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Synthesis, Characterization and Docking Studies of Some New Alkyne Containing Thiazole Derivatives

Navneet P. Mori[1], Priti K. Parmar[1], Vijay M. Khedkar[2], Gaurav Sanghavi[3] and Ranjan C. Khunt[1,✉]

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ABSTRACT

Thiazole derivatives are potential candidates for drug development. They can be efficiently synthesized and are extremely active against several diseases, including antimicrobial screening. A series of 2-(2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazinyl)-4-(*p*-tolyl)-4,5-dihydrothiazole **(5a-f)** and 2-((2-(4-(4-bromophenyl)-thiazol-2-yl)hydrazono)methyl)-5-(diethylamino)phenol (**8g-j**). The synthesized compounds' have been characterized by spectral analysis, such as mass, FT-IR, ^{1}H & ^{13}C NMR. All the synthesized compounds were screened for *in vitro* antibacterial activity against some Gram-positive (*Staphylococcus aureus*, *Streptococcus pyogenes*) and Gram-negative (*Escherichia coli*, *Klebsila*) bacteria. The thiazole derivatives with a pharmacologically potent group provide the valued therapeutic involvement in the treatment of microbial diseases, especially against bacterial and fungal infections. Furthermore, to gauze their plausible mechanism of action and thermodynamic interaction governing these molecules' binding, a molecular docking study was carried out against crucial target bacterial DNA, Gyrase.

KEYWORDS

Antimicrobial agents, Binding affinity study, Alkyne, Thiazole scaffold.

INTRODUCTION

In the present scenario, the microbial infection's omni-presence is the primary concern to the public, health worldwide and treatment for microbial infection remains an important and thought irritating problem for researchers due to multi drugs resistant strain [1,2]. The major complication in anti-microbial drug therapy has original to be drug resistance. However, numerous new antimicrobial agents and their medical ethics are inadequate to treat an emergency range of life-threatening universal infections due to the high risk of toxicity, irrelevance in their therapeutic activity [3,4]. Therefore, the spread of antibiotic resistance among pathogenic microbes has become a serious mystery for the clinical management of infectious diseases and resulted in demand for new and better than traditional antibacterial agents [5,6].

During the literature survey, it was noticed that the first effective antibiotics used for the treatment of microbial infections are sulphathiazole, fentiazac and niridazole, bearing thiazole ring (Fig. 1). Thiazole derivatives are a prominent group of the

Author affiliations:

[1]Chemical Research Laboratory, Department of Chemistry, Saurashtra University, Rajkot-360005, India
[2]School of Pharmacy, Vishwakarma University, Pune-411048, India
[3]Department of Microbiology, Marwadi University, Rajkot-360003, India

✉To whom correspondence to be addressed:

E-mail: navneetmori44@gmail.com; drrckhunt12@yahoo.com

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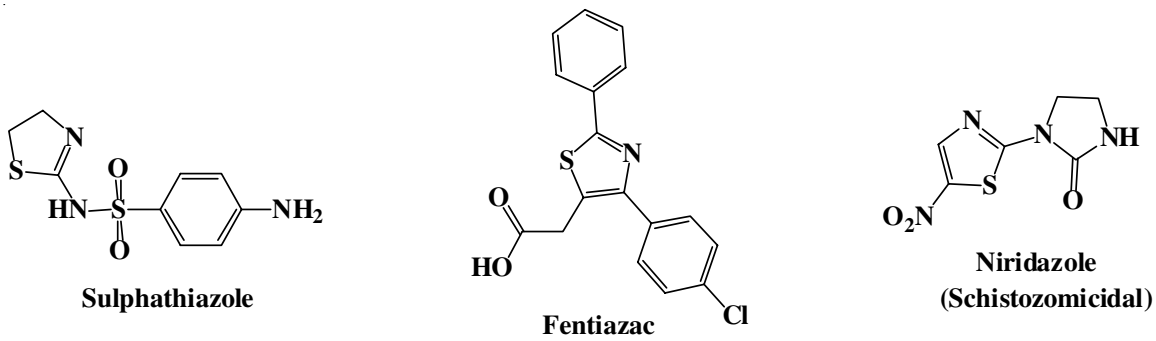


Fig. 1. Thiazole bearing active drugs

heterocyclic compound that has a therapeutic effect against several diseases [7-11]. Moreover, the thiazole ring is also associated with many biological activities such as antimicrobial [12,13], alkaline phosphatase inhibitors [14], rabies antiviral agents [15], anticancer agents [16-18], anticytotoxic agents against human breast cancer cell line [19] as well as antitumor agents [20]. Thiosemicarbazide is a very good synthon to construct sulphur or nitrogen containing rings, or both heteroatoms are present in five or six-membered heterocycles [21]. Many researchers have reported the S/N regioselective nucleophilic completion in heterocyst construction by intramolecular cyclization. The involvement of nitrogen or sulphur, depending on reaction condition, resulted in a different ring system formation. Moreover, thiosemicarbazide attachment, with an aromatic ring, enhances the various biological activities [22-24].

Because of these instances and together with our research concerns of developing new convenient approaches for the synthesis of different heterocyclic systems with auspicious pharmacological activities [25], we herein report the synthesis of thiazole derivatives bearing terminal alkyne with the variant in base scaffolds in two-step procedure. The starting material was selected based on of their nitrogen and oxygen atom dependency to enhance the antimicrobial efficacy. Additionally, we have assessed a biological activity for the newly synthesized compounds that demonstrated their potential antimicrobial effectiveness.

EXPERIMENTAL

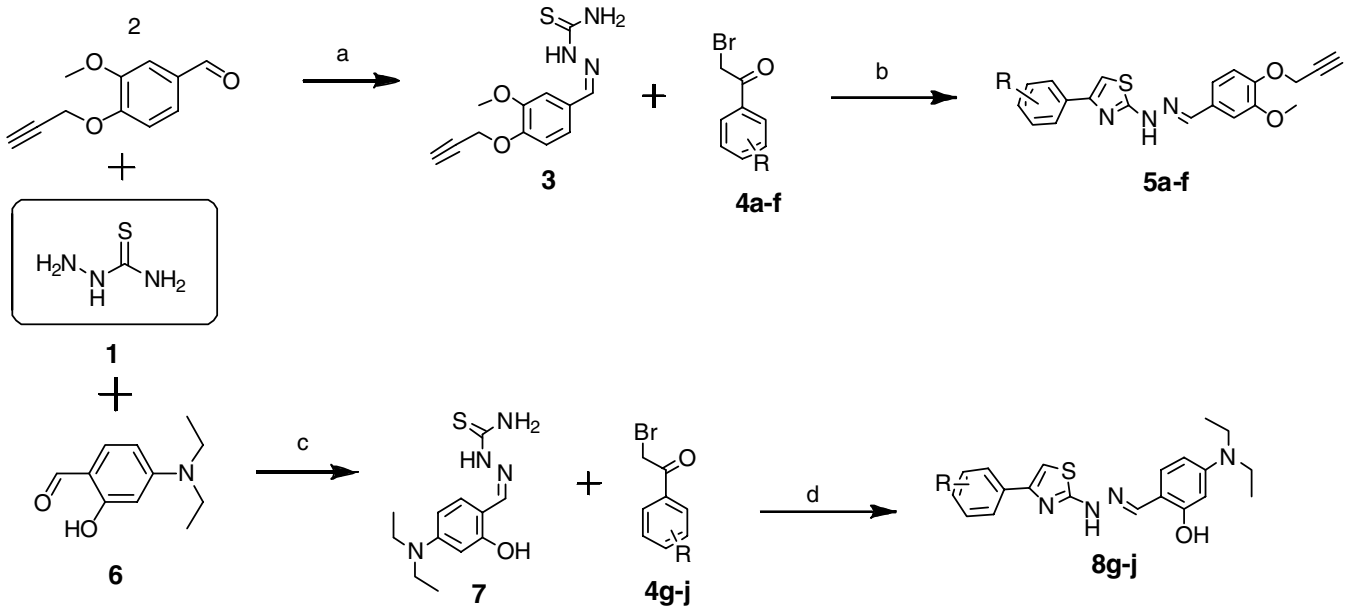
The raw material used for the synthesis were commercially available as an analytical grade reagent. Precoated silica gel plates G60 F_{254} (0.2 mm, Merck) were used for thin-layer chromatography. Visualization was made under UV light (254 and 365 nm) or with iodine vapour. FT-IR spectra were recorded on an FT-IR Affinity-1S spectrophotometer (Shimadzu). ^{1}H (400.1 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker AVANCE III spectrometer in $(CD_3)_2SO$. Chemical shifts are expressed in δ ppm downfield from tetramethyl silane (TMS). Mass spectra were recorded on GC-MS-QP 2010 mass spectrometer (Shimadzu). Melting points were measured using Digital Auto Melting Point Device (Labronics).

