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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SOME NOVEL FURAN-AZETIDINONE HYBRID COMPOUNDS

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ABSTRACT

A series of furan-azetidinone hybrid compounds were synthesized with the objective of arriving at potential lead antimicrobial compounds. The synthesis of 2-phenylcyano-N-phenylacetamide (1) was carried out by the condensation of ethyl cyanoacetate and aniline. This was the precursor for the synthesis of 2-amino-N, 4, 5-triphenyl furan-3-carboxamide (2). A series of Schiff bases 3 (a-h), were synthesized from 2-amino-N, 4, 5-triphenyl furan-3-carboxamide (2) by refluxing with various substituted aromatic aldehydes in ethanol using concentrated sulphuric acid as the catalyst. These were cyclized to give the furan-azetidinone hybrids 4 (a-h). Structures of the novel compounds were characterized by infrared (IR), ^{1}H nuclear magnetic resonance (NMR) and mass spectral analysis. The title compounds were screened for their antibacterial and antifungal activity by the cup plate method. All the compounds exhibited moderate activity against the screened microorganisms compared with the standard drugs. Compound 4b was found to be the most active against the screened bacterial and fungal strains.

KEY WORDS: ***Furan, Azetidinone, Antibacterial, Antifungal.***

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INTRODUCTION

Spread of drug-resistant bacteria has adversely affected the efficiency of many existing antibacterial agents.[1] Moreover there has been a significant rise of fungal infections in immune compromised populations over the past decades.[2] Antimicrobial resistance (AMR) is a significant health threat globally.[3-6] According to the world health organization (WHO), new resistance mechanisms are evolving and spreading worldwide, decreasing our ability to treat common infections resulting in prolonged illness, disability and death.[7] This has dictated the need for the synthesis of novel antibacterial and antifungal agents. The most widely prescribed antibiotics contain the azetidinone moiety or the β-lactam ring.[8-11] Nevertheless, the long term use of antibiotics has resulted in the emergence of resistant organisms. Azetidinone derivatives display antimicrobial, antifungal, antibacterial, antiviral, anticonvulsant, antioxidant, antimycobacterial, anthelmintic and cytotoxic activities.[12-13] Furan is an important moiety in medicinal chemistry. Synthetic compounds containing furan nucleus possess various pharmacological activities such as antibacterial, antifungal, antiviral, antidepressant, anti-inflammatory, anti-ulcer, diuretic and antihypertensive properties.[14-15] Literature review reveals that the synergistic antimicrobial efficacy of furan-azetidinone hybrids have not been explored. Keeping in view the enormous biological potential of both the moieties, novel furan- azetidinone hybrids were synthesized with the objective of obtaining more potent antimicrobials.

MATERIALS AND METHODS

All the chemicals and reagents used for the synthesis were purchased from Merck, Ranchem and SD fine-chem were of laboratory reagent grade, and used without further purification. The reactions were monitored by using a thin layer chromatography (TLC) on silica gel 60 F254 plates (Merck) for completion of the reaction; mobile phase solvents were selected as n-hexane and ethyl acetate (at different ratios for the various steps). Melting points of the compounds were determined in open capillary tubes using melting point apparatus (RAAGA) and were uncorrected. The purity of the compounds was checked on precoated TLC plates. All the compounds were characterized by FTIR spectrometer (FTIR-8400S, Shimadzu) using attenuated total reflection (ATR) method in the range of 400-4000 cm^{-1}mHz; ^{1}HNMR spectra were obtained from Brucker spectrometer operating at 400MHz using dimethyl sulphoxide (DMSO-d_6) as solvent. Chemical shifts were measured as parts per million downfield from tetramethylsilane (TMS) which is used as internal standard. The MS analyses were obtained in the scan range 100–1000 m/z, using the ESI (Electrospray ionization) mode.

Experimental

Procedure for the synthesis of 2-cyano-N-phenyl acetamide (1)

A mixture of aniline 0.1mol (9.3 mL) and ethyl cyanoacetate 0.1 mol (11.3 mL) were taken in a conical flask, mixed well and heated on a heating mantle at 160-170 °C for 4 hrs. The reaction mixture was left at room temperature overnight. The solid product obtained was washed with ethanol and dried in air. It was purified by recrystallization using n-propanol. White crystalline solid was obtained. Percentage Yield, 87.50%; mp 172°C; Rf value 0.72 ethyl acetate : n-hexane (6:4); Molecular formula $C_9H_8N_2O$; Molecular Weight 160; IR(KBR): 3232 (NH str, amide); 3120 (Ar CH, str); 2973(CH str); 2233 (CN str, nitriles); 1677 (C=O, str);1588,1433 (Ar C=C ring str)

Synthesis of 2-amino-N, 4, 5-triphenylfuran-3-carboxamide (2)[16-19]

Diethylamine (13.8g, 0.13mol) was added dropwise over a period of 30 minutes to a mixture of benzoin (10.6g, 0.05mol) and phenyl cyanoacetamide (8.0g, 0.05mol) in dimethylformamide (30mL) at 0-5□C. The reaction mixture was stirred at room temperature for 16 hours. The resulting mixture was added slowly with stirring to 100 mL of ice-cold water and left at room temperature for 1 hour. The solid obtained was filtered, washed with water (3x10mL) and recrystallized from methanol. The TLC solvent system used was ethylacetate: n-Hexane (6:4). Percentage Yield, 48.5%; mp 190°C; Rf value 0.77; Molecular formula $C_{23}H_{18}N_2O_2$; Molecular Weight 354 IR(KBR): 3308 and 3240, broad peak, doublet (-NH, str of H-bonded NH_2 group); 3096 (Ar C-H str); 1631(C=O str of amide); 1598, 1514, 1471 (Ar C=C ring str); 1293 (C-N str, aromatic amines); 1184 (C-O-C str); 709 (Substituted phenyl rings).

