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Design, characterization and molecular docking study of the new isoxazolidine-1,2,3-triazole hybrids

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Abstract: Polycyclics are considered among the most widely used compounds in drug discovery. Isoxazolidine-triazole hybrids have multiple medicinal properties, including anti-inflammatory and anti-tumor agents. In this work, we synthesized a series of isoxazolidines and study molecular docking of the synthesized compounds to determine the binding interactions with target protein PIKα (PDB ID: 3ZIM). With a docking score of -10.4 kcal/mol, **7e** demonstrated good binding affinity to the active site of PI3K among all synthesized compounds.

Keywords: Docking; pyrroloisoxazolidines; isoxazolidine-triazole hybrids, click chemistry, 1,3-dipolar cycloaddition.

1. INTRODUCTION

Isoxazolidines obtained from 1,3-DCs between nitrones and olefins is one of the privileged structures in medicinal chemistry [1-6]. They gained prominence by exploring broad biological activity spectrum such as antioxidant and antibacterial effects as well as α-amylase and α-glucosidase inhibitors [7-9]. There are also natural compounds that contain the isoxazolidine ring and are used to treat diseases [10]. Additionally, the ability to convert isoxazolidines *via* cleavage of the NO bond in the ring to open-chain derivatives makes them valuable for the preparation of natural bioactive compounds such as amino-alcohols [11], amino-acids [12] and amino-sugars [13]. Triazole derivatives have received great attention due to their wide range of biological activities [14,15] and their use as starting materials

for a large number of compounds in many different applications such as agrochemistry [16], materials chemistry [17] and medicine [18]. Furthermore, the synthesis of polyheterocycles containing different heterocyclic rings, such as isoxazolidines and triazoles, represents an important strategy in medicinal chemistry [19]. Indeed, molecules containing at least two heterocyclic pharmacophores could have a significant improvement in biological effectiveness [20].

Based on the biological properties of heterogeneous isoxazolidine and triazole rings, we propose in this research to combine these parts into a single molecule in order to obtain new hybrid molecules and study the molecular docking of the synthesized compounds to determine the binding interactions with target protein PIKα (PDB ID: 3ZIM).

2. MATERIALS AND METHODS

2.1. Molecular docking (MD)

In order to investigate the preferred orientation of the ligands at the binding site of the receptor, interactions between produced derivatives and PI3Kα as a therapeutic target of high interest in anticancer drug research, were assessed using in silico molecular docking. The crystal structures for PI3Kα (PDB code: 3ZIM) were retrieved from the Protein Data Bank. All H_2O molecules, as well as the co-crystallized ligand, have been removed from the structures. To assign polar hydrogens and Gasteiger charges, AutoDockTools1.5.2 (ADT) was utilized, and the PDBQT file format was generated [21-24]. Discovery Studio Visualizer [25] depicts receptor-ligand interactions.

2.2. Chemistry

5:(Z)-N-benzyl-1-(4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl) methanimine oxide

To a solution of aldehyde (1 eq.) in EtOH was added 1.2 eq of sodium acetate and 1.2 eq. of N-benzylated hydroxylamine. The mixture is kept stirring for 24 h at r.t. After evaporation of the solvent, the residue was extracted with DCM. The combined organic phases were dried with Na_2SO_4 and concentrated to give the desired nitrone **5** (91%). White solid; Mp134-136 °C (Et_2O); **^{1}HNMR** (400MHz,$CDCl_3$) 2.20 (s, 3H); 2.26 (s, 3H); 4.73 (s, 2H,); 5.31 (s 2H); 6.88 (dd, 1H, *J* 8.2, 1.3 Hz); 7.09 (ddd, 2H, *J*8.3, 1.2, 0.5 Hz);7.18 (dd,1H, *J*8.2, 7.7 Hz);7.29-7.49 (8H, 7.35 (dt, 1H, *J* 7.7, 1.3 Hz); 7.36 (m, 2H); 7.39 (m, 2H);7.39 (dd, 1H, *J* 7.7, 1.3 Hz);7.43 (ddd, 2H, *J* 8.3, 1.8, 0.5 Hz);7.75 (s, 1H); 8.70 (s, 1H).