Synthesis of 2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazine-1-carbothioamide (3): In a round bottom flask, to a suspension of thiosemicarbazide (**1**) (5 g, 0.026 mol) in methanol (2 mL), 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde (**2**) (2.39 g, 0.026 mol) was added in a dropwise manner. The resulting mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was poured into ice-cold water (10 mL). The mixture was filtered and dried using a vacuum drier. The dried product was recrystallized from ethanol to afford analytically pure products compound **3** (yield: 85%). m.p.: 182-195 ºC. The reaction's progress was monitored on a TLC plate using *n*-hexane:ethyl acetate (7:3) as a mobile phase.

Synthesis of 2-(4-(diethylamino)benzylidene)hydrazine-1-carbothioamide (7): To a solution of 4-(diethylamino)-2-hydroxybenzaldehyde (**6**) (0.026 mmol) in methanol (2 mL), the stock of thiosemicarbazide was added to compound **1** (0.026 mol) in a dropwise manner. The resulting mixture was stirring at room temperature for 2.5 h. The reaction was monitored on a TLC plate using ethyl acetate:*n*-hexane (3:7). After completion of the reaction, the reaction mixture was poured into crushed ice and the desired solid product (**7**) was separated out. It was filtered, washed with *n*-hexane to afford the pure product (**7**). This product was used in the next step without purification (yield: 93%). m.p.: 179-186 ºC.

Synthesis of 4-(4-fluorophenyl)-2-(2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazinyl)thiazole (5a-f): A mixture of intermediate (**3**) (10 mmol) and substituted phenacyl bromide (**4a**) (10.5 mmol) was dissolved in 5 mL methanol into a round bottom flask. The reaction mass was stirred continuously for 7 h at room temperature. The reaction was monitored on the TLC plate (10% *n*-hexane:ethyl acetate). After completion of the reaction, the reaction mass was cooled onto the ice and the white precipitate was collected. It was washed with *n*-hexane, dried, pure product as an off-white powder (yield: 87-92%) was isolated (**Scheme-I**).

4-(4-Bromophenyl)-2-(2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazinyl)thiazole (5a): Yield: 83%; m.p.: 170 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3363.97 (-NH *str.* hydrazone), 2939.31 (C-H *str.*), 1689.70 (C=N *str.*), 1504.53 (aromatic ring skeleton), 1265.35 (C-H bending); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ ppm: 8.95 (1H, s, -NH), 8.08 (1H, t, J = 0.96 Hz), 7.80-7.72 (2H, m, CH, Ar), 7.59-7.51 (2H, m, CH Ar), 7.49 (1H, ddd, J = 0.93 Hz, -CH Ar), 7.30 (1H, dd, J = 1.97 Hz, CH Ar), 7.24 (1H, s, CH Ar), 7.13 (1H, d, J = 8.37 Hz, CH Ar), 4.84-4.78 (2H, d, J = 2.92 Hz, -CH_2), 3.86-3.80 (3H, s, -CH_3), 3.60 (1H, t, J = 3.00 Hz, -CH acetylene); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 170.0 (C=S), 149.2 (C=O),148.70 (C, Ar), 146.9 (N-C), 133.5 (C, Ar), 132.8 (C_2, Ar), 131.0 (C, Ar), 128.3 (C, Ar), 127.7 (C, Ar), 127.5 (C_2, Ar), 124.7 (C, Ar), 121.8 (C, Ar), 117.6 (C, Ar), 109.4 (C, Ar), 78.9 (O= C), 76.1 (O-C), 56.5 (O-CH_3), 56.3 (O-C); MS: *m/z* 442.33 (M^+); Elemental analysis



where R = -H, -Br, -Cl, -CH_3, -OCH_3, -F; Reaction conditions: (a) Methanol, CH_3COOH, RT, 3 h, stirring; (b) Methanol, RT, 8 h, stirring, (c) Ethanol, RT, 4 h, stirring; (d) Methanol, RT, 7 h, stirring

Scheme-I: Reaction scheme of compounds **5a-f** & **8g-j**

of $C_{20}H_{16}N_3O_2SBr$ calcd. (found) (%): C, 54.31 (54.34); H, 3.65 (3.68); N, 9.50 (9.55); O, 7.23 (7.20); S, 7.25 (7.22).

2-(2-(3-Methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazinyl)-4-(*p*-tolyl)thiazole (5b): Yield: 89%; m.p.: 178 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3255.95 (-NH *str.* hydrazone), 2924.18 (-C-H *str.*), 1689.70 (C=N *str.*), 1573.97 (aromatic ring skeleton), 1419.66 (C-H bending), 817.85 (arom. C-H mono substitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 8.949 (1H, s, *sec*. -NH), 8.101 (1H, t, *J* = 0.97 Hz, CH Ar), 7.858-7.779 (2 H, m, CH Ar), 7.407 (1H, ddd, *J* = 0.85 Hz, CH Ar), 7.337-7.180 (4 H, m, CH Ar), 7.1485 (1H, d, *J* = 8.37 Hz, CH Ar), 4.847-4.784 (2 H, d, *J* = 2.92, -CH_2), 3.868-3.807 (3H, s, -CH_3), 3.605 (1H, t, *J* = 3.00 Hz, -CH acetylene), 2.398-2.335 (3H, d, *J* = 0.74 Hz, -CH_3); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 168.6 (C=S),150.7 (C=N), 149.8 (C, Ar), 148.1 (C, Ar), 141.7 (C=N), 137.8 (C, Ar), 132.9 (C, Ar), 129.9 (-CH), 129.6 (CH), 128.8 (C, Ar), 128.5 (C, Ar), 125.3 (CH), 120.2 (CH),114.3 (CH), 109.2 (C=S), 103.0 (C, thiazole), 79.5 (CH), 78.9 (C, acetylene), 56.5 (CH_3), 55.9 (CH_2), 21.2 (CH_3); MS: *m/z* 379 (M^+); Elemental analysis of $C_{21}H_{19}N_3O_2S$ calcd. (found) (%): C, 66.82 (66.85); H, 5.07 (5.10); N, 11.13 (11.15); O, 8.48 (8.50); S, 8.49 (8.52).

