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Synthesis, docking, and biological studies of phenanthrene β -diketo acids as novel HIV-1 integrase inhibitors

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Abstract

In the present study we report the synthesis of halogen-substituted phenanthrene β -diketo acids as new HIV-1 integrase inhibitors. The target phenanthrenes were obtained using both standard thermal- and microwave-assisted synthesis. 4-(6-Chlorophenanthren-2-yl)-2,4-dioxobutanoic acid (**18**) was the most active compound of the series that inhibited both 3'-end processing (3'-P) and strand transfer (ST) with IC₅₀ values of 5 and 1.3 μ M, respectively. Docking studies revealed two predominant binding modes that were distinct from the binding modes of raltegravir and elvitegravir, and suggest a novel binding region in the IN active site. Moreover, these compounds do not interact significantly with some of the key amino acids (Q148 and N155) implicated in viral resistance. Therefore, this series of compounds can further be investigated for a possible chemotype to circumvent resistance to clinical HIV-1 IN inhibitors.

Keywords

HIV-1; HIV-1 Integrase; Phenanthrene β -diketo acids; ST inhibitors; Docking

Acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) has resulted in the deaths of about 30 million people since it was first reported in 1981.^{1,2} Most of the approved anti-retroviral drugs target mainly viral reverse transcriptase or protease, two essential enzymes involved in viral replication.^{3,4} To circumvent viral resistance, which is a major bottleneck in anti-HIV therapy, the currently

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Supplementary data

Supplementary data (Docking poses of compounds **15** and **16** and Chemistry experimental data) associated with this article can be found, in the online version, at

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available regimens include cocktails of drugs from two or more classes. Although, highly active antiretroviral therapy (HAART) has been successful in reducing morbidity and mortality, the emergence of multi-drug resistant viral strains, along with the issues of toxicity, and dosing have rendered the current therapy ineffective.^{5–12} Thus, there is an urgent need to target other essential enzymes involved in viral survival and replication. Towards this end, IN has been shown to be a promising target with the entry of raltegravir (MK-0518), elvitegravir (GS-9137) and dolutegravir (GSK-1349572) into the clinic, in clinical trials for the management of AIDS.^{13,14}

IN, a 32 kDa 288 amino acid protein is an important enzyme involved in viral replication. Since IN has no homologue in human cells, it offers a promising strategy for anti-retroviral drug development. β -Diketo acids and isosteres are the most advanced class to have shown promising HIV-1 IN inhibitory activity.¹⁵ S1360 was the first IN inhibitor to enter clinical trials followed by a naphthyridine carboxamide L-870, 810.¹⁶ Although, over the last two decades promising IN inhibitors (Fig. 1) were designed based on the diketo acid functionality, raltegravir (MK-0518), elvitegravir (GS-9137) and dolutegravir are the only IN inhibitors approved by the FDA.¹⁷ Unfortunately, clinical studies have reported viral mutants particularly G148H, N155H, and double mutant G148H G140S, that are resistant to both raltegravir and elvitegravir.^{18,19} Thus, it is highly imperative to design new chemical classes as new generation HIV-1 IN inhibitors that not only have potent inhibitory activities, but also have the potential to circumvent the viral resistance to present IN inhibitors.

In our previous study, we reported 5(*H*)-phenanthridin-6-one diketo acids and their phenanthrene DKA analogs as a novel class of HIV-1 IN inhibitors that also showed cell culture antiviral activity.²⁰ Herein, we report the synthesis of a new series of phenanthrene β -diketo acids incorporating halogen substituents to provide better metabolic stability than the parent non-halogenated compounds.²⁰ These also turned out to have substantial IN inhibitory activities. Selected compounds were then tested for their abilities to inhibit HIV-1 replication in cell culture. Furthermore, to gain understanding of their binding modes at the IN active site, docking studies were conducted using our recently reported homology model of full-length HIV-1 IN in complex with DNA,²¹ which was built using the foamy IN-DNA structure²² as a template. In the previous docking studies²⁰ we used the structures of IN that was not bound to DNA, and therefore was less biologically relevant.

