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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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Keywords:

Thiazolidinediones, Anti-Cancer Properties.

ABSTRACT

Thiazolidinediones (TZDs) are five-membered heterocyclic having sulfur, nitrogen, and oxygen atoms in their ring structure and exhibiting potent as well as wide range of pharmacological activities. In the past few decades, research has reached to the mark with an increased interest in capturing novel methodologies and targets that forcefully worked for the preparation of 2,4- Thiazolidinediones (TZD) nucleus for their various pharmacological properties like anticancer, antioxidants, anti-malarial, antiviral, anti-infammatory, anti-HIV, anti-TB, antimicrobial etc. This review covers updated information of molecular docking of anti-cancer and anti-microbial activity. Thiazolidinediones are sulfur containing pentacyclic compounds that are widely found throughout nature in various forms. Thiazolidinediones are agonists of the nuclear receptor Peroxisome Proliferator Activated Receptor gamman (PPARγ). There are several synthetic compounds which are known for a long-time anticancer potencies and numerous studies have been performed to understand their mechanism of action. Thymidylate synthase (TS) has been an attention-grabbing area of research for the treatment of cancers due to their role in DNA biosynthesis. In the present study, we have synthesized a library of thiazolidinedione- 1,3,4-oxadiazole hybrids as TS inhibitors. A new series of mannich bases of thiazolidine-2,4-diones have been synthesized by mannich base reaction between 5-substituted thiazolidine-

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2,4-dione, acetanilide and aromatic aldehydes. The substituted thiazolidinone linked to benzothiazoles and benzoxazoles or substituted 5-benzylidene-4-thiazolidinones were synthesized. The antitumor activity of the prepared compounds was evaluated against human breast MCF7 and liver HEPG2 cancer cell lines using Sulphorhodamine-B (SRB) assay method, doxorubicin was used as a reference standard.

Introduction

Background

The thiazolidinediones are the oral antidiabetic drugs which has been available since the late 1990s. These are five-membered heterocyclic molecules containing thiazole nucleus with carbonyl group on second and fourth carbon such as 2,4-thiazolidinedione derivatives. The five membered thiazole system comprising of three carbon atoms, one nitrogen atom, and one sulfur atom with two double bonded oxygen on 2 and 4 positions is of considerable interest in different areas of medicinal chemistry. In recent times 2,4-thiazolidinediones are gaining more importance as antidiabetic 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. Among them rosiglitazone displays superior antihyperglycemic activity and therefore used to treat type 2 diabetes mellitus. The thiazolidinediones also known as 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, antimalarial, antiproliferative, antitubercular, antioxidant, antiviral hypolipidemic and antibacterial etc. A.A. Napoleon et al (2).

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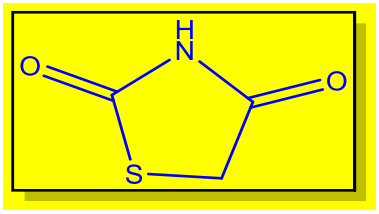

Fig. (1) 1-2, 4 - Thiazolidinediones Nucleus

Anti-Cancer Property

The anticancer effects of TZD can be associated with several processes including cell differentiation, cell cycle arrest, apoptosis and autophagy. The involvement of PPARγ in these effects of TZD is really unclear since increasing PPARγ-independent events have been reported. Intensive researches are now focusing on the underlying molecular mechanisms. Here we review the current knowledge about major PPARγ-independent effects of TZD. The role of some of them is still unclear whereas others have been clearly involved in the anticancer action. These data will be essential in order to develop new TZD derivatives devoid of toxicity and more efficient in cancer therapeutics. Ovarian cancer is the fifth leading cause of cancer death in women. Of the three main types of ovarian cancer (epithelial, germ cell, and sex cord stromal cancers), epithelial ovarian cancer accounts for about 90% of all cases, and is the first cause of death from gynecological malignancies. Linah Al-Alem et al (8).

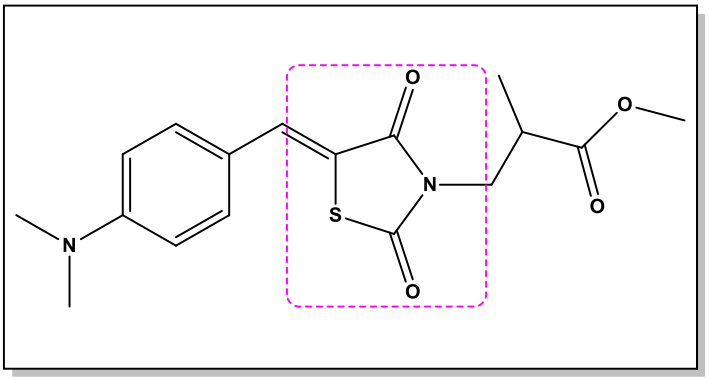

Fig. (2) Anticancer Agent

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Anti-Microbial Property

Development of novel synthetic antimicrobial agents is an important and challenging problem because, some microorganisms have developed resistance to available antibiotics in the market. 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 antihyperglycemic, anti-inflammatory, bactericidal, fungicidal etc. The reported potential activities of "glitazones" initiated to synthesize N-substituted-2,4-TZD derivatives with good antimicrobial activity. Swapna D et al (1).

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

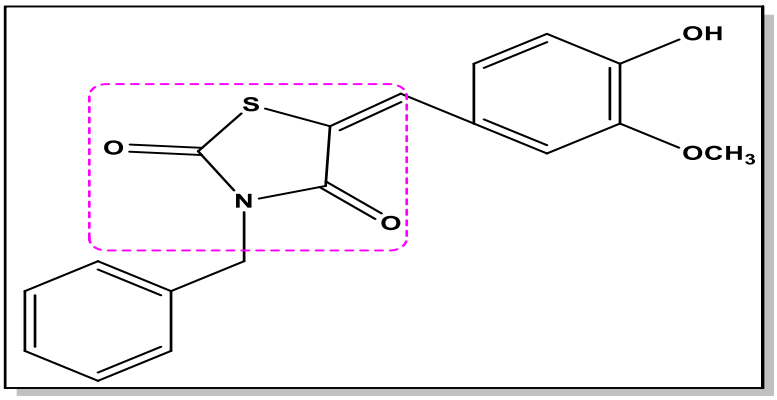

Fig. (3). Antimicrobial Agent

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Anti-Hyperglycmic Property

Diabetes is a chronic metabolic syndrome which relates to impaired insulin secretion and peripheral insulin resistance. It consists of an array of dysfunctions characterized by hyperglycaemia as its initial symptoms which when left unnoticed leads to vascular diseases, nephropathy, vascular neuropathy, cardiovascular diseases etc. Categorized 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 changes in lifestyle and proper medications. thiazolidinediones (Glitazones) introduced in late 1990's are orally acting hypoglycaemic agents which have attracted attention round the globe because of their diverse biological profile showing anti-hyperglycaemic, anti-tumour, anti-oxidant, anti-malarial, anti-obesity & anti-microbial activities. TZD's acts as specific 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. Being an important molecular target; it is further classified as PPAR-a (NR1C1), PPAR-d (NR1C2) & PPAR-c (NR1C3) among which 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. In spite of its excellent anti-diabetic action, TZD derivatives also possess undesirable side effects including weight gain, edema, anaemia, bone deformities. Being with a specified & well-planned objective, it's still a challenge for medicinal chemists to avoid their undesirable effects while retaining the hypoglycaemic property of TZD derivatives. M.J. Naim et al. (6)

