Benzimidazole-heterocyclic hybrids as potential anticancer agents: A review on outstanding research

Pham Canh Em
Hong Bang International University, Vietnam

ABSTRACT
Cancer is one of the most serious medical problem and second leading cause of death in the world, characterized by a deregulation of the cell cycle which mainly results in a progressive loss of cellular differentiation and uncontrolled cellular growth. Benzimidazole-heterocyclic hybridization, involving a combination of benzimidazole nucleus and other pharmacophores of bioactive heterocyclic scaffolds to generate a single molecular architecture with improved affinity and activity, in comparison to their parent molecules, has emerged as a promising strategy in recent drug discovery research. Hybrid anticancer drugs are of great therapeutic interests since they can potentially overcome most of the pharmacokinetic drawbacks encountered with conventional anticancer drugs. Strategically, the design of anticancer drugs involved the blending or linking of an anticancer drug with another anticancer drug or a carrier molecule which can efficiently target cancer cells with improved biological potential. Major advantages of hybrid anticancer drugs involved increased specificity, better patient compliance, and lower side effects along with reduction in chemo-resistance. This review is intended to provide an overview of discovery and development in benzimidazole-heterocyclic anticancer hybrids, as well as inspire the design and synthesis of new anticancer molecules.

Keywords: *benzimidazole, triazine, purine, pyrazole, thiazole, anticancer hybrid*

1. INTRODUCTION

According to the 2020 World Cancer Report, slightly over 18 million new cases of cancer and nearly 10 million cancer-related deaths occurred across the globe in 2018 [1]. Cancer is also the first or second leading cause of premature death in people of ages 30-69 in most countries worldwide. It is characterized by uncontrolled cell growth which may spread to other parts of the body (known as metastasis) and invade other tissues. Although prevention efforts are critical to limit cancer incidence, the treatment of cancer often involves pharmacologic intervention. Cytotoxic chemotherapeutic agents continue to play an important role in cancer pharmacotherapy, but discovery efforts have increasingly turned to targeted therapies (drugs interfering with processes unique to the proliferation and spread of cancer cells) and immunotherapy (boosting the immune system or changing how the immune system works) as effective and less toxic forms of pharmacotherapy for cancer [2, 3]. While numerous anticancer drugs are available, many forms remain difficult to cure, resulting in the mortality rates mentioned above. The toxicity, rapid development of resistance, and limited efficacy associated with currently available anticancer agents highlight the urgency to discover new compounds that can overcome the limitations of existing drugs [4].

