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Original article

Synthesis and anti-integrase evaluation of novel calix[4]arene derivatives containing the triazolyl 1,3-diketo moiety

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ABSTRACT

A series of novel calix[4]arene derivatives incorporating two triazolyl 1,3-diketo subunits in alternate positions at the lower rim were synthesized and screened for HIV integrase inhibition activity. The chemical structures of these compounds were confirmed by means of ^{1}H NMR, ^{13}C NMR, and ESI-MS. Preliminary bioassays indicated that calix[4]arene derivatives proved to be more active than *p-tert*-butylcalix[4]arene derivatives. In particular, compound **4g** presented the most potent integrase strand transfer inhibitory activity with an IC_{50} value of 6.1 μmol/L.

1. Introduction

HIV-1 integrase (IN), belongs to the superfamily of polynucleotidyl transferases, which insert a double-stranded DNA copy of the viral RNA genome into the chromosomes of an infected cell through a multistep process that involves 3′-processing (3′-P) and strand transfer (ST) or integration [1]. Considering that HIV-IN plays a key role in stable infection and that there is no known human counterpart of HIV-IN, it is understandable why this enzyme is an attractive therapeutic target [1]. Numerous small-molecule HIV-1 integrase inhibitors have been described, with the most predominant class of inhibitors being the diketo acids (DKA) [2]. The structures of the DKA moiety can be replaced by various bioisosteres [3–5]. The structure of the HIV-1 integrase core domain complexed with the inhibitor 5-CITEP (Fig. 1) has been described as a platform for the structure-based design of novel HIV-1 integrase inhibitors [3]. It is believed that their IN-binding mechanism is connected to the presence of the DKA pharmacophoric motif, which could be involved in functional sequestration of one or both divalent metal ions in the enzyme catalytic site to form a ligand-M^{2+}-IN complex. This would subsequently block the transition state of the IN-DNA complex by competing with the target DNA substrate, acting as an "interfacial inhibitor" [6]. The global research efforts to identify drugs that inhibit HIV integrase recently led to new strand-transfer inhibitors MK-0518 and GS9137 (Fig. 1), which have been approved by the FDA.

Calixarenes, which constitute a major class of supramolecular organic host compounds, have been paid special attention as new molecular platforms for the design and development of new drugs [7–9]. During the last 10 years, calixarene derivatives have been the subject of growing interest in the biology. Many pharmacological properties are described for calixarenes (antiviral, antibacterial, antifungal, and anticancer activities) [10–12]. In particular, calixarenes have been increasingly studied for their anti-HIV activity [13,14]. The 1,2,3-triazole ring is not only a hydrogen-bond donor but also as a linking unit in the structure scaffold. Its planar structure may facilitate the π stacking interaction with target enzymes similar to phenyl rings. 1,2,3-Triazole moiety can be synthesized by application of a synthetic strategy using organoazide and acetyl acetone [15]. Further, many known 1,2,3-triazoles have anti-HIV properties [16,17].

In recent years, we also engaged in the development of new anti-IN inhibitors [18–20]. To synthesize novel molecules with potential biological activities, we used the calix[4]arene skeleton as a platform to design a new class of integrase inhibitors in the present study. Therefore, we detail the synthesis of a series of new

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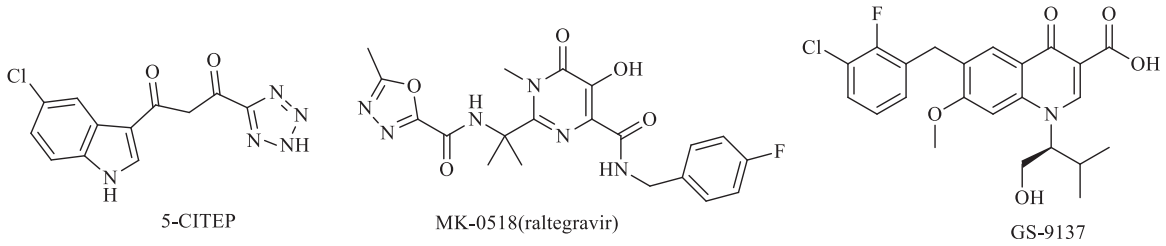


Fig. 1. Structures of IN inhibitors.

calix[4]arene derivatives **4a–h** (Scheme 1) incorporating two triazolyl 1,3-diketo subunits in alternate positions at the lower rim, and evaluation of their anti-IN activities against HIV-1 with baicalein as a reference compound.

