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SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL ACTIVITY OF PYRAZOLE CAPPED 2-AZITIDINONE DERIVATIVES

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ABSTRACT: A series of compound 3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)- 1H-pyrazol-4-yl)-1-(substituted phenyl)azetidin-2-one **(4a-n)** have been synthesized from 1-(4- ((E)-(substituted phenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone **(3a-n)** by the action of chloacetylchloride and TEA. The series of compound **(3a-n)** has been synthesized from the condensation reaction between 3-(4-fluorophenyl)-1-(2-phenylacetyl)- 1H-pyrazole-4-carbaldehyde **(2)** and aromatic amines in acidic media. Compound **(2)** has been synthesized from N'-(1-(4-fluorophenyl)ethylidene)-2-phenylacetohydrazide **(1)** by well-known Vilsmeier-haack reagent. The reaction conditions were established in well-equipped laboratory and by monitoring thoroughly. The structures of synthesized compounds were confirmed by elemental analysis and spectroscopic Techniques. Mainly FT-IR, ^{1}HNMR, ^{13}CNMR and Mass Spectrometry. Antimicrobial activities studied by using controlled standard i.e. 19±0.28 and 17.5±0.58 against Gram positive as well as Gram negative bacterial strains respectively. Compound **4-e** showed encourageous anti-bacterial activity and compound **4-h** and **4-n** showed moderate activity. The results promoted us to continue our research work to established further investigational study. Also to enhance the value of NCEs wish synthesized with modification.

KEYWORDS: Schiff Base, Pyrazole, Vilsmeier-haack reaction, 2-azetidinone, antibacterial, New Chemical Entities (NCEs), Structure Activity Relationship (SAR)

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1. INTRODUCTION

In order to synthesize the NCEs by capping different and established the synthetic strategy is the area of interest of researchers. It's actually a part of the drug designing and development. To synthesize the targeted molecule with reducing the different undesirable factors is the main aim of synthetic organic chemist. We expanded our criteria for enhancing our applicable research. Selected moieties like Pyrazole, 4-Oxo-quinazolines, 4-thiazolidinones, 2-azitidinones, 1,3,4-triazole, Oxadiazole and thiadiazole are having a special attention in the field of Advanced Medicinal Chemistry Research. Not even that but it's capped with other four, five or six member heterocycle to enhance their biological actions. Fused as well as capped ring systems with structural modification resulted in series of compounds for broadening their applications. Our broad literature survey[1], was with aim to study fused heterocycles which were subjected to their important biological applications. The most life threatening diseases nowadays are cancer and HIV. We targeted to start with established studies of these types of fused systems. Recently Khanam R.and et al. reported Piperazine clubbed with 2-azetidinone[2]. Some of reported compounds are able to suppresses proliferation, migration and induces apoptosis in human cervical cancer HeLa cells through oxidative stress mediated intrinsic mitochondrial pathway. 2-azetidinone pharmacophores which is also known as Piperazine scaffolds were reported for mechanistic studies.These scaffolds get involved in induction of apoptosis addressing these two moieties for human cervical cancer cells remain uncertain. Antimicrobial,antifungal and antitubercular activities have been reported by Tailor J H and et al.[3]. They synthesised 2-azetidinone and thiazolidine-4-one derivatives under mild reaction conditions. Dibenzothiazepine nucleus containing compounds produced via the reaction of (Z)-11-(2-(substituted benzylidene) hydrazinyl) dibenzo[b,f][1,4] thiazepine with chloro acetyl chloride and another via thiogycolic acid to produce thiazolidin-4-one. Some anti-diabetic and renoprotective activity have been showed by researchers[4], by incorporating benzazole, thiazolidinone and azetidin-2-one derivatives to pyrazole moiety. Some compounds showed moderate to good anti-diabetic potency. Some pyrazole scaffolds have catched eye to investigate and study to keep continue our this study of fused systems. As a five membered hetrocycle with two same hetero atoms with in sequence position is offering broad rang of applications. In drug development and in synthetic dye-stuff. The moiety,which capable to fused with β-lactam ring system and broading biological actions. Literature review resulted in numerous applicable studies. In extent of same interested moiety pyrazole, a nitrogen-containing heterocyclic compound and its derivatives have been invaluable as a source of biologically active agents[5]. In order to create opportunities to harness the full potentials of such studies pyrazole derivatives have been reported. In part, pharmaco-dymamic properties along with their structure–activity relationships (SAR) attempted to reveal the wide range of these compounds. Targeted for discovery of new drugs is to synthesize pyrazole derivatives and shows that this class of compounds are owing some recent

advances in synthetic medicinal chemistry as anticonvulsant[6]. Its now priority for researchers to keep keen interest in the pyrazole moiety for capping with another heterocycle which having broad range of pharmacological applicationss. These scaffolds are always attracted area for the point of view of their biological activities. In this presented work is focused the combine 2-azetidinone and pyrazole in a one molecule these are reported for their therapeutic use like, antidepressant and nootropic agents[7], antiproliferative[8], antioxidant[9], Antifungal[10-11], antitubercular and cholesterol absorption inhibitor[12], Antimicrobial[13]. The presented work is focused on syntheses 2-azitidinone derivatives capped with pyrazole ring. According to our broad literature survey, β-lactam moiety gives numerous biological activities. On the other hand second base moiety, which was selacted for the study and invastigation is Pyrazole. Both the system are having with our previously studied base moieties[14]. The multiple sustible activities of different pyrazole derivatives[15-21] and 2-azitidinones[22-31] have been prompetd us to deal with and keep contineued until hit the target of designed NCEs. We have planned to synthesised capped moieties with keeping its potentails and enhance their multiple activity. Synthesised hydrazone was cyclised by well known vilsmeier-haack reaction[32] to form corsponding pyrazole contain aldehyde goup. For expanding our research problem to creat a new ara for investigetion and open new window for further research we synthesized the presented molecules for its biological applications. The results are very promissing and encourageous.

