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Review Article

BENZIMIDAZOLE: AS POTENTIAL BIOLOGICALLY ACTIVE AGENT

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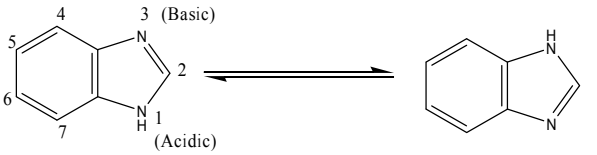
ABSTRACT
The benzimidazole ring system is an important pharmacophore in medicinal chemistry and modern drug discovery**.** Benzimidazole and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different biological activities. This review article covers the most active benzimidazole derivatives and discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing benzimidazole moiety that could be better agents in terms of efficacy and safety.
Keywords: Benzimidazoles, synthesis, biological activities, tautomerism.

INTRODUCTION

Benzimidazole is a bi cyclic ring system in which benzene ring fused with 4- and 5- position of the imidazole ring, imidazole ring contain two nitrogen atoms at nonadjacent position. In 1950, when 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole was found as a integral part of the structure of vitamin B_{12}, interest have been generated to develop potential chemotherapeutic agent with benzimidazole as a nucleus[1]. Benzimidazole is a very important pharmacophore in drug discovery, and its derivatives are used as an important class of bioactive molecules in the field of new drug development. Some of them exhibit significant biological activity against several viruses, and have potent anti parasitic agents, anti tumor agents, antimicrobial agents, and inhibitors of the hepatitis C virus RNA polymerase. Benzimidazoles as a veterinary drug are also widely used for prevention and treatment of parasitic infections in agriculture and aquaculture. In addition, some of them it also used as pre- or post-harvest fungicides for the control of a wide range of fungi, which affect field crops, stored fruit and vegetables[2].

Tautomerism in benzimidazole

Tautomers are isomers of organic compounds that readily interconvert by a chemical reaction called tautomerization. This reaction results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. The concept of tautomerizations is called tautomerism[3]. The systematic numbering of the benzimidazole ring system is shown in structure-I although benzimidazole is depicted in I as possessing the proton at N_1 there actually exists a rapid exchange between the -NH- and =N- nitrogen atoms, and two tautomers, I and II, may be drawn for the benzimidazole molecule[1]. Tautomerism occurs through either an intermolecular process involving two or more benzimidazole molecules or through interactions with a protic solvent such as water[3].



Structure-I **Structure-II**

Antibacterial activity

Synthesis and *in-vitro* antibacterial activity of some novel substituted benzimidazole derivatives (1) having potent activity against methicillin-resistant *S. aureus* (MRSA) were reported by Meral Tuncbilek *et al*[4]. From the synthesized compounds (1a-1c) having the free NH group of the benzimidazole moiety exhibited excellent activity with MIC 3.12 µg/ml against methicillin-resistant *S. aureus* (MRSA).

Anti-tubercular activity

A new series of novel 5-(nitro/bromo)-styryl-2-benzimidazole (2) derivatives has been synthesized by Hosamani M. K. *et al*[5]. Screening of *in-vitro* anti-tubercular activity of synthesized compounds (1a-12l) against *Mycobacterium tuberculosis* strain H_{37} Rv. The compounds 2g, 2h, 2i and 2k showed good anti-tubercular activity whereas compound 2e showed moderate activity. All compounds tested at concentration of 7.25 µg/ml and standard drug taken was streptomycin.

Anthelmintic activity

The synthesis of 2-alkyl and aryl substituted benzimidazole (3) derivatives are screened for their anthelmintic activity were reported by Sreena K. *et al*[6]. All the synthesized compounds (3a-3d) showed significant anthelmintic activity. Among the synthesized compounds 2-Phenyl benzimidazole showed potent anthelmintic activity 0.931 ± 0.231 and 1.317 ± 0.149 minute for paralysis and death time respectively when compared with the standard Piperazine citrate 15 mg/ml.

Antiprotozoal activity

A series of 2-(Trifluromethyl)-1*H*-benzimidazole derivatives (4a-4i) synthesized by Lilian Y. Mulia *et al* (7). The compounds 4a-4i was evaluated *in-vitro* antiprotozoal activity against *G. intestinalis, E. histolytica, T. vaginalis* and *L. Mexicana*. Compounds 4b, 4c and 4e showed most potent activity. The order of parasite susceptibility found was: *E. histolytic > G. intestinalis > T. vaginalis > L. Mexicana.*

Anticoagulant

A series of Halothiophene benzimidazoles (5) as P_1 surrogates of inhibitors of blood coagulation factor Xa was synthesized by Werner W. K. R. Mederski *et al*[8]. All synthesized compounds were assayed against human fXa, thrombin and trypsin. The compounds 5a and 5b showed potent activity.

Antifungal activity

Synthesis of phenyl hydrazine substituted benzimidazole (6) derivative and their biological activity by Tiwari A. *et al*[9]. The 6-nitro derivative of benzimidazole shows good activity against *Aspergillus niger* and *Aspergillus flavus.*

Analgesic, Anti-inflammatory activity

A series of 2-Methyl aminobenzimidazole derivatives (7a-7k) were synthesized by Hosamani M. K. *et al*[10]. The synthesized compounds were screened for analgesic and anti-inflammatory activity on acetic acid induced writhing in mice and carrageenan induced paw oedema in rats. Compounds (7g) and (7b) showed a potent analgesic (89 % at 100 mg/kg b.w.) and anti-inflammatory (100 % at 100 mg/kg b.w.) activities compared with standard drug Nimesulide (100 % at 100 mg/kg b.w.) respectively. The other compounds showed good analgesic and anti-inflammatory activities.