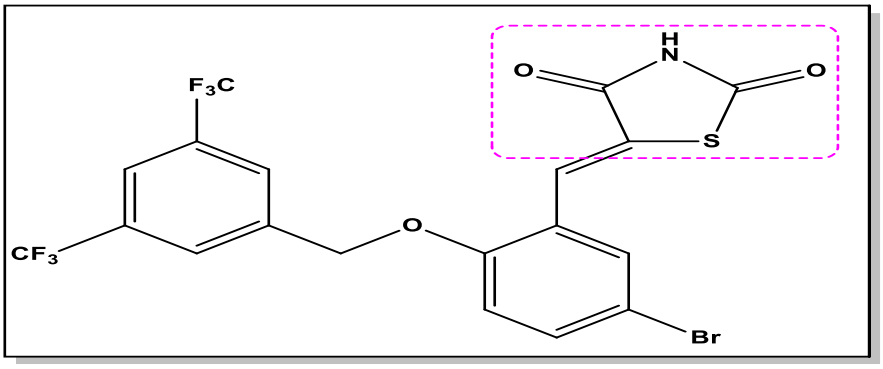

Fig. (4). Anti-Hyperglycaemic Agent

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Anti-Oxidants Properties

Antioxidants are the substances, which when present at low concentrations compared to those of an oxidisable substrate, significantly delay or prevent oxidation of that substrate. The key role of antioxidants is to intercept and react with free radicals so that cascade effect of ROS propagation is prevented by readily donating its proton to the ROS (Reactive Oxygen Species). The antioxidant property of a compound is attributed to its ability of Inhibiting cellular Microsomal P-450 linked Mixed Function oxidation (MFO) reaction, Oxygen radical scavenging, Suppressing the formation of ROS. *In vitro* antioxidant activity of the synthesized compounds was quantitatively measured by DPPH radical scavenging assay. DPPH (2, 2-diphenyl 1-picrylhydrazyl) is a stable free radical at room temperature and accepts an electron or hydrogen radical to become stable diamagnetic molecule. DPPH radical is scavenged by antioxidants through the donation of protons forming the reduced DPPH. 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)

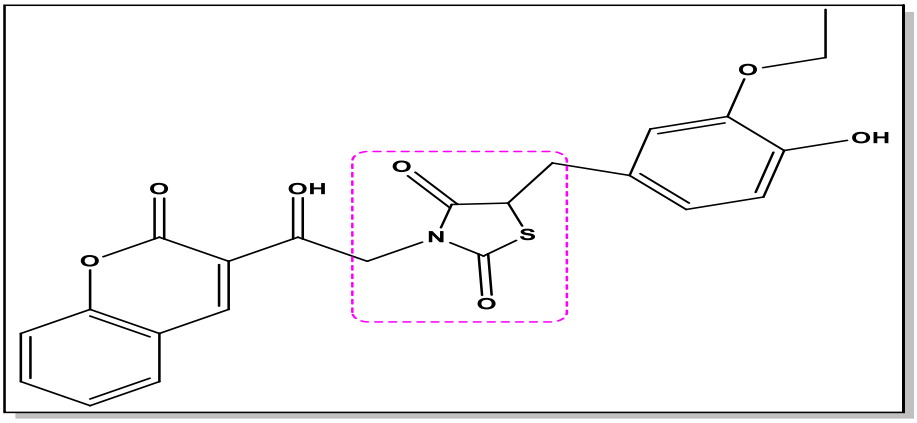

Fig. (5). Antioxident Agent

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LITRATURE REVIEW

1.Swapna D, Rajitha G et al. (1) synthesize a new series of mannich bases of thiazolidine-2,4-diones. A new series 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 structure of these two compounds was established by IR,1H NMR and Mass spectrosopy. The synthesized mannich bases of thiazolidine-2,4-diones were subjected to 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 sstandard drugs streptomycin and griseofulvin. Molecular docking studies showed the compound 3h showed good docking score of -5.419 with target 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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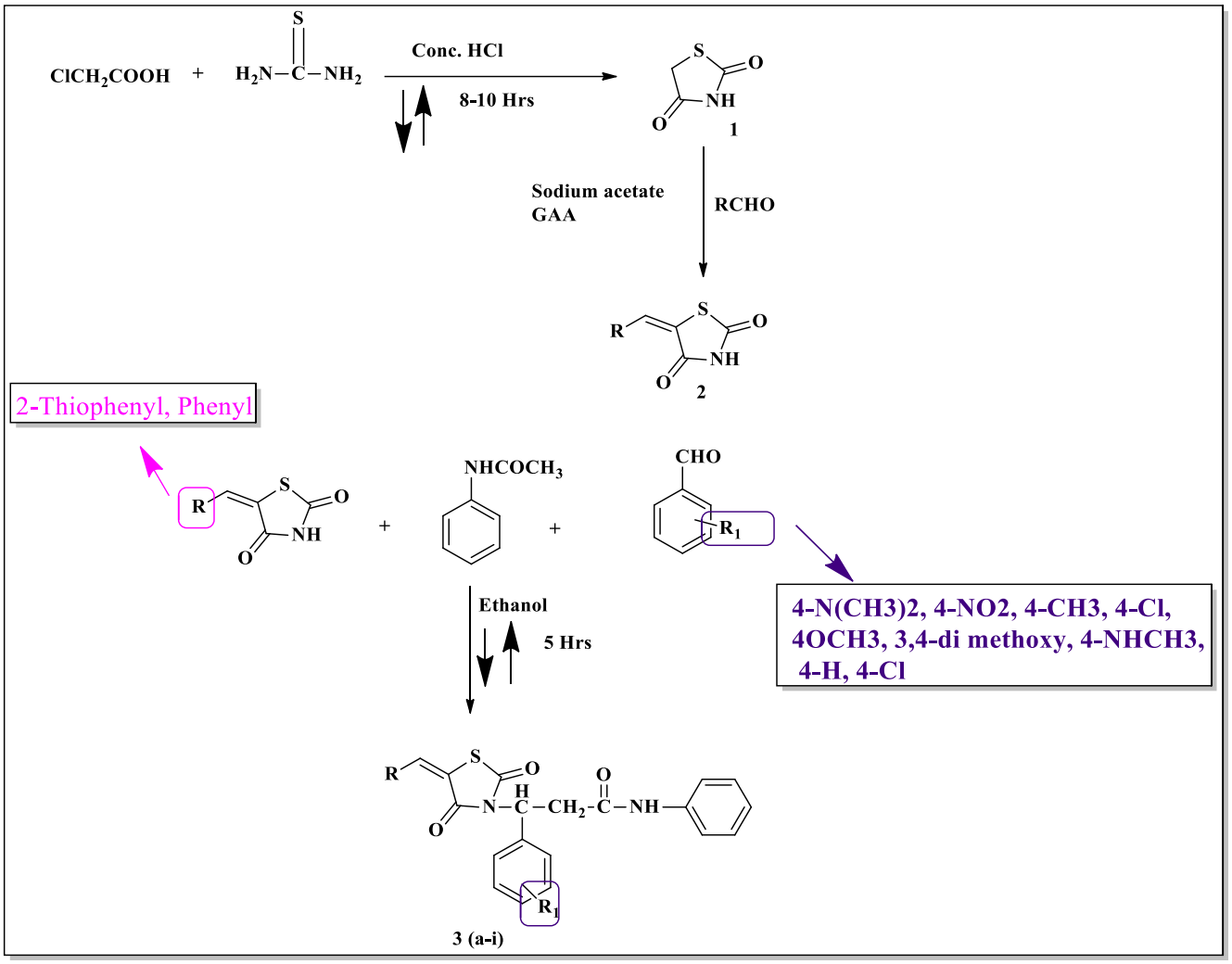

Fig. (6) Schematic Representation of Mannich Bases of Thiazolidine-2,4-Diones

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. Different spectral techniques (1H-NMR, IR, MS etc.) were used to confirm the chemical structures of the synthesized analogues. These synthesized compounds were screened for their antioxidant and antimicrobial potential.

