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Recent Updates on Anticancer Potential of Benzimidazole Derivatives: A Review

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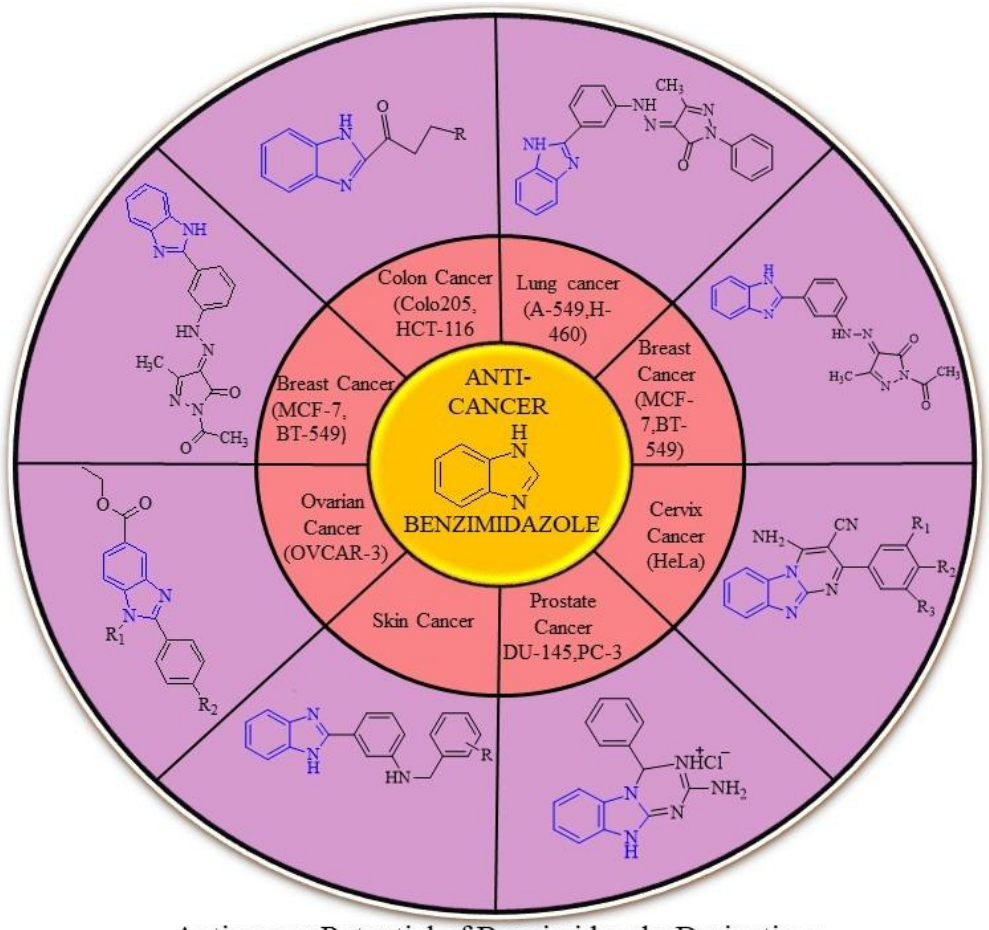
Abstract

Benzimidazole is a heterocyclic compound containing benz annulated bicyclic nucleus that consists of a benzo-fused imidazole ring with a heteroatom at 1st and 3rd positions. Benzimidazole has shown many significant advances in synthetic chemistry as it grabbed the attention of many researchers and scientists because of its numerous pharmacological application such as Antiviral, Anti-HIV, Antiprotozoal, Antihypertensive, Anti-inflammatory, Analgesics, Antioxidants, and Anticonvulsants. Therefore, this review is compromised on the benzimidazole derivatives and their therapeutic activity that will further play a vital role in the discovery of a novel and active drug molecule.

Graphical Abstract



Anticancer Potential of Benzimidazole Derivatives

Keywords: Cancer, Benzimidazole, Synthesis, Anticancer activity, Structure-activity relationship, Patents.

1. Introduction

Cancer is the second most commonly leading cause of mortality nearly 10 million deaths have been reported in 2020 worldwide, and the World Health Organization estimates that 12-14 million people will develop cancer each year **[1-3]**. Cancer is a deadly disease whose prevalence is steadily increasing around the world. It is defined by the uncontrolled growth and multiplication of abnormal cells **[4].** Death, continuous weight loss, paralysis, and bowel alteration are all possible symptoms of cancer **[5].** According to the report of the American cancer society, cancer is a global health problem associated with the lung, breast, and central nervous system. Around 15.5 million living Americans have a history of cancer as of January 2016 **[6, 7].** Chemotherapy and radiotherapy are the most often used treatment method but have suffered setbacks in the long-fought war against various tumors with multidrug resistance considered the most significant obstacle **[8].** Some anticancer medicines such as carboplatin, oxaliplatin, and cisplatin are

commonly used in clinical practices around the world for the treatment of a variety of tumors **[9]** butthese anticancer drugs show troublesome results such as harmfulness, bioavailability, and resistance**.** The complete eradication of cancer is medicine's greatest challenge **[10].** Because of these issues, cancer therapy requires a significant focus on research and development. It has been observed that nitrogen-containing heterocyclic compounds play an essential part in the treatment of cancer. Benzimidazole belongs to the same class of heterocyclic compounds which exhibited several therapeutic potentials **[11]** such as antifungal **[14-16],**antibacterial **[12,13],** antiviral **[17,18],** glucosidase inhibitor **[19,20],**anthelminthic **[23,24],** antihypertensive **[21,22]**, anti-inflammatory **[25-27],** antiprotozoal **[28-30],** anticonvulsant **[31-33]** etc., along with anticancer activity **[34-37].** It is a bicyclic hetero-aromatic ligand that consists of a fused benzene ring with a 5-membered imidazole ring. The key mechanisms behind the anticancer potential of benzimidazole via inhibition of cyclin-dependent kinase, tyrosine kinase,and destroying DNA **[38, 39, 41].** Benzimidazole derivatives have shown substantial anticancer action, particularly on the MCF-7 breast cancer cell line **[42].** It has also been shown to limit endothelial cell development and decrease *in vivo* and *in vitro* angiogenesis **[43].** In 1963, bendamustine is the first benzimidazole-based anticancer drug marketed successfully as the alkylating agent which is used in the management of indolent non- Hodgkin Lymphoma **[44].** Further, two others are marketed as anticancer drugs such as Nocodazole and dovitinib (TKI258). Nocodazole acts via interference with apical protein in cultured intestinal epithelial cells ($CaCo_2$), and Dovotinib acts as a tyrosinase kinase receptor inhibitor **[45, 46]** other than these anticancer agents, several marketed drugs are also available which contain benzimidazole rings such as Omeprazole and Rabeprazole as proton pump inhibitors**[47, 48]**, Albendazole, and Thiabendazole as antihelmintic**[49, 50]**, and candesartan as anti-hypertensive agent **[51]**. Keeping the view of the importance of benzimidazole in mind, this review highlights the synthetic approaches for anticancer benzimidazole derivatives with their structure-activity relationship studies. To provide a piece of vast knowledge to the medicinal chemist for the future development of anticancer agents.

