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A REVIEW ON BENZIMIDAZOLE-BASED MEDICINAL CHEMISTRY

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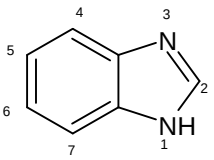
ABSTRACT
Benzimidazole is an aromatic, heterocyclic and bicyclic organic compound. It is the combination of imidazole and benzene ring which exhibits potential pharmacological actions such as anti-microbial, anti-cancer, anti-viral, analgesic, anti-protozoal, anti-tubercular, anthelmintic and more. Various methods for benzimidazole preparation and their various reaction gave great scope in medicinal chemistry. There are several drugs which are available for treating the diseases but have several side effects so there is a need for synthesizing better efficacy and novel mechanism of action. Benzimidazole ring is essential pharmacophore for discovery of new drugs. There are many ongoing researches for this compound because of its versatility, it would help in obtaining many better medicinal agents.

KEYWORDS: Benzimidazole, anti-microbial activity, synthesis of benzimidazole, anti-cancer activity, anti-viral activity and anti-protozoal activity.

INTRODUCTION
Benzimidazole are the heterocyclic aromatic organic molecule. This bicyclic molecule can be thought of as benzene and imidazole's aromatic rings fused together. It is a solid with no coloration.



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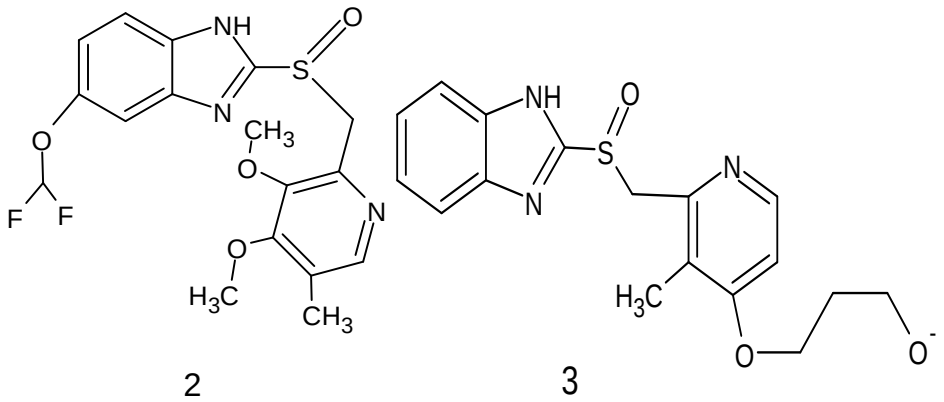
A benzene ring is fused to an imidazole ring to produce the benzimidazole nucleus. For a very long time, benzimidazole chemistry has been a significant field of study. One of the most attractive moieties, it has a variety of biological functions and is used in several clinically useful medications.

The benzimidazole fragment corresponds with the necessary structural minimums for anti-inflammatory compounds. Different benzimidazole derivatives' natural and synthetic sources are crucial in medical chemistry. Purine and 2-aminobenzimidazole have structural similarities which provide insight into how such nuclei were developed for various biological activities. It has been reported that several drugs with the benzimidazole nucleus are potent analgesics and anti-inflammatory drugs. Additionally, there are multiple accounts of the anti-fungal activity of benzimidazole-substituted compounds. Antibacterial, anti-hypertensive, anti-infective[3], and Male contraception, drugs that are antagonistic to the human glucagon receptor. These compounds are also effective lymphocyte tyrosine kinase inhibitors kinase and the chemokine receptor and derivatives of 1H-benzimidazoleare effective at reducing the harm that inflammation inhibitors do to the stomach. Research offers a current overview of several benzimidazole syntheses derivatives and includes the most present healthcare use compositions of benzimidazoles. A variety of lead molecules are available from the benzimidazole nucleus, a privileged scaffold with a fused heterocyclic system that can be researched for usage as potential multi-targeting drugs against multi-factorial disorders. A variety of processes involved in the derivatized nucleus pathophysiology of different disorders. In 1944, a compound called benzimidazole was identified as a possible nucleus. Based on the report, its structural homology enables it to behave similarly to purines and cause some biological reactions. Later,5, 6-dimethylbenzimidazole, a novel contender found by Brink, vitamin B12 degradation byproduct from acid hydrolysis was identified similar activity to vitamin B12, and that its derivatives. The studies described above inspired researchers to thoroughly examine this nucleus against numerous diseases and create several hybrids to enhance the parent nucleus' pharmacological profile against complex disorders including such as malaria, diabetes, cancer, and

Alzheimer's disease. Multiple causal factors and pathways are included in these complex diseases. For the unusual disease's course. It is critical to target numerous pathways at once to halt the spread of these diseases because they are multifactorial. Designing hybrids of the parent molecule and other molecules is one method of hitting various targets. changing the focus from a single-targeting strategy to a multi-targeting one. A few years ago, the idea of molecular hybridization was introduced on years ago and is popular today. For instance, a combination of benzimidazole and mesalamine exhibits strong immune-modulating and antioxidant effects. The most accurate explanation of a synthetic chemical having two or more different types of structural regions exhibiting various biological roles. As according Choudhary, hybrid compounds function as two different Overall, developing benzimidazole-based on hybrids using various hybrid designing techniques can be an intriguing way to solve some issues are related to parent drugs and to increase their pharmacokinetics properties. Several comprehensive reviews on the chemistry, synthesis, and hybrid has the advantages of improving the solubility and helping to increase the bioavailability of a conjugated medication.[4] There are also some comprehensive reports on particular nucleus's pharmacological characteristics. However, this nucleus' hybrids have not yet been identified. described previously. This review is an attempt to assemble in a single publication, the pharmacological characteristics of benzimidazole hybrids are discussed together with their SAR profiles pharmacophores.

Antimicrobial property and preparation of benzimidazole

The heterocyclic moities of benzimidazole and benzoxazole are significant and have been widely utilised in medical chemistry. A part of vitamin B12, benzimidazole is related to both the stimulant caffeine and the DNA nucleotide purine. A variety of pharmacologically active compounds, including omeprazole, pantoprazole, rabeprazole, mebendazole, and thiabendazole, contain substituted benzimidazole, which has a wide range of possible pharmacological actions.



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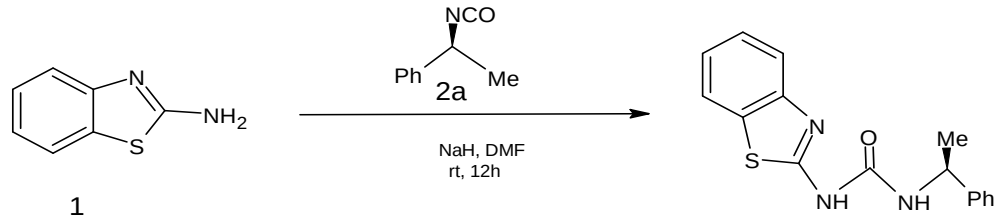
Structure of Biologically Active Pharmaceutical Ingredient (API) Molecules.

The synthesis of these heterocycles has been observed using a number of different techniques, such as the condensation of carboxylic acids, orthoesters, acid chlorides, nitriles, amides, aldehydes, and esters with o-substituted amino aromatics derived from orthoesters.



