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ARTICLE

# Synthesis, Molecular Docking and DFT Studies on Biologically Active 1,4-Disubstituted-1,2,3-Triazoles-Semicarbazone Hybrid Molecules.

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Some biologically active semicarbazone-triazole hybrid molecules have been designed and synthesized from semicarbazone linked terminal alkyne and aromatic azides via Cu(I)-catalyzed cycloaddition reaction. All newly synthesized compounds were successfully characterized by IR, $^{1}$H-NMR, $^{13}$C-NMR, and HRMS spectral techniques. The synthesized molecules were screened in vitro for anti-bactericidal property on *E. coli* (MTCC 16521), *B. subtilis* (MTCC441), *S. Aureus* (MTCC 3160), *P. aeruginosa* (MTCC 424) *and S. epidermidis* (MTCC 6880). The antibacterial property results revealed that the semicarbazone-triazoles hybrid molecules (**9b**, **9e**, and **9f**) are better alternative to the existing antibacterial drug ciprofloxacin. The docking study on most active compound **9b** and its alkyne precursor **8** of DNA Gyrase enzyme of *E. coli* bacteria supported the biological activity results.

## Introduction

In the last few years, a steady increase in various infectious microbial diseases observed in day-to-day life. Most of the infections in the human body are asymptomatic and latent. According to the World Health Organisation in 2015, about one in ten latent infection progresses to active diseases. This situation becomes more complicated by the evolution of various microbial strains resistant to some single or combination of drugs.[1-6] This instigated an immediate concern for the discovery of peculiar chemical substances of significant biological potential with different modes of action to eradicate the drug-resistant microbes.[7-9] The molecular assimilation method comes up as an important route to synthesize competent chemicals with improved properties. This involved the combination of two or more pharmacophore fragments in order to generate much effective hybrid molecule with better properties than the pre-existing parent molecules.

Semicarbazide and its derivatives are an interesting class of organic compounds as they are crystalline and stable. The semicarbazide, a raw material of semicarbazone known for various biological activities for some common species of bacteria.[10-14] Also, semicarbazones known for a broad range of antibacterial properties.[15-16] Various workers have reported the interesting biological activities of semicarbazones like antimicrobials,[16,17-18] anti-inflammatory,[19-20] anticonvulsant,[21-26] antioxidant,[27-28] antiepileptic,[29-30] antiproliferative etc.[31-32]

1,2,3-Triazoles and their derivatives have gained considerable attention of both theoretical and synthetic organic chemists for the progression of advanced biologically active compounds having utility in chemical,[33-34] biological and medicinal chemistry.[33,35-36] Besides these 1,2,3-triazole moieties are very much stable to acidic and basic hydrolysis. Also, remain inert for various oxidizing and reducing chemicals. Huisgen introduced cycloaddition reaction between azide and terminal alkyne resulting a regioisomers of 1,2,3-triazole.[37] However, the improved method discovered by Sharpless and Meldal through the term “click chemistry” involves dipolar cycloaddition reaction of alkynes and azides using Cu(I) as catalyst results in facile, efficient and regioselective formation of triazoles under mild reaction condition.[38-40] The copper-catalyzed reactions are easy to perform, flexible, high yielding and brought excellent selectivity of the product. The superior regioselectivity, quantitative yield, extensive scope and compatibility with biological entity have made this one of the most classical methods. In the recent studies, various catalysts were reported for the selective synthesis of 1,4-disubstituted-1,2,3-triazoles.[41-43] The absolute formation of 1,4-disubstituted-1,2,3-triazoles have centred the consideration of researchers due to broad spectrum of pharmacological activities like anticancer,[44-50] antimicrobial,[51-55] antitubercular,[56-62] anti-inflammatory,[63] antioxidants,[64-65] antimalarial,[66] antiprotozoal,[67] antivirals,[68] antibiotics,[69] anti-HIV,[70-71] anti-obesity agent etc.[72]

Considering the above mentioned pharmacological applications of 1,2,3-triazoles, semicarbazide and semicarbazone moieties in our mind, we thought to club concerned triazoles and semicarbazones together in order to develop 1,4-disubstituted-1,2,3-triazoles-semicarbazone hybrid (**Figure 1**) molecules with much improved pr--operties. Thus, we prepared [2-(1-aryl-1H-[1,2,3]triazol-4-ylmethoxy)-benzylidene]-semicarbazone hybrid molecules. The synthesized triazole hybrids were successfully characterized by FTIR,

