Shandong NormCollege of Chemistry[1], Chemical Engineering and Materials Science, Collaborative Innovation Center of Functionalized Probes for Chemical Imaging in Universities of Shandong, Key Laboratory of Molecular and Nano Probes, Ministry of Education, Shandong Provincial Key Laboratory of Clean Production of Fine Chemicalsal University, Jinan; Key Laboratory of Agro-Products Processing Technology of Shandong Province[2], Key Laboratory of Novel Food Resources Processing Ministry of Agriculture, Institute of Agro-Food Science and Technology, Shandong Academy of Agricultural Sciences; Jinan Asia Pharma Tech Co. Ltd[3], Jinan; School of Chemistry and Chemical Engineering[4], Henan Normal University, Xinxiang; College of Chemistry and Chemical Engineering[5], Lanzhou University, Lanzhou; Department of Thyroid Surgery[6], The First Affiliated Hospital of Shandong First Medical University, Jinan; Department of Ultrasound Diagnosis and Treatment Department[7], Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

Novel compounds with promising IDO1 inhibitory activity as new cancer drug candidates: Derivatives of N,N'-diphenylurea linked with 1,2,3-triazole

Bin Sun[1], Xiaofei Liu[2,3], Xiuwei Sun[2,3], Yingjie Zhou[4], Xiaoqing Gong[5], Longfei Mao[2,4], Weichen Shi[2,6,*], Peng Deng[2,*], Lin Shi[7,*]

Received November 6, 2022, accepted December 31, 2022

**Corresponding authors: Weichen Shi, Peng Deng, Key Laboratory of Agro-Products Processing Technology of Shandong Province, Key Laboratory of Novel Food Resources Processing Ministry of Agriculture, Institute of Agro-Food Science and Technology, Shandong Academy of Agricultural Sciences, Jinan 250100, China*
shiweichen0304@163.com, dengpeng2017@163.com
Lin Shi, Department of Ultrasound diagnosis and treatment department, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, China
shilinmaomao@126.com

Pharmazie 78: 2-5 (2023) *doi: 10.1691/ph.2023.2552*

To explore potential indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors, we designed a series of compounds incorporating urea and 1,2,3-triazole structures. IDO1 enzymatic activity experiments with the synthesized compounds were used to verify their molecular-level activity; for instance, the half maximal inhibitory concentration value of compound **3c** was 0.07 μM. Our research has yielded a series of novel IDO1 inhibitors which may be beneficial in the development of drugs targeting IDO1 for cancer treatment.

1. Introduction

Urea has an extensive history in medicinal chemistry applications as a structure fragment, often playing an important role in the regulation of drug–target interactions. Its two amino groups and the carbonyl that connect them render it highly druggable (Fig. 1) (Owen et al. 1993). In the design of molecular drugs, the use of a urea structure fragment may improve the drug's bioactivity, increase its selectivity, and optimize its physico-chemical properties. Furthermore, urea incorporation can be helpful in overcoming metabolic stability issues and removing toxic pharmacophores, leading to fewer side effects (Nakagawa et al. 2009). N,N′-Diphenylurea (DPU) is the earliest known phenylurea compound with a symmetrical structure; it is widely found in plants, where it plays an important role in growth regulation (Nauck et al. 2013). The function of DPU is similar to that of cytokinin; they both promote chlorophyll synthesis and inhibit oxidase activity. DPU is the earliest plant growth regulator used to help maintain plant freshness and delay aging (Kiser et al 2012). Derivates of DPU also play important roles in drug design. For example, sorafenib incorporates the DPU structure and acts as a multi-kinase inhibitor that can inhibit the activity of b-Raf, c-KIT, c-Raf, fms-like tyrosine kinase 3 (FLT3), platelet-derived growth factor (PDGFR)-α/β and vascular endothelial growth factor (VEGFR)-1/2/3. Its typical clinical application is in the treatment of cancerous tumors, notably in cases of acute myeloid leukemia (Escudier 2007; Liu et al.2007).

