Drug Design, In Silico-Profiling of New Pyrrole Derivatives: Promising Anticancer Agents Against Acute Myeloid Leukemia

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Abstract:

Molecular docking simulation and synthesis of five compounds of N2, N4-bis (2-(4-substituted phenyl)-4-oxothiazolidin-3-yl)-3,5-dimethyl-1H-pyrrole-2,4-dicarboxamide was carried out to evaluate their theoretical binding affinities, targeting acute myeloid leukemia (AML). The chemical structure of the molecules was accurately drawn using ChemDraw Professional 19.1 software.

The designed compounds were evaluated for their selectivity towards FLT3's ATP pocket (PDB ID:6JQR) in comparison with the reference ligand (Gilteritinib) by using GOLD suite from the Cambridge Crystallographic Data Centre (CCDC) software (Version 2021.2.0). All the designed compounds exhibited good binding energies with the receptor active pocket and had promising activity. Compounds **2E** and **3E** showed the highest PLP Fitness (83.30, 80.86 respectively) and it is higher than that of Gilteritinib (71.91). In-silico ADME and drug-likeness studies were performed by using the Swiss ADME server. The results showed that most of the designed compounds expected to be absorbed from the GIT. Compounds **2B-E** have high expected GI absorption. All the investigated compounds have no predicted BBB penetration. Additionally, compounds **2A, 2C, 2D**, and **3A** are not a substrate to P-gps which may indicate a lower expected incidence of resistance by cancer cells in vitro studies. Finally, all of the investigated compounds are not considered to inhibit CYP1A2 enzyme, except for compounds **2A** and **3D**.

Key words: in silico-profiling, pyrrole derivatives, Schiff bases, thiazolidinones, acute myeloid leukemia

التصميم الدوائي وتحديد السمات الحاسوبي لمشتقات البيرول الجديدة: عوامل واعدة لمكافحة سرطان الدم النخاعي الحاد

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الخلاصة:

تم اجراء محاكاة الالتحام الجزيئي لخمسة مركبات من N2,N4-bis (2-(4-substituted phenyl) -4-(oxothiazolidin-3-yl) -3,5-dimethyl-1H-pyrrole-2,4-dicarboxamide لتقييم الميول النظري للارتباط الخاص بها لاستهداف سرطان الدم النخاعي الحاد. تم رسم التركيب الكيميائي للجزيئات بدقة باستخدام برنامج ChemDraw

19.1 الاحترافي وتم تقييم المركبات المصممة من حيث انتقائها لجيب ادينوسين ثلاثي الفوسفات الخاص ب FLT3 (معرَف بنك معلومات البروتينات: JQR٦) بالمقارنة مع دواء Gilteritinib كمصدر مرجع (Gilteritinib) باستخدام مجموعة GOLD من برنامج مركز كامبريدج للبيانات البلورية (CCDC) (الإصدار ٢٠٢١,٢,٠). أظهرت جميع المركبات المصممة طاقات ربط جيدة مع الجيب النشط للمستقبل وكان لها نشاط واعد. أظهر المركبان (E٢) و (E٣) أعلى مستوى للفاعلية PLP (٨٣,٣٠، ٨٠,٨٦ على التوالي) وهو أعلى من مركب Gilteritinib (٧١,٩١). تم اجراء الدراسات الحاسوبية الخاصة ب (الامتصاص والتوزيع والتمثيل الغذائي والإفراز (ودراسات مشابَهَة الادوية باستخدام خادم Swiss ADME وأظهرت النتائج أن معظم المركبات المصممة يتوقع امتصاصها من الجهاز الهضمي. تحتوي المركبات (B٢) و (E٢) نسبة عالية من الامتصاص المتوقع بالجهاز الهضمي. جميع المركبات التي تم فحصها ليس لها اختراق متوقع لحاجز الدم في الدماغ. بالإضافة لذلك المركبات (A٢) و (C٢) و (D٢) و (A٣) ليست مادة أساس للبروتينات السكرية الناقلة (P-GPS) مما قد يشير إلى انخفاض متوقع لمقاومة الخلايا السرطانية في الدراسات المختبرية. أخيرًا، لا تعتبر جميع المركبات التي تم فحصها مثبطًا لإنزيم الكبد CYP1A2، باستثناء المركبات (A2) و (D٣).

الكلمات المفتاحية: تحديد السمات الحاسوبي، مشتقات البيرول، قاعدة شف، ثايازوليدينون، سرطان النخاع الحاد.

