Regular Article

Synthesis and Biological Evaluation of 3,9-Dioxatetraasteranes as C₂-Symmetric HIV-1 Protease Inhibitors and Docking Study

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A series of tetraethyl 2,4,8,10-tetramethyl-6,12-diaryl-3,9-dioxahexacyclo[6.4.0.0²,7·0⁴,11·0⁵,10]dodecane-1,5,7,11-tetracarboxylates (simplified as 3,9-dioxatetraasteranes) with C₂-symmetric structural characteristics were synthesized through the [2 + 2] photocycloaddition of the diethyl 2,6-dimethyl-4-aryl-4H-pyran-3,5-dicarboxylates. Besides, their anti-human immunodeficiency virus (HIV)-1 activities were evaluated by enzyme-linked immunosorbent assay (ELISA) assay against HIV-1 (IIIB) replication in MT-4 cell culture. The result showed that the tested compounds exhibited potential activities with IC₅₀ values less than 110 nM. Furthermore, docking study was carried out to study the binding mode of these compounds. The results indicated that the overall orientation of the inhibitors in the active site were similar to that of the cyclic urea AHA001 and a hydrogen bond with the protein residues might play a crucial role in their anti-HIV-1 activities. Such results will provide a theoretical foundation for further investigations on the biological activity of 3,9-dioxatetraasteranes.

Key words 3,9-dioxatetraasterane; synthesis; docking study; pharmacological activity; human immunodeficiency virus (HIV)-1 protease inhibitor

INTRODUCTION

AIDS, caused by human immunodeficiency virus (HIV) infection, is still one of the important challenges for the chemotherapy. The introduction of combined antiretroviral therapy (cART) was a mark of breakthrough treatment for patients with AIDS. cART treatment regimens with reverse transcriptase inhibitors and protease inhibitors improved HIV-related disease progression and mortality. HIV protease inhibitors (PIs) are critical components of cART regimens particularly for salvage treatments. The HIV-1 protease (PR) is an essential enzyme for HIV-1 replication and constitutes an important target in the treatment of HIV/AIDS. The X-ray crystal structure of HIV-1 PR shows the enzyme to consist of a C₂-symmetric homodimer, with the binding groove lying perpendicular to the 2-fold symmetry axis. The C₂ symmetry of the protease and of its active sites have served as useful guideline in the design of inhibitors: C₂-symmetric and nearly C₂-symmetric inhibitors have been tested under the assumption of better drug-active site fit, due to the similar shape. One of the strategies that exploit the enzyme structure more directly and use the element of symmetry in the design and synthesis of HIV-1 PIs has also been pursued.

Early efforts have been made to develop non-peptidic PIs, thus promising a better oral bioavailability. From the series of cyclic ureas the most potent representatives DMP 323 and DMP 450 failed in clinical trials because of a disappointing bioavailability. While DMP 323 showed poor absorption and extensive oxidative metabolism of the hydroxymethylene groups, the therapeutically necessary blood levels of DMP 450 were not achieved because of high plasma protein binding. Cage 3,9-diazatetraester have recently been developed as a novel class of non-peptidic PIs with moderate but promising activities of their first representatives. With a hitherto unknown substituted tetraasterane-analogous drug skeleton, 3,9-dioxatetraasterane (1, tetraethyl 2,4,8,10-tetramethyl-6,12-diaryl-3,9-dioxapentaacyclo[6.4.0.0²,7·0⁴,11·0⁵,10]dodecane-1,5,7,11-tetracarboxylate) are synthesized by photocycloaddition of 4-aryl-4H-pyranes (Fig. 1). These compounds possessed a steady structure, high energy and large lipophilic property, especially, the C₂-symmetric characteristic would be the key to ensuring potential HIV-1 PR inhibition activities. In this paper, our efforts have resulted in the synthesis and evaluation of 3,9-dioxatetraasterane as potent inhibitors of HIV-1 PIs.

