Trends in advanced sciences and technology

Trends in Advanced Sciences and Technology

Volume 1 Article 21

2024

Dual Activity of Aromatic and Heterocyclic Compounds as Anti-inflammatory and Anticancer promising agents

Samar Said Fatahala
Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Helwan University, Helwan, Cairo,11795, Egypt

Rania Helmy Abd El-Hameed
Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Helwan University, Helwan, Cairo,11795, Egypt

Mosaad Sayed Mohamed
Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Helwan University, Helwan, Cairo,11795, Egypt

Neama Abdallah Abd El-tawab
Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Helwan University, Helwan, Cairo,11795, Egypt, neama.hussein@pharm.helwan.edu.eg

How to Cite This Article

Fatahala, Samar Said; El-Hameed, Rania Helmy Abd; Mohamed, Mosaad Sayed; and El-tawab, Neama Abdallah Abd (2024) "Dual Activity of Aromatic and Heterocyclic Compounds as Anti-inflammatory and Anticancer promising agents," *Trends in advanced sciences and technology*: Vol. 1, Article 21.
DOI: https://doi.org/10.62537/2974-444X.1022
Available at: https://tast.researchcommons.org/journal/vol1/iss1/21

REVIEW

Dual Activity of Aromatic and Heterocyclic Compounds as Anti-inflammatory and Anticancer Promising Agents

Samar Said Fatahala, Rania Helmy Abd El-Hameed, Mossad Sayed Mohamed, Neama Abdallah Abd El-tawab*

Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Helwan University, Helwan, Cairo, Egypt

Abstract

As the second leading cause of mortality worldwide, cancer poses a severe threat to human health. Chronic inflammation has recently been linked to an increased risk for several malignancies, suggesting that reducing inflammation could be a useful approach to both cancer prevention and treatment. This review delves into the connection between inflammation and cancer and outlines the current use of anti-inflammatory drugs as potentially effective cancer prevention and therapy strategies. We herein describe the main relation and the mechanisms underlying the anti-cancer outcomes of anti-inflammatory agents; namely nonsteroidal anti-inflammatory drugs, Cyclooxygenase-2 inhibitors, lipoxygenase-inhibitors, Toll-inhibitors, and antioxidant agents.

Keywords: Anticancer, non-steroidal anti-inflammatory drugs, anti-inflammatory, antioxidant, Aromatics, cyclooxygenase-2 inhibitor, heterocyclic compounds, lipoxygenase-inhibitor, toll-inhibitor

1. Introduction

Inflammation is closely linked to cancer and is essential to the genesis and spread of tumors. It is now evident that long-term inflammation suppresses the immune system's and chemotherapeutic drugs' effectiveness and increases the growth, angiogenesis, and metastasis of cancer cells (Zhao *et al.*, 2021).

Pro-inflammatory molecules in chronic inflammation include NF-kB, reactive oxygen species (ROS), cytokines, and inducible nitric oxide synthase. All these mechanisms work together to create an environment that is ideal for the rapid proliferation of cancerous cells. So, inflammation may supply the essential mutations and the ideal conditions for tumor growth (Sarkar & Fisher, 2006).

Tumor cells express cytokines, chemokines, and their receptors, which gives them phenotypic similarities to inflammatory cells at the beginning of their development. Prolonged elevation of these inflammatory mediators can cause damage to DNA and tissue, which in turn promotes the accumulation of mutations in epithelial cells. A tumor inflammatory microenvironment is created by mutated cells, which continue to generate cytokines and attract inflammatory cells, that contribute to angiogenesis, migration, and metastasis. Studies have shown that tumors express higher levels of inflammatory mediators than normal tissues do (Philip *et al.*, 2004).

Many anti-inflammatory drugs including nonsteroidal anti-inflammatory drugs (NSAIDs), Cyclooxygenase (COX-2), lipoxygenase (LOX), and Toll-inhibitors can interfere with tumor microenvironment.

2. Inflammation

Inflammation is a physiological action triggered by infection with microorganisms and wound

Received 13 January 2024; revised 7 May 2024; accepted 13 October 2024.
Available online 11 November 2024

* Corresponding author at: Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Helwan University, Helwan, Cairo 11795, Egypt.
E-mail address: neama.hussein@pharm.helwan.edu.eg (N.A.A. El-tawab).

https://doi.org/10.62537/2974-444X.1022

healing. When tissue is damaged, activated endothelium, macrophages, and mast cells in the tissues quickly attract neutrophils to the inflammatory areas by secreting certain mediators (Balkwill & Mantovani, 2001). Neutrophil immobilization on the vascular endothelium, leukocyte integrin activation, transmigration to the inflammatory sites, and P-, L-, and E-selectin-mediated activation to encourage the rolling of cells along the endothelium are the four steps that recruit neutrophils, which are the first effectors of the inflammatory response (Wright *et al.*, 2010). Following their activation, macrophages generate cytokines and growth factors that draw different kinds of inflammatory cells to the inflammatory sites. The maintenance of the defense against injury is facilitated by each of these inflammatory response effectors (Duque & Descoteaux, 2014). The duration of the self-limiting inflammatory response is controlled by several substances that have pro- and anti-inflammatory dual actions (Megha *et al.*, 2020). Among these chemicals is the anti-inflammatory mediator transforming growth factor-β, which is released upon the phagocytosis of apoptotic cells and aids in the prompt elimination of inflammatory cells, ultimately leading to the resolution of inflammation. Chronic inflammation, which is defined by the presence of macrophages and lymphocytes with abnormal morphology, persistent growth factor, and cytokine secretion, may develop from an overly protracted inflammatory response. Prolonged production of inflammatory mediators can cause harm to DNA and tissue by creating an environment that encourages cell division and increases the risk of cancer (Philip *et al.*, 2004).

3. Cancer and inflammation

Cancer can be linked to Numerous etiologic variables, such as genomic instability and environmental stress (Mbemi *et al.*, 2020). The development of cancer is a multi-step process that is first triggered by genetic alterations induced by chemical or viral carcinogens. Subsequently, exposure to hormones, irritants, or inflammatory mediators that encourage cell division, and slow down DNA repair processes further advances the process. Eventually, cells have a growth advantage and develop into malignant cancer cells, which have uncontrolled cell division and increased angiogenesis (Hanahan & Weinberg, 2000).

Chronic inflammation is directly linked to the risk of cancer, due to its hallmarks of increased cell proliferation and decreased DNA repair (Guo *et al.*, 2017). In response to microorganisms that cause long-lasting tissue damage and DNA changes, macrophages and other leukocytes located in inflammatory regions release large amounts of ROS and mutagenic agents (Kawanishi *et al.*, 2017). Additionally, T cells and macrophages can create tumor necrosis factor-α and macrophage migration inhibitory factor, which disrupt the p53- and Rb-E2F pathways and aid in the development of tumors (Zhao *et al.*, 2017). It takes a multitude of genetic and epigenetic alterations associated with persistent inflammation to transform starting cells into malignant cells. Chronic inflammation is defined by ongoing damage to tissue and DNA, which causes epithelial cells to accumulate with mutations (Riabov *et al.*, 2014).