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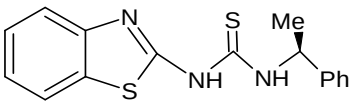

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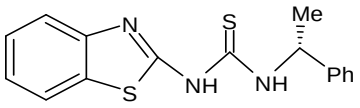

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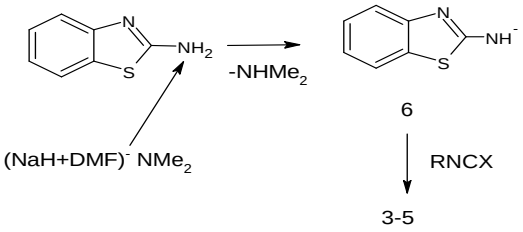
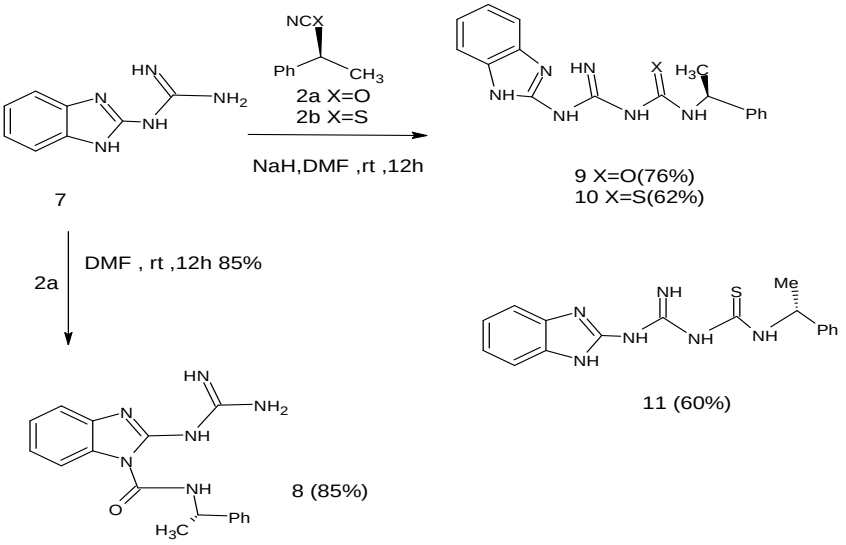
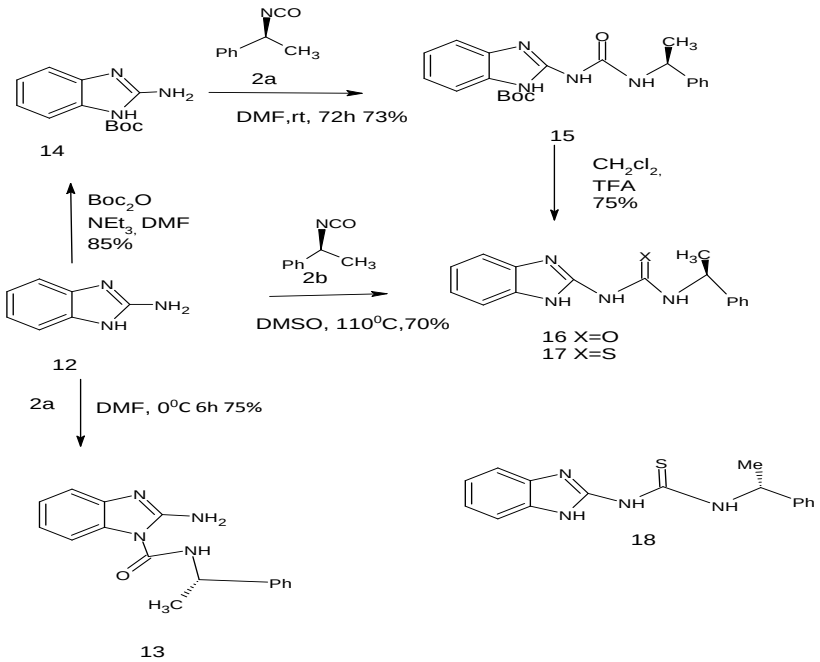


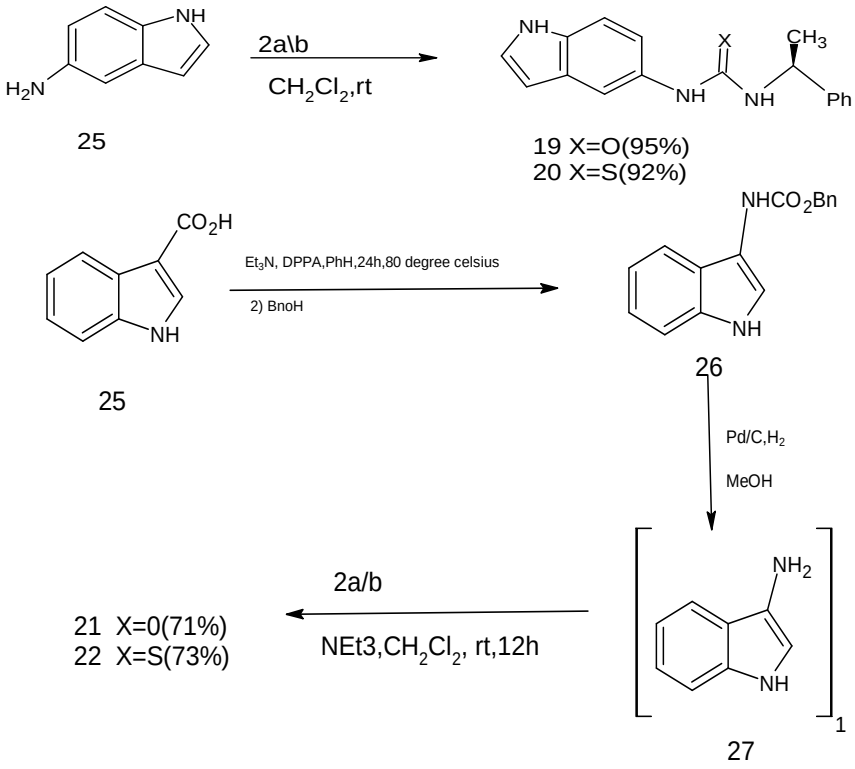
In our initial research on the synthesis of urea and thiourea, the reaction conditions were optimised using the reagents 2- aminobenzothiazole (1) and (S)-1-phenylethyl isocyanate (2a). However, using sodium hydride as a base in DMF at ambient temperature for 12 hours enabled the high yield synthesis of benzothiazole-urea compound 3. The synthetic process used to produce the desired urea/thiourea derivatives 3-5 is shown. Under the same experimental circumstances, the corresponding thioureas 4 and 5 were produced by coupling (S)- and (R)-1-phenylethyl isothiocyanates with 2-aminobenzothiazole (1) for the production of thiourea enantiomeric pairs 4 and 5. When it came to isocyanate 2a, both molecules worked as ambident nucleophiles. While the identical reaction with NaH produced guanidine-isocyanate coupling to produce urea 9 in 76%, the base free reaction of 2-guanidobenzimidazole (7) with and (S)-1-phenylethyl isocyanate (2a) generated the urea derivative 8 (85%). The yields for the thiourea derivatives 10 and 11 with the (S) or (R) configuration were 62% and 60%, respectively.