Corresponding author: MS. Pham Canh Em
Email: empc@hiu.vn

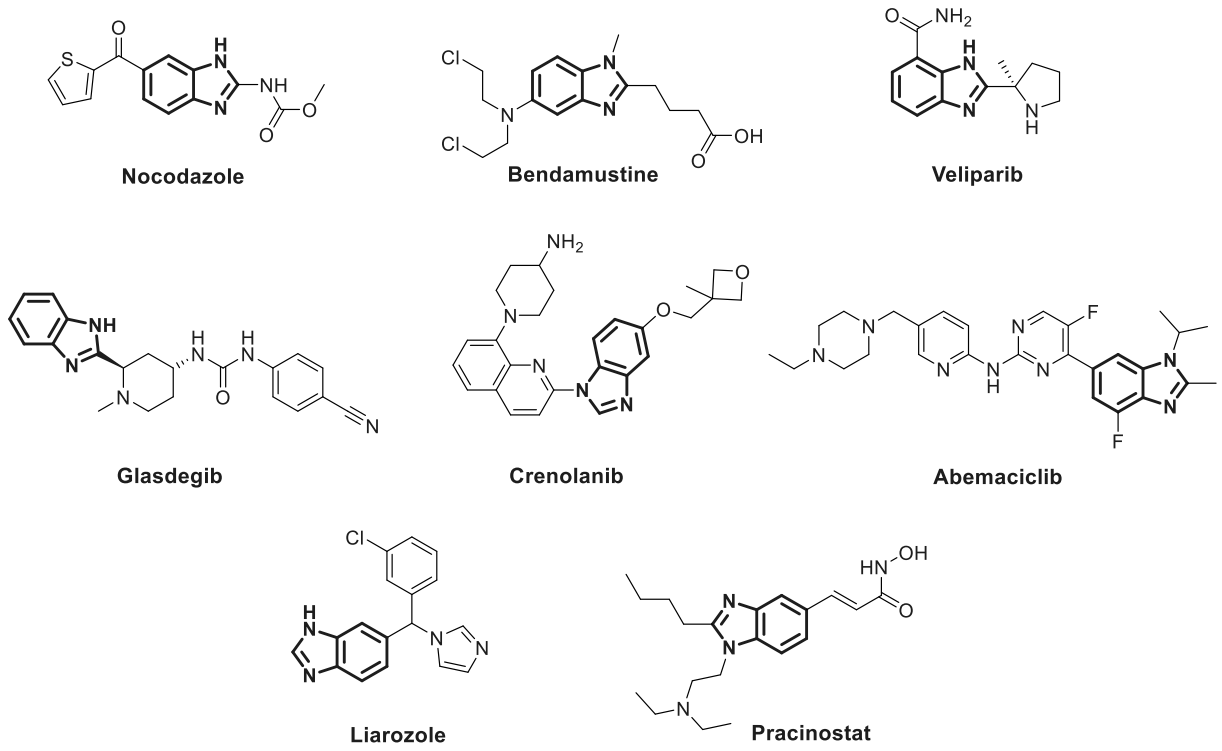

Figure 1. Marketed drugs having benzimidazole moiety

Benzimidazole is also named as 3-azaindole, azindole, benziminazole, benzoglyoxaline, 3-benzodiazole, 1,3-diazaindene having melting point of 170-172°C and occurs as white crystals [5]. Benzimidazole is an important structural motif found in extensive number of natural and pharmacologically active molecules. Especially the benzimidazoles might be considered as auxiliary isosters of nucleotides having attached heterocyclic cores in their structures, cooperate effortlessly with biopolymers and have potential action for chemotherapeutic applications [6]. The benzimidazole moiety itself is an urgent pharmacophore in present day and has been used as privileged scaffolds to synthesize selective drugs of interest in numerous therapeutic areas including HIV-RT inhibitor [7], anticancer [8], antimicrobial [9], antihistamine [10], antihelmintic [11], antioxidant [12], antihypertensive [13], antiviral [14], anticoagulant [15] and antiulcer activity [16]. The marketed drugs having benzimidazole moiety (Figure 1).

Anticancer drugs have been categorized in consonance with their mechanism of action as molecular targeting hybrids, antimetabolites, antitubulin and DNA-interactive hybrids, monoclonal antibodies and hormones [17, 18]. However, the single target approach also leads to cytotoxicity, predominantly on normal proliferating tissues such as hematopoietic system [19, 20]. Consequently, in the development of effectual and discerning anticancer drugs having low incidence of side effects, toxicity and emergence of drug resistance is of high priority [21]. To address this issue, combination therapy was considered, where numerous cytotoxic hybrids were pooled in anticancer behaviour regimes that endorse improved results with fewer side effects. However, the advantage of combination pattern is compromised with poor patient compliance [22, 23].

The hybrid anticancer drug approach is an innovative synthetic strategy that involves either the merging or blending of hepatophoric moieties of different drugs in a new molecular structure or combining two or more potential

anticancer pharmacophores directly through cleavable/noncleavable linkages, based on the ability of moieties to retain their affinity and activity for biological targets in the newly synthesized molecular hybrid. It is believed that the presence of two or more pharmacophores in a single unit not only synergises their biological effect but also upsurge their ability to inhibit more than one biological target. Recently, the molecular hybrid approach has resulted in several novel chemical entities with improved anticancer activity and selectivity with reduced side effects. This review focuses on the diverse strategies for pharmacomodulation focused on innovative benzimidazole-heterocyclic hybrid compounds exhibiting promising anticancer activities, along with a brief summary of their structure activity relationship (SAR).

2. ANTICANCER MOLECULAR HYBRIDS

2.1. Benzimidazole-triazine hybrid

Benzimidazole core has emerged as an important heterocyclic scaffold because of its wide range of activities as well as synthetic potential. Benzimidazole exhibits its structural resemblance with purines, because of which it can easily interact with various biomolecules. Recent reports have shown the anti-cancer potential of substituted benzimidazoles while its hybrids with other heterocyclic moieties have displayed improved anticancer activities [24].

Singla et al. reported the synthesis and anticancer evaluation of benzimidazole-triazine hybrids (Figure 2) against NCI-60 cell panel including nine tumour cell lines [25]. Among the evaluated hybrids, three compounds viz. 1a, 1b and 1c displayed prominent cell growth inhibition at a concentration of 10^{-5}M against variety of cancer cell lines. These compounds were further chosen for screening against a panel of 60 different tumour cell lines at 5-dose concen-tration range viz. 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} M. Hybrid 1a showed good antitumor activity with growth inhibition (GI_{50}) values in the range of 3.56-19.0 µM against nine tumour subpanels with the mean graph mid-point (MG-MID) GI_{50} value of 9.79 µM. Further, dihydrofolate reductase (DHFR) inhibition assay of the promising hybrids 1a, 1b and 1c was performed to investigate their mechanism of action. Hybrids 1a and 1c revealed excellent inhibition potential while hybrid 1b was found to be ineffective towards DHFR assay. The presence of chloro substituent at the C-6 position of triazine significantly improved the inhibitory activity.

