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Research Article

Synthesis and *in silico* evaluation of some new 2,4-disubstituted thiazole derivatives

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ABSTRACT

The synthesis and antiproliferative activity investigation of methyl 3/4-[[4-(2-substituted thiazol-4-yl)phenyl]amino]-3-oxopropanoate/(4-oxobutanoate) (**3a-h**) derivatives were aimed in this work. The synthesis of the new compounds was carried out by a simple, multiple-step synthetic procedure. The physicochemical properties of the compounds were determined using SwissADME and QikProp software systems. Additionally, virtual target and toxicity predictions were carried out for all final compounds. The pharmacokinetics/physicochemical, druglikeness properties and biological target and toxicity predicitions of the compounds were determined to possess satisfying findings. Since the target determination of the compounds according to literature is point out their cytotoxic properties, the DNA gyrase enzyme was chosen as common enzymatic pathway, and evaluated via docking studies. Compound **3b**, namely methyl 4-[[4-(2-methylthiazol-4-yl)phenyl] amino]-4-oxobutanoate was detected to possess a potential to inhibit DNA gyrase-ATPase activity.

Keywords: DNA gyrase inhibition, druglikeness, molecular docking, pharmacokinetic properties, thiazole

1. INTRODUCTION

The thiazole ring is an aromatic heterocyclic ring commonly found in natural and synthetic molecules. It is existing in the structure of alkaloids, steroids, vitamins (Thiamine-vit B1), flavones, pigments and secondary metabolites [1-3]. Secondary metabolites are organic intermediates and products produced by bacteria, fungi, or plants metabolism which of those constitute important drugs in treatment [4]. Thiazole including seconder metabolites are quite large scale that some of them are penicillins, epothilones, ascidians, tubulysins, cystothiazoles, scleritodermin, leinamycin, lyngbyabellin thiostrepton and micrococcin P1 known with various biological activity potential [5].

In 1887, Hantzsch and Weber described thiazole ring, synthesis and properties [6]. In this method, known today as the Hanzsch method, α-haloketones and thioamides are reacted to form thiazoles [7]. In later years, Prop and coworkers synthesized new thiazole derivatives, in particular 2- aminothiazoles. Gabriel acquired various thiazoles by using a different implementation of Robinson-Gabriel oxazole synthesis. Tcherina obtained thiazole derivatives by cyclization reaction of α-thiocyanoketones whereas Erlenmeyer used the reaction of mercaptoketons and nitrilles. Lastly, Cook and Heilborn were developed synthetic method via α-aminonitriles, α-aminoamides and carbon disulfide. In following years, thiazole synthesis was carried out using these methods and continued in this context [8,9]. In this direction, the

synthetic suitability of the thiazole ring leads to new applications in industrial and medicinal chemistry [10]. Mono/di/polysubstituted aromatic/nonaromatic and condensed thiazoles were widely studied and it was observed that the variety of biological activities increased with changes in substitution [3,11,12].

Thiazole derivatives were reported with a broad range of biological activities such as antifungal, antibacterial, antiviral, analgesic, anticancer, anticholinesterase, antihypertensive, and antiproliferative [13-17]. Besides, in present day, thiazole core is existing in many clinically used drugs; abafungin and ravuconazole (antifungal), ritonavir (anti-HIV), febuxostat (antigut), nizatidine (antiulcer), imidacloprid (insecticide), myxothiazols and melithiazols (fungicide), fatostatin (sterol regulatory element-binding proteins (SREBPs) inhibitor), tiazofurin, bleomycin and dasatinib (anticancer), fanetizole, meloxicam and fentiazac (anti-inflammatory) sulfathiazole (antimicrobial), and nitazoxanide (antiparasitic agent) and penicillin (antibiotic) [18-20].

According to previous studies, DNA gyrase inhibition by thiazole derivatives was investigated and obtained remarkable enzyme inhibition results, even against drug-resistance pathogens [21-23]. The action mechanism of the DNA gyrase enzyme is need ATP energy. The role of the gyrase subunit B (GyrB) is to provide the energy necessary for the DNA ligation process through ATP hydrolysis, hence, the inhibition of this subunit cause stopping ATP hydrolysis, so bacteria cells lose their functions. According to literature, thiazole ring is generally linked to GyrB subunit [24,25]. Therefore, we determined the GyrB as a target.

Furthermore, in many of our studies, we conducted biological activity studies on similar [26-28] and different thiazole derivatives [29,30]. Likewise, we synthesized eight novel thiazole derivatives and evaluated their *in silico* physicochemical properties and evaluated their anti-DNA-gyrase activity, in this study.

2. MATERIALS AND METHODS

2.1. Chemistry

All chemicals were purchased from Sigma-Aldrich Chemical Co., (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck (Merck, Darmstadt, Germany). All melting points (m.p.) were determined by Electrothermal 9300 digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) using Silica gel 60 F254 TLC plates (Merck, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: IR, Shimadzu 8400S spectrophotometer (Shimadzu, Tokyo, Japan); ^{1}H-NMR, Bruker 500 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA); ^{13}C-NMR, Bruker 100 FT spectrometer (Bruker Bioscience, Billerica, MA, USA); MS, MS-FAB, VG Quattro Mass spectrometer (Fisons Instruments GmbH, Mainz, Germany) and elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyser (Perkin Elmer, Norwalk, CT, USA).