^{13}C NMR ($CDCl_3$, 100MHz) 17.3; 21.0; 49.1; 62,1; 114.2; 114.4; 115.6; 121.4; 123.9; 124.3; 127.7; 127.8; 127.9; 128.2; 128.4; 128.9; 129.1; 130.1; 130.2; 131.4; 136.8; 138.6; 140.3; 142.9; 158.5.

Anal.Calcd. for $C_{25}H_{24}N_4O_2$ (412.49): C,72.80; H, 5.86; N, 13.58, Found: C,72.53; H, 5.79; N, 13.46.

7a:(3R,3aS,6aR)-2-benzyl-3-(4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl) methoxy) phenyl) tetrahydro-4H-pyrrolo[3,4-d] isoxazole-4,6(5H)-dione

Nitrone **5** (1 eq.) was reacted with maleimide **6a** (1 eq.) under microwave activation (MWA, a power of 280 W) in toluene at reflux for 1h to give hybrid **7a** (85%). MP158-160 °C (hexane); **^{1}H NMR** (400MHz, $CDCl_3$)2.20 (s, 3H); 2.26 (s, 3H);3.66 (1H, dd, *J* 8.1, 7.1 Hz); 4.25 (s, 2H); 4.26 (d, *J* 7.1 Hz); 5.11 (1H, d, *J*8.1 Hz); 5.25 (s, 2H); 6.87 (ddd, 1H, *J* 8.4, 1.2, 0.6 Hz), 6.88 (dd, 2H, *J* 8.2, 1.3 Hz); 7.18 (dd, 1H, *J* 8.2, 7.7 Hz); 7.27 (dt, 1H, *J* 7.7, 1.3 Hz); 7.28 (ddd, 2H, *J* 8.4, 1.0, 0.6 Hz);7.29 (m, 2H); 7.31(m, 2H); 7.39 (dd, *J*7.7, 1.3 Hz); 7.73 (s, 1H).

^{13}C NMR ($CDCl_3$, 100MHz) 16.0; 20.0; 24.0; 40.6; 56.6; 61.8; 62.1; 73.9; 114.3; 115.6; 121.5; 124.3; 127.0; 127.1; 127.6; 127.7; 127.8; 128.3; 128.4; 128.9; 129.0; 137.21; 138.8; 138.9; 140.4; 142.9; 158.5; 173.5; 176.3.

Anal.Calcd. for $C_{29}H_{27}N_5O_4$ (509.57): C,68.36; H, 5.34; N, 13.74, Found: C,67.95; H, 5.33; N, 13.67.

7b:(3R,3aS,6aR)-2-benzyl-3-(4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-5-methyl tetrahydro-4H-pyrrolo[3,4-d] isoxazole-4,6(5H)-dione

Nitrone **5** (1 eq.) was reacted with maleimide **6b** (1 eq.) under MWA in toluene at reflux for 1h to give hybrid **7b** (81%). MP141-143°C (hexane). **^{1}H NMR** (400MHz,$CDCl_3$) 2.20 (s, 3H); 2.26 (s, 3H); 3.40 (s, 3H); 3.66 (1H, dd, *J* 8.3 and 7.4 Hz); 4.25 (s, 2H); 4.26 (d, 1H, *J* 7.1 Hz); 5.11 (1H, d, *J*8.3 Hz), 5.25(s, 2H); 6.87 (ddd, 2H, *J* 8.4, 1.2, 0.6 Hz); 6.88 (1H, dd, *J*8.2, 1.3 Hz); 7.18 (dd, 1H, *J*8.2, 7.7 Hz); 7.27 (dt, 1H, *J*7.7, 1.3 Hz); 7.28 (ddd, 2H, *J* 8.4, 1.0, 0.6 Hz); 7.29 (m, 2H);7.31 (m, 2H);7.39 (dd, 1H, *J*7.7, 1.3 Hz); 7.73 (s, 1H).

^{13}C NMR ($CDCl_3$, 100MHz) 14.0; 20.0; 24.0; 40.7; 56.6; 61.8; 62.1; 73.9; 114.2; 114.3; 115.6; 121.5; 124.3; 127.0; 127.2; 127.7 (2C), 127.8; 128.4 (2C); 128.9; 129.0; 137.2; 138.8; 138.9; 140.4; 142.9; 158.5; 173.5; 176.3.