2. Experimental

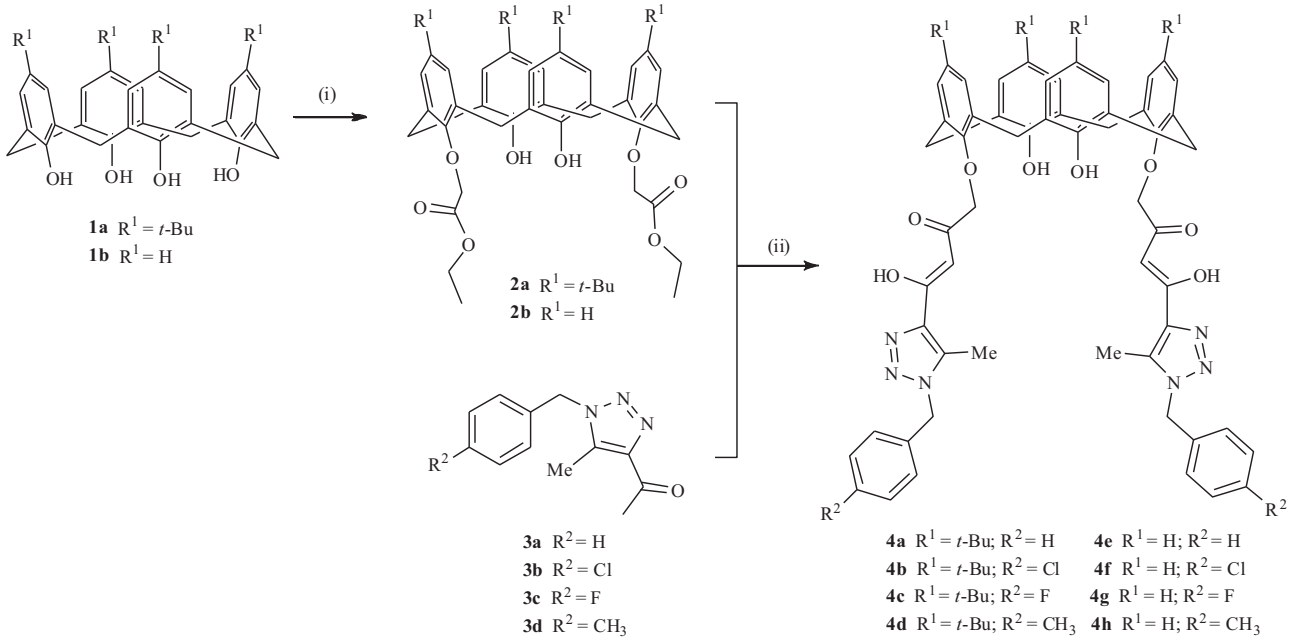
Unless otherwise noted, all materials were obtained from commercial suppliers and dried and purified by standard procedures. The melting point was measured on an SGW X-4 monocular microscope melting point apparatus with an unadjusted thermometer. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker Avance-400 MHz spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. The chemical shifts were reported in δ (ppm). Mass spectra (MS) data were obtained using an Esquire 6000 Mass Spectrometer. Column chromatography was performed with silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd., China).

The synthesis of our target calix[4]arene derivatives is outlined in Scheme 1. Compounds **1** [21], **2** [22], and **3** [23] were prepared according to the corresponding literature. Compound **2** underwent Claisen condensation with variable 4-acetyl-5-methyl-1,2,3-triazoles **3** to afford the novel calix[4]arene derivatives **4a–h** incorporating two triazolyl 1,3-diketo subunits in alternate positions at the lower rim in the alkaline medium (NaH) with a moderate yield (33%–52%).

General procedure for the synthesis of calix[4]arene derivatives **4a–h**: To a suspension of sodium hydride (60% dispersion in oil), 30 mmol in dry THF (10 mL) was slowly added to variable 1,2,3-triazoles **3** (22 mmol) in dry THF (10 mL) at 0 °C, and the mixture was stirred for 10 min. After that, calix[4]arenes **2** (10 mmol) in dry THF (15 mL) was added to the above solution at 0 °C, and then the reaction mixture was slowly heated to reflux for about 90 min with stirring until TLC confirmed that the reaction had finished. The cooled mixture was poured into a mixture of ice-water (20 mL) and concentrated HCl (5 mL), extracted with EtOAc, and purified by flash chromatography on silica gel eluted with petroleum ether/ethyl acetate (15:1–8:1).

