

A Review on Some Proposed Targets and its Effective Molecules in Cancer Disease

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ABSTRACT

Development of anticancer drugs with fewer or no side effects is important for the treatment of cancer as chemotherapeutic agents having lots of side and/or toxic effects in cancer treatment. The search for such potential anticancer drugs have led to the discovery of synthetic small molecules with anti-carcinogenic activity and limited harmful side effects particularly with respect to the immune system. In the decade, there have been numerous advances in understanding of pathogenesis of cancer as a result there are many novel targets found and still in the researchers interest. The aim of this review is to provide overview on some novel targets and some effective molecule on those targets. They are proposed and helpful targets for treatment of cancer. This review focus on various proposed novel targets like HIF, CYP450, TNF- α , protein kinase, COX-2, NF-kB, Phosphodiesterase (PDs), Peroxisome proliferator-activated receptors (PPARs), Carbonic anhydrase, Farnesyltransferase, Histone deacetylase and its role in cancer with some effective inhibitor molecules on those targets. More research in those targets will helpful for development of newer anticancer agents on targeted based drug discovery. Furthermore in the area of combination of this target inhibitors with existing treatment or new targeted therapy may prove to be useful clinically.

Keywords: Cancer disease, effective molecules, link between target and cancer, proposed targets

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INTRODUCTION

Within last half a century there have been major developments in our understanding of cancer at the molecular level. Various growth factors, hormones, cytokines, oncogenes, viruses, bacteria, and carcinogens have been identified that initiate and promote cancer. Many of the sub cellular mechanisms that promote hyper proliferation, invasion, angiogenesis and metastasis, have also been delineated. The structure of entire human genome consisting of almost 25,000 genes and at least some of those genes that mediate tumorigenesis, is also quite apparent now. In spite of this tremendous increase in knowledge about cancer, its prevention and treatment is still lacking. As a result of these advances there are many targets like inhibitors of HIF, CYP450, TNF- α , protein

kinase etc. found out to treat the cancer. This review includes more updated information about novel targets and its effective molecules as potential anticancer agents.

This review focus on various proposed novel targets like HIF, CYP450, TNF- α , protein kinase, COX-2, NF-kB, Phosphodiesterase (PDs), Peroxisome proliferator-activated receptors (PPARs), Carbonic anhydrase, Farnesyltransferase, Histone deacetylase and its role in cancer with some effective inhibitor molecules on those targets. More research in those targets will helpful for development of newer anticancer agents. Furthermore in the area of combination of this target inhibitors with existing treatment or new

targeted therapy may prove to be useful clinically.

1. Hypoxia inducible factor (HIF) -I:

HIF1 is a heterodimeric basic helix-loop-helix structure [1] that is composed of HIF1A, the alpha subunit (this protein), and the aryl hydrocarbon receptor nuclear translocator (Arnt), the beta subunit. HIF1A contains a basic helix-loop-helix domain near the C-terminal, followed by two distinct PAS (PER-ARNT-SIM) domains, and a PAC (PAS-associated C-terminal) domain [2, 3]. The HIF1A polypeptide also contains a nuclear localization signal motif, two transactivating domains CTAD and NTAD, and an intervening inhibitory domain (ID) that can repress the transcriptional activities of CTAD and NTAD [4]. There are a total of three HIF1A isoforms formed by alternative splicing, however isoform1 has been chosen as the canonical structure, and is the most extensively studied isoform in structure and function [5, 6].

HIF-1 is over expressed in many human cancers [7,8]. HIF-1 over expression is heavily implicated in promoting tumor growth and metastasis through its role in initiating angiogenesis and regulating cellular metabolism to overcome hypoxia [9]. Hypoxia promotes apoptosis in both normal and tumor cells [10]. However, hypoxic conditions in tumor microenvironment especially, along with accumulation of genetic alternations often contribute to *HIF-1* over expression [11].

Significant HIF-1 expression has been noted in most solid tumors studied, which include cancers of the colon, breast, pancreas, kidneys, prostate, ovary, brain, and bladder [12, 13]. Clinically, elevated HIF-1 α levels in a number of cancers, including cervical cancer, non-small-cell lung carcinoma, breast cancer (LV-positive and negative), oligodendroglioma, oropharyngeal cancer, ovarian cancer, endometrial cancer, esophageal cancer, head and neck cancer, and stomach cancer, have been associated with aggressive tumor progression, and thus has been implicated as a predictive and prognostic marker for resistance to radiation treatment, chemotherapy, and increased mortality [14-17].

