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Novel furocoumarins as potential HIV-1 integrase inhibitors

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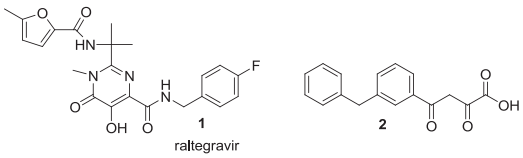
ABSTRACT

A series of seven novel, rationally designed *N*-substituted 3-{3,5-dimethylfuro[3,2-*g*]coumarin-6-yl} propanamides have been prepared as potential HIV-1 integrase (IN) inhibitors *via* a five-step pathway commencing with resorcinol and diethyl 2-acetylglutarate, and the HIV-1 IN inhibition potential of these compounds has been examined relative to raltegravir, a known HIV-1 IN inhibitor.

1. Introduction

Earlier research on the development of effective anti-HIV agents has focussed on inhibitors of the critical HIV-1 enzymes, reverse transcriptase (RT) and protease (PR) [1,2]. The emerging challenges of drug resistance have been addressed using combinations of RT and PR inhibitors in what is known as 'Highly Active Anti-Retroviral Therapy (HAART)' – an approach which has enjoyed considerable success [3]. Nevertheless, there is an urgent need to develop new and more effective therapeutics and the drug targets have been extended to include HIV-1 integrase (IN) inhibitors [4], which either block the strand transfer of viral DNA into the host genome or disrupt the 3′-processing of the viral DNA LTR units [5]. Since the approval of raltegravir **1** [6] for clinical use by the FDA in 2007, other potential scaffolds have been explored, *inter alia* the β-diketo acid (DKA) moiety [7], which is present in compound **2** [8] and which is capable of coordinating metal ions in the enzyme active site.



2. Results and discussion

Computer modelling studies suggested that the endocyclic oxygens in furocoumarin derivatives, such as compound **3a** (Fig. 1), could also coordinate metal ions in the HIV-1 IN enzyme active site and inhibit the integration of viral DNA. The coumarin moiety is found in various medicinally active natural products, including umbelliferone (7-hydroxycoumarin) [9] and warfarin [10]. In our own research on applications of Baylis–Hillman chemistry, we have reported several approaches to coumarins and their elaboration to novel analogues [11] of the clinically established HIV-1 PR inhibitor, ritonavir, and, more recently, the synthesis and evaluation of coumarin-AZT conjugates as potential dual-action HIV-1 PR/RT inhibitors [12,13]. In our approach to the synthesis of the furocoumarins **3a–g** as potential HIV-1 IN inhibitors, however, we decided to follow the five-step pathway outlined in Scheme 1.

Resorcinol **4** was reacted overnight with diethyl 2-acetylglutarate **5** at 0 °C in an ethanolic solution of HCl, generated *in situ* by the cautious addition of acetyl chloride to dry ethanol (CAUTION! exothermic reaction), and the known coumarin derivative **6** [14] was isolated in 64% yield (Scheme 1). Following a literature procedure [15], alkylation of the phenolic hydroxyl group in compound **6** was achieved by treatment with highly lachrymatory chloroacetone in the presence of freshly calcined K_2CO_3; the intermediate **7** was obtained, after recrystallisation, in 73% yield. The critical furanocoumarin scaffold **8** was obtained in good yield (79% after recrystallisation) by heating the ether **7** under basic conditions [15]. This mechanistically interesting cyclisation is considered [16] to proceed *via* initial opening of the coumarin ring to afford a phenoxide ion which, in turn, activates the *para*-position to

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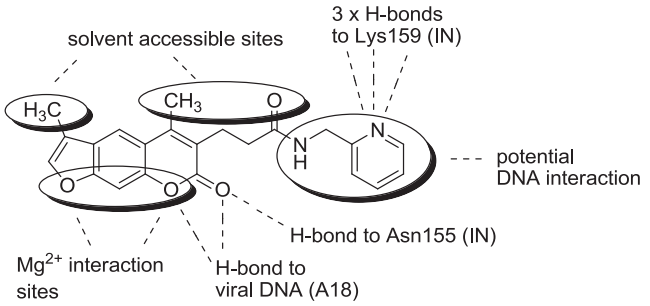


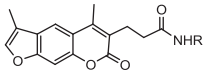
Fig. 1. Computer-modelled 2-D interactions of compound **3a** with the HIV-1 IN active site obtained using Tripos Sybyl molecular modelling software.

intramolecular cyclisation and formation of the furan ring - processes presumably accompanied by saponification of the ester group; subsequent protonation and acid-catalysed dehydration then regenerates the coumarin moiety.

