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Design, Synthesis And Pharmacological Activity Of Novel Furan-Azetidinone Derivatives For Antimicrobial Activity

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ABSTRACT

It is now necessary to create new, efficient agents with various scaffolds due to rising drug resistance and significant toxicity to the current medications. A technique was developed to hybridise the various heterocyclic moieties with the goal of discovering new antibacterial and antifungal compounds. Drawing from prior research, the four most promising derivatives were chosen and synthesised. When o-toluidine and ethyl cyanoacetate were condensed at 160–190 °C, 2-cyano-N-2(methylphenyl) acetamide (1) was produced. By reacting with benzoin, 2-amino-N-(2-methylphenyl) 4, 5-diphenylfuran-3-carboxamide (2) was produced. As a catalyst, concentrated sulphuric acid was used to reflux (2) with different substituted aromatic aldehydes in ethanol to create a series of Schiff bases ARJJ03 (A-B). By cyclizing ARJJ03 (A-B) with chloroacetyl chloride in 1, 4-dioxane while triethylamine was present, the title compounds ARJJ04 (A-B) were produced. The UV, IR, NMR, and mass spectral data were used to characterise the synthesised derivatives. Ciprofloxacin and ketoconazole were used as reference medications in the agar streak dilution method to investigate the in-vitro antibacterial activity of compounds [ARJJ04 (A-B)].

Keywords: *Azetidinones, Furan, Methodology, Antimicrobial- screening*

1. INTRODUCTION

Human mucosal health is significantly impacted by a variety of parasite bacteria, including Salmonella typhimurium, Escherichia coli, Staphylococcus aureus, and S. pyogenes. Salmonella typhimurium, E. coli, S. aureus, and S. pyogenes infections may have caused severe tissue damage and perhaps fatal illnesses. Millions of people in impoverished nations suffer from food poisoning, rheumatic fever, and diarrhoea as a result of these bacterial parasites. [1, 2] Over 50 million individuals are afflicted globally, and up to 1,10,000 of them pass away each year. The most widely prescribed medications for this bacterial infection are amoxicillin, norfloxacin, and ciprofloxacin; however, they are linked to serious adverse effects.

[3] There is a serious risk of treatment failures and problems if the incidence of illnesses brought on by bacteria resistant to one or more antibiotic classes keeps rising. [4] As a result, numerous research teams have worked hard to identify novel antibacterial compounds.

Often referred to as 2-azetidinone (Azetidin-2-ones) or β-lactams, azetidinones are heterocyclic compounds with a carbonyl group at position 2. Even though the ring system has been understood since 1907, research into its chemistry didn't start until 1947. These are being used to treat bacterial infections with chemotherapy. Its distinct and deadly antibacterial effect is caused by specific inhibition during bacterial cell wall production [5]. Among pharmaceutical chemicals, β-lactams are well-known heterocyclic compounds due to their various pharmacological actions, which mostly involve antibacterial activity. Today Pencillins, cephalosporins, carbapenems, and monobactams are the main antibiotics that contain azetidinone in their fundamental structure. [6, 7] When β-lactam medications are used effectively, they put pressure on bacteria and prevent the growth of resistant organisms by preventing the manufacturing of their cell walls. Bacteria are fatally affected by this. However, bacteria that are resistant to beta-lactam antibiotics are present in lesser numbers within their population. By expressing the beta-lactamase gene or genes, they are able to achieve this resistance. [8] Numerous bacterial species have been shown to contain over 1000 distinct β-lactamase enzymes.