RESULTS AND DISCUSSION

Chemistry C₂-Symmetrical 3,9-dioxatetraasterane (1) were synthesized according to the reported strategy, which was realized by exposing a solution of 2 in methanol (0.15 M) to irradiated with a 500 W high-pressure mercury lamp using benzophenone as photosensitizer (Chart 1). Subsequently, the inhibitory activity of 1 was evaluated against HIV-1 (IIIB) replication in MT-4 cell culture using enzyme-linked immunosorbent assay (ELISA) assay and the results were summarized in Table 1. From Table 1, potential inhibitory activities of 1 could be observed. For example, 1c, 1f, 1k and 1m displayed potent anti-HIV-1 activities with IC₅₀ values less than 29 nM. Regrettably, due to the poor solubility of 1d, e and 1g, their IC₅₀ values could not be determined. Overall, it was found that the introduction of electron-donating groups into the benzene ring would increase the inhibitory activity, especially for 1f (4-OC₃H₇) and 1m (4-NH₂). Moreover, the IC₅₀ value of 1m (4-NH₂) was determined at 26.77 nM, which is better than that of the control compound AHA001 (IC₅₀ = 84.12 nM), indicating the 3,9-dioxatetraasterane has the potential to become a novel HIV-1 protease inhibitor drug
skeleton.

**Theoretical Analysis** To understand the structure–activity relationships (SARs) observed at HIV-1 protease, molecular docking of compounds 1 into active site of HIV-1 PR was performed based on the HIV-1 PR complex structure (PDB code 1ajx). Before performing docking calculations, ligand AHA001 was extracted from the crystal structure, the structural water molecules were removed, and hydrogen atoms were added in standard geometry. For each compound, 100 docking experiments were initiated with randomized populations and solutions for individual runs were clustered if their final docked positions were within a tolerance of 2 Å RMSD. The grid size for the search of docking space was set at $60 \times 60 \times 60$ distributed around the binding domain with a default grid spacing of 0.375 Å. AHA001 is a cyclic, $C_{2}$-symmetric HIV-1 PI, which is also docked as a control compound. Binding affinities are reported as the binding free energies ($\Delta G$) and inhibition constants ($K_{i}$), as shown in Table 2. It can be seen that photodimers 1 exhibited a certain binding affinities ($\Delta G$ ranging from $-5.35$ to $-6.16$ kcal/mol and $K_{i}$ ranging from 12.23 to 30.22 $\mu$M), 1m ($R = 4-NH_{2}$) exhibited relative better binding capacity with $\Delta G = -6.16$ kcal/mol. Photodimers 1 with electron-donating groups on the benzene ring (such as $-OCH_{3}, -OH, -NH_{2}$), exhibited more potent binding capacity with HIV-1 PR than those with electron-withdrawing substituents, which is consistent with the results of biological evaluation.

Photodimers 1f and 1m were chosen as the representative compounds and docked into the active site of HIV-1 PR to identify the key interactions between those two molecules and HIV-1 PR. Molecular docking modeling of compounds 1f, 1m and AHA001 are given to visualize the orientation and binding mode of the active compounds. As shown in Fig. 2, the comparable potencies of 1f and 1m could be explained by similar binding interactions. Both 1f and 1m showed high overlap ratios with AHA001 in the active site of the HIV-1 PR (Figs. 2A, B), which was consistent with the biological activities results. For 1f, the carbonyl oxygen of the carbethoxyl group formed hydrogen bond with IleA50 (C=O $\cdots$ HN, $\Delta d = 3.29$ Å). In addition, two $\pi$–alkyl interactions between the phenyl ring and the amino acid IleA50 (C=O $\cdots$ HN, $\Delta d = 3.29$ Å). In addition, two $\pi$–alkyl interactions between the phenyl ring and the amino acid IleA50 ($\Delta d = 3.29$ Å). In addition, two $\pi$–alkyl interactions between the phenyl ring and the amino acid IleA50 ($\Delta d = 3.29$ Å).

Table 1. Structures and Inhibitory Effect of 1 against HIV-1 Infecting MT-4 Cells in Vitro

| Compd. | R        | IC$_{50}$ (nM)$^{a}$ | Compd. | R        | IC$_{50}$ (nM)$^{a}$ |
|--------|----------|----------------------|--------|----------|----------------------|
| 1a     | H        | 30.51                | 1h     | 4-OH     | 32.83                |
| 1b     | 4-Cl     | 34.69                | 1i     | 3,4-diCl | 106.05               |
| 1c     | 4-CH$_{3}$ | 28.54                | 1j     | 4-NHCOCH$_{3}$ | 56.08          |
| 1d     | 3-Cl     | — ($^{b}$)           | 1k     | 3,4-diF  | 28.57                |
| 1e     | 4-F      | — ($^{b}$)           | 1l     | 4-CF$_{3}$ | 75.52                |
| 1f     | 4-OCH$_{3}$ | 27.89                | 1m     | 4-NH$_{2}$ | 26.77                |
| 1g     | 3-NHCOCH$_{3}$ | — ($^{b}$)        | AHA001 | —        | 84.12                |

$^{a}$ Values are the means of at least three independent experiments S.D. < 10%. $^{b}$ Due to the poor solubilities, the values could not be determined.

