WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 17, 80-87. Review Article ISSN 2277– 7105

REVIEW ON ANTIMICROBIAL ACTIVITY OF 2- SUBSTITUDE-BENZIMIDAZOLE COMPOUDS

Budhwant Balaji G.*, Bavage S. B., Patel A. C. and Ingle P. V.

India.

Article Received on
28 October 2022,

Revised on 18 Nov. 2022,
Accepted on 08 Dec. 2022,

DOI: 10.20959/wjpr202217-26074

***Corresponding Author**
Budhwant Balaji G.
India.

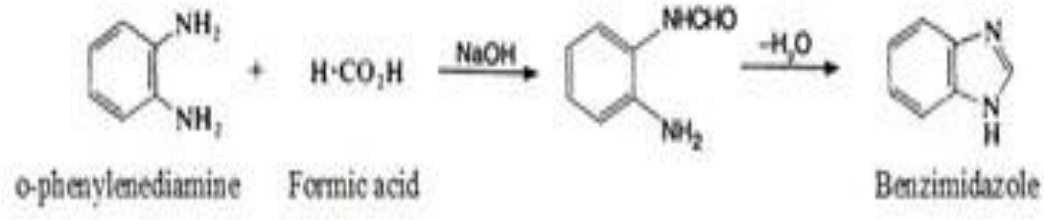
ABSTRACT

Benzimidazole is the heterocyclic compound formed from benzene and imidazole ring containing nitrogen, oxygen Sulphor and its derivatives are of wide interest because of their diverse biological activity and clinical applications, They are remarkably effective compounds both with respect to their inhibitory activity and their favourable selectivity Ratio. Reported nucleus is a constituent of vitamin-B12. Benzimidazoles are regarded as a promising class of bioactive Heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-Cancer activity, numerous anti-oxidant, anti-parasitic, anti-helmintics, anti-proliferative, anti-HIV, anti-convulsant, Anti-inflammatory, anti-hypertensive, anti-neoplastic, proton pump inhibitor and anti-trichinellosis. Benzimidazoles Exhibit significant activity as potential antitumor agents, smooth muscle cell proliferation inhibitors, a treatment for Intestinal cystitis, and in diverse area of chemistry. Some of the important benzimidazole derivatives have been Reported as thyroid receptor agonist gonadotropin releasing hormone receptor antagonists, non-nucleoside HIV-1 Reverse transcriptase inhibitors and interestingly alkynylbenzimidazoles as modulators of metabotropic glutamate Receptors. The imidazole core is a common moiety in a large number of natural products and pharmacologically Active compounds. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. This comprehensive overview summarizes the chemistry of different derivative of substituted benzimidazole along With their anti-microbial activity containing anti-malarial anti-fungal, anti-bacterial, anti-viral activities.

KEYWORDS: benzimidazoles, anti-malarial, anti-fungal, anti-bacterial, anti-viral.

INTRODUCTION

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Benzimidazoles areregarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleusis a constituent of vitamin-B12. This ring system is present innumerous antioxidant, antiparasitic, antihelmintics, antiproliferative, anti-HIV,anticonvulsant, anti-inflammatory, antihypertensive, antineoplastic and antitrichinellosis activities. Varied bioactivities exhibitedby benzimidazoles, efforts have been made from time to time to gener-ate libraries of these compounds and screened them for potentialbiological activities. Also it is well documented that oxadiazole nucleusis associated with a variety of pharmacological actions. It displays pronounced anticonvulsant, antifungal and antimycobacterial activities.



The diverse parasitic bacteria such as Staphylococcus aureus, S. pyogenes, Salmonella typhimurium and Escherichia coli have significant impact on the mucosal health of humans. Infection with S. aureus, S. pyogenes, Salmonella typhimurium and E. coli may have resulted in massive destruction of host tissue and life-threatening diseases. These bacterial parasites cause food poisoning, rheumatic fever and diarrhea, which affect millions of individuals in developing countries. More than 50 million people worldwide are infected and up to 1,10,000 of these die every year. Amoxicillin, Norfloxacin and Ciprofloxacin are the most commonly used drugs for this bacterial infection but are associated with severe side-effects.