Anticancer Activity

The synthesis of various series of 2-Substituted benzimidazoles (8) by Hanan M. Refaat *et al*[11]. All the synthesized compounds screened for *in-vitro* anticancer activity against three cell lines human hepatocellular carcinoma cell line (HEPG2), human breast adenocarcinoma cell line (MCF7), and colon carcinoma cell line (HCT 116) with IC50's <10 µg/ml. Compounds 8a and 8c showed the highest potency against HEPG2 while compounds 8f, 8h and 8g were most active against MCF7, Compounds 8h and 8c were moderately potent against HCT116.

Anti-HIV activity

A series of novel benzofuran and related benzimidazole derivatives (9) for evaluation of *In-Vitro* Anti-HIV-1 by Hesham T.Y. Fahmy *et al*[12]. All synthesized compounds were evaluated for their effects on HIV-1-induced cytopathogenicity in human T_4 lymphocyte cell line (CEM). The compounds 9a and 9b showed potent activity.

Molluscicidal Activities

A series of benzimidazole Schiff's bases, thiosemicarbazides, Pyrimidinobenzimidazoles, trizinobenzimidazoles, and 2-(acetonylamino)-1-methyl-benzimidazole (10) were prepared by Z. M. Nofal *et al*[13]. All the synthesized compounds were screened in vitro mollouscicdal activity against *Biomphalaria alexandrina* snails, specific host of *Schistosoma mansoni*. The compounds (10a) and (10b) showed potent molluscicidal activity.

Antiulcer Activity

A series of novel Pyrimidylthiomethyl benzimidazole (11a) and Pyrimidylsulfinylmethyl benzimidazole (11b) were reported by Bariwal J. B. *et al*[14]. All synthesized compounds evaluated for the antiulcer activity by pylorus ligation of rats. Compounds (11a) and (11b) when evaluated significantly decreased the gastic acid secretion, free acidity, as well as gastric ulcers in the pylorus ligated rats and the effects are dose dependent and comparable to omeprazole. The compound 11b (Sulfinyl derivative) was more effective than 11a (Thio derivative).

Antiviral activity

The series of 2-(Alkylthio) and 2-(Benzylthio)-5, 6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (12) synthesized by Leroy B. Townsend *et al*[15]. All synthesized compounds were evaluated for antiviral activity against human cytomegalovirus (HCMV) and herpes simplex virus type-1 (HSV-1). The compound 12d showed potent activity in the series.

Antihistaminic

A series of substituted (3-phenoxypropyl)amines (13) were reported by Robert Aslanian *et al*[16]. All the synthesized compounds evaluated for antihistaminic activity. Compound 13a showed potent H_1 antagonist possessing a good pharmacokinetic profile in the rat.

Anti pneumonial activity

A series of dicationically substituted bis-benzimidazole (14) synthesized by R. R. Tidwell *et al*[17]. All synthesized compounds evaluated for activity in the rat model of *Pneumocystis carinii* pneumonia. The compound 14 h was found to be more potent and less toxic.

Antinociceptive activity

The series of 1-[(Benzoxazole/benzimidazole-2-yl)thioacetyl]pyrazoline (15) derivatives synthesized by Gulhan Turan Zitouni *et al*[18]. The synthesized compounds exhibited statistically significant antinociceptive activities against thermal and chemical noxious stimuli. The compounds 15b and 15e showed highest antinociceptive activities. It can be suggested that dimethyl substitution on phenyl at third position of the pyrazole ring increases the antinociceptive activities.

Antioxidant activity

Synthesis of some 1-[(substituted thiocarbamoylhydrazine carbonyl) methyl]-2-phenyl-1H-benzimidazoles (16) were reported by Canan Kus *et al*[19]. *In-vitro* antioxidant effect on the rat liver microsomal NADPH-dependent lipid peroxidation (LP) levels was determined. The most active compound 16c caused an 84 % inhibition of LP at 10^{-3} M, which is better than that of butylated hydroxytoluene (BHT) (65 %) used as standard.

Anti arrhythmic agent

The series of *N*-(1,3-Dimethyl-1*H*-2,3-dihydrobenzimidazol-2-ylidene)acetamido (17) derivatives synthesized by Hamad A. Alkhamees[20]. The compounds 17a and 17b exhibited significantly anti arrhythmic activity.

Anti-diabetic activity

Synthesis of some novel and functionalized benzimidazole (18) derivatives were reported by Ramanatham Vinod Kumar

et al[21]. All synthesized compounds were tested for anti-diabetic activity against DPP-IV and PTP-1B. Compound 18b shown potent inhibitory activity against PTP-1B (27.67 %) at 30 μM dose and 6a shown potent inhibitory activity against DPP-IV (9 %) at 0.3 μM doses.

Anti-Asthmatic Activity

Syntheses of some novel and functionalized benzimidazole (19) derivatives were reported by Ramanatham Vinod Kumar *et al*[21]. All synthesized compound were tested against PDE-1V for potential anti-asthmatic effect, compound 19a shown potent inhibitory activity (22.56 %) at 1 μm doses.

