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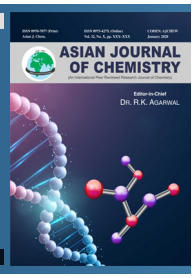

Synthesis, Characterization and *in vitro* Antimicrobial Screening of Some Novel Series of 2-Azetidinone Derivatives Integrated with Quinoline, Pyrazole and Benzofuran Moieties

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A series of 5-(benzofuran-2-yl)-*N*-(3-chloro-4-(2-(*p*-tolyloxy) substituted quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide derivatives (**4a-f**) were synthesized with excellent yields by cyclocondensation reaction of 5-(benzofuran-2-yl)-*N*′-(2-(*p*-tolyloxy) substituted quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**3a-f**) with chloroacetyl chloride in presence of triethylamine in DMF. One pot condensation of 5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**1**) with 2-(*p*-tolyloxy) substituted quinoline-3-carbaldehyde (**2a-f**) in ethanol solvent in presence of catalytic amount of acetic acid gave intermediate compounds (**3a-f**). The structures of newly synthesized compounds have been substantiated through elemental analysis and spectral studies *viz.* ^{1}H NMR, ^{13}C NMR, IR and mass spectra. All the synthesized compounds were screened for their *in vitro* antibacterial activity against pathogenic bacteria such as *S. aureus* and *E. coli* at different concentrations.

Keywords: Azetidinones, *p*-Tolyloxy, Quinoline carbaldehyde, Pyrazole, Carbohydrazides.

INTRODUCTION

An incredible position has been given to 2-azetidinone compounds in research because these structural moieties are associated with wide spectrum β-lactam antibiotics, containing cephalosporin, penicillin, cephamycin, carbapenem and monobactam that have been extensively used as pharmacological agents to treat bacterial infections and microbial diseases [1]. This diversity in the medicinal prominence of 2-azetidinone ring frequently attracted chemist from numerous years for synthetic challenges in drug design to explore this skeleton to its multiple potential against a number of activities. Azetidinone nucleus is considered as versatile nucleus having all types of biological activities predominantly antifungal and antimicrobial activity. 2-Azetidinone is a cyclic system more usually designated as β-lactam, a 2-carbonyl derivative of azetidine having four membered heterocyclic ring having nitrogen as heteroatom and amide function in ring which was exploring the Baeyer′s strain associated with it [2]. Azetidin-2-ones and its derivatives play an important role as antimicrobial [3-6], anticancer [7], anti-inflammatory [8], biological activity [9-12], antitubercular [13], pharmacological [14,15], antifungal [16], antiproliferative [17], antileishmanial [18], cytotoxic [19], cholesterol absorption inhibitors [20] and antihyperlipidemic [21].

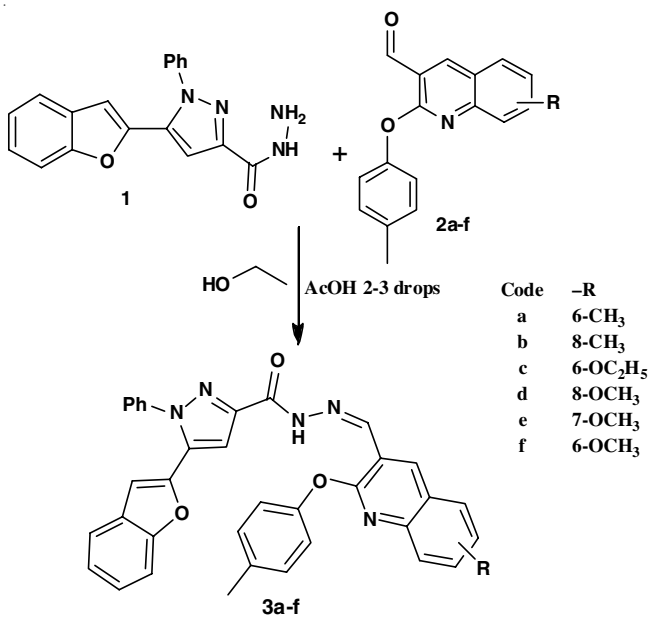
It is also revealed that quinoline moiety acts as a core nucleus in novel heterocyclic compounds and its prominence in the field of medicinal chemistry is worth mentioning. A wide range of its application has drawn huge attention to the researchers to yield different quinoline derivatives, which may have novel therapeutic efficiency. Pharmaceutically, a wide variety of substituted quinoline derivatives possess a broad range of bioactivities [22,23], such as anticancer [24], antibacterial [25], antituberculosis [26], anti-inflammatory [27], analgesic [28], antioxidant [29], antimalarial [30], anti-HIV [31], anticonvulsant [32], antiviral [33], *etc*. Nowadays, researchers are seeking to synthesize hybrids or fused heterocycles to improve the therapeutically activities. Triggered by these interpretations and in extension of our efforts towards the synthesis of novel heterocyclic compounds with antimicrobial property, we planned to frame a molecule which syndicates two bio labile rings 2-azetidinone and 2-(*p*-tolyloxy) quinoline-3-carbaldehyde with