2. MATERIALS AND METHODS

Melting points of all synthesized compounds were determined by an open capillary method using SSU melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-affinity-1 FT-IR spectrophotometer using ATR plate. Mass spectra taken by Shimadzu GC-MS. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400MHz spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. Frequency for ^{1}H resonance is 400 MHz and for ^{13}C resonance frequency is 100MHz. Elemental analysis of was carried out using Vario-El Cube Elemental analyzer within ±0.5% of the theoretical (calculated) values. All the data and results are tabulated in table1 and 2.

2.1 Synthesis

Synthesis of N'-(1-(4-fluorophenyl)ethylidene)-2-phenylacetohydrazide (1)

A mixture of Phenylacetic acid hydrazide (0.1mol, 15.0g) and 4-fluoroacetophenone (0.1mol, 12.0 ml) were dissolved separately in ethanol then mix well. Followed by addition of catalytic amount of glacial acetic acid mixture was refluxed for 4 hours. Completion of reaction was checked by TLC using n-hexane:ethylacetate eluent (60:40 v/v). After completion of the reaction obtained mass poured in crushed ice, filtered, dried and recrystallized in ethanol. M.P.162□. 87% yield was obtained. **IR cm^{-1}:** 1620(C=N), 1666(C=O), 3015(C-H aromatic); **^{1}H NMR**(δ ppm DMSO-d_6)**:** 3.44(-CH_2-), 7.06 to 7.6 (9 aromatic proton), 8.0(-NH-), 8.1(-N=CH-); **^{13}C NMR:**19.5(-CH_3),

42.55(-CH_2-), 116 to135 (Aromatic C), 165(C-F), 167(CH-CH_3), 176(C=O); MS: m/z: 257(M^{+1}); Mol. Wt.: 256.27; Anal. Calcd. for $C_{15}H_{13}FN_2O$: C, 70.30; H, 5.11; N, 10.93.Found: C, 70.26; H, 5.14; N, 10.97.

Synthesis of 3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazole-4-carbaldehyde (2)

0.08 mol (20.50g) of N'-(1-(4-fluorophenyl) ethylidene)-2-phenylacetohydrazide (1) was dissolved in anhydrous DMF. Stirred the reaction mixture for 10 minutes in cold condition at 0□ in this mixture 10 eq. of Vilsmeier reagent (DMF-$POCL_3$) was added drop-wise. After completion of the addition it was stirred at room temp for more 30 minutes then at 80□ for 5 hours. Reaction monitored by TLC. After completion of reaction obtained mass was poured in crushed-ice and basify by drop wise addition of 10% NaOH until solution brownish. The product precipitated out was filtered dried and recrystallized in ethanol.

M.P. 115□; 68% yield. **IR cm^{-1}:**1605(C=N), 1692(-CHO), 1665(C=O), 3032(C-H aromatic),**^{1}H NMR** δ ppm DMSO-d_6: 3.66(-CH_2-), 7.03 to 7.46 (9 aromatic proton), 7.5(CH Pyrazole), 9.61(-CHO); **^{13}C NMR:** 34.5(-CH_2-), 115-136(Aromatic C), 182(C=O); 194(-CHO); **MS:** m/z: 309(M^{+1}); Mol. Wt.: 308.31; **Anal. Calcd.** for $C_{18}H_{13}FN_2O_2$; C, 70.12; H, 4.25; N, 9.09; found: C, 70.18; H, 4.19; N, 9.14.

General procedure for Synthesis of 1-(4-((E)-(substituted phenylimino)methyl)-3- (4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone(3a-n)

Dissolved 3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazole-4-carbaldehyde (0.005 mol, 1.54g) **(2)** and aromatic amines (0.01mol) in 30 ml of ethanol catalytic amount of glacial acetic acid was added. Refluxed the mixture in a oil bath for 4 hours**.** Reaction was monitored by TLC. After completion of reaction whole reaction mass poured in cursed ice, crude product was filtered, dried and recrystalised in ethanol to give corresponding imines.

1-(4-((E)-(phenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3a)

IR cm^{-1}: 1508 (Ar, C=C), 1627(C=N), 1667(C=O), 3058(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.82(-CH_2-), 7.02 to 7.88 (14 aromatic proton), 7.35(CH Pyrazole), 7.44(CH=N); **^{13}C NMR:** 53.2(-CH_2-), 116-137(Aromatic C), 160.8(-CH=N-), 183(C=O); **MS:** m/z: 384(M^{+1}); Mol. Wt.: 383.42; **Anal. Calcd** for $C_{24}H_{18}FN_3O$; C, 75.18; H, 4.73; N, 10.96; found: C, 75.21; H, 4.69; N, 10.92.

