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Biodynamic Potential of Benzimidazole Derivatives: A Review

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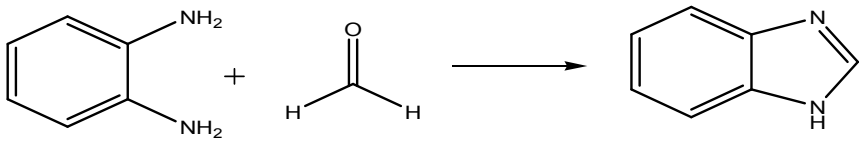
Abstract: The benzimidazole derivatives is an important drug in a therapeutics application of medicine, having varieties of biological activities including antihistamine, analgesics, antifungal, antivral, antitumor, antiparasitic and use in endocrinology, cardiovascular disease, neurology and their synthesis is privileged scaffold. The literature reviews indicate that the substituted benzimidazole derivatives showed more potent biological activity. The benzimidazole derivatives are summarized in this review to know about pharmacological activities as well as chemistry.

Key Words: Benzimidazole, Antibacterial activity, Antiglycation activity and cytoprotective effect.

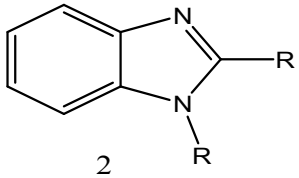
Introduction:

Benzimidazole moieties are the class of heterocyclic aromatic organic compound has many applications in pharmaceutical industries. The bicyclic benzimidazole compound contains benzene and imidazole fussed ring. Benzimidazole nucleus is a versa-tile pharmacophore showed varies range of biological activities. Generally the condensation reactions of o-phenylene diamine with formic acid give benzimidazole.



1

Several methods are accessible for the synthesis of benzimidazoles (2). The synthesis of benzimidazole by the derivatization of benzimidazole by electron donating group and substitution with long chain of propyl, thio, thiazole-amino, acetamido, tetramethyl piperidine on pyridine showed good antiulcer activity. On the basis of their excellent biological activity, benzimidazole derivatives are used in medicine as antimicrobial agents, anti-viral agents, anti-ulcer and antitumor.



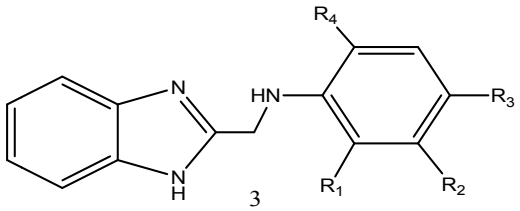
2

The benzimidazole derivatives showed varied pharmacological activity due to the potent antimicrobial properties. The different substituents on heterocyclic ring of benzimidazole causes a certain change of activity. Some pharmaceutical drugs which contain a benzimidazole group include etonitazene, pantoprazole, mavatrep, albendazole, rabeprazole, lansoprazole, omeprazole etc. The drugs like pimozide,

droperidol and benperidol anti protozoal agents which contains benzimidazole nucleus. The antiprotozoal drugs such as metronidazole, benznidazole containing imidazole nucleus.

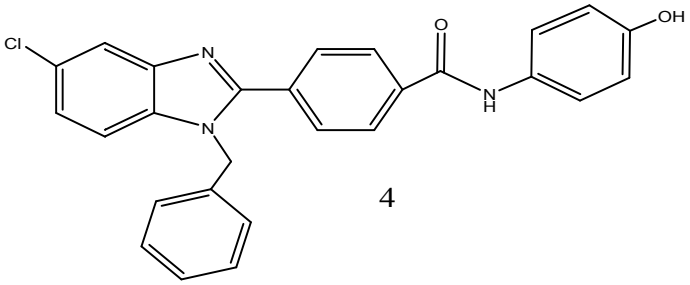
Biological Activities:

Some of the benzimidazole derivatives are biological potent and have wild importance in drug discovery. The series of 2-substituted benzimidazole derivatives (3) synthesized and tested for their anti-inflammatory and analgesic activities. All the synthesized compounds showed potent analgesic and anti-inflammatory activity in comparison with pentazocine and diclofenac sodium as standard drug respectively; **G. Mariappan et al[1].**