an anticipation to obtain compounds having better enhanced qualitative pharmacological activities.

EXPERIMENTAL

The reactions were monitored by E. Merck TLC aluminium sheet silica gel 60 F_{254} and visualizing the spot in UV cabinet and iodine chamber. The melting points were recorded in open capillary in 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 in Shimadzu IR Spectrophotometer. ^{1}H & ^{13}C NMR spectra were recorded on a Bruker AM 400 instrument using tetramethylsilane as an internal reference and DMSO-d_6 and $CDCl_3$ as solvent. Elemental analysis was done using Thermo Scientific Flash-2000. The ESI-MS spectra were obtained in Mass Spectrophotometer with Micromass Q-TOF.

General protocol for the synthesis of 5-(benzofuran-2-yl)-*N*′-(2-(*p*-tolyloxy) substituted quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (3a-f): 5-(Benzo furan-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**1**, 0.01 mol) and 2-(*p*-tolyloxy) substituted quinoline-3-carbaldehyde (**2**, 0.01mol) were dissolved in ethanol containing 2-3 drops of acetic acid and the reaction mixture was refluxed for 2 h (**Scheme-I**). The resulting mass was cooled and transferred into crushed ice, filtered and recrystallized using 1,4-dioxane.

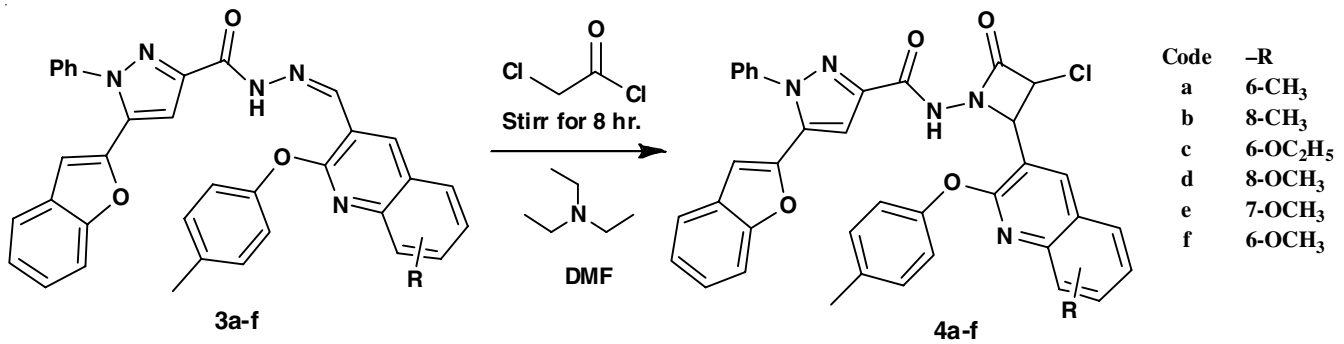


Scheme-I

5-(Benzofuran-2-yl)-*N*′-((6-methyl-2-(*p*-tolyloxy)-quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (3a): Yellow crystalline solid; m.p.: 263-265 ºC; Yield: 81 %; IR (KBr, ν_{max}, cm^{-1}): 3293, 3412, (N-H *str*.), 3062, 3029 (C-H *str*., arom.), 2958 (C-H asym. str., aliph.), 2857,2915 (C-H *str*. sym., aliph.), 1688 (C=O *str*.), 1650-1600 (C=N *str*.), 1240 (C-O-C sym. *str*., ether), 1058 (C-O-C asym. *str*., ether). ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, Ar-CH_3), 2.47 (s, 3H, CH_3 attached to quinoline ring), 6.51 (s, 1H, at C_4 of pyrazole ring), 12.21 (s, 1H, NHCO), 7.14-9.08 (m, 19H, arom.+ heterocycl. ring protons); MS: *m/e* 577 M^+, 578 $[M+H]^+$, 579 $[M+2]^+$, 600 $[M+Na]^+$. Elemental analysis (%) calcd. (found) $C_{36}H_{27}N_5O_3$: C, 74.85 (74.05); H, 4.71 (4.50); N, 12.12 (12.06).

