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SULFONAMIDE-CONTAINING HETEROCYCLIC COMPOUNDS WERE SYNTHESISED

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ABSTRACT
Sulfonamide moieties were added to certain quinoline and pyrimido[4,5-b]quinoline compounds in the hunt for novel cytotoxic agents with better anticancer properties. In vitro anticancer screening was performed on all freshly synthesised target compounds using a human breast cancer cell line (MCF7). In vitro anticancer screening identified the most effective chemicals, which were then tested in conjunction with -radiation for their in vitro anticancer efficacy. It was also discovered that novel chemicals made in the lab docked with the carbonic anhydrase enzyme.

INTRODUCTION

1.1 Sulfonamides as carbonic anhydrase inhibitors

1.1.1 Carbonic anhydrases

They are zinc-containing metalloenzymes, carbonic anhydrases. A total of four gene families encode carbonic anyhdrases, which are found in both prokaryotes and eukaryotes. Sixteen distinct isozymes of the -CA, or CA-related proteins (CARPs), have been identified in mammals, each with a unique subcellular location and tissue distribution. CA I-III, CA VII, and CA XIII are all cytosolic forms, whereas CA IV, CA IX, CA XII, CA XIV, and CA XV are membrane-bound isozymes. CA VI is released in saliva and milk. Additional three acatalytic forms are found in the cytosol (CARP VIII, CARP X and CARP XI).

At physiological pH, all of these CAs are capable of catalysing the hydration of CO2 into bicarbonate (Figure 1). Gluconeogenesis, the biosynthesis of numerous amino acids, lipogenesis, ureagenesis, and pyrimidine synthesis all rely on this chemical interconversion since bicarbonate provides the substrate for various carboxylation processes. Additionally, some of the CAs are engaged in a number of physiological activities, including respiration and the transfer of CO2/bicarbonate between metabolising tissues and the lungs, pH homeostasis in various tissues/organs, and electrolyte secretion in a wide range of tissues.

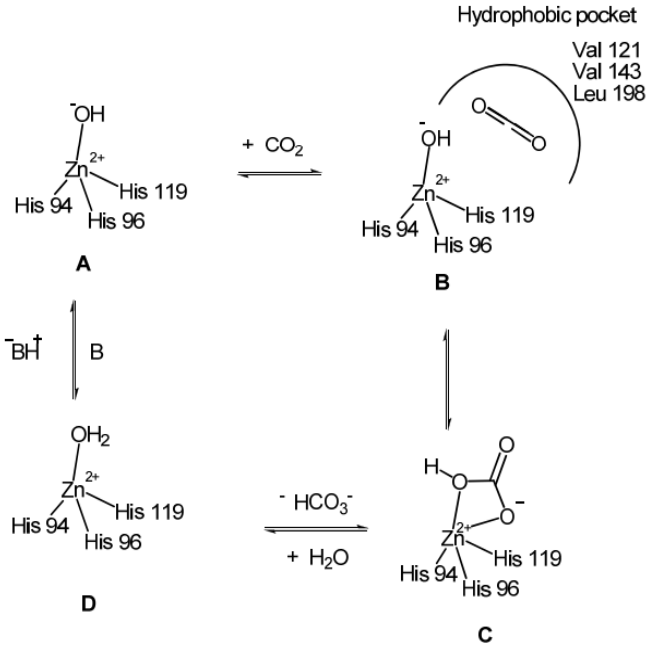


Figure (1): The catalytic process for -CA catalysed CO2 hydration is shown schematically. Schematically represented at step one is the hydrophobic pocket for the binding of substrates (B)

1.1.2 Carbonic anhydrases inhibition

As antiglaucoma, antithyroid, hypoglycemic, and anticancer medicines, CA inhibitors are widely utilised. It is well known that sulfonamides have a zinc binding group (ZBG) that interacts with the metal ion in the active site of the enzyme and residues Thr 199, Glu 106 in the vicinity of the ZBG. Figure 2 depicts the

wide variety of novel ZBGs that have been reported in the last several years. ZBGs now comprise hydroxamates, urea and hydroxyurea derivatives, sulfamide modified sulfonamides, and a variety of other novel compounds, in addition to the more traditional sulfuramides.

