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Mechanism of Action of Many Drugs Depend on Enzyme Inhibition

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Abstract

Enzyme inhibition is an important process in the mode of action of many drugs used in the treatment of various diseases. Antibiotics, anti-hypertensive agents, anti-hyperlipidaemic, anti-glaucoma, and anti-malarial drugs act on specific enzymes, leading to bacteriostatic or bactericidal effects, lower blood pressure, reduce cholesterol levels, and cause smooth muscle relaxation of blood vessels. Understanding the mode of action of these drugs and how they affect enzymes is crucial for the development of new drugs and the optimization of existing therapies. This article highlights some various drugs that act through enzyme inhibition and their mechanisms of action.

Keywords: enzyme inhibition, beta-lactamase inhibitors, gyrase enzyme inhibitors, pteridine synthetase inhibitors, dihydrofolate inhibitors, angiotensin-converting enzyme inhibitors, HMG-CoA reductase inhibitors, phosphodiesterase inhibitors, cholinesterase inhibitors, carbonic anhydrase inhibitors, bacteriostatic, bactericidall, antibiotic, anti-hypertensive

1. Introduction

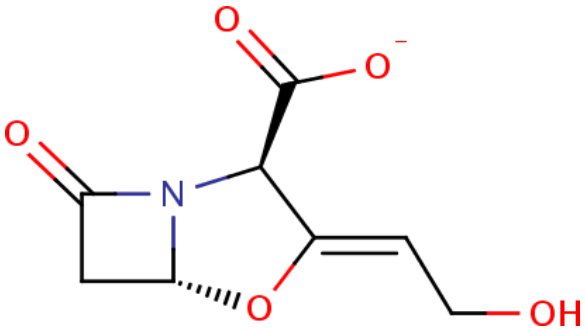
Many drugs rely on enzyme inhibition as a critical mechanism of action. Antibiotics for example often target key enzymes in microorganisms, such as beta lactamases inhibitors e.g., Clavulanic acid sulbactam and tazobactam are inhibit the beta lactamase enzyme which attack the beta lactam compounds (Penicillins and Cephalosporins) the beta lactamases not have strong antibacterial but it potentiate the activities of beta lactam containing compounds, not merely the quinolone i.e., Ofloxacin and levofloxacin which inhibit the gyrase Enzyme required for protein Synthesis of bacteria, and the Sulfonamides which used as antibacterial drugs act through the Inhibition of dihydropteroic acid which convert into dihydro folate and tetrahydrofolate to synthesize protein of microorganisms. Lastly the trimethoprim which used to inhibit the tetrahydrofolate reductase enzyme and used also antimalarial agent and combined with sulfamethoxazole where the affinity of

trimethoprim to dihydropteridin and tetrahydrofolate enzymes in microorganisms nearly 100,000 times as human, and also on enzyme inhibition to lower blood pressure or reduce cholesterol synthesis as angiotensin converting Enzyme Inhibition, where the chemical structure of Compound inhibit Synthesis of Angiotensin2 into Angiotensin1 which act on smooth muscle of blood vessels (contraction) cause elevation in blood pressure, also the cholesterol Synthesis in the body through Enzyme called 3-Hydroxy methyl glutrate reductase which act on 3-hydroxy methyl glutrate (HMG) (is a key step in cholesterol Synthesis) mevalonate for Formation of cholesterol, which precipitation on wall of blood vessels cause elevate in blood pressure. As well as the indirect cholinomimetics which inhibited by Cholinesterase Enzyme either reversible or irreversible e.g., Drugs used in glaucoma, also the carbonic anhydrase enzyme act via formation of carbonic acid from water and carbon dioxide which led to un excreted the water and cause increase in blood volume followed by high blood pressure. The Phosphodiesterase enzyme play an important role in smooth muscle contraction through formation of ATP, when the patient takes nitrates or nitrates the phosphodiesterase inhibit and hence no contraction so occurs smooth muscle relaxation of blood vessels cause vasodilatation lead to lowering the blood pressure.

