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# Total Synthesis and Anti-HIV Activity Evaluation of Desmosdumotin D and Analogues

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**Abstract:** The natural product Desmosdumotin D (hereafter referred to as **Des-D**), isolated from the plant *Desmos dumosus*, showed potent anti-HIV activity. However, the subsequent pharmacological activity and clinical studies are limited due to the low content of **Des-D** in the plant. Therefore, the total synthesis path of **Des-D** was optimized in this paper, and the total yield was increased from 4.4% to 11.9%. Additionally, twelve analogues were obtained following the synthesis route of **Des-D**. The anti-HIV activity evaluation results in vitro showed that **Des-D** had the highest activity, with an $IC_{50}$ value of 13.6 μM, and compounds **17** and **11** had the lowest anti-HIV activity, with $IC_{50}$ values of 101.3 μM and 161.0 μM, respectively. Through the molecular docking of compounds **Des-D** and **17** with HIV-IN, the results show that phenolic hydroxyl groups and two benzene rings interact with HIV-IN and are possible pharmacodynamic groups.

**Keywords:** Desmosdumotin D; chemical synthesis; analogue; HIV-1



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## 1. Introduction

The AIDS pandemic has been a serious medical and public health problem for nearly half a century. AIDS, acquired immunodeficiency syndrome (AIDS), is a systemic disease caused by body infection with the human immunodeficiency virus (HIV) [1]. HIV is a lentivirus, a type of retrovirus that infects cells of the human immune system [2]. Currently, the essential treatment for AIDS is highly effective antiretroviral therapy, commonly known as cocktail therapy, which combines several antiretroviral drugs to improve the quality of survival and prolong the life span of infected patients by inhibiting HIV replication and rebuilding and maintaining the body's immune function [3]. Among the antiretroviral drugs, integrase inhibitors could inhibit the replication process of the retrovirus and block the integration of viral DNA and host chromosome DNA [4]. Raltegravir has the characteristics of a rapid and efficient antiviral, showing good curative effects compared with traditional antiviral drugs; however, it has its own shortcomings, and antiviral drugs have certain toxic and side effects [5,6].

Natural products are often used as lead compounds in developing new drugs due to their unique chemical structure, good pharmacological activity and low toxicity, and natural products with anti-HIV activity are studied [7]. **Des-D** (Figure 1) was first discovered in 1976 by Joshi et al. [8] from the plant *Unona lawii*, which belonged to the *chalcone* class. In 1999, Wu et al. [9,10] isolated **Des-D** from the roots of the domestic genus *Pseudohawpaw* of *Phyllanthaceae* family in China, which was found to have significant inhibitory activity against HIV.

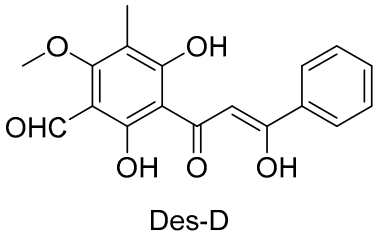



**Figure 1.** Structure of **Des-D**.

However, due to the extremely low content of Des-D, i.e., 0.04 ‰, in the plant [10], the synthesis of **Des-D** exhibited great potential and low cost, which could help to obtain enough products for subsequent biological activity studies. Nakagawa-Goto and Lee reported the total synthesis of **Des-D** first, showing a short route without the use of any protecting groups (Figure 2) [11].

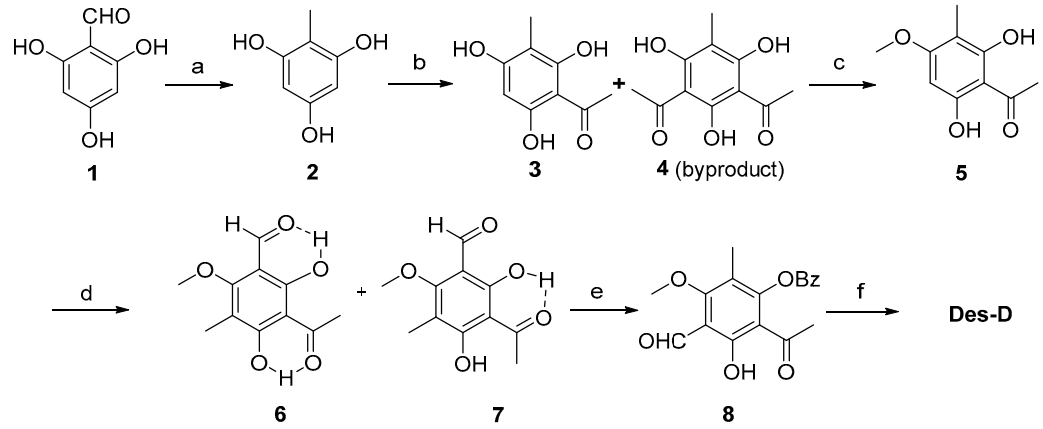



**Figure 2. Des-D** synthesis route by Nakagawa-Goto and Lee Reagents and conditions: (**a**) $NaBH_3CN$, THF, rt, 15 h, 53.0%; (**b**) $Ac_2O$, $BF_3{\cdot}Et_2O$, AcOH, 100 °C, 3 h, 75.0%; (**c**) EtOAc, MeOH, $TMSCHN_2$, −40 °C, 9 h, 47.0%; (**d**) $TiCl_4$, $CH_2Cl_2$, $Cl_2CHOCH_3$, overnight, 68.0%; (**e**) BzCl, Py, DMAP, 60 °C, 26 h, 55.3%; (**f**) Py, DMAP, KOH, 50 °C, 4.5 h, 63.0%.

However, the high cost of this route could make the product uneconomical. Additionally, the instability of the reagent $NaBH_3CN$ and the relatively harsh reaction conditions could lead to poor efficiency and a low yield for the synthesis of **Des-D**. Due to the complex by-products and difficult purification process, the total yield was only 4.4% for the six steps, which posed difficulties for their massive synthesis [12].

Therefore, in this study, the synthesis of **Des-D** was optimized, and the total yield was further increased to 11.9% by using cheap starting materials, convenient reaction reagents, and a simplified separation and purification process. Meanwhile, 12 analogues were obtained by structural modification of **Des-D**, and the structure–activity relationship was discussed by in vitro anti-HIV activity.

## 2. Results

### *2.1. Synthesis*

We obtained 2,4,6-trihydroxy benzaldehyde (compound **1**) in high yield via the Vilsmeier–Haack reaction with phloroglucinol dihydrate as the starting material to reduce costs [13]. Then, we chose different catalysts, reagents, temperatures, and other conditions to optimize each step of the reported procedure.

Compound **1** was obtained by dissolving phloroglucinol dihydrate in ethyl acetate (EtOAc) and *N*,*N*-dimethylformamide (DMF) and then adding the appropriate amount of phosphorus oxychloride ($POCl_3$) via the Vilsmeier–Haack reaction for two hours, and the product could be recrystallized by water.

Then, compound **1** was dissolved in EtOAc via the slow dropwise addition of concentrated hydrochloric acid under nitrogen condition and ice bath condition, and then the reaction mixture was stirred overnight to obtain compound **2** in a yield of 86.4% after adding the reducing agent, zinc [14]. Compound **3** and the by-product deacetylation product **4** (2,4,6-trihydroxy-3-methyl-5-acetylacetophenone; this by-product could be used for the synthesis of analogues of **Des-D**) were obtained via the Friedel–Crafts acylation reaction from compound **2** in the presence of acetic acid (AcOH), $Ac_2O$, and $BF_3{\cdot}Et_2O$ [15]. Compound **5** was obtained by treating compound **3** with excess (Diazomethyl)trimethylsilane ($TMSCHN_2$) and reacting at a low temperature for 7 h. Formylation of **5** with Dichloromethyl methyl ether ($Cl_2CHOCH_3$) in the presence of $TiCl_4$ gave compounds **6** and **7**, as shown in Figure 3. This reaction should be carried out at −40 °C before moving to room temperature. Then, each of the rotated isomers was obtained, and both structures were verified through NMR, in which the shifts of the phenolic hydroxyl hydrogen protons of **6** are 15.02 ppm and 14.09 ppm, while those of **7** are 14.03 ppm and 12.56 ppm. The results showed that the main isomer, **6**, was more stable than the minor isomer, **7**, and more easily separated with a high yield [16].