2.1.1. General procedure for the synthesis of methyl 3/4-[[4-(2-substituted thiazol-4-yl)phenyl]amino]-3-oxopropanoate/(4-oxobutanoate) derivatives (3a-h)

4-(2-Substituted-4-thiazolyl)aniline derivatives (0.05 mol) **(2a-d)** were solved in tetrahydrofuran (75 mL) and triethylamine (0.06 mol). Methyl malonyl chloride/methyl succinyl chloride (0.06 mol) was added dropwise over 15 min to a magnetically stirred solution at 0-5^{o}C. After the reaction was completed, the solvent was evaporated under reduced pressure, the residue was reacted with water and filtered. The obtained resulting solid was crystallized from ethanol after dryness to gain pure final products.

Methyl 3-[[4-(2-methylthiazol-4-yl)phenyl]amino]-3-oxopropanoate **(3a)**

80-82 % yield; mp 175-179 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.76 (s, 3H, CH_3), 3.49 (s, 2H, CH_2),

3.66 (s, 3H, OCH_3), 7.63 (d, 2H, *J*=8.5 Hz, Ar-H), 7.81 (s, 1H, thiazole C_5-H), 7.88 (d, 2H, *J*=8.5 Hz, Ar-H), 10.29 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.39, 43.97, 53.45, 113.07, 119.66, 126.93, 130.09, 138.91, 153.98, 164.48, 165.87, 168.57. For $C_{14}H_{14}N_2O_3S$ calculated: 57.92 % C, 4.86 % H, 9.65 % N; found: 57.81 % C, 4.94 % H, 9.55 % N. MS $[M+1]^+$: *m/z* 291.

Methyl 4-[[4-(2-methylthiazol-4-yl)phenyl]amino]-4-oxobutanoate **(3b)**

76-80 % yield; mp 162-165 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.61-2.65 (m, 4H, CH_2), 2.70 (s, 3H, CH_3), 3.37 (s, 3H, OCH_3), 7.63 (d, *J*=8.5 Hz, 2H, Ar-H), 7.78 (s, 1H, thiazole C_5-H), 7.85 (d, 2H, *J*=8.5 Hz, Ar-H), 10.09 (s, 1H, N-H). For $C_{15}H_{16}N_2O_3S$ calculated: 59.19 % C, 5.30 % H, 9.20 % N; found: 59.11 % C, 5.15 % H, 9.35 % N. MS $[M+1]^+$: *m/z* 305.

Methyl 3-[[4-(2-phenylthiazol-4-yl)phenyl]amino]-3-oxopropanoate **(3c)**

76-78 % yield; mp 147-150 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.51 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 7.51-7.56 (m, 3H, Ar-H), 7.69 (d, 2H, *J*=8.5 Hz, Ar-H), 7.99-8.03 (m, 5H, Ar-H), 8.08 (s, 1H, thiazole C_5-H), 10.36 (s, 1H, N-H). For $C_{19}H_{16}N_2O_3S$ calculated: 64.76 % C, 4.85 % H, 7.95 % N; found: 64.61 % C, 4.96 % H, 7.85 % N. MS $[M+1]^+$: *m/z* 353.

Methyl 4-[[4-(2-phenylthiazol-4-yl)phenyl]amino]-4-oxobutanoate **(3d)**

71-74 % yield; mp 203-206 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.62-2.64 (m, 4H, CH_2), 3.61 (s, 3H, OCH_3), 7.51-7.54 (m, 3H, Ar-H), 7.69 (d, 2H, *J*=8.5 Hz), 7.98 (d, 2H, *J*=8.5 Hz, Ar-H), 8.02 (d, 2H, *J*=8.5 Hz, Ar-H), 8.06 (s, 1H, thiazole C_5-H), 10.14 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.92, 31.36, 51.85, 113.77, 119.49, 126.66, 127.08, 129.31, 129.74, 130.81, 133.53, 139.71, 155.51, 167.27, 170.38, 173.34. For $C_{20}H_{18}N_2O_3S$ calculated: 65.55 % C, 4.95 % H, 7.64 % N; found: 65.64 % C, 4.99 % H, 7.75 % N. MS $[M+1]^+$: *m/z* 367.

Methyl 3-[[4-(2-(4-methoxyphenyl)thiazol-4-yl) phenyl]amino]-3-oxopropanoate **(3e)**

65-68 % yield; mp 153-158 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.51 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 7.08 (d, 2H, *J*=9 Hz, Ar-H), 7.67 (d, 2H, *J*=9.0 Hz, Ar-H), 7.95-8.0 (m, 5H, Ar-H), 10.34 (s, 1H, N-H). For $C_{20}H_{18}N_2O_4S$ calculated: 62.81 % C, 4.74 % H, 7.33 % N; found: 62.88 % C, 4.82 % H, 7.36 % N. MS $[M+1]^+$: *m/z* 383.