The transcription factor NF-kB can be activated by a variety of inflammatory and carcinogenic substances. Once triggered, it attaches to certain nucleus DNA sequences to cause the synthesis of COX enzymes and pro-inflammatory cytokines. Certain metalloproteinases (MMP-2 and MMP-9) and cytokines (VEGF, IL-6, etc.) are produced by activated immune cells. Growth factors and IL-6 can activate STAT3 by encouraging cell survival and proliferation, whereas metalloproteases break down the membrane basement and encourage cell invasion. Furthermore, ROS and mutagenic agents are secreted by macrophages in response to microbial agents that cause chronic tissue damage and change DNA through their role in carcinogenesis (Fig. 1) (Riabov *et al.*, 2014).

4. Anti-inflammatory drugs with anticancer activity

Various anti-inflammatory agent proved to have anticancer activity such as: nonsteroidal anti-inflammatory drugs (NSAIDs), Selective COX-2 inhibitors, LOX-inhibitors, Toll- inhibitors, and antioxidant agents.

4.1. Nonsteroidal anti-inflammatory drugs (NSAIDs) and their role in cancer

COX is an essential enzyme involved in prostaglandin (PG) production and plays a crucial role in the pathophysiological mechanism of inflammation. There are three isoforms of the COX enzyme: COX-1, COX-2, and COX-3. Normal tissues contain COX-1 and it regulates PG synthesis, so it is necessary for normal physiological processes. COX-2 is created during inflammation and cancer development (Zarghi & Arfaei, 2011). NSAIDs block COX-1 and COX-2 enzymes and decrease PG production. One of the most frequent consequences of COX-1

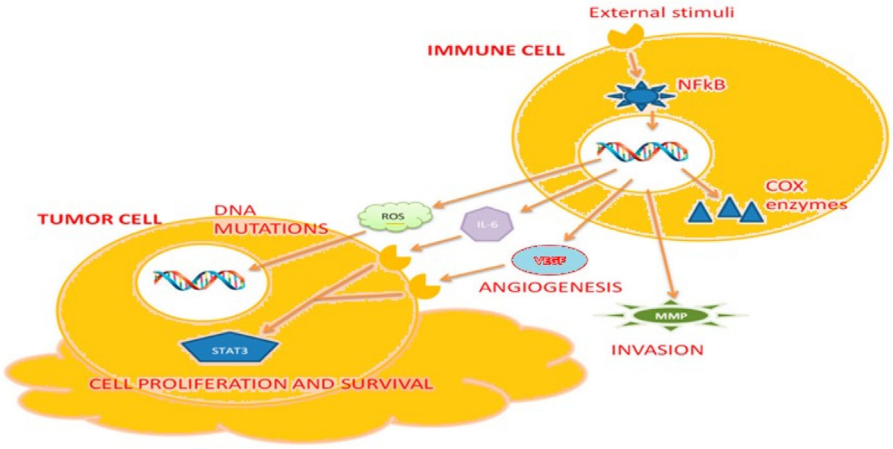


Fig. 1. Simple representative for the relation between inflammation and Cancer.

inhibition is GIT ulceration (Hörl, 2010). The key mediator of inflammation, COX-2, has an upregulated expression level during inflammation. Anti-inflammatory agents have therefore long targeted COX-2. Because it prevents apoptosis and initiates the angiogenesis process, the COX-2 enzyme plays an important role in the development of cancer. It has been noted that colorectal (60%), breast (40%), pancreatic, esophageal, lung, and melanoma cancers have higher levels of COX-2 (Mohsin *et al.*, 2022).

NSAIDs are widely used to manage pain and inflammation associated with cancer. Certain NSAIDs have been shown to suppress COX-2, which has prevented the growth of cancer. Diclofenac (a potent inhibitor of PG E2 production and COX-2) exhibits diverse impacts on the angiogenic cascade, the immune system, and tumor metabolism (Pantziarka *et al.*, 2016). Aspirin inhibits COX-1 in platelets (in the pre-systemic circulation) completely and persistently, but it also has a modest and quickly reversible inhibitory impact on COX-2 and/or COX-1 produced in nucleated cells (Dovizio *et al.*, 2012). Sulindac; a potent inhibitor of COX-1 and COX-2 and selective for COX-2 over COX-1. Reports have indicated that Sulindac can decrease the number and size of adenomas in FAP patients (Familial adenomatous polyposis) by 60–70% in randomized clinical trials (Piazza *et al.*, 2020), as revealed in Fig. 2 (Ali & Elsaman, 2016).

In 2021 X. He *et al.* synthesized novel organoselenides (NSAIDs-Se derivatives) as possible anticancer agents. Derivatives 1, 2, and 3 demonstrated the potential to trigger apoptosis in BGC-823 cells by modulating the expression of pro apoptotic caspase-8 protein, anti-apoptotic Bcl-2 protein, and pro-inflammatory cytokines (IL-2) (Fig. 3) (He *et al.*, 2021).

Recently in 2023, M. Zhong *et al.* synthesized series of NSAIDs-EBS derivatives from the hybridization of NSAIDs skeleton with Ebselen (synthetic organoselenium drug molecule has anti-inflammatory, cytoprotective, and antioxidant activity), and their cytotoxicity was evaluated against (BGC-823, SW480, MCF-7, HeLa and A549) human cell lines. NSAIDs-EBS derivative (4) showed most potent cytotoxicity activity against five cancer cell lines (Fig. 4) (Zhong *et al.*, 2023).

4.2. Selective COX-2 inhibitors with anticancer activity

The COX-2 enzyme has been found to exhibit persistent overexpression in a multitude of premalignant, malignant, and metastatic human

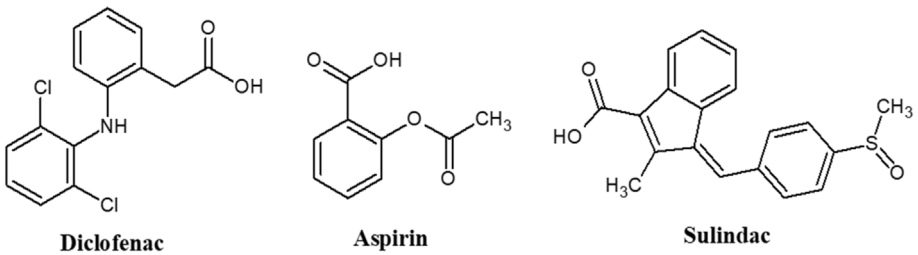


Fig. 2. Nonsteroidal anti-inflammatory drugs proved to have remarkable anticancer activity.

