DESIGN, SYNTHESIS, EVALUATION OF BENZOXAZOLE DERIVATIVES FOR ANTI-TUBERCULAR AND ANTI-BACTERIAL ACTIVITY

Vinod Madhaorao Thakare [1], Akshaykumar Baban Kadam [2], Archana Shaha [3]*, Bishwanath Mishra [4], Sazedur Rahman Akanda [5], Boi Basanta Kumar Reddy [6], Pavankumar D Chopade [7], Dhruv Kishor Vishwakarma [8]

1. Professor and Principal, Nagpur College of Pharmacy, Wanadongri, Hingna Road, Nagpur, Pin Code: 441110
2. Assistant professor, Department of Pharmaceutical Chemistry, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, Pin Code: 415539
3. Assistant Professor, Department of Pharmacy, Vishwakarma University, Pune, Maharashtra, Pin Code: 411048
4. Associate Professor, Institute of Pharmacy & Technology, Salipur, At/Po- Salipur, District-Cuttack, Odisha, Pin Code: 754202
5. Assistant Professor and Research Scholar School of Pharmaceutical Sciences, University of Science and Technology Meghalaya, Techno city, Pin Code: 793101
6. Professor, Danteswari College of Pharmacy, Borapadar, Raipur Road, Jagdalpur, Chattiagarh, Pin Code: 494221
7. Assistant professor, Oriental College of Pharmacy Sanpada Navi Mumbai, Maharashtra, Pin Code: 400705
8. Assistant professor, Shri Rawatpura Sarkar Institute of Pharmacy Chitrakoot, Pin Code: 485334

Corresponding Author: Archana Shaha
Designation and Affiliation: Assistant Professor, Department of Pharmacy, Vishwakarma University, Pune, Maharashtra, Pin Code: 411048
Email Id: archana.shaha@gmail.com

ABSTRACT

The antibacterial and antimycobacterial properties of a novel class of benzoxazole compounds were tested in vitro. The produced benzoxazole compounds were screened for their in vitro antibacterial activity against Gram-positive bacteria S. aureus and Gram-negative bacteria E. coli using IR, 1H-NMR, and mass. The antibacterial activity was then tested using a serial dilution experiment. All medications and antimycobacterial activities against M. tuberculosis are evaluated for MIC. For antibacterial activity, the serial dilution method (MIC test) was employed, and for antitubercular activity, the Alamar blue assay test was employed. Compounds 4a, 4c, 4f, and 4i had strong antibacterial activity against E. coli and S. aureus at 100 and 50 µg/ml, while Compounds 4c and 4i demonstrated strong antitubercular activity against Mycobacterium tuberculosis (H-37RV) at 100 and 50 µg/ml.

Keywords: Benzoxazole, *M. tuberculosis,* Antibacterial and Antimycobacterial

INTRODUCTION

Infectious infections are causing a significant number of deaths worldwide [1]. Multidrug-resistant diseases have been found to be rapidly increasing these days, leading to an increase