Methyl 4-[[4-(2-(4-methoxyphenyl)thiazol-4-yl)phenyl] amino]-4-oxobutanoate **(3f)**

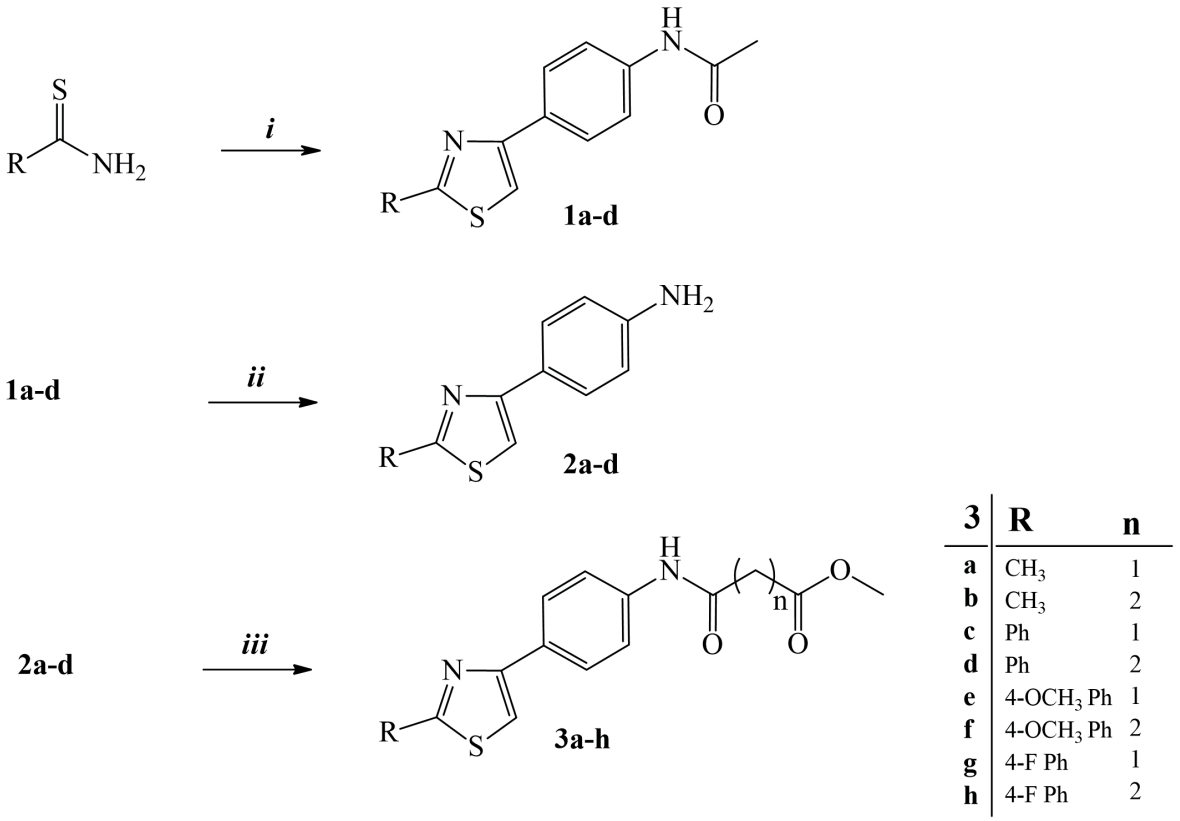
71-74 % yield; mp 203-206 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.61-2.65 (m, 4H, CH_2), 3.61 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 7.08 (d, 2H, *J*=8.5 Hz, Ar-H), 7.66 (d, 2H, *J*=8.5 Hz, Ar-H), 7.94-7.97 (m, 5H, Ar-H), 10.12 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.51, 52.03, 55.40, 112.54, 114.64, 119.23, 125.98, 126.54, 127.43, 129.52, 138.71, 154.62, 160.90, 164.11, 166.87, 168.12. For $C_{21}H_{20}N_2O_4S$ calculated: 63.62 % C, 5.08 % H, 7.07 % N; found: 63.66 % C, 4.98 % H, 7.15 % N. MS $[M+1]^+$: *m/z* 397.

Methyl 3-[[4-(2-(4-fluorophenyl)thiazol-4-yl)phenyl] amino]-3-oxopropanoate **(3g)**

63-68 % yield; mp 184-186 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.67 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 7.37 (brs, 2H, Ar-H), 7.69 (brs, 2H, Ar-H), 7.99-8.21 (m, 5H, Ar-H), 10.33 (s, 1H, N-H). For $C_{19}H_{15}FN_2O_3S$ calculated: 61.61 % C, 4.08 % H, 7.56 % N; found: 61.69 % C, 4.19 % H, 7.65 % N. MS $[M+1]^+$: *m/z* 370.