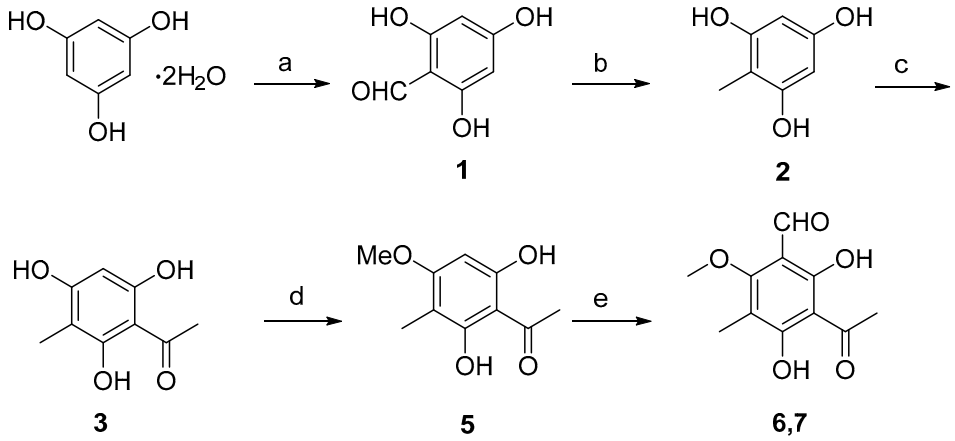
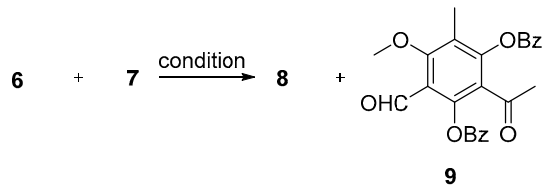



**Figure 3.** Synthesis of **6** and **7** in this work. Reagents and conditions: (**a**) (i) $POCl_3$, DMF, EtOAc, rt, 2 h; (ii) $H_2O$, 100 °C, 5 min, 88.5%. (**b**) EtOAc, $Et_2O$ or THF, Zn, HCl, 0 °C, 79.3%. (**c**) $Ac_2O$, $BF_3{\cdot}Et_2O$, AcOH, 100 °C, 3 h, 86.9%. (**d**) EtOAc, MeOH, $TMSCHN_2$, −40 °C, 49.6%. (**e**) $TiCl_4$, $CH_2Cl_2$, $Cl_2CHOCH_3$, −40 °C, 71.2%.

Next, monoacylated product **8** and diacylated product **9** (3-methyl−4-methoxy-5-formyl-2,6-benzyloxy-acetophenone) were obtained after the addition of BzCl to the mixture of activated 4Å-type molecular sieves and compounds **6** and **7** under a nitrogen atmosphere (Table 1). Subsequently, we tried to optimize the conditions for a high yield and regioselectivity. The excess BzCl (**2** equiv) could lead to the obtainment of more **9** (Entry 1), while the equimolar BzCl (**1** equiv.) did not obtain the corresponding **8** (Entry 2). The half of BzCl in Entry 2 was used for **9** and less than one-third for **8**, which indicated that the low equivalent BzCl did not have a significant enough promoting effect on the generation of **8**. The data also showed that the higher temperature of the reaction could lead to the high yield (Entries 1 and 3; Entries 2 and 4). In addition, the change in the reaction system (Entries 3 and 5) could not increase the yield of **8** or **9**. The reason might be that the low temperature leads to the low yield, while the high temperature leads to the trend of compound **9**′s production. Compound **8** was identified by $^1H$ NMR and $^{13}C$ NMR as an inseparable isomer mixture, which may be caused by the interaction of aldehyde, hydroxyl, and acetyl groups on the benzene ring (similar to **6** and **7**). Compound **9** was obtained by recrystallization, using methanol.

**Table 1.** Screening of benzoylation reaction conditions.




**9**

| Entry | Solvent | BzCl (eq) | Alkali/Catalyst | Temperature | Yield (8) | Yield (9) |
|---|---|---|---|---|---|---|
| 1 | Py | 2 | DMAP (0.2 eq) | 60 °C (12 h) | 14.4% | 73.5% |
| 2 | Py | 1 | DMAP (0.2 eq) | 60 °C (12 h) | 32.5% | 24.7% |
| 3 | Py | 2 | DMAP (0.2 eq) | rt (12 h) | ↓ [a] | ↓ |
| 4 | Py | 1 | DMAP (0.2 eq) | rt (12 h) | ↓ | ↓ |
| 5 | $CH_2Cl_2$ | 2 | $Et_3N$ (2 eq) | rt (4 h) | — [b] | — |
| 6 | $CH_2Cl_2$ | 1 | $Et_3N$ (1 eq) | rt (4 h) | — | — |

[a] The yield was less than 10%; [b] no products were determined.

Compound **8** was used as raw material with pyridine (Py), DMAP, and KOH for the Baker–Venkataraman rearrangement. However, the experiment failed due to the difficulty in separation and purification. Then, we optimized the conditions according to similar reports [12,17], which used **8** and **9** in dry dimethyl sulfoxide (DMSO) reacted with potassium tert-butoxide (*t*-BuOK) as the base (Figure 4) [18]. There was no obvious difference in the yield of **Des-D** from **8** or **9**, so we chose the crude residue of **8** and **9** via the benzoylation of **6** and **7** to simplify operations and increase productivity. **Des-D** obtained from our works was confirmed by NMR as a mixture of enol and diketone structures coexisting, and the molar ratio of enol to diketone was about 2:1 at about 30 °C. The proportion of diketone structures would gradually increase as the temperature increased. The total yield of the entire synthetic route (raw material compound **1**) was 11.9%.

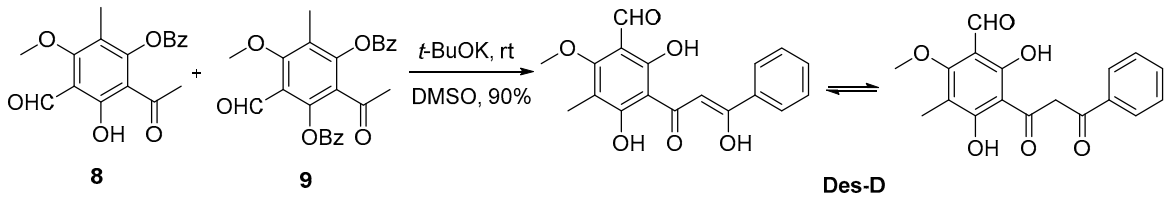



**Figure 4.** The synthesis of **Des-D**.

### *2.2. Analogues*

Using 2,6-dihydroxy acetophenone as a raw material and 4-chlorobenzene chloride as an acylating agent, monoacylated product **10** and diacylated product **12** were obtained. Subsequently, compounds **10** and **12** were reacted from the reaction system of DMSO and *t*-BuOK. After, recrystallization in methanol was used to obtain derivatives **11** and **13**, respectively; the reaction process is shown in Figure 5. The yield of **13** showed that the method might be a potential procedure for the synthesis of flavones, and diacylated intermediates without hydrogen bonding next to hydroxyl groups could not yield the desired products instead of flavones. Since the low yield of the rearrangement step of 2,6-dihydroxy acetophenone as the raw material was insufficient for further modification studies as a substrate, we tried to use compound **2** for the synthesis.

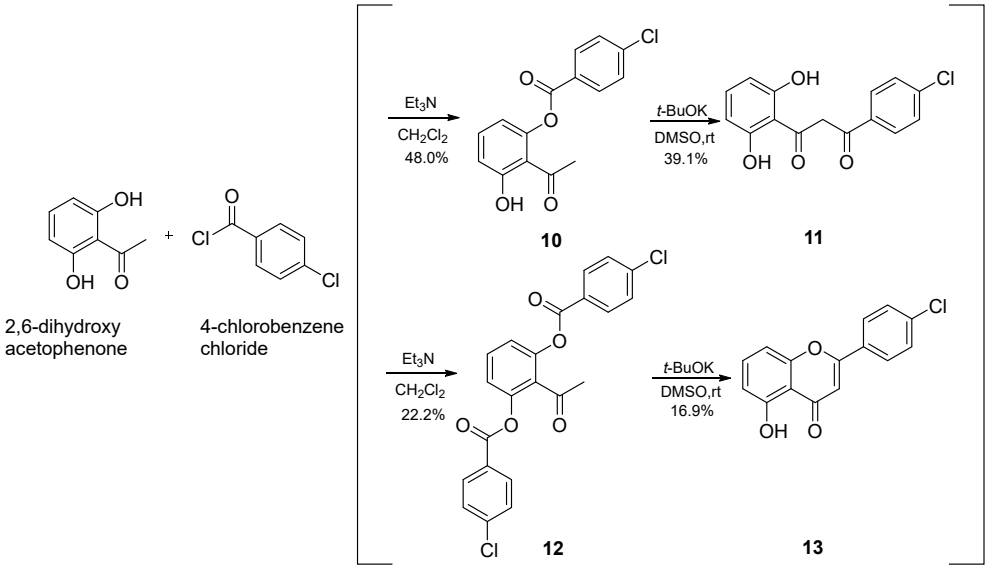



**Figure 5.** Synthesis of analogues **11** and **13**.

The diacetylation product **4** was obtained via the acetylation of compound **2**, which could increase the yield by the additional $Ac_2O$. And then the benzoylation products **14**, **15**, and **16** were obtained in the presence of $CH_2Cl_2$ and $Et_3N$ via the one-pot reaction from **2**. Then, **14** could react with NaOH in the presence of DMSO to give **17** via the Baker–Venkataraman rearrangement, and the structure was confirmed as shown in Figure 6 below.

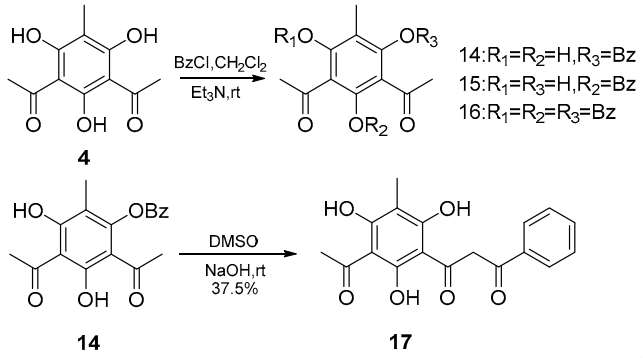



**Figure 6.** Synthesis of analogue **17**.

Moreover, the yield for compound **17** was only 37.5%, and the benzoylation of **4** caused **3** isomers, which made the yield low and difficult to separate and purify. Therefore, we screened another intermediate for total synthesis. The low yields of **8**, **11**, and **17** indicated that a hydroxyl group next to the acetyl group might reduce the efficiency of rearrangement reactions.

