WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 5, 632-647. Review Article ISSN 2277– 7105

AN UPDATE AND LITERATURE REVIEW: BENZIMIDAZOLES AS ANTI CANCER AGENTS

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Article Received on
29 February. 2020,
Revised on 19 March 2020,
Accepted on 09 April 2020
DOI: 10.20959/wjpr20205-17329

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ABSTRCTCT

Cancer is the most important dreadful diseases in the world. It is characterized by uncontrolled proliferation of cells. The women are more prone to cause the cancer compare to men. World wise the most of the peoples are suffering by breast, lung, and colorectal cancer. There are some factors responsible to cause the cancer they are genetical factors, behavioral risk factors, physicalrisk factors. Global data announced that there may be a chance to a rise 21.4 million cases per year with 13.2 million deaths by 2030. Benzimidazole and its are important heterocyclic compounds having wide variety of pharmacological actions like anticancer, acetylchlinesterase, antimicrobial, anti inflammatory, analgesic, antileishmanial activities hence its attracts the researcher to develop many active compounds in medicinal chemistry. The present review reveals that many substituted benzimidazoles as anti cancer agents against many type of cancer celllines.

KEYWORDS: Antiancer, Benzimidazoles, Acetylchlinesterase, Pharmacological, Antileishmanial.

INTRODUCTION

Cancer is one of the most important dreadful diseases in the world. It is characterized by uncontrolled proliferation of cells. The most effective cancers are breast, lung, and colorectal cancer. World wise one women in six womens, one men in eight mens are suffering from cancer during lifetime. Gobal data estimated there is chance to a rise 21.4 million cases per year with 13.2 million death by 2030. The main factors responcible for the development of

cancers are Behavioral risk factors usage tobacco, smoking; Physical risk factors exposure toionizing radiations; Genetic factors areresponcible to cause the cancer.[1-3]

Chemistry of Benzimidazole Benzimidazole is heterocyclic compound in which benzene ring fused with imidazole ring. It shows important role in medicine its shows many pharmacological activities like anticancer,[4] acetylchlinesterase,[5] anti-microbial,[6] anti-inflammatory,[7] analgesic,[8] antiviral,[9] anti-protozoal,[10] anti-malarial,[11] anti-leishmanial.[12] Hence it is attracting many researchers to develop new benzimidazole derivatives with significant pharmacological activities.

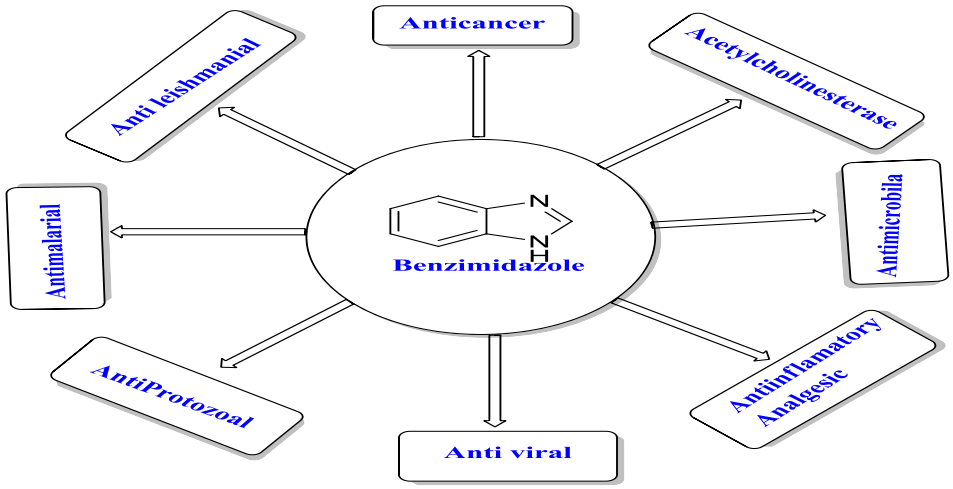

Fig. 1: Representation of pharmacological activities of Benzimidazoles.