2-(2-(3-Methoxy-4-(prop-2-yn-1-yloxy)benzylidene)-hydrazinyl)-4 (4-methoxyphenyl)thiazole (5c): Yield: 89%; m.p.: 180 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3333.10 (-NH *str.* hydrazone), 3010.50 (C-H *str.*), 1681.98 (C=N *str.*), 1512.24 (aromatic ring skeleton), 1482.73 (C-H bending), 833 (arom. C-H mono substitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 8.043 (1H, s, -NH), 7.859-7.742 (2 H, m, CH Ar), 7.367 (1H, m, CH Ar), 7.303-7.124 (2 H, m, CH Ar), 7.122 (1H, d, *J* = 8.37 Hz, CH Ar), 7.040-6.946 (2H, m, CH Ar), 4.868-4.774 (2H, d, *J* = 2.42 Hz, CH_2), 3.944-3.647 (7 H, m, CH Ar), 3.630 (1H, t, *J* = 2.43 Hz, -CH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 170.0 (C=S), 155.4 (C=O), 149.2 (C, Ar), 148.7 (C, Ar), 145.9 (HC=N), 133.5 (C, Ar), 128.4 (C, Ar), 128.3 (C, Ar), 128.3 (CH), 127.9 (C, Ar), 124.2 (C, Ar), 117.4 (C, Ar), 113.8 (C, Ar), 109.3 (C, Ar), 78.9 (C= C), 76.2 (-CH), 56.5 (-CH_2), 56.3 (-CH_3), 55.3 (-CH_3); MS: *m/z* 394. (M^+); Elemental analysis of $C_{21}H_{19}N_3O_3S$ calcd. (found) (%): C, 64.11 (64.15); H, 4.87 (4.88); N, 10.68 (10.65); O, 12.20 (12.22); S, 8.15 (8.18).

4-(4-Fluorophenyl)-2-(2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazinyl)thiazole (5d): Yield: 91%; m.p.: 188 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3350.50 (-NH *str.* hydrazone), 3070.71 (C-H *str.*), 1627.97 (C=N *str.*), 1512.24 (aromatic ring skeleton), 1419.66 (C-H bending), 840 (arom. C-H mono substitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 8.94 (1H, s, -NH), 8.10 (1H, t, *J* = 0.96, HC=N), 7.84-7.75 (2 H, m, Ar), 7.41 (1H, ddd, *J* = 8.28 Hz, CH Ar), 7.298-7.15 (4 H, m, CH Ar), 7.11 (1H, d, *J* = 8.31 Hz, Ar), 4.85-4.78 (2 H, d, *J* = 3.08 Hz, -CH_2), 3.86-3.80 (3 H, s, CH, Ar), 3.60-3.53 (1H, t, *J* = 3.00 Hz, -CH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 168.8 (C=S), 163.3 (Ar),160.8 (C, Ar), 149.8 (C=S), 149.3 (C, Ar),148.2 (C, Ar), 142.2 (HC-N), 131.4 (C, Ar),128.5 (C, Ar),120.3 (C, Ar),115.8 (Ar),109.2 (C, Ar), 103.7 (C, thiazole), 79.5 (C, acetylene), 78.9 (C), 56.5 (-CH_3),55.9 (C-O); MS: *m/z* 380.9 (M^+); Elemental analysis of $C_{20}H_{16}N_3O_2SF$ calcd. (found) (%): C, 62.97 (62.95); H, 4.23 (4.27); N, 11.02 (11.05); O, 8.39 (8.36); S, 8.41 (8.46).

2-(2-(3-Methoxy-4-(prop-2-yn-1-yloxy)benzylidene)-hydrazinyl)-4-phenylthiazole (5e): Yield: 95%; m.p.: 168 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3286.81 (-NH *str.* hydrazone), 3063.06 (C-H *str.*), 1681.98 (C=N *str.*), 1589.40 (aromatic ring skeleton), 1450.52 (C-H bending), 884 (arom. C-H mono substitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 12.14 (1H, s, -NH), 8.00 (1H, s, CH, Ar), 7.90-7.83 (2H, m, CH Ar), 7.46-7.3 (2H, t, *J* = 7.55 Hz, CH Ar), 7.35-7.28 (3 H, m, CH Ar), 7.22 (1H, dd, *J* = 8.33 Hz, CH Ar), 7.12 (1H, d, *J* = 8.37 Hz, CH Ar), 4.87-4.81 (2H, d, *J* = 2.46 Hz, CH), 3.86-3.81 (3 H, s, -CH_3), 3.58 (1H, t, *J* = 2.35 Hz, CH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 170.0 (C=S), 149.2 (C, Ar), 148.7 (C, Ar), 146.9 (C-N),

139.3 (C, Ar), 131.4 (C, Ar), 129.84 (C, Ar), 128.9 (C_2, Ar), 127.7 (C_2, Ar), 127.4 (C, Ar), 125.5 (C, Ar), 124.2 (C, Ar), 117.4 (C, Ar), 109.3 (C, Ar), 78.9 (C, acetylene), 76.2 (CH, acetylene), 56.5 (C-O), 56.3 (-CH_3); MS: *m/z* 364.8 (M^+); Elemental analysis of $C_{20}H_{17}N_3O_2S$: calcd. (found) (%): C, 66.10 (66.11); H, 4.72 (4.74); N, 11.56 (11.59); O, 8.80 (8.88); S, 8.82 (8.85).

4-(4-Chlorophenyl)-2-(2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazinyl)thiazole (5f): Yield: 93%; m.p.: 193 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3225.09 (-NH *str.* hydrazone), 3001.34 (C-H *str.*), 1626.97 (C=NS *str.*), 1512.24 (arom. ring skeleton), 1445.73 (C-H bending), 833 (arom. C-H mono substitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 12.00 (1H, s, -NH), 8.02 (1H, s, CH Ar), 7.95-7.77 (2 H, m, CH Ar), 7.59-7.42 (2 H, m, CH Ar), 7.42 (1H, s, CH Ar), 7.36-7.25 (1H, d, *J* = 2.01 Hz, CH Ar), 7.25-7.15 (1H, dd, *J* = 8.32 Hz, CH Ar), 7.14 (1H, d, *J* = 8.25,CH Ar), 4.87-4.73 (2 H, d, *J* = 2.41 Hz, CH Ar), 3.93-3.73 (3 H, s, CH_2), 3.70– 3.534 (1H, t, *J* = 2.41 Hz, CH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 170.0 (C=S), 149.9 (C, Ar), 148.7 (C, Ar), 146.2 (HC=N), 139.1 (C=S), 131.3 (C, Ar), 129.4 (C_2, Ar), 128.0 (C_2, Ar), 127.6 (C, Ar), 127.2 (C, Ar), 125.6 (C=S), 124.7 (C, Ar), 117.6 (C, Ar), 109.4 (C, Ar), 78.3 (O-C), 76.1 (C, acetylene), 56.5 (CH_2), 56.3 (CH_3); MS: *m/z* = 396.7. (M^+); Elemental analysis of $C_{20}H_{16}N_3O_2SCl$ calcd. (found) %: C, 60.38 (6.39); H, 4.05 (4.04); N, 10.56 (10.57); O, 8.04 (8.08); S, 8.06 (8.07).

Synthesis of 2-((2-(4-(4-bromophenyl)thiazol-2-yl)-hydrazono)methyl)-5-(diethylamino)phenol (8g-j): In a round bottom flask, a mixture of intermediate (**7**) (0.01 mmol) and substituted phenacyl bromide (**4a**) (0.015 mmol) was dissolved in methanol (5 mL). The reaction mass was stirred continuously for 7 h at room temperature. The reaction was monitored on the TLC plate using *n*-hexane:ethyl acetoacetate (6:4) as a mobile phase. After the completion of reaction, a mass was cooled into the ice and the white precipitate was collected by filtration. It was washed with *n*-hexane, dried, pure product as an off-white powder (yield: 88-95%) was isolated (**Scheme-I**).