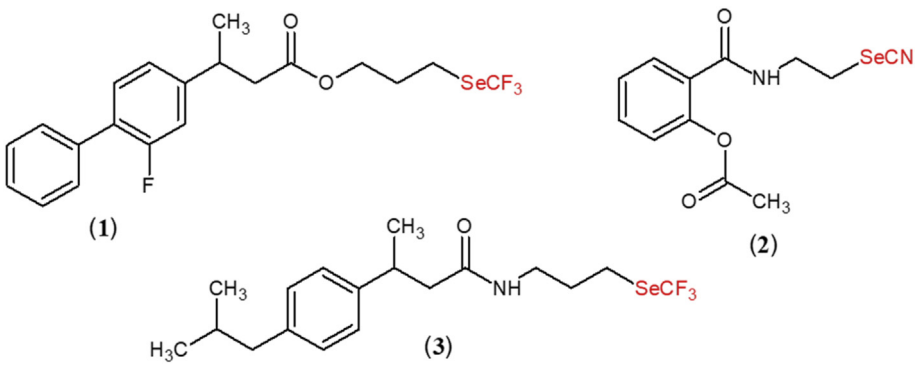


Fig. 3. Nonsteroidal anti-inflammatory drugs-Se derivatives with anticancer activity.

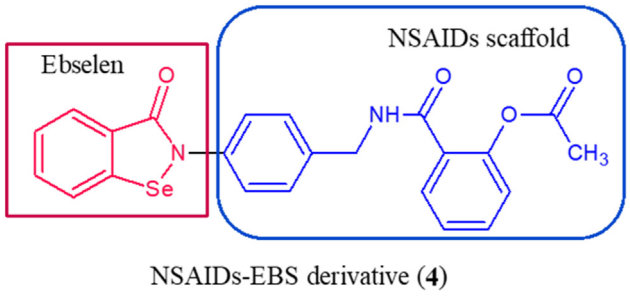


Fig. 4. Nonsteroidal anti-inflammatory drugs-EBS derivative with potent anticancer activity.

malignancies, such as those of the breast, liver, and colon. As a result, it contributes significantly to several malignant diseases, and its inhibition provides a crucial target for cancer treatment (Fig. 5) (Gasparini *et al.*, 2003).

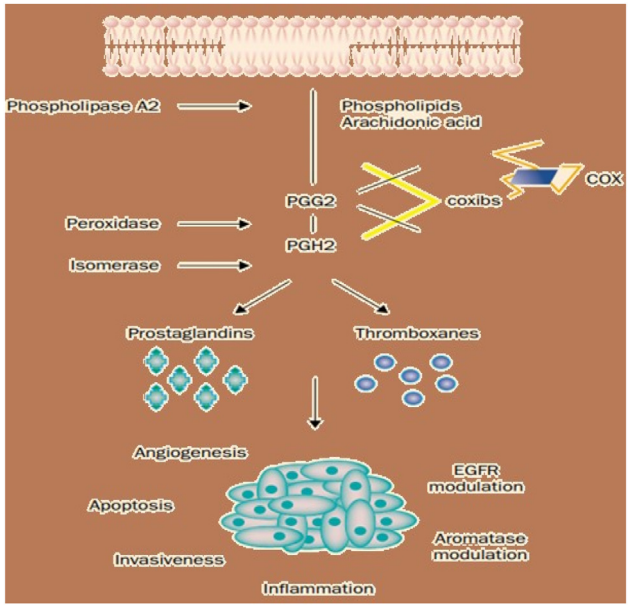


Fig. 5. The pathways which stimulate tumor growth through cyclo-oxygenase-2 and the mechanisms of action of coxibs.

N containing heterocyclic as pyrazole derivatives have demonstrated encouraging anti-inflammatory and anticancer properties, suggesting that the pyrazole motif can be a strong foundation for new therapeutics (Zhang *et al.*, 2023).

The pyrazole framework as well as the mono and di hetero five-membered rings are known to be important components of several well-known selective COX-2 inhibitors bearing an anticancer activity, including Celecoxib, Valdecoxib, and Rofecoxib (Fig. 6) (Shaker *et al.*, 2022).

In 2014, Diphenylthiazole substituted thiazolidinone derivatives were prepared by Abdelazeem *et al.* and investigated their anticancer behavior against a set of cancer cell lines. Thiazolo derivatives 5 and 6; showed potent anticancer agents toward the human cell lines (MCF-7, HCT-116, PC-3, Caco-2, and DU-145) and good COX-2 inhibition percentages comparable to celecoxib (Fig. 7) (Abdelazeem *et al.*, 2014).

Later on, Abdellatif *et al.* synthesized a novel series of blend structures containing thiohydantoin (anti-cancer agent) and pyrazole core (selective COX-2) possessing SO_2Me pharmacophore, and evaluated for their anti-cancer and anti-inflammatory activities. Methoxy derivatives 7 showed higher COX-2 inhibitory activity in comparison with COX-2 selective drug celecoxib, higher cytotoxic activity, and potent inhibitory activity of human Topo-1 enzyme (Fig. 8) (Abdellatif *et al.*, 2019).

In addition to the reported activities of the novel oxadiazole derivatives 8 and 9 based molecules, prepared by El-Sayed *et al.* as potent COX-2 inhibition compared to the known COX-2 selective inhibitor Celecoxib, a good cytotoxic activity and inhibition of the tyrosine kinase EGFR are also notices (Fig. 9) (El-sayed *et al.*, 2019).

In 2020, a series of sulfonyl hydrazones were synthesized by Senkardes and colleagues and assessed for their cytotoxic and apoptotic effects on

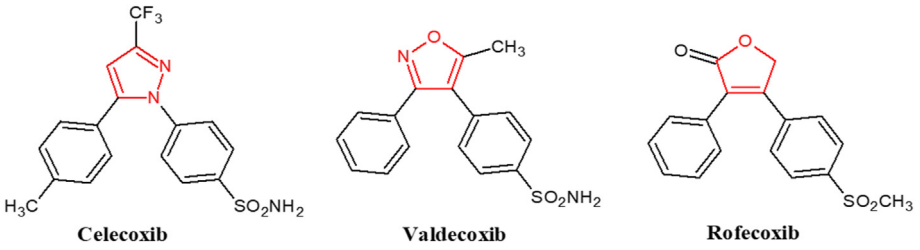


Fig. 6. Selective Cyclooxygenase-2 inhibitors with anticancer activity.

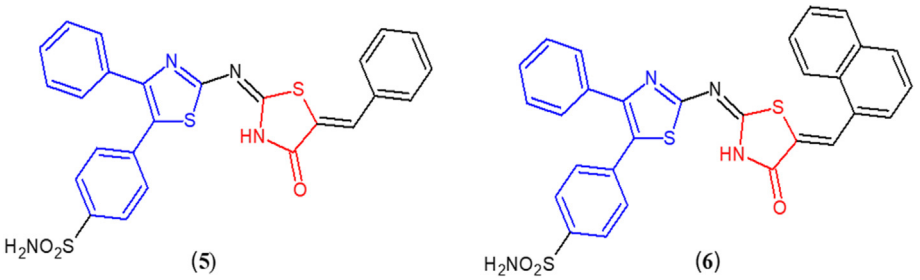


Fig. 7. Diphenyl thiazole- based Cyclooxygenase-2 inhibitors with anticancer activity.