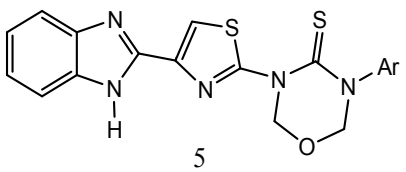
3

The series of 1-benzyl-1H-benzimidazole derivatives synthesized and tested for their in vitro anticancer activity. Among the synthesized compounds, 4-(1- benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)-N-(4-hydroxyphenyl) benzamide (4) showed potent anticancer activity; **N.S. Goud, et al[2].**



4

K. Gullapelli et al synthesized new benzimidazoles compounds and tested for antibacterial activity. Among the synthesized compounds, 5 and 6 showed a promising activity in comparison with Gentamycin as standard drug. The electron withdrawing substituent on benzene ring such as nitro and chloro showed more antibacterial activity. The docking study showed that compounds 5d and 6d showed good binding energy for topoisomerase II and for DNA gyrase subunit b respectively [3].



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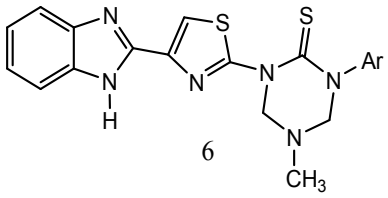
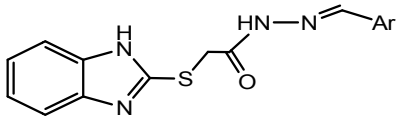


6

5 a and 6a = C_6H_5, 5 b and 6b = 4-CH_3 C_6H_4
5 c and 6c = 4-OCH_3 C_6H_4, 5 d and 6d = 4-NO2 C_6H_4
5 e and 6e = 4-Cl C_6H_4

S. Yadav et al. synthesized benzimidazole derivatives (7-8) and tested for biological activities. Among the synthesized derivatives most of them were highly potent as antimicrobial agents in comparison with fluconazole and cefadroxil as standard drug. All the synthesized derivatives in comparison with the standard drug fluconazole showed high antifungal activity. Some compounds showed promising antifungal

activity against *C. albicans*. The synthesized benzimidazole derivatives showed potent anticancer activity as compared with the 5-flourouracil and carboplatin as standard[4].



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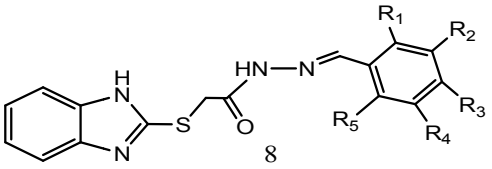
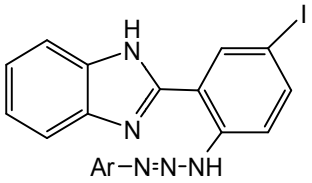


8

1. R1= OCH_3, 2. R2= OCH_3, 3. R3= OCH_3, 4. R1=R3= OCH_3, 5. R2=R3=R4= OCH_3
6. R3= OH, 7. R1= Cl, 8. R3= Cl, 9. R3= F, 10. R3= Br
11. R3= NO_2, 12. R2= OCH_3, R3= OH, 13. R2= OCH_2CH_3, R3= OH.
14. R3= CHO, 16. R1= OH, 17. R3= $N(CH_3)_2$, 18. R3= $N(CH_2CH_3)_2$.

S.K. Mohanty et al. synthesized benzimidazole azo derivatives (9-10) showed promising cytotoxic and antibacterial activities against *E. Coli*, *B. subtilis* and excellent potency against M. Tuberculosis. The result indicated that, the electron withdrawing group enhances the biological activity[5].