General procedure for the synthesis of 2-[aryl-2-yl methylidene) amino]-N,4,5-triphenyl furan -3-carboxamides [3a-p][20-22]

To a mixture of 2-amino-N,4,5-triphenyl furan-3-carboxamide (0.01 mol, 3.54 g) and the appropriate aromatic aldehyde (0.01mol) in absolute ethanol (20 mL) a few drops of concentrated sulphuric acid was added. The reaction mixture was refluxed for 6-8 hrs. After completion of the reaction it was allowed to cool, the solid obtained was filtered and recrystallized from ethanol.

Physicochemical data and spectral data of the intermediate schiff bases

2-[benzylidene amino]-N,4,5-triphenylfuran -3-carboxamide (3a)

Percentage Yield, 67.87%; mp 185 □C; Rf value 0.71 Ethyl acetate: n-Hexane (7:3); Molecular formula $C_{30}H_{22}N_2O_2$; Molecular Weight 442; IR (KBR v_{max} cm^{-1}): 3288 (NH str of CONH); 3031(Ar CH, str); 1683 (C=O str of amide);1610 (imine C=N str); 1450,1469,1505 (Ar C=C ring str); 1230 (C-O str); 1184 (C-O-C str); 682 (Substituted phenyl rings). ^{1}H NMR (400 MHz, DMSO) δ (ppm): δ 7.1-7.5 (20H,m, Ar-H)); δ 7.9 (1H, NH); δ 8.3 (1H, CH=N) MS (ESI): m/z = found 442 $[M^+]$ and 443 $[M+1]^+$ peak; calcd. 442. The $[M]^+$ peak is very stable and forms the base peak. Other fragments at m/z 353, 231, 148.

2-[(2-hydroxybenzylidene)amino]-*N*,4,5-triphenyl furan-3-carboxamide (3b)

Percentage Yield, 56.56%; mp 188 □C; Rf value 0.71 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{22}N_2O_3$; Molecular Weight 458;IR(KBR): 3209 (NH, str of CONH); 3172(OH str); 3070 (Ar CH, str); 1681

(C=O str of amide);1605 (imine C=N str); 1452,1504 (Ar C=C ring str); 1230 (C-O str); 1174 (C-O-C str); 684 (Substituted phenyl rings).

2-[(4-ethyl benzylidene) amino]-*N*,4,5-triphenyl furan-3-carboxamide (3c)
Percentage Yield, 57.44%; mp 182 °C; Rf value 0.61 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{32}H_{26}N_2O_2$; Molecular Weight 470;IR(KBR): 3222 (NH str of CONH); 3070 (Ar CH, str); 2945(CH str);1670 (C=O str of amide);1611 (imine C=N str); 1423,1452,1502 (Ar C=C ring str); 1230 (C-O str); 1188 (C-O-C str).

2-[(4-chlorobenzylidene)amino]-*N*,4,5-triphenylfuran-3-carboxamide (3d)
Percentage Yield, 63.02 %; mp 175 °C; Rf value 0.63 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{21}N_2ClO_2$; Molecular Weight 476.95;IR(KBR): 3357 (NH, str of CONH); 3076(Ar CH, str); 1683 (C=O, str);1612 (imine C=N str); 1440,1502 (Ar C=C ring str); 1224 (C-O str); 1172 (C-O-C str); 761 (Ar-Clstr); 696 (Substituted phenyl rings).

2-[(2,4-dichloro benzylidene)amino]-*N*,4,5-triphenylfuran-3-carboxamide (3e)
Percentage Yield, 58.7%; mp 182 °C; Rf value 0.64 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{20}N_2Cl_2O_2$; Molecular Weight 511.IR(KBR): 3294 (NH, str of CONH); 2941 (CH, str); 1666 (C=O, str); 1618 (imine C=N str); 1461,1502 (Ar C=C ring str); 1232 (C-O str); 1180 (C-O-C str); 788 (Ar-Clstr); 690 (Substituted phenyl rings).

2-[(2-nitrobenzylidene)amino]-*N*,4,5-triphenyl furan -3-carboxamide (3f)
Percentage Yield, 47.84%; mp 180 °C; Rf value 0.66 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{21}N_3O_4$; Molecular Weight 487;IR(KBR):3321 (NH str of CONH); 3060 (Ar CH str); 2983 (CH, str); 1676 (C=O str of amide);1604 (imine C=N str); 1442,1452,1504 (Ar C=C ring str); 1323 (NO_2str); 1236 (C-O str); 1180 (C-O-C str); 680 (Substituted phenyl rings).

2-[(4-nitrobenzylidene)amino]-*N*,4,5-triphenyl furan -3-carboxamide (3g)
Percentage Yield, 51.33%; mp 185 °C; Rf value 0.72 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{21}N_3O_4$; Molecular Weight 487;IR(KBR):3290 (NH str of CONH); 3096 (Ar CH, str); 2918 (CH str); 1683 (C=O str of amide); 1596 (imine C=N str); 1450,1504 (Ar C=C ring str); 1361 (NO_2str); 1226 (C-O str); 1176 (C-O-C str); 686 (Substituted phenyl rings).