Introduction

Cancer is the world's second significant cause of death. Overall, the incidence of cancer is growing. As a result, cancer is a severe issue that affects the health of all human communities. Unfortunately, it is a tissue-level variety disorder, and this variation is a big problem for its particular diagnosis, followed by therapy effectiveness [1]. Tumors are uncontrolled cell growth, some of which may be benign, when tumor cell proliferation is restricted to the area of origin, it is less dangerous unless it is located close to any major organs. Others are malignant tumors when the cells are unusual and have the potential to expand out of control [2]. Most mutations cause functional loss. However, the overall effect of mutations that alter an inhibitory pathway may be an increase in function. Such a loss often causes malignant cells to proliferate more and/or have the capacity to attack nearby structures or expand outside of the original tissue (metastasize). Tumor cells exhibit morphological changes in their cytological appearance (cellular atypia) and growth pattern (dysplasia). Understanding how the cell manages its growth may help prevent and treat the tumor [3].

Problems in Antineoplastic Drug Development include creating medications that specifically target tumor cells rather than healthy cells. Despite targeted therapy has come a long way, there remain a lot of inevitable side effects, one distinguishing feature of cancer is being resistant to many treatments [4].

Despite medical and scientific advances, there are still few effective ways to cure cancer. Cancer metastasis and recurrence are major causes of morbidity and death, but their underlying processes have yet to be fully elucidated. [5]. Acute myeloid leukemia (AML) is a rare disease that can be very dangerous and has historically high death rates. The standard of care hasn't changed in decades, but recent discoveries regarding the genetic causes of disease development have made new medicines for AML possible. Studies are working hard to personalize treatment by finding molecular targets, finding risk factors that are unique to each patient and disease, and determining which combination of procedures and medicines responds effectively [6].

AML research and treatment have advanced considerably in recent years. There have been nine agents authorized for use in AML between 2017 and 2021. Targeted therapies such as venetoclax, FLT3 inhibitors, IDH inhibitors, and others were among those used [7].

Type III receptor tyrosine kinase FMS, first identified as the gene implicated in Feline McDonough Sarcoma, links to macrophage or monocyte colony-stimulating factor (M-CSF or CSF-1). This binding trigger signal cascade that promotes the survival, multiplication, and differentiation of the monocyte/macrophage lineage. Several

diseases have been linked to the overexpression of CSF-1 and/or FMS, including the development of metastasis in several cancer types, the promotion of osteoclast development in bone osteolysis, and numerous inflammatory conditions [8].

Fms-like Tyrosine Kinase 3 (FLT3) is a receptor tyrosine kinase found mostly in the hematopoietic component that has been associated to a number of illnesses, including the appearance of metastasis in numerous cancer types. FLT3 expression and modification are significantly associated to the development and occurrence of AML. It has been found that FLT3 alterations appear in around 30% of recently identified AML patients [9].

FLT3 stimulatory mutations may include potentially the juxta membrane domain [internal tandem duplication mutations (FLT3-ITD)] or the tyrosine kinase domain (FLT3-TKD) [10]. FLT3 inhibitors of type I can stop both FLT3-ITD and TKD but type II inhibitors can only stop FLT3-ITD and not TKD. The first-generation FLT3i drugs aren't specific for FLT3 and stop many downstream RTKs from working. This could lead to more side effects that aren't intended. FLT3i's of the second generation work better and more specifically on FLT3 and have less of an effect on other things [11].

Gilteritinib, an FDA-approved second-generation targeted FLT3 inhibitor with efficacy in recurring or refractory FLT3-mutated AML, was discovered to be linked to FLT3's pocket (PDB ID:6JQR) [12][13].

Multiple molecules with anti-inflammatory, antimicrobial, anti-dyslipidemia, and anticancer properties have been related back to the pyrrole moiety[14]. The pyrrole carboxamide core possesses unique characteristics and has been subjected to limited research until now. It plays a crucial role in numerous marine natural products, such as (agelastatin A and yatakemycin), which have demonstrated anticancer properties [15]. The synthetic pyrrole carboxamides have been observed to exhibit a range of pharmacological effects, including the inhibition of tyrosine kinase [16].

Schiff bases are recognized in biological chemistry for their broad range of biological actions, including anticancer properties[17]. Several thiazolidinedione derivatives are currently being studied due to their diverse biological activities, which include antibacterial, anti-diabetic, and cytotoxic activities on various cell lines[18].