2. Table 1. Marketed Anticancer drugs containing benzimidazole ring

S.No	Drug	Structure	Uses

01	Bendamustine		Indolent B-cell non-Hodgin's lymphoma (NHL) and Chronic lymphocytic leukemia.
02	Nocodazole		Cdk4- and Cdk2-cyclin complexes inhibitors.
03	Dovitinib		Prostate cancer cell line inhibitor via FGFR1 mediates the anticancer activity.

3. Synthetic approach for anticancer benzimidazole derivatives

Raka *et al*.,reported and evaluated substituted 2-benzyloxymethyl-benzimidazoles **(1 and 2)shown in figure 1,** for *in vitro* cytotoxicity. Among the reported derivatives 1-(4-hydroxybenzyl)-2-(4-hydroxyphenyl)-1H-benzimidazole **(1)**, 1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1H-benzimidazole **(1),**1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1H benzimidazole **(1)**and 2-Benzyloxymethyl-1H-benzimidazole **(2)** showed good anticancer activity **[52].**

Sathyanarayana*et al*., reported several novel benzimidazole derivatives **(3)shown in figure 1,** and these wereassayed for *in vitro* cytotoxic activity on cell lines i.e., HeLa and A549. Among the reported derivatives ethyl 2-(4-((4-chlorobenzyl) oxy)-3-methoxyphenyl)-1-pentyl-1H-benzo[d]imidazole-5-carboxylate **(3)** caused maximum cell death in both cell lines **[53].**

Sireesha*et al*., reported several benzimidazole-linked β-carbolines based derivatives **(4)shown in figure 1,** all new derivatives were evaluated for their anti-proliferative action on Colo-205, A549, MCF-7 and A2780 cell lines by MTT method. Among the reported derivatives 1-(2-(5,6-dimethoxy-1H-benzo[d]imidazol-2-yl) thiazol-4-yl) -9H-pyrido[3,4-

b] indole **(4)** and 1-(2-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl) thiazol-4-yl) -9H-pyrido[3,4-b] indole **(4)** were found to be most potent against all cell lines **[54].**

Ren *et al.,* reported pyrazole containing benzimidazole analogues**(5) shown in figure 1,** and their*in vitro* cytotoxicity was determined on different cell lines such as, Huh-7, MCF-7 and HCT116. Results revealed that compound 2-[3-(4-Bromo-phenyl)-1-phenyl-1H-pyrazol-4-yl]-1-methyl-1H-benzoimidazole (**5**)showed imperative anti-proliferative action on HCT-116 cell lines**[55].**

Chen *et al.,*reportedamide analogues of 2-ethoxy-3-[2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl]-3H-benzoimidazole-4-carboxylic acid **(6)shown in figure 1,**these derivatives were evaluated for their *in vivo* cytotoxicity against A549 cancer cell line by neddylation inhibition method.Analogue 1-((2'-(1H-tetrazol-5-yl)-[1,10-biphenyl]-4-yl)methyl)-N-(2,4-dichlorophenethyl) -2-ethoxy 1H-benzo[d]imidazole-7-carboxamide**(6)** exhibited higher neddylation enzyme inhibition compared with CDC, along with promising inhibitory potential of target and killing selective cancer cell **[56].**

Tang *et al.,*reported and evaluated 2- (1- (4,4-difluorocyclohexyl) piperidine-4-yl) -1H-benzo [d] imidazole-4- carboxamide derivatives **(7)shown in figure 1,** for their*in vitro* cytotoxicity against MDA-MB-231, PARP1, PARP2, MCF-7, MDA-MB-436, and CAPAN-1, using veliparib as standard. The synthesized compound exhibited a higher anticancer potential to tumor cell lines and have a significant effect on PARP1/2 inhibitory action **[57].**

Atmaca*et al.,* reported 2-[5,6-dichloro-2-ethyl-1H-benzimidazol-1-yl]-N-[4-bromophenylene] acetohydrazide **(8)shown in figure 1**. The cytotoxic activity of the compound was evaluated against HEK-293 and selected human cancer cell lines assessed by the MTT test. The compound showed prominent cytotoxic activity against DU-145, MCF-7, HEK-293 (human embryonic kidney), and H69AR cell lines **[58]**.

Haoran*et al.,* reported 2-(1H-benzoimidazol-2-ylmethylsulfanyl)-4-(4-methoxy-phenyl)-pyrimidine-5-carbonitriles **(9) shown in figure 1,** and Cytotoxic activity of reported compounds was tested by National Cancer Institute.Results showed that 2-{(1H-benzimidazol-2-yl) methylthio}-4-(4-methoxyphenyl)-6-morpholinopyrimidine-5-carbonitrile **(9)** exhibited the most potent activity against T-47D and HOP-92 cancer cell lines **[59].**

Li *et al.,* reported metal transition analogues based on benzimidazole-quinoline derivatives **(10)**that is [Cu(L)Br_2]2, [Cu(L)Cl_2]2 and Pt(L)Cl2 **(**where L = 2-((2-(pyridin-

2-yl)-1H-benzo[*d*] imidazolyl) methyl) quinolone)**shown in figure 1**. All the reported derivatives tested for cytotoxicity against SMMC7721. Compound [Cu(2-(2-(pyridin-2-yl)-1H-benzo[*d*]imidazolyl) methyl) quinolone) $Cl_2]_2$ **(10)** showed most potent cytotoxicity **[60]**.