Urea 13 was produced in a 75% yield after 2-aminobenzimidazole (12) was treated with isocyanate 2a under base-free conditions. Benzimidazole ring nitrogen is protected by a Boc group using Et3N and Boc2O. regioselectively produced compound 14.



After being Boc-protected, the 14 was linked to isocyanate 2a in room-temperature NaH/DMF and then deprotected with TFA in CH2Cl2 to produce urea 16, when compound 12 combined with 2-aminobenzimidazole, DMSO at 100 treated with (S)-1-phenylethyl isothiocyanate (2b)°C, 70% of the equivalent thiourea 17 was produced. Compounds of urea/thiourea based on indole 19–20.



A synthetic route to compounds 21 and 22 was planned. The creation of intermediate 27 through a Curtius rearrangement was crucial. In actuality, the present urea/thiourea 21 and 22 synthesis was carried out simply and without any unforeseen complications. Indole-3-carboxylic acid[25] was easily converted into compounds 21 and 22 utilising a literature approach[32,33] in three steps with high yields. The equivalent carbamate 26 was created through a Curtius rearrangement of indole-3-carboxylic acid[25] using diphenylphosphoryl azide (DPPA) and Et3N in refluxing benzene, followed by in situ trapping with benzyl alcohol. 3-aminoindole was produced by catalytically hydrogenating the benzyl group of 26 on Pd/C in methanol and then decarboxylating it.[27] Since the amine 27 has not been refined, it is used directly in the subsequent process to produce the urea/thiourea 21 (71%) and 22 (73%), without more purification.

Using the disc diffusion assay, the antibacterial activity of the produced compounds was assessed against Gram-positive (S. aureus and B. cereus) and Gram-negative (E. coli and P. aeruginosa) bacteria. Only an antibacterial action against Gram-positive bacteria was demonstrated by the compounds (8-11, 13, 16-18, 20 and 21). Additionally, a microwell dilution assay for the substances constituting the inhibitory zone against S. aureus and B. cereus was performed. The MIC values for compounds 9, 16, and 20 were determined to be 62.5 g/mL for both S. aureus and B. cereus. Additionally, compound 17's MIC value for B. cereus was 62.5 g/mL. It's interesting that only Gram-positive bacteria were inhibited by all of the compounds. This may be because Gram-negative bacteria have a poor rate of compound penetration into their outer membranes.

Anticancer property of benzimidazole

Benzimidazole which is structurally similar to purine nucleosides which is the main bases for the development of various anticancer agents (Jawaid Akhtar et al., 2018, Shrivastava et al., 2017). Many researchers have examined that the benzimidazole derivatives exhibits anticancer activity through various mechanisms such as DNA intercalation, dihydrofolate reductase (DHFR) enzymes, microtubule inhibiting activity, androgen receptor antagonistic effect, poly (ADP-ribose) polymerase (PARP) and topoisomerases-I & II inhibition.

The new styryl sulfones were examined for its anticancer property against various cell lines which causes lung, renal, ovarian, breast, colon, melanoma, CNS and prostrate cancer. The synthesized compound, 6-chloro-1H- (benzo[d]imidazol-2-yl) methyl [(E)-2-(4-chloro-3-methyl phenyl)-1-ethenyl] sulphone, compound 4 have reported 51% cancer cell growth inhibition in the mice which was injected with HT-29 human carcinoma at 400mg/kg orally.[7]

It is found that the nitro group at 5 position of benzimidazole is optimum for activity. Examination of substituted 2-methyl-5-nitro benzimidazoles at 1-position with different heterocycles disclose that thiadiazole ring connected through a methylene group at 1-position 5 contains the maximum antitumor activity.[8]

Ni et al. prepared some 2-(substituted quinolinon-3-yl)benzimidazoles as serine/ threonine checkpoint kinase (CHK-1) inhibitors for treating the cancer.[9]

Benzimidazole-thiazolidinedione hybrid derivatives which have highly potent anticancer agents, described by Sharma et al. 6 and 7 compounds have shown high anticancer property against cancer cell line with IC50 value of in range of 0.13-10.24µM, against prostate cancer cell line PC-3, bone cancer (HT1080), cervical cancer (HeLa), breast cancer (MDAMB-231) and lung cancer (A549) cell lines.[11]

There are some metal complex bearing benzimidazole like Pt(II) complexes with 2-phenyl benzimidazole 8 and 2-mercapto methyl benzimidazoles 9a and 9b which have potent cytotoxic activity against human RD Rhabdomyosarcoma cell lines and less mutagenic against Salmonella thyphimurium strains TA 98 and TA 100,this leads to consider them as effective antitumor agent.[12]

Bistrovic et al. have described novel hybrid derivatives of benzimidazole-1,2,3-triazole which has high anticancer property. 10 and 11 compound have reported highest inhibitory activity with IC50 value of 0.05 and 6.18 against A549 cancer cell line and an IC50 value of 17.53 and 8.80 against HeLa cancer cell line respectively.[13]

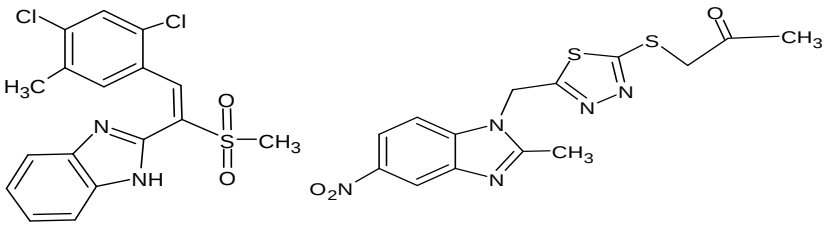
Sivaramakarthikeyan et al. were described the novel hybrid derivatives of benzimidazole and pyrazole as the potential anticancer agents. The demonstration of compounds 12 and 13 for potency of anticancer property against SW1990 and AsPC1 which are selected human pancreatic cancer cell lines with an IC50 value in range of 30.9–61.8µM respectively.[14]

McBride et al. described the preparation of 3-benzimidazol-2-yl-1H-indazoles which act as inhibitors of RTK. The compound **11a** and **11b** shows remarkable tumour growth inhibitor activity against various cell lines tested.[15]

The recent progress on 2-substituted benzimidazoles have shown that various heterocycles at position to give a potent anticancer drug at different carcinoma cell lines. These compound contains pyrimidine derivatives 14[16], pyrazoline derivatives 15[17], and thiazole derivatives 16.[12]

Tangeda et al. were described the preparation and evaluation of a new series of benzomidazole dithiocarbamates 17 for its antitumor activity against the three cancer cell lines A-549,MDA-MB and HT-29. The compounds were not toxic, it fulfilled the requirements for the solubility and oral bioavailability criteria. In the series, the compound containing benzylamino side chain with 5-methyl group provide potential anticancer property with IC value between 0.1 to 43µM.[13]