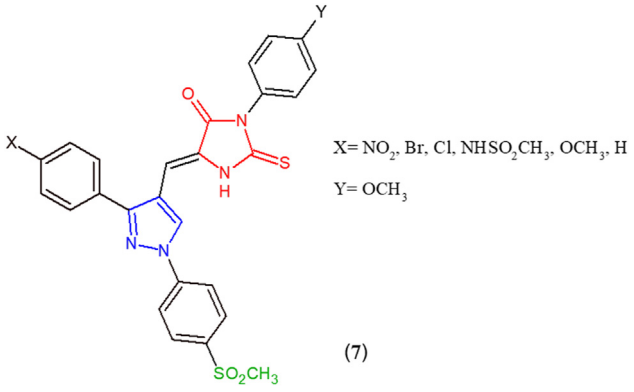


Fig. 8. Thiohydantoin derivatives with pyrazole core as Cyclooxygenase-2 and human Topo-1 inhibitors.

PC3 and MCF-7 cell lines in addition to COXs activities. Sulfonyl hydrazone derivatives 10 showed high COX-2 inhibition and potent anticancer activity by induction of apoptosis through the mitochondrial pathway, along with upregulation of Bax and down regulation of Bcl-2 protein expression (Fig. 10) (Şenkardeş *et al.*, 2020).

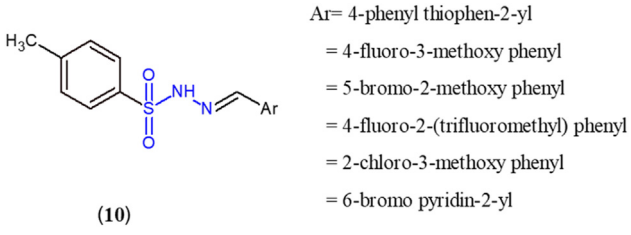


Fig. 10. Sulfonyl hydrazone derivatives with potent Cyclooxygenase-2 inhibition and anticancer activity.

One year later, Abolhasani and colleagues synthesized novel spiroisoxazoline derivatives with indanone Spiro bridge, and assessed for their ability to selectively inhibit COX-2 and for their cytotoxicity on various cell lines. Spiroisoxazoline derivatives 11 showed effective inhibition COX-2 enzyme as it fit better within the active site of COX-2, and showed more cytotoxicity against malignant cells but not against healthy cells. This provides evidence that, the COX-2 enzyme selective inhibitors may have more potent anticancer effects (Fig. 11) (Abolhasani *et al.*, 2021).

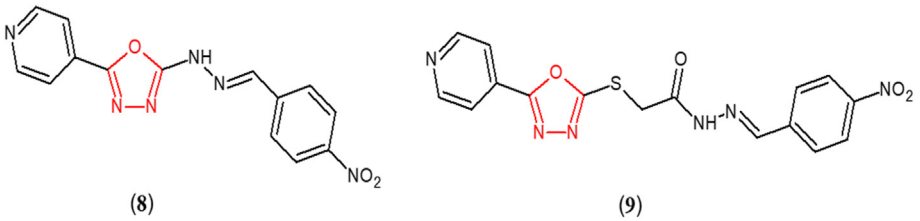


Fig. 9. 2- substituted -5- (4-pyridyl)-1,3,4-oxadiazoles with selective cyclooxygenase-2 inhibitory activity.

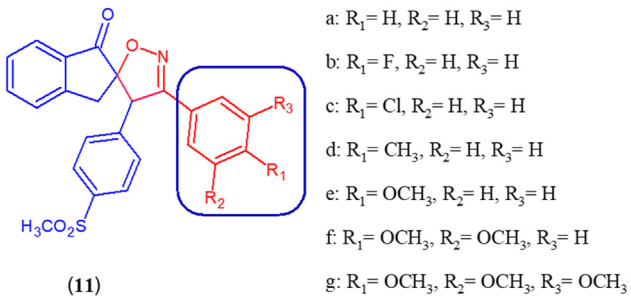


Fig. 11. Indanonic spiroisoxazoline compounds with selective cyclooxygenase-2 inhibition as anticancer agents.

Furthermore, in 2022, Novel diarylpyrazole derivatives containing methyl sulfonyl moiety were prepared and evaluated for their ability to inhibit COX enzyme. Diarylpyrazole derivatives 12 and 13 exhibited potent and selective COX-2 inhibitory activity comparable to celecoxib and indomethacin and showed remarkable cytotoxicity against malignant cells (HCT-116, MCF-7, and HePG-2). These derivatives regulate the G1 and S stages of the cell cycle, which causes MCF-7 cells to undergo apoptosis by cell cycle arrest (Fig. 12) (Shaker *et al.*, 2022).

Recently in 2023, Halim and colleagues prepared novel substituted pyrazole derivatives, and their anticancer activity was evaluated. Pyrazole derivative 14 demonstrated strong anti-proliferative action against (MCF-7 and HT-29) cancer cell lines as well as specific suppression of the COX-2 enzyme. The compound stopped cell cycle at G1/S phase in HT-29 treated cells, displayed accumulation of cells in G0 phase, and increased in percentage of cells in the early and late phases of apoptosis. The ability to induce apoptosis was verified by down-regulating Bcl-2, up-regulating BAX, and activating the levels of the caspase-3/9 protein. Also, inhibition of both EGFR and Topomerise-1 (Topo-1) aimed to interrupt DNA replication in cancer cells (Fig. 13) (Halim *et al.*, 2023).

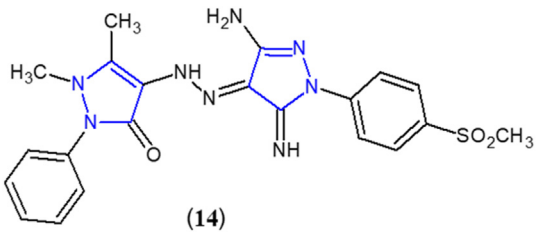


Fig. 13. Cyclooxygenase-2 inhibitors based on pyrazole with potential anticancer activity.

4.3. LOX-inhibitors with anticancer activity

The polyunsaturated fatty acid arachidonic acid (AA), which is derived from membrane phospholipids, is one of the powerful mediators of inflammation. The two main metabolic processes for AA are the LOX pathway, which generates a variety of leukotrienes (LTs) and hydroxyeicosatetranoic acids (HETEs), and the COX system, which converts AA to PGs and thromboxanes (TXs) (Wang *et al.*, 2021).

5-LOX (human nonheme enzyme) is an essential component of LOXs, and produces leukotriene B4 (LTB4) and 5-HETE, which may stimulate the growth of cancer cells, inhibit apoptosis, and enhance cell proliferation (Fig. 14) (Steinhilber *et al.*, 2010).

