

An Overview of Antibiotics Used in Cancer Treatment and Drugs that Act as Antimicrotubules

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Abstract

The cancer in general is an abnormal growth with no causes and route of transportation in the body, which is the difficult of treatment or limited of its spread.

One of the methods of treatment is the chemotherapeutic agents, we will overview on Antibiotics and Antimicrotubules act as Anticancer. The Anticancer Antibiotics are Bleomycin, Dactinomycin, Daunorubicin, Epirubicin, Plicamycin, Doxorubicin, Mitomycin.

Antimicrotubules, mostly, they are naturally compounds which inhibit the microtubules which responsible for the cell division and proliferation of the cancer cell specifically as Colchicine, Vincristine, Vinblastine, hence the Antibiotic Anticancers and Antimicrotubules are important to know its importance in cancer treatment.

Keywords: anticancer, Antimicrotubules, chemotherapeutic agents, antibiotics, colchicine, vincristine, vinblastine, microtubules, cell division

1. Introduction

The cancer disease is a dangerous due to unknown of its raising from any tissue, spread to the other tissues.

The cancer cell not plays the bioactivity which

required for the cell, tissue and organ (whole body). The tumor tissues convert into necrotic mass which diffuse in the body till die the cancerous human (animal), so the Antibiotics anticancer play an important role in stopped of the growth of cancer, if responded to the

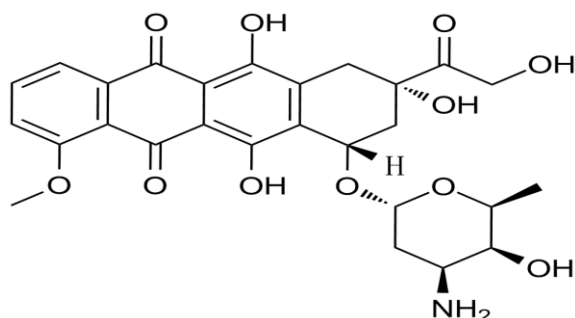
antibiotics, also the growth of cell cancer will stopped or may be decreased (by inhibit the new cancer cell), in related to that, the antimicrotubules its mechanism of action depend on inhibition of cell division, sometimes there are many drugs specific for the tumor cells (benign and malignant).

In many states the benign tumors with times convert into malignant tumors, whereas the tumor is increase in number of cell either benign or malignant, the antimicrotubules will stopped the increase of tumor cells (numbers or size).

2. Chemistry and Pharmacology

Doxorubicin

It is a tetracycline antibiotic which used in breast, bladder cancers, Kaposi's sarcoma, lymphoma and leukemia (acute with other chemotherapeutic drugs).



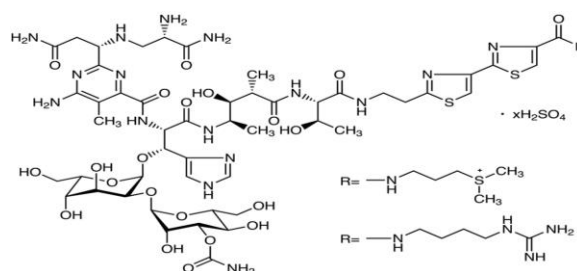
The Doxorubicin is biosynthesized from the *Streptomyces* strains.

The doxorubicin intercalates with DNA and prevent the biosynthesis of macromolecules.

For example, Topoisomerase II an enzyme which relaxes supercoiling of DNA and hence no formation of new cells, where the Topoisomerase II enzyme present largely in tumor cells so its inhibition will inhibit the DNA synthesis in cancer cell, hence, the macromolecules is not formed and many of DNA strands will be relaxed and broken.

The chromophoric properties (i.e., the many of double bonds and carbonyl, hydroxyl groups) responsible for intercalation with DNA, where the sugar moiety downs amine which contains six atoms in cyclic structure act as groove which catch the DNA inside it (the previous means doxorubicin inhibit the Protein synthesis of the cell via inhibition of Topoisomerase II enzyme present of tumor cell).

Bleomycin.