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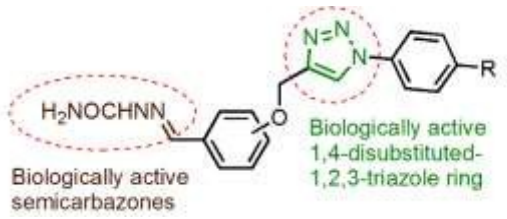
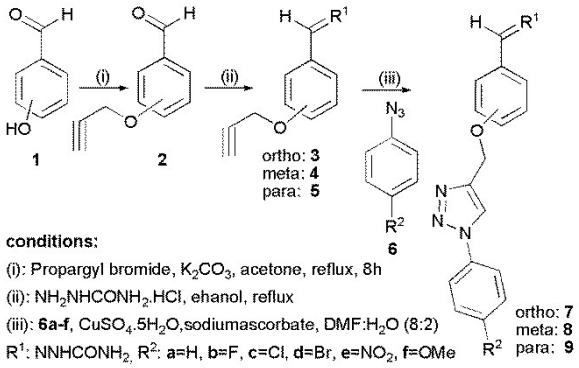



**Fig. 1** 1,4-disubstituted-1,2,3-triazole-semicarbazone hybrid

$^1$H-NMR, $^{13}$C-NMR, and HRMS spectroscopic data. These characterized triazole hybrids were then screened for their antimicrobial properties.

## Results and discussion

The preparation of semicarbazone-linked triazoles was performed in three steps. In the first step, propergylation of commercially available ortho-hydroxy benzaldehyde **1** (**Scheme 1**) was carried out by refluxing *O*-hydroxy benzaldehyde with propergyl bromide in acetone with $K_2CO_3$ using a standard procedure.[51] In the second step, semicarbazone **3** was prepared by the condensation reaction of so formed propargyloxy-benzaldehyde with semicarbazide.[73] Wherein, respective aldehyde was refluxed with semicarbazide in dry ethanol for 4 h. The light brown solid product appeared out in the reaction mixture at the cold condition. The solid obtained was purified by recrystallization from alcohol in 93% yield. The formation of semicarbazide-linked alkyne **3** was confirmed by IR, $^1$H-NMR and $^{13}$C-NMR spectroscopy. In the IR spectrum of propergylated semicarbazone, the band appeared at $\nu_{max}$ 3263 and 1606 cm$^{-1}$ because of alkyne ≡CH and C=N stretching frequency showed the formation of semicarbazone. The $^1$H-NMR spectrum of alkyne **3** showed a peak at δ 10.27 ppm equivalent to one hydrogen due to HC=N group, it again confirmed the formation




of semicarbazones.

**Scheme 1** Synthesis of semicarbazone-triazoles hybrid molecules (**7a-f**, **9a-f**).

The so formed semicarbazone alkyne **3** was then reacted with organic azide **6a** for cycloaddition reaction with copper catalyzed condition using $CuSO_4.5H_2O$ in DMF/water (8:2 v/v) solvent to furnish semicarbazone-linked triazole hybrids **7a** in 92% yield. In turn, organic azides **6a** was prepared by the reaction of corresponding aniline with $NaNO_2$ in acidic medium using well known diazotization reaction.[74] The reproducibility of product and generalization of reaction condition was realized by successively extending reaction condition to other derivatives of alkyne **5** and organic azides **6a-f**. All necessary details for the formation of alkynes **3** & **5** and triazoles-hybrids **7** & **9** are given in **table 1**.

**Table 1** Reaction of terminal alkyne (**3** & **5**) with organic azides (**6a-f**).[a]

| S. No. | Compounds | R | Time (h) | Yield %[b] |
|---|---|---|---|---|
| 1 | **3** | --- | 4 | 93 |
| 2 | **7a** | H | 3 | 92 |
| 3 | **7b** | F | 2.5 | 90 |
| 4 | **7c** | Cl | 2.5 | 91 |
| 5 | **7d** | Br | 2.5 | 94 |
| 6 | **7e** | $NO_2$ | 2 | 95 |
| 7 | **7f** | $OCH_3$ | 3 | 92 |
| 8 | **5** | --- | 4 | 94 |
| 9 | **9a** | H | 3 | 94 |
| 10 | **9b** | F | 2.5 | 92 |
| 11 | **9c** | Cl | 2.5 | 90 |
| 12 | **9d** | Br | 2 | 88 |
| 13 | **9e** | $NO_2$ | 2 | 93 |
| 14 | **9f** | $OCH_3$ | 3 | 92 |