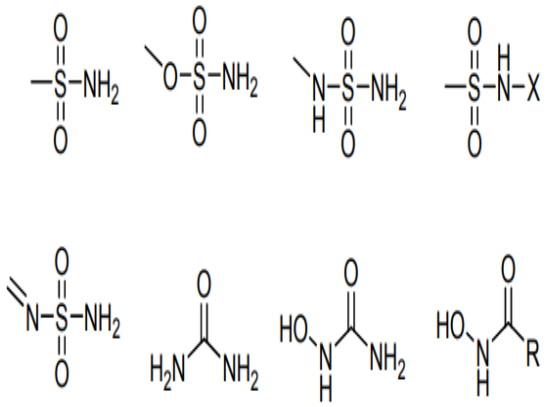


Figure (2): Zinc binding groups: sulfonamides, sulfamates, sulfamides, substituted sulfonamides, Schiff's base, urea, hydroxyurea and hydroxamates

According to Thiry et al., the carbonic anhydrase inhibitory sulfonamide compounds have a common pharmacophore (Figure 3). Based on an examination of the active site of CAs and the structures of known inhibitors, we came up with this pharmacophore.

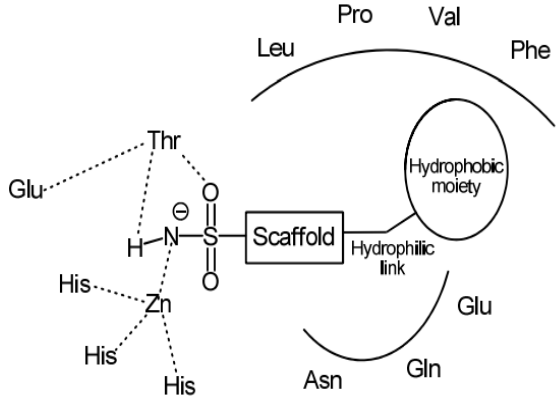


Figure (3): Structural elements of CA inhibitors in the CA enzymatic active site

1.1.3 Role of carbonic anhydrases in cancer

A huge variety of isoforms (which may be differentiated in activity and are situated in various parts of the cell) and the relevance of this family of enzymes for bicarbonate absorption by many species make the CAs an unquestionable part of cell growth. Three CA isozymes (CA XII, CA XIV) have been shown to be closely linked to malignancies. Because cancer cells need a faster rate of replication than normal cells, CAs play an important role in the development of cancer. In this case, a large flow of bicarbonate into the cell is necessary to provide the cell with the necessary substrate for the production of either nutrients or cell structural components (membrane lipids).

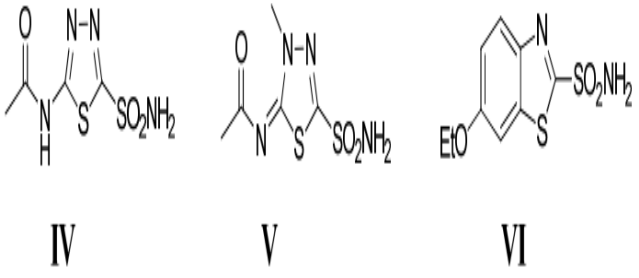
1.1.4. The action of sulfonamides as anticancer agents through CA inhibition

Inhibitors of carbamoyl phosphate synthetase II, sulfonamides CA, limit the availability of bicarbonate for the production of nucleotides and other cell components, such as membrane lipids (mediated by pyruvate carboxylase). CA II and CA V are expected to have a role in such a system.

These powerful CA inhibitors may also have an extra mechanism that causes acidification of the intracellular environment. The CA isozymes CA IX, XII, and XIV, which are known to be abundant in tumour cells, may also be inhibited by the sulfonamides. It is also feasible to combine any or all of the techniques outlined above.