Based on the known active fragments of methoxy at the C-4 position, compound **3** was first treated with an excess of $TMSCHN_2$ at room temperature. The main product, **18** (3-methyl-2-hydroxy-4,6-dimethoxy-acetophenone), was obtained after stirring for 24 h, which was found to be efficiently purified by recrystallization in methanol instead of column chromatography. Then, compound **19** (3-methyl-2-benzyloxy-4,6-dimethoxy-acetophenone) was obtained after introducing the benzyloxy group to compound **18**. Afterward, compound **20** (tautomer) was obtained in 93.0% yield via Baker–Venkataraman rearrangement. The structure and procedure are shown in Figure 7; compound **18** was available as an important intermediate for the synthesis of other Des-D analogues on B-ring modification.

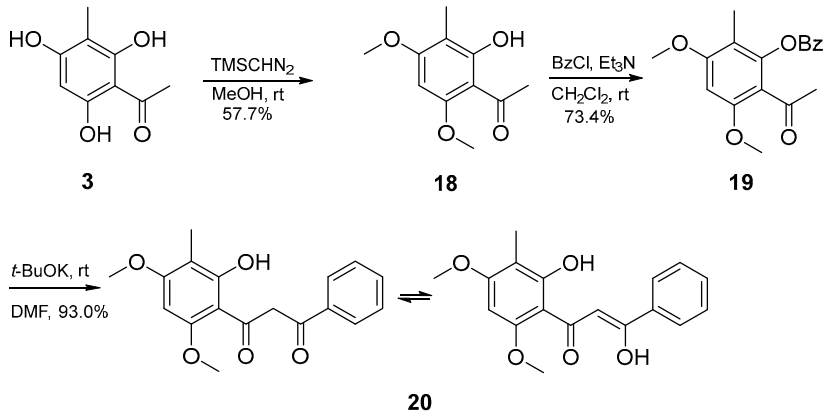



**Figure 7.** Synthesis of analogue **20**.

According to the successful procedure of analogue **20**, the B ring was modified using different acylating agents to introduce halogenated benzene or alkylbenzene. A series of acylated products, **21**, **23**, **25**, **27**, **29**, **31**, **33**, and **35**, were obtained via the Baker–Venkataraman rearrangement, in which the corresponding products, **22**, **24**, **26**, **28**, **30**, **32**, **34**, and **36**, were all reciprocal isomers; see Figure 8 and Table 2.

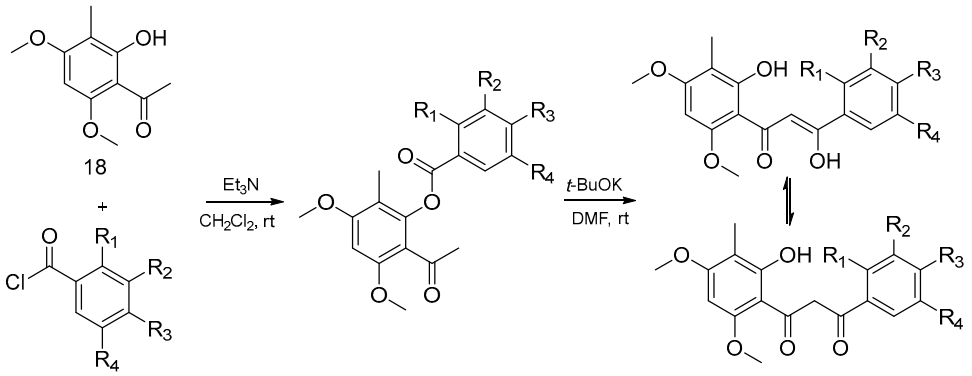



**Figure 8.** Synthesis of chalcone analogues.

**Table 2.** Structure of B-ring analogues.

| Analogue | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **22** | H | H | Cl | H |
| **24** | Cl | H | H | H |
| **26** | H | Cl | H | H |
| **28** | H | Cl | H | Cl |
| **30** | H | H | F | H |
| **32** | H | H | Br | H |
| **34** | H | H | $CH_3$ | H |
| **36** | H | H | $CH_2CH_3$ | H |

### *2.3. Biological Activity*

Subsequently, the HIV-1 integrase inhibitory activities of Des-D and its analogues were studied. As shown in Table 3, the positive control was Raltegravir (HIV integrase inhibitor), with the lowest $IC_{50}$ value of 0.08 ± 0.04 μM. The lead compound, Des-D, showed the highest anti-HIV activity with a $IC_{50}$ value of 13.6 ± 1.75 μM. However, the $IC_{50}$ values of its derivatives, **17** and **11**, were 101.3 ± 3.80 μM and 161.0 ± 3.27 μM, respectively, showing low HIV activity. And compounds **22**, **24**, **26**, **28**, **30**, and **32** showed no inhibitory activity against HIV-1.

**Table 3.** Activity data of target compounds for HIV-1 integrase inhibition.

| Compound | HIV-1 Integrase Activity $IC_{50}$ (μM) |
|---|---|
| **Des-D** | 13.6 ± 1.75 |
| **17** | 101.3 ± 3.80 |
| **11** | 161.0 ± 3.27 |
| **20** | >200 |
| **34** | >200 |
| **22** | / |
| **24** | / |
| **26** | / |
| **27** | / |
| **30** | / |
| **32** | / |
| **Raltegravir** | 0.08 ± 0.04 |

Note: "/" means "no activity".

### *2.4. Molecular Docking*

Finally, the binding mechanism of compounds **Des-D** and **17** was studied using computer-simulated molecular docking. The docking data are shown in Figures 9 and 10. The phenolic hydroxyl groups of **Des-D** and **17** form salt bridges, binding regions of A396 and A397, and the two aromatic benzene rings interact with HIV-IN by forming π-π stacks with D16 and D17. The binding free energy of **Des-D** and HIV-IN is −10.4 kcal/mol, and the binding free energy of **17** and HIV-IN had a binding free energy of −9.6 kcal/mol.

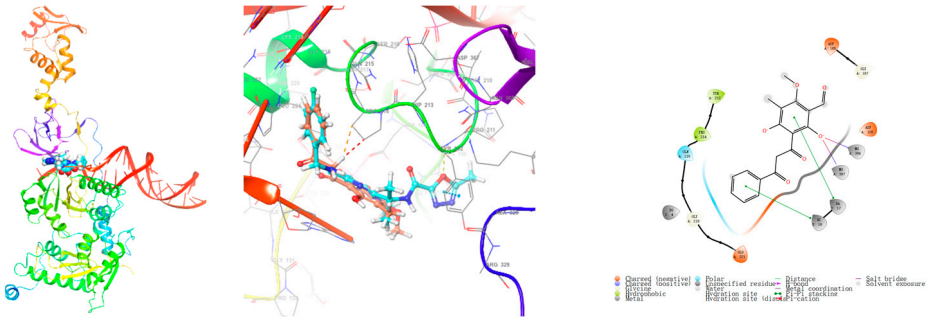


**Figure 9.** Docking of **Des-D** with HIV-1 integrase protein molecule.

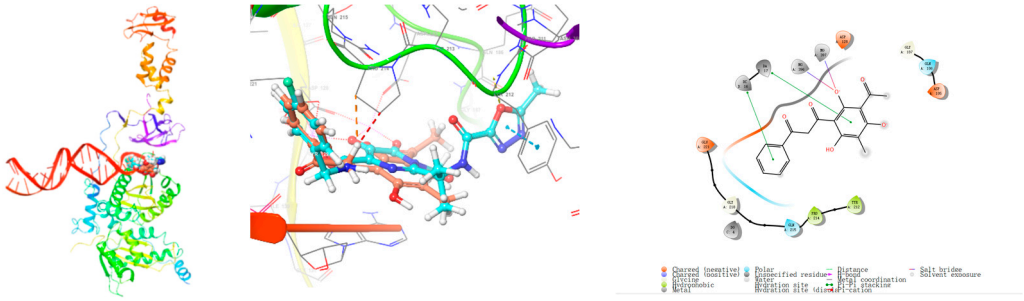


**Figure 10.** Docking of **17** with HIV-1 integrase protein molecule.

Through the molecular docking of compounds **Des-D** and **17** with HIV-IN, the results show that phenolic hydroxyl groups and two aromatic benzene rings of **Des-D** and **17** are active functional groups that bind to HIV-IV. Because hydroxyl groups can bind to the core domain of HIV-IN, they cannot be protected. At the same time, the binding free energy of **Des-D** and HIV-IN is lower than that of **17** and HIV-IN, showing that **Des-D** is easier to bind to HIV-IN than **17**, and the results can be mutually corroborated with the activity research test.

## 3. Materials and Methods

### *3.1. General*

Reagents were analytically or chemically purified and did not require further purification unless otherwise specified. All anhydrous solvents were dried and redistilled before being used in the usual manner. Thin-layer chromatography (TLC) was performed on pre-coated E. Merck silica gel 60 F254 plates (Kenneworth, NJ, USA). Flash column chromatography was performed on silica gel (300–400 mesh). $^{1}$H NMR and $^{13}$C NMR spectra were performed on a Bruker DPX 400 NMR transmission spectrometer (Saarbrucken, Germany) at 400 MHz, using tetramethylsilane as an internal standard, and chemical shifts were recorded as d-values. Mass spectral data were obtained using Bruker Apex IV RTMS, using ESI conditions. The synthesis procedures and spectral data of some compounds were reported [11].