During hypoxia, tumor suppressor p53 over expression may be associated with HIF-1 α

dependent pathway to initiate apoptosis. Moreover, p53-independent pathway may also induce apoptosis through the Bcl-2 pathway [18]. However, over expression of HIF-1 α is cancer-and individual-specific, and depends on the accompanying genetic alternations and levels of pro- and anti-apoptotic factors present. One study on epithelial ovarian cancer shows HIF-1 α and nonfunctional tumor suppressor p53 is correlated with low levels of tumor cell apoptosis and poor prognosis [19]. Further, early-stage esophageal cancer patients with demonstrated overexpression of HIF1 and absence of BCL2 expression also failed photodynamic therapy [20]. Studies of glioblastoma multiform show striking similarity between HIF-1 α protein expression pattern and that of VEGF gene transcription level.

While research efforts to develop therapeutic drugs to target hypoxia-associated tumor cells have been ongoing for many years, there has not yet been any breakthrough that has shown selectivity and effectiveness at targeting HIF-1 α pathways to decrease tumor progression and angiogenesis [21]. Successful therapeutic approaches in the future may also be highly case-specific to particular cancers and individuals, and seem unlikely to be widely applicable due to the genetically heterogenous nature of the many cancer types and subtypes.

Several series of pyrazolopyridines (1) reported as potent inhibitor of HIF-1 α prolyl hydroxylase. These analogs were potent VEGF inducers in a cell-based assay [22].

Several series of sulfonamides (2) was reported as a new scaffold for hypoxia inducible factor pathway inhibitors. Among these compounds, the most potent ones showed an IC₅₀ of 0.5 μ M in the hypoxia-responsive element (HRE)-luciferase reporter system [23]. Similarly mun et al reported Structure-activity relationship of 2,2-dimethyl-2H-chromene based arylsulfonamide analogs of 3,4-dimethoxy-N-[(2,2-dimethyl-2H-chromen-6-yl)methyl]-N phenylbenzene sulfonamide, (3) a novel small molecule hypoxia inducible factor-1 (HIF-1) pathway inhibitor and anti-cancer agent. A 3,4-dimethoxybenzenesulfonyl

group in region 1 showed the strongest inhibition among five arylsulfonyl groups tested. The presence of propan-2-amine in region 2 conferred the strongest inhibitory effect of the compound on HIF-1 activated transcription in a reporter assay. These findings are important as they help define the structural motifs where the 3,4-dimethoxy-N-[(2,2-dimethyl-2H-chromen-6-yl)methyl]-N-phenylbenzenesulfonamide can be chemically modified to improve its pharmacological properties towards

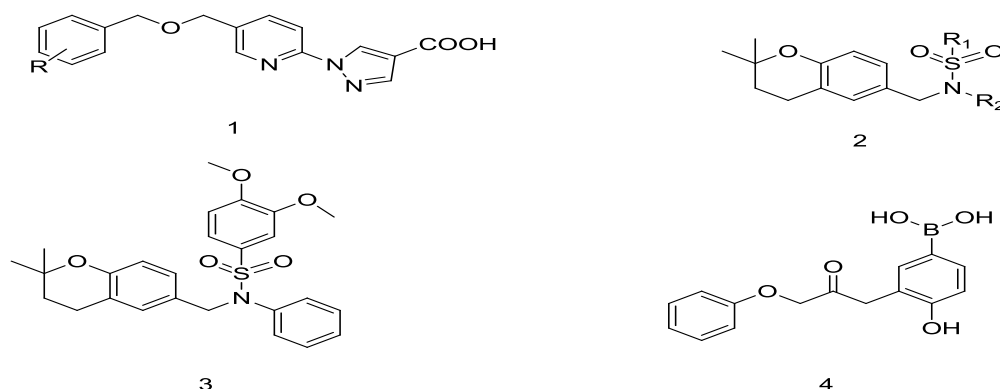


Figure 1: Examples of some effective molecules act as HIF inhibitors

2. Proteinkinase:

A protein kinase inhibitor is a type of enzyme inhibitor that blocks the action of one or more protein kinases. Protein kinases are enzymes that add a phosphate (PO_4) group to a protein or other organic molecule. Phosphate groups can turn a protein off. The phosphate groups are usually added to the serine, threonine, or tyrosine amino acid on the protein. Hence, protein kinase inhibitors can be subdivided or characterised by the amino acids whose phosphorylation is inhibited: most kinases act on both serine and threonine, the tyrosine kinases act on tyrosine, and a number (dual-specificity kinases) act on all three. There are also protein kinases that phosphorylate other amino acids, including histidine kinases that phosphorylate histidine residues. Phosphorylation is a necessary step in some cancers and inflammatory diseases. Inhibiting the protein kinases, and therefore the phosphorylation, can treat these diseases. Therefore, protein kinase inhibitors are used as drugs. Kinase inhibitors such as dasatinib are often used in the treatment of cancer and inflammation.

