

REVIEW



“SAR OF INDENOISOQUINOLINE DERIVATIVES AS TOPOISOMERASE I INHIBITOR” -A REVIEW

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ABSTRACT

Topoisomerase I (TOP I) is a valuable molecular target for the development of clinically used anticancer agents. Topoisomerase I is important for DNA replication and cell division, making it an attractive drug target for anticancer therapy. Camptothecin (CPT) is the first agent identified as a TOP-I inhibitor. Camptothecin and its derivatives bind the interface of the TOP-I-DNA complex and exert their pharmacological activity. They are effective in S-phase rather than in the G1 or G2/M phases of the cell cycle. Camptothecin derivatives are not ideal drug molecules, suffering from pharmacokinetic problems, inherent instability due to lactone ring opening and rapid reversibility of the cleavage complexes after drug removal. Therefore developed noncamptothecin Top1 inhibitors as anticancer agents. Recently, a number of analogues of the indenoisoquinolines have been reported as novel anticancer agents. Indenoisoquinolines have emerged as potent topoisomerase I inhibitors. They have several advantages over the camptothecins: (a) They are synthetic and chemically stable, (b) The Top1 cleavage sites trapped by the indenoisoquinolines have different genomic locations, implying differential targeting of cancer cell genomes, (c) The Top1 cleavage complexes trapped by indenoisoquinolines are more stable, indicative of prolonged drug action. Indenoisoquinolines have become important new lead for rational design of anticancer drugs due to their greater physiological and DNA-enzyme cleavage complexes stabilities. The SAR of various indenoisoquinolines as topoisomerase I inhibitors with potential clinical application in the treatment of cancer in humans.

KEYWORDS: -TOPOISOMERASE I (TOP I) INHIBITORS, ANTICANCER, CAMPTOTHECIN (CPT), INDENOISOQUINOLINES, SAR

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1. INTRODUCTION

Cancer is the leading cause of mortality in most countries after cardiovascular disease. There is no other disease which parallels cancer in diversity of its origin, nature and treatments.¹ It is likely to become the major reason of the death in the upcoming years. In spite of the progress made, the index of cancer therapy remains low and its treatment is a challenge.² There are over a hundred different types of cancer. Although it can strike people of all ages older people get cancer more often than younger ones. Cancer is not one single illness. It can attack all parts of the body and spread to other areas. Cancer is a disease of cell characterized by progressive, persistent, abnormal, and uncontrolled proliferations of tissues. Deaths from cancer worldwide are projected to continue rising. By 2030, it is projected that there will be an estimated 26 million new cancer cases and 17 million cancer deaths per year.³

1.1 CHEMOTHERAPY

Chemotherapy is the treatment of cancer with anticancer drugs. The main purpose of chemotherapy is to kill cancer cells. It usually is used to treat patients with cancer that has spread from the place in the body where it originated (metastasized). Chemotherapy destroys cancer cells anywhere in the body. It even kills cells that have broken off from the main tumor and traveled through the blood or lymph systems to other parts of the body. Most chemotherapy drugs interfere

with the ability of cells to grow or multiply. Although these drugs affect all cells in the body, many useful treatments are most effective against rapidly growing cells. The possible advantages of chemotherapy are:-reduction in symptoms, a better quality of life, it can possibly prolong life.⁴

1.2 DNA TOPOISOMERASE - I

DNA Topoisomerase-I (TOP-I) is an effective molecular target for the development of clinically based anticancer agents. They show excellent activity against various types of tumors, especially lung cancer and colon cancer.¹ Human topoisomerase type I (Top1) is a member of the topoisomerase family of enzymes that resolve the topological problems associated with DNA supercoiling during various essential cellular processes.⁵⁻⁶ It forms a covalent link with the 3'-end of the cut DNA strand in the Top1-DNA cleavage complex at its catalytic tyrosine 723 residue, relieving torsional strain in DNA via reversible single-strand nick.^{7,8} Top1 is important for the successful replication, transcription and recombination of DNA, as well as chromatin remodeling, making it an attractive drug target for anticancer therapy.⁹

1.3 CAMPTOTHECIN

Camptothecin (CPT) is the first agent identified as a TOP-I inhibitors. Camptothecin and its derivatives bind the interface of the TOP-I-DNA complex and exert their pharmacological activity. They are effective in S-phase rather than in the G1 or G2/M phases of the cell cycle.^{1, 25-27}