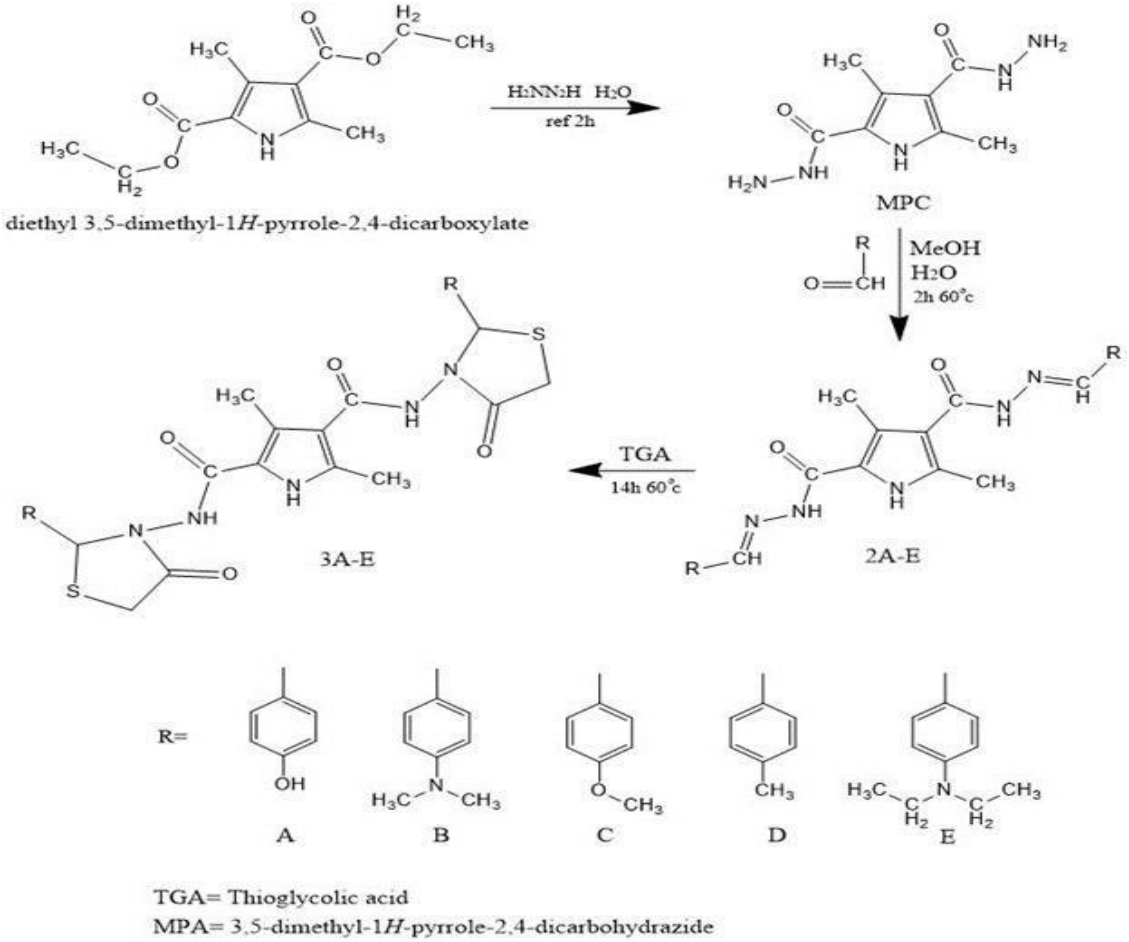
Given these results, as well as the remarkable biological capabilities of thiazolidinones and Schiff base derivatives, a reasonable structure of five novel compounds containing oxothiazolidin and the five Schiff bases from which they were generated was proposed. This technique may result in an improvement of the suggested compounds' pharmacological properties, particularly their anticancer activity.

Experimental work

Five new compounds were designed by selecting pyrrole as core scaffold which is linked symmetrically to two substituted thiozolidinone moieties, a scheme was proposed to synthesize the designed compounds **3A-E**, **Scheme 1**, which was constructed by using ChemOffice software (ChemDraw Professional 19.1). Basically, it includes

- base-promoted ester aminolysis reaction of starting material (1,1'-(3,5-dimethyl-1H-pyrrole-2,4-diyl) bis(propan-1-one)) (10 mmol, 2.11g) was mixed with (20 ml) of 99% hydrazine hydrate and 5 ml distilled water (DW) in a round bottle flask and the mixture boiled under reflux for 2 hrs, then allowed to cool and washed with diethyl ether then filtered. The residue was recrystallized by ethanol, filtered, and collected. resulting in the formation of the hydrazide intermediate [19].