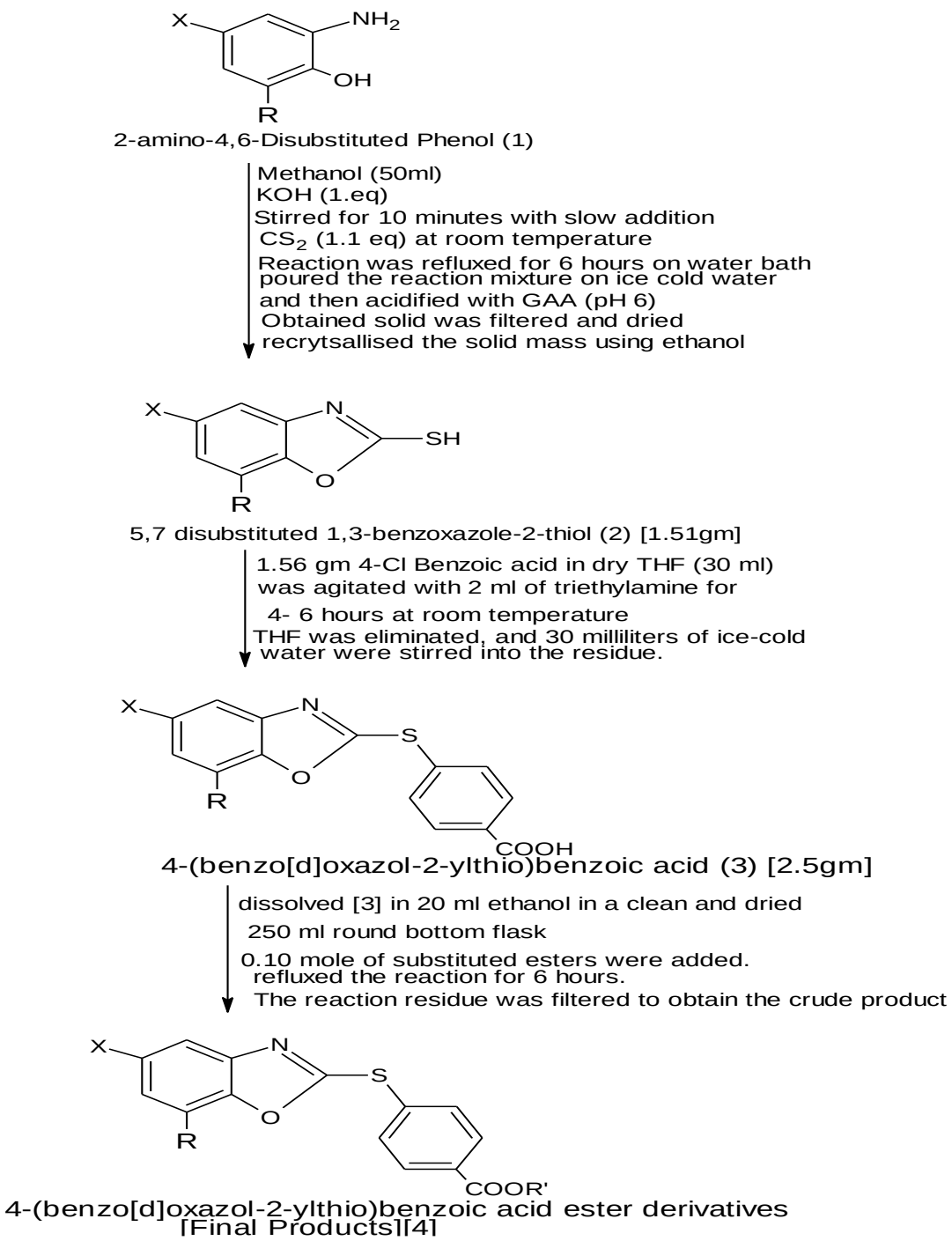
in a number of public health issues. Clinicians must rely on limited medications like vancomycin to address a number of disorders that are currently difficult to treat with conventional antibiotics [2]. The need to create more advanced antimicrobial drugs has grown as a result [3]. Cancer is one of the most deadly illnesses in the world, and despite significant medical progress, it continues to rank as the second most common cause of death in both industrialised and developing nations. Even though chemotherapy is the most common treatment for cancer, the ineffectiveness of current chemotherapeutics highlights the necessity of creating novel chemical entities [4]. The third most frequent cancer to be detected in humans is colorectal cancer (CRC), which has a dismal prognosis. Better efficacy, fewer side effects, and higher survival rates are desperately needed in therapy [5].