The chemical makeup and catalytic efficiency of these enzymes differ greatly. When beta-lactam drugs are used to treat bacterial populations that contain these resistant fractions, the resistant strain may become more common and, consequently, more virulent. [9] There is a growing need for medications with more specific and effective antibacterial activity today, and the pharmaceutical industry has developed several semi-synthetic and synthetic β-lactam antibiotics as a result of the alarming rise in bacterial resistance to β-lactam drugs when comparing current antibiotics with those from previous decades. [10] Many 3-chloro Monocyclic β-lactams have strong antifungal [11], antibacterial [12], anticonvulsant [13], anti-parkinsonian [14], anti-inflammatory [15], anti-HIV [16], antidiabetic [17], and antitubercular [18] properties, according to the paper. For many years, azetidinone-based penicillins and cephalosporins have been produced and used to treat a variety of illnesses. [19] They also have an effect on the central nervous system and act as enzyme inhibitors [20]. The enzymes human tryptase, chymase, thrombin, leukocyte elastase, human CMV protease, and serine protease have all been shown to be strongly inhibited by 2-azetidinones, according to reports [21]. In the realm of medicinal chemistry, furan is crucial. Derivatives of furan exhibit anti-inflammatory, anti-hypertensive, analgesic, antibacterial, antifungal, and anticancer effects [22]. A survey of the literature shows that no research was done on the anti-cancer potential of furan-azetidinone hybrids. Novel furan-azetidinone hybrids were created and synthesised in order to provide more powerful anti-cancer medications, taking into account the immense biological potential of both moieties.

2. EXPERIMENTAL WORK

Materials and Methods: All chemicals and solvents of LR grade were bought from Spectrochem Pvt Ltd. in Mumbai and utilised without additional purification. Uncorrected melting points were obtained using the open capillary method. Using silica gel-G as the stationary phase and suitable solvents for the mobile phase, thin-layer chromatography was utilised to determine the compounds' purity. A UV detector and an iodine chamber were used to see the spots. The Shimadzu 1900 was used to measure the synthesised compounds' λ max value. Using the DRS probe KBr pallet, IR spectra were captured using an FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan). The produced compounds' 1HNMR spectra were captured in DMSO-d6 solvent using a Bruker-Avance-II (400 MHz).Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan).

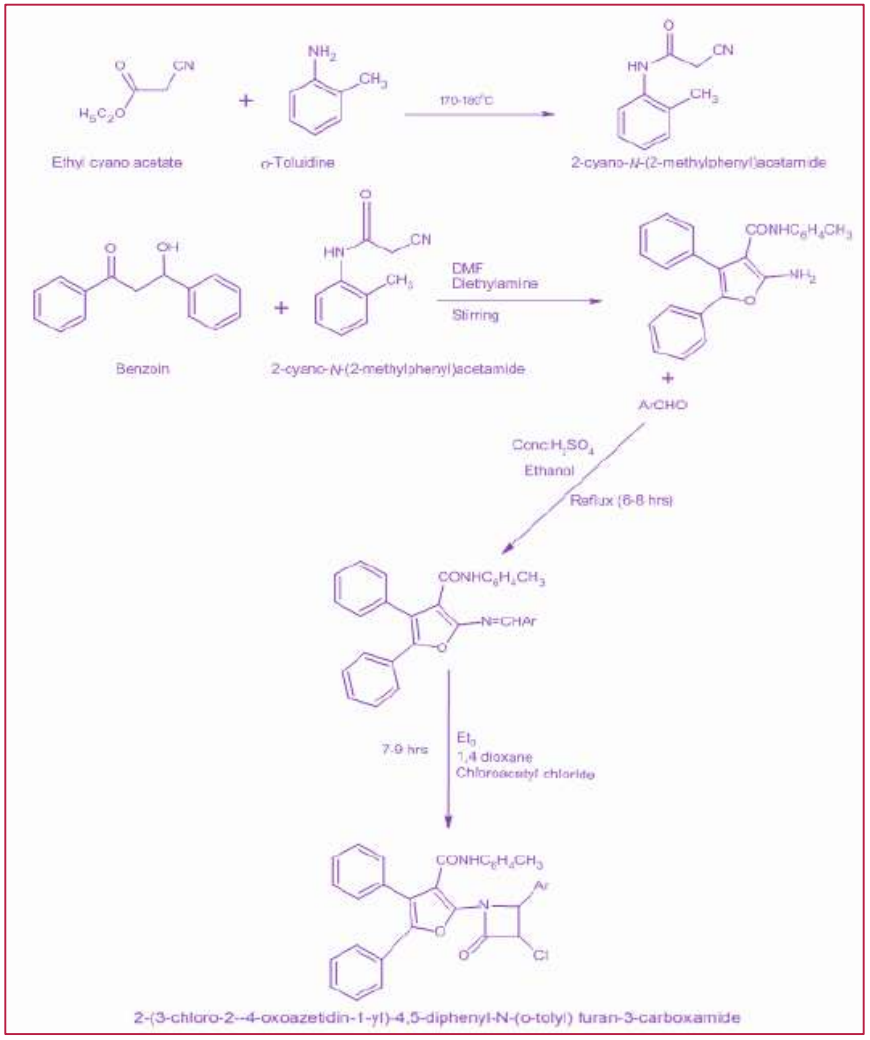
Synthesis of Furan-Azetidinone derivatives:

Procedure for Synthesis of 2-cyano-N-2(methylphenyl) Acetamide (1): In a conical flask, 0.1 mol (10.4 mL) of o-toluidine and 0.1 mol (11.3 mL) of ethyl cyanoacetate were combined, thoroughly mixed, and heated to 160–190 °C for four hours. Overnight, the reaction mixture was allowed to sit at room temperature. After obtaining a solid result, it was cleaned with ethanol and allowed to air dry. Isopropyl alcohol was used for recrystallisation in order to purify it. The result was a white, crystalline substance. [25]

Procedure for Synthesis of 2-amino-N-(2-methylphenyl) 4, 5 – diphenyl – furan – 3 – carboxamide (2): Benzoin (10.6g, 0.05mol) and methyl phenyl cyanoacetamide (8.0g, 0.05mol) were combined in 30mL of dimethylformamide at 0–5 °C, then diethyl amine (13.8g, 0.13mol) was added dropwise over the course of 30 minutes. For 16–18 hours, the reaction mixture was agitated at room temperature. 100 mL of ice-cold water was gradually added to the resultant mixture while stirring, and it was then allowed to sit at room temperature for an hour. After filtering and washing with three 10 mL of water, the solid was recrystallised from methanol. [26]

Procedure for synthesis of 2-((benzylidene) amino)-4,5-diphenyl-N-furan-3carboxamide (ARJJ03(1)-ARJJ03(2)) (3): A few drops of concentrated sulphuric acid were added to a combination of 2-amino-N-(2-methylphenyl)4, 5-diphenylfuran-3-carboxamide (0.01mol), and the corresponding aromatic aldehyde (0.01mol) in 30 millilitres of 100% ethanol. For eight to ten hours, the reaction mixture was refluxed. Ethanol was used to recrystallise the chemicals. [27]

Procedure for synthesis of 2-(3-chloro-2--4-oxoazetidin-1-yl) - 4, 5 – diphenyl – N - (o-tolyl) furan-3-carboxamide (ARJJ04(1)-ARJJ04(2)) (4A & 4B): Drop by drop, chloroacetyl chloride (0.01 mol) was added to a well-agitated solution of 1, 4-dioxane (25 ml) and substituted Schiff bases (0.01 mol). For one hour, the reaction mixture was stirred and refluxed for eight to twelve hours. The mixture was placed onto crushed ice, filtered, and dried once the reaction was complete. Absolute ethanol was used to perform recrystallisation. [28]



Scheme 1: Synthesis of Furan-Azetidinone derivatives [23, 24]

Antimicrobial activity: The agar streak dilution method was used in this investigation to screen all of the synthesised compounds for antibacterial activity. Four Gram-positive bacteria (Staphylococcus aureus ATCC 9144, Staphylococcus epidermidis ATCC 5634, Micrococcus luteus ATCC 8743, and Bacillus cereus ATCC 5433) and three Gram-negative bacteria (Escherichia coli ATCC 64322, Pseudomonas aeruginosa ATCC 644332, and Klebsiella pneumoniae ATCC 64332) were used to test the compounds' antibacterial activity. Two fungus, Aspergillus niger ATCC 7543 and Aspergillus fumigatus ATCC 6433, were used to test the synthetic compounds' antifungal efficacy. For testing of antibacterial and antifungal activities, bacterial strains were cultivated overnight in Mueller Hinton broth at 37°C, whereas yeast was cultivated overnight in YEPDE agar at 30°C. Test strains were suspended in nutrient agar to give a final density of 5 × 10-5 cfu/mL. [29-31]