Methyl 4-[[4-(2-(4-fluorophenyl)thiazol-4-yl)phenyl] amino]-4-oxobutanoate **(3h)**

65-69 % yield; mp 200-203 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.62-2.64 (m, 4H, CH_2), 3.80 (s, 3H, OCH_3), 7.38 (brs, 2H, Ar-H), 7.72 (brs, 2H, Ar-H), 7.98-8.20 (m, 5H, Ar-H), 10.35 (s, 1H, N-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.42, 30.93, 51.42, 113.34, 116.25, 116.38, 126.68, 128.42,



3	R	n
a	CH_3	1
b	CH_3	2
c	Ph	1
d	Ph	2
e	4-OCH_3 Ph	1
f	4-OCH_3 Ph	2
g	4-F Ph	1
h	4-F Ph	2

Scheme 1. The synthetic protocol of the compounds **3a-h.** Reactants and conditions: : ***i*** : 4-(2-bromoacetyl)acetanilide, EtOH, r.t., 8h; ***ii*** : 10 % HCl , EtOH, reflux; ***iii*** : methyl malonyl chloride/methyl succinyl chloride, TEA, THF, r.t.

125.53, 128.79, 129.76, 139.25, 155.0, 162.25, 164.23, 165.65, 169.80, 172.83. For $C_{20}H_{17}FN_2O_3S$ calculated: 62.49 % C, 4.46 % H, 7.29 % N; found: 62.59 % C, 4.35 % H, 7.25 % N. MS $[M+1]^+$: *m/z* 384.

2.2. *In Silico* Prediction

The physicochemical properties of the compounds were calculated using SwissADME [31] and Qikprop [32] software programs. Potential activity and toxicity profiles were predicted using SwissTargetPrediction [33] and pkCSM–pharmacokinetics [34] software programs. The DNA-gyrase crystal was retrieved from RCSB Protein Data Bank (PDBID: 4DUH), and the protein and final compounds prepared using protein preparation and ligand preparation wizards at 7.4±1.0 pH. Their binding modes were investigated using Maestro software program.

3. RESULTS AND DISCUSSION

Present study was undertaken to synthesize methyl 3/4-[[4-(2-substituted thiazol-4-yl)phenyl] amino]-3-oxopropanoate/(4-oxobutanoate) (**3a-h**) derivatives and to evaluate their *in silico* physicochemical properties. The synthetic protocol was realized according to previously reported studies [26] and it was depicted in **Scheme 1**. Initially, thiazole derivatives were synthesized according to Hantzsch thiazole synthesis with the reaction of alkyl/aryl thioamides and α-bromo-(4'-acetylamino)acetophenone. Then the obtained thiazole intermediates (**1a-d**) were hydrolyzed to convert acetanilide to corresponding aniline. Lastly, the acquired 4-(2-substituted-4-thiazolyl)aniline derivatives (**2a-d**) were reacted with methyl malonyl chloride or methyl succinyl chloride at acetylation conditions to reach ester compounds (**3a-h**). The

Table 1. Some properties of synthesized compounds from SwissADME

	HBA	HBD	TPSA	Log $P_{o/w}$	SC	Log K_p	GIA	RoF (V)	Ghose	Leadlikeness (V)
3a	4	1	96.53	2.38	Moderately	6.11	High	0	Yes	Yes
3b	4	1	96.53	2.48	Moderately	6.77	High	0	Yes	Yes
3c	4	1	96.53	3.50	Poorly	5.59	High	0	Yes	No (2)
3d	4	1	96.53	3.62	Poorly	6.26	High	0	Yes	No (2)
3e	5	1	105.76	3.48	Poorly	5.79	High	0	Yes	No (3)
3f	5	1	105.76	3.60	Poorly	6.46	High	0	Yes	No (2)
3g	5	1	96.53	3.77	Poorly	5.63	High	0	Yes	No (2)
3h	5	1	96.53	3.93	Poorly	6.29	High	0	Yes	No (2)

MW: Molecular Weight, **HBA:** H-bond acceptor, **HBD:** H-bond acceptor, **TPSA:** Topologic polar surface area (Å²) **Log $P_{o/w}$:** *Consensus* Log $P_{o/w}$ (Average of all five predictions), **SC:** Solubility Class (Water), **GIA:** Gastrointestinal absorption, **Log K_p:** skin permeation **(-cm/s)**, **RoF (V)**: Rule of Five (violation number), **Ghose:** Ghose Filter, **Leadlikeness (V):** Suitability score (violation number).