Synthesis of 5-(benzofuran-2-yl)-*N*′-(3-chloro-4-(2-(*p*-tolyloxy) substituted quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (4a-f): Mixture of 5-(benzofuran-2-yl)-N′-(2-(*p*-tolyloxy) substituted quinolin-3-yl)methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**3**, 0.01mol) and chloroacetyl chloride (0.01 mol) was taken in DMF (30 mL) and the reaction condition was maintained cold by using ice bath; then to this triethylamine (0.69 mL, 0.01 mol) was added dropwise and the mixture was stirred for 15 min and refluxed for 8 h. The reaction content was then allowed to cool and transferred in crushed ice, product obtained was filtered, washed, dried and recrystallized from DMF as yellow solid (**Scheme-II**).

5-(Benzofuran-2-yl)-*N*-(3-chloro-4-(6-methyl-2-(*p*-tolyloxy)quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (4a): Yellow crystalline solid; recrystallizing solvent, DMF; m.p.: 212-214 ºC; yield, 64 %; R_f value: 0.58. IR (KBr, ν_{max}, cm^{-1}): 3176 (N-H *str*., -CONH-), 2926 (C-H asym. *str*., aliph.), 2801 (C-H sym. *str*., aliph.), 1452 (C-H asym. def., aliph.), 1361 (C-H sym. def., aliph.), 1059 (C-H. i.p.def., arom.), 823 (C-H. o.o.p. def., arom.), 1664, 1771 (C=O *str*., azetidinone), 1592 (-C=N *str*., pyrazole moiety), 1059 (C-O-C sym. *str*., ether), 1234 (C-O-C asym. *str*., pyrazole moiety), 1011 (N-N *str*.), 747 (C-Cl *str*. azetidinone). ^{1}H NMR (DMSO-d_6): δ (ppm) 2.75 (s, 6H, two CH_3 group attached to two diff-erent aromatic ring), 6.54 (s,1H, at C_4 of pyrazole ring), 12.35 (s, 1H, NH at -CONH- linkage), 7.14-9.08 (m, 20 H, CH-Cl at C_3 and N-CH C_4 at C4 of azetidinones ring, aromatic and hetero aromatic ring protons). ESI-MS (*m/z*): 654 $[M+H]^+$, 676 $[M+Na]^+$. Elemental analysis (%) calcd. (found) for $C_{38}H_{28}N_5O_4Cl$: C, 69.77 (69.84); H, 4.31 (4.38); N, 10.71 (10.68).