Minimum inhibitory concentration (MIC): The agar streak dilution method was used to find the compound's MIC. [30] Graded amounts of the test compounds were added to a predetermined amount of molten sterile agar (Sabouraud's dextrose agar medium for antifungal activity and nutritional agar for antibacterial activity) after a stock solution of the synthesised compound in dimethyl formamide was created. A predetermined amount of the compound-containing medium (40–50°C) was added to a Petri dish until it reached a depth of 3–4 mm, and it was left to harden. For testing, a suspension of the microorganism containing around 5 × 10-5 cfu/mL was put to plates containing serially diluted substances in dimethyl formamide. The plates were then incubated at 37°C for 24 hours for bacteria and 48 hours for fungi. The minimum inhibitory

concentration (MIC) was defined as the concentration of the test material at which no discernible bacterial or fungal growth occurred on the plate. [32–35] In Tables 1 and 2, the observed MIC is displayed.

3. RESULTS AND DISCUSSION

A number of novel analogues, including 1, 2, 3, 4A, and 4B, were created and described in this paper. 2-cyano-N-2(methylphenyl) acetamide (1) was produced by condensation of o-toluidine and ethyl cyanoacetate at 160–190 °C. When (1) and benzoin were combined, 2-amino-N-(2-methylphenyl) 4, 5-diphenylfuran-3-carboxamide (2) was produced. Using concentrated sulphuric acid as a catalyst, (2) was refluxed with different substituted aromatic aldehydes in ethanol to create a series of Schiff bases ARJJ03 (A-B). By cyclizing ARJJ03 (A-B) with chloroacetyl chloride in 1, 4-dioxane while triethylamine was present, the title compounds ARJJ04 (A-B) were produced. Synthetic Scheme 1 provides a summary of the chemical reactions that were involved in the synthesis of the title compounds. The compounds were prepared and isolated using a process that produced materials with good purity, as shown by TLC and their spectrum studies. The UV, IR, NMR, and mass spectral data were used to characterise the synthesised derivatives.

Physicochemical Data and Spectral Analysis of the Synthesized Furan-Azetidinones:

2-cyano-N-2(methylphenyl) Acetamide (1): Percentage Yield, 78.64%; melting point 153°C; Rf value 0.45; Molecular formula $C_{11}H_{13}N_2O$; Molecular Weight 193; IR(KBR): 3245 (NH str, amide); 3132 (Ar CH, str); 3064 (CH str); 2674 (CN str); 1723 (C=O, str);1543,1543 (Ar C=C ring str). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 2.65–2.54 (d, 2H, CH_2 of acetamide), 3.76–3.76 (t, 1H, CH of acetamide), 4.54 (s, 2H, CH_2), 5.65 (s, 1H, NH), 7.65–8.75 (m, 18H, Ar–CH). MS ESI m/e= found 193 (M+) calculated: 193.

2-amino-N-(2-methylphenyl) 4, 5 – diphenyl – furan – 3 – carboxamide (2): Percentage Yield, 64.45%; melting point 134°C; Rf value 0.62; Molecular formula $C_{23}H_{22}N_2O_2$; Molecular Weight, 201; IR(KBR): 3311 (-NH str); 3123 (Ar C-H str); 1823 (C=O str of amide); 1611, (Ar C=C ring str); 1356 (C-N str, aromatic amines); 1276 (C-O-C str); 8633 (Substituted phenyl rings); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 2.64 (s, 3H, OCH_3), 2.86–3.19 (d, 2H, CH_2 of carboxamide), 3.34–3.54 (t, 1H, CH of carboxamide), 4.55 (s, 2H, CH_2), 5.62 (s, 1H, NH), 5.74 (s, 1H, OH), 7.07–8.09 (m, 17H, Ar–CH).; MS ESI m/e= found 201 (M+) calculated: 201.