Benzimidazole Derivatives as Anti Cancer Agents

Sumit et al., 2019, synthesized the 4-2-(1*H*-Benzo[d]imidazol-2-ylthio)acetamido)-*N*-substistuted phenyl benzamides, evaluated the anti cancer activity. Among all, the compound **N9, N18** (**1, 2, Fig. 2**) showed best anti-cancer activity with IC_{50} value of 5.85µM, 4.53µM against the human colorectal cancer cell line.[4]

Brech et al., 2018, synthesized the Gold (III) Pyridine-Benzimidazole Complexes, evaluated the anti cancer activity. Among all, the compound **C9, C10, C11** (**3, 4, 5, Fig. 2**) with EC_{50} value of 5 ± 2µM, 12 ± 2 µM, 13±2 µM against the melanoma (A375) cells.[13]

Sumit et al., 2018, synthesized the 3-(2-(1*H*-benzo[*d*]imidazol-2-ylthio) acetamido)-*N*-(substituted phenyl)benzamide derivatives , evaluated the anti cancer activity. Among all, the compound **W17** (**6, Fig. 2**) showed best anticancer activity with IC_{50} value of 4.12µM against the human colorectal carcinoma cell line (HCT116).[14]

Lamia et al., 2018, synthesized the New Benzimidazole Derivatives, evaluated the anti cancer activity. Among all, the compound **viib** (**7, Fig. 2**) showed best anti-cancer activity with IC_{50} value of 80µg/ml,. 35µg/ml, 72µg/ml against the against human breast adenocarcinoma (MCF-7), human lung carcinoma(A549), human epitheloid cervix carcinoma (HELA).[15]

Gohary et al., 2017, synthesized the new benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **3f (8, Fig. 2)** with IC_{50} value of 0.032µM, 0.031µM, 0.037µM, compound **3p (9, Fig. 2)** with IC_{50} value of 0.022 µM, 0.014µM, 0.015µM showed best anticancer activity against the against liver cancer (HepG2), colon cancer (HCT-116), breast cancer (MCF-7) cell.[16]

Wang et al., 2017, synthesized the chrysin benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **18** (**10, Fig. 2**) showed best anti-cancer activity with IC_{50} values of 25.72 ± 3.95µM against MFC cells.[17]

Snehlata et al., 2017, synthesized the 2-(1*H*-benzo[*d*]imidazol-2-ylthio) acetami do)-*N*-(substituted-4-oxothiazolidin-3-yl) acetamides, evaluated the anti cancer activity. Among all, the compound **5l, 5k** (**11, 12, Fig. 2**) showed best anti-cancer activity with IC_{50} value of 0.00005µM/ml, 0.00012 µM/ml against HCT116 cell line.[18]

Valentina al., 2016, synthesized the new benzimidazolehydrazones, evaluated the anti cancer activity. Among all, the compound **10** (**13, Fig. 2**) showed best anti-cancer activity with IC_{50} values of 1.6 ± 0.9µM, 0.98± 0.02µM, 4.0 ±0.4µM, 6.3 ±3.2µM against murine leukemia (L1210), human T-lymphoblastic leukemia (CEM), human cervixcarcinoma (HeLa) human pancreas carcinoma (Mia Paca-2) cells.[19]

Mohammad et al., 2015, synthesized the 2-substituted benzimidazoles, evaluated the anti cancer activity. Among all, the compound **1** (**14, Fig. 2**) showed best anti-cancer activity 72-88% and 82-95% growth of inhibition and compound **2** (**15, Fig. 2** Fig.) showed 68- 93% and 71-96% growth of inhibition against breast (MCF-7), leukemia (THP-1), prostrate (PC-3) and lungs (A-549) cancer cell lines.[20]

Chunmei et al., 2015, synthesized the benzimidazole acridine derivatives, evaluated the anti cancer activity. Among all, the compound **8l** (**16, Fig. 2**) showed best anti-cancer activity with IC_{50} value of 2.68µM against K562 and HepG-2 cells.[21]

Ahmed et al., 2015, synthesized the 2-aryl-1,2,4-oxadiazolo-benzimidazoles, evaluated the anti cancer activity. Among all, the compound **5x** (**17, Fig. 2**) showed best anti-cancer activity with IC_{50} value of 1.8µM against most of the tumor cell lines.[22]