Table 2. Some properties of synthesized compounds from Schrodinger (QikProp)

	HBA	HBD	PSA	Log $P_{o/w}$	AS	-Log K_p	%HOA	RoF (V)	RoT (V)	Similar Molecules
3a	5	0	81.10	2.74	-4.20	-2.56	96	0	0	Azapropazone
3b	6	1	82.09	2.75	-4.76	-2.53	96	0	0	Diloxanide
3c	5	0	79.52	4.08	-5.80	-1.83	100	0	1	Phenylbutazone
3d	6	1	80.51	3.98	-6.20	-1.80	100	0	1	Oxyphenbutazone
3e	5.75	0	88.0	4.09	-5.84	-1.94	100	0	1	Bisacodyl
3f	6.75	1	88.99	4.09	-6.35	-1.91	100	0	1	Famprofazone
3g	6	1	80.51	4.28	-6.60	-1.94	100	0	1	Bisacodyl
3h	5	0	79.5	4.32	-6.17	-1.96	100	0	1	Tribuzone

HBA: H-bond acceptor (2 / 20), **HBD:** H-bond acceptor (0 / 6), **PSA:** vdW Polar SA (7.0 / 200.0), **%HOA:** % Human Oral Absorption in GI (poor<%25), **Log $P_{o/w}$:** Log $P_{o/w}$ (-6.5 / 0.5), **AS:** log S for aqueous solubility (-6.5 / 0.5), **Log K_p:** skin permeability **(cm/hr)**, **RoF (V)**: Rule of Five (violation number), **RoT (V):** Jorgensen Rule of 3 Violations, **Similar Molecules:** At least 90% similarity and above were considered, but if there is nothing, at this time the closest one indicated.

structure of final compounds was assigned on the basis of spectroscopic and analytical data. In the ^{1}H-NMR spectra of the compounds, singlet peaks at about 3.37-3.83, 7.78-8.08 and 10.09-10.36 ppm were assigned to methoxy proton (OCH_3), thiazole C_5 proton and NH protons, respectively. The other alkylic and aromatic protons were determined at about 2.61-3.51 ppm and 7.08-8.21 ppm. In the ^{13}C-NMR spectra of the compounds, peaks at about 51.85-53.45 ppm indicated the methoxy carbon existed in ester structure, the signals observed in the down field over 160 ppm were defined for carbonyl carbons and vicinal aromatic carbons to heteroatoms as expected. M+1 peaks were determined for all compounds. Elemental analyses results for C, H, and N elements were satisfactory within calculated values of the compounds.

The physicochemical/pharmacokinetic and druglikeness properties of the final compounds (**3a-h**) were predicted using SwissADME (**Table 1**) and QikProp (**Table 2**) softwares. ADME parameters (for Absorption, Distribution, Metabolism and Excretion) including H-bond acceptor (HBA), H-bond acceptor (HBD), polar surface area (PSA/TPSA), partition coefficient (Log Po/w), skin permeability (Log Kp), Rule of five (violation number-RoF) and Gastrointestinal absorption (GIA) were calculated virtually in both programs. Additionally, water solubility (Log S), Jorgensen Rule of 3 Violations (RoT(V), Molecular Weight (MW) were identified and evaluated [35]. According to the Lipinski Rule of Five, all compounds were detected in the compliant with the rule to be an oral bioavailable drug. The rule suggests that a high absorption is available for an