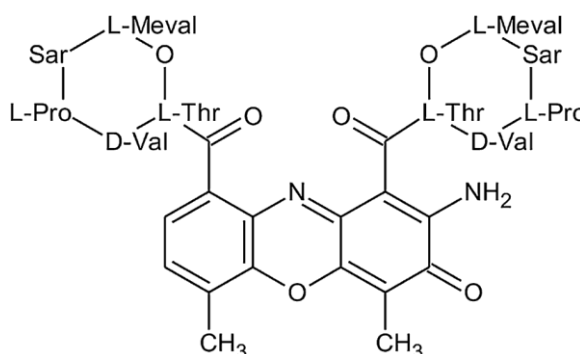
Is peptide non ribosomal meaning peptide polyketide natural product. Bleomycin has aglycon part, bleomycin is mega synthetase and polyketide synthetase modules synthesized from amino acids and short carboxylic acids.

Bleomycin acts by induction of DNA strands break and also inhibit the incorporation of thymidine into DNA strands.

Bleomycin chelates metal ions (iron), release enzymes that interact with oxygen to form reactive oxygen (ROS) species that cause destruction of DNA, also maybe it binds to specific region on DNA and induce session of its strands.

Also, it is Antibiotic anticancer act on Topoisomerase II enzyme which is characteristic in more of tumor cells.

Dactinomycin.

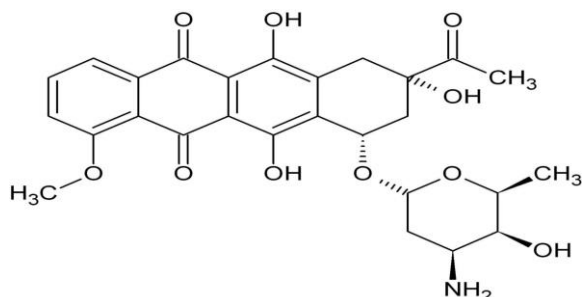


Also known as Actinomycin-D as chemotherapeutic agents which used as intra venous in treatment of Wilms tumor, rhabdomyosarcoma, Ewing's sarcoma, testicular cancers and certain ovarian benign tumors.

Dactinomycin is composed of chromophoric Phenoxazinone and formed from cyclic peptides, the dactinomycin resulted from fermentation from tryptophan and dextro-glutamic acid as precursor substrates, the *Streptomyces chrysomallus cluster* used in synthesis of Dactinomycin.

The DNA transcript into RNA, the Dactinomycin binds to DNA which initiate the complexation and elongation of RNA chain by RNA polymerase which inhibited by action of dactinomycin on DNA.

Daunorubicin.



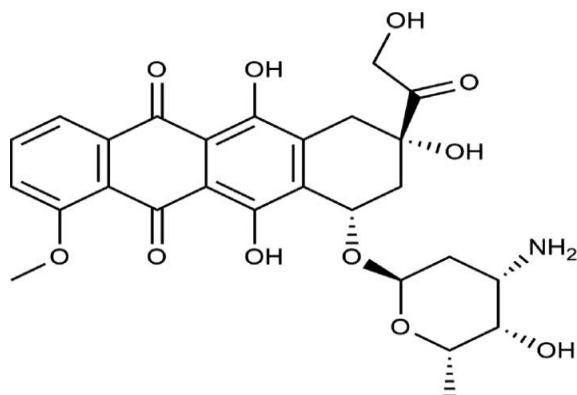
Daunorubicin is a chemotherapeutic agent known as daunomycin used in treatment of leukemia (Acute Myeloid and lymphoblastic and chronic myelogenous), Kaposi sarcoma too.

The Daunomycin is used intravenous after liposomal formulation of Daunomycin.

The Daunorubicin was essential isolated from bacteria which is from *Streptomyces* family.

Its mechanism of action Daunorubicin interact with DNA via intercalation and prevention of macromolecule synthesis, this occur across inhibition of Topoisomerase II which is relaxes the supercoil of DNA, hence this action is prevent the Topoisomerase II enzyme, also lead to break the DNA chains and no further replication of DNA strands (no DNA double helix stands) specifically of the tumor cells.

Epirubicin.



The Epirubicin is a tetracyclic compound attached with sugar part which is called Anthracycline, Chemotherapeutic agent which

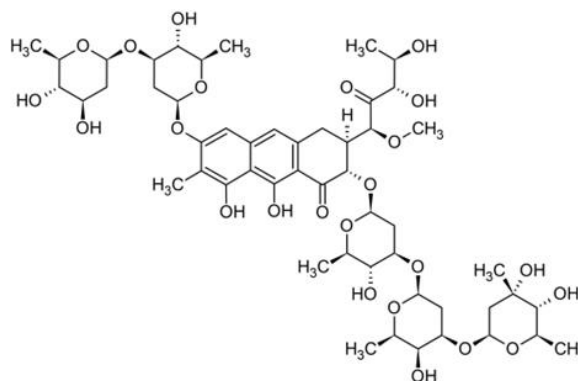
combined with anticancer drugs which used in mammary cancers and used after surgical removal of breast.