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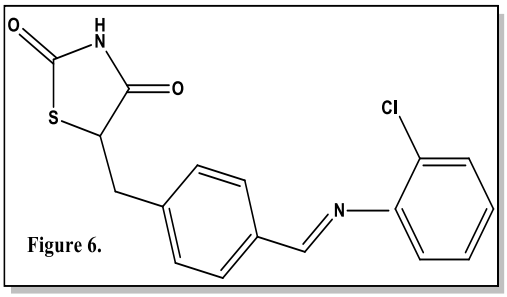

Fig. (7). 5-((E)-4-((E)-((2-Chlorophenyl) Imino) Methyl) Benzylidene) Thiazolidine -2,4-Dione

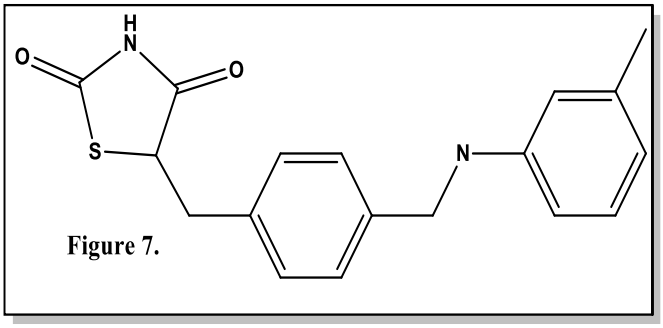

Fig. (8). 5-((E)-4-((E)-(M-Tolylimino) Methyl) Benzylidene) Thiazolidine-2,4-Dione

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

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

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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.

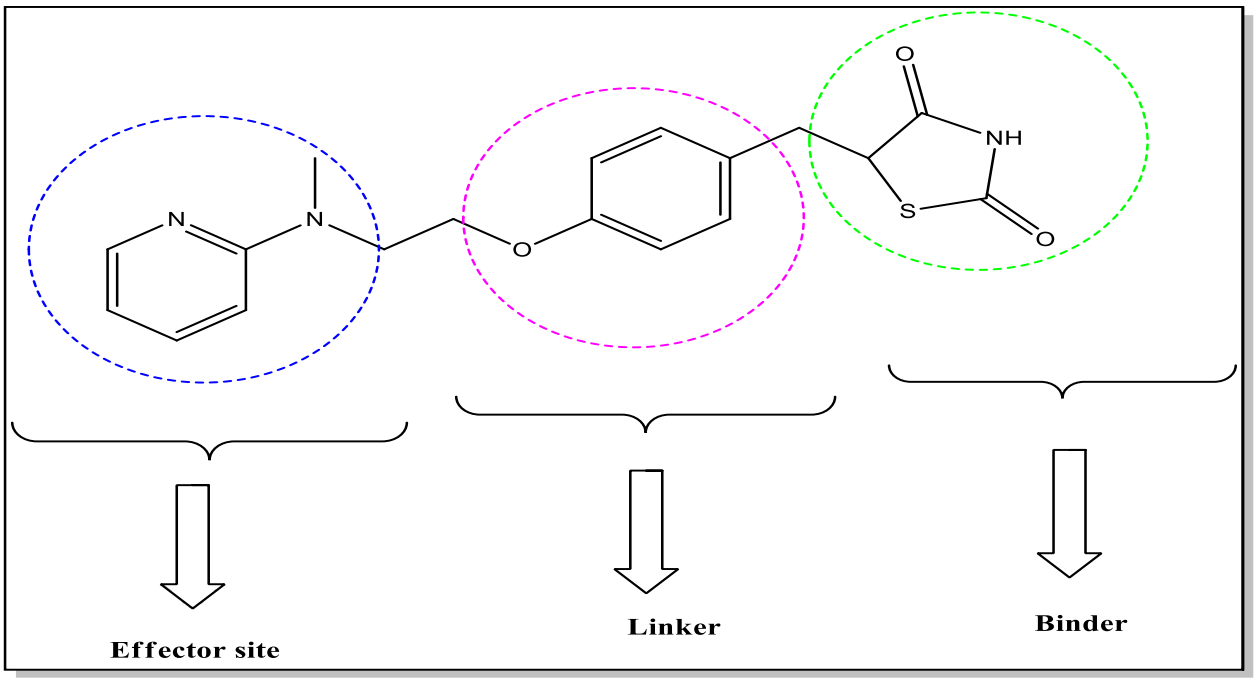

Fig. (9). Three Regions of Thiazolidinediones Based Upon QSAR Study of Various Anti-Diabetic Compounds.

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. 11 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 those 4 compounds (6c, 6e, 6m & 6n) showed significantly good antidiabetic activity in comparison to rosiglitazone and pioglitazone as reference drugs. Compound 6c appeared as the most potent derivative in lowering blood glucose level and showed excellent interaction with SER 342, ILE 281, pi-pi interaction with ARG 288 and halogen bond interaction with LYS 367. Further, PPARc transactivation and gene expression studies of compound 6c were carried out to investigate the possible mechanism of action through PPARc

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modulation. Compound 6c exhibited 53.65% transactivation and elevated PPARc gene expression by 2.1 folds. The biochemical parameters (AST, ALT and ALP levels) were found within the range with no noteworthy damage to liver.

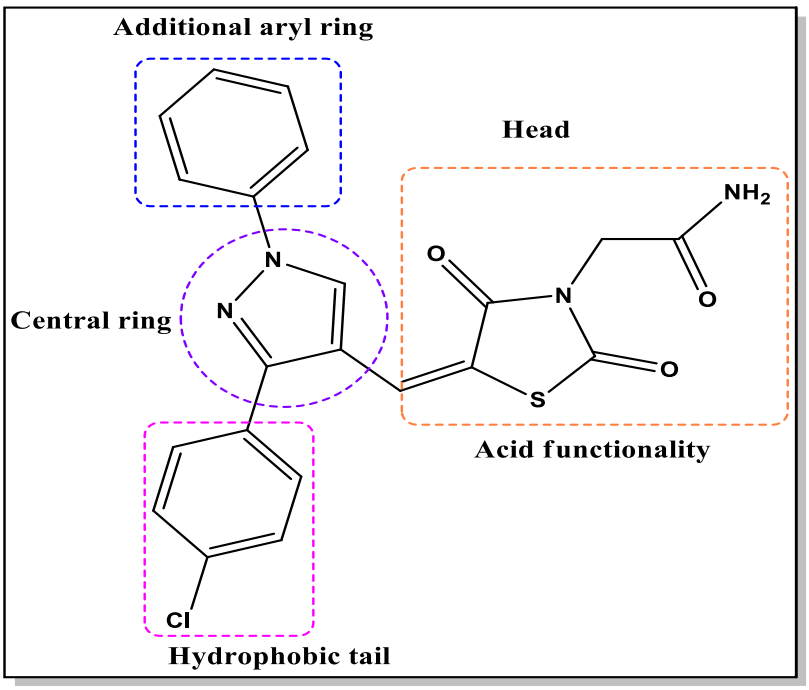

Fig. (10). Designed Molecule.

5.Fawad Naeem et al. (7) works on 2,4-Thiazolidinedione and its derivatives exhibit a variety of pharmacological activities including antidiabetic, antiviral, antifungal, anti-inflammatory, anti-cancer and aldose reductase inhibitory activities. Keeping in mind the pharmacological potential of 2,4-Thiazolidinedione derivatives as antidiabetic agents, seven arylidene derivatives of 2,4-thiazolidinedione 1(a-g) and four corresponding acetic acid derivatives 2(a-d) have been synthesized by a three-step procedure.

