PIONEER
ACADEMIC PUBLISHING LIMITED

Current Research in Medical Sciences
ISSN 2958-0390
www.pioneerpublisher.com/crms
Volume 4 Number 1 January 2025

Sulfa Drugs Are the Leader of Drug Discovery via Its Side Effects

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doi:10.56397/CRMS.2025.01.03

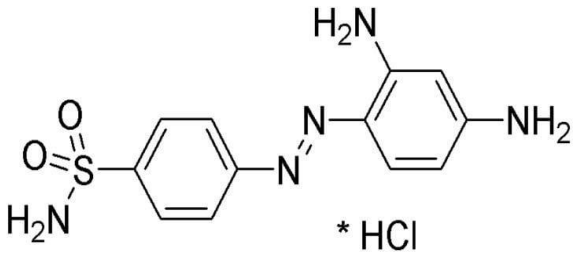
Abstract

The sulfa drugs are bacteriostatic when used side effects appear as a decrease in blood glucose level which led us to oral hypoglycemics (Sulfonylurea drugs), and diuretic action which led us to diuretics (Thiazide drugs), these side effects attention us to the discovery of diuretics and oral hypoglycemics. Sulfonamides are synthetic antibacterial which were the first antibacterial compounds till the presence of Penicillins, the sulfonamides are used as urinary tract infection treatment and treatment of certain forms of malaria and prevent infection of burns, the sulfa drugs act via inhibition of di hydro folate reductase enzyme (DHFR), they act by interfering with synthesis of folic acid which is vitamin B_9 (Member of Vit. B complex) which required by all living cells.

Keywords: sulfa drugs, oral hypoglycemics, diuretics, di hydro folate reductase inhibitor, (DHFR)

1. Introduction

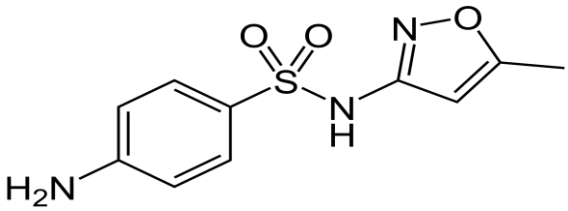
In 1932, the German Bacteriologist Gerhard Domagk noted the effect of the red dye Prontosil is effective in vivo, but inactive in vitro due to the azo reductase enzyme which hydrolyzes the prontosil to liberate the sulfanilamide (the first member of sulfa drug), the sulfonamides are widely used through the world war before the discovery of penicillin, all sulfa drugs to Para Amino Benzoic Acid (PABA) which used in the synthesis of folic acid, hence the sulfonamide compete with PABA and inhibit the synthesis of folic acid.



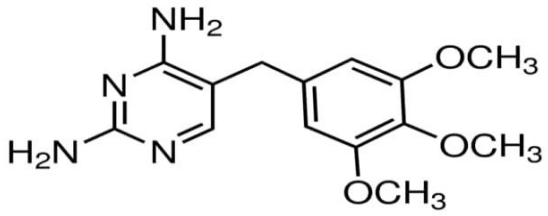
Prontosil

2. Pharmacology and Chemistry

Sulfamethoxazole



Trimethoprim



The mechanism of action of sulfonylurea differs from the sulfonamides as bacteriostatic, where sulfonylurea acts through the close ATP-sensitive K channel in the β-cell of Pancreas which secrete insulin from islets of Langerhans.

The side effects of lowering blood glucose levels have led us to discover oral hypoglycemics.

Thiazides (Chlorothiazide, Hydrochlorothiazide)

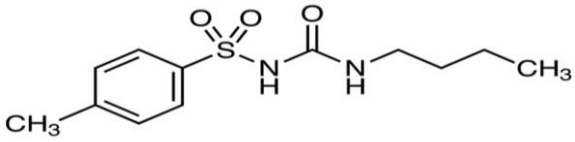
The combination of trimethoprim and sulfamethoxazole worldwide is used in medicine systemically (oral use).

The sulfamethoxazole inhibits DHFR and trimethoprim (non-sulfa) inhibits tetra hydro folate reductase.

The combination of sulfamethoxazole and trimethoprim gives full inhibition of folic acid synthesis which is required for microorganisms but not essential for humans due to the takes the folic acid from diet source.