With the common scaffold, 3-{3,5-dimethylfuro[3,2-*g*]coumarin-6-yl}propanoic acid **8**, in hand, access to the targeted furanocoumarin carboxamides **3a–g** was achieved in two steps, *viz.*, activation of the carboxylic acid group by treatment with *N*-hydroxysuccinimide and *N*,*N*′-diisopropylcarbodiimide (DIC) to generate the succinimido intermediates **9** (Scheme 1), followed by *in situ* reaction with each of the amines **10a–g**. The resulting, novel carboxamides **3a–g** were obtained in moderate to good yield (63–83% after recrystallisation; Table 1) and fully characterised. Chromatographed samples were tested for their inhibition of the HIV-1 IN strand-transfer process using the method adapted from Hazuda et al. [17].

Percentage enzyme inhibition values for compounds **3a–g** and raltegravir (a known HIV-1 IN inhibitor) are reported in Table 1. While some of the synthetic ligands exhibited negligible inhibition activities at a concentration of 10 μM, a number of compounds exhibited statistically significant inhibition ($p > 0.05$) at this concentration [*viz.*, **3a** (16.61%); **3d** (10.31%); **3e** (11.12%); and **3g** (15.92%)] and may warrant further investigation in the development of possible lead compounds. While compounds **3a** and **3d** contain pyridyl moieties with hydrogen-bonding potential, compounds **3e** and **3g** contain non-polar moieties (benzyl and propyl, respectively). *In silico* docking studies of these specific compounds is expected to guide future developments.

Table 1
Yields and % HIV-1 IN strand-transfer enzyme inhibition activities for compounds **3a–g** at 10 μM