Oxazole is a heterocyclic molecule that contains nitrogen and oxygen atoms in five-membered rings. [6] When benzene rings are joined to oxazole rings, benz-oxazole is created. There are numerous techniques available for making the benz-oxazole derivative. Because it contains N and O in a structure that can undergo ring organisation processes, ortho-aminophenol is the optimum starting material for the synthesis of benzo-oxazole heterocyclic rings. [7, 8] Although it is a heterocyclic molecule with several reactive sites, the stability of the benz-oxazole moiety is due to its aromaticity. These days, Mycobacterium tuberculosis is the cause of tuberculosis, a serious health concern with a wide range of symptoms. The lungs are the primary organ affected by tuberculosis. [9] According to recent research, over 33% of the population is infected with mycobacterium tuberculosis germs. Treatment for this pathogenic bacterium now takes longer. As a result, new medications with different mechanisms of action from previously utilised medications, like isoniazid, streptomycin, pyrazinamide, and rifampicin, must be prepared. [10, 11, 12] Numerous activities, including anticancer, antihyperglycemic, antitumor, immunomodulatory, antifungal, antibacterial, analgesic, anti-tubercular, anti-inflammatory, antihypertensive, and anticonvulsant properties, have been demonstrated by the novel derivative that contains benz and oxazole rings. [13–18] The newly made derivative (4a–4i) was applied for its antibacterial and antitubercular properties.

MATERIAL AND METHODS

Materials: Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and Central Drug House (P) Ltd. (Delhi, India) provided all of the analytical-grade solvents and chemicals utilised in the research.

Synthesis:



Schem 1: Synthesis of Benzoxazole derivatives [19-20]

Anti-bacterial Activity: Bacteria that are Gram-positive Gram-negative bacteria and S. aureus The antibacterial activity was tested using a serial dilution experiment with E. coli. Every medication must be diluted nine times with thioglycollate broth for MIC. Fill a first tube with 20 µl of the medication and 380 µl of thioglycollate broth. Nine tubes were individually diluted with 200µl of thioglycollate. It was filled with 200 µl of the thioglycollate broth from the first

tube. It was determined that the dilution was 10-1. The 10-2 dilution was made by moving 200 µl from the 10-1 diluted tube to the second tube. [21, 22] Serial dilutions were performed up to a 10-9 dilution for every medication. From the routinely maintained stock culture of the required organisms, 5µl were taken and added to 2 ml of thioglycollate broth. 200µl of the previously described culture solution was added to each serially diluted tube. Every tube was kept in anaerobic jars at 37°C for two to three days while the turbidity was tracked. [23-27]

Anti-tubercular Activity: Using the Alamar blue assay method, the anti-tubercular activity of the vaccine strain of Mycobacterium TB, H37 RV strain (ATCC No. 27543) was evaluated. This process uses a non-toxic, thermally stable reagent. 200µl of sterile deionised water was added to each outer perimeter well of a sterile 96-well plate to stop the medium in the test well from evaporating too quickly during incubation. After adding 100 µl of the middle-brook 7H-9 broth to the 96-well plates, serial dilutions of the derivatives were made directly on the plate. [28-29] The final drug levels that were analysed were between 100 and 0.2 µg/ml. After being parafilm-enclosed, the plates were incubated for 120 hours at 37°C. The plate was then incubated for one day after receiving 25µl of a freshly prepared solution [1:1] of alamar blue reagent and 10% tween 80. Bacterial growth in the wells was shown by pink colour, whilst no bacterial growth was indicated by blue. [30-32]

RESULTS AND DISCUSSION

All of the benzoxazole derivatives used in this study were successfully made using the synthetic root scheme. 1. All produced derivatives' physiochemical data (4a–4i) are displayed in Table 1. Serial dilution was employed to test for antibacterial activity, and the interpretation of LCMS, NMR, and IR data validated all freshly produced compounds. On the other hand, anti-tubercular activity was tested using the Alamar Blue Assay.

Table 1: List of compounds synthesized

Derivatives	X	R	R’	Colour	Rf value	% yield
4a	F	OCH_3	CH_3	white solid powder	0.56	68.30%
4b	F	OCH_3	C_2H_5	Off white solid	0.68	59.30%
4c	F	OCH_3	C_3H_7	Pale yellow solid	0.61	69.40%
4d	Br	OCH_3	CH_3	Yellowish brown crystals	0.49	59.70%
4e	Br	OCH_3	C_2H_5	Pale brown solid	0.68	62.20%
4f	Br	OCH_3	C_3H_7	Yellowish brown solid	0.57	57.98%
4g	I	OCH_3	CH_3	Off white solid	0.68	59.30%

4h	I	OCH_3	C_2H_5	Off white solid	0.71	61.30%
4i	I	OCH_3	C_3H_7	Off white solid	0.75	51.25%