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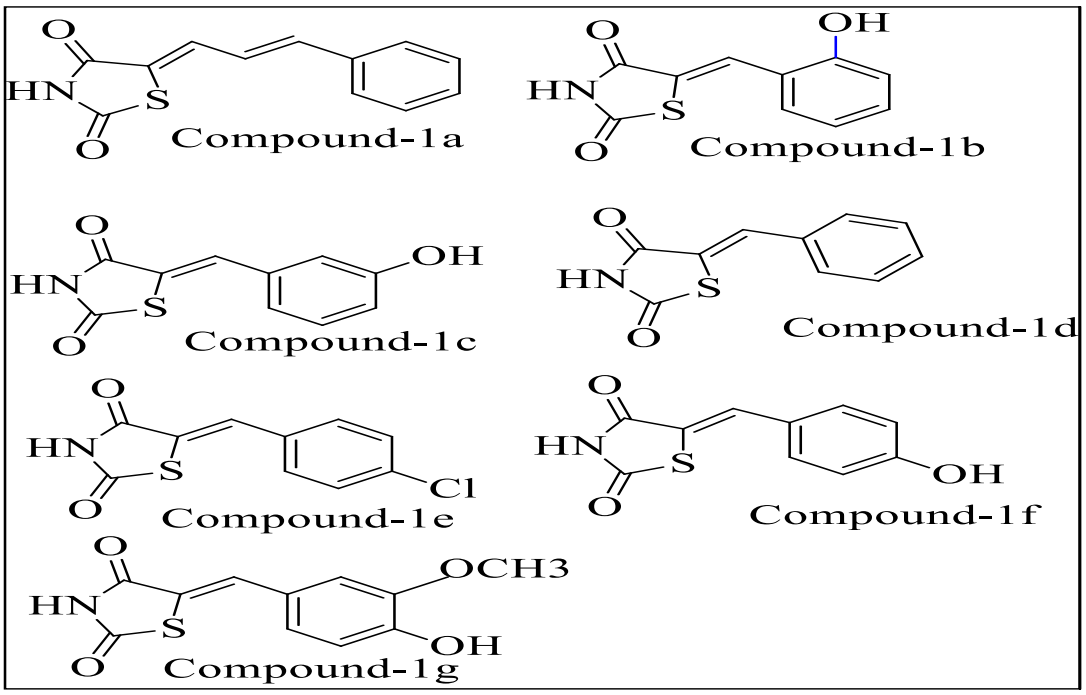

Fig. (11). Chemical Structures of The Compounds 1(a-g).

6. Tamer Nasr et al. (10) works on microbial resistance to the available drugs poses a serious threat in modern medicine. They report the design, synthesis and in vitro antimicrobial evaluation of new functionalized 2,3-dihydrothiazoles and 4-thiazolidinones tagged with sulfisoxazole moiety. Compound 8d was most active against Bacillis subtilis (MIC, 0.007 mg/mL). Moreover, 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). 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 hand, compounds 7e and 9c were fourfolds more active than amphotericin B against Syncephalastrum racemosum. Molecular docking studies showed that the synthesized compounds could act as inhibitors for the dihydropteroate synthase enzyme (DHPS). This study is a platform for the future design of more potent antimicrobial agents.

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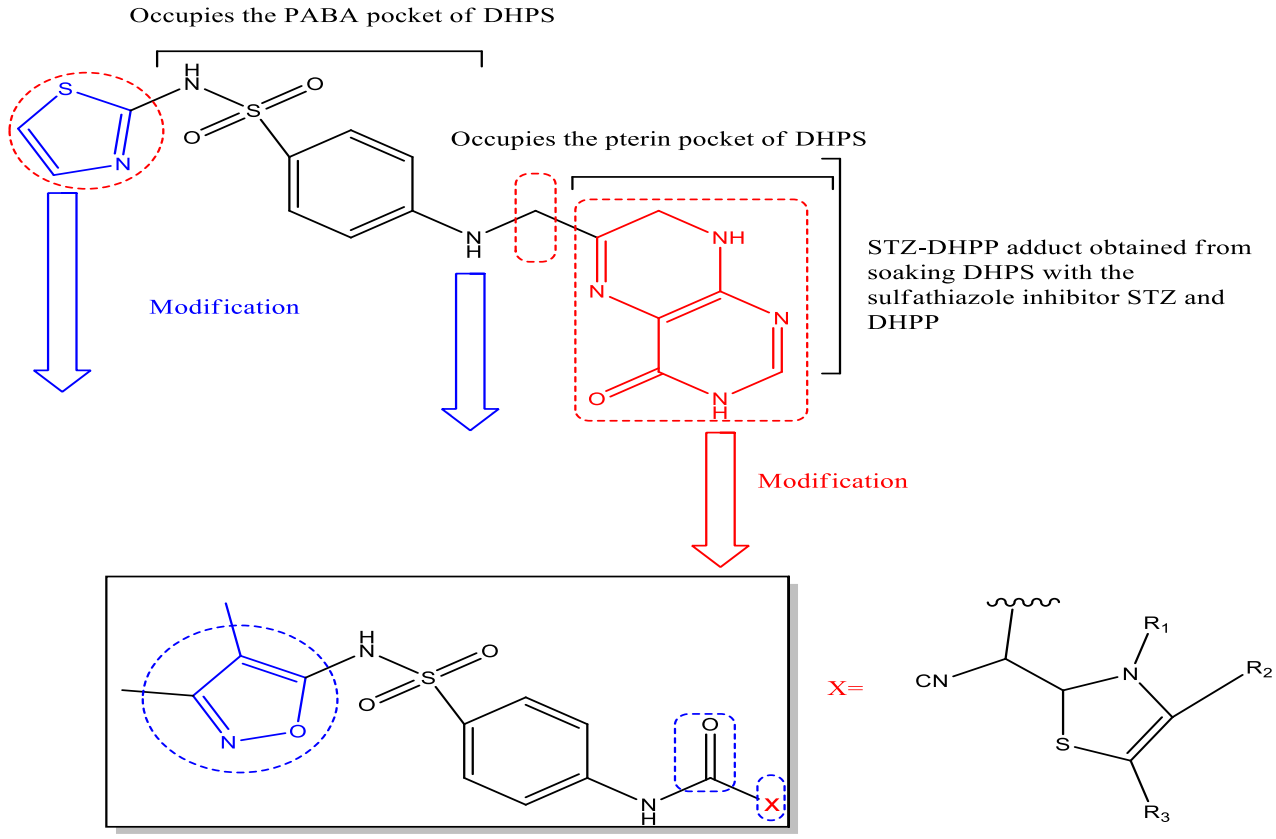

Fig. (12). Design of Thaizole Derivatives Bearing Sulfisoxazole Moiety as DHPS Inhibitors.

7. Marc et al. (13) works on the series of 12 new thiazolidine-2,4-dione derivatives were obtained by microwave-assisted synthesis. All compounds were physicochemically characterized by quantitative elemental *C, H, N, S* analysis and spectral data (mass spectrometry [MS], infrared [IR], and nuclear magnetic resonance [NMR]), with the results being in agreement with the expected data. An in vitro screening performed on *Candida albicans* ATCC 10231 showed their moderate antifungal activity, which was further investigated by determining the minimum inhibitory concentration and minimum fungicidal concentration values for the most active compounds on four strains of *Candida*. The molecular docking studies, performed against a fungal lanosterol 14α-demethylase, emphasized the importance of different molecular fragments in the compounds' structures for their antifungal activity. The synthesized compounds were subjected to in silico screening for the prediction of their absorption, distribution, metabolism,

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excretion, and toxicity (ADMET) and molecular properties. The results of the antifungal activity assays, docking study, and ADMET predictions revealed that the synthesized compounds are potential anti-*Candida* agents that might act by interacting with the fungal lanosterol 14α-demethylase and could be further optimized and developed as antifungal agents.

