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Synthesis, Characterization, Docking and *In Silico* Pharmacokinetics Study of New Triazole Derivatives as TDP1 Enzyme Inhibitor Compounds

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Abstract

Numerous research groups across the globe have been dedicatedly studying the mechanism involved in carcinogenesis and cancer progression focusing on developing various strategies for the prevention and treatment of cancer. Chemotherapy is a treatment used for the whole body to fight recurrent tumors using conventional anticancer drugs which can be made more effective by using chemosensitizers, which can decrease the required dosage for treatment. TDP-1 inhibitors have the potential to enhance the effectiveness of topotecan by increasing the sensitivity of tumors to the drug, both in laboratory and living organism settings. A new triazole derivatives were synthesized starting from Naproxen and Vanillic acid through multisteps reactions. The final compounds and their intermediates were monitored by chromatography (TLC) and characterized by ^{1}HNMR. The final compounds were docked against the target *TDP1 enzyme.* The docking analysis for the titled compounds 5A and 5B revealed better binding affinity values against *(TDP1 enzyme)* target site compared with the reference (co-crystallized) ligand as well as they showed good *ADMET* and *in silico* toxicity profile.

تحضير وتوصيف ونمذجة إرساء ودراسة الحرائك الدوائية الحاسوبية لمشتقات تريازول جديدة كمركبات مثبطة لإنزيم TDP1

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الخلاصة

كرّست العديد من مجموعات البحث حول العالم جهودها لدراسة الآليات المشتركة في تكوين السرطان وتطوره، مع التركيز على تطوير استراتيجيات متنوعة للوقاية من السرطان وعلاجه. يعد العلاج الكيميائي وسيلة علاجية تشمل الجسم بأكمله لمحاربة الأورام المتكررة باستخدام أدوية تقليدية مضادة للسرطان، والتي يمكن تعزيز فعاليتها باستخدام محفزات كيميائية تقلل الجرعة المطلوبة للعلاج. تُظهر مثبطات TDP-1 إمكانية تعزيز فعالية عقار التوبوتيكان عن طريق زيادة حساسية الأورام للدواء، سواء في التجارب المخبرية أو على الكائنات الحية. تم تصنيع مشتقات جديدة من التريازول انطلاقًا من نابروكسين وحمض الفانيليك عبر تفاعلات متعددة المراحل. تم متابعة المركبات النهائية والمركبات الوسيطة باستخدام الكروماتوغرافيا (TLC) وتوصيفها بواسطة ^{1}HNMR ثم تم إجراء نمذجة إرساء للمركبات النهائية ضد إنزيم TDP1 المستهدف. كشفت تحليلات الإرساء للمركبين 5A و 5Bعن قيم ارتباط أفضل مع الموقع المستهدف لإنزيم TDP1 مقارنةً بالربيط المرجعي (المتبلور مع الإنزيم)، بالإضافة إلى إظهارهما لملف جيد فيما يتعلق بـ ADMET والسلامة السمية الحاسوبية.

الكلمات المفتاحية: المحفزات الكيميائية، العلاج الكيميائي، النمذجة الحاسوبية، TDP-1، التريازول.

Introduction:

Cancer initiation and progression are multistep processes and are regulated by different internal factors, including growth factors and their receptors, cytokines, chemokines and transcriptional factors [1,2]. In addition, a variety of factors outside the body can trigger the development of different types of cancer by activating various elements that promote tumor growth. These factors include smoking, exposure to carcinogens in the diet, environmental factors, and certain chemicals [3]. It has been observed that cell cycle checkpoints undergo mutations in all cancer types [4]. The development of tumor cells is facilitated by the mutations of tumor suppressor genes, which regulate the cell cycle checkpoints, by enabling the progression of damaged cells through the cell cycle [5].

Chemotherapy is a treatment used for the whole body to fight recurrent tumors using conventional anticancer drugs [6]. However, this treatment leads to serious clinical side effects due to the high dose, non-specific distribution, severe toxicity to normal cells, inadequate drug concentrations at cancerous cells, and the development of multidrug resistance [7]. To address these issues, researchers have focused on developing chemosensitizers to enhance the effectiveness of chemotherapy in the last two decades [8,9].

Chemotherapy drugs can be made more effective by using chemosensitizers, which can decrease the required dosage for treatment [8,9]. TDP1 inhibitors have the potential to enhance the effectiveness of topotecan by increasing the sensitivity of tumors to the drug, both in laboratory and living organism settings [10]. Anticancer therapies based on topoisomerase inhibitors 1 (TOP1) rely on TDP1 as a key target, given its important role in eliminating TOP1-DNA adducts that are stabilized by TOP1 inhibitors. Additionally, TDP1 can also hydrolyze apurinic sites and repair them. This is particularly important for repairing DNA damage caused by antitumor alkylating drugs like temozolomide (TMZ) and ionizing radiation [11].