Table 2: Chemical Properties of synthesized compounds(4a-4i)

Derivatives	Chemical Formula	M.W	Composition C								M.P. (°C)
			C	H	N	O	S	F	Br	I	
4a	$C_{16}H_{12}NO_4SF$	333.33	57.65%	3.63%	4.20%	19.20%	8.30%	5.70%	-	-	106°C
4b	$C_{17}H_{14}NO_4SF$	347.36	58.78%	4.06%	4.03%	18.42%	9.23%	5.47%	-	-	109°C
4c	$C_{18}H_{16}NO_4SF$	361.38	59.82%	4.46%	3.88%	17.71%	8.87%	5.47%	-	-	102°C
4d	$C_{16}H_{12}NO_4SBr$	394.23	48.74%	3.07%	3.55%	16.23%	8.13%	-	20.27%	-	138°C
4e	$C_{17}H_{14}NO_4SBr$	408326	50.01%	3.46%	3.43%	15.68%	7.85%	-	19.57%	-	143°C
4f	$C_{18}H_{16}NO_4SBr$	422.29	51.19%	3.82%	3.32%	15.15%	7.59%	-	18.92%	-	157°C
4g	$C_{16}H_{12}NO_4SI$	441.24	43.55%	2.74%	3.17%	14.50%	7.27%	-	-	28.76%	167°C
4h	$C_{17}H_{14}NO_4SI$	455.26	44.85%	3.10%	3.08%	14.06%	7.04%	-	-	27.87	157°C
4i	$C_{18}H_{16}NO_4SI$	469.29	46.07%	3.44%	2.98%	13.64%	6.83%	-	-	27.04%	141°C

Spectral data of final compounds (4a-4i)

Methyl 4-[(5-fluoro-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4a): 1HNMR (400 MHz, DMSO) δ- 2.11 (3-H, s, -CH_3),indicate the Prescence of methyl group, δ-6.45-6.34 (2-H, m, Ar-H, δ-5.76 (1-H, dd, 1.7Hz, Ar-H), show the presence of aromatic ring, 7.45 (0.5Hz), 7.37 (0.5Hz)), IR (KBr): 1656 cm^{-1} (stretching C=N), 2798 cm^{-1} (stretching Ar-H), 1511 cm^{-1} (stretching Ar-CH_3) and 788.87 cm^{-1} (stretching, C-S), Mass, (ESI-MS): m/z 169 (M+H).

Ethyl 4-[(5-fluoro-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4b): ^{1}HNMR (400 MHz, DMSO) δ2.95 (3H, s,-CH3), show the presence of methyl group, 7.11-7.39 (H, m, Ar-H,) indicate the presence of aromatic ring, 12.5 (1H, -NH-), 4.45 (2H,s, -CH_2-), indicate methylene group, 7.56 (1H,1.2 Hz, Ar-H) , IR (KBr): 3123 cm^{-1} (stretching, Ar-H), 1701 cm^{-1} (stretching C=N), 1534 cm^{-1} (stretching Ar-CH_3), 2278 cm^{-1} (stretching N-H, Secondary Amine), and 756.4 cm^{-1} (stretching, C-S), Mass (ESI-MS): m/z 269 (M+H).

Propyl 4-[(5-fluoro-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4c): 1HNMR (400 MHz, DMSO) δ-2.27 (3H, s, -CH_3) indicates the presence of a methyl group, 4.34 (2H,s, -CH_2-), indicate the presence of methylene group 4.67 (2H,s,-CH_2-), δ-6.67-7.54 (11-H, m, Ar- H), indicate the presence of aromatic ring. IR interpretation, IR (KBr): 3023 cm^{-1} (stretching, Ar-

H), 1721 cm^{-1} (stretching C=N), 1516 cm^{-1} (stretching Ar-CH3), 1213 cm^{-1} (stretching C-F) & 737.6 cm^{-1} (stretching C-S), LCMS interpretation, Mass (ESI-MS): m/z 378 (M+H).

