WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.632
Volume 12, Issue 7, 878-886 Review Article ISSN 2278 – 4357

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.

S. V. Manohare[1]* and S. S. Thakare[2]

[1*]Department of Chemistry, Adarsha Science, J. B. Arts and Birla Commerce Mahavidyalaya, Dhamangaon Rly., 444709, Maharashtra, India.

[2]Rajarshee Shahu Science College, Chandur Rly., 444704, Maharashtra.

Article Received on
16 May 2023,

Revised on 05 June 2023,
Accepted on 26 June 2023

DOI: 10.20959/wjpps20237-25341

***Corresponding Author**
S. V. Manohare
Department of Chemistry, Adarsha Science, J. B. Arts and Birla Commerce Mahavidyalaya, Dhamangaon Rly., 444709, Maharashtra, India.

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-chlorophenyl)-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 the newly synthesized compounds were screened for their antibacterial activity against four microorganisms: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa and Klebsiella pneumoniae*. All compound 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.

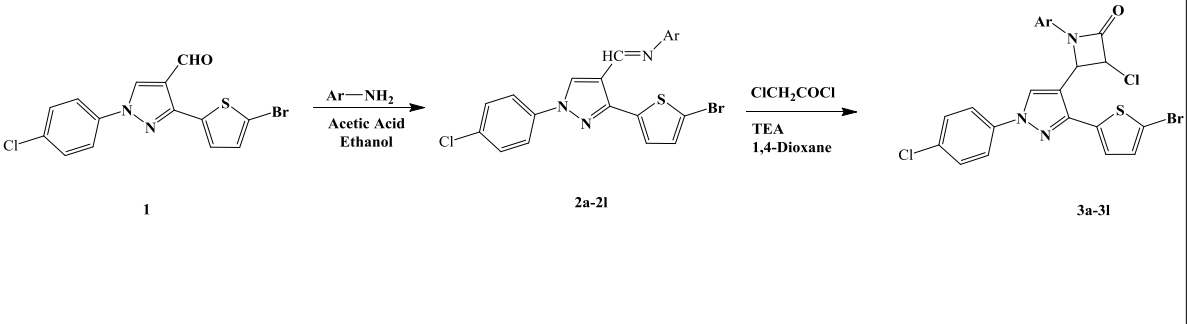
2-Azetidinones are an important group of heterocyclic compounds with broad spectrum of pharmacological activities. Structural modification of β-lactam ring gives on to compounds with enhance pharmacological activities inducing cholesterol absorption inhibition, human tryptase, thrombin and chymase inhibition, 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 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); ^1H 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); ^1H 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); ^1H 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, ^1H 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 2d, 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.

ACKNOWLEDGEMENT

The authors are thankful to SAIF, IISc. Bangalore for ^{1}H NMR analysis, SAIF, CDRI, Lucknow for Mass analysis and Shri Shivaji Science College, Amravati for IR analysis. One of the authors is grateful to UGC, for the award of teacher fellowship under XII plan of UGC (File no. 29-19/14 WRO.).