Rashid et al., 2015, synthesized the benzimidazoles containing substituted oxadiazole, thiadiazole and triazolothiadiazines, evaluated the anti cancer activity. Among all, the compound **4f** (**18, Fig.3**) showed best anticancer activity with MG-MID value GI_{50} (2.09), $\log_{10} GI_{50}$(6.04), $\log_{10}$TGI(4.38) and $\log_{10}LC_{50}$ (4.02).[23]

Srinivasa reddy et al., 2015, 1,3-diphenyl-1*H*-pyrazole derivatives containing benzimidazole, evaluated the anti cancer activity. Among all, the compound **9, 17, 28** (**19, 20, 21, Fig. 3**) showed best anti-cancer activity with IC_{50} values of (Compound 9)1.81±0.4µM, 0.83±0.3µM, 1.76±0.7µM, (Compound 17) 1.13±0.2 µM, 0.95±0.3µM, 1.57±0.3µM (Compound 28) 1.34±0.2µM, 1.17±0.2µM, 1.63±0.3µM against lung (A549), breast (MCF-7), cervical (HeLa) human tumor cell lines,[24]

Alexey et al., 2015, synthesized the ferrocenylalkyl mercaptoazoles, evaluated the anti cancer activity. Among all, the compound **3b** (**22, Fig. 3**) showed best anti-cancer activity with 87% tumor growth inhibition on carcinoma755.[25]

Sharma et al., 2015, synthesized the novel hybrids of purine-benzimidazole, evaluated the anti cancer activity. Among all, the Compound **6** (**23, Fig. 3**) showed best anti-cancer activity with GI_{50} values of 3.16 µM, 2.00 µM and 1.36 µM against colon cancer, CNS cancer and ovarian cancer.[26]

Wang et al., 2015, synthesized the novel 1-benzene-acyl-2-(1-methylindol-3-yl)-benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **11f** (**24, Fig.3**) showed best anti-cancer activity with GI_{50} values of 2.4± 0.42µM, 3.8 ±0.5µM, 5.1 ± 0.42µM against human lung adenocarcinoma cells(A549), human liver hapatocellular carcinoma (HepG2), human breast carcinoma cells (MCF-7).[27]

Yeong et al., 2014, synthesized the novel benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **5j, 5l** (**25, 26, Fig. 3**) showed best anti-cancer activity with CI_{50} value of 49.63µM, 46.33µM and 62.43µM, 42.30 µM against breast cancer cells (MCF-7), triple-negative breast cancer cells (MDA-MB-468).[28]

Wenna et al., 2014, synthesized the new benzimidazole-2-urea derivates, evaluated the anti cancer activity. Among all, the compound **6o** (**27, Fig. 3**) showed best anti-cancer activity with 0.006 ± 0.001µM, 0.026 ± 0.003µM, 1.774 ± 0.374µM, 0.452 ± 0.129µM, 0.052 ± 0.025µM against the K562, A431, HepG2, Hela, MDA-MB-435S cancer cells.[29]

Salahuddin et al., 2014, synthesized the 2-(naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1-[5-(substitutedphenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1Hbenzimidazole derivatives, evaluated the anti cancer activity. Among all,the compound **7c** (**28, Fig. 3**) showed best anti-cancer activity with growth percentage of 36.23 and 47.56 against Breast cancer (MDA-MB-468) and Melanoma (SK-MEL-28).[30]

Kamaldeep et al., 2014, synthesized the primary amine substituted quinazoline linked benzimidazole, evaluated the anti cancer activity. Among all, the compound **11** (**29, Fig. 3**) showed best anti-cancer activity with GI_{50} values of 0.34µM, 0.31 µM aganst colon cancer cell lines and prostate cancer cell lines.[31]

Sridhar et al., 2014, synthesized the novel thioureas, evaluated the anti cancer activity. Among all, the compound **5h** (**30, Fig. 3**) showed best anti-cancer activity with IC_{50} values of 5.2 ± 0.24µM, 9.8 ± 0.26µM, 12.3 ± 0.44µM, 11.1 ± 0.52µM against A549, MCF7, DU145, HeLa human cancer cell lines.[32]