Capan*et al.*,reported substituted benzimidazole analogues **(11)shown in figure 1,**the cytotoxic potential on Panc-1, MDA-MB-231, Ovcar3, and A549 cell lines via MTT test was assayed. Among the reported analogues 4-[1-(2-Chloro-benzoyl)-1H-benzoimidazol-2-yl]-4-aza-tricyclo [5,2,1,2,6] dec-8-ene-3,5-dione **(11)** demonstrated most potent cytotoxic potential against all cell lines **[61].**

Shinde *et al.*,reportedbenzimidazole nucleosides **(12)shown in figure 1,**all reported compounds assayed cytotoxicity on MDA-MB-231 cancer cell line using standard etoposide. Among the reported compounds 3′-azide nucleosides 4-azido-2-benzoimidazol-1-yl-5-hydroxymethyl-tetrahydro-furan-3-ol **(12),** 4-azido-5-hydroxymethyl-2-(2-methyl-benzoimidazol-1-yl)-tetrahydro-furan-3-ol **(12),** 4-azido-5-hydroxymethyl-2-(2-phenyl-benzoimidazol-1-yl)-tetrahydro-furan-3-ol **(12),** and 4-azido-5-hydroxymethyl-2-(2-anthryl-benzoimidazol-1-yl)-tetrahydrofuran-3-ol **(12)** have potent anticancer activity **[62].**

Kacar *et al.*, reported the compound Copper (II)-1-(4-(trifluoromethyl) benzyl)-1H-benzimidazole (**13)shown in figure 2.** Anti-cancer activity of copper (II) complex was evaluated via MTT assay. It was found that compound exhibited good anticancer activity **[63].**

Karadayi*et al.*, reported novel ethyl-sulfonyl indole-benzimidazole derivatives **(14)shown in figure 1,**and their anticancer activity was screened on MCF-7 and TP53 (breast cancer cells) against tivozanib, bazedoxifene, and vincristine, as standard. Among the reported derivatives 2-(5-bromo-1H-indol-3-yl)-5-(ethylsulfonyl)-1-(4-fluorobenzyl)-1H-benzo[d]imidazole **(14)** found to have most significant activity **[64].**

Yuan *et al.*,reported and evaluated6-amide-2-aryl-benzimidazole **(15)shown in figure 2,**for *in vitro* antitumor potential on various cell lines, MDA-MB-231, HUVEC, A549 and HepG2 and selective inhibition on VEGFR-2. Compound N-(2-(4-chlorophenyl)-1H-benzo[d]imidazol-5-yl)-2-(4-methoxyphenyl) acetamide **(15)** showed the most potent effect on HepG2 and HUVEC cell lines **[65]**.

Mostafa *et al.*, reported 2-phenyl benzimidazole-based analogues **(16,17)shown in figure 2,** these derivatives were tested for *in vitro* cytotoxicity against MCF-7 cell line. Compound 3-(1H-benzo[d]imidazol-2-yl)-N-(4-nitrobenzyl) aniline **(16)**, 3-(1H-

benzo[d]imidazol-2-yl)-N-(2,6-dichlorobenzyl) aniline **(16)** and 1-(3-(1H-benzo[d]imidazol-2-yl) phenyl)-3-(4-nitrophenyl) thiourea (**17)** showed most significant cytotoxic potential against MCF-7 cell lines **[66].**

Jian *et al.,* reported novel tertiary N-[2-(1H-benzoimidazol-2-yl)-ethyl]-4-methyl-N-(3,4,5-trimethoxy-phenyl)-benzenesulfonamide analogues **(18)shown in figure 2,**and anti-cancer activity of the reported analogues was screened against tumour cell lines such as PC-3, MGC-803 and MCF-7 via *in vitro* method and used 5-fluorouracil as standard. Analogue N-((3a,7a-dihydro-1H-benzo[d]imidazol-2-yl) methyl)-4-Methyl-N-(3,4,5-trimethoxyphenyl) benzene-sulfonamide **(18)** showed the prominent inhibition of proliferation of SGC-7901, and HGC-27 with good selectivity between normal and abnormal cells **[67]**.

Goud *et al.,*reportedvarious 1-benzyl-benzimidazole derivatives by using N^1-Benzyl-4-chlorobenzene-1,2-diamine **(19)shown in figure 2,**and the anticancer activity was tested against various cell lines MCF-7, A-549, HT-29, HCT-116, MDA-MB-231 and DU-145 with reference of 5-fluorouracil.Compound 4-(1-benzyl-5- chloro-1H-benzo[d]imidazol-2-yl)-N-(4-hydroxyphenyl) benzamide **(19)** exhibited most significant activity against MCF-7 **[68].**

Cevik*et al.,*reported 4-(5(6)-substituted-1H-benzimidazol-2-yl)-N-furan-2-yl/ thiophene methylene) benzo hydrazides**(20)shown in figure 2,** and *in vitro* anticancer activity of the compound was evaluated by MTT assay against cell lines: MCF-7, A549, and NIH/3T3. Among the reported derivatives4-(5(6)-chloro-1*H*-benzimidazol-2-yl)-*N*-(5-methyl thiophene-2-yl-methylene) benzo hydrazide**(20)** showed higher cytotoxicity against MCF-7 cell line with respect to reference cisplatin**[69].**

Yadav *et al.,* reported a series of benzimidazole derivatives **(21)shown in figure 2,** and *in vitro* anticancer activity of the derivatives were assessed against breast cancer cell line. Results showed that (1H-benzoimidazol-2-ylsulfanyl)-acetic acid (4-hydroxy-naphthalen-1-ylmethylene)-hydrazide **(21)** displayeda potent anticancer agent than 5-fluorouracil against breast cancer cell line **[70].**