The synthesis of target halogenated phenanthrene β -diketo acids was accomplished by first synthesizing the halogenated acetyl phenanthrene intermediates **9a–9h** using Scheme 1. On the basis of commercial availability, two different sets of starting materials were used to perform the Suzuki coupling reaction. Thus, either the acetyl boronic acid derivatives (**1a–1d**) were reacted with the aldehyde containing halogen partners (**2a–2d**) to synthesize intermediates **5a–5d**, or alternatively, the formyl boronic acid derivatives (**3e–3h**) were coupled with iodo acetyl starting materials (**4e–4h**) to synthesize intermediates **5e–5h**. The coupling reaction was optimized by using a polymer bound Pd (PPh₃)₄ with triethyl amine as a base in a dioxane-ethanol solvent under an inert atmosphere.²³ Conditions varied from ice-cold (0 °C) to reflux, and the reaction was stirred from 6 to 48 h depending upon the starting materials used. The aldehyde intermediates were converted to the corresponding alkynes by Seyferth-Gilbert homologation under which, a mixture of intermediates **5a–5h**, dimethyl-(1-diazo-2-oxopropyl) phosphonate, and K₂CO₃ in methanol was stirred in ice for 7–17 h.²⁴ The alkyne intermediates **6a–6h** were then subjected to a 6-endo dig cyclization using PtCl₂ as catalyst and refluxing in toluene for 24 h under inert conditions to yield acetyl phenanthrenes intermediates **9a–9h**.²⁵ An alternative efficient microwave synthesis shown in Scheme 2 was used to synthesize the acetyl phenanthrene derivatives **9i** and **9j**. This one-pot synthesis of phenanthrenes was accomplished by a step-wise Suzuki-Miyaura coupling reaction followed by an intramolecular aldol condensation.²⁶ Thus, **7a** and **7b** phenyl

propanone starting materials were coupled with (2-formyl-4-methoxyphenyl) boronic acid (**8**) using Pd (PPh₃)₄ with Cs₂CO₃ as a base and S-Phos as a catalyst. The reaction was performed in a toluene/ethanol (2:1) mixture and irradiated at 60–80 W and 150 °C for 10 min. The acetyl phenanthrene intermediates **9i–9j** were then subjected to oxalation reaction. Our initial attempt with diethyl oxalate did not yield the desired product. A literature report²⁷ suggests that *tert*-butyl methyl oxalate is an efficient oxalylating agent for halogen-substituted acetophenones. Thus, we used of *tert*-butyl methyl oxalate (**11**), which was prepared according to a previously reported method,²⁸ by the reaction of methyl chlorooxo acetate, *tert*-butanol and pyridine in anhydrous ether. This resulted successful formation of the corresponding diketo esters **12i–12j**. The ester derivatives were then hydrolyzed with aq NaOH to their corresponding desired diketo acid final products **13–22**.