Anthracycline is a drug which extracted from *Streptomyces* bacteria this compound used in treatment in addition to breast cancer used in leukemias, bladder, stomach, ovarian, uterine and lung cancers.

N.B. The first anthracycline discovered is daunorubicin, doxorubicin and daunorubicin are an important antibiotic anticancer.

Generally, the anthracycline has been widely studied for their interaction with cellular components and impact on cellular processing, this includes cultured cells and animal system as whole, must be noted the mechanisms (DNA intercalation, topoisomerase II poison, reactive oxygen species (ROS) and DNA adduct formation) production and which occurred at clinically relevant drug concentrations are the most important.

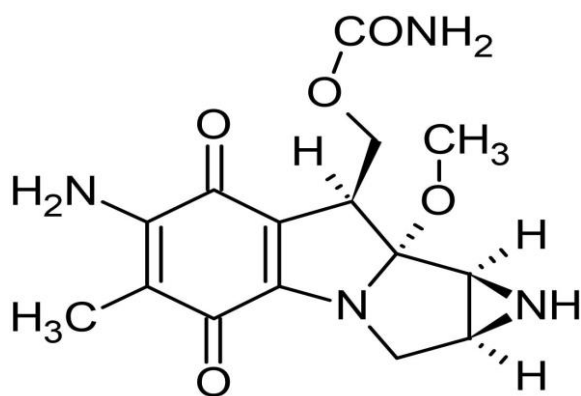
Plicamycin.



Plicamycin named as mithramycin antineoplastic antibiotic resulted from *Streptomyces plicatus*, it is a RNA synthesis inhibitor. The plicamycin is stopped or discontinued production due to Prescence of many different structures are currently reported in different places of the world which have the same core of plicamycin (chromomycin).

The importance difference is stereochemistry of the glycoside chain.

Mitomycin.

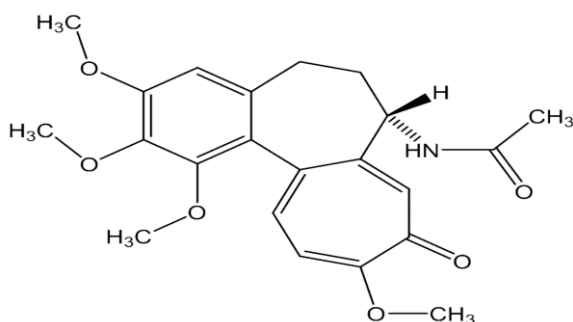


Mitomycins are family of aziridine compounds, natural, isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae*. Mitomycins are A, B and C when mention mitomycin only is indicate to Mitomycin-C (the only has medical importance), the mitomycin synthesized from combination of 3-amino, 5-hydroxy benzoic acid, D-glucose amine and carbamoyl phosphate to produce the mitosan core followed by tailoring steps the key intermediate, which is precursor for other anticancer compounds e.g. rifamycin and ansamycin.

Mitomycin-C is strong DNA cross linker which links per genome has shown to be effective in killing bacteria, which accomplished by reductive activation of mitomycin to form mitocyne which react with DNA where alkylate the two bases of the DNA bases, so occur denaturation of DNA double helix, hence the mitomycin gel is an alkylating agent, inhibits the transcription of DNA to RNA which stop protein synthesis and lead to away the multiplication of the cancer cell.

The drugs which act as Antimicrotubules

Colchicine.



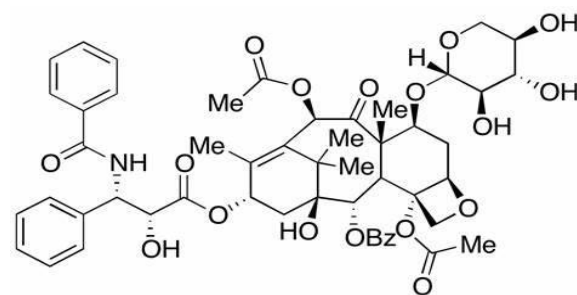
Is a natural alkaloid which used in treatment of gout, Behcet's disease and also management of pericarditis and Familial Mediterranean fever,

used (oral and intraarticular), also the therapeutic index is a risk significant.

