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Review Article

INHIBITORS OF BROMODOMAIN-4 AND CYCLOOXYGENASE-2: A REVIEW ON THE ADVANTAGEOUS EFFECT OF DUAL-TARGET APPROACH IN CANCER TREATMENT

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ABSTRACT

The main objective of this review article is to establish a correlation between the roles of BRD-4 and COX-2 inhibitors in anticancer treatment. This article aims to project the synergistic benefits of a dual-target approach. A Literature review was conducted using the keywords such as BRD-4, cyclooxygenase-2, COX-2, Anticancer, anti-proliferative BRD-4 inhibitors, COX-2 inhibitors and dual-target therapy. Searches were made using the mentioned keywords individually as well as in combinations in PubMed, Science Direct and Google Scholar for the past ten years. The correlation between inflammatory mediators, particularly COX-2 and bromodomain in particular BRD-4 in cancers has been studied in a few research articles. These targets have been used for the development of anti-proliferative drugs individually as well as in combination. Combination therapy has been proposed to be better than mono-drug therapy. The need for a dual target concept has arisen to improve the efficacy of chemotherapy. The cancers where BRD-4 is over-expressed and inflammation is observed, it may be very much advantageous to give a combination therapy of BRD-4 and COX-2 inhibitors. Moreover, if the COX-2 inhibitors show anti-proliferative action, then the combination therapy is expected to work better than mono chemotherapy.

Keywords: Bromodomain, BRD-4, Cyclooxygenase-2, COX2, Antiproliferative activity, dual target

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INTRODUCTION

According to the World Health Organization in 2018, one out of six deaths is due to cancer. Cancer is the second largest cause of death globally. In 2020 the most common causes of cancer deaths are lung cancer, colon and rectum cancer, liver cancer, stomach cancer, and breast cancer [1]. Bromodomain-containing protein 4 (BRD4) is a protein that in humans, is encoded by the BRD gene. It is located in human chromosome 19. Other members of the mammalian Bromodomain and Extra Terminal (BET) family contain BRD2, BRD3, BRD4, and BRDT [2, 3]. BRD1 contains one gene and is associated with transcriptional regulation, brain development, and susceptibility to brain disorders [4]. BRD-4 is also known as SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4 (Smarca4). It is also referred to as Mitotic Chromosome Associated Protein (MCAP), Hormonal Upregulated Neu-Tumour associated Kinase (HUNK1). It contains two bromodomains that recognize acetylated lysine residue. Brd4 is an atypical kinase that phosphorylates serine 2 of RNA polymerase II [5, 6] and helps in cellular growth, cell cycle progression, and cancer development.

Cyclooxygenase-2 (COX-2) is an inducible form of the enzyme that catalyzes the first step for the synthesis of prostanoids. COX-2 contributes to immune evasion and contributes to resistance towards cancer immunotherapy, which plays a crucial role in the innate and adaptive immune response. The activity of the COX-2 signal pathway can suppress Dendritic cells (DCs), natural killer (NK), T cells and type-1 immunity, excluding type-2 immunity, which promotes tumor immune evasion. COX-2 and the prostaglandin cascade play important roles in the "inflammogenesis of cancer". Overexpression of COX-2 is also observed in cancer cells [7].

MATERIALS AND METHODS

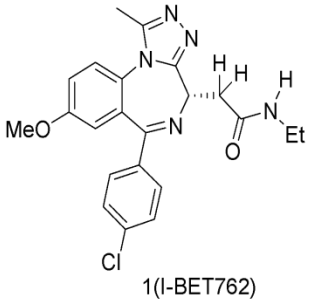
A literature review was conducted using the keywords such as BRD-4, cyclooxygenase-2, COX-2, Anticancer, anti-proliferative BRD-4 inhibitors, COX-2 inhibitors, and dual-target therapy. Searches were made using the mentioned keywords individually as well as in combinations in PubMed, Science Direct, and Google Scholar for the past ten years. The research articles which have reported small molecules as BRD4 inhibitors and COX2 inhibitors as anticancer agents have been referenced. The reported structures in those research articles are included in this review.