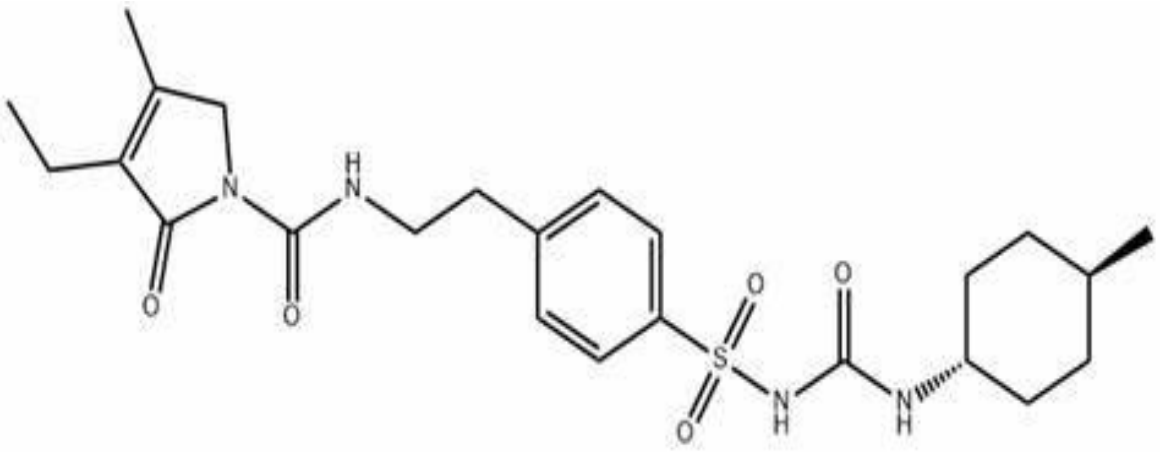
The observation of blood glucose levels during the treatment with sulfa we discover the sulfonylurea drugs.

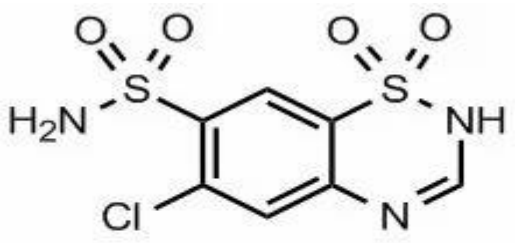
Tolbutamide



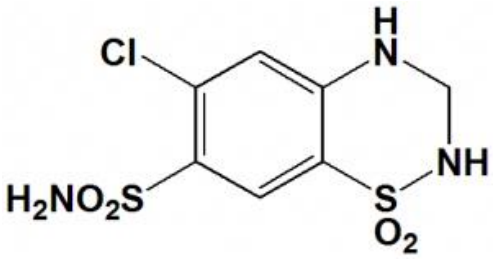
Tolbutamide is the first compound of oral hypoglycemic which is developed.

Glimepiride





chlorothiazide



Hydrochlorothiazide

The sulfonamides when used as bacteriostatic, noted the diuresis of the patient, which led us to the thiazide diuretics discovery.

The thiazides are sulfa drugs like sulfonylurea and usual sulfonamides.

The mechanism of action of thiazide inhibition of Na/Cl cotransporter (NCC) in the renal distal convoluted tubule, where NCC facilitates the absorption of sodium from the distal convoluted tubules back to the interstitial.

Mechanism of action of three groups of sulfa drugs sulfonamides as bacteriostatic, sulfonylurea as oral hypoglycemics, and thiazides as diuretic, they are completely different in their action.

The first sulfa drugs as bacteriostatic are the leader of drug discovery depending on their side effects the lowering of blood glucose levels and diuresis actions and led us to know the mechanism of action of oral hypoglycemics and diuretic of the sulfa compounds.

N.B. The sulfa drugs it is the compounds that contain the sulfamoyl group (SO_2, NH_2), either free (side chain) as sulfonylurea or sulfonamide all in the ring as thiazides.

3. Conclusion

In conclusion, the discovery of sulfa drugs, specifically sulfonamides, played a significant role in the development of oral hypoglycemics and diuretics. Initially used as bacteriostatic agents, the side effects of sulfa drugs, such as a decrease in blood glucose levels and diuretic action, prompted further exploration into their potential therapeutic applications. This led to the discovery of sulfonylurea drugs, which act by regulating insulin secretion in the pancreas and are used for the treatment of diabetes. Additionally, the observation of diuresis in patients treated with sulfa drugs led to the discovery of thiazide diuretics, which inhibit the Na/Cl cotransporter in the renal tubules, resulting in increased urine production.