2-((2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)-methyl)-5-(diethylamino)phenol (8g): Yield: 82%; m.p.: 166 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3394.83 (-NH *str.* hydrazone), 2955.04 (C-H *str.*), 1597.11 (C=N *str.*), 1527.67 (aromatic ring skeleton), 1440.60 (C-H bending), 840 (aromatic C-H mono substitution), 717 (arom. C-H disubstitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 11.77 (1H, s, -NH), 9.55 (1H, s, -OH), 8.29 (1H, d, *J* = 0.99 Hz, CH), 7.76-7.67 (2 H, m, CH, Ar), 7.51-7.43 (2 H, m, CH, Ar), 7.25 (1H, s, CH, Ar), 7.23 (1H, dd, *J* = 8.40 Hz, CH, Ar), 6.38 (1H, dd, *J* = 8.35 Hz, CH, Ar), 6.08 (1H, d, *J* = 2.25 Hz, CH, Ar), 3.46-3.35 (4 H, q, *J* = 7.20 Hz, -CH_2), 1.22-1.13 (6 H, t, *J* = 7.20 Hz, -CH_3); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 168.6 (C=S),157.5 (C, Ar), 137.9 (C, Ar), 133.5 (C, Ar), 132.3 (C, Ar), 131.4 (C, Ar), 129.3 (C_2, Ar),129.3 (C_2, Ar), 129.3 (C, Ar), 128.3 (C_2, Ar),128.1 (C, Ar), 125.9 (C, Ar), 40.6 (C_2), 40.5 (C, Ar), 40.4 (C, Ar),12.4 (-CH_3); MS: *m/z* 385.9 (M^+); Elemental analysis of $C_{20}H_{21}N_4OSCl$ calcd. (found) %: C, 59.92 (59.85); H, 5.28 (5.20); N, 13.97 (13.80); O, 3.99 (3.55); S, 8.00 (8.12).

5-(Diethylamino)-2-((2-(4-(*p*-tolyl)thiazol-2-yl)hydrazono)methyl)phenol (8h): Yield: 93%; m.p.: 120 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3302.24 (-NH *str.* hydrazone), 2970.48 (C-H *str.*), 1635.60 (C=N *str.*), 1519.96 (arom. ring skeleton), 1404.42 (C-H bending), 817 (arom. C-H monosubstitution), 632 (arom. C-H disubstitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 11.71 (1H, s, -NH), 9.48 (1H, s, -OH), 8.32 (1H, d, *J* = 0.99 Hz, CH), 7.85-7.78 (2 H, m, CH, Ar), 7.358-7.27 (2H, dq, *J* = 7.46 Hz, CH Ar), 7.28-7.25 (2 H, m, CH, Ar), 6.36 (1H, dd, *J* = 8.42 Hz, CH, Ar), 6.04 (1H, d, *J* = 2.29 Hz, CH, Ar), 3.45-3.35 (4H, q, *J* = 7.24 Hz, -CH_2), 2.394-2.34 (3H, m, -CH_3), 1.221-1.13 (6 H, t, *J* = 7.20 Hz, -CH_3). ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 168.6 (C=S), 157.5 (C, Ar), 137.29 (C, Ar), 132.3 (C, Ar), 129.6 (C_2, Ar), 129.3 (C_2, Ar), 129.3 (C_2, Ar), 128.3 (C_2, Ar), 128.2 (C_2, Ar), 125.9 (C_2, Ar), 40.46 (C_2), 21.2 (CH_3), 12.9 (C_2); MS: *m/z* = 379. (M^+); Elemental analysis of $C_{21}H_{24}N_4OS$: calcd. (found) (%): C, 66.29 (66.28); H, 6.36 (6.38); N, 14.72 (14.25); O, 4.20 (4.30); S, 8.43 (8.44).

2-((2-(4-(4-Bromophenyl)thiazol-2-yl)hydrazono)-methyl)-5-(diethylamino)phenol (8i): Yield: 97%; m.p.: 152 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3309.96 (-NH *str.* hydrazone), 2970.48 (C-H *str.*), 1689.70 (C=N *str.*), 1519.96 (arom. ring skeleton), 1473.66 (C-H bending), 817 (arom. C-H monosubstitution), 686 (arom. C-H disubstitution), ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 11.62 (1H, s, -OH), 8.24-7.16 (8 H, m, CH, Ar), 7.00-6.51 (2 H, s, CH, CH, Ar), 5.45-5.07 (1H, s, CH, Ar), 3.73-2.91 (3 H, m, -CH_2), 1.33-0.86 (6 H, t, *J* = 6.99, CH_3); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 168.6 (C=S), 157.5 (C=O), 133.5 (C, Ar), 132.8 (C, Ar), 132.3 (C, Ar), 131.0 (C, Ar), 129.3 (C_2, Ar), 129.5 (C, Ar), 128.3 (C_2, Ar), 127.5 (C, Ar), 125.9 (C, Ar), 121.1 (C-Br), 40.6 (C_2), 40.5 (C_2), 40.4 (CH), 12.4 (-CH_3); MS: *m/z* 431. (M^+); Elemental analysis of $C_{20}H_{21}N_4OSBr$ calcd. (found) (%): C, 53.94 (53.96); H,4.75 (4.50); N, 12.58 (12.50); O, 3.59 (3.55); S, 7.20 (7.20).

5-(Diethylamino)-2-((2-(4-phenylthiazol-2-yl)hydrazono)methyl)phenol (8j): Yield: 97%; m.p.: 172 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3310.20 (-NH *str.* hydrazone), 3063.04 (C-H *str.*), 1689.70 (C=N *str.*), 1597.11 (arom. ring skeleton), 1435.09 (C-H bending), 894 (arom. C-H monosubstitution), 709 (arom. C-H disubstitution); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ ppm: 11.90 (1H, s, -OH), 8.01 (1H, s, -NH), 7.977 (1H, s, CH, Ar), 7.89-7.82 (2H, d, *J* = 7.65 Hz, CH, Ar), 7.41-7.36 (2H, t, *J* = 7.57 Hz, CH, Ar), 7.32-7.24 (2H, q, *J* = 7.28 Hz, CH, Ar), 7.12-7.12 (2H, s, CH, Ar), 6.73-6.68 (2H, s, CH, Ar), 1.19-1.05 (9H, t, *J* = 7.09 Hz, CH_3). ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ ppm: 168.2 (C=S), 157.9 (C-O), 139.1 (C=N), 132.4 (C=N), 131.3 (C, Ar), 129.4 (C, Ar), 129.9 (C, Ar), 129.0 (C, Ar), 128.9 (C_2, Ar), 127.4 (C, Ar), 125.4 (C, Ar), 125.6 (C, Ar), 40.6 (C_2), 40.6 (C_2), 12.3 (C_3); MS: *m/z* = 365. (M^+); Elemental analysis of $C_{20}H_{22}N_4OS$ calcd. (found) (%): C, 66.55 (66.54); H, 6.05 (6.02); N, 15.29 (15.28); O, 4.37 (4.35); S, 8.75 (8.74).

Molecular docking: Microbial DNA gyrase, an extensively explored biological target, is present in almost all bacteria and is known to play a significant role in bacterial DNA replication, making it critical for the survival of the microorganism [26]. Furthermore, a low structural homology exhibited by this enzyme with human topoisomerases qualifies DNA gyrase as an attractive drug target for antibacterial drug discovery. The B-subunit of DNA gyrase (GyrB) consists of an ATP binding pocket and small molecule inhibition of this pocket has resulted in several lead compounds with antibacterial properties [27].

Thus to gain a better understanding of the antimicrobial potency of 4-aryl-2-(2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazine)thiazole derivatives, to elucidate their plausible mechanism of antimicrobial activity and to guide further SAR, a molecular docking study was performed against DNA gyrase subunit b (PDB ID:1KZN) using the standard protocol implemented in the GLIDE (Grid-Based Ligand Docking with Energetics) module of the Small Drug Discovery Suite (Schrödinger, LLC, New York, NY) [28-31].

RESULTS AND DISCUSSION

The synthetic procedure adopted for the titled compound is outlined in the reaction scheme. The key intermediate 2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazine-1-carbothioamide (**3**) and 2-(4-(diethylamino)benzylidene)-hydrazine-1-carbothioamide (**7**) was synthesized by the condensation of thiosemicarbazide with 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde (**2**) and 4-(diethylamino)-2-hydroxy-benzaldehyde (**6**), respectively. The structure of intermediates **3** and **7** was confirmed based on the spectroscopic data. The Michael addition of phenacyl bromide to hydrazinyl-thiocarbamide followed by intramolecular cyclization led to our target molecules' formation. The reaction optimization was carried out using different solvents and a high yield was formed in the case of methanol as a solvent.