2-[(4-methoxybenzylidene)amino]-*N*,4,5triphenyl furan -3-carboxamide (3h)
Percentage Yield, 63.55%; mp 187 °C; Rf value 0.74 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{31}H_{24}N_2O_3$; Molecular Weight 472;IR(KBR):3288 (NH str of CONH); 2929 (CH str); 1689 (C=O str of amide); 1612 (imine C=N str); 1448,1500 (Ar C=C ring str); 1228 (C-O str); 1174 (C-O-C str); 754 (Substituted phenyl rings).

2-[(3-methoxybenzylidene)amino]-*N*,4,5triphenyl furan -3-carboxamide (3i)
Percentage Yield, 68.25%; mp 182°C; Rf value 0.77Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{31}H_{24}N_2O_3$; Molecular Weight 472;IR(KBR):3285 (NH str of CONH); 2920 (CH str); 1673 (C=O str of amide); 1612 (imine C=N str); 1448,1500 (Ar C=C ring str); 1235 (C-O str); 1174 (C-O-C str); 760 (Substituted phenyl rings).

2-[(3-nitrobenzylidene)amino]-*N*,4,5-triphenyl furan -3-carboxamide (3j)
Percentage Yield, 50.36%; mp 182°C; Rf value 0.69 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{21}N_3O_4$; Molecular Weight 487;IR(KBR):3321 (NH str of CONH); 3060 (Ar CH str); 2983 (CH, str); 1676 (C=O str of amide);1606 (imine C=N str); 1442,1452,1504 (Ar C=C ring str); 1325 (NO_2str); 1236 (C-O str); 1182 (C-O-C str); 685 (Substituted phenyl rings).

2-[(3-chlorobenzylidene)amino]-*N*,4,5-triphenyl furan-3-carboxamide (3k)
Percentage Yield, 65.84 %; mp 170°C; Rf value 0.69Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{21}N_2ClO_2$; Molecular Weight 476.95;IR(KBR): 3357 (NH, str of CONH); 3076(Ar CH, str); 1683 (C=O, str);1612 (imine C=N str); 1440,1502 (Ar C=C ring str); 1224 (C-O str); 1172 (C-O-C str); 761 (Ar-Clstr); 696 (Substituted phenyl rings).

2-[(4-dimethylaminobenzylidene)amino]-*N*,4,5-triphenyl furan-3-carboxamide (3l)
Percentage Yield, 63.02 %; mp 175 °C; Rf value 0.63 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{21}N_2ClO_2$; Molecular Weight 485.55;IR(KBR): 3357 (NH, str of CONH); 3076(Ar CH, str); 1683 (C=O,str);1612 (imine C=N str); 1450,1512 (Ar C=C ring str); 1231 (C-O str); 1169 (C-O-C str); 696 (Substituted phenyl rings).

2-[(3, 4-dimethoxybenzylidene)amino]-*N*,4,5triphenyl furan -3-carboxamide (3m)
Percentage Yield, 68.25%; mp 184°C; Rf value 0.73 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{32}H_{26}N_2O_4$; Molecular Weight 472; IR(KBR): 3285 (NH str of CONH); 2920 (CH str); 1673 (C=O str of amide); 1612 (imine C=N str); 1448,1500 (Ar C=C ring str); 1235 (C-O str); 1174 (C-O-C str); 760 (Substituted phenyl rings).

2-[(3,4,5-trimethoxybenzylidene)amino]-*N*,4,5triphenylfuran -3-carboxamide (3n)
Percentage Yield 72.55%; mp 195°C; Rf value 0.77 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{33}H_{28}N_2O_5$; Molecular Weight 472;IR(KBR): 3289 (NH str of CONH); 2926 (CH str); 1673 (C=O str of amide); 1610 (imine C=N str); 1453,1502 (Ar C=C ring str); 1230 (C-O str); 1181 (C-O-C str); 767 (Substituted phenyl rings).

2-[(2,6-dichloro benzylidene)amino]-*N*,4,5-triphenyl furan-3-carboxamide (3o)
Percentage Yield 61.5%; mp 182 °C; Rf value 0.64 Ethyl acetate : n-Hexane (7:3); Molecular formula $C_{30}H_{20}N_2Cl_2O_2$; Molecular Weight 511.IR(KBR): 3292

(NH, str of CONH); 2939 (CH, str); 1666 (C=O, str); 1619 (imine C=N str); 1461,1502 (Ar C=C ring str); 1232 (C-O str); 1180 (C-O-C str); 792 (Ar-Clstr); 692 (Substituted phenyl rings).

2-[(furan-2-yl methylidene) amino]-N,4,5-triphenyl furan -3-carboxamide (3p)

Percentage Yield, 67.87%; mp 185 □C; Rf value 0.71 Ethyl acetate: n-Hexane (7:3); Molecular formula $C_{30}H_{22}N_2O_2$; Molecular Weight 442; IR (KBR ν_{max} cm^{-1}): 3286 (NH str of CONH); 3033(Ar CH, str); 1680 (C=O str of amide);1608 (imine C=N str); 1451,1469,1505 (Ar C=C ring str); 1230 (C-O str); 1184 (C-O-C str); 682 (Substituted phenyl rings).

General procedure for the synthesis of 2-[3-chloro-2-aryl-4-oxo azetidin-1-yl]-N, 4, 5-triphenyl furan-3-carboxamides.[23-25]

Chloroacetyl chloride (0.01 mol) was added drop wise to a well stirred solution of substituted schiff base 4(a-p) (0.01 mol) and triethylamine (0.01 mol) in 1,4-dioxane (25mL) at 5-10^0 C. The reaction mixture was stirred for an hour and refluxed for 6 hrs. The contents were cooled to room temperature and poured onto crushed ice. The precipitate obtained was filtered, washed with water, air dried and recrystallized from ethanol.