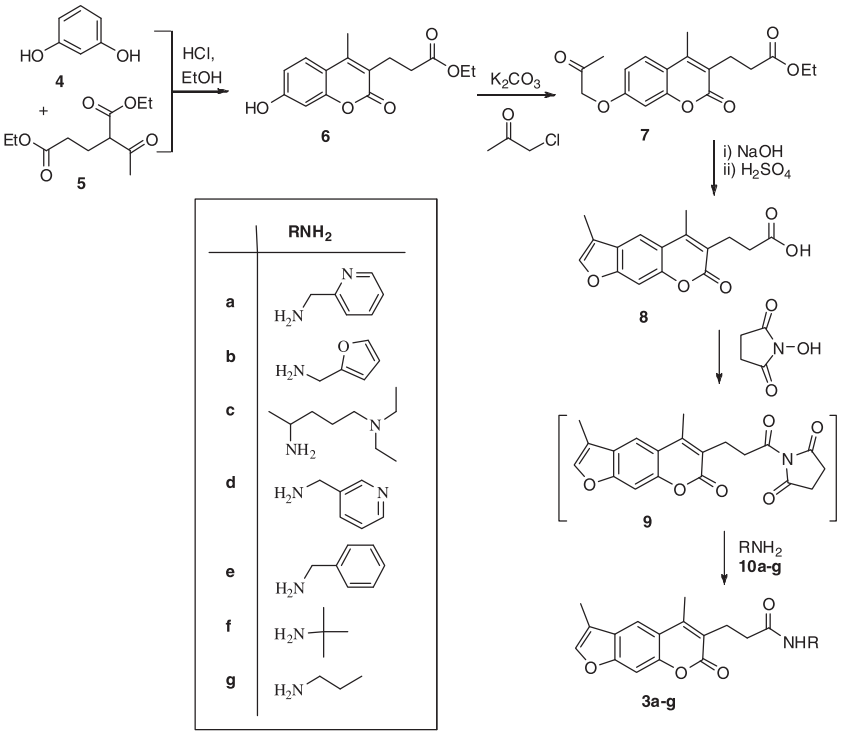


Compound	R	% Yield	% Inhibition[a]
3a	(Pyridine-2-yl)methyl	78	16.61 (3.11)
3b	(Furan-2-yl)methyl	80	5.21 (7.94)
3c	5-(Diethylamino)pent-2-yl	76	4.98 (5.96)
3d	(Pyridine-3-yl)methyl	81	10.31 (6.62)
3e	Benzyl	82	11.12 (7.48)
3f	*tert*-Butyl	63	8.48 (7.44)
3g	Propyl	83	15.92 (7.66)
Raltegravir	–	–	92.77 (0.61)

[a] Standard deviation in parentheses.

3. Conclusions

The structure of a potential HIV-1 IN inhibitor has been identified from an examination of its virtual interactions with a model of the HIV-1 IN active site based on available sub-domain X-ray crystal structures and NMR structures. This compound and a series of six analogues have been successfully synthesised and HIV-1 IN inhibition studies reveal that some of the ligands exhibit statistically significant inhibition at 10 μM concentrations. Ongoing research in this area at Rhodes is being focussed on the development of cinnamate ester-AZT and DKA analogue-AZT conjugates as potential dual-action HIV-1 integrase/reverse transcriptase inhibitors.



Scheme 1. Synthetic route to furocoumarin analogues **3a–g**.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AMX 400 spectrometer at 303 K in $CDCl_3$ or DMSO-d_6 and calibrated using solvent signals [δ_H: 7.26 ppm for residual $CHCl_3$ and 2.50 ppm for residual DMSO; δ_C: 77.0 ppm ($CDCl_3$) and 39.5 (DMSO-d_6)]. Melting points were measured using a hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with a diamond window, and compounds were analysed neat. High-resolution mass spectra (HRMS) were recorded on a Waters API Q-TOF Ultima spectrometer (University of Stellenbosch, Stellenbosch, South Africa). All computational protein manipulations were performed on a dual-core desktop PC with a Red Hat Enterprise Linux Version 5.0 operating system. All protein visualisations, manipulations and docking runs were performed using the commercial software package Sybyl™ version 8.0, licensed from Tripos™ (Tripos Inc., St. Louis, MO, USA, 2008).

4.2. Computer modelling

A three-dimensional model of the HIV-1 IN active site was prepared based on sub-domain X-ray crystal structures and NMR structures available in the Protein Data Bank (PDB1QS4, PDB1B9F, PDB1EX4, PDB1K6Y, PDB2B4J, PDB1MM8 and PDB1TQR). A virtual, drug-like compound database of 731 compounds was prepared through filtering of the ZINC commercial database according to Lipinski's Rule of 5. Ten different orientations of each compound were docked into the prepared HIV-1 IN active site using the SurflexDock™ application. Compound **3a** was identified as a potential inhibitor based on the virtual interactions with the enzyme active site predicted by the docking studies.

4.3. Chemistry

4.3.1. Synthesis of intermediates ***6–8***

The intermediates were obtained using reported methods: ethyl 3-(7-hydroxy-4-methylcoumarin-3-yl)propanoate **6** as a pale yellow solid (44.2 g, 64%), m.p. 126–127 °C (lit. [14] 124 °C); ethyl 3-[7-(2-oxopropoxy)-4-methylcoumarin-3-yl]propanoate **7** as white crystals (28.1 g, 73%), m.p. 122–123 °C (lit. [15] 115–116 °C); and 3-{3,5-dimethylfuro[3,2-*g*]coumarin-6-yl}propanoic acid **8** as a yellow solid (16.9 g, 79%), m.p. 220–221 °C (lit. [15] 215–216 °C). The general procedure for the synthesis of the novel furocoumarin carboxamides **3a–g** is illustrated by the following example; analytical data for the other compounds are detailed below.