It is obtained from plant origin (*Autumn crocus Colchicum autumn*). The previous researches are mentioned various mechanisms by which colchicine may interfere with gouty inflammation (the inflammation is a type of tumor "benign"), colchicine act via inhibit the microtubules polymerization by binding with tubulin.

The tubulin is essential for mitosis; hence the colchicine inhibits the mitosis. Colchicine inhibits migration of neutrophils to site of inflammation, where interfere with the inflammasome complex in neutrophils and monocytes that mediates interleukin 1-beta and also cause inhibition of super oxide anion which formed in urate crystals, further more interrupts mast cells and lysosome degranulation, inhibits the release of glycoproteins that promote the chemotaxis from synovial cells and neutrophils, collectively colchicine inhibit multiple pro inflammatory mechanisms and increase the levels of anti inflammatory mediator in addition inhibition of mitosis.

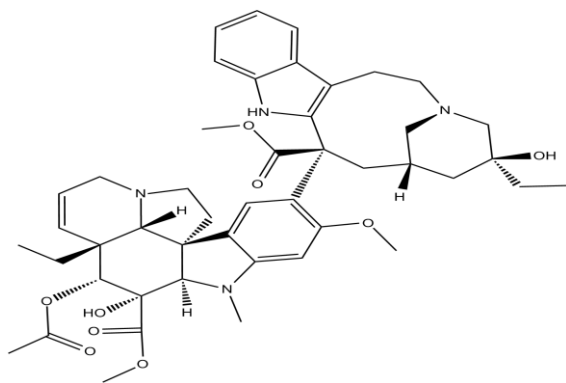
Vincristine.



Vincristine is a chemotherapeutic agent of the drugs obtained from *Vinca* alkaloid (natural drug from plant source), which acts through binding with microtubular proteins of the mitotic spindle, which lead to prevent cell division during Anaphase of mitosis, hence they (vincristine and vinblastine) arrest mitosis so cause cell death, M-phase it is the target site of vinca alkaloid.

N.B. Vincristine is fatal in 85% of patients when injected intrathecal, where vincristine is included on the CHS (high risk medicine).

Vinblastine.



It is similar to vincristine obtained from *Vinca* alkaloid, also acts as vinblastine.

3. Conclusion

In conclusion, cancer is a complex disease characterized by abnormal cell growth and limited treatment options. Chemotherapeutic agents, including antibiotics and antimicrotubules, play a crucial role in the treatment of cancer. Antibiotic anticancer drugs such as Bleomycin, Dactinomycin, Daunorubicin, Epirubicin, Plicamycin, Doxorubicin, and Mitomycin act through various mechanisms, such as inhibiting DNA synthesis and interfering with the function of enzymes like Topoisomerase II. These antibiotics have shown efficacy in treating different types of cancers.

Antimicrotubule agents, such as Colchicine, Vincristine, and Vinblastine, inhibit microtubule formation, which is essential for cell division and proliferation of cancer cells. By disrupting microtubule function, these agents prevent the growth and spread of tumors.

Understanding the chemistry and pharmacology of these anticancer agents is crucial for their effective use in cancer treatment. Each drug has its unique mechanism of action and specific indications for different types of cancers.

In summary, antibiotics and antimicrotubules are important components of chemotherapy regimens and have demonstrated their significance in cancer treatment. Further research and development in this field will likely lead to the discovery of more effective and targeted anticancer agents, improving outcomes for patients with cancer.

N.B. from the above survey, noted that the antibiotics which used in cancer treatment obtained from specific microorganisms.