Anticonvulsant Activity

A series of 2-mercaptobenzimidazole (20) derivatives were reported by K. Anandarajagopal *et al*[22]. All synthesized compounds evaluated for anticonvulsant activity by maximum electrical shock induced convulsion method and compared with the standard drug phenytoin. Compounds 20a, 20b and 20c exhibited excellent anticonvulsant activity.

Angiotensin II Receptor Antagonist and antihypertensive activity

A series of 5-(alkyl and aryl)carboxamido benzimidazole (21) derivatives were reported by Gulshan bansal *et al*[23]. All synthesized compounds evaluated for *in-vitro* angiotensin II receptor antagonist and *in-vivo* antihypertensive activities. Compounds 21a and 21b showed potent activity because it contain lower alkyl group at 5-position of benzimidazole nucleus.

Radio protectors

A series of disubstituted bisbenzimidazoles and terbenzimidazole (22) reported by Urmila Tawar *et al*[24]. Compounds 5 and 6 showed 82 % and 37 % protection against radiation-induced cell death (macrocolony assay) while 100 % protection was observed against growth inhibition. Compound 22a and 22b contain electron donating groups on the phenyl ring , complex with DNA was formed and this prevent the formation of free radical species on the bases and also scavenge the free radicals being generated in the vicinity and thereby afford better protection against radiation induced DNA damage.

Anti-Trypanosomatid agent

A series 2H-Benzimidazole 1,3-dioxide (23) derivatives were reported by Mercedes Gonzalez *et al*[25]. All synthesized compounds evaluated for their activity against trypanosomatid parasites (*Trypanosoma cruzi* and *Leishmania* spp.). Compounds 23a, 23b and 23c most potent (IC_{50} < 5 μM) against the epimastigote form of *T. cruzi* and 23a, 23d and 23e most potent against the promastigote from of *Leishmania spp.*

DNA repair enzyme Poly (ADP-ribose) Polymerase inhibitor

A series of 2-phenyl-1*H*-benzimidazole (24) derivatives were reported by Alex W. White *et al*[26]. Compound 24a showed important hydrogen binding and hydrophobic interactions with protein (Ki = 6 nM).

5-HT_4 Receptor Antagonist Activity

A series of benzimidazolone-3-carboxamides (25) were reported by John M. Schaus *et al*[27]. All synthesized compounds evaluated for antagonist affinity at the 5-HT_4 receptor in rat oesophagus. Compounds 25a, 25b and 25c have been identified as a potent and selective 5-HT_4 receptor antagonist with pharmacodynamic properties.

$GABA_A$ receptor agonist activity

A series of *N*-substituted 2-phenyl-benzimidazole (26) were reported by Jose Luis Falco *et al*[28]. All synthesized compounds evaluated spontaneous motor activity in mice. Compound 26a showed potent activity.

Cyclooxygenase-2 inhibitors

A series of 2-[[(2-alkoxy-6-pentadecylphenyl) methyl]thio]-1*H*-benzimidazole (27) reported by Srinivasa Rao *et al*[29]. Compounds 27a and 27b showed potent COX-2 inhibitor. Compound 27a is 384 times more selective towards COX-2 when compared to COX-1(COX-1 IC_{50} = 384μM, COX-2 IC_{50} = 1 μM) and compound 27b is 470 times more selective towards COX-2 inhibition than COX-1(COX-1 IC_{50} = >500, COX-2 IC_{50}=1.06 μM).

Hypolipidmic

A novel series of benzimidazole-based analogues of the potent microsomal triglyceride transfer protein inhibitors were reported by Jeffrey A. Robl *et al*[30]. Incorporation of an unsubstituted benzimidazole moiety in place of piperidine group afforded potent inhibitors of microsomal triglyceride transfer protein. All synthesized compounds in this series reduces plasma lipids (cholesterol, VLDL/LDL, TG) in both hamsters and cynomolgus monkeys.

Cannabinoid receptor CB2 agonist

A novel series of 5-sulfonyl benzimidazole (28) derivatives were reported by Harrie J.M. Gijsen *et al*[31]. The synthesized compound 28b showed potent activity, it is more selective for peripherically cannabinoid receptor CB2.

Chemokine receptor CXCR3 antagonist

High-throughput screening identified a low molecular weight antagonist of CXCR3 displaying micro molor activity in a membrane filtration binding assay was reported by Martin E. Hayes *et al*[32]. Compound 29a exhibited potent activity.

Human Bradykinin B_2 receptor agonist

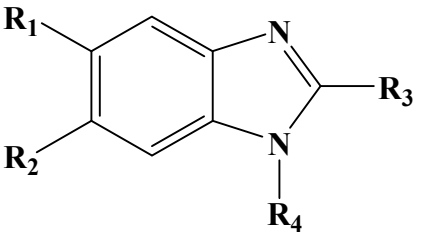
A novel series of 1-(2-picolyl)benzimidazole (30) derivatives were reported by Hiroshi Kayakiri *et al*[33]. The synthesized compound 30c showed potent activity it increased PGE_2 production at 1 μM conc.

Melanin concentrating hormone (MCH-1R) receptor antagonist

The novel series of *N*-methyl substituted benzimidazole (31) derivatives were reported by Hazel J. Dyke *et al*[34]. The synthesized compounds 31a, 31b, 31c showed potent activity it's IC_{50} valu 9, 9, 28 nM.