Therefore, inhibiting TDP1 activity can significantly enhance the therapeutic effects of some anticancer agents and provide selectivity when combined with TOP1 [11,12]. Figure 1 showing the mechanism of action of TDP-1 and the effect of its inhibitors [13].

There is a wide variety of therapeutic drugs that are based on 1,2,4-Triazole, which includes analgesics, antiseptics, antimicrobials, antioxidants, anti-urease agents, anti-inflammatory agents, diuretics, anticancer agents, anticonvulsants, antidiabetic agents, and antimigraine agents. These diverse biological activities make triazole an important building block in drug discovery and development [14].

One of the advantages of this ring system is its ability to provide good water solubility, which is important for drug molecules to be effectively absorbed and distributed throughout the body. In addition, the 1,2,4-triazole ring has the potential to Interact with a number of enzymes involved in cancer growth. This is due to Its ability to form hydrogen bonds with receptors [15].

Molecular docking predicts molecule interaction in drug discovery. Its samples ligand conformation and ranks them. It calculates druggability and specificity against targets for optimization. Flexible docking is more accurate and currently an active research area [16-20].

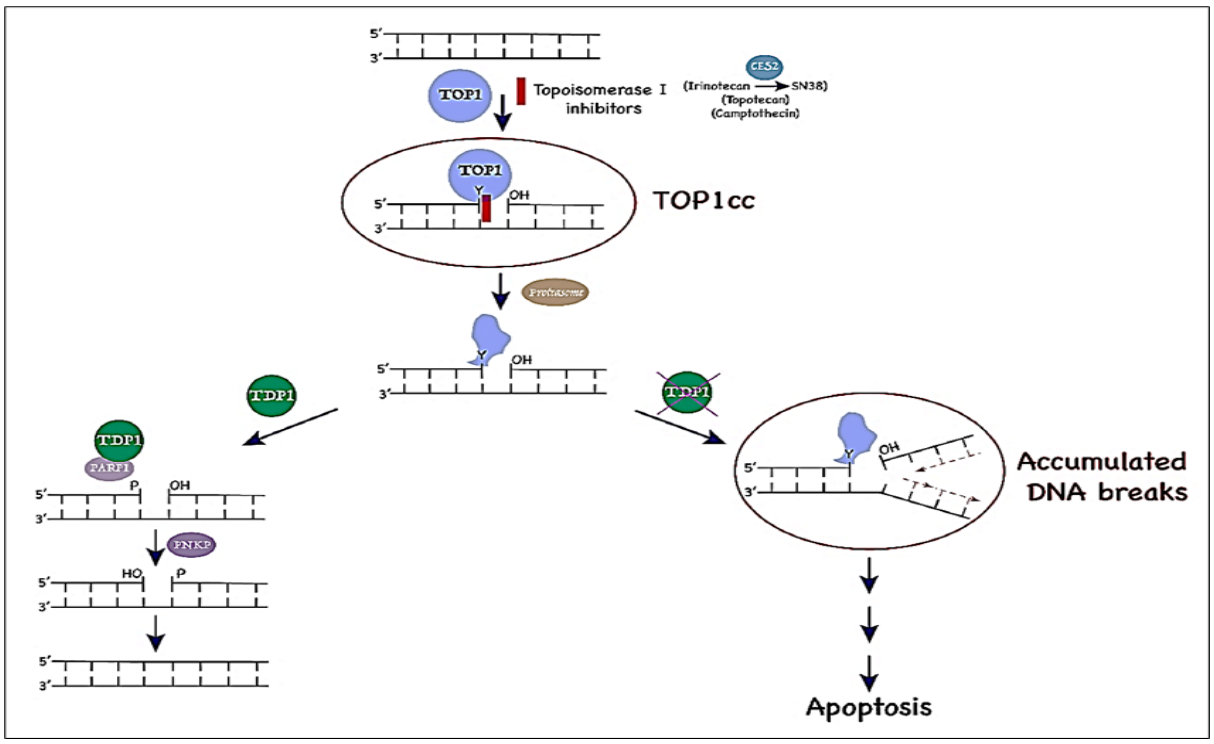
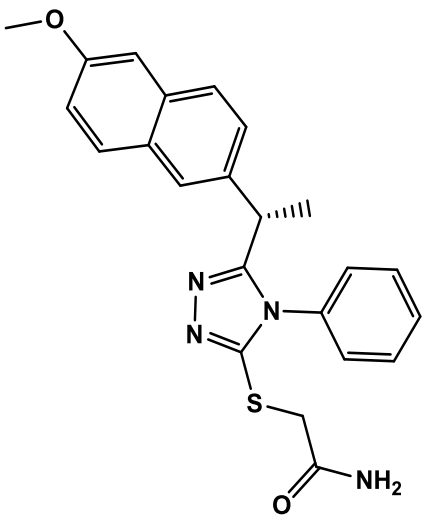
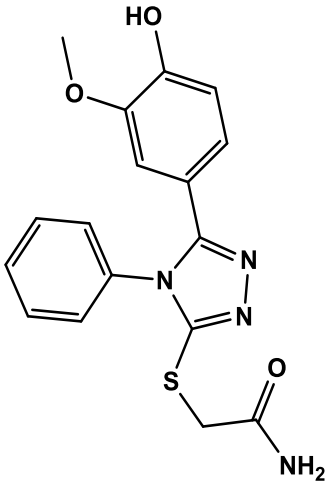