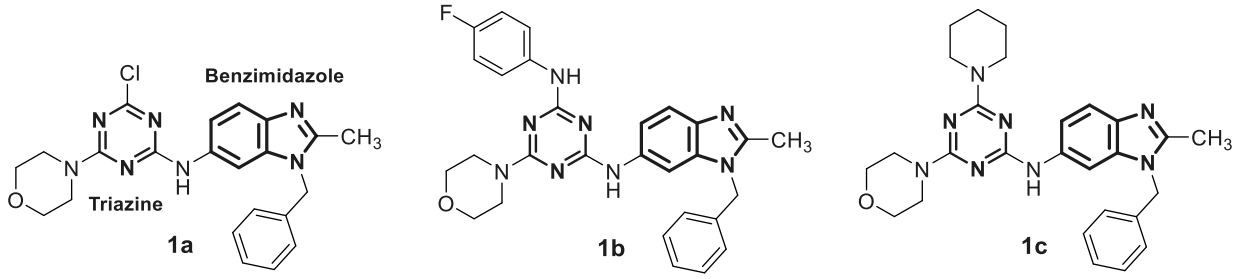

Figure 2. Benzimidazole-triazine hybrids with the potent compounds 1a-c

Singla and co-workers reported the synthesis and anticancer studies of benzimidazole-triazine hybrids (Figure 3) against the NCI-60 cell panel [26]. Four hybrids, 2a, 2b, 2c and 2d exhibited remarkable activity against leukemia cancer cell lines (SR) with GI_{50} values of 731, 125, 539 and 31 nM, respectively. Moreover, these hybrids also showed promising activity against renal cancer cell lines RXF393 (GI_{50} < 750 nM). The presence of an aryl moiety on the triazine ring positively influenced the anticancer activity of the

hybrids. The strong binding affinity of hybrids with the bovine serum albumin (BSA) was also established based on UV and fluorescence studies.

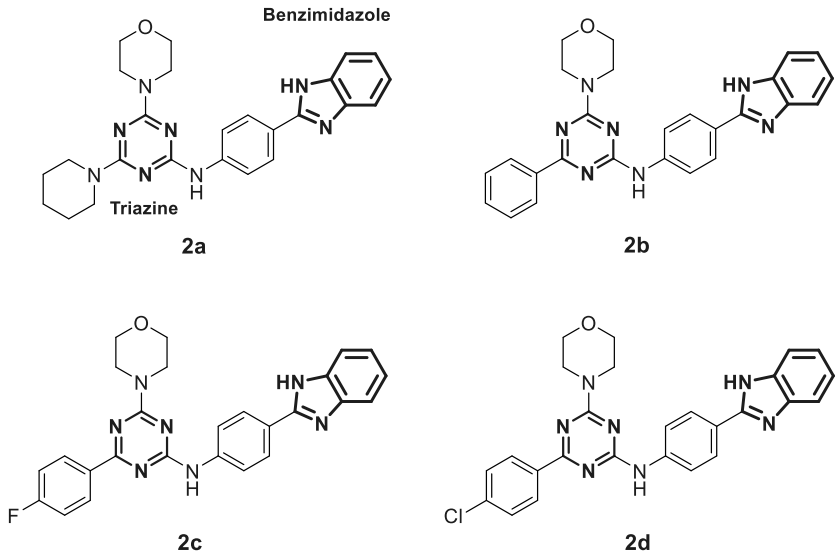

Figure 3. Benzimidazole-triazine hybrids with the potent compounds 2a-d

Wu et al. synthesized a novel series of molecules possessing a triazine-benzimidazole hybrids (Figure 4) based on the PI3K inhibitor gedatolisib designed to act as potential anticancer agents through the inhibition of PI3K/mTOR [27]. All but one of the target hybrids inhibited PI3K and mTOR with IC_{50} values below 200 nM. Hybrids 3a and 3b were among the most potent target compounds and were more active towards PI3Kδ compared to other PI3K isoforms, with IC_{50} values of 5.1 and 13.0 nM, respectively, compared to gedatolisib (IC_{50} = 156 nM). Hybrids 3a and 3b displayed IC_{50} values of 0.9 and 0.3 µM against the HCT116 cell line, while gedatolisib displayed an IC_{50} value of 1.4 µM. Western blotting studies in this cell line showed that 10 µM concentrations of hybrids 3a and 3b almost completely inhibited the phosphorylation of AKT and p70S6K, the latter protein being downstream of the PI3K/AKT/mTOR signaling pathway.

