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AN EFFICIENT SYNTHESIS OF SOME NOVEL BIOACTIVE AZETIDINONE DERIVATIVES INCLUDING 5-(BENZOFURAN-2-YL) AND 1-PHENYL-1*H*-PYRAZOLE-3-CARBOXAMIDE MOIETY

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Keywords:

Benzofuran, Pyrazole, Carbohydrazides, Azetidinones, Carbohydrazones

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ABSTRACT: In continuation of our efforts in the development of novel drugs, in the present article we have described synthesis of a series of novel azetidinones derivatives (4a-i) containing 5-(benzofuran-2-yl) and 1-phenyl-1H-pyrazole-3-carboxamide moiety, with excellent yields and without formation of undesirable side products from cyclo condensation reaction of N'- (benzylidene) -5- (benzofuran- 2- yl) -1 -phenyl -1*H* -pyrazole- 3-carbohydrazide derivatives (3a-i) with chloro acetyl chloride in the presence of triethylamine in DMF. Carbohydrazones of aryl aldehydes (3a-i) used as the starting compound was obtained by one-pot condensation of 5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (1) with various substituted aromatic aldehydes (2a-i) and a catalytic amount of acetic acid in ethanol. The structures of newly synthesized compounds have been established through elemental analysis and spectral studies like IR, ^{1}H NMR, ^{13}C-NMR and Mass spectra. All the synthesized compounds were screened for their *in-vitro* antibacterial activity against different strains of microbes such as *S. aureus*, *E. coli*, *P. vulgaris* and *S. typhi* at different concentration. The result of the bioactivity confirmed that most of the newly synthesized compounds showed the significant activity when compared with the standard drug Chloramphenicol which might be due to the cyclic carbonyl group present in azetidinones.

INTRODUCTION: The 2-carbonyl derivative of azetidine (four-membered heterocyclic ring with nitrogen as the heteroatom) is designated as 2-azetidinone or, more commonly, *β*-lactam which is well known for the synthesis of a large number of molecules by exploring the Baeyer's strain associated with it. It is the smallest cyclic system that is of accommodating the amide function as a consistent which is also known as the *β*-lactam ring.

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The unique chemotherapeutic properties of *β*-lactam antibiotics continue to attract the attention of the chemical community as they present a variety of synthetic challenges. The development of the chemistry of the *β*-lactam was initiated by Staudinger and his collaborators during his classical studies of ketenes.

The tremendous impetus has been given to the study and reactivity of these compounds because structural moieties are associated with wide spectrum *β*-lactam antibiotics, including Penicillin, Cephalosporin, Carbapenem and Monobactam that have been widely used as pharmacological agents to treat bacterial infections and microbial diseases. Azetidine-2ones and its derivatives play an important role as pharmacological [1, 2], biological activity [3, 4, 5, 6] they show very good antifungal [7],

antimicrobial [8, 9, 10, 11, 12, 13], cholinesterase enzymes [14], anti-inflammatory [15], anticancer [16], anti-tubercular [17], cholesterol absorption inhibitors [18], anti-proliferative [19], antihyperlipidemic[20], cytotoxic [21], antileishmanial [22] activities. Considering the bio potency of these heterocycles, it impelled us to continue our research and to synthesize, some novel 2-azetidinone derivatives from Schiff's bases that can be used in the future as better pharmacological and biological agents.

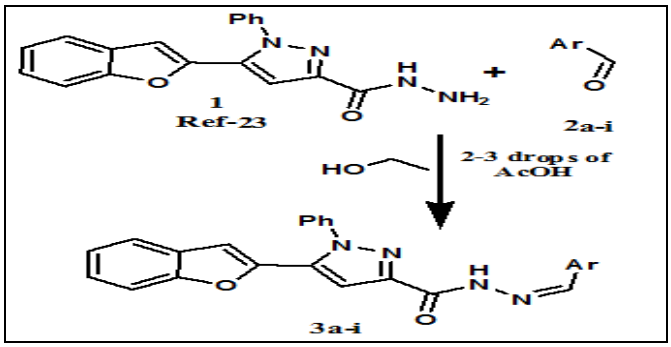
MATERIALS AND METHODS: The reactions were monitored by E. Merck TLC aluminum sheet silica gel$_{60}F_{254}$ and visualizing the spot in UV cabinet and iodine chamber. The melting points were recorded in the open capillary in a paraffin bath and are uncorrected. All the chemicals used for the synthesis were of AR grade of Merck, S.D. Fine and Aldrich. IR spectra were recorded on a Shimadzu IR spectrophotometer (KBr, υ_{max} in cm^{-1}).

^{1}H NMR and ^{13}C NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-*d6* and $CDCl_3$ as a solvent. Chemical shifts are given in parts per million (ppm). NMR data are given as multiplicity and number of protons. Elemental analysis (CHN) was done using Thermo Scientific (Flash-2000). The compounds were analyzed for carbon, hydrogen, nitrogen and the results obtained were found to be in good agreement with the calculated values. Positive-ion electrospray ionization (ESI) Mass spectra were obtained with a Waters Micromass Q-TOF Micro, Mass spectrophotometer. All the obtained products were screened for their antibacterial activities.