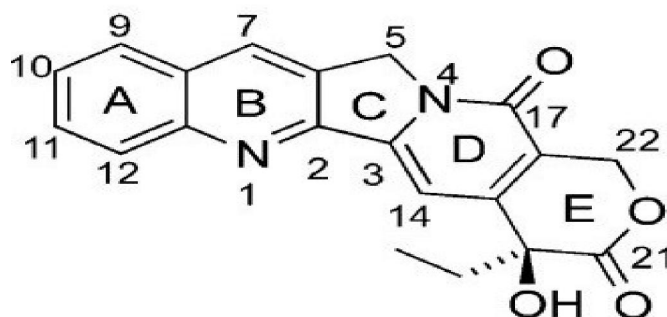


FIGURE 1 STRUCTURE OF CAMPTOTHECIN

IUPAC NAME: (S)-4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione.

CPT is a cytotoxic quinoline alkaloid. It was discovered in 1966 by M. E. Wall and M. C. Wani in systematic screening of natural products for anticancer drugs. It was isolated from the bark and stem of *Camptotheca acuminata* (*Camptotheca*,

Happy tree). Camptothecins and its derivatives exert their pharmacological activity via binding at the interface of the TOP I-DNA complex.⁹

¹⁰ Camptothecin derivatives irinotecan and topotecan approved by the Food and Drug Administration (FDA) validate Top1 as a therapeutic target for anticancer drug development.¹¹

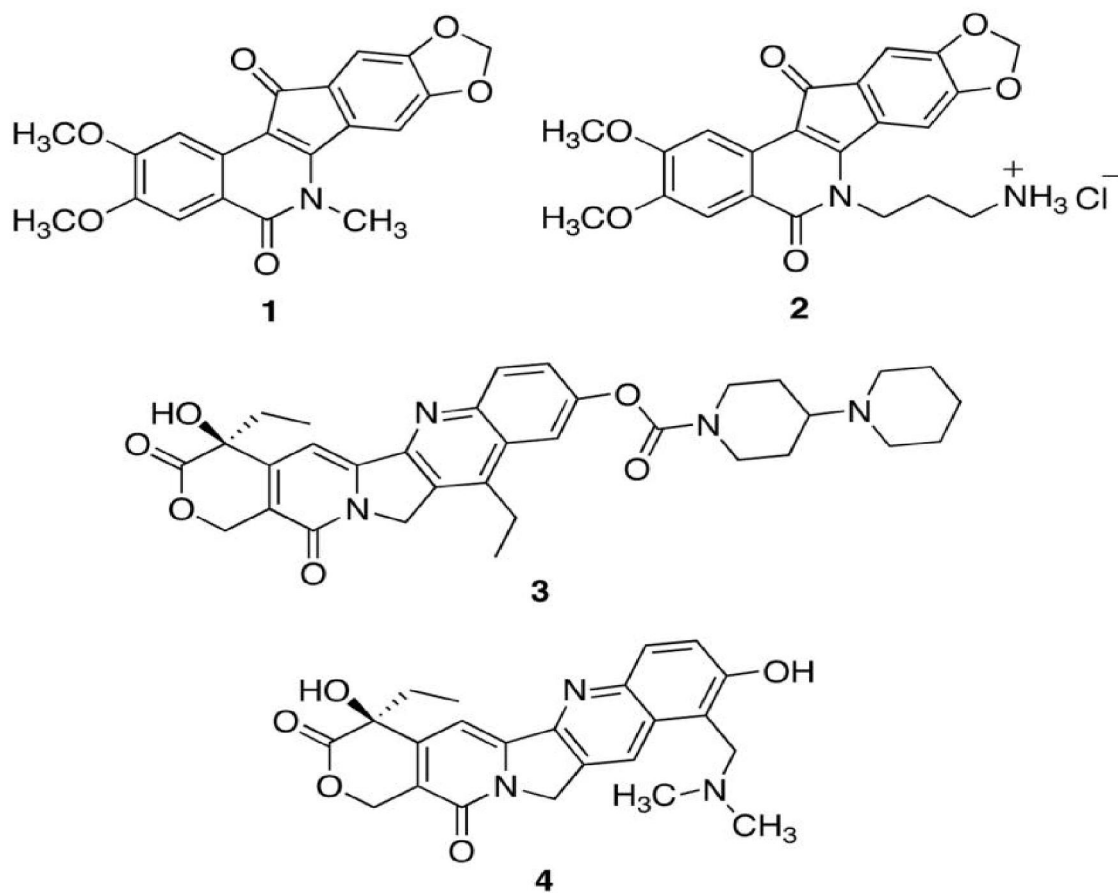


FIGURE 2 REPRESENTATIVE INDENOISOQUINOLINE AND CAMPTOTHECIN TOP1 INHIBITORS [IRINOTECAN (3) AND TOPOTECAN (4)]

