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# Four Novel Bis-(naphtho-γ-pyrones) Isolated from *Fusarium* Species as Inhibitors of HIV-1 Integrase

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**Abstract**—Integration of viral DNA into host cell DNA is an essential step in retroviral (HIV-1) replication and is catalyzed by HIV-1 integrase. HIV-1 integrase is a novel therapeutic target and is the focus of efforts to identify effective inhibitors that will prevent/or cure HIV infections. Four novel naphtho-γ-pyrones, belonging to the chaetochromin and ustilaginoidin family, were discovered as inhibitors of HIV-1 integrase from the screening of fungal extracts using a recombinant in vitro assay. These compounds inhibit both the coupled and strand transfer activity of HIV-1 integrase with $IC_{50}$ values of 1–3 and 4–12 μM, respectively. The discovery, structure elucidation, chemical modification and the structure–activity relationship of these compounds are described.

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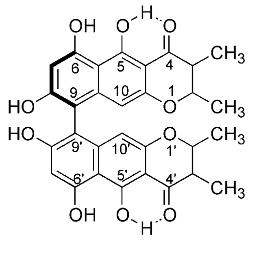
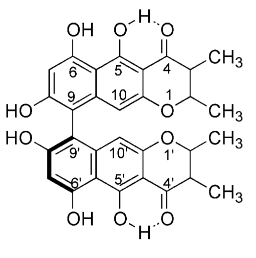
Integration, a three-step process, is an essential step in the life cycle of HIV-1 that includes assembly of proviral DNA onto integrase, endonucleolytic processing of the proviral DNA, and strand transfer of the proviral DNA into the host cell DNA.[1] This process is unique to retroviral proliferation and the entire reaction is catalyzed by a single viral enzyme, HIV-1 integrase. This enzyme is absent in mammalian cells and therefore represents a potentially safe target for development of anti HIV therapy. Treatment by these inhibitors could be either used alone or in combination with existing therapies (drugs that inhibit HIV-1 protease and reverse transcriptase). The recent discovery of diketo acid (DKA)-based inhibitors helped validate this target.[2] Unfortunately, none of the inhibitors has been clinically tested as yet and the clinical outcome of any given class of compounds is inherently uncertain. Therefore, new classes of inhibitors are urgently needed to further elucidate and define whether HIV-1 integrase is a clinically effective target.



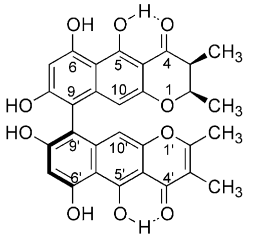
**1** (isochaetochromin $B_1$)

$[\alpha]_D$=+142.6°



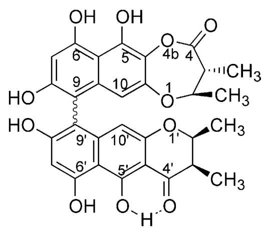
**2** (isochaetochromin $B_2$)

$[\alpha]_D$=-543.9°



**3** (isochaetochromin $D_1$)

$[\alpha]_D$=-228.6°



**4** (oxychaetochromin B)

$[\alpha]_D$=+20°

Screening of natural product extracts against recombinant HIV-1 integrase led to the discovery of several classes of natural product inhibitors exemplified by equisetin,[3] integric acid,[4] complestatin,[5] and integracins.[6]

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Continued screening of fungal extracts led to the discovery of four new compounds of the unsymmetrical bis-naphtho-γ-pyrone family named herein isochaetochromin $B_1$ (**1**), isochaetochromin $B_2$ (**2**), isochaetochromin $D_1$ (**3**) and oxychaetochromin B (**4**). These compounds inhibited the recombinant HIV-1 integrase coupled reaction with $IC_{50}$ values of 1–3 μM. The isolation, structure elucidation, stereochemistry, chemical modification and biological activities of these compounds are herein described.