DISCUSSION

Role of bromodomain in cancer

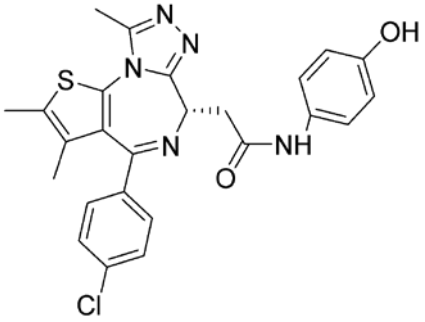
Cancer is the undesirable and uncontrolled growth of abnormal cells where bromodomain (BRD) proteins perform a crucial role in translating histone modifications with powerful transcriptional consequences. Histone acetylation is important in chromatin remodeling and gene activation. Nearly all known histone-acetyl transference-associated transcriptional co-activators contain bromodomain [8]. Thirty bromodomain-containing proteins are present in humans. BRD2, BRD3, and BRD4 are the proteins that interact with acetylated histone H3/H4. Among them, BRD4 is known to be a protein involved in the cell cycle and gene expression. Hence, the selective inhibition of bromodomains across the family creates varied opportunities as novel therapeutic agents in human cell division dysfunction. BRD-4 and COX-2 are overexpressed in breast cancer [9-12], skin cancer [13], gastric cancer [14-17], colorectal cancer [18-22], cervical cancer [23], prostate cancer [24-27], pancreatic cancer [28], acute myeloid leukemia [29, 30] and lung cancer [31, 32],

Benzodiazepine derivatives were studied for their anticancer activity. I-BET762 a potent molecule, was reported as a bromodomain inhibitor. It was also reported to show anti-inflammatory activity in a rat model [33]. Its bromodomain inhibitory activity was studied in phase I clinical trial [34].



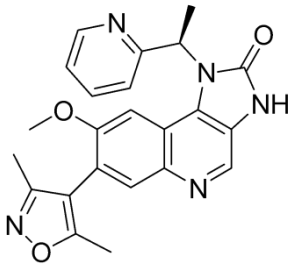
1(I-BET762)

Birabresib (OTX015 or, MK-8628) has also been reported as a BRD4 inhibitor. It inhibits the gene transcription phase of the cell cycle. A study reveals the antiproliferative activity of Birabresib on cell lines and *in vivo* tumors. In this study, Birabresib was used alone and the anticancer activity was noticed in patients with resistant acute myeloid leukemia related to myeloid malignancies [37]



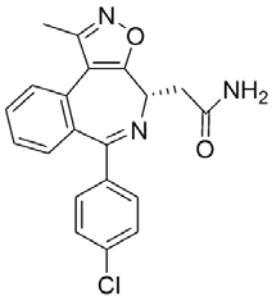
Birabresib (OTX015)

A novel series of BET family bromodomain inhibitors were reported to have an anti-inflammatory effect. The crystallographic images show good binding interactions with the BRD2 N-terminal bromodomain. The reported molecule showed good activity toward LPS-induced sepsis and inflammation in the mice model [38]. The same molecule has been studied for antiproliferative activity in other studies.



I-BET151

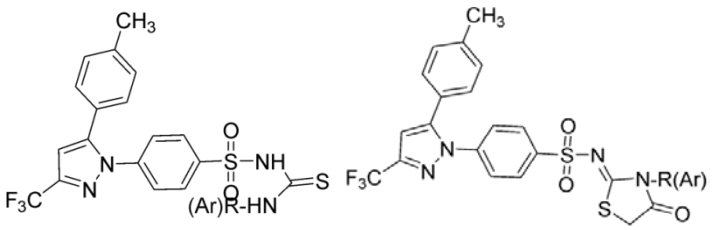
Clinical trials on Pelabresib (CPI-0610) for its anticancer activity suggest that it is active against myelofibrosis (NCT04603495). It arrests cell line growth in the G1 cell cycle and causes caspase-dependent apoptosis [39].