[a]**Reaction condition**: Phenyl azides **6a-f** and alkynes **3** & **5** (1 mmol each); $CuSO_4.5H_2O$ (10 mol %) and sodium ascorbate (20 mol %), rt, 2-3 h.
[b]Yield refer to purification by recrystallization.

The structures of semicarbazone linked alkynes (**3** & **5**) and semicarbazone-linked triazole hybrids (**7a-f** & **9a-f**) were efficiently characterized by IR, $^1$H-NMR, $^{13}$C-NMR, and HRMS. For instance, in the IR spectrum of **9a**, a specific band at $\nu_{max}$ 3140 cm$^{-1}$ confirmed the existence of a triazole ring. In addition, the absorption band at $\nu_{max}$ 1606 and 3462 cm$^{-1}$ were assigned to C=N and N-H stretching frequencies. However, in the $^1$H-NMR spectrum of semicarbazone triazole hybrid **9a**, a peak appeared at δ 7.8 ppm due to the presence of NH group. The –CH of a triazole ring gave a sharp and distinctive singlet peak at δ 8.97 ppm. However, the $^{13}$C-NMR spectrum of **9a** showed peaks at δ 144.21 and 123.41 ppm for C-4 and C-5 atoms of the triazole ring. Finally, structure was supported by the HRMS spectrum which showed m/z peak at 359.123 value due to $[M+Na]^+$.

The compound library was tested in vitro for antibacterial potency by typical serial dilution approach for *E. coli* (MTCC 16521), *B. subtilis* (MTCC441), *S. Aureus* (MTCC 3160), *P. aeruginosa* (MTCC 424) and *S. epidermidis* (MTCC 6880). The minimum inhibitory concentration (MIC in µmol/mL) of synthesized alkyne and semicarbazone-triazole hybrid molecules was compared with commonly used antibacterial drug ciprofloxacin and results are summarized in **table 2**.

**Table 2** In vitro antibacterial results of compounds **3**, **5**, **7a-f**, **5**, **9a-f** (MIC in µmol/mL)

| S No | Comp | R | A | B | C | D | E |
|---|---|---|---|---|---|---|---|
| 1 | **3** | --- | 0.1152 | 0.1152 | 0.1152 | 0.1152 | 0.2304 |
| 2 | **7a** | H | 0.0744 | 0.0744 | 0.0372 | 0.0744 | 0.0744 |
| 3 | **7b** | F | 0.0706 | 0.0706 | 0.0706 | 0.0706 | 0.0706 |
| 4 | **7c** | Cl | 0.0675 | 0.0675 | 0.0675 | 0.0675 | 0.0337 |
| 5 | **7d** | Br | 0.0602 | 0.0602 | 0.0602 | 0.0602 | 0.0602 |
| 6 | **7e** | $NO_2$ | 0.1312 | 0.0656 | 0.0656 | 0.0656 | 0.0328 |
| 7 | **7f** | OMe | 0.0683 | 0.0683 | 0.0683 | 0.0683 | 0.0683 |
| 8 | **5** | --- | 0.2304 | 0.1152 | 0.0576 | 0.1152 | 0.2304 |
| 9 | **9a** | H | 0.0744 | 0.0744 | 0.0372 | 0.0744 | 0.1488 |
| 10 | **9b** | F | 0.0706 | 0.0706 | 0.0177 | 0.0353 | 0.1412 |
| 11 | **9c** | Cl | 0.1350 | 0.0675 | 0.0337 | 0.0675 | 0.1349 |
| 12 | **9d** | Br | 0.1205 | 0.1205 | 0.1205 | 0.1205 | 0.1205 |
| 13 | **9e** | $NO_2$ | 0.0656 | 0.0656 | 0.0328 | 0.0656 | 0.1312 |
| 14 | **9f** | OMe | 0.0683 | 0.0683 | 0.0342 | 0.0683 | 0.1366 |
| 15 | **Ciprofloxacin** | | **0.0732** | **0.1465** | **0.0366** | **0.0732** | **0.1465** |

