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SYNTHESIS AND ANTIBACTERIAL SCREENING OF 4-(3-(5-BROMOTHIOPHEN-2-YL)-1-(4-CHLOROPHENYL)-1H-PYRAZOL-4-YL)-3- CHLORO-1-(ARYL) AZETIDIN-2-ONE FROM SCHIFF BASES CONTAINING PYRAZOLE MOIETY.

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ABSTRACT

A new series of 4-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3- chloro-1-(aryl) azetidin-2-one was prepared from pyrazole containing Schiff bases,1-(3-(5-bromo thiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4- yl)-N-(aryl)methanimine. 1-(3-(5-bromo thiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-N-(aryl) methanimine were prepared from 3-(5-bromothiophen-2-yl)-1-(4-chloro phenyl)-1H-pyrazole-4-carbaldehyde and aromatic amines. The structures of newly synthesized compounds were confirmed on the basis of IR, ^{1}H NMR and Mass spectroscopy data. All newly synthesized compounds were screened for their antibacterial activity against four microorganisms: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa and Klebsiella pneumoniae*. All compounds showed nearly good to better activity against the test organisms. The synthesized compounds were significantly active against *Klebsiella pneumoniae* and compounds 3a, 3b and 3l were highly active, showing zone of inhibition 18, 16 and 16 mm respectively.

KEYWORDS: Pyrazole, Schiff bases, 2-Azetidinones, Antibacterial Activity.

INTRODUCTION

Microbial resistance is one of the major issues going through medical science and searching new powerful antimicrobial agents against multi-resistant pathogens is one of the main

concerns in modern pharmaceutical research.[1] Heterocyclic compounds are very important and unique class of compounds. These compounds revels broad spectrum of physical, chemical and biological distinctive properties. In nature, heterocyclic compounds are extensively disbursed and display an important part in metabolism because of their structural framework associated with number of natural products, consisting hormones, antibiotics, alkaloids, vitamins and many more.[2] Among heterocyclic compounds, nitrogen containing heterocyclic compounds are extensively observed as a core framework in massive library of heterocyclic compounds and shows several applications in chemical and medical sciences.[3] This nitrogen containing heterocyclic compounds are part of many natural products for example vitamins, hormones and alkaloids.[4-5] Pyrazole and 2-azetidinones are potential scaffolds of nitrogen containing compounds. Pyrazole is an important five membered heterocyclic compound found in number of drugs.[6-9] Due to wide spectrum of biological activities, pyrazole is the framework of interest for the synthetic chemist, it has also wide applications in number of therapeutic areas like central nervous system, cancer and metabolic disease.[10-12] It shows antimicrobial.[13-16], anticancer[17], anti-inflammatory[18] and antioxidant[19] activity.

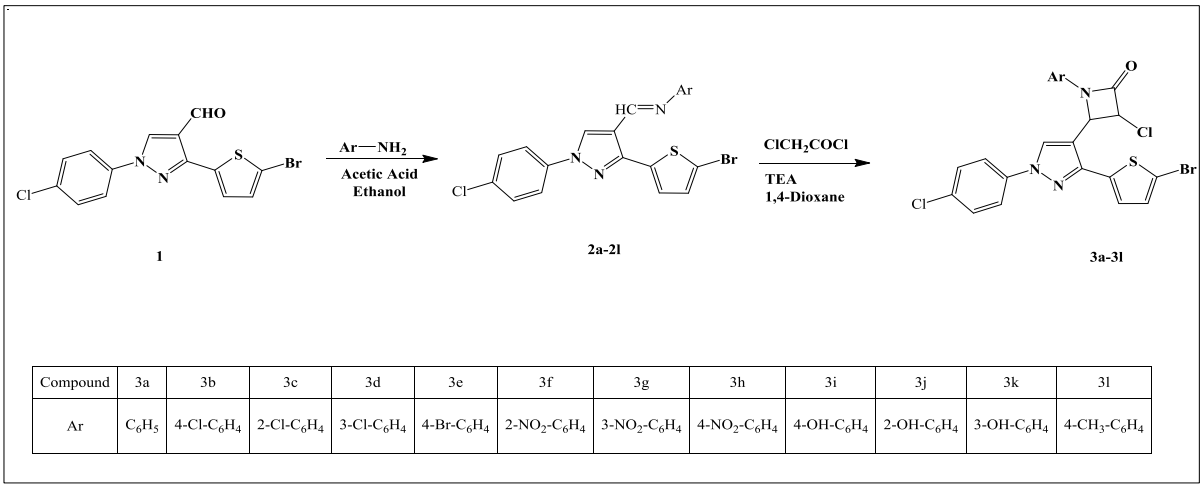
2-Azetidinones are an important group of heterocyclic compounds with broad spectrum of pharmacological activities. Structural modification of β-lactam ring gives on to compounds with enhance pharmacological activities inducing cholesterol absorption inhibition, human tryptase, thrombin and chymase inhibition, vasopressin V1a antagonist activity, antibacterial[20-24], antitubercular[25-26], cyclooxygenase-2 inhibitors[27], anticancer[28-29], antimalarial[30] and antifungal[31-32] activity.