CPI-0610

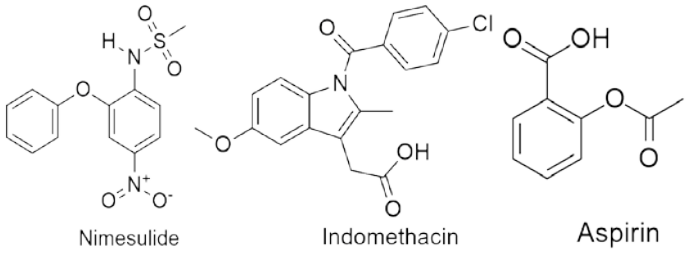
Role of cyclooxygenase-2 in cancer

Several clinical trials using COX-2 inhibitors are in progress, and the results from these studies will increase our understanding of COX-2 inhibition in both cancer treatment and its prevention [40]. Several reports suggest that chronic inflammation leads to cancer. So, some anti-inflammatory drugs were derivatized and tested for their anticancer activity. Celecoxib, a COX-2 inhibitor, has been studied for its anticancer activity in clinical trial number NCT02429427 (against breast cancer). Some derivatives of celecoxib (1a-e and 2a-e) were developed and studied as anticancer molecules [41]. However, more shreds of evidence are needed for the effectiveness of celecoxib in the treatment of cancer.



1a-e 2a-e

Other established COX-2 inhibitors and their derivatives have been studied for anticancer properties. To name a few, derivatives of Nimesulide [42, 43], Indomethacin [44, 45] and Aspirin [46, 47] have been reported to show anti-cancer activity.



Nimesulide Indomethacin Aspirin

Dual target approach

BRD residue within key chromatin serves to control distinctive disease-associated transcriptional pathways like cancer, inflammation, and viral replication. Disrupting the BRD4-acetyl lysine interactions by BRD-4 inhibitors arrests the growth of cancer cells. On the other hand, COX-2 is majorly involved in the biosynthesis of pain mediators. Combining these two targets in the study could be advantageous and needs attention of the scientists.

Cancer drug resistance has been a major problem in cancer therapy. Almost any therapy (except surgery) that is being used in the treatment of cancer can result in resistance. A large group of patients has the problem of intrinsic resistance or acquired resistance. Sometimes patients can become one-drug resistant; another group of patients may become multiple-drug resistant. Designing drugs for dual targets i. e for both COX-2 and BRD-4 may help in the development of novel molecules used for the treatment of cancers where these two targets are over-expressed.

Another aspect of the dual target approach involving BRD-4 and COX-2 is the reduction of pain in cancer patients as shown in fig. 1. The COX-2 inhibitor which reduces pain mediators and is anticancer, can be studied for combination therapy with BRD-4.