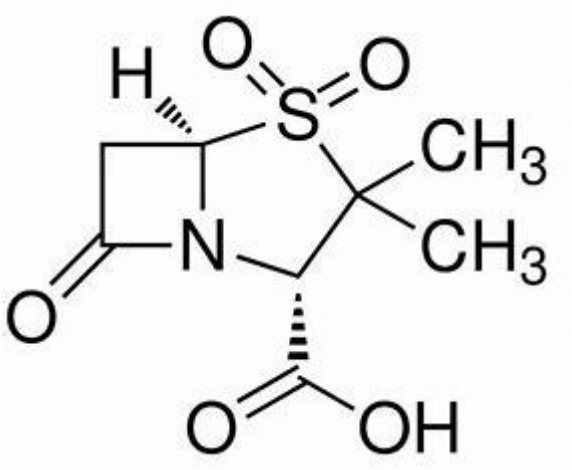
2. Chemistry and Discussion

Beta-lactamase inhibitors. Although β-lactamase inhibitors have little antibiotic activity of their own, they prevent bacterial degradation of beta-lactam antibiotics and thus extend the range of bacteria the drugs are effective against.

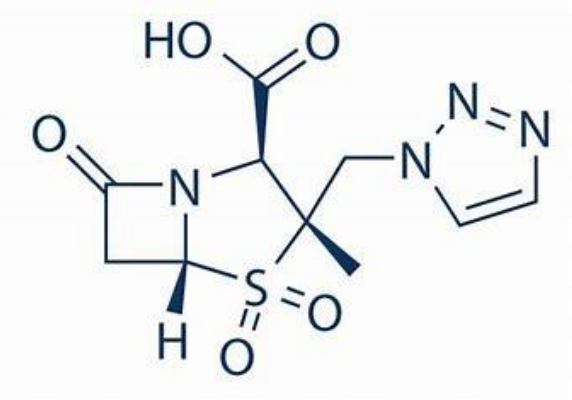
Clavulanic acid



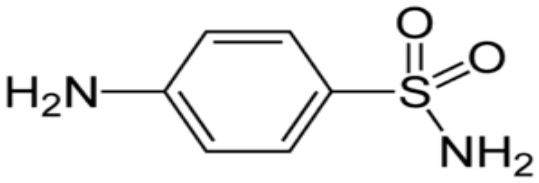
Sulbactam



Tazobactam

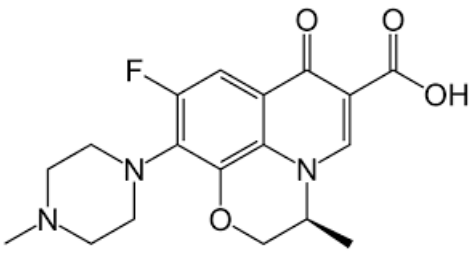


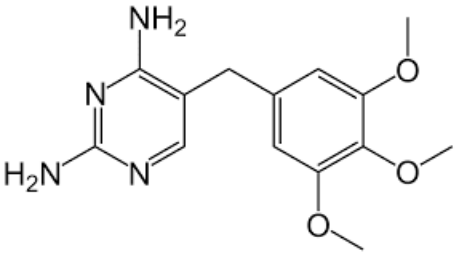
Sulfanilamide is a competitive inhibitor of bacterial enzyme dihydropteroate synthetase. This enzyme normally uses para-aminobenzoic acid (PABA) for synthesizing the necessary folic acid. The inhibited reaction is normally necessary in these organisms for the synthesis of folic acid.



Levofloxacin is a bactericidal antibiotic of the fluoroquinolone drug class that directly inhibits bacterial DNA synthesis. Levofloxacin promotes the breakage of DNA strands by inhibiting.