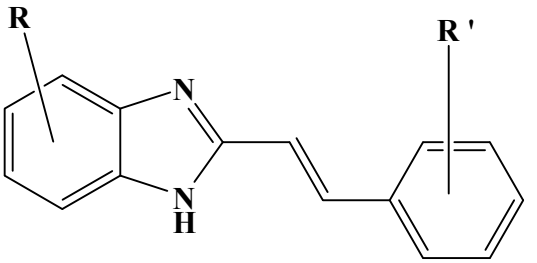
Mammalian DNA topoisomerase I inhibitor

A series of substituted 1*H*-benzimidazole (32) derivatives reported by Zeki Topcu *et al*[35]. All synthesized compounds were screened for *in-vitro* supercoil relaxation assay, compounds 32a, 32b, 32c showed potent activity.



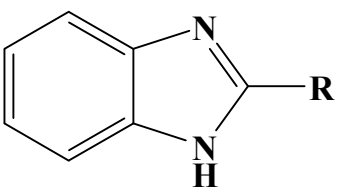
Compound	R_1	R_2	R_3	R_4
1a	Cl	Cl	$-C_6H_4F$	H
1b	Cl	Cl	$-C_6H_4Cl$	H
1c	Cl	Cl	$-C_6H_4-C-(CH_3)_3$	H

(1)



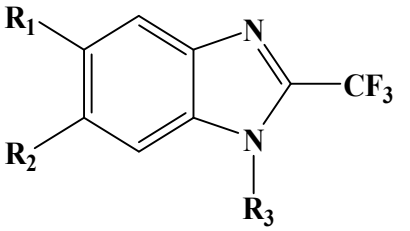
Compound	R	R'
2a	NO_2	H
2b	NO_2	3,4-OCH_3
2c	NO_2	4-CH_3
2d	NO_2	3,4-O_2CH_2
2e	NO_2	2,4-Cl
2f	NO_2	3-OH
2g	Br	H
2h	Br	3,4-OCH_3
2i	Br	4-CH_3
2j	Br	3,4-O_2CH_2
2k	Br	2,4-Cl
2l	Br	3-OH

(2)



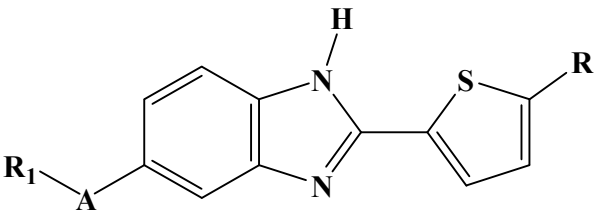
Compound	R
3a	CH_3
3b	C_6H_5
3c	4-$NH_2.C_6H_4$
3d	$(CH_2).C_6H_5$

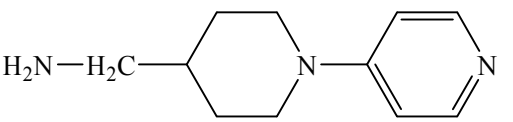
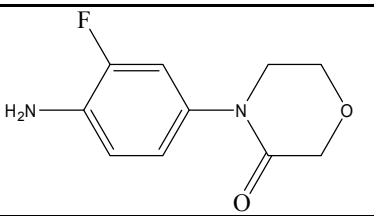
(3)



Compounds	R_1	R_2	R_3
4a	2,3-$Cl_2C_6H_3O$	H	H
4b	2,3-$Cl_2C_6H_3O$	H	CH_3
4c	H	2,3-$Cl_2C_6H_3O$	CH_3
4d	2,3-$Cl_2C_6H_3O$	Cl	H
4e	$C_{10}H_7O$	Cl	H
4f	$C_{10}H_7O$	Cl	CH_3
4g	Cl	$C_{10}H_7O$	CH_3
4h	Cl	Cl	H
4i	Cl	H	CH_3

(4)



Compound	R	A	R_1
5a	Br	$CH_2(C=O)$	
5b	Cl	$CH_2CH_2(C=O)$	

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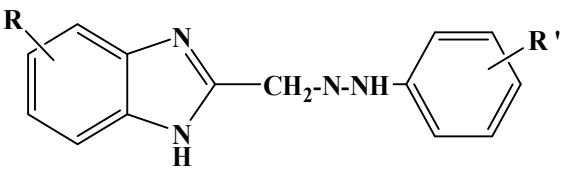
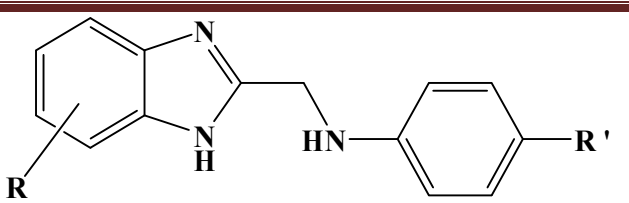


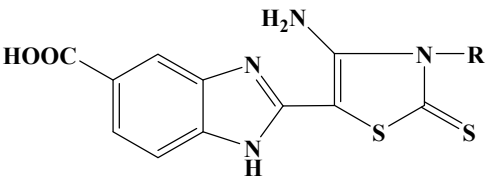
Compound	R	R'
6a	H	H
6b	H	-4-NO_2
6c	H	-2,4-NO_2
6d	H	-4-Cl
6e	-6-NO_2	H
6f	-6-NO_2	-4-NO_2
6g	-6-NO_2	-2,4-NO_2
6h	-6-NO_2	-4-Cl