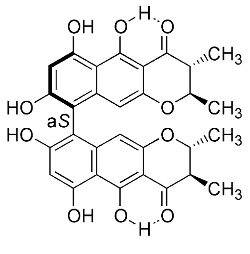
## Producing Organism, Fermentation and Isolation

The culture (MF6252, ATCC74396) that produced these compounds was isolated from leaf litter collected under *Podocarpus dacryoides* in Te Anau, New Zealand. It was identified as a *Fusarium* sp. and was grown in CYS80 media.[7] A 1.2-L fermentation broth was extracted with methyl ethyl ketone and the extract was chromatographed on Sephadex LH-20 in MeOH yielding three consecutive fractions containing the active components. The first and third fractions were chromatographed by RPHPLC (Zorbax RX C-8, aqueous $CH_3CN + 0.1\%$ TFA gradient) to give **4** (300 mg/L) and **3** (5 mg/L), respectively.[8] The middle LH-20 active fraction was subjected to silica gel chromatography followed by RPHPLC to give **1** (25 mg/L) and **2** (800 mg/L).

## Structure elucidation

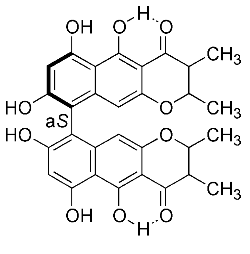
HREIMS analysis of **1** and **2** indicated that they were isomeric and gave a parent ion at *m/z* 546 suggesting a molecular formula $C_{30}H_{26}O_{10}$. The $^{13}C$ NMR spectra revealed the presence of 30 carbons and supported the formula. The formula search of these compounds in the Chapman and Hall database provided chaetochromins A (**5**),[9] B (**6**)[9] and ustilaginoidin D (**7**)[10] as hits which was further narrowed to the unsymmetrical dimer chaetochromin B by a $^{13}C$ NMR similarity search in the SIMSER database.[11] Chaetochromin A (**5**) is a symmetrical dimer and its structure and absolute stereochemistry including 9,9′-axial stereochemistry was thoroughly established by CD and X-ray crystallography of a *p*-bromobenzoate derivative.[9b] The stereochemistry of the other symmetrical dimer ustilaginoidin D and unsymmetrical dimers chaetochromins B and D were originally elucidated by comparative CD spectroscopy.[9a] Ustilaginoidins exhibited negative first (294 nm) and positive second (267 nm) Cotton effects in the CD spectrum indicating 9,9′-axial stereochemistry as a*R*. On the other hand chaetochromins A-D displayed the opposite CD spectra and hence a*S* 9,9′-axial stereochemistry.[9a,10a]

The $^1H$ and $^{13}C$ NMR spectra (Table 1) of **1** and **2** were essentially identical to the published data of chaetochromin B[9a] except for downfield shifted pairs of the aromatic and methyl signals in the $^1H$ spectra of **1** (δ 6.15, 6.75, 1.44, 1.25) and **2** (δ 6.13, 6.72, 1.43, 1.23) compared to chaetochromin B (δ 5.95, 5.93, 1.31, 1.18). Like chaetochromin B, each of these two compounds possess a pair of *cis* ($J_{2,3} = \sim 3$ Hz) and *trans* ($J_{2,3} = \sim 10$ Hz) methyl groups. The specific rotation of both of these compounds (**1**: +143° and **2**: −544°) were significantly different than chaetochromin B (+524°) indicating that **1** and **2** were diastereomers of chaetochromin B. The CD spectrum of **1** showed positive first (294 nm) and negative second (269 nm) Cotton effects just like chaetochromin B whereas a negative first and positive second Cotton effects were observed in the CD spectrum of **2** as in ustilaginoidins suggesting 9,9′-axial stereochemistries as a*S* and a*R*, respectively. However, the complete stereochemical assignment of these compounds would require X-ray crystallography.