Physicochemical data and spectral analysis of the synthesized azetidinones

2-[3-chloro-2phenyl-4-oxo azetidin-1-yl]-N,4,5-triphenyl furan-3-carboxamide (4a)

Percentage Yield 79.34%; mp 150 □C; Rf value 0.68; Molecular formula $C_{32}H_{23}O_3N_2Cl$; Molecular Weight 519; IR(KBR): 3199 (amide N-H str),3078 (Ar C-H str), 2952 (C-H str),1713 (lactam C=O str), 1689 (amideC=O str), 1605,1468 (Ar C=C ring str),1163 (C-O-C str),754 (Ar-Cl str); ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.5 (1H,s, CH); δ 6.6 (1H,s, CHCl); δ 7.1-7.6 (20H,m, Ar-H)); δ 7.9 (1H, NH). MS (ESI): m/z = found 519 [M$^+$], 520 [M$^+$ +1] and 521 [M$^+$+ 2]; calcd. 518.98. [M+ 2] peak is due to isotopic effect of Cl. A fragment ion peak is formed at m/z 365 and 235. They correspond to the fragments [M]$^+$ formed after cleavage of the beta lactam ring and losing the C_6H_5NHCO- group respectively.

2-[3-chloro-2(2-hydroxyphenyl)-4-oxo azetidin-1-yl]-N,4,5-triphenyl furan-3-carboxamide (4b)

Percentage Yield 65.54%; mp 155 □C; Rf value 0.62; Molecular formula $C_{32}H_{23}$ O_4N_2Cl; Molecular Weight 535; IR(KBR): 3419 (OH str), 3191 (amide N-H str), 3078 (Ar C-H str), 2980 (C-H str),1731 (lactam C=O str),1684 (amide C=O str),1605,1517,1492 (Ar C=C ring str), 1151 (C-O-C str), 682 (Ar-Cl);^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.5 (1H, CH), 6.7 (1H, CHCl), 7.1-7.6 (19H, Ar) , 7.9 (1H, NH), 9.5 (1H, OH); MS (ESI): m/z = found 535 [M$^+$]; calcd. 534.98.

2-[3-chloro-2-(2-ethylphenyl)-4-oxo azetidin-1-yl]-*N,4,5*-triphenyl furan-3-carboxamide (4c)

Percentage Yield, 49.70 ; mp 150 □C; Rf value 0.45; Molecular formula $C_{34}H_{27}O_3N_2Cl$; Molecular Weight 547; IR(KBR): 3114 (amide N-H str), 3031 (Ar C-H str), 2879 (C-H str), 1766 (lactam C=O str), 1697 (amide C=O str), 1598,1461 (Ar C=C ring str), 1213 (C-O-C str), 763 (Ar-Cl str);^{1}H NMR (400 MHz, DMSO) δ (ppm): 1.2 (3H, CH_3), 2.6 (2H, CH_2), 5.5 (1H, CH), 6.7 (1H, CHCl), 7.1-7.8 (19H, Ar) , 7.9 (1H, NH); MS (ESI): m/z = found 547 [M$^+$]; calcd. 547.04.

2-[3-chloro-2-(4-chlorophenyl)-4-oxo azetidin-1-yl]-*N,4,5*-triphenyl furan-3-carboxamide (4d)

Percentage Yield, 54.24% ; mp 162 □C; Rf value 0.58; Molecular formula $C_{32}H_{22}O_3N_2Cl_2$;Molecular Weight 553.4; IR(KBR): 3172 (amide N-H str), 3076 (Ar C-H str). 2948 (C-H str), 1749 (lactam C=O str), 1697 (amide C=O str), 1605,1585,1492 (Ar C=C ring str), 1151 (C-O-C str), 688 (Ar-Cl str); ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.6 (1H, CH), 6.9 (1H, CHCl),7.1-7.7 (19H, Ar), 7.8 (1H, NH). MS (ESI): m/z = found 553 [M$^+$]; calcd. 553.43.

2-[3-chloro-2(2,4-dichlorophenyl)-4-oxo azetidin-1-yl]-N,4,5-triphenyl furan-3-carboxamide (4e)

Percentage Yield, 51.10% ; mp 165 □C; Rf value 0.61; Molecular formula $C_{32}H_{21}O_3N_2Cl_3$; Molecular Weight 588; IR(KBR): 3191 (amide N-H str), 3004 (Ar C-H str), 2962 (C-H str), 1766 (lactam C=O str), 1686 (amide C=O str), 1604,1581,1492 (Ar C=C ring str), 1153 (C-O-C str), 786 (Ar-Cl str); ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.6 (1H, CH), 7.0 (1H, CHCl), 7.1-7.8 (18H, Ar) , 7.9 (1H, NH); MS (ESI): m/z = found 588 [M$^+$]; calcd. 587.87.