### *3.2. Intermediates and Derivatives*

#### 3.2.1. 3-acetyl-2,4-dihydroxy-6-methoxy-5-methylbenzaldehyde (**6** and **7**)

Compound 5 (631.1 mg, 3.2 mmol) was dissolved in 5 mL of dry dichloromethane, and then $TiCl_4$ (16 mL, 16 mmol, dissolved in 16 mL of dry $CH_2Cl_2$ and $Cl_2CHOCH_3$ (2.7 mL, 30.4 mmol) was added at −40 °C. After sufficient dissolution, the reaction device was transferred to a room-temperature environment and stirred overnight. The next day, the reaction was quenched by slowly adding an appropriate amount of ice water dropwise to the reaction solution at 0 °C, and the reaction was stopped after stirring for one hour. After adding dichloromethane and distilled water to both phases and extracting three times, the organic phase was collected and washed once with NaCl (aq) and desiccated with anhydrous $Na_2SO_4$. Compounds **6** and **7** were purified via column chromatography (eluent, EtOAc/PE = 1/12 to 1/8) after vacuum concentration (513.5 mg, 71.2% yield, white solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/10). Compound **6**: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.74 (s, 3H), 3.89 (s, 3H), 9.98 (s, 1H), 14.09 (s, 1H), 15.02 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 8.08, 33.19, 63.03, 106.58, 107.29, 111.07, 166.66, 167.58, 172.57, 192.74, 204.76; HRMS (ESI) calcd for $C_{11}H_{11}O_5$[M-H]$^-$: 223.0606, found 223.0602. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); Compound **7**:$^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.72 (s, 3H), 3.96 (s, 3H), 10.07 (s, 1H), 12.56 (s, 1H), 14.03 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 6.78, 31.48, 66.82, 108.23, 108.47, 109.62, 166.07, 167.95, 168.96, 192.51, 203.37; HRMS(ESI) calcd for $C_{11}H_{11}O_5$[M-H]$^-$: 223.0606, found 223.0606.

#### 3.2.2. 2-acetyl-4-formyl-5-methoxy-6-methyl-1,3-phenylene dibenzoate (**9**)

The 4Å-type molecular sieve was activated and loaded into a reaction flask. Compounds **6** and **7** (448 mg, 2.0 mmol) were added and dissolved in 5 mL of Py, DMAP (48.9 mg, 0.4 mmol) was added, and then BzCl (0.7 mL, 4.0 mmol) was added slowly, dropwise. The reaction was carried out at 60 °C for 12 h under nitrogen protection. After the reaction, the molecular sieve was removed via filtration, using diatomaceous earth; the reaction solution was diluted with dichloromethane; and then Py was removed via extraction with **1** N HCl. The organic phase was collected and washed once with NaCl (aq), and the desiccant was anhydrous $Na_2SO_4$. The purification was carried out via column chromatography after concentration under reduced pressure (eluent, EtOAc/PE = 1/8 to 1/6) to give compound **8** (94.5 mg, 14.4% yield, white solid) and compound **9** (635.1 mg, 73.5% yield, white solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.20–2.25 (s, 3H), 2.40–2.47 (s, 3H), 3.94–4.00 (s, 3H), 7.49–7.57 (q, J = 7.5 Hz, 4H), 7.62–7.71 (m, 2H), 8.13–8.21 (d, J = 6.6 Hz, 4H), 10.28–10.37 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 197.67, 187.41, 164.61, 164.09, 163.78, 151.59, 146.18, 134.53, 134.16, 130.61, 130.57, 129.03, 128.87, 128.76, 128.13, 127.09, 125.17, 120.44, 63.91, 31.52, 9.80; HRMS(ESI) calcd for $C_{25}H_{21}O_7$[M+H]$^+$: 433.1282, found 433.1267.

3.2.3. 2-acetyl-3-hydroxyphenyl 4-chlorobenzoate (**10**) and 2-acetyl-1,3-phenylene bis(4-chlorobenzoate) (**12**)

2,6-dihydroxy acetophenone (500 mg, 3.29 mmol) was dissolved in 5 mL of dry dichloromethane, and 4-chlorobenzoyl chloride (0.5 mL, 4 mmol), $Et_3N$ (0.5 mL, 4 mmol) was added slowly, dropwise, at room temperature (30 °C). The reaction was terminated after 4 h. After that, we added dichloromethane and distilled water to both phases and extracted three times. The organic phase was collected and washed once with NaCl (aq), desiccated with anhydrous $Na_2SO_4$, concentrated under vacuum, and purified via column chromatography (eluent, EtOAc/PE = 1/20 to 1/15) to give compound **10** (458.1 mg, 48.0% yield, yellow solid) and compound **12** (312.8 mg, 22.2% yield, yellow solid). TLC: Rf = 0.3 (EtOAc/PE = 1/16); compound **10**: $^1$H NMR (400 MHz, $CDCl_3$) δ 2.54–2.57 (s, 3H), 6.64–6.70 (d, J = 8.0 Hz, 1H), 6.91–6.98 (d, J = 8.5 Hz, 1H), 7.44–7.50 (t, J = 7.6 Hz, 1H), 7.52–7.57 (d, J = 8.5 Hz, 2H), 8.12–8.20 (d, J = 8.4 Hz, 2H), 12.69–12.72 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.13, 164.20, 164.15, 151.50, 141.20, 135.69, 131.82, 129.54, 127.38, 116.84, 114.82, 114.12, 32.52; HRMS(ESI) calcd for $C_{15}H_{10}ClO_4[M\text{-}H]^-$: 289.0268, found 289.0269.TLC: $R_f$ = 0.3 (EtOAc/PE = 1/12); compound **12**: $^1$H NMR (400 MHz, $CDCl_3$) δ 2.41–2.50 (s, 3H), 7.19–7.25 (d, J = 8.3 Hz, 2H), 7.46–7.57 (m, 5H), 8.05–8.15 (d, J = 7.0 Hz, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 198.19, 163.87, 148.02, 140.89, 131.80, 131.15, 129.32, 128.38, 127.22, 120.86, 31.47; HRMS(ESI) calcd for $C_{22}H_{15}Cl_2O_5[M+H]^+$: 429.0291, found 429.0261.

3.2.4. 1-(4-chlorophenyl)-3-(2,6-dihydroxyphenyl)propane-1,3-dione (**11**)

Compound **10** (145 mg, 0.5 mmol) was dissolved in 2 mL of dry DMSO, then *t*-BuOK (112.2 mg, 1 mmol) was added, and the reaction was carried out at room temperature (26 °C) for 12 h. After the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$, concentrated under reduced pressure, and purified via column chromatography (eluent, EtOAc/PE = 1/15) to give compound **11** (56.7 mg, 39.1% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/12); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.99–3.09 (s, 2H), 6.49–6.56 (d, J = 8.1 Hz, 1H), 6.57–6.62 (d, J = 8.4 Hz, 1H), 7.37–7.46 (t, J = 8.4 Hz, 3H), 7.60–7.66 (d, J = 8.4 Hz, 2H), 11.47–11.57 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 196.26, 161.83, 157.82, 140.41, 138.44, 135.63, 129.11, 126.74, 110.62, 108.21, 101.34, 48.90; HRMS(ESI) calcd for $C_{15}H_{10}ClO_4[M\text{-}H]^-$: 289.0268, found 289.0251.

3.2.5. 2-(4-chlorophenyl)-5-hydroxy-4H-chromen-4-one (**13**)

Compound **12** (214 mg, 0.5 mmol) was dissolved in 3 mL of dry DMF, then *t*-BuOK (112.2 mg, 1 mmol) was added, and the reaction was carried out at room temperature (16 °C) for 12 h. After the reaction, ethyl acetate and distilled water were added to both phases. After three extractions, the organic phase was collected and washed once, using NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$, concentrated under reduced pressure, and purified via column chromatography (eluent, EtOAc/PE = 1/12). The crude product was obtained as 46.8 mg, and the pure compound **13** was obtained after recrystallization in methanol (23 mg, 16.9% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/10); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.65–6.73 (s, 1H), 6.77–6.85 (d, J = 8.2 Hz, 1H), 6.93–7.02 (d, J = 8.4 Hz, 1H), 7.46–7.59 (m, 3H), 7.78–7.89 (d, J = 8.2 Hz, 2H), 12.38–12.56 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 183.55, 163.48, 160.94, 156.46, 138.54, 135.68, 129.78, 129.61, 127.79, 111.78, 110.95, 107.15, 106.28; HRMS(ESI) calcd for $C_{15}H_{10}ClO_3[M+H]^+$: 273.0313, found 273.0252.

