

NOVEL DUAL ACTION ANTI-NEOPLASTIC DRUGS

Meyer Elazar, Ph.D

214 Haalon St., Matta, Israel

Correspondence e-mail: elime11g@gmail.com

Abstract. A novel drug structure (a Markush structure) is presented including molecules that can be effective as dual action drugs namely as inhibitors of epidermal growth factor kinase domain as well as having anti-angiogenic activity. The novel Markush structure includes molecules that might have dual anti-neoplastic activity leading to the development of a novel effective cancer drug for treating e.g., pancreatic cancer.

Keywords: dual action, anti-neoplastic, Markush, pancreatic cancer, epidermal growth factor receptor, vascular endothelial growth factor, computer-assisted molecular modeling, structure-activity-relation, drug model explanation.

Introduction

Pancreatic cancer is one of the most lethal malignancies due to its late diagnosis and limited response to treatment²⁻⁷. Tractable methods to identify and interrogate pathways involved in pancreatic tumorigenesis are urgently needed. Pancreatic ductal adenocarcinoma (PDAC) is characterized by an extremely poor overall survival compared to other solid tumors. Since treatment options are limited, PDAC is projected to be the 2nd leading cause of cancer-related deaths in the United States by 2030¹. A majority of patients are not eligible for curative resection at the time of diagnosis, and those that are resected will often relapse within the first few years after surgery. A presently common treatment includes using the nucleoside analogue gemcitabine as standard treatment for patients with non-resectable PDAC with only marginal effect on overall survival. Gemcitabine-free FOLFIRINOX regimen (folinic acid, fluorouracil, irinotecan and oxaliplatin) shows a significant survival advantage for patients with metastatic PDAC. Metastatic pancreatic adenocarcinoma with nano-formulated albumin-bound paclitaxel (nab-paclitaxel) in combination with

gemcitabine also results in a significant survival extension compared to gemcitabine mono-therapy. However, both intensified therapy regimens show a broad spectrum of side effects and patients need to be carefully selected for the most appropriate protocol.

Neo-adjuvant therapies exist such as using 5-fluorouracil and radiation, gemcitabine and radiation, gemcitabine/nab-paclitaxel or FOLFIRINOX followed by 5-fluorouracil and radiation, or gemcitabine/docetaxel/capecitabine followed by 5-fluorouracil and radiation.

The current treatments for treating pancreatic cancer do not cure the disease and serve only to prolong the lives of the patients. In addition, existing drug therapies fail to overcome the problem of RAS mutations (see page 5). Therefore, there is a need for more efficient drugs with decreased side effects.

Methodology

The proposed novel Markush drug structure affords theoretical dual therapeutic action, which may consequently lead to the discovery of more effective drugs for treating cancer. The novel drug has a reversible kinase domain, which may act on the epidermal growth factor receptor (EGFR) as tyrosine kinase inhibitor and a second domain possessing anti-angiogenic activity.

The phrase "theoretical" means that the Markush structure includes molecules that have never been disclosed prepared or tested before.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene, which encodes aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a trans-membrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. It is known that such kinases are frequently aberrantly expressed in common human cancers such as pancreatic cancer. It has also been shown that EGFR, which possesses tyrosine kinase activity, is mutated and/or overexpressed in many human cancers. A computer-assisted molecular modeling may be used to determine whether or not at least one molecule of the Markush structure may act as a suitable inhibitor of epidermal growth factor kinase domain by fitting into an active site thus leading to reversible binding to the active site.

Angiogenesis or formation of new blood capillaries from preexisting vessels results of a complex balance of positive and negative regulators, and vascular endothelial growth factor (VEGF) is one of the most important pro-angiogenic factors involved in tumor angiogenesis.

The potent role of VEGF in tumor angiogenesis has been described in the literature, being expressed in most types of non-digestive and digestive cancers.

VEGF and its receptors play a central role in tumor angiogenesis and therefore the inhibition of this pathway is a promising therapeutic strategy for inhibiting angiogenesis and tumor growth.