Benzimidazoles and their analogs are well-known biologically active N-containing heterocycles reported to possess various biological activities. On the other hand, pharmacologically, pyrazole and its derivatives represent one of the most important classes of organic heterocyclic compounds possessing antibacterial, antifungal, herbicidal and antiviral activities. Some of its derivatives have been reported to exhibit significant anti-arrhythmic, sedative, hypoglycemic and anti-inflammatory activities.

Chemistry of Benzimidazol

All solvents used were of laboratory grade and were obtained from SD Fine Chemicals (Mumbai, India) and Merck (Mumbai, India). Ciprofloxacin and Ketoconazole were received as gift samples from Dr. Reddys Laboratories, Hyderabad, India. Melting points were determined in open glass capillary tubes and were uncorrected. Compounds were routinely checked for their purity on Silica gel G (Merck) Thin layer chromatography (TLC) plates; iodine chamber and UV lamp were used for visualization of TLC spots. The IR spectra were recorded in KBr pellets on a BIO-RAD FTS FT-IR spectrophotometer. 1H-NMR spectra were recorded on a Bruker DPX-300 NMR spectrometer in CDCl3 using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported on a ppm scale. Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. Elemental analyses were performed on a Perkin Elmer model 2400 CHN analyzer and were within ±0.4% of the theoretical values.

Synthesis of Benzimidazol

Benzimidazole was prepared according to the reported literature. Briefly, a mixture of o-phenylenediamine 1 (2.7 g, 0.025 mol) and 90% formic acid (1.56 g, 0.034 mol) was refluxed at 100°C for 2 h. The resulting solution was cooled and made alkaline to litmus with 10% sodium hydroxide solution. The product 2 obtained was filtered, washed with water and dried at 100°C. Yield 79%, m.p. 169-172°C. IR (KBr, cm-1): 3285 (NH), 3062 (Ar–CH). 1H-NMR (CDCl3, 300 MHz) δ ppm: 5.24 (s, 1H, NH), 7.18-7.89 (m, 5H, Ar–CH). ESI-MS: m/z 118 [M+]. Anal. Cald for C7H6N2: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.35; H, 5.11; N, 23.65.

Synthesis of 1-(4-((1H-benzimidazol-1-yl) methylamino)phenyl)-3- substitutedprop- 2-en-1-one

A mixture of 1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl) ethanone 3 (2.65 g, 0.01 mol) and different aromatic aldehydes (0.01 mol) was dissolved in a minimum quantity of ethanol. To this, a few drops of 10% sodium hydroxide solution was added and stirred for 5 h and kept in a refrigerator for 24 h. Then, the reaction mixture was poured in crushed ice and stirred well. The product separated out 4a-4l was filtered, dried and recrystallized from ethanol.

Synthesis of 1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl) ethanone

Benzimidazole 2 (1.18 g, 0.01 mol) and p-aminoacetophenone (1.35 g, 0.01 mol) was dissolved in 40 mL of ethanol. To the above solution, formaldehyde (0.3 g, 0.01 mol) was added and stirred magnetically at room temperature for 3 h. Then, the resulting solution was refluxed on a water bath for 1 h and cooled in an ice bath. The product thus separated 3 was filtered, dried and crystallized from ethanol. Yield 72%, m.p. 145-147°C. IR (KBr, cm-1): 3270 (NH), 3079 (Ar–CH), 2953 (CH3–CH), 1697 (C = O). 1H-NMR (CDCl3, 300 MHz) δ ppm: 2.91 (s, 3H, CH3), 4.50 (s, 2H, CH2), 5.06 (s, 1H, NH), 7.05-8.14 (m, 9H, Ar–CH). ESI-MS: m/z 265 [M+]. Anal. Cald for C16H15N3O: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.70; H, 5.68; N, 15.79.