1-(4-((E)-(2-chlorophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3b)

IR cm^{-1}: 1515 (Ar, C=C), 1622(C=N), 1662(C=O), 3052(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.95(-CH_2-), 7.03 to 7.87 (13aromatic proton), 7.32(CH Pyrazole), 7.48(CH=N); **^{13}C NMR:** 54.78(-CH_2-), 116-135(Aromatic C), 161.21(-CH=N-), 188(C=O); **MS:** m/z: 418(M^{+1}); Mol. Wt.: 417.86; **Anal. Calcd** for $C_{24}H_{17}ClFN_3O$; C, 68.98; H, 4.10; N, 10.06; found: C, 68.96; H, 4.15; N, 10.04.

1-(4-((E)-(4-chlorophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3c)

IR cm^{-1}: 1518 (Ar, C=C), 1626(C=N), 1664(C=O), 3049(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.93(-CH_2-), 7.03 to 7.89 (13 aromatic proton), 7.29(CH Pyrazole), 7.46(CH=N); **^{13}C NMR:** 55.83(-

CH_2-), 116-162(Aromatic C), 160.34(-CH=N-), 192.01(C=O); **MS:** m/z: 419(M^{+2}); Mol. Wt.: 417.86; **Anal. Calcd** for $C_{24}H_{17}ClFN_3O$; C, 68.98; H, 4.10; N, 10.06; found: C, 68.96; H, 4.15; N, 10.04

1-(4-((E)-(2-bromophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3d)

IR cm^{-1}: 1508 (Ar, C=C), 1630(C=N), 1663(C=O), 3054(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.95(-CH_2-), 7.03 to 7.89 (13 aromatic proton), 7.28(CH Pyrazole), 7.50(CH=N); **^{13}C NMR:** 56.42(-CH_2-), 112-163(Aromatic C), 160.08(-CH=N-), 191.13(C=O); **MS:** m/z: 463(M^{+1}); Mol. Wt.: 462.31; **Anal. Calcd** for $C_{24}H_{17}BrFN_3O$; C, 62.35; H, 3.71; N, 9.09; found: C, 62.41; H, 3.69; N, 9.11.

1-(4-((E)-(3-bromophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3e)

IR cm^{-1}: 1510(Ar, C=C), 1626(C=N), 1666(C=O), 3047(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.93(-CH_2-), 7.04 to 7.91 (13 aromatic proton), 7.31(CH Pyrazole), 7.46(CH=N); **^{13}C NMR:** 56.38(-CH_2-), 111-162(Aromatic C), 159.77(-CH=N-), 191.07(C=O); **MS:** m/z: 463(M^{+1}); Mol. Wt.: 462.31; **Anal. Calcd** for $C_{24}H_{17}BrFN_3O$; C, 62.35; H, 3.71; N, 9.09; found: C, 62.39; H, 3.66; N, 9.12.

1-(4-((E)-(4-bromophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3f)

IR cm^{-1}: 1506(Ar, C=C), 1634(C=N), 1667(C=O), 3053(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.95(-CH_2-), 7.02 to 7.88 (13 aromatic proton), 7.25(CH Pyrazole), 7.42(CH=N); **^{13}C NMR:** 56.44(-CH_2-), 113-164(Aromatic C), 160.04(-CH=N-), 192.07(C=O); **MS:** m/z: 463(M^{+1}); Mol. Wt.: 462.31; **Anal. Calcd** for $C_{24}H_{17}BrFN_3O$; C, 62.35; H, 3.71; N, 9.09; found: C, 62.43; H, 3.64; N, 9.17.

1-(4-((E)-(2-fluorophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3g)

IR cm^{-1}: 1519(Ar, C=C), 1623(C=N), 1665(C=O), 3046(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.98(-CH_2-), 7.04 to 7.90 (13 aromatic proton), 7.24(CH Pyrazole), 7.47(CH=N); **^{13}C NMR:** 56.54(-CH_2-), 114-163(Aromatic C), 160.29(-CH=N-),191.26(C=O); **MS:** m/z: 402(M^{+1}); Mol. Wt.: 401.41; **Anal. Calcd** for $C_{24}H_{17}F_2N_3O$; C, 71.81; H, 4.27; N, 10.47; found: C, 71.78; H, 4.30; N, 10.52.

1-(4-((E)-(4-fluorophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3h)

IR cm^{-1}: 1513(Ar, C=C), 1618(C=N), 1662(C=O), 3049(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.94(-CH_2-), 7.03 to 7.89 (13 aromatic proton), 7.26(CH Pyrazole), 7.51(CH=N); **^{13}C NMR:** 56.49(-CH_2-), 115-164(Aromatic C), 160.33(-CH=N-), 191.08(C=O); **MS:** m/z: 402(M^{+1}); Mol. Wt.: 401.41; **Anal. Calcd** for $C_{24}H_{17}F_2N_3O$; C, 71.81; H, 4.27; N, 10.47; found: C, 71.83; H, 4.32; N, 10.55.