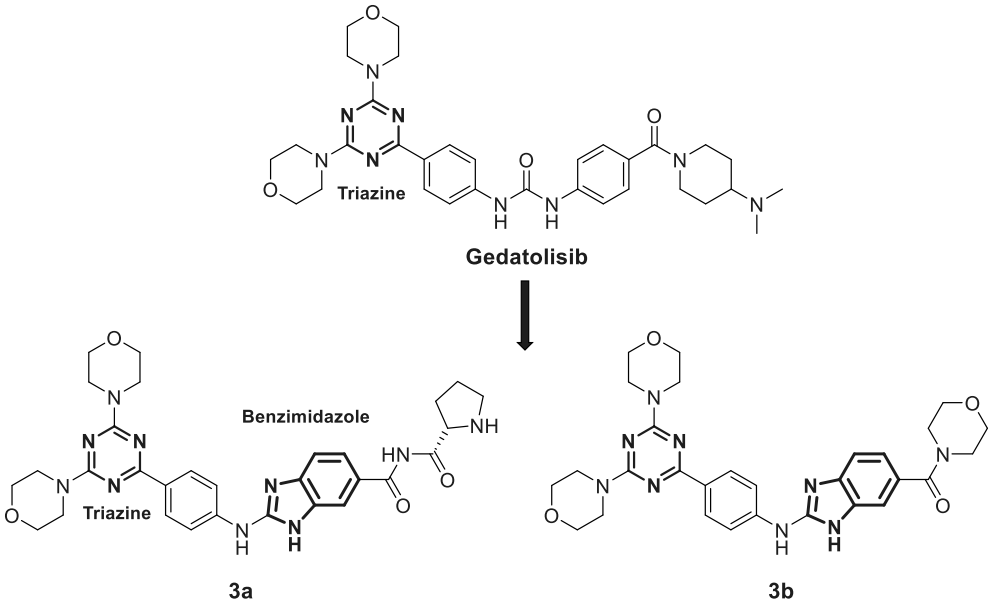

Figure 4. Benzimidazole-triazine hybrids with the potent compounds 3a-b

2.2. Benzimidazole-purine hybrid

Sharma et al. reported the synthesis and anticancer evaluation of benzimidazole-purine hybrids (Figure 5) against the NCI-60 cell panel at a single dose of 10 µM concentration [28]. The representative hybrid 4a exhibited considerable inhibition towards ovarian cancer, CNS cancer and colon cancer cell lines with GI_{50} values of 1.34, 2.00 and 3.16 µM, respectively. Also, hybrid 4a (MG-MID Gi_{50} = 18.12 µM) presented 1.25 fold greater activity than 5-fluorouracil (5-FU), and was selective (IC_{50} = 0.01 µM) towards Aurora-A kinase inhibition. Subsequently, QSAR model was developed with good predictive ability for the affinity of this series of Aurora-A kinase inhibitors with physicochemical descriptors. Molecular docking studies explored the favourable binding of 4a with the active site residues (His644, Asp622, Ser625 and Arg626) of Aurora-A.

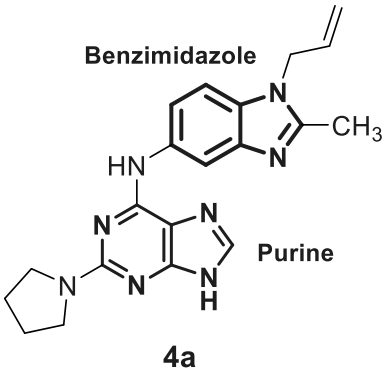

Figure 5. Benzimidazole-purine hybrid with the potent compound 4a

2.3. Benzimidazole-pyrazole hybrid

Reddy et al. conjugated benzimidazole and pyrazole nuclei, and subjected the resultant hybrids (Figure 6) to anti-proliferative evaluation against three cancer cell lines viz. MCF-7 (breast), A-549 (lung) and HeLa (cervical) [28]. Hybrids 5a, 5b and 5c exhibited superior growth inhibition (IC_{50} ranges 0.83-1.81 µM) as compared to 5-fluorouracil (IC_{50} ranges 2.13-4.16 µM) against the tested cancer cell lines. Mono-substitution of halogens (F, Br and I) on the benzimidazole ring noticeably increased the anticancer activity of these hybrids. The most potent hybrid 5a, exhibited the highest activity among the test compounds with IC_{50} of 0.83 µM against MCF-7 cell lines, due to cell cycle arrest in the G1 phase of cell cycle as confirmed by flow cytometry analysis. The apoptotic effects of these compounds on MCF-7 cells suggested that the hybrids induced apoptosis due to increased production of ROS, elevation of Bax/Bcl-2 ratio, and activation of caspase-3 and 7.