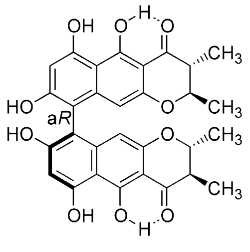
**5** (chaetochromin A)

$[\alpha]_D = +600°$



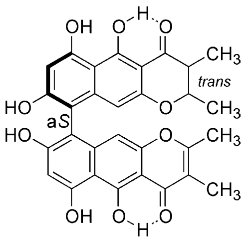
**6** (chaetochromin B)

$[\alpha]_D = +524°$



**7** (ustilaginoidin D)

$[\alpha]_D = -188°$



**8** (chaetochromin D)

$[\alpha]_D = +411°$

**Isochaetochromin $D_1$ (3).** HREIMS analysis of **3** gave a molecular ion at *m/z* 544 and a molecular formula $C_{30}H_{26}O_{10}$ which corresponded to a dehydro derivative of compounds **1** and **2**. The $^1H$ NMR spectrum (Table 1) of **3** indicated that the *trans* methyl group signals were replaced with two olefinic methyl groups (δ 1.96, 2.29), thus confirming the presence of the olefin in the pyrone ring. Isochaetochromin $D_1$ (**3**) showed a negative specific rotation (−288°) and exhibited a negative first (294 nm) and positive second (269 nm) Cotton effects in the CD spectrum indicating an a*R* 9,9′-axial stereochemistry. This compound is a *cis*-dimethyl ($J_{2,3} = \sim 3$ Hz) isomer of chaetochromin D with the opposite axial stereochemistry.[9a]

**Oxychaetochromin B (4).** HREIMS analysis of **4** afforded a molecular formula $C_{30}H_{26}O_{11}$ (*m/z* 562.1458) indicating the presence of an extra oxygen atom compared to **1** and **2**. One of the γ-pyrone carbon (δ 202.3) signals was replaced with an ester carbonyl (δ 170.9) in the $^{13}C$ NMR spectrum of **4** (Table 1). The $^1H$ NMR spectrum of **4** indicated that it was a 1:1 of diastereomer mixture and exhibited smaller separation between the two *trans*-dimethyl groups (Δδ 0.08) indicating the location of the ester group next to these methyls. This observation was confirmed by the HMBC correlation

(Fig. 1) of one of the methyl signals (δ 0.91) to the ester carbonyl. The HMBC correlations from the other methyl groups, aromatic, and hydroxy protons further supported this substitution and established the structure for oxychaetochromin B (**4**). The $\delta_C$ values were in full agreement with the assigned structure. HREIMS fragmentation of **4** further corroborated the assigned structure (Fig. 2). It produced two fragment ions at *m*/*z* 274 and 290 as a result of the cleavage of 9,9′-bond. In addition, the mass spectrum of **4** contained fragment ions at *m*/*z* 83 and *m*/*z* 480 for the five-carbon acyl unit and due to its loss, respectively. Oxychaetochromin B exhibited a positive but low specific rotation (+20°). The CD spectrum of **4** did not show the characteristic strong Cotton effects observed for other chaetochromins and ustilaginoidins and indicated that it may be inseparable mixture of 9,9′-axial isomers. This was also apparent in the $^1$H NMR spectrum of **4**, which

