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A REVIEW ON DOCKING STUDY OF 3-SUBSTITUTED AND 3,5-DISUBSTITUTED 2,4-THIAZOLIDINEDIONE DERIVATIVES FOR THEIR ANTI-CANCER PROPERTIES.

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ABSTRACT

Thiazolidinediones (TZDs) are five-membered heterocyclic compound have sulfur, nitrogen, and oxygen atoms in their ring and exhibiting potent and wide range of pharmacological activities. In previous few decades, research has reached to the mark with an increased interest in capturing the novel methodologies and targets that forcefully worked for the preparation of 2,4- Thiazolidinediones (TZD) nucleus for their more than one pharmacological properties like anticancer, antioxidants, anti-malarial, antiviral, anti-HIV, anti-TB, antimicrobial. This review covers updated information of molecular docking of anti-cancer and anti-microbial activity. Thiazolidinediones contain sulfur and they are pentacyclic compounds which are widely found throughout nature in various forms. The thiazolidinediones are agonist of the nuclear receptor Peroxisome Proliferator Activated Receptor gamman (PPARγ). There are several synthetic compounds which are known for a long-time anticancer dominance and various studies have been performed for their mechanism. Thymidylate synthase (TS) has been an remarkable area of research for the treatment of cancers due to their role in DNA biosynthesis. In the ongoing study, the researchers synthesized a library of thiazolidinedione- 1,3,4- oxadiazole hybrids as TS inhibitors. A new sequence of mannich bases of thiazolidine-2,4-diones have been synthesized by mannich base reaction between 5-substituted thiazolidine-2,4-dione, acetanilide and aromatic aldehydes. The substituted thiazolidinone linked to benzothiazoles and benzoxazoles or substituted 5-benzylidene-4- thiazolidinones

Keywords:

Thiazolidinediones, Anti-Cancer Properties.

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were synthesized. The antitumor activity of the prepared compounds, the researchers evaluated the compound against human breast MCF7 and liver HEPG2 cancer cell lines using assay method Sulphorhodamine-B (SRB), taking doxorubicin was used as a reference standard.

Introduction

Background

The thiazolidinediones are the oral antidiabetic drugs which has been available since the late 1990s.Thiazolidinediones are 5-membered heterocyclic molecules containing thiazole nucleus with carbonyl group on second and fourth carbon such as 2,4-thiazolidinedione. The five membered thiazole system comprising of three carbon atoms, one nitrogen atom, and one sulfur atom with 2 double bonded oxygen on 2 and 4 positions is of considerable interest in different areas of med. chem. In past times 2,4-thiazolidinediones are acquire more importance as anti-diabetic agents and their mechanism of action has been thoroughly investigated. The main representatives of this group are pioglitazone, rosiglitazone, troglitazone and ciglitazone, are found to display significant antidiabetic activity. Between them rosiglitazone displays superior anti-hyperglycemic activity and therefore used to treat type 2 diabetes mellitus. The thiazolidinediones going by the name glitazones are a class of medications used in the treatment of diabetes mellitus type 2. The TZD moiety is reported to possess extensive biological potential such as antifungal, analgesic, anti-inflammatory, hypoglycemic, anti-malarial, anti-proliferative, anti-tubercular, anti-oxidant and anti-viral. A.A. Napoleon et al (2).

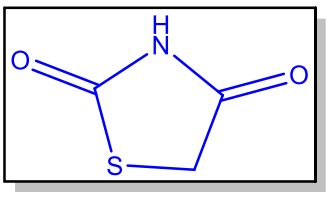

Figure 1: -2,4-Thiazolidinediones Nucleus

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Anti-Cancer Property

The anticancer effects of TZD can be related with many processes including cell differentiation, cell cycle arrest, apoptosis and autophagy. The action of PPARγ in these effects of TZD is really unclear since increasing PPARγ-independent events have been reported. Concentrated researches are now focusing on the underlying molecular mechanisms. As per the researchers on current knowledge about major PPARγ-independent effects of TZD. The activity of some of them is still unclear but some others have been clearly involved in the anticancer action. These data will be important in order to develop new TZD derivatives devoid of toxicity and more efficient in cancer therapeutics. Ovarian cancer is the 5th leading cause of cancer death in women of the 3 major types of ovarian cancer (epithelial, sex cord stromal cancers), epithelial ovarian cancer accounts for about 90% of all cases. Linah Al-Alem etal(8).

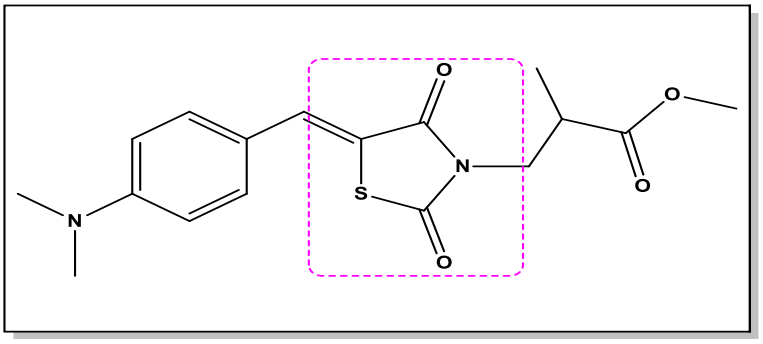

Figure 2: Anticancer Agent

Anti-Microbial Property

Evolution of novel synthetic antimicrobial agents is an important and challenging problem because, some microorganisms have developed resistance to available antibiotics in the vend. Hence it is essential to develop new compounds for treating infectious disease1.Thiazolidine-2,4- diones (TZDs) are important class of heterocyclic compounds, because of their various biological applications such as anti-hyperglycemic, anti-inflammatory, bactericidal, fungicidal etc. The reported potential activities of “glitazones”

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initiated to synthesize N-substituted-2,4- TZD derivatives with good antimicrobial activity. Swapna D et al (1).

The expand rate of microbial infection and development of drug resistance amongst different microbial strains are the major cause of worry for human life worldwide. Several of these resistant strains, such as multidrug resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE) are skilled of surviving the effects of most, if not all, antibiotics currently in use. Exposure of new infectious ailments and development of multidrug resistance are amongst the biggest obstacles in the treatment of microbial infections. Small heterocyclic rings having sulfur and nitrogen atoms like thiazolidine-2,4-dione (TZD) are in study for a long time due to their synthetic variety and therapeutic relevance. Isabelle Grillier-Vuissoz et al. (3).

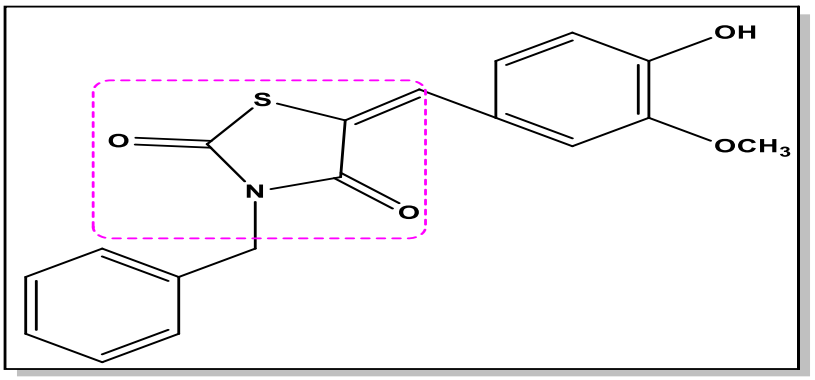

Figure 3: Antimicrobial Agent

Anti-Hyperglycmic Property

Diabetes is a long-term metabolic syndrome which relates to impaired insulin secretion and peripheral insulin resistance. It composed of an array of dysfunctions characterized by hyperglycaemia as its initial symptoms which when ignored leads toseveral disease. These are classified as Type I & II; Type II is found to be the most common among 80% of the affected population worldwide which can be tackled with right medications and changes in lifestyle. Glitazones a class Thiazolidinedionesfound in late 1990's are orally acting hypoglycaemic agents which have attracted attention round the globe

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because of their diverse biological profile showing anti-hyperglycaemic, anti- tumour, anti-oxidant, anti-malarial, anti-obesity & anti-microbial activities. TZD is acts as particular ligand for PPAR to ameliorate diabetes without causing hypoglycaemia. PPAR's (Peroxisome proliferated activated receptors) are ligand activated transcription factors of nuclear receptor superfamily with a leading role in adipogenesis activation and insulin sensitivity. Because of important molecular target; it is further classified as PPAR-a (NR1C1), PPAR-d (NR1C2) & PPAR-c (NR1C3) from them PPAR-c is the most widely researched protein receptor. Rosiglitazone and pioglitazone are thiazolidinedione derivatives which act as PPAR-c full agonist in ameliorating diabetes. Because it has excellent anti-diabetic action, TZD derivatives also possess undesirable side effects including weight gain, edema, anaemia, bone deformities. M.J. Naim et al. (6)

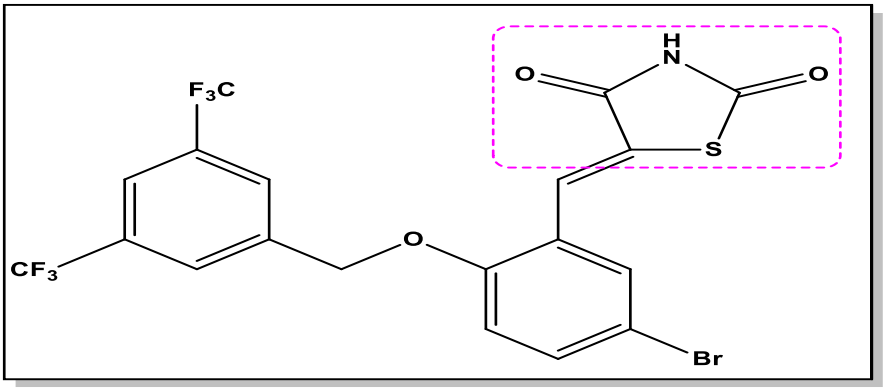

Figure 4: Anti-Hyperglycaemic Agent

Anti-Oxidants Properties

Antioxidants are the compound, which when present at low concentrations compared to those of an oxidisable substrate, significantly delay or prevent oxidation of that substrate.