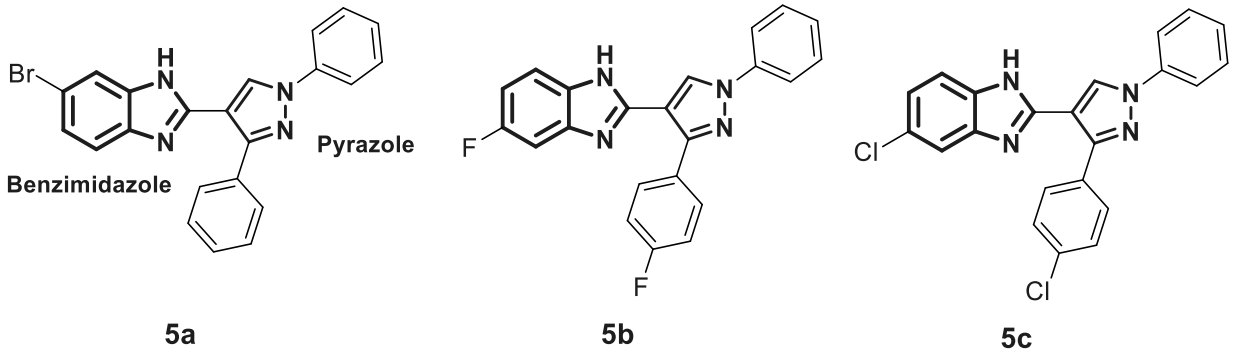

Figure 6. Benzimidazole-pyrazole hybrids with the potent compounds 5a-c

Akhtar et al. synthesized new benzimidazole-pyrazole hybrids (Figure 7) as potential anticancer agents targeting EGFR [29]. Among the synthesized hybrids, 6a and 6b displayed the greatest inhibition of EGFR phosphorylation in the KB cell line as assessed by ELISA, exhibiting IC_{50} values of 0.97 µM and 1.7 µM, respectively. The reference standard gefitinib exhibited an IC_{50} value of 0.011 µM in this assay. Of the four cancer cell lines examined, hybrids 6a and 6b displayed the greatest antiproliferative activity against A549 cells, with IC_{50} values of 2.2 and 2.8 µM, respectively. When incubated with A549 cells at 5 and 10 µM for 24 h, hybrid 6a caused a dose-dependent increase in the percentage of cells in the G2/M cell cycle phase. No mortality was observed 24 h post-administration when a single 500 mg dose of hybrid 6a was given to female albino rats by oral gavage.