VEGF increases vascular permeability, which might facilitate tumor dissemination via the circulation causing a greater delivery of oxygen and nutrients; it recruits circulating endothelial precursor cells, and acts as a survival factor for immature tumor blood vessels. The endotheliotropic activities of VEGF are mediated through the VEGF-specific tyrosine-kinase receptors: VEGFR-1, VEGFR-2 and VEGFR-3.

Targeting VEGF activity, inhibiting VEGF receptor function is proposed herein as a possible strategy for treating cancer by inhibiting VEGF signal transduction.

VEGF family members play an important role in the development of pancreatic cancer (especially VEGF-A, VEGF-C, VEGF-D, VEGFR-1 and VEGFR-2). VEGF-A is the most specific and prominent angiogenic factor among all family members and VEGFR-2 is the most important receptor in evaluating the angiogenesis in pancreatic cancer. Thus, VEGF overexpression may be considered as a diagnostic marker and as a poor prognostic factor of the disease⁸.

The proposed Markush structure relates to compounds of formula I and to stereoisomers and pharmaceutically acceptable salts and pro-drugs thereof;

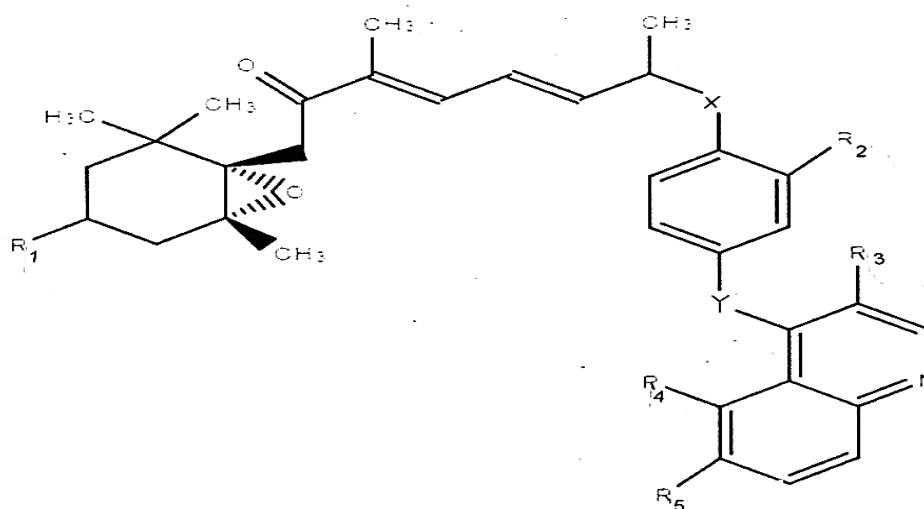


Fig.1 Compounds of formula I

wherein X and Y are independently selected from CH₂, O, S, NH, NR, wherein R is a (C₁-C₄)-alkyl;

R₁ is selected from H, OH, (C₁-C₄)-alkyl, O(C₁-C₄)-alkyl, OCO(C₁-C₄)-alkyl;

R₂, R₃ and R₄ are independently selected from (C₁-C₆)-alkyl, un-substituted or substituted with substituents selected from phenyl, benzyl and naphthyl and substituted phenyls bearing one or more substituents on the aromatic ring selected from (C₁-C₆)-alkyl such as methyl and ethyl, CF₃, OH, OR₆, wherein R₆ is (C₁-C₆)-alkyl, NO, NO₂, CN, F, Cl, Br, I, CHO, SO₂H, SO₂Me, NH₂, NHR₇ wherein R₇ is (C₁-C₆)-alkyl or OCOR₈, wherein R₈ is (C₁-C₆)-alkyl, N(R₉)₂ wherein R₉ is (C₁-C₆)-alkyl, CO₂H, CO₂R₁₀ wherein R₁₀ is (C₁-C₆)-alkyl, CO₂NHR₁₁, wherein R₁₁ is (C₁-C₆)-alkyl.