Figure 1. Mode of action of TDP-1.

The aim was to synthesize new 1,2,4-triazole derivatives figure 2, docked them against Tdp-1 as potential anticancer target and *in silico* ADMET profile prediction.



5A



5B

Figure 2. Structures of targeted compounds.

Materials and Methods

Commercially supplied chemicals were used to synthesize compounds. Thin-layer chromatography (TLC) was used to monitor reactions and test compound purity depending on toluene:ethylacetate:ethanol (**2:2:1)** as solvent system. TLC plates were coated with Silica gel GF254 and exposed to UV-254 nm. The synthesized compounds were characterized using FTIR at Samarra drugs industry (SDI) or ^{1}HNMR at Basrha-University.

Chemical Synthesis

The synthesis of the targeted compounds (**comp. A5 and B5**) was proceeding as following:

Synthesis of the first intermediates; comp. A1 and comp. B1 [21]

The amount of absolute methanol required to dissolve a certain quantity (specified below) of either Naproxen or Vanillic acid was measured. The solutions were then cooled to -10°C and 5 milliliters of concentrated H2SO4 was slowly added. After continuous stirring for 10 minutes in an ice bath, the mixture was left to sit at room temperature for 15 minutes. It was then refluxed for a specified period of time (see below) and stirred overnight. The developed precipitate was filtered, collected, and rinsed with a 10% aqueous solution of NaHCO3. The precipitate was then collected, dried, and used directly without any further purification.

Methyl (S)-2-(6-methoxynaphthalen-2-yl)propanoate: White powder, yield (74%), R_f = 0.82.

^{1}HNMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 7.81-7.15 (m, aromatic H_s), 3.92 (q, 1H, *benzylic proton*), 3.86 (s, 3H of OCH_3), 3.59 (s, 3H of ester OCH_3), 1.46 (d, 3H of CH_3)

Methyl 4-hydroxy-3-methoxybenzoate: brown powder, yield 85%, R_f value (0.8).

^{1}HNMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 10.00 (s, 1H, OH proton), 7.48-7.44 and 6.88-6.86 (m, 3H, aromatic H_s), 3.82 (s, 3H of OCH_3), 3.80 (s, 3H of ester OCH_3).

Compound	Quantity	Required methanol	Reflux time
Naproxen	0.0535 mol, 9.0g	180 ml	2 hrs
Vanillic acid	0.042 mol, 9.5g	70 ml	7 hrs

Synthesis of the second intermediates; comp. A2 and comp. B2 [22]

Specific quantity (see below) of each ester was dissolved in absolute ethanol, excess amount of hydrazine hydrate 80% (see below) was added to the formed solution and refluxed with stirring for specific time (see below) and left to stir overnight. The formed precipitates were filtered, washed with hot ethanol and dried for using in the next step.

(S)-2-(6-methoxynaphthalen-2-yl)propanehydrazide: White powder, yield 71%, R_f = 0.64.

^{1}HNMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 9.27 (s, 1H, NH proton), 7.79-7.13 (m, 6H, aromatic H_s), 4.24 (s, 2H, NH_2 protons), 3.86 (s, 3H of OCH_3), 3.66 (q, 1H, *benzylic proton*), 1.42 (d, 3H of CH_3)

***4-hydroxy-3-methoxybenzohydrazide*:** white powder, yield 72%, R_f value 0.55.

^{1}HNMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 9.55 (s, 2H, OH and NH protons), 7.41-7.31 and 6.81-6.78 (m, 3H, aromatic H_s), 4.43 (s, 2H of NH_2), 3.80 (s, 3H of OCH_3).