Table 2. Molecular Docking Results of 1 with HIV-1 Protease

| Compd. | R         | $\Delta G$$^{a}$ | $K_{i}$$^{a}$ | Compd. | R         | $\Delta G$$^{a}$ | $K_{i}$$^{a}$ |
|--------|-----------|------------------|---------------|--------|-----------|------------------|---------------|
| 1a     | H         | $-5.8$           | 55.9          | 1h     | 4-OH      | $-5.92$          | 45.28         |
| 1b     | 4-Cl      | $-5.81$          | 54.56         | 1i     | 3,4-diCl  | $-5.53$          | 88.15         |
| 1c     | 4-CH$_{3}$ | $-5.9$           | 47.14         | 1j     | 4-NHCOCH$_{3}$ | $-5.77$          | 58.43         |
| 1d     | 3-Cl     | $-5.62$          | 76.25         | 1k     | 3,4-diF   | $-5.76$          | 60.21         |
| 1e     | 4-F      | $-5.81$          | 55.10         | 1l     | 4-CF$_{3}$ | $-5.62$          | 75.43         |
| 1f     | 4-OCH$_{3}$ | $-5.99$          | 40.58         | 1m     | 4-NH$_{2}$ | $-6.16$          | 30.22         |
| 1g     | 3-NHCOCH$_{3}$ | $-5.35$          | 120.23        | AHA001 | —        | $-7.62$          | 2.58          |

$^{a}$ Binding free energy (kcal/mol). $^{b}$ Inhibition constant ($\mu$M).
Moreover, the introduction of methoxy group on phenyl ring of 1f permitted deeper immersion into the bottom of the binding site, prompting good binding affinities (Fig. 2E). 1m was involved in three hydrogen bonds with the enzyme backbone: one involved the carbonyl oxygen of carbethoxyl group and the main chain NH group of IleB50 (C=O⋯HN, \(d = 3.16\) Å), one occurred between the nitrogen atom substituent on the benzene ring and the amino acid AspA30 (N⋯HC, \(d = 3.96\) Å) and the other involved the nitrogen atom and the amino acid AspB30 (N⋯HC, \(d = 4.45\) Å) (Fig. 2H). Besides, a π–σ interaction between the phenyl ring and the amino acid IleB84 (Ar⋯HC, \(d = 5.44\) Å), a π-alkyl interaction between phenyl ring and the amino acid IleA50 (Ar⋯HC, \(d = 4.35\) Å) and a π-alkyl interaction between phenyl ring and the amino acid AspB30 (N⋯HC, \(d = 4.45\) Å).
acid AlaA28 (Ar· · · HC, d = 4.8 Å) were detected. And the other moieties of this compound were involved in Van der Waals contacts and hydrophobic interactions with residues (Fig. 2H). The analog 1f and 1m were more active than other photodimers, suggesting that the hydrogen bond donating ability plays a key role in bonding pattern and affinity. Moreover, 1f also exhibited that the introduction of alkyl side chains on phenyl ring may assist to form interactions with amino acid residues in the bottom of the binding cavity.

The results of molecular docking indicated that the photodimers 1 had a certain overlap ratios and affinities and the interactions of a hydrogen bond and a π-cation with the protein residues in the active site might play a crucial role in their HIV-1 PR inhibition. Good correlation between the docking study and anti-HIV-1 activities supported targeting of the residues in the active pocket was nicely occupied by 1p (Fig. 4E).

In order to improve the solubility and further enhance the inhibitory activity of the photodimers, another four photodimers (1n–q) were designed (Fig. 3) and the binding affinities with HIV-1 PR and presented photodimer 1p and 1m as promising and attractive anti-HIV-1 agents that might be promising lead compounds for further optimization.

| Compd. | $\Delta G$ (kcal/mol) | $K_i$ ($\mu$M) |
|--------|----------------------|----------------|
| 1n     | −7.46                | 3.38           |
| 1o     | −7.03                | 7.04           |
| 1p     | −7.66                | 2.42           |
| 1q     | −7.29                | 4.51           |
| AHA001 | −7.62                | 2.58           |