However, these camptothecin derivatives are not ideal drug molecules. Camptothecins are compromised by the reversibility of the Top1-DNA cleavage complex, which necessitates long infusion times for maximum activity, and they are inherently unstable and suffer from lactone ring opening to form a hydroxy acid that has a high affinity for human serum albumin. As a result of the pharmacokinetic problems of the camptothecins, there is great interest in the development of non-camptothecin Top1 inhibitors as anticancer agents.^{13, 28} Top1 inhibitors such as the indenoisoquinolines are not limited by the same pharmacokinetic problems that limit the camptothecins. Some of the more potent indenoisoquinolines stabilize the Top1-DNA cleavage complex to a greater extent than camptothecin, they are more stable chemically, and the *in vitro* biological activities of certain derivatives are comparable.²⁹ Furthermore, it is known that clinically useful topoisomerase II

(Top2) inhibitors have preferential activity for different cancers, and it can be expected that different Top1 inhibitors will display different spectra of anticancer activity as well.³⁰

1.4 INDENOISOQUINOLINE

The indenoisoquinoline Top1 inhibitors were examined for antiproliferative activity against different cancer cell lines. These novel noncamptothecin Top1 inhibitors could be potential agents for the treatment of a variety of cancers. Two indenoisoquinolines have been selected currently for clinical development by the National Cancer Institute (NCI): National Screening Committee (NSC) (725776) (Indimitecan), and NSC (724998) (Indotecan).^{15, 24} Both exert antiproliferative activity in submicromolar concentrations in cultured human cancer cell lines. Although CPTs are very potent but often shows dose related toxicities and pharmacokinetic

problems. As compared to camptothecins, the indenoisoquinolines as a class of cytotoxic TOP I inhibitors offer certain advantages, including the

greater stabilities of the compounds themselves, as well as the greater stabilities of their drug enzyme-DNA cleavage complexes.¹²

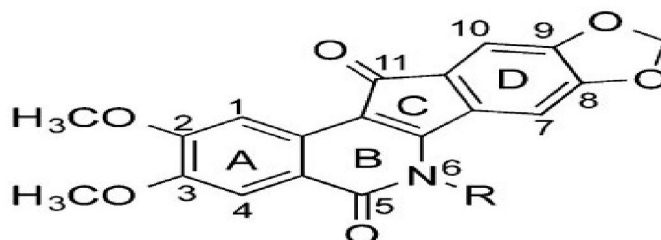


FIGURE 3 INDENOISOQUINOLINE

2. MATERIALS AND METHOD

This study is to examine the SAR of various indenoisoquinolines as topoisomerase I inhibitors with potential clinical application in the treatment of cancer in humans. To investigate the possible biological roles of the di (methoxy) and methylenedioxy substituents present on the

aromatic rings of the previously synthesized indenoisoquinoline topoisomerase I inhibitors, a series of compounds lacking these substituents was synthesized and tested for both cytotoxicity in cancer cell cultures and for enzyme inhibitory activity. The most cytotoxic of the presently synthesized indenoisoquinolines has a 4-amino-n-butyl group on the lactam nitrogen.¹⁴