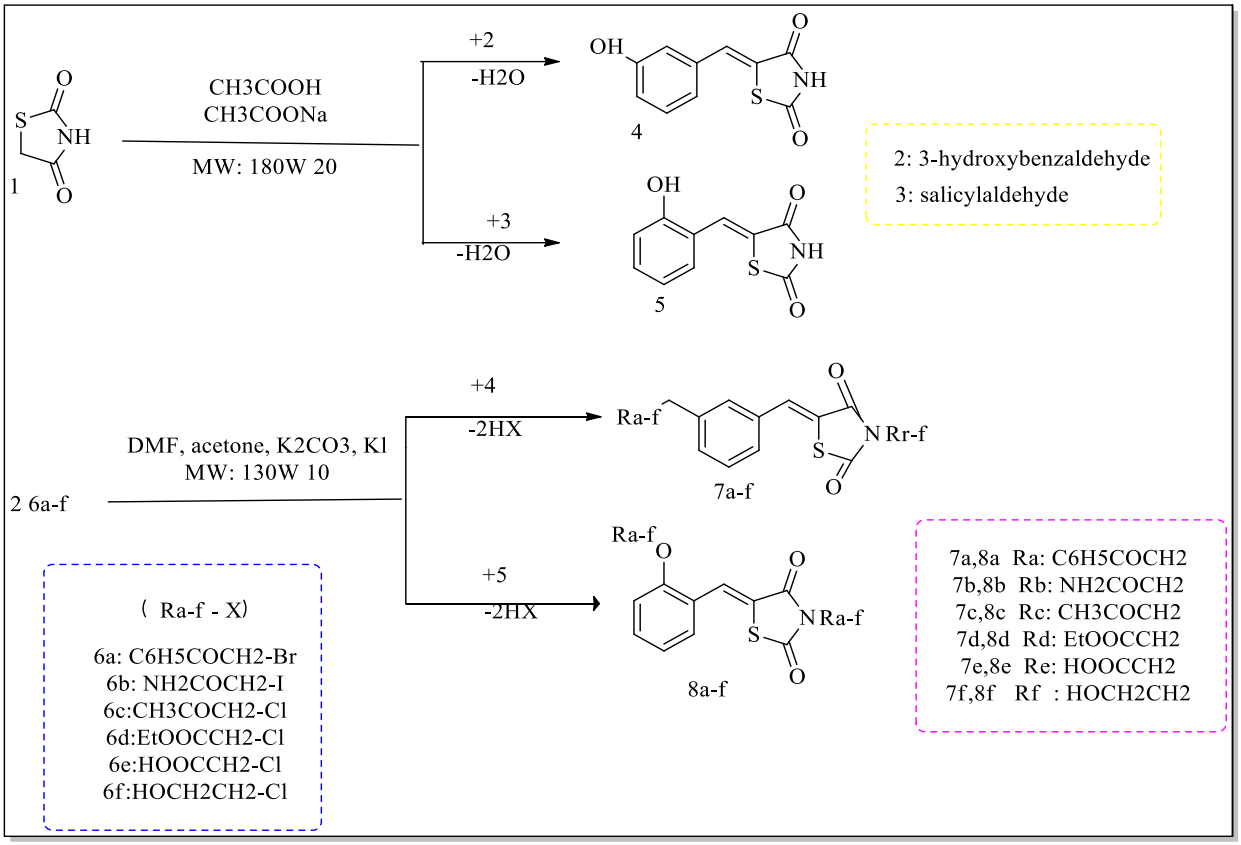

Fig. (13). Route Followed in Order to Obtain the Thiazolidine- 2,4-Dione Derivatives 7a–f and 8a–f.

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 anticancer activity.

9. K. Srikanth Kumar et al (29) works on Various thiazolidine-2,4-dione derivatives 3a-l possessing indole moiety were designed, synthesized using appropriate conventional heating as well as microwave irradiation methods. All the synthesized compounds were

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characterized physically and spectrally. The compounds were evaluated for in vitro antibacterial activity, in vitro antioxidant activity and in vivo hypoglycemic activity in relation to the standard drugs. Most of the new compounds exhibited moderate activity and some showed considerable activity. Molecular docking studies were carried out using AutoDock software and revealed that compound 3b has significant binding interaction with PPARg receptor compared with the standard ligand Rosiglitazone.

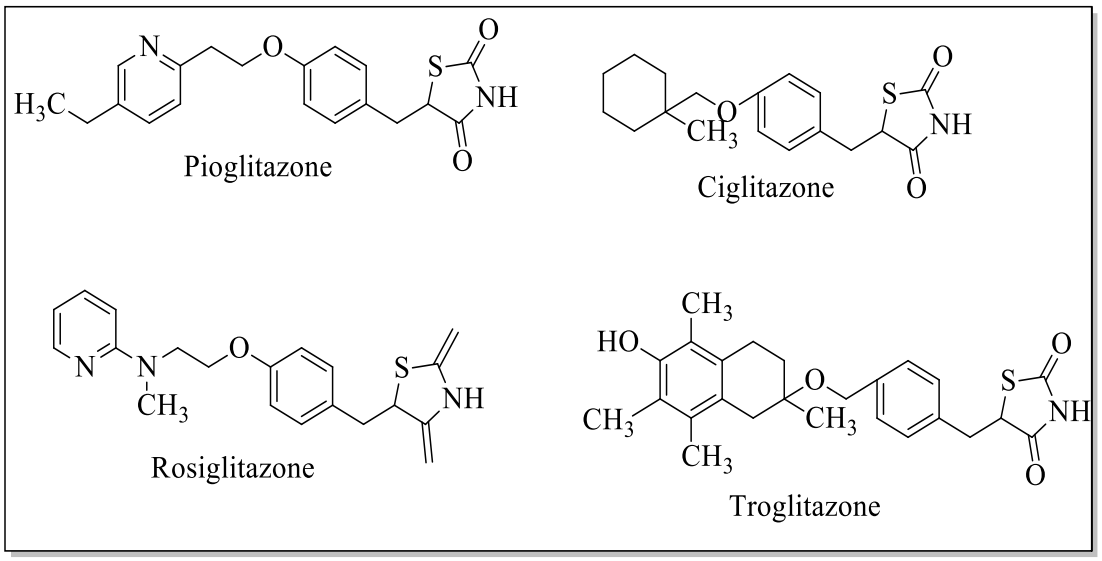

Fig. (14). Structures of Pioglitazone, Rosiglitazone, Ciglitazone and Troglitazone

10. Syed Nazreen et al. (20) studied on new thiazolidine-2,4-dione hybrids were designed and synthesized as potential peroxisome proliferator-activated receptor (PPAR)-γ agonists and thymidylate synthase inhibitors. All the synthesized compounds follow Lipinski's and Veber's rules and possess the desired pharmacokinetics properties. The PPAR-γ transactivation results displayed that compound **12** (78.9%) and **11** (73.4%) were the most active compounds and they increased PPAR-γ gene expression by 2.2- and 2.4-fold, respectively. Compounds **12**, **11**, and **8** showed promising cytotoxicity, with IC_{50} values ranging from 1.4 to 4.5 µM against MCF-7 cells and from 1.8 to 8.4 µM against HCT-116 cells. Compounds **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

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thymidylate synthase inhibitors. Finally, molecular docking studies supported the in vitro biological activity results.

11. Lamia H.T. Amine et al. (21) studied that cancer is a perplexing and challenging problem for researchers. In this study, a series of 6-aryl-5-cyano-pyrimidine derivatives were designed, synthesized and evaluated for their anticancer activity against HePG-2, MCF-7 and HCT-116 cell lines. Compounds **2, 3d, 4a-c**, **5, 8** and **12** displayed high anticancer activity, comparable to that of 5-fluorouracil. Additionally, those compounds with effective anticancer activity were further assessed for their ability to inhibit thymidylate synthase (TS) enzyme. All the tested compounds demonstrated a marked TS inhibitory activity (33.66–74.98%), with IC_{50} ranging from 3.89 to 15.74 nM. Moreover, apoptosis studies were conducted on the most potent compound **8**, to evaluate its proapoptotic potential. Interestingly, 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 between the active compounds and the thymidylate synthase active site.