development as a cancer therapeutic [24]. Boron-containing phenoxyacetanilide derivatives (4) were reported as hypoxia-inducible factor HIF-1 α inhibitors. Among the compounds synthesized, carboranyl-phenoxyacetanilide (GN26361) was found to be a potent inhibitor against HIF-1 α accumulation under hypoxic conditions and inhibited the hypoxia-induced HIF-1 transcriptional activity in HeLa cells ($\text{IC}_{50} = 0.74 \mu\text{M}$) [25].

Some of the kinase inhibitors used in treating cancer is inhibitors of tyrosine kinases. The effectiveness of kinase inhibitors on various cancers can vary from patient to patient. A tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to a protein in a cell. It functions as an "on" or "off" switch in many cellular functions. Tyrosine kinases are a subclass of protein kinase. The phosphate group is attached to the amino acid tyrosine on the protein. Tyrosine kinases are a subgroup of the larger class of protein kinases that attach phosphate groups to other amino acids (serine and threonine). Phosphorylation of proteins by kinases is an important mechanism in communicating signals within a cell (signal transduction) and regulating cellular activity, such as cell division. Protein kinases can become mutated, stuck in the "on" position, and cause unregulated growth of the cell, which is a necessary step for the development of cancer. Therefore, kinase inhibitors, such as imatinib, are often effective cancer treatments.

Most tyrosine kinases have an associated protein tyrosine phosphatase, which

removes the phosphate group. A serine/threonine protein kinase is a kinase enzyme that phosphorylates the OH group of serine or threonine (which have similar sidechains). At least 125 of the 500+ human protein kinases are serine/threonine kinases (STK). Serine/Threonine Kinase receptors play a role in the regulation of cell proliferation, programmed cell death (apoptosis), cell differentiation, and embryonic development [26].

A series of 4-anilinoquinazolines (5) with C-C multiple bond substitutions at the 6-position were synthesized and investigated for their potential to inhibit epidermal growth factor receptor (EGFR) tyrosine kinase activity. Among the compounds synthesized, alkyne and allenes derivatives significantly inhibited EGFR tyrosine kinase activity [27].

Series of a novel class of imidazo[2,1-b]thiazoles (6) were synthesised as multi target inhibitors of both the insulin-like growth factor receptor and members of the epidermal growth factor family of receptor tyrosine kinases and found that imidazothiazole scaffolds provide potent and balanced enzyme and cellular activity against IGF-IR, EGFR, and ErbB2 [28].

N4-phenylsubstituted-6-phenylmethylsubstituted-7H-pyrrolo[2,3-d]pyrimidin-4-amines (7) were synthesized to evaluate the importance of the 2-NH₂ moiety for multiple receptor tyrosine kinase (RTK) inhibition [29].

A novel series of 8-(2-tetrahydropyranyl)-12,13-dihydroindazolo[5,4-a]pyrrolo[3,4-c]carbazoles (THPDHI) (8) was synthesized and evaluated as dual TIE-2 and VEGF-R2 receptor tyrosine kinase inhibitors. Development of the structure-activity relationships (SAR) with the support of X-ray crystallography led to identification of 7f and 7g as potent, selective dual TIE-2/VEGF-R2 inhibitors with excellent cellular potency and acceptable pharmacokinetic properties. Compounds 7f and 7g were orally active in tumor models with no observed toxicity [30].

A series of benzothiazole derivatives (9) was synthesised as tyrosine kinase inhibitors among the compounds tested with MTT assay, mono fluoro substitution on benzothiazole nucleus and 4_-methyl variations at 2-phenyl position demonstrated highest percent growth inhibition of MCF-7 cells. Docking studies of the synthesised compounds was done on EGFR using GRIP batch docking method to study their observed activity [31].

4-(Pyridin-3-yl)-1H-pyrazol-1-yl-phenyl-3-benzamide derivatives (10) have been proposed as new tyrosine kinase inhibitors by using combinational strategies of scaffold hopping and conformational constraint. The interesting activities of these compounds may make them promising candidates as therapeutic agents for chronic myelogenous leukemia [32].