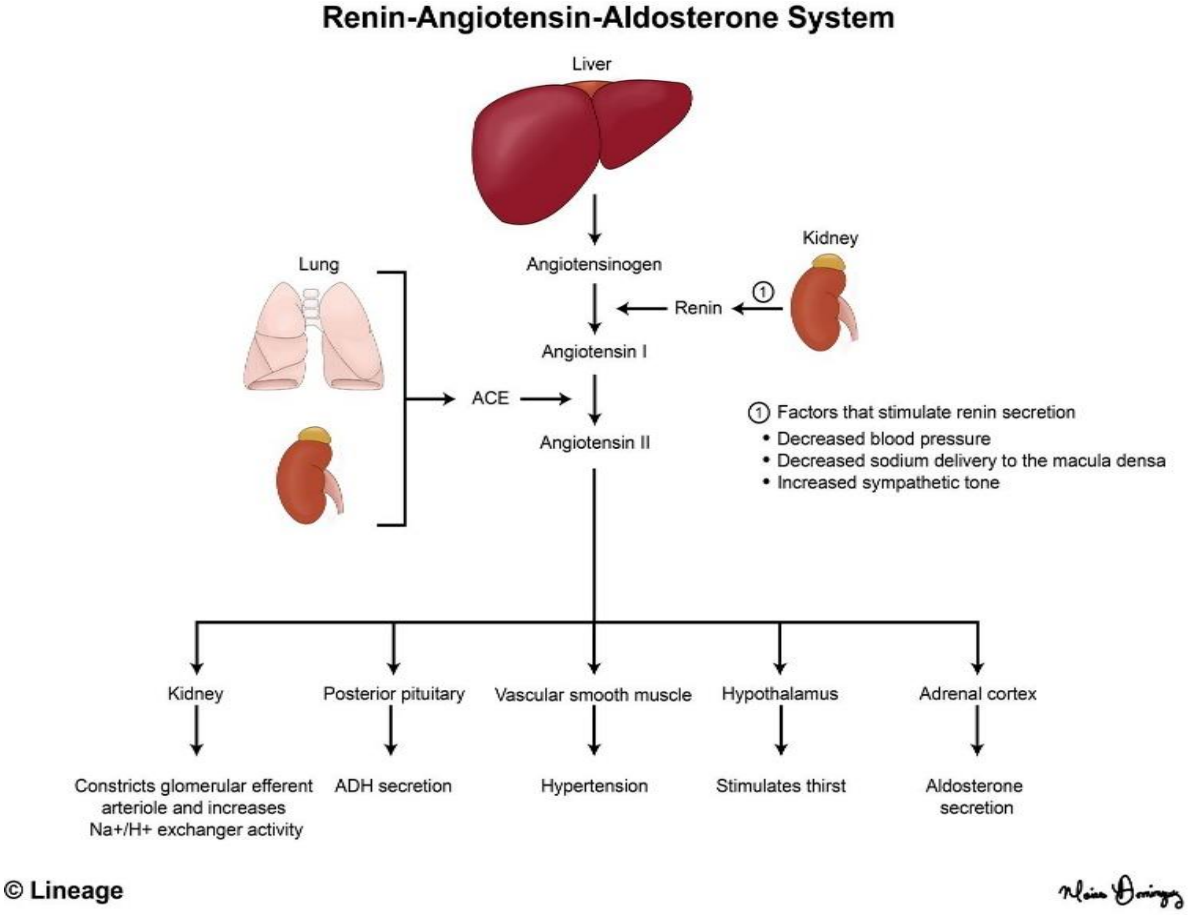
DNA-gyrase in susceptible organisms, which inhibits the relaxation of supercoiled DNA.

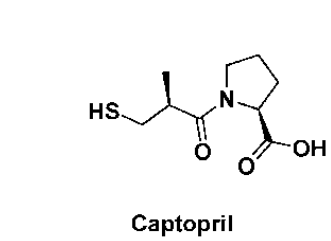




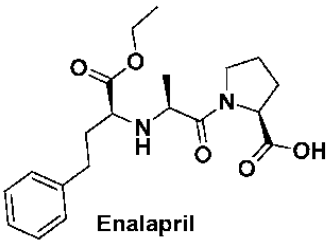
Trimethoprim exerts antimicrobial activity by blocking the reduction of dihydrofolate to tetrahydrofolate, the active form of folic acid, by susceptible organisms. It has inhibitory activity for most gram-positive aerobic cocci and some gram-negative aerobic bacilli.

ACE inhibitors prevent an enzyme in the body from producing angiotensin II, a substance that narrows blood vessels, this narrowing can cause high blood pressure and forces the heart to work harder. Angiotensin II also releases hormones that raise blood pressure, according to the mode of action of ACE inhibitors the inhibition lead to Treat the elevation of blood pressure.