The cyclization of thiosemicarbazide intermediate **3** and **7** depends on the reaction conditions (Table-1). Thus, the ring is constructed using intermediate **3** and **7** by the condensation of different phenacyl bromide in acidic media. The signal of -NH proton belongs to the thiazole ring was confirmed by appearing at δ 11.97 ppm as a singlet, further established by CMR at δ 168.66 ppm. In infrared spectroscopic studies of the title compound shown, the characteristic bands at 3300 and 1640 cm^{-1} demonstrated NH- groups. The *m/z* value in the mass spectrum also supported the builtup ring system.

Antimicrobial assay: All the synthesized compounds have been tested against Gram-positive stain *(Staphylococcus aureus* and *Bacillus subtillis*) and Gram-negative (*E. coli* and *Pseudomonas*) bacteria and determine the minimum inhibitory concentration (MIC) by performing turbidometry method [32]. The result of the MIC value against microorganisms is shown in Table-2. All compounds showed the MIC value in the range of 10-80 µg/mL. We have drawn the diversity at position-2 & 5 of the thiazole rings using 3-methoxy-4-(prop-2-yn-1-yloxy)-benzaldehyde (**2**) and 4-(diethylamino)benzaldehyde as well as various substituted phenyl, respectively. The SAR study from the MIC value proves that *p*-tolyl substitution behaves as a broad-spectrum molecule in 3-methoxy-4-(prop-2-yn-1-yloxy) benzaldehyde substitution at position-2 while active against Gram-negative bacteria in case of 4-*N,N*-dimethyl-benzaldeyde at position-2 of thiazole ring. The response of *B. cereus* strain against all the compounds is resistant. The 3-methoxy-4-(prop-2-yn-1yloxy)benzaldehyde enhances the activity at position-2 compared to 4-*N,N*-dimethylamino benzaldehyde, which may prove that the extended alkyne chain is better than the alkylamino group as an electron donor. Two aldehyde groups made a correlation with antimicrobial study, *i.e.* 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde (**2**) and 4-(diethylamino)benzaldehyde (**6**). Literature shows that donating part on the phenyl ring may serve as good mediators in medicinal chemistry. The table also supported that none of the electron-withdrawing features subsidizes to enhance biological activity. It was concluded that compound **8i** exhibited MIC in the range of *E. coli* and *Pseudomonas* strain with MIC values 10 and 15 µg/mL, respectively. Those of compounds **5b** were active only against *Staphylococcus* and *Bacillus cereus* strain with MIC values 15 and 20 µg/mL.

TABLE-1
OPTIMIZATION OF REACTION CONDITION

Solvent	Time	Temp. (°C)	Yield (%)
Methanol	3 h	RT	92
Ethanol	7 h	RT	82
Isopropyl alcohol	10 h	RT	53
Ethyl acetate	8 h	RT	59
THF	12 h	RT	47
Dichloromethane	7 h	RT	35
Toluene	3 days	RT	–
Methanol	7 h	60-70	64
Ethanol	9 h	70-80	51
Isopropyl alcohol	11 h	80-82	50
Ethyl acetate	9 h	80-90	56
THF	15 h	60-70	45
Dichloromethane	1 day	40-50	30
Toluene	4 days	110-120	–

Molecular docking: It was observed that all the molecules could dock well into the active site of DNA gyrase with good to excellent binding affinities, which is attributed to significant

TABLE-2
ANTIMICROBIAL ACTIVITY OF COMPOUNDS AS A MIC (**5a-e** and **8g-j**)

Compd. No.	R_1	Gram-positive		Gram-negative	
		S. aureu	*Bacillus sps*	*E. coli*	*Pseudomonas*
5a	-Br	25	70	20	30
5b	$-CH_3$	15	20	15	35
5c	$-OCH_3$	30	20	20	20
5d	-F	30	35	30	30
5e	-H	65	60	25	25
8g	-Cl	35	35	30	30
8h	$-CH_3$	20	25	40	20
8i	-Br	65	80	10	15
8j	-H	35	50	70	75
Standard Drug	Chloramphenicol	16	26	23	22
	Penicillin	24	34	64	32

bonded and non-bonded interactions (steric and electrostatic) with residues lining the active site of the enzyme (Table-3). The per-residue interaction analysis for one of the most active analog **5b** showed that the molecule is embedded into the active site through a series of significant van der Waals interactions observed with Val167 (-1.585 kcal/mol), Met166 (-1.024 kcal/mol), Thr165 (-3.11 kcal/mol), Ala96 (-1.479 kcal/mol), His95 (-1.672 kcal/mol), Ile90 (-3.854 kcal/mol), Asp73 (-2.639 kcal/mol), Val71 (-1.821 kcal/mol), Ala47 (-2.053 kcal/mol), Asn46 (-3.582 kcal/mol) and Val43 (-1.416 kcal/mol) residues through the 2-(2-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazinyl component while the 4-(*p*-tolyl) thiazole section was seen to be engaged in similar type of interactions with Arg136 (-1.711 kcal/mol), Ser121 (-1.339 kcal/mol), Val120 (-2.428 kcal/mol), Gly119 (-1.208 kcal/mol), Val118 (-1.713 kcal/mol), Pro79 (-3.445 kcal/mol), Ile78 (-4.943 kcal/mol), Gly77 (-2.596 kcal/mol), Arg76 (-5.822 kcal/mol) and Glu50 (-2.512 kcal/mol) residues lining the active site of the enzyme. Further, the high binding affinity demonstrated by this molecule is also attributed to favourable electrostatic interactions observed with Arg136 (-2.791 kcal/mol), Gly119 (-1.376 kcal/mol), His95 (-1.118 kcal/mol), Arg76 (-1.751 kcal/mol), Asp73 (-3.111 kcal/mol), Glu50 (-1.558 kcal/mol) and Asn46 (-1.674 kcal/mol) residues of active site. Though these non-bonded (steric and electrostatic) interactions were observed to be the major driving force for the mechanical interlocking of the molecule into the binding site, compound **5b** also showed two prominent hydrogen bonding interactions: firstly, with Arg136 (2.547 Å) through the thiazole (-N-) ring while the second hydrogen bond was formed through Asn46 (2.542 Å) with methoxy substituent. A very close π-π stacking interaction was observed through the thiazole ring with Arg136 (2.021 Å) and Arg76 (2.088 Å) residues. Such hydrogen bonding and π-stacking interactions "anchor" the ligand to guide into the 3D space of into the active site and facilitate the non-bonded interactions. A very similar network of bonded and non-bonded interactions was exhibited by other analogues in the series, contributed to their binding affinity towards bacterial DNA gyrase (Figs. 2-10). The information gained from these *in silico* binding analyses is now being utilized for the structure-based lead optimization to arrive at potent molecules with higher potency and selectivity.

Conclusion

It is concluded that the condensation of phenacyl bromide derivatives with different thiosemicarbazide in the presence of acetic acid and alcohol as a solvent to furnished thiazole ring system. It is confirmed that thiazole ring system provides more efficiency to bind with DNA Gyrase as a hydrogen bond donor with amino acid residue specifically with alanine indirectly it increases the potency of a molecule as an antimicrobial agent. The compound's MIC value concludes that the group present at position-2 is more important than position-5 to play the effective antimicrobial agents.