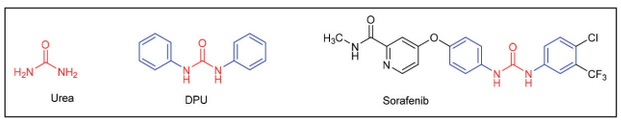


Fig. 1: Structures of urea, DPU and sorafenib

The 1,2,3-triazole moiety is a prominent structure element of nitrogen-containing heterocyclic compounds (Bonandi et al. 2017; Mao et al. 2020a; Bozorov et al. 2019). Bearing a five-membered heterocyclic ring comprising three nitrogen and two carbon atoms (molecular formula: $C_2N_3H_3$), 1,2,3-triazole has a unique rigid planar structure, which imparts strong DNA intercalation ability. Its large dipole moment facilitates a variety of non-covalent interactions with different biological targets; these include hydrophobic interactions, hydrogen bonding, van der Waals forces, and dipole–dipole interactions. In addition, the structural characteristics of 1,2,3-triazole allow its use as an electronically equivalent substitute for amide, ester, carboxylic acid, and alkene rigid analogues. Thus, 1,2,3-triazole has a broad range of biological activities and is often used as a molecular building block in the synthesis of active compounds, such as antibacterial (Zhang 2019), anti-malarial (Dantas et al. 2021; Feng et al. 2021), anti-fungal (Santos et al. 2020), anti-viral (Tan et al. 2021), anti-tubercular, and anti-tumor drugs (Alam 2022; Linag et al. 2021). The modification of several drugs in clinical use with 1,2,3-triazole enhances their biological activity and can lead to the discovery of new biological activities (Fig. 2). For example, when a terminal alkyne group is introduced into the parent structure of dolutegravir, an HIV integrase inhibitor, it reacts with 2-trifluoromethylphenyl azide to produce DTHP. In *in vivo* experiments in mice, DTHP substantially inhibited the proliferation of various lung cancer cells, especially H1975, by inducing apoptosis and increasing the reactive oxygen species concentration (Wang et al. 2020). Icotinib, an epidermal growth factor receptor (EGFR) inhibitor, reacts with 3-chlorophenyl azide via the terminal alkyne moiety in its structure, to form a7 (Mao et al. 2020b), which has a strong inhibitory effect on both mutant lung cancer cells (PC-9) and wild-type lung cancer cells (H460 and A549). Thus, a7 is more effective than icotinib in the clinical

treatment of lung cancer. In a similar study, 1,2,3-triazole was introduced into naphthoquinone to produce **7a** (Mao et al. 2020), which inhibits the growth of Caco-2 cells [half maximal inhibitory concentration (IC_{50}) = 23.92 μM] by blocking topoisomerases I and IIα, and shows selectivity. An indole-2-one derivative containing the 1,2,3-triazole moiety (**13d**) induces a strong inhibitory effect on the VEGFR-2 kinase (IC_{50} = 26.38 nM) and various tumor cells (Wang et al. 2021).

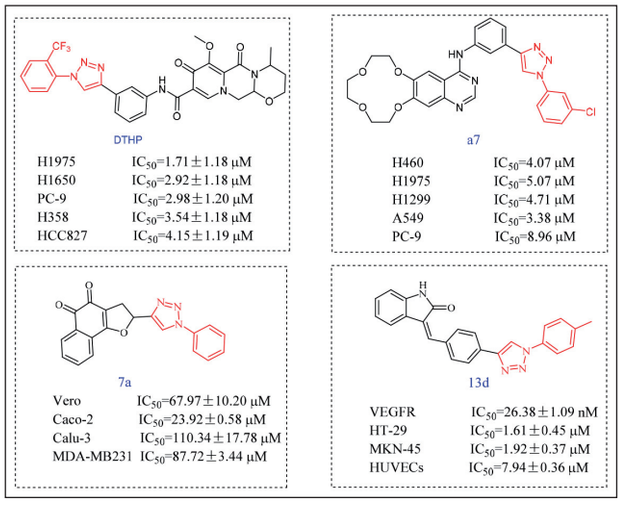


Fig. 2: Structure of 1,2,3-triazole compounds

Thus, the incorporation of the 1,2,3-triazole group into the molecular structure of a drug can considerably improve its anti-tumor performance. In this study, we explored the possibility of improving the anti-tumor efficiency of N,N′-diphenylurea (DPU) by introducing various 1,2,3-triazole groups into its structure.