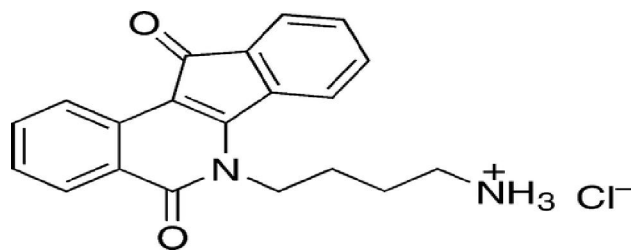


FIGURE 4 4-AMINO-N-BUTYL GROUP ON THE LACTAM NITROGEN

Compounds were evaluated for Top1 inhibition and for cytotoxicity in the National Cancer Institute's human cancer cell screen. Some of the more potent derivatives were also screened for in vivo activity in a hollow fiber assay. The results of these studies indicate that lactam substituents possessing nitrogen heterocycles can provide highly cytotoxic

compounds with potent Top1 inhibition. Molecular modeling of these compounds in complex with DNA and Top1 suggests that some of the lactam substituents are capable of interacting with the DNA base pairs above and below the site of intercalation and/or with Top1 amino acid residues, resulting in increased biological activity.¹³

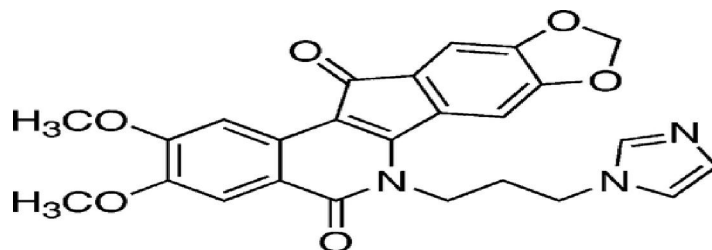


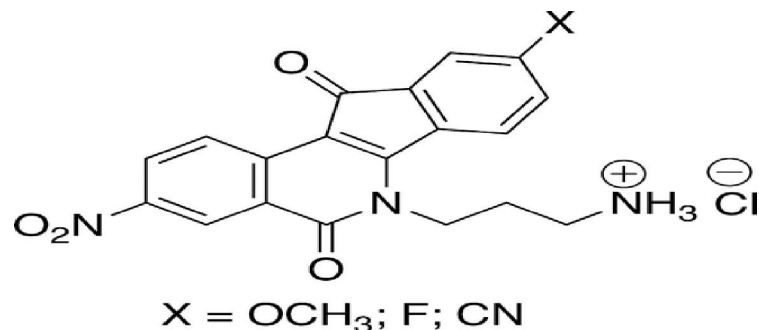
FIGURE 5 NITROGEN HETEROCYCLES ON THE LACTAM NITROGEN

Two series of indenoisoquinoline topoisomerase I inhibitors have been prepared to investigate optimal substituents on the indenone ring at the 9-

position. The more exhaustive series was prepared using a nitrated isoquinoline ring that has been previously demonstrated to enhance biological

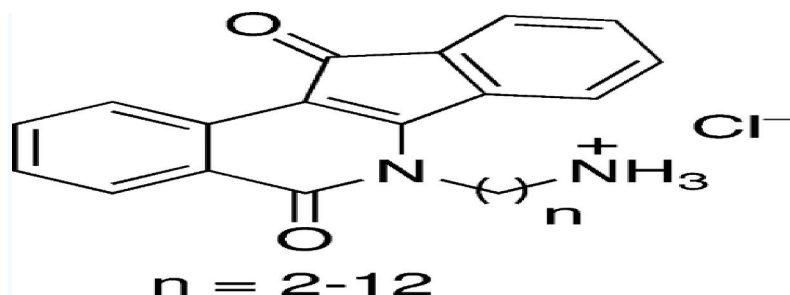
activity. After preliminary biological evaluation, a more focused series of inhibitors was prepared utilizing a 2, 3-dimethoxy-substituted isoquinoline ring. The results of the two series indicate the existence of superior functional groups such as

methoxy, fluorine, and cyano for the indenoisoquinoline 9-position. Interestingly, these functional groups coincide with established structure-activity relationships for the 11-position of camptothecin.²⁰



Indenoisoquinoline with lactam substituents such as ethyl amino, propyl amino, and butyl amino has previously demonstrated potent biological activity, but an optimal length has never been established. A series of simplified indenoisoquinoline analogues possessing a linker spacing of 0-12 carbon atoms between the lactam terminal and nitrogen and the

terminal amino group determining that 2-4 atom lengths are optimal for topoisomerase I inhibition and cytotoxicity. Using these lengths, with the amino group and portions of the linker replaced by a pyridine ring. A three-carbon spacer within the pyridine series still demonstrated potent topoisomerase I inhibition.²¹