1-(4-((E)-(4-nitrophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3i)

IR cm^{-1}: 1505(Ar, C=C), 1631(C=N), 1667(C=O), 3057(Ar, C-H);**^{1}H NMR** δ ppm DMSO-d_6: 4.95(-CH_2-), 7.28 to 7.85(13 aromatic proton), 7.29(CH Pyrazole), 7.46(CH=N); **^{13}C NMR:** 56.58(-

CH_2-), 114-163(Aromatic C), 160.09(-CH=N-), 191.03(C=O); **MS:** m/z: 429(M^{+1}); Mol. Wt.: 428.42; **Anal. Calcd** for $C_{24}H_{17}FN_4O_3$; C, 67.28; H, 4.00; N, 13.08; found: C, 67.23; H, 3.98; N, 13.11.

1-(4-((E)-(2-methoxyphenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3j)

IR cm^{-1}: 1512(Ar, C=C), 1625(C=N), 1663(C=O), 2829(OCH_3), 3047(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.65(OCH_3), 4.97(-CH_2-), 7.17 to 7.88(13 aromatic proton), 7.26(CH Pyrazole), 7.45(CH=N); **^{13}C NMR:** 54.87(OCH_3), 56.74(-CH_2-), 114-164(Aromatic C), 160.12(-CH=N-), 191.15(C=O); **MS:** m/z: 414(M^{+1}); Mol. Wt.: 413.44; **Anal. Calcd** for $C_{25}H_{20}FN_3O_2$; C, 72.63; H, 4.88; N, 10.16; found: C, 72.59; H, 4.92; N, 10.14.

1-(4-((E)-(3-methoxyphenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone(3k)

IR cm^{-1}: 1523(Ar, C=C), 1628(C=N), 1664(C=O), 2832(OCH_3), 3049(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.68(OCH_3), 4.94(-CH_2-), 7.15 to 7.86(13 aromatic proton), 7.24(CH Pyrazole), 7.47(CH=N); **^{13}C NMR:** 54.92(OCH_3), 56.69(-CH_2-), 113-162(Aromatic C), 159.87(-CH=N-), 191.01(C=O); **MS:** m/z: 415(M^{+2}); Mol. Wt.: 413.44; **Anal. Calcd** for $C_{25}H_{20}FN_3O_2$; C, 72.63; H, 4.88; N, 10.16; found: C, 72.65; H, 4.86; N, 10.20.

1-(4-((E)-(pyridin-2-ylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3l)

IR cm^{-1}: 1514(Ar, C=C), 1590(C=N), 1665(C=O),3025(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 4.96(-CH_2-), 7.08 to 7.87(13 aromatic proton), 7.27(CH Pyrazole), 7.45(CH=N); **^{13}C NMR:** 56.58(-CH_2-), 115-163(Aromatic C), 160.06 (-CH=N-), 191.05(C=O); **MS:** m/z: 385(M^{+1}); Mol. Wt.: 384.41; **Anal. Calcd** for $C_{23}H_{17}FN_4O$; C, 71.86; H, 4.46; N, 14.57; found: C, 71.82; H, 4.43; N, 14.61.

1-(4-((E)-(4-methylpyridin-2-ylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3m)

IR cm^{-1}: 1514(Ar, C=C), 1590(C=N), 1665(C=O), 3025(Ar, C-H); **^{1}H NMR** δ ppm DMSO-d_6: 2.45(-CH_3), 4.96(-CH_2-), 7.08 to 7.87(13 aromatic proton), 7.27(CH Pyrazole), 7.45(CH=N); **^{13}C NMR:** 56.58(-CH_2-), 115-163(Aromatic C), 160.06 (-CH=N-), 191.05(C=O); **MS:** m/z: 385(M^{+1}); Mol. Wt.: 384.41; **Anal. Calcd** for $C_{23}H_{17}FN_4O$; C, 71.86; H, 4.46; N, 14.57; found: C, 71.82; H, 4.43; N, 14.61.

1-(4-((E)-(2-chloro-4-nitrophenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone (3n)

IR cm^{-1}: 1502(Ar, C=C), 1587(C=N), 1664(C=O), 3023(Ar, C-H);**^{1}H NMR** δ ppm DMSO-d_6: 4.87(-CH_2-), 7.04 to 7.92(12 aromatic proton), 7.31(CH Pyrazole), 7.48(CH=N); **^{13}C NMR:** 56.56(-CH_2-), 117-164(Aromatic C), 160.09 (-CH=N-), 191.14(C=O); **MS:** m/z: 464(M^{+1}); Mol. Wt.: 462.86; **Anal. Calcd** for $C_{24}H_{16}ClFN_4O_3$; C, 62.28; H, 3.48; N, 12.10; found: C, 62.31; H, 3.52; N, 12.08.

General procedure for synthesis of 3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)- 1H-pyrazol-4-yl)-1-(substituted phenyl)azetidin-2-one(4a-n)

In a three neck RBF dissolved compound **3a-n** (0.0001 mol) in a 25ml of dry DMF. Then after a mixture of chloroacetylchloride (0.015mole) and TEA(Triethylamine) (0.015mol) in 15 ml of dry DMF was added at 0-5 °C with constant stirring. After completion of addition the reaction mixture was stirred at RT for 2 hours, then reaction mass was transferred to single neck RBF and refluxed for 6 hours. The reaction progress was monitored by TLC. After completion of reaction, was cooled to room temperature, and then poured into crushed-ice. The solid thus obtained mass solid was filtered, washed with cold-water and recrystallized by DMF.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(phenyl)azetidin-2-one (4a)