Guan et al., 2014, synthesized the benzimidazole carbamates bearing indole moieties, evaluated the anti cancer activity. Among all, the compound **10a** (**31, Fig. 3**) showed best anti-cancer activity with IC_{50} values of 0.098 ± 0.002µM, 0.15 ± 0.05 µM, 0.13 ± 0.07µM against SGC-7901, A-549, HT-1080 human cancer cell lines.[33]

Sharma et al., 2013, synthesized the benzimidazole quinazoline hybrids, evaluated the anti cancer activity. Among all, the compound **9** (**32, Fig. 3**) showed best anti-cancer activity with percentage growth of inhibition of 98, 50, 45, 94.2, 76.6, 80.3, 94.3, 97.5 against Leukemia (K-562, MOLT-4, RPMI-8226, SR), Colon (HCC-2998, HCC-116, HT29), Melanoma (LOX IMVI) human cancer cell lines.[34]

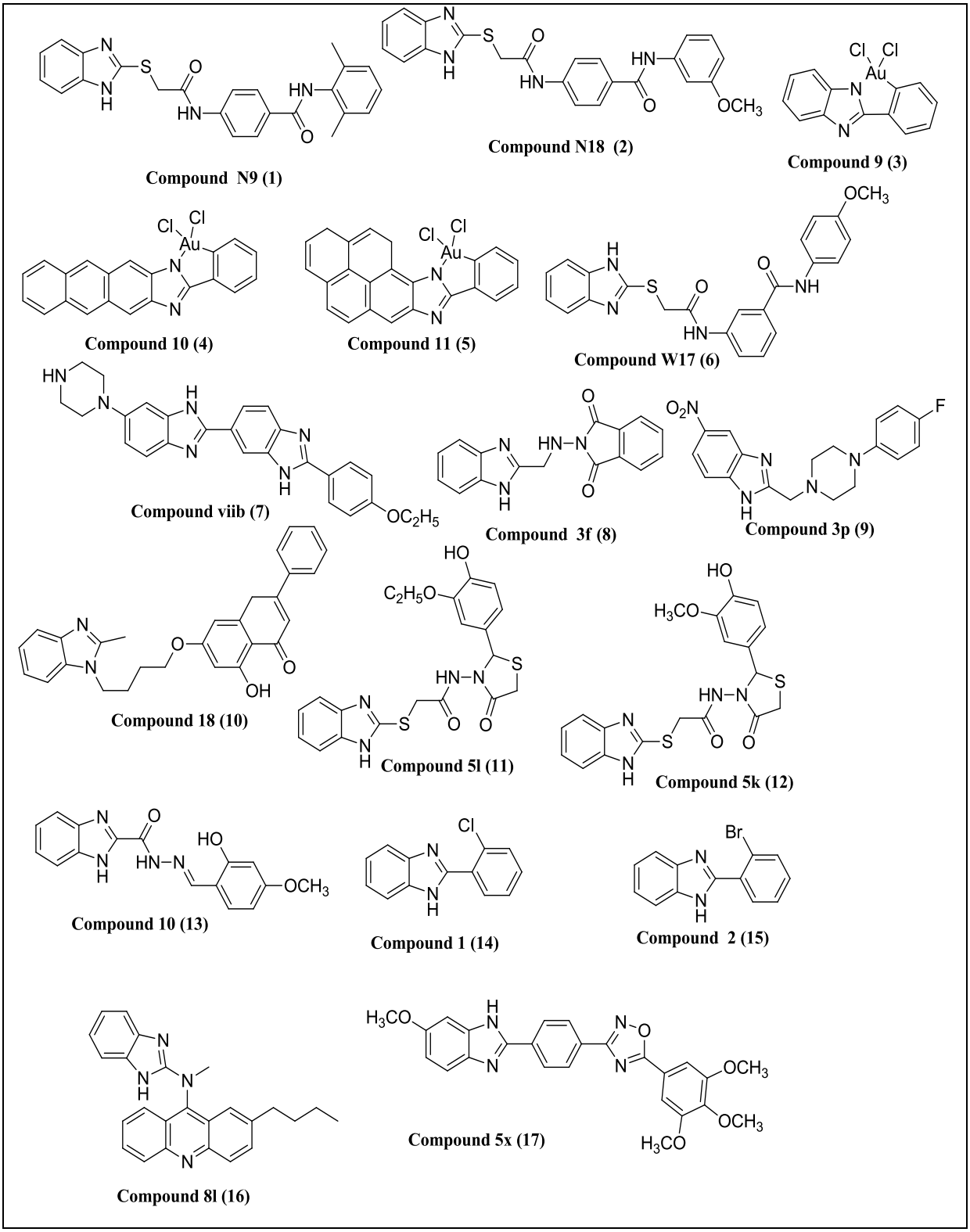

Fig. 2: Structures of effective anticancer compounds.