Scheme-II

5-(Benzofuran-2-yl)-*N*-(3-chloro-4-(8-methyl-2-(*p*-tolyloxy)quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (4b): Yellow crystalline solid; recrystallizing solvent, DMF; m.p.: 147-148 ºC; yield, 60 %; R_f value: 0.59. IR (KBr, ν_{max}, cm^{-1}): 3178 (N-H *str*., -CONH-), 2925 (C-H asym. *str*., aliph.), 2805 (C-H sym. *str.*, aliph.), 1456 (C-H asym. def., aliph.), 1364 (C-H sym. def., aliph.), 1057 (C-H i.p.def., arom.), 825 (C-H o.o.p.def., arom.), 1666, 1776 (C=O *str*., azetidinone), 1595 (-C=N *str.*, pyrazole moiety), 1060 (C-O-C sym. *str.*, ether), 1237 (C-O-C asym. *str*., pyrazole moiety), 1015 (N-N *str*.), 749 (C-Cl *str*., azetidinone). ^{1}H NMR (DMSO-d_6): δ (ppm): 2.65 (s, 6H, two CH_3 group attached to two different aromatic ring), 6.5 (s, 1H, at C4 of pyrazole ring), 12.25 (s, 1H, NH at –CONH– linkage), 7.2-8.9 (m, 20H, CH-Cl at C_3 and N-CH at C_4 of azetidinones ring, aromatic and hetero aromatic ring protons). ESI-MS (*m/z*): 654 $[M+H]^+$, 676 $[M+Na]^+$. Elemental analysis (%) calcd. (found) for $C_{38}H_{28}N_5O_4Cl$: C, 69.77 (69.71); H, 4.31 (4.27); N, 10.71 (10.66).

5-(Benzofuran-2-yl)-*N*-(3-chloro-4-(6-ethoxy-2-(*p*-tolyloxy)quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (4c): Yellow crystalline solid; recrystallizing solvent, DMF; m.p.: 168-170 ºC; yield, 65 %; R_f value: 0.45. IR (KBr, ν_{max}, cm^{-1}): 3173 (N-H *str.*, -CONH-), 2925 (C-H asym. *str*., aliph.), 2800 (C-H sym. *str.*, aliph.), 1450 (C-H asym. def., aliph.), 1364 (C-H sym. def., aliph.), 1054 (C-H i.p.def., arom.), 825 (C-H o.o.p. def., arom.), 1667, 1770 (C=O *str.*, azetidinone), 1595 (-C=N *str.*, pyrazole moiety), 1061 (C-O-C sym. *str*., ether), 1235 (C-O-C asym. *str.*, pyrazole moiety), 1010 (N-N *str.*), 749 (C-Cl *str*., azetidinone). ^{1}H NMR (DMSO-d_6): δ (ppm): 3.95 (q, 2H, O-C<u>H$_2$</u>-CH$_3$), 1.35 (t, 3H, O-CH$_2$-C<u>H$_3$</u>), 2.35 (s, 3H, CH_3 group attached to aromatic ring), 6.52 (s, 1H, at C4 of pyrazole ring), 12.38 (s, 1H, NH at –CONH– linkage), 7.01-8.73 (m, 20 H, CH-Cl at C_3 and N-CH at C_4 of azetidinones ring, aromatic and hetero aromatic ring protons). ESI-MS (*m/z*): 684 $[M+H]^+$, 696 $[M+Na]^+$. Elemental analysis (%) calcd. (found) for $C_{39}H_{30}ClN_5O_5$: C, 68.47 (C, 68.40); H, 4.42 (H, 4.40); N, 10.24 (N, 10.10).

5-(Benzofuran-2-yl)-*N*-(3-chloro-4-(8-methoxy-2-(*p*-tolyloxy)quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (4d): Yellow crystalline solid; recrystallizing solvent, DMF; m.p.: 192-194 ºC; yield, 62 %; R_f value: 0.52. IR (KBr, ν_{max}, cm^{-1}): 3178 (N-H *str*., -CONH-), 2921 (C-H asym. *str*. aliph.), 2810 (C-H sym. *str*., aliph.), 1450 (C-H asym. def., aliph.), 1368 (C-H sym. def., aliph.), 1064 (C-H i.p. def., arom.), 826 (C-H o.o.p.def., arom.), 1668, 1770 (C=O *str*., azetidinone), 1595 (-C=N *str*., pyrazole moiety), 1061 (C-O-C sym. *str*., ether), 1231 (C-O-C asym. *str.*, pyrazole moiety), 1010 (N-N *str.*), 740(C-Cl *str*., azetidinone). ^{1}H NMR (DMSO-d_6): δ (ppm): 3.73 (s, 3H, O-CH_3 attached to quinoline ring), 2.33 (s, 3H, CH_3 group attached to aromatic ring), 6.56 (s, 1H, at C_4 of pyrazole ring), 12.34 (s, 1H, NH at –CONH– linkage), 6.89-8.85 (m, 20 H, CH-Cl at C_3 and N-CH at C_4 of azetidinones ring, aromatic and hetero aromatic ring protons). ESI-MS (*m/z*): 684 $[M+H]^+$, 696 $[M+Na]^+$. Elemental analysis (%) calcd. (found) for $C_{38}H_{28}ClN_5O_5$: C, 68.11 (68.05); H, 4.21 (4.16); N, 10.45 (10.38).