3.2.6. 2,4-diacetyl-3,5-dihydroxy-6-methylphenyl benzoate (**14**); 2,6-diacetyl-3,5-dihydroxy -4-methylphenyl benzoate (**15**); 2,4-diacetyl-6-methylbenzene-1,3,5-triyl tribenzoate (**16**)

Compound **4** (249 mg, 1.11 mmol) was placed in 3 mL of dichloromethane, with thorough stirring, and BzCl (0.14 mL, 1.22 mmol) and $Et_3N$ (0.17 mL, 1.22 mmol) were added under an ice bath. The reaction was allowed to continue at room temperature for

4 h. After the reaction was completed, dichloromethane and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq), and the desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography after vacuum concentration (eluent, EtOAc/PE = 1/35 to 1/30 to 1/20) to give compound **14** (79.7 mg, 21.9% yield, yellow solid), compound **15** (70.1 mg, 19.3% yield, yellow solid), and compound **16** (113.1 mg, 19.0% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/30). Compound **14**: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.92–2.02 (s, 3H), 2.48–2.60 (s, 3H), 2.75–2.86 (s, 3H), 7.55–7.62 (t, J = 7.6 Hz, 2H), 7.67–7.76 (t, J = 6.9 Hz, 1H), 8.19–8.29 (d, J = 6.3 Hz, 2H), 14.86–15.21 (s, 1H), 15.45–15.77 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 205.65, 202.23, 169.98, 168.59, 163.70, 155.47, 134.75, 130.57, 129.24, 128.28, 111.98, 108.46, 107.45, 33.66, 31.97, 8.73; HRMS(ESI) calcd for $C_{18}H_{15}O_6[M\text{-}H]^-$: 327.0869, found 327.0868. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/25). Compound **15**: $^1$H NMR (400 MHz, $CDCl_3$) δ 2.11–2.18 (s, 3H), 2.47–2.57 (s, 6H), 7.57–7.65 (t, J = 7.8 Hz, 2H), 7.72–7.80 (t, J = 7.5 Hz, 1H), 8.21–8.30 (d, J = 8.3 Hz, 2H), 13.59–13.80 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 202.36, 166.37, 164.76, 154.09, 135.20, 130.66, 129.56, 128.39, 111.96, 109.38, 32.65, 7.55; HRMS(ESI) calcd for $C_{18}H_{15}O_6[M\text{-}H]^-$: 327.0869, found 327.0869. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/15). Compound **16**: $^1$H NMR (400 MHz, $CDCl_3$) δ 2.07–2.17 (s, 3H), 2.43–2.54 (d, J = 1.5 Hz, 6H), 7.47–7.60 (dt, J = 7.3, 13.8 Hz, 6H), 7.62–7.73 (m, 3H), 8.09–8.26 (m, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 197.58, 164.35, 163.82, 147.87, 142.82, 134.50, 130.58, 129.03, 128.99, 128.16, 127.96, 124.75, 31.24, 10.69; HRMS(ESI) calcd for $C_{32}H_{28}NO_8[M+NH_4]^+$: 554.1815, found 554.1793.

3.2.7. 1-(3-acetyl-2,4,6-trihydroxy-5-methylphenyl)-3-phenylpropane-1,3-dione (**17**)

Compound **14** (100 mg, 0.3 mmol) was dissolved in 2 mL of dry DMSO, followed by NaOH (24.4 mg, 0.61 mmol), and reacted for 12 h at room temperature (21 °C). After the completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once, using NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and concentrated under reduced pressure via column chromatography (eluent, EtOAc/PE = 1/30) to give compound **17** (36.9 mg, 37.5% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/25); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.04–2.09 (s, 3H), 2.68–2.75 (s, 3H), 3.05–3.13 (s, 2H), 7.42–7.51 (d, J = 6.9 Hz, 3H), 7.64–7.71 (d, J = 7.3 Hz, 2H), 13.95–14.04 (s, 1H), 14.88–14.97 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.09, 194.62, 171.00, 166.08, 159.99, 141.27, 129.39, 128.74, 124.72, 105.21, 104.73, 101.36, 100.44, 47.77, 32.71, 7.11; HRMS(ESI) calcd for $C_{18}H_{17}O_6[M+H]^+$: 329.1020, found 329.1016.

3.2.8. 1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl)ethan-1-one (**18**)

Compound **3** (364 mg, 2 mmol) was dissolved in 6 mL of ethyl acetate, 0.6 mL of methanol was added, and then $TMSCHN_2$ (2.95 mL, 20 mmol, dissolved in 2.95 mL of ether) was added under an ice bath. Then, the reaction device was moved to a room-temperature environment, and the reaction was allowed to continue for 24 h. After the reaction was completed, the reaction was quenched by the addition of acetic acid, dropwise. After adding ethyl acetate and distilled water in both phases and extracting three times, the organic phase was collected and washed once, using NaCl (aq); dried using anhydrous $Na_2SO_4$; and purified via column chromatography (eluent, EtOAc/PE = 1/10 to 1/4) after vacuum concentration to yield compound **18** (242.3 mg, 57.7% yield, white solid) and compound **5** (99.6 mg, 25.4% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/8); $^1$H NMR (400 MHz, $CD_3OD$) δ 1.91–1.97 (s, 3H), 2.55–2.61 (s, 3H), 3.86–3.97 (d, J = 8.5 Hz, 6H), 6.13–6.19 (s, 1H); $^{13}$C NMR (101 MHz, $CD_3OD$) δ 204.79, 165.34, 164.44, 163.37, 106.58, 106.03, 87.32, 56.13, 56.05, 33.29, 7.26; HRMS(ESI) calcd for $C_{11}H_{15}O_4[M+H]^+$: 211.0965, found 211.0956.

3.2.9. 2-acetyl-3,5-dimethoxy-6-methylphenyl benzoate (**19**)

Compound **18** (63.1 mg, 0.3 mmol) was dissolved in 1 mL of dry dichloromethane, and then BzCl (0.07 mL, 0.6 mmol) and $Et_3N$ (0.09 mL, 0.6 mmol) were added slowly, dropwise, under an ice bath. After that, the reaction was moved to room temperature (16 °C) and

ended after 4 h. After adding dichloromethane and distilled water to both phases and extracting three times, the organic phase was collected and washed once, using NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to yield compound **19** (69.2 mg, 73.4% yield, white solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.93–2.04 (s, 3H), 2.43–2.53 (s, 3H), 3.83–3.95 (s, 6H), 6.37–6.42 (s, 1H), 7.45–7.53 (t, J = 7.1 Hz, 2H), 7.58–7.65 (t, J = 8.1 Hz, 1H), 8.13–8.20 (d, J = 8.3 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.91, 164.81, 160.35, 157.05, 147.57, 133.69, 130.41, 129.29, 128.68, 116.97, 112.68, 92.88, 56.11, 55.90, 32.12, 8.79; HRMS(ESI) calcd for $C_{18}H_{19}O_5[M+H]^+$: 315.1227, found 315.1217.

3.2.10. (Z)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl)-3-phenylprop-2-en-1-one and 1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl)-3-phenylpropane-1,3-dione (**20**)

Compound **19** (39.8 mg, 0.13 mmol) was dissolved in 1 mL of dry DMF, then *t*-BuOK (29.2 m, 0.26 mmol) was added, and the reaction was carried out at room temperature (16 °C) for 12 h. After the completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$, concentrated under reduced pressure, and purified via column chromatography (eluent, EtOAc/PE = 1/10) to yield compound **20** (37 mg, 93.0% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol: diketonic) of 2:3. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.99–2.08 (d, J = 10.1 Hz, 3H), 3.46–3.99 (m, 6H), 4.55 [s, 1.2H, C(O)$CH_2$C(O) for 1,3-diketo form], 5.85 (s, 0.6H, ArH for 1,3-diketo form), 6.01 (s, 0.4H, ArH for enol form), 7.34 (s, 0.4H, olefin for enol form), 7.41–7.66 (m, 3H), 7.83–8.05 (dd, J = 8.1, 32.0 Hz, 2H), 13.34 (s, 0.4H, ArOH for enol form), 13.68 (s, 0.6H, ArOH for 1,3-diketo form), 15.55 (s, 0.4H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 198.87, 194.88, 194.27, 175.64, 164.16, 164.13, 163.24, 163.13, 160.77, 160.45, 136.86, 134.63, 133.42, 131.78, 128.88, 128.75, 128.25, 126.76, 106.45, 106.26, 105.54, 104.68, 98.54, 86.73, 85.86, 55.99, 55.62, 55.48, 55.35, 55.05, 7.47, 7.27; HRMS(ESI) calcd for $C_{18}H_{19}O_5[M+H]^+$: 315.1227, found 315.1217.

3.2.11. 2-acetyl-3,5-dimethoxy-6-methylphenyl 4-chlorobenzoate (**21**)

Compound **18** (400 mg, 1.9 mmol) was dissolved in 3 mL of dry dichloromethane and 4-chlorobenzoyl chloride (0.27 mL, 2.1 mmol), and then $Et_3N$ (0.3 mL, 2.1 mmol) was added slowly, dropwise, under an ice bath. The reaction was terminated after 4 h at room temperature (27 °C). After adding dichloromethane and distilled water to both phases and extracting three times, the organic phase was collected and washed once, using NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to give compound 21 (619.54 mg, 93.7% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.94–2.00 (s, 3H), 2.43–2.50 (s, 3H), 3.85–3.94 (s, 6H), 6.36–6.43 (s, 1H), 7.42–7.50 (d, J = 8.6 Hz, 2H), 8.03–8.14 (d, J = 8.6 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.70, 164.02, 160.49, 157.31, 147.54, 140.21, 131.79, 129.06, 127.82, 116.64, 112.68, 92.95, 56.11, 55.91, 32.15, 8.76; HRMS(ESI) calcd for $C_{18}H_{18}ClO_5[M+H]^+$: 349.0837, found 349.0823.