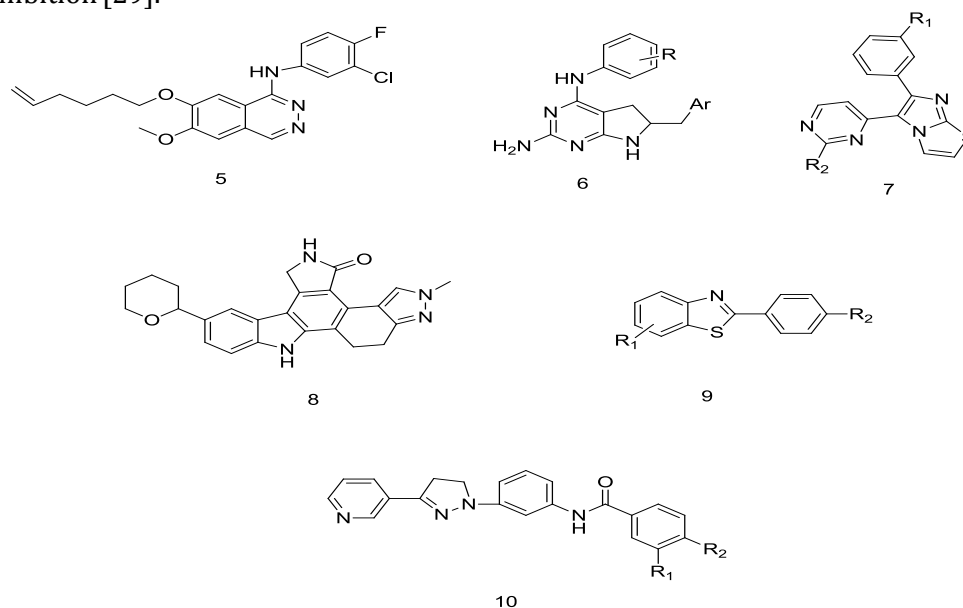


Figure 2: Protein Kinase inhibitors

3. COX-2:

It is well admitted that the link between chronic inflammation and cancer involves cytokines and mediators of inflammatory pathways, which act during the different steps of tumorigenesis. The cyclooxygenases (COXs) are a family of enzymes, which catalyze the rate-limiting step of prostaglandin biosynthesis. COX-2 was described to modulate cell proliferation and apoptosis mainly in solid tumors, that is, colorectal, breast, and prostate cancers, and, more recently, in hematological malignancies [33]. Over expression of COX-2 has been detected in a number of tumors, such as colorectal, breast as well as pancreatic and lung cancers [34-36], where it correlates with a poor prognosis. Moreover, over expression of COX-2 has been reported in hematological cancer models such as RAJI (Burkitt's lymphoma) and U937 (acute promonocytic leukemia) [37, 38] as well as in patient's blast cells [39, 40]. Data suggested that COX-2 may play a role in different steps of cancer progression, by increasing proliferation of mutated cells, thus favoring tumor promotion as well as by affecting programmed cell death and affecting the efficacy of anticancer therapies [41, 42] to be, finally, implicated in metastasis formation, for example, by affecting apoptosis induced by loss of cell anchorage (anoikis) [43].

4. NF- κ B:

NF- κ B controls many genes and is apparently involved in many diseases, including cancer [44, 45]. When bound to I κ B proteins, the NF- κ B heterodimer is trapped in the cytoplasm. Phosphorylation of I κ B in response to inducers such as cytokines, results in its degradation and activation of NF- κ B. As a result, NF- κ B translocates to the nucleus and binds to the NF- κ B binding site in the regulatory region of target genes, thereby promoting the transcription of several genes including COX-2, c-myc and cyclin D1. Many reports demonstrate that members of the NF- κ B and I κ B families are involved in the development of cancer [46]. For example, aspirin inhibits the activation of NF- κ B without interfering with gene transcription [47].

5. Phosphodiesterases (PDEs):

Phosphodiesterases regulate the levels of cAMP. Their importance to cancer pharmacology stems from findings that high intracellular cAMP levels arrest the growth induce apoptosis and attenuate cancer cell migration [48, 49]. Agents like theophylline or cholera toxin, which increase intracellular cAMP trigger apoptosis in human cancer cells such as lung and ovarian cells alone or synergizing with chemotherapeutic agents [50]. Sulindac sulfone inhibits PDE2 and PDE5, increasing cellular concentrations of cGMP, leading to activation of cGMP-dependent protein kinase which in turn down regulates β -catenin, suggesting a mechanism for its apoptotic actions [51].