Experimental:

Procedure for the synthesis of *N'*-(4-methoxy benzylidene)-5-(benzofuran-2-yl)-1-phenyl -1*H*-pyrazole-3-carbohydrazide (3a): A mixture of 5-(benzofuran-2 -yl) -1 -phenyl -1*H* -pyrazole -3-carbohydrazide (3.18, 10 mmol) and 4-methoxy benzaldehyde (1.21 ml, 10 mmol) in absolute ethanol (25 ml), was taken in a round bottom flask and to this 2-3 drops of acetic acid was added as a catalyst, the reaction mixture was refluxed for 2h. The resulting mass was allowed to cool, filtered and the product was recrystallized from absolute ethanol to get 3a **Scheme 1**. Similarly, 3b-i was synthesized from condensing 1 and 2b-i by following the same procedure as for 3a.

***N'*-(4-methoxybenzylidene)-5 -(benzofuran-2-yl) -1-phenyl-1*H* -pyrazole-3 -carbohydrazide (3a):** Pale yellow amorphous solid; mp, 228-230 °C; yield, 92%; R_f, 0.72; (from absolute ethanol); M.F. $C_{26}H_{20}N_4O_3$; IR (KBr, υ_{max} in cm^{-1}): 3143, 3308, 3370 (NH str.), 3068 (CH str., aromatic), 1694 (C=O str., amide), 1205, 1256 (C-O-C sym. str.), 1020, 1068 (C-O-C asym. str.), 1605 (C=N str., azomethine), 1308 (C-N str., pyrazole), 1570,1508, 1536(C=C str. aromatic), 1068, 1135 (CH i.p.def., aromatic), 830, 813 (CH o.o.p.def., aromatic), 2968 (C-H asym. str., aliphatic), 2840 (CH sym. str., aliphatic), 1458 (CH sym. def., aliphatic), 1458 (C-H asym.def. aliphatic), ^{1}H NMR δ ppm (DMSO-*d6*): 3.83 (s, 3H, -OCH_3 attached to aromatic ring), 8.48 (s,1H, of CH=N), 6.59 (s, 1H, C_4 of pyrazole ring), 7.012-7.67 (m,14H, Ar-H and benzofuran ring), ^{13}C NMR δ ppm (DMSO-*d6*): 144 (s, 1C, C_3 of pyrazole ring), 146 (s,1C,- CH=N-), 156.90 (s, 1C, amide -CONH-), 55.27(s, 1C,-OCH_3), 153.88 (s,1C, C_9 of benzofuran ring), 160.82 (s, 1C, C of benzene attached to OCH_3), LCMS (m/z), 437 $[M+1]^+$, 459$[M+Na]^+$, 460$[M+Na+H]^+$ Elemental anal. calcd. for $C_{26}H_{20}N_4O_3$; calculated: C, 71.55; H, 4.62; N, 12.84 found: C, 71.67; H, 4.62; N, 12.80.



SCHEME 1: REACTION

Code	Ar
3a	4-OCH_3-C_6H_4-
3b	2-Cl-C_6H_4-
3c	2-F-C_6H_4-
3d	4-$OCH_2C_6H_4$-C_6H_4-
3e	-CH=CH-C_6H_5
3f	2-C_4H_3O-
3g	2-C_4H_3S-
3h	1-$C_{10}H_7$
3i	-C_6H_5

***N'*-(2-chlorobenzylidene)-5-(benzofuran-2 -yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (3b):** Pale

yellow amorphous solid; mp, 220-222 °C; yield, 90 %; R_f, 0.72; (from absolute ethanol); M. F. $C_{25}H_{17}ClN_4O_2$; IR(KBr, υ_{max} in cm^{-1}): 3150, 3310, 3365(NH str.), 3065(CH str., aromatic), 1696 (C=O str., CONH), 1204, 1250 (C-O-C sym. str.), 1020, 1068 (C-O-C asym. str.), 1610 (C=N str., azomethine), 1300 (C-N str., pyrazole), 1575, 1515, 1536 (C=C str. aromatic), 1080, 1140 (CH i.p.def., aromatic), 840, 818 (CH o.o.p.def., aromatic); Elemental anal. calcd. for $C_{25}H_{17}ClN_4O_2$; calculated: C, 68.11; H, 3.89; N, 12.71; found: C, 68.05; H, 3.82; N, 12.73.

***N′*-(2-fluorobenzylidene)-5-(benzofuran-2 -yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (3c):** Pale yellow amorphous solid; mp, 245-247 °C; yield, 88%; R_f, 0.71; (from absolute ethanol); M. F. $C_{25}H_{17}FN_4O_2$; IR(KBr, υ_{max} in cm^{-1}): 3130, 3305, 3355 (NH str.), 3060 (CH str., aromatic), 1698 (C=O str., CONH), 1210, 1245 (C-O-C sym. str.), 1025, 1065 (C-O-C asym. str.), 1615 (C=N str., azomethine), 1308 (C-N str., pyrazole), 1580, 1515, 1540 (C=C str., aromatic), 1085, 1150 (CH i.p.def., aromatic), 845, 820 (CH o.o.p. def., aromatic), Elemental anal. calcd. for $C_{25}H_{17}FN_4O_2$; calculated, 70.75; H, 4.04; N, 13.20; found: C, 70.05; H, 4.00; N, 13.20.