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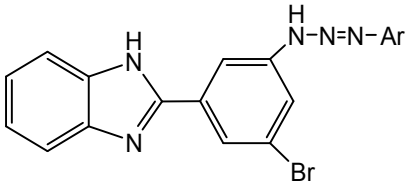
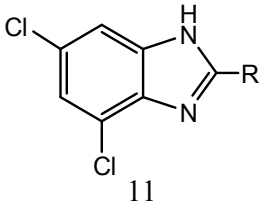


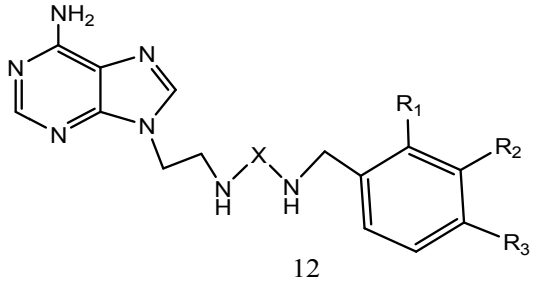
10

Some derivatives of benzimidazole (11) synthesized from 3,5-dichlorobenzene-1,2-diamine with of arylaldehyde and tested for their antiglycation and antioxidant activity . Among the synthesized compounds, some showed most potent antiglycation activity. In comparison with synthesized compounds, 2,5-dihydroxy compound showed potent activity. The compounds 3,4-dihydroxy analog and 2,5-dihydroxy analog showed greater antioxidant potential as compared to standard propyl gallate. The studies showed that an active compound contains hydroxyl substituents thus showed antiglycation and antioxidant potential; **M. Taha et al[6].**



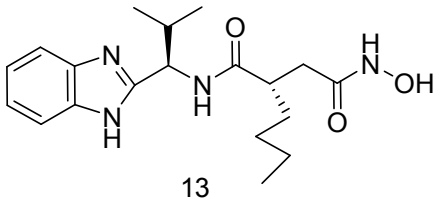
11

The synthesized adenines based benzimidazole derivatives and were tested for their antibacterial activity. The synthesized compound fluoro-substituted adenine-based sulfamide (12a) showed good activity against *C. albicans*. The diamine (12c) and adenine-based thiourea (12b) showed potent antibacterial acticity against *B. anthracis;* **A.G. Eissa et al[7].**



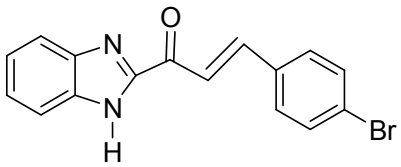
12

12a (x-SO_2, R_1& R_2-H, R_3-F), 12b(x- C=S, R_1 R_2 R_3-H), 12c(x-Ethyl, R_1 R_2 R_3-H), A novel actinonin incorporateed benzimidazole derivative (13) synthesized and tested for antibacterial activity against *K. pneumoniae, S. aureus, and S. lutea*. The unsubstituted benzimidazole ring compound (13) showed potent antibacterial activities; **D. Zhang et al[8].**



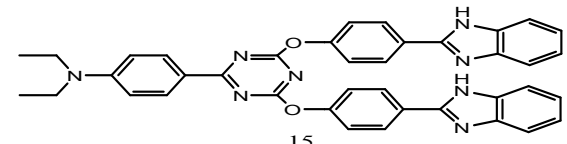
13

P. Janaki et al. synthesized substituted styryl 2-benzimidazole ketones were found to reflect satisfactory antifeedant activity. Some compounds showed good to modarate antifeedant activity. The result showed that the benzimidazole derivatives (14) showed an good antifeedant activity. The antifeedant activity of this compound depends on the concentration[9].



14

The new benzimidazole (15-16), benzothiazole(17) and benzoxazole(18) derivatives screened for antimicrobial activity. These synthesized derivatives showed potent antibacterial activity and antifungal activity against bacterial strains. The result showed that oxazole moites containing derivatives gave better antifungal and antibacterial activity than benzothiazole and benzimidazole derivatives; **V.S. Padalkar et al[10].**



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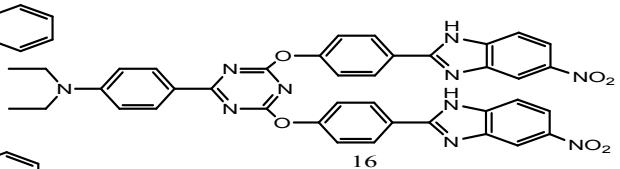

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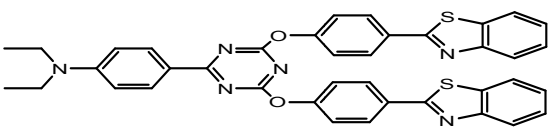