The key factor of antioxidants is to intercept and react with free radicals so that rapid effect of reactive oxygen species propagation is prevented by readily donating its proton to the ROS. The antioxidant property of a compound

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is attributed to its ability of Inhibiting cellular Microsomal P-450 linked Mixed Function oxidation (MFO) reaction, Oxygen radical scavenging, Suppressing the formation ROS. The researchers studied that the *in vitro* antioxidant activity of the synthesized compounds was quantitatively measured by DPPH radical scavenging assay. The DPPH (2, 2-diphenyl 1- picrylhydrazyl) is a stable free radical at room temperature and accepts an electron or hydrogen radical. The DPPH radical is scavenged by antioxidants through the donation of protons forming the reduced DPPH. The Antioxidant molecule can quench DPPH free radicals and convert them to a colorless / bleached product ultimately resulting in a decrease in absorbance. The medicinal properties of thiazolidinediones initiated us to synthesize N-substituted-5-benzylidene-2, 4- TZD derivatives and evaluate their antioxidant activity. The synthesized 2, 4-thiazolidinedione derivatives were substituted at N-3 with secondary amines to obtain their Mannich bases. Archana Kapoor et al. (16)

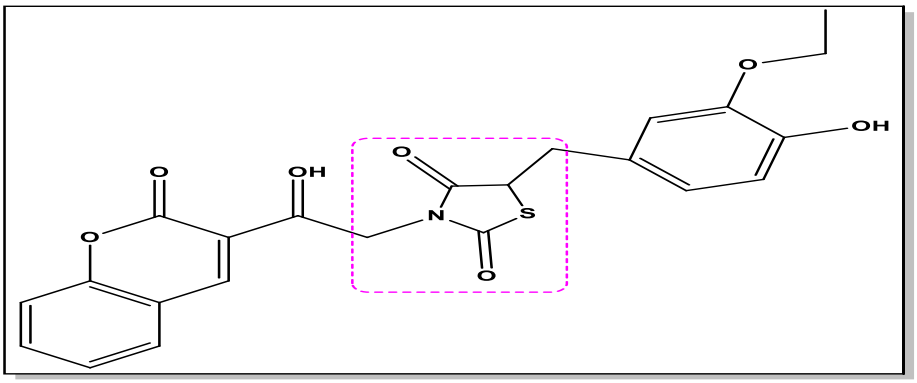

Figure 5: Antioxident Agent

LITRATURE REVIEW

1. Swapna D, Rajitha G et al. (1) Synthesize a new series of mannich bases of thiazolidine-2,4- diones. The synthesized a new series of mannich bases of thiazolidine-2,4-diones is synthesized by mannich base reaction between 5-substituted thiazolidine-2,4-dione, acetanilide and aromatic aldehydes. The structure of these two compounds was established by IR,1H NMR and Mass spectrosopy. The Mannich bases of

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thiazolidine-2,4-diones are going for molecular docking studies with dihydropteroate synthase (DPHS, PDB ID: 3TYE) by using XP GLIDE module. These new compounds (3a–3i) evaluated for their antimicrobial activity. The compounds 3g and 3h showed great activity against Salmonella paratyphi, Escherichia coli and fungi Aspergillus niger, Colletotrichum coffeanum comparable to the standard drugs streptomycin and griseofulvin. Molecular docking studies showed the compound 3h showed good docking score of -5.419 when it targets with protein dihydropteroate synthase.

Table 1: Molecular Docking Score and Binding Energy of Title Compounds 3a-3i

S. No.	DHPS(3TYE) with Compound	Docking Score	Binding Free Energy (kcl/mol)
1	3a	-3.33	-48.116
2	3b	-3.245	-43.26
3	3c	-2.068	-49.498
4	3d	-3.34	-43.246
5	3e	-3.212	-41.88
6	3f	-3.513	-44.27
7	3g	-3.725	-64.84
8	3h	-5.419	-48.673
9	3i	-1.604	-50.018
10	Crystal ligand (XTZ)	-8.332	-63.875

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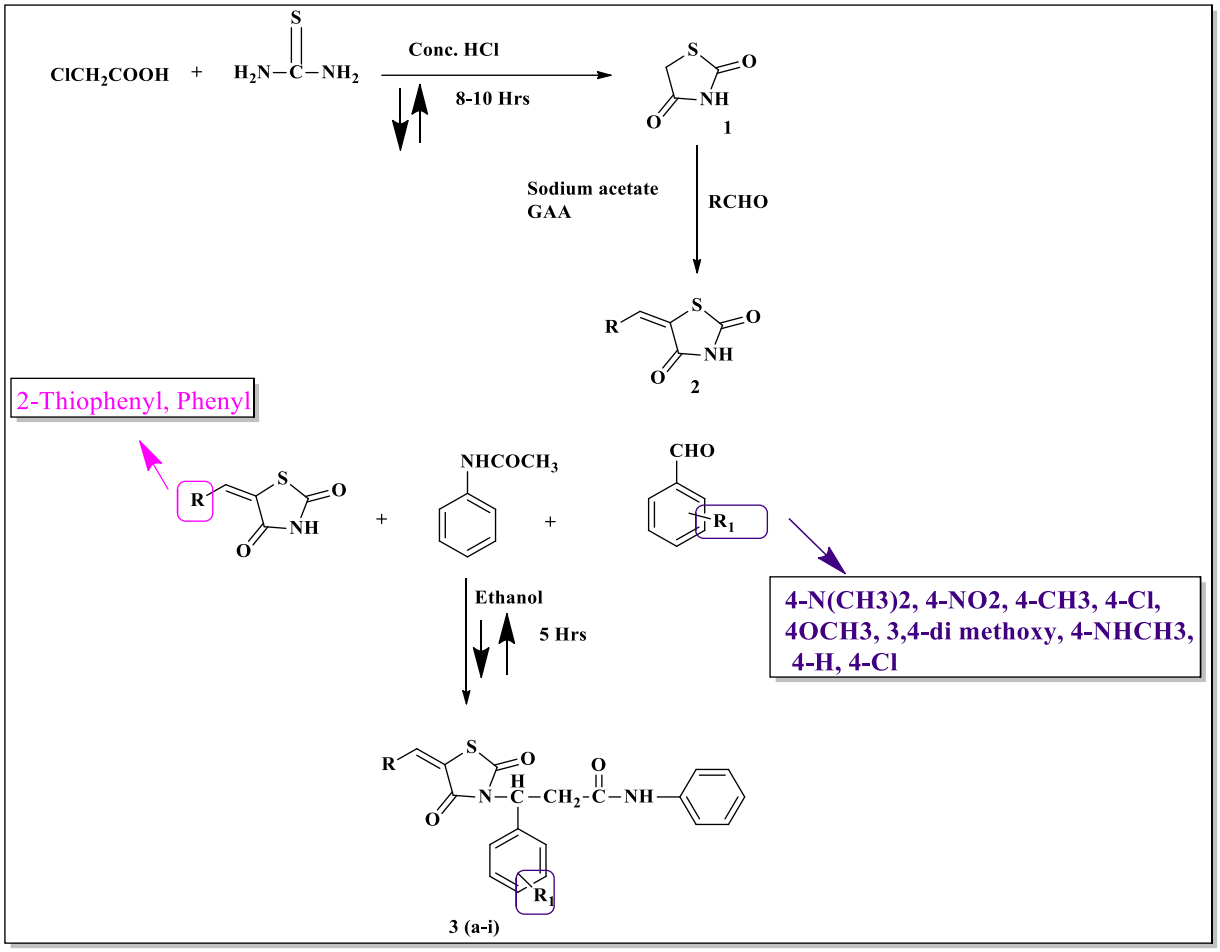

Figure 6: Schematic Representation of Mannich Bases of Thiazolidine-2,4-Diones

2. Harsh kumar et al., (4) work on the extensive biological potential of thiazolidine-2,4-dione (TZD) moiety, a new series of thiazolidine-2,4-dione analogues was synthesized. Various spectral techniques (1H-NMR, IR, MS etc.) were used to clear the chemical structures of the synthesized analogues. These synthesized compounds were screened for the antioxidant and antimicrobial potential.