Zileuton (benzothiophene *N*-hydroxyurea) is the only approved 5-lipoxygenase (5-LOX) inhibitor, and is assumed to work by inhibiting the biosynthesis of LT, which can help with inflammatory and allergy disorders (Rossi *et al.*, 2010). The drug is a member of the class of iron ligand-type inhibitors of 5-LOX, which chelates the iron in the enzyme's active site while also having some weak reducing abilities. Considering the significant role that LTs play in inflammation of the airway, zileuton offers an extra therapeutic choice for the treatment of persistent and chronic asthma.

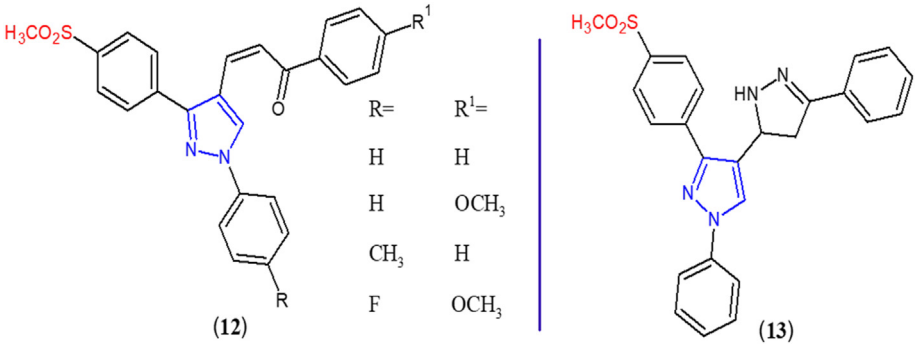


Fig. 12. Diaryl pyrazole derivatives with dual anticancer and anti-inflammatory activity.

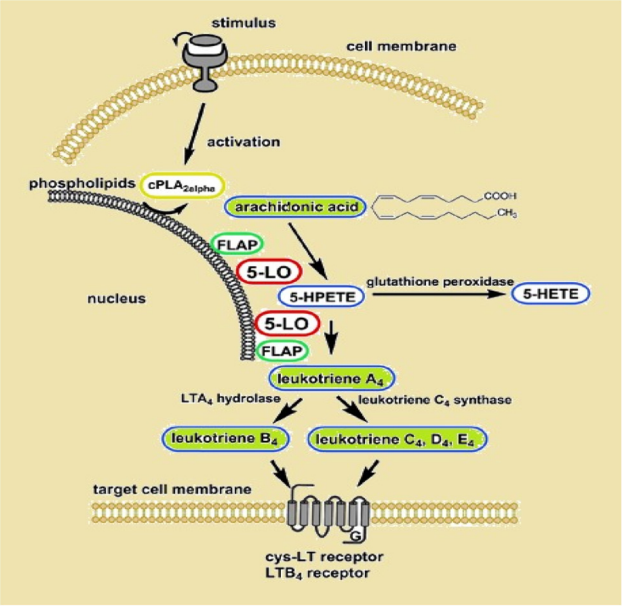
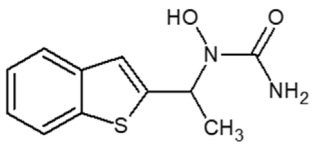


Fig. 14. Lipoxygenase (LOX) pathway for leukotriene B4 (LTB4) and 5-HETE production.

Zileuton showed anticancer activity against cervical cancer cells in preclinical study by inhibiting the ALOX5-5-HETE axis (Fig. 15) (Li *et al.*, 2021).

In 2019, Li and colleagues synthesized new blend compounds with morpholine and diaryl-1,5-diazole structures that function as dual COX-2/5-LOX inhibitors. The pyrazole-amide derivative 15 showed potent antiproliferative activities as well as COX-2/5-LOX inhibitory *in vitro*. Also, showed potency against cancer cell lines (HeLa, A549, and MCF-7 cells), and excellent inhibitory activities on COX-2 and 5-LOX (Fig. 16) (Li *et al.*, 2019).

Recently in 2022, Ahmed and colleagues synthesized new series of pyrazole-chalcone analogs of Lonazolac and the anticancer activity against four cancer cell lines *in vitro* were investigated. Compound 16 showed potent activity against cancer cell lines, potent inhibition against tubulin polymerization, and significant Induction of pre-G1 apoptosis and G2/M cell cycle arrest; it also showed promising inhibitory activity towards 5-LOX. High levels of inducible nitric oxide synthase and PGE2 (Prostaglandin E2) inhibitory actions in LPS (lipopolysaccharide)-stimulated



Zileuton

Fig. 15. Zileuton as 5-lipoxygenase inhibitor.

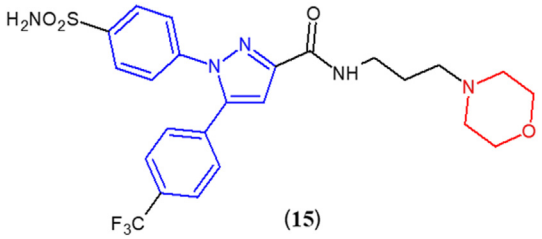


Fig. 16. Diaryl-1,5-diazole derivative containing morpholine function as dual cyclooxygenase-2/5-lipoxygenase inhibitor and anticancer agent.

RAW cells (It is a mouse Macrophage cell lines), along with a strong suppression of NO release, validated the anti-inflammatory action (Fig. 17) (Ahmed *et al.*, 2022).

4.4. Toll-inhibitors

The core of the innate sensor, toll-like receptors (TLRs) are a family of pattern recognition receptors that also help to shape and connect the innate and adaptive immune responses. They can identify the two most powerful inflammatory response inducers: internal damage-associated molecular patterns (DAMPs) and external pathogen-associated molecular patterns (Yu & Feng, 2018).

In order to defend against invaders and repair injured tissue, TLR activation triggers signaling cascades in the host. This results in the production of many immunological modulators and inflammatory cytokines (Wang *et al.*, 2016).

Excessive TLR activation contributes to the onset and progression of numerous disorders, including cancer and Alzheimer's disease, by persistently producing pro-inflammatory cytokines and chemokines that disturb immunological homeostasis (Momtazmanesh *et al.*, 2020; So & Ouchi, 2010).

TLRs are divided into two subgroups: cell membrane TLRs (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10) that are expressed on the cell surface. On the other hand, intracellular TLRs or nucleic acids sensors (TLR3, TLR7, TLR8, and TLR9) that are found in the endoplasmic reticulum, lysosomes, and endosomes (Gay *et al.*, 2014).

It has been demonstrated that TLR4, the first human toll protein homolog identified, can stimulate the production of genes related to inflammatory reactions. Because TLR2 and TLR4 are cell surface TLRs, their significance has increased greatly (Elzayat & Sibaii, 2019).

TLR2 and TLR4 inhibitors prevent cascades of inflammatory cytokines and immune modulators, act as potent anti-inflammatory agent and can be used as a target for promising anticancer therapy (Neill *et al.*, 2009).