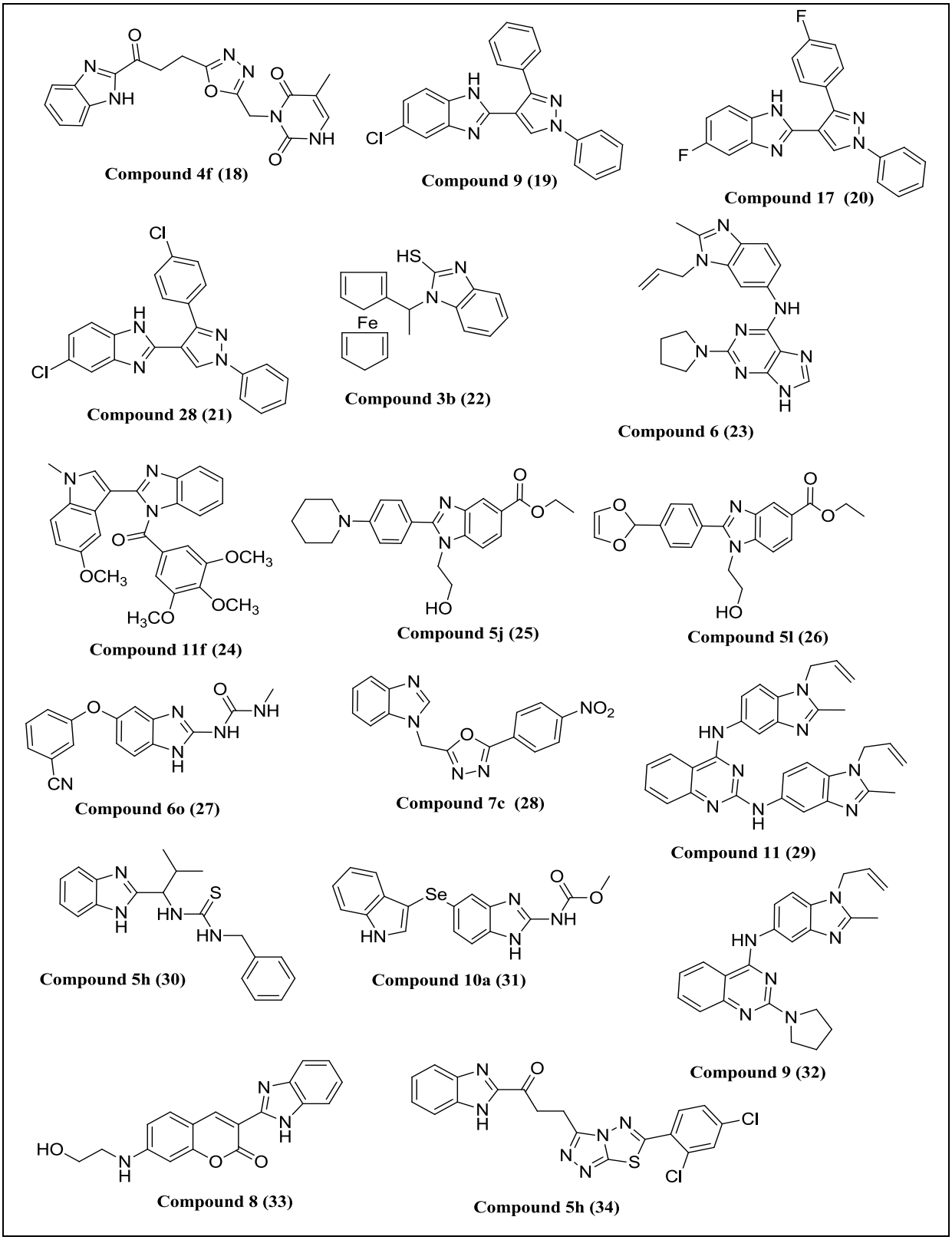

Fig. 3: Structures of effective anticancer compounds.