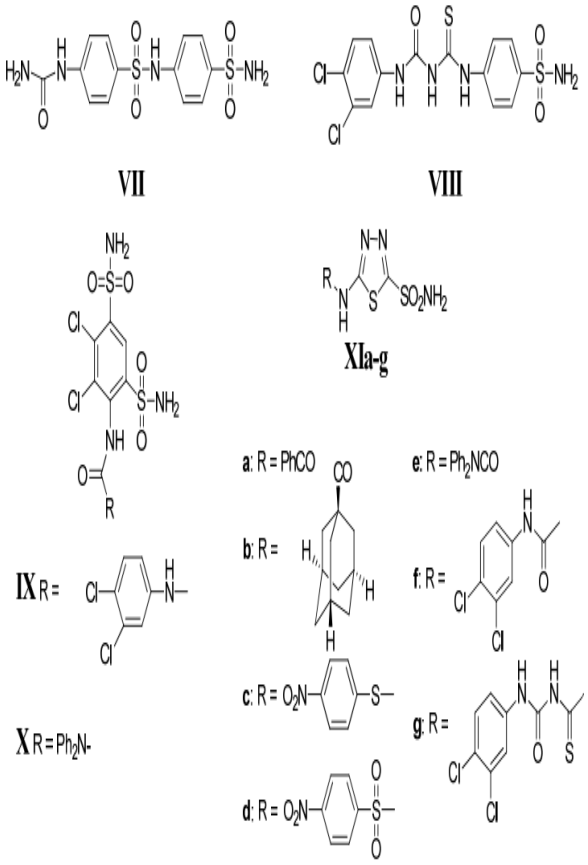
1.1.5 Examples of sulfonamides acting as anticancer agents by CA inhibition

Human lymphoma cells can be inhibited by several clinically effective sulfonamide CA inhibitors, including acetazolamide IV, methazolamide V, and ethoxzolamide VI.



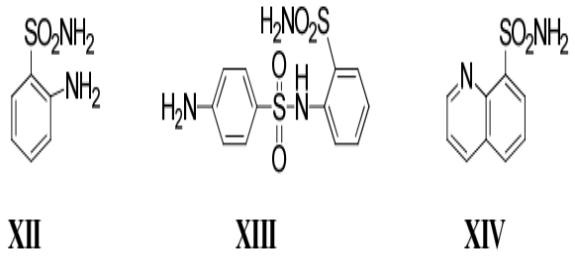
IV V VI

Sulfonamide CA inhibitors (both aromatic and heterocyclic derivatives) have been screened against a panel of 60 cancer cell lines from the National Cancer Institute of the United States, and derivatives VII-XI have been identified as promising leads in this effort. Anti-cancer properties of these compounds were shown against cancer cell lines such as leukaemia and non-small cell lung cancer as well as melanoma and colon cancer cell lines.



1.1.6 Examples of Sulfonamides acting as selective CA inhibitiors

Vullo et al. have synthesised and evaluated a variety of sulfonamides in an effort to find selective CA inhibitors, particularly for CA IX and CA XII. XII-XIV were discovered to be extremely effective CA IX inhibitors, while being moderate to medium-weak inhibitors of CA I, II, and IV as a whole.



SULFONAMIDES TARGETING THE G1 PHASE OF CELL CYCLE

A cell's destiny is mostly determined during the G1 phase of the cell cycle, when a variety of signals combine to either promote cell growth, quiescence, differentiation, or death (Figure 4).