Methyl 4-[(5-bromo-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4d): 1HNR (400 MHz, DMSO) δ- 2.36 (3H, s, -CH_3), indicate methyl group, 3.45 (3H, s, -OCH_3) show presence of Methoxy group δ-4.32 (2-H,s, -CH_2-), show methylene group δ-4.56 (2-H, s, -CH_2-) δ-7.21-7.57 (11H, m, Ar-H) indicate presence of aromatic ring, IR (KBr): 2987 cm^{-1} (stretching Ar-H), 2796 cm^{-1} (stretching, Ar-OCH_3), 1702 cm^{-1} (stretching C=N), 1489 cm^{-1} (stretching Ar-CH3), and 723.54 cm^{-1} (stretching, C-S), Mass (ESI-MS): m/z 411(M+H).

Ethyl 4-[(5-bromo-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4e): 1HNMR (400-MHz, DMSO) δ-2.56 (3H, s, -CH_3), show presence of methyl group 3.45 (2H, s, -CH2-), δ-3.79 (2H, s,-CH_2-), indicate methylene group δ-6.56-7.33 (11H, m, Ar-H), indicate aromatic ring, IR (KBr): 3011 cm^{-1} (stretching, Ar-H), 1783 cm^{-1} (stretching C=N), 1559 cm^{-1} (stretching Ar-CH_3), 756.5 cm^{-1} (stretching C-S) & 737.64 cm^{-1} (stretching C-Br), Mass (ESI-MS): m/z 423 (M+H).

Propyl 4-[(5-bromo-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4f): 1HNMR (400-MHz, DMSO) δ-2.08 (3-H, s, -CH_3), 3.90 (2-H, s, -CH2-), 4.57 (2-H, s, -CH_2-), δ-6.65-7.16 (11H, m, Ar-H), IR (KBr): 3065 cm^{-1} (stretching, Ar-H), 1729 cm^{-1} (stretching C=N), 1576 cm-1 (stretching Ar-CH^3), 763.6 cm-1 (stretching C-Cl) & 756.5 cm-1 (stretching C-S), Mass (ESI-MS): m/z 398(M+H).

Methyl 4-[(5-iodo-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4g): 1HNMR (400-MHz, DMSO) δ-4.24 (s, 2H, –CH_2S), 2.51 (s, 2H, –NH_2), 7.90 (s, 1H, –NH), 4.57 (2-H, s, -CH_2-), δ-7.41-7.78 (8H, m, Ar-H), IR (KBr): 3031 (C–H str., aromatic), 1472 (C=C str., aromatic), 1674 (C=N, N=CH str.), 1240 (C–N str.), 694 (CH2S, C–S str.), 1194 (C–O–C str. of oxazole), 1624 (CONH str., amide), 1778 (C=O str.), 3392 (C–NH_2 str.), Mass (ESI-MS): m/z 387(M+H).

Ethyl 4-[(5-iodo-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4h): 1HNMR (400-MHz, DMSO) δ-4.59 (s, 2H, –CH_2S), 4.63 (s, 2H, –NCH_2), 7.95 (s, 1H, –NH), 8.15 (s, 1H, N=CH–Ar), δ-7.34–7.69 (m, 13H, ArH), IR (KBr): 3212 cm^{-1} (stretching, Ar-H), 1455 cm^{-1} (stretching C=N), 1666 (C=N, N=CH str.), 1252 (C–N str.), 705 cm-1 (stretching C-Cl) & 711 cm-1 (stretching C-S), Mass (ESI-MS): m/z 411(M+H).

Propyl 4-[(5-iodo-7-methoxy-1,3-benzoxazol-2-yl)sulfanyl]benzoate (4i): 1HNMR (400-MHz, DMSO) δ-4.58 (s, 2H, –CH_2S), 4.62 (s, 2H, –NCH_2), 7.89 (s, 1H, –NH), 8.24 (s, 1H, N=CH–Ar), δ-6.85–7.69 (m, 12H, ArH), IR (KBr): 3053 (C–H str., aromatic), 1456 (C=C str., aromatic), 1671 (C=N, N=CH str.), 1248 (C–N str.), 675 (CH2S, C–S str.), 1167 (C–O–C str. of oxazole), 1625 (CONH str., amide), 2941 (C–H str., –OCH_3), Mass (ESI-MS): m/z 411 (M+H).