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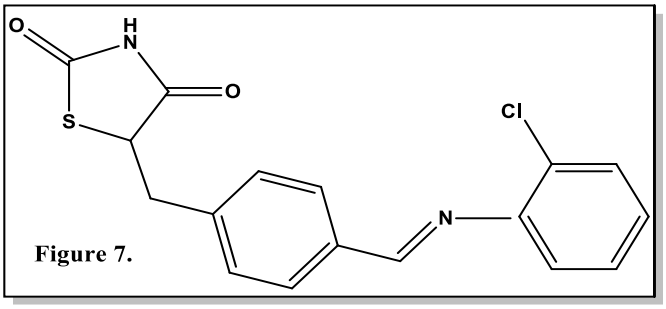

Figure 7: 5-((E)-4-((E)-((2-Chlorophenyl) Imino) Methyl) Benzylidene) Thiazolidine -2,4-Dione

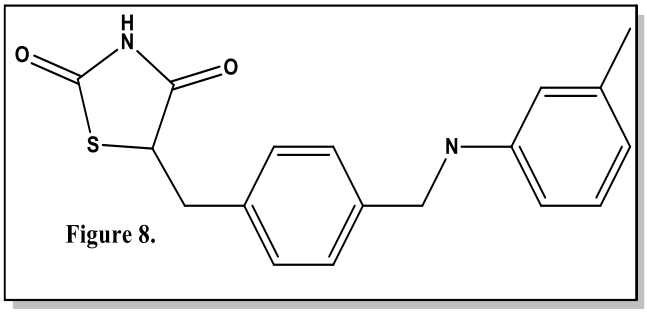

Figure 8: 5-((E)-4-((E)-(M-Tolylimino) Methyl) Benzylidene) Thiazolidine-2,4-Dione

Table. (2). Docking Score of The Compound Compaired with Standard Drug Ofloxacin.

S. No.	Compound	Docking Score
1	5-((E)-4-((E)-((2-chlorophenyl) imino) methyl) benzylidene) thiazolidine -2,4-dione	-4.73
2	5-((E)-4-((E)-(m-tolylimino) methyl) benzylidene) thiazolidine-2,4-dione	-4.61
3	Ofloxacin	-5.107

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3. B. Geetha et al., (5) identified the series of new thiazolidinedione derivatives have been designed and synthesized through microwave-assisted technique. The synthesized compounds were screened by Insilco methods like molecular docking, QSAR studies in order to explore the anti-diabetic and anti-cancer activity, synthetic assessability of compounds against the peroxisome proliferator-activated the receptor (PPAR_). Compounds which showed higher glide score than standard (Pioglitazone) were synthesized using the microwave. Compounds were characterized with the help of FT Infrared spectroscopy, Proton NMR, C-13 NMR spectroscopic studies and Lc-Ms.

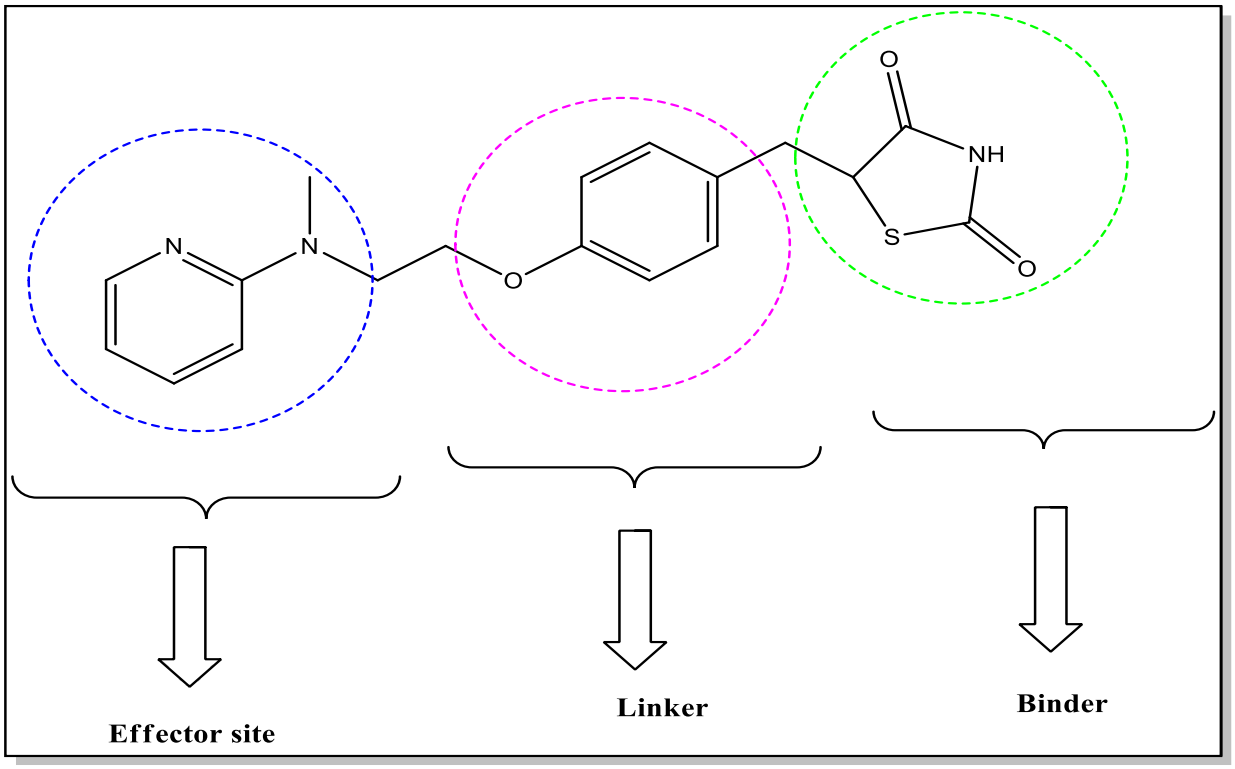

Figure 9: Three Regions of Thiazolidinediones Based Upon QSAR Study of Various Anti-Diabetic Compounds

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4. M.J. Naim et al. (6) work on the series of thiazolidinedione (TZD) based amide derivatives were designed, synthesized and docked against the PPARc receptor target. Various compounds from the series with good glide scores were selected for in vivo antidiabetic study based on streptozotocin induced diabetic rat model. It was seen that 4 compounds (6c, 6e, 6m & 6n) showed significantly good antidiabetic activity in comparison to rosiglitazone and pioglitazone as reference drugs. The compound 6c appeared as the most potent derivative in lowering blood glucose level and have excellent interaction with SER 342, ILE 281, pi-pi interaction with ARG 288 and shows halogen bond interaction with the LYS 367. Further, PPARc transactivation and gene expression studies of compound 6c were carried out to investigate the possible mechanism of action through PPARc modulation. The compound 6c exhibited 53.65% transactivation and elevated PPARc gene expression by 2.1 folds. All biochemical parameters (AST, ALT and ALP levels) were found within the range with no damage of liver.