2-[3-chloro-2(2-nitrophenyl)-4-oxo azetidin-1-yl]-N, 4,5-triphenyl furan-3-carboxamide (4f):-

Percentage Yield, 71.04%; mp 160 □C; Rf value 0.54; Molecular formula $C_{32}H_{22}O_5N_3Cl$; Molecular Weight 564; IR(KBR): 3107 (amide N-H str), 3078 (Ar C-H str), 2965 (C-H str), 1750(lactam C=O str), 1686 (amide C=O str), 1602,1421 (Ar C=C ring str), 1552,1365 (NO_2, asym, sym str), 1145 (C-O-C str), 763 (Ar-Cl str);^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.5 (1H, CH), 6.6 (1H, CHCl), 7.0-7.8 (19H, Ar) , 7.9 (1H, NH);MS (ESI): m/z = found 563 [M$^+$]; calcd. 563.04

2-[3-chloro-2(4-nitrophenyl)-4-oxo azetidin-1-yl]-N,4,5-triphenyl furan-3-carboxamide (4g):-

Percentage Yield, 62.16%; mp 164 □C; Rf value 0.64; Molecular formula $C_{32}H_{22}O_5$ N_3Cl; Molecular Weight 564; IR (KBR): 3191 (amide N-H str), 3033 (Ar C-H str), 2943 (C-H str), 1770 (lactam C=O str), 1686 (amide C=O str), 1596,1492 (Ar C=C ring str), 1548,1384 (NO_2, asym, sym str), 1157 (C-O-C str), 711 (Ar-Cl str);^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.3 (1H, CH), 6.9 (1H, CH), 7.2-7.6 (19H, Ar), 7.9 (1H, NH);MS (ESI): m/z = found 563 [M$^+$]; calcd. 563.04.

2-[3-chloro-2(4-methoxyphenyl)-4-oxo azetidin-1-yl]-N, 4, 5-triphenyl furan-3-carboxamide (4h)

Percentage Yield, 72.85%; mp 143 □C; Rf value 0.70; Molecular formula $C_{33}H_{25}O_4$ N_2Cl; Molecular Weight 549; IR(KBR): 3110 (amide N-H str), 3076 (Ar C-H str), 2964 (C-H str), 1780(lactam C=O str), 1691 (amide C=O str), 1606,1490 (Ar C=C ring str), 1153 (C-O-C str), 796 (Ar-Cl str) ^{1}H NMR (400 MHz, DMSO) δ (ppm): 3.3 (3H, CH_3), 5.5 (1H, CH), 6.7 (1H, CH), 7.4-7.7 (19H, Ar), 7.9 (1H, NH); MS (ESI): m/z = found 549 [M$^+$]; calcd. 549.01.

2-[3-chloro-2(3-methoxyphenyl)-4-oxoazetidin-1-yl]-N,4,5-triphenylfuran-3-carboxamide (4i)

Percentage Yield, 75.38%; mp 147 °C; Rf value 0.72; Molecular formula $C_{33}H_{25}O_4N_2Cl$; Molecular Weight 549; IR(KBR): 3160 (amide N-H str), 3070 (Ar C-H str), 2967 (C-H str), 1785 (lactam C=O str), 1694 (amide C=O str), 1601,1497 (Ar C=C ring str), 1156 (C-O-C str), 799 (Ar-Cl str):^{1}H NMR (400 MHz, DMSO) δ (ppm): 3.4 (3H, OCH_3),5.5 (1H, CH), 6.9 (1H, CHCl), 7.3-7.7 (19H, Ar) , 7.9 (1H, NH); MS (ESI): m/z = found 549 [M^+]; calcd. 549.01.

2-[3-chloro-2(3-nitrophenyl)-4-oxo azetidin-1-yl]-N,4,5-triphenyl furan-3-carboxamide (4j)

Percentage Yield, 79.41%; mp 162 °C; Rf value 0.58; Molecular formula $C_{32}H_{22}O_5N_3Cl$; Molecular Weight 564; IR(KBR): 3120 (amide N-H str), 3063 (Ar C-H str), 2958 (C-H str), 1765(lactam C=O str), 1684 (amide C=O str), 1591,1460 (Ar C=C ring str), 1541,1345 (NO_2, asym, sym str), 1150 (C-O-C str), 757 (Ar-Cl str);^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.4 (1H, CH), 6.8 (1H, CHCl), 7.0-7.8 (19H, Ar) , 7.9 (1H, NH);MS (ESI): m/z = found 563 [M^+]; calcd. 563.04.

2-[3-chloro-2-(3-chlorophenyl)-4-oxoazetidin-1-yl]-N,4,5-triphenylfuran-3-carboxamide (4k)

Percentage Yield, 74.42% ; mp 166 °C; Rf value 0.54; Molecular formula $C_{32}H_{22}O_3N_2Cl_2$; Molecular Weight 553; IR(KBR): 3153 (amide N-H str), 3039 (Ar C-H str). 2928 (C-H str), 1751 (lactam C=O str), 1693 (amide C=O str), 1587,1498 (Ar C=C ring str), 1148 (C-O-C str), 710 (Ar-Cl str); ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.6 (1H, CH), 7.0 (1H, CHCl),7.1-7.7 (19H, Ar), 7.9 (1H, NH); MS (ESI): m/z = found 553 [M^+]; calcd. 553.43

2-[3-chloro-2(4-dimethylaminophenyl)-4-oxo azetidin-1-yl]-N,4,5-triphenyl furan-3-carboxamide (4l)

Percentage Yield, 77.25%; mp 194 °C; Rf value 0.63; Molecular formula $C_{34}H_{28}O_3N_3Cl$; Molecular Weight 562; IR(KBR): 3155 (amide N-H str), 3053 (Ar C-H str), 2894 (C-H str), 1757(lactam C=O str), 1689 (amide C=O str), 1593,1486 (Ar C=C ring str), 1188 (C-O-C str), 762 (Ar-Cl str)

^{1}H NMR (400 MHz, DMSO) δ (ppm): 3.1 [6H, $N(CH_3)_2$],5.5 (1H, CH), 6.7 (1H, CHCl), 7.4-7.7 (19H, Ar) , 7.9 (1H, NH); MS (ESI): m/z = found 562 [M^+]; calcd. 562.05.