References

- Abdel-Aziz, A. A. M., El-Azab, A. S., Alanazi, A. M., Asiri, Y. A., Al-Suwaidan, I. A., Maarouf, A. R., ... & Shawer, T. Z. (2016). Synthesis and potential antitumor activity of 7-(4-substituted piperazin-1-yl)-4-oxoquinolines based on ciprofloxacin and norfloxacin scaffolds: in silico studies. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 31(5), 796-809.
- Al Ward, M. M. S., Abdallah, A. E., Zayed, M. F., Ayyad, R. R., & El-Zahabi, M. A. (2024). Design, synthesis and biological evaluation of newly triazolo-quinoxaline based potential immunomodulatory anticancer molecules. *Journal of Molecular Structure*, 1298, 137041.
- Al Ward, M., Abdallah, A. E., Zayed, M., Ayyad, R., & El-Zahabi, M. (2023). New immunomodulatory anticancer quinazolinone based thalidomide analogs: Design, synthesis and biological evaluation.
- Alaa, A. M., Abou-Zeid, L. A., ElTahir, K. E. H., Ayyad, R. R., Magda, A. A., & El-Azab, A. S. (2016). Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4 (3H)-quinazolinones. *European Journal of Medicinal Chemistry*, 121, 410-421.
- Alaa, A. M., El-Azab, A. S., Abou-Zeid, L. A., ElTahir, K. E. H., Abdel-Aziz, N. I., Ayyad, R. R., & Al-Obaid, A. M. (2016). Synthesis, anti-inflammatory, analgesic and COX-1/2 inhibition activities of anilides based on 5, 5-diphenylimidazolidine-2, 4-dione scaffold: molecular docking studies. *European journal of medicinal chemistry*, 115, 121-131.
- Alanazi, A. M., Abdel-Aziz, A. A. M., Shawer, T. Z., Ayyad, R. R., Al-Obaid, A. M., Al-Agamy, M. H., ... & El-Azab, A. S. (2016). Synthesis, antitumor and antimicrobial activity of some new 6-methyl-3-phenyl-4 (3 H)-quinazolinone analogues: in silico studies. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 31(5), 721-735.
- Al-Suwaidan, I. A., Abdel-Aziz, A. A. M., Shawer, T. Z., Ayyad, R. R., Alanazi, A. M., El-Morsy, A. M., ... & El-Azab, A. S. (2016). Synthesis, antitumor activity and molecular docking study of some novel 3-benzyl-4 (3H) quinazolinone analogues. *Journal of enzyme inhibition and medicinal chemistry*, 31(1), 78-89.