2-((benzylidene) amino)-4,5-diphenyl-N-furan-3carboxamide (ARJJ03(1)-ARJJ03(2)) (3): Percentage Yield, 81.76%; melting point 145°C; Rf value 0.56; Molecular formula $C_{29}H_{24}N_3O_2$; Molecular Weight 354; IR (KBR cm^{-1}): 3345 (NH str of CONH); 3234 (Ar CH, str); 1875 (C=O str of amide);1743 (imine C=N str); 1643, 1442, 1411 (Ar C=C ring str); 1122 (C-O str); 1083 (C-O-C str); 704 (Substituted phenyl rings). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 3.46–3.56 (d, 2H, CH_2 of carboxamide), 3.65–3.79 (t, 1H, CH of carboxamide), 4.54 (s, 2H, CH_2), 5.53 (s, 1H, NH), 6.56–7.85 (m, 19H, Ar–CH), 8.23–8.49 (m, 2H, -CH = CH-). MS (ESI): m/z = found 354 [M+2]; cald. 354.

2-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-4,5-diphenyl-N- (o-tolyl) furan-3-carboxamide ARJJ04(4A). Percentage Yield, 73.59%; melting point 152 °C; Rf value 0.71; Molecular formula, $C_{31}H_{23}N_2O_2Cl_2$; Molecular Weight 576; IR (KBR): 3375 (N-H str), 3123 (SP^2 CH str), 2942 (SP^3 CH str), 1823 (C=O str), 1563 Ar (C=C str), 1411 (CH_2 bend), 1355 (CH3 bend), 1057(Ar Cl str), 875 (C-Cl str); ^{1}H NMR (400 MHz, DMSO) δ (ppm): 4.4 (1H, CH), 6.6 (1H, CH), 7.31- 7.45 (19H, Ar), 8.2 (1H, NH); MS (ESI): m/z = found 576 [M+2]; cald. 576.

2-(3-chloro – 2 - (3-nitrophenyl) – 4 - oxoazetidin-1-yl)-4, 5 – diphenyl – N - (o - tolyl) furan-3-carboxamide ARJJ04 (B). Percentage Yield, 79.65%; melting point 155 °C; Rf value 0.74; Molecular formula, $C_{34}H_{23}O_5N_3Cl_2$; Molecular Weight 583; IR (KBR): 3211 (amide N-H str), 3123 (Ar C-H str), 3084 (C-H str), 1843 (lactam C=O str), 1731 (amide C=O str), 1564, 1322 (Ar C=C ring str), 1533, 1421 (N-O str), 1256 (C-O-C str), 823 (Ar-Cl str); ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.64 (4H,Ar),7.64 (4H, Ar), 6.64 (2H,Ar), 6.87 (2H,Ar), 5.3 (2H, Ar) 8.1 (1H, NH);MS (ESI): m/z = found 583 [M+]; cald. 583.

IR, 1H NMR, and mass spectrum data were used to confirm the structures of the compounds listed in the title. While the intermediate ARJJ03 is verified by the disappearance of the doublet and the appearance of peaks at 1743 (imine C=N str) and [M]+ peak at 476, which is also the base peak indicating the stability of the Schiff's base, the intermediate 2-amino furan displays a broad peak, doublet at 3234 (-NH, str of H-bonded NH2 group).

The development of IR peaks at 1843 (lactam C=O str) and the NMR signals at δ 8.1 (1H, NH) and δ 7.31- 7.45 (1H, CH-Cl) of the azetidinone ring verified the presence of the β-lactam ring in the title compounds. In the typical area, the aromatic protons were seen as multiplets between δ 7.31 and 7.45. The M+ peak, which is also the base peak, is present in every molecule, suggesting that the molecular ion is rather stable. Two compounds were tested for anti-cancer activity based on the docking score.

Antimicrobial activity

The agar streak dilution method was used to screen all of the title compounds for their in vitro antibacterial activity. In parallel trials, the MICs of ketoconazole and ciprofloxacin were established in order to regulate the sensitivity of the test

organisms. The MIC values were identified as the lowest concentration at which the microorganisms' observable growth was completely suppressed. Tables 1 and 2 effectively display the MICs of the conventional medications and test compounds 1, 2, 3, 4A, and 4B.

