Lung cancer predominantly occurs in two forms, small cell lung cancer (SCLC) (20%) and non-small cell lung cancer (NSCLC) (80%). Research into therapies to combat lung cancer has revealed an effective drug target: the enzyme topoisomerase II (topoII).

Combination therapy with topoII poisons, black gate closes, and topoII dissociates from DNA (6). Inhibitors and their inhibition points are shown. Red – topoII poisons, black – catalytic inhibitors, green – drugs under evaluation, 1, 4-

Catalytic Cycle of Topoisomerase II

Fig. 2: The catalytic cycle of DNA topoisomerase II. Light blue – ATPase domain, dark blue – core domain, yellow – G-segment, green – T-segment. Free topoi binds to the G-segment of duplex DNA (1). ATP (red circle) binds to the ATPase domains promoting T-segment capture and ATPase dimerization (2). N-gate closure induces G-segment cleavage and hydrolysis of one ATP (3). The DNA-gate opens and the T-segment passes through the G-segment (4). Hydrolysis of the second ATP reglatis the G-segment, the C-gate opens, and the T-segment dissociates (5). Both ADPs dissociate from the ATPase domain, the N-gate opens, the C-gate closes, and topoi dissociates from DNA (6). Inhibitors and their inhibition points are shown. Red – topoII poisons, black – catalytic inhibitors, green – drugs under evaluation.

Compounds Exhibit Significant Antiproliferation Activity

Fig. 3 – 9-aminoacridine derivatives shown alongside the parent structure of 9-aminoacridine. 2

Chemical Structure of Experimental Compounds

Fig. 1: Chemical structures of substituted 9-aminoacridine derivatives shown alongside the parent structure of 9-aminoacridine. 2

Topoisomerase II is a Major Target of Lung Cancer Therapy

• Cancer is the leading cause of death in the developed world, claiming over 7.6 million lives in 2008 alone.
• Lung cancer is one of the most common cancers and has one of the highest mortality rates, accounting for nearly 18% of all cancer-related deaths each year. 7
• Lung cancer predominantly occurs in two forms, small cell lung cancer (SCLC) (20%) and non-small cell lung cancer (NSCLC) (80%).
• Research into therapies to combat lung cancer has revealed an effective drug target: the enzyme topoisomerase II (topoII).
• Present drugs that inhibit topoi are called topoi poisons and stabilize the topoDNA covalent complex, inducing DNA damage and cell death.
• Topoi poisons have a major drawback: they are very toxic and can lead to chemotherapy-related leukemia in patients.
• This has prompted the search for drugs of similar action with reduced toxicity, which led to the discovery of the catalytic inhibitors.
• Catalytic topoi inhibitors interfere with topoi’s function without inducing DNA damage by acting either before the DNA is broken or after it is rejoined.
• Recently, a small library of substituted 9-aminoacridines was discovered that have been shown to be catalytic inhibitors of topoi.
• In this study, we tested these compounds’ antiproliferative abilities in human lung cancer cell lines. 2

Future directions

• Substituted 9-aminoacridine compounds exhibit significant anticancer activity in human lung cancer in vitro.
• The potency of compounds as antiproliferative agents is greater in NSCLC lines than SCLC lines, showing a greater ability to inhibit cell growth and division.
• Compounds display differential potency with compounds ranked in decreasing order of potency from 4 > 3 > 2 > 1.
• NSCLC lines undergo apoptosis when treated with acridine compounds.
• SCLC lines undergo both apoptosis and apoptosis simultaneously when treated with acridine compounds.
• Combination therapy with cisplatin show additive drug effects with compound 3 showing the greatest effect.
• Future directions:
  • Further studies are needed to understand the mechanism behind the difference in programmed cell death observed between SCLC and NSCLC cancers.
  • In vivo studies should be initiated to determine drug activity and toxicity in animal models. The dosage of compound necessary for activity in humans is unlikely to be achieved in vivo.
  • However, further drug refinement through chemical modification may increase potency and lead to improved therapies in the future to combat this disease.

References