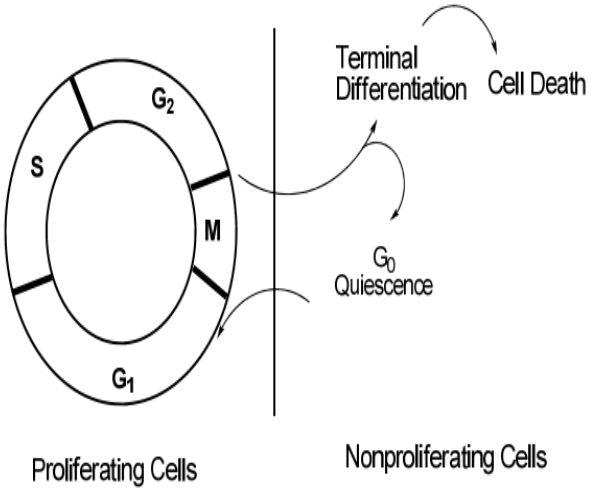


Figure (4): The cell cycle

When it comes to carcinogenesis and tumour growth, cell cycle control in G1 phase is among the most crucial molecular bases. In this regard, a tiny chemical targeting the control mechanism in G1 phase might be a novel kind of treatment that is effective against resistant clinical malignancies.

Using E7070 III, researchers discovered that it prevented human NSCLC A549 cells from entering the S phase, resulting in a buildup of cells in late G1. In addition, E7070 treatment of A549 cells led in the suppression of pRb phosphorylation, a critical step in the transition from G1 to S phase. The inhibition of pRb phosphorylation by E7070 may be due to the downregulation of CDK2 and cyclin A expression, as well as the suppression of CDK2

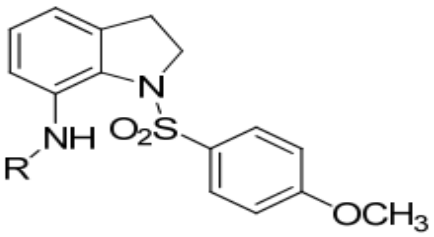
catalytic activity with the activation of p53 and p21.

The phosphorylation of CDK2 was also demonstrated to be inhibited by E7070, which led to a decrease in CDK2 catalytic activity. In human NSCLC cells, a growth-inhibitory pathway reliant on pRb was damaged, and our findings imply that E7070 may repair that route. CDK2 catalytic activity is inhibited in order to achieve this.

2.1 Sulfonamides causing disruption of microtubules

There were no longer any cytoplasmic microtubules or mitotic spindles in colon 38 cells after treatment with E7010, according to research done on the drug. Researchers found that E7010 inhibited microtubule assembly, which is responsible for its growth-inhibiting properties.

Chang et al. discovered a new class of very effective antitubulin compounds in the form of a novel series of 7-aroylaminoindoline-1-benzenesulfonamides. A range of human cancer cell lines, including MDR-positive cells, show antiproliferative activity with IC50 values of 8.6 to 11.1 nM for the two lead compounds, XXX and XXXI. It was shown that the 7-amide bond formation in the indoline-1-sulfonamines contributed to a large amount for maximum activity, rather than the carbamate, carbonate, urea, alkyl, sulfonamide linkers.



XXX: R = isonicotinoyl
XXXI: R = 2-furoyl

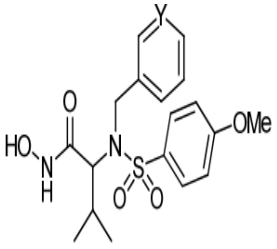
2.2 Sulfonamides as matrix metalloproteinase (MMP) inhibitors

MMPs, zinc-containing endopeptidases, have been demonstrated to play an important role in a variety of physiological and pathological processes, including angiogenesis and tumour invasion. Our primary focus is on the impact of these enzymes in these processes.

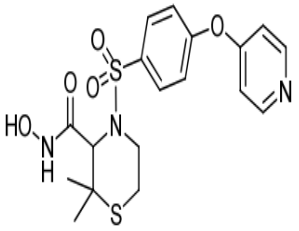
A total of at least 20 members of the same enzyme family have been identified. Zinc (ZnII), three histidines, and a further nucleophile (water/hydroxide) make up the enzyme's four-ligand structure.

Metal ion coordination of the inhibitor molecule (neutral or ionised) to the catalytic metal ion, with or without replacement of the water molecule, is connected with MMP inhibitory activity. This means that MMP inhibitors (MMPIs) must have a zinc-binding activity coupled to a scaffold that may interact with other binding areas of the enzymes.