IR cm^{-1}: 1646 (C=O Amide),1760 (C=O, β-lactam), 759 (-C-Cl), 3039(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.57(-CH_2-), 4.12(>CH-Cl), 7.05 to 7.53(14 aromatic proton), 7.16(CH Pyrazole); **^{13}C NMR:** 36.23(-CH_2-), 57.6,63.8,163.24(β-lactam), 117-138(Aromatic C), 194.17(C=O); **MS:** m/z: 461(M^{+1}); Mol. Wt.: 459.9; **Anal. Calcd** for $C_{26}H_{19}ClFN_3O_2$; C, 67.90; H, 4.16; N, 9.14; found: C, 67.82; H, 4.23; N, 9.35.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(2-chlorophenyl)azetidin-2-one (4b)

IR cm^{-1}: 1672(C=O Amide),1758(C=O, β-lactam), 748(-C-Cl), 3035(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.62(-CH_2-), 4.25(>CH-Cl), 7.03 to 7.52(13 aromatic proton), 7.23(CH Pyrazole); **^{13}C NMR:** 36.03(-CH_2-), 56.42, 64.11, 164.53(β-lactam), 115-142(Aromatic C), 195.54(C=O); **MS:** m/z: 495(M^{+1}); Mol. Wt.: 494.34; **Anal. Calcd** for $C_{26}H_{18}Cl_2FN_3O_2$; C, 63.17; H, 3.67; N, 8.50; found: C, 63.25; H, 3.70; N, 8.49.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(4-chlorophenyl) azetidin-2-one (4c)

IR cm^{-1}: 1668(C=O Amide),1754(C=O, β-lactam), 750(-C-Cl), 3019(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.65(-CH_2-), 4.31(>CH-Cl), 7.04 to 7.49(13 aromatic proton), 7.33(CH Pyrazole); **^{13}C NMR:** 36.01(-CH_2-), 56.39, 64.08, 164.62(β-lactam), 116-143(Aromatic C), 194.85(C=O); **MS:** m/z: 493(M^{-1}); Mol. Wt.: 494.34; **Anal. Calcd** for $C_{26}H_{18}Cl_2FN_3O_2$; C, 63.17; H, 3.67; N, 8.50; found: C, 63.13; H, 3.69; N, 8.44.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(2-bromophenyl)azetidin-2-one (4d)

IR cm^{-1}: 1664(C=O Amide),1743(C=O, β-lactam), 750(-C-Cl), 3027(Ar C-H);**^{1}H NMR** δ ppm DMSO-d_6: 3.71(-CH_2-), 4.36(>CH-Cl), 7.07 to 7.50(13 aromatic proton), 7.28(CH Pyrazole); **^{13}C NMR:** 36.42(-CH_2-), 56.50, 64.31, 164.08(β-lactam), 114-160(Aromatic C), 194.39(C=O); **MS:** m/z: 540(M^{+1}); Mol. Wt.: 538.8; **Anal. Calcd** for $C_{26}H_{18}BrClFN_3O_2$; C, 57.96; H, 3.37; N, 7.80; found: C, 57.87; H, 3.42; N, 7.76.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(3-bromophenyl)azetidin-2-one (4e)

IR cm^{-1}: 1662(C=O Amide),1756(C=O, β-lactam), 754(-C-Cl), 3031(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.69(-CH_2-), 4.28(>CH-Cl), 7.04 to 7.52(13 aromatic proton), 7.24(CH Pyrazole); **^{13}C NMR:** 36.11(-CH_2-), 56.37, 64.20, 164.49(β-lactam), 116-162(Aromatic C), 195.03(C=O); **MS:** m/z: 540(M^{+1}); Mol. Wt.: 538.8; **Anal. Calcd** for $C_{26}H_{18}BrClFN_3O_2$; C, 57.96; H, 3.37; N, 7.80; found: C, 57.85; H, 3.47; N, 7.72.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(4-bromophenyl)azetidin-2-one (4f)

IR cm^{-1}: 1663(C=O Amide),1752(C=O, β-lactam), 751(-C-Cl), 3026(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.64(-CH_2-), 4.27(>CH-Cl), 7.02 to 7.53(13 aromatic proton), 7.27(CH Pyrazole); **^{13}C NMR:** 36.07(-CH_2-), 56.50, 64.21, 164.49(β-lactam), 116-143(Aromatic C), 195.62(C=O); **MS:** m/z: 540(M^{+1}); Mol. Wt.: 538.8; **Anal. Calcd** for $C_{26}H_{18}BrClFN_3O_2$; C, 57.96; H, 3.37; N, 7.80; found: C, 57.89; H, 3.42; N, 7.83.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(2-fluorophenyl)azetidin-2-one (4g)

IR cm^{-1}: 1666(C=O Amide),1749(C=O, β-lactam), 751(-C-Cl), 3024(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.59(-CH_2-), 4.31(>CH-Cl), 7.02 to 7.50(13 aromatic proton), 7.27(CH Pyrazole); **^{13}C NMR:** 36.05(-CH_2-), 56.34, 64.23, 164.49(β-lactam), 114-143(Aromatic C), 195.72(C=O); **MS:** m/z: 479(M^{+1}); Mol. Wt.: 477.89; **Anal. Calcd** for $C_{26}H_{18}ClF_2N_3O_2$: C, 65.35; H, 3.80; N, 8.79; found: C, 65.29; H, 3.77; N, 8.87.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(4-fluorophenyl)azetidin-2-one (4h)