(6)

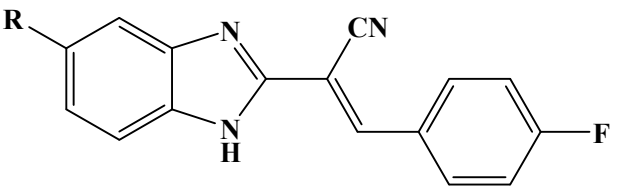


Compound	R	R'
7a	H	H
7b	H	Cl
7c	H	Br
7d	H	OMe
7e	Br	H
7f	Br	Cl
7g	Br	Cl
7h	Br	Br
7i	Br	OMe
7j	Br	Me
7k	NO_2	Br

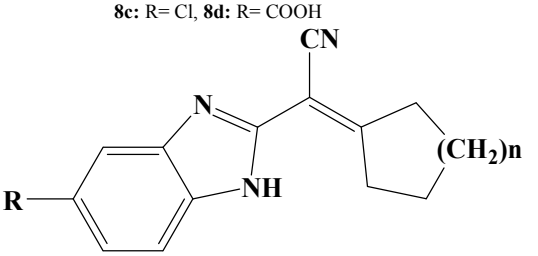
(7)



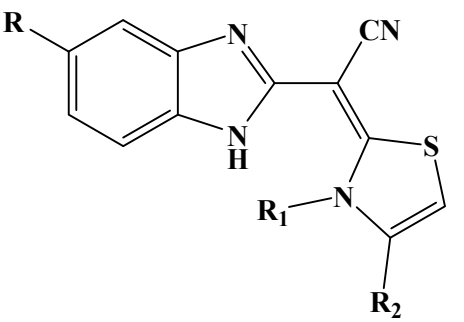
8a: R= $CH_2C_6H_5$, **8b:** R= C_6H_5



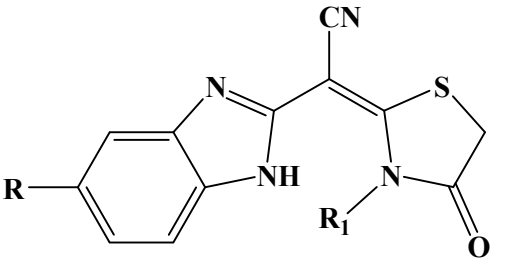
8c: R= Cl, **8d:** R= COOH



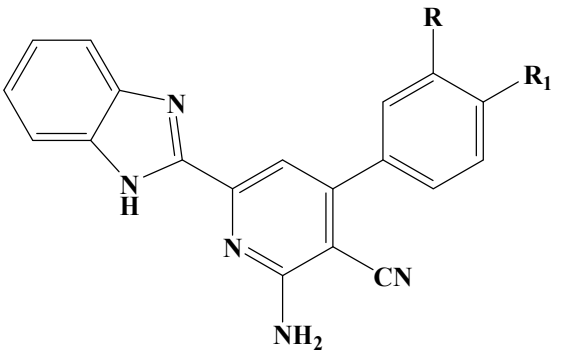
8e: R=Cl n=1, **8f:** R=COOH n=2



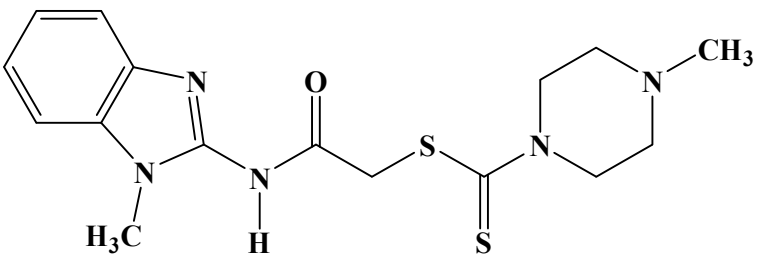
8g: R= COOH, R_1= 4-Br-C_6H_4, R_2= 2-OCH_3-C_6H_4



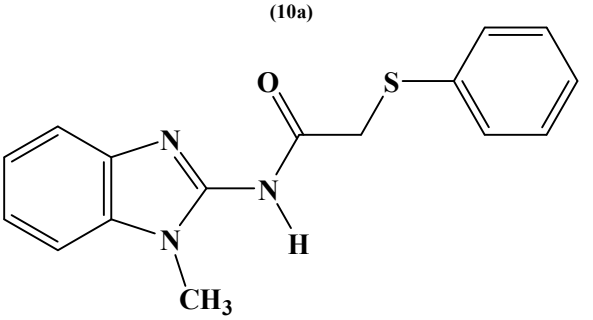
8h: R= Cl, $R_1 = C_6H_5$



9a: R=H, R_1=Cl
9b: R=OCH_3, R_1=OCH_3



(10a)