***N′*-(4-(benzyloxy)benzylidene)-5-(benzofuran -2-yl)- 1- phenyl-1*H* –pyrazole -3 -carbohydrazide (3d):** Pale yellow amorphous solid; mp, 218-220°C; yield, 85%; R_f, 0.73; (from absolute ethanol); M. F. $C_{32}H_{24}N_4O_3$; IR (KBr, υ_{max} in cm^{-1}): 3140, 3315, 3365 (NH str.,), 3065 (CH str., aromatic), 1690 (C=O str., CONH), 1205, 1250 (C-O-C sym.str.), 1030, 1068 (C-O-C asym.str.), 1620 (C=N str., azomethine), 1305 (C-N str., pyrazole), 1578, 1515, 1546 (C=C str., aromatic), 1080, 1140 (CH i.p.def. aromatic), m850, 818 (CH o.o.p.def., aromatic), 2972(C-H asym.str., aliphatic) 2838(CH sym.str. aliphatic), 1425 (C-H sym.def., aliphatic), 1435 (C-H assym.def., aliphatic), Elemental anal. calcd. for $C_{32}H_{24}N_4O_3$; calculated, 74.99; H, 4.72; N, 10.93; found: C, 74.05; H, 4.70; N, 11.10.

5- (benzofuran-2 -yl) -1 –phenyl -*N′* -(3-phenyl allylidene) -1*H* -pyrazole-3-carbohydrazide (3e): Pale yellow amorphous solid; mp, 215-217 °C; yield, 82%; R_f, 0.67; (from absolute ethanol); M.F. $C_{27}H_{20}N_4O_2$; IR (KBr, υ_{max} in cm^{-1}): 3160, 310, 3365 (NH str.,), 3060 (CH str., aromatic), 1696 (C=O str., CONH), 1210, 1240 (C-O-C sym.str.), 1030, 1078 (C-O-C asym.str.), 1615 (C=N str., azomethine), 1300 (C-N str., pyrazole), 1578, 1515, 1536 (C=C str., aromatic), 1080, 1140 (CH i.p.def., aromatic), 845, 818 (CH o.o.p.def., aromatic), Elemental anal. for calcd. $C_{27}H_{20}N_4O_2$; calculated C, 74.98; H, 4.66; N, 12.95; O, 7.40; found: C, 73.05; H, 4.62; N, 12.98.

5- (benzofuran-2-yl) -*N′* -(furan-2-ylmethylene) -1-phenyl-1*H* -pyrazole-3 -carbohydrazide (3f): Pale yellow amorphous solid; mp, 220-222 °C; yield, 86%; R_f, 0.69; (from absolute ethanol); M.F. $C_{23}H_{16}N_4O_3$; IR(KBr, υ_{max} in cm^{-1}): 3130, 3320, 3375 (NH str.), 3075 (CH str., aromatic), 1690 (C=O str., CONH), 1214, 1260 (C-O-C sym. str.), 1020, 1068 (C-O-C asym. str.), 1620 (C=N str., azomethine), 1300 (C-N str., pyrazole), 1585, 1525, 1546 (C=C str., aromatic), 1070, 1140 (CH i.p.def., aromatic), 830, 818 (CH o.o.p.def., aromatic); Elemental anal. calcd. for $C_{23}H_{16}N_4O_3$; calculated; C, 69.69; H, 4.07; N, 14.13; found: C, 69.63; H, 4.10; N, 14.17.

5- (benzofuran-2-yl) -1 -phenyl-*N′* -(thiophen-2-ylmethylene) -1*H* -pyrazole-3 -carbohydrazide (3g): Pale yellow amorphous solid; mp, 210-212°C; yield, 90%; R_f, 0.68; (from absolute ethanol); M.F. $C_{23}H_{16}N_4O_2S$; IR(KBr, υ_{max} in cm^{-1}): 3148, 3320, 3365 (NH str.,), 3070 (CH str., aromatic), 1690 (C=O str., CONH), 1214, 1250 (C-O-C sym. str.), 1030, 1068 (C-O-C asym. str.), 1600 (C=N str., azomethine), 1320 (C-N str., pyrazole),1575, 1515, 1536 (C=C str., aromatic), 1080, 1140 (CH i.p.def. aromatic), 840, 818(CH o.o.p.def., aromatic); Elemental anal. calcd. for $C_{23}H_{16}N_4O_2S$; calculated; C, 66.97; H, 3.91; N, 13.58; S,7.77; found: C, 66.89; H, 3.93; N, 13.56, S,7.72.