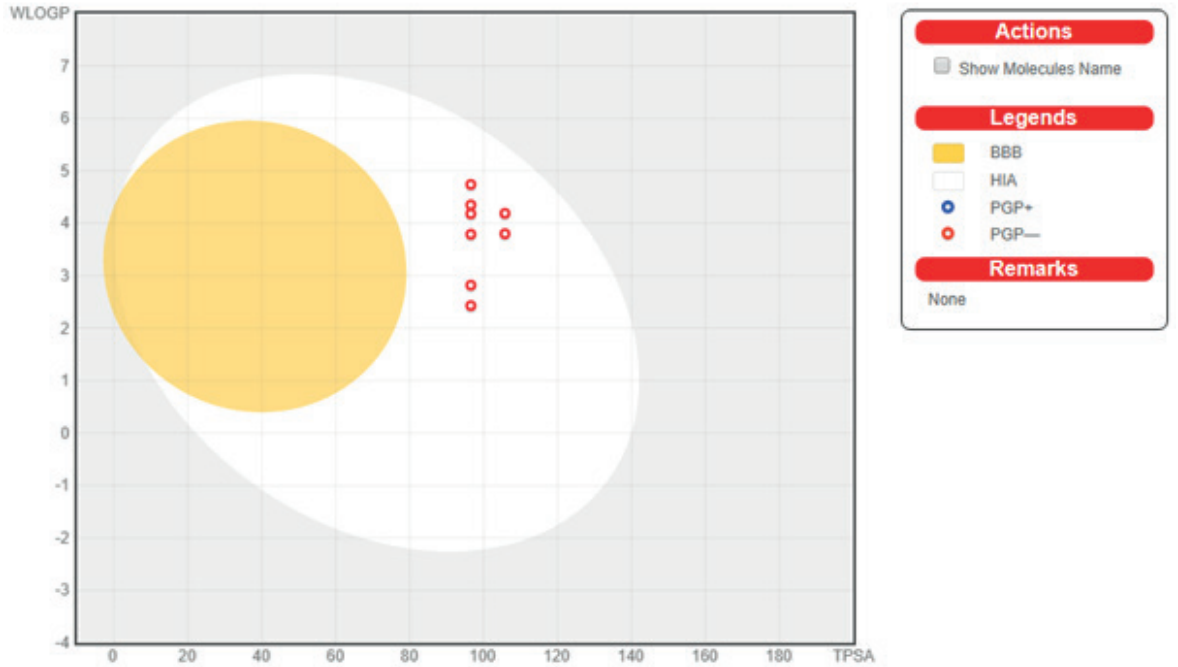


Figure 1. Boiled-egg plot of the compounds **3a-h**

oral drug when it possesses HBD less than 5, HBA less than 10, MW less than 500, and log P less than 5 [36]. All compounds passed Ghose filter developed by him [37] for drug discovery. Leadlikeness is the filter identified by Teague and co-workers which only compounds **3a** and **3b** passed through this filter [38]. Also, similar molecules (anti-inflammatory, antiprotozoal and laxative drugs) to these compounds were detected by QikProp software The boiled-egg plot between WLOGP and TPSA was also studied in SwissADME to predict gastrointestinal absorption and brain penetration of the selected molecules. According to **Figure 1**, none of the compounds have BBB permeability but they possess gastrointestinal absorption. Besides, red dots show molecules predicted not to be effluated from central nervous system by P-glycoprotein [39].

Table 3. SwissTarget prediction of the compounds **3a-h** in percentage (%)

	Kinase	Enzyme	Family A G protein-coupled receptor
3a	33.3	13.3	13.3
3b	26.7	13.3	13.3
3c	60	-	-
3d	53.3	-	13.3
3e	40	-	13.3
3f	40	20	-
3g	53.3	13.3	-
3h	33.3	20	20

Target prediction of the final compounds was identified using SwissTarget prediction software. Top fifteen targets were estimated; frequently predicted target regions were given in **Table 3** and over 10 % were in explanation. Compounds **3a-h** were determined to target on kinase, enzyme and Family A G protein-coupled receptor with percentages of 26.7-60, 13.3-20 and 13.3-20 %, respectively. Additionally, compound **3a** and **3c** exhibited phosphodiesterase target with 13.3 and 26.7 %. Compound 3b showed Family B G protein-coupled receptor (13.3%) whereas **3d** showed nuclear receptor (26.7%). Besides, compound **3e**, **3f** and **3g** represented targets phosphatase, electrochemical