6. Peroxisome proliferators-activated receptors (PPAR):

PPARs (a, b, and δ) function as heterodimers with the retinoic acid receptor (RXR), their obligate partner, and regulate transcription of genes involved in apoptosis, differentiation, and inflammation [52]. Higher PPAR expression is observed in human non-small-cell lung cancer compared to normal tissue [53]. Troglitazone, a PPAR γ ligand, increased PPAR γ transcriptional activity in lung adenocarcinoma cells (A549) and inhibited their growth predominantly due to inhibition of cell proliferation [54]. Indomethacin binds and activates PPAR γ ; other NSAIDs, including ibuprofen, and flufenamic acid, are also PPAR γ ligands [55].

7. NSAID activated gene (NAG-1):

NSAID activated gene is a divergent member of the TGF- β family of genes. The TGF- β superfamily of genes plays roles in adult and embryonic growth and development, in inflammation, and in repair including angiogenesis [56]. Multiple lines of evidence suggest that the TGF- β signaling pathway is a potent tumor suppressor of human colorectal carcinogenesis. NAG-1 is of interest because of its characteristics and relation to COX activity: NAG-1 has antitumorigenic and proapoptotic properties. Some NSAIDs (aspirin, indomethacin, sulindac sulfide, and ibuprofen) regulate the expression of NAG-1. NAG-1 expression is up-regulated in human colorectal cancer cells by several

NSAIDs that are known to have anti-tumorigenic and pro-apoptotic activities [57].

8. Wnt pathway:

Wnt binds to membrane receptors encoded by the Frizzled genes (FZD1-10). Its canonical pathway involves Wnt binding to FZD receptors, which leads to phosphorylation of the cytoplasmic protein Dishevelled (Dsh), which then binds to axin and causes dissociation of the APC/axin/GSK complex, accumulation of β -catenin and its subsequent translocation to the nucleus. There, β -catenin inactivates gene transcription, some of it (e.g., c-Myc, cyclin D1) relevant to cancer. The properties of this pathway and the fact that NSAIDs appear to inhibit the initial stages of the adenoma-carcinoma sequence, prompted studies of the effect of NSAIDs and COX-2 inhibitors on this pathway. McEntee et al. provided one of the earliest indications that the regression of intestinal tumors in Min mice by sulindac was accompanied by changes in β -catenin expression [58].

9. Carbonic anhydrase:

Carbonic anhydrases are a group of zinc-containing metalloenzymes that catalyze the hydration of CO_2 to bicarbonate at physiological pH. Virtually ubiquitous in living systems, they facilitate many

biosynthetic processes including the synthesis of nucleotides [59]. Carbonic anhydrase expression has been studied most extensively in colorectal tumors and to a lesser extent in hepatobiliary, pancreatic, esophageal, gastric and other tumors. It appears quite likely that some carbonic anhydrase isoenzymes play a role in carcinogenic processes such as uncontrolled cell proliferation and malignant cell invasion [60].

The use of monoclonal antibodies targeting CA IX in the treatment of RCC has progressed into clinical trials. The use of CA IX immunotherapy in non-RCC tumors such as mouse monoclonal antibody VII/20 in colorectal carcinoma shows a potential anticancer effect in mice [61].

10. TNF- α :

The TNF receptor-associated factor (TRAF) family is a group of adapter proteins that link a wide variety of cell surface receptors. Including the TNF and IL-1 receptor super family to diverse signaling cascades, which lead to the activation of NF- κ B and mitogen-activated protein kinases. In addition, TRAFs interact with a variety of proteins that regulate receptor-induced cell death or survival. Thus, TRAF-mediated signals may directly induce cell survival or interfere with the death receptor-induced apoptosis [62].