3.2.12. (Z)-3-(4-chlorophenyl)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) prop-2-en-1-one and 1-(4-chlorophenyl)-3-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) propane-1,3-dione (**22**)

Compound **21** (367.5 mg, 1.06 mmol) was dissolved in 3 mL of DMF, and then *t*-BuOK (235.6 mg, 2.1 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After the completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound **22** (295.1 mg, 80.3% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol-form:diketonic) of 1:1. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.01–2.03 (d, J = 9.5 Hz, 3H), 3.51–3.98 (m, 6H), 4.51 [s, 1H, C(O)$CH_2$C(O) for 1,3-diketo

form], 5.86 (s, 0.5H, ArH for 1,3-diketo form), 6.01 (s, 0.5H, ArH for enol form), 7.30 (s, 0.5H, olefin for enol form), 7.40–7.50 (dd, J = 7.9, 21.0 Hz, 2H), 7.77–7.95 (dd, J = 8.5, 38.4 Hz, 2H), 13.27 (s, 0.5H, ArOH for enol form), 13.60 (s, 0.5H, ArOH for 1,3-diketo form), 15.50 (s, 0.5H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 198.41, 194.31, 193.72, 174.17, 164.26, 164.14, 163.30, 160.74, 160.49, 139.89, 137.86, 135.21, 133.13, 131.05, 129.69, 129.24, 129.04, 128.05, 106.55, 106.40, 105.49, 104.67, 98.59, 86.75, 85.90, 65.71, 56.02, 55.66, 55.42, 54.97, 7.47, 7.28; HRMS(ESI) calcd for $C_{18}H_{18}ClO_5[M+H]^+$: 349.0837, found 349.0813.

3.2.13. 2-acetyl-3,5-dimethoxy-6-methylphenyl 2-chlorobenzoate (**23**)

Compound **18** (210 mg, 1 mmol) was dissolved in 3 mL of dry dichloromethane, and 2-chlorobenzoyl chloride (0.19 mL, 1.5 mmol), $Et_3N$ (0.21 mL, 1.5 mmol) was added slowly, dropwise, under an ice bath. The reaction was terminated after 4 h at room temperature (29 °C). After adding dichloromethane, and distilled water to both phases and extracting three times, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to give compound 23 (278.9 mg, 80.1% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.01–2.09 (s, 3H), 2.46–2.56 (s, 3H), 3.84–3.97 (s, 6H), 6.36–6.44 (s, 1H), 7.34–7.42 (t, J = 7.2 Hz, 1H), 7.42–7.52 (d, J = 7.8 Hz, 2H), 8.02–8.11 (d, J = 7.8 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.97, 163.61, 160.55, 157.34, 147.38, 134.14, 133.06, 132.11, 131.14, 129.47, 126.91, 116.58, 112.77, 93.00, 56.11, 55.93, 32.22, 8.89; HRMS(ESI) calcd for $C_{18}H_{18}ClO_5[M+H]^+$: 349.0837, found 349.0801.

3.2.14. (Z)-3-(2-chlorophenyl)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) prop-2-en-1-one and 1-(2-chlorophenyl)-3-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) propane-1,3-dione (**24**)

Compound **23** (115.0 mg, 0.33 mmol) was dissolved in 2 mL of dry DMF, and *t*-BuOK (74.8 mg, 0.66 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After the completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound **24** (94 mg, 81.7% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol: diketonic) of 3:2. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.00–2.03 (d, J = 8.8 Hz, 3H), 3.62–4.62 (m, 6H), 4.62 [s, 0.8H, C(O)$CH_2$C(O) for 1,3-diketo form], 5.88 (s, 0.4H, ArH for 1,3-diketo form), 5.98 (s, 0.6H, ArH for enol form), 7.28 (s, 0.6H, olefin for enol form), 7.35–7.72 (m, 4H), 13.24 (s, 0.6H, ArOH for enol form), 13.61 (s, 0.4H, ArOH for 1,3-diketo form), 15.35 (s, 0.6H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 197.77, 194.47, 173.95, 163.39, 160.70, 132.47, 131.20, 131.05, 130.81, 130.46, 130.34, 126.94, 106.24, 103.94, 86.53, 85.68, 58.70, 55.79, 55.53, 55.34, 7.33, 7.15; HRMS(ESI) calcd for $C_{18}H_{18}ClO_5[M+H]^+$: 349.0837, found 349.0805.

3.2.15. 2-acetyl-3,5-dimethoxy-6-methylphenyl 3-chlorobenzoate (**25**)

Compound **18** (210 mg, 1 mmol) was dissolved in 3 mL of dry dichloromethane and 3-chlorobenzoyl chloride (0.19 mL, 1.5 mmol), and then $Et_3N$ (0.21 mL, 1.5 mmol) was added slowly, dropwise, under an ice bath. The reaction was terminated after 4 h at room temperature (29 °C). After adding dichloromethane and distilled water to both phases and extracting three times, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to give compound **25** (307.6 mg, 88.4% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.96–2.03 (s, 3H), 2.44–2.52 (s, 3H), 3.86–3.97 (s, 6H), 6.35–6.49 (s, 1H), 7.40–7.46 (t, J = 7.9 Hz, 1H), 7.55–7.61 (d, J = 8.0 Hz, 1H), 8.02–8.08 (d, J = 7.9 Hz, 1H), 8.11–8.17 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.69, 163.72, 160.54, 157.39, 147.52, 134.85, 133.70, 131.10,

130.39, 130.03, 128.53, 116.52, 112.65, 92.99, 56.11, 55.91, 32.18, 8.75; HRMS(ESI) calcd for $C_{18}H_{18}ClO_5[M+H]^+$: 349.0837, found 349.0806.

3.2.16. (Z)-3-(3-chlorophenyl)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) prop-2-en-1-one and 1-(3-chlorophenyl)-3-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) propane-1,3-dione (**26**)

Compound **25** (115.0 mg, 0.33 mmol) was dissolved in 2 mL of dry DMF, and *t*-BuOK (74.8 mg, 0.66 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After the completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound **26** (95.4 mg, 83.0% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol: diketonic) of 1:1. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.97–2.11 (d, J = 8.8 Hz, 3H), 3.50–4.00 (m, 6H), 4.51 [s, 1.00H, C(O)$CH_2$C(O) for 1,3-diketo form], 6.01 (s, 0.50H, ArH for 1,3-diketo form), 5.86 (s, 0.50H, ArH for enol form), 7.30 (s, 0.44H, olefin for enol form), 7.35–7.97 (m, 4H), δ13.25 (s, 0.50H, ArOH for enol form), δ 13.59 (s, 0.50H, ArOH for 1,3-diketo form), δ 15.42 (s, 0.50H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 198.22, 194.45, 193.65, 173.56, 164.29, 164.13, 163.41, 163.35, 160.72, 160.56, 138.40, 136.53, 135.27, 134.90, 133.38, 131.55, 130.25, 129.99, 128.30, 126.86, 126.38, 124.78, 106.52, 106.39, 105.45, 104.65, 99.01, 86.74, 85.91, 56.03, 55.65, 55.45, 55.00, 7.45, 7.27; HRMS(ESI) calcd for $C_{18}H_{18}ClO_5[M+H]^+$: 349.0837, found 349.0806.

3.2.17. 2-acetyl-3,5-dimethoxy-6-methylphenyl 3,5-dichlorobenzoate (**27**)

Compound **18** (210 mg, 1 mmol) was dissolved in 3 mL of dry dichloromethane and 2,4-dichlorobenzoyl chloride (0.19 mL, 1.5 mmol); $Et_3N$ (0.21 mL, 1.5 mmol) was added slowly, dropwise, under an ice bath; and the reaction was terminated after 4 h at room temperature (29 °C). After adding dichloromethane and distilled water in both phases and extracting three times, the organic phase was collected and washed once, using NaCl (aq); the desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to give compound **27** (354.1 mg, 92.7% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.91–2.03 (s, 3H), 2.41–2.55 (s, 3H), 3.82–4.01 (s, 6H), 6.35–6.47 (s, 1H), 7.53–7.65 (s, 1H), 7.96–8.12 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.39, 162.69, 160.68, 157.69, 147.50, 135.61, 133.46, 132.24, 128.73, 116.05, 112.59, 93.06, 56.11, 55.93, 32.25, 8.71; HRMS(ESI) calcd for $C_{18}H_{17}Cl_2O_5[M+H]^+$: 383.0448, found 383.0386.

3.2.18. (Z)-3-(3,5-dichlorophenyl)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) prop-2-en-1-one and 1-(3,5-dichlorophenyl)-3-(2-hydroxy-4,6-dimethoxy -3-methylphenyl) propane-1,3-dione (**28**)

Compound **27** (126.0 mg, 0.33 mmol) was dissolved in 2 mL of dry DMF, and *t*-BuOK (74.8 mg, 0.66 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound 28 (110.0 mg, 87.3% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol: diketonic) of 4:1. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.01–2.05 (d, J = 9.4 Hz, 3H), 3.78–4.06 (m, 6H), 4.31 [s, 0.34H, C(O)$CH_2$C(O) for 1,3-diketo form], 5.96 (s, 0.17H, ArH for 1,3-diketo form), 6.02 (s, 0.76H, ArH for enol form), 7.28 (s, 0.76H, olefin for enol form), 7.47–7.72 (m, 3H), δ 13.16 (s, 0.76H, ArOH for enol form), δ 13.96 (s, 0.17H, ArOH for 1,3-diketo form), δ 15.33 (s, 0.76H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 197.88, 195.98, 194.59, 174.07, 164.25, 164.17, 163.50, 163.39, 160.82, 160.70, 137.81, 134.57, 132.59, 132.33, 132.01, 131.31, 131.16, 130.92, 130.58, 130.47, 127.05, 106.36, 105.48,

104.65, 104.06, 86.64, 85.78, 58.84, 55.91, 55.65, 55.63, 55.46, 7.45, 7.27; HRMS(ESI) calcd for $C_{18}H_{15}Cl_2O_5[M\text{-}H]^-$: 381.0297, found 381.0244.