TABLE-3
MOLECULAR DOCKING SCORE (**5a-e** and **8g-j**)

Compd. No.	R_1	Glide score	Glide energy (kcal/mol)	H-bond (Å)	Pi-pi stacking (Å)
5a	Br	-5.364	-45.229	Glu50 (2.455)	–
5b	CH_3	-7.941	-40.234	Arg136 (2.547), Asn46 (2.542)	Arg136 (2.021), Arg76 (2.088)
5c	$-OCH_3$	-7.774	-38.540	Asn46 (2.542)	Arg136 (2.021)
5d	F	-7.397	-35.023	–	Arg136 (2.624)
5e	H	-7.473	-36.837	Glu50 (2.557)	–
8g	Cl	-7.285	-33.434	Glu50 (2.631)	–
8h	CH_3	-7.175	-33.62	Glu50 (2.637)	–
8i	Br	-7.813	-39.722	Glu50 (2.759)	–
8j	H	-7.011	-31.723	Glu50 (2.587)	–

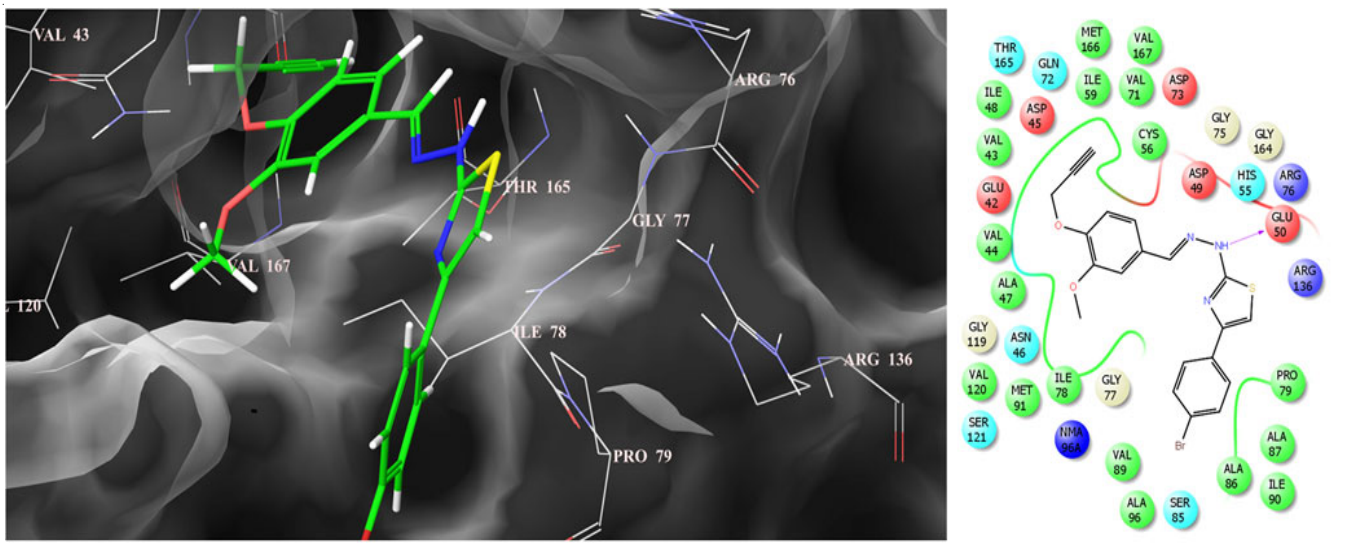


Fig. 2. Binding mode of **5a** into the active site of DNA gyrase subunit b (on right side: pink lines represent hydrogen bonding interactions)

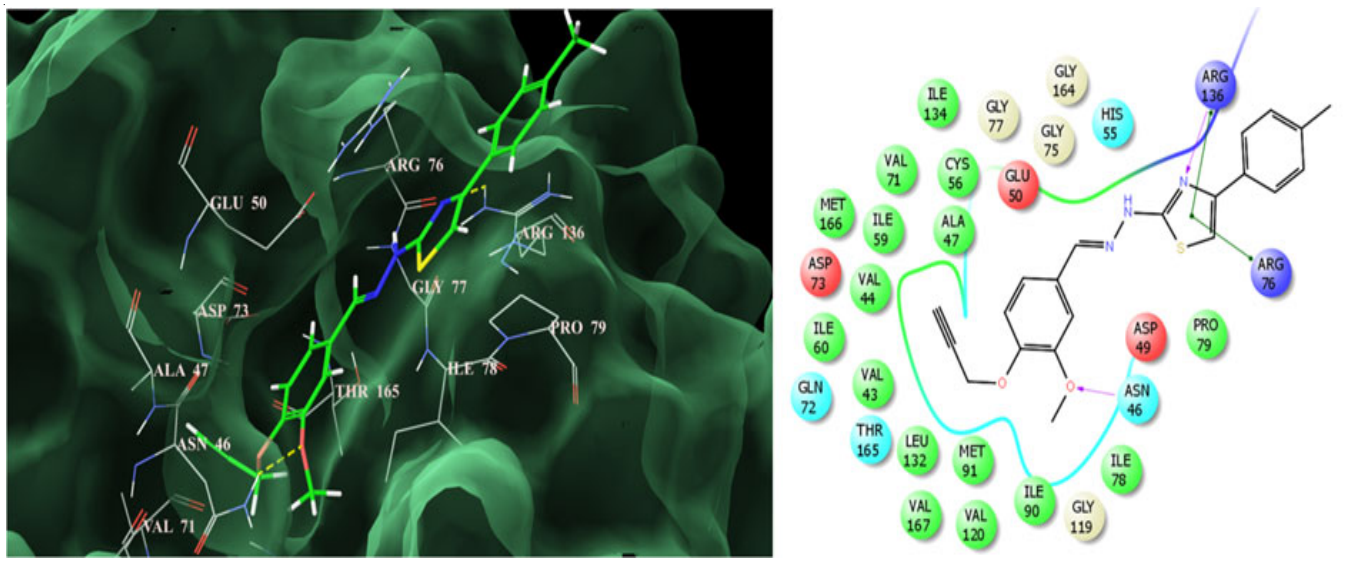


Fig. 3. Binding mode of **5b** into the active site of DNA gyrase subunit b (on the right side: most significantly interacting residues, pink lines correspond to H-bonding interactions, Green lines signify pi-pi stacking interaction)

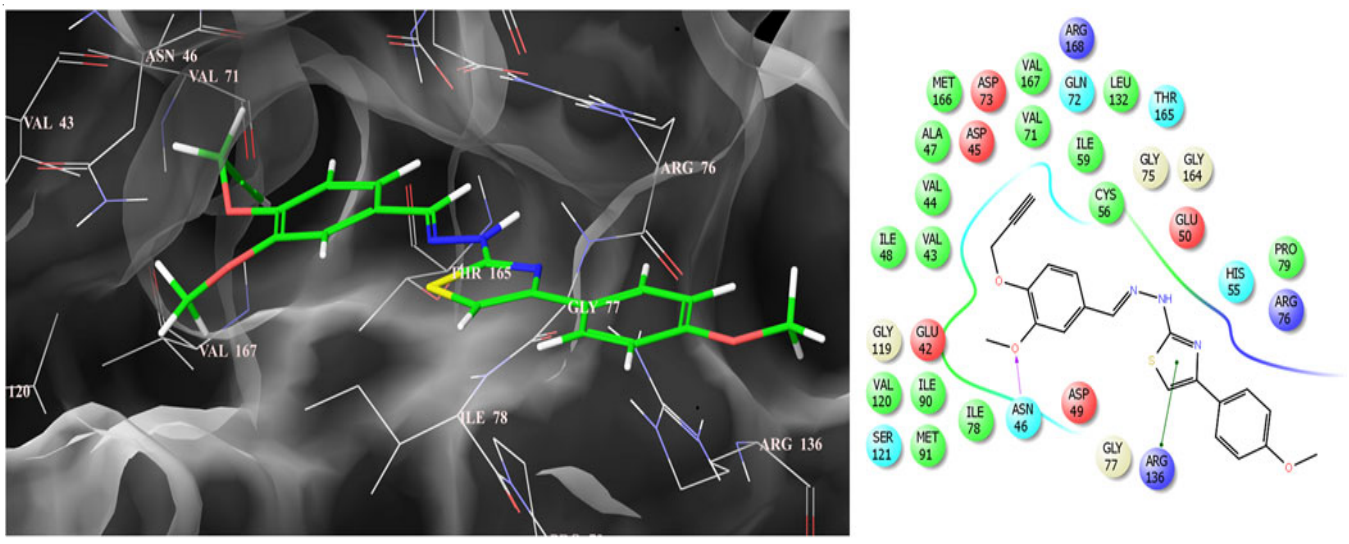


Fig. 4. Binding mode of **5c** into the active site of DNA gyrase subunit b (on right side: pink lines represent hydrogen bonding and green lines signify pi-pi stacking interactions)