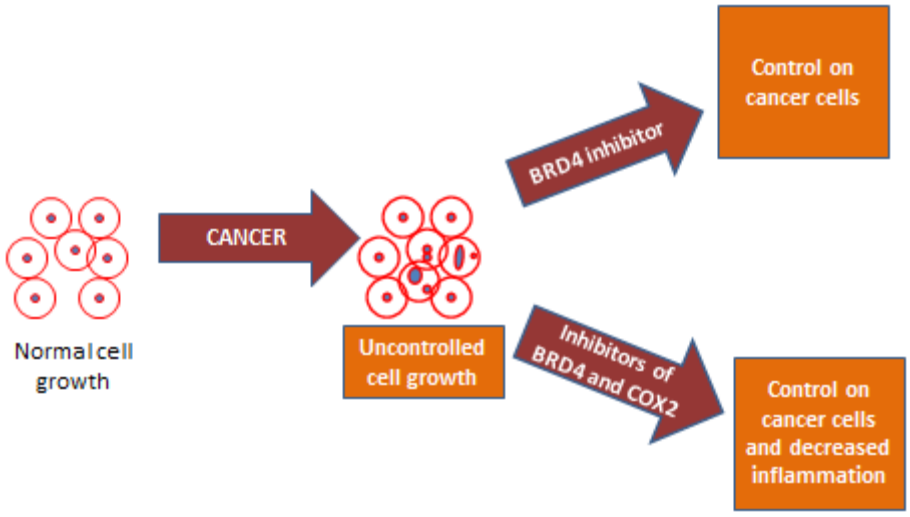


Fig. 1: Advantageous effect of dual-target in cancer chemotherapy

In lung cancer cell lines, bromodomain, PHD finger transcription factor (BPTF) and COX-2 were found to be over-expressed. BPTF regulates the expression of COX-2 by NF-kB pathway. Knockdown of BPTF evaded the binding of the Nf-kB with COX-2. Thus, the poor prognosis in lung cancer can be managed by a dual target approach. This information provides the rationale for the selection of these targets for developing a potent antiproliferative drug for lung cancer [48].

CONCLUSION

Extensive literature review exhibits the relation between inflammation and cancer. A number of clinical trials using **mono-targeted** COX-2/BRD4 inhibitors are in progress and the results from these studies increase our understanding on these inhibitors. Dual target approach including BRD-4

and COX-2 may be used in both cancer treatment and prevention. The combination of **dual-targeted** COX-2 and BRD4 inhibitors may be more effective in cancers where these two targets are over-expressed.

ABBREVIATION

SWI/SNF: SWItch/Sucrose Non-Fermentable

BRD: Bromodomain containing protein

BET: Bromodomain and Extra Terminal

MCAP: Mitotic Chromosome Associated Protein

CONSENT FOR PUBLICATION

The author gives consent for the publication of this manuscript in the International Journal of Chemistry Research

AVAILABILITY OF DATA AND MATERIALS

Nil

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The author declares no conflict of interest.