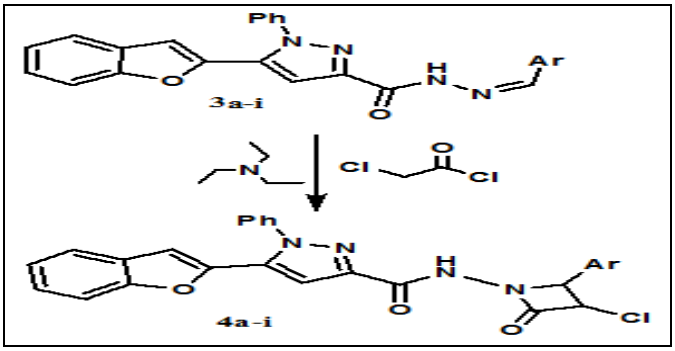
5- (benzofuran -2 -yl) -*N′* -(naphthalen-1 -yl methylene) -1 –phenyl -1*H* –pyrazole -3-carbohydrazide (3h): Pale yellow amorphous solid; mp, 195-197°C; yield, 85%; R_f, 0.70; (from absolute ethanol); M.F. $C_{29}H_{20}N_4O_2$; IR(KBr, υ_{max} in cm^{-1}): 3155, 3315, 3370(NH str.), 3070 (CH str., aromatic), 1690 (C=O str., CONH), 1200, 1260 (C-O-C sym. str.), 1030, 1070(C-O-C asym. str.), 1600 (C=N str., azomethine), 1320 (C-N str., pyrazole), 1575, 1525, 1536 (C=C str., aromatic), 1080,1140(CH i.p.def., aromatic), 840, 818(CH

o.o.p.def., aromatic), Elemental anal. calcd $C_{29}H_{20}N_4O_2$ for calculated C, 76.30; H, 4.42; N, 12.27; found: C, 76.25; H, 4.42; N, 12.73.

5 -(benzofuran -2-yl) -N' -benzylidene-1-phenyl-1H-pyrazole-3-carbohydrazide (3i): Pale yellow amorphous solid mp, 202-204°C; yield,88%; R_f.;0.65 (from absolute ethanol); M.F; $C_{25}H_{18}N_4O_2$. IR(KBr, υ_{max} in cm^{-1}): 3145, 3325, 3365 (NH str.), 3065 (CH str., aromatic), 1694 (C=O str., CONH), 1220, 1260 (C-O-C sym. str.), 1020, 1078 (C-O-C asym. str.), 1620 (C=N str., azomethine), 1300 (C-N str., pyrazole), 1575, 1515, 1536(C=C str., aromatic), 1080, 1140(CH i.p.def., aromatic), 840, 818 (CH o.o.p.def., aromatic); Elemental anal. for $C_{25}H_{18}N4O_2$; Calcd. calculated; C, 73.88; H, 4.46; N, 13.78; found: C, 73.75; H, 4.42; N, 13.73.

Procedure for the synthesis of 5-(benzofuran-2-yl)- *N′* -(3 –chloro -2 -(4 -methoxyphenyl)-4-oxoazetidin -1-yl) -1 –phenyl -1*H* -pyrazole-3-carboxamide (4a): Mixture of *N′*-(4-methoxy benzylidene)-5 -(benzofuran-2-yl)-1 -phenyl -1*H*-pyrazole-3-carbohydrazide (3a, 2.18g, 0.005 mol) and chloro acetyl chloride (0.40 ml, 0.005mol) was taken in DMF (30 ml) and the condition was maintained cold by using ice bath then to this triethylamine (0.69 ml, 0.005 mol) was added drop wise and the mixture was stirred for 15 min. The reaction mixture was refluxed for 8h, at 90 ºC, allowed to cool and poured on crushed ice; product obtained was filtered, washed, dried and recrystallized from ethanol as white amorphous solid 4a **Scheme 2**. Similarly, 4b-i was synthesized from 3b-i by following the same procedure for 4a.

5 -(benzofuran -2 -yl)-*N′*-(3-chloro-2-(4-methoxy phenyl) -4 –oxoazetidin -1 -yl) -1 –phenyl -1*H*-pyrazole -3 -carboxamide (4a): Dirty white amorphous solid; mp, 240-242 °C; yield, 89%; R_f, 0.75; (from absolute ethanol); M.F. $C_{28}H_{21}ClN_4O_4$; IR (KBr, υ_{max} in cm^{-1}):1693(C=O in CONH str.), 1790 (C=O str., azetidinone), 3308, 3143 (NH str.), 3069 (CH str., aromatic and heterocyclic), 1257 (C-O-C str.), 1604 (C=N str.), 1508, 1537(C=C str., aromatic), 1363, 1308 (C-N str. *β*-lactam ring), 701, 752 (C-Cl str.), 1206, 1257 (C-O-C sym. str.), 1026, 1068 (C-O-C asym. str.), 830, 812 (CH o.o.p.def. aromatic), 1068, 1134 (CH i.p.def. aromatic), 2969 (CH-asym. str., aliphatic), 2841 (CH, sym. str. aliphatic), 1459 (CH, sym.def. aliphatic), 1508 (CH, asym.def. aliphatic); ^{1}H NMR δ ppm (DMSO-*d6*): 3.81 (s, 3H, OCH_3 attached to aromatic ring), 6.59 (s, 1H, C_4 of pyrazole ring), 5.41 (s, 1H,C_4-H at azetidinone ring),11.82 (s,1H, NH attached to –NHCO- linkage), 7.01-7.67 (m, 15H, aromatic, benzofuran ring and1H of CH-Cl at azetidinone ring), ^{13}C NMR δ ppm: (DMSO-*d6*), 55.26 (s,OCH_3), 163.41 (s, CO of azetidinone), 160.82 (s, CONH), 144.71 (s, C_3 of pyrazole ring), 153.88 (s, C_9 of benzofuran ring), 156.91 (s, carbon atom of benzene to which OCH_3 is attached) 62.40, 64.10, 105.90, 107.85, 111.15, 114.30, 121.74, 123.55, 126.24, 127.55, 129.45, 135.41, 139.19, 146.40, 148.06, LCMS (m/z), 512 M^+, 535 $[M+Na]^+$, Elemental anal. calcd. for $C_{28}H_{21}ClN_4O_4$; Calculated: C, 65.56; H, 4.13; N, 10.92; found: C, 65.59; H, 4.18; N, 10.96.