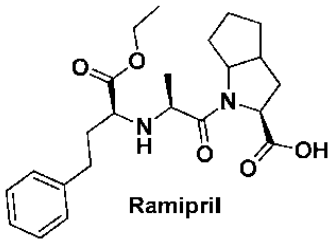




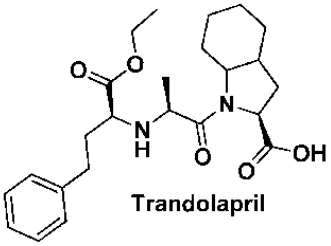
Captopril



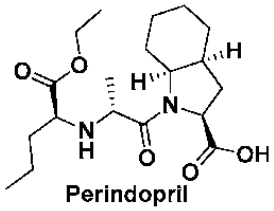
Enalapril



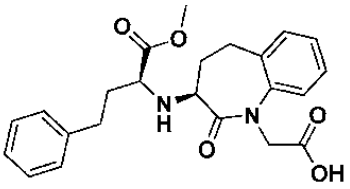
Ramipril



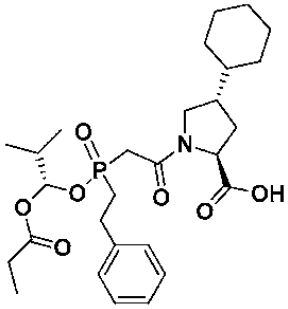
Trandolapril



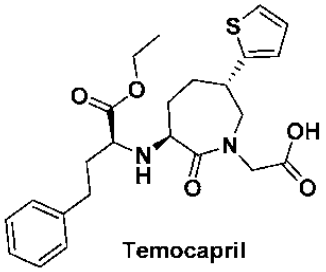
Perindopril



Benazepril

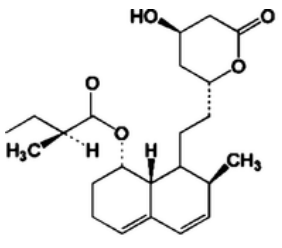


Fosinopril

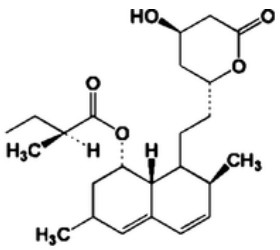


Temocapril

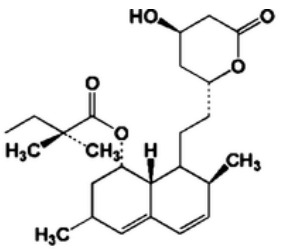
Statins work by competitively blocking the active site of the first and key rate-limiting enzyme in the mevalonate pathway (HMG-CoA reductase enzyme), inhibition of this site prevents substrate access, thereby blocking the conversion of HMG-CoA to mevalonic acid.



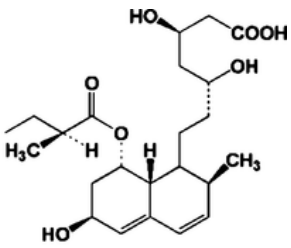
Mevastatin (Compactin)



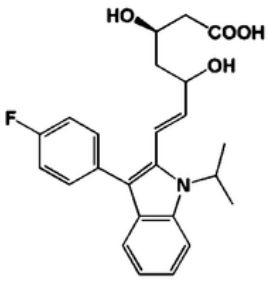
Lovastatin (Mevacor, Altocor, Altoprev)



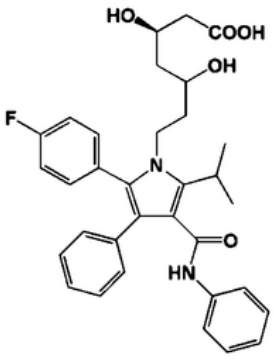
Simvastatin (Zocor, Lipex)



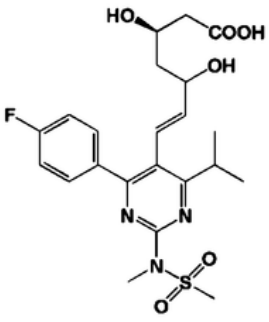
Pravastatin (Selektine, Pravachol, Lipostat)



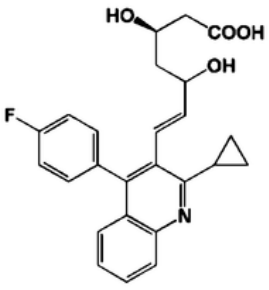
Fluvastatin (Lescol)