- Al-Warhi, T., Almahli, H., Maklad, R. M., Elsayed, Z. M., El Hassab, M. A., Alotaibi, O. J., ... & El-Ashrey, M. K. (2023). 1-Benzyl-5-bromo-3-hydrazonoindolin-2-ones as Novel Anticancer Agents: Synthesis, Biological Evaluation and Molecular Modeling Insights. *Molecules*, 28(7), 3203.
- Al-Warhi, T., El Kerdawy, A. M., Aljaeed, N., Ismael, O. E., Ayyad, R. R., Eldehna, W. M., ... & Al-Ansary, G. H. (2020). Synthesis, biological evaluation and in silico studies of certain oxindole-indole conjugates as anticancer CDK inhibitors. *Molecules*, 25(9), 2031.
- Ayyad, R. (2012). Synthesis and Biological Evaluation of Novel Iodophthalazinedione Derivatives as Anticonvulsant Agents. *Al-Azhar Journal of Pharmaceutical Sciences*, 45(1), 1-13.
- Ayyad, R. (2014). Synthesis and Anticonvulsant Activity of 6-Iodo Phthalazinedione Derivatives. *Al-Azhar Journal of Pharmaceutical Sciences*, 50(2), 43-54.
- Ayyad, R. A., Sakr, H. M., & El-Gamal, K. M. (2016). Design, Synthesis, Computer Modeling and Analgesic Activity of Some New Disubstituted Quinazolin-4 (3H)-ones. *Med. Chem*, 6(5), 299-305.
- Ayyad, R. A., Sakr, H., & El-Gamal, K. (2016). Synthesis, modeling and anticonvulsant activity of some phthalazinone derivatives. *American Journal of Organic Chemistry*, 6(1), 29-38.
- Ayyad, R. R., Mansour, A. M., Nejm, A. M., Hassan, Y. A. A., & Ayyad, A. R. (2024). Stereo Selectivity of Histaminic Receptors Play an Important Role of Anti-histaminic Activity. *Current Research in Medical Sciences*, 3(1), 10-17.
- Ayyad, R. R., Nejm, A. M., & Ayyad, A. R. (2023). The Activity of Some Antibiotics Depend on Stereochemistry of Them (Its Structure). *Journal of Progress in Engineering and Physical Science*, 2(2), 5-7.
- Ayyad, R. R., Nejm, A. M., & Ayyad, A. R. (2023). The Isomers of Some Drugs One Effective and the Other Is Toxic or Ineffective. *Current Research in Medical Sciences*, 2(2), 58-62.
- Ayyad, R. R., Nejm, A. M., Abdelaleem, Y. H., & Ayyad, A. R. (2023). Hydrophobicity, Transport and Target Sites of Action Are Important for the Activity of Many Drugs. *Current Research in Medical Sciences*, 2(3), 15-19.
- Ayyad, R. R., Nejm, A. M., Elbahat, E. T., Elnagar, A. M., Aljazar, M. A., Al-Hassan, Y. A., & Ayyad, A. R. (2023). The Configuration of Some Hormonal Compounds Play an Important Role in Pharmacological Action (Agonist, Antagonist, Active, More Active). *Journal of Progress in Engineering and Physical Science*, 2(3), 23-29.
- Ayyad, R. R., Nejm, A. M., Hassan, Y. A. A., & Ayyad, A. R. (2023). Mechanism of Action of Many Drugs Depend on Enzyme Inhibition. *Current Research in Medical Sciences*, 2(4), 1-9.
- Ayyad, R. R., Nejm, A. M., Hassan, Y. A. A., & Ayyad, A. R. (2023). The Lipid Solubility of Most Drugs Play Important Role of Its Pharmacological Action and Duration of Action. *Journal of Progress in Engineering and Physical Science*, 2(4), 1-6.
- Ayyad, R. R., Sakr, H. M., El-Gamal, K. M., Eissa, I. H., HA, A., Tita, A. S., ... & Mansour, A. M. (2017). Anti-Inflammatory, Proton Pump Inhibitor and Synthesis of Some New Benzimidazole Derivatives. *Der Chemica Sinica*, 8(1), 184-97.
- Ayyad, R., Sakr, H., & Gaafer, A. (2022). Design and Synthesis of New Compounds Derived from Phenyl Hydrazine and Different Aldehydes as Anticancer Agents. *International Journal of Organic Chemistry*, 12(1), 28-39.
- Eissa, I. H., Metwaly, A. M., Belal, A., Mehany, A. B., Ayyad, R. R., El-Adl, K., ... & ElSohly, M. A. (2019). Discovery and antiproliferative evaluation of new quinoxalines as potential DNA intercalators and topoisomerase II inhibitors. *Archiv der Pharmazie*, 352(11), 1900123.
- El-Adl, K., El-Helby, A. G. A., Ayyad, R. R., Mahdy, H. A., Khalifa, M. M., Elnagar, H. A., ... & Eissa, I. H. (2021). Design, synthesis, and anti-proliferative evaluation of new quinazolin-4 (3H)-ones as potential VEGFR-2 inhibitors. *Bioorganic & Medicinal Chemistry*, 29, 115872.
- El-Adl, K., El-Helby, A. G. A., Sakr, H., Ayyad, R. R., Mahdy, H. A., Nasser, M., ... & El-Hddad, S. S. (2021). Design, synthesis, molecular docking, anticancer evaluations, and in silico pharmacokinetic studies of novel 5-[(4-chloro/2, 4-dichloro) benzyldiene]