SCHEME 2: REACTION

Code	Ar
4a	4-OCH_3-C_6H_4-
4b	2-Cl-C_6H_4-
4c	2-F-C_6H_4-
4d	4-$OCH_2C_6H_4$-C_6H_4-
4e	-CH=CH-C_6H_5
4f	2-C_4H_3O-
4g	2-C_4H_3S-
4h	1-$C_{10}H_7$
4i	-C_6H_5

5 -(benzofuran- 2 -yl) -*N′* -(3 –chloro -2 -(2-chlorophenyl) -4 -oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole -3 -carboxamide (4b): Dirty white amorphous solid; mp, 235-237 °C; yield, 85%; R_f, 0.72 (from absolute ethanol); M.F. $C_{27}H_{18}Cl_2N_4O_3$; IR (KBr, υ_{max} in cm^{-1}): 1695 (C=O str., CONH str.), 1788 (CO str., 2-azetidinone), 3300, 3145(NH str.), 3072 (CH str., aromatic), 1256 (C-O-C str.), 1610 (C=N str.), 1500, 1535 (C=C str., aromatic), 1363-1257 (C-N str. *β*-lactam ring), 705, 757 (C-Cl str.), 1200, 1256 (C-O-C sym. str.), 1025, 1067 (C-O-C asym. str.), 840, 815 (CH o.o.p. def. aromatic),

1070, 1144 (CH i.p. def. aromatic), Elemental anal. calcd. for $C_{27}H_{18}Cl_2N_4O_3$; calculated: C, 62.68; H, 3.51; N, 10.83; found: C, 62.71; H, 3.45; N, 10.89.

5 -(benzofuran -2- yl) -*N′* -(3 –chloro -2 -(2-fluorophenyl) -4 –oxoazetidin -1 -yl) -1 -phenyl-1*H* –pyrazole -3 -carboxamide (4c): Dirty white amorphous solid; mp, 236-238 °C; yield, 80%; R_f, 0.73 (from absolute ethanol); M.F. $C_{27}H_{18}ClFN_4O_3$; IR (KBr, υ_{max} in cm^{-1}): 1698 (C=O str., CONH str.), 1792 (CO str., 2-azetidinone), 3300, 3135 (NH str.), 3079 (CH str., aromatic), 1363-1257 (C-N str. β-lactam ring), 703, 751 (C-Cl str.), 1251 (C-O-C str.), 1600 (C=N str.), 1500, 1532 (C=C str., aromatic), 1214, 1269 (C-O-C sym. str.), 1025, 1065 (C-O-C asym. str.), 835, 818 (CH o.o.p. def. aromatic), 1069, 1142 (CH i.p.def. aromatic),. Elemental anal. calcd. for $C_{27}H_{18}ClFN_4O_3$; calculated, C, 64.74; H, 3.62; N, 11.19; found: C, 64.78; H, 3.58; 11.28.

5 -(benzofuran -2 -yl) -*N′* -(2 -(4 -(benzyloxy) phenyl) -3 –chloro -4-oxoazetidin-1-yl)-1-phenyl-1*H* -pyrazole-3 -carboxamide (4d): Dirty white amorphous solid; mp, 232-234°C; yield, 83%; R_f, 0.70 (from absolute ethanol); M.F. $C_{34}H_{25}ClN_4O_4$**.** IR(KBr, υ_{max} in cm^{-1}): 1691 (C=O str., CONH), 1792 (CO str., 2-azetidinone), 3315, 3145 (NH str.), 3063 (CH str., aromatic), 1260 (C-O-C str.), 1604 (C=N str.), 1510, 1537 (C=C str., aromatic), 1363-1257 (C-N str. β-lactam ring), 702, 753 (C-Cl str.), 1212, 1257 (C-O-C sym. str.), 1026, 1065 (C-O-C asym. str.,), 835, 822 (CH o.o.p.def. aromatic), 1085, 1134 (i.p.def., aromatic), 2972 (CH asym. str. aliphatic), 2840(CH, sym. str. aliphatic), 1459 (CH sym.def. aliphatic), 1500 (CH asym. def. aliphatic). Elemental anal. calcd. for $C_{34}H_{25}ClN_4O_4$; calculated C, 69.33; H, 4.28; N, 9.51; found: C, 69.38; H, 4.33; N, 9.48.