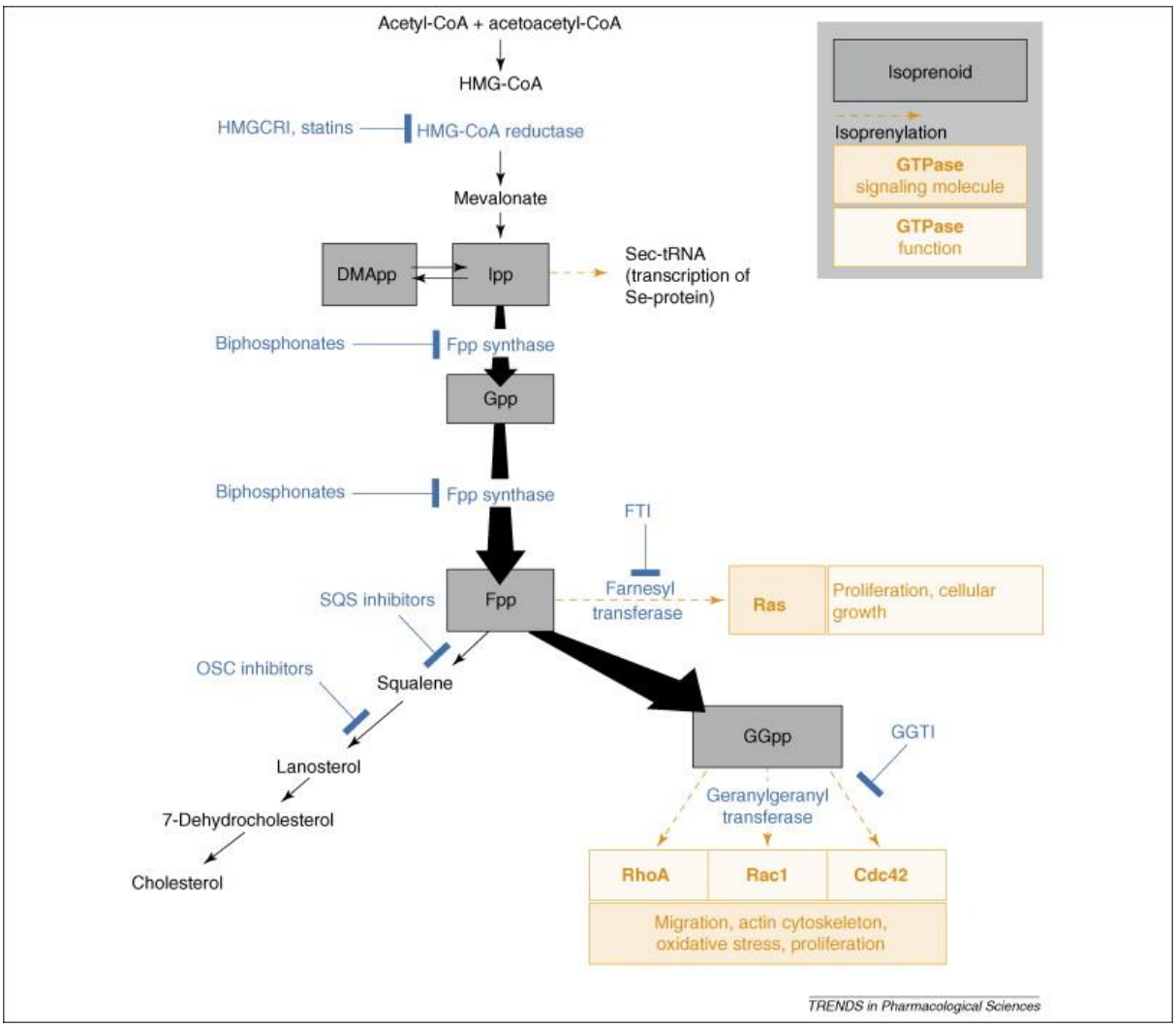
Atorvastatin (Lipitor)



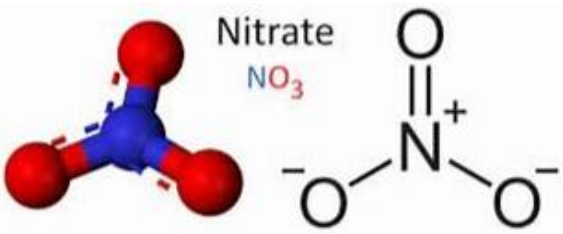
Rosuvastatin (Crestor)



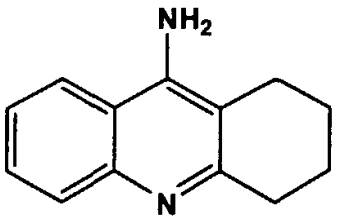
Pitavastatin (Livalo, Pitava)