2-[4-chloro-2(3,4-dimethoxyphenyl)-4-oxoazetidin-1-yl]-N,4,5-triphenylfuran-3-carboxamide (4m)

Percentage Yield, 67.48%; mp 155 °C; Rf value 0.67; Molecular formula $C_{34}H_{27}O_5N_2Cl$; Molecular Weight 579; IR(KBR): 3191 (amide N-H str), 3056 (Ar C-H str), 2934 (C-H str), 1784(lactam C=O str), 1676 (amide C=O str), 1596,1487 (Ar C=C ring str), 1164 (C-O-C str), 766 (Ar-Cl str) ^{1}H NMR (400 MHz, DMSO) δ (ppm): 3.5 (6H, CH_3), 5.5 (1H, CH), 6.8 (1H, CHCl), 7.3-7.7 (18H, Ar), 7.9 (1H, NH); MS (ESI): m/z = found 579 [M^+]; calcd. 579.04.

2-[3-chloro-2(3,4,5-trimethoxyphenyl)-4-oxoazetidin-1-yl]-N,4,5-triphenylfuran-3-carboxamide (4n)

Percentage Yield, 71.45%; mp 164 °C; Rf value 0.57; Molecular formula $C_{35}H_{29}O_6N_2Cl$; Molecular Weight 609; IR(KBR): 3121 (amide N-H str), 3067 (Ar C-H str), 2976 (C-H str), 1782 (lactam C=O str), 1689 (amide C=O str), 1602,1485 (Ar C=C ring str), 1149 (C-O-C str), 784 (Ar-Cl str) ^{1}H NMR (400 MHz, DMSO) δ (ppm): 3.7 (9H, CH_3), 5.5 (1H, CH), 6.9 (1H, CHCl), 7.2-7.7 (17H, Ar), 7.9 (1H, NH); MS (ESI): m/z = found 609 [M^+]; calcd.609.06

2-[3-chloro-2(2,6-dichlorophenyl)-4-oxoazetidin-1-yl]-N,4,5-triphenylfuran-3-carboxamide (4o)

Percentage Yield, 56.50% ; mp 168 °C; Rf value 0.63; Molecular formula $C_{32}H_{21}O_3N_2Cl_3$;Molecular Weight 587;IR(KBR): 3210 (amide N-H str), 3044 (Ar C-H str), 2982 (C-H str), 1760 (lactam C=O str), 1684 (amide C=O str), 1600,1551,1490 (Ar C=C ring str), 1150 (C-O-C str), 775 (Ar-Cl str); ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.6 (1H, CH), 6.9 (1H, CHCl), 7.1-7.8 (18H, Ar) , 7.9 (1H, NH); MS (ESI): m/z = found 587 [M^+]; calcd. 587.02.

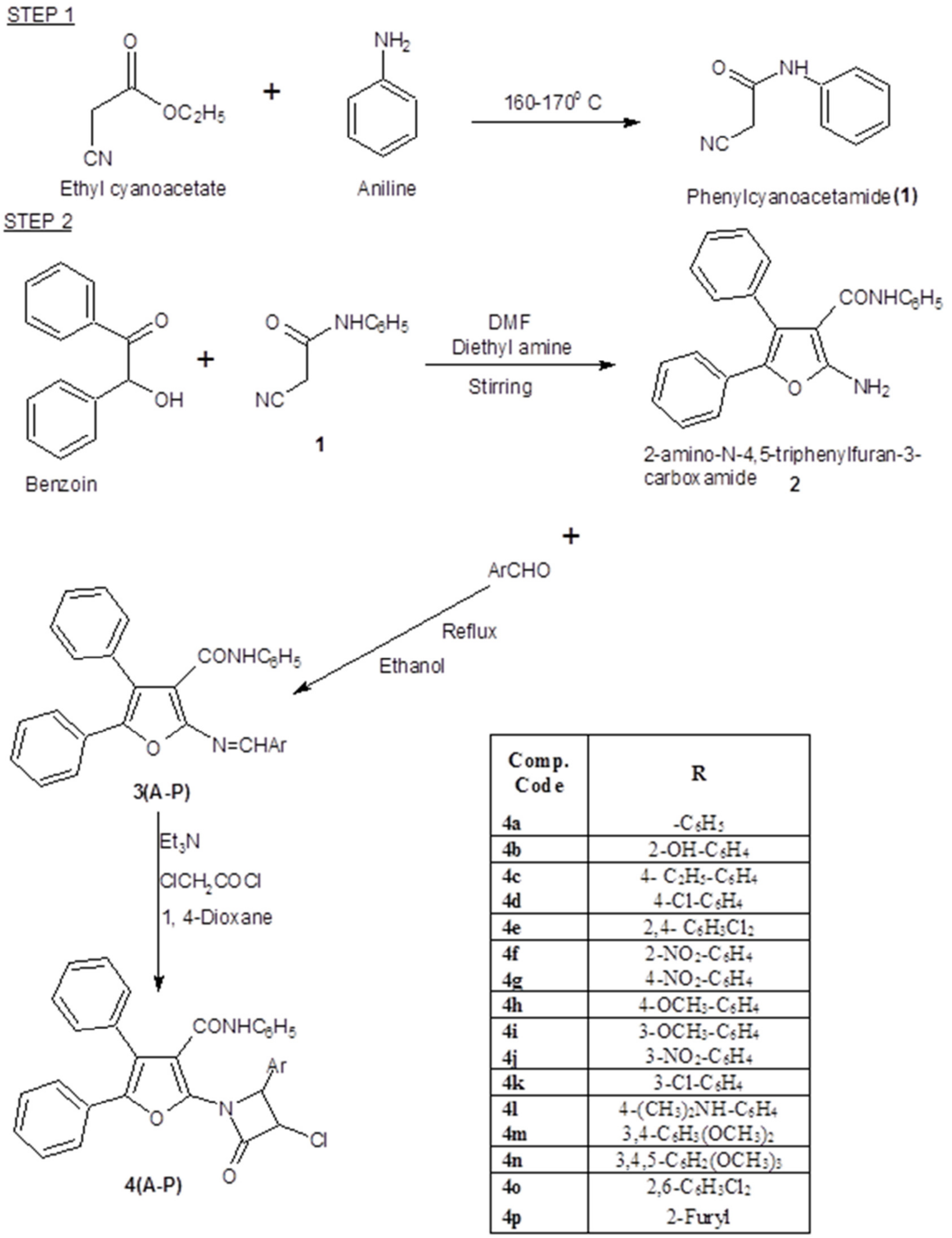
2-[3-chloro-2(furyl)-4-oxo azetidin-1-yl]-N,4,5-triphenyl furan-3-carboxamide (4p)