There were some novel benzimidazole derivative 2-(4-amino-2-arylaminothiazol-5-oyl)-N-methylbenzimidazoles 18 which was developed and investigated for its antitumor property by Selvin et al.[14]



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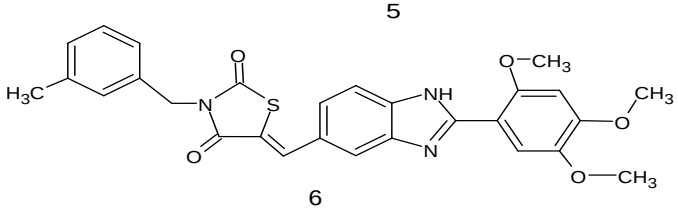

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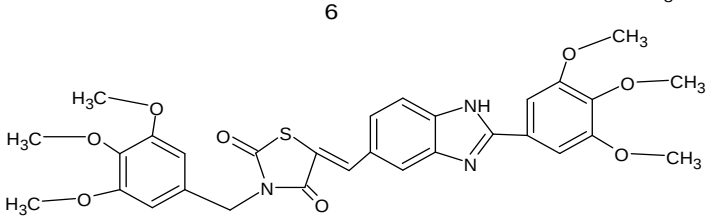

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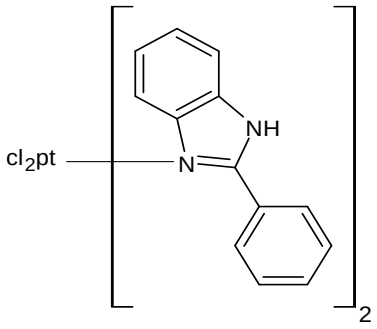

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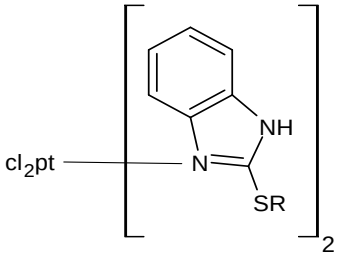
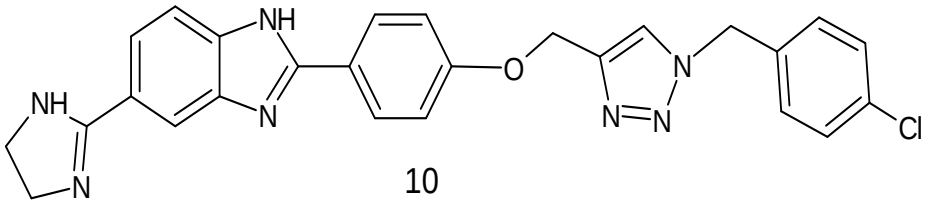


9a R=H
9b R=CH3



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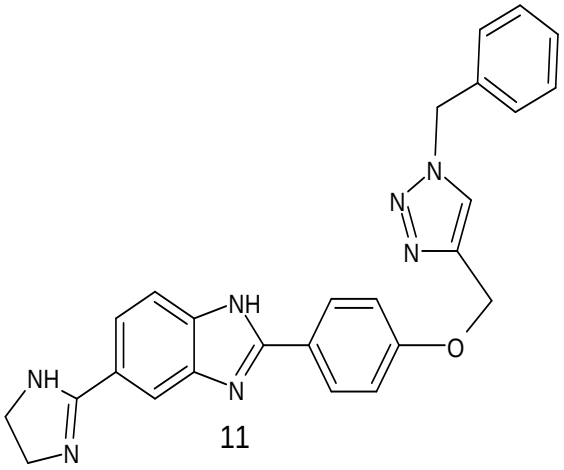

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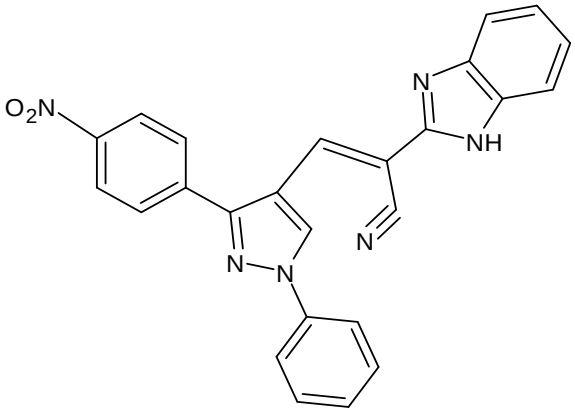

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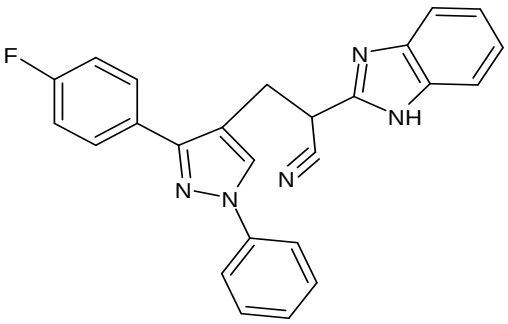

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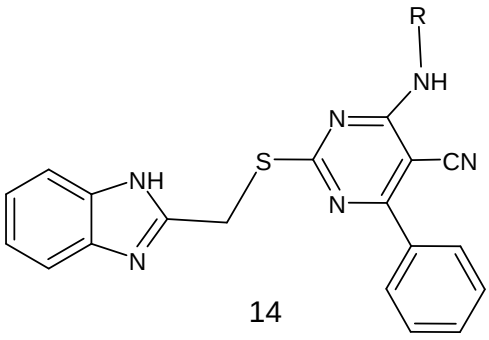

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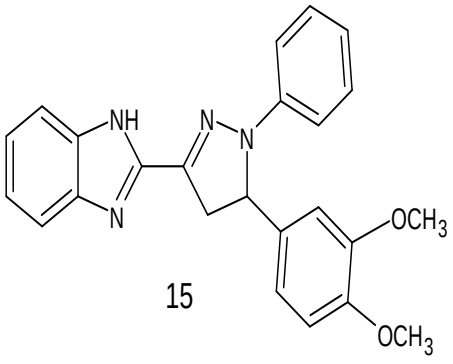