1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl)-3- phenylprop-2-en-1-one

Yield 75%, m.p. 231-233°C. IR (KBr, cm-1): 3309 (NH), 3065 (Ar–CH), 2852 (CH2–CH), 1753 (C = O). 1H-NMR (CDCl3, 300 MHz) δ ppm: 4.15 (s, 2H, CH2), 5.21 (s, 1H, NH), 7.24-7.99 (m, 14H, Ar–CH), 8.32-8.50 (m, 2H, CH = CH). ESI-MS: m/z 353 [M+]. Anal. Cald for C23H19N3O: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.01; H, 5.44; N, 11.92.

1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl)-3- (4-methoxyphenyl) prop-2-en-1-one

Yield 79%, m.p. 184-186°C. IR (KBr, cm-1): 3272 (NH), 3077 (Ar–CH), 2878 (CH2–CH), 1745 (C = O). 1H-NMR (CDCl3, 300 MHz) δ ppm: 2.95 (s, 3H, OCH3), 3.82 (s, 2H, CH2), 5.57 (s, 1H, NH), 7.08-8.14 (m, 13H, Ar–CH), 8.29-8.46 (m, 2H, CH = CH). ESI-MS: m/z 383 [M+]. Anal. Cald for C24H21N3O2: C, 75.18; H, 5.52; N, 10.96. Found: C, 75.38; H, 5.50; N, 10.93.

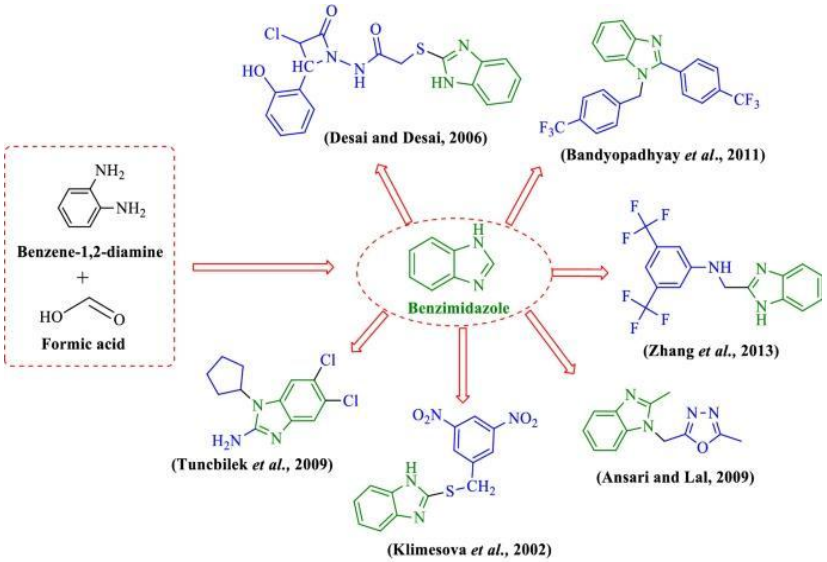
1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl)-3- p-tolylprop-2-en-1-one

Yield 72%, m.p. 217-220°C. IR (KBr, cm-1): 3348 (NH), 3102 (Ar–CH), 2855 (CH2–CH), 1750 (C = O). 1H-NMR (CDCl3, 300 MHz) δ ppm: 3.22 (s, 3H, CH3), 4.38 (s, 2H, CH2), 5.33 (s, 1H, NH), 7.10-8.31 (m, 13H, Ar–CH), 8.37-8.64 (m, 2H, CH = CH). ESI-MS: m/z 367 [M+]. Anal. Cald for C24H21N3O: C, 78.45; H, 5.76; N, 11.44. Found: C, 78.71; H, 5.74; N, 11.47.