3.2.19. 2-acetyl-3,5-dimethoxy-6-methylphenyl 4-fluorobenzoate (**29**)

Compound **18** (210 mg, 1 mmol) was dissolved in 3 mL of dry dichloromethane and 4-fluoro benzoyl chloride (0.19 mL, 1.5 mmol), and then $Et_3N$ (0.21 mL, 1.5 mmol) was added slowly, dropwise, under an ice bath. The reaction was terminated after 4 h at room temperature (29 °C). After adding dichloromethane and distilled water to both phases and extracting three times, the organic phase was collected and washed once, using NaCl (aq); the desiccant was used as anhydrous $Na_2SO_4$, and it was purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to give compound **29** (318.4 mg, 95.9% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.92–2.06 (s, 3H), 2.39–2.56 (s, 3H), 3.82–3.98 (s, 6H), 6.32–6.46 (s, 1H), 7.07–7.23 (t, J = 8.6 Hz, 2H), 8.09–8.28 (t, J = 7.1 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.80, 167.57, 165.03, 163.86, 160.45, 157.24, 147.54, 133.09, 132.99, 125.62, 125.59, 116.77, 116.00, 115.79, 112.70, 92.93, 56.11, 55.91, 32.14, 8.77; HRMS(ESI) calcd for $C_{18}H_{18}FO_5[M+H]^+$: 333.1133, found 333.1076.

3.2.20. (Z)-3-(4-fluorophenyl)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) prop-2-en-1-one and 1-(4-fluorophenyl)-3-(2-hydroxy-4,6-dimethoxy-3 -methylphenyl) propane-1,3-dione (**30**)

Compound **29** (109.6 mg, 0.33 mmol) was dissolved in 2 mL of dry DMF, and *t*-BuOK (74.8 mg, 0.66 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound **30** (83.5 mg, 76.2% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol: diketonic) of 2:3. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.11–2.25 (d, J = 9.9 Hz, 3H), 3.64–4.15 (m, 6H), 4.66 [s, 1.20H, C(O)$CH_2$C(O) for 1,3-diketo form], 6.01 (s, 0.60H, ArH for 1,3-diketo form), 6.16 (s, 0.40H, ArH for enol form), 7.28 (s, 0.40H, olefin for enol form), 7.29–7.47 (m, 2H), 7.95–8.33 (m, 2H), 13.42 (s, 0.40H, ArOH for enol form), 13.77 (s, 0.60H, ArOH for 1,3-diketo form), 15.75 (s, 0.40H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 198.55, 194.15, 193.36, 174.59, 167.21, 164.68, 164.23, 164.14, 163.24, 163.20, 160.77, 160.44, 133.33, 130.96, 130.86, 129.05, 128.96, 116.14, 115.99, 115.92, 115.77, 106.53, 106.37, 105.52, 104.62, 98.23, 86.75, 85.90, 56.02, 55.65, 55.41, 54.96, 32.06, 29.84, 22.83, 14.26, 7.47, 7.28; HRMS(ESI) calcd for $C_{18}H_{18}FO_5[M+H]^+$: 333.1133, found 333.1082.

3.2.21. 2-acetyl-3,5-dimethoxy-6-methylphenyl 4-bromobenzoate (**31**)

Compound **18** (210 mg, 1 mmol) was dissolved in 3 mL of dry dichloromethane and 4-bromobenzoyl chloride (0.19 mL, 1.5 mmol), and then $Et_3N$ (0.21 mL, 1.5 mmol) was added slowly, dropwise, under an ice bath. The reaction was terminated after 4 h at room temperature (29 °C). After adding dichloromethane, and distilled water to both phases and extracting three times, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to give compound **31** (381.8 mg, 97.4% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.89–2.07 (s, 3H), 2.37–2.56 (s, 3H), 3.80–3.98 (s, 6H), 6.32–6.46 (s, 1H), 7.52–7.73 (d, J = 8.8 Hz, 2H), 7.94–8.10 (d, J = 8.8 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.69, 164.18, 160.49, 157.32, 147.53, 132.07, 131.90, 128.93, 128.28, 116.62, 112.68, 92.96, 56.12, 55.92, 32.16, 8.76; HRMS(ESI) calcd for $C_{18}H_{18}BrO_5[M+H]^+$: 393.0332, found 393.0267.

3.2.22. (Z)-3-(4-bromophenyl)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) prop-2-en-1-one and 1-(4-bromophenyl)-3-(2-hydroxy-4,6-dimethoxy -3-methylphenyl) propane-1,3-dione (**32**)

Compound **31** (129.4 mg, 0.33 mmol) was dissolved in 2 mL of dry DMF, and *t*-BuOK (74.8 mg, 0.66 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After the completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound **32** (107.2 mg, 82.8% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol: diketonic) of 2:3. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.97–2.07 (d, J = 9.4 Hz, 3H), 3.47–4.05 (m, 6H), 4.51 [s, 1.20H, C(O)$CH_2$C(O) for 1,3-diketo form], 5.86 (s, 0.60H, ArH for 1,3-diketo form), 6.01 (s, 0.40H, ArH for enol form),7.30 (s, 0.40H, olefin for enol form), 7.52–7.89 (m, 4H), 13.27 (s, 0.40H, ArOH for enol form), 13.60 (s, 0.60H, ArOH for 1,3-diketo form), 15.48 (s, 0.40H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 198.38, 194.33, 193.92, 174.19, 164.26, 164.13, 163.31, 160.73, 160.49, 135.60, 133.59, 132.24, 132.01, 129.79, 128.62, 128.21, 126.35, 106.54, 106.40, 105.48, 104.66, 98.61, 86.75, 85.90, 56.02, 55.66, 55.43, 54.94, 29.84, 22.83, 14.26, 7.47, 7.28; HRMS(ESI) calcd for $C_{18}H_{16}BrO_5$[M-H]$^-$: 391.0181, found 391.0122.

3.2.23. 2-acetyl-3,5-dimethoxy-6-methylphenyl 4-methylbenzoate (**33**)

Compound 18 (210 mg, 1 mmol) was dissolved in 3 mL of dry dichloromethane, and p-Toluoyl chloride (0.19 mL, 1.5 mmol) and $Et_3N$ (0.21 mL, 1.5 mmol) were added slowly, dropwise, under an ice bath. The reaction was terminated after 4 h at room temperature (29 °C). After adding dichloromethane and distilled water to both phases and extracting three times, the organic phase was collected and washed once, using NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration to give compound **33** (294.2.4 mg, 89.7% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.93–2.02 (s, 3H), 2.43 (s, 3H), 2.48 (s, 3H), 3.83–3.96 (s, 6H), 6.34–6.44 (s, 1H), 7.26–7.34 (d, J = 7.9 Hz, 2H), 7.98–8.11 (d, J = 8.1 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.95, 164.82, 160.29, 156.93, 147.59, 144.52, 130.46, 129.40, 126.54, 117.17, 112.72, 92.87, 56.11, 55.88, 32.08, 21.86, 8.79; HRMS(ESI) calcd for $C_{19}H_{21}O_5$[M+H]$^+$: 329.1384, found 329.1332.

3.2.24. (Z)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl)-3-(p-tolyl)prop-2-en-1-one and 1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl)-3-(p-tolyl) propane-1,3-dione (**34**)

Compound **33** (108.0 mg, 0.33 mmol) was dissolved in 2 mL of dry DMF, and *t*-BuOK (74.8 mg, 0.66 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was collected and washed once with NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound **34** (82.1 mg, 76.0% yield, yellow solid) as a reciprocal isomer with a molar ratio (enol: diketonic) of 3:7. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.97–2.11 (d, J = 10.3 Hz, 3H), 2.37–2.55 (d, J = 6.4 Hz, 3H), 3.49–3.98 (m, 6H), 4.53 [s, 1.40H, C(O)$CH_2$C(O) for 1,3-diketo form], 5.86 (s, 0.70H, ArH for 1,3-diketo form), 6.02 (s, 0.30H, ArH for enol form),7.27 (s, 0.30H, olefin for enol form), 7.28–7.36 (m, 2H), 7.75–7.94 (dd, J = 8.3, 31.1 Hz, 2H), 13.36 (s, 0.30H, ArOH for enol form), 13.71 (s, 0.70H, ArOH for 1,3-diketo form), 15.63 (s, 0.30H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.10, 194.54, 194.01, 176.06, 164.11, 163.16, 162.99, 160.81, 160.37, 144.24, 142.47, 134.41, 131.79, 129.55, 129.48, 128.38, 126.77, 106.43, 106.21, 105.59, 104.69, 98.01, 86.74, 85.87, 55.99, 55.61, 55.36, 55.01, 29.83, 21.81, 21.72, 7.48, 7.27; HRMS(ESI) calcd for $C_{19}H_{21}O_5$[M+H]$^+$: 329.1384, found 329.1334.