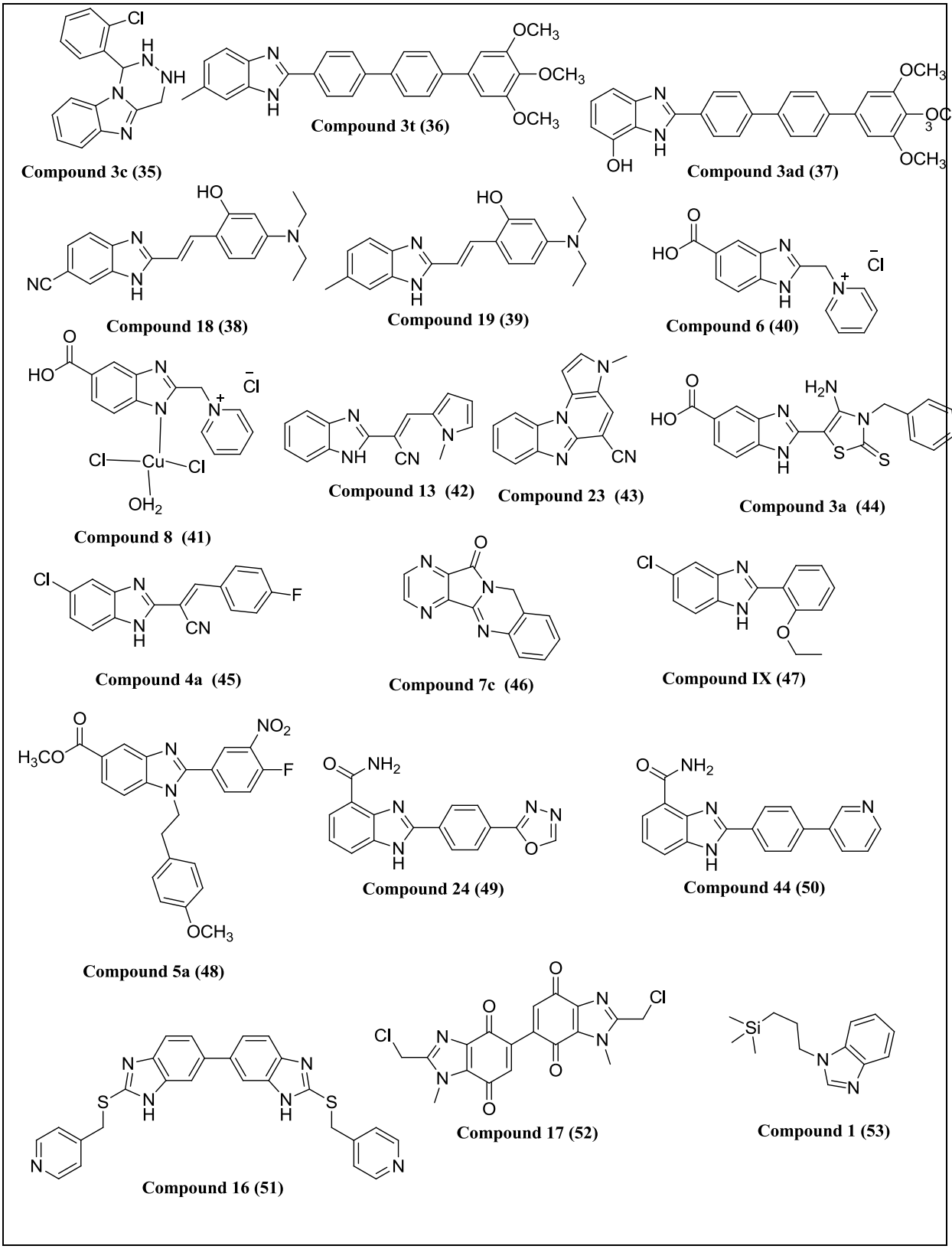

Fig. 4: Structures of effective anticancer compounds.