**A:** *E. Coli*; **B:** *B. Subtilis*; **C:** *S. Aureus;* **D:** *P. Auroginosa;* **E:** *S. epidermidis*

The antibacterial testing results of the synthesized semicarbazone-triazole hybrid molecules exhibited good antibacterial activity. Compound **7d** demonstrated excellent activity

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results for all tested strains of bacteria with MIC value 0.0602 µmol/mL as compared to the commonly used antibacterial drug ciprofloxacin except *S. Aureus* which show MIC 0.0366 µmol/mL. The triazole **9b** with the fluorine functional group on aryl ring established to be very active for all the five tested bacterial strains with MIC value 0.0706 , 0.0706, 0.0177, 0.0353 and 0.1412 µmol/mL, respectively. Compound **7e** with $NO_2$-group found to be more potent against *S. epidermidis* wih MIC value 0.0328 µmol/mL, while in case of *P. auroginosa* the compound **9b** showed better potency (MIC 0.0353 µmol/mL). After scrutiny and study of the antibacterial data and their structure-activity relationship, an augmentation in the biological activity observed by the incorporation or linking semicarbazide unit with various 1,2,3-triazoles rings. Overall result showed that semicarbazone-triazoles hybrid molecules **9e** and **9f** are better potent for all bacterial strains as compared to commonly used antibacterial drug and hence as a better alternative to the existing antibacterial drug ciprofloxacin.[75]

The docking study on DNA gyrase topoisomerase II (1 kzn) enzyme of *E. coli* bacteria studied exclusively on heterocycles including triazoles. In the present paper, docking study of most active triazole hybrid molecule **9b** and its alkyne precursor **5** conducted for the active sites of *E. coli* bacterial enzyme DNA Gyrase. The conformations with very good binding affinity represented in **fig. 2** and **3**. The alkyne CH of **5** found involved in π-alkyl interaction with ALA47 and VAL43. The middle phenoxy ring of alkyne **5** showed π-anion interaction with GLU50 and π-alkyl interaction with ILE78. The carbonyl oxygen of semicarbazone moiety showed conventional H-bond interaction with ARG136. The amide group of semicarbazone moiety showed conventional H-bond interaction with GLU50 and GLY77. The amide group of semicarbazone moiety of compound **9b** showed conventional H-bond interaction with VAL93 and ILE90. Carbonyl oxygen of semicarbazone moiety showed conventional H-bond interaction with VAL120 and SER121. Phenoxy ring of the compound showed π-alkyl interaction with ILE90. The triazole ring showed π-alkyl interaction with ILE78. The benzene ring of triazole showed π-alkyl interaction with ALA47 and π-**σ** interaction with THR165.

The triazole derivative **9b** found to have high binding energy (-7.5 kcal/mol) as compare to semicarbazone substituted alkyne derivative 8 (-6.0 kcal/mol). Therefore, it can be hypothesized that both fragments of the triazole hybrid molecule i.e. semicarbazone and triazole are essential for the antibacterial activity. The docked semicarbazone substituted alkyne **5** and semicarbazone-triazole hybrid molecule **9b** together with co-crystallized ligand chlorobiocin (CBN) represented in **fig. 4**.

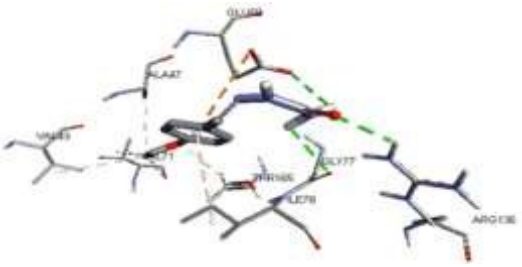

**Fig. 2** Binding mode of compound **5** docked with *E. coli* DNA Gyrase Topoisomerase II (1 kzn); Green: Hydrogen bond (dotted lines), Yellow: π-anion, Light pink: σ-alkyl interactions.