Indenoisoquinoline analogues combinations of nitro groups, methoxy groups, and hydrogen atoms in an effort to understand the contribution of each group toward cytotoxicity and Top I inhibition. Analysis of the biological results suggests that the nitro group is important for Top I inhibition and the methoxy group improves cytotoxicity. In addition previously identified structure-activity

relationships were utilised to select favourable lactam side chain functionalities for incorporation on the aromatic skeleton of analogues in this study. As a result, this investigation has provided optimal Top I inhibitors equipotent to camptothecin that demonstrate low nanomolar cytotoxicities toward cancer cell.²²

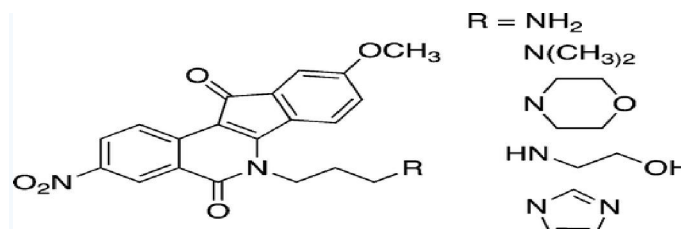
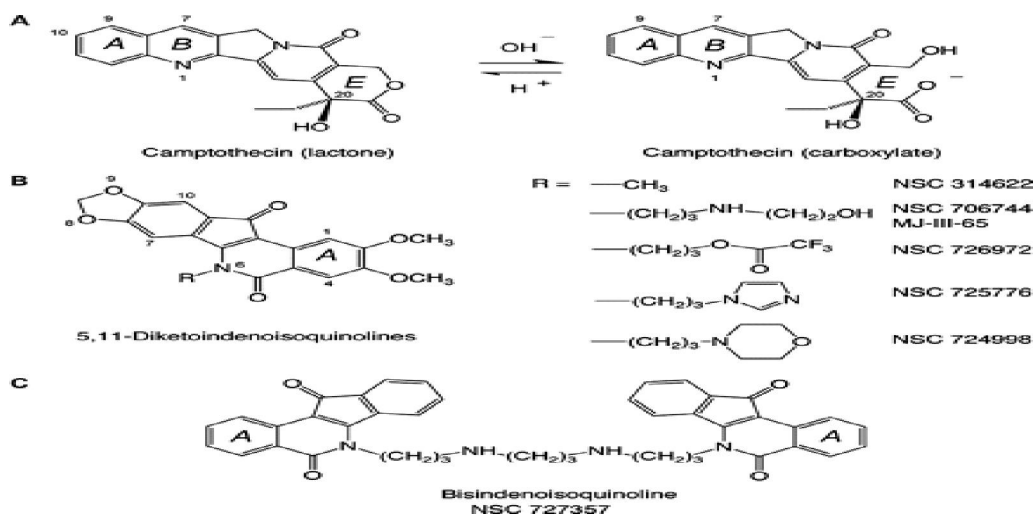


FIGURE 6 DIFFERENT FUNCTIONALITIES ON THE LACTAM NIROGEN

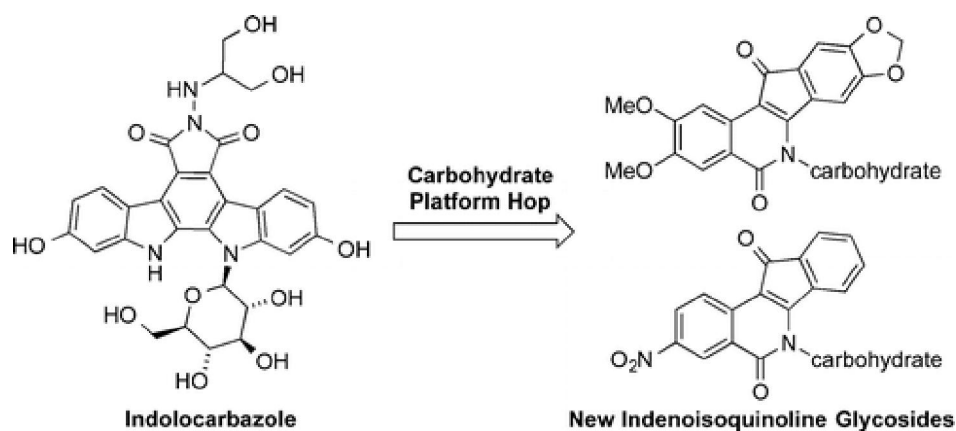
Camptothecins are effective against previously resistant tumors and are the only class of topoisomerase I (Top1) inhibitors approved for cancer treatments. Like camptothecins, the indenoisoquinolines selectively trap Top1-DNA cleavage complexes and have been cocrystallized