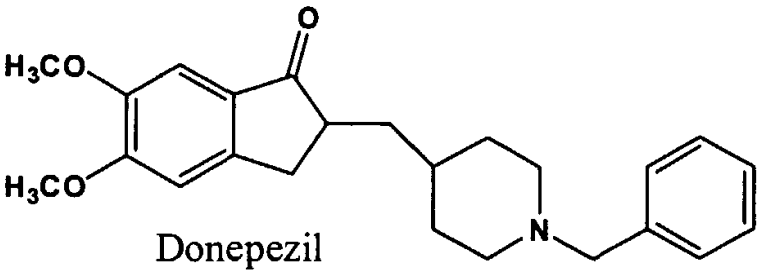
Organic nitrate esters have a direct relaxant effect on vascular smooth muscles, and the dilation of coronary vessels improves oxygen supply to the myocardium, the dilation of peripheral veins, and in higher doses peripheral arteries, reduces preload and afterload, and thereby lowers myocardial oxygen consumption, Mechanism of Action Phosphodiesterase inhibitors exert their effects on their targeted phosphodiesterase enzymes (PDE-3, PDE-4, PDE-5), preventing cGMP or cAMP degradation, further increasing their levels in smooth muscle cells, causing relaxation and vasodilatory effect in target cells.



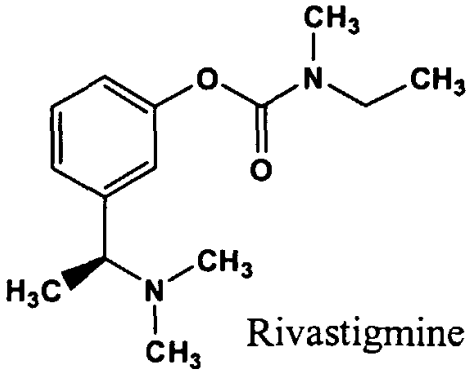
AChE inhibitors or anti-cholinesterases inhibit the cholinesterase enzyme from breaking down ACh, increasing both the level and duration of the neurotransmitter action, according to the mode of action, AChE inhibitors can be divided into two groups: irreversible and reversible.



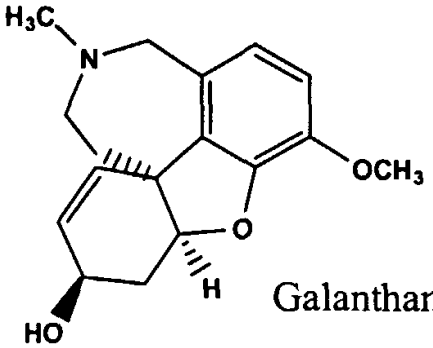
Tacrine



Donepezil

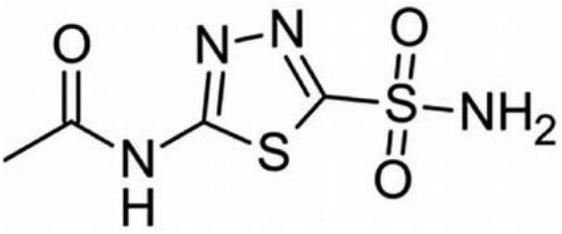


Rivastigmine



Galanthamine

Acetazolamide is a carbonic anhydrase inhibitor. That means this drug works to cause an accumulation of carbonic acid by preventing its breakdown. The result is lower blood pH (i.e., more acidic), given the increased carbonic acid, which has a reversible reaction into bicarbonate and a hydrogen ion.



3. Conclusion

In conclusion, enzyme inhibition is a critical mechanism of action for many drugs used in the treatment of various diseases. Antibiotics, for instance, target key enzymes in microorganisms to stop their growth and proliferation, so the inhibition of some Enzymes indicate to the mechanism of action or mode of action for some Antibiotics and these Mechanisms tell us if the antibacterial are bacteriostatic or bactericidal.

Similarly, anti-hypertensive agents act on enzymes involved in blood pressure regulation that means any matters formed by enzymes and cause elevation in blood pressure treated by enzyme inhibitor, also any substance formed by enzyme and narrowing the blood vessels treated by Enzyme inhibition and if presence matters causing contraction of the blood vessels inhibited by enzyme inhibition, and also some of anti-hyperlipidaemic reduce cholesterol levels by acting on different enzymes, understanding the mode of action of these drugs and how they affect enzymes is crucial for the development of new drugs and the optimization of existing therapies. Therefore, continued research in this area is imperative to enhance our knowledge of enzyme inhibition and its potential applications in drug development and treatment of diseases.

References

A Ibrahim, HM Sakr, RR Ayyad, MM Khalifa. (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.

AA El-Helby, MK Ibrahim, AA Abdel-Rahman, RRA Ayyad, MA Menshawy, ... (n.d.). Synthesis, molecular modeling and anticonvulsant activity of benzoxazole derivatives. *Al-Azhar J Pharm Sci*, *40*, 252-70.