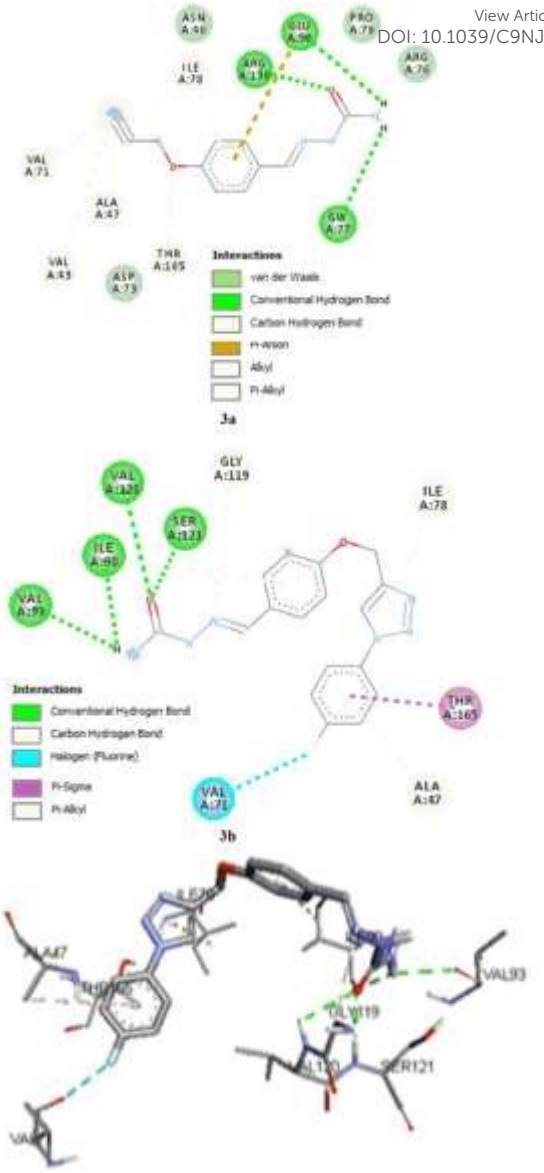


**Fig. 3** Binding mode of compound **9b** docked with *E. coli* DNA Gyrase Topoisomerase II (1 kzn); Green: Hydrogen bond (dotted lines), Violet: π-σ interaction, Light pink: π-alkyl interactions.

Molinspiration bioactivity score (**Table SI-1** and **Table SI-2**) showed that all the synthesized molecules (**3**, **5**, **7a-f** and **9a-f**) demonstrated fairly good conformational flexibility due to a sufficient number of rotational bonds (4-7). The formula % ABS = 109 - (0.345 × TPSA) is used to measure % absorption.[76] All the synthesized alkyne and semicarbazone-triazole hybrid molecules exhibited good absorption (% ABS = 56.13 to 82.53). According to the Lipinski rule of five, a chemical compound considered biologically active for an oral drug in humans if it must not violate more than one rule out of the following proposed rules:

- The octanol-water partition coefficient must be ≤5
- The molecular weight must be <500 daltons
- The number of H-bond acceptors must be ≤10
- A number of H-bond donor ≤5.

In all the above-mentioned rules, all numbers are an exact multiple of five, hence named Lipinski's rule of five, which is also, called

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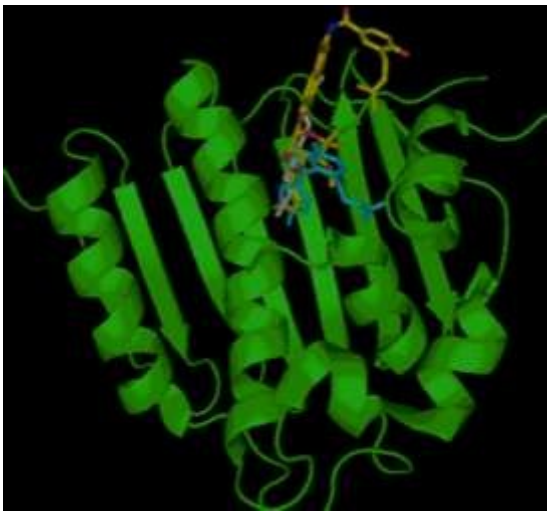

**Fig. 4** Cartoon diagram of **5** and **9b** docked in the active site of *E. coli* DNA Gyrase Topoisomerase II.

Pfizer's rule of five. It observed that all the synthesized alkyne and triazole hybrid compounds obeyed to Lipinski's rule of five and possessed bioavailability. Hence, the predicted properties of alkyne **3** & **5** and semicarbazone-triazole hybrids **7a-f** and **9a-f** showed good drug-like properties.

