

6-(1-Benzyl-1*H*-pyrrol-2-yl)-2,4-dioxo-5-hexenoic Acids as Dual Inhibitors of HIV-1 Integrase and Reverse Transcriptase Ribonuclease H Domain, Synthesized by a Parallel Synthesis Approach

Roberta Costi,^{,#,†} Mathieu Métifiot,^{#,‡} Francesca Esposito,[†] Giuliana Cuzzucoli Crucitti,[†] Luca Pescatori,[†] Antonella Messori,[†] Luigi Scipione,[†] Silvano Tortorella,[†] Luca Zinzula,[†] Ettore Novellino,[§] Yves Pommier,[‡] Enzo Tramontano,[†] Christophe Marchand,^{*,‡} and Roberto Di Santo[†]*

[†]Dipartimento di Chimica e Tecnologie del Farmaco, Istituto Pasteur-Fondazione Cenci Bolognetti, “Sapienza” Università di Roma, Italy, [‡]Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Building 37, Room 5068, Bethesda, Maryland 20892-4255, [†]Department of Life and Environmental Sciences, University of Cagliari, Italy, [§]Dipartimento di Farmacia, Università di Napoli “Federico II”, Via D. Montesano 49, I-80131 Napoli, Italy

Contents:

Pages 2-3: Spectroscopic data of representative compounds within the derivatives **9a-y** and **10a-y**;

Pages 3-5: Table 1: chemical, physical and analytical data of derivatives **9a-y** and **10a-y**.

Pages 5-9: Analysis of derivatives **7a-y** and **8a-y**.

1. Spectroscopic data

1-[(4-Methylphenyl)methyl]pyrrole-2-carboxaldehyde (9d). White solid; IR ν 1652 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 2.36 (s, 3H, CH_3), 5.67 (s, 2H, CH_2), 6.30 (m, 1H, pyrrole β -proton), 6.98-7.02 (m, 3H, pyrrole β -proton and benzene H), 7.08-7.19 (m, 3H, pyrrole α -proton and benzene H), 9.60 (s, 1H, aldehyde CH).

1-[(2-Fluorophenyl)methyl]pyrrole-2-carboxaldehyde (9e). White solid; IR ν 1650 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 5.67 (s, 2H, CH_2), 6.32 (m, 1H, pyrrole β -proton), 7.01 (m, 1H, pyrrole β -proton), 7.09-7.14 (m, 4H, benzene H), 7.30 (m, 1H, pyrrole α -proton), 9.60 (s, 1H, aldehyde CH).

3-[(2-Formyl-1*H*-pyrrol-1-yl)methyl]benzonitrile (9k). White solid; IR ν 2224 (CN), 1656 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 5.64 (s, 2H, CH_2), 6.40 (m, 1H, pyrrole β -proton), 7.07-7.08 (m, 2H, pyrrole β -proton and benzene H), 7.39-7.50 (m, 3H, benzene H), 7.61 (m, 1H, pyrrole α -proton), 9.60 (s, 1H, aldehyde CH).

1-[(2,3-Difluorophenyl)methyl]pyrrole-2-carboxaldehyde (9q). Brown oil; IR ν 1655 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 5.71 (s, 2H, CH_2), 6.35 (m, 1H, pyrrole β -proton), 6.89 (m, 1H, pyrrole β -proton), 7.02-7.15 (m, 4H, pyrrole α -proton and benzene H), 9.62 (s, 1H, aldehyde CH).

1-[(3,4-Difluorophenyl)methyl]pyrrole-2-carboxaldehyde (9u). Yellow solid; IR ν 1650 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 5.56 (s, 2H, CH_2), 6.36 (m, 1H, pyrrole β -proton), 6.93-7.05 (m, 4H, pyrrole β -proton, pyrrole α -proton and benzene H), 7.18 (m, 1H, benzene H), 9.60 (s, 1H, aldehyde CH).

4-[2-Formyl-1-[(4-methylphenyl)methyl]-1*H*-pyrrol-2-yl]-3-buten-2-one (10d). Yellow oil; IR ν 1660 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 2.25 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 6.30 (m, 1H, pyrrole β -proton), 6.50 (d, 1H, $J_t = 15.7$ Hz, butenoate C4-H), 6.80 (m, 1H, pyrrole β -proton), 6.91

(m, 1H, pyrrole α -proton), 6.99 (d, 1H, benzene H), 7.17 (d, 1H, benzene H), 7.45 (d, 1H, $J_t = 15.7$ Hz, butenoate C3-H).