REFERENCES

1. World Health Organization. Cancer details. Available from. https://www.who.int/news-room/fact-sheets/detail/cancer. [Last accessed on 03 Feb 2022]
2. Andrieu GP, Denis GV. BET proteins exhibit transcriptional and functional opposition in the epithelial-to-mesenchymal Transition Distinct. Mol Cancer Res. 2018;16(4):580-6. doi: 10.1158/1541-7786.MCR-17-0568. PMCID PMC5882530.
3. Taniguchi Y. The bromodomain and extra-terminal domain (BET) family: functional anatomy of BET paralogous proteins. Int J Mol Sci. 2016;17(11):1849. doi: 10.3390/ijms17111849, PMID 27827996.
4. Fryland T, Christensen JH, Pallesen J, Mattheisen M, Palmfeldt J, Bak M. Identification of the BRD1 interaction network and its impact on mental disorder risk. Genome Med. 2016;8(1):53. doi: 10.1186/s13073-016-0308-x. PMID 27142060.
5. Devaiah BN, Lewis BA, Cherman N, Hewitt MC, Albrecht BK, Robey PG. BRD4 is an atypical kinase that phosphorylates serine2 of the RNA polymerase II carboxy-terminal domain. Proc Natl Acad Sci USA. 2012;109(18):6927-32. doi: 10.1073/pnas.1120422109, PMID 22509028.
6. Donati B, Lorenzini E, Ciarrocchi A. BRD4 and cancer: going beyond transcriptional regulation. Mol Cancer. 2018;17(1):164. doi: 10.1186/s12943-018-0915-9, PMID 30466442.
7. Hashemi Goradel N, Najafi M, Salehi E, Farhood B, Mortezaee K. Cyclooxygenase-2 in cancer: a review. J Cell Physiol. 2019;234(5):5683-99. doi: 10.1002/jcp.27411, PMID 30341914.
8. Dhalluin C, Carlson JE, Zeng L, He C, Aggarwal AK, Zhou MM. Structure and ligand of a histone acetyltransferase bromodomain. Nature. 1999;399(6735):491-6. doi: 10.1038/20974, PMID 10365964.
9. Shi J, Cao J, Zhou BP. Twist-BRD4 complex: potential drug target for basal-like breast cancer. Curr Pharm Des. 2015;21(10):1256-61. doi: 10.2174/1381612821666141211153853, PMID 25506891.
10. Wu SY, Lee CF, Lai HT, Yu CT, Lee JE, Zuo H. Opposing functions of BRD4 isoforms in breast cancer. Mol Cell. 2020;78(6):1114-1132.e10. doi: 10.1016/j.molcel.2020.04.034. PMID 32446320.
11. Liu B, Liu X, Han L, Chen X, Wu X, Wu J. BRD4-directed super-enhancer organization of transcription repression programs links to chemotherapeutic efficacy in breast cancer. Proc Natl Acad Sci USA. 2022;119(6). doi: 10.1073/pnas.2109133119. PMID 35105803.
12. Lu L, Chen Z, Lin X, Tian L, Su Q, An P. Inhibition of BRD4 suppresses the malignancy of breast cancer cells via regulation of Snail. Cell Death Differ. 2020;27(1):255-68. doi: 10.1038/s41418-019-0353-2, PMID 31114028.
13. Jing X, Shao S, Zhang Y, Luo A, Zhao L, Zhang L. BRD4 inhibition suppresses PD-L1 expression in triple-negative breast cancer. Exp Cell Res. 2020;392(2):112034. doi: 10.1016/j.yexcr.2020.112034. PMID 32339606.
14. Andrieu G, Tran AH, Strissel KJ, Denis GV. BRD4 regulates breast cancer dissemination through Jagged1/Notch1 signaling BRD4. Cancer Res. 2016;76(22):6555-67. doi: 10.1158/0008-5472.CAN-16-0559. PMID 27651315.
15. Moon H, White AC, Borowsky AD. New insights into the functions of Cox-2 in skin and esophageal malignancies. Exp Mol Med. 2020;52(4):538-47. doi: 10.1038/s12276-020-0412-2, PMID 32235869.
16. Qin ZY, Wang T, Su S, Shen LT, Zhu GX, Liu Q. BRD4 promotes gastric cancer progression and metastasis through acetylation-dependent stabilization of snail. Cancer Res. 2019;79(19):4869-81. doi: 10.1158/0008-5472.CAN-19-0442. PMID 31311807.
17. Dong X, Hu X, Chen J, Hu D, Chen LF. BRD4 regulates cellular senescence in gastric cancer cells via E2F/miR-106b/p21 axis. Cell Death Dis. 2018;9(2):203. doi: 10.1038/s41419-017-0181-6, PMID 29434197.
18. Song H, Shi L, Xu Y, Xu T, Fan R, Cao M. BRD4 promotes the stemness of gastric cancer cells via attenuating miR-216a-3p-mediated inhibition of Wnt/β-catenin signaling. Eur J Pharmacol. 2019;852:189-97. doi: 10.1016/j.ejphar.2019.03.018. PMID 30876979.
19. Ba M, Long H, Yan Z, Wang S, Wu Y, Tu Y. BRD4 promotes gastric cancer progression through the transcriptional and epigenetic regulation of c-MYC. J Cell Biochem. 2018;119(1):973-82. doi: 10.1002/jcb.26264, PMID 28681984.
20. Hu Y, Zhou J, Ye F, Xiong H, Peng L, Zheng Z. BRD4 inhibitor inhibits colorectal cancer growth and metastasis. Int J Mol Sci. 2015;16(1):1928-48. doi: 10.3390/ijms16011928, PMID 25603177.
21. Otto C, Schmidt S, Kastner C, Denk S, Kettler J, Müller N. Targeting bromodomain-containing protein 4 (BRD4) inhibits MYC expression in colorectal cancer cells. Neoplasia. 2019;21(11):1110-20. doi: 10.1016/j.neo.2019.10.003. PMID 31734632.