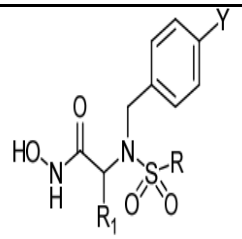
Only lately have sulfonylated amino acid hydroxamates been shown to be effective MMPIs. XXXIV and (CGS 25966) XXXV are the first of this class to be tested in clinical studies. XXXVI, for example, is one of the strongest and most selective inhibitors of its class known to date. Many new forms of N-benzyl hydroxamates generated from glycine, as well as from L-alanine and valine and leucine, were also discovered at this time. The CAI activity of hydroxamates structurally similar to MMPIs has also been shown.



XXXIV: Y = N
XXXV: Y = CH

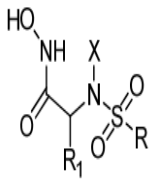


XXXVI



Y = H, Cl, NO_2 R_1 = H (Gly derivatives)
R = alkyl, aryl = Me (Ala derivatives)
= *i*-Pr (Val derivatives)
= *i*-Bu (Leu derivatives)

XXXVII

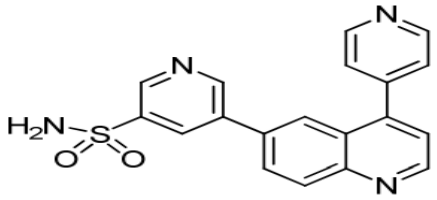


R_1 = H, Me, *i*-Pr, *sec*-Bu
R = Aryl
X = H
X = Benzyl, *i*-Pr

XXXVIII

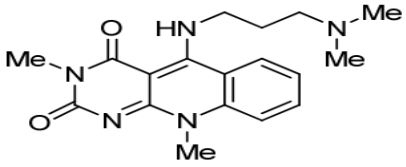
QUINOLINES AS ANTICANCER AGENTS

Anticancer activity has been shown for quinolines and fused quinoline derivatives. For example, quinolines and fused quinoline derivatives have anticancer properties that include DNA intercalation, topoisomerase inhibition and cell cycle arrest. Inhibition of PI3 kinase by quinoline derivatives such as drug XXXIX has recently been discovered. Proliferation and survival are two of the primary functions of PI3Ks, enzymes that have a protein kinase activity and influence a variety of signalling pathways. Human malignancies and other disorders are caused by dysregulation of these mechanisms.



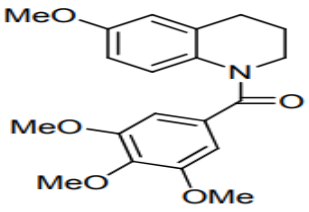
XXXIX

Genetic changes that allow for abnormal cell proliferation, including the creation of tumour cells, may contribute to the development of cancer. Cells undergoing oncogenic alterations are protected against such abnormal development by many systems that function by triggering apoptosis in such cells. Tumor cells must thus acquire genetic mutations that disrupt the relationship between aberrant growth and cell death if they are to survive. Anti-tumor proteins are important because they may promote cell death and prevent tumours from growing. A strong anticancer effect has been shown by the pyrimidoquinoline derivatives like drug XL, which modulate or stabilise p53 activity.



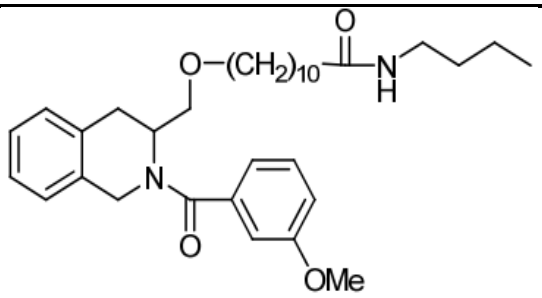
XL

Several reduced quinoline derivatives, such as compound XLI synthesised by Liou et al. and tested against oral epidermoid carcinoma KB cells, non-small lung carcinoma H460 cells, stomach carcinoma MKN45 cells, and one type of MDR-positive cell line, the KB-vin 10 cell line, have shown anticancer activity as well. Compound XLI demonstrated substantial antiproliferative activity against the four cell lines previously stated, and working by inhibiting tubulin polymerization.