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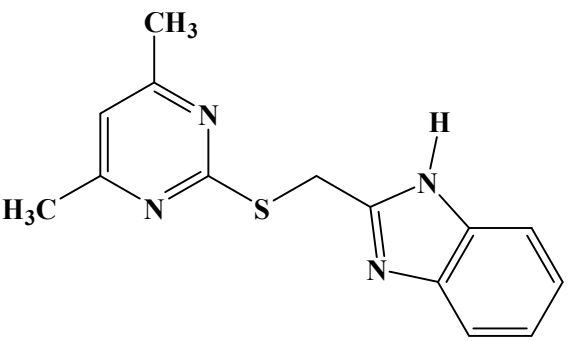
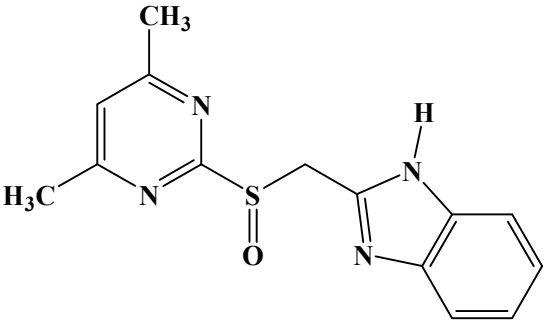
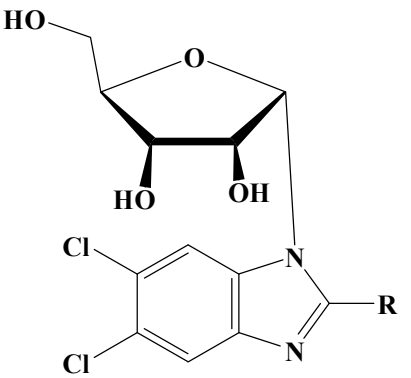


(11a)

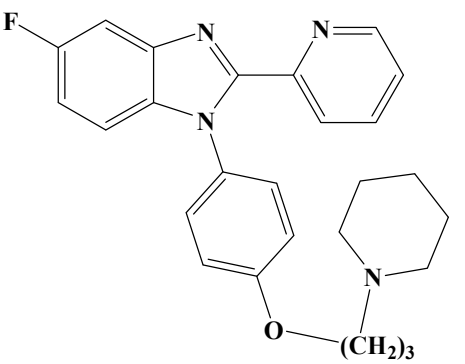


(11b)

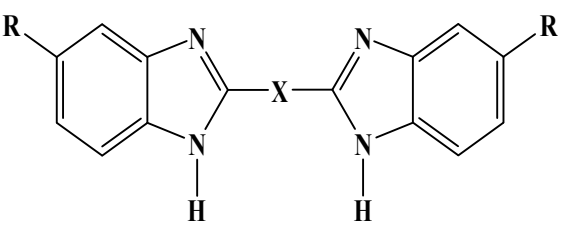


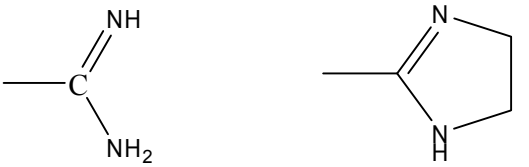
Compound	R
12a	SH
12b	SCH_3
12c	SO_2CH_3
12d	$SCH_2C_6H_5$
12e	$SCH_2C{=}CH_2$
12f	$SCH_2CH{=}CH_2$
12g	$SCH_2C{=}NH$

(12)



(13a)

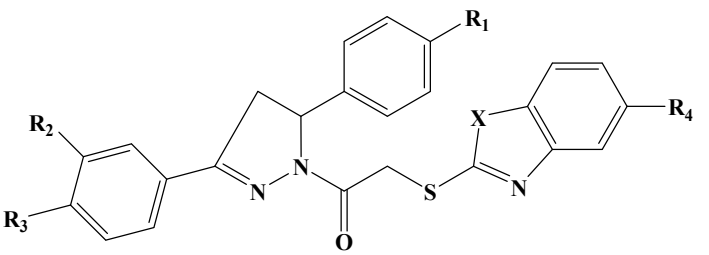




Am Im

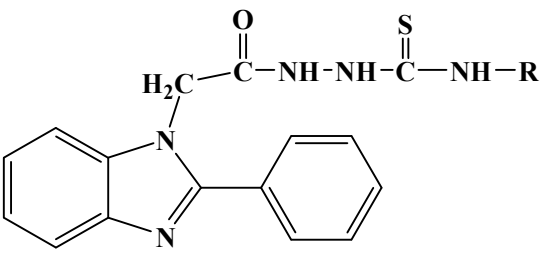
Compound	X	R
14a	CH_2	Am
14b	CH_2	Im
14c	$(CH_2)_2$	Am
14d	$(CH_2)_2$	Im
14e	$(CH_2)_3$	Am
14f	$(CH_2)_3$	Im
14g	$(CH_2)_4$	Am
14h	**$(CH_2)_4$**	**Im**
14i	$(CH_2)_8$	Am
14j	-CH=CH-	Am

(14)



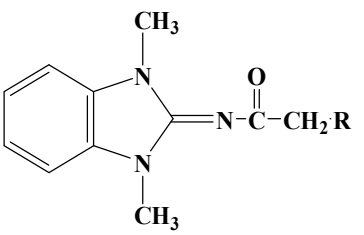
Compound	R_1	R_2	R_3	R_4	X
15a	H	H	H	Cl	O
15b	H	CH_3	CH_3	Cl	O
15c	OCH_3	H	H	Cl	O
15d	H	H	H	H	NH
15e	H	CH_3	CH_3	H	NH
15f	OCH_3	H	H	H	NH

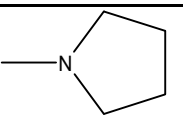
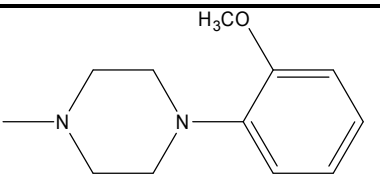
(15)