The frontier orbitals of the chemical compounds are very significant parameters in drug design and in recognizing their reactivity.[77-79] The higher value of highest occupied molecular orbital (HOMO) of a molecule can give electrons to suitable acceptor molecules with low energy and empty molecular orbitals. Predicted frontier orbital energies, the chemical potential (μ), chemical hardness (η), and electrophilicity index (ω) presented in the **Table SI-3** (Please, refer SI). The results of μ, η, and ω obtained by using HOMO and LUMO energies according to Koopmans' theorem and Parr approximation expressed as follow:[80]

$$\mu = (E_{HOMO} + E_{LUMO})/2 \quad (1)$$

$$\eta = (E_{LUMO} - E_{HOMO})/2 \quad (2)$$

$$\omega = \mu^2/2\eta \quad (3)$$

All the molecular structures of alkynes (**3** & **5**) and semicarbazone-triazole hybrid molecules (**7a-f** & **9a-f**) in the present paper optimized at the B3LYP level of theory using 6-311G(d,p) basis set of the Gaussian 09 program suite.[81] The hardness η shows the reactivity of the molecule, where a larger η value indicates less reactive nature than a molecule having smaller η. A hard molecule possesses large HOMO-LUMO gap means high excitation energies required to manifold of excited states, less reactive and their electron density less easily changed than a soft molecule. FMOs distribution patterns of alkynes and semicarbazone-triazole hybrid molecules are presented in **Table SI-4** and **Table SI-5** (Please, refer SI). However, for reference FMOs distribution patterns at ground state of alkynes **3** & **5** and representatives of triazole hybrids **7a** & **9a** are shown in **Fig 5**. From our calculations, it follows that the hardness of selected molecules increases in the following order:

**9e<7e<7a<7c≈9d<7d<7b≈7f<9a≈9c<9b<9f**

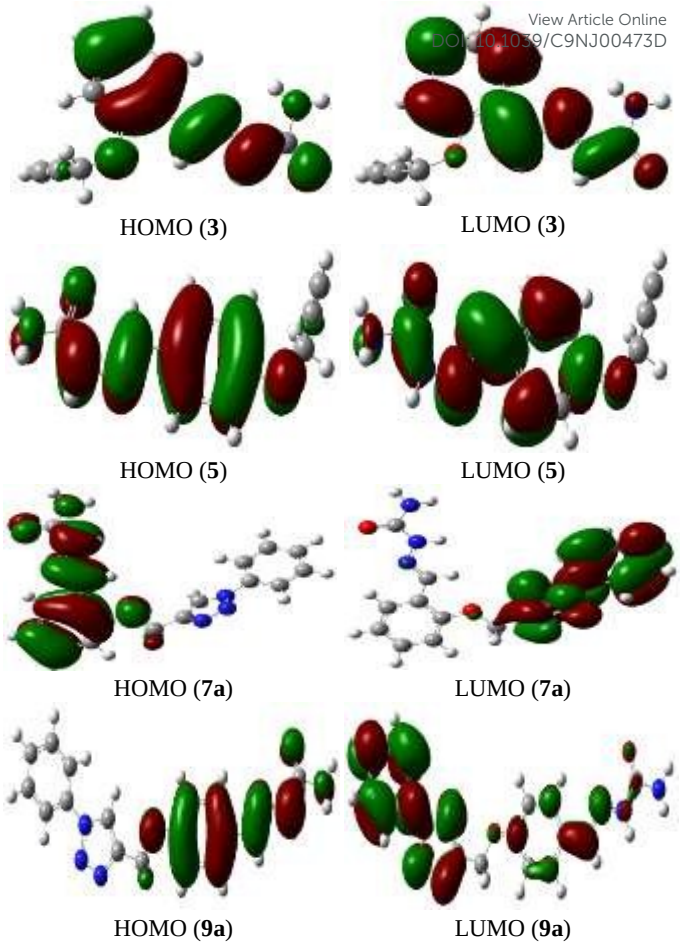


**Fig 5**. HOMO and LUMO orbital of alkyne **3** & **5** and triazoles **7a** & **9a**.

It shows that **9f** is the least reactive while **9e** and **7e** are the most reactive molecules among the selected molecules. The electrophilicity index (ω) reveals the stabilization energy when the system augmented by an electronic charge from the surrounding environment. In addition, results showed that semicarbazone-triazoles hybrid molecules bearing $NO_2$ functional group on the aryl are more reactive and hence are more active as highlighted in the antibacterial study for compound **7e** with $NO_2$ group found to be more potent against *S. epidermidis* with MIC value 0.0328 μmol/mL. Thus, experimental and computational results are in good agreement to each other for compound **7e** bearing $NO_2$-substitution on aryl of 1,4-disubstituted-1,2,3-triazoles-semicarbazone hybrid molecule.