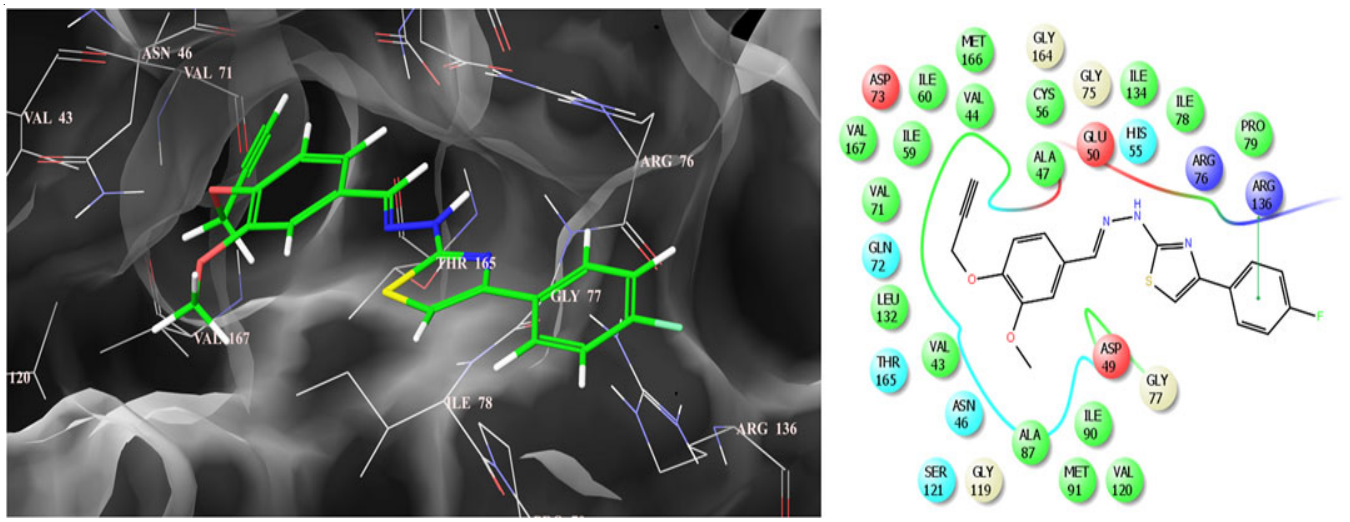


Fig. 5. Binding mode of **5d** into the active site of DNA gyrase subunit b (on right side: green lines signify pi-pi stacking interactions)

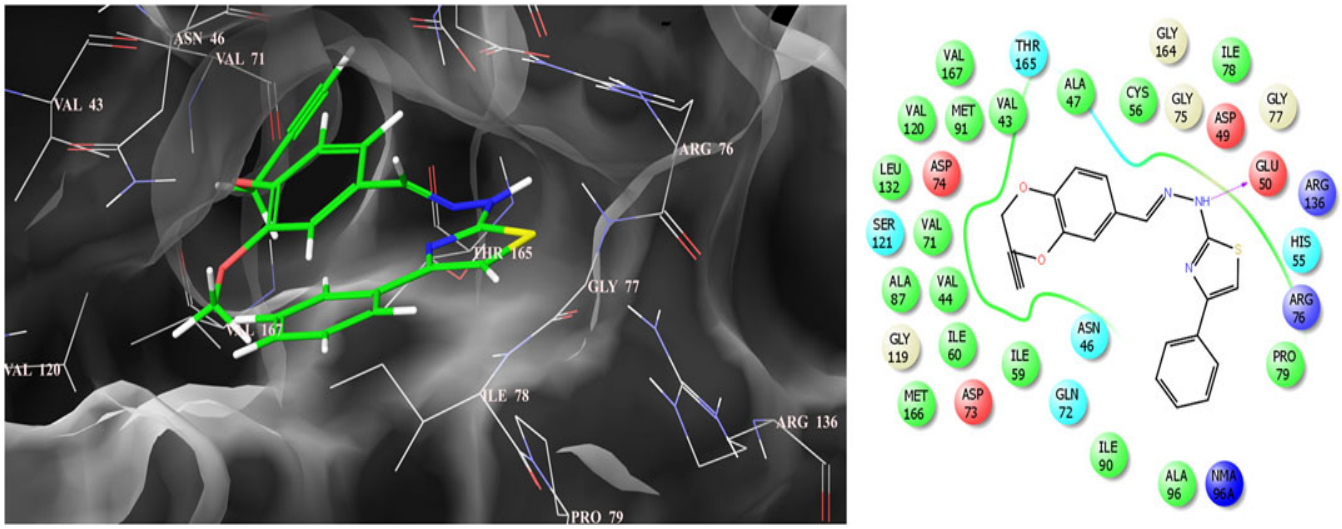


Fig. 6. Binding mode of **5f** into the active site of DNA gyrase subunit b (on right side: pink lines represent hydrogen bonding interactions)

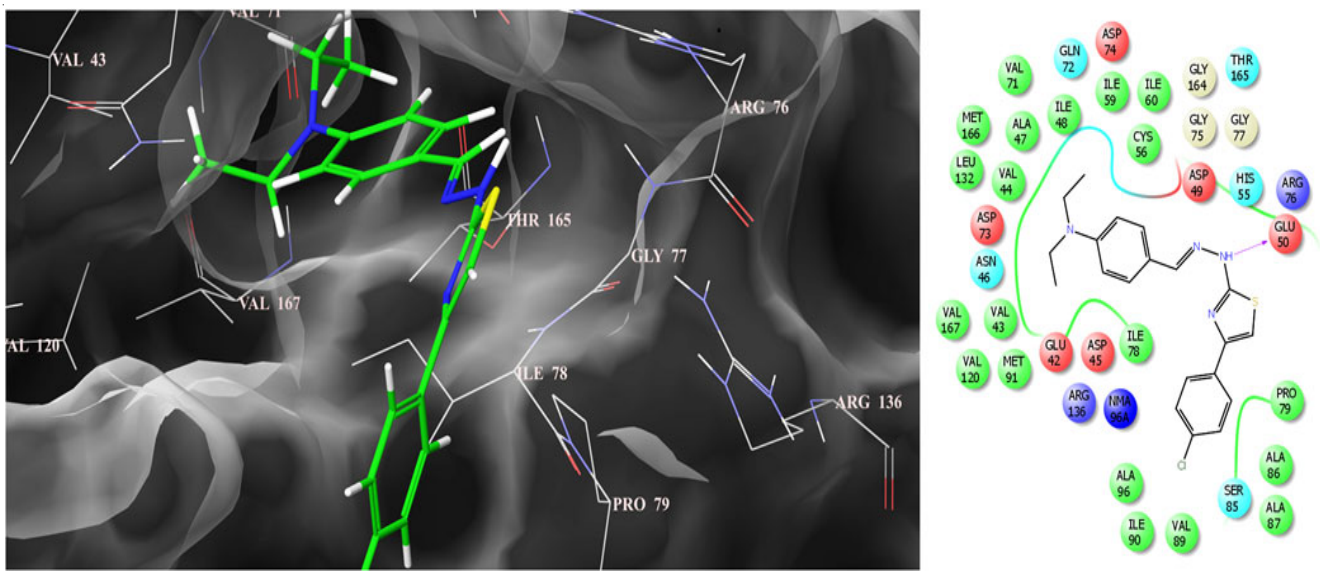


Fig. 7. Binding mode of **8g** into the active site of DNA gyrase subunit b (on right side: pink lines represent hydrogen bonding interactions)