R₅ is selected from (C₁-C₆)-alkyl or NHCOR₁₂, wherein R₁₂ is selected from (C₁-C₆)-alkyl un-substituted or substituted with substituents selected from phenyl, benzyl, naphthyl, pyridyl, imidazolyl, pyrrole or piperidinyl and substituted phenyl, benzyl, naphthyl, pyridyl, imidazolyl, pyrrole or piperidinyl bearing one or more substituents on the aromatic ring selected from (C₁-C₆)-alkyl such as methyl and ethyl, NO, NO₂, CN, F, Cl, Br, I, CHO, SO₂H, SO₂Me, NH₂CF₃, OH, OR₁, NHR₇ wherein R₇ is (C₁-C₆)-alkyl or OCOR₈, wherein R₈ is (C₁-C₆)-alkyl, N(R₉)₂ wherein R₉ is (C₁-C₆)-alkyl, CO₂H, CO₂R₁₀ wherein R₁₀ is (C₁-C₆)-alkyl, CO₂NHR₁₁, wherein R₁₁ is (C₁-C₆)-alkyl.

An example of a dual action compound belonging to the Markush structure of formula I, is the compound of formula Ia, wherein X=O, Y=NH, R₁=OH, R₂=Cl, R₃=CN, and R₄=NHCCH₂-imidazol and R₅=OMe:

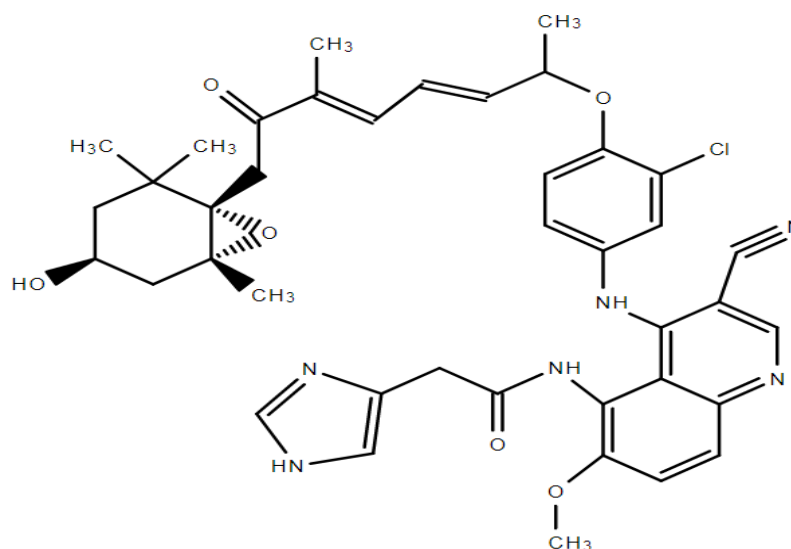


Fig.2 Compound of formula Ia

Another example of a dual action compound belonging to the Markush structure of formula I, is the compound of formula Ib, wherein X=O, Y=NH, R₁=OH, R₂=OMe, R₃=OMe, R₄=Cl and R₅=F:

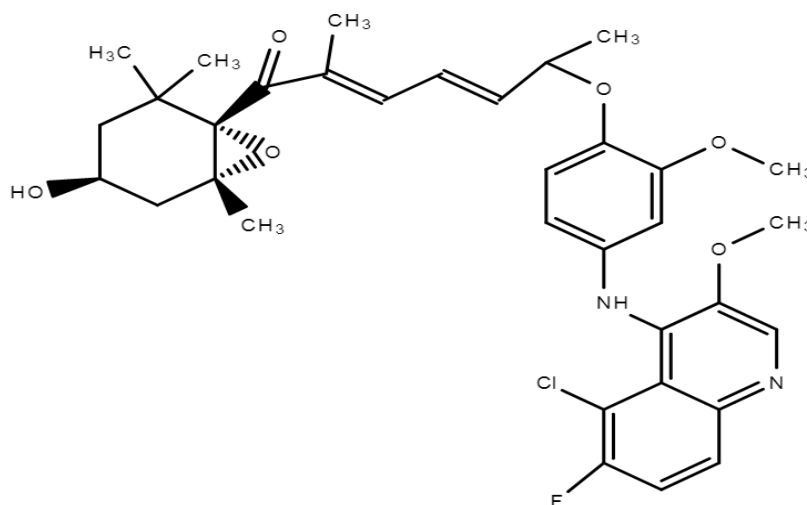


Fig.3 Compound of formula Ib

The structure-activity-relation and drug model explanation are the following: it is predicted that the substituted aromatic ring that is connected (via a linker atom) to the substituted quinoline ring of the proposed Markush (hereinafter the 3-ring system) might fit well into the well-known active site of the epidermal growth factor receptor which possesses tyrosine activity⁹, thus it might act as an irreversible covalent inhibitor of EGFR. Specially, the 3-ring system might fit well into the pocket of said EGFR between Tyr845 and Glu842.

Additionally, is predicted that the substituted cyclohexyl ring to which a stereo epoxide ring is connected and an aliphatic tail that includes two double bonds and a keto group of the proposed Markush, might possess angiogenesis inhibitory activity by binding to a VEGF receptor. According to Comba et al.¹⁰, compounds such as apo-13-fucoxanthinone might significantly decrease the expression of VEGF in certain kinds of cancers such as Sarcoma 180.

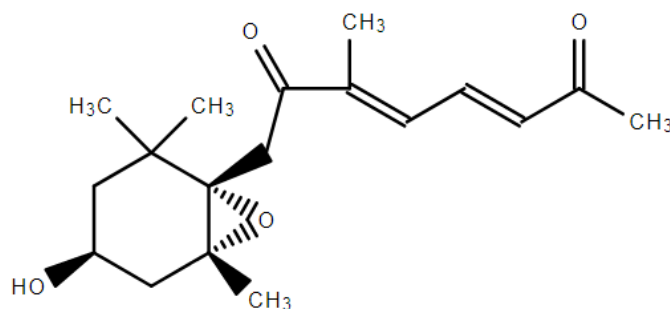


Fig.4 apo-13-fucoxanthinone

These results imply that molecules having structures such as apo-13-fucoxanthinone possess antiangiogenic activity that might be useful in preventing angiogenesis-related diseases¹¹.

It is further proposed that the aliphatic tail that includes two double bonds and a keto group of the Markush of formula I may contribute to both effects described herein by fitting to the pocket of EGFR and by VEGF inhibition.

Rat Sarcoma Virus (*RAS*) gene mutations are among the most frequently mutated genes in human cancers, found in approximately 30% of all tumor types and in approximately 50% of colorectal cancer. Clinically, *RAS* mutations have proven to be an elusive target despite the substantial amount of research investigating strategies to inhibit oncogenic *RAS* mutations. The *KRAS* mutations exist in more than 90% of pancreatic cancers. Oncogenic *RAS* mutations act through different pathways to elicit its tumor promoting effects and cause acquired resistance to EGFR therapies such as cetuximab and panitumumab (monoclonal antibodies).

The aliphatic tail of the Markush structure might also interfere with formation of *RAS* gene mutations by blocking *RAS*-effector protein interactions¹². Unless given by IV administration, a drug must cross several semipermeable cell membranes before reaching the systemic circulation. Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. The membranes are composed primarily of a bimolecular lipid matrix, which determines membrane permeability characteristics. Combining the two effects in one molecule might lead to the development of a drug with improved activity in treating cancer and at the same time avoiding the limitations of administering two drugs simultaneously which may lead to reduced drugs absorption.

Conclusion

The presented novel drug structure includes molecules having potential dual anti-neoplastic activity, thus at least one of these molecules can be effective as inhibitor of epidermal growth factor kinase domain as well as having anti-angiogenic activity for treating e.g., pancreatic cancer. Research is needed to establish the potential activity by carrying out molecular modeling to tack the most potent candidates, synthesis and pharmacological tests.

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