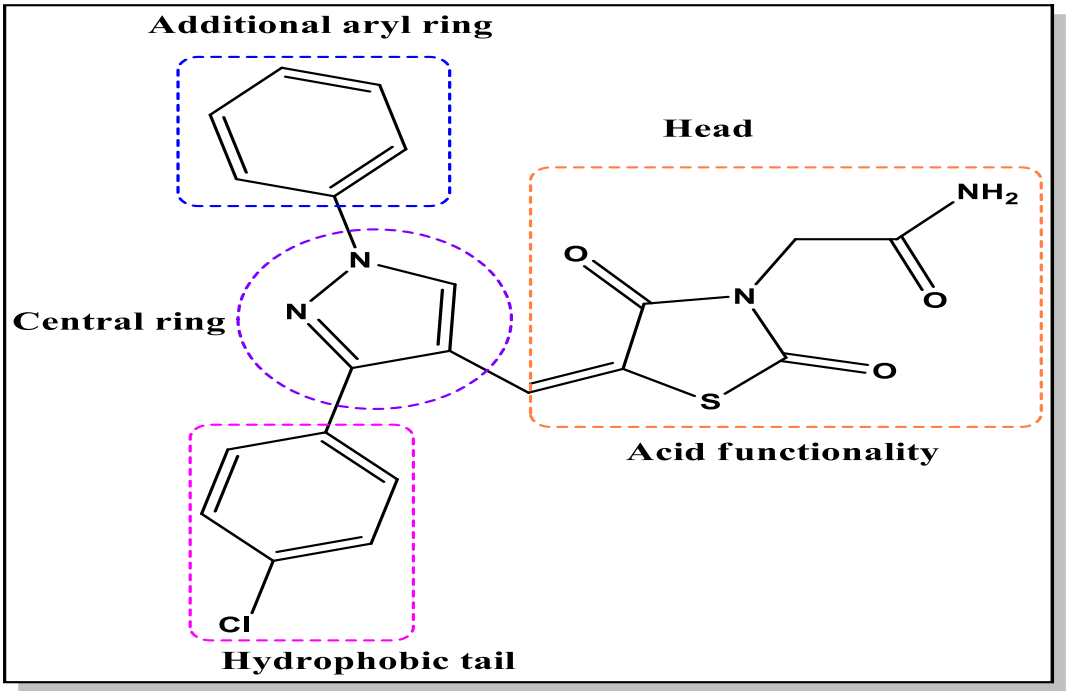

Figure 10: Designed Molecule

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5. Fawad Naeem et al. (7) works on 2,4-Thiazolidinedione and its derivatives and have a variety of pharmacological activities including anti-diabetic, antiviral, anti-fungal, anti-inflammatory, anti- cancer. The pharmacological potential of 2,4- Thiazolidinedione derivatives as anti-diabetic agents, seven arylidene derivatives of 2,4-thiazolidinedione 1(a-g) and 4 corresponding acetic acid derivatives 2(a-d) have been synthesized by a 3-step procedure.

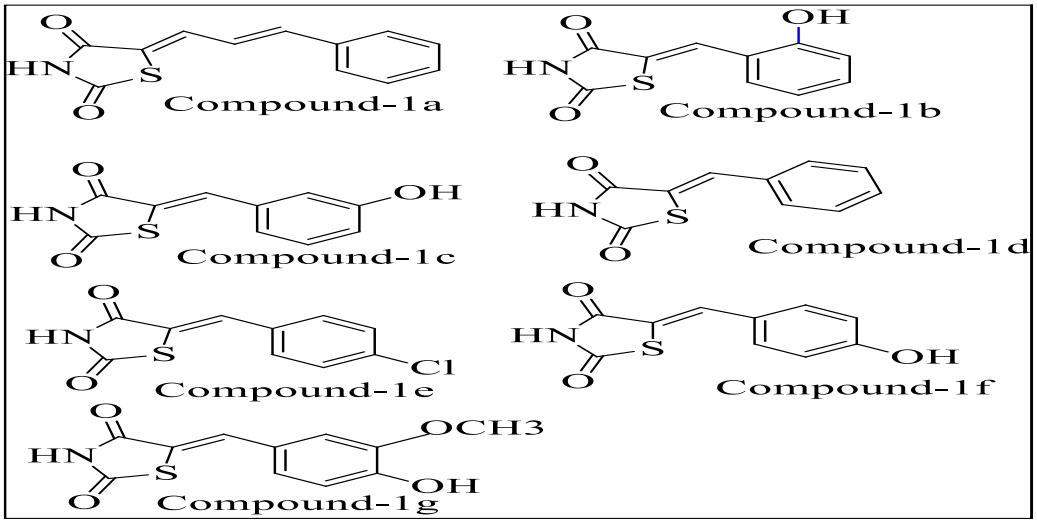

Figure 11: Chemical Structures of The Compounds 1(a-g)

6. Tamer Nasr et al., (10) works on microbial resistance to the available drugs poses a serious threat in modern medicine. The researchers report the design, synthesis and in vitro antimicrobial activity of new functionalized 2,3-dihydrothiazoles and 4-thiazolidinones tagged with sulfisoxazole moiety. The compound 8d was most active against Bacillissubtilis (MIC, 0.007 mg/mL). The compounds 7c–d and 8c displayed significant activities against B. subtilis and Streptococcus pneumoniae (MIC, 0.03– 0.06 mg/mL and 0.06–0.12 mg/mL versus ampicillin 0.24 mg/mL and 0.12 mg/mL; respectively). The compounds 7a and 7c–d were highly potent against Escherichia coli (MIC, 0.49–0.98 mg/mL versus gentamycin 1.95 mg/mL). On the other side, compounds 7e and 9c were fourfolds more active than amphotericin B against

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Syncephalastrumracemosum. The molecular docking studies showed that the synthesized compounds could act as inhibitors for the dihydropteroate synthase enzyme (DHPS). That study is a platform for the future design of more potent anti-microbial gents.

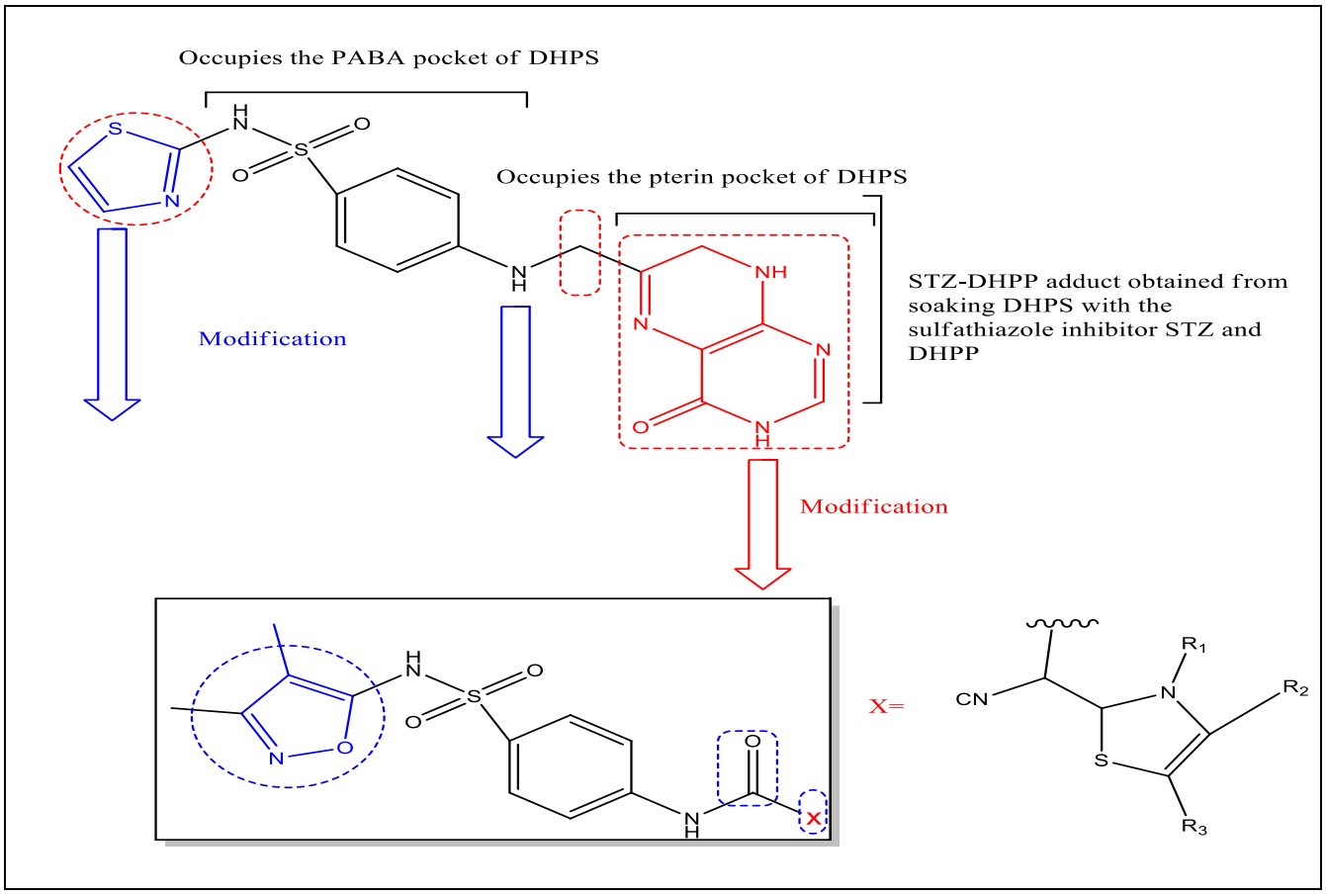

Figure 12: Design of Thaizole Derivatives Bearing Sulfisoxazole Moiety as DHPS Inhibitors

7. Marc et al., (13) Studied the series of 12 new thiazolidine-2,4-dione derivatives were obtained by microwave-assisted synthesis. All synthesized compounds were physicochemically characterized by quantitative elemental *C, H, N, S* analysis and data spectral, with the results being in agreement with the expected data. The in vitro screening performed on *Candida albicans* ATCC 10231 showed their moderate antifungal activity, which was further investigated

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to determine the minimum inhibitory concentration and minimum fungicidal concentration values for the most active compounds on four strains of *Candida*. Molecular docking studies, were performed against a fungal lanosterol 14α-demethylase, emphasized the importance of different molecular fragments in the compounds' structures for their antifungal activity. In silico screening of synthesized compounds were subjected to the prediction of their absorption, distribution, metabolism, excretion, and toxicity (ADMET) and molecular properties. The result of the antifungal activity assay, docking study, and ADMET prediction revealed that th synthesized compound are potential anti-*Candid* agent that may act by interacting with the fungal lanosterol 14α-demethylase and could be further optimized and developed as anti-fungal agent.