The synthesized target compounds **13–22** (Table 1) were then tested for their ability to inhibit strand transfer (ST) and 3'-end processing (3'-P) according to the assay we have previously reported.²⁹ The structure activity relationship around these halogen-substituted phenanthrene derivatives suggests that the β -diketo acid functionality is well tolerated at R¹ and R² positions. Thus, compounds **17**, **18**, and **20** have potent and similar ST IC₅₀ values of 1.4, 1.3, and 1.2 μ M, respectively. Moreover, compound **18** showed potent activities against both 3'-P and ST reactions with IC₅₀s of 5.0 μ M and 1.3 μ M, respectively. Comparison of **20** vs. **19** and **13** vs. **14** indicates that the β -diketo acid functionality is slightly more favorable at the R² position than the R¹ position. In particular, compound **20** was found to be about four times more active than compound **19** against ST reaction. Our laboratory has previously reported unsubstituted phenanthrene derivative **23** with diketo acid at the R² position which had an ST IC₅₀ value of 2.7 μ M.²⁰ With respect to compound **23**, while substitution of a chlorine atom at R⁶ position (compound **20**) improved activity, a fluoro substituent at this position (compound **13**) resulted in a slight loss of potency; also implying that the chloro substituent did better than the fluoro counterpart (compare compounds **20** and **13**) at this position. That fluorine may not be an optimal substituent at the R⁶ position is also evident when one considers that compound **22** (ST IC₅₀ = 3 μ M) was two-folds more active than compound **21** (ST IC₅₀ = 6 μ M). Chlorine was also found to improve activity at positions R⁴ and R⁵. Compounds **18** and **17** were about four times more potent than their unsubstituted counterpart (compound **24**, ST IC₅₀ of 4.8 μ M).²⁰ Chlorine substitution at R⁵ position in compound **17** also improved selectivity (nine-folds) for the ST step. The reason for the dramatic loss of potency for both ST and 3'-P with compound **15** is not apparent. It might be due to ineffective metal chelation by the β -diketo acid functionality considering, the electron withdrawing effect of the adjacent fluorine substituent. The improvement of activity of compound **16** (ST IC₅₀ = 8.0 μ M), relative to compound **15**, implies a favorable effect of the fluoro substituent at the R⁵ position. This may be one of the reasons why compound **17**, having a more hydrophobic Cl at the R⁵ position, had improved activity over compound **16**; also implying that hydrophobic interaction at this position may be an important contributing factor to activity. Compound **22**, with an electron donating methoxy group at the R¹ position, and the diketo acid moiety at R⁷ showed an IC₅₀ of 3 μ M against ST. This is a significant loss of activity when compared to its parent unsubstituted diketo acid analog **25** (ST IC₅₀ of 0.38 μ M) that our laboratory has previously reported.²⁰ This suggests that the R¹ position is sensitive to modifications and could be further exploited to determine the structure activity relationship around this novel class of IN inhibitors.

Next, to determine their potential as anti-HIV agents, potent analogs of the series, compounds **18**, and **17** were tested for their ability to inhibit HIV-1 replication in primary human peripheral blood mononuclear cells (PBMC) according to the previously reported procedure.³⁰ Both compounds showed moderate inhibition of HIV replication with IC₅₀s of 20.7 and 27.5 μ M, respectively (Table 2). The reduced antiviral potency might be because of

poor solubility, binding to serum proteins and/or cellular distribution factors. Cytotoxicity assays^{31,32} showed that the selected compounds, **17** and **18**, have toxicities when tested against PBMC, human CEM lymphoblastic leukemia cells and African green monkey Vero cells. However, the non-halogenated compound **23**, had an EC₅₀ of 8.0 μ M for inhibition of HIV replication in cell culture and a selectivity index of 10 against PBMCs in our previous study²⁰ suggesting that there is potential for optimization to improve selectivity index along with their anti-viral activities.

After synthesis and biological evaluation, a homology model of the structure of full HIV-1 integrase bound to DNA that we recently constructed based on the foamy virus crystal structure,²¹ was used to determine binding modes of the compounds. The docking studies revealed two distinct poses. The docked conformations of compound **18**, active against both ST and 3'-P, are shown in Fig. 2. In both orientations, the β -diketo acid chelating pharmacophore interacted with the two Mg²⁺ ions in the IN active site, thus contributing to IN inhibition in accordance with the proposed mechanism of action of ST inhibitors. The phenanthrene ring in one binding mode interacted with residues Glu92, Ser119, Asn120, and Phe121 in a possible novel binding region in the IN active site. In the other mode, the phenanthrene ring made contacts with Pro142, Tyr143, Asn117, and Gly118. It is important to note that because of steric hindrance, the phenanthrene ring does not dock into the DNA-IN interface cavity²¹ into which the characteristic halobenzyl moieties of clinically used IN inhibitors insert; thus making no contacts with Gln146 or viral DNA. The present docking simulation on HIV-DNA complex structure is a major improvement over our previous studies on partial IN structure without DNA and provide more detailed insights into the binding modes of the target phenanthrene β -diketo acids. More importantly, there were no significant interactions with Gln148 and Asn155, key residues implicated in viral resistance.