Table 3. Molecular Docking Results of 1n–q with HIV-1 Protease

EXPERIMENTS

Chemistry All chemicals were purchased from commercial sources and used without further purification. TLC was conducted on silica gel 60 F254 plates (Merck KGaA, Germany). Melting points were determined on a XT-5A digital melting point apparatus and are uncorrected. IR spectra were recorded as thin films on KBr plates with a Bruker vertex 70 spectrophotometer. $^1$H-NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400MHz using CDCl$_3$ or acetone-$d_6$ as the solvent and tetramethylsilane (TMS) as the internal standard. Electrospray ionization (ESI)-MS were measured on a ZAB-HS & ESQUIRE6000 mass spectrometer. Elemental analyses, as indicated by the symbols of the elements, were within ±0.3% of the theoretical values and were performed using a Leco CHNS-932 apparatus. Sonication was performed in a GE750-5C ultrasonic processor and irradiation for the photochemical reactions was conducted using an Osram HBO 500 W high-pressure mercury lamp.

General Procedure for Synthesis of the 3,9-Dioxatetraasterane (1) Diethyl 2,6-dimethyl-4-aryl-4H-pyran-3,5-dicarboxylate (2) (2.5 g) containing 0.05 eq of benzophenone was dissolved in 50 mL methanol in an ACE glass of chemical reactor fitted with a centrally positioned quartz cooling jacket. The solution was irradiated with a 500 W high-pressure mercury lamp from a distance of 10 mm. After completion of the reaction as indicated by TLC, the photodimers 1 precipitated from the solution after reduction of the solution volume. The precipitate was recrystallized in methanol–dichloromethane solution.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-diphenyl-3,9-dioxapentacyle[6.4.0]2,7.04,11.05,10-tetracarboxylate (1a) Yield 10.0%, mp 268–270°C. IR (ATR, cm$^{-1}$): 2922, 2854, 1603, 1487, 1456, 1380, 1192, 1034, 710. $^1$H-NMR (CDCl$_3$) $\delta$: 1.12 (t, 12H, CH$_2$CH$_3$), 1.70 (s, 12H, CH$_3$), 3.83–3.99 (m, 8H, CH$_2$CH$_3$), 4.26 (s, 2H, Ar-CH), 7.15–7.55 (m, 10H, Ar-H). MS (ESI) m/z (%): 661.3 [M + H]$^+$;

Calculd for C$_{38}$H$_{54}$O$_{10}$: C, 68.97; H, 6.85; O, 24.18. Found: C, 68.90; H, 6.87; O, 24.23.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(4-chlorophenyl)-3,9-dioxapentacyle[6.4.0]2.7.04,11.05,10-tetracarboxylate (1b)
Yield 9.3%, mp >300°C. IR (KBr, cm⁻¹): 2983, 2939, 1493, 1450, 1416, 1271, 1201, 861, 718. ¹H-NMR (acetone-d₆, 400 MHz) δ: 1.13 (t, 12H, CH₂CH₃), 1.66 (s, 12H, CH₃), 3.84–4.02 (m, 8H, CH₂CH₃), 4.3 (s, 2H, Ar-CH), 7.33 (d, 4H, J = 8.5 Hz, Ar-H), 7.61 (d, 4H, J = 8.5 Hz, Ar-H). MS (ESI) m/z (%): 753.1 [M + Na]⁺; Anal. Calcd for C₃₈H₄₂Cl₂O₁₀: C, 62.55; H, 5.80; Cl, 9.72. Found: C, 62.67; H, 5.79; Cl, 9.74.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(4-methylphenyl)-3,9-dioxapentacyclo[6.4.0.0²,7.0⁴,11.0⁵,10]dodecane-1,5,7,11-tetracarboxylate (1c)

Yield 9.5%, mp >300°C. IR (KBr, cm⁻¹): 2983, 2939, 1739, 1493, 1450, 1416, 1271, 1201, 861, 718. ¹H-NMR (acetone-d₆, 400 MHz) δ: 1.14 (t, 12H, CH₂CH₃), 1.69 (s, 12H, CH₃), 3.83–4.02 (m, 8H, CH₂CH₃), 4.30 (s, 2H, Ar-CH), 7.02 (d, 4H, J = 8 Hz, Ar-H), 7.39 (d, 4H, J = 8 Hz, Ar-H). MS (ESI) m/z (%): 711.8 [M + Na]⁺; Anal. Calcd for C₄₀H₄₈O₁₀: C, 69.75; H, 7.02; O, 23.23. Found: C, 69.78; H, 7.04; O, 23.18.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(3-chlorophenyl)-3,9-dioxapentacyclo[6.4.0.0²,7.0⁴,11.0⁵,10]dodecane-1,5,7,11-tetracarboxylate (1d)