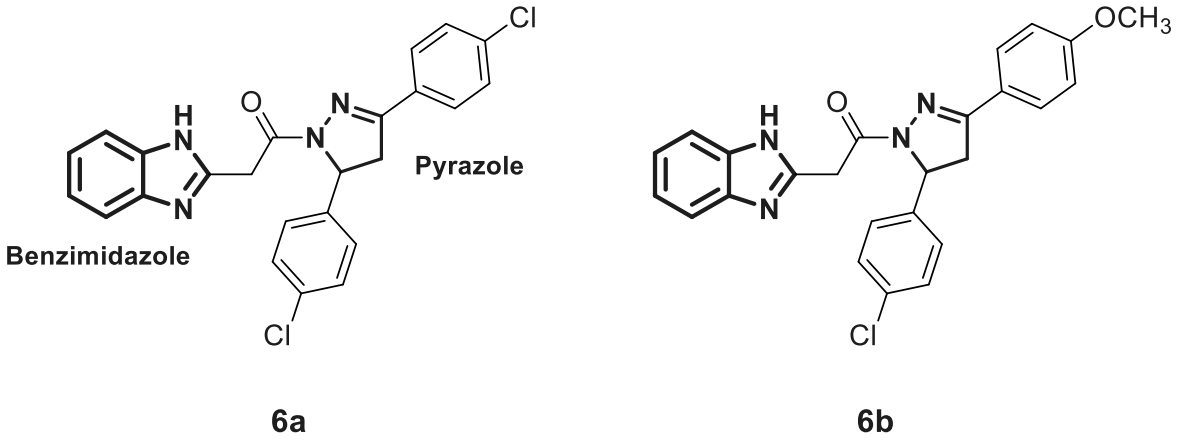

Figure 7. Benzimidazole-pyrazole hybrids with the potent compounds 6a-b

Analogs bearing a benzimidazole-pyrazole hybrids (Figure 8) were synthesized by Galal et al. and were tested for their cytotoxic activity on MCF-7, HeLa, and HepG2 cell lines and were also tested *in vitro* for Chk2 inhibition [30]. Chk2 inhibitory activity was in the range 9.95-65.07 nM for these molecules. Hybrids 7a and 7b were among the most potent of these derivatives against Chk2, exhibiting IC_{50} values of 11.49 and 11.13 nM, respectively. Assays on HepG2, HeLa, MCF-7 and baby hamster kidney (BHK) cells showed that hybrid 7b displayed a GI_{50} value of 6.5 µM against MCF-7 cells, while hybrids 7c and 7a exhibited GI_{50} values of 11.7 µM and 6.6 µM against HeLa cells, respectively. Some of these analogs enhanced the activity of the cytotoxic anticancer agent's doxorubicin and cisplatin in MCF-7 cells, while some did not. For example, a potentiation index of 276 was determined for the combination of doxorubicin with hybrid 7c in MCF-7 cells, while no potentiation was observed for doxorubicin paired with target hybrids 7a and 7b. Of the compounds evaluated, 7c was the least toxic *in vivo* and was, thus, further tested alone and in combination with doxorubicin in an MNU-induced breast cancer model in rats. Serum Chk2 activity was lower in MNU-induced animals receiving hybrid 7c at an oral dose of 50 mg/kg/day for 10 days compared to MNU-treated animals that did not receive this compound, and the serum of MNU-induced animals receiving a combination of doxorubicin and hybrid 7c at this same dose displayed lower Chk2 activity compared to MNU-induced rats receiving doxorubicin alone.