Percentage Yield, 82.65% ; mp 170°C; Rf value 0.66; Molecular formula $C_{30}H_{21}O_4N_2Cl$; IR(KBR v_{max} cm^{-1}): 3167 (amide N-H str), 3035 (Ar C-H str), 8296 (C-H str), 1770(lactam C=O str), 1697 (amide C=O str), 1595,1485 (Ar C=C ring str), 1168 (C-O-C str), 805 (Ar-Cl str);^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.5 (1H, CH), 6.8 (1H, CHCl), 7.3-7.7 (18H, Ar) , 7.9 (1H, NH); MS (ESI): m/z = found 509 [M^+]; calcd. 508.95.

Biological Activity [26, 27]

The title compounds 4 (a-p) were assessed for their antibacterial activity against gram positive bacteria *Staphylococcus aureus*, and *Bacillus subtilis,* and gram negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*. The cup plate method using the Mueller-Hinton agar medium was followed. Cups were formed in the nutrient agar with the help of a sterile borer. The test and standard solutions at concentrations of 1000µg/mL were added in this cup. The diameter of the zone of inhibition around each well was measured after incubation at 37±1°C for 24 hours. Standard drugs used for antibacterial activity were amoxicillin and ciprofloxacin. The title compounds were tested for their *in-vitro* antifungal activity against *Aspergillus Niger* and *Candida albicans* by the cup plate method. After incubation at 37±1°C for 72 hours, the zone of inhibition was measured in mm. Clotrimazole and Ketoconazole were used as the standards. The zone of inhibition of the compounds were measured and tabulated. All the experiments were carried out in triplicate and the results were taken as a mean of three determinations.

Scheme for the synthesis



Comp. Code	R
4a	$-C_6H_5$
4b	$2-OH-C_6H_4$
4c	$4-\ C_2H_5-C_6H_4$
4d	$4-Cl-C_6H_4$
4e	$2,4-\ C_6H_3Cl_2$
4f	$2-NO_2-C_6H_4$
4g	$4-NO_2-C_6H_4$
4h	$4-OCH_3-C_6H_4$
4i	$3-OCH_3-C_6H_4$
4j	$3-NO_2-C_6H_4$
4k	$3-Cl-C_6H_4$
4l	$4-(CH_3)_2NH-C_6H_4$
4m	$3,4-C_6H_3(OCH_3)_2$
4n	$3,4,5-C_6H_2(OCH_3)_3$
4o	$2,6-C_6H_3Cl_2$
4p	2-Furyl

RESULTS AND DISCUSSION

Synthesis of furan-azetidinone hybrids by the described method resulted in good yields of the products. Condensation of ethyl cyanoacetate and aniline at 160-170□C yielded 2-phenyl cyano-N-phenylacetamide (1). The reaction between (1) and benzoin yielded 2-amino-N,4,5-triphenyl furan-3-carboxamide (2). A series of schiff bases 3 (a-h), were synthesized from 2-amino-N,4,5-triphenyl furan-3-carboxamide (2) by refluxing it with various substituted aromatic aldehydes in ethanol using concentrated sulphuric acid as the catalyst. The title compounds 2-[3-chloro-2-(2-aryl)-4-oxo azetidin-1-yl]-*N,4,5*-triphenyl furan-3-carboxamides 4(a-p)were obtained by the cyclization of 3a-p with chloroacetyl chloride in dioxane in the presence of triethylamine. Melting points were determined by the open capillary tube method and were uncorrected. The course of the reaction and the purity of the compounds were checked by TLC using different solvent systems. The physical constants of the compounds and their spectral data are given in the experimental section. The structures of the title compounds were confirmed by IR, ^{1}H NMR and mass spectral data. The intermediate 2-amino furan (2), exhibits a broad peak, doublet at 3308 and 3240 (-NH, str of H-bonded NH_2 group); while intermediate 3a is confirmed by the disappearance of the doublet and appearance of peaks at 1610 (imine C=N str) and $[M]^+$ peak at 442 which is the also the base peak indicating the stability of the schiff's base. The presence of β-lactam ring in the title compounds were confirmed by the appearance of IR peaks at 1713-(lactam C=O str) and the NMR signals at δ 5.5 (1H, C*H*-N) and δ 6.6-6.9 (1H, C*H*-Cl) of azetidinone ring. The aromatic protons were observed in the usual region as multiplet between δ 7.1-7.8. All the compounds have shown the M^+ peak, which is also the base peak indicating that the molecular ion is quite stable. All the synthesized compounds were subjected to *in vitro* antimicrobial screening. The results of the antibacterial and antifungal activity of the compounds are given in Table 1 and Table 2 respectively. The preliminary screening indicated that most of the compounds exhibited mild to moderate antimicrobial activity against the tested strains of microorganisms.