Yield 11.6%, mp >300°C. IR(KBr, cm⁻¹): 2983, 2939, 1739, 1493, 1450, 1416, 1383, 1200, 1038, 861, 686. ¹H-NMR (acetone-d₆, 400 MHz) δ: 1.14 (t, 12H, CH₂CH₃), 1.69 (s, 12H, CH₃), 3.89–4.00 (m, 8H, CH₂CH₃), 4.30 (s, 2H, Ar-CH), 7.26–7.64 (m, 8H, Ar-H). MS (ESI) m/z (%): 753.1 [M + Na]⁺; Anal. Calcd for C₃₈H₄₂Cl₂O₁₀: C, 62.55; H, 5.80; Cl, 9.72. Found: C, 62.70; H, 5.79; Cl, 9.70.
Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(4-fluorophenyl)-3,9-
dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)6,12-bis(3,4-difluorophenyl)-3,9-
dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)6,12-bis(4-trifluoromethyl-
phényl)-3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)6,12-bis(4-
methoxyphenyl)-3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)
-15,11-tetracarboxylate (Ie)

Yield 9.1%, mp 273–275°C (Dec.). IR (KBr, cm\(^{-1}\)): 2989,
1715, 1602, 1504, 1478, 1372, 1260, 1023, 836. \(^{1}H\)-NMR (CDCl\(_3\), 400 MHz) \(\delta\): 1.14 (t, 12H, CH\(_2\)CH\(_3\)), 1.67 (s, 12H,
CH\(_3\)), 3.83–4.00 (m, 8H, CH\(_2\)CH\(_3\)), 4.25 (s, 2H, Ar-CH), 6.91
(m, 4H, \(J = 8.71\) Hz, Ar-H), 7.51 (m, 4H, \(J = 8.71\) Hz, Ar-H). MS
(ESI) m/z (%): 719.2 [M + Na]+; Anal. Calcd for C\(_{40}\)H\(_{32}\)F\(_{10}\)O\(_{10}\):
C, 56.51; H, 6.02; F, 4.54. Found: C, 56.55; H, 6.07; F, 4.56.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(3-acetamidophenyl)-
3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)6,12-bis(4-
methoxyphenyl)-3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)
-15,11-tetracarboxylate (Ig)

Yield 8.0%, mp 267–269°C. IR (KBr, cm\(^{-1}\)): 2989, 2942,
1739, 1612, 1514, 1449, 1382, 1255, 1043, 847, 762. \(^{1}H\)-NMR (CDCl\(_3\), 400 MHz) \(\delta\): 1.15 (t, 12H, CH\(_2\)CH\(_3\)), 1.68 (s,
12H, CH\(_3\)), 3.75 (s, 6H, OCH\(_3\)), 3.84–3.98 (m, 8H, CH\(_2\)CH\(_3\)),
4.20 (s, 2H, Ar-CH), 4.18 (d, 4H, \(J = 8.85\) Hz, Ar-H), 7.44 (d,
4H, \(J = 8.85\) Hz, Ar-H). MS (ESI) m/z (%): 743.2 [M + Na]+;
Anal. Calcd for C\(_{39}\)H\(_{26}\)F\(_{10}\)O\(_{10}\): C, 66.65; H, 6.71; O, 26.64. Found:
C, 66.74; H, 6.69; O, 26.57.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(4-hydroxyphenyl)-3,9-
dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)6,12-bis(3,4-
difluorophenyl)-3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)
-15,11-tetracarboxylate (Ih)

Yield 7.4%, mp >300°C. IR (KBr, cm\(^{-1}\)): 2924, 2853,
1739, 1655, 1637, 1560, 1539, 1488, 1458, 1385, 1256, 1180,
1051, 866, 742. \(^{1}H\)-NMR (acetone-\(d_{6}\), 400 MHz) \(\delta\): 1.13 (t,
12H, CH\(_2\)CH\(_3\)), 1.68 (s, 12H, CH\(_3\)), 2.81(s, 6H, NHCOCH\(_3\)),
3.82–3.99 (m, 8H, CH\(_2\)CH\(_3\)), 4.26 (s, 2H, Ar-CH), 7.16–7.96
(m, 8H, Ar-H), 9.109 (s, 2H, NHCOCH\(_3\)). MS (ESI) m/z (%):
797.2 [M + Na]+; Anal. Calcd for C\(_{39}\)H\(_{30}\)F\(_{10}\)N\(_2\)O\(_{10}\): C, 65.10; H,
6.50; N, 3.63. Found: C, 65.22; H, 6.51; N, 3.63.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(3-dichlorophenyl)-
3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)6,12-bis(3,4-
difluorophenyl)-3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)
-15,11-tetracarboxylate (Ii)