Anal.Calcd. for $C_{30}H_{29}N_5O_4$ (523.59): C,68.82; H, 5.58; N, 13.38, Found: C,68.77; H, 5.53; N, 13.27.

7c:(3R,3aS,6aR)-2-benzyl-3-(4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-5-phenyl tetrahydro-4H-pyrrolo[3,4-d] isoxazole-4,6(5H)-dione

Nitrone **5** (1 eq.) was reacted with maleimide **6c** (1 eq.) under MWA in toluene at reflux for 1h to give hybrid **7c** (79%). MP129-131°C (hexane); **^{1}H NMR** (400MHz,$CDCl_3$)2.20 (s, 3H); 2.26 (s, 3H);3.64 (1H, dd, *J*8.3, 7.2 Hz); 4.25 (s, 2H); 4.30 (d, 1H, *J* 7.1 Hz); 5.21 (d, 1H, *J*8.2 Hz); 5.25 (s, 2H); 6.87 (dd, *J*8.2, 1.3 Hz);6.88 (ddd, 2H, *J*8.4, 1.2, 0.8 Hz), 7.13 (m, 2H); 7.18 (dd, *J*8.2, 7.7 Hz); 7.27 (dt, *J*7.7, 1.3 Hz); 7.29 (m, 2H); 7.31 (m, 2H); 7.37 (m, 1H); 7.39 (dd, *J*7.7, 1.3 Hz); 7.43 (ddq, 2H, *J*8.7, 1.4, 0.5 Hz);7.63 (m, 2H); 7.73 (m, 1H).

^{13}C NMR ($CDCl_3$, 100MHz) 16.0; 20.1; 40.7; 56.6; 61.8; 62.1; 73.9; 114.1; 114.2; 115.6; 121.5; 124.3; 124.4; 127.1; 127.2; 127.6, 127.7; 127.8; 128.1; 128.2; 128.3; 128.4; 128.9; 129.0; 130.1; 137.2; 138.8; 138.9; 140.4; 142.9; 158.5; 173.5; 176.3.

Anal.Calcd. for $C_{35}H_{31}N_5O_4$ (585.66): C,71.78; H, 5.34; N, 11.96, Found: C,71.66; H, 5.27; N, 11.85.

7d:(3R,3aS,6aR)-2-benzyl-5-(4-chlorophenyl)-3-(4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl) methoxy) phenyl) tetrahydro-4H-pyrrolo[3,4-d] isoxazole-4,6(5H)-dione

Nitrone **5** (1 eq.) was reacted with 4-chloromaleimide **6d** (1 eq.) under MWA in toluene at reflux for 1h to give hybrid **7d** (76%). MP166-168°C (hexane); **^{1}H NMR** (400MHz,$CDCl_3$) 2.21 (s, 3H); 2.26 (s, 3H); 3.66 (1H, dd, *J* 7.9, 7.2 Hz); 4.25 (s, 2H); 4.30 (d, 1H, *J* 7.1 Hz); 5.18 (d, 1H, *J*7.9 Hz); 5.25 (s, 2H); 6.88 (dd, *J*8.2, 1.3 Hz); 6.89 (ddd, 2H, *J*8.4, 1.2, 0.8Hz), 7.13 (m, 2H); 7.18 (dd, *J*8.2, 7.7 Hz); 7.27 (dt, *J*7.7, 1.3 Hz); 7.29-7.31 (m, 4H); 7.39 (dd, *J* 7.7, 1.6 Hz); 7.451 (m, 2H); 7.52 (m, 2H); 7.73 (m, 1H).

^{13}C NMR ($CDCl_3$, 100MHz) 15.5; 20.0; 40.7; 56.6; 61.8; 62.1; 73.9; 114.2; 114.3; 115.6; 121.5; 124.3; 125.7; 125.9; 127.1; 127.2; 127.6, 127.7; 127.8; 128.1; 128.2; 128.3; 128.8; 129.9; 129.0; 130.1; 133.7; 137.2; 138.8; 138.9; 140.4; 142.9; 158.6; 173.3; 176.5.