Anti-tubercular and Anti-bacterial Activity: Against the bacteria Mycobacterium tuberculosis (H-37RV), the newly synthesised derivative of benzoxazole (4a–4i) showed anti-tubercular activity sensitive at 100 and 50 µg/ml, whereas compounds 4c and 4i showed sensitivity at 100 and 50 µg/ml (Fig. 1). Furthermore, 4a, 4c, and 4i showed antibacterial activity that was sensitive at 100 g/ml against gram-negative bacteria like E. coli. Using the serial dilution method (MIC), Table 4 showed antibacterial activity sensitive to 100 µg/ml dosages against gramme-positive bacteria S. aureus.

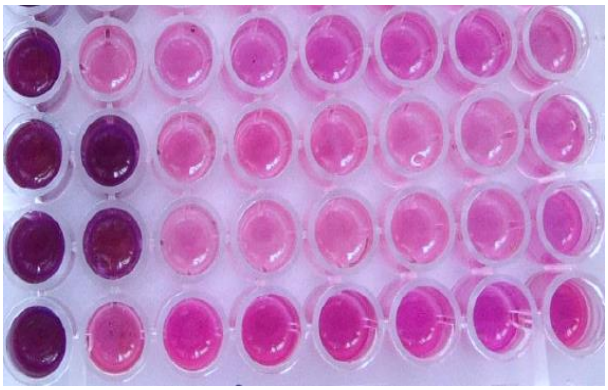


Figure 1: Result of Anti-Tubercular Activity (Bacteria-M. Tuberculosis), Dark Bluish Color Shows Sensitivity, And Pink Colour Shows Resistivity

Table 3: Minimum Inhibitory Concentration Data of Anti-Bacterial Activity Against Gram-Negative Bacteria E. coli

Code	µg/ml									
	100	50	25	12.5	6.25	3.12	1.6	0.8	0.4	0.2
4a	S	R	R	R	R	R	R	R	R	R
4b	S	R	R	R	R	R	R	R	R	R
4c	S	S	R	R	R	R	R	R	R	R
4d	R	R	R	R	R	R	R	R	R	R
4e	S	R	R	R	R	R	R	R	R	R
4f	S	S	R	R	R	R	R	R	R	R
4g	S	R	R	R	R	R	R	R	R	R

4h	R	R	R	R	R	R	R	R	R	R
4i	S	S	S	R	R	R	R	R	R	R

Table 4: Minimum Inhibitory Concentration Data of Anti-bacterial Activity Against Gram-Positive *S. aureus*

Code	µg/ml									
	100	**50**	**25**	**12.5**	**6.25**	**3.12**	**1.6**	**0.8**	**0.4**	**0.2**
4a	S	S	R	R	R	R	R	R	R	R
4b	R	R	R	R	R	R	R	R	R	R
4c	S	S	R	R	R	R	R	R	R	R
4d	R	R	R	R	R	R	R	R	R	R
4e	S	R	R	R	R	R	R	R	R	R
4f	R	S	R	R	R	R	R	R	R	R
4g	S	R	R	R	R	R	R	R	R	R
4h	R	R	R	R	R	R	R	R	R	R
4i	S	S	S	R	R	R	R	R	R	R

Where, R- Resistant and S- sensitive

CONCLUSION

Because of their diverse range of pharmacological actions, benzoxazoles are important in medicinal chemistry. By using spectral analysis, such as liquid chromatography-mass spectrometry, infrared spectroscopy, and proton nuclear magnetic resonance, all of the newly synthesised benzoxazole derivatives (4a–4i) were verified. Compounds 4c and 4i shown strong anti-tubercular activity against Mycobacterium tuberculosis (H-37RV) at 100 and 50 µg/ml, while Compounds 4a, 4c, 4f, and 4i demonstrated strong anti-bacterial activity against S. aureus and E. coli at 100 and 50 µg/ml.