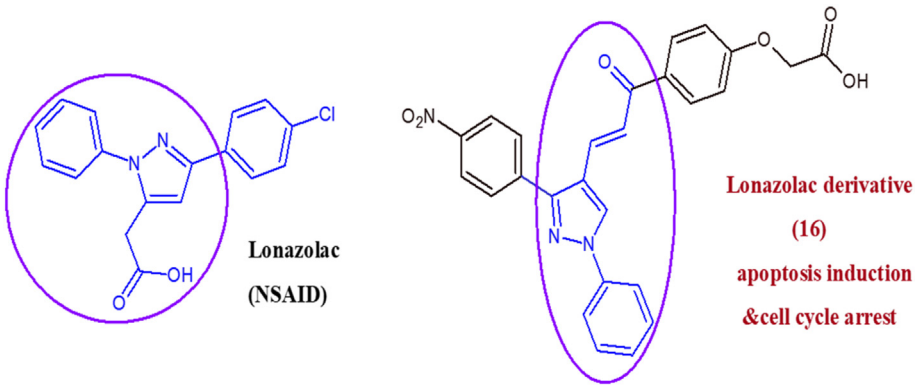


Fig. 17. Pyrazole-Chalcone analog of lonazolac as potential anti-inflammatory and antitumor agents.

In 2022, Sayed and colleagues synthesized new fused pyrrolopyrimidine derivatives with promising antioxidant and anti-inflammatory activities. Compounds 17, 18, and 19 showed significant anti-inflammatory action *via* inhibition of TLR4, TLR2, and COX-2 enzyme. Also these derivatives showed promising anti-oxidative activities (potent scavenging properties against the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical) compared to the reference, BHT (Butylated hydroxytoluene) (Fig. 18) (Sayed *et al.*, 2022).

4.5. Anti-inflammatory agents as antioxidant

The oxidation mechanism that takes place in human bodies eventually results in serious illness by destroying different cells and tissues (Muhammad *et al.*, 2014). It has been noted that the oxidation procedure might result in serious diseases like skin issues, heart diseases, and cancer (Mahnashi *et al.*, 2022). Currently, several methods and strategies are employed to eliminate the impact of free radicals (Sadiq *et al.*, 2015).

Natural sources are among the main suppliers of antioxidants, which may also be beneficial in unseen disorders such as stress (Hassan *et al.*, 2021). New antioxidants derived from synthetic and natural resources are developing daily for the benefit of humans (Bibi *et al.*, 2019). Natural products, especially fruits, have unique compounds showing significant antioxidant properties; nevertheless, certain synthetic compounds that have been discovered recently also have a great antioxidant capacity (Kumar *et al.*, 2021).

Anti-inflammatory agents with antioxidant properties are crucial in preventing serious diseases, particularly cancer (Małecka *et al.*, 2021).

In 2020, Novel coumarin-sulfonamide derivatives were synthesized and assessed for their anti-inflammatory and antioxidant outcomes. Compound 20 was the most active towards COX-2 isozyme and demonstrated significant antioxidant activity (the DPPH microplate-based method) (Fig. 19) (Alshibl *et al.*, 2020).

Later in 2022, Mahmood and colleagues synthesized novel series of (2*S*,3*S*)-2-(4-isopropylbenzyl)-

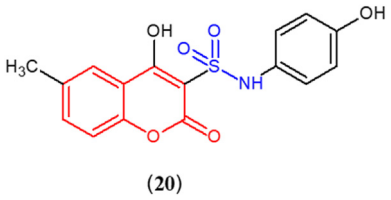


Fig. 19. New coumarin derivative as antioxidant and anti-inflammatory agents.

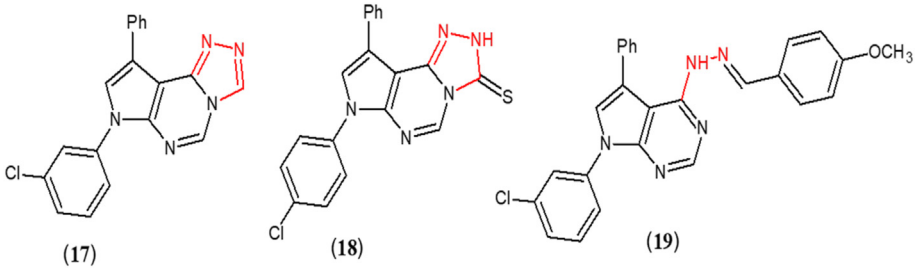


Fig. 18. Fused pyrrolopyrimidine derivatives with promising anti-inflammatory and antioxidant activity.

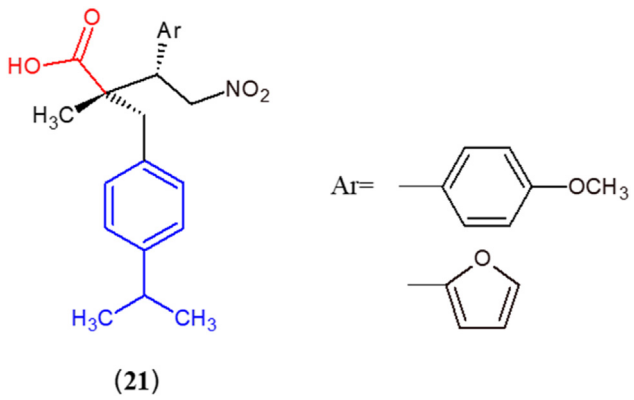


Fig. 20. Carboxylic acid analogues as potential anti-inflammatory and antioxidant.

2-methyl-4-nitro-3- phenylbutanals and their corresponding carboxylic acid analogs, and their anti-inflammatory and antioxidant activity were evaluated. Carboxylic acid analogues 21 showed potent anti-inflammatory action toward COX-1, COX-2, and 5-LOX targets *in vitro*, and promising antioxidant activity (DPPH Free Radical Scavenging Assay) (Fig. 20) (Mahmood *et al.*, 2022).

4.6. Conclusion

Inflammation is directly linked to cancer and is essential to the growth and spread of tumors. Thus, it is imperative to target inflammation for the early detection and therapy of cancer, either in isolation or in conjunction with chemotherapeutic drugs. Anti-inflammatory medicine use has been linked to a lower incidence and recurrence of cancer, according to several studies. Numerous anti-inflammatory drugs can be added to traditional treatments as adjuvants. Reducing the development of cancer may be possible by treating chronic inflammation early on.

Ethics information

This is a review article, so there is no ethics information.

Funding

The authors conducting this research are self-funded, and no specific grant from any funding organization has been obtained for it.

Authors contribution

Each participating researcher made a contribution to this project. The final manuscript was read and approved by all authors.

Conflicts of interest

There are no conflicts of interest.

References

Abdelazeem, A. H., Gouda, A. M., Omar, H. A., & Tolba, M. F. (2014). Design, synthesis and biological evaluation of novel diphenylthiazole-based cyclooxygenase inhibitors as potential anticancer agents. *Bioorganic Chemistry, 57*, 132–141.