Anal.Calcd. for $C_{35}H_{30}ClN_5O_4$ (620.11): C,67.79; H, 4.88; N, 11.29, Found: C,67.55; H, 4.81; N, 11.19.

7e:(3R,3aS,6aR)-2-benzyl-3-(4-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl) methoxy) phenyl)-5-(naphthalen-2-yl) tetrahydro-4H-pyrrolo[3,4-d] isoxazole-4,6(5H)-dione

Nitrone **5** (1 eq.) was reacted with naphthylmaleimide **6e** (1 eq.) under MWA in toluene at reflux for 1h to give hybrid **7e** (75%). MP174-176°C (hexane); **^{1}H NMR** (400MHz,$CDCl_3$)2.20 (s, 3H); 2.26 (s, 3H); 3.67 (1H, dd, *J* = 7.8, 7.2 Hz); 4.25 (s, 2H);4.30 (d, 1H, *J* 7.1 Hz); 5.18 (d, 1H, *J* 7.8 Hz); 5.25 (s, 2H); 6.88 (ddd, 2H, *J*8.4, 1.2, 0.6 Hz), 6.87 (dd, *J* = 8.2, 1.3 Hz); 7.13 (m, *2H*), 7.18 (dd, 1H, *J*8.2, 7.7 Hz); 7.27 (dt, 1H, *J* 7.7, 1.3 Hz); 7.29 (m, 2H); 7.31 (m, 2H); 7.37 (m, 1H); 7.39 (dd, *J*7.7, 1.3 Hz); 7.45 (ddq, *J* 8.7, 1.4, 0.5 Hz); 7.50 (m, 1H); 7.59 (ddq, *J*2.5, 1.8, 0.5 Hz); 7.73 (s, 1H); 7.78 (ddd, 1H, *J*8.7, 1.8, 0.5 Hz); 7.79 (m, 1H); 7.88 (m, 1H).

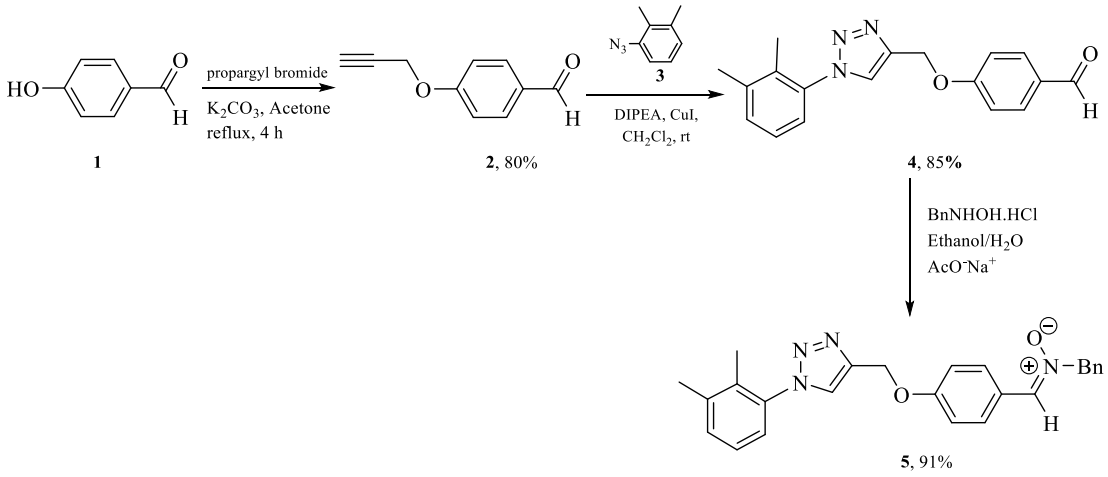
^{13}C NMR ($CDCl_3$, 100MHz) 14.9; 20.0; 40.7; 56.6; 61.8; 62.1; 73.9; 106.9; 114.3; 115.6; 117.1; 121.5; 124.3; 126.4; 126.4; 127.2 (3C); 127.7 (4C); 127.8, 128.4 (2C); 128.8; 128.9; 129.0; 130.9; 132.7; 137.2; 138.8; 138.9; 140.4; 142.9; 145.1; 158.5; 173.5; 176.3.