12. Malihe Akhavan et al. (22) studied that the magic scaffolds rhodanine and thiazolidine are very important heterocyclic compounds in drug design and discovery. Those are important heterocyclic compounds that have attracted a great deal of attention due to the fact that they exhibit a variety of bioactivities including antibacterial, antifungal, antiviral, antimalarial, and anti-inflammatory activities. These agents often exhibit selective toxicity. The goal of this study was molecular docking, green and solvent-free efficient synthesis of a new series of hetero/aromatic substituted rhodanine and thiazolidine analogues and then investigation of their antimicrobial activity.

13. Sergio Hidalgo-Figueroa et al. (23) This work presents the synthesis of two hybrid compounds (**1** and **2**) with thiazolidine-2,4-dione structure as a central scaffold which were further screened *in combo* (*in vitro* as PTP-1B inhibitors, *in vivo* antihyperglycemic activity, *in silico* toxicological profile and molecular docking). Compound **1** was tested in the enzymatic assay showing an IC_{50} = 9.6 ± 0.5 μM and compound **2** showed about a 50% of inhibition of PTP-1B at 20 μM. Therefore, compound **1** was chosen to test its antihyperglycemic effect in a rat model for non-insulin-dependent diabetes mellitus

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(NIDDM), which was determined at 50 mg/kg in a single dose. The results indicated that compound showed a significant decrease of plasma glucose levels that reached 34%, after a 7 h post-administration. Molecular docking was employed to study the inhibitory properties of thiazolidine-2,4-dione derivatives against Protein Tyrosine Phosphatase 1B (PDB ID: 1c83). Concerning to the two binding sites in this enzyme (sites A and B), compound **1** has shown the best docking score, which indicates the highest affinity. Finally, compounds **1** and **2** have demonstrated an in silico satisfactory pharmacokinetic profile. This shows that it could be a very good 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 derivatives were synthesized in excellent yield using OxymaPure/N, N0-diisopropylcarbodimide coupling methodology and were characterized by chromatographic and spectrometric methods, and elemental analysis. The antimicrobial and antifungal activity of these derivatives was 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.

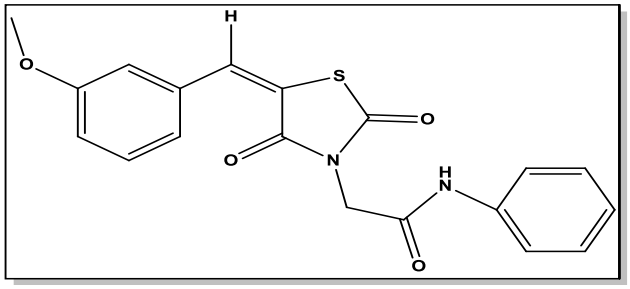

Fig. (15). Structure of Compound 4b.

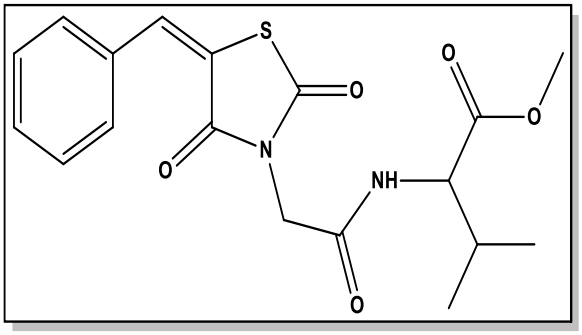

Fig. (16). Structure Of Compound 5g.

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

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

16. Mohamed A. Abdelgawad et al (12) Substituted thiazolidinone linked to benzothiazoles and benzoxazoles 3a, b or substituted 5-benzylidene-4- thiazolidinones 4a-h were synthesized. The antitumor activity of the prepared compounds was evaluated against human breast MCF7 and liver HEPG2 cancer cell lines using Sulphorhodamine-B (SRB) assay method, doxorubicin was used as a reference standard. Most of the tested compounds showed potent antitumor activity especially the pmethoxy- 5-benzylidine-4-thiazolidinone derivative of benzoxazole 4c and benzothiazole 4d, their IC50 against liver HEPG2 cancer cell line are 0.027 nM and 0.026 nM respectively. The IC50 of p-chloro-5 benzylidine-4- thiazolidinone linked to benzoxazole 4e against breast MCF7 cancer

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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 lines, its IC50 is 36 and 48 nM respectively. The most active compounds were docked against VEGFR-2 using Moe program and 1Y6A (pdb file) to investigate if these compounds had a similar binding mode to VEGFR-2 inhibitors.

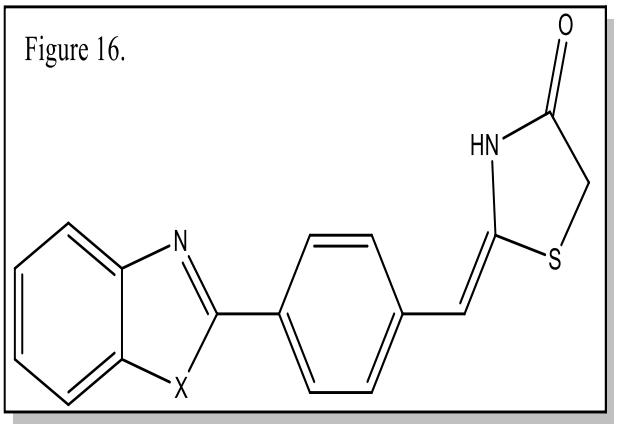

Fig. (17). Synthesize A Series of Substituted Benzothaizoles/Benzoxazoles to Be Linked onto 4-Thiazolidinone

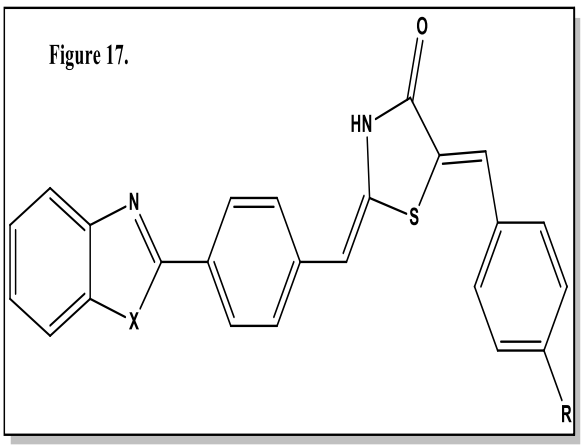

Fig. (18). Substituted 5-Benzylidine-4-Thiazolidinones.