4.3.2. Synthesis and analytical data for the furocoumarin ligands ***3a–g***

*4.3.2.1. General procedure: Synthesis of 3-{3,5-dimethylfuro[3,2-g]coumarin-6-yl}-N-[(pyridin-2-yl)methyl]-propanamide **3a**.* 3-{3,5-Dimethylfuro[3,2-*g*]coumarin-6-yl}propanoic acid **8** (1.0 g, 3.5 mmol) was dissolved in dry dioxane (50 mL) in a 2-necked round-bottomed flask and *N*-hydroxysuccinimide (0.44 g, 3.8 mmol) was added. The solution was stirred under N_2 for 20 min.; *N*,*N*′-diisopropylcarbodiimide (0.6 mL, 4 mmol) was then added through a septum and the solution stirred vigorously for 2 h. 2-Picolylamine **10a** (0.4 mL, 4 mmol) was then introduced through the septum and the mixture stirred for 4 h at r.t. under N_2. Ice-cooled water was then added to the mixture and the resulting precipitate was filtered off. Recrystallisation from 2-propanol gave 3-{3,5-dimethylfuro[3,2-*g*]coumarin-6-yl}-*N*-[(pyridin-2-yl)methyl]propanamide **3a** as a yellow solid (1.03 g, 78%), m.p. 212–213 °C [HRMS: *m*/*z* calculated for $C_{22}H_{21}N_2O_4$ (MH^+) 377.1501. Found 377.1498]; δ_H (400 MHz; DMSO-d_6) 2.26 (3H, s, 3-CH_3), 2.41 (2H, t, *J* = 7.5 Hz, CH_2Ar), 2.45 (3H, s, 5-CH_3), 2.85 (2H, t, *J* = 7.5 Hz, CH_2CO), 4.32 (2H, d, *J* = 5.7 Hz, NCH_2), 7.18 (2H, m, ArH), 7.57 (2H, m, ArH), 7.83 (1H, s, ArH), 7.90 (1H, s, ArH), 8.42 (1H, d, *J* = 4.3, ArH) and 8.51 (1H, t, *J* = 5.7 Hz, NH); δ_C (100 MHz; DMSO-d_6) 7.6 and 15.2 (CH_3), 23.7, 33.9 and 44.2 (CH_2), 98.8, 115.6, 116.0, 116.3, 120.9, 122.0, 122.4, 125.9, 136.5, 143.6, 147.9, 148.8, 149.7, 155.2 and 158.6 (Ar—C), 160.7 and 171.5 (C=O).

*4.3.2.2. Analytical data for the furocoumarin ligands **3b–g**.*

*4.3.2.2.1. 3-{3,5-Dimethylfuro[3,2-g]coumarin-6-yl}-N-[(furan-2-yl) methyl]propanamide **3b**.* A yellow solid (1.02 g, 80%), m.p. 215–217 °C [HRMS: *m*/*z* calculated for $C_{21}H_{20}NO_5$ (MH^+) 366.1342. Found 366.1331]; δ_H (400 MHz; $CDCl_3$) 2.28 (3H, s, 3-CH_3), 2.53 (5H, overlapping s and t, 5-CH_3 and CH_2Ar), 3.02 (2H, t, *J* = 7.4 Hz, CH_2CO), 4.39 (2H, d, *J* = 5.5 Hz, NCH_2), 6.14 (1H, d, *J* = 2.1 Hz, ArH), 6.20 (1H, m, ArH), 6.24 (1H, br s, NH), 7.17 (1H, s, ArH), 7.29 (1H, s, ArH), 7.43 (1H, s, ArH) and 7.66 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 7.9 and 15.5 (CH_3), 24.1, 34.9 and 36.4 (CH_2), 99.2, 107.3, 110.2, 114.9, 115.6, 116.6, 122.4, 126.3, 142.0, 142.9, 148.3, 150.2, 151.2 and 155.9 (Ar—C), 162.0 and 171.8 (C=O)