3-[[2-(3-Oxo-1-propen-1-yl)-1H-pyrrol-1-yl]methyl]benzonitrile (10k). Orange oil; IR ν 2230 (CN), 1659 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 2.27 (s, 1H, CH_3), 5.31 (s, 2H, CH_2), 6.37 (m, 1H, pyrrole β -proton), 6.54 (d, 1H, $J_t = 15.6$ Hz, butenoate C4-H), 6.85 (m, 1H, pyrrole β -proton), 6.92 (m, 1H, pyrrole α -proton), 7.26 (s, 1H, benzene H), 7.30-7.36 (m, 2H, benzene H and butenoate C3-H), 7.49 (t, 1H, benzene H), 7.62 (d, 1H, benzene H).

4-[2-Formyl-1-[(2,3-difluorophenyl)methyl]-1H-pyrrol-2-yl]-3-buten-2-one (10q). Yellow oil; IR ν 1659 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 2.31 (s, 3H, CH_3), 5.34 (s, 2H, CH_2), 6.34 (m, 1H, pyrrole β -proton), 6.52-6.61 (m, 2H, pyrrole β -proton and butenoate C4-H), 6.83 (m, 1H, pyrrole α -proton), 6.96 (m, 1H, benzene H), 7.06 (m, 1H, benzene H), 7.15 (m, 1H, benzene H), 7.45 (d, 1H, $J_t = 15.7$ Hz, butenoate C3-H).

4-[2-Formyl-1-[(3,4-difluorophenyl)methyl]-1H-pyrrol-2-yl]-3-buten-2-one (10u). Yellow oil; IR ν 1660 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 2.27 (s, 3H, CH_3), 5.23 (s, 2H, CH_2), 6.34 (m, 1H, pyrrole β -proton), 6.53 (d, 1H, $J_t = 15.8$ Hz, butenoate C4-H), 6.83-6.86 (m, 3H, pyrrole β -proton and benzene H), 6.91 (m, 1H, pyrrole α -proton), 7.16 (m, 1H, benzene H), 7.38 (d, 1H, $J_t = 15.8$ Hz, butenoate C3-H).

2. Table 1. Chemical, Physical and Analytical Data of Derivatives **9a-y** and **10a-y**.

Cpd	R ₂	R ₃	R ₄	R ₅	R ₆	mp ($^{\circ}\text{C}$)	recryst solvent ^a	Yield (%)
9a	H	H	H	H	H	oil	oil	76
9b	CH_3	H	H	H	H	38-40	b	100
9c	H	CH_3	H	H	H	oil	oil	82
9d	H	H	CH_3	H	H	49-51	b	86

9e	F	H	H	H	H	34-36	b	100
9f	H	F	H	H	H	oil	oil	100
9g	H	H	F	H	H	oil	oil	65
9h	H	Cl	H	H	H	oil	oil	100
9i	H	H	Cl	H	H	78-80	b	96
9j	CN	H	H	H	H	138-140		85
9k	H	CN	H	H	H	98-100	c	70
9l	H	H	CN	H	H	-	-	100
9m	OCH ₃	H	H	H	H	56-58	b	100
9n	H	H	OCH ₃	H	H	oil	oil	77
9o	OC ₂ H ₅	H	H	H	H	oil	oil	71
9p	H	CH ₃	H	CH ₃	H	oil	oil	52
9q	F	F	H	H	H	oil	oil	71
9r	F	H	F	H	H	40-41	b	100
9s	F	H	H	F	H	50-52	b	87
9t	F	H	H	H	F	oil	oil	87
9u	H	F	F	H	H	47-49	b	69
9v	H	F	H	F	H	56-58	b	100
9w	Cl	H	Cl	H	H	75-77	c	100
9x	Cl	H	H	H	Cl	70-72	b	72
9y	H	Cl	H	Cl	H	61-63	b	100
10a	H	H	H	H	H	oil	oil	100
10b	CH ₃	H	H	H	H	76-77	a	58
10c	H	CH ₃	H	H	H	65-67	a	81
10d	H	H	CH ₃	H	H	oil	oil	87
10e	F	H	H	H	H	46-47	a	92
10f	H	F	H	H	H	oil	oil	69
10g	H	H	F	H	H	oil	oil	83
10h	H	Cl	H	H	H	78-80	a	63

10i	H	H	Cl	H	H	oil	oil	100
10j	CN	H	H	H	H	87-89	c	75
10k	H	CN	H	H	H	oil	oil	68
10l	H	H	CN	H	H	95-98	c	32
10m	OCH ₃	H	H	H	H	120-122	a	37
10n	H	H	OCH ₃	H	H	oil	oil	100
10o	OC ₂ H ₅	H	H	H	H	81-82	a	47
10p	H	CH ₃	H	CH ₃	H	76-78	b	72
10q	F	F	H	H	H	oil	oil	81
10r	F	H	F	H	H	63-65	c	28
10s	F	H	H	F	H	oil	oil	72
10t	F	H	H	H	F	86-88	a	100
10u	H	F	F	H	H	oil	oil	87
10v	H	F	H	F	H	62-64	c	35
10w	Cl	H	Cl	H	H	88-90	c	58
10x	Cl	H	H	H	Cl	89-90	c	47
10y	H	Cl	H	Cl	H	75-77	a	85