22. Zhang P, Li R, Xiao H, Liu W, Zeng X, Xie G. BRD4 inhibitor AZD5153 suppresses the proliferation of colorectal cancer cells and sensitizes the anticancer effect of PARP inhibitor. Int J Biol Sci. 2019;15(9):1942-54. doi: 10.7150/ijbs.34162, PMID 31523195.
23. Zheng R, Zhang K, Tan S, Gao F, Zhang Y, Xu W. Exosomal circLPAR1 functions in colorectal cancer diagnosis and tumorigenesis through suppressing BRD4 via METTL3-eIF3h interaction. Mol Cancer. 2022;21(1):49. doi: 10.1186/s12943-021-01471-y. PMID 35164758.
24. Wang W, Tang YA, Xiao Q, Lee WC, Cheng B, Niu Z. Stromal induction of BRD4 phosphorylation results in chromatin remodeling and BET inhibitor resistance in colorectal cancer. Nat Commun. 2021;12(1):4441. doi: 10.1038/s41467-021-24687-4. PMID 34290255.
25. Ni M, Li J, Zhao H, Xu F, Cheng J, Yu M. BRD4 inhibition sensitizes cervical cancer to radiotherapy by attenuating DNA repair. Oncogene. 2021;40(15):2711-24. doi: 10.1038/s41388-021-01735-3, PMID 33712705.
26. Dai X, Gan W, Li X, Wang S, Zhang W, Huang L. Prostate cancer–associated SPOP mutations confer resistance to BET inhibitors through stabilization of BRD4. Nat Med. 2017;23(9):1063-71. doi: 10.1038/nm.4378, PMID 28805820.
27. Shafran JS, Andrieu GP, Gyorffy B, Denis GV. BRD4 regulates metastatic potential of castration-resistant prostate cancer through AHNAK. Mol Cancer Res. 2019;17(8):1627-38. doi: 10.1158/1541-7786.MCR-18-1279. PMID 31110158.
28. Guan H, You Z, Wang C, Fang F, Peng R, Mao L. MicroRNA-200a suppresses prostate cancer progression through BRD4/AR signaling pathway. Cancer Med. 2019;8(4):1474-85. doi: 10.1002/cam4.2029, PMID 30784214.
29. Shafran JS, Jafari N, Casey AN, Gyorffy B, Denis GV. BRD4 regulates key transcription factors that drive epithelial–mesenchymal transition in castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2021;24(1):268-77. doi: 10.1038/s41391-020-0246-y, PMID 32690869.
30. Wang SP, Li Y, Huang SH, Wu SQ, Gao LL, Sun Q. Discovery of potent and novel dual PARP/BRD4 inhibitors for efficient treatment of pancreatic cancer. J Med Chem. 2021;64(23):17413-35. doi: 10.1021/acs.jmedchem.1c01535. PMID 34813314.
31. Zuber J, Shi J, Wang E, Rappaport AR, Herrmann H, Sison EA. RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. Nature. 2011;478(7370):524-8. doi: 10.1038/nature10334, PMID 21814200.
32. Szczepanski AP, Zhao Z, Sosnowski T, Goo YA, Bartom ET, Wang L. ASXL3 bridges BRD4 to BAP1 complex and governs enhancer activity in small cell lung cancer. Genome Med. 2020;12(1):63. doi: 10.1186/s13073-020-00760-3, PMID 32669118.
33. Zong D, Gu J, Cavalcante GC, Yao W, Zhang G, Wang S. BRD4 levels determine the response of human lung cancer cells to BET degraders that potently induce apoptosis through suppression of Mcl-1BET. Cancer Res. 2020;80(11):2380-93. doi: 10.1158/0008-5472.CAN-19-3674. PMID 32156781.
34. Xu W, Sun D, Wang Y, Zheng X, Li Y, Xia Y. Inhibitory effect of microRNA-608 on lung cancer cell proliferation, migration, and invasion by targeting BRD4 through the JAK2/STAT3 pathway. Bosn J Basic Med Sci. 2020;20(3):347-56. doi: 10.17305/bjbms.2019.4216, PMID 31621555.
35. Piha Paul SA, Hann CL, French CA, Cousin S, Braña I, Cassier PA. Phase 1 study of molibresib (GSK525762), a bromodomain and extra-terminal domain protein inhibitor, in NUT carcinoma and other solid tumors. JNCI Cancer Spectr. 2020;4(2):pkz093. doi: 10.1093/jncics/pkz093, PMID 32328561.