5 -(benzofuran -2 -yl) -*N′* -(3 –chloro -2 -oxo-4-(styryl)azetidin -1 -yl) -1 –phenyl -1*H* -pyrazole-3-carboxamide (4e): Dirty white amorphous solid; mp, 237-239 °C; yield, 79%; Rf, 0.76 (from absolute ethanol); M.F. $C_{29}H_{21}ClN_4O_3$; IR (KBr, υ_{max} in cm^{-1}):1696 (C=O str., CONH), 1790 (CO str., 2-azetidinone), 3312, 3153 (NH str.), 3066 (CH str., aromatic), 1254 (C-O-C str.), 1614 (C=N str.), 1510, 1535 (C=C str., aromatic), 1363-1257 (C-N str. *β*-lactam ring), 700, 750 (C-Cl str.), 1216, 1243 (C-O-C sym. str.), 10263, 1068 (C-O-C asym. str.), 826, 815 (CH o.o.p.def. aromatic), 1062,1134(CH i.p.def. aromatic). Elemental anal. calcd. for $C_{29}H_{21}ClN_4O_3$ calculated, C, 68.44; H, 4.16; N, 11.01; found: C, 68.54; H, 4.14; N, 11.11.

5-(benzofuran-2-yl)-*N′* -(3-chloro-2-(furan-2-yl)-4-oxoazetidin-1 -yl) -1 –phenyl -1*H* pyrazole-3-carboxamide (4f): Dirty white amorphous solid; mp, 236-240 °C; yield, 74%; R_f, 0.74 (from absolute ethanol); M.F. $C_{25}H_{17}ClN_4O_4$; IR(KBr, υ_{max} in cm^{-1}): 1694 (C=O str., CONH str.), 1785 (CO str., 2-azetidinone), 3300, 3140 (NH str.), 3075 (CH str., aromatic), 1257 (C-O-C str.), 1600 (C=N str.), 1505, 1533(C=C str., aromatic), 1363-1257 (C-N str. *β*-lactam ring), 702, 754 (C-Cl str.), 1203, 1252 (C-O-C sym. str.), 1023, 1074 (C-O-C asym. str.), 835, 818 (CH o.o.p.def. aromatic), 1069, 1136 (CH i.p. def. aromatic); Elemental anal. calcd. for $C_{25}H_{17}ClN_4O_4$; calculated, C, 63.50; H, 3.62; N, 11.85; found :63.43; H, 3.67; N, 11.88.

5 -(benzofuran -2 -yl) -*N′* -(3 –chloro -2 -oxo-4-(thiophen -2 -yl) azetidin -1 -yl) -1-phenyl-1*H*-pyrazole -3 -carboxamide (4g): Dirty white amorphous solid; mp, 230-234 °C; yield, 81%; R_f, 0.68 (from absolute ethanol); M.F. $C_{25}H_{17}ClN_4O_3S$; IR(KBr, υ_{max} in cm^{-1}): 1690 (C=O str., CONH str.), 1785 (CO str. of 2-azetidinone), 3300, 3144 (NH str.), 3062 (CH str., aromatic), 1255 (C-O-C str.), 1600 (C=N str.), 1502, 1535 (C=C str., aromatic), 1363-1257 (C-N str. *β*-lactam ring), 705, 758 (C-Cl str.), 1204, 1253 (C-O-C sym. str.), 1025, 1072 (C-O-C asym. str.), 820, 811 (CH o.o.p.def. aromatic), 1065, 1132 (i.p.def., aromatic); Elemental anal. calcd. for $C_{25}H_{17}ClN_4O_3S$; calculated, C, 61.41; H, 3.50; N, 11.46; S,6.56; found: C, 61.45; H, 3.55; N, 11.26; S, 6.60.

5-(benzofuran-2-yl)-*N′*-(3-chloro-2-(naphthalen-1-yl)-4-oxoazetidin-1-yl) -1-phenyl-1*H*-pyrazole-3-carboxamide (4h): Dirty white amorphous solid; mp, 242-244 °C; yield, 78%; R_f, 0.78 (from absolute ethanol); M.F. $C_{31}H_{21}ClN_4O_3$; IR (KBr, υ_{max} in cm^{-1}): 1697 (C=O str., CONH str.), 1785 (CO str., 2-azetidinone), 3300, 3141 (NH str.), 3070 (CH str., aromatic), 1252 (C-O-C str.), 1605 (C=N str.), 1500, 1535 (C=C str., aromatic), 1363-1257 (C-N str. *β*-lactam ring), 703, 751 (C-Cl str.), 1200, 1260 (C-O-C sym. str.), 1024, 1070 (C-O-C asym. str.), 827, 812 (CH o.o.p.def. aromatic), 1070, 1134 (CH i.p.def. aromatic); Elemental anal.

calcd. for $C_{31}H_{21}ClN_4O_3$; calculated, C, 69.86; H, 3.97; N, 10.51; found: C, 69.82; H, 3.97; N, 10.59.