Anal.Calcd. for $C_{39}H_{33}N_5O_4$ (635.72): C,73.68; H, 5.23; N, 11.02, Found: C,73.60; H, 5.11; N, 10.99.

3. RESULTS AND DISCUSSION

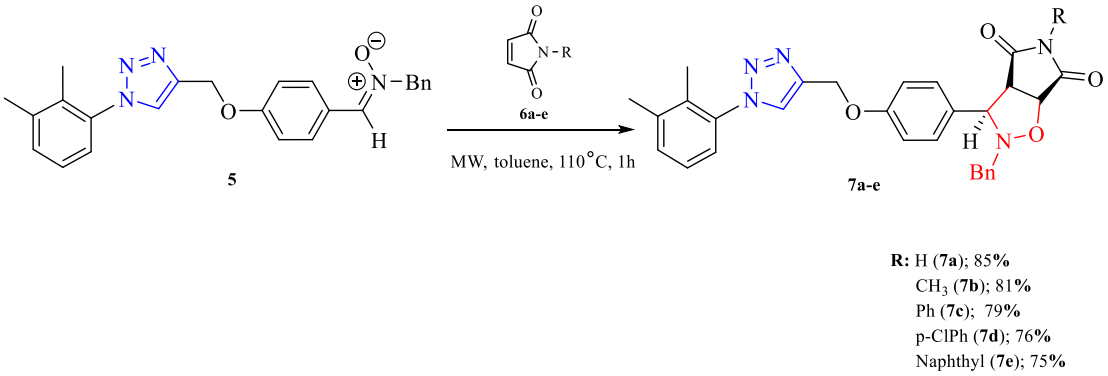
3.1. Chemistry

4-Hydroxybenzaldehyde was reacted with propargyl bromide at reflux of acetone and in the presence of K_2CO_3 to give intermediate **2** [26]. Alkyne **2** was engaged in a click chemistry reaction (CuAAC) in the presence of arylazide **3**, Cu(I) and diisopropylethylamine (DISPEA) to produce compound **4**. The condensation of intermediate **4** in an EtOH/H_2O mixture and in the presence of NaOAc gave the expected nitrone **5** (scheme 1).



Scheme 1. Synthesis of nitrone **5**

The maleimide derivatives **6a-e** were engaged in 1,3-DC reactions with nitrone **5** under the activation of microwave irradiation and toluene reflux for 1h to access a new series of triazole-isoxazolidine hybrids **7a-e** (scheme 2).



Scheme 2. Preparation of isoxazolidines **7a-e**

The synthesis of pyrroloisoxazolidines by 1,3-DC between a nitrone and maleimide derivatives has been widely studied in the literature [27]. Under appropriate conditions, this reaction preferentially leads to the *cis* isomer. For the cis isomer, the coupling constants between the protons H3/H4 in *syn* position ($J_{3,4}$ (syn)), are greater than or equal to 7.1 Hz [28]. On the other hand, the *trans* isomer has a vicinal coupling constant $J_{3,4}$ (*trans*) was lower or zero [27]. Indeed, the analysis of the 1H NMR spectra of the synthesized pyrroloisoxazolidine derivatives **7a-e** shows coupling constants between the protons H3 and H4 close to 7 Hz (table 1), this indicates that the two protons point in the same direction. These results support the stereochemistry proposed in Figure 1.