XLI

Compound XLII, a tetrahydroisoquinoline derivative used to treat breast and prostate cancer, was also discovered to work as an antiestrogen and an antiandrogen. Although the particular processes involved in the formation of breast cancers are unknown, it is widely accepted that oestrogen and oestrogen receptors play an important role. Agents that modify oestrogen receptors may be effective in the therapy of prostate cancer as well, since oestrogen receptors play a role in the disease. In the early stages of prostate cancer, the androgen plays a critical role in its development, and antiandrogen deprivation treatment may significantly decrease its growth.



3.1 Chemoradiotherapy

Chemoradiotherapy (CRT) is a significant advancement in cancer treatment. For many forms of cancer, it is now normal practise to combine chemotherapy with radiation therapy.

3.1.1 Therapeutic ratio

Sigmoid curves are often used to explain the connection between radiation dosage and tumour response and normal tissue damage (Figure 5). To calculate the therapeutic ratio, researchers divide the dosage that provides a particular likelihood of normal tissue damage by the dose that produces the same chance for tumour control (50 percent is the most usually utilised in experimental investigations). A change in the tumour control curve and the response curve for normal tissue damage occurs when CT is used in conjunction with RT. In order to maximise the anticancer impact while reducing the toxicity to vital normal tissues, CT and RT should be used together.

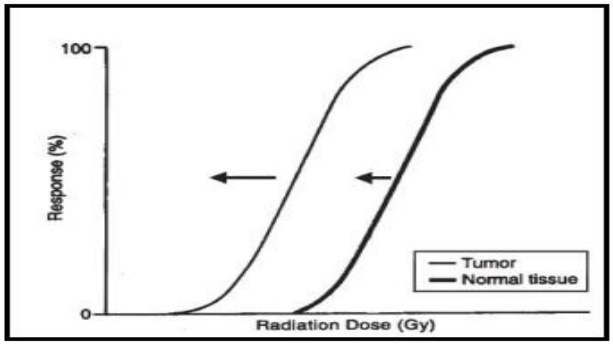


Figure (5): Tumor-control and normal tissue damage dose-response curves are shown below. A change in the tumour control curve (long arrow) and a shift in the response curve for normal tissue damage (short arrow) may be seen when chemotherapy (CT) and radiation (RT) are used together.

3.1.2 Rationale for combining chemotherapy and radiotherapy

There are two key reasons for combining CT and RT: spatial cooperation and an increase in radiation effects. In order for spatial collaboration to be beneficial, CT must be active enough to destroy subclinical metastases and RT must be effective in treating the main local tumour. No interaction between RT and CT is necessary, but different toxicities are needed so that both modalities may be employed at effective doses.

In individuals with common solid tumours, anticancer medicines have a rather low effectiveness. Small subclinical metastases might be difficult to remove with CT scans. Many tumour locations have substantial local failure rates after RT for a primary tumour. The improvement of RT effects is required in order to reduce the local failure rate. Chemotherapeutic medicines augment the irradiated volume's reaction, such as enhancement. Radiation damage to normal tissues is exacerbated by almost all chemotherapeutic drugs. When tumours respond more favourably than normal tissues, therapeutic benefits can be realised.

3.1.3 Mechanisms responsible for CT-RT interactions

New studies have demonstrated that combining CT and RT may increase local control and survival, indicating that the two treatments work in concert. The next paragraphs explore five key processes that underlie CT-RT interactions.

CONCLUSION

Finally, our docking investigation shows that the produced compounds with a free sulfonamide moiety display comparable conformations and binding interactions with hCA II as other sulfonamide compounds that operate as CA inhibitors. Anticancer action may

be at least in part due to the fact that these chemicals may serve as CA inhibitors.

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