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Synthesis and Molecular Docking Analysis of New Thiazo-isoindolinedione Hybrids as Potential Inhibitors of the SARS-CoV-2 Main Protease

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ABSTRACT

Herein, we report the synthesis of novel thiazo-isoindolinedione derivatives in excellent yields (up to 92%) from the reaction of thiazolidinedione and isoindoline-dione. The structures of the novel compounds were elucidated by ^{1}H-, ^{13}C-NMR, and MS analyses. Furthermore, molecular docking analysis was performed to study the potential inhibition of the SARS-CoV-2 main protease (M^{pro}) by the new thiazo-isoindolinediones. The present study revealed that the new thiazo-isoindolinediones could inhibit the M^{pro} and represent a promising platform for the experimental development of new antiviral drugs based on thiazo-isoindolinedione scaffolds.

Keywords: Condensation, COVID-19, Isoindolinedione, Thiazolidinedione, Molecular docking.

INTRODUCTION

In December 2019, the World Health Organization (WHO) declared COVID-19, a disease caused by the coronavirus 2 (SARS-CoV-2), a global health emergency[1,2]. According to the WHO statistics, SARS-CoV-2 resulted in over 33 million infections and caused more than 1 million deaths[3]. There is currently no approved specific treatment for COVID-19; however, immunization can reduce the risk of severe illness and death. The essential chymotrypsin-like cysteine protease

(M^{pro}) is among the potential targets proposed for SARS-CoV-2 inhibition, which plays a crucial role in viral transcription and replication[4-6]. Within this context, heterocyclic compounds have been extensively studied as potential lead inhibitors of the SARS-CoV-2 M^{pro} owing to their diverse biological properties, including antiviral, antiparasitic, and antimicrobial activities, making them among the most investigated pharmacologically active scaffolds[7].

Furthermore, nitrogen- and sulfur-based heterocycles demonstrated favorable binding affinities to various biological targets due to their ability to form exceptionally high intermolecular interactions via the nitrogen and sulfur heteroatoms[8]. In this regard, isoindoline-diones serve as a core structure for several medically essential agents. Furthermore, they are commonly utilized as starting building blocks for synthesizing alkaloids, pesticides, and polymers[9]. In addition, isoindoline-diones derivatives also manifested potent pharmaceutical properties, such as antiviral, anti-inflammatory, anticancer, and anti-HIV properties[10].

Within this context, isoindolinedione scaffolds were used to synthesize the α-glucosidase inhibitor I[11]. Furthermore, isoindoline II is a potent papain-like cysteine protease (P^{Lpro}) 11 inhibitor. Moreover, norcantharimide III is a bioactive isoindoledione with potential antitumor activity against breast and lung cancers[12]. The 1,3-isoindolinedione tethered triazole IV possessed a promising antituberculosis mycobacterium activity[13].

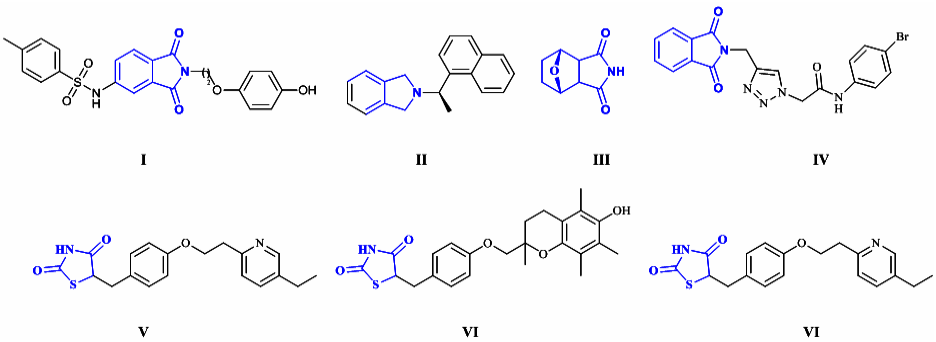


Fig. 1. Bioactive isoindolinedione-(I-IV) and thiazolidinedione-(V-VI) containing agents

Conversely, the thiazolidinedione motif is a common building block of numerous drugs with interesting bioactivity, such as antiviral, antihyperglycemic, antitubercular, and anticancer properties[14-16]. The thiazolidinedione-based drug family includes the antidiabetic drugs pioglitazone V, troglitazone VI, and Troglitazone VII[17].