- thiazolidine-2, 4-dione derivatives as VEGFR-2 inhibitors. *Archiv der Pharmazie*, 354(2), 2000279.
- El-Azab, A. S., Alaa, A. M., Ayyad, R. R., Ceruso, M., & Supuran, C. T. (2016). Inhibition of carbonic anhydrase isoforms I, II, IV, VII and XII with carboxylates and sulfonamides incorporating phthalimide/phthalic anhydride scaffolds. *Bioorganic & medicinal chemistry*, 24(1), 20-25.
- Eldehna, W. M., Abo-Ashour, M. F., Al-Warhi, T., Al-Rashood, S. T., Alharbi, A., Ayyad, R. R., ... & El-Haggar, R. (2021). Development of 2-oxindolin-3-ylidene-indole-3-carbohydrazide derivatives as novel apoptotic and anti-proliferative agents towards colorectal cancer cells. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 36(1), 320-329.
- Eldehna, W. M., Abou-Seri, S. M., El Kerdawy, A. M., Ayyad, R. R., Hamdy, A. M., Ghabbour, H. A., ... & Abou El Ella, D. A. (2016). Increasing the binding affinity of VEGFR-2 inhibitors by extending their hydrophobic interaction with the active site: Design, synthesis and biological evaluation of 1-substituted-4-(4-methoxybenzyl) phthalazine derivatives. *European Journal of Medicinal Chemistry*, 113, 50-62.
- Eldehna, W. M., Salem, R., Elsayed, Z. M., Al-Warhi, T., Knany, H. R., Ayyad, R. R., ... & El-Haggar, R. (2021). Development of novel benzofuran-isatin conjugates as potential antiproliferative agents with apoptosis inducing mechanism in Colon cancer. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 36(1), 1423-1434.
- Elhelby, A. A., Ayyad, R. R., & Zayed, M. F. (2011). Synthesis and biological evaluation of some novel quinoxaline derivatives as anticonvulsant agents. *Arzneimittelforschung*, 61(07), 379-381.
- El-Helby, A. A., Ibrahim, M. K., Abdel-Rahman, A. A., Ayyad, R. R. A., Menshaw, M. A., & El-Adl, K. (2009). Synthesis, molecular modeling and anticonvulsant activity of benzoxazole derivatives. *Al-Azhar J Pharm Sci*, 40, 252-70.
- El-Helby, A. G. A., Ayyad, R. R., El-Adl, K., & Elkady, H. (2019). Phthalazine-1, 4-dione derivatives as non-competitive AMPA receptor antagonists: design, synthesis, anticonvulsant evaluation, ADMET profile and molecular docking. *Molecular diversity*, 23, 283-298.
- El-Helby, A. G. A., Ayyad, R. R., El-Adl, K., & Elwan, A. (2017). Quinoxalin-2 (1 H)-one derived AMPA-receptor antagonists: Design, synthesis, molecular docking and anticonvulsant activity. *Medicinal Chemistry Research*, 26, 2967-2984.
- El-Helby, A. G. A., Ayyad, R. R., El-Adl, K., Sakr, H., Abd-Elrahman, A. A., Eissa, I. H., & Elwan, A. (2016). Design, molecular docking and synthesis of some novel 4-acetyl-1-substituted-3, 4-dihydroquinoxalin-2 (1 H)-one derivatives for anticonvulsant evaluation as AMPA-receptor antagonists. *Medicinal Chemistry Research*, 25, 3030-3046.
- El-Helby, A. G. A., Ayyad, R. R., Sakr, H. M., Abdelrahim, A. S., El-Adl, K., Sherbiny, F. S., ... & Khalifa, M. M. (2017). Design, synthesis, molecular modeling and biological evaluation of novel 2, 3-dihydrophthalazine-1, 4-dione derivatives as potential anticonvulsant agents. *Journal of Molecular Structure*, 1130, 333-351.
- El-Helby, A. G. A., Ayyad, R. R., Sakr, H., El-Adl, K., Ali, M. M., & Khedr, F. (2017). Design, synthesis, molecular docking, and anticancer activity of phthalazine derivatives as VEGFR-2 inhibitors. *Archiv der Pharmazie*, 350(12), 1700240.
- El-Helby, A. G. A., Ayyad, R. R., Zayed, M. F., Abulkhair, H. S., Elkady, H., & El-Adl, K. (2019). Design, synthesis, in silico ADMET profile and GABA-A docking of novel phthalazines as potent anticonvulsants. *Archiv Der Pharmazie*, 352(5), 1800387.
- El-Helby, A. G. A., Sakr, H., Ayyad, R. R., El-Adl, K., Ali, M. M., & Khedr, F. (2018). Design, synthesis, in vitro anti-cancer activity, ADMET profile and molecular docking of novel triazolo [3, 4-a] phthalazine derivatives targeting VEGFR-2 enzyme. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, 18(8), 1184-1196.
- El-Helby, A. G. A., Sakr, H., Ayyad, R. R., El-Adl, K., Ali, M. M., & Khedr, F. (2018). Design, synthesis, in vitro anti-cancer activity, ADMET profile and molecular docking of