Compound	Quantity	Required ethanol	Hydrazine hydrate	Reflux time
Comp. 1A	0.028 mol, 7g	Minimum amount	0.28 mol, 14g	12 hrs
Comp. 1B	0.038mol, 7g	Minimum amount	0.38mole, 19g	4 hrs

Synthesis of the third intermediates; comp. A3 and comp. B3 [23]

Phenyl isothiocyanate (**0.0164mol, 2.2g**) was added to a ethanolic solution (**0.0082mol, 2.0g in 50ml of ethanol**) of **comp. 2A** or (**0.022mol, 2.96g**) of Phenyl isothiocyanate was added to suspension of **comp. 2B** (**0.011mol, 2.0g in 25ml ethanol**) in both cases the reaction mixtures were stirred at 40-50 ^{o}C on water bath for 4 h, then kept stirred overnight. The reactions were stopped depending on TLC result and the precipitates were filtered and recrystallized from boiled MeOH to yield the corresponding **comp. 3A and 3B**, respectively.

***(S)-2-(2-(6-methoxynaphthalen-2-yl)propanoyl)-N-phenylhydrazine-1-carbothioamide*:** white crystals, yield 64%, R_f = 0.84.

^{1}HNMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 10.18, 9.64, 9.52 (3s, 3H, NH(C=S)NH(C=O) protons), 7.81-7.15 (m, 11H, aromatic H_s), 3.87 (s, 4H of OCH_3 and *benzylic proton*), 1.49 (d, 3H of CH_3)

2-(4-hydroxy-3-methoxybenzoyl)-N-phenylhydrazine-1-carbothioamide: white powdered, yield 57%, R_f= 0.75.

^{1}H NMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 10.33, 9.77, 9.73 (3s, 3H, NH(C=S)NH(C=O) protons), 9.67 (s, 1H, OH proton), 7.55-6.84 (m, 8H, aromatic H_s), 3.82 (s, 3H of OCH_3).

Synthesis of the fourth intermediates; comp. 4A and comp. 4B [24]

Comp. 3A (2.0g, 0.0053mol) or **Comp. 3B** (2.0g, 0.0063mol) were placed in RBF then 2N NaOH (6ml) was added to each one of them and stirred r.t for (15 min) after that they were refluxed for 5 h and left to stir over night. The reaction mixtures were acidified with 2N HCl to pH 3. The precipitates were filtered, and recrystallized from boiled EtOH to yield **comp. 4A and 4B**.

***(S)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-4-phenyl-4H-1,2,4-triazole-3-thiol*:** yellow powder, yield 65%, R_f =0.92

^{1}H NMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 7.63-7.02 (m, 11H, aromatic H_s), 6.89 (*br* s, 1H, SH proton), 3.93 (q, 1H, *benzylic proton*), 3.84 (s, 3H of OCH_3), 1.54 (d, 3H of CH_3).

5-(4-hydroxy-3-methoxyphenyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione: yellow powder, yield 80%, R_f = 0.90

^{1}H NMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 14.03 (s, 1H, NH thioamide group), 9.63 (s, 1H, OH proton), 7.52-6.70 (m, 8H, aromatic H_s), 3.48 (s, 3H of OCH_3).

Synthesis of the final products; comp. A5 and comp. B5 [25]

Comp. 4A and **4B** were dissolved by 7mL of absolute ethanol in RBF with aid of triethylamine (as base catalyst) and stirred until clear solutions were obtained, to these clear solution, 2-chloroacetamide was added and the reaction mixtures were refluxed for 2h and left to stir overnight. Depending on TLC results the reactions stopped and the precipitates were filtered, washed with hot methanol and dried. Below the specific quantities required for each reagents for the synthesis.

***(S)-2-((5-(1-(6-methoxynaphthalen-2-yl)ethyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetamide*:**

off-white powder, yield 68%, R_f = 0.59

^{1}H NMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 7.72-7.03 (m, 11H, aromatic H_s and 2H of acetamide group), 4.16 (q, 1H, *benzylic proton*), 3.90 (s, 2H of -S-CH_2), 3.84 (s, 3H of OCH_3), 1.64 (d, 3H of CH_3).

2-((5-(4-hydroxy-3-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetamide:

white powder, yield 68%, R_f=0.59.

^{1}H NMR (400 MHz, DMSO-$_{d6}$, δ=ppm): 9.56 (s, 1H, OH proton), 7.73-6.70 (m, 8H, aromatic H_s and 2s, 2H, acetamide protons),, 3.94 (s, 2H of -S-CH_2), 3.52 (s, 3H of OCH_3).