5-(benzofuran-2-yl)-*N'*-(3-chloro-2-oxo-4-phenyl azetidin -1 -yl) -1 –phenyl -1*H* –pyrazole -3-carboxamide (4i): Dirty white amorphous solid; mp, 230-232 °C; yield, 83%; R_f, 0.76 (from absolute ethanol); M.F. $C_{27}H_{19}ClN_4O_3$; IR(KBr, υ_{max} in cm^{-1}): 1692 (C=O str., CONH), 1786 (CO str. of 2-azetidinone), 3304, 3145(NH str.), 3071 (CH str., aromatic.), 1260 (C-O-C str.), 1600 (C=N str.,), 1502, 1534 (C=C str., aromatic), 1363-1257 (C-N str., *β*-lactam ring), 700, 753 (C-Cl str.), 1203, 1259 (C-O-C sym. str.), 1021, 1068 (C-O-C asym. str.), 820, 809(CH o.o.p.def. aromatic), 1069, 1134 (CH i.p.def., aromatic); Elemental anal. calcd. for $C_{27}H_{19}ClN_4O_3$; calculated, C, 67.15; H, 3.97; N, 11.60; found: C, 67.12; H, 3.95; N, 11.65.

Antibacterial Activity:

A procedure of Paper Disc-Diffusion Method: The novel synthesized heterocyclic compounds (4a-i) were screened for their *in-vitro* antimicrobial activity by using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai. The test solution was prepared by dissolving known weight of each compound in dimethyl sulphoxide (DMSO) as a solvent and diluted suitably to give the resultant concentration of 31-1000 µg/mL. Petri plates were prepared by pouring 10 ml of Mueller Hinton agar was allowed to solidify. The microorganism culture was inoculated in fresh 10 ml fresh nutrient broth to yield an initial suspension and maintained in nutrient agar medium at 37°C. The bacterial culture was spread over nutrient agar in the plate. Whatmann no.1 sterile paper discs (6 mm) were impregnated with solution were then applied on the plates and incubated at 37°C for 24 h. The inhibition zone was measured in mm in four directions and expressed as mean. The results were compared using Chloramphenicol as a standard antibacterial drug.

RESULTS AND DISCUSSION: An efficient, simple and reproducible method afforded various azetidine-2-one 4a-i derivatives in excellent yields, and without formation of undesirable side products. The synthetic protocol has been outlined in **Scheme 1** and **2**. At every stage, the reaction was monitored with TLC. The physical constants like melting point and solubility were determined for all the intermediate and final products. Spectral data have characterized the newly synthesized compound, and elemental analysis such as FT-IR, ^{1}HNMR, ^{13}C NMR and mass spectra and they were also screened for antimicrobial activities.

5 -(benzofuran -2 -yl) -1-phenyl -1*H*-pyrazole-3-carbohydrazide (1) was reacted with aromatic substituted aldehydes (2a-i) in ethanol as solvent to get intermediate *N'*-(benzylidene)-5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides (3a-i) in good yield. The IR spectrum of 3a supported these structures by different absorption bands mainly at 1605 cm^{-1} due to C=N stretch in azomethine. The ^{1}H NMR of 3a revealed a characteristic singlet at 8.48 ppm due to one proton of azomethine. Another singlet appeared at 3.83 ppm is due to three protons of methoxy group attached to the aromatic ring. ^{13}C NMR spectra showed a singlet at 146 ppm due to the carbon atom of CH=N. LCMS indicated the M^{+1} peak at 437 similarly; the elemental analysis also proved that the percentage of the elements is in good agreement with the calculated value which determines the molecular formula to be $C_{26}H_{20}N_4O_3$.

4a was obtained by cyclocondensation reaction of *N'*-(4-methoxybenzylidene) -5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (3a) with chloro acetyl chloride in the presence of triethylamine as a base in DMF. The IR spectra of 4a showed a characteristics absorption band at 1790 cm^{-1} due to the CO stretch of the 2-azetidinone ring. The CN stretch in the *β*-lactam ring was observed at their usual range from 1257-1363 cm^{-1}. ^{1}H NMR of 4a revealed singlet at 5.41 ppm due to one proton of azetidinone ring attached at a fourth carbon atom.

Another characteristic singlet was observed at 11.82 ppm which supported the position of one proton attached to NH in amide moiety. A singlet at 163.41ppm in ^{13}C NMR also supported the presence of carbon of CO group of azetidinone while another singlet appeared at 160.82 ppm due to a carbon atom of the amide group. Further, confirmation came from the percentage of C, H and N obtained in the elemental analysis of 4a which is in good agreement with calculated values. A molecular ion peak at 512 obtained in Mass spectra

supported the molecular formula to be $C_{28}H_{21}ClN_4O_4$. Thus all the above spectral data obtained by spectral analysis favors confirmation of structure of the synthesized compound.

Antibacterial Activity: The results of *in-vitro* antibacterial activity of entire synthesized compounds against bacterial strains at the different concentration ranging from 31-1000 µg/mL are depicted in **Table 1** and **2**. It is found that most of the title compounds 4a-i exhibited significant antibacterial activity when these results were compared with std. drug.