5-(Benzofuran-2-yl)-*N*-(3-chloro-4-(7-methoxy-2-(*p*-tolyloxy)quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (4e): Yellow crystalline solid; recrystallizing solvent, DMF; m.p.: 118-120 ºC; yield, 72 %; R_f value: 0.37. IR (KBr, ν_{max}, cm^{-1}): 3174 (N-H *str*., -CONH-), 2924 (C-H asym. *str.*, aliph.), 2808 (C-H sym. *str.*, aliph.), 1445 (C-H asym. def., aliph.), 1369 (C-H sym. def., aliph.), 1050 (C-H i.p. def., arom.), 825 (C-H o.o.p.def., arom.), 1660, 1775 (C=O *str*., azetidinone), 1595 (-C=N *str.*, pyrazole moiety), 1060 (C-O-C sym. *str*., ether), 1235 (C-O-C asym. *str.*, pyrazole moiety), 1017 (N-N *str.*), 749 (C-Cl *str*., azetidinone). ^{1}H NMR (DMSO-d_6): δ (ppm): 3.76 (s, 3H, O-CH_3 attached to quinoline ring), 2.37 (s, 3H, CH_3 group attached to aromatic ring), 6.52 (s, 1H, at C_4 of pyrazole ring), 12.38 (s, 1H, NH at –CONH– linkage), 6.97-8.96 (m, 20 H, CH-Cl at C_3 and N-CH at C_4 of azetidinones ring, aromatic and hetero aromatic ring protons). ESI-MS (*m/z*): 684 $[M+H]^+$, 696 $[M+Na]^+$. Elemental analysis (%) calcd. (found) for $C_{38}H_{28}N_5O_5Cl$: C, 68.11 (68.09); H, 4.21 (4.11); N, 10.45 (10.34).

5-(Benzofuran-2-yl)-*N*-(3-chloro-4-(6-methoxy-2-(*p*-tolyloxy)quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (4f): Yellow crystalline solid; recrystallizing solvent, DMF; m.p.: 238-240 ºC; yield, 61 %; R_f value: 0.40. IR (KBr, ν_{max}, cm^{-1}): 3172 (N-H *str*., -CONH-), 2921 (C-H asym. *str*., aliph.), 2802 (C-H sym. *str.*, aliph.), 1458 (C-H asym. def., aliph.), 1363 (C-H sym. def., aliph.), 1054 (C-H. i.p. def., arom.), 826 (C-H. o.o.p. def., arom.), 1667, 1769 (C=O *str*., azetidinone), 1595 (-C=N *str*., pyrazole moiety), 1051 (C-O-C sym. *str*., ether), 1233 (C-O-C asym. *str.*, pyrazole moiety), 1016 (N-N *str*.,), 741(C-Cl *str*., azetidinone). ^{1}H NMR (DMSO-d_6): δ (ppm): 3.78 (s, 3H, O-CH_3 attached to quinoline ring), 2.40 (s, 3H, CH_3 group attached to aromatic ring), 6.59 (s, 1H, at C_4 of pyrazole ring), 12.34 (s, 1H, NH at –CONH– linkage), 6.93-9.05 (m, 20 H, CH-Cl at C_3 and N-CH at C_4 of azetidinones ring, aromatic and hetero aromatic ring protons). ESI-MS (*m/z*): 684 $[M+H]^+$, 696 $[M+Na]^+$. Elemental analysis (%) calcd. (found) for $C_{38}H_{28}N_5O_5Cl$: C, 68.11 (68.05); H, 4.21 (4.15); N, 10.45 (10.39).