Sr.No.	Name of Compounds
A	Synthesis of 1-(4-((1H-benzimidazol-1-yl) methylamino)phenyl)-3- substitutedprop-2-en-1-one
B	Synthesis of 1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl) ethanone
C	1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl)-3- phenylprop-2-en-1-one
D	1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl)-3- (4-methoxyphenyl) prop-2-en-1-one
E	1-(4-((1H-benzimidazol-1-yl) methylamino) phenyl)-3- p-tolylprop-2-en-1-one

Antimicrobial Activity

In this study, all the synthesized compounds were screened for antimicrobial activity by the agar streak dilution method. The antibacterial activity of the compounds was evaluated against four Gram-positive bacteria: Staphylococcus aureus ATCC 9144, Staphylococcus epidermidis ATCC 155, Micrococcus luteus ATCC 4698 and Bacillus cereus ATCC 11778, and three Gram-negative bacteria: Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 2853 and Klebsiella pneumoniae ATCC 11298. The antifungal activity of the synthesized compounds were evaluated against two fungi, Aspergillus niger ATCC 9029 and Aspergillus fumigatus ATCC 46645. Bacterial strains were cultured overnight at 37°C in Mueller Hinton broth, and the yeast was cultured overnight at 30°C in YEPDE agar for antibacterial and antifungal activity tests. Test strains were suspended in nutrient agar to give a final density of 5 × 10-5 cfu/mL.



Benzimidazole derivatives as antimicrobial agents

Antimicrobial Screening

All the title compounds were screened for their in vitro antimicrobial activity by the agar streak dilution method. To control the sensitivity of the test organisms, the MICs of

Ciprofloxacin and Ketoconazole were determined in parallel experiments. The MIC values were determined as the lowest concentration that totally inhibited visible growth of the microorganisms. From the results, it was found that compound 5e, 5g and 5i (MIC: 15.62 µg/mL) displayed comparable activity like Ciprofloxacin against S. aureus. Compounds 5g and 5i displayed an equivalent activity (MIC: 7.81 µg/mL) against S. epidermidis, whereas the rest of the sequence displayed lesser activity (MIC: 15.62–62.5 µg/mL). Against M. luteus, compound 5i showed superior activity (MIC: 3.9 µg/mL) than standard drug, whereas compounds 5e and 5g exhibited comparable activity (MIC: 7.81 µg/mL) as Ciprofloxacin, while the others demonstrated trivial activity than the standard. Compounds 5g and 5i demonstrated equal activity (MIC: 7.81 µg/mL) as Ciprofloxacin, whereas the rest of the series exhibited shoddier activities than the standard against B. cereus. Compound 5i displayed potent activity (MIC: 7.81 µg/mL) than the standard, while the rest of the series exhibited lower activity against E. coli (MIC: 31.25–62.5 µg/mL) except 5e, 5g and 5h. Compounds 5e and 5g displayed an equivalent activity (MIC: 7.81 µg/mL) as standard against P. aeruginosa. None of the synthesized compounds displayed the same activity (MIC: 3.9 µg/mL) as Ciprofloxacin against K. pneumoniae. Against A. niger, except compound 5i, the rest of the compounds showed weaker activity (MIC: 31.25–125 µg/mL) than Ketoconazole. Compounds 5g and 5i showed comparable activity (MIC: 7.81 µg/mL) against A. fumigates, while the others had lower activity (MIC: 15.62–125 µg/mL) than the standard. Of the various tested derivatives, N-((1H-benzimidazol-1-yl) methyl)-4-(1-phenyl-5-(4-(trifluoromethyl) phenyl)-4,5-dihydro-1H-pyrazol-3-yl) benzenamine 5i was found to be the more potent compound. This compound exhibited better activity against M. leutus and E. coli, while it displayed equal activity as standard against S. aureus, S. epidermidis, B. cereus, A. niger and A. fumigatus.

Structural Activity Relationship (Sar)

From the antimicrobial studies, it was found that compounds 5e, 5g, 5h, 5i and 5l showed potent antimicrobial activity, which might be due to the presence of electron-withdrawing substituents like chloro, fluoro, nitro and trifluoromethyl groups on phenyl ring attached at the C-5 of the pyrazole nucleus. Compounds possessing electron-donating substituents like methoxy, methyl, amino and hydroxyl groups (5b, 5c, 5d, 5f and 5k) demonstrate less in vitro antimicrobial activity. SAR studies reveal that compounds possessing an electron-withdrawing group displayed better activity than the compounds containing electron-donating groups, whereas the unsubstituted derivatives displayed moderate activity.