- then the formation of Schiff bases through an acid-catalyzed imine formation by reacting the tydrazide intermediate (1 mmol, 0.21 g) with different aldehydes (2 mmol) which occure by dissolving them in 14 ml methanol and 6 ml DW with continuous stirring. A few minutes later, three drops of acetic acid were applied. The combination was warmed up to 60 ^{o}C under reflux for 2 hrs. Afterward, solvent evaporated, and the residue was washed with DW (to get rid of the MPC) and allowed to dry. The resulting powder was washed with diethyl ether (to remove the excess unreacted aldehyde), filtered, and collected [20]
- (Compounds **2A-E**). Finally, undergo intramolecular ring cyclization to yield bisheterocyclic (thiozolidinone) pyrrole compounds **3A-E** (ring closure reaction by reacting them with thioglycolic acid (TGA)) [21]**.** they were solubilized within a 3-milliliter volume of thioglycolic acid (TGA) then heated to 60°C under reflux for 14 hrs then stirring at room temperature overnight. Afterward, 5 ml ethyl acetate was poured into the mixture and subsequently transported to a separating funnel. The organic layer underwent a series of three washes with a saturated solution of sodium bicarbonate, each wash utilizing a volume of 20 milliliters. Subsequently, it was further rinsed with a volume of 10 milliliters of distilled water and concentrated by a rotatory evaporator to give an oily residue which was washed with diethyl ether to give the final compounds.



Scheme 1. A proposed pathway for synthesizing the designed compounds 3A-E

Molecular docking

Molecular docking is a type of computer modeling that enables the prediction of the preferable binding position of one molecule (e.g., ligand) to another (e.g., Receptor) when the two interact to create a stable complex [22]. The goal of molecular docking is to determine the most likely method of ligand binding to a specific molecular partner (protein). This is becoming increasingly important in the drug development process as more protein structures are identified experimentally using methods such as X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy [23].

Drawing of the 2D chemical structure of the designed compounds and their energy minimization were carried out by ChemDraw Professional 19.1 and they were saved as SYBYL2 (mol2) format. The 3D structure of the target enzyme (FLT3, PDB ID: 6JQR) was obtained and retrieved from the protein data bank (PDB) website (https://www.rcsb.org/) and uploaded to the GOLD software program (Hermes 2021.2.0.). Hydrogen atoms were added and unnecessary metals, ligands (except the reference ligand, Gilteritinib), enzyme chains (except chain A), and water molecules were deleted. The binding site was defined by the reference ligand and cavity size was determined by all atoms within 10 ◦A. The saved compounds (2mol format) were uploaded and the GOLD run was allowed to proceed. When the run ended, the highest PLP scores for each compound and their images (which show the interaction of each compound with the amino acid residues in the binding site) were recorded. Docking scores and images were shown in table 1 and Figures 1 and 2, respectively.

Computational methods for the characterization of the investigated molecules by the ADME program

Early ADME (absorption, distribution, metabolism, and excretion) screening tests developed for low cost and high throughput in pharmaceutical research and manufacturing facilitate the discovery of the most potential lead compound since poor pharmacokinetics (PK) and toxicity are the most frequent reasons for drug discovery failure [24].

The SwissADME server was used to predict the ADME parameters (Absorption, Distribution, Metabolism, and Excretion) and the other physicochemical properties of the investigated molecules [25]. ChemAxon's Marvin JS was used to draw the chemical structures of the investigated compounds, 2A-E and 3A-E, and their SMILES notations. The BOILED EGG was used to assess the possibility of passive gastrointestinal absorption and brain penetration, or the polarity and lipophilicity of the investigated compounds, Figure 3 and 4 [26].

Results and Discussion

All the investigated compounds, 2A-E and 3A-E showed a comparable binding pattern with the amino acids' residues of the active site of FLT3 (PDB ID: 6JQR) to the reference ligand, Gilteritinib, as shown in Figures 1 and 2, and Table 1. However, they have higher PLP fitness scores than Gilteritinib might be due to covalently binding to amino acid residues of the active site in addition to electron rich aromatic and heterocyclic rings that could fill the pocket with high possibility of producing hydrophobic interactions more the giltertinib except for compounds 2A and 3A, as shown in Table 1. Moreover, Compound 2E, which is a bis-hydroxybenzaldehyde Schiff base of compound 1, recorded the highest docking score (83.3). This may indicate that this compound has the highest FLT3 inhibitory activity among the other designed molecules. The highest predicted activity of compound 2E may be due to the interaction of this compound with three amino acid residues (Cys 694, Asp 698, Val 624 with bond distances 2.237, 3.065 and 2.855 ◦A, respectively). These interactions maximize the binding affinity and the docking score, as shown in table 1 and Figure 1.