2. Investigations and results

2.1. IDO1 inhibition study

Based on literature surveys, we selected the HeLa cell-based functional assay to study the indoleamine 2,3-dioxygenase 1 (IDO1) inhibition activities of the designed compounds (Yue et al. 2009; Malachowski et al 2016; Qian et al. 2016). We employed Amg-1 as a positive control; its IC_{50} value was measured to be 3.97 μM under our experimental conditions (which is close to the actual value). As shown in the Table, the activities of compounds **3a**–**3e** against IDO1 were all below 6 μM, with **3c** reaching 0.07±0.04 μM. This indicates that all the synthesized compounds **3a**–**3e** have good inhibitory activity against IDO1.

Table: IDO1 inhibitory activities of designed derivatives

Compounds	IDO1 IC_{50} (μM)
3a	0.36±0.09
3b	1.67±0.52
3c	0.07±0.04
3d	5.09±1.31
3e	5.56±1.09
Amg-1	3.97±0.88

IC_{50} values were fitted from single point inhibition curves, and two parallel experiments were performed for each compound. IC_{50} values were calculated using Graph Pad Prism 8.0 software. These results are reported as the averages ± SD.

2.2. Molecular docking studies of compound 3c

To better understand the potential of the designed compounds against IDO1, we selected compound **3c**, which had the best inhibitory activity, for binding mode analysis. The docking score of compound **3c** was measured as −7.808, with the distance between the triazole ring and heme iron being 4.3 Å. The two N atoms of the urea group act as hydrogen bond donors to form hydrogen bond interactions with heme. Hydrophobic amino acids such as V125, Y126, C129, V130, F163, F164, F226, F227, R231, L234, A260, A264 and F291, I354 and L384 formed hydrophobic interactions with compound **3c**, similar to co-crystal complexes. Among the amino acids, F226 and R231 are essential for IDO1 inhibitory activity. Figure 3 shows the interaction of compound **3c** and the IDO1 protein.

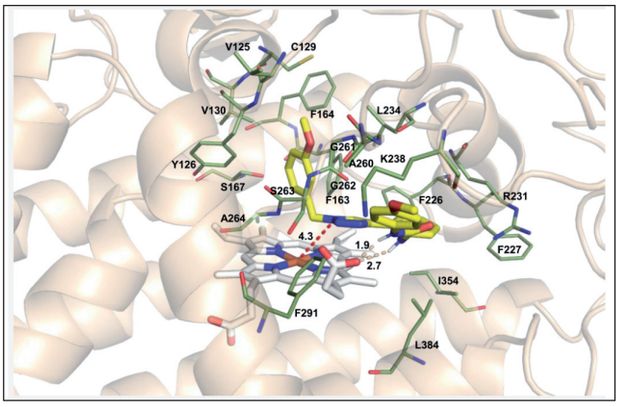


Fig 3: The 3D binding mode of compound **3c**

2.3. Conclusions

In this study, five compounds containing urea and 1,2,3-triazole structures were designed. Compound **3c** exhibited the best inhibitory effect on IDO1 (IC_{50}=0.07μM), and molecular docking studies confirmed compound **3c** to be the most promising of the devised compounds. Therefore, we plan to optimize this compound and carry out further experimental studies at cellular and animal levels.

3. Experimental

3.1. Materials and chemistry

1,2,3-Triazole derivatives were synthesized independently by our research group. All reagents were gained from commercial source without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded by Bruker 600 spectrometer in DMSO-d_6 solution. Chemical shifts (d) were showed in parts per million. Tetramethylsilane (TMS) was used as internal reference, while coupling constants were expressed in hertz. High-resolution mass spectra (HR MS) measurements were carried out using a Bruker Micro ToF II mass spectrometer.