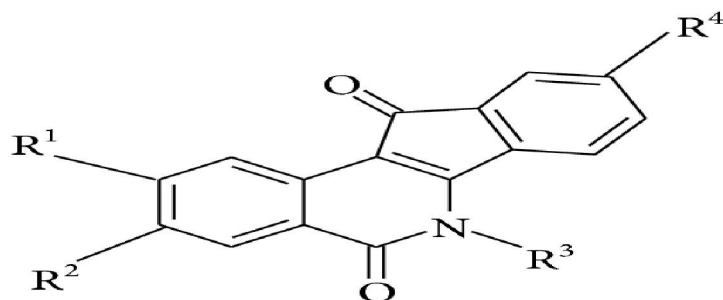
with the Top1-DNA cleavage complexes. Indenoisoquinolines show antitumor activity in animal models. The trapping of Top1 cleavage complexes by indenoisoquinolines in cells results in the rapid and sustained phosphorylation of histone H2AX (-H2AX).¹⁵



Carbohydrate moieties were strategically transported from the indolocarbazole topoisomerase I (Top1) inhibitor class to the indenoisoquinoline system in search of structurally novel and potent Top1 inhibitors. The syntheses and biological evaluation of 20 new indenoisoquinolines glycosylated with linear and cyclic sugar moieties are reported. Aromatic ring

substitution with 2, 3-dimethoxy-8, 9-methylenedioxy or 3-nitro groups exerted strong effects on antiproliferative and Top1 inhibitory activities. While the length of the carbohydrate side chain clearly correlated with antiproliferative activity, the relationship between stereochemistry and biological activity was less clearly defined.¹⁸





In recent year's topoisomerase I inhibitors like indenoisoquinolines have become important new lead for rational design of anticancer drugs due to their greater physiological and DNA-enzyme cleavage complexes stabilities. As a starting point a complete pharmacophore based 3D-QSAR study was performed on a series of 104

indenoisoquinolines and their derivatives. The best pharmacophore model consisted of one Hydrophobe (HY), one Positive Ionizable (PI) and one Ring Aromatic (RA) characteristics which are a necessary requirement for good topoisomerase I inhibitory activity.¹⁶

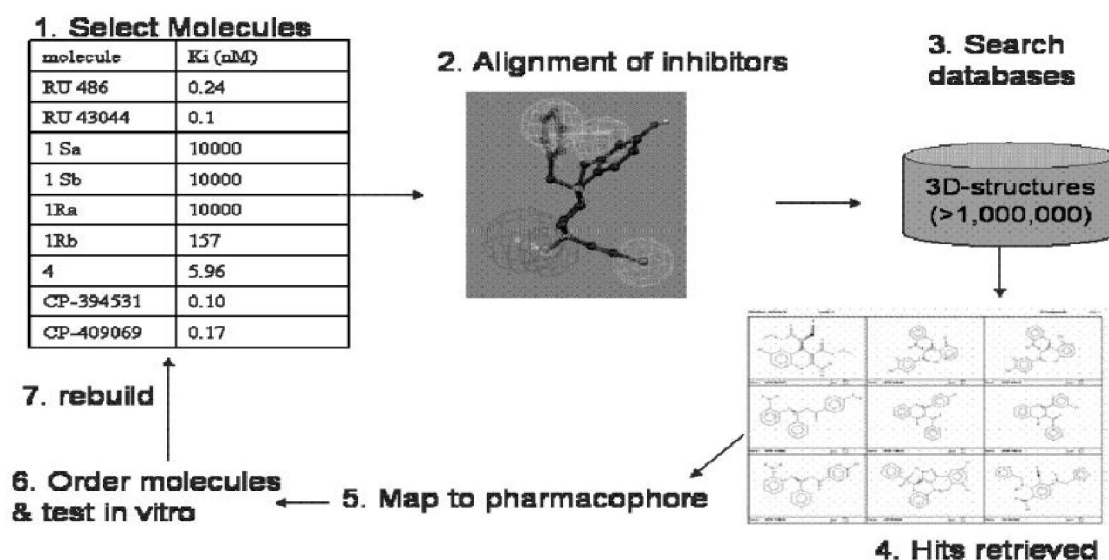
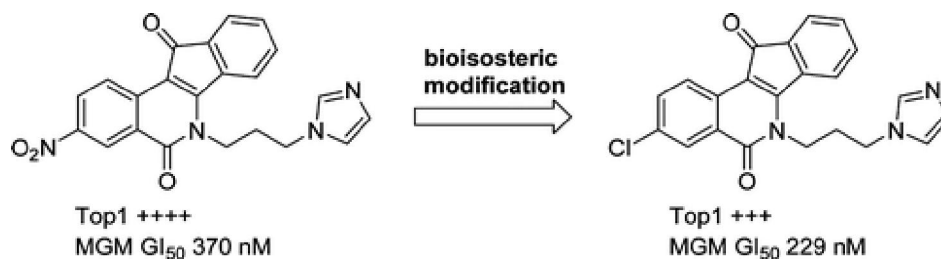