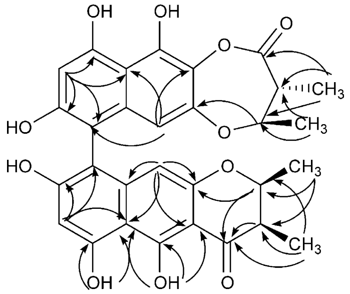


**Figure 1.** HMBC correlations ($^nJ_{XH}$ = 5 and 7 Hz) of **4**.

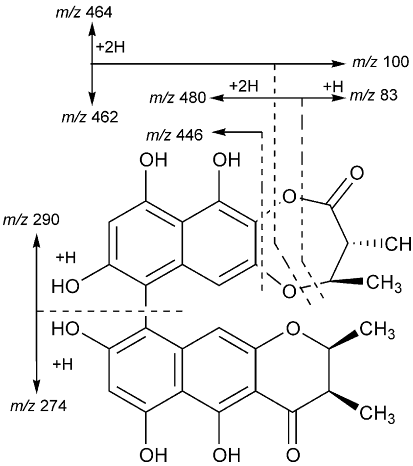


**Figure 2.** EIMS fragmentation of oxychaetochromin B (**4**).

**Table 1.** $^1$H and $^{13}$C NMR assignments of naphtho-γ-pyrones **1**–**4** in $CDCl_3$

| Carbon # | **1** (δC) | **2** (δC) | **4** (δC)[b] | **1** (δH) | **2** (δH) | **3** (δH)[a] | **4** (δH)[b] |
|---|---|---|---|---|---|---|---|
| 2,2′ | 78.4 | 78.4 | 82.6 | 4.17, dq, 10.8, 6.3 | 4.14, dq, 11.1, 6.3 | 4.65, dq, 3.0, 6.4 | 4.15, dq, 10.4, 6.4 |
|  | 75.6 | 75.6 | 74.7 | 4.64, dq, 3.0, 6.6 | 4.62, dq, 3.0, 6.6 |  | 4.42, dq, 3.6, 6.8 |
| 3,3′ | 46.1 | 46.2 | 41.2 | 2.66, dq, 10.8, 6.9 | 2.66, dq, 10.8, 6.9 | 2.80, dq, 2.4, 6.4 | 2.67, dq, 10.8, 6.4 |
|  | 44.4 | 44.4 | 43.1 | 2.75, dq, 3.0, 7.0 | 2.72, dq, 3.0, 7.5 |  | 2.55, dq, 3.6, 6.0 |
| 4,4′ | 202.3 | 202.3 | 170.9 |  |  |  |  |
|  | 200.7 | 200.7 | 201.3 |  |  |  |  |
| 4a, 4a′ | 101.5 | 101.5 | 126.6* |  |  |  |  |
|  | 101.4 | 101.4 | 100.2 |  |  |  |  |
| 5, 5′ | 165.6 | 165.6 | 142.4 |  |  |  |  |
|  | 164.7 | 164.7 | 165 |  |  |  |  |
| 5a, 5a′ | 105.6 | 105.6 | 107.6 |  |  |  |  |
|  | 105.1 | 105 | 103.9 |  |  |  |  |
| 6, 6′ | 158.5 | 158.6 | 154.5 |  |  |  |  |
|  | 158.3 | 158.2 | 157.2 |  |  |  |  |
| 7, 7′ | 100.1 | 100.1 | 100.4 | 6.55, s | 6.56, s | 6.54, s | 6.37, s |
|  | 99.8 | 99.9 | 100.9 | 6.57, s | 6.56, s | 6.48, s | 6.45, s |
| 8, 8′ | 161.1 | 161.1 | 153.3 |  |  |  |  |
|  | 159.5 | 159.7 | 159.4 |  |  |  |  |
| 9, 9′ | 102.1 | 102.4 | 102.6 |  |  |  |  |
|  | 102 | 102 | 104.4 |  |  |  |  |
| 9a, 9a′ | 142.6 | 142.6 | 132.6* |  |  |  |  |
|  | 141.3 | 141.2 | 141.3 |  |  |  |  |
| 10, 10′ | 99 | 99.1 | 108.6 | 6.15, s | 6.13, s | 6.42, s | 6.24, s |
|  | 99 | 99.1 | 99.8 | 6.75, s | 6.72, s | 6.68, s | 6.32, s |
| 10a, 10a′ | 156.1 | 156.2 | 142.9 |  |  |  |  |
|  | 155.5 | 155.4 | 154.2 |  |  |  |  |
| 2-$CH_3$ | 19.7 | 19.7 | 16.5 | 1.44, d, 6.6 | 1.43, d, 6.3 | 1.37, d, 6.8 | 0.99, d, 6.4 |
| 2′-$CH_3$ | 16.6 | 16.5 | 15.3 | 1.44, d, 6.6 | 1.43, d, 6.3 | 2.29, s | 1.19, d, 6.8 |
| 3-$CH_3$ | 10.2 | 10 | 12.1 | 1.26, d, 7.5 | 1.26, d, 7.2 | 1.26, d, 7.2 | 0.91, d, 6.4 |
| 3′-$CH_3$ | 9.7 | 9.7 | 8.43 | 1.25, d, 7.2 | 1.23, d, 6.9 | 1.96, s | 1.02, d, 7.2 |
| 5-OH |  |  |  | 15.53,s | 15.48, s | 16.64, s |  |
| 5′-OH |  |  |  | 15.39, s | 15.36, s | 15.64, s | 15.5, s |
| 6-OH |  |  |  | 9.93, s | 9.93, s | 9.94, s |  |
| 6′-OH |  |  |  | 9.77, s | 9.76, s | 9.72, s | 9.6, s |
| 8-OH |  |  |  | 5.49, brs | 5.69, brs | 5.69, brs |  |
| 8′-OH |  |  |  | 5.28, brs | 5.29, brs | 5.29, brs |  |