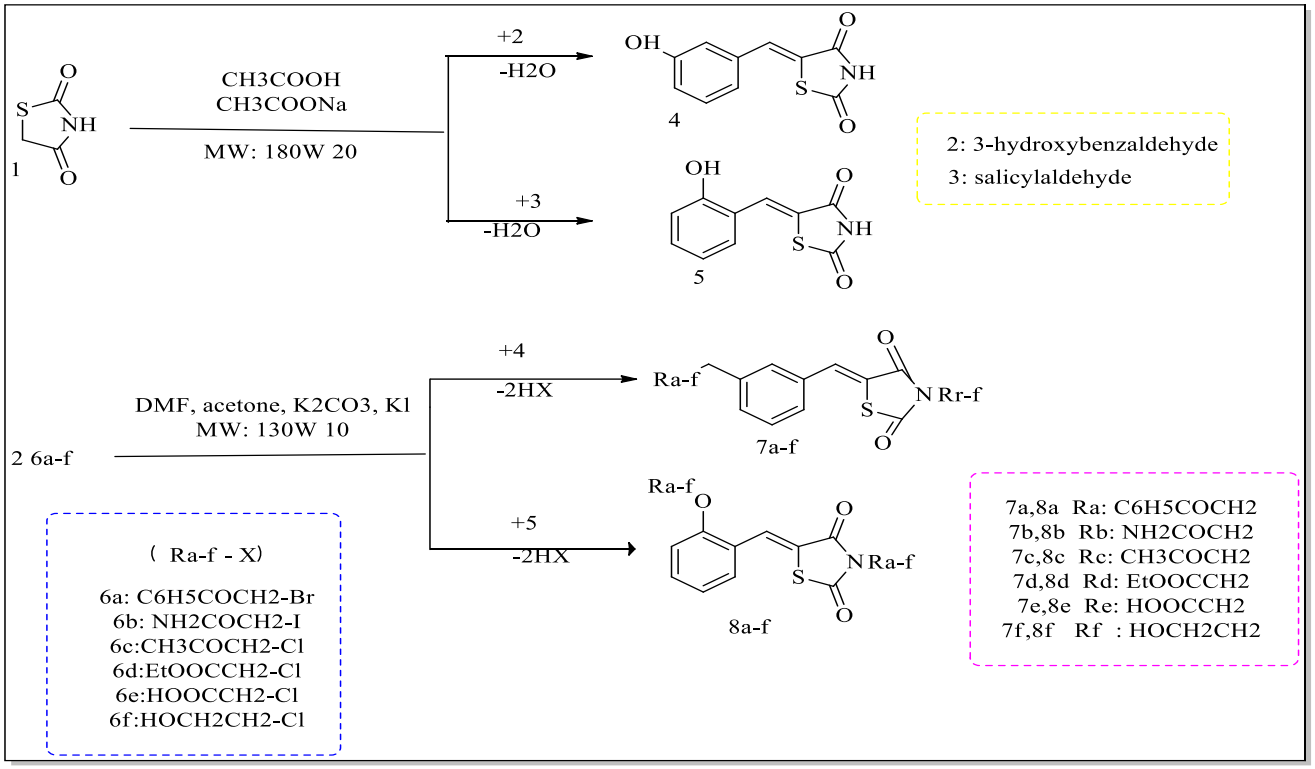

Figure 13: Route Followed in Order to Obtain the Thiazolidine- 2,4-Dione Derivatives 7a–-F And 8a–F

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8. Harshitha. T et al., (14) Performs *in silico* molecular docking and *in vitro* anticancer studies of proposed 1,2,4-triazole derivatives for the determination of their anti-cancer activity.

9. K. Srikanth Kumar et al (29) works on Various thiazolidine-2,4-dione derivative 3a-l possessing indole moiety was designed, synthesized using appropriate conventional heating as well as microwave irradiation method. All the synthesized compound was characterized physically and spectrally. The compound were evaluated for in vitro anti-bacterial activity, in vitro anti-oxidant activity and in-vivo hypoglycemic activity in relation to the standard drug. Most of the new compounds exhibited moderate activity or some showed considerable activity. Molecular docking study was carried out using Auto-Dock software and reveal that compound 3-b has significant binding interaction with PPARg receptor compared with the standard ligand Rosiglitazone.

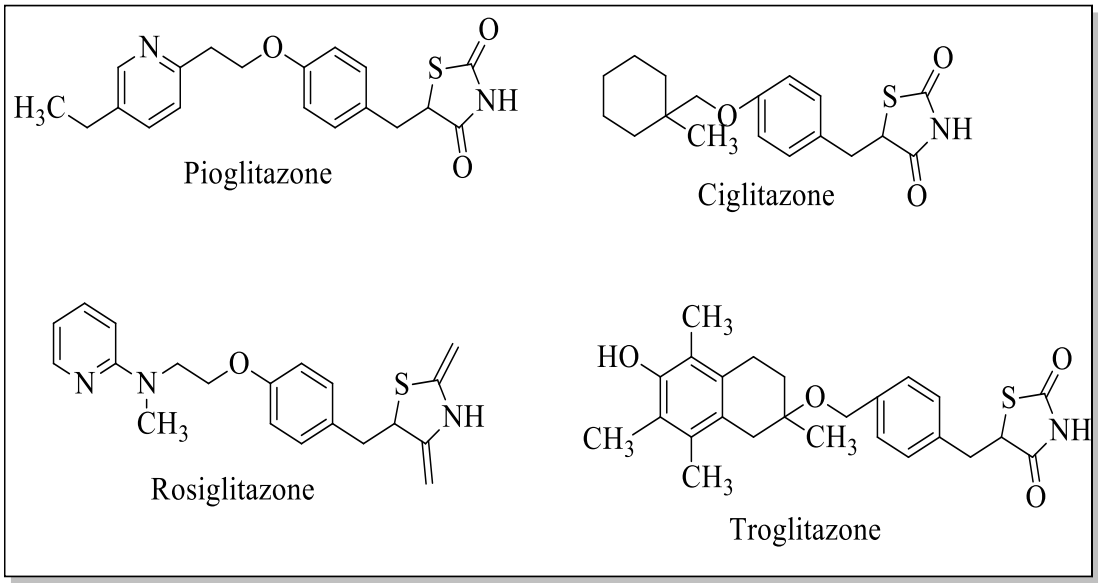

Figure 14: Structures of Pioglitazone, Rosiglitazone, Ciglitazone and Troglitazone.

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10. Syed Nazreen et al., (20) studied on new thiazolidine 2,4-dione hybrid were designed and synthesized as potential peroxisome proliferator activated receptor (PPAR)-γ agonist and thymidylate-synthase inhibitor. All the synthesized compound follows Lipinski's and Veber's rules and possesses the desired pharmacokinetic properties. The PPAR-γ transactivation result displayed that compound **12** (78.9%) and **11** (73.4%) was the most active compound and they increase PPAR-γ gene expression by 2.2- fold and 2.4-fold, respectively. Compounds 12, **11**, and **8** shows promising cytotoxicity, with IC_{50} value ranging from1.4to4.5 μM against MCF-7 cell and from 1.8 to 8.4 μ Magainst HCT-116 cells. Compound **11** and **12** also inhibited thymidylate synthase with IC_{50} values of 5.1 and 3.2 μM, respectively, confirming their mode of action as thymidylate synthase inhibitor. Finally, molecular docking study supported the in vitro biological activity result.

11 Lamia H.T. Amine et al. (21) studied that cancer is a perplexing and challenging problem for researcher. In this study, a series of 6-aryl-5-cyano-pyrimidine derivative was designed, synthesized and evaluated for their anticancer activity against HePG-2, MCF-7 and HCT-116 cell lines Compound **2, 3d, 4a-c**, **5, 8** and **12** displayed high anticancer activity, compared to that of 5-fluorouracil. Additionally, those compounds with effective anticancer activity were further assesses for their ability to inhibit thymidylate synthase (TS) enzyme. All the tested compound demonstrated a marked TS inhibitory activity (33.66–74.98%), with IC_{50} ranging from 3.89 to 15.74 nM. Moreover, apoptosis study was conducted on the most potent compound **8**, to evaluate its proapoptotic potentials. Ironically, compound **8** induced the level of active caspase 3, and elevated the Bax/Bcl2 ratio 44 folds in comparison to the control. Finally, a molecular docking study was conducted to detect the probable interaction among the active compounds and the thymidylate synthase active site.