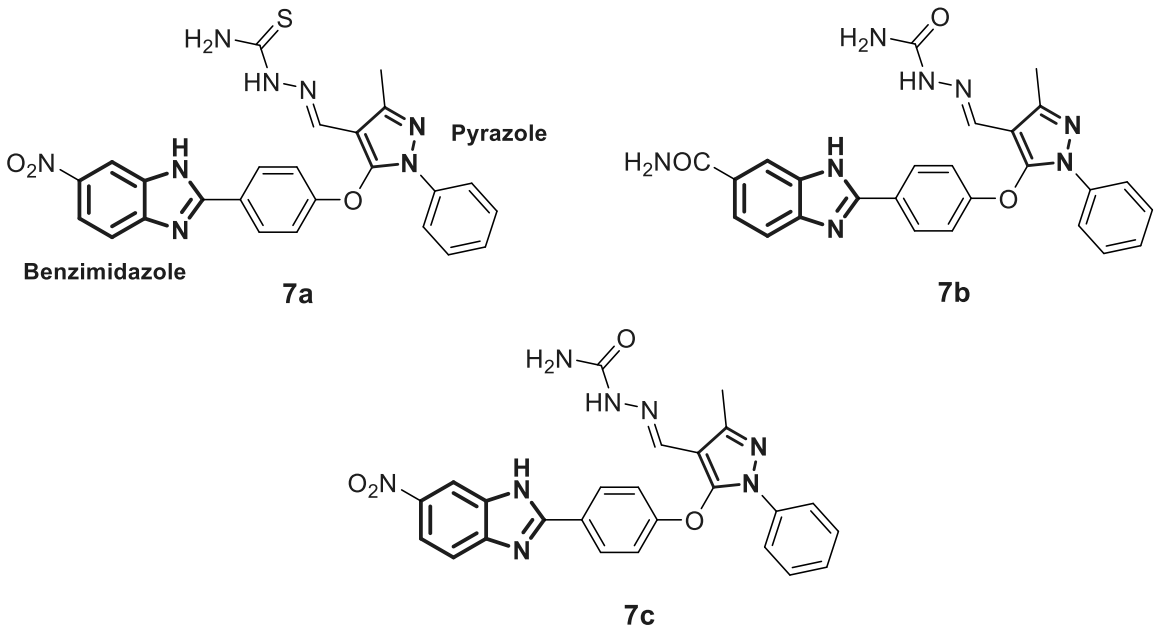

Figure 8. Benzimidazole-pyrazole hybrids with the potent compounds 7a-c

Wang et al. synthesized a series of benzimidazole sulfonamides containing a substituted pyrazole ring (Figure 9) at the C2 position [31]. These derivatives displayed IC_{50} values in the range between 0.15-7.26 µM against A549, HeLa, HepG2, and MCF-7 cancer cell lines. Hybrid 8a was the most potent derivative, displaying IC_{50} values of 0.15, 0.21, 0.33, and 0.17 µM against A549, HeLa, HepG2, and MCF-7 cells, respectively. This compound also showed low toxicity to murine primary hepatocytes and 293T cells (CC_{50} values of 132 and 223 µM, respectively). In terms of the SAR for these derivatives against the cancer cell lines, placement of the benzene sulfonyl group on the benzimidazole nitrogen enhanced activity and the inclusion of 2,5-dimethyl, 4-methyl and 4-methoxy groups on the phenylsulfonyl ring increased potency. Hybrid 8a displayed an IC_{50} value of 1.52 µM against porcine brain tubulin polymerization, while colchicine and combretastatin A4 displayed IC_{50} values of 2.26 µM and 1.61 µM in the same assay, respectively. At a concentration of 5 µM, hybrid 8a inhibited the binding of [*3H*] colchicine (5 µM) to tubulin by 91%. Incubation with this compound at a concentration of 0.5 µM resulted in an increase in the percentage of A549 cells in the G2/M phase.

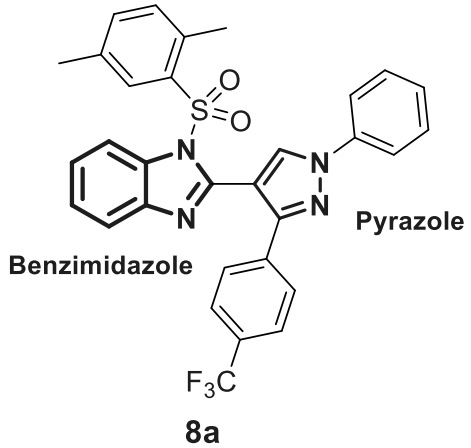

Figure 9. Benzimidazole-pyrazole hybrid with the potent compound 8a

Ashok et al. prepared 1,2,3-triazole-based pyrazole-benzimidazole hybrids through conventional, as well as microwave-assisted, synthesis and evaluated their *in vitro* antiproliferative activity against C6 and MCF-7 cell lines [32]. These derivatives were obtained in higher yields using microwave-assisted synthesis (77 - 89%) compared to conventional heating in DMF (57 - 66%). Hybrid 9a displayed an IC_{50} value of 0.102 µM against the C6 cell line, while the standard drug cisplatin exhibited an IC_{50} value of 0.122 µM. Hybrids 9a and 9b displayed IC_{50} values of 0.110 and 0.144 µM against the MCF-7 cell line, while the IC_{50} value for cisplatin against these cells was 0.596 µM.