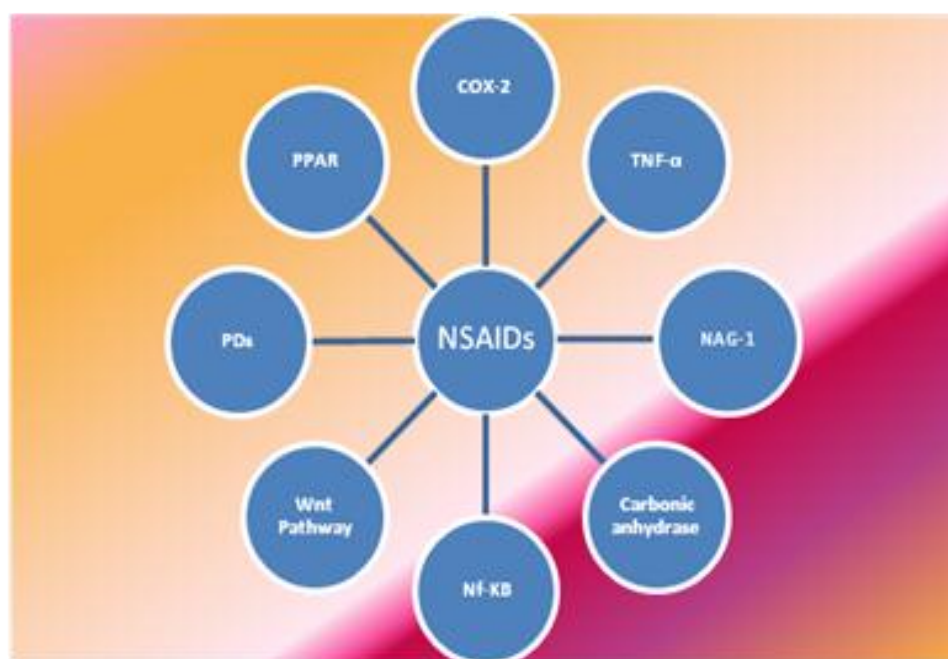
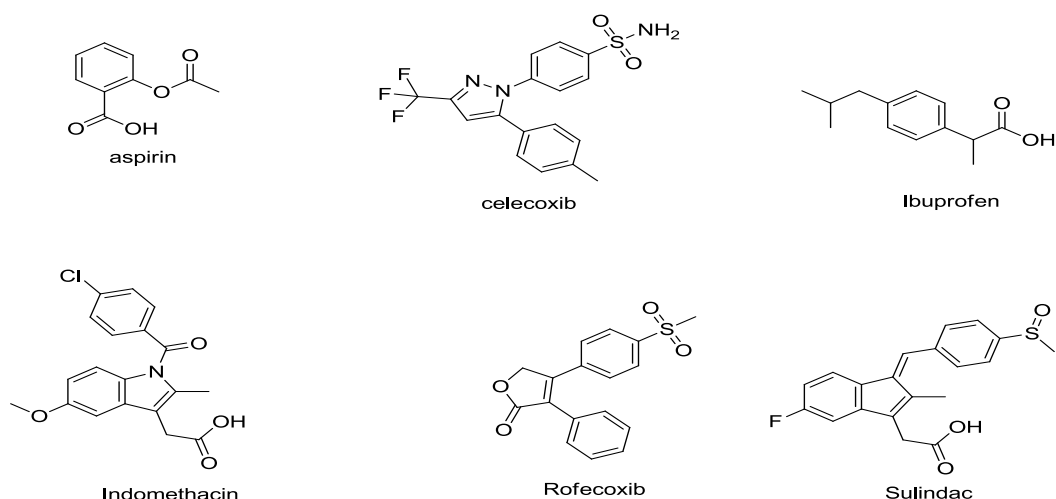


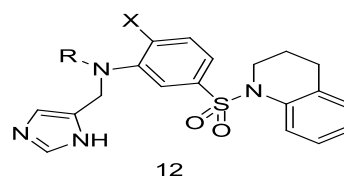
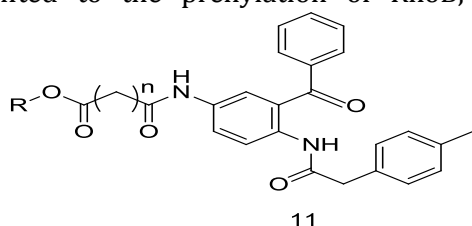
Figure 3: various molecular targets affected by NSAIDs. All of them are potentially relevant to carcinogenesis.

**Figure 4: NSAIDs****11. Farnesyltransferase:**

Inhibition of farnesyltransferase has become a major strategy for the development of novel potential anticancer drugs [63, 64]. Farnesyltransferase catalyzes the transfer of a farnesyl residue from farnesylpyrophosphate to the thiol of a cysteine side chain of proteins bearing C-terminal the CAAX-tetrapeptide sequence (C: cysteine, A: aliphatic amino acid, X: serine or methionine) [65]. Farnesylation is a prerequisite for the transforming activity of oncogenic Ras which is found in approximately 30% of all cancers in humans. However, there is accumulating evidence that prevention of Ras farnesylation may not be the crucial cellular event responsible for the antiproliferative effect of farnesyltransferase inhibitors [66]. Focus has shifted to the prenylation of RhoB,

another member of the class of small GTPases which is involved in receptor trafficking [67]. Disregarding the unresolved mechanism of action of farnesyltransferase inhibitors, the efficacy of these compounds and their low toxicity has been demonstrated [68].

Schlitzer et al studied structure-activity relationships of benzophenone-based bisubstrate analogues (11) of farnesyltransferase inhibitors. Some of the analogues showed good results against inhibition of farnesyltransferase [69]. Some molecules are also under clinical trials which were found to be effective in lung cancer [70]. A series of 3-Imidazolylmethylaminophenylsulfonyltetrahydroquinolines (12) was synthesised and reported as novel series of Farnesyltransferase Inhibitors [71].