In view of above literature survey and in continuation to our work, here we report the synthesis a new series of 2-azetidinones from Schiff bases containing pyrazole moiety and its antibacterial activity.

MATERIALS AND METHOD

All the Chemicals and solvents were of analytical grade and were procured from SDFCL. Melting points were determined in open capillary tube and are uncorrected. The progress and purity of compounds was checked by thin-layer chromatography using with F-252 silica gel precoated aluminium plates using petroleum ether-ethyl acetate (9:1) as a developing solvent and spots were visualised by exposing the plates in iodine vapours. Infrared spectra were recorded on Shimadzu spectrophotometer using KBr pellets technique (λ_{max} in cm^{-1}). ^{1}H

Nuclear magnetic resonance spectra were recorded on BRUKER ADVANCE (400 FT- NMR) spectrophotometer using dimethyl sulfoxide (DMSO- d_6) as a solvent and tetramethyl silane as an internal reference (chemical shifts, δ in ppm). Mass spectra were observed on Waters UPLC- TQC Mass Spectrometer.



Compound	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l
Ar	C_6H_5	4-Cl-C_6H_4	2-Cl-C_6H_4	3-Cl-C_6H_4	4-Br-C_6H_4	2-NO_2-C_6H_4	3-NO_2-C_6H_4	4-NO_2-C_6H_4	4-OH-C_6H_4	2-OH-C_6H_4	3-OH-C_6H_4	4-CH_3-C_6H_4

Scheme- Synthesis of 2-azetidinones (3a-3l) from corresponding Schiff bases.

Synthesis of 4-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3- chloro-1-(aryl) azetidin-2-one (3a-3l)

A mixture of 1-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-N-(aryl) methanimine (2a -2l) (0.01 mol) and triethylamine (TEA) (0.01 mol) was dissolved in 40 ml 1,4-dioxane, cooled and stirred at 0 – 5^{O}C. To this well-stirred cooled solution chloroacetyl chloride (0.01 mol) was added drop wise over the period of half an hour. The reaction mixture was then stirred for 5 hours, the white precipitate of amine hydrochloride thus obtained was filtered off. The filtrate was then refluxed for 8 to 15 hours. The reaction mixture then cooled and poured into ice-cold water. The resulting solid was filtered, washed with water and purified by recrystallization from ethanol/ dioxane.

Table No. 1: Analytical data of compounds (3a-3l).

Sr. No.	Compound	Ar	Molecular Formula	Colour	Melting Point in ^{0}C	% Yield
1	3a	C_6H_5	$C_{22}H_{14}BrCl_2N_3OS$	Yellow	156	59
2	3b	4-Cl C_6H_4	$C_{22}H_{13}BrCl_3N_3OS$	Yellow	142	61
3	3c	2-Cl C_6H_4	$C_{22}H_{13}BrCl_3N_3OS$	Yellow	134	56
4	3d	3-Cl C_6H_4	$C_{22}H_{13}BrCl_3N_3OS$	Brown	158	54
5	3e	4-Br C_6H_4	$C_{22}H_{14}Br_2Cl_2N_3OS$	Yellow	162	58
6	3f	2-NO_2 C_6H_4	$C_{22}H_{13}BrCl_2N_4O_3S$	Yellow	137	60
7	3g	3-NO_2 C_6H_4	$C_{22}H_{13}BrCl_2N_4O_3S$	Yellow	147	50

8	3h	4-NO_2 C_6H_4	$C_{22}H_{13}BrCl_2N_4O_3S$	Brown	155	62
9	3i	4-OH C_6H_4	$C_{22}H_{14}BrCl_2N_3O_2S$	Pale yellow	153	68
10	3j	2-OH C_6H_4	$C_{22}H_{14}BrCl_2N_3O_2S$	Yellow	132	54
11	3k	3-OH C_6H_4	$C_{22}H_{14}BrCl_2N_3O_2S$	Yellow	130	58
12	3l	4-$CH_3C_6H_4$	$C_{23}H_{16}BrCl_2N_3OS$	Yellow	146	48

4-(3-(5-bromo thiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3-chloro-1-phenyl azetidin-2-one (3a)

IR (KBr) cm^{-1}: 1685 (C=O, *β*-lactam) 1597 (C=N), 1469 (C=C) 3097 (C-H) 698 (C-Br); ^{1}H NMR: δ 8.1 (s, 1H, H-pyrazole), 3.4 (d, 1H, H-C-N), 4.8 (d, 1H, H-C-Cl), 7.1-8.4 (m, 11H, Ar-H); Mass: m/z = 522 (M^+ +3).