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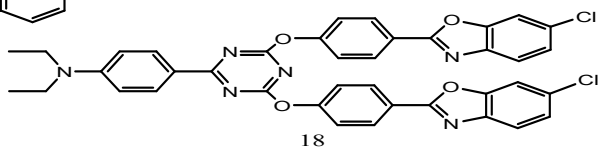
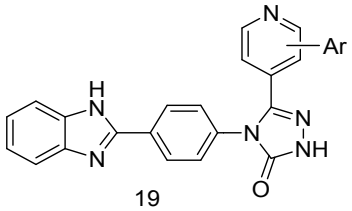


18

The synthesis of benzimidazole derivatives and tested for their antifungal and antibacterial activities. The synthesized benzimidazole derivatives 24, 29 and 30 showed good antibacterial activity. The compounds 15 and 19 showed moderate to good antifungal activity. The result showed that carbon atom of side chain at second position of benzimidazole derivatives increases which increase in the biological activity against *C. albicans, B. subtilis* and *S. aureus;* **K.P. Barot et al[11].**



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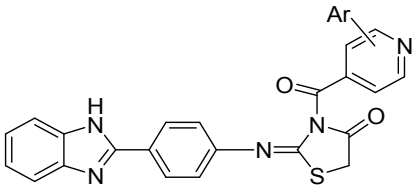

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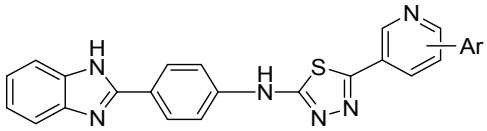
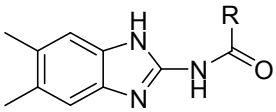


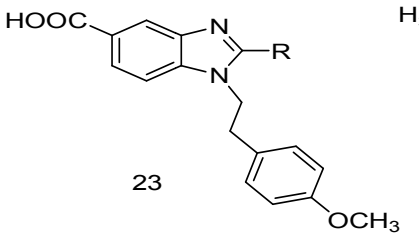
21

A.S. M. et al. synthesized benzimidazole compounds showed remarkable antimicrobial and antioxidant activities. The synthesized benzimidazole compound (22) showed promising antimicrobial activity bacterial strains and potent ion chelating and radical scavenging activity. The substitution of a heterocyclic ring and electron with substituents at second position of the benzimidazole moiety showed more potent biologically active compounds[12].



22

M.C. Sharma et. al. Synthesized benzimidazole derivatives (23 - 24) and tested for antileukaemic activity, The incorporation of fluorine, chlorine, methyl, nitro, substitution on aromatic ring at the R position would enhance the antileukaemic activity[13].



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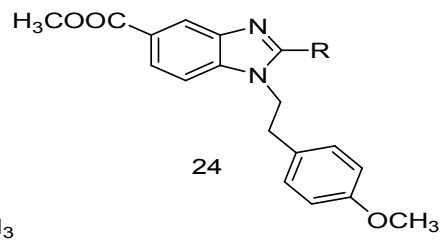
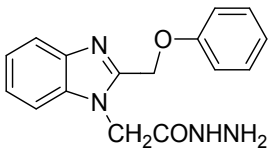


24

The benzimidazole derivatives (25-26) synthesized and tested for the shown anticonvulsant activity and neurotoxicity. The compounds 25 and 26 exhibits potent anticonvulsant activity and lower neurotoxicity the study showed that electron withdrawing substituents such as NO_2, F and Cl enhance the activities of synthesized

compound than the other substituents. The study showed that these compounds have potential anticonvulsant activity; **M. Shaharyar et al[14].**



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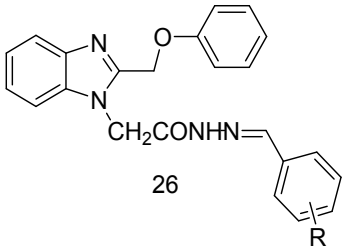
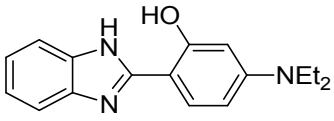
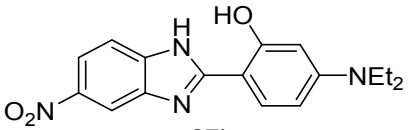