Compound	Quantity	Triethylamine	2-chloroacetamide
Comp. 4A	0.0007mol, 0.25g	97 microliter	0.0007mol, 0.075g
Comp. 4B	0.00083mol, 0.25gm	117 microliter	0.00083mol, 0.08g

Molecular docking study

A server (https://prediction.charite.de/index.php) was utilized to select the molecular targets and the TDP1 enzyme was the suggested target. The selection of the target site was done through the use of the protein data bank (https://www.rcsb.org/), which contains several isoforms of TDP1 and the best one was 6N0D. For molecular docking MOE 2022 software was used. The binding sites were generated from the co-crystallized ligand within the crystal protein (PDB codes: 6N0D). The first step of the protocol was to eliminate water molecules present in the complex. After that, any crystallographic disorders and unfilled valence atoms were addressed using the protein report, utility, and clean protein options. To minimize the protein's energy, AMBER10 force fields was employed, and a protein's rigid binding site using a fixed atom constraint was obtained followed by identification of the critical amino acids in the proteins and made them ready for docking. The SMILE structures of the tested compounds were created using Chem-Bio Draw Ultra13.0 and generated in 3D form in the MOE 2022 software. The 3D structures were protonated with a 0.1 Å RMSD AMBER10 force field to minimize the energy, after which they were prepared for docking using a ligand protocol [18,26].

Results and Discussion

Chemistry

Stepwise synthesis of the targeted compounds showed in figure 3 A and B at the end of this section. To create either **comp. A1** or **B1** the carboxylic acid group was transformed into a methyl ester. Esterification, a conventional method, was done by reacting the carboxylic acid with MeOH in the presence of conc.H2SO4. The **comp. A1** displayed marked signal in the ^{1}HNMR spectrum at δ = 3.59 ppm, attributed to CH_3 of -OCH_3 as singlet, while for **comp. B1** the signal of CH_3 of -OCH_3 appeared at δ = 3.82 ppm.

For synthesis of **Comp. A2 or B2,** the reaction mechanism is primarily based on the hydrolysis that is catalyzed by a base (44). In this reaction, the transfer of a proton between two hydrazine molecules is the rate-determining step. The subsequent step involves the slow reaction of one hydrazine molecule with one alcohol molecule. The ^{1}HNMR spectrum of hydrazides,

comp. A2 and **B2**, exhibited the appearance of two *singlet* peaks, at δ = 4.24 & 9.27 ppm for **comp. A2**, and at δ = 4.43 & 9.55 ppm for **comp. B2** due to the presence of NH_2 and NH groups of the hydrazides.

The synthesis of thiosemicarbazides derivatives **comp. A3 and B3** were the results of nucleophilic additions of carbohydrazides to isothiocyanates.

The ^{1}HNMR spectrum disclosed a characteristic *singlet* peak related to (S=C-**NH**-Ar) and neighboring (2**NH**) groups, at δ =10.18ppm, δ=9.64 and 9.52 ppm for **comp. A3** while comp. B3 showed the same peaks at δ =10.33 ppm, δ=9.77 and 9.73 ppm.

Comp. 4A and 4B were the results of intramolecular cyclization of **comp. A3 and B3** while being refluxed in 2N sodium hydroxide solution. Comp. **4A** was a derivative of triazole-2-thiole, displayed a s*inglet* peak at δ= 7.17 for one proton, due to (**SH**) group while comp. **4B** was a derivative of triazole-2-thione, displayed a s*inglet* peak at δ= 14.03 for one proton, due to **(NH)** group of thioamides. all signals due to thiosemicarbazide are disappeared as an indication of intramolecular cyclization.

Comp. 5A and **5B** were the results of a nucleophilic substitution (SN^2) reaction either between **comp. 4A** and **4B** and 2-chloroacetamide in absolute ethanol and in the presence of triethylamine as a catalyst. Comp. **(5A and 5B)** are thioether derivatives characterized by appearance of new signals relate to **CH_2** of **S-CH_2** as *singlet* at δ= 3.90 ppm for **5A** and at 3.94 ppm for **5B**; and signals related to **CONH_2** at δ= 7.28 and 7.72 ppm for **comp. 5A** and at 7.30 and 7.73 for **comp. 5**

Molecular docking analysis

The molecular docking procedure was carried out using MOE software, which is a grid-based method for docking ligands into receptor binding sites. The binding sites were found by SITE FINDER in plate number 1. During the refinement process, the receptor remained rigid while the ligands were allowed to be flexible.Five distinct interactions with the protein were allowed for each molecule. The docking scores of the best-fitting pose with the active site were noted, and subsequently, the TDP1 binding site was identified and recorded in Table 1. The above information was utilized to anticipate the recommended binding mode (pose) and affinity. The binding free energy (ΔG) of the compounds tested with TDP1 (6N0D) was represented by the predicted affinity.