DMEM medium, fetal bovine serum and Hela cell line were purchased from ATCC (Virginia, USA). Recombinant Human IFN-γ was purchased from R&D systems (Emeryville, CA, USA). Acetic acid, 3.05 N trichloroacetic acid and 4-(dimethylamino)benzaldehyde and were obtained from Sigma Aldrich.

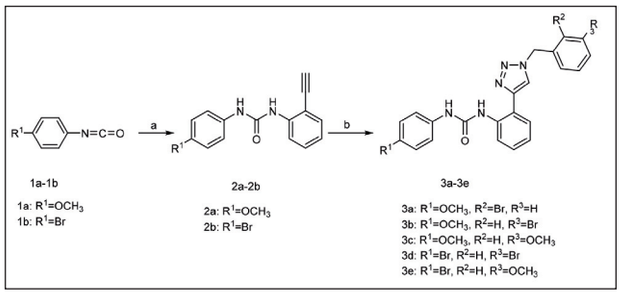
The phenyl isocyanate derivatives **1a–1b** were reacted with 2-aminophenylacetylene, N,N-Diisopropylethylamine (DIPEA) and 2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in N,N-dimethylformamide (DMF) to form compounds **2a–2b**, which were then reacted with various azide derivatives to yield compounds **3a–3e** (Gimeno et al. 2010; Guo et al. 2022). The molecular structures of these compounds were analyzed using ^{1}H NMR, ^{13}C NMR, and MS. These five compounds were then tested for their anti-IDO1 activity.

3.2. General procedure for preparation of compounds 2

To a solution of 4-bromophenyl isocyanate (2.0 g, 0.01mol) in CH_2Cl_2 (100 mL) was added 2-aminophenylacetylene (1.2 g, 0.01mol) in one portion. After stirring at room temperature for 2.5 h, the mixture was concentrated, and the residue was purified by column chromatography on silica gel (eluent: PE/EA = 2:1) to give compound **2a** as pale yellow solid.

3.2.1. 1-(2-Ethynylphenyl)-3-(4-methoxyphenyl)urea (2a)

White solid-^{1}H NMR (600 MHz, DMSO- d_6) δ 9.26 (s, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.62 (dd, J_1 = 7.8 Hz, J_2 =1.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 9.0 Hz, 2H),7.15 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 3.65 (s, 3H), 2.89 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.74, 153.89, 142.68, 135.65, 132.26, 128.63, 124.84, 121.36, 119.23, 117.36, 114.61, 79.15, 71.53, 55.23.



Conditions: a). Isocyanate (0.01 mol) in 100 mL CH_2Cl_2 and 2-aminophenylacetylene (0.01 mol) was added, then stirring at r.t. for 2.5 hours; b) Urea (1.0 mmol) and azido (1.2 mmol) added to 15 mL of mixed solvent (water: *tert*-butanol=2:1), then the reaction was operated under copper sulfate pentahydrate (0.1 mmol) and sodium ascorbate (0.2 mmol) at 80 °C for 4 hours.
Scheme: Reaction routes and structures of compounds **3a**–**3e**

*3.2.2. 1-(4-Bromophenyl)-3-(2-ethynylphenyl)urea (**2b**)*

White solid; ^{1}H NMR (600 MHz, DMSO- d_6) δ 9.56 (s, 1H), 9.03 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.78-7.75 (m, 1H), 7.54 (dd, J_1 = 7.8 Hz, J_2 =1.2 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 2H),7.17 (m, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 2.97 (s, 1H). ^{13}C NMR (151 MHz, DMSO- d_6)) δ 154.64, 153.45, 141.94, 136.68, 132.75, 129.53, 124.64, 121.65, 118.63, 116.16, 112.71, 78.24, 72.74.

