128.2 (2C, s), 128.4 (1C, s), 129.2 (1C, s), 129.4 (1C, s), 138.4 (1C, s), 143.0 (1C, s), 148.0 (1C, s), 157.0 (1C, s), 201.6 (1C, s).

5-bromo-3-(furan-2-yl)-2,4-diphenylisoxazolidine-5-carbaldehyde (3g)

^{1}H NMR: δ 4.34 (1H, d, *J* = 8.1 Hz), 5.19 (1H, d, *J* = 8.1 Hz), 6.25 (1H, dd, *J* = 1.8, 1.1 Hz), 7.00-7.16 (4H, 7.06 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.11 (dd, *J* = 1.1, 0.9 Hz)), 7.18-7.46 (8H, 7.24 (tt, *J* = 7.7, 1.8 Hz), 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5

Hz), 7.33 (tdd, *J* = 7.7, 1.9, 0.5 Hz), 7.36 (dd, *J* = 1.8, 0.9 Hz), 7.39 (dddd, *J* = 7.6, 1.8, 1.6, 0.5 Hz)), 9.97 (1H, s).

^{13}C NMR: δ 40.7 (1C, s), 64.9 (1C, s), 89.2 (1C, s), 109.2 (1C, s), 115.9 (2C, s), 127.6 (2C, s), 127.8-127.8 (2C, 127.8 (s), 127.8 (s)), 128.2 (2C, s), 128.4 (2C, s), 129.2 (1C, s), 138.4 (1C, s), 139.2 (1C, s), 143.0 (1C, s), 148.0 (1C, s), 190.9 (1C, s).

3-(furan-2-yl)-4-(4-hydroxy-3-(methylperoxy)phenyl)-2-phenylisoxazolidine-5-carbaldehyde (3h)

^{1}H NMR: δ 3.73 (3H, s), 3.95 (1H, dd, *J* = 8.1, 6.9 Hz), 4.96 (1H, d, *J* = 8.1 Hz), 5.13 (1H, dd, *J* = 6.9, 3.8 Hz), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.76 (1H, dd, *J* = 8.4, 0.5 Hz), 6.83-6.97 (2H, 6.89 (dd, *J* = 8.4, 2.7 Hz), 6.91 (dd, *J* = 2.7, 0.5 Hz)), 6.99-7.15 (4H, 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz)), 7.24-7.41 (3H, 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz)), 9.73 (1H, d, *J* = 3.8 Hz).

^{13}C NMR: δ 40.7 (1C, s), 55.7 (1C, s), 64.9 (1C, s), 73.9 (1C, s), 109.2 (1C, s), 110.6 (1C, s), 115.8 (1C, s), 115.9 (2C, s), 127.8 (1C, s), 128.2 (2C, s), 128.7 (1C, s), 129.2 (1C, s), 138.4 (1C, s), 139.2 (1C, s), 143.0 (1C, s), 146.1 (1C, s), 148.0 (1C, s), 153.2 (1C, s), 201.6 (1C, s).

3-(furan-2-yl)-4-(4-nitrophenyl)-2-phenylisoxazolidine-5-carbaldehyde (3i)

^{1}H NMR: δ 3.98 (1H, dd, *J* = 8.1, 6.9 Hz), 4.94 (1H, d, *J* = 8.1 Hz), 5.13 (1H, dd, *J* = 6.9, 3.8 Hz), 6.24 (1H, dd, *J* = 1.8, 1.1 Hz), 6.99-7.41 (11H, 7.05 (tt, *J* = 8.1, 1.2 Hz), 7.08 (dtd, *J* = 8.2, 1.2, 0.5 Hz), 7.10 (dd, *J* = 1.1, 0.9 Hz), 7.21 (ddd, *J* = 8.2, 1.3, 0.5 Hz), 7.27 (ddd, *J* = 8.2, 1.2, 0.5 Hz), 7.32 (dddd, *J* = 8.2, 8.1, 1.4, 0.5 Hz), 7.35 (dd, *J* = 1.8, 0.9 Hz)), 9.72 (1H, d, *J* = 3.8 Hz).

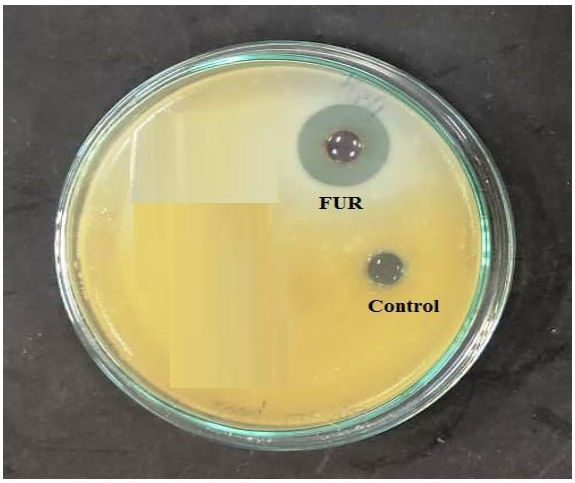
^{13}C NMR: δ 40.7 (1C, s), 64.9 (1C, s), 73.9 (1C, s), 109.2 (1C, s), 114.8 (2C, s), 115.9 (2C, s), 127.8 (1C, s), 128.2 (2C, s), 128.7 (2C, s), 129.2 (1C, s), 138.4 (1C, s), 139.2 (1C, s), 143.0 (1C, s), 148.0 (1C, s), 164.6 (1C, s), 201.6 (1C, s).

Antibacterial activity

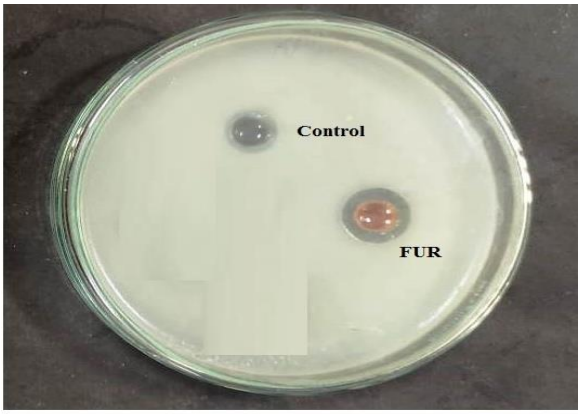
In this study, the disc diffusion method is used to examine antibacterial activity. Placing antimicrobial-soaked paper circles over a yard of bacteria grown on the outer layer of an agar medium, hatching the plate for the time being, and detecting the presence or absence of an inhibitory zone around the circles is the method used. Antibacterial activity of isoxazolidines has been demonstrated [27],[28]. As a consequence, an antibacterial susceptibility test using synthesized Isoxazolidine 3 in the inhibitory zone diameter at a dose of 20mg/ml of DMSO was performed. Compound 3 inhibits the development of two different bacteria. It is effective against Pseudomonas aeruginosa and Bacillus marisflavi. (Table II)

Table II 20mg/ml of DMSO

Organisms	Compound 3
Bacillus Marisflavi	15 mm
Pseudomonas aeruginosa	13 mm
Exiguobacterium indicum	-



Bacillus marisflavi



Pseudomonas aeruginosa

CONCLUSION

The heterocyclic ring system isoxazolidines were synthesised here using dipolarophiles, stable nitrone, and unique cinnamaldehyde. The antibacterial properties of the newly synthesised isoxazolidines have been confirmed using ^{1}H, ^{13}C, FT-IR, and UV-visible methods. As a consequence, all of the heterocyclic compounds listed above have been successfully developed.

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