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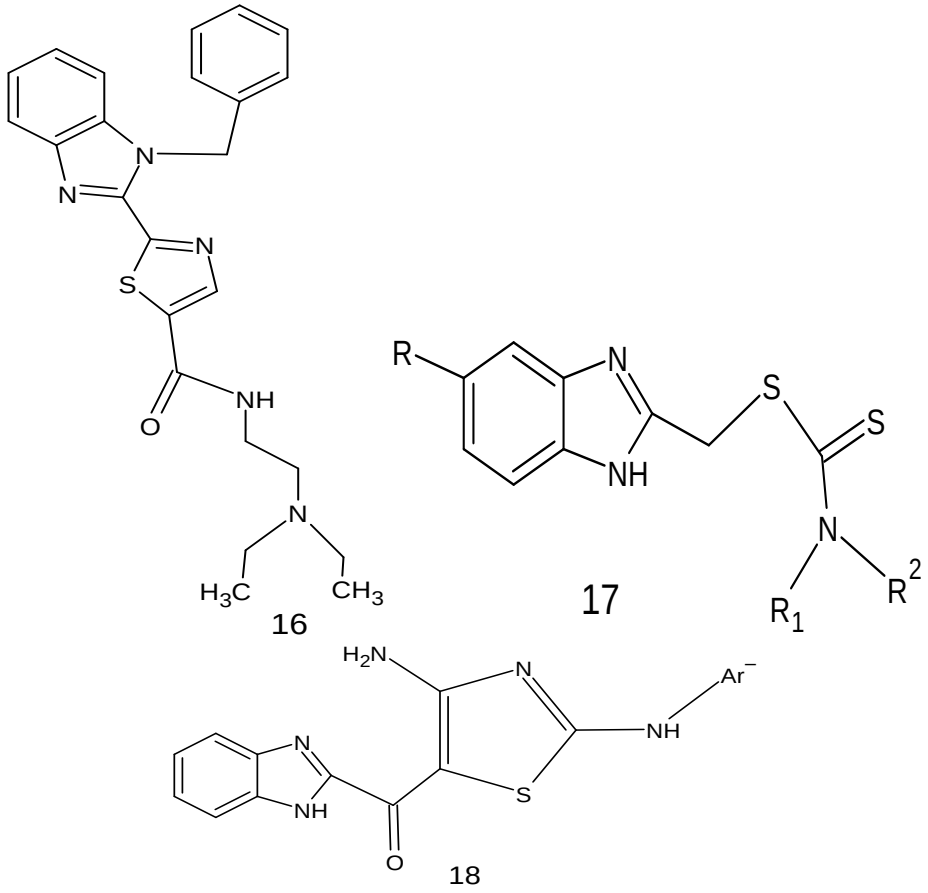


Antiviral property of benzimidazole

Recent studies have shown that most of this heterocycle's derivatives have remarkable antiviral potential. In accordance with the type of substitution and side chain functionalities, benzimidazole derivatives have anti-HCV, anti-HBV, anti-HIV, anti-HSV, anti-Coxsackie virus, anti-rotavirus, anti-mosquito larvae, anti-PRSV, anti-adenovirus, anti-tobacco mosaic, and anti-Sunn-hemp rosette viruses, and other properties.

1-[(dialkylamino)alkyl]-2-[(benzotriazol-1/2-yl)methyl]benzimidazoles have potential anti RSV action was reported by Yu et al.[21]

In 2004, Fonseca et al were accounted the preparation of various benzimidazole derivatives, by introduction into the naphthalene and hydrophenanthrene scaffolds. All the compounds were undergone for evaluation for its in vitro antiviral activity against few RNA and DNA viruses.[22] The prepared benzimidazole derivative compounds 18,19 and 20 indicated high activity against VZV(varicella-zoster virus) and CMV(cyto-megalo virus) with potency IC50 >0.2, 1.1–3.2 and 1.0–1.2 μg/mL, respectively.

In a study by Lu et al.[23] on the anti-HBV activity of thiazolylbenzimidazole compounds, compound 21 showed excellent anti-HBV activity with an IC50 value of 1.1 M.

Luo, et al.[24] described a series of pyrrole-substituted benzimidazoles, of which benzyl-2-(2-(1-methyl-1H-pyrrol-2-yl)ethyl)-1H-benzoimidazole 22 exhibited highly potent anti-HBV activity with an IC50 value of 0.41 M.

As non-nucleoside reverse transcriptase inhibitors (Is), sulfonylbenzimidazoles were identified and their effectiveness against mutant HIV-1 strains was tested. In comparison to nevirapine, the reference medication, sulfonylbenzimidazole compound 23 shows excellent action against HIV-1 (IIIB) with IC50 values of 0.003-0.0003 M.[25]

The hybrid of benzimidazole-triazole which were evaluated against flavivirus and pestivirus are potent anti-HSV agent. For respiratory syncytial virus(RSV),compound 24 exhibit excellent activity with an EC50 value of 0.02μM.[26]

The synthesis of 5-acetyl-2-aryl benzimidazole and its derivatives which was described by Vitale, et al.[27] were studied of the activity against viral RNA, compound 25 was highly potent with EC 50 value of 0.80μM. Another compound,new 2-substituted phenylbenzimidazole and its derivatives which were described and synthesised by Tonelli, et al.[28] The compound was evaluated against RNA and DNA viruses such as vaccinia virus(VV), Reo-1, respiratory syncytial virus (RSV) and bovine viral

diarrhea(BDVD).Compound 26 had great action against VV 1with an EC50 value of 0.1 µM.

Benzyl 2-((2, 4-dichlorophenoxy) methyl)-1H-benzo[d]imidazole-1-carboxylate 27 and some new synthesised benzimidazole derivatives which was demonstrated by Gupta and Jaiswal[29], showed good antiviral property against papaya ring spot virus(PRSV).

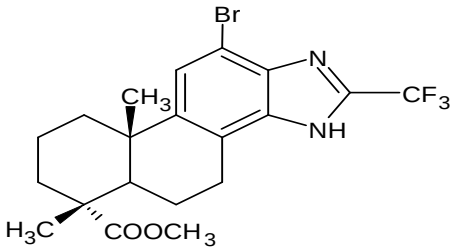
2005 Cheng et al. were reported the preparation of different novel benzimidazole derivatives and later undergone for estimation for its antiviral activity against CVB3 (Coxsackie virus B3) in the Vero cells also known as African green monkey kodney (GMK)cells.[30]

2014, Monforte et al. were showed a preparation and evaluation of HIV-1[human immunodficiency virus type-1] inhibitor potency of new benzimidazole, among which compound 28, 29, 30 had shown highest activity excluding toxicity with IC50 values 0.18, 0.55, and 0.12µM. The results were compared with Nevirapine and Efavirenz, the standard drug.[31]

There was reported that benzimidazole derivatives were effective anti-hepatitis C virus (HCV) and anti-hepatitis B virus (HBV) medicines. Triazole-substituted benzimidazole derivatives have been shown to have anti-HCV activity. With an EC50 value of 7.6 mol L-1, compound 31 from the series demonstrated have high anti-HCV activity.[32] A new class of benzimidazole and pyrimidine hybrid compounds that suppressed HCV were synthesized by Diwani et al.[33], with compound 32 exhibiting excellent results.