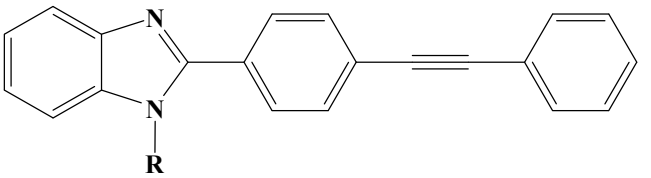
Compound	R
16a	Phenyl
16b	4-tolyl
16c	2-chlorophenyl
16d	4-fluorophenyl
16e	2-bromophenyl

(16)

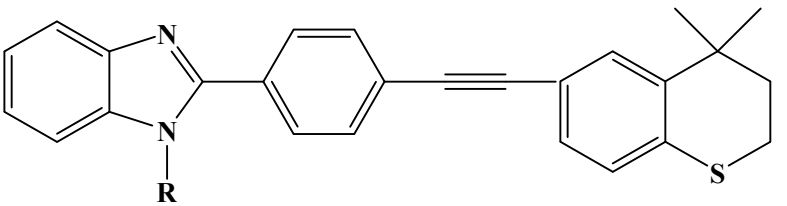


Compound	R
17a	
17b	

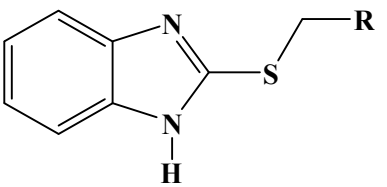
(17)



18a R= Methyl, **18b** R=Ethyloxycarbonyl, **18c** R= 4-Methylphenylsulfonyl

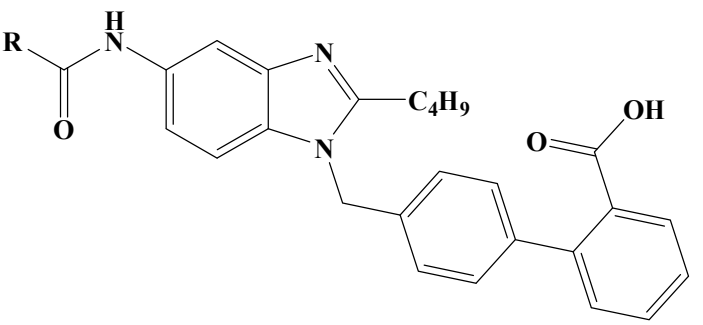


19a R=Trifluoromethanesulfonyl



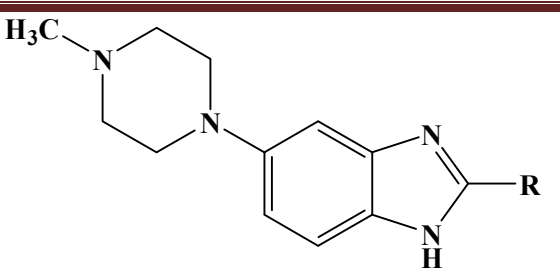
Compound	R
20a	Piperazine
20b	Morpholine
20c	N-pheny benzamide

(20)



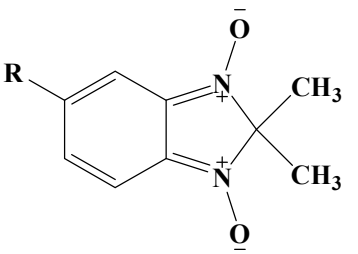
Compound	R
21a	CH_3
21b	C_2H_5

(21)



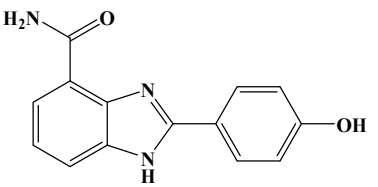
(22)

Compound	R
22a	2-(3,4-dimethoxyphenyl)-1*H*-benzo[*d*]imidazole
22b	4-(6-(1*H*-benzo[*d*]imidazole-2-yl)-1*H*-benzo[*d*]imidazole-2-yl)-2-Methoxyphenol

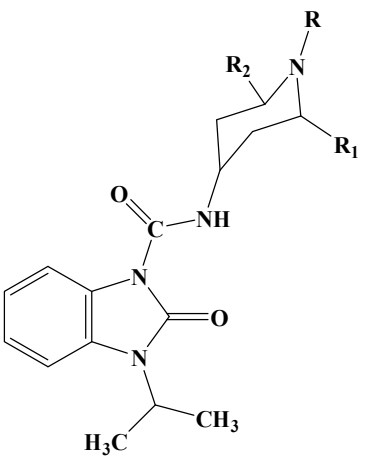


Compound	R
23a	H
23b	CH_3
23c	(E/Z)-CH=CHPh
23d	CH=NOH
23e	1,3-dioxolane

(23)

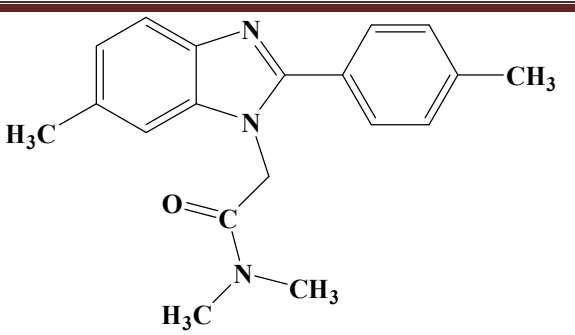


(24a)