12. MaliheAkhavan et al. (22) studies that the magic scaffoldrhodanine and thiazolidine are very important heterocyclic compounds in drug design and discovery. Those are important heterocyclic compound that have attracted a great deal of attention because they exhibit a variety of bioactivitiy including antibacterial, antifungal, antiviral, antimalarial, and anti-inflammatory action. The selective toxicity exhibits by these agents. The aim of this study was molecular docking,

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green and solvent-free efficient synthesis of a new series of hetero/aromatic substituted rhodanine and thiazolidine analogue and then investigation of their antimicrobial activity.

13. Sergio Hidalgo-Figueroa et al. (23) This work present the synthesis of two hybrid compounds (**1** and **2**) with thiazolidine2,4-dione structure as a central scaffold which were further screened *in combo* (*in vitro* as PTP-1B inhibitors, *in vivo* anti-hyperglycemic activity, molecular docking and *in silico* toxicological profile. The compound **1** was tested in the enzymatic assay showing an $IC_{50}=9.6\pm0.5\mu M$ and the compound **2** showed about a 50% of inhibition of PTP-1B at 20 μM. Therefore, the compound **1** was chosen to test its anti-hyperglycemic effects in a rat model for type-1 diabetes mellitus, which was determined at 50mg/kg in single dose. The results indicated that compound showed a significant decrease of plasma glucose level that reached 34%, after a 7 h post administration. Molecular docking was employed to study the inhibitory property of thiazolidine-2,4-dione derivative against Protein Tyrosine Phosphatase 1B (PDB ID: 1c83). If we talk about two binding sites in this enzyme (sites A and B), compound **1** has shown the best docking score, which indicates the highest affinity. In the end compounds **1** and **2** have demonstrated an in silico satisfactory pharmacokinetic profile. This shows that it could be a very best candidate or leader for new series of compounds with this central scaffold.

14. Rakia Abd Alhameed et al. (9) Studied on novel thiazolidine-2,4-dione carboxamide and amino acid derivative were synthesized in excellent yield using OxymaPure/N, N0-diisopropyl-carbodimide coupling methodology and were characterized by chromatographic and spectrometric method, and elemental analysis. The antimicrobial and antifungal activity of these derivatives were evaluated against two Gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis), two-Gram negative bacteria (Escherichia coli and Pseudomonas aeruginosa), and one fungal isolate (Candida albicans). Interestingly, several samples demonstrated weak to moderate antibacterial activity against Gram-negative bacteria, as well as antifungal activity. However, only one compound namely, 2-(5-(3-methoxybenzylidene)-2,4-dioxothiazolidin-3- yl) acetic acid, showed antibacterial activity against Gram-positive bacteria, particularly S. aureus.

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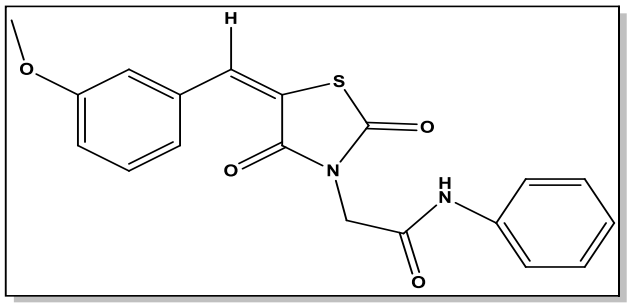

Figure 15: Structure of Compound 4b

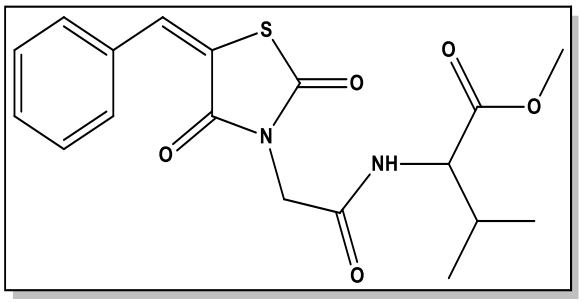

Figure 16: Structure of Compound 5g

15 Z.M.M. Alzhrani et al., (11) works on Thymidylate synthase (TS) has been an attention- grabbing area of researchers for the treatment of cancer due to their role in DNA biosynthesis. In the present studies, the researchers synthesised a library of thiazolidinedione- 1,3,4-oxadiazole hybrids as TS inhibitor. All the synthesized hybrid followed Lipinski and Veber rules which indicated good drug likeness property upon oral administration. Among the synthesized hybrid, compound 9 and 10 displayed 4.5- and 4.4-fold activity of 5-Fluorouracil, respectively against MCF-7 cell line whereas 3.1- and 2.5-fold cytotoxicity against HCT-116 cell lines. Furthermore, compound 9 and 10 also inhibit TS enzyme with IC50 ¼ 1.67 and 2.21mM, respectively. Finally, the docking study of 9 and 10 was found to be consistent with in-vitro TS result. From these study, compound 9 and 10 has the potential to be developed as TS inhibitor.

Table 3: Docking Scores of Active Compounds Against Human Thymidylate Synthase Protein 6QXG

S. No.	Compound	Docking Score
1	methoxybenzylidene)-3-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl) methyl) thiazolid ine-2,4-dione	-9.09
2	5-(4-methoxybenzylidene)-3-((5-(4-bromophenyl)-1,3,4-oxadiazol-2 yl) methyl) thiazolid ine-2,4-dione	-8.67
3	5-FU	-4.22

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16. Mohamed A. Abdelgawad et al., (12) Substituted thiazolidinone linked to benzothiazole and benzoxazole 3a, b or substituted 5-benzylidene-4- thiazolidinones 4a-h were synthesized. The antitumor activity of the prepared compound was evaluated against human breast MCF7 and liver HEPG2 cancer cell lines using Sulphorhodamine-B (SRB) assays method, doxorubicin was used as a reference standard. Most of the tested compound showed potent antitumor activity especially the pmethoxy- 5-benzylidine-4-thiazolidinone derivatives of benzoxazoles 4c and benzothiazoles 4d, their IC50 against liver HEPG2 cancer cell line is 0.026 nM & 0.027. The IC50 of p-chloro-5 benzylidine-4-thiazolidinone linked to benzoxazole 4e againsts breast MCF7 cancer cell line, is 19 nM but, p-nitro-5-benzylidine- 4-thiazolidinone derivative of benzothiazole 4h showed a broad-spectrum antitumor activity against MCF7 and HEPG2 cell line, its IC50 is 36 and 48 nM respectively. The most active compound was docked against VEGFR-2 using Moe program and 1Y6A (pdb file) to investigates if this compound has a similar binding mode to VEGFR-2 inhibitor.

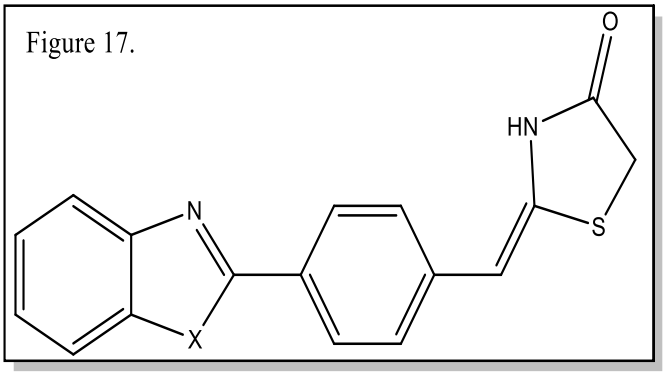

Figure 17: Synthesize A Series Of Substituted Benzothaizoles/Benzoxazoles To Be Linked Onto 4-Thiazolidinone

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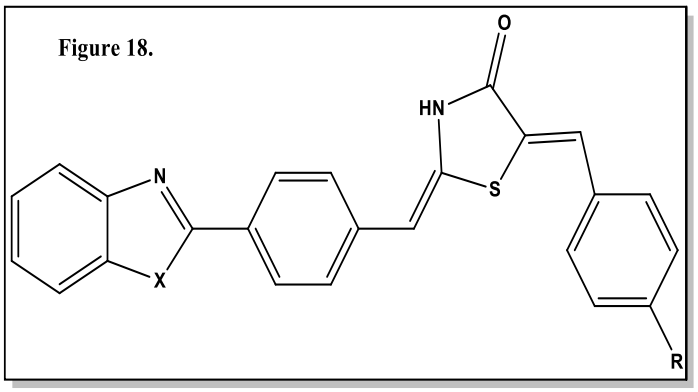