REFERENCES

1. Chilumula NR, Gudipati R, Ampati S, Manda S, Gadhe D (2010) Synthesis of some novel methyl-2-(2-(arylideneamino)oxazol-4-ylamino)benzoxazole-5-carboxylate derivatives as antimicrobial agents. Int J Chem Res 1(2):1–6
2. Ram Prasad S, Saraswathy T, Niraimathi V, Indhumathi B (2012) Synthesis, characterization and antimicrobial activity of some hetero benzocaine dervivatives. Int J Pharm Pharm Sci 4(5):285–287

3. Kamal A, Dastagiri D, Ramaiah MJ, Reddy JS, Bharathi EV, Reddy MK, Sagar MP, Reddy TL, Pushpavalli S, Bhadra MP (2011) Synthesis and apoptosis inducing ability of new anilino substituted pyrimidine sulfonamides as potential anticancer agents. Eur J Med Chem 46(12):5817–5824
4. Vishvakrama P, Sharma S. Liposomes: an overview. Journal of Drug Delivery and Therapeutics. 2014 Jun 24:47-55.
5. Vishvakarma P. Design and development of montelukast sodium fast dissolving films for better therapeutic efficacy. Journal of the Chilean Chemical Society. 2018 Jun;63(2):3988-93.
6. Vishvakarma P, Mandal S, Verma A. A review on current aspects of nutraceuticals and dietary supplements. International Journal of Pharma Professional's Research (IJPPR). 2023;14(1):78-91.
7. Prabhakar V, Agarwal S, Chauhan R, Sharma S. Fast dissolving tablets: an overview. International Journal of Pharmaceutical Sciences: Review and Research. 2012;16(1):17
8. Davidson JP, Corey EJ (2003) First enantiospecific total synthesis of the antitubercular marine natural product pseudopteroxazole revision of assigned stereochemistry. J Am Chem Soc 125(44):13486–13489
9. Smith P, Ward DN (2011) Heterocyclic benzoxazole compositions as inhibitors of hepatitis c virus. US 2012/0208856_01
10. Sun LQ, Chen J, Bruce M, Deksus JA, Epperson JR, Takaki K, Johnson G, Iben L, Mahle CD, Ryan E, Xu C (2004) Synthesis and structure–activity relationship of novel benzoxazole derivatives as melatonin receptor agonists. Bioorg Med Chem Lett 14(14):3799–3802
11. Razavi H, Palaninathan SK, Powers ET, Wiseman RL, Purkey HE, Mohamedmohaideen NN, Deechongkit S, Chiang KP, Dendle MTA, Sacchettini JC, Kelly JW (2003) Benzoxazoles as transthyretin amyloid fibril inhibitors: synthesis, evaluation, and mechanism of action. Angew Chem Int Ed 42(24):2758–2761
12. Sessions EH, Yin Y, Bannister TD, Weiser A, Griffin E, Pocas J, Cameron MD, Ruiz C, Lin L, Schürer SC, Schröter T, LoGrasso P, Feng Y (2008) Benzimidazole- and benzoxazole-based inhibitors of Rho kinase. Bioorg Med Chem Lett 18(24):6390
13. Babul reddy A, Hymavathi RV, Narayana Swamy G (2013) A new class of multi-substituted oxazole derivatives: synthesis and antimicrobial activity. J Chem Sci 125(3):495–509