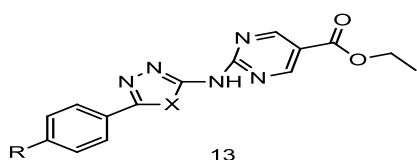
**Figure 5: Farnesyltransferase Inhibitors****12. Histone deacetylase:**

Histone deacetylases (HDACs) regulate gene expression through the deacetylation of histone tails and are promising targets in drug development for cancer therapy [72-76]. They have been linked mechanistically to the pathogenesis of cancer and several other diseases [77-81]. Small-molecule

inhibitors of HDACs have significant effects in preclinical models of cancer [82, 83]. The increased focus on HDAC inhibitors for cancer treatment stems from their ability to alter several cellular functions known to be important in cancer cells. The anticancer properties of these drugs may, for example, be due to the accumulation of acetylated histones that leads to the activation (and/or

repression) of transcription of genes, and inhibition of tumor cell growth [84].

A series of 2,5-Disubstituted-1,3,4-oxadiazoles/thiadiazole as histone deacetylase inhibitors, (13) The results of the present studying indicates 2,5-disubstituted 1,3,4-oxadiazole/thiadiazole as promising surface recognition moiety for development of newer hydroxamic acid based histone deacetylase inhibitor [85]. Novel indeno[1,2-d]thiazole hydroxamic acids were designed, synthesized, (14) and evaluated for histone deacetylases (HDACs) inhibition and antiproliferative activities on tumor cell lines. Most of the tested compounds exhibited HDAC inhibition and antiproliferative activity against both MCF7



and HCT116 cells with GI50 values in the sub-micromolar range [86].

A novel series of N-hydroxy-4-(3-phenylpropanamido)benzamide (HPPB) derivatives (15) comprising N-hydroxybenzamide group as zinc-chelating moiety were designed, synthesized and evaluated for their ability to inhibit histone deacetylases. These compounds possessed inhibitory activity against the enzymes with IC50 values as low as 4.0 mM. Among them, the thiophene substituted derivative 5j (IC50¼ 0.3 mM) and benzo[d][1,3]dioxole derivative 5t (IC50¼ 0.4 mM) exhibited good antiproliferative activity against the growth of human colon carcinoma cell line HCT116 and non-small cell lung cancer cell (NSCLC) line A549 [87].

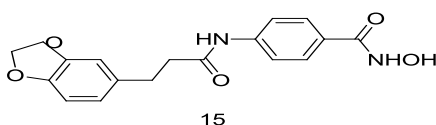
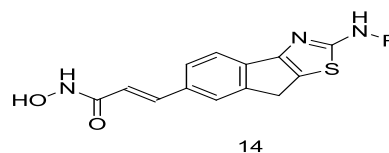


Figure 6: Histone deacetylase inhibitors

13. Poly (ADP-ribose) polymerases (PARPs):

Poly (ADP-ribose) polymerases (PARPs) are a family of nuclear enzymes that polymerize (poly adenosine diphosphate-ribose) on substrate proteins critical for cellular regulations including DNA repair, gene transcription, and chromatin architecture. Members in the PARP super family share a common and highly homologous catalytic domain that catalyzes the transfer of ADP-ribose units from intracellular nicotinamide adenine dinucleotide (NAD⁺) to the acceptor proteins, leading to the formation of mostly branched ADP-ribose polymers (PARs). This cellular event is a key process during base excision repair (BER) of single-strand DNA breaks caused by ionizing radiation or DNA-damaging chemotherapeutic treatments, and contributes to the resistance mechanism that often develops after these cancer

therapies [88]. Some PARP inhibitors are also under clinical trials [89]. (Fig. 7)

14. Cytochrome P450 enzymes:

Cytochrome P450s (CYPs) are a large ubiquitous family of proteins containing a single iron protoporphyrin IX prosthetic heme group. The majority of CYPs (designated Class I and II) act as versatile monooxygenases. These enzymes catalyze a multitude of reactions, including the hydroxylation of alkanes to alcohols, conversion of alkenes to epoxides, arenes to phenols, sulfides to sulfoxides and sulfones, and the oxidative split of C-N, C-O, C-C or C-S bonds. Functionally, CYPs can be classified into two groups those with specific roles in the metabolism of endogenous molecules such as hormones, and those that non-specifically process exogenous molecules (drugs, chemicals, natural products, etc.). Both classes of CYPs offer potential targets in chemotherapeutic and chemo preventative strategies.