Figure 18: Substituted 5-Benzylidine-4-Thiazolidinones

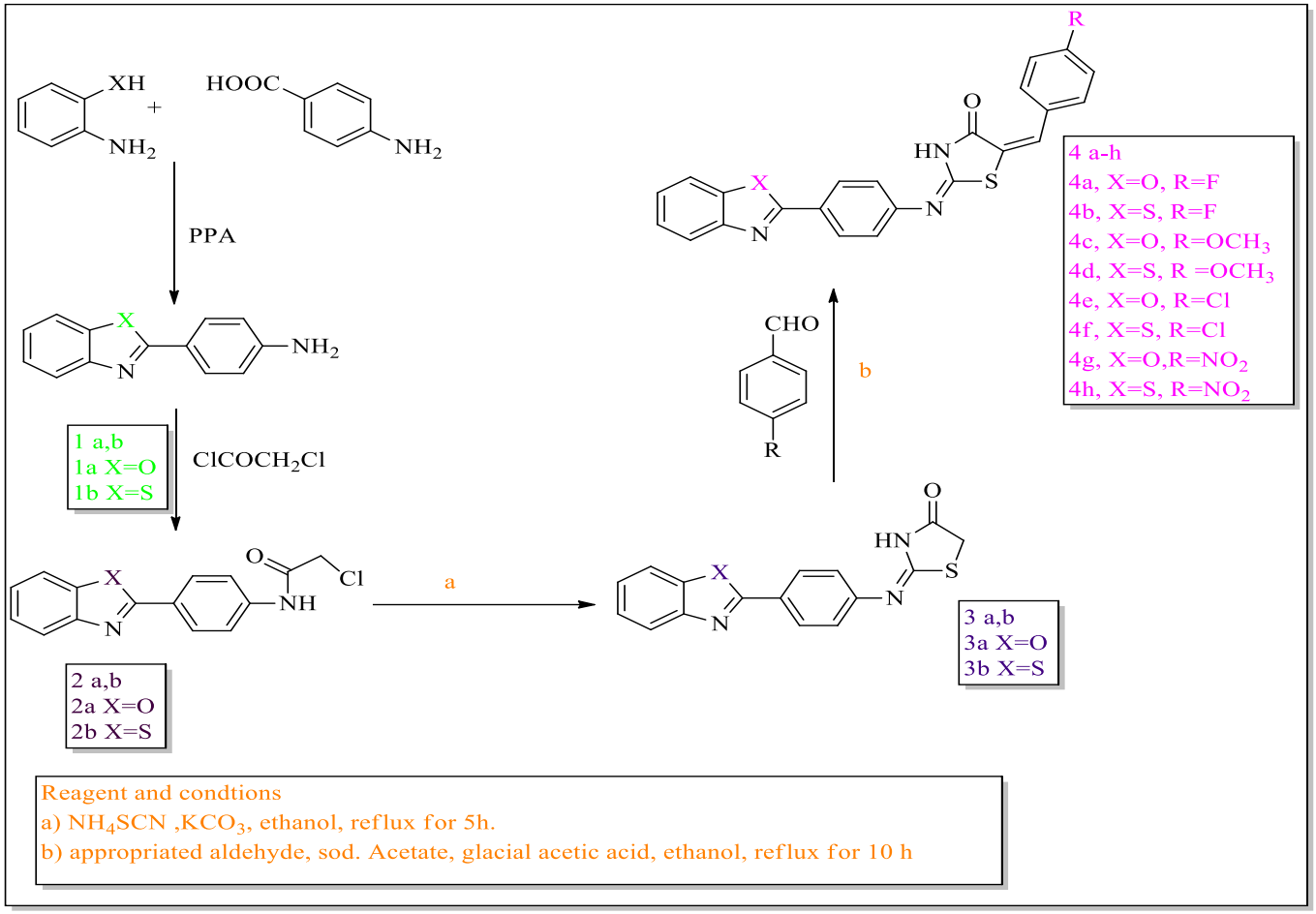

Figure 19: Synthesis of Compounds 3a, b and 4a-h

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17. ThirumalaswamyKottha et al. (15) Studied on the series of naphthalene-based hybrid heterocyclic were designed and synthesized by the replacement of benzene ring with napthalene on 4-substituted *4H*-chromene. As a part of their continuous efforts in accessing the bioactive compound by using simple technique, we report the synthesis of azolidinedione/ thiazolidinedione tethered 4-substituted benzo[f] chromene derivative under greener reaction condition and *in silico*evaluation of anticancer activity. Docking study showed that the synthesized compound exhibit good predicted binding affinity at the colchicine binding site of tubulin.

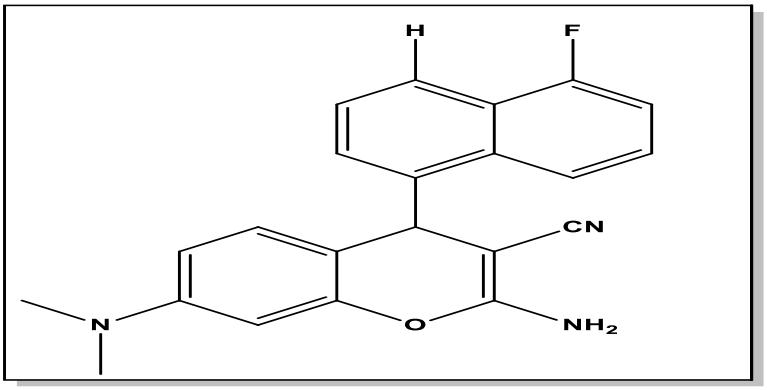

Figure 20: Naphthalene Tethered 4-Substituted-4*H*-Chromene Analogue.

18. Metta Madhuri et al. (17) studied on Molecular docking studies was performed on a series of 2,4-Thiazolidinedione MM1-MM24 as potential epiderma1 growth factor receptors (EGFRR) inhibitor. The techniques of docking were applied to dock a set of representative compounds within the active site region of 1M17 using Molegro Virtual Docker v 5.0. For these compounds, the binding free energy (kcal/mol) was determined. The docking simulation prediction is that the binding mode that is nearly similar to the crystallographic binding mode with 1.34Ao RMSD. Based on the validation and hydrogen bond interactions made by R substituents were considered for evaluation. The result avail to understand the type of interaction that occur between thiazolidinedione with 1M17 binding site region and explains the importance of R substitution on thiazolidinedione basicnucleus.

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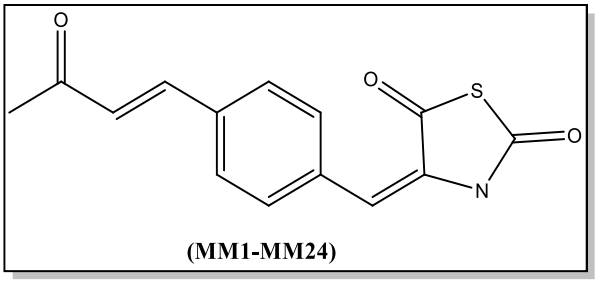

Figure 21: Structure of 24 Thiazolidinediones MM1-MM24

19. Yuichi sawaguchi et al., (18) Works on Pim kinases. Pim kinase are overexpressed in various type of hematological malignancies and solid carcinomas, and promote cell proliferation and survivals. Here in this study, we investigated the preclinical profiles of novel pan-Pim kinase inhibitor with imidazopyridazine and thiazolidinedione structures. Imidazopyridazine-thiazolidinedione inhibits activities of Pim kinases with IC50 value of tens to hundreds nanomolar. With YPC-21440 and/or YPC-21817, which exhibits especially high inhibitory activity against Pim kinases, we investigated in vitro and in vivo activities of imidazopyridazine-thiazolidinedione. In silico analysis of binding mode of YPC-21440 and Pim kinases revealed thats it directly bound to ATP-binding pocket of Pim kinases. In the kinase panels tested, YPC-21440 and YPC-21817 were highly specific to Pim kinases. These compounds exerted antiproliferative activity against various cancers cell lines derived from hematological malignancies and solid carcinomas. Furthermore, they suppressed phosphorylation of Pim kinase substrate, arrested cells cycle at the G1 phase, and induced apoptosis in cultured cancer cell. In tumor xenograft model, YPC-21440 methanesulfonate and YPC- 21817 methanesulfonate exerted antitumor activitiy. The pharmacodynamic analysis done with a xenograft model suggested that YPC-21817 methanesulfonate inhibited Pim kinases in tumors. In conclusion, our data revealed that imidazopyridazine thiazolidinedione are novel Pim kinases inhibitor, effective on various type of cancer cell lines both in- vitro and in-vivo.

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20. Nadine Uwabagira et al. (19) studied on the compounds 3- {[(2,3 Dichlorophenyl) amino] methyl}-5-(furan-2-ylmethylidene)-1,3- thiazolidine-2,4-dione has been designed, synthesized, and screened for its in-vitro anti breast cancers activity, using human breast adenocarcinoma cell line (MCF-7) and in-vitro anti-inflammatory activity. By hemolysis assays, it shows that it has a non-hemolytic and nontoxic effect on human blood cell. The title compound 5, subjected to in vitro activity, showed that it is cytotoxic with an IC50 of 42.30 _M and a good anti-inflammatory agent. The docking result against cyclin dependent kinase 2 (CDK2) (PDB ID: 3QQK) gave insight on its inhibitory activity.