TABLE 1: ANTIBACTERIAL ACTIVITY OF THE SYNTHESISED COMPOUNDS 4a-i

Compound Code	Zone of Inhibition (mm)											
	Gram +ve						Gram –ve					
	S. aureus						*P. vulgaris*					
	Conc. µg/mL						Conc. µg/mL					
	1000	500	250	125	63.5	31	1000	500	250	125	63.5	31
4a	25	22	21	20	17	13	27	24	21	18	17	10
4b	24	21	20	18	16	18	25	22	19	16	14	09
4c	25	21	19	20	16	15	28	23	21	17	15	11
4d	23	22	21	19	18	15	27	24	20	18	17	12
4e	19	20	16	15	13	14	21	19	15	14	13	09
4f	24	23	21	20	17	16	25	23	21	19	15	08
4g	23	20	18	17	16	13	23	22	21	16	14	10
4h	20	18	16	15	13	11	26	21	17	15	12	09
4i	21	18	17	16	14	12	22	20	16	14	13	08
DMSO	-	-	-	-	-	-	-	-	-	-	-	-
Std. drug	24	22	20	19	17	15	28	24	20	17	16	13

TABLE 2: ANTIBACTERIAL ACTIVITY OF THE SYNTHESISED COMPOUNDS 4a-i.

	Zone of Inhibition (mm)											
	Gram –ve											
	E. coli						*S. typhi*					
	Conc. (µg/mL)						Conc. (µg/mL)					
	1000	500	250	125	63.5	31	1000	500	250	125	63.5	31
4a	27	24	22	20	18	15	17	13	11	10	09	07
4b	24	22	20	19	16	13	16	15	12	09	08	06
4c	25	24	22	20	18	16	17	16	14	10	09	07
4d	26	25	24	22	19	13	18	15	13	11	10	06
4e	21	22	18	17	15	14	12	10	08	05	07	04
4f	26	25	22	19	17	15	17	16	13	12	08	07
4g	25	22	21	20	16	13	15	13	09	07	09	07
4h	23	20	19	17	15	10	16	12	11	10	08	06
4i	21	19	18	16	13	11	14	11	10	09	07	05
DMSO	-	-	-	-	-	-	-	-	-	-	-	-
Std. drug	26	24	23	21	17	14	17	15	12	11	09	08

Std. drug: Chloramphenicol

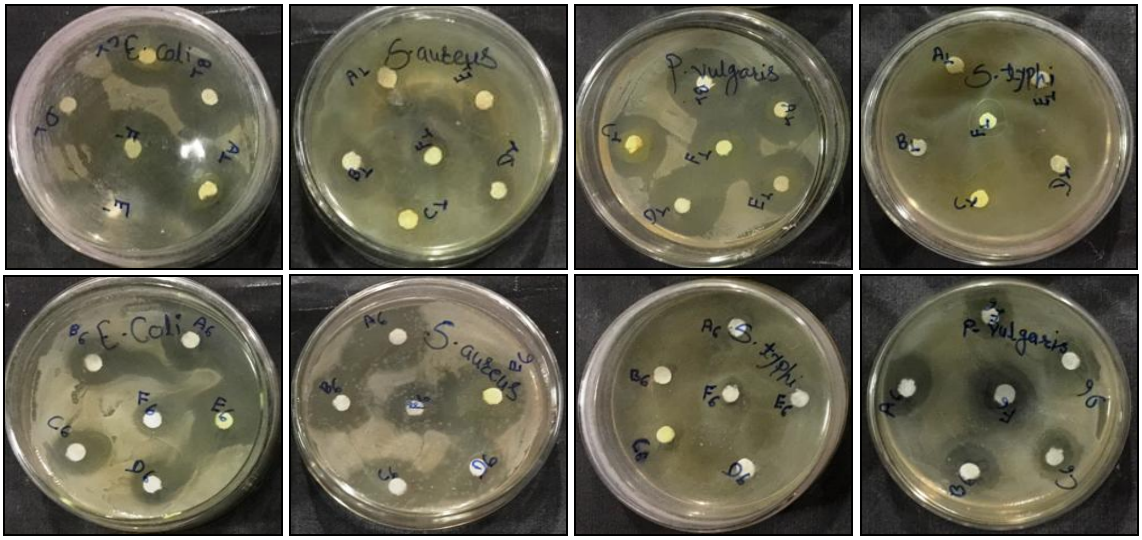


FIG. 1: ZONE OF INHIBITION OF SYNTHESISED AZETIDINONES (4a-f) FOR DIFFERENT MICROORGANISMS

The test compounds 4a, 4c, 4d and 4f showed better activity than the standard drug against *S. aureus, P. vulgaris* and *E. coli.* The better activities of these synthesized heterocyclic compounds towards the microbial strains is due to the presence of different functional groups or rings which tends to inhibit the growth of microorganism at a minimum concentration of applied title compounds. Activities at rest of concentrations were found to be good to moderate for these bacterial strains. But it was found that the entire series of the synthesized compounds showed poor activity against *S. typhi.*

CONCLUSION: In summary, we have reported here a new series of 5-(benzofuran-2-yl)-*N'*-(3-chloro -2 -(substituted aryl) -4 -oxoazetidine-1 -yl) -1-phenyl -1*H* -pyrazole -3-carboxamide derivatives (4a-i) from carbohydrazones of aryl aldehydes (3a-i) respectively**.** The presented series of compounds were synthesized in good yields. The structure and purity of newly synthesized compounds were confirmed by spectroscopic investigation and chemical analysis. Among the synthesized compounds most of the compounds showed good to moderate activity against selected strains *S. aureus, P. vulgaris*, and *E. coli* while poor activity was evaluated for *S. typhi*.

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CONFLICT OF INTEREST: Author wishes to declare that there is no conflict of interest.

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