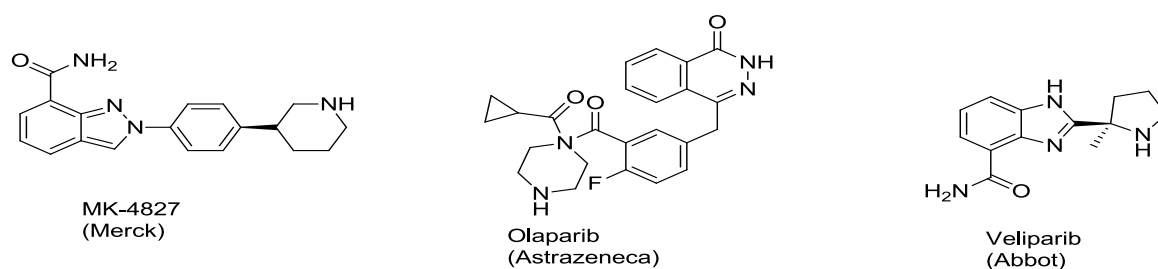


Figure 7: Current PARP inhibitors in clinical trials

Most CYPs were once considered liver specific enzymes, but now their extrahepatic expression has been well established. It has long been known that CYP17 and CYP19—the enzymes responsible for the production of androgens and estrogens, respectively—are expressed in the testes, ovaries, and adrenals. However, CYP19 has subsequently been found expressed locally in the adipose tissue of the breast, and indirect evidence suggests CYP17 may be expressed in adipose tissue as well [90, 91]. It is also now well established that expression of CYPs responsible for the metabolism of anti-cancer metabolites of vitamin A (all-trans-retinoic acid; ATRA) and vitamin D (1 α ,25-dihydroxyvitaminD₃; 1,25-D₃) are induced by their substrates in target cells. [92-96] Members of CYP families 1, 2, and 3 have also been identified in both healthy and cancerous extrahepatic tissues. [97-100] The enzymes in these families are involved

in the metabolism of xenobiotic substances such as carcinogens, Pro-carcinogens and chemotherapeutics [101,102]. Recently, CYP2W1 have been identified as having tumor-specific expression [103].

These observations have led to a greater appreciation for the role of CYPs in tumor formation and development. Targeting of these enzymes with natural or synthetic small molecules offers potential benefits in cancer prevention and therapy. Because crystal structures for nearly all CYPs are yet to be determined, drug design strategies rely on the knowledge of substrate structure and the enzyme's mechanism of action. Strategies to target these enzymes include: (i) designing molecules that inhibit the enzymes; (ii) designing prodrugs that are activated by the enzymes; (iii) immune-based therapies that target immune responses toward the enzymes; (iv) genetic therapy strategies to express specific CYPs in cancer cells [104].

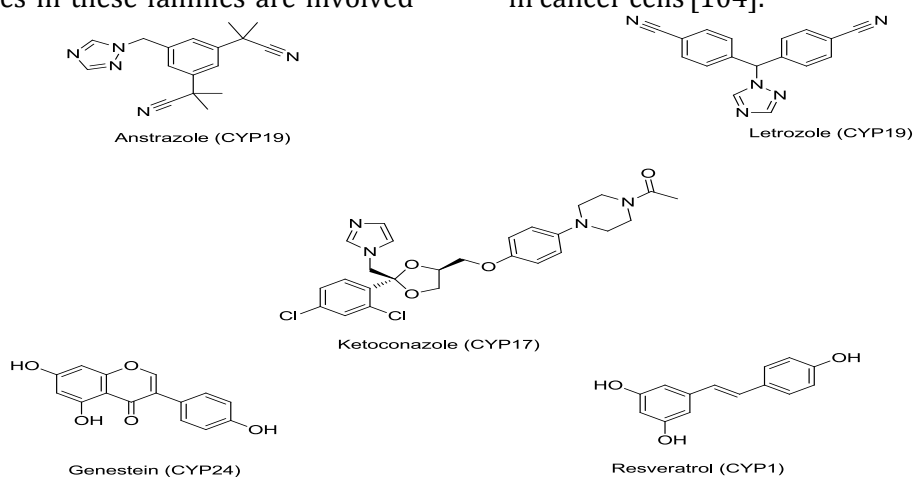


Figure 8: Examples of CYP inhibitors

CONCLUSION

In this review total 14 different targets and its role in cancer were described. Some examples of effective molecules which act on those targets were also given. Furthermore in the area of combination of

this target inhibitors with existing treatment or new targeted therapy may prove to be useful clinically. This review will helpful for the targeted based drug discovery in cancer disease.

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