Interestingly, combining bioactive pharmacophores targeting different pathways into a single compound is a major challenge for developing and discovering novel drugs acting simultaneously on multiple targets[18]. This strategy has shown considerable success and is currently employed to develop new therapies for diseases such as tuberculosis, malaria, anticancer, and Alzheimer's diseases[19,20].

Within this context, we envisage the synthesis of novel thiazo-isoindolinedione hybrids. The synthetic strategy involves a nucleophilic substitution reaction key step between thiazolidine-2,4-dione and bromo-substituted *N*-alkyl phthalimides. The target compounds are designed to comprise thiazolidine-2,4-dione and 1,3-isoindolinedione linked together by three carbon atoms, as illustrated in Fig. 2. Additionally, a molecular docking tool will be used to explore the chemical and electrical properties of the new compounds to inhibit the M^{pro} required for SARS-CoV-2 replication.

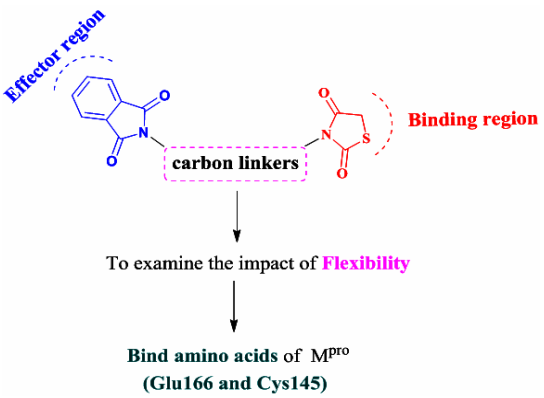


Fig. 2. The design criteria of the thiazo-isoindolinedione hybrids

MATERIAL AND METHODS

Chemistry

Compounds 2-(2-bromoethyl)isoindoline-1,3-dione (4)[21] and 2-(3-bromopropyl)isoindoline-1,3-dione (5)[21,22] were synthesized from the reaction of 2-bromoethan-1-amine hydrobromide (2) and 3-bromopropylamine hydrobromide (1) with phthalic anhydride under neat conditions at 110°C, respectively. Furthermore, thiazolidine-2,4-dione (6)[23] was prepared from thiourea and chloroacetic acid reaction using water as the solvent and at 100°C for 4 hours. The potassium salt 7 was synthesized by treating an ethanolic solution of thiazolidine-2,4-dione (6) with potassium hydroxide according to the reported literature methods[24]. Copies of the ^{1}H- & ^{13}C-NMR, IR, and MS can be found in the Supporting information.

The synthesis of compound 8

Compound 7 (1.2 mmol) and compound 4 (1 mmol) (1 mmol) were dissolved in DMF (10 ml) and heated at 80°C for 4 hours. TLC was used to monitor the process, and after completion, the reaction was poured onto ice to give a white powder. Compound 8 was obtained from the reaction of compound 4 (1 mmol, 253 mg) with thiazolidine-2,4-dione potassium salt 7 (1.2 mmol, 186 mg) in DMF (10 mL) at 80°C for 4 hours. The reaction was followed by TLC (EtOAc/heptane 1:3; Rf=0.32), isolated as a white solid with 88% yield (and its m.p. =158–159°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 4H, Ar-H), 4.08 (s, 1H, 2H, CH_2S), 3.82–3.66 (m, 4H, CH_2CH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.92, 172.46, 168.21, 134.99, 131.80, 123.59, 40.25, 35.73, 34.21; MS (ESI): m/z=found 327.3 [M^++Na]; calcd. 327.0 [M^++Na].

The synthesis of compound 9

Compound 9 was obtained from the reaction of compound 7 (1.2 mmol) with compound 5 (1 mmol) in DMF (10 mL) at 80°C for 4 hours. The mixture was cooled to room temperature and then poured over ice to give a white powder.