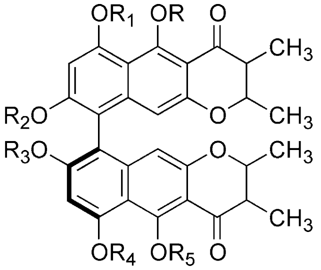
[a] $CD_3CN$.
[b] $CDCl_3$–$CD_3CN$ (4:1), only one isomer is listed.
*Assignment may be interchanged.

**Table 2.** HIV-1 inhibitory activities of naphtho-γ- pyrone derivatives

| Compd | Coupled $IC_{50}$ (μM) | ST $IC_{50}$ (μM) |
|---|---|---|
| **1** | 2 | 12 |
| **2** | 2 | 12 |
| **3** | 1 | 4 |
| **4** | 3 | 9 |
| **9a** | 50 | > 100 |
| **9b** | 60 | > 100 |
| **9c** | 40 | > 100 |
| **9d** | 80 | > 100 |
| **9e** | 40 | > 100 |
| **9f** | 8 | > 100 |

displayed approximately 1:1 ratios of the two isomers. Heating of the sample up to 55 °C did not alter the ratio of the isomers in the $^1$H NMR spectrum but led to the decomposition. Oxychaetochromin B containing unprecedented oxalactone ring is potentially biosynthesized by Bayer-Villiger type oxidation of **1** or **2** and probably both. If it were equally produced from both compounds it would result in isomeric axial isomers. It is not clear why these isomers are inseparable.

**Chemical modification.** Acetylation of **2** with acetic anhydride in pyridine gave exclusively hexa-acetate derivative **9a**. Methylation of **2** with freshly prepared diazomethane in $CH_2Cl_2$ at 0 °C to room temperature furnished hexa- and penta-methyl ethers **9b** and **9c** (δ 10.08, OH), respectively, in a ratio of 7:5. In contrast, methylation with trimethylsilyl-diazomethane in a mixture of $CH_2Cl_2$–MeOH produced a mixture of three tetramethyl ethers [**9d** (δ 14.6, 10.05, 2×OH), **9e** (δ 14.6, 10.05, 2×OH) and **9f** (δ 10.05 2×OH)] in a ratio of 12:2:3, respectively.[12]



**9a**: $R = R_1 = R_2 = R_3 = R_4 = R_5 = COCH_3$
**9b**: $R = R_1 = R_2 = R_3 = R_4 = R_5 = CH_3$
**9c**: $R_4 = H$, $R = R_1 = R_2 = R_3 = R_4 = R_5 = CH_3$
**9d**: $R = R_1 = H$, $R_2 = R_3 = R_4 = R_5 = CH_3$
**9e**: $R = R_1 = R_2 = R_3 = CH_3$, $R_4 = R_5 = H$
**9f**: $R = R_2 = R_3 = R_5 = CH_3$, $R_2 = R_4 = H$