26

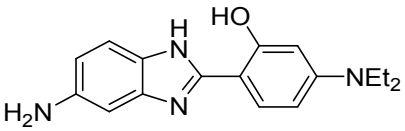
New class of 2-substituted benzimidazole derivatives (27) were synthesized and evaluated for antibacterial activities and antifungal activity against bacterial strains. The compounds 27a–27h showed good antibacterial activity. The compounds 27a–27c showed excellent antibacterial activities and 27d–27i derivatives showed moderate inhibitory action. The compound 27i shows excellent antifungal activity against bacterial strain. The study revealed most of the synthesized compounds showed excellent antibacterial activity and benzothiazole give excellent antifungal activity against fungal strain; **V.S. Padalkar et al[15].**



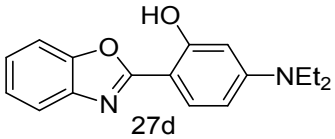
27a



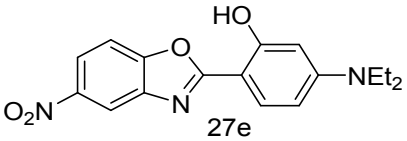
27b



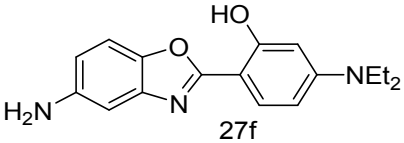
27c



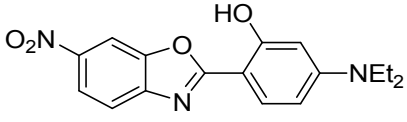
27d



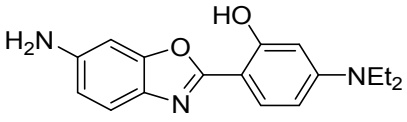
27e



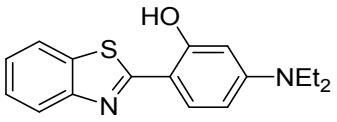
27f



27i



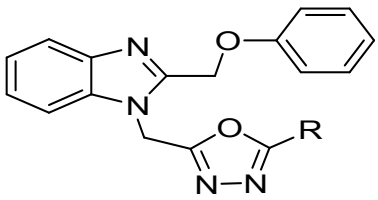
27j



27k

(27a-k)

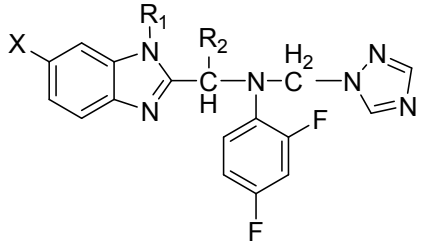
The novel synthesized benzimidazole derivatives (28) were tested for their antimicrobial activity. The result showed that compound 28a, 28b, 28c and 28d is a most potent against bacterial strains. The compounds having electron withdrawing group were the showed potent antibactreial activity and antifungal activity against bacterial strains; **Salahuddin et al[16].**



28

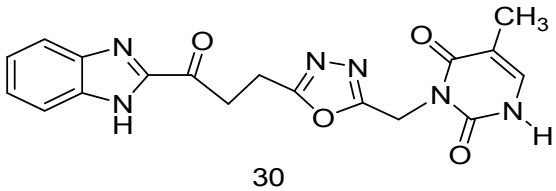
R= 28a-4-$CH_3C_6H_4$, 28b-4-ClC_6H_4, 28c-4-BrC_6H_4, 28d-2-$NO_2C_6H_4$.