36. Zhao Y, Yang CY, Wang S. The making of I-BET762, a BET bromodomain inhibitor now in clinical development. J Med Chem. 2013;56(19):7498-500. doi: 10.1021/jm4014407, PMID 24107192.
37. Berthon C, Raffoux E, Thomas X, Vey N, Gomez Roca C, Yee K. Bromodomain inhibitor OTX015 in patients with acute leukaemia: a dose-escalation, phase 1 study. Lancet Haematol. 2016;3(4):e186-95. doi: 10.1016/S2352-3026(15)00247-1, PMID 27063977.
38. Seal J, Lamotte Y, Donche F, Bouillot A, Mirguet O, Gellibert F. Identification of a novel series of BET family bromodomain inhibitors: binding mode and profile of I-BET151 (GSK1210151A). Bioorg Med Chem Lett. 2012;22(8):2968-72. doi: 10.1016/j.bmcl.2012.02.041. PMID 22437115.
39. Siu KT, Ramachandran J, Yee AJ, Eda H, Santo L, Panaroni C. Preclinical activity of CPI-0610, a novel small-molecule bromodomain and extra-terminal protein inhibitor in the therapy of multiple myeloma. Leukemia. 2017;31(8):1760-9. doi: 10.1038/leu.2016.355, PMID 27890933.
40. Xu XC. COX-2 inhibitors in cancer treatment and prevention, a recent development. Anticancer Drugs. 2002;13(2):127-37. doi: 10.1097/00001813-200202000-00003, PMID 11901304.
41. Kucukguzel SG, Coskun I, Aydın S, Aktay G, Gursoy S, Cevik O. Synthesis and characterization of celecoxib derivatives as possible anti-inflammatory, analgesic, antioxidant, anticancer and anti-HCV agents. Molecules. 2013;18(3):3595-614. doi: 10.3390/molecules18033595, PMID 23519201.
42. Zhong B, Cai X, Chennamaneni S, Yi X, Liu L, Pink JJ. From COX-2 inhibitor nimesulide to potent anti-cancer agent: synthesis, *in vitro*, *in vivo* and pharmacokinetic evaluation. Eur J Med Chem. 2012;47(1):432-44. doi: 10.1016/j.ejmech.2011.11.012. PMID 22119125.
43. Gungor T, Ozleyen A, Yılmaz YB, Siyah P, Ay M, Durdagı S. New nimesulide derivatives with amide/sulfonamide moieties: selective COX-2 inhibition and antitumor effects. Eur J Med Chem. 2021;221:113566. doi: 10.1016/j.ejmech.2021.113566. PMID 34077833.
44. El-Kashef H, El-Emary T, Verhaeghe P, Vanelle P, Samy M. Anticancer and anti-inflammatory activities of some new pyrazolo[3,4-b]pyrazines. Molecules. 2018;23(10):2657. doi: 10.3390/molecules23102657, PMID 30332801.
45. Sever B, Altıntop MD, Kuş G, Ozkurt M, Ozdemir A, Kaplancıklı ZA. Indomethacin based new triazolothiadiazine derivatives: synthesis, evaluation of their anticancer effects on T98 human glioma cell line related to COX-2 inhibition and docking studies. Eur J Med Chem. 2016;113:179-86. doi: 10.1016/j.ejmech.2016.02.036. PMID 26927686.
46. Tran PHL, Lee BJ, Tran TTD. Current studies of aspirin as an anticancer agent and strategies to strengthen its therapeutic application in cancer. Curr Pharm Des. 2021;27(18):2209-20. doi: 10.2174/1381612826666201102101758, PMID 33138752.
47. Lin S, Zhang Y, Wang Z, Zhang S, Li Y, Fan Y. Preparation of novel anthraquinone-based aspirin derivatives with anti-cancer activity. Eur J Pharmacol. 2021;900:174020. doi: 10.1016/j.ejphar.2021.174020. PMID 33741381.
48. Dai M, Hu S, Liu CF, Jiang L, Yu W, Li ZL. BPTF cooperates with p50 NF-κB to promote COX-2 expression and tumor cell growth in lung cancer. Am J Transl Res. 2019;11(12):7398-409. PMID 31934287.