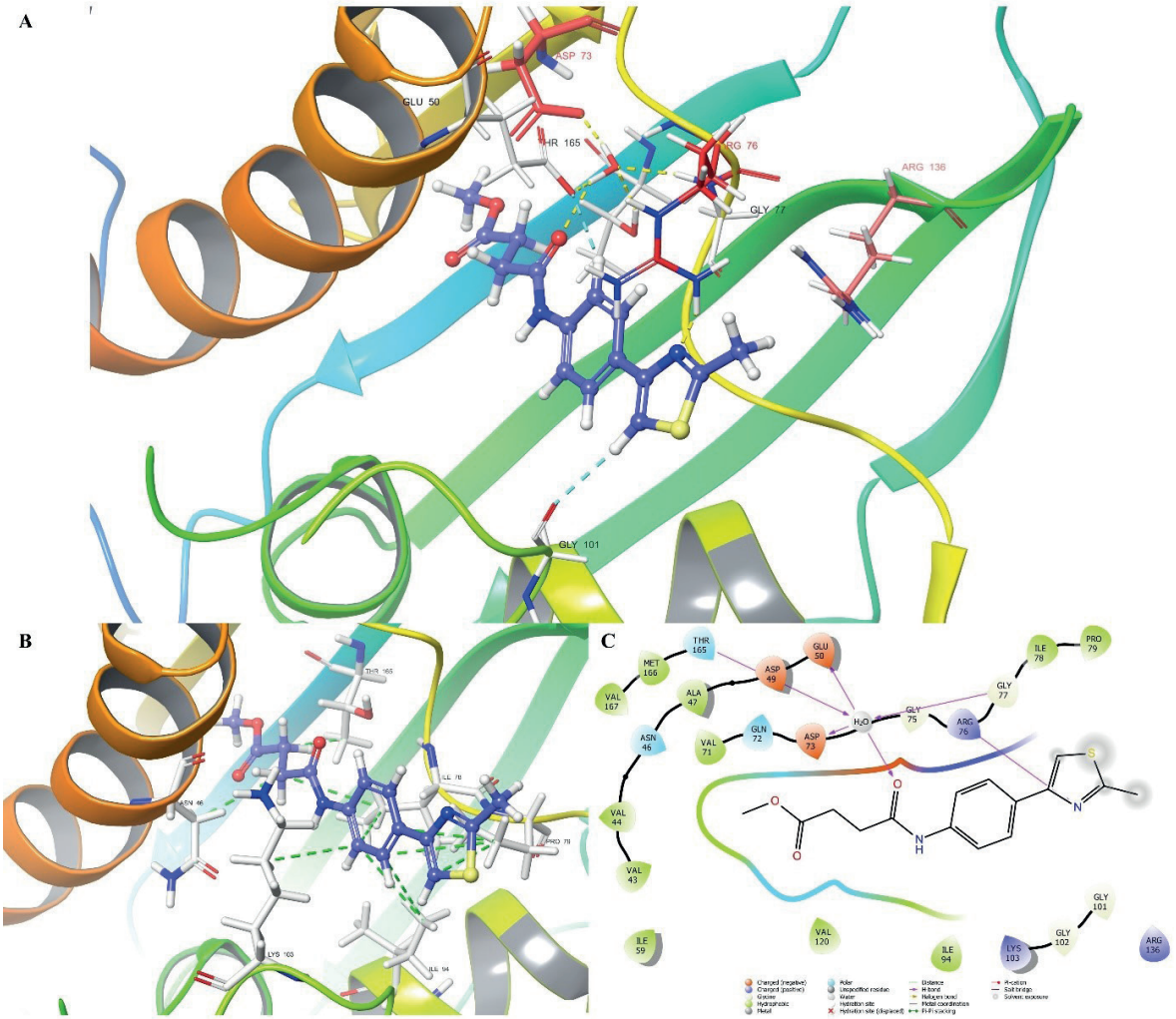


Figure 2. The best 2D and 3D poses of compound **3b. A)** The carbon atoms of key amino acids were represented as red, the carbon atoms interacted residues were represented as white. **B)** Hydrophobic interactions were represented as green dashes. **C)** The ligand, the residues around its 5 Å, and the important water molecule were displayed.

transporter and protease with percentages 13.3, 13.3 and 20 %, respectively. The possible sites of target which the compound may bind to are mostly the targets which are predicted by the software and the probability score are very less that is between 0.153 to 0.097. This makes an inference that the small compound may have high target attraction towards the specific binding site it is directed to [40].

In addition to the above information, we investigated the probable antimicrobial action mechanism of the final compounds through the docking study. The docking study point out that compound **3b** may have potent antimicrobial activity via ATP-competitive DNA gyrase B inhibition. Obtained 2D and 3D pose showed that compound **3b** interacted with Asp49, Glu50, Asp73 and Gly77 amino acids via water-mediated H-bonds. On the other hand, there were one direct H-bond with Arg76 and also 2 aromatic H-bonds with Gly101 and Thr165 residues. Moreover, compound **3b** have showed van der Waals

interactions with Asn46, Ile78, Pro79, Ile94, Lys103 and Thr165 amino acids. All those connections were envisaged as binding action (**Figure 2**). The role of the GyrB subunit is to provide the energy necessary for the DNA ligation process through ATP hydrolysis, hence, the inhibition of this subunit cause stopping ATP hydrolysis, so bacteria cells lose their functions. In previous studies, Asp73 and Gly101 residues have been described as key amino acids for inhibition of the GyrB subunit [41,42]. However, Gly101 amino acid and the other loop amino acids (Gly102, Lys103, and Phe104) could stabilize the loop region, which reduces the flexibility of the enzyme. Therefore, it can be concluded that be a direct proportion between the strong inhibition potential and those loop amino acids interactions. Moreover, final compounds except **3b**, could not properly enter the cavity, thus, not dock with important amino acids well at GyrB active pocket (**Figure 3**). For compounds **3c-3h**, It is probably caused by their bulky structures due to phenyl substitutions at the 4th position of the thiazole ring. On the other hand, compound **3a** has a small moiety (methyl) at thiazole ring like **3b**, but its localization was observed like other derivatives. It may be related to the absence of one carbon at the side chain. This absence may have led to unfavorable localization between ligand and protein. Indeed, there weren't any connections between **3a** and Gly101. It's clear that only compound **3b** was found as an appropriate analog to inhibit DNA gyrase via blocking ATP hydrolysis. In further studies, the advanced experimental studies should be improved. Although this potential hit was determined, this compound may also be useful for developing more powerful molecules.