The novel binding mode of these compounds could be exploited to develop agents active against the current drug-resistant strains of HIV. Since, compound **15** exhibited a significant loss of activity (ST IC₅₀ of 63 μ M), its binding pose was also evaluated. It was observed that compound **15** predominantly docked in a different binding mode (Supplementary material, Figure S1). In this orientation, while the phenanthrene ring interacted with Thr66, His67, and Leu68, only the acid and the enolic oxygen of the β -diketo acid motif chelated the two Mg²⁺ ions. The loss of potency may be attributed to a disruption of chelation by an adjacent electron withdrawing fluorine substituent. The structurally similar derivative **16** had a similar binding pose as compound **15** (Supplementary material, Figure S2). However, the improved activity of compound **16** might result from a favorable contact that the R⁵ position fluoro makes with the side chain of Leu68.

In summary, a series of new phenanthrene- β -diketo acid derivatives bearing mostly halogen substituents were synthesized and evaluated as HIV-1 integrase inhibitors. In general, compounds were active against the ST catalytic step but some also showed good activities against 3'-P as well. Selected compounds were also found to moderately inhibit HIV-1 replication. Docking studies with a more refined structure than we previously used to dock earlier parent phenanthrene DKAs suggest that these derivatives bind to a potential novel region in the IN active site. In particular, the bulky phenanthrene ring system does not dock into the cavity characteristically occupied by the halobenzyl groups of IN inhibitors in clinical use, and does not appear to interact with Gln146 and viral DNA. Furthermore, no contacts with two of the most critical residues implicated in viral resistance, Asn155 and Gln148, were observed. This series of compounds could be further optimized to develop agents to overcome viral resistance against currently used HIV-1 IN inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References and notes