The newly synthesised N-substituted benzimidazole analogs, along with 3-(1-Benzyl-1H-benzo[d]imidazol-2-yl)propanoic acid 33 have activity against tobacco mosaic and sunn-hemp rosette(mosaic) virus was reported by Tewari and Mishra.[34]

Francesconi et al. (2020) reported the preparation of several new (thio) semicarbazone-based benzimidazole derivatives which have potent antiviral agent against the human respiratory virus such as RSA, influenza A/H3N2, influenza A/H1N1 and coronavirus 229E. the compounds, 34, 35 and 36, these benzimidazole derivatives show great potential antiviral actions.[35]



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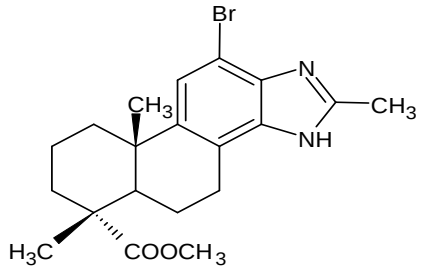

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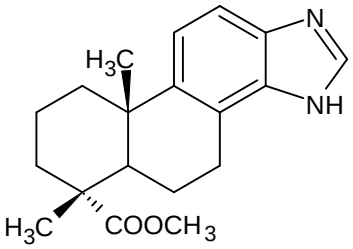

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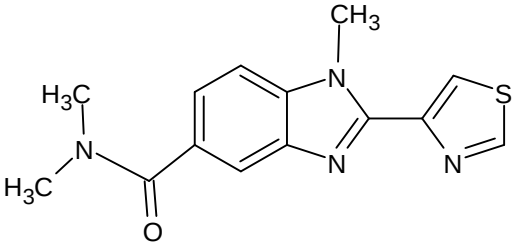

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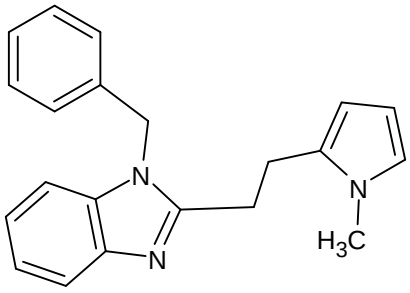

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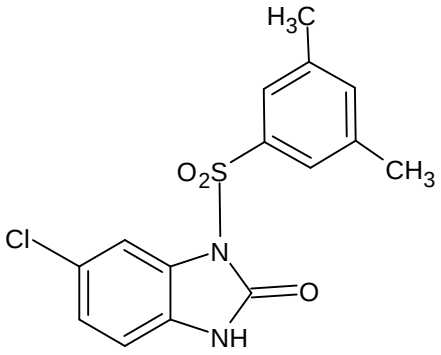

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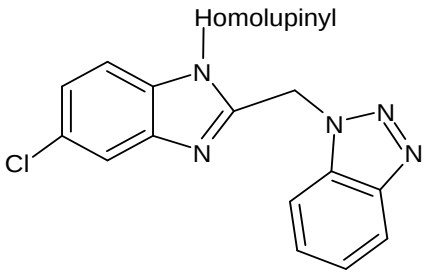

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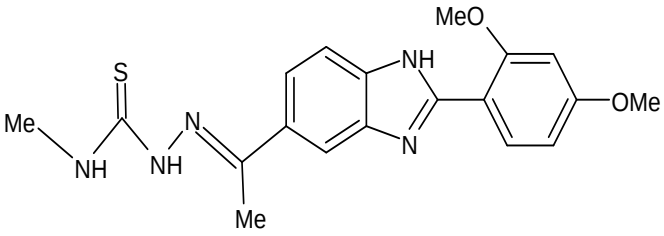

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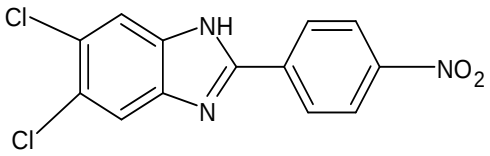

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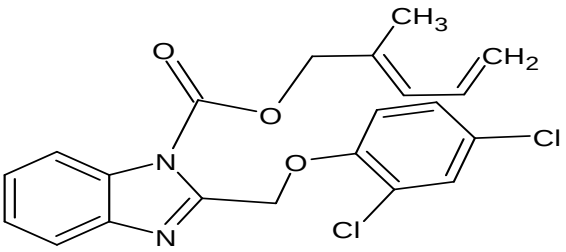

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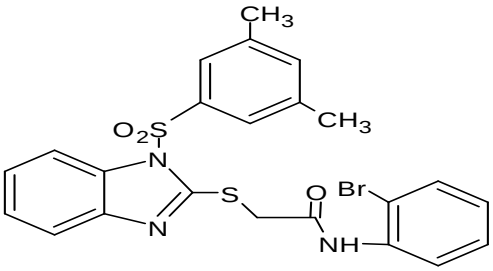

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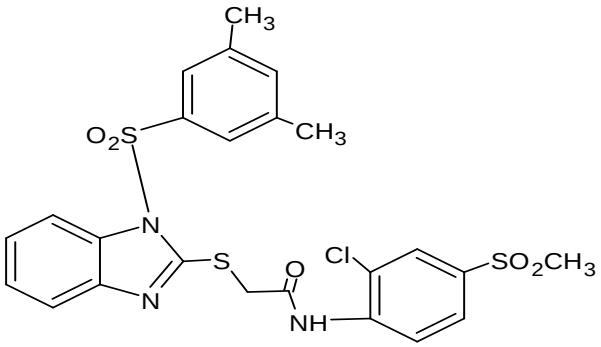

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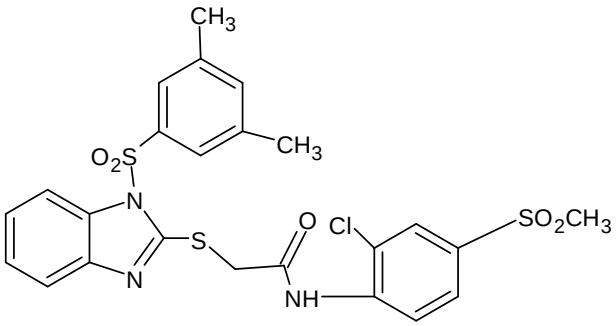

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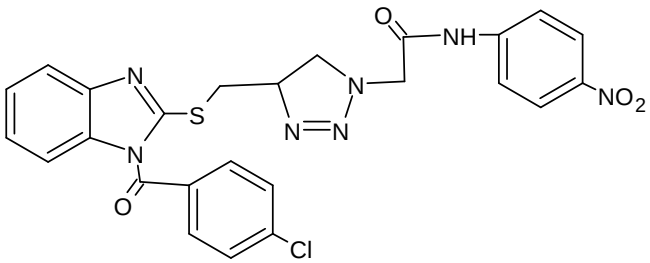

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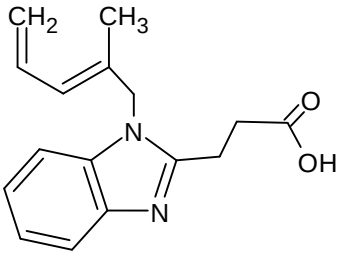

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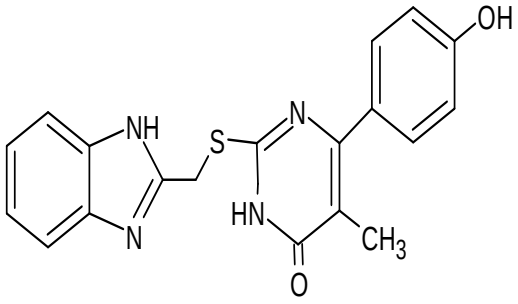

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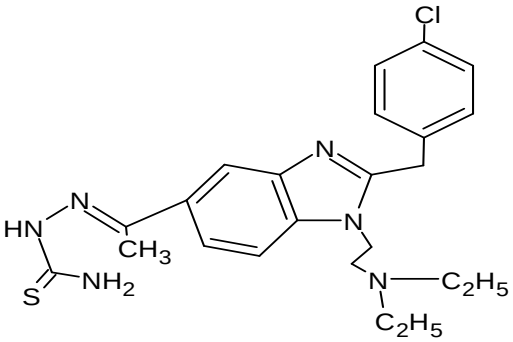