FIGURE 7 PHARMACOPHORE BASED 3D-QSAR STUDY ON INDENOISOQUINOLINES AND THEIR DERIVATIVES

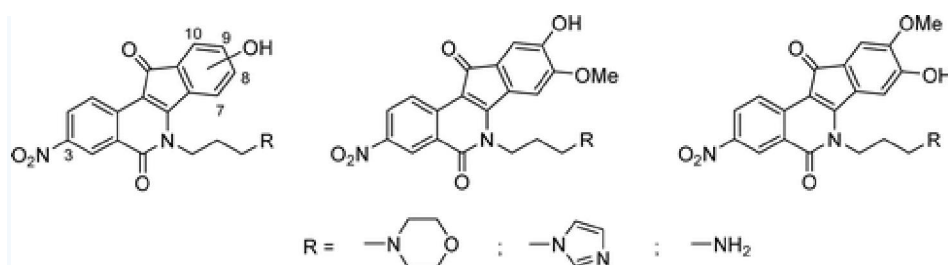
3-Nitroindenoisoquinoline human topoisomerase IB (Top1) poisons have potent antiproliferative effects on cancer cells. The undesirable nitro toxicophore could hypothetically be replaced by other functional groups that would retain the desired biological activities and minimize potential safety risks. Eleven series of indenoisoquinolines bearing 3-nitro bioisosteres were synthesized. The

molecules were evaluated in the Top1-mediated DNA cleavage assay and in the National Cancer Institute's 60 cell line cytotoxicity assay. The data reveal that fluorine and chlorine may substitute for the 3-nitro group with minimal loss of Top1 poisoning activity. The new information gained from these efforts can be used to design novel indenoisoquinolines with improved safety.¹⁷



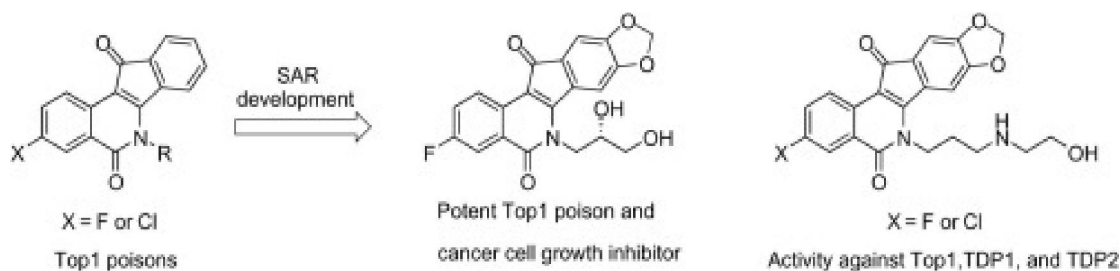
The structure activity relationships and hit-to-lead optimization of dual Top1-TDP 1 inhibitors in the indenoisoquinoline drug class were investigated. A series of nitrated 7-, 8-, 9-, and 10-hydroxyindenoisoquinolines were synthesized and evaluated. Several compounds displayed potent dual Top 1-TDP 1 inhibition. The hydroxyl series exhibited potencies and cytotoxicities vs Top 1 that

surpassed those of camptothecin (CPT), the natural alkaloid that is being used as standard in the Top 1 mediated DNA cleavage assay. One member of this series was a more potent Top 1 inhibitor at a concentration of 5 nM and produced a more stable ternary drug-DNA-Top1 cleavage complex than CPT.²³