Kamaldeep et al., 2013, synthesized the coumarin–benzimidazole hybrids, evaluated the anti cancer activity. Among all, the compound **8** (**33, Fig. 3**) showed best anti-cancer activity with

percentage growth of inhibition of 80.51, 72.52, 57.34, 57.34, 46.65, 70.68, 58.91, 48.37, 33.10, 62.25, 72.67, 54.29, 56.69 against leukemia (HL-60 (TB), CCRF-CEM, K-562, MOLT-4, RPMI-8226), breast tumor (T-47D, MDA-MB231/ATCC, MDA-MB-468, BT-549), colon tumor (HCT-116, HCT-15), melanoma cancer (LOX IMVI), prostate cancer (PC-3).[35]

Asif et al., 2013, synthesized the Benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines, evaluated the anti cancer activity. Among all, the compound **5h** (**34, Fig. 3**) showed best anti-cancer activity with growth inhibition with GI_{50} values ranging from 0.20 to 2.58mM against eukemia cell lines.[36]

Nassan et al., 2012, synthesized the novel 1,2,3,4-tetrahydro[1,2,4]triazino[4,5-a] benzimidazoles, evaluated the anti cancer activity. Among all, the compound **3c** (**35, Fig. 4**) showed best anti-cancer activity with IC_{50} value of 0.0390µM against human breast adenocarcinoma cell line (MCF7).[37]

Ahmed et al., 2012, synthesized the terphenyl benzimidazoles, e valuated the anti cancer activity. Among all, the compound **3t , 3ad** (**36, 37, Fig. 4**) showed best anti-cancer activity with IC_{50} values of (Compound 3t) 0.1µM, 0.17µM, 0.19 µM, 0.1 µM, 0.19µM, 0.17µM, 0.19 µM, 2.11µM, 0.19µM, 0.17µM, 0.17 µM (Compound 3ad) 0.1µM, 0.17µM, 2.37 µM, 0.17µM, 0.19µM, 0.19µM, 0.17 µM, 2.11µM, 0.19µM, 0.18µM, 0.17 µM against lung (A549, Gurav, Hop62), breast (MCF-7, ZR-75-1), ovarian (A2780), oral (DWD, KB), colon (Colo205), prostate (PC3), cervix (SiHa) cancer cell lines.[38]

Marijana et al., 2012, synthesized the novel benzimidazoles Schiff bases, evaluated the anti cancer activity. Among all, the compound **18, 19** (**38, 39, Fig. 4**) showed best anti-cancer activity with IC_{50} values of 4.73µM, 9.23µM, 49.15µM, 27.92 µM, 0.96µM, 3.24 µM, 15.27µM, 52.04 µM, 22.24µM, 1.67µM against HeLa, MCF-7, SW620, MiaPaCa-2, WI38 cell lines.[39]

Shadia et al., 2010, synthesized the novel benzimidazole-5-carboxylic acid derivatives, evaluated the anti cancer activity. Among all, the compound **6, 8** (**40, 41, Fig. 4**) showed best anti-cancer activity with GI_{50} values of 0.095µM, 0.091µM Compound 6 against gastric cancer cells, Compound 8 against lung cancer cell lines.[40]

Marijana et al., **2010**, synthesized the benzimidazole derivatives related to 2,3-acrylonitriles, benzimidazo[1,2-a] quinolines and fluorenes, evaluated the anti cancer activity. Among all, the compound **13, 23** (**42, 43, Fig. 4**) showed best anti-cancer activity with IC_{50} values of (Compound 13) 0.8±0.4µM, 4±2µM, 30 ±5µM, 13 ±3µM, 26±13µM (Compound 23) 0.7± 0.2 µM, 4±2µM, 25±4µM, 11±1µM, 22±2µM against HeLa, MiaPaCa-2, SW 620, MCF-7, H 460 cancer cells.[41]