3.3. General procedure for preparation of compounds 3

The reaction reagents were compound **2a** (0.32 g, 1.0 mmol) and 1-(azidomethyl)-2-bromobenzene (0.2g, 1.2 mmol), which were added to 15 mL of mixed solvent (water: tert-butanol=2:1). The reaction was performed in copper sulfate pentahydrate (0.1 mmol) and sodium ascorbate (0.2 mmol) at 80 °C for 4 h. The reaction status was monitored by TLC, and after completion of the reaction, the mixture was extracted through dichloromethane (15 mL×3). The organic phase was combined and washed successively with water and brine, then dried over sodium sulfate and concentrated in vacuo. The desired compound **3a** was isolated by column chromatography (CH_2Cl_2/MeOH=20:1).

*3.3.1. 1-(2-(1-(2-Bromobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-3-(4-methoxyphenyl)urea (**3a**)*

Brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.33 (s, 1H), 8.70 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.67 (dd, J_1 = 7.8 Hz, J_2 =1.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 9.0 Hz, 2H), 7.33 (td, J_1 = 7.8 Hz, J_2 =1.8 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.79 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (151 MHz, DMSO- d_6) δ 154.95, 153.38, 146.47, 137.19, 135.03, 133.42, 131.21, 131.02, 128.81, 128.74, 128.43, 123.86, 123.51, 122.68, 122.28, 120.89, 118.96, 114.35, 55.62, 53.79.

*3.3.2. 1-(2-(1-(3-Bromobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-3-(4-methoxyphenyl)urea (**3b**)*

White solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.69 (s, 1H), 9.32 (s, 1H), 8.74 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, J_1 = 7.8 Hz, J_2 =1.8 Hz, 2H), 7.56 (dt, J_1 = 7.2 Hz, J_2 =1.8 Hz, 1H), 7.39 (dd, J_1 = 7.2 Hz, J_2 =1.8 Hz, 3H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.10 – 7.03 (m, 1H), 6.89 – 6.83 (m, 2H), 5.73 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.97, 153.37, 146.61, 138.75, 137.19, 133.37, 131.65, 131.51, 131.40, 128.76, 128.46, 127.89, 127.69, 123.63, 122.67, 122.37, 122.19, 120.91, 118.95, 114.36, 55.62, 53.12, 52.84.

*3.3.3. 1-(2-(1-(3-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-3-(4-methoxyphenyl)urea (**3c**)*

Brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.72 (s, 1H), 9.34 (s, 1H), 8.71 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.30 (q, *J* = 7.8 Hz, 2H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.99 (s, 1H), 6.93 (t, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.67 (s, 2H), 3.75 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.96, 154.96, 153.37, 146.60, 137.60, 137.19, 133.40, 130.47, 128.70, 128.43, 123.48, 122.64, 122.18, 120.90, 120.60, 118.99, 114.36, 114.10, 55.61, 53.62.

*3.3.4. 1-(2-(1-(3-Bromobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-3-(4-bromophenyl)urea (**3d**)*

White solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.67 (s, 1H), 8.75 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.67 (dd, J_1 = 7.8 Hz, J_2 =1.2 Hz, 1H), 7.65 (s, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.49 – 7.44 (m, 4H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 153.05, 146.52, 139.87, 138.73, 136.73, 131.89, 131.66, 131.51, 131.41, 128.81, 128.49, 127.70, 123.71, 123.12, 122.46, 122.37, 120.91, 119.31, 113.74, 52.85.

*3.3.5. 1-(4-Bromophenyl)-3-(2-(1-(3-methoxybenzyl)-1H-1,2,3-triazol-4-yl)phenyl)urea (**3e**)*

White solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.69 (s, 1H), 8.73 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 2H), 7.33 – 7.29 (m, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.00 (s, 1H), 6.93 (t, *J* = 8.4 Hz, 2H), 5.67 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.95, 153.06, 146.51, 139.89, 137.57, 136.72, 131.88, 130.46, 128.74, 128.46, 123.54, 123.09, 122.44, 120.91, 120.60, 119.34, 114.36, 114.09, 113.73, 55.60, 53.63.