1. Curran JW. *N Engl J Med*. 1983; 309:609. [PubMed: 6877290]
2. Curran JW. *R I Dent J*. 1984; 16:19, 21. [PubMed: 6591331]
3. Von Hentig N. *Drugs Today*. 2008; 44:103. [PubMed: 18389089]
4. MacArthur RD, Novak RM. *Clin Infect Dis*. 2008; 47:236. [PubMed: 18532888]
5. Clavel F, Hance AJ. *N Engl J Med*. 2004; 350:1023. [PubMed: 14999114]
6. Moyle G, Gatell J, Perno CF, Ratanasuwan W, Schechter M, Tsoukas C. *AIDS Patient Care STDs*. 2008; 22:459. [PubMed: 18479200]
7. Johnson VA, Brun-Vezinet F, Clotet B, Gunthard HF, Kuritzkes DR, Pillay D, Schapiro JM, Richman DD. *Top HIV Med*. 2010; 18:156. [PubMed: 21245516]
8. Emini EA, Graham DJ, Gotlib L, Condra JH, Byrnes VW, Schleif WA. *Nature*. 1993:364.
9. Calmy A, Hirschel B, Cooper DA, Carr A. *Antivir Ther*. 2009; 14:165. [PubMed: 19430091]
10. Marcello A. *Retrovirology*. 2006; 3:7. [PubMed: 16412247]
11. Geeraert L, Kraus G, Pomerantz RJ. *Annu Rev Med*. 2008; 59:487. [PubMed: 17845138]
12. Malta M, Magnanini MM, Strathdee SA, Bastos FI. *AIDS Behav*. 2010; 14:731. [PubMed: 19020970]
13. Summa V, Petrocchi A, Bonelli F, Crescenzi B, Donghi M, Ferrara M, Fiore F, Gardelli C, Gonzalez Paz O, Hazuda DJ, Jones P, Kinzel O, Laufer R, Monteagudo E, Muraglia E, Nizi E, Orvieto F, Pace P, Pescatore G, Scarpelli R, Stillmock K, Witmer MV, Rowley M. *J Med Chem*. 2008; 51:5843. [PubMed: 18763751]
14. Sato M, Motomura T, Aramaki H, Matsuda T, Yamashita M, Ito Y, Kawakami H, Matsuzaki Y, Watanabe W, Yamataka K, Ikeda S, Kodama E, Matsuoka M, Shinkai H. *J Med Chem*. 2006; 49:1506. [PubMed: 16509568]
15. Hazuda DJ, Felock P, Witmer M, Wolfe A, Stillmock K, Grobler JA, Espeseth A, Gabryelski L, Schleif W, Blau C, Miller MD. *Science*. 2000; 287:646. [PubMed: 10649997]
16. Hazuda DJ, Anthony NJ, Gomez RP, Jolly SM, Wai JS, Zhuang L, Fisher TE, Embrey M, Guare JP Jr, Egbertson MS, Vacca JP, Huff JR, Felock PJ, Witmer MV, Stillmock KA, Danovich R, Grobler J, Miller MD, Espeseth AS, Jin L, Chen IW, Lin JH, Kassahun K, Ellis JD, Wong BK, Xu W, Pearson PG, Schleif WA, Cortese R, Emini E, Summa V, Holloway MK, Young SD. *Proc Natl Acad Sci USA*. 2004; 101:11233. [PubMed: 15277684]
17. U.S. Food and Drug Administration. [Accessed Aug 29 2013] <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>
18. Marinello J, Marchand C, Mott BT, Bain A, Thomas CJ, Pommier Y. *Biochemistry*. 2008; 47:9345. [PubMed: 18702518]
19. Goethals O, Clayton R, Van Ginderen M, Vereycken I, Wagemans E, Geluykens P, Dockx K, Strijbos R, Smits V, Vos A, Meersseman G, Jochmans D, Vermeire K, Schols D, Hallenberger S, Hertogs K. *J Virol*. 2008; 82:10366. [PubMed: 18715920]
20. Patil S, Kamath S, Sanchez T, Neamati N, Schinazi RF, Buolamwini JK. *Bioorg Med Chem*. 2007; 15:1212. [PubMed: 17158051]
21. Sharma H, Cheng X, Buolamwini JK. *J Chem Inf Model*. 2012; 52:515. [PubMed: 22256860]
22. Hare S, Gupta SS, Valkov E, Engelman A, Cherepanov P. *Nature*. 2010; 464:232. [PubMed: 20118915]

23. Jang SB. *Tetrahedron Lett.* 1997; 38:1793.
24. Roidl G, Enkelmann V, Adams RD, Bunz UH. *J Organomet Chem.* 1999; 578:144.
25. Furstner A, Mamane V. *J Org Chem.* 2002; 67:6264. [PubMed: 12182677]
26. Kim YH, Lee H, Kim YJ, Kim BT, Heo JN. *J Org Chem.* 2008; 73:495. [PubMed: 18154352]
27. Jiang XH, Song LD, Long YQ. *J Org Chem.* 2003; 68:7555. [PubMed: 12968921]
28. Bucher G, Halupka M, Kolano C, Schade O, Sander W. *Eur J Org Chem.* 2001; 3:545–552.
29. Sharma H, Patil S, Sanchez TW, Neamati N, Schinazi RF, Buolamwini JK. *Bioorg Med Chem.* 2011; 19:2030. [PubMed: 21371895]
30. Stuyver LJ, Lostia S, Adams M, Mathew JS, Pai BS, Grier J, Tharnish PM, Choi Y, Chong Y, Choo H, Chu CK, Otto MJ, Schinazi RF. *Antimicrob Agents Chemother.* 2002; 46:3854. [PubMed: 12435688]
31. Schinazi RF, Sommadossi JP, Saalman V, Cannon DL, Xie MY, Hart GC, Smith GA, Hahn EF. *Antimicrob Agents Chemother.* 1990; 34:1061. [PubMed: 2393266]
32. Sommadossi JP, Carlisle R, Schinazi RF, Zhou Z. *Antimicrob Agents Chemother.* 1988; 32:997. [PubMed: 3190201]

S-1360 **MK-0518** **GS-9137** **GSK-1349572**

Figure 1.
Representative structures of potent HIV-1 integrase inhibitors.