Sinem*et al.,*reported some novel 4-(5-chloro-1H-benzimidazol-2-yl)-benzoic acid benzylidene hydrazides **(22)shown in figure 2,**and were evaluated for their antitumor potential on MCF-7 and A549 cell lines by using positive control cisplatin. The 4-(5-chloro-1H-benzimidazol-2-yl) benzoic acid 2,4-dichlorobenzylidene hydrazide **(22)** and

4-(5-Chloro-1H-benzimidazol-2-yl) benzoic acid 2-nitrobenzylidene hydrazide **(22)**compounds showed significant inhibitor potential against cancer cells **[71].**

Abdelgawad *et al*.,reported 2-acetyl-4-[(3-(1H-benzimidazol-2-yl)-phenyl]-hydrazono-5-methyl-2,4-dihydropyrazol-3-one**(23)** and 4-{[3-(1H-Benzoimidazol-2-yl)-5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one **(24)shown in figure 2.** The compound was evaluated against A549 and MCF-7 cell lines for cytotoxic activity and exhibits excellent activity**[72].**

Kartikeyan*et al.,* reported 2-(phenyl)-3H-benzo[d]imidazole-5-carboxylic acid derivatives **(25)shown in figure 2,** and screened them for their *in vitro* cytotoxicity against cancer cell lines i.e., MDA-MB468, MDA-MB231 and MCF7 by using cisplatin as a standard**.** The compound Methyl-2-(5-fluoro-2-hydroxyphenyl)-1Hbenzo[d]imidazole-5-carboxylate **(25)**showed the most promising activity against MCF-7 cell lines **[73].**

Wu *et al*., reported novel benzimidazole-2-substituted phenyl or pyridine propyl-ketenes**(26)shown in figure 3,** and *in vitro* anticancer activity was analysed for all the reported compounds against MCF-7, HepG2, and HCT116 cell lines. Among the reported analogues 1-(1H-benzo[d]imidazol-2-yl)-3-(pyridin-2-yl)-prop-2-enone **(26)**, 1-(1H-benzo[d]imidazol-2-yl)-3-(3-chlorophenyl)-prop-2-enone (**26)** and 1-(1H-benzo[d]imidazol-2-yl)-3-(3-methoxyphenyl)-prop-2-enone (**26)**exhibited most significant activity against irinotecan as positive control **[74].**

Sharma *et al*., reported several benzo[*d*]imidazol-2-yl) methylene) indolin-2-ones **(27)shown in figure 3,**and tested for their cytotoxicity on MCF-7,4T1, A549, HGC, MCF10A, PC-3, DU-145, BT-549 and MDA-MB-231 cell lines.Results revealed that 5-bromo-3-((1-isopropyl-benzo[d]imidazol-2-yl)methylene)indolin-2-one (**27)** found to be active on MDA-MB-231, whereas compounds 5-fluoro-3-((1-isopropyl-benzo[d]imidazol-2-yl)methylene)indolin-2-one (**27)**, 5-chloro-3-((1-isopropyl-benzo[d]imidazol-2-yl)methylene)indolin-2-one **(27)**, **a**nd 3-((1-isopropyl-benzo[d]imidazol-2-yl)methylene)-5-methylindolin-2-one (**27)** showed good activity against MCF-10A **[75]**.

Lonel*et al*., reported the 2-benzimidazol-1-yl-N-quinolin-8-yl-acetamide **(28)shown in figure 3,** and evaluated for tumour inhibitory potential against MDA-MB-468 and A-498 cell lines. The reported derivative exhibited the most potent activity against the tested cell lines **[76]**.

Shaaban *et al.*, reported2-substituted benzimidazoles **(29-34)shown in figure 3,** andcompounds tested for *in vitro* anti-proliferative activity on SF-268 NCI-H460 and MCF-7 by using doxorubicin as standard. Among the reported compounds2-(2-(1-(1H-benzo[d]imidazol-2-yl) -3-bromo-2-oxopropylidene)hydrazine)benzoic acid **(29),** 2-[3-(1H-benzo[d]imidazol-2-yl)-5-cyano-4-methyl-6-oxopyridazin-1(6H)-yl]benzoic acid **(30),** 2-(2-(1-amino-11-oxobenzo[4,5] imidazo[1,2-a]thieno[3,4-d]pyridin-4(11H)ylidene)hydrazinyl)benzoic acid **(31),** 2-(2-((1H-benzo[d]imidazol-2-yl)(2-(cyanomethyl)-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-5-yl)methylene)hydrazine)benzoic acid **(32)**, 2-{4-(1H-benzo[d]imidazol-2-yl)-7-[(4-fluoro-benzylidene)-amino]-1-oxo-1H-thieno[3,4-d] pyridazin-2-yl]benzoic acid **(33),** 2-[2-(2-amino-1-(1H- benzo[d]imidazol-2-yl)-2-hydrazonoethylidene) hydrazine]benzoic acid **(34)** showed excellent cytotoxicityagainst tested cell lines **[77]**.

Abdallah *et al*., design and reported a series of benzimidazoles **(35-38)shown in figure 3,**andevaluated them *in vitro*for anticancer activity against human cancer cell line NUGC, DLDI, HA22T, HEPG2, HONEI, HR, MCF, WI38 by using reference drug CHS828. Results showed that 2-[2-(1H-benzimidazol-2-yl)-1-methyl-ethylidene]-malononitrile**(35),** 1-(1H-benzimidazol-2-yl)-1-hydrazono-propan-2-one**(36)**, 1H-benzimidazol-2-yl-hydrazono-acetonitrile **(37)** and 3-imino-2-phenyl-hydrazono-3,4-dihydro-2H-benzo[4,5]-imidazo[1,2-c] pyrimidine-1-thione **(38)**possess most potent anticancer activity**[78].**

Reddy *et al*.,reported novel pyrazole containing benzimidazole derivatives **(39)shown in figure 3,**further the compounds were tested for their cytotoxicity against several tumour cell lines i.e., A-549, MCF-7, and HeLa. Derivatives 6-bromo-2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole **(39),**5-fluoro-2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole **(39)**, and 5-chloro-2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole **(39)** found to have considerable growth inhibitory capability against all cancer cell lines as compare to standard 5-fluorouracil **[79].**