The key binding site consists of the amino acids: Ser 200, Tyr 204, Cys 205, Ala 258, Phe 259, Gly 260, Thr 261, His 263, Lys 265, Asn 283, Ile 285, Asp 288, Ser 399 and 400, Val 401, Gly 402, Ser 403, Leu 404, Gly 458, Ser 459, Pro 461, Tyr 462, Ser 463, Serianine 466, Hist 493, Lys 495, Asn 516, Leu 517, Ser 518, Lys 519, Ala 520, Ala 521, and Arg 522.The binding mode of the **comp. 5A** exhibited an affinity value of **-7.187**kcal/mol formed (six hydrophobic interactions by VDW forces through naphthalene ring and two methyl groups with Tyr 204, His 263 and 493 and Ala 521) and (three hydrogen bonds by acetamido group with Val 401, Pro 461 and Ser 463, figure 4.

The binding mode of the **comp. 5B** exhibited an affinity value of **-6.582**kcal/mol. The phenyl ring formed hydrophobic interactions by VDW forces with Ala 521; methoxy groups bounded by hydrogen bond and VDW forces with Ser 518 and Ser 400, respectively; triazole ring bounded by two hydrogen bonds and two VDW forces with Asn 516, His 263, Pro 461 and His 263; acetamide group bonded by three hydrogen bonds Asn 283, Ser 459 and His 493, figure 5.

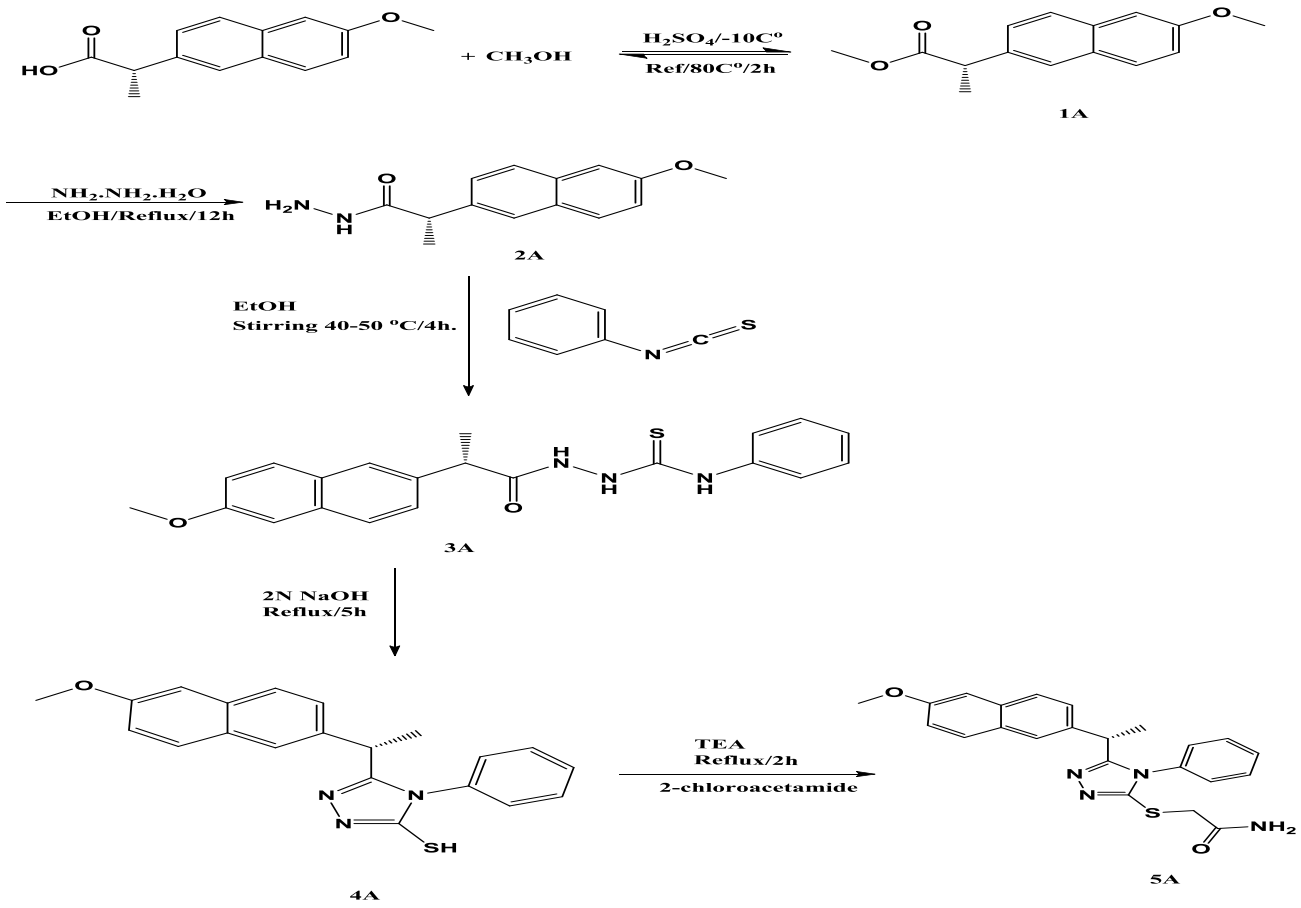


Figure 3 A. scheme for synthesis of targeted compound 5A.