3.4. IDO1 enzymatic inhibition assay

To demonstrate the inhibitory effect of the designed compounds against IDO1, Hela cell density was adjusted using DMEM complete medium and subsequently seeded into 96-well cell culture plates at 100 μL per well for a total of 50,000 cells, and then incubated at 37 °C, 5% CO_2 overnight. The next day, 100 μL various concentrations of the compounds were diluted by medium containing 100 ng/mL human IFNγ, and added into 96-well then incubated for 18 h. The third day, 140 μL of medium was removed into a new 96-well plate and added 10 μL of 6.1 N TCA to precipitate the protein at 50 °C for 30 min. Sediment was centrifuged at 2500 rpm for 10 min. Then supernatant was transferred to another 96-well plate and mixed with 100 μL [2% (w/v)] of 4-(dimethylamino) benzaldehyde in acetic acid. The plate was incubated at room temperature for 10 min, the yellow color derived from kynurenine was recorded by measuring absorbance at 480 nm using a microplate reader (PE, USA). Graphs of inhibition curves with IC_{50} values were generated using Prism 6.0 (Mao et al. 2020a).

3.5. Molecular docking

Molecular docking was performed with standard precision in Schrödinger 2015. The crystal structure of IDO1 complexed with Amg-1 (PDB: 4PK5) was obtained from RCSB PDB database. Protein and compounds were processed by Protein Preparation Wizard and LigPrep module, respectively. IDO1 protein was prepared by assigning bond orders, adding hydrogens, creating zero-order bonds to metals, creating disulfide bonds, deleting waters beyond 5.00 Å from het groups, structural optimization and energy minimization. Compounds were optimized under the OPS2005 force field. A grid of size 20 × 20 × 20 Å is generated centered on Amg-1 while generating metal coordination constraints centered on heme. 3D binding mode of the compound **3c** was visualized by PyMOL (version 2.4.0) software with best docking score.

Acknowledgements: The Project was supported by grants from the Shandong Provincial Key Laboratory of Biomass Gasification Technology (No. BG-KFT-04), Qilu University of Technology (Shandong Academy of Sciences). Youth-Supporting Foundation (No. 2022PX057) of Qilu University of Technology (Shandong Academy of Sciences) and Shandong Provincial Natural Science Foundation ZR2020QB066 and ZR2021QC025. We would like to thank Editage (www.editage.cn) for English language editing.

Conflicts of interest: None declared.

References

Alam MM (2022) 1,2,3-Triazole hybrids as anticancer agents: A review. Arch Pharm 355: e2100158.

Bonandi E, Christodoulou MS, Fumagalli G, Perdicchia D, Rastelli G, Passarella D (2017) The 1,2,3-triazole ring as a bioisostere in medicinal chemistry. DrugDiscov Today 22: 1572–1581.

Bozorov K, Zhao J, Aisa HA (2019) 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview. Bioorgan Med Chem 27: 3511–3531.

Dantas WM, de Oliveira VNM, Santos DAL, Seabra G, Sharma PP, Rathi B. Searching anti-Zika virus activity in 1H-1,2,3-triazole based compounds. Molecules 26: 5869.

Escudier B (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. New Engl J Med 356: 125–134.

Feng LS, Zheng MJ, Zhao F, Liu D (2021) 1,2,3-Triazole hybrids with anti-HIV-1 activity. Arch Pharm 354: e2000163.

Gimeno A, Medio-Simón M, de Arellano CR, Asensio G, Cuenca AB (2010) NHC-Stabilized gold(I) complexes: Suitable catalysts for 6-exo-dig heterocyclization of 1-(o-ethynylaryl)ureas, Org Lett 12: 1900–1903.

Guo YJ, Wang X, Wang ZZ, Mao LH, Wang JH, Peng LZ, Xu GQ (2022) Synthesis and anti-tumor effects of novel pomalidomide derivatives containing urea moieties. Pharmaceuticals 15: 1479–1491

Kiser JJ, Burton JR, Anderson PL, Everson GT (2012) Review and management of drug interactions with boceprevir and telaprevir. Hepatology, 55: 1620--1628.