Risley*et al.*, reportedpyrimido-[1,2-a] benzimidazole-based analogues**(40)shown in figure 3,** and these compounds were tested on two types of breast and pancreatic cancer cell lines.The compound 4-amino-2-(3,5-dibromophenyl) pyrimido[1,2-a] benzimidazole-3-carbonitrile **(40)** and 4-amino-2-(3,4,5-trimethoxyphenyl) pyrimido[1,2-a] benzimidazole-3-carbonitrile **(40)** exhibited prominent cytotoxicity **[80].**

Swiatkiewicz*et al*., reported the novel N-oxide of benzimidazole-4,7-diones**(41)shown in figure 3,** and the derivative was tested cytotoxicity on A549 cell lines using WST-1 test. According to the results 2-(4-chlorophenyl)-1H-benzimidazol-4,7-dione N-oxide **(41)** and 2-(2-nitrophenyl)-1H-benzimidazol-4,7-dione N-oxide **(41)** was found to be the more potent anti-proliferative agent **[81].**

Yoon *et al.,* reported novel 2-phenyl-3H-benzimidazole-5-carboxylic acid ethyl ester derivatives **(42)shown in figure 3,**and investigated them for their SIRT1 and SIRT2 inhibition and MDA-MB-468, HCT-116 and CCRF-CEM cancer cells lines. According to the results ethyl-2-(4-(dimethyl amino)-phenyl)-1-phenyl-1H-benzo [d]imidazole-5-carboxylate **(42)** have the inhibitory action for SIRT1 as well as for SIRT2 and significant activity against the tested cell lines **[82]**.

Noolvi*et al.,*reported 3-chloro-1-(1-methyl-1H-benzimidazol-2-yl)- (4'-substituted)-phenylazetidin-2-one derivatives **(43)shown in figure 3,**these derivatives were investigated for *in vitro* proliferative inhibition of MCF-7 cell lines using cyclophosphamide as standard. Results showed that 3-Chloro-4-(2,5-dimethoxyphenyl)-1-(1-methyl-1Hbenzimidazol-2-yl)azetidin-2-one **(43)** and 3-Chloro-4-(2-chlorophenyl)-1-(1-methyl-1H-benzimidazol-2-yl)azetidin-2-one **(43)** exhibited significant cytotoxic activity **[83].**

Paul *et al.,* reported coumarin–Benzimidazole hybrid 7-(substituted)-amino-3-(benzimidazol-2-yl)-2H-1-benzopyran-2-one derivatives **(44) shown in figure 4,***in vitro* cytotoxicity of compound tested against cancer cell lines by using standard drug 5-fluorouracil.Derivative 7-ethanolamino-3-(1H-benzimidazol-2-yl)-2H-1-benzopyran-2-one **(44)** showed pronounced activity against HCC-2998, HCT-116, CCRF-CEM, MCF-7, LOX IMVI cell lines. **[84]**.

Yurttas *et al.,*reported 1-(2-aryl-2-oxoethyl)-2-[(morpholine-4-yl)-thioxo-methyl] benzimidazoles**(45) shown in figure 4,** screened them for anti-proliferative activity using MTT and BrdU methods against C6, A549 and MCF-7 tumour cell lines. Compound 1-[2-(4-chlorophenyl)-2-oxoethyl]-2-[(morpholine-4-yl)-thioxomethyl] benzimidazole (**45**) exhibited substantial selectivity on the C6 cell and MCF-7 line **[85].**

Shekeil*et al.,* reportedand screened 4-amino-2-phenyl-benzo[4,5]imidazo [1,2-a]pyrimidine-3-carbonitrile derivatives **(46) shown in figure 4,** for *in vitro* anti-cancer activity on HeLa and PC3 cancer cell lines. The compound (N- (3,4-dimethoxyphenyl) methylene]- 1H- benzimidazol- 2- amine **(46),** and (N- (3,4,5- trimethoxy-

phenyl)methylene]- 1H- benzimidazol- 2- amine **(46)** showed restricted cytotoxicity except for compound (N- (4- methoxyphenyl) methylene] - 1H- benzimidazol - 2- amine **(46)** that exhibited moderate cytotoxic potential towards HeLa cell line **[86].**

Hranjec *et al.,* reported 2-amino-4-aryl-4,10-dihydro[1,3,5] triazino[1,2-a]benzimidazole hydrochloride salts **(47) shown in figure 4,** andanti-proliferative activity of these analogues was assayed against HCT116, MCf-7, H460 cell lines. Among the reported analogues 2-amino-4-(4'-diethylamino-biphenyl-4-yl)-4,10-dihydro-benzo [4,5] imidazole[1,2-a] [1,3,5] triazin-3-ium chloride (**47)** was found to be most active cytotoxic at the highest concentration [**87**].

Refaat *et al.,* reported a novel series of substituted 1-oxo-1,5-dihydro-benzo[4,5] imidazo[1,2-a]pyridine-4-carbonitrile **(48) shown in figure 4,**and these derivatives were tested for *in vitro* antitumor action against MCF-7 cell line using standard drug doxorubicin. Among the reported derivatives 8-chloro-3-methyl-1-oxo-1,5-dihydro-benzo [4,5] imidazole[1,2-a] pyridine-4-carbonitrile **(48)**, 8-chloro-1-oxo-3-phenyl-1,5-dihydro-benzo [4,5] imidazo[1,2-a]pyridine-4-carbonitrile **(48)**, and 4-cyano-1-oxo-3-phenyl-1,5-dihydro-benzo[4,5]imidazo[1,2-a]pyridine-8-carboxylic acid **(48)** exhibited most significant anticancer activity against MCF7 **[88].**

Rashid *et al.,* reported1-(1H-benzo[d]imidazol-2-yl)-3-(1,3,4-oxadiazol-5-substituted) analogues **(49) shown in figure 4,**these ligands tested for *in vitro* proliferation inhibition for the management of cancer. Thecompound 1-(1H-benzimidazol-2-yl)-3-[5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl] propan-1-onehave **(49)** showed significant proliferation inhibition activity **[89].**