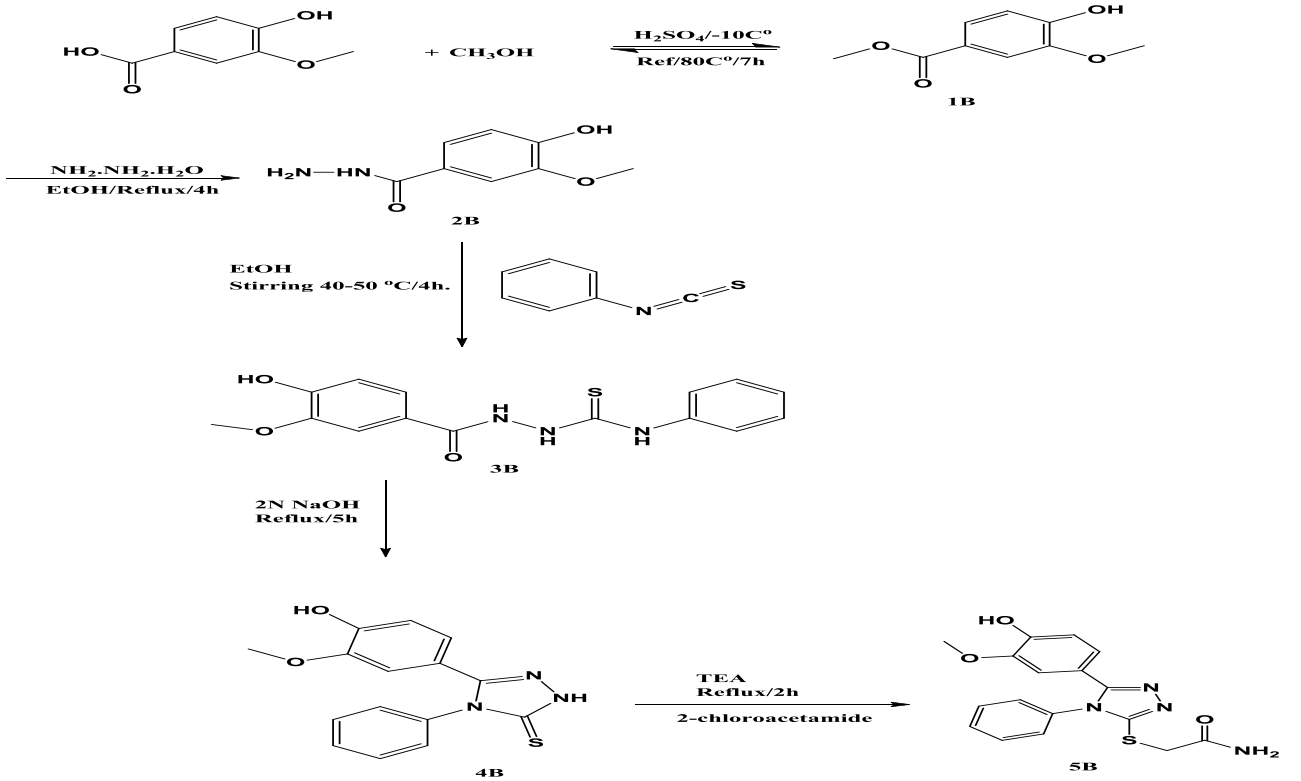


Figure 3 A. scheme for synthesis of targeted compound 5A.

Table 1: The scores for docking of the tested compounds against the target site of the co-crystallized ligand are represented in ΔG values measured in kcal/mol.

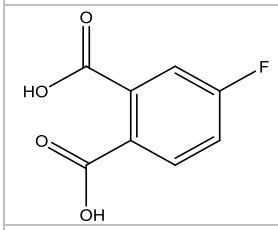
Ligand	RMSD value	Docking score (Kcal/mol)	Interactions	
			H.B	VDW
	1.474	-6.568	5	6
Comp. 5A	1.633	-7.187	3	6
Comp. 5B	1.19	-6.582	5	5

Table 2: The properties related to physical and chemical characteristics of the compounds that were synthesized

Comp.	Clog p	Ali class	n. H-bond acceptors	n. H-bond donors	n. rotatable bonds	TPSA / ºA
5A	3.7	Poorly sol.	4	1	7	108.33
5B	1.99	Moderately sol.	5	2	6	128.56

Table 3: Analysis of ADMET properties has been predicted for the mentioned compounds

Comp.	CYP2C9	CYP2D6	CYP3A4	BBB	GI absorption	P-gp subst.
5A	Yes	Yes	Yes	No	High	No
5B	Yes	No	No	No	High	No

Table 4: The toxicity prediction for the titled compounds.