IR cm^{-1}: 1667(C=O Amide),1755(C=O, β-lactam), 740(-C-Cl), 3020(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.59(-CH_2-), 4.28(>CH-Cl), 7.02 to 7.49(13 aromatic proton), 7.19(CH Pyrazole); **^{13}C NMR:** 36.28(-CH_2-), 56.31, 64.27, 164.68(β-lactam), 116-164(Aromatic C), 196.03(C=O); **MS:** m/z: 479(M^{+1}); Mol. Wt.: 477.89; **Anal. Calcd** for $C_{26}H_{18}ClF_2N_3O_2$; C, 65.35; H, 3.80; N, 8.79; found: C, 65.40; H, 3.74; N, 8.82.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(4-nitrophenyl)azetidin-2one(4i)

IR cm^{-1}: 1659(C=O Amide),1753(C=O, β-lactam), 751(-C-Cl), 3025(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.72(-CH_2-), 4.33(>CH-Cl), 7.04 to 8.27(13 aromatic proton), 7.32(CH Pyrazole); **^{13}C NMR:** 36.25(-CH_2-), 56.16, 64.29, 164.62(β-lactam), 114-145(Aromatic C), 196.14(C=O); **MS:** m/z: 495(M^{+1}); Mol. Wt.: 504.9; **Anal. Calcd** for $C_{26}H_{18}ClFN_4O_4$; C, 61.85; H, 3.59; N, 11.10; found: C, 61.79; H, 3.62; N, 11.17.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(2-methoxyphenyl)azetidin-2-one (4j)

IR cm^{-1}: 1660(C=O Amide),1757(C=O, β-lactam), 754(-C-Cl), 2845(OCH_3), 3034(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.68(-CH_2-) 4.97(OCH_3), 4.29(>CH-Cl), 7.02 to 7.48(13 aromatic proton), 7.21(CH Pyrazole); **^{13}C NMR:** 36.12(-CH_2-), 52.17(OCH_3), 56.55, 64.23, 164.64(β-lactam), 117-154(Aromatic C), 196.78(C=O); **MS:** m/z: 495(M^{+1}); Mol. Wt.: 489.93; **Anal. Calcd** for $C_{27}H_{21}ClFN_3O_3$; C, 66.19; H, 4.32; N, 8.58; found: C, 66.23; H, 4.28; N, 8.66.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(3-methoxyphenyl)azetidin-2-one (4k)

IR cm^{-1}: 1662(C=O Amide),1754(C=O, β-lactam), 750(-C-Cl), 2838(OCH_3), 3028(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.45(-CH_2-) 4.92(OCH_3), 4.36(>CH-Cl), 7.03 to 7.49(13 aromatic proton), 7.26(CH Pyrazole); **^{13}C NMR:** 36.25(-CH_2-), 52.30(OCH_3), 56.70, 64.29, 164.72(β-lactam), 115-154(Aromatic C), 196.43(C=O); **MS:** m/z: 495(M^{+1}); Mol. Wt.: 489.93; **Anal. Calcd** for $C_{27}H_{21}ClFN_3O_3$; C, 66.19; H, 4.32; N, 8.58; found: C, 66.16; H, 4.37; N, 8.49.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(pyridin-2-yl)azetidin-2-one (4l)

IR cm^{-1}: 1666(C=O Amide),1759(C=O, β-lactam), 749(-C-Cl), 3023(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.71(-CH_2-), 4.26(>CH-Cl), 7.02 to 8.54(13 aromatic proton), 7.29(CH Pyrazole); **^{13}C NMR:** 36.14(-CH_2-), 55.87, 64.75, 164.63(β-lactam), 114-144(Aromatic C), 196.07(C=O); **MS:** m/z: 461(M^{+1}); Mol. Wt.: 460.89; **Anal. Calcd** for C25H18ClFN4O2; C, 65.15; H, 3.94; N, 12.16; found: C, 65.09; H, 3.88; N, 12.21.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(4-methylpyridin-2-yl)azetidin-2-one(4m)

IR cm^{-1}: 1665(C=O Amide), 1752(C=O, β-lactam), 738(-C-Cl), 3022(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 2.44(-CH_3), 3.70(-CH_2-), 4.34(>CH-Cl), 7.01 to 8.22 (12 aromatic proton), 7.27(CH Pyrazole); **^{13}C NMR:** 25.07(CH_3), 36.24(-CH_2-), 56.19, 64.43, 164.73 (β-lactam), 114-152 (Aromatic C), 197.01(C=O); **MS:** m/z: 476(M^{+1}); Mol. Wt.: 474.9; **Anal. Calcd** for $C_{26}H_{20}ClFN_4O_2$; C, 65.75; H, 4.24; N, 11.80 found: C, 65.82; H, 4.26; N, 11.76.

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(2-chloro-4-nitrophenyl) azetidin-2-one (4n)

IR cm^{-1}: 1666(C=O Amide),1758(C=O, β-lactam), 756(-C-Cl), 3061(Ar C-H); **^{1}H NMR** δ ppm DMSO-d_6: 3.72(-CH_2-), 4.25(>CH-Cl), 7.05 to 8.15(12 aromatic proton), 7.38(CH Pyrazole); **^{13}C NMR:** 36.27(-CH_2-), 54.16, 63.03, 163.67(β-lactam), 115-163(Aromatic C), 197.64(C=O); **MS:** m/z: 540(M^{+1}); Mol. Wt.: 539.34; **Anal. Calcd** for $C_{26}H_{17}Cl_2FN_4O_4$; C, 57.90; H, 3.18; N, 10.39; found: C, 57.83; H, 3.23; N, 10.47.