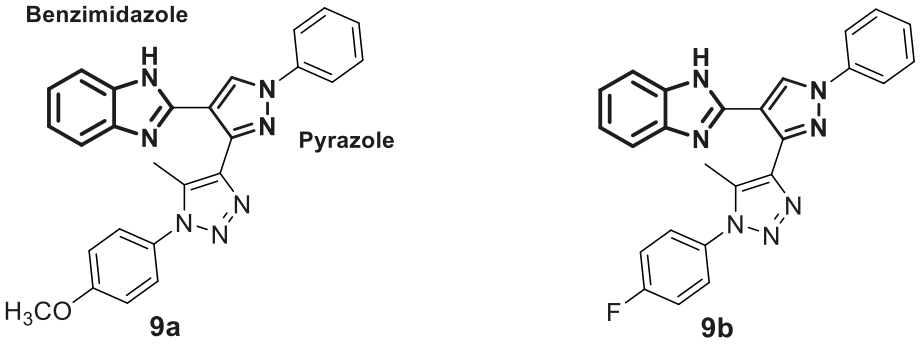

Figure 10. Benzimidazole-pyrazole hybrids with the potent compounds 9a-b

2.4. Benzimidazole-thiazole hybrid

Srour et al. synthesized thiazole-benzimidazole hybrids as potential anticancer agents directed against EGFR [33]. These compounds displayed IC_{50} values against EGFR kinase in the range between 71.7-1235 nM. Hybrids that showed potent activity against EGFR were evaluated for their cytotoxicity to the MCF-7 cell line. Of these, hybrids 10a and 10b possessed the greatest potency against the MCF-7 cells, exhibiting IC_{50} values of 6.30 µM and 5.96 µM, respectively, while the IC_{50} of the standard drug erlotinib was 4.15 µM against this cell line (Figure 11). Considering that EGFR inhibitory activity did not directly correlate with activity against MCF-7 cells for these molecules, the authors speculated that other mechanisms of action may also be responsible for their anti-cancer activity. When tested at its IC_{50} concentration in MCF-7 cells, hybrid 10a caused the accumulation of these cells in the pre-G1 and G2/M cell cycle phases. At this same concentration, hybrid 10a increased the percentage of early and late apoptotic cells compared to the DMSO treated controls as assessed by annexin V/propidium iodide staining. Moreover, at its IC_{50} concentration, 10a increased the levels of the pro-apoptotic markers p53, Bax, and caspase-3 by 9.85-, 4.95-, and 12.28-fold in MCF-7 cells compared to control, while the anti-apoptotic marker Bcl-2 was decreased by approximately 2-fold in treated MCF-7 cells.

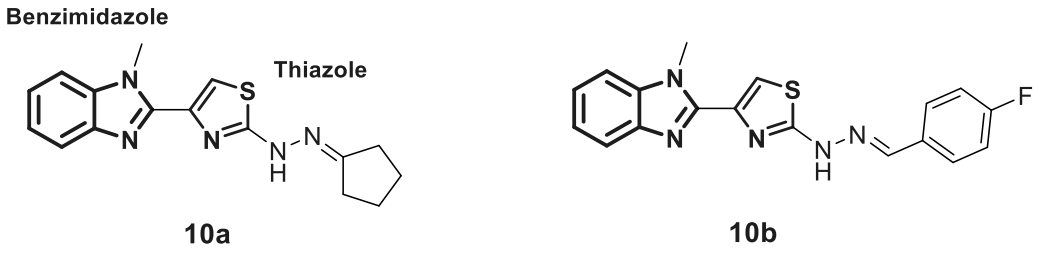

Figure 11. Benzimidazole-thiazole hybrids with the potent compounds 10a-b

3. CONCLUSION

The concept of anticancer hybridization is ever evolving and innovative for the development of promising drugs. The intent of this approach is to synthesize new molecular frameworks via covalent-amalgamation of two or more active compounds with specific mechanism of action and biological targets, so as to achieve improved activity and selectivity. In some cases, minor modifications in a particular benzimidazole-heterocyclic anticancer hybrids can result in promising new anticancer activities. Many of the synthesized hybrids reported here display similar or greater potency compared to the reference drugs and promising activity in animal models of cancer, reinforcing both the versatility and utility of the benzimidazole-heterocyclic hybrids in modern medicinal chemistry. The prerequisite to the design of such multi-factorial anticancer compounds, however include the in-depth knowledge of synthetic strategies, SAR as well as disease-associated signaling pathways.

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Tạp chủng benzimidazol-dị hoàn như tác nhân kháng ung thư tiềm năng: Phê bình về nghiên cứu nổi bật

Phạm Cảnh Em

TÓM TẮT

Ung thư là một trong những vấn đề y tế nghiêm trọng nhất và là nguyên nhân gây tử vong đứng thứ hai trên thế giới, mang đặc điểm là sự bất thường trong chu kỳ tế bào dẫn đến sự mất dần biệt hóa tế bào và sự phát triển tế bào không kiểm soát. Sự tạp chủng benzimidazol-dị hoàn là sự kết hợp giữa nhân benzimidazol với nhân dị hoàn có hoạt tính sinh học khác để tạo ra một phân tử mới với ái lực và hoạt tính được cải thiện so với phân tử ban đầu, đây là một chiến lược đầy tiềm năng trong nghiên cứu khám phá thuốc hiện nay. Thuốc tạp chủng kháng ung thư có hiệu quả điều trị cao vì khắc phục hầu hết các nhược điểm dược động học của thuốc kháng ung thư thông thường. Về mặt chiến lược, thiết kế thuốc kháng ung thư liên quan đến sự trộn lẫn hoặc liên kết thuốc kháng ung thư này với thuốc kháng ung thư khác hoặc chất mang có thể hướng mục tiêu đến tế bào ung thư hiệu quả góp

phần cải thiện hoạt tính sinh học. Ưu điểm chính của tạp chủng kháng ung thư bao gồm: tăng độ đặc hiệu, tăng mức độ tuân thủ điều trị và giảm tác dụng phụ do giảm sự chịu đựng hóa học. Đánh giá này cung cấp một cái nhìn tổng quan về khám phá và phát triển tạp chủng kháng ung thư benzimidazol-dị hoàn, cũng như truyền cảm hứng cho thiết kế và tổng hợp các hợp chất kháng ung thư mới.

Keywords: *benzimidazol, triazin, purin, pyrazol, thiazol, tạp chủng kháng ung thư*

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