Abdellatif, K. R. A., Fadaly, W. A. A., Mostafa, Y. A., Zaher, D. M., & Omar, H. A. (2019). Thiohydantoin derivatives incorporating a pyrazole core: Design, synthesis and biological evaluation as dual inhibitors of topoisomerase-I and cycloxygenase-2 with anti-cancer and anti-inflammatory activities. *Bioorganic Chemistry, 91*(May), Article 103132.

Abolhasani, H., Zarghi, A., Komeili, T., & Abolhasani, A. (2021). Design, synthesis and biological evaluation of novel indanone containing spiroisoxazoline derivatives with selective COX-2 inhibition as anticancer agents. *Bioorganic & Medicinal Chemistry, 32*(November 2020), Article 115960.

Ahmed, A. H. H., Mohamed, M. F. A., Allam, R. M., Nafady, A., Mohamed, S. K., Gouda, A. E., & Beshr, E. A. M. (2022). Design, synthesis, and molecular docking of novel pyrazole-chalcone analogs of lonazolac as 5-LOX, iNOS and tubulin polymerization inhibitors with potential anticancer and anti-inflammatory activities. *Bioorganic Chemistry, 129*(September), Article 106171.

Ali, M., & Elsaman, T. (2016). Nonsteroidal anti-inflammatory drugs (NSAIDs) derivatives with anti-cancer activity. *American journal of research communication, 4*, 4.

Alshibl, H. M., Al-abdullah, E. S., Haiba, M. E., Alkahtani, H. M., Awad, G. E. A., Mahmoud, A. H., et al. (2020). Synthesis and evaluation of new coumarin derivatives as antioxidant, antimicrobial, and anti-inflammatory agents. *Molecules, 25*, 1–28.

Balkwill, F., & Mantovani, A. (2001). Inflammation and cancer: Back to virchow? *Lancet, 357*, 539–545.

Bibi, A., Shah, T., Sadiq, A., Khalid, N., Ullah, F., & Iqbal, A. (2019). L-Isoleucine-catalyzed michael synthesis of N-alkyl-succinimide derivatives and their antioxidant activity assessment. *Russian Journal of Organic Chemistry, 55*, 1749–1754.

Dovizio, M., Tacconelli, S., Sostres, C., Ricciotti, E., & Patrignani, P. (2012). Mechanistic and pharmacological issues of aspirin as an anticancer agent. *Pharmacy Times, 5*, 1346–1371.

Duque, G. A., & Descoteaux, A. (2014). Macrophage cytokines: Involvement in immunity and infectious diseases. *Frontiers in Immunology, 5*(October), 1–12.

El-sayed, N. A., Nour, M. S., Salem, M. A., & Arafa, R. K. (2019). New oxadiazoles with selective-COX-2 and EGFR dual inhibitory activity: Design, synthesis, cytotoxicity evaluation and in silico studies. *European Journal of Medicinal Chemistry, 183*, Article 111693.

El-zayat, S. R., & Sibaii, H. (2019). Toll-like receptors activation, signaling, and targeting: An overview. *Bulletin of the National Research Centre, 43*, 1–12.

Gasparini, G., Longo, R., Sarmiento, R., & Morabito, A. (2003). Inhibitors of cyclo-oxygenase 2: A new class of anticancer agents. *The Lancet Oncology, 4*(October), 605–615.

Gay, N. J., Symmons, M. F., Gangloff, M., & Bryant, C. E. (2014). Assembly and localization of Toll-like receptor signalling complexes. *Nature Publishing Group, 14*(August), 546–558.

Guo, Y., Nie, Q., Maclean, A. L., Li, Y., Lei, J., & Li, S. (2017). Multiscale modeling of in fl ammation-induced tumorigenesis reveals competing oncogenic and oncoprotective roles for infl ammation. *Cancer Research, 77*, 6429–6441.

Hörl, W. H. (2010). Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmacy Times, 3*, 2291–2321.

Halim, P. A., Sharkawi, S. M. Z., & Labib, M. B. (2023). Novel pyrazole-based COX-2 inhibitors as potential anticancer

agents: Design, synthesis, cytotoxic effect against resistant cancer cells, cell cycle arrest, apoptosis induction and dual EGFR/Topo-1 inhibition. *Bioorganic Chemistry, 131*(October 2022), Article 106273.

Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. *Cell, 100*, 57−70.

Hassan, S. S. U., Muhammad, I., Abbas, S. Q., Hassan, M., Majid, M., Jin, H. Z., & Bungau, S. (2021). Stress driven discovery of natural products from actinobacteria with antioxidant and cytotoxic activities including docking and ADMET properties. *International Journal of Molecular Sciences, 22*, Article 11432.

He, X., Nie, Y., Zhong, M., Li, S., Li, X., Guo, Y., et al. (2021). New organoselenides (NSAIDs-Se derivatives) as potential anticancer agents: Synthesis, biological evaluation and in silico calculations. *European Journal of Medicinal Chemistry, 218*, Article 113384.

Kawanishi, S., Ohnishi, S., Ma, N., Hiraku, Y., & Murata, M. (2017). Crosstalk between DNA damage and inflammation in the multiple steps of carcinogenesis. *International Journal of Molecular Sciences, 18*, 1808.

Kumar, D., Kumar, R., Ramajayam, R., Lee, K. W., & Shin, D. (2021). Synthesis, antioxidant and molecular docking studies of (−) -catechin derivatives. *Journal of the Korean Chemical Society, 65*, 106−112.

Li, Z., Wang, Z., Li, X., Abbas, M., Wu, S., Ren, S., et al. (2019). Design, synthesis and evaluation of novel diaryl-1, 5-diazoles derivatives bearing morpholine as potent dual COX-2/5-LOX inhibitors and antitumor agents. *European Journal of Medicinal Chemistry, 169*, 168−184.

Li, L., Xiao, Y., Xu, Z., & Wang, S. (2021). Zileuton inhibits arachidonate - 5 - lipoxygenase to exert antitumor effects in preclinical cervical cancer models. *Cancer Chemotherapy and Pharmacology, 88*, 953−960.

Małecka, M., Hikisz, P., Budzisz, E., Mucha, P., & Skoczy, A. (2021). Overview of the antioxidant and anti-inflammatory activities of selected plant compounds and their metal ions complexes. *Molecules, 26*, 4886.

Mahmood, F., Khan, J. A., Mahnashi, M. H., Jan, M. S., Javed, M. A., Rashid, U., et al. (2022). Anti-inflammatory, analgesic and antioxidant potential of new (2S,3S)-2-(4-isopropylbenzyl)-2-methyl-4-nitro-3-phenylbutanals and their corresponding carboxylic acids through in vitro, in silico and in vivo studies. *Molecules, 27*, 1−20.

Mahnashi, M. H., Alyami, B. A., Alqahtani, Y. S., Alqarni, A. O., Jan, M. S., Hussain, F., et al. (2022). Antioxidant molecules isolated from edible prostrate knotweed: Rational derivatization to produce more potent molecules. *Oxidative Medicine and Cellular Longevity, 2022*, 1−15.