REFERENCES

1. Maria M. Synthesis of Antimicrobial Benzimidazole–Pyrazole Compounds and Their Biological Activities. Antibiotics, 2021; 10: 1002, https://doi.org/10.3390/ antibiotics10081002.
2. Muhammad F, Aamer S, Sarwat H, Parsa D. Fayaz Ali L. Recent developments in synthetic chemistry and biological activities of pyrazole derivatives. J. Chem. Sci, 2019; 131: 70, https://doi.org/10.1007/s12039-019-1646-1.
3. Ardiansah B. Recent reports on pyrazole-based bioactive compounds as candidate for anticancer agents. Asian J. Pharm. Clin. Res, 2017; 10(12): 45-51.
4. Srivastava M, Singh J, Singh S B, Tiwari K, Pathak K V, Singh J. Synthesis of novel fused heterocycle-oxa-aza-phenanthrene and anthracene derivatives via sequential one-pot synthesis in aqueous micellar system. Green Chem. 2012; 14**:** 901-905.
5. Pai G and Chattopadhyay A P. N-arylation of nitrogen containing heterocycles with aryl halides using copper nanoparticle catalytic system. Tetrahedron Lett, 2016; 57(29): 3140-3145.
6. Dai H, Ge S S, Guo J, Chen S, Huang M L, Yang J Y, Sun S Y, Ling Y, Shi Y. Development of novel bis-pyrazole derivatives as antitumor agents with potent apoptosis induction effects and DNA damage. Eur. J. Med. Chem, 2018; 143: 1066–1076. DOI: 10.1016/j.ejmech.2017.11.098.
7. Padalkar V S, Borse B N, Gupta V D, Phatangare K R, Patil V S, Sekar N. Synthesis and antimicrobial activities of Novel 2-[substituted-1H -pyrazol-4-yl] benzothiazoles, benzoxazoles, and benzimidazoles. J. Heterocyclic Chem, 2016; 53(5): 1347–1355 DOI: 10.1002/jhet.1506.
8. Radi S, Attayibat A, El-Massaoudi M, Salhi A, Eddike D, Tillard M, Mabkhot Y N. X-Ray single crystal structure, DFT calculations and biological activity of 2-(3-methyl-5-

(pyridin-2'-yl)-1H-pyrazol-1-yl) ethanol. Molecules, 2016; 21(8): 1020. DOI: 10.3390/molecules21081020.

9. Gomha S M, Abdel-Aziz H M, El-Reedy A A M. Facile synthesis of pyrazolo [3,4-c] pyrazoles bearing coumarine ring as anticancer agents. J. Heterocyclic Chem, 2018; 55(8): 1960–1965. DOI: 10.1002/jhet.3235.
10. Caddick S, Joshi S A. Regioselective synthesis of heteroaromatic stannanes via radical displacement of heteroaromatic tosylates. Synlett, 1992; 1992(10): 805-806.
11. Viale M, Anzaldi M, Aiello C, Fenoglio C, Albicini F, Emionite L, Gange R, Balbi A. Evaluation of the anti-proliferative activity of three new pyrazole compounds in sensitive and resistant tumor cell lines. Pharmacol. Rep, 2013; 65(3): 717-723.
12. Mert S, Yaghoglu A S, Demirtas I, Kasmogullar R. Synthesis and antiproliferative activities of some pyrazole-sulfonamide derivatives. Med. Chem. Res, 2014; 23: 1278-1289.
13. Desai N C, Vaja D V, Jadeja K A, Joshi S B, Khedkar V M. Synthesis, biological evaluation and molecular docking study of pyrazole, pyrazoline clubbed pyridine as potential antimicrobial agents, 2019; 17(1): DOI:10.2174/2211352517666190627144315.
14. Kendre B V, Landge M G, Bhusare S R. Synthesis and biological evaluation of some pyrazole, isoxazole, benzoxazepine, benzothiazepine and benzodiazepine derivatives bearing an aryl sulfonate moiety as antimicrobial and anti-inflammatory agents, 2019; 12(8): 2091-2097.
15. El Shehry M F, Ghorab M M, Abbas S Y, Fayed E A, Shedid S A, Ammar Y A. Quinoline derivatives bearing pyrazole moiety: Synthesis and biological evaluation as possible antibacterial and antifungal agents. Eur. J. Med. Chem, 2018; 1(143): 1463-1473.
16. Sood S, Kumari P, Yadav A N, Kumar A, Singh K. Microwave-assisted synthesis and biological evaluation of pyrazole-4-carbonitriles as antimicrobial agents. J. Heterocyclic Chem, 2020; 57(7): 2936-2944.
17. Ali G M E, Ibrahim D A, Elmetwali A M, Ismail N S M. Design, synthesis and biological evaluation of certain CDK2 inhibitors based on pyrazole and pyrazolo[1,5-a] pyramidine scaffold with apoptotic activity. Bioorg Chem, 2019; 86: 1-14.
18. Taher A T, Mostafa Sarg M T, El-Sayed Ali N R, Elnagdi N H. Design, synthesis, modelling studies and biological screening of novel pyrazole derivatives as potential analgesic and anti-inflammatory agents. Bioorg. Chem, 2019; 89: 103023, doi: 10.1016/j.bioorg.2019.103023.