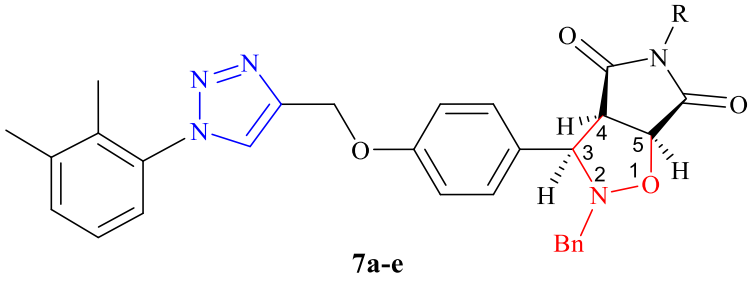
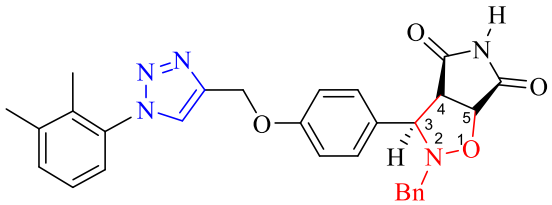
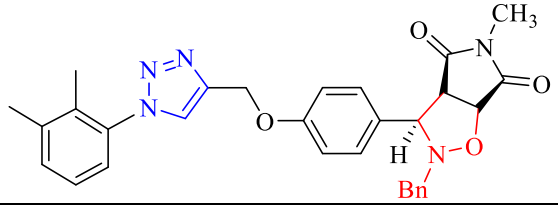
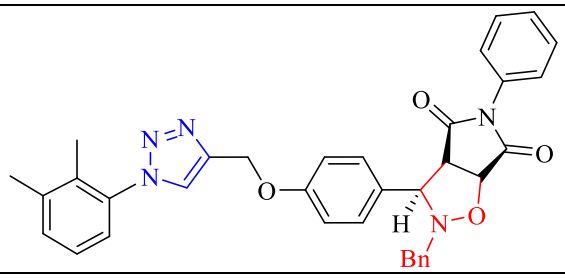
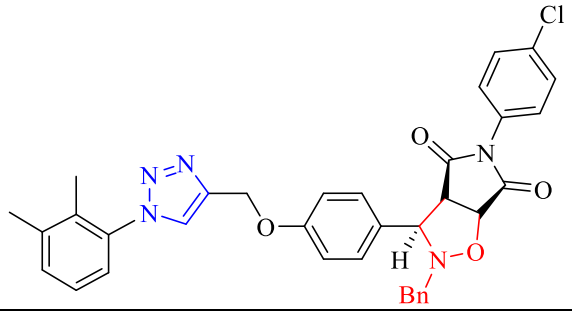
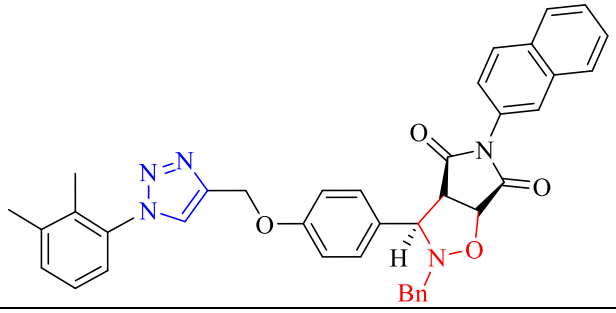


Figure 1. stereochemistry of pyrroloisoxazolidine derivatives **7a-e**

Table 1. structures of the synthesized pyrroloisoxazolidine derivatives **7a-e**

Entry	Structure	Coupling constant $J_{3,4}$ and $J_{4,5}$
7a		7.1 and 8.1 Hz
7b		7.4 and 8.3 Hz

7c		7.2 and 8.2 Hz
7d		7.2 and 7.9 Hz
7e		7.2 and 7.8 Hz

3.2. Docking

In order to explore the binding mode of the isoxazolidine-triazole hybrids, molecular docking was performed [29-33]. Cancer is a complex disease caused by unregulated cell growth with the potential to infiltrate other organs of the body [34,35]. PI3Kα is a crucial target for drug discovery [36-41]. The MD analysis of synthesized compounds was performed using the Autodock vina to find binding contacts with the target protein PI3Kα (PDB ID: 3ZIM) to virtually evaluate their potency in binding to the PI3Kα protein. Table 1 displays the top-ranked complex pose scores for each compound, as well as their binding energies (BE). The MD data of synthesized compounds revealed that compound **7e** had the highest docking score of -10.4 kcal mol^{-1} compared to the reference ligand KKR, which had a docking value of -10.4 kcal mol^{-1}. All of the compounds had compelling dock scores ranging from -9.2 kcal mol^{-1} to -10.4 kcal mol^{-1} (see Table 2), indicating that the created molecules have the same manner of binding and binding affinity against the protein as the reference ligand.