Table 1. Docking scores of Gilteritinib, compounds 2A-E and 3A-E, and their interaction with the amino acid residues in the active site of FLT3 (PDB ID: 6JQR).

Compound	ER binding energy (PLPfitness)	**Amino acids residues involved in the interaction with FLT3's pocket (PDB ID:6JQR)**
2A	67.97	Cys 694, Asp 698,
2B	80.72	Cys 694, Val 675
2C	75.48	Cys 694, Leu 616
2D	72.29	Cys 694
2E	83.30	Cys 694, Asp 698, Val 624
3A	80.86	Glu 692, Asp 698, Tyr 696, Cys 695
3B	80.43	Glu 692
3C	79.04	Cys 694
3D	77.31	Cys 694, Leu 616, Tyr 693
3E	69.47	Cys 694
Reference Ligand: Gilteritinib	71.91	Glu 692, Cys 694

The SwissADME server was employed for the prediction of the physicochemical and ADME properties of the investigated molecules. The pharmacokinetic parameters of the investigated molecules have been recorded and there was a variation in properties according to chemical structures, as illustrated in Tables **2** and **3**. As shown from the predicted results, all of the Schiff bases don't violate the drug-likeness parameters, except compound **2A** (1 violation, 1 violation: TPSA>131.6) might be due to the polarity of hydroxide moiety and compound **2B** (1 violation 1 violation: MR>130). Therefore, compounds **2A-E** displayed a high predicted GI absorption, except for compound **2A**. The low predicted GI absorption of compound **2A** is due to its high TPSA (139.17) which is a violation to Egan parameter (TPSA>131.6). Compounds **3A-E** have low expected GI absorption due to their violation to all the drug-likeness parameters. The low expected oral bioavailability of compounds **2A** and **3A-E** may indicate that these compounds should be administered parentally or could be evaluated for colon targeting in the future.

All of the proposed compounds don't show an expected penetration though the blood brain barrier (BBB). Furthermore, compounds **2A**, **2C**, **2D**, and **3A** are not a substrate to P-gps which may indicate a lower expected incidence of resistance by cancer cells in vitro studies [(27)(28)]. Finally, all of the investigated compounds are not considered to inhibit CYP1A2 enzyme, except for compounds **2A** and **3D**, as shown in table **2** and **3**.

Table 2 ADME and drug-likeness parameters of compounds 2A-2E and 3A-3E

Compound	MW (g/ mol)	nHBD	nHBA	MR	TPSA (Å)	GI	BBB	P-gp substrate	CYP1A2 inhibitor
2A	419.43	5	6	117.11	139.17	Low	No	No	Yes
2B	473.57	3	4	141.48	105.19	High	No	Yes	No
2C	447.49	3	6	126.05	117.17	High	No	No	No
2D	415.49	3	4	122.99	98.71	High	No	No	No
2E	529.68	3	4	160.70	105.19	High	No	Yes	No
3A	567.64	5	6	153.94	205.67	Low	No	No	No
3B	621.77	3	4	178.31	171.69	Low	No	Yes	No
3C	595.69	3	6	162.88	183.67	Low	No	Yes	No
3D	583.69	3	4	159.83	165.21	Low	No	Yes	Yes
3E	677.88	3	4	197.54	171.69	Low	No	Yes	No
Gilteritinib	552.71	3	7	168.43	121.11	High	No	No	No

Table 2. Drug likeness parameters for SAHA and compounds 2A-E

Compound	**Drug likeness according to**				
	Lipinski	**Ghose**	**Veber**	**Egan**	**Muegge**
Gilteritinib	Yes	Yes	Yes	Yes	Yes
2A	Yes	Yes	Yes	1 violation: TPSA>131.6	Yes
2B	Yes	1 violation: MR>130	Yes	Yes	Yes
2C	Yes	Yes	**Yes**	Yes	Yes
2D	Yes	Yes	Yes	Yes	Yes
2E	1 violation: MW>500	3 violations: MW.480, MR.130, #atoms>70	1 violation: Rotors>10	Yes	1 violation: XLOGP3>5
3A	2 violations: MW>500, NorO>10	2 violations: MW>480, MR>130	1 violation: TPSA>140	1 violation: TPSA>131.6	1 violation: TPSA>150
3B	2 violations: MW>500, NorO>10	3 violations: MW.480, MR.130, #atoms>70	1 violation: TPSA>140	1 violation: TPSA>131.6	2 violations: TPSA>150, MW>600
3C	2 violations: MW>500, NorO>10	2 violations: MW>480, MR>130	1 violation: TPSA>140	1 violation: TPSA>131.6	1 violation: TPSA>150
3D	1 violation: MW>500	2 violations: MW>480, MR>130	1 violation: TPSA>140	1 violation: TPSA>131.6	1 violation: TPSA>150,
3E	2 violations: MW>500, NorO>10	3 violations: MW.480, MR.130, #atoms>70	2 violations: TPSA>140 Rotors>10	1 violation: TPSA>131.6	3 violations: TPSA>150, MW>600, XLOGP3>5