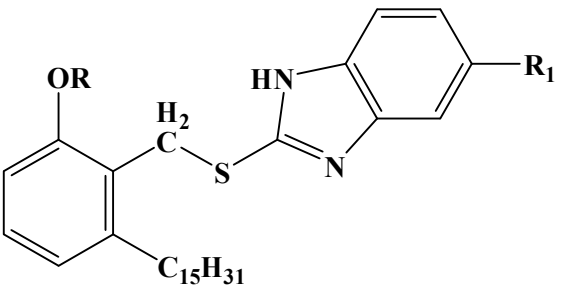


(25)

Compound	R	R_1	R_2
25a	CH_2	CH_2	1-butoxy-4-flurobenzene
25b	H	H	CH_3
25c	H	H	1-butoxy-4-flurobenzene

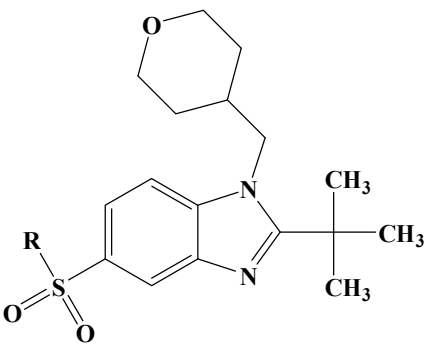


(26a)



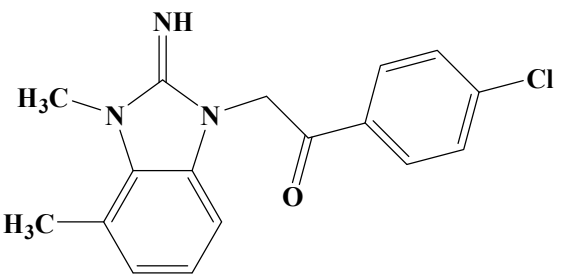
Compound	R	R_1
27a	H	OCH_3
27b	CH_3	H

(27)

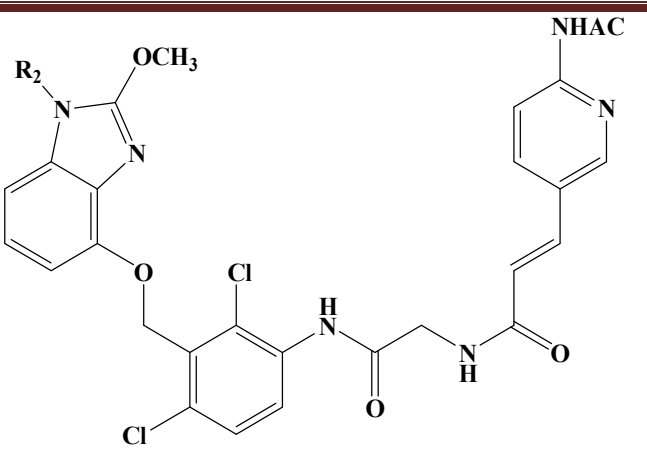


(28)

Compound	R
28a	3-CH_3-4-pyridine
28b	3-HOC_2H_5-4-pyridine
28c	3-F-4-pyridine

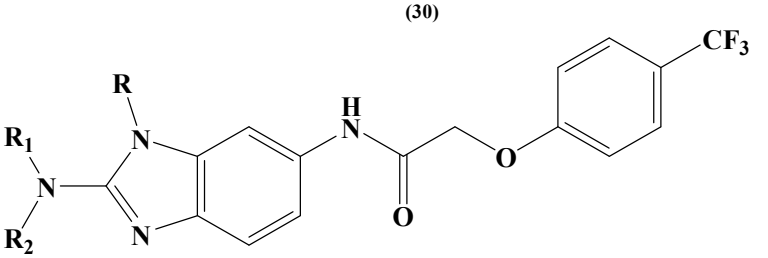


(29a)



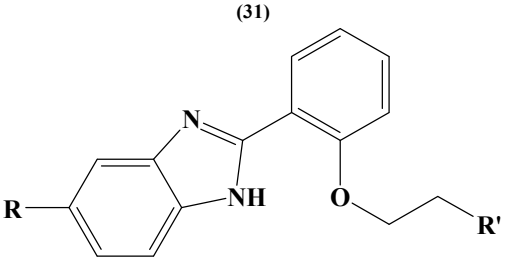
Compound	R_2
30a	H
30b	CH_2COOEt
30c	CH_2Ph
30d	CH_2-2Py

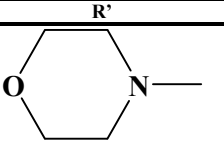
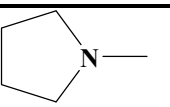
(30)



Compound	R_1R_2N	R
31a	Pyrrolidine	H
31b	Pyrrolidine	CH_3
31c	$(CH_3)_2N(CH_2)_2N(CH_3)$	CH_3

(31)



Compound	R	R'
32a	H	
32b	H	
32c	Cl	$-N(C_2H_5)_2$

(32)

CONCLUSION

Modifications on benzimidazole moiety displayed valuable biological activities. Substituted benzimidazole a major class of anti-infective agent with significant potential for development of therapeutic agent in medicinal chemistry

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