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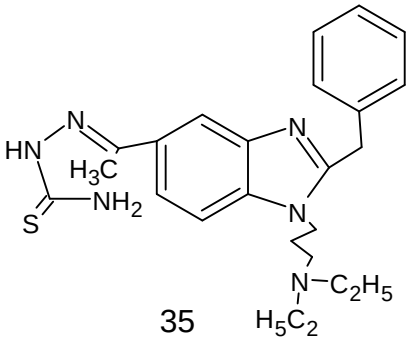

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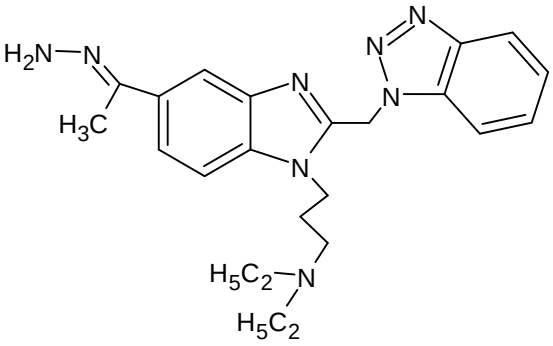

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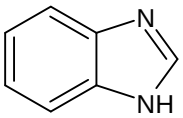
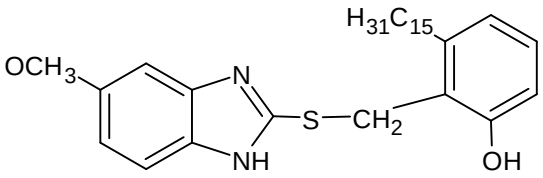
Benzimidazole as Anti -Inflammatory

It has been determined that the benzimidazole nucleus produces effective analgesic and anti-inflammatory agents when substituted at positions 1, 2, 5, and 6 with different substituents. However, the nucleus' positions 4 and 7 cannot be swapped. TRPV-1 antagonists may have the 1-position of the benzimidazole unsubstituted, or the substituents may change from methyl or phenylsulfonyl groups, polyhydroxy sugars, and cycloalkanes to appropriately substituted aryl/heteroaryl moieties with electronic, heterocyclic, or alkyl groups. The 2-position could be substituted with an alkyl or a large lipophilic aryl substituting alkyl, electronic, or heterocyclic groups into heteroaryl moieties. The nucleus's position 5 or 6 can remain un substituted. or substitutes may include functional groups such as halogens, hydroxyl, alkoxy, nitro, amino, methyl, trifluoromethyl, or Aryl/heteroaryl replaced with N-sulfonamide. Various writers have examined a variety of pharmacological activities that benzimidazole and its derivatives exhibit. Here, we'll discuss about the use of benzimidazole derivatives as relievers.



Benzimidazole nucleus structural criteria for analgesic and anti-inflammatory action. Benzimidazoles execute active analgesic and anti-inflammatory effects on clinically recognized targets. European Journal of Medicinal Chemistry 76 (2014) 494e505-495, M. Gaba et al. and painkillers that work on a variety of beneficial targets like the momentary receptor and the cyclooxygenase (COX)enzyme Cannabinoid receptors, potential vanilloid-1 (TRPV-1) ion channels, particular cytokines, bradykinin receptors, and 5-lipoxygenase activating protein (FLAP) compound 37.



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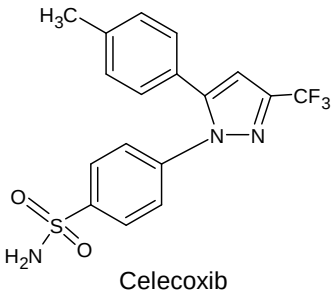
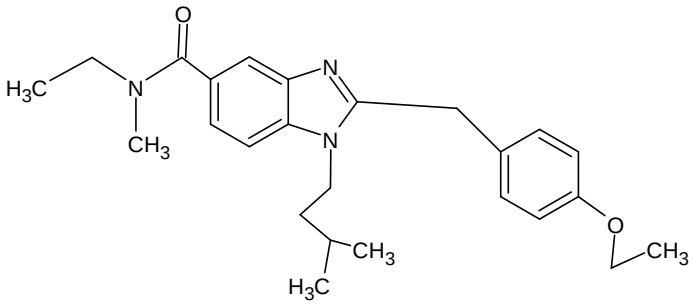


Celecoxib

Cannabinoid receptor agonists are beneficial at reducing pain in several neuropathic and inflammatory pain models, as according recent studies. Two subtypes of cb1 receptors situated centrally and obliquely mediate these actions. CB1, in peripheral tissues, immunological cells, or peripheral tissues (CB2). A significant body of preclinical evidence supports the idea that either CB1 agonists acting at peripheral locations, CB2-selective agonists, or with little exposure to the central nervous system (CNS), Within the CNS, there isn't any side effect but inflammation and neuroinflammation. Selective COX-2 inhibitors (3.1) The primary enzyme that facilitates the conversion of prostaglandins and thromboxane from arachidonic acid.[18,19]

The discovery of cannabinoid agonists has attracted renewed importance. For the treatment of pain and inflammation, AstraZeneca has disclosed a number of benzimidazole derivatives as specific CB2 agonists as well as CB1/CB2 dual agonists. 7 Compound. It was revealed that was a highly selective CB2 agonist having selectivity of 970fold over CB1 receptors, Ki = 3170 n M, and3.3 n M and 3.3 n M, respectively, for human CB1 and CB2 receptors.

Replacement Additional cannabinoid receptor agonist was identified as compound 38 carbo-amido group at C5 with sulfamoyl group. highlighted by compound 39.



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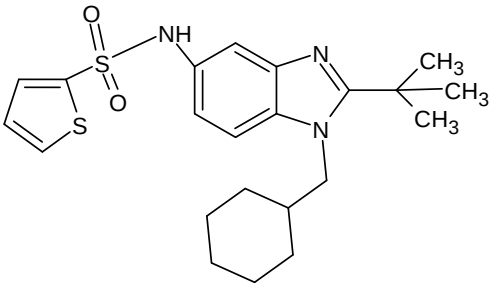