Comp.	Hepatotoxicity	Renal toxicity	Carcinogenicity	LD50 mg/kg
5A	Yes	No	No	1000
5B	No	No	No	1500

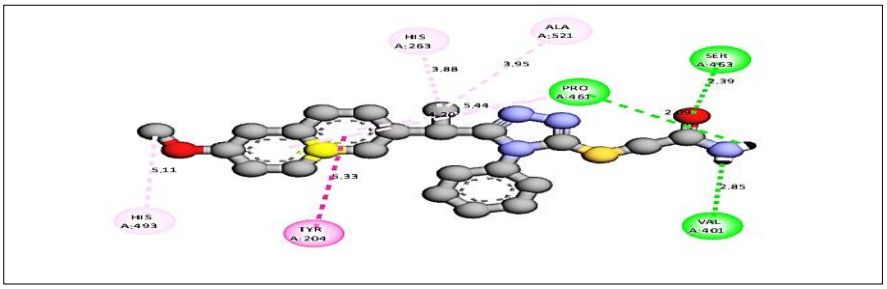


Figure 4. Binding interactions of compound 5A with the target.

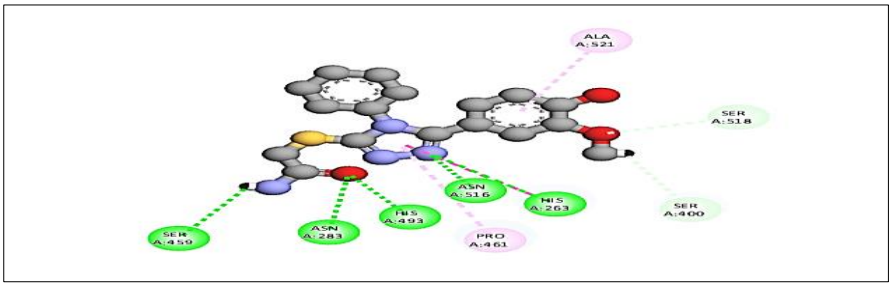


Figure 4. Binding interactions of compound 5B with the target.

Physicochemical properties

Understanding the physical characteristics of drugs is essential for improving their molecular activity. One parameter that plays a key role in this aspect is the partition coefficient (clogP), which predicts how drugs move within the human body. However, it is worth noting that all target compounds have a clogP value of less than 5, which violates the widely accepted Lipinski's rule of five. The total polar surface area (TPSA) is another important parameter that defines the surface area occupied by polar atoms in a compound. Lower TPSA values are much more desirable for drug-like properties since they are associated with higher membrane permeability. Therefore, by carefully analyzing these parameters, it's possible to enhance the therapeutic properties of drugs and achieve better treatment outcomes for patients, table 2 [35,36].

In-silico ADMET and toxicity properties

ADMET properties of synthesized compounds were examined using Swiss ADME cheminformatics software to identify safer drug candidates and exclude compounds with adverse ADMET properties for further drug development stages. Table 3 shows the expected ADMET analysis of the target compounds, while in-silico toxicities of the new compounds are presented in table 4. The LD50 was obtained from PROTOX II webserver, while admetSAR provided the remaining data.

Conclusion

New compounds (**5A** and **5B**) were successfully synthesized and characterized. The activities were predicted using Docking study which reveals better binding modes of **5A** and **5B** than the co-crystallized ligand with the target enzyme TDP1. The grater binding affinity of **5A** than that of **5B** may explain the importance of hydrophobic interactions to increase affinity for the enzyme. The predicted ADMET and toxicology profile gave good indications about the synthesized compounds regarding their pharmacokinetics and safety profile.

Conflicts of Interest

Not found.

Funding

Not found.

Author Contribution

The authors confirm contribution to the paper as follows: supplying of Naproxen and Vanillic acid, study design, supervision on the progress of the reactions, interpretation of FTIR and ^{1}HNMR, and interpretation of docking results: Mostafa F. Tawfeeq; interpretation of ^{1}HNMR and providing essential references: Ali H. Abbas and Emad M. Yousif. All authors reviewed the results and approved the final version of the manuscript.

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Ethics Statements

The study did not need ethical approval from an ethics committee.

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