R.S. Kankate et al synthesised a novel benzimidazole derivatives (29) which contains tertiary amine moiety and triazole ring and screened for antifungal activity against *C. albicans* in comparistion with fluconazole as standard[17]**.**



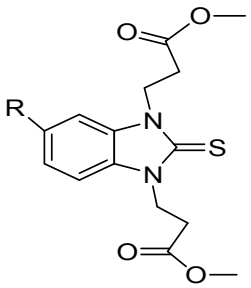
29

The benzimidazole derivatives were prepared and screened for anticipated antiproliferative activity. Among the synthesized compounds, 30 was exhibiting excellent antiproliferative activity. The cytotoxic effects of this molecule were tested against standard chlorambucil and bendamustine; **M. Rashid et al[18].**

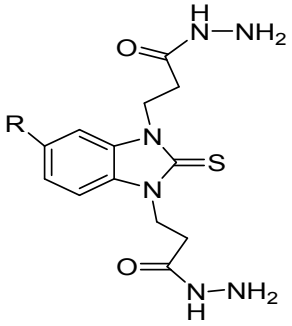


30

N.O. Anastassova et al. synthesized series of novel benzimidazole derivatives using aza-Michael addition and screening for their hepatotoxicity and the antioxidant activity. The compounds (31) and (32), showed lowest cytotoxic effects and exhibited significant cytoprotective and antioxidant effects similar to the quercetin[19].

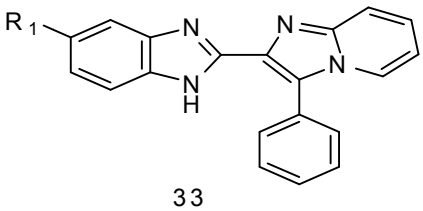


31



32

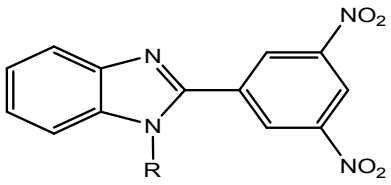
The synthesis of novel benzimidazole derivatives (33) and tested for antiproliferative activity. The compounds 33a, 33b and 33c showed promising antiproliferative activity. The compound 33a with treatment of MCF-7 cells showed moderate effect; **P.V. Sri Ramya et al**[20].



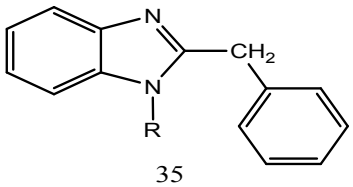
33

R_1=33a-H, 33b-CH_3, 33c-F

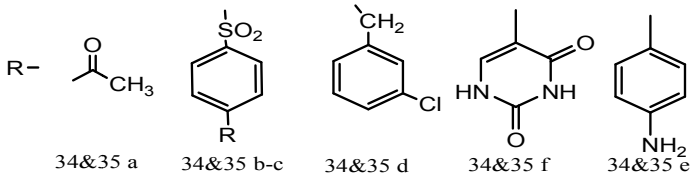
O.O. Ajani et al synthesized mono- and disubstituted benzimidazole derivatives. Among the synthesized compounds, the 34 and 35b-c showed most potent activity[21].



34

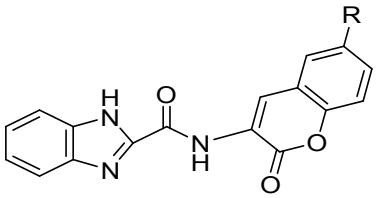


35

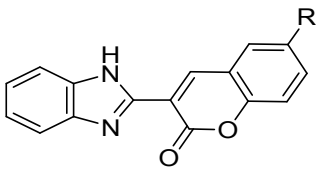


34&35 a 34&35 b-c 34&35 d 34&35 f 34&35 e

The coumarin–benzimidazole derivatives (36–37) synthesized by coupling coumarin derivatives and tested for antioxidant and anti-inflammatory activities. The compounds 36c, 36d and 37a showed good anti-inflammatory inhibition, and antioxidant activities; **Radha Krishan Arora et al[22].**



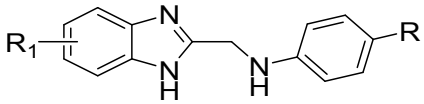
36



37

(R =36&37a-H, 36&37b-OCH_3, 36&37c-Br, 36&37d-Cl, 36&37e-NO_2)

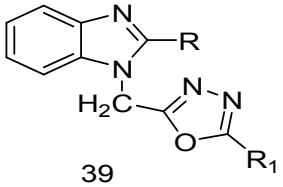
K.C.S. Achar et al synthesized benzimidazole derivatives (38) and screened for analgesic and anti-inflammatory activities. Some of the synthesized compounds showed highest analgesic activity and some compounds showd good to moderate analgesic activity. The studies showed that the compounds which contain chloro group in the meta position of aniline ring substituent increases the anti-inflammatory[23].