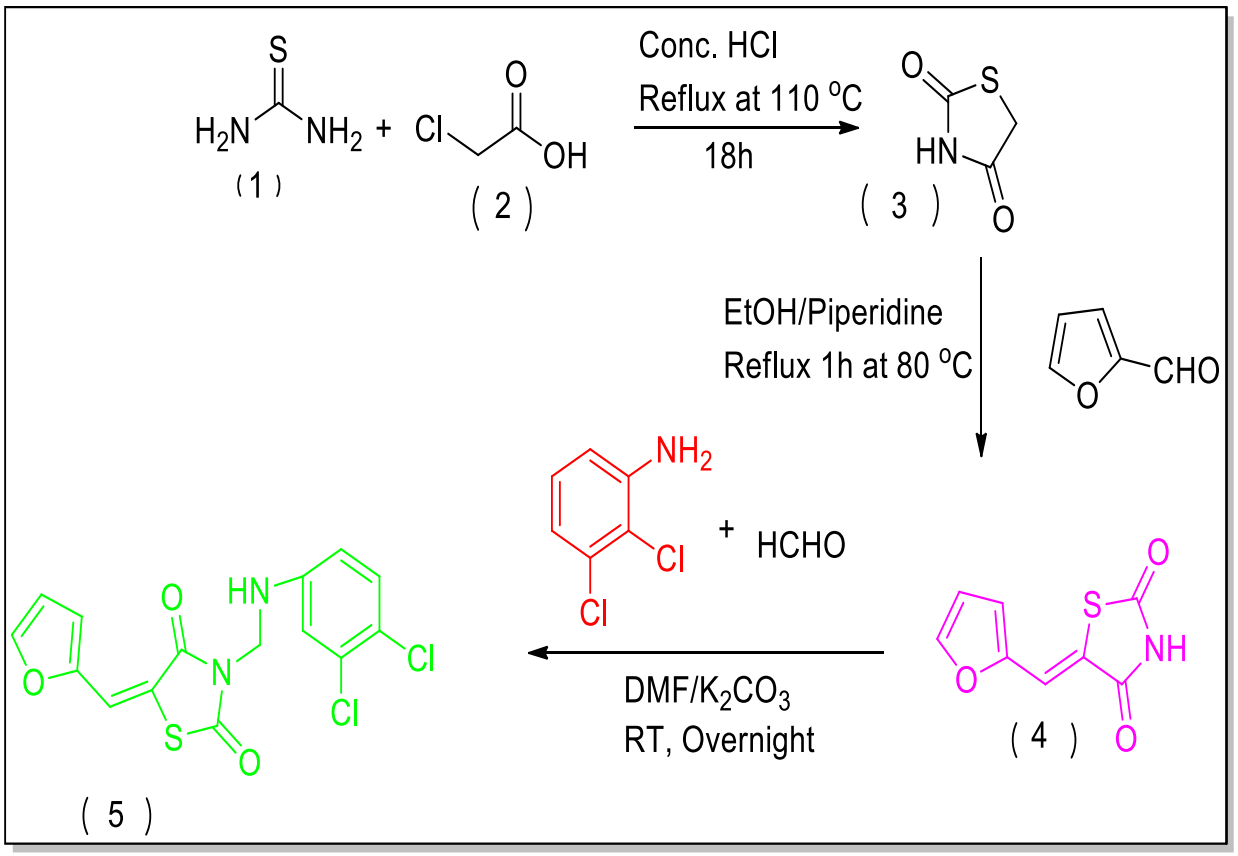

Figure 22: The Synthesis Of 3-{[(2,3-Dichlorophenyl) Amino] Methyl}-5-(Furan-2-Ylmethylidene)-1,3- Thiazolidine-2,4-Dione

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21. Sethi Navjotet. al (23) Literature studies also reveal that the attachments of more heterocyclic ring, containing nitrogen on 5th position of 2,4-TZD, can enhance the antimicrobial activities. Hence, attachment of various moiety on the benzylidene ring may produce safe and effective compound in the future.

The *in vitro* cytotoxicity study was performed for human breast cancer (MCF-7) and human lung cancer (A549) cells and HepG2 cell-lines and compared to standard drugs doxorubicin by MTTassays. Antimicrobial activitiy of the synthesized 2,4-thiazolidinediones derivatives was carried out using the cup plate method with slight modification. The result obtained showed that derivatives with heterocyclic rings like benzimidazole and Aromatic amine group exhibited good antiproliferative activity againsts A549 cancer cell-line, whereas derivatives with Phenolic group exhibited moderate antiproliferative activities against HepG2 cell-line when compared to standard drug doxorubicin.

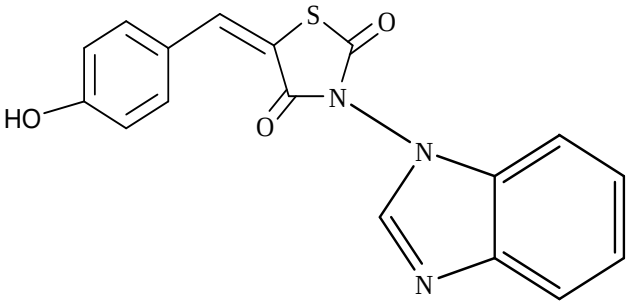

Figure 23: 2,4-TZD Derivative with Benzimidazole Ring

CONCLUSION

In recent past, a variety of molecules base on thiazolidinedione have been evaluated and synthesized to improve its pharmacological activity. Due to wide ranges of pharmacological activities and clinically used 2,4-thiazolidinediones, these molecules have attracted much attention and encouraged the chemists and biologist to be extensive investigations or molecular manipulations, and as a result further improved protocol with

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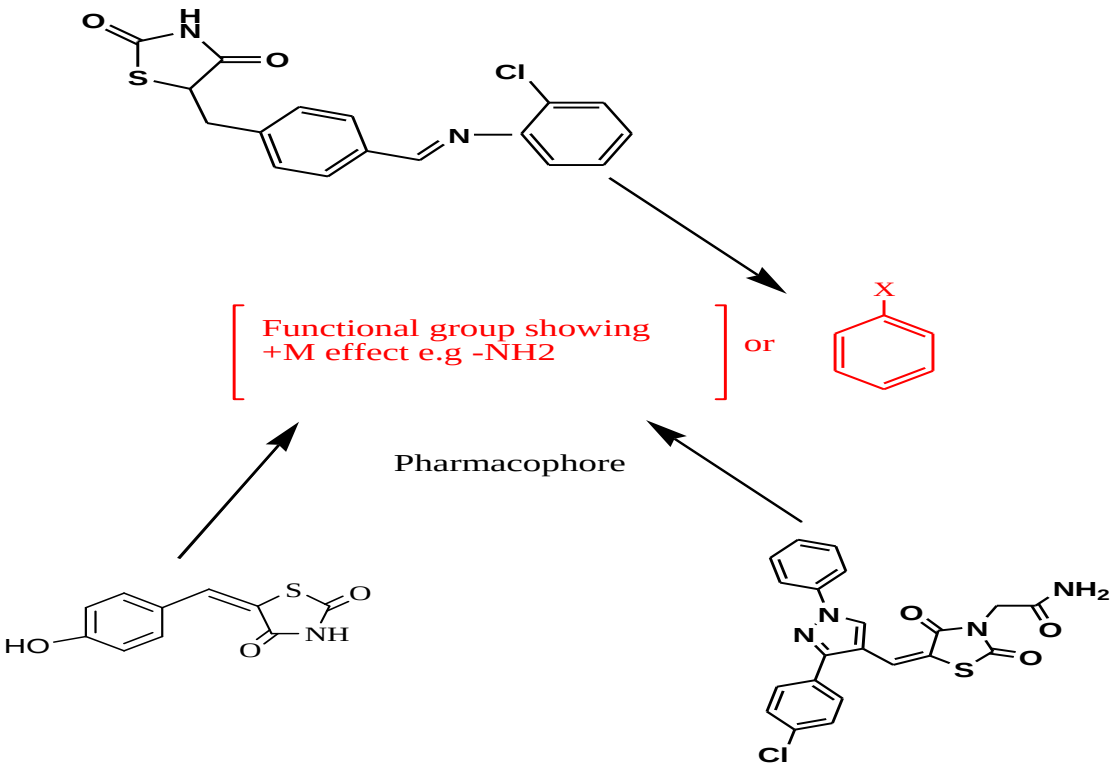
better observation is still ongoing. The purpose of the review is to systemize the information available in the literature regarding the molecular docking study of noval thiazolidinedione-based compounds. The molecular docking evaluation for antimicrobial activity was carried out to find out the interaction between synthesized thiazolidine-2,4-dione compounds with DNA gyrase protein. When the substituted thiazolidinone linked to benzothiazoles and benzoxazoles it shows good anticancer activity the compounds which was formed is evaluated against human breast MCF7 and liver HEPG2 cancer cell lines and it shows effective machanism. Some of the recent and effective chemical synthetic pathway is also illustrated to understand the parameters of the compound's formation. The results of this work indicate efficient computational tools are capable of identify potential ligand.



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