Mbemi, A., Khanna, S., Njiki, S., Yedjou, C. G., & Tchounwou, P. B. (2020). Impact of gene − environment interactions on cancer development. *International Journal of Environmental Research and Public Health, 17*, 8089.

Megha, K. B., Joseph, X., Akhil, V., & Mohanan, P. V. (2020). Cascade of immune mechanism and consequences of inflammatory disorders. *Phytomedicine, 91*(January), Article 153712.

Mohsin, A., Aslam, S., Ahmad, M., Irfan, M., Al-hussain, S. A., & Zaki, M. E. A. (2022). Cyclooxygenase-2 (COX-2) as a target of anticancer agents: A review of novel synthesized scaffolds having anticancer and COX-2 inhibitory potentialities. *Pharmaceuticals, 15*, 1471.

Momtazmanesh, S., Perry, G., & Rezaei, N. (2020). Toll-like receptors in Alzheimer' s disease. *Journal of Neuroimmunology, 348*(June), Article 577362.

Muhammad, S., Shah, M., Sadiq, A., Muhammad, S., Shah, H., & Ullah, F. (2014). Antioxidant, total phenolic contents and antinociceptive potential of Teucrium stocksianum methanolic extract in different animal models. *BMC Complementary and Alternative Medicine, 14*, 1−7, 2014.

Neill, L. A. J. O., Bryant, C. E., & Doyle, S. L. (2009). Therapeutic targeting of toll-like receptors for infectious and inflammatory diseases and cancer. *Pharmacological Reviews, 61*, 177−197.

Pantziarka, P., Sukhatme, V., Bouche, G., Meheus, L., & Sukhatme, V. P. (2016). Repurposing drugs in oncology (ReDO)— diclofenac as an anti-cancer agent. *Ecancermedicalscience, 10*, 1−28.

Philip, M., Rowley, D. A., & Schreiber, H. (2004). Inflammation as a tumor promoter in cancer induction. *Seminars in Cancer Biology, 14*, 433−439.

Piazza, G. A., Chen, X., Ward, A., Coley, A., Zhou, G., Buchsbaum, D. J., et al. (2020). Oncology Signaling Targeting cGMP/PKG signaling for the treatment or prevention of colorectal cancer with novel sulindac derivatives lacking cyclooxygenase inhibitory activity. *Oncology Signaling, 3*, 1−6.

Riabov, V., Gudima, A., Wang, N., Mickley, A., Orekhov, A., Red, G., & Blood, C. (2014). Role of tumor associated macrophages in tumor angiogenesis and lymphangiogenesis. *Frontiers in Physiology, 5*(March), 1−13.

Rossi, A., Pergola, C., K, A., Hoffmann, M., D, F., Bramanti, P., et al. (2010). The 5-lipoxygenase inhibitor, zileuton, suppresses prostaglandin biosynthesis by inhibition of arachidonic acid release in macrophages. *British Journal of Pharmacology, 161*, 555−570.

Şenkardeş, S., Han, M.İ., Kulabaş, N., Abbak, M., Çevik, Ö., & Küçükgüzel, İ. (2020). Synthesis, molecular docking and evaluation of novel sulfonyl hydrazones as anticancer agents and COX - 2 inhibitors. *Molecular Diversity, 24*, 673−689.

Sadiq, A., Mahmood, F., Ullah, F., Ayaz, M., Ahmad, S., Haq, F. U., et al. (2015). Synthesis, anticholinesterase and antioxidant potentials of ketoesters derivatives of succinimides: A possible role in the management of Alzheimer's. *Chemistry Central Journal, 9*, 1−9.

Sarkar, D., & Fisher, P. B. (2006). Molecular mechanisms of aging-associated inflammation. *Cancer Letters, 236*, 13−23.

Sayed, A. I., Mansour, Y. E., Ali, M. A., Aly, O., Zainab, M., Said, A. M., et al. (2022). Novel pyrrolopyrimidine derivatives: Design, synthesis, molecular docking, molecular simulations and biological evaluations as antioxidant and anti-inflammatory agents. *Journal of Enzyme Inhibition and Medicinal Chemistry, 37*, 1821−1837.

Shaker, A. M. M., Shahin, M. I., Aboulmagd, A. M., Abdel, S. A., Abdel-rahman, H. M., Abou, D. A., & Ella, E. (2022). Novel 1, 3-diaryl pyrazole derivatives bearing methylsulfonyl moiety: Design, synthesis, molecular docking and dynamics, with dual activities as anti-inflammatory and anticancer agents through selectively targeting. *Bioorganic Chemistry, 129*(September), Article 106143.

So, E. Y., & Ouchi, T. (2010). The application of Toll like receptors for cancer therapy. *International Journal of Biological Sciences, 6*, 675−681.

Steinhilber, D., Fischer, A. S., Metzner, J., Steinbrink, S. D., Roos, J., & Maier, T. J. (2010). 5-Lipoxygenase: Underappreciated role of a pro-inflammatory enzyme in tumorigenesis. *Frontiers in Pharmacology, 1*, 8074.

Wang, Y., Song, E., Bai, B., & Vanhoutte, P. M. (2016). Toll-like receptors mediating vascular malfunction: Lessons from receptor subtypes. *Pharmacology & Therapeutics, 158*, 91−100.

Wang, B., Wu, L., Chen, J., Dong, L., & Chen, C. (2021). Metabolism pathways of arachidonic acids: Mechanisms and potential therapeutic targets. *Signal Transduction and Targeted Therapy, 6*, 94.

Wright, H. L., Moots, R. J., Bucknall, R. C., & Edwards, S. W. (2010). Neutrophil function in inflammation and inflammatory diseases. *Rheumatology, 49*(March), 1618−1631.

Yu, L., & Feng, Z. (2018). The role of toll-like receptor signaling in the progression of heart failure. *Mediators of Inflammation, 2018*, 11.

Zarghi, A., & Arfaei, S. (2011). Selective COX-2 inhibitors: A review of their structure-activity relationships. *Iranian Journal of Pharmaceutical Research, 10*(September), 655−683.

Zhang, Y., Wu, C., Zhang, N., Fan, R., & Ye, Y. (2023). Recent advances in the development of pyrazole derivatives as anticancer agents. *International Journal of Molecular Sciences, 24*, Article 12724.

Zhao, H., Liu, J., Song, L., Liu, Z., Han, G., Yuan, D., & Wang, T. (2017). Oleanolic acid rejuvenates testicular function through attenuating germ cell DNA damage and apoptosis via deactivation of NF- j B, p53 and p38 signalling pathways. *Journal of Pharmaceutics & Pharmacology, 69*, 295−304.

Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., & Li, Y. (2021). Inflammation and tumor progression: Signaling pathways and targeted intervention. *Signal Transduction and Targeted Therapy, 263*(May), 1−43.

Zhong, M., Lu, Y., Li, S., Li, X., Liu, Z., He, X., & Zhang, Y. (2023). Synthesis, cytotoxicity, antioxidant activity and molecular modeling of new NSAIDs-EBS derivatives. *European Journal of Medicinal Chemistry, 259*(May), Article 115662.