3. Results and discussion

All of the final products were new compounds and their structures were fully confirmed by MP, ^{1}H NMR, ^{13}C NMR, and mass spectra (ESI-MS). The data of the NMR spectra of the title compounds revealed that the calix[4]arene moiety maintains the cone conformation. The bridging methylene groups of the compounds **4a–h** exhibit two sets of doublets (absorptions of the doublets near δ 3.4 and 4.5 ppm, J = 13.2 Hz for $ArCH_2Ar$ protons) in their ^{1}H NMR spectra and absorptions near 31 ppm in their ^{13}C NMR spectra, respectively. The chemical shift values are close to those reported for other calix[4]arene molecules in the same conformations [24,25]. Moreover, the 1,3-diketo moieties of the title compounds possess enol-keto tautomerism in the solvent [23,26], and the conformation of the 1,3-diketo moieties of the title compounds exist almost completely with an enol configuration in $CDCl_3$ [26], which was readily proven by their ^{1}H NMR absorptions



Scheme 1. Synthetic route for calix[4]arene derivatives **4a–h**. Reagents and conditions: (i) $BrCH_2COOEt$, K_2CO_3, DMF, 70–90 °C, 12–24 h (86% for **2a** and 78% for **2b**); (ii) NaH, THF, reflux, 1.5–2 h (33–52%).

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near 7 or 8 ppm for the methylene proton of the 1,3-diketo moiety and ^{13}C NMR absorptions for the methylene carbon of the 1,3-diketo moiety near 97 ppm, respectively. In the negative ion MS (ESI) spectrum, the loss of hydrogen ion substances $[M-H]^-$ were usually observed as the base peak ion for all target compounds. Selected characterization data of the targeted compounds are listed below.

4a: White solid, yield: 41%; mp: 155–158 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 18H, C(CH_3)$_3$), 1.33 (s, 18H, C(CH_3)$_3$), 2.44 (s, 6H, CH_3), 3.42 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.45 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.75 (s, 4H, ArOCH_2), 5.56 (s, 4H, ArCH_2), 6.85 (s, 2H, COCH), 6.90 (s, 4H, ArH), 7.12 (s, 4H, ArH), 7.18–7.21 (m, 4H, ArH), 7.30–7.36 (m, 6H, ArH), 7.78 (s, 2H, ArOH), 15.31 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.7, 181.5, 150.8, 149.8, 147.3, 141.3, 141.1, 136.4, 134.3, 132.5, 129.0, 128.3, 127.4, 127.1, 125.7, 125.0, 96.7, 75.7, 51.6, 33.9, 33.8, 31.8, 31.6, 30.9, 9.36; MS(ESI): m/z 1157.8 $[M-H]^-$.

4b: White solid, yield: 52%; mp: 182–185 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 18H, C(CH_3)$_3$), 1.31 (s, 18H, C(CH_3)$_3$), 2.45 (s, 6H, CH_3), 3.49 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.50 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.75 (s, 4H, ArOCH_2), 5.52 (s, 4H, ArCH_2), 6.68–6.73 (m, 4H, ArH), 6.83 (s, 2H, COCH), 7.01 (d, 4H, J = 7.6 Hz, ArH), 7.12–7.17 (m, 8H, ArH), 7.36 (d, 4H, J = 8.4 Hz, ArH), 7.80 (s, 2H, ArOH), 15.30 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 181.6, 150.7, 151.3, 151.0, 147.1, 136.4, 134.5, 133.2, 132.7, 129.3, 128.6, 127.6, 125.8, 119.0, 118.7, 97.0, 75.7, 51.0, 34.0, 33.8, 31.8, 31.5, 30.9, 9.30; MS (ESI): m/z 1225.6 $[M-H]^-$.