4-(3-(5-bromothio phen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3-chloro-1-(4-chlorophenyl) azetidin -2-one (3b)

IR (KBr) cm^{-1}: 1700 (C=O, *β*-lactam) 1597 (C=N), 1469 (C=C) 3036 (C-H) 663 (C-Br); ^{1}H NMR: δ 8.6 (s, 1H, H-pyrazole), 3.3 (d, 1H, H-C-N), 4.5 (d, 1H, H-C-Cl), 7.3-8.0 (m, 10H, Ar-H); Mass: m/z = 556 (M^+ +3).

1-(4-bromophenyl)-4-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3-chloroazetidin-2-one (3e)

IR (KBr) cm^{-1}: 1710 (C=O, *β*-lactam) 1593 (C=N), 1469 (C=C) 3078 (C-H) 705 (C-Br); ^{1}H NMR: δ 8.4 (s, 1H, H-pyrazole), 3.4 (d, 1H, H-C-N), 4.2 (d, 1H, H-C-Cl), 7.1-8.0 (m, 10H, Ar-H); Mass: m/z = 562 (M^+).

RESULTS AND DISCUSSION

4-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3-chloro-1-(aryl) azetidin-2-one (3a-3l) were prepared by condensing corresponding Schiff bases with chloroacetic acid in presence of triethyl amine in dry 1,4-dioxane. The corresponding Schiff bases,1-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-N-(aryl) methanimine (2a -2l) were prepared from 3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde (1) by the reported method and published in our previous work.[33] The newly synthesized 2-azetidinones have been characterized on the basis of IR, ^{1}H NMR and Mass spectroscopy data. Spectral data of all the synthesized compounds are in full agreement with the proposed structures. In IR spectra of synthesized compounds, a strong band in the region at 1600-1710 cm^{-1} is assigned to the stretching of CO of β-lactam. All compounds showed a signal due to C=N stretching at around 1500-1600 cm^{-1}. ^{1} H NMR spectrum of the

compounds (3a-3l) showed a sharp singlet in the range of δ 8-8.5 ppm for pyrazole proton while a doublet at δ 3.3 ppm and δ 4.4 ppm appeared for H -C-N and H-C-Cl. The aromatic protons appeared in the form of multiplet at δ 7-8.4 ppm. The m/z values obtained from Mass spectra for the characterized 2-azetidinones are in good agreement with the molecular weights.

Antibacterial screening of compounds (3a-3l)

All newly synthesized compounds were screened for their antibacterial activity against four microorganisms: *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella pneumoniae.* All compounds showed nearly good to better activity against the test organisms. The synthesized compounds were significantly active against *Klebsiella pneumoniae.* Compounds 3a, 3b and 3d were the more active towards *Escherichia coli*, Compounds 3d, 3k and 3l showed good activity against *Staphylococcus aureus*, compound 3j showed significant activity against *Pseudomonas aeruginosa*, and compounds 3a, 3b and 3l were highly active, showing zone of inhibition 18, 16 and 16 mm respectively.

Table No. 2: Antibacterial Activity of compounds (3a-3l).

Sr. No.	Compound	Test organism			
		E. coli	***S. aureus***	***P. aeruginosa***	***K.pneumoniae***
1	3a	18	12	11	18
2	3b	16	12	11	16
3	3c	15	14	11	12
4	3d	17	15	12	12
5	3e	14	12	12	14
6	3f	15	13	12	13
7	3g	13	<10	<10	12
8	3h	14	<10	12	11
9	3i	11	13	<10	11
10	3j	11	13	14	14
11	3k	13	18	11	14
12	3l	12	17	<10	16
13	Streptomycin	28	27	27	19
14	Chloramphenicol	21	24	20	28

CONCLUSION

A new series of 4-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-3-chloro-1-(aryl) azetidin-2-one (3a-3l) was prepared from 1-(3-(5-bromo thiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4- yl)-N-(aryl)methanimine (2a-2l). The synthesized compounds were characterized on the basis IR, ^{1}H NMR and Mass spectroscopy data. Spectral data of

compounds and proposed structures are in full agreement. All newly synthesized compounds were screened for their antibacterial activity against four microorganisms. All compounds showed nearly good to better activity against the test organisms.

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