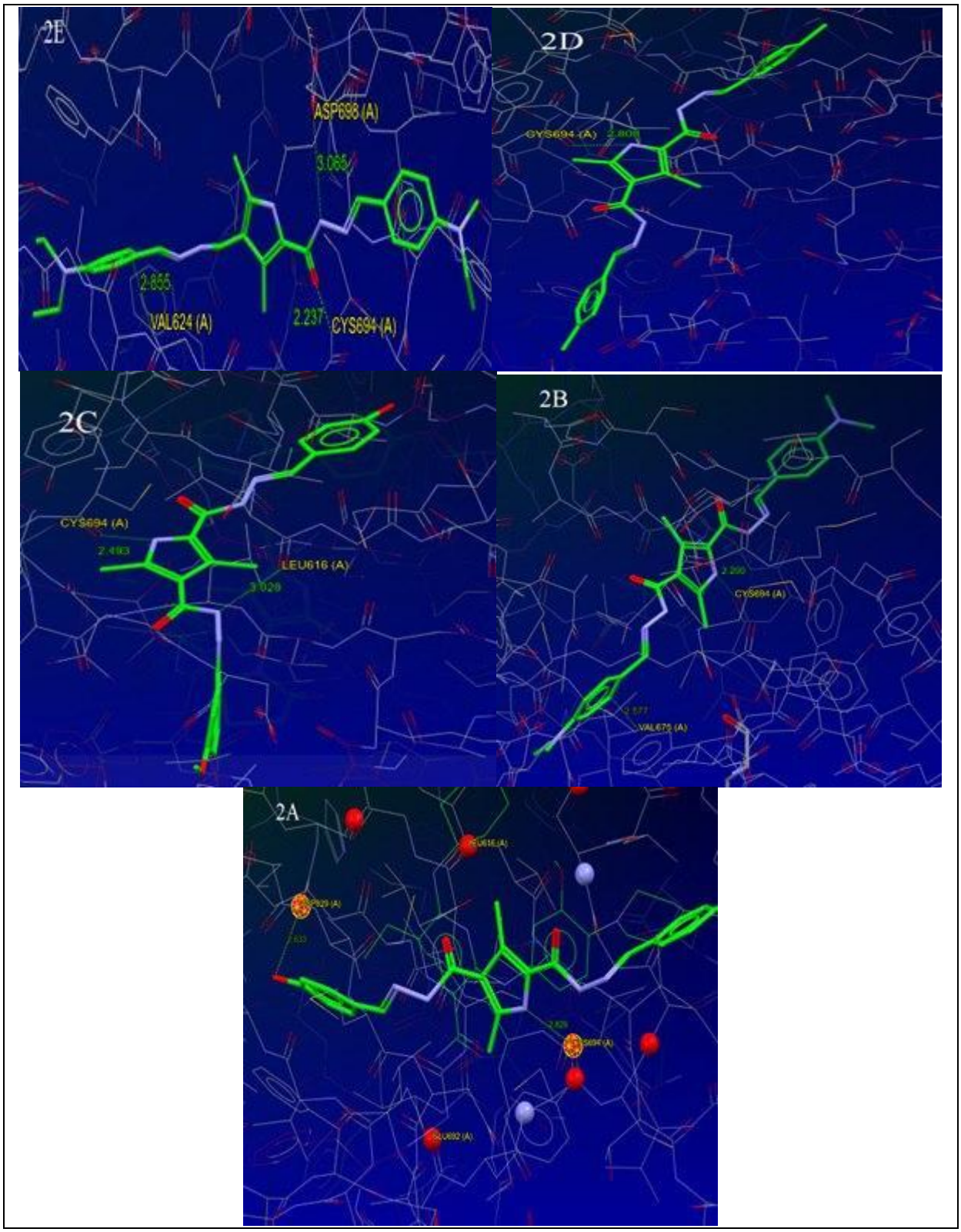


Figure 1. Interaction of Compounds 2A-E with the amino acids residues of FLT3 catalytic pocket (PDB ID: 6JQR)