Demirayak*et al*., reported 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles**(50) shown in figure 4,** and these analogues were investigated for *in vivo* cytotoxic activity in comparison with standard drugs melphalan and cisplatin. Among the reported analogues 2-(2-benzoyl-benzoimidazol-1-yl)-1-phenyl-ethanone (**50)**, 2-(2-benzoyl-benzoimidazol-1-yl)-1-p-tolyl-ethanone (**50)**, and 1-(2-(4-methoxyphenyl)-2-oxoethyl)-2-benzoylbenzimidazole **(50)** showed the most promising anticancer activity **[90].**

Li *et al.,* reported the 2-aryl benzimidazole derivatives **(51) shown in figure 4,** and these were tested for their cytotoxicity against HepG-2 and kinases cell lines. According to the results 2-chloro-N-(2-p-tolyl-1H-benzo[d]imidazol-5-yl) acetamide (**51)** and2-chloro-N-(2-(1-methyl-1H-pyrrol-2-yl)-1H-benzo[d]imidazol-5-yl) acetamide showed great EGFR inhibitory in kinase assay and limited inhibitory activities against PDGFR, VEGFR-2,

and compound 2-chloro-N-(2-(1-methyl-1H-pyrrol-2-yl)-1H-benzo[d]imidazol-5-yl) acetamide (**51)** exhibited high cytotoxicity against HepG-2 cells **[91].**

Aziz *et al.,* reported ethyl 6-bromo-3-methyl-1,3-thiazolo[3,2-a] benzimidazole-2-hydrazide and carboxylate derivatives **(52) shown in figure 4,***in vivo* anti-proliferative activity were tested for all the reported derivatives on Hep-G2 and HCT-11.Compounds amino-1-[(6-bromo-3-methyl-1,3-thiazolo[3,2-a] benzimidazol-2-yl) carbonyl]-pyrazole-4-carbonitrile **(52)** and ethyl 5-amino-1- [(6-bromo-3-methyl [1,3] thiazolo[3,2-a] benzimidazol-2-yl) carbonyl]-pyrazole-4-carboxylate (**52)** showed most potent activity as compared to paclitaxel as reference drug **[92].**