According to the findings, compounds 1, 4A, and 4B showed activity against S. aureus that was comparable to that of ciprofloxacin. Compounds 4A and 4B displayed an equivalent activity (MIC: 7.81 µg/mL) against S. epidermidis, whereas the rest of the sequence displayed lesser activity (MIC: 31.25–62.5 µg/mL). Against M. luteus, compound 4B showed superior activity (MIC: 3.9 µg/mL) than standard drug, whereas compounds 1 and 4A exhibited comparable activity (MIC: 15.62 and 7.81 µg/mL) as Ciprofloxacin, while the others demonstrated trivial activity than the standard. Compounds 4A and 4B demonstrated equal activity (MIC: 7.81 µg/mL) as Ciprofloxacin, whereas the rest of the series exhibited shoddier activities than the standard against B. cereus. Compound 4B displayed potent activity (MIC: 7.81 µg/mL) than the standard, while the rest of the series exhibited lower activity against E. coli (MIC: 31.25–62.5 µg/mL). When tested against P. aeruginosa, compounds 1 and 4A showed comparable activity (MIC: 31.25 & 7.81 µg/mL) to the standard. Against K. pneumoniae, none of the synthesised compounds showed the same activity (MIC: 3.9 µg/mL) as Ciprofloxacin.

Table 1. Minimum inhibitory concentration in µg/mL of the synthesized compounds 1, 2, 3, 4A and 4B

Der.	***S. aureus***	***S. epidermidis***	***M. luteus***	***B. cereus***	***E. coli***	***P. aeruginosa***	***K. pnemoniae***
1	31.25	31.25	15.62	62.5	31.25	31.25	15.62
2	125	62.5	31.25	125	62.5	125	31.25
3	125	62.5	125	125	62.5	62.5	31.25
4A	15.62	7.81	7.81	7.81	15.62	7.81	31.25
4B	15.62	7.81	3.9	7.81	7.81	7.81	15.62
Cip.	15.62	7.81	7.81	7.81	7.81	7.81	3.9

Cip=Ciprofloxacin

With the exception of compounds 4A and 4B, all of the other compounds exhibited lower activity (MIC: 62.5–125 µg/mL) against A. niger than ketoconazole. While the other compounds displayed lower activity (MIC: 15.62 µg/mL) than the standard, compounds 4A and 4B demonstrated comparable activity (MIC: 7.81 µg/mL) against A. fumigates. 2-(3-chloro – 2- (3-nitrophenyl) – 4-oxoazetidin-1-yl)-4,5-diphenyl – N - (o - tolyl) furan-3-carboxamide (4B) was determined to be the more potent of the different investigated derivatives. While this chemical showed equivalent activity as standard against S. aureus, S. epidermidis, B. cereus, A. niger, and A. fumigatus, it shown superior action against M. leutus and E. coli.

Table 2. Minimum inhibitory concentration in µg/mL of the synthesized compounds 1, 2, 3, 4A and 4B

Der.	**A. niger**	**A. fumigates**
1	62.5	31.25
2	125	125
3	125	62.5
4A	15.62	7.81
4B	7.81	7.81
Cip.	7.81	7.81

Cip=Ciprofloxacin

4. CONCLUSION

FT-IR, 1H-NMR, mass spectroscopy, and elemental analysis were used to characterise a series of novel furan-attached azetidinone that were synthesised by a multistep chemical synthesis with the goal of creating a powerful antibacterial agent. The agar streak dilution method was used to screen all of the title compounds for in vitro antibacterial activity, and the minimum inhibitory concentration (MIC) was established against a range of microorganism strains. -(3-chloro - 2- (3-nitrophenyl) - 4- oxoazetidin-1-yl)-4, 5- diphenyl - N - (o - tolyl) furan-3-carboxamide (4B) shown superior activity among

the several compounds examined. This chemical could therefore be a lead molecule for the production of an antibacterial drug that is clinically beneficial.

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