^a Recrystallization solvent: (a) ligroin; (b) *n*-hexane; (c) cyclohexane

3. Analysis

Compd	Elemental Analyses Calculated/ Found				
	C	H	N	Cl	F
7a	70.13	5.89	4.31		
	70.29	5.97	4.10		
7b	70.77	6.24	4.13		
	70.78	6.21	4.01		
7c	70.77	6.24	4.13		
	70.53	6.34	4.31		

7d	70.77	6.24	4.13	
	70.49	6.21	4.18	
7e	66.45	5.29	4.08	5.54
	66.20	5.25	4.39	5.69
7f	66.45	5.29	4.08	5.54
	66.51	5.25	4.03	5.50
7g	66.45	5.29	4.08	5.54
	66.40	5.39	4.01	5.50
7h	63.41	5.04	3.89	9.86
	63.65	5.08	3.87	9.90
7i	63.41	5.04	3.89	9.86
	63.55	5.08	3.96	9.77
7j	68.55	5.18	8.00	
	68.35	5.36	7.95	
7k	68.55	5.18	8.00	
	68.50	5.20	7.99	
7l	68.55	5.18	8.00	
	68.69	5.13	8.18	
7m	67.58	5.96	3.94	
	67.61	5.93	3.80	
7n	67.58	5.96	3.94	
	67.53	6.17	4.11	
7o	68.26	6.28	3.79	
	68.53	6.99	3.70	
7p	71.36	6.56	3.97	
	71.10	6.66	3.80	
7q	63.14	4.74	3.88	10.52

	63.21	4.79	3.63		10.47
7r	63.14	4.74	3.88		10.52
	63.22	4.58	3.83		10.64
7s	63.14	4.74	3.88		10.52
	63.28	4.64	3.62		10.55
7t	63.14	4.74	3.88		10.52
	63.09	4.58	4.05		10.64
7u	63.14	4.74	3.88		10.52
	63.13	4.61	3.74		10.50
7v	63.14	4.74	3.88		10.52
	63.19	4.56	3.75		10.51
7w	57.86	4.35	3.55	18.00	
	57.62	4.25	3.46	17.89	
7x	57.86	4.35	3.55	18.00	
	57.71	4.55	3.89	18.10	
7y	57.86	4.35	3.55	18.00	
	57.89	4.08	3.60	17.95	
8a	68.66	5.09	4.71		
	68.40	4.78	4.76		
8b	69.43	5.51	4.50		
	69.53	5.64	4.59		
8c	69.43	5.51	4.50		
	69.40	5.57	4.51		
8d	69.43	5.51	4.50		
	69.41	5.51	4.56		
8e	64.74	4.48	4.44		6.03
	64.90	4.53	4.50		7.79

8f	64.74	4.48	4.44	6.03
	64.70	4.51	4.49	6.99
8g	64.74	4.48	4.44	6.03
	65.00	4.51	4.68	6.10
8h	61.53	4.26	4.22	10.69
	61.46	4.30	4.18	10.73
8i	61.53	4.26	4.22	10.69
	61.70	4.33	4.41	10.66
8j	67.06	4.38	8.69	
	67.07	4.24	8.72	
8k	67.06	4.38	8.69	
	66.91	4.30	8.71	
8l	67.06	4.38	8.69	
	67.10	4.40	8.71	
8m	66.03	5.24	4.28	
	65.85	5.12	4.31	
8n	66.03	5.24	4.28	
	65.90	5.21	4.28	
8o	66.84	5.61	4.10	
	66.76	5.93	3.98	
8p	70.13	5.89	4.31	
	70.03	5.92	4.54	
8q	64.95	4.17	4.46	6.05
	65.00	4.12	4.51	6.10
8r	64.95	4.17	4.46	6.05
	65.01	4.13	4.52	5.99
8s	64.95	4.17	4.46	6.05
	64.87	4.20	4.57	6.07
8t	64.95	4.17	4.46	6.05

	65.01	4.22	4.40		6.16
8u	64.95	4.17	4.46		6.05
	64.88	4.18	4.50		6.03
8v	64.95	4.17	4.46		6.05
	65.11	4.17	4.44		6.12
8w	61.72	3.96	4.24	10.73	
	61.54	3.98	4.22	10.70	
8x	61.72	3.96	4.24	10.73	
	61.70	4.04	4.23	10.75	
8y	61.72	3.96	4.24	10.73	
	61.54	3.99	4.32	10.77	