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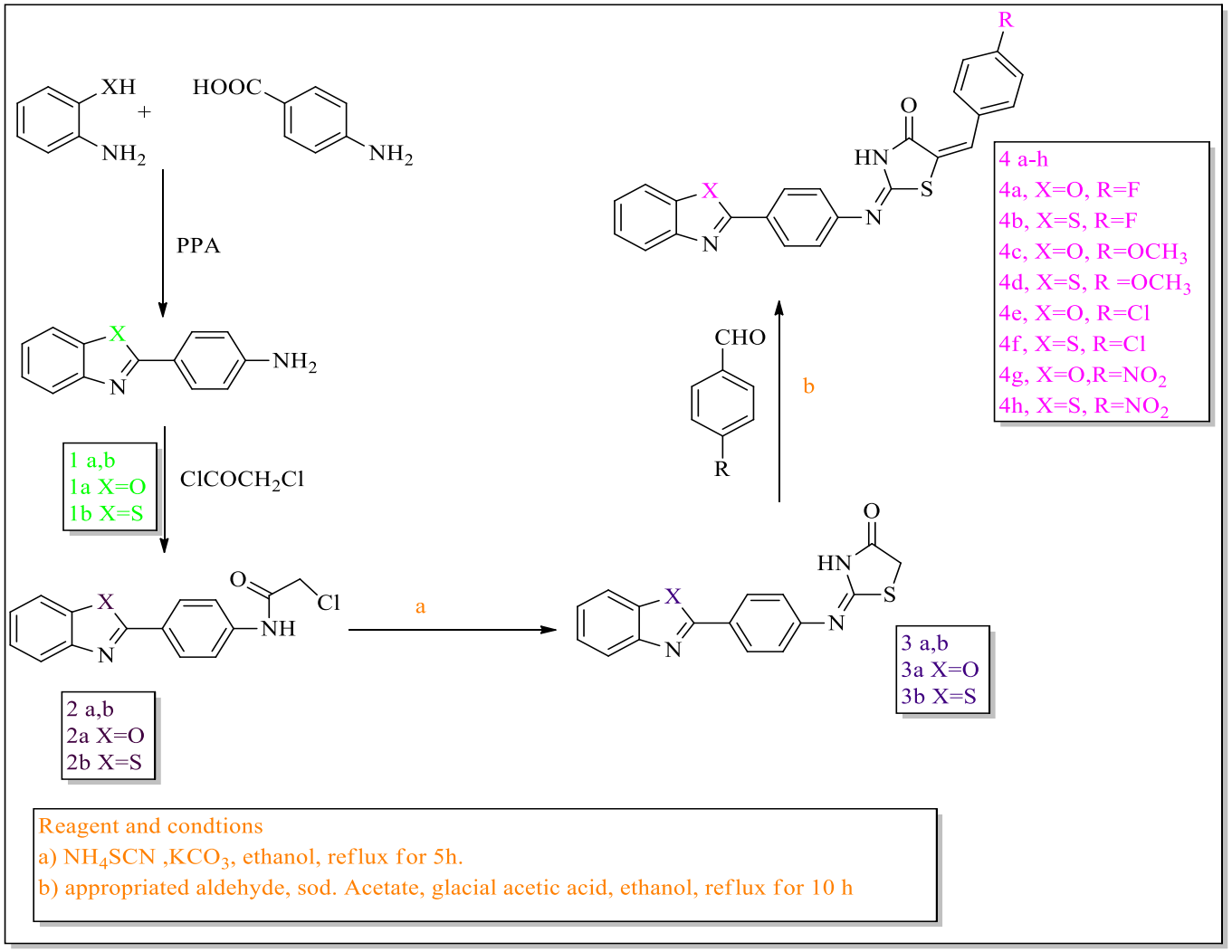

Fig. (19). Synthesis of Compounds 3a, b and 4a-h.

17. Thirumalaswamy Kottha et al. (15) studied on the series of naphthalene-based hybrid heterocyclics were designed and synthesized by the replacement of benzene ring with napthalene on 4-substituted *4H*-chromenes. As a part of our continuous efforts in accessing the bioactive compounds by using simple techniques, we report the synthesis of azolidinedione/thiazolidinediones tethered 4-substituted benzo[f] chromene derivatives under greener reaction conditions and *in silico* evaluation of anticancer activity. Docking studies showed that the synthesized compounds exhibit good predicted binding affinities at the colchicine binding site of tubulin.

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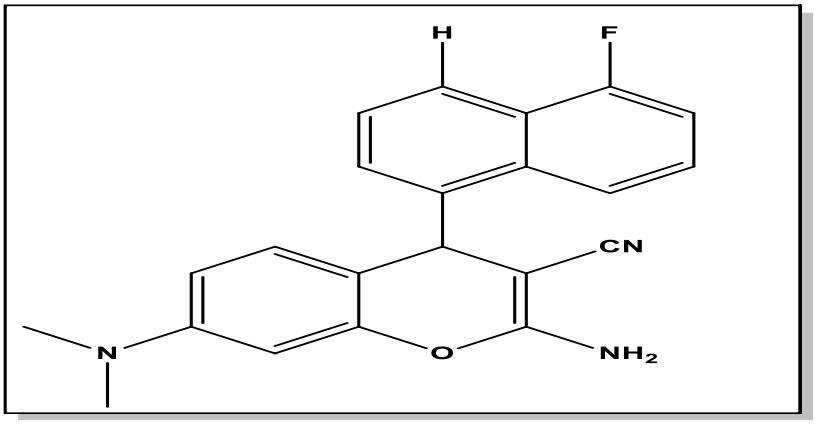

Fig. (20). Naphthalene Tethered 4-Substituted-4*H*-Chromene Analogue.

18. Metta Madhuri et al. (17) studied on Molecular docking study was performed on a series of 24 Thiazolidinediones MM1-MM24 as potential epiderma1 growth factor receptor (EGFRR) inhibitors. The docking technique was 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 clearly predicted the binding mode that is nearly similar to the crystallographic binding mode with 1.34Ao RMSD. Based on the validations and hydrogen bond interactions made by R substituents were considered for evaluation. The results avail to understand the type of interactions that occur between thiazolidinediones with 1M17 binding site region and explain the importance of R substitution on thiazolidinedione basic nucleus.

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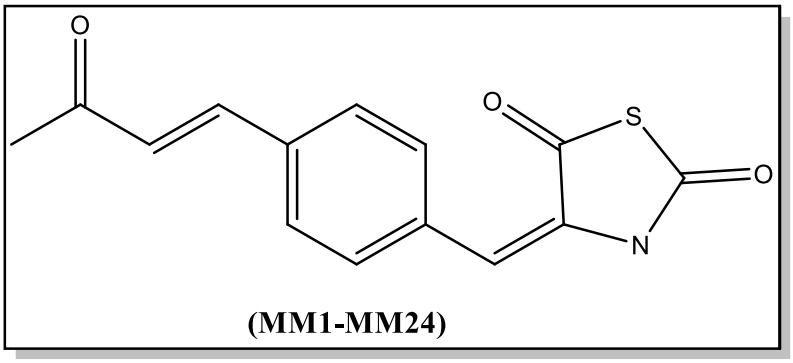

Fig. (21). Structure of 24 Thiazolidinediones MM1-MM24.

19. Yuichi Sawaguchi et al. (18) Works on Pim kinases. Pim kinase are overexpressed in various types of hematological malignancies and solid carcinomas, and promote cell proliferation and survival. Here in this study, we investigated the preclinical profile of novel pan-Pim kinase inhibitors with imidazopyridazine and thiazolidinedione structure. Imidazopyridazine-thiazolidinediones inhibited activities of Pim kinases with IC50 values of tens to hundreds nanomolar. With YPC-21440 and/or YPC-21817, which exhibited especially high inhibitory activities against Pim kinases, we investigated in vitro and in vivo activities of imidazopyridazine-thiazolidinediones. In silico analysis of binding mode of YPC-21440 and Pim kinases revealed that it directly bound to ATP-binding pockets of Pim kinases. In the kinase panel tested, YPC-21440 and YPC-21817 were highly specific to Pim kinases. These compounds exerted antiproliferative activities against various cancer cell lines derived from hematological malignancies and solid carcinomas. Furthermore, they suppressed phosphorylation of Pim kinase substrates, arrested cell cycle at the G1 phase, and induced apoptosis in cultured cancer cells. In tumor xenograft models, YPC-21440 methanesulfonate and YPC- 21817 methanesulfonate exerted antitumor activities. Furthermore, pharmacodynamic analysis with a xenograft model suggested that YPC-21817 methanesulfonate inhibited Pim kinases in tumors. In conclusion, our data revealed that imidazopyridazine-thiazolidinediones are novel Pim kinases inhibitors, effective on various types of cancer cell lines both in vitro and in vivo.

20. Nadine Uwabagira et al. (19) studied on the compound 3-{[(2,3-Dichlorophenyl) amino] methyl}-5-(furan-2-ylmethylidene)-

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1,3- thiazolidine-2,4-dione has been designed, synthesized, and screened for its in vitro anti breast cancer activity, using human breast adenocarcinoma cell lines (MCF-7) and in vitro anti-inflammatory activity. By hemolysis assay, it showed that it has a nonhemolytic and nontoxic e_ect on human blood cell. The title compound 5, subjected to in vitro activities, showed that it is cytotoxic with an IC50 of 42.30 _M and a good anti-inflammatory agent. The docking results against cyclin dependent kinase 2 (CDK2) (PDB ID: 3QQK) gave insights on its inhibitory activity.