Table 2: MD energies (kcal mol^{-1}) of the docked compounds **7a-e** into the active site of 3ZIM

Compound	Free BE (kcal mol^{-1})
7a	-10.2
7b	-9.2
7c	-10.0

7d	-10.1
7e	-10.4

The molecule **7e** fits nicely into the binding site of human PI3Kα by hydrogen bonds and other tight interactions. Figure 2 depicts the interaction of the PI3Kα protein and molecule **7e**. The docking of compound **7e** revealed that one hydrogen bond interaction is present with SER774 (bond distance of 3.05 Å). Non-bonded interactions have been seen between the molecule **7e** and the residues VAL850, VAL851, LYS802, GLN 859, ILE932, TRP780, MET922, and TYR836. Many of these residues, such as VAL850, VAL851, LYS802, GLN 859, and ILE932, have been found in prior interactions of molecules with 3ZIM [42].

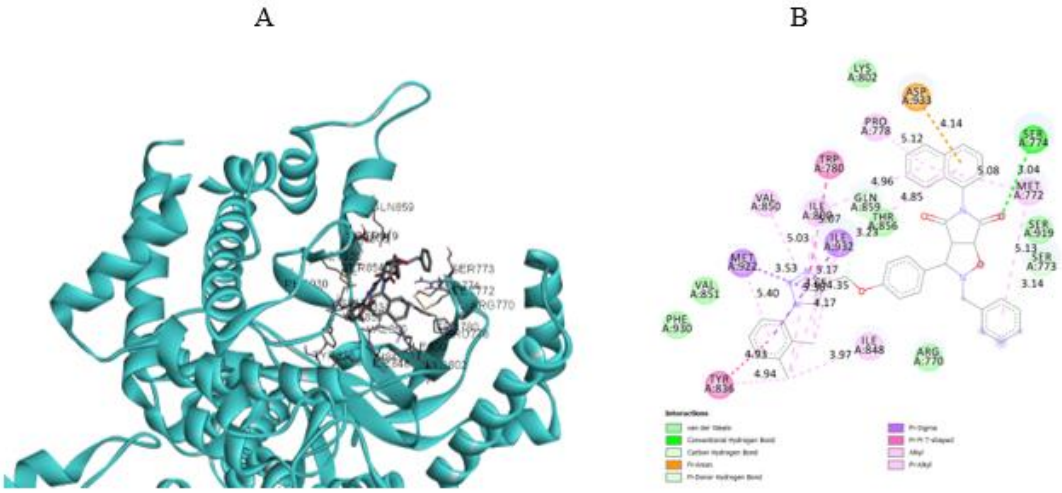


Figure 2. 3D (A) and 2D (B) view of interaction type of 7e with surrounding amino acids of 3ZIM.

4. Conclusion

We designed and synthesized a new series of isoxazolidine-triazole hybrids. The 1,3-DC reaction between nitrone **5** and the maleimide derivatives led mainly to the *cis* isomer. With a docking score of -10.4 kcal/mol, **7e** had the highest binding affinity to the active site of PI3K of any of the synthesized compounds.

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الملخص باللغة العربية

تصميم وتوصيف ودراسة الالتحام الجزيئي للهجينات الجديدة من الإيزوكسازوليدين-3،2،1-ترايازول

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تعتبر المركبات متعددة الحلقات من بين المركبات الأكثر استخدامًا في اكتشاف الأدوية. تمتلك المركبات الهجينة من إيزوكسازوليدين-ترياز ول خصائص طبية متعددة، بما في ذلك العوامل المضادة للالتهابات والمضادة للأورام. في هذا العمل، قمنا بتصنيع سلسلة من إيزوكسازوليدينات ودراسة الالتحام الجزيئي للمركبات المصنعة لتحديد تفاعلات الارتباط مع البروتين المستهدف PIKα (معرف قاعدة بيانات البروتينات: ZIM3). مع درجة الالتحام 10.4- كيلو كالوري/مول، أظهر **7e** تقاربًا جيدًا للارتباط بالموقع النشط لـ PI3K بين جميع المركبات المصنعة.

الكلمات المفتاحية: الالتحام؛ بيرولوايزوكسازوليدينات؛ هجينات إيزوكسازوليدين-ترايازول، كيمياء النقر، إضافة حلقية 3،1- ثنائية القطب