*4.3.2.2.2. N-[5-(diethylamino)pent-2-yl]-3-{3,5-dimethylfuro[3,2-g]coumarin-6-yl}propan-amide **3c**.* A yellow solid (1.02 g, 76%), m.p. 59–60 °C [HRMS: *m*/*z* calculated for $C_{25}H_{35}N_2O_4$ (MH^+) 427.2597. Found 427.2611]; δ_H (400 MHz; $CDCl_3$) 0.93 (6H, t, *J* = 6.5 Hz, 2 × CH_2CH_3), 1.04 (3H, d, *J* = 5.9 Hz, $CHCH_3$), 1.37 (4H, m, $CHCH_2CH_2$), 2.25 [5H, m (overlapping s and t), 3-CH_3 and CH_2-Ar], 2.39–2.48 (6H, series of signals, 3 × NCH_2), 2.54 (3H, s, 5-CH_3), 2.99 (2H, t, *J* = 6.5 Hz, CH_2CO), 3.90 (1H, br s, NCH), 6.22 (1H, d, *J* = 6.7 Hz, NH), 7.29 (1H, s, ArH), 7.41 (1H, s, ArH) and 7.65 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 7.8, 11.2, 15.4 and 20.6 (CH_3), 23.3, 24.3, 34.6, 35.3, 46.6 and 52.6 (CH_2), 45.0 (NCH), 99.2, 114.8, 115.6, 116.6, 122.7, 126.3, 142.9, 148.1, 150.1 and 155.9 (Ar—C), 162.0 and 171.3 (C=O).

*4.3.2.2.3. 3-{3,5-Dimethylfuro[3,2-g]coumarin-6-yl}-N-[(pyridin-3-yl) methyl]propanamide **3d**.* An off-white solid (1.07 g, 81%), m.p. 234–236 °C [HRMS: *m*/*z* calculated for $C_{22}H_{21}N_2O_4$ (MH^+) 377.1501. Found 377.1513]; δ_H (400 MHz; DMSO-d_6) 2.25 (3H, s, 3-CH_3), 2.37 (2H, t, *J* = 7.5 Hz, CH_2Ar), 2.43 (3H, s, 5-CH_3), 2.83 (2H, t, *J* = 7.5 Hz, CH_2CO), 4.25 (2H, d, *J* = 5.7 Hz, NCH_2), 7.17 (1H, m, ArH), 7.50–7.51 (2H, overlapping s and m, ArH), 7.80 (1H, s, ArH), 7.86 (1H, s, ArH), 8.37 (1H, d, *J* = 3.9, ArH) and 8.43 (2H, overlapping s and m, ArH and NH); δ_C (100 MHz; DMSO-d_6) 7.5 and 15.1 (CH_3), 23.7, 33.9 and 39.9 (CH_2), 98.7, 115.5, 115.9, 116.2, 122.3, 123.3, 125.8, 134.9, 135.0, 143.5, 147.8, 147.9, 148.7, 149.7 and 155.2 (Ar—C), 160.6 and 171.4 (C=O).

*4.3.2.2.4. N-benzyl-3-{3,5-dimethylfuro[3,2-g]coumarin-6-yl}propan-amide **3e**.* An off-white solid (1.07 g, 82%), m.p. 230–232 °C [HRMS: *m*/*z* calculated for $C_{23}H_{22}NO_4$ (MH^+) 376.1549. Found 376.1565]; δ_H (400 MHz; DMSO-d_6) 2.26 (3H, s, 3-CH_3), 2.37 (2H, t, *J* = 7.5 Hz, CH_2Ar), 2.45 (3H, s, 5-CH_3), 2.84 (2H, t, *J* = 7.5 Hz, CH_2-CO), 4.21 (2H, s, NCH_2), 7.15 (5H, s, ArH), 7.58 (1H, s, ArH), 7.85 (1H, s, ArH), 7.92 (1H, s, ArH) and 8.42 (1H, br s, NH); δ_C (100 MHz; DMSO-d_6) 7.6 and 15.2 (CH_3), 23.8, 34.0 and 42.1 (CH_2), 98.8, 115.7, 116.1, 116.4, 122.5, 125.9, 126.7, 127.2, 128.2, 139.5, 143.7, 148.0, 149.8 and 155.2 (Ar—C), 160.7 and 171.3 (C=O).