Compound 9 was obtained from compound 5 (1 mmol, 269 mg) and thiazolidine-2,4-dione potassium salt (1.2 mmol, 186 mg) in DMF (10 mL). The reaction was followed by TLC (EtOAc/heptane 1:3; Rf=0.31), isolated as a white solid with 92% yield and its m.p.=167–168°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (m, 4H, Ar-H), 4.13 (s, 2H, CH_2S), 3.52 (dt, *J*=20.3, 7.3 Hz, 4H, $2CH_2$), 1.90–1.77 (m, 2H, CH_2); ^{13}C NMR (101 MHz, DMSO-d_6)δ 172.75, 172.34, 168.27, 134.84, 132.03, 123.47, 39.38, 35.58, 34.39, 26.42; MS (ESI): m/z=found 376.3 [M^+++2Na+K]; calcd. 376.0 [M^++2Na+K].

In silico studies

Molecular docking

The novel two thiazo-isoindolinedione hybrids 8 and 9 were subjected to a molecular docking study using the MOE software[25,26] to investigate their potential inhibitory effect on the SARS-CoV-2 M^{pro}. Besides, the co-crystal (O6K) was inserted as a reference standard in the docking process.

Each examined compound was sketched in the ChemDraw and then transferred to the MOE window, subjected to partial charge corrections and energy minimization, as mentioned before[27]. Next, the target Mpro protein receptor of SARS-CoV-2 was extracted from the Protein Data Bank (PDB ID: 6Y2G, https://www.rcsb.org/structure/6Y2G) and opened in the MOE window. The M^{pro} protein was corrected and 3D hydrogenated before energy minimization as a final step of protein preparation[28]. Finally, a general docking process was performed by inserting a database of compounds 8 and 9 with the co-crystal (O6K) of SARSCoV-2 M^{pro}. The default setting options were adjusted to match the selected docking methodology[29].

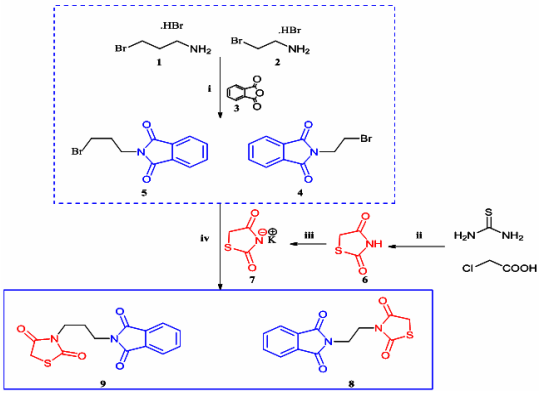
Notably, a validation process by redocking O6K of SARSCoV-2 Mpro within its receptor pocket was carried out, and the validly applied forcefield was confirmed by obtaining low Root Mean Square Deviation (RMSD) values<2 Å 30.

RESULTS AND DISCUSSION

Synthesis and characterization

Thiazo-isoindolinedione hybrids 8 and 9 were synthesized according to the synthetic Scheme 1. The condensation of phthalic anhydride with 2-aminoethyl bromide hydrobromide (2) and 3-aminopropyl bromide hydrobromide (3) under neat conditions afforded compound 4 and compound 5. Furthermore, the reaction of chloroacetic acid and thiourea in water afforded the corresponding 2,4-thiazolidinedione 6. The latter is converted to the corresponding potassium salt via reaction with KOH at room temperature and in ethanol. The nucleophilic substitution reaction of the

potassium salt 7 with the bromo derivatives 4 and 5 afforded the corresponding compound 8 and 9 in 88% and 92% yields, respectively.



Scheme 1. The synthesis of thiazo-isoindolinedione hybrids 8 and 9. Reagents: (i) phthalic anhydride (1 mmol) with 2-aminoethyl bromide hydrobromide (1 mmol) (2) or 3-aminopropyl bromide hydrobromide (3) (1 mmol) heating at 110°C under neat conditions for 4 h; (ii) thiourea (2 mmol) and chloroacetic acid (2 mmol), water, reflux for 4 h; (iii) KOH (1 mmol) and 2,4-thiazolidinedione (6) (1 mmol) in EtOH (20 mL); (iv) potassium salt 7 (1.2 mmol) and compound (4) (1 mmol) or 2-(3-bromopropyl) isoindoline-1,3-dione (5) in DMF, 80°C, 4 hours