Figure 2.
(a) Two-binding modes of compound **18** within the active site of IN-DNA homology model, (b) binding interactions of one of the pose of compound **18**. Ligand is colored by yellow carbons and represented by tubes, (c) binding interactions of the second pose of compound **18**. Ligand is colored with gray carbons and represented by ball and stick. Residues are shown within 4 Å of the ligand in the IN active site. Mg²⁺ ions are represented by magenta spheres. Active site residues is represented by tubes and colored by element.

Scheme 1.

Reagent and Conditions: (a) Pd[P(Ph)₃]₄ (polymer bound) (1mol%), Et₃N, dioxane, EtOH ice/reflux, 6h-2 days (b) dimethyl- (1-diazo-2-oxopropyl) phosphonate, K₂CO₃, MeOH, ice, 7–17 h (c) PtCl₂, Toluene, reflux, 24 h.

Scheme 2.

Reagent and Conditions: (a) Microwave: 10 min, 150 °C, $Pd[P(Ph)_3]_4$ (4 mol%), S-Phos (6 mol%), Cs_2CO_3 , Toluene:EtOH 2:1.

Scheme 3.

Reagent and Conditions: (a) t-butanol, pyridine, ether, rt, 2h (b) NaOMe, MeOH, 60 °C, 4h

(c) aq. NaOH, MeOH, THF, 6h.

Table 1

Structure and HIV-1 IN inhibitory activities of phenanthrene β -diketo acids

Comp.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	Activity (IC ₅₀ μM)	
								3-P ^a	ST ^b
13	H	DKA ^c	H	H	H	F	H	11 ± 2	3 ± 2
14	DKA	H	H	H	H	F	H	35 ± 13	4 ± 1
15	H	DKA	F	H	H	H	H	83 ± 15	63 ± 16
16	H	DKA	F	H	F	H	H	63 ± 12	8 ± 2
17	DKA	H	H	H	Cl	H	H	12 ± 3	1.4
18	DKA	H	H	Cl	H	H	H	5 ± 3	1.3 ± 0.1
19	DKA	H	H	H	H	Cl	H	19 ± 2	4 ± 1
20	H		H	H	H	Cl	H	11 ± 4	1.2 ± 0.3
		DKA							
21	OCH ₃	H	H	H	H	F	DKA	44 ± 10	6 ± 2
22	OCH ₃	H	H	H	H	H	DKA	32 ± 12	3 ± 2
23 ^d	H	DKA	H	H	H	H	H	25 ± 7	2.7 ± 2

Comp.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	Activity (IC ₅₀ μM)	
								3'-p ^a	ST ^b
24 ^d	DKA	H	H	H	H	H	H	23 ± 6	4.8 ± 2
25 ^d	H	H	H	H	H	H	DKA	9 ± 2	0.38 ± 0.11
S-1360 ^e								11 ± 2	0.6 ± 0.1

^aRepresents 3'-processing.

^bRepresents strand transfer.

^cRepresents β-diketo acid.

^dCompounds synthesized previously.

^eStandard.

Table 2

Anti-HIV activity of selected novel potent derivatives

Comp.	Anti-HIV-1 Activity in PBMCs ^a , EC ₅₀ ^b (μM)	Cytotoxicity (IC ₅₀ , μM)		
		PBMC	CEM ^c	VERO
17	20.9 ± 15.8	14.1	12.1	7.2
18	27.5 ± 10.2	4.0	13.1	4.5
AZT (control)	0.005 ± 0.0009	>100	14.3	56.0

^a Human peripheral blood mononuclear cells.^b Effective concentrations inhibiting 50 % HIV replication.^c Human CEM lymphoblastic leukemia cells.