Table 1: Physical properties of 1-(4-((E)-(substituted phenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone(3a-n)

Sr. No.	Comp. No.	R	% yield	M.P. ^{0}C
1.	3a	-C_6H_5	73.26	107
2.	3b	2-Cl, C_6H_4	80.05	126
3.	3c	4-Cl, C_6H_4	74.40	121
4.	3d	2-Br, C_6H_4	73.19	132
5.	3e	3-Br, C_6H_4	70.31	140
6.	3f	4-Br, C_6H_4	73.47	151
7.	3g	2-F, C_6H_4	69.24	124
8.	3h	4-F, C_6H_4	70.05	133
9.	3i	4-NO_2, C_6H_4	70.89	139
10.	3j	2-OCH_3, C_6H_4	76.34	122
11.	3k	3-OCH_3, C_6H_4	70.63	127
12.	3l	NC_5H_4	68.12	109
13.	3m	4-$CH_3NC_5H_4$	70.03	119
14.	3n	2-Cl, 4-NO_2, C_6H_3	69.13	114

Table 2: Physical properties of 3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(substituted phenyl)azetidin-2-one(4a-n)

Sr. No.	Comp. No.	R	% yield	M.P. 0C
1.	4a	$-C_6H_5$	68.32	168
2.	4b	2-Cl, C_6H_4	70.54	145
3.	4c	4-Cl, C_6H_4	64.75	152
4.	4d	2-Br, C_6H_4	71.62	155
5.	4e	3-Br, C_6H_4	69.33	139
6.	4f	4-Br, C_6H_4	67.49	166
7.	4g	2-F, C_6H_4	72.81	158
8.	4h	4-F, C_6H_4	70.79	144
9.	4i	4-NO_2, C_6H_4	68.70	164
10.	4j	2-OCH_3, C_6H_4	73.46	149
11.	4k	3-OCH_3, C_6H_4	66.23	155
12.	4l	NC_5H_4	59.46	123
13.	4m	4-$CH_3NC_5H_4$	60.78.	145
14.	4n	2-Cl, 4-NO_2, C_6H_3	70.18	149

2.2 Microorganisms and growth media

Two pathogenic strains one gram negative and one gram positive organisms were selected based on their clinical and pharmacological importance, i.e. *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) respectively. The bacterial strains were acquired from ATCC Hi-media. The bacterial culture was grown in Mueller-Hinton agar (MHA) plates at 37°C for 24 hours incubation.