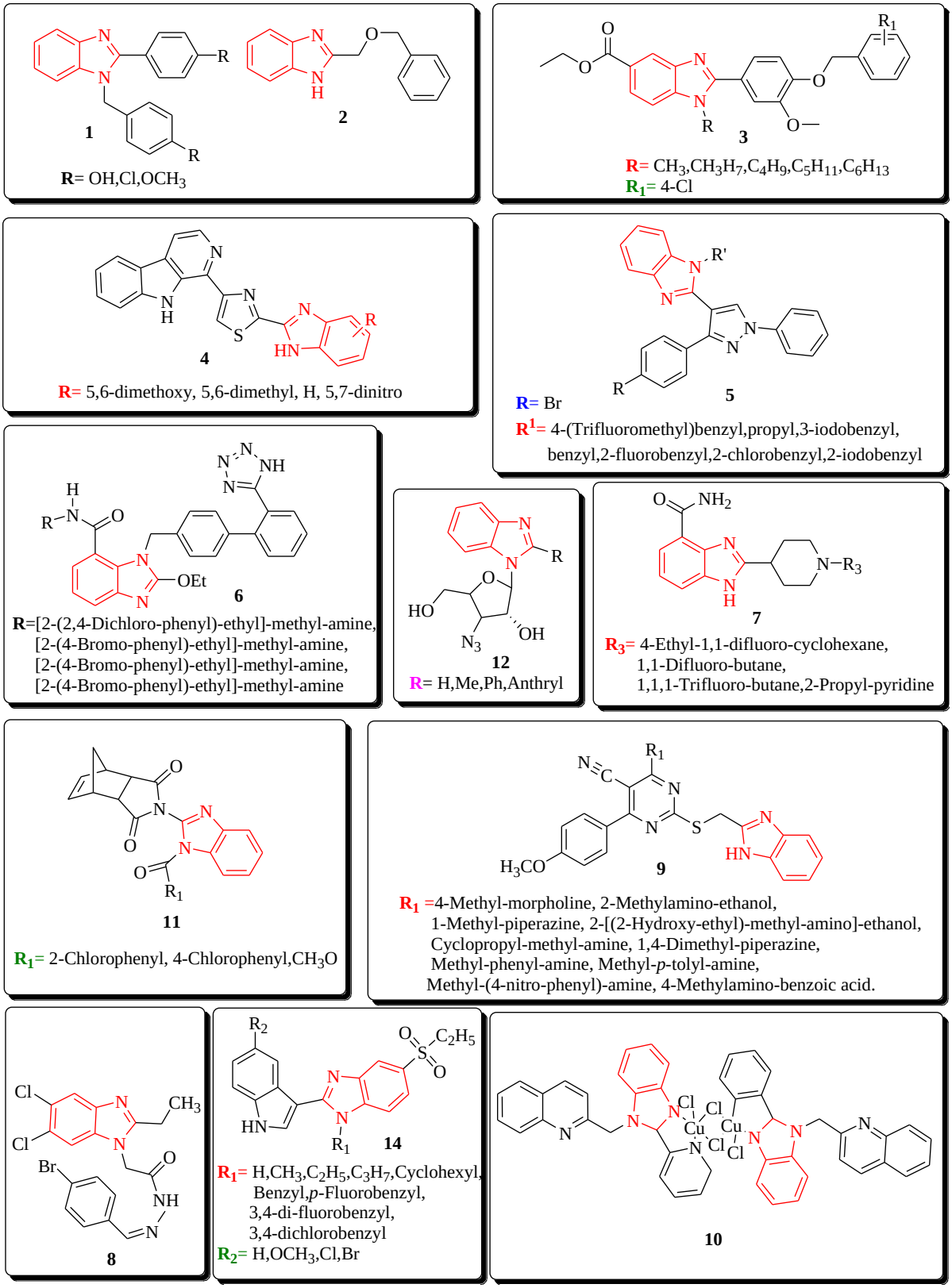


Figure 1: Anticancer potential of benzimidazole derivatives

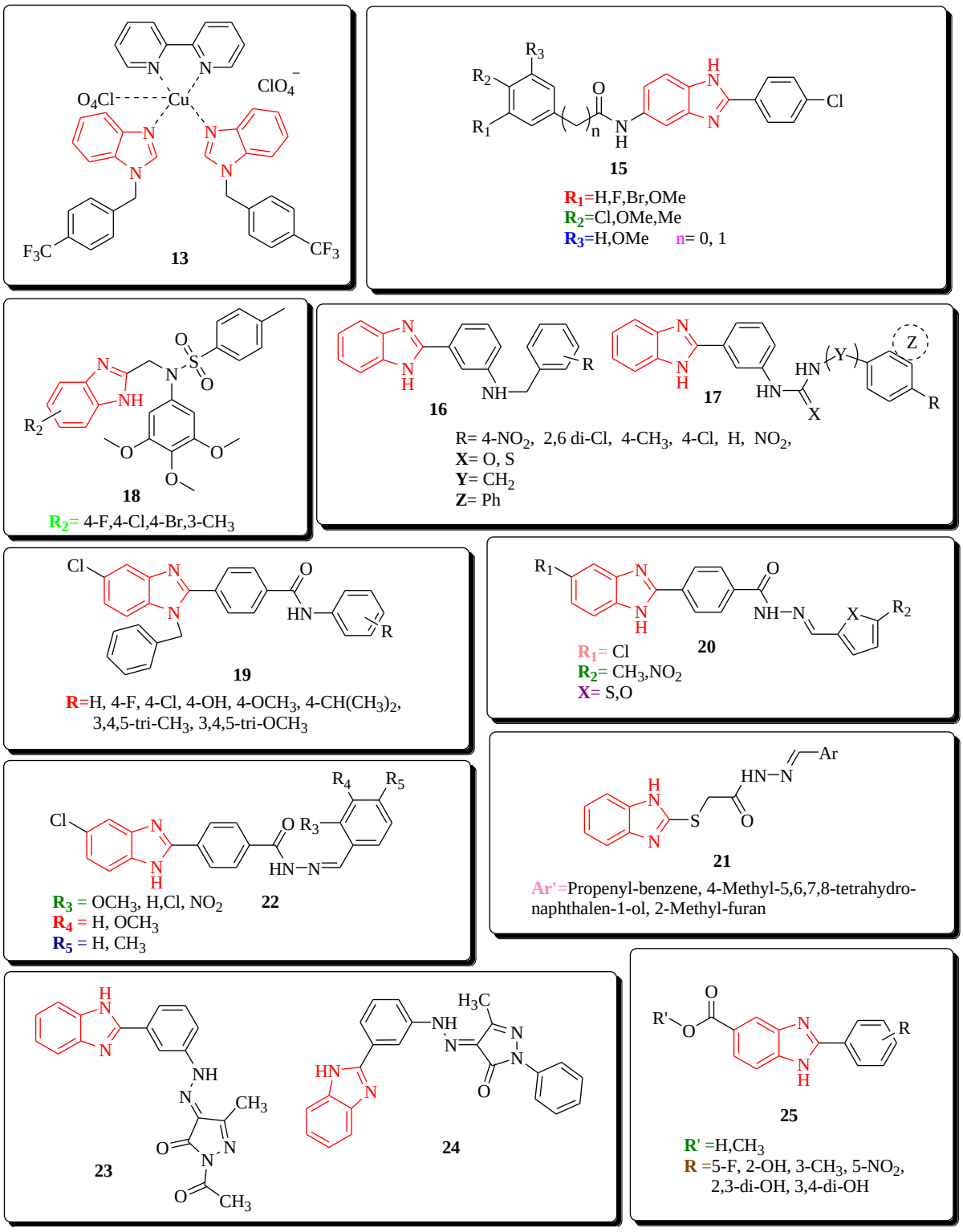


Figure 2: Anticancer potential of benzimidazole derivatives

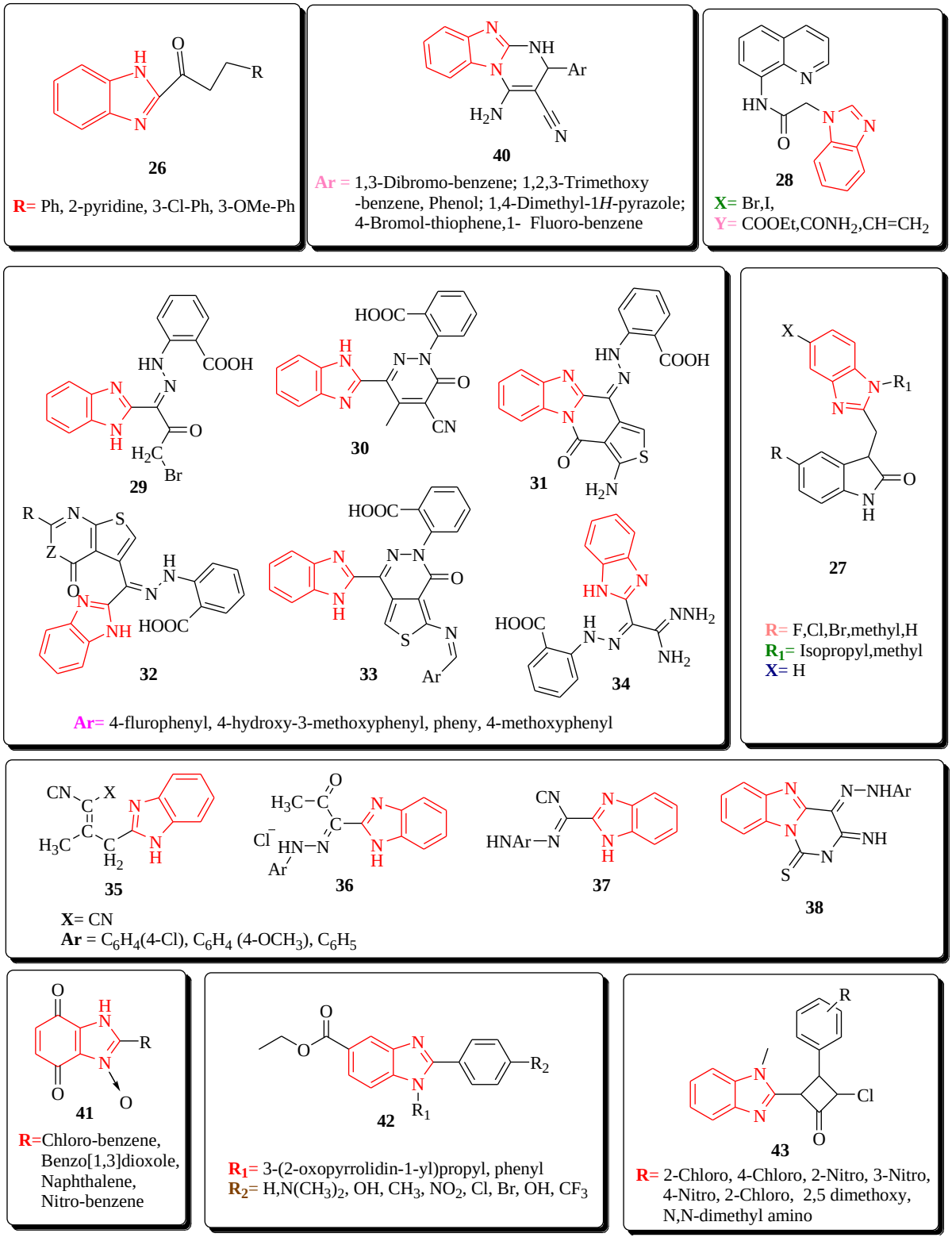


Figure 3: Anticancer potential of benzimidazole derivatives

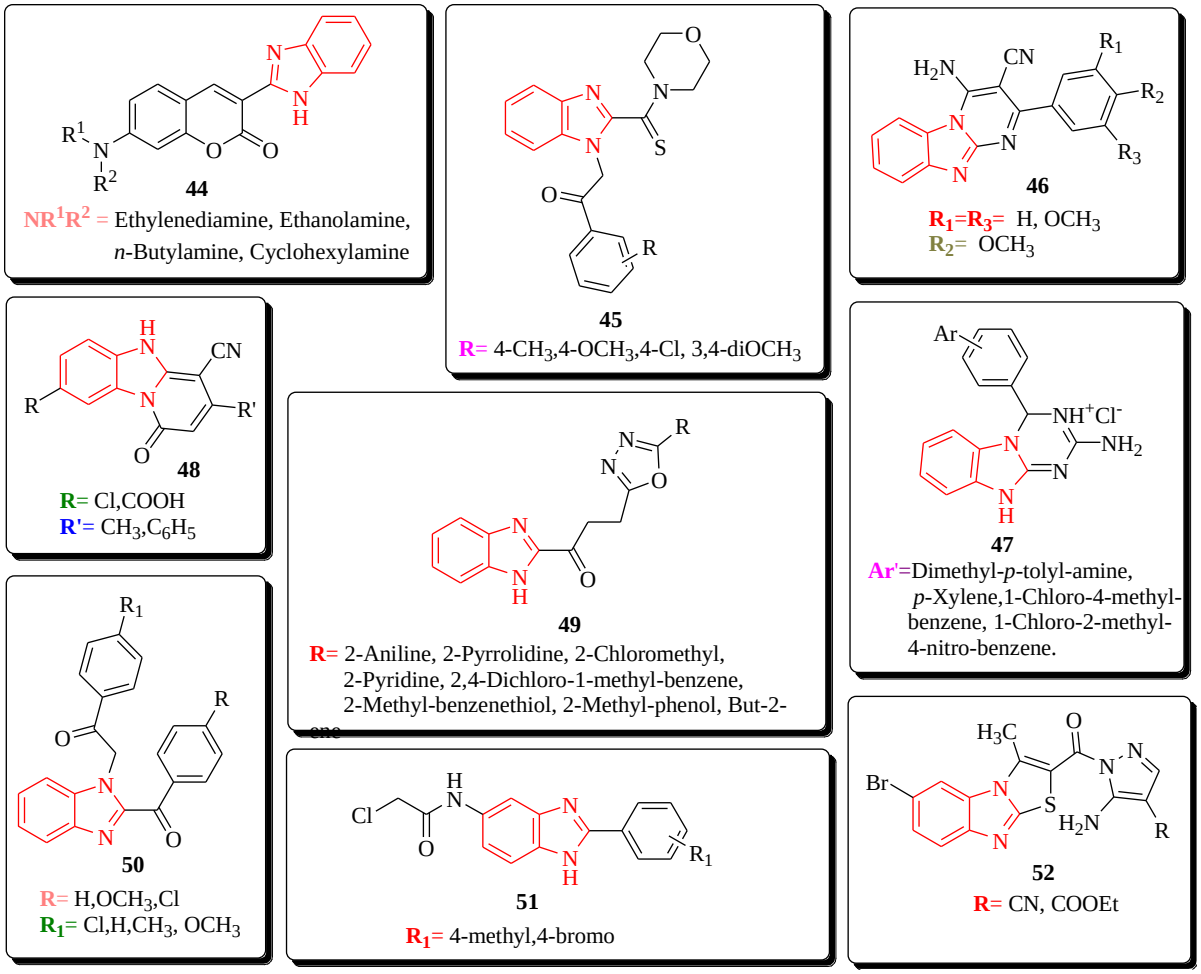


Figure 4: Anticancer potential of benzimidazole derivatives

Conclusion

This study summarizes the different benzimidazole derivatives and their pharmacological potential, and further based on this study and on the published data we conclude that benzimidazole scaffolds is versatile molecule and have potent anticancer activity. However, the activity of benzimidazole derivatives can be enhanced by the addition of different moieties. Thus, the attachment of different moieties and their effect should be considered in future studies so that benzimidazole can be used effectively.

Conflict of Interest

The authors confirm that this article's content has no conflict of interest.

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