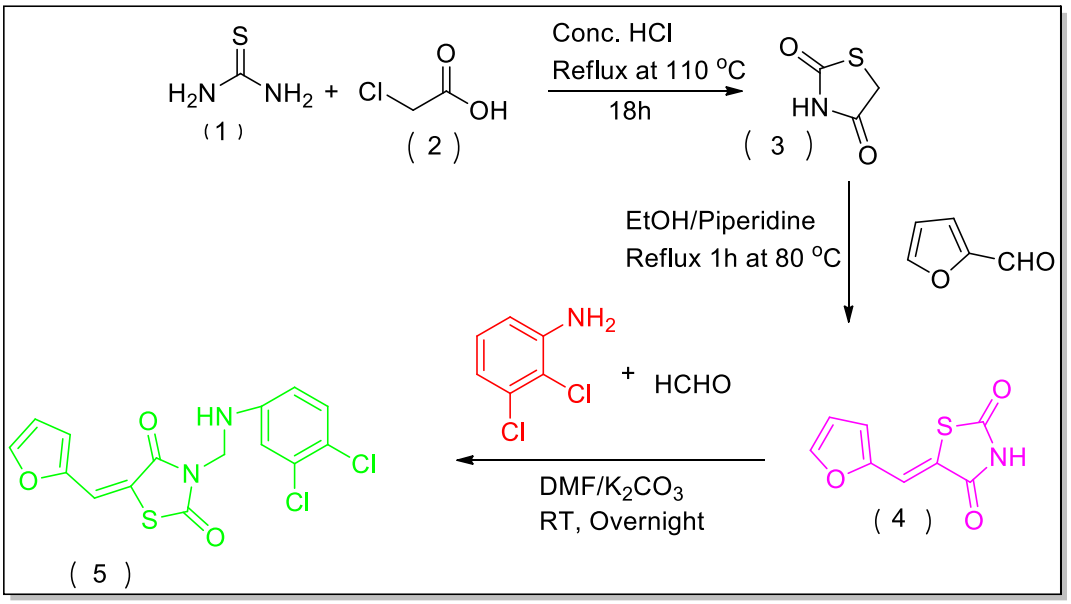

Fig. (22). The Synthesis of 3-{[(2,3-Dichlorophenyl) Amino] Methyl}-5-(Furan-2-Ylmethylidene)-1,3- Thiazolidine-2,4-Dione.

Sethi Navjot et. al (2020) Literature studies also revealed that the attachment of more heterocyclic rings, containing nitrogen on 5th position of 2,4-TZD, can enhance the antimicrobial activity. Hence, attachment of various moieties on the benzylidene ring may produce safe and effective compounds in the future and antibacterial activity.

The *in vitro* cytotoxicity studies were performed for human breast cancer (MCF-7) and human lung cancer (A549) cells and HepG2 cell-line and compared to standard drug doxorubicin by MTTassay. Antimicrobial activity of the synthesized 2,4-thiazolidinediones derivatives was carried out using the cup plate method with slight

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modification. The results obtained showed that derivatives with heterocyclic ring like benzimidazole and Aromatic amine group exhibited good antiproliferative activity against A549 cancer cell-line, whereas derivative with Phenolic group exhibited moderate antiproliferative activity against HepG2 cell-line when compared to standard drug doxorubicin.

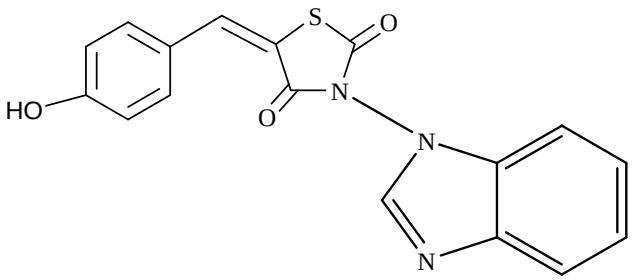

Fig. (23) 2,4-TZD Derivative with Benzimidazole Ring

CONCLUSION

In recent past, a variety of molecules base on thiazolidinedione have been evaluated and synthesized to improve its pharmacological activity. Due to wide range of pharmacological activities and clinically used 2,4-thiazolidinediones, these molecules have attracted much attention and encouraged the chemists and biologists to be extensive investigations or molecular manipulations, and as a result further improved protocol with better observation is still under progress. 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 compounds formation. The results of this work

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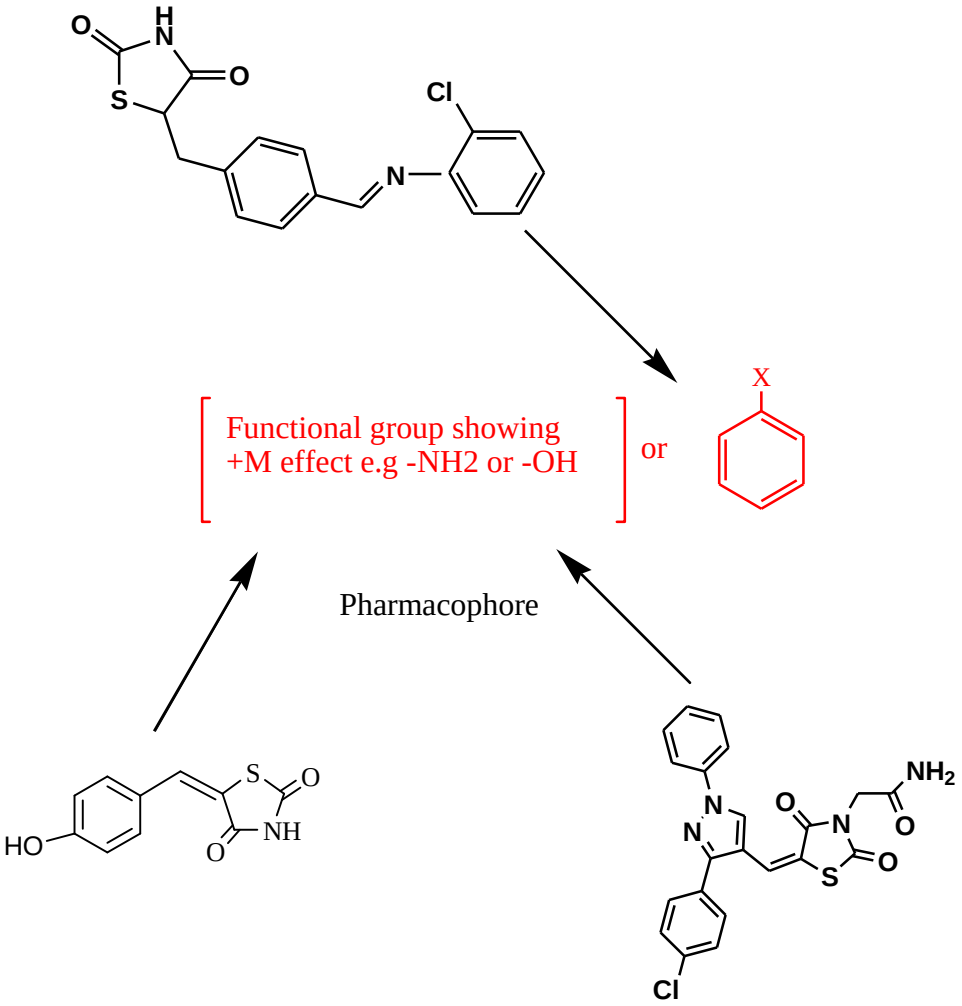
indicate efficient computational tools are capable of identify potential ligand.



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