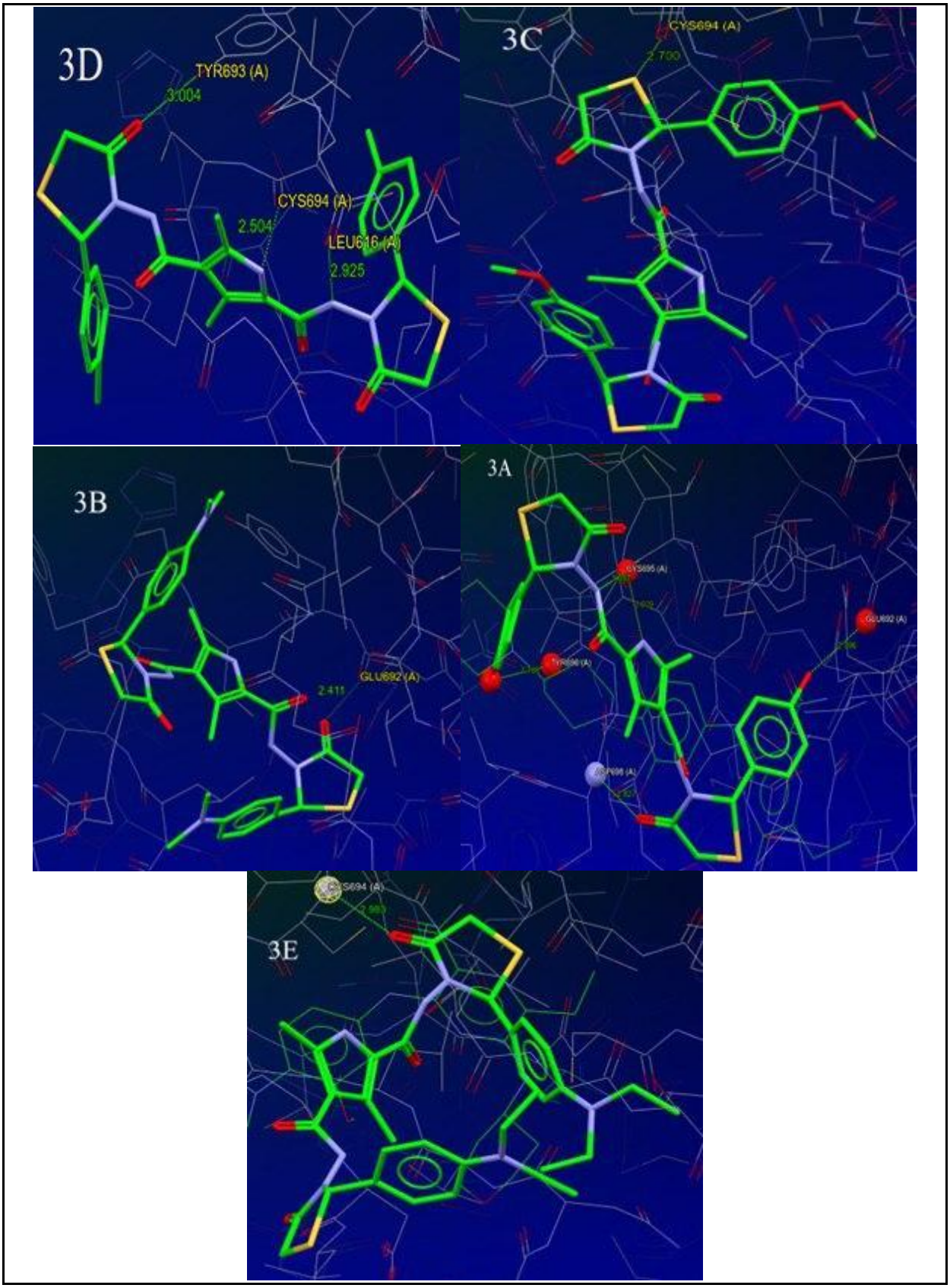


Figure 2. Interaction of Compounds 3A-E and Gilteritinib with the amino acids residues of FLT3 catalytic pocket (PDB ID: 6JQR)