4c: White solid, yield: 46%; mp: 189–192 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 18H, C(CH_3)$_3$), 1.32 (s, 18H, C(CH_3)$_3$), 2.44 (s, 6H, CH_3), 3.43 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.42 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.75 (s, 4H, ArOCH_2), 5.52 (s, 4H, ArCH_2), 6.85 (s, 2H, COCH), 6.90 (s, 4H, ArH), 7.10–7.16 (m, 8H, ArH), 7.30–7.37 (m, 4H, ArH), 7.85 (s, 2H, ArOH), 15.33 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 181.3, 150.8, 149.8, 147.2, 141.4, 141.0, 136.3, 134.4, 132.7, 132.4, 129.2, 128.5, 127.3, 125.7, 125.0, 96.8, 75.6, 50.9, 34.0, 33.8, 31.8, 31.6, 30.9, 9.37; MS (ESI): m/z 1193.6 $[M-H]^-$.

4d: White solid, yield: 43%; mp: 145–147 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 18H, C(CH_3)$_3$), 1.31 (s, 18H, C(CH_3)$_3$), 2.33 (s, 6H, CH_3), 2.43 (s, 6H, CH_3), 3.42 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.44 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.76 (s, 4H, ArOCH_2), 5.52 (s, 4H, ArCH_2), 6.86 (s, 2H, COCH), 6.92 (s, 4H, ArH), 7.11–7.17 (m, 7H, ArH), 7.29–7.37 (m, 4H, ArH), 7.85 (s, 2H, ArOH), 15.33 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 181.1, 150.8, 149.7, 147.2, 141.2, 141.0, 136.2, 134.3, 132.7, 132.3, 129.1, 128.2, 127.3, 125.5, 125.0, 97.0, 75.2, 50.9, 34.1, 33.7, 31.5, 31.4, 30.9, 21.1, 9.35; MS (ESI): m/z 1185.3 $[M-H]^-$.

4e: White solid, yield: 38%; mp: 177–180 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 6H, CH_3), 3.45 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.50 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.76 (s, 4H, ArOCH_2), 5.52 (s, 4H, ArCH_2), 6.70 (t, 4H, J = 7.2 Hz, ArH), 7.00 (d, 4H, J = 7.6 Hz, ArH), 7.12 (d, 4H, J = 7.6 Hz, ArH), 7.19 (d, 4H, J = 7.6 Hz, ArH), 7.34–7.40 (m, 6H, ArH), 8.02 (s, 2H, COCH), 8.10 (s, 2H, ArOH), 15.20 (s, 2H, OH); ^{13}C NMR (100 Hz, $CDCl_3$): δ 187.4, 181.8, 153.8, 152.1, 141.5, 136.6, 134.7, 133.6, 129.6, 129.0, 128.5, 128.3, 127.7, 127.3, 126.0, 119.0, 96.9, 75.6, 51.6, 31.6, 9.31; MS (ESI): m/z 933.4 $[M-H]^-$.

4f: White solid, yield: 36%; mp: 147–149 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 6H, CH_3), 3.49 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.50 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.75 (s, 4H, ArOCH_2), 5.52 (s, 4H, ArCH_2), 6.68–6.73 (m, 4H, ArH), 7.01 (d, 4H, J = 7.6 Hz, ArH), 7.12–7.17 (m, 8H, ArH), 7.36 (d, 4H, J = 8.4 Hz, ArH), 8.11 (s, 2H, COCH), 8.15 (s, 2H, ArOH), 15.19 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 181.6, 153.7, 153.3, 151.9, 141.1, 136.4, 134.5, 133.2, 132.7, 129.3, 128.6, 127.6, 125.8, 119.0, 118.7, 97.0, 75.7, 51.0, 31.5, 9.30; MS (ESI): m/z 1001.3 $[M-H]^-$.

Table 1
Inhibition of HIV-1 integrase strand transfer catalytic activities.[a]

Compound	R^1	R^2	IC_{50} (μmol/L)[b]
4a	*t*-Bu	H	–[c]
4b	*t*-Bu	Cl	–[c]
4c	*t*-Bu	F	–[c]
4d	*t*-Bu	CH_3	–[c]
4e	H	H	7.4
4f	H	Cl	8.8
4g	H	F	6.1
4h	H	CH_3	10.9
Baicalein			1.06

[a] HIV-1 IN inhibitory activities were measured according to the procedure described [27].
[b] Inhibition of strand transfer with the initial concentration at 25 μmol/L.
[c] –: indicates that the HIV-IN inhibitory effect was less than 50% at the initial concentration.