19. Masaret G S. A new approach for the synthesis and biological activities of novel thiazolyl-pyrazole derivatives. Chemistry Select, 2021; 6: 947-982.
20. Kayarmar R, Nagaraja G K, Naik P, Manjunatha H, Revanasiddappa B C, Arulmoli T. Synthesis and characterization of novel imidazoquinoline based azetidinones as potent antimicrobial and anticancer agents. Journal of Saoudi Chemical Society, 2017; 21: S434-S444.
21. Swami M B, Kaminwar N S, More Y W, Pathare P G, Kotai L, Kendrekar P K, Pawar R P. Synthesis, characterization and biological activities of 4-thiazolidinone and 2- azetidinone derivatives, 2017; 6(3): 98-100.
22. Kakkerla R, Marri S, Merugu R, Satyanarayana M. Synthesis and antibacterial activity of isoxazolyl azetidine-2-ones and thiazolidine-4-ones RASAYAN J. Chem, 2018; 11(2): 886-893.
23. Zangade S, Shinde A, Nalwar Y, Patil P. Microwave assisted synthesis and antimicrobial study of some novel 2-azetidinones derived from 2-(1-phenylimino microwave assisted synthesis-ethyl)-naphthalen-1-ol. Current Pharma Research, 2019; 10(1): 3565-3576.
24. Khan T, Yadav R, Gound S S. An effective synthesis and antibacterial activity of some novel 2-azetidinone derivatives of 4H-1,2,4-triazoles under mild conditions. J. Heterocyclic Chem, 2018; 55(4): 1042-1047.
25. Das R, Mehta D K. Evaluation and docking study of pyrazine containing 1,3,4-oxadiazoles clubbed with substituted azetidine-2-one: A new class of potential antimicrobial and antitubercular. Drug. Res, 2021; 71: 26-35.
26. Kumar S S, Shettar A, Joshi S D, Patil S A. Design, synthesis, molecular docking and biological activity study of novel coumarino-azetidinones. Journal of Molecular Structure, 2021; 1231(5): 130016.
27. Arefi H, Naderi N, Shemirani A B I, Falvarjani M K, Movahed M A, Zarghi A. Design, synthesis and biological evaluation of new 1,4-diarylazetidin-2-one derivatives (β-lactams) as selective cyclooxygenase -2 inhibitors. Arch Pharm, 2020; 353(3): e1900293
28. Tripodi F, Dapiaggi F, Orsini F, Pagliarin R, Sello G, Coccetti P. Synthesis and biological evaluation of new 3-amino-2-azetidinone derivatives as anti-colorectal cancer agents. Med. Chem. Commun, 2018; 9: 843-852
29. Mohmadzadeh M, Zarei M. Anticancer activity and evaluation of apoptotic genes expression of 2-azetidinones containing anthraquinone moiety. Molecular Diversity, 2020; 25(4): 2429-2439.

30. Jarrahpour A, Heiran R, Sinour V, Latour C, Bouktab L D, Brunel J M, Sheikh J, Hadda T B. Synthesis of new β-lactams bearing the biologically important morpholine ring POM analysis of their antimicrobial and antimalarial activities. Iranian Journal of Pharmaceutical Research, 2019; 18(1): 34-38.
31. Patel N B, Patel M D. Synthesis and evaluation of antibacterial and antifungal activities of 4-thiazolidinones and 2-azetidinones derivatives from chalcone. Medicinal Chemistry Research, 2017; 26: 1772-1783.
32. Mishra M K, Singh V N, Ahmad K, Sharma S. Synthesis and antimicrobial activities of some novel diastereoselective monocyclic cis β-lactams using 2-ethoxy carbonyl DCPN as a carboxylic acid activator. Molecular Diversity, 2020; 25: 2973-2087.
33. Manohare S V, Thakare S S. Synthesis and antibacterial screening of Schiff bases derived from 3-(5-bromothiophene-2-yl)-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde. IJPSR, 2019; 10: 3741-3745.