The mechanism of action of sulfa drugs, oral hypoglycemics, and diuretics differs significantly. Sulfa drugs act by inhibiting dihydrofolate reductase (DHFR) and interfering with the synthesis of folic acid, which is essential for the growth of microorganisms. Oral hypoglycemics, such as sulfonylurea drugs, exert their effects by modulating ATP-sensitive potassium channels in pancreatic beta cells, leading to increased insulin secretion. Thiazide diuretics, on the other hand, inhibit the Na/Cl cotransporter in the renal tubules, reducing sodium reabsorption and promoting diuresis.

Overall, the discovery of sulfa drugs and their subsequent exploration for different therapeutic purposes not only revolutionized the field of antibacterial agents but also paved the way for the development of oral hypoglycemics and diuretics. By understanding the diverse mechanisms of action of these compounds, healthcare professionals have been able to utilize them effectively in the treatment of various conditions, improving patient outcomes and quality of life.

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. *Chemistry Select*, *7*(14), e202104590.

AA El-Helby, MK Ibrahim, AA Abdel-Rahman, RRA Ayyad, MA Menshawy, ... (2009). 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, ... (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.

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 inhibitors. *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. *Anti-cancer agents in medicinal chemistry, 18*(8), 1184-1196.

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(1H)-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(1H)-one derivatives for anticonvulsant evaluation as AMPA- receptor antagonists. *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, 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 Alaa, LA Abou-Zeid, KEH ElTahir, RR Ayyad, AA Magda, AS El-Azab. (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.

AM Alanazi, AAM Abdel-Aziz, TZ Shawer, RR Ayyad, AM Al-Obaid, ... (2016). Synthesis, antitumor and antimicrobial activity of some new 6-methyl-3-phenyl-4(3H)-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. (2024). 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. (2022). RECENT ADVANCES IN DRUGS TARGETING PROTEIN KINASES FOR CANCER THERAPY. *Al-Azhar Journal of Pharmaceutical Sciences, 66*(2), 56-86.

H Sakr, I Otify, RR Ayyad, A Elwan. (2023). VEGFER-2 INHIBITORS AND QUINAZOLINE-BASED ANTICANCER AGENTS. *Al-Azhar Journal of Pharmaceutical Sciences, 68*(2), 111-129.

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, ... (2021). Design, synthesis, molecular docking, anticancer evaluations, and in silico pharmacokinetic studies of novel 5-[(4-chloro/2, 4-dichloro) benzylidene] thiazolidine-2, 4-dione derivatives as VEGFR-2 inhibitors. *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. (2024). New immunomodulatory anticancer quinazolinone based thalidomide analogs: Design, synthesis and biological evaluation. *Future Medicinal Chemistry, 16*(23), 2523-2533.

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.

MA Mohamed, RR Ayyad, TZ Shawer, AM Alaa, AS El-Azab. (2016). Synthesis and antitumor evaluation of trimethoxyanilides based on 4 (3H)-quinazolinone scaffolds. *European Journal of Medicinal Chemistry*, *112*, 106-113.

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, ... (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.

MK Ibrahim, AEA El-Helby, AH Ghiaty, AH Biomy, AA Abd-El Rahman, ... (n.d.). 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.

MMS Al Ward, AE Abdallah, MF Zayed, RR Ayyad, MA El-Zahabi. (2024). Design, synthesis and biological evaluation of newly triazolo-quinoxaline based potential immunomodulatory anticancer molecules. *Journal of Molecular Structure, 1298*, 137041.

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 Mansour, AM Nejm, YAA Hassan, AR Ayyad. (2023). Stereo Selectivity of Histaminic Receptors Play an Important Role of Anti-histaminic Activity. *Current Research in Medical Sciences, 3*(1), 10-17.

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, ELT Elbahat, AM Elnagar, MA Aljazar, ... (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.

RR Ayyad, AM Nejm, YAA Hassan, AR Ayyad. (2023). Mechanism of Action of Many Drugs Depend on Enzyme Inhibition. *Current Research in Medical Sciences, 2*(4), 1-9.

RR Ayyad, AM Nejm, YAA Hassan, AR Ayyad. (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.

RR Ayyad, AM Nejm, YAA Hassan, AR Ayyad. (2024). Repair of Destroyed Liver Cells or Protection Liver Cells from Destruction by Silymarin and Minor Concentration of Vitamin E and Vitamin K. *Journal of Progress in Engineering and Physical*.

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, ... (2017). 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, ... (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.

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.

WM Eldehna, SM Abou-Seri, AM El Kerdawy, RR Ayyad, AM Hamdy, ... (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.