*4.3.2.2.5. N-tert-butyl-3-{3,5-dimethylfuro[3,2-g]coumarin-6-yl}propanamide **3f**.* A white solid (0.75 g, 63%), m.p. 84–85 °C [HRMS: *m*/*z* calculated for $C_{20}H_{24}NO_4$ (MH^+) 342.1705. Found 342.1698]; δ_H (400 MHz; $CDCl_3$) 1.28 [9H, s, $C(CH_3)_3$], 2.26 (3H, s, 3-CH_3), 2.39 (2H, t, *J* = 7.5 Hz, CH_2Ar), 2.54 (3H, s, 5-CH_3), 2.97 (2H, t, *J* = 7.5 Hz, CH_2CO), 5.67 (1H, br s, NH), 7.28 (1H, s, ArH), 7.41 (1H, s, ArH) and 7.65 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 7.8, 15.5 and 28.6 (CH_3), 24.2 and 36.0 (CH_2), 51.0 [$C(CH_3)_3$], 99.1, 114.8, 115.6, 116.6, 122.8, 126.3, 142.8, 148.0, 150.1 and 155.8 (Ar—C), 162.0 and 171.3 (C=O).

4.3.2.2.6. 3-{3,5-Dimethylfuro[3,2-g]coumarin-6-yl}-N-propylpropanamide ***3g***. A yellow solid (0.95 g, 83%), m.p. 211–213 °C [HRMS: *m*/*z* calculated for $C_{19}H_{22}NO_4$ (MH^+) 328.1549. Found 328.1561]; δ_H (400 MHz; DMSO-d_6) 0.75 (3H, t, J = 7.2 Hz, CH_3), 1.33 (2H, m, CH_2CH_3), 2.24–2.29 (5H, overlapping s and t, 3-CH_3 and CH_2Ar), 2.47 (3H, s, 5-CH_3), 2.79 (2H, t, J = 7.2 Hz, CH_2CO), 2.95 (2H, m, NCH_2), 7.55 (1H, s, ArH), 7.82 (1H, s, ArH) 7.88 (1H, m, NH) and 7.92 (1H, s, ArH); δ_C (100 MHz; DMSO-d_6) 7.6, 11.4 and 15.3 (CH_3), 23.9, 34.1, 39.5 and 40.4 (CH_2), 51.0 (CH_2CH_3), 98.8, 115.7, 116.0, 122.6, 125.9, 143.7, 147.9, 149.8 and 155.2 (Ar—C), 160.8 and 171.2 (C=O).

4.4. Biological evaluation

The HIV-1 IN strand transfer inhibition assay was adapted from previously described methods [17]. Briefly, 0.15 μM double-stranded biotinylated donor DNA (5′-biotin-GTGTGGAAAATCTC-TAGCA-3′ and 5′-ACTGCTAGAGATTTTCCACAC-3′) was added to the wells of streptavidin-coated 96-well microtiter plates (R&D Systems, USA). Following incubation at room temperature for 60 min and a stringent wash step, 1 μM purified recombinant HIV-1 subtype B IN (in the presence of $MgCl_2$ and $MnCl_2$) was assembled onto the pre-processed donor DNA through incubation for 30 min at 22 °C. Following a wash step, compounds **3a–g** and raltegravir were titrated into individual wells at a final concentration of 10 μM. The microtiter plates were incubated for 30 min at 37 °C, washed and the strand transfer reaction was initiated through the addition of 0.25 μM double-stranded FITC-labelled target DNA (5′-TGACCAAGGGCTAATTCACT-FITC-3′ and 5′-AGT-GAATTAGCCCTTGGTCA-FITC-3′) in Hepes buffer containing $MgCl_2$ and $MnCl_2$. After an incubation period of 60 min at 37 °C, the plates were washed as before and an alkaline phosphatase (AP) – conjugated anti-FITC secondary antibody (Sigma, USA) was added. Finally, the plates were washed and substrate (BluePhos, KPL, USA) was added to allow for detection at 620 nm using a microplate reader (xMark™, Bio-Rad, USA). All inhibition values are the average of triplicate experiments.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bioorg.2014.07.008.

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