4g: White solid, yield: 35%; mp: 170–172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 6H, CH_3), 3.45 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.54 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.77 (s, 4H, ArOCH_2), 5.50 (s, 4H, ArCH_2), 6.91 (s, 4H, ArH), 7.10–7.16 (m, 8H, ArH), 7.30–7.37 (m, 4H, ArH), 8.09 (s, 2H, COCH), 8.13 (s, 2H, ArOH), 15.15 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 181.3, 152.8, 149.8, 141.2, 136.3, 134.4, 132.5, 132.4, 129.2, 128.5, 127.3, 125.7, 125.0, 119.3, 119.0, 96.8, 75.6, 50.9, 31.6, 9.31; MS (ESI): m/z 970.1 $[M-H]^-$.

4h: White solid, yield: 33%; mp: 149–151 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 6H, CH_3), 2.39 (s, 6H, CH_3), 3.46 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.48 (d, 4H, J = 13.2 Hz, ArCH_2Ar), 4.72 (s, 4H, ArOCH_2), 5.48 (s, 4H, ArCH_2), 6.65 (t, 4H, J = 7.6 Hz, ArH), 6.95 (d, 4H, J = 7.6 Hz, ArH), 7.05–7.09 (m, 8H, ArH), 7.13 (d, 4H, J = 7.6 Hz, ArH), 7.97 (s, 2H, COCH), 8.06 (s, 2H, ArOH), 15.16 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2, 181.9, 153.7, 152.1, 141.1, 138.2, 136.4, 133.2, 131.3, 129.7, 129.3, 128.5, 127.7, 127.2, 125.7, 118.7, 96.9, 75.7, 51.5, 31.5, 21.1, 9.36; MS (ESI): m/z 961.4 $[M-H]^-$.

The inhibition effects of the calix[4]arene derivative **4a**–**h** were measured by the HIV-1 integrase strand transfer activity assay, which was carried out as described previously [27] with some minor modifications. Compounds diluted in DMSO were pre-incubated with 800 ng integrase at 37.8 °C in the reaction buffer in the absence of Mn^{2+} for 10 min. Subsequently, 1.5 pmol donor DNA and 9 pmol target DNA were added, and the reaction was initiated by the addition of 10 mmol/L Mn^{2+} into the final reaction volume. The reactions were carried out at 37.8 °C for 1 h, and a subsequent detection procedure was applied to detect the assay signals. An integrase inhibitor, baicalein, was used as the control compound (positive control), whereas no compound but only DMSO in the reaction mixture was set as the drug-free control (negative control). The inhibition effects of compounds **4a-h** were calculated based on the positive and negative controls, and the data are summarized in Table 1.

As shown in Table 1, *p*-*tert*-butylcalix[4]arene derivatives **4a**–**d** proved to be inactive in the ST assay at the concentration of 25 μmol/L. The calix[4]arene derivatives **4e**–**h** presented anti-IN activity in the low micromolar range (6.1–10.9 μmol/L). The most potent derivative was compound **4g**, which had an IC_{50} value for strand transfer of 6.1 μmol/L. Moreover, the anti-IN activity of the compounds **4e**–**h** with electron withdrawing groups or electron donating groups on the benzene rings of the 1,3-diketo subunits in alternate positions at the lower rim shows no clear difference. This experimental observation seems to indicate that the bulky *tert*-butyl groups reduced combination ability with integrase comparable to H atoms at the upper rim of calix[4]arene. In addition, an appropriate water-soluble anionic group incorporated at the upper rim, including sulfonates, carboxylates, or phosphonates, seems essential to enhance potential anti-integrase activity [13].

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4. Conclusion

In summary, a series of calix[4]arene derivatives incorporating two 1,3-diketo subunits in alternate positions at the lower rim were synthesized and their preliminary bioassays were also evaluated. The biological results showed that the *tert*-butyl groups at the upper rim of calix[4]arene have a negative effect on inhibiting HIV-1 integrase ST reaction. Calix[4]arene derivatives afforded more potent anti-IN activity in this series. Specifically, compound **4g** was the most potent candidate among the tested compounds, which inhibited the ST step of IN at 6.1 μmol/L concentration. Further work based on these structures is in progress.

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