- novel triazolo [3, 4-a] phthalazine derivatives targeting VEGFR-2 enzyme. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, 18(8), 1184-1196.
- El-Helby, A. G. A., Sakr, H., Ayyad, R. R., Mahdy, H. A., Khalifa, M. M., Belal, A., ... & Eissa, I. H. (2020). Design, synthesis, molecular modeling, in vivo studies and anticancer activity evaluation of new phthalazine derivatives as potential DNA intercalators and topoisomerase II inhibitors. *Bioorganic chemistry*, 103, 104233.
- Ibrahim, A., Sakr, H. M., Ayyad, R. R., & Khalifa, M. M. (2022). Design, Synthesis, In-Vivo Anti-Diabetic Activity, In-Vitro α -Glucosidase Inhibitory Activity and Molecular Docking Studies of Some Quinazolinone Derivatives. *ChemistrySelect*, 7(14), e202104590.
- Ibrahim, M. K., Abd-Elrahman, A. A., Ayyad, R. R., El-Adl, K., Mansour, A. M., & Eissa, I. H. (2013). Design and synthesis of some novel 2-(3-methyl-2-oxoquinoxalin-1 (2H)-yl)-N-(4-(substituted) phenyl) acetamide derivatives for biological evaluation as anticonvulsant agents. *Bulletin of Faculty of Pharmacy, Cairo University*, 51(1), 101-111.
- Ibrahim, M. K., El-Helby, A. E. A., Ghiaty, A. H., Biomy, A. H., Abd-El Rahman, A. A., Ayyad, R. R., & Menshaw, M. A. (2009). Modeling, Synthesis and Antihyperglycemic Activity of Novel Quinazolinones Containing Sulfonylurea. *J. Biol. Pham. Sci*, 7(1).
- Khalifa, M. M., Sakr, H. M., Ibrahim, A., Mansour, A. M., & Ayyad, R. R. (2022). Design and synthesis of new benzylidene-quinazolinone hybrids as potential anti-diabetic agents: In vitro α -glucosidase inhibition, and docking studies. *Journal of Molecular Structure*, 1250, 131768.
- M Sakr, H., R Ayyad, R., Mahmoud, K., M Mansour, A., & Ahmed, G. (2021). Design, Synthesis of Analgesics and Anticancer of Some New Derivatives of Benzimidazole. *International Journal of Organic Chemistry*, 11(03), 144-169.
- Mahdy, H., & Shaat, M. (2022). RECENT ADVANCES IN DRUGS TARGETING PROTEIN KINASES FOR CANCER THERAPY. *Al-Azhar Journal of Pharmaceutical Sciences*, 66(2), 56-86.
- Mohamed, M. A., Ayyad, R. R., Shawer, T. Z., Alaa, A. M., & El-Azab, A. S. (2016). Synthesis and antitumor evaluation of trimethoxyanilides based on 4 (3H)-quinazolinone scaffolds. *European journal of medicinal chemistry*, 112, 106-113.
- Nassar, E., El-Badry, Y. A., Eltoukhy, A. M. M., & Ayyad, R. R. (2016). Synthesis and antiproliferative activity of 1-(4-(1H-Indol-3-yl)-6-(4-Methoxyphenyl) Pyrimidin-2-yl) hydrazine and its pyrazolo pyrimidine derivatives. *Med chem (Los Angeles)*, 6, 224-233.
- Osman, I. A., Ayyad, R. R., & Mahdy, H. A. (2022). New pyrimidine-5-carbonitrile derivatives as EGFR inhibitors with anticancer and apoptotic activities: design, molecular modeling and synthesis. *New Journal of Chemistry*, 46(24), 11812-11827.
- Sakr, H., Ayyad, R. R., El-Helby, A. A., Khalifa, M. M., & Mahdy, H. A. (2021). Discovery of novel triazolophthalazine derivatives as DNA intercalators and topoisomerase II inhibitors. *Archiv der Pharmazie*, 354(6), 2000456.
- Sakr, H., Otify, I., Ayyad, R. R., & Elwan, A. (2023). VEGFER-2 INHIBITORS AND QUINAZOLINE-BASED ANTICANCER AGENTS. *Al-Azhar Journal of Pharmaceutical Sciences*, 68(2), 111-129.
- Salem, M. M., Ayyad, R., & Sakr, H. (2022). Design and Synthesis of Some New Oxadiazole Derivatives as Anticancer Agents. *International Journal of Organic Chemistry*, 12(02), 64-74.
- Zayed, M. F., & Ayyad, R. R. (2012). Some novel anticonvulsant agents derived from phthalazinedione. *Arzneimittelforschung*, 62(11), 532-536.