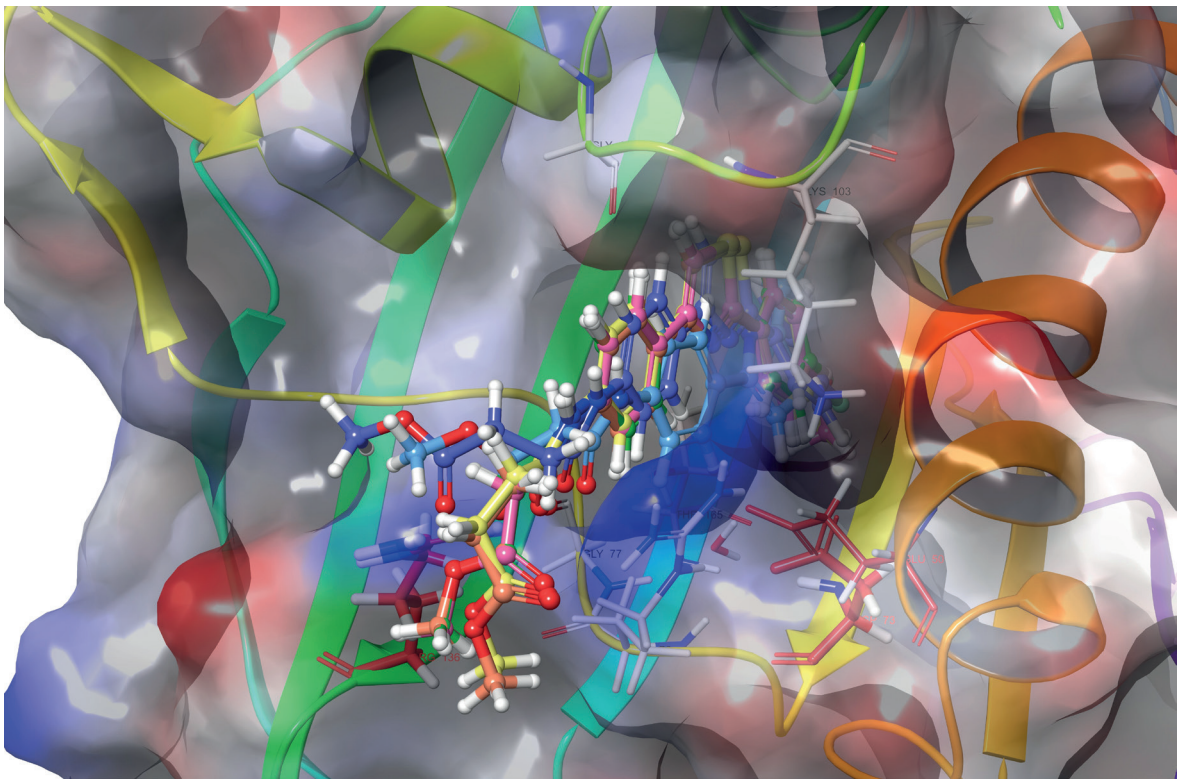


Figure 3. The final compounds at DNA gyrase active region

Table 4. Toxic profiles of the compounds (**3a-h**) predicted using pkCSM software

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
Ames toxicity	No	No	No	No	No	No	No	No
Max. tolerated dose (human, log mg/kg/day)	-0.156	-0.198	-0.054	-0.025	-0.118	-0.107	-0.102	-0.089
hERG I inhibitor	No	No	No	No	No	No	No	No
hERG II inhibitor	No	No	No	No	No	No	No	No
Oral Rat Acute Toxicity (LD50, mol/kg)	2.686	2.643	2.243	2.147	2.447	2.37	2.38	2.304
Oral Rat Chronic Toxicity (LOAEL, log mg/kg_bw/day)	1.178	1.169	0.911	0.909	1.01	0.936	0.974	0.901
Hepatoxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Skin sensitisation	No	No	No	No	No	No	No	No
***T. pyriformis* toxicity (log µg/L)**	0.887	1.127	0.567	0.562	0.46	0.451	0.462	0.455
Minnow toxicity (log mM)	0.881	0.719	-0.382	-0.511	-0.837	-0.966	-0.631	-0.76

Toxic profiles of the compounds were also predicted using pkCSM software and the results were displayed in **Table 4**. The website can provide details of toxicology effects in the fields of AMES toxicity, human maximum tolerance dose, hERG-I inhibitor, hERG-II (human Ether-à-go-go-Related Gene) inhibitor, LD_{50} (lethal dose), chronic oral rat toxicity, hepatotoxicity, skin toxicity, *T. pyriformis* toxicity and minnow toxicity. None of the compounds possessed Ames toxicity which mean they have no mutagenic potential and also skin sensitization, however they all cause hepatotoxicity. They don't inhibit hERG-I and hERG-II which is a satisfying finding that provides non-cardiotoxic profile to the compounds [43]. Acute oral rat toxicity (LD_{50}) of the compounds were found in between 2.147-2.686 mol/kg, whereas chronic oral rat toxicity (LOAEL) were found 0.901-1.178 log mg/kg_bw/day. Toxicity to *T. pyriformis* which is a ciliate protozoan was found between the range of 0.451-1.127 log µg/L. Compounds **3a** and **3b** including alkyl function (methyl) which differ from others showed the highest toxicity to the protozoan and minnow (fish species), too.

4. CONCLUSION

New eight thiazole compounds (**3a-h**) were synthesized containing ester and amide function using known synthetic procedures and starting from Hantzsch thiazole ring cyclization reaction. Final ester compounds were evaluated for their physicochemical/pharmacokinetic and druglikeness properties. All compounds were found to be in compliance with such rules, Lipinski and Ghose. Kinases were *in silico* determined as the main biological target for these compounds and toxicity profile of them was identified at the acceptable ranges, virtually. Compound **3b** was found a hit molecule to inhibit DNA gyrase B subunit enzyme.

Ethical approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Author contribution

Concept: LY, YÖ; Design: LY, YÖ; Supervision: YÖ; Materials: LY; Data Collection and/or Processing: LY, AEE; Analysis and/or Interpretation: LY, YÖ, AEE; Literature Search: LY, AEE; Writing: LY, AEE; Critical Reviews: LY, AEE.

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Conflict of interest

The authors declare that there is no conflict of interest.

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