14. Padmavathi V, Kumara CP, Venkatesh BC, Padmaja A (2011) Synthesis and antimicrobial activity of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles. Eur J Med Chem 46(11):5317–5326
15. Sączewski F, Stencel A, Bieńczak AM, Langowska KA, Michaelis M, Werel W, Hałasa R, Reszka P, Bednarski PJ (2008) Structure activity relationships of novel heteroaryl-acrylonitriles as cytotoxic and antibacterial agents. Eur J Med Chem 43(9):1847–1857
16. Skehan P, Storeng R, Scudiero D, Monks A, McMahon J, Vistica D, Warren JT, Bokesch H, Kenney S, Boyd MR (1990) New colorimetric cytotoxicity assay for anticancer-drug screening. J Natl Cancer Inst 82(13):1107–1112.
17. Kuzu, B., Hepokur, C., Turkmenoglu, B., Burmaoglu, S. & Algul, O. Design, synthesis and in vitro antiproliferation activity of some 2-aryl and-heteroaryl benzoxazole derivatives. Future Med. Chem. 14, 1027–1048. https://doi.org/10.4155/fmc-2022-0076 (2022).
18. Kamal, U., Javed, N. M. & Arun, K. Biological potential of benzoxazole derivatives: An updated review. Asian J. Pharm. Clin. Res. 13, 28–41 (2020).
19. Pathak, N., Rathi, E., Kumar, N., Kini, S. G. & Rao, C. M. A review on anticancer potentials of benzothiazole derivatives. Mini Rev. Med. Chem. 20, 12–23. https://doi.org/10.2174/1389557519666190617153213 (2020).
20. Abdelgawad, M. A., Belal, A., Omar, H. A., Hegazy, L. & Rateb, M. E. Synthesis, anti-B reast cancer activity, and molecular modeling of some benzothiazole and benzoxazole derivatives. Arch. Pharm. 346, 534–541. https://doi.org/10.1002/ardp.201300044 (2013).
21. Omar, A., AboulWafa, O. M., El-Shoukrofy, M. S. & Amr, M. E. Benzoxazole derivatives as new generation of anti-breast cancer agents. Bioorg. Chem. 96, 103593. https://doi.org/10.1016/j.bioorg.2020.103593 (2020).
22. Osmaniye, D. et al. Synthesis of some new benzoxazole derivatives and investigation of their anticancer activities. Eur. J. Med. Chem. 210, 112979. https://doi.org/10.1016/j.ejmech.2020.112979 (2021).
23. Srivastava, A., Aggarwal, L. & Jain, N. One-pot sequential alkynylation and cycloaddition: regioselective construction and biological evaluation of novel benzoxazole–triazole derivatives. ACS Comb. Sci. 17, 39–48. https://doi.org/10.1021/co500135z (2015).

24. Bérubé, G. An overview of molecular hybrids in drug discovery. Exp. Opin. Drug Discov. 11, 281–305. https://doi.org/10.1517/17460441.2016.1135125 (2016).
25. Adachi, K., Michigami, K. & Hayashi, M. Simple three steps synthesis of potential medicine for metabolic syndrome. Heterocycles 82, 857–865. https://doi.org/10.3987/COM-10-S(E)45 (2010).
26. Anand K and Wakode S: Synthesis, characterization and biological evaluation of benzimidazole derivatives, International Journal of Pharmaceutical Sciences and Research 2018; 9(2): 617-624.
27. Alheety NF: synthesis, characterization and antimicrobial activity study of some new substituted benzoxazole derivatives, Baghdad Science J 2019; 16(3): 616-625.
28. Nguyen TT, Nguyen XTT, Nguyen TLH and Tran PH: Synthesis of benzoxazoles, benzimidazoles and benzothiazoles using a brønsted acidic ionic liquid gel as an efficient heterogeneous catalyst under a solvent free condition, ACS Omega Journal 2019; 4: 368-373.
29. Mohammad OA and Dahham OS: Synthesis, characterization and study of anti-bacterial activity of some new formazan dye derivatives, derived from 2-Mercepto benzoxazole, International Conference of Materials Engineering and sciences 2018; 454:1-12.
30. Vishvakarma P, Mandal S, Pandey J, Bhatt AK, Banerjee VB, Gupta JK. An Analysis of The Most Recent Trends In Flavoring Herbal Medicines In Today's Market. Journal of Pharmaceutical Negative Results. 2022 Dec 31:9189-98
31. Anusha P, Rao JV and Mohan GK: Synthesis, characterization and biological evaluation of new benzoxazole derivatives as anti-bacterial agents, International Journal of Pharmacy and Biological Sciences 2018; 8(2): 709-714.
32. Kamal U, Javed NM and Kumar A: Biological potential of benzoxazole derivatives, Asian Journal of Pharmaceutical and Clinical Research 2020; 13(8): 1-14.