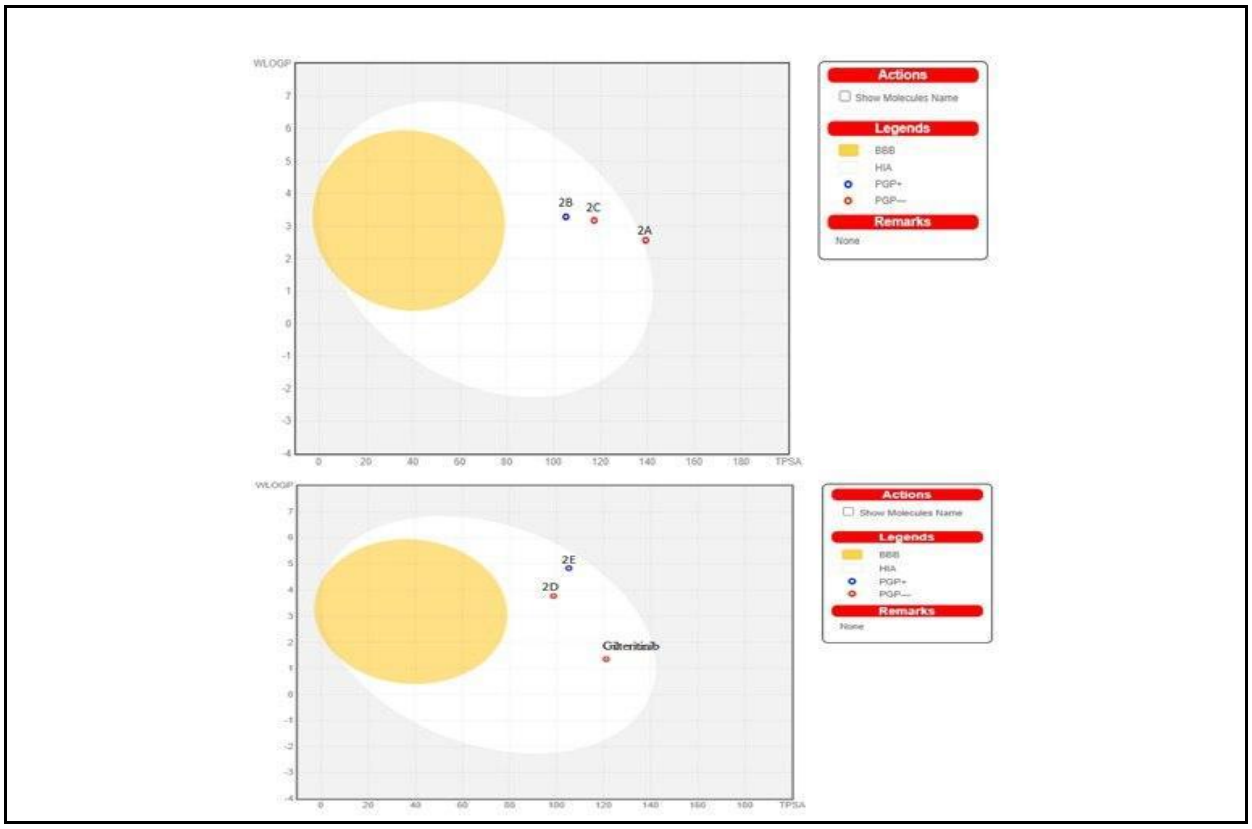


Figure 3. Overview of the BOILED-Egg construction for Gilteritinib and compounds 2A-E

Figure 4. Overview of the BOILED-Egg construction for compounds 3A-E

Conclusion

New compounds containing pyrrole as a scaffold and linked symmetrically to either various aromatic Schiff bases or substituted thiazolidinones were designed and investigated to evaluate their binding to FLT3 (PDB ID: 6JQR) and to predict their physicochemical properties and the other ADME parameters. All the investigated compounds displayed a higher binding affinity to FLT3 (except compounds 2A and 3E) compared with the reference ligand, Gilteritinib. Compounds 2B-E have high expected GI absorption. All the investigated compounds have no predicted BBB penetration. Additionally, compounds 2A, 2C, 2D, and 3A are not a substrate to P-gps which may indicate a lower expected incidence of resistance by cancer cells in vitro studies. Finally, all of the investigated compounds are not considered to inhibit CYP1A2 enzyme, except for compounds 2A and 3D. These interesting results were found to be encouraging for the synthesis of the designed compounds in the future and performing further evaluation studies such as, in vitro and in vivo biological studies.

Conflicts of interests

The authors declare no conflict of interests.

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