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REFERENCE

1. Heba E, Hashem, Youness EL Bakri; An overview on novel synthetic approaches and medicinal applications of benzimidazole compounds. [Arabian journal of chemistry].
2. Shalki Choudhary, Mohit Arora, Himanshu verma, Manoj kumar, Om Silakari; Benzimidazole based hybrids against Complex diseases: A catalogue of the SAR profile. [European journal of Pharmacology].
3. (Ku c u kbay et al., 2003; KU C U KBAY et al., 2011) (Sharma, 2013), anthelmintic, antiproliferative (Karminski-zamola, 2012; Ts antiviral (Evans et al., 2015),
4. (Simon, 2006). pectral characteristics of benzimidazoles have already been written (Preston, 1974).
5. Bharat B. Kashid,a* Anil A. Ghanwat,a* Vijay M. Khedkar,b Balasaheb B. Dongare,a Mubarak H. Shaikh, Prathmesh P. Deshpande,c and Yogesh B. Wakchaure ; Design, Synthesis, *In Vitro* Antimicrobial, Antioxidant Evaluation, and Molecular Docking Study of Novel Benzimidazole and Benzoxazole Derivatives.
6. Ferruh Lafzi, Deryanur Kilic, Melike Yildiz, Nurullah Saracoglu; Design, synthesis, antimicrobial evaluation, and molecular docking of novel chiral urea/thiourea derivatives bearing indole, benzimidazole, and benzothiazole scaffolds; Journal of Molecular Structure, 2021; 1241: 130566.
7. M.J. Akhtar, A.A. Khan, Z. Ali, R.P. Dewangan, M.d. Rafi, M.Q. Hassan, M.S. Akhtar, A.A. Siddiqui, S. Partap, S. Pasha, M.S. Yar Bioorg. Chem., 2018; 78: 158-169.
8. Vedula, M.S.; Pulipaka, A.B.; Venna, C.; Chintakunta, V.C.; Jinnapally, S.; Kattuboina, V.A.; Vallakati, R.K.; Basetti, V.; Akella, V.; Rajgopal S.; Reka, A.K.; Teepireddy, S.K.; Mamnoor, P.K.; Rajagopalan, R.; Bulusu, G.; Khandelwal, A.; Upreti. V.V.; Mamidi. S.R. New styryl sulfones as anticancer agents. Eur. J. Med. Chem., 2003; 38: 811-824.
9. Ramla, M. M.; Omar, M. A.; El-Khamry, A. M. M.; El-Diwani, H. I. Bioorg. Med. Chem., 2006; 14: 7324.

10. Ni, Z. J.; Barsanti, P.; Brammeier, N.; Diebes, A.; Poon, D. J.; Ng, S.; Pecchi, S.; Pfister, K.; Renhowe, P. A.; Ramurthy, S.; Wagman, A. S.; Bussiere, D. E.; Le, V.; Zhou, Y.; Jansen, J. M.; Ma, S.; Gesner, T. G. Bioorg. Med. Chem. Lett., 2006; 16: 3121.
11. Sharma P, Reddy TS, Kumar NP, Senwar KR, Bhargava SK, Shankaraiah N. Conventional and microwave-assisted synthesis of new 1H-benzimidazole-thiazolidinedione derivatives: A potential anticancer scaffold. European Journal of Medicinal Chemistry, 2017; 138: 234-245.
12. Gumus F.; Pamuk I.; Ozden T.; Yildiz S.; Dirl N.; Oksuzoglu E.; Gur S.; Ozkul A., Synthesis, characterization and in vitro cytotoxic, mutagenic and antimicrobial activity of platinum(II) complexes with substituted benzimidazole ligands. J. Inorg. Biochem., 2003; 94: 255-262.
13. Bistrović A, Krstulović L, Harej A, Grbčić P, Sedić M, Koštrun S, et al. Design, synthesis and biological evaluation of novel benzimidazole amidines as potent multi-target inhibitors for the treatment of non-small cell lung cancer. European Journal of Medicinal Chemistry, 2018; 143: 1616-1634.
14. Sivaramakarthikeyan R, Iniyaval S, Saravanan V, Lim WM, Mai CW, Ramalingan C. Molecular hybrids integrated with benzimidazole and pyrazole structural motifs: Design, synthesis, biological evaluation, and molecular docking studies. ACS Omega, 2020; 5(17): 10089-10098
15. Zien P.; Bretner M.; Zastapilo K.; Szyzyka R.; Shugar D. Selectivity of 4,5,6,7-tetrabromobenzimidazole as an ATP competitive potent inhibitor of protein kinase CK2 from various sources. Biochem. Biophys. Res. Commun., 2003; 306: 129-133.
16. Abdel-Mohsen, H. T.; Ragab, F. A. F.; Ramla, M. M.; El Diwani, H. I. Eur. J. Med. Chem., 2010; 45: 2336.
17. Shaharyar, M.; Abdullah, M. M.; Bakht, M. A.; Majeed, J. Eur. J. Med. Chem., 2010; 45: 114.
18. Luo, Y.; Xiao, F.; Qian, S.; Lu, W.; Yang, B. Eur. J. Med. Chem., 2011; 46: 417.
19. Tangeda SJ, Sandala AB, Garlapati A. Synthesis, cytotoxic evaluation and molecular properties studies of novel benzimidazole derivatives with dithiocarbamate side chain. Pharmacophore, 2014; 5: 417-29.
20. Selvin PPS, Yardly A, Rajasekharan KN, Abbs FRTF. Synthesis of anticancer compounds 2-(4-amino-2-arylaminothiazol-5-oyl)-N-methylbenzimidazoles. Indian J Chem., 2013; 52B: 560-4.
21. K.-L. Yu, Y. Zhang, R. L. Civiello, K. F. Kadow, C. Cianci, M. Krystal, N. A. Meanwell, Bioorg. Med. Chem. Lett., 2003; 13: 2141.
22. Fonseca, T., Gigante, B., Marques, M.M., Gilchrist, T.L., De Clercq, E., Bioorganic & Medicinal Chemistry, 2004; 12: 103.
23. Y. Lu, J. P. Yao, L. Yang, et al., Arch. Pharm. Chem. Life Sci., 2011; 2: 78–83.
24. Y. Luo, J. P. Yao, L. Yang, et al., Bioorg. Med. Chem., 2010; 18: 5048–5055.
25. M. L. Barreca, A. Rao, L. D. Luca, et al., Bioorg. Med. Chem. Lett., 2007; 17: 1956–1960.
26. M. Tonelli, G. Paglietti, V. Boido, et al., Chem. Biodiversity, 2008; 5: 2386–2401.
27. G. Vitale, P. Corona, M. Loriga, et al., Eur. J. Med. Chem., 2012; 53: 83–97.
28. M. Tonelli, M. Simon, B. Tasso, et al., Bioorg. Med. Chem., 2010; 18: 2937–2953.
29. H. C. Gupta and V. Jaiswal, J. Ind. Council Chem., 2010; 27: 159–162.
30. Cheng, J., Xie, J., Luo, X., Bioorganic & Medicinal Chemistry Letters, 2005; 15: 267.
31. Monforte, A.M., Ferro, S., De Luca, L., Lo Surdo, G., Morreale, F., Pannecouque, C., Balzarini, J., Chimirri, A., Bioorganic & Medicinal Chemistry, 2014; 22: 1459.
32. B. G. M. Youssif, Y. A. M. Mohamed, M. T. A. Salim, et al., Acta Pharm., 2016; 66: 219–231.
33. H. I. E. Diwani, H. T. A. Mohsin, I. Salama, et al., Chem. Pharm. Bull., 2014; 62: 856–866.
34. A. K. Tewari and A. Mishra. Indian J. Chem., 2006; 45: 489–493.
35. Francesconi, V., Cichero, E., et al, Molecules, 2020; 25: 1487.
36. Benzimdazole an emerging scaffold for analgesic and anti –inflammatory agents. European journal of medicinal chemistry, 2014; 76: 494-505.