Antibacterial activity: The novel synthesized compounds (**4a-f**) were screen for *in vitro* antimicrobial activity at various concentrations by agar disc diffusion method. Test solution were organized by dissolving each compound in DMSO solvent and diluted suitably to give the subsequent concentration of 31-1000 µg/mL. Petri plates were set by pouring 10 mL of nutrient agar. The stock culture of *S. aureus* and *E. coli* were evaluated by inoculating in broth media and grown at 37 ºC for 18 h. The bacterial culture was banquet over nutrient agar in plate. Whatmann No. 1 sterile filter paper circle of 6 mm diameter were soaked in the arranged solution and dried at room temperature then put on the plates and incubated at 37 ºC for 24 h. The inhibition zones were measured in mm. The results were compared using chloramphenicol as a standard antibacterial drug.

RESULTS AND DISCUSSION

An effective and facile process to afford azetidin-2-one derivatives (**4a-f**) in excellent yields. Newly synthesized compounds have been corroborated on spectroscopic investigation such as ^{1}H & ^{13}C NMR, FT-IR and mass spectra.

The carbohydrazide derivatives (**3a-f**) on treatment with chloroacetyl chloride in the presence of triethylamine in DMF solvent at ice cold condition furnished final products, 5-(benzofuran-2-yl)-N′-(3-chloro-4-(2-(*p*-tolyloxy) substituted quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (**4a-f**) as given in **Scheme-II**.

IR spectra of compound **4a** shows characteristic absorption band at 1664, 1771 cm^{-1} due to C=O stretch of carbonyl group of β-lactam ring, respectively. Another absorption bands appeared at 773, 747 cm^{-1} are due to C-Cl stretch. Yet one more band at 1375 cm^{-1} was observed due to C-N stretching. All other absorptions bands for various stretching and bending vibrations for aromatic and aliphatic group were observed at the expected region in the infrared spectra. ^{1}H NMR spectrum of compound **4a** showed a singlet at δ 2.75 ppm due to six protons of two -CH_3 groups; one attached to phenyl and other to the quinoline ring. Another singlet appeared at δ 6.54 ppm due to one proton present at C_4 of pyrazole ring. An additional singlet displayed at δ 12.35 ppm was due to one proton of -CONH- linkage, and a multiplet due to twenty aromatic protons including azetidinones, aromatic and hetero aromatic ring appeared in the range of δ 7.14-9.08 ppm.

Mass spectra of compound **4a** shows also supported *m/z* ion peaks at 654 $[M+H]^+$ and 676 $[M+Na]^+$. Elemental analysis of compound **4a** showed percentage of carbon, hydrogen and nitrogen in good agreements with the calculated values.

Antibacterial activity: The results of *in vitro* antibacterial activity of entire synthesized compounds against bacterial strains at different concentration ranging from 31-1000 µg/mL are given in Table-1. It is found that most of the compounds **4a-f** exhibited significant antibacterial activity when these results were compared with standard drug chloramphenicol. The activities of these synthesized heterocyclic compounds towards the microbial strains may be due to presence different heterocyclic rings present in the concluding structure *p*-tolyloxy quinoline in combination with 2-azetidinone ring which is bonded with pyrazole and benzofuran, all these have tendency to inhibit the growth of microorganism.

TABLE-1
ANTIBACTERIAL ACTIVITY OF
THE SYNTHESIZED COMPOUNDS **4a-f**

Entry	Zone of inhibition in mm at 1000 µg/mL	
	Gram-positive *S. aureus*	Gram-negative *E. coli*
4a	10	13
4b	11	12
4c	10	11
4d	12	10
4e	11	11
4f	11	10
Chloramphenicol	10	13

Conclusion

In conclusion, the synthesis and characterization of some novel 5-(benzo-furan-2-yl)-*N*′-(3-chloro-4-(2-(*p*-tolyloxy) substituted quinolin-3-yl)-2-oxoazetidin-1-yl)-1-phenyl-1*H*-pyrazole-3-carboxamide (**4a-f**) derivatives from 5-(benzofuran-2-yl)-*N*′-(2-(*p*-tolyloxy) substituted quinolin-3-yl)-methylene)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**3a-f**) are reported. The presented series of compounds were synthesized in excellent yields and most of the compounds exhibited good activity against selected strains *S. aureus* and *E. coli*.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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