AA Elhelby, RR Ayyad, MF Zayed. (2011). Synthesis and biological evaluation of some novel quinoxaline derivatives as anticonvulsant agents. *Arzneimittelforschung*, *61*(07), 379-381.

AAM Abdel-Aziz, AS El-Azab, AM Alanazi, YA

Asiri, IA Al-Suwaidan, ... (n.d.). 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.

AGA El-Helby, H Sakr, RR Ayyad, HA Mahdy, MM Khalifa, A Belal, ... (2020). Design, synthesis, molecular modeling, in vivo studies and anticancer activity evaluation of new phthalazine derivatives as potential DNA intercalators and topoisomerase II … *Bioorganic chemistry, 103*, 104233.

AGA El-Helby, H Sakr, RRA Ayyad, K El-Adl, MM Ali, F Khedr. (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. *Anticancer Agents Med Chem*, *18*(8), 1184-1196.

AGA El-Helby, H Sakr, RRA Ayyad, K El-Adl, MM Ali, F Khedr. (n.d.). Anti-Cancer Agents Med. *Chem, 18*(8), 1184.

AGA El-Helby, RR Ayyad, HM Sakr, AS Abdelrahim, K El-Adl, FS Sherbiny, ... (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.

AGA El-Helby, RRA Ayyad, H Sakr, K El-Adl, MM Ali, F Khedr. (2017). Design, synthesis, molecular docking, and anticancer activity of phthalazine derivatives as VEGFR-2 inhibitors. *Archiv der Pharmazie, 350*(12), 1700240.

AGA El-Helby, RRA Ayyad, K El-Adl, A Elwan. (2017). Quinoxalin-2(1*H*)-one derived AMPA-receptor antagonists: Design, synthesis, molecular docking and anticonvulsant activity. *Medicinal Chemistry Research, 26*, 2967-2984.

AGA El-Helby, RRA Ayyad, K El-Adl, H Elkady. (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.

AGA El-Helby, RRA Ayyad, K El-Adl, H Sakr, AA Abd-Elrahman, IH Eissa, ... (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 … *Medicinal Chemistry Research, 25*, 3030-3046.

AGA El-Helby, RRA Ayyad, MF Zayed, HS Abulkhair, H Elkady, K El-Adl. (2019). Design, synthesis, in silico ADMET profile and GABA-A docking of novel phthalazines as potent anticonvulsants. *Archiv Der Pharmazie, 352*(5), 1800387.

AM Alaa, AS El-Azab, AM Alanazi, YA Asiri, IA Al-Suwaidan, AR Maarouf, ... (n.d.). Synthesis and potential antitumor activity of 7-(4-substituted piperazin-1-yl)-4-oxoquinolines based on ciprofloxacin and norfloxacin scaffolds: in silico studies.

AM Alaa, AS El-Azab, LA Abou-Zeid, KEH ElTahir, NI Abdel-Aziz, ... (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.

AM Alanazi, AAM Abdel-Aziz, TZ Shawer, RR Ayyad, AM Al-Obaid, ... (2015). 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.

AS El-Azab, AM Alaa, RR Ayyad, M Ceruso, CT Supuran. (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.

E Nassar, YA El-Badry, AMM Eltoukhy, RR Ayyad. (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.

H M Sakr, R R Ayyad, K Mahmoud, A M Mansour, G Ahmed. (2021). Design, Synthesis of Analgesics and Anticancer of Some New Derivatives of Benzimidazole.

International Journal of Organic Chemistry, 11(03), 144-169.

H Mahdy, M Shaat, R Ayyad. (2022). Recent Advances in Drugs Targeting Protein Kinases for Cancer Therapy. *Al-Azhar Journal of Pharmaceutical Sciences, 66*(2), 56-86.

H Sakr, RR Ayyad, AA El-Helby, MM Khalifa, HA Mahdy. (2021). Discovery of novel triazolophthalazine derivatives as DNA intercalators and topoisomerase II inhibitors. *Archiv der Pharmazie, 354*(6), 2000456.

IA Al-Suwaidan, AAM Abdel-Aziz, TZ Shawer, RR Ayyad, AM Alanazi, ... (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.

IA Osman, RR Ayyad, HA Mahdy. (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.

IH Eissa, AM Metwaly, A Belal, ABM Mehany, RR Ayyad, K El-Adl, ... (2019). Discovery and antiproliferative evaluation of new quinoxalines as potential DNA intercalators and topoisomerase II inhibitors. *Archiv der Pharmazie, 352*(11), 1900123.