Yield 9.2%, mp >300°C. IR (KBr, cm\(^{-1}\)): 1732, 1509,
1394, 1259, 1047. \(^{1}H\)-NMR (CDCl\(_3\), 400 MHz) \(\delta\): 1.26 (t,
12H, CH\(_2\)CH\(_3\)), 1.63 (s, 12H, CH\(_3\)), 3.78–3.94 (m, 8H,
CH\(_2\)CH\(_3\)), 4.20 (s, 2H, Ar-CH), 7.08 (s, 2H, Ar-H), 7.13(d, 4H,
Ar-H). MS (ESI) m/z (%): 822.1 [M + Na]+; Anal. Calcd for C\(_{39}\)H\(_{30}\)Cl\(_{10}\)O\(_{10}\):
C, 57.16; H, 5.05. Found: C, 57.14; H, 5.06.

Tetraethyl 2,4,8,10-Tetramethyl-6,12-bis(4-acetamidophenyl)-
3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)6,12-bis(3,4-
difluorophenyl)-3,9-dioxapentacyclo[6.4.0.0\(^{1}\)2,7\(^{6}\)
-15,11-tetracarboxylate (Ij)

Yield 8.6%, mp >300°C. IR (KBr, cm\(^{-1}\)): 2853, 1739,
1637, 1560, 1539, 1488, 1256, 1180, 1051. \(^{1}H\)-NMR (CDCl\(_3\),
400 MHz) \(\delta\): 1.15 (t, 12H, CH\(_2\)CH\(_3\)), 1.73 (s, 12H, CH\(_3\)),
2.18 (s, 6H, NHCOCH\(_3\)), 3.87–4.01 (m, 8H, CH\(_2\)CH\(_3\)), 4.29 (s,
2H, Ar-CH), 7.01–7.34 (m, 8H, Ar-H). MS (ESI) m/z (%): 797.2 [M + Na]+; Anal. Calcd for C\(_{39}\)H\(_{30}\)N\(_2\)O\(_{10}\): C,
65.10; H, 6.50; N, 3.62. Found: C, 65.06; H, 6.53; N, 3.59.
mented through the graphical user interface Auto-DockTools (ADT 1.5.2). AutoDockTools (ADT) was used to add polar hydrogens and gasteiger charges. Ligands were prepared by drawing the 2D structure in CambridgeSoft’s ChemDraw, and converted to PDB format using Chem3D. Ligands were then energy minimized using Discovery Studio 2.1 before using ADT to add polar hydrogens and gasteiger charges. All bound water and ligands were eliminated from the protein and the polar hydrogen was added. The whole HIV-1 PR complex was defined as a receptor, then the ligand AHA001 molecule was removed and new ligand was placed during the molecular docking procedure. Types of interactions of the docked protein with ligand were analyzed after the end of molecular docking.

CONCLUSION

In this paper, a series of 3,9-dioxatetraesteranes with C2-symmetric structural characteristics were synthesized by the photodimerization of 4-aryl-4H-pyran as a HIV-1 protease inhibitors. The bioactivities test of the titled compounds were conducted by ELISA assay in MT-4 cell culture. The inhibitors. The bioactivities test of the titled compounds revealed that were conducted by ELISA assay in MT-4 cell culture. The inhibitors. The bioactivities test of the titled compounds photodimerization of 4-aryl-4H-pyran as a HIV-1 protease inhibitors. The bioactivities test of the titled compounds were conducted by ELISA assay in MT-4 cell culture. The result showed that inhibitors displayed the most activities with the IC50 values of 27.89 and 26.77 nM, respectively.

Molecular docking of inhibitors revealed that the overall orientation of inhibitors in the active site was similar to that of the cyclic urea HIV-1 protease inhibitor AHA001. Besides, hydrogen bond involvement between inhibitors and the protein residues might play a crucial role in controlling their anti-HIV-1 activities. In order to improve the solubility of the inhibitors and further enhance their inhibitory activities, another four photodimers (1f–q) were designed and docked with the HIV-1 protease, the docking result suggested that photodimers have similar or even better binding affinities to the cyclic urea HIV-1 PI AHA001(ΔG = −7.62 kcal/mol). Such result will provide theoretical foundations for further investigations on the biological activity of 3,9-dioxatetraesteranes.

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Conflict of Interest The authors declare no conflict of interest.