3.2.25. 2-acetyl-3,5-dimethoxy-6-methylphenyl 4-ethylbenzoate (**35**)

Compound **18** (100 mg, 0.48 mmol) was dissolved in dry dichloromethane, and 4-ethylbenzoyl chloride (76 μL, 0.52 mmol) was added slowly, dropwise, under an ice bath, followed by $Et_3N$ (72 μL, 0.52 mmol), and the reaction was terminated by thorough stirring for 4 h. After adding dichloromethane, adding distilled water in both phases, and extracting three times, the organic phase was collected and washed once, using NaCl (aq); the desiccant was used as anhydrous $Na_2SO_4$ and purified via column chromatography (eluent, EtOAc/PE = 1/8) after vacuum concentration, yielding compound 35 (105.6 mg, 64.3% yield, yellow solid). TLC: $R_f$ = 0.3 (EtOAc/PE = 1/6); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.92–2.02 (s, 3H), 2.42–2.50 (s, 3H), 2.67–2.78 (q, J = 7.7 Hz, 2H), 3.81–3.96 (s, 6H), 6.34–6.42 (s, 1H), 7.27–7.35 (d, J = 8.1 Hz, 2H), 8.01–8.14 (d, J = 8.3 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.98, 164.83, 160.30, 156.94, 150.70, 147.62, 130.59, 128.25, 126.74, 117.18, 112.76, 92.88, 56.13, 55.90, 32.10, 29.20, 15.40, 8.80; HRMS(ESI) calcd for $C_{20}H_{23}O_5$[M+H]$^+$: 343.1540, found 343.1522.

3.2.26. (Z)-3-(4-ethylphenyl)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-3-methylphenyl) prop-2-en-1-one and 1-(4-ethylphenyl)-3-(2-hydroxy-4,6-dimethoxy-3 -methylphenyl) propane-1,3-dione (**36**)

Compound **35** (24 mg, 0.07 mmol) was dissolved in 2 mL of dry DMF, and *t*-BuOK (15.71 mg, 0.14 mmol) was added. The reaction was carried out at room temperature (27 °C) for 12 h. After the completion of the reaction, ethyl acetate and distilled water were added to both phases, and after three extractions, the organic phase was washed once, using NaCl (aq). The desiccant was used as anhydrous $Na_2SO_4$, and it was purified via column chromatography (eluent, EtOAc/PE = 1/10) after vacuum concentration to yield compound **36** (14.6 mg, 60.8% yield, yellow solid) as a reciprocal isomer with a molar ratio (enolic: diketonic) of 1:4. TLC: $R_f$ = 0.3 (EtOAc/PE = 1/9); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.27–1.36 (d, J = 9.9 Hz, 3H), 1.99–2.07 (d, J = 9.9 Hz, 3H), 2.67–2.80 (q, J = 7.6 Hz, 2H), 3.50–3.97 (m, 6H), 4.53 [s, 1.56H, C(O)$CH_2$C(O) for 1,3-diketo form], 5.86 (s, 0.77H, ArH for 1,3-diketo form), 6.02 (s, 0.22H, ArH for enol form), 7.28 (s, 0.22H, olefin for enol form), 7.31–7.33 (m, 2H), 7.80–7.90 (m, 2H), 13.36 (s, 0.22H, ArOH for enol form), 13.71 (s, 0.77H, ArOH for 1,3-diketo form), 15.62 (s, 0.22H, OH for enol form); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.13, 194.59, 194.02, 176.09, 164.11, 163.16, 162.96, 160.82, 160.36, 150.39, 148.72, 134.60, 132.03, 128.49, 128.36, 128.31, 126.90, 106.43, 106.22, 105.60, 104.69, 98.07, 86.71, 85.85, 56.00, 55.63, 55.39, 55.05, 29.09, 29.04, 15.45, 15.29, 7.49, 7.29; HRMS(ESI) calcd for $C_{20}H_{23}O_5$[M+H]$^+$: 343.1540, found 343.1514.

*3.3. Biological Activity*

The synthesized Des-D and 10 analogs were evaluated for anti-HIV-1 activity, using the method of HTRF. Recombinant HIV-1 integrase (HIV-1 integrase, referred to as HIV-IN) expressed in bacteria was selected as the model for evaluating the anti-HIV-1 integrase activity of the derivatives synthesized herein.

3.3.1. Experimental Materials

The reagents used for the experiments were Tris-HCl buffer, NaCl, 3-[(3-cholamidopropyl) dimethylammonium]-1-propane sulfonic acid (CHAPS), imidazole, EDTA 2Na, DTT, and glycerol in black solid-bottom 96-well plates (Greiner), along with europium chelate–streptavidin (purchased from Aladdin Reagent Company, shanghai). Protein purification preloading columns: HisTrap FF (5 mL) and Hitrap heparin (5 mL) (purchased from Aladdin Reagent Company, Shanghai, China). Experimental instruments were Perkin Elmer EnSpire multimode plate reader and Nanodrop 2000 (from PerkinElmer, Inc. Waltham, MA, USA).

3.3.2. Experimental Methods

(1) Protein expression and purification

The recombinant HIV-1 integrase protein expressed in bacteria must be purified [18,19]. Briefly, the pellet was resuspended in A {25 mM Tris-HCI (pH 7.4), 1 M NaCl, 7.5 mM CHAPS}, and 25 mM imidazole protease inhibitor tablets. After sonication, the lysate was centrifuged at 45,000× *g* for 30 min. The supernatant was loaded into 5 mL of HisTrap FF and washed. The integrase was eluted with Buffer A containing 200 mM imidazole. Protein samples were concentrated and injected into a 5 mL Hitrap heparin column, and bound proteins were eluted in a linear gradient with 0.25 M~1 M NaCl in 25 mM Tris-HCl (pH 7.4)−7.5 mM CHAPS. The IN-containing fraction was pooled and dialyzed in buffer {25 mM HEPES (pH 7.6), 1 M NaCl 7.5 mM CHAPS, 0.1 mM EDTA, 1 mM DTT, and 10% glycerol}. The protein concentration was determined spectrophotometrically, frozen rapidly in liquid nitrogen, and stored at −80 °C.

(2) HTRF-based integrase activity assay

Experiments were performed using an HTRF-based method [20,21]. Wild-type integrase (final concentration 250 nM) was preincubated with serial dilutions of the compounds for 15 min at room temperature. Raltegravir was used as a positive control. Then, 12.5 nM Cy-5-labeled donor DNA and 5 nM biotinylated target DNA were added and incubated for 120 min at 37 °C. Europium–streptavidin was then added to the plates. After incubating the plates for 16 h at room temperature, the HTRF signal was recorded using a Perkin Elmer EnSpire multimode plate reader. Raw counts at 665 and 620 nm were collected, and the signal was expressed as a ratio of (cps at 665 nm/cps at 620 nm) × 1000.

(3) Calculation

The inhibition rate of integrase was calculated according to the following equation:

$$\text{Inhibition rate}(\%) = (1 - \frac{\text{OD value of experimental group} - \text{Blank group OD}}{\text{Control group OD} - \text{Blank group OD}}) \times 100\%$$

*3.4. Molecular Docking*

The binding of compounds **Des-D** and **17** to HIV-IN [22] was examined dynamically via molecular docking simulations.

The protein 3D structure of HIV-IN was downloaded from the Protein Data Bank database (Protein Data Bank code: 3OYA). **Des-D** and compound **17** were first preprocessed for hydrogen bonding, using Mastero2020V22 software. Then, the HIV-IN protein was pre-processed for ligand compound extraction and dehydrogenation, and the format was converted to a pdbqt file. The structural formula files of **Des-D** and **17** after pretreatment were opened in Autodock4.2 software and converted into pdbqt files, while the protein–ligand compound files were opened to determine the active region of the HIV-IN protein with the active region set to x = 90.86, y = 50.504, and z = 114.826. Finally, AutoDock and Vina 4.2 software were used to perform molecular docking of **Des-D** and **17** with HIV-IN proteins, and the results were analyzed using PyMol molecular graphics system2.4 software.

## 4. Conclusions

In this paper, the total synthesis of the natural product **Des-D** was optimized and completed with a yield of 11.9% compared with the work of Nakagawa-Goto and Lee (4.4%) [11]. Then, **Des-D** and 12 analogues were designed and synthesized, and the HIV-IN inhibitory activity indicated that the natural product, **Des-D**, exhibited the most potent anti-HIV-IN activity, with an $IC_{50}$ value of 13.6 μM, while compounds **17** and **11** had low HIV-IN inhibition activity, with $IC_{50}$ values of 101.3 μM and 161.0 μM, respectively. The result of the computer-simulated molecular docking showed that the phenolic hydroxyl groups of **Des-D** and **17** formed salt bridges with the $Mg^{2+}$-binding regions of A396 and A397, and the two aromatic benzene rings formed π-π stacks with D16 and D17, which

interacted with HIV-IN. Although our work did not yield compounds with a stronger performance than the natural product **Des-D**, it provided important guidance for the optimization of compounds against HIV-IN. Because phenolic hydroxyl and two benzene rings interact with HIV-IN, they are possible pharmacodynamic groups, and they should be preserved as much as possible in future structural modification.

Though the compounds either have or do not have activity, it was still shown that the derivatives of Des-D have potential in this study. In the future, we will continue to carry out a more in-depth synthesis and anti-HIV activity evaluation of Des-D and its analogues on this basis, hoping to pave the way for the development of new compounds with anti-HIV activity.

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