K El-Adl, AGA El-Helby, H Sakr, RR Ayyad, HA Mahdy, M Nasser, ... (2020). Design, synthesis, molecular docking, anticancer evaluations, and in silico pharmacokinetic studies of novel 5-[(4-chloro/2, 4-dichloro) benzylidene] thiazolidine-2, 4-dione… *Archiv der Pharmazie, 354*(2), 2000279.

K El-Adl, AGA El-Helby, RR Ayyad, HA Mahdy, MM Khalifa, HA Elnagar, ... (2021). Design, synthesis, and anti-proliferative evaluation of new quinazolin-4 (3H)-ones as potential VEGFR-2 inhibitors. *Bioorganic & Medicinal Chemistry, 29*, 115872.

M Al Ward, AE Abdallah, M Zayed, R Ayyad, M El-Zahabi. (2023). New immunomodulatory anticancer quinazolinone based thalidomide analogs: Design, synthesis and biological evaluation. *Research Square*.

M Salem, R Ayyad, H Sakr. (2022). Design and Synthesis of Some New Oxadiazole Derivatives as Anticancer Agents. *International Journal of Organic Chemistry, 12*(02), 64-74.

MF Zayed, RR Ayyad. (2012). Some novel anticonvulsant agents derived from phthalazinedione. *Arzneimittelforschung, 62*(11), 532-536.

MK Ibrahim, AA Abd-Elrahman, RRA Ayyad, K El-Adl, AM Mansour, ... (2012). 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.

MK Ibrahim, AEA El-Helby, AH Ghiaty, AH Biomy, AA Abd-El Rahman. (2009). Modeling, Synthesis and Antihyperglycemic Activity of Novel Quinazolinones Containing Sulfonylurea.

MM Khalifa, HM Sakr, A Ibrahim, AM Mansour, RR Ayyad. (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.

R Ayyad, H Sakr, A Gaafer. (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.

R Ayyad. (2012). Synthesis and Biological Evaluation of Novel Iodophthalazinedione Derivatives as Anticonvulsant Agents. *Al-Azhar Journal of Pharmaceutical Sciences, 45*(1), 1-13.

R Ayyad. (2014). Synthesis and Anticonvulsant Activity of 6-Iodo Phthalazinedione Derivatives. *Al-Azhar Journal of Pharmaceutical Sciences, 50*(2), 43-54.

RA Ayyad, HM Sakr, KM El-Gamal. (2016). Design, Synthesis, Computer Modeling and Analgesic Activity of Some New Disubstituted Quinazolin-4 (3H)-ones. *Med. Chem, 6*(5), 299-305.

RR Ayyad, AM Nejm, AR Ayyad. (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.

RR Ayyad, AM Nejm, AR Ayyad. (2023). The Isomers of Some Drugs One Effective and the Other Is Toxic or Ineffective. *Current Research in Medical Sciences, 2*(2), 58-62.

RR Ayyad, AM Nejm, YH Abdelaleem, AR Ayyad. (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.

RR Ayyad, HM Sakr, KM El-Gamal, IH Eissa, A HA, AS Tita, FF Sherbini, ... (2018). Anti-Inflammatory, Proton Pump Inhibitor and Synthesis of Some New Benzimidazole Derivatives. *Der Chemica Sinica, 8*(1), 184-97.

RRA Ayyad, H Sakr, K El-Gamal. (2016). Synthesis, modeling and anticonvulsant activity of some phthalazinone derivatives. *American Journal of Organic Chemistry, 6*(1), 29-38.

T Al-Warhi, AM El Kerdawy, N Aljaeed, OE Ismael, RR Ayyad, ... (2020). Synthesis, biological evaluation and in silico studies of certain oxindole–indole conjugates as anticancer CDK inhibitors. *Molecules, 25*(9), 2031.

T Al-Warhi, H Almahli, RM Maklad, ZM Elsayed, MA El Hassab, ... (2023). 1-Benzyl-5-bromo-3-hydrazonoindolin-2-ones as Novel Anticancer Agents: Synthesis, Biological Evaluation and Molecular Modeling Insights. *Molecules, 28*(7), 3203.

WM Eldehna, MF Abo-Ashour, T Al-Warhi, ST Al-Rashood, A Alharbi, ... (2020). 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.

WM Eldehna, R Salem, ZM Elsayed, T Al-Warhi, HR Knany, RR Ayyad, ... (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.