Liang T, Sun X, Li W, Hou G, Gao F (2021) 1,2,3-Triazole-containing compounds as anti-lung cancer agents: current developments, mechanisms of action, and structure-activity relationship. Frontiers Pharmacol 12: 661173.

Liu J, Cao Y, Chen C, Zhang X, Carter C (2007) Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 66: 11851–11858.

Malachowski WP, Winters M, DuHadaway JB, Lewis-Ballester A, Badir S, Wai J, Rahman M, Sheikh E, LaLonde JM, Yeh SR, Prendergast GC, Muller A (2016) O-Alkylhydroxylamines as rationally-designed mechanism-based inhibitors of indoleamine 2,3-dioxygenase-1. Eur J Med Chem 108: 564–576.

Mao LF, Wang YW, Zhao J, Xu GQ, Yao XJ, Li YM (2020a) Discovery of icotinib-1,2,3-triazole derivatives as IDO1 inhibitors. Frontiers Pharmacol 11: 579024.

Mao L, Sun G, Zhao J, Xu G, Yuan M, Li YM (2020b) Design, synthesis and anti-tumor activity of icotinib derivatives. Bioorg Chem 105: 104421.

Nakagawa T, Lomb DJ, Haigis MC, Guarente LP (2009) SIRT5 deacetylates carbamoyl phosphate synthetase 1 and regulates the urea cycle. Cell 137: 560–570.

Nauck M, Frid A, Hermansen K, Thomsen AB, During M, Shah N, Tankova T, Mitha I, Matthews DR (2013) Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2: year results from the LEAD- 2 study, Diab Obes Metabol 15: 204–212.

Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM (1993) The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis, N Engl J Med 329: 1001–1006.

Qian S, He T, Wang W, He Y, Zhang M, Yang L, Li G, Wang Z (2016) Discovery and preliminary structure-activity relationship of 1H-indazoles with promising indoleamine-2,3-dioxygenase 1 (IDO1) inhibition properties. Bioorg Med Chem 24: 6194–6205.

Santos BMD, Gonzaga DTG, da Silva FC, Ferreira VF (2020) Plasmodium falciparum knockout for the GPCR-like PfSR25 receptor displays greater susceptibility to 1,2,3-triazole compounds that block malaria parasite development. Biomolecules 10: 1197.

Tan Z, Deng J, Ye Q, Zhang (2021) Triazole-containing hybrids with anti-mycobacterium tuberculosis potential – part I: 1,2,3-Triazole. Fut Med Chem 13: 643–662.

Wang WJ, Mao LF, Lai HL, Wang YW, Jiang ZB, Li W, Huang JM, Xie YJ, Xu C, Liu P, Li YM, Leung ELH, Yao XJ (2020) Dolutegravir derivative inhibits proliferation and induces apoptosis of non-small cell lung cancer cells via calcium signaling pathway Pharmacol Res 161: 105129.

Wang DP, Liu KL, Li XY, Lu GQ, Xue WH, Qian XH, Mohamed OK, Meng FH (2021) Design, synthesis, and in vitro and in vivo anti-angiogenesis study of a novel vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor based on 1,2,3-triazole scaffold. Eur J Med Chem 211: 113083.

Yue EW, Douty B, Wayland B, Bower M, Liu X, Leffet L, Wang Q, Bowman KJ, Hansbury MJ, Liu C, Wei M, Li Y, Wynn R, Burn TC, Koblish HK, Fridman JS, Metcalf B, Scherle PA, Combs AP (2009) Discovery of potent competitive inhibitors of indoleamine 2,3-dioxygenase with in vivo pharmacodynamic activity and efficacy in a mouse melanoma model, J Med Chem 52: 7364-7367.

Zhang B (2019) Comprehensive review on the anti-bacterial activity of 1,2,3-triazole hybrids. Eur J Med Chem 168: 357–372.