## Experimental

### General procedure for the synthesis of semicarbazone linked triazoles (7a-f & 9a-f)

A mixture of substituted phenyl azide 6a-f (1.0 mmol), alkyne 3 or 5 (1.0 mmol) in DMF/water (8:2 v/v), $CuSO_4.5H_2O$ (10 mol %) and sodium ascorbate (20 mol %) was stirred for 2-3 h at room temperature. The progress of the reaction was monitored by TLC and after completion of the reaction; the reaction mixture was diluted with ice cold water (30 mL). The solid residues were filtered, washed with aqueous ammonium chloride:ammonia (9:1 v/v) solution followed by water and recrystallized with ethyl

acetate:hexane (4:1 v/v) to get the desired semicarbazone linked-triazoles 7 & 9 in 88-95 % yield.

## Conclusions

In summary, we have synthesized some semicarbazone-triazole hybrid molecules through Cu(I)-catalyzed cycloaddition reaction of semicarbazone o/p-substituted alkyne with various organic azides under green condition. The synthesized compounds exhibited potent antibacterial activities against the tested bacterial strains. An improvement in biological properties was observed by clubbing semicarbazide units with suitably substituted 1,2,3-triazoles. Further, the computational results of active semicarbazone-triazole hybrid molecule **9b** and its alkyne precursor **5** were in agreement with the in vitro antimicrobial results.

## Conflicts of interest

There are no conflicts to declare.

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# Synthesis, Molecular Docking and DFT Studies on Biologically Active 1,4-Disubstituted-1,2,3-Triazoles-Semicarbazone Hybrid Molecules.

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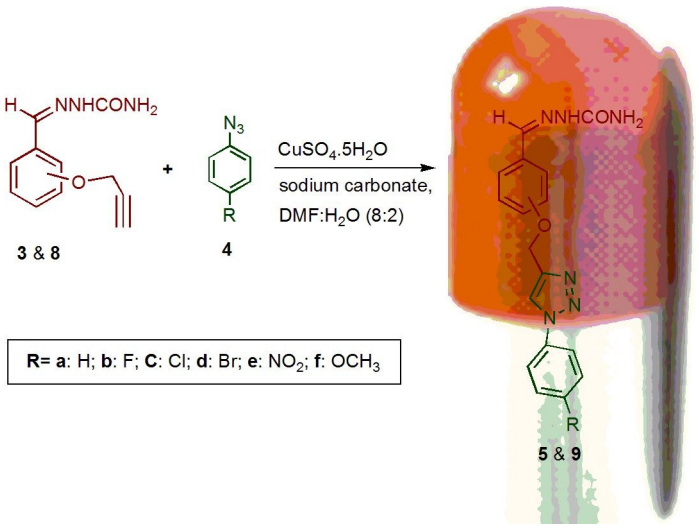


Biologically active semicarbazone-triazole hybrid molecules designed and synthesized from semicarbazone linked with a terminal alkyne and aromatic azides via Cu(I)-catalyzed cycloaddition reaction. All newly synthesized compounds successfully characterized by IR, $^{1}$H-NMR, $^{13}$C-NMR, and HRMS spectroscopy. The synthesized molecules screened in vitro for anti-bactericidal property on *Bacillus subtilis* (MTCC441), *Staphylococcus epidermidis* (MTCC 6880), *Escherichia coli* (MTCC 16521) and *Pseudomonas aeruginosa* (MTCC 424). The antibacterial property results revealed that the semicarbazone-triazoles hybrid molecules (**9b**, **9e**, and **9f**) are the better alternative to the existing antibacterial drug ciprofloxacin. The docking study on most active compound **9b** and its alkyne precursor **8** of DNA Gyrase enzyme of E. coli bacteria supported the biological activity results.