CONCLUSION

With an aim of developing potent antimicrobial agent, a series of novel pyrazole-attached benzimidazoles were synthesized from o-phenylenediamine by the multistep reaction synthesis and characterized by FT-IR, 1H-NMR, mass spectroscopy and elemental analysis. All the title compounds were screened for their in vitro antimicrobial activity by the agar streak dilution method, and its MIC was determined against various strains of microorganisms. Results revealed that compounds containing an electron-withdrawing group at the phenyl group attached to C-5 of pyrazole displayed superior antimicrobial activities than compounds possessing an electron-releasing group. Moreover, the unsubstituted derivatives displayed moderate activity. Among several tested compounds, N-((1H-benzimidazol-1-yl) methyl)-4-(1-phenyl-5-(4-(trifluoromethyl) phenyl)-4, 5-dihydro-1H-pyrazol-3-yl) benzenamine 5i showed better activity. Hence, this compound may serves as a lead molecule to obtain clinically useful antimicrobial agent.

REFERENCES

1. Synthesis, characterization and antimicrobial activity of some novel benzimidazole derivatives Immadisetty Sri Krishnanjaneyulu, Govindaraj Saravanan, Janga Vamsi, Pamidipamula Supriya, Jarugula Udaya Bhavana, Mittineni Venkata Sunil Kumar.
2. Husain, A.; Varshney, M. M.; Rashid, M.; Mishra, R.; Akhter, A. Benzimidazole: A valuable insight into the Recent Advances and Biological Activities. J. Pharm. Res., 2011; 4(2): 413-419.
3. Puertoa SA, Fernandeza GJ, Castillob LDJ, Jose M, Pinoa S, Anguloa PG. In vitro activity of β-lactam and non β-lactam antibiotics in extended spectrum β-lactamase producing clinical isolates of Escherichia coli. Diagn Microbiol Infect Dis., 2006; 54: 135–9. [PubMed] [Google Scholar]
4. Nolan CM, Chalhub GE, Nash GD, Yamauchi T. Treatment of bacterial meningitis with intravenous Amoxicillin. Antimicrob Agents Chemother, 1979; 16: 171–5. [PMC free article] [PubMed] [Google Scholar]
5. Budow, S., Kozlowska, M., Gorska, A., Kazimierczuk, Z., Eickmeier, H., Colla, P.L., Gosselin, G., Seela, F. Substituted benzimidazoles: anti-viral activity and synthesis of nucleosides. ARKIVOC, 2009; iii: 225- 250.
6. Ansari KF, Lal C, Synthesis, physicochemical properties and antimi-crobial activity of some new benzimidazole derivatives, EuropeanJournal of Medicinal Chemistry, 2009; 1–6.

7. El-masry AH, Fahmy HH, Abdelwahed SHA, Synthesis and Antimi-crobial Activity of Some New Benzimidazole Derivatives, Molecules, 2000; 5: 1429–1438.
8. Boruah CR, Skibo EB, synthesis-and-antimicrobial-activities-of-some-benzimidazolyl-pyrazoles, J. Med. Chem., 1994; 37: 1625.28.
9. Ansari KF, Lal C, Synthesis and evaluation of some new benzimida-zole derivatives as potential antimicrobial agents, Eur. J. Med. Chem., 2009; 44: 2294–2299.
10. Basavaraja HS, Nagamani JE, Vijay Kumar MM, Padmashali B. Antimicrobial evaluation of novel substituted pyrimidinopyrazoles and pyrimidinotriazoles. J Adv Pharm Technol Res., 2010; 1: 236–44. [PMC free article] [PubMed] [Google Scholar]
11. Boiani M, Gonzalez M. Imidazole and benzimidazole derivatives as chemotherapeutic agents. Mini Rev Med Chem, 2005; 5: 409–24. [PubMed] [Google Scholar]
12. Kazimierczuk Z, Andrzejewska M, Kaustova J, Klimesova V. Synthesis and antimycobacterial activity of 2-substituted halogenobenzimidazoles. Eur J Med Chem, 2005; 40: 203–8. [PubMed] [Google Scholar]