Fluorine and chlorine are metabolically stable, but generally less active replacements for a nitro group at the 3-position of indenoisoquinoline topoisomerase IB (Top1) poisons. A number of strategies were employed in the present investigation to enhance the Top1 inhibitory potencies and cancer cell growth inhibitory activities of halogenated indenoisoquinolines. In several cases, the new compounds' activities were found to rival or surpass those of similarly

substituted 3-nitroindenoisoquinolines, and several unusually potent analogs were discovered through testing in human cancer cell cultures. A hydroxyl ethyl amino propyl side chain on the lactam nitrogen of two halogenated indenoisoquinoline Top1 inhibitors was found to also impart inhibitory activity against tyrosyl DNA phosphodiesterases 1 and 2 (TDP1 and TDP2), which are enzymes that participate in the repair of DNA damage induced by Top1 poisons.¹⁹



3. RESULTS AND DISCUSSION

Topoisomerase I (TOP I) is a valuable molecular target for the development of clinically used anticancer agents. Indenoisoquinolines as a class of cytotoxic TOP I inhibitors offer certain advantages, including the greater stabilities of the compounds themselves. 4-amino-n-butyl group on the lactam nitrogen shows significant Top I inhibitory activity. Indenoisoquinoline topoisomerase I inhibitors substituted with nitrogen heterocycles appended to the lactam side chain shows potent Top1 inhibition. In lactam side chain 2-4 carbon chain lengths are optimal for topoisomerase I inhibition and cytotoxicity. Along with the carbohydrate substitution, aromatic ring substitution with 2, 3-dimethoxy-8, 9-methylenedioxy or 3-nitro groups exerted strong effects on antiproliferative and Top1 inhibitory activities. Hydrophobe (HY), one Positive Ionizable (PI) and one Ring Aromatic (RA) characteristics which are a necessary requirement for good topoisomerase I inhibitory activity. Optimal substituents such as methoxy, fluorine, chlorine and cyano for the indenoisoquinoline on the indenone ring at the 9-position of indenoisoquinoline possess topoisomerase I inhibitors. Nitrated 7-, 8-, 9-, and 10-hydroxyindenoisoquinolines displayed potent dual Top 1-TDP 1 inhibition. Fluorinated and chlorinated indenoisoquinoline metabolically stable

rival or surpass those of similarly substituted 3-nitroindenoisoquinolines.

4. CONCLUSION

The substituted heteroatom within the lactam side chain has a significant impact on both Top1 inhibition and cytotoxicity. The new information gained from these efforts can be used to design novel indenoisoquinolines with improved safety. Indenoisoquinoline has a great scope for the discovery of new, better, safer and more potent chemotherapeutic agents. It has been noticed so far that the structural modifications of indenoisoquinoline moiety displayed various biological activities especially anticancer activities. Also it will be interesting to observe that this modification can be utilised to produce potent anticancer agent in future. Indenoisoquinoline derivatives can be synthesized relatively easily and Top1-DNA indenoisoquinoline additional optimization will lead to novel drugs selectively targeted to Top1 with significant activity against cancers.

5. ACKNOWLEDGEMENT

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6. AUTHOR CONTRIBUTIONS

All authors equally contributed to this review. All authors were participated in the collection of data, preparation of manuscript and finally approved the review.

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9. ABBREVIATIONS:-

CPT-Camptothecin

DNA-Deoxyribo Nucleic Acid

FDA -Food and Drug Administration

G1-First growth phase

G2-Second growth phase

H2AX-Histone H2AX (H2A histone family, member X.

HY-Hydrophobe

NCI-National Cancer Institute

NSC-National Screening Committee

PI-Positive Ionizable

QSAR-Quantitative Structure Activity Relationship

SAR-Structure Activity Relationship

RA-Ring Aromatic

TDP1-Tyrosyl DNA Phosphodiesterases 1

TDP2-Tyrosyl DNA Phosphodiesterases 2

Top 1(TOP 1)-Topoisomerase 1

Top 2 (TOP 2)-Topoisomerase 2

CONFLICT OF INTEREST REPORTED: NIL;

SOURCE OF FUNDING: NONE REPORTED