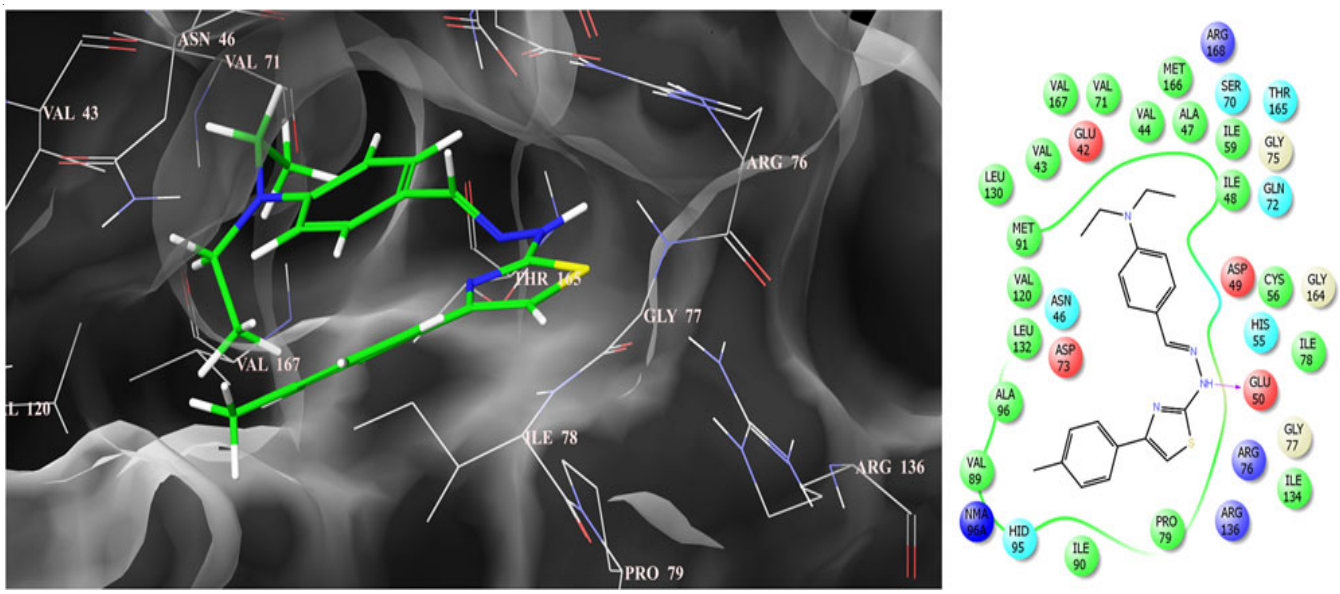


Fig. 8. Binding mode of **8h** into the active site of DNA gyrase subunit b (on right side: pink lines represent hydrogen bonding interactions)

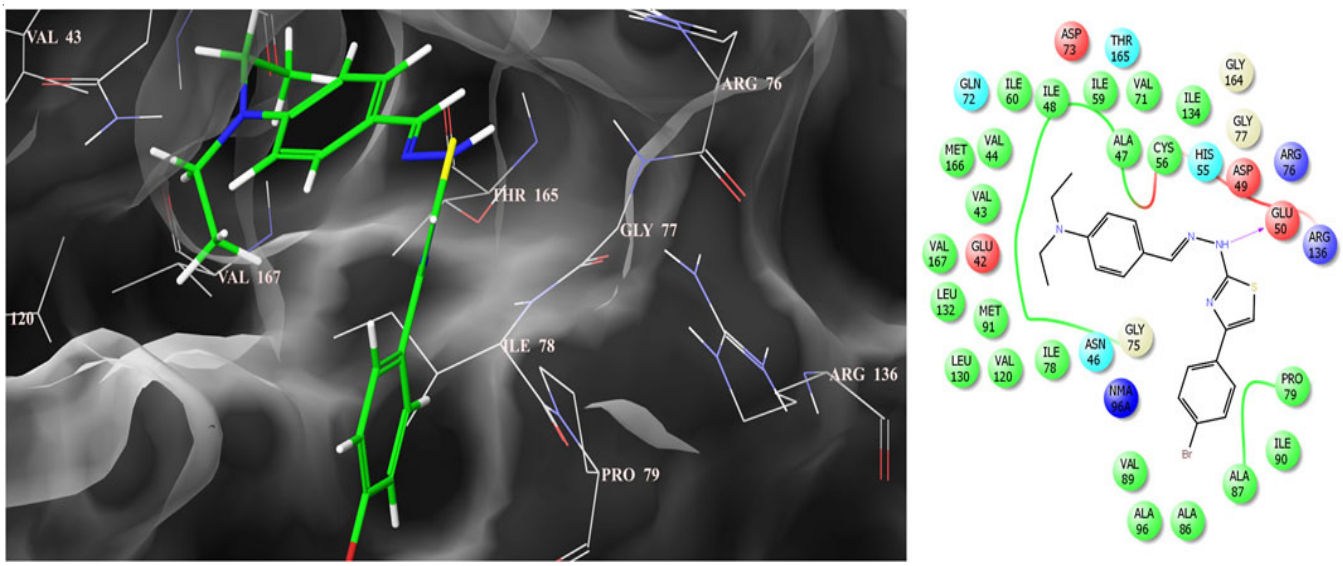


Fig. 9. Binding mode of **8i** into the active site of DNA gyrase subunit b (on right side: pink lines represent hydrogen bonding interactions)

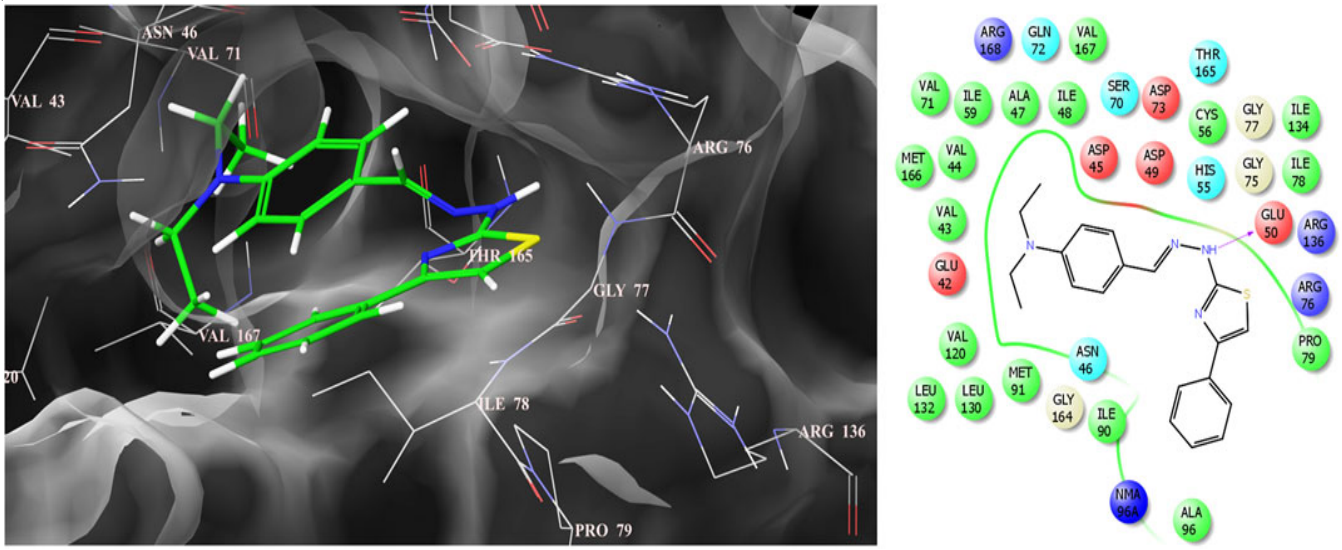


Fig. 10. Binding mode of **8j** into the active site of DNA gyrase subunit b (on right side: pink lines represent hydrogen bonding interactions)

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