In silico studies

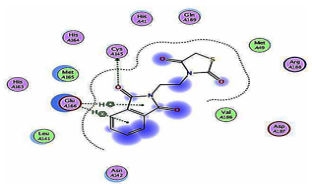
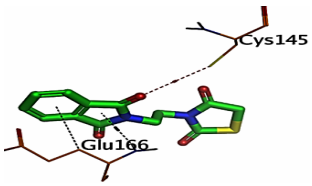
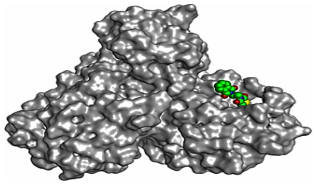
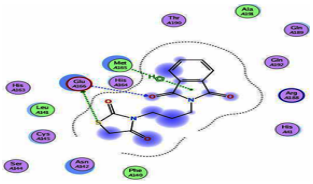
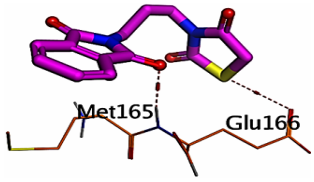
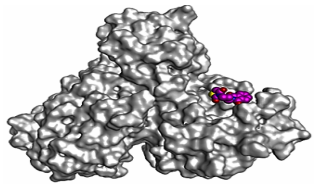
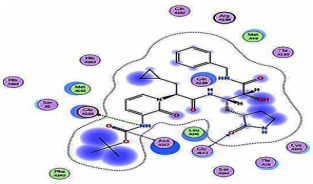
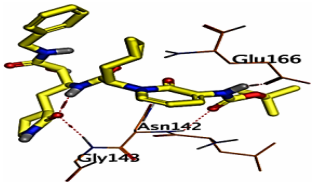
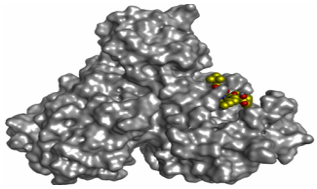
Molecular docking

The novel two thiazo-isoindolinedione hybrids 8 and 9 were subjected to a molecular docking study to investigate their potential inhibitory effect on the SARS-CoV-2 M^{pro}. Besides, the co-crystal (O6K) was inserted as a reference standard in the docking process.

Observing the O6K binding mode, it was clear that Glu166 and Cys145 are the most crucial amino acids to produce their inhibitory potential towards the SARS-CoV-2 M^{pro}. The docked O6K achieved a binding score of -8.41 kcal/mol (RMSD=1.58 Å) and could bind Glu166, Asn142, and Gly143 with three hydrogen bonds. On the one hand, compound 8 showed a binding score of -5.83 kcal/mol (RMSD=1.16 Å). It bound crucial amino acids (Glu166 and Cys145) with two pi-hydrogen interactions and one hydrogen bond, respectively. On the other hand, compound 9 interacted with Glu166 (two hydrogen bonds) and Met165 (one pi-hydrogen bond), Table 1. Its binding score was recorded at -6.05 kcal/mol (RMSD=1.50 Å), superior to compound 8.

Based on the above, compound 9 with the three carbons bridge (propylene) between the 1,3-dioxoisoindoline and thiazolidine-2,4-dione moieties was superior to compound 8 with the two carbons bridge (ethylene) as SARS-CoV-2 M^{pro} inhibitor. This may be attributed to the flexibility of compound 9, which produced more and deeper fitting within the SARS-CoV-2 M^{pro} target receptor.

Table 1: 2D interactions, 3D interactions, and 3D positioning of compounds 8 and 9 within the binding pocket of the SARS-CoV-2 M^{pro} (PDB ID: 6Y2G) target receptor

	2D interactions	3D interactions	3D positioning
8			
9			
O6K			

CONCLUSION

In this study, we designed and synthesized new thiazo-isoindolinedione hybrids from readily available starting materials and in good yields (up to 92%). The chemical structures of the new compounds were characterized by IR, ^{1}H- and ^{13}C-NMR, and MS techniques. In addition, a molecular docking study clarified that compound 9 with the three carbons bridge (propylene) between the 1,3-dioxoisoindoline and thiazolidine-2,4-dione moieties was superior to compound 8 with the two carbons bridge (ethylene) as SARS-CoV-2 M^{pro} inhibitor. This may be attributed to the flexibility of compound 9, which produced more and deeper fitting within the SARS-CoV-2 Mpro target receptor.

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Conflict of interest

The author declare that we have no conflict of interest.

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