## HIV-1 integrase activity and SAR

Naphtho-γ-pyrones (**1**–**4**) and semisynthetic derivatives were evaluated in HIV-1 integrase coupled and strand transfer assays[2a] and the $IC_{50}$ values are reported in Table 2. Compounds **1** and **2** were indistinguishable in these assays, exhibiting $IC_{50}$ values of 2 and 12 μM in coupled and strand transfer assays, respectively. The dehydro compound **3** was slightly more active with $IC_{50}$ values of 1 and 4 μM in the corresponding assays. Oxychaetochromin B (**4**) was slightly less active ($IC_{50} = 3$ μM) in the coupled assay, but was slightly more active ($IC_{50} = 9$ μM) than **1** and **2** in the strand transfer assay. Compounds **1** and **2** were selected for further biological evaluation. These compounds exhibited viral protection in a 24 h HIV-1 viral infectivity assay with an $IC_{50}$ of 3 and 2 μM, respectively. Toxicity was noted in a 7-day infectivity assay and compounds **1**–**2**, at 50 μM, exhibited toxicity in a MTT assay.

The semisynthetic derivatives of compound **2** were consistently less active or inactive in the coupled and strand transfer assays (Table 2) and thus indicated the requirement of the phenolic groups for the activity.

This class of compounds have shown a variety of biological activities including a calmodulin-sensitive cyclic nucleotide phosphodiesterase activity (SCH 45752, $IC_{50}$ 40-47 nM),[13] and antileukemic activity in mice.[9b]

In conclusion, in this letter, we have reported four new naphtho-γ-pyrones of the chaetochromin/ustilaginoidin type that are good inhibitors of HIV-1 integrase. The isolation of compounds with opposite axial stereochemistry from the same extract is quite interesting and to be best of our knowledge it appears to be the first example of this type. Although the epimerization of the methyl groups next to a keto group have been reported[9b] and the racemization of the bis-naphthyl bond is possible, the compounds in this report are not isolation artefacts as determined by RPHPLC analysis of the initial extract.

## Acknowledgements

The authors thank Delia Valentino for fermentation studies.

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8. **1**: Orange yellow powder, $t_R = 5.65$ min (RPHPLC, Zorbax RX C-8, 4.6×250 mm, 65% aq $CH_3CN + 0.1\%$ TFA, 1 mL/min), $[\alpha]_D^{25} = +827°$ (*c* 0.13, MeOH); $[\alpha]_D^{25} = +142.6^o$ (*c* 0.12, dioxane), CD (dioxane) $[\theta]^{22}$ (nm): −488,500 (269), +824,600 (294), HREIMS (*m/z*): 546.1505 ($M^+$, calcd For $C_{30}H_{26}O_{10}$: 546.1525); **2**: orange yellow powder, $t_R = 6.02$ min, $[\alpha]_D^{25} = -188°$ (*c* 0.13, MeOH); $[\alpha]_D^{25} = -543.9°$ (*c* 1.07, dioxane), CD (dioxane) $[\theta]^{22}$ (nm): +5,464,400 (269), −6,174,800 (294), HREIMS (*m/z*) 546.1501 (M+, calcd For $C_{30}H_{26}O_{10}$: 546.1525); **3**: $t_R = 7.28$ min, orange yellow powder, $[\alpha]_D^{25} = -228.6°$ (*c* 0.14, dioxane); CD (dioxane) $[\theta]^{22}$ (nm): +1,867,704 (269), −1,556,400 (294), HREIMS (*m/z*) 544.1365 (M+, calcd For $C_{30}H_{24}O_{10}$: 544.1369); **4**: $t_R = 3.99$ min, dark brown powder, $[\alpha]_D^{25} = +20°$ (*c* 0.2, dioxane), CD (dioxane) $[\theta]^{22}$ (nm): 0 (240), +455311 (254), 0(276), −78,695 (288), 0 (303), +95,559 (324), 0 (335), −32602 (343), 0 (351), HREIMS (*m/z*) 562.1458 (M+, calcd For $C_{30}H_{26}O_{11}$: 562.1475).

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12. The structural assignments of **9d** and **9e** could be interchanged.

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