Hanan et al., **2010**, synthesized the novel 2-substituted benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **3a, 4a** (**44, 45, Fig. 4**) showed best anti-cancer activity with IC_{50} values of (Compound 3a) 0.55 ±0.05µM, 3.51 ±0.50µM, 4.23± 0.04µM, (Compound 4a) 0.55± 0.03µM, 3.41 ± 0.17µM, 8.40 ±0.10µM against human hepatocellular carcinoma (HEPG2), human breast adenocarcinoma (MCF7), human colon carcinoma cell lines(HCT 116).[42]

Sham et al., 2010, synthesized the tetracyclic benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **7c** (**46, Fig. 4**) showed best anti-cancer activity with percentage growth of inhibition 48, 23, 46, 55, 56, 66 against ovary (IGR-OV-1), breast (MCF-7), CNS(SF-295) human cancer cell lines.[43]

Gunes et al., 2009, synthesized the benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **IX** (**47, Fig. 4**) showed best anti-cancer activity with IC_{50} values of 6.16 µM, 6.04 µM, 6.94 µM against skin epidermoid carcinoma(A431), cervix adenocarcinoma(HeLa), breast adenocarcinoma(MCF7) cells.[44]

Thimme gowda et al., 2009, synthesized the novel 1-(4-methoxyphenethyl)-1*H*benzimidazole-5-carboxylic acid derivatives, evaluated the anti cancer activity. Among all, the compound**5a** (**48, Fig. 4**) showed best anti-cancer activity with IC_{50} values of 3 µM, 4 µM against leukemic (K562, CEM) cell lines.[45]

Yunsong et al., 2009, synthesized the new generation of orally efficacious benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **24, 44** (**49, 50, Fig. 4**) showed best anti-cancer activity with EC_{50} values of 3.7 nM, 7.8 nM using B16F10 murine melanoma model.[46]

Yang et al., 2009, synthesized the new novel symmetrical bis-benzimidazoles derivatives, evaluated the anti cancer activity. Among all, the compound **16** (**51, Fig. 4**) showed best anti-

cancer activity with IC_{50} values of 2.81µM, 32.4µM, 11.0µM against SKOV-3, HeLa, and BGC-823 cell lines.[47]

Armand et al., 2009, synthesized the some benzimidazole-4,7-diones, evaluated the anti cancer activity. Among all, the compound **17**(**52, Fig. 4**) showed best anti-cancer activity with IC_{50} values of 3 ± 1µM, 3 ± 1 µM, 3 ± 1µM against breast (T47D), lung (A549) and colon (HT29) cancer cells.[48]

Edmunds al., 2001, synthesized the tetracyclic benzimidazole derivatives, evaluated the anti cancer activity. Among all, the compound **1** (**53, Fig. 4**) showed best anti-cancer activity with TD_{50} value of 2.13µg/ml, 1.2µg/ml, 0.6µg/ml, 0.55 µg/ml, 3.6µg/ml against mouse hepatoma (MG-22A), human fibrosarcoma (HT-1080), mouse melanoma(B16), Neuro mouse neuroblastoma (2A) and normal mouse fibroblast(3T3) cells.[49]

CONCLUSION

Benzimidazole is a bioactive heterocyclic compound. It exhibit wide variety of biological activities one of the important activity is anti cancer activity hence it attract the many researcher to synthesize bioactive compounds towards the target site. The present review focused on anti cancer activity of many bioactive substituted benzimidazoles. It may serves as valuable source of information to researchers who wish to synthesize new benzimidazole derivative having anticancer activity as well as further investigation benzimidazole derivatives having anticancer activity.

ACKNOWLEDGEMENTS

The author thankful to Head of Jayamukhi Institute of Pharmaceutical Sciences, Warangal, Telangana, for providing facilities to carry out this research work.

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