38

R_1 = H, Br, NO_2 and R= H, Cl, Br, CH_3, OCH_3

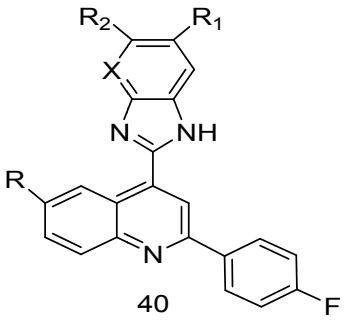
The benzimidazole derivatives (39) synthesized and screened for antimicrobial activity. Some compounds showed good to moderate antifungal and antibacterial activities. The study sowed that with increase in the carbon atom in the side chain of oxadiazole ring on second position enhance the antimicrobial activity against bacterial strains and chemotherapeutic activity; **K.F. Ansari, C. Lal[24].**



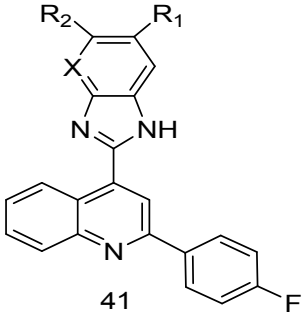
39

B. Garudachari et al. synthesized quinoline incorporated benzimidazole derivatives (40-41) and screenedd for their in-vitro antibacterial activity against bacterial strains. Some of the compounds exhibits good inhibition and some compounds showed significant antibacterial against microbial strains. Remaining all compounds showed

good to moderate antibacterial activity. Some tested compounds showed significant antifungal activity against microbial strains some compounds active against fungal strains. The result concludes that pyridine ring and 4- fluorophenyl group in benzimidazole and quinoline ring respectively increases the antimicrobial activity[25].



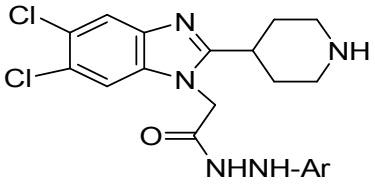
40



41

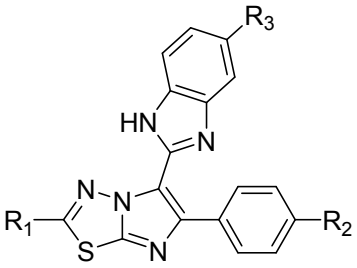
(40 R= H, Cl, F; R_1= Cl, F; R_2= H, Cl; X= CH, N) (41 R_1= H, Cl, F; R_2= H, Cl; X= CH, N)

Y. He et al. synthesized new benzimidazole derivatives and were screened against both *S. Aureus* and *E. coli.* The most of these benzimidazole derivatives showed good antibacterial activities. Some tested compounds exhibited low mM broad-spectrum activities[26].



42

J. Ramprasad et al. synthesized benzimidazole derivatives and tested for in vitro anti-tuberculosis activity against *M. tuberculosis* strain. The studies showed potent anti-tubercular activity this compounds. A substituents such p-tolyl or p-chlorophenyl in the imidazo[2,1-b][1,3,4]thiadiazole ring enhance anti-tuberculosis activity whereas a chloro group in the benzimidazole ring increases anti-tuberculosis activity and nitro group reduces the activity of benzimidazole moiety. The imidazo[2,1-b][1,3,4]thiadiazole-benzimidazole derivatives showed promising antibacterial activity against bacterial strains and showed significant antioxidant activity[27].



43

Conclusion:

The benzimidazole derivatives are an important in drug discovery and design. The reviewed benzimidazole derivatives showed wield varies of potent biological activities including antimicrobial, analgesics, antitumor, antiparasitic, in cardiovascular disease, endocrinology and neurology. Literature survey revealed that some adenine, actinonin, thaiazole, cumarine or quinoline derivatives of

benzemidazole showed potent antimicrobial, anti-inflammatory and antioxidant activities.

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