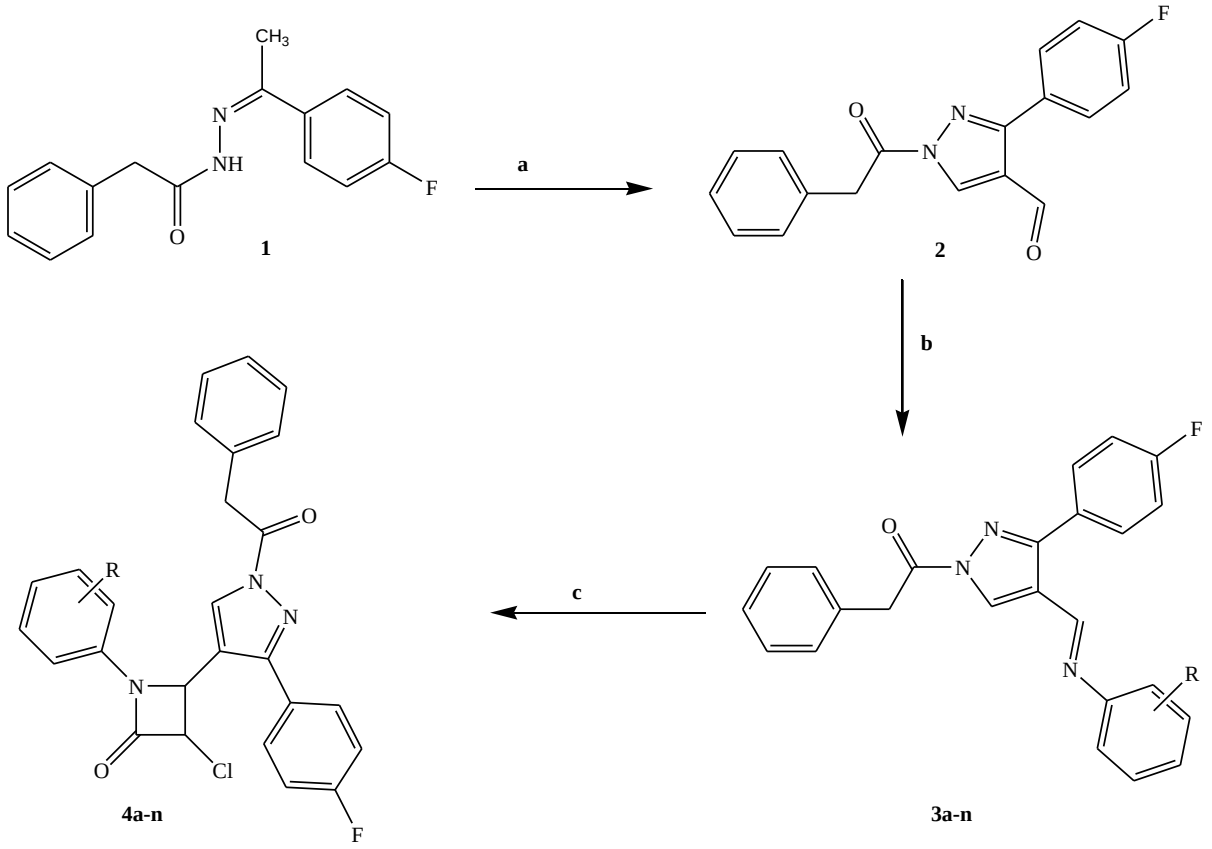
2.3 Antimicrobial activity

Antibacterial activity was performed for 4(a-n) synthesized products against *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923). Standard drugs Tetracycline and Imipenem were selected for gram positive and gram negative organisms respectively. Muller-Hinton sterile agar plates were seeded with both the strains with synthesized compounds from 4a-n and kept at 37°C for 24 hours. The zone of growth inhibition around the drugs and synthesized compounds were measured after 24 hours incubation. The sensitivity of the organisms against synthesized compounds were checked by measuring the size if inhibitory zone on the agar surface. 4e shows best result compare to standard i.e. 19±0.28 and 17.5±0.58 from gram positive and gram negative

respectively. While compound 4h shows weakest sensitivity 9.5±0.68 against gram positive and compound 4n shows weakest sensitivity 8±0.75 against gram positive organisms compared to other synthesized compounds.

Table 3: Antibacterial screening of the compounds 4a-n

Comp. No.	Zone of inhibition (mm)	
	E.coli	S.aureus
4a	17.5±0.63	12±0.48
4b	12±0.53	13.5±0.60
4c	16.6±0.23	10.5±0.80
4d	14.5±0.84	14±1.40
4e	19±0.28	17.5±0.58
4f	12.5±0.75	12.5±0.74
4g	18.5±0.46	11.5±0.49
4h	9.5±0.68	14.5±0.66
4i	16±0.87	10.5±0.87
4j	16.5±0.50	8.5±0.54
4k	15.5±0.60	10.5±0.94
4l	18±0.48	11±0.69
4m	18.5±0.53	13.5±0.65
4n	13.5±0.55	8±0.75
STD for Bac.	Tetracycline (gram +ve) Imipenem (gram –ve)	>19 >23



Scheme-1

Reaction conditions

a= addition at 0^0C about 10 minutes, stirred for 30 minutes to mix thoroughly, refluxed for 5 hours at 80^0C.; **b**= in presence of catalytic acetic acid, refluxed in ethanol for 4 hours. ; **c**= Addition of chloroacetyl chloride and TEA in dry DMF at 0-5^0C, Stirred the mixture at RT for 2 hours, Refluxed for 6 hours.

3. RESULTS AND DISCUSSION

3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(substituted phenyl)azetidin -2-one **(4a-n)** have been synthesized by step-up conventional method. Phenylacetic acid hydrazide and 4-flouroacetophenone condensed in acidic media using ethanol solvent to form N'-(1-(4-fluorophenyl)ethylidene)-2-phenylacetohydrazide**(1).** This Schiff's base (1) is accelerated in DMF to get 3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazole-4-carbaldehyde **(2)** by Vilsmeier-haack reagent (DMF-$POCL_3$). Which was confirmed by IR frequency found at 1695cm^{-1} and ^{1}H NMR 9.6 δ ppm of –CHO group. Compound (2) reacts with different aromatic amines in ethanol in the presence of catalytic amount of glacial acetic acid to get 1-(4-((E)-(substituted phenylimino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)-2-phenylethanone **(3a-n).** Imines group (-CH=N-) of compounds **(3a-n)** were confirmed by IR frequency found between 1615-1630cm^{-1} and ^{1}H NMR shift between 7.48-7.55 δ ppm. The targeted compounds 4(a-n) were produced by the final step-up reaction by the action of chloroacetylchloride and triethylamine in dimethyl formamide. Carbonyl group of β-lactam ring has been confirmed by IR spectra. Which showed absorption

between 1743-1760 $cm^{-1}$and ^{1}H NMR spectra of compounds 4(a-n) showed between 4.12-4.36 δ ppm, indicating the presence of -CH-Cl. These characterization data are supporting to confirm the formation of β-lactam ring. All the targeted compounds were also subjected for their anti-microbial activities. Our findings are encourageous and boosts for further expansion of area.

4. CONCLUSION

A new series of 3-chloro-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1H-pyrazol-4-yl)-1-(substituted phenyl) azetidin-2-one **(4a-n)** were synthesized in multistep-up procedure. The cyclisation of compounds 3(a-n) is the key initiator to hit the targeted compounds 4(a-n). Structures of all the synthesized compounds were confirmed by spectral analysis using IR, NMR, mass and elemental analysis. Synthesized targeted molecules were considered for their medicinal value by the help of our previous and current research work. The series of compounds were subjected to study their potential biological zest. Out of 14 compounds, 2 were showed promising result.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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