Biological activity

The results of the antibacterial evaluation revealed that all the compounds showed moderate activity against *S.aureuas, B.subtilis and P.aeruginosa*. The compounds were comparatively lesser effective against *E.coli*, however compound 4c (4-ethyl derivative) exhibited reasonable activity against it. The compound 4b (4-hydroxy derivative), was found to be the most active against the screened gram positive strains. While compounds 4b and 4m (3, 4-dimethoxy derivative) exhibited the maximum activity against *P.aeruginosa*. The antifungal screening revealed that the compounds 4b (4-hydroxy derivative) and 4h (4-methoxy derivative) showed reasonable activity against *C.albicans* and *A.niger* when compared with the standard drugs. The other derivatives were only moderately active against both the fungal species, while the unsubstituted derivative 4a showed the least activity. Based on the results, it can be concluded that among the synthesized compounds, 4b is the most active against the screened bacterial and fungal strains. This indicates that the presence of electron donating hydroxyl group in the *para* position of the phenyl ring increases the antimicrobial activity. Hence 4b can be considered as a lead molecule for structural modifications and design of more effective antimicrobials.

Table 1
Antibacterial activity of 4[a-p]

Sl No.	**Comp. code**	**R**	**Zone of inhibition (mm)**			
			S.aureus	***B.subtilis***	***P.aeruginosa***	***E.coli***
1	4a	$-C_6H_5$	18	14	19	13
2	4b	$2-OH-C_6H_4$	20	21	18	14
3	4c	$4-C_2H_5-C_6H_4$	17	18	17	18
4	4d	$4-Cl-C_6H_4$	16	15	17	10
5	4e	$2,4-\ C_6H_3Cl_2$	14	12	15	11
6	4f	$2-NO_2-C_6H_4$	17	16	16	12
7	4g	$4-NO_2-C_6H_4$	15	14	17	10
8	4h	$4-OCH_3-C_6H_4$	19	18	16	12
9	4i	$3-OCH_3-C_6H_4$	13	12	14	11
10	4j	$3-NO_2-C_6H_4$	17	18	17	13
11	4k	$3-Cl-C_6H_4$	15	17	16	14
12	4l	$4-(CH_3)_2NH-C_6H_4$	16	16	14	15
13	4m	$3,4,-C_6H_3(OCH_3)_2$	18	17	18	10
14	4n	$3,4,5-C_6H_2(OCH_3)_3$	14	15	16	11
15	4o	$2,6-\ C_6H_3Cl_2$	17	16	17	15
16	4p	2-furyl	19	18	15	12
	Ciprofloxacin		36	41	34	35
	Amoxicillin		40	39	32	38
	Control (50% DMF)		NI	NI	NI	NI

Note: Average zone diameter of triplicate readings

Table 2
Antifungal activity of 4[a-p]

Sl No.	**Comp. code**	**R**	**Zone of inhibition (mm)**	
			C. albicans	***A.niger***
1	4a	$-C_6H_5$	18	10
2	4b	$2-OH-C_6H_4$	23	22
3	4c	$4-C_2H_5-C_6H_4$	19	18
4	4d	$4-Cl-C_6H_4$	13	14
5	4e	$2,4-\ C_6H_3Cl_2$	15	14

6	4f	2-NO_2-C_6H_4	14	12
7	4g	4-NO_2-C_6H_4	14	15
8	4h	4-OCH_3-C_6H_4	20	21
9	4i	3-OCH_3-C_6H_4	18	16
10	4j	3-NO_2-C_6H_4	15	17
11	4k	3-Cl-C_6H_4	16	15
12	4l	4-$(CH_3)_2NH$-C_6H_4	15	16
13	4m	3,4,-$C_6H_3(OCH_3)_2$	19	17
14	4n	3,4,5-$C_6H_2(OCH_3)_3$	17	18
15	4o	2,6- $C_6H_3Cl_2$	15	13
16	4p	2-furyl	14	17
	Clotrimazole		31	29
	Ketoconazole		28	27
	Control (50% DMF)		**NI**	**NI**

Note: Average zone diameter of triplicate readings

CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the antimicrobial activity of some novel furans containing an azetidinone nucleus. The compounds have been successfully synthesized according to the scheme. The products were obtained in good yields and no side products were formed. Physical characteristics like melting point, solubility, and Rf value have being determined. The structures of the title compounds were fully supported by the spectral data. The compounds were screened for their *in vitro* antibacterial and antifungal activity by the cup plate method. It was observed that some of the derivatives have shown moderate to reasonable antibacterial and anti-fungal activities against the representative panel of microorganisms. With these encouraging results, all the synthesized compounds can further be explored for structural modification and detailed microbiological investigations to arrive at possibly newer and more potent antimicrobials.

CONFLICT OF INTEREST

Conflict of interest declared none.

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