Supporting Information

Discovery of the first Thumb Pocket 1 NS5B
polymerase inhibitor (BILB 1941) with demonstrated
antiviral activity in patients chronically infected with
genotype 1 hepatitis C virus (HCV).

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¹H NMR spectra for all inhibitors: S10-S119

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
A1										
A2										
A3										
A4										
A5										
A6										
A7										
A8										
A9										
A10										
A11										
A12										
A13	0.017	0.047	7.6	167	61	0.25*	0.08	Y	99	592.4 (H+)
A14	0.023	0.062	2.2	136	45	0.3	0.23	Y	96	606.3 (H+)
A15	0.017	0.091		111				Y	98.9	606.3 (H+)
A16										
A17										
A18										
A19										
A20	0.019	0.02	2.9	>300		0.09*	0.03	Y	94	607.3 (H+)
A21										
A22	0.03	0.067	0.9	200		0.1	0.08	Y	96.3	606.3 (H+)
A23										
A24										
A25	0.011	0.06	10.4	>300		0.57*	0.17	Y	94.5	593.3 (H+)
A26										
A27										
A28										

* Single compound rat PK: Cmax at 10 mpk p.o.

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
B1										
B2	0.056	0.093		182		0	0	Y	98.5	611.3 (H+)
B3										
B4	0.011	0.17						Y	95.1	612.3 (H+)
B5										
B6										
B7										
B8										
B9										
B10										
B11										
B12										
B13	0.011	0.13	0.2	>300				Y	100	606.3 (H+)
B14	0.016	0.14	0	274		0	0	Y	95	620.4 (H+)
B15	0.014	0.075	0.3	67		0	0	Y	98	620.4 (H+)
B16	0.037	0.17						Y	97.8	640.3 (H+)
B17										
B18										
B19										
B20	0.012	0.11	0.1	>300				Y	97.9	621.4 (H+)
B21										
B22	0.032	0.18						Y	96.4	620.4 (H+)
B23										
B24										
B25	0.005	0.53						Y	98.8	607.3 (H+)
B26										
B27										
B28										

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
C1	0.034	0.068	6	124		0.61*	0.18	Y	98	540.2 (H+)
C2	0.14	0.11	2.6	>300	22	0.1	0.08	Y	98.8	554.3 (H+)
C3	0.012	0.15						Y	98.8	541.3 (H+)
C4	0.05	0.13	1.9	62	24	0	0	Y	93.1	557.2 (H+)
C5	0.021	0.17	7	196	31	0.5	0.38	Y	93.9	557.3 (H+)
C6	0.031	0.041	6.1	51		0.4	0.3	Y	98.3	571.2 (H+)
C7	0.032	0.12	2.8	147	52			Y	97.3	572.3 (H+)
C8	0.043	0.079	1.1	>300	68	0.5	0.38	Y	93.7	614.3 (H+)
C9	0.056	0.12	3	45	34	0.7	0.53	Y	97.8	586.3 (H+)
C10	0.068	0.033	2.8	19		0.2	0.15	Y	96.9	600.2 (H+)
C11	0.54	0.27		>300	80			Y	90.4	633.3 (H+)
C12	0.53	0.088		>300	>300	0	0	Y	97.4	582.3 (-H)
C13	0.06	0.067	6.5	208	83	6.37*	1.91	Y	95	551.3 (H+)
C14	0.065	0.085	9.7	33	26	0.7**	0.7	Y	98.9	565.3 (H+)
C15	0.051	0.066	6.9	37	23	1.1	0.83	Y	98.1	565.3 (H+)
C16	0.071	0.067	1.8	236		1.7	1.28	Y	97	585.2 (H+)
C17										
C18	0.32	0.2	6.8	>300	120	0.1	0.08	Y	100	619.3 (H+)
C19										
C20	0.023	0.052	1.7	141	43	0.5**	0.5	Y	99	566.2 (H+)
C21	0.13	0.048	27.7	70	33	0	0	Y	100	581.3 (H+)
C22	0.12	0.12	3.8	79	45	0.1**	0.1	Y	98.7	565.3 (H+)
C23	0.16	0.057	2.3	211	51	0**	0	Y	99.1	581.3 (H+)
C24	0.044	0.058	2.2	>300	71	0.1	0.08	Y	100	551.2 (H+)
C25	0.014	0.11	2.2	173	98	0	0	Y	99.2	552.3 (H+)
C26										
C27	0.59	0.18	1.1	135	55	0.2**	0.2	Y	95.1	601.3 (H+)
C28	0.15	0.12	1.1	187	34	0.6	0.45	Y	97.1	601.3 (H+)

* Single compound rat PK: Cmax at 10 mpk p.o.

** 3 mg/kg p.o. cassette

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
D1	0.069	0.067	7.5	162		0.6	0.45	Y	98	552.2 (H+)
D2	0.17	0.094		>300	31	0.7	0.53	Y	98.8	568.3 (H+)
D3	0.059	0.17						Y	98.6	553.3 (H+)
D4										
D5	0.06	0.14						Y	95.3	569.2 (H+)
D6	0.072	0.11	3.6	40				Y	95.6	583.3 (H+)
D7	0.097	0.15	1.3			0.4	0.3	Y	93	584.3 (H+)
D8	0.083	0.06	0.8	>300		0.2	0.15	Y	98.3	626.2 (H+)
D9	0.16	0.14						Y	97.3	598.3 (H+)
D10										
D11										
D12	0.69	0.089		>300	>300	2.3	1.73	Y	96	596.3 (H+)
D13	0.06	0.084	11.2	85	31	3.2	2.4	Y	99	563.3 (H+)
D14	0.084	0.062	6.9	53	24	6.7**	6.7	Y	100	577.3 (H+)
D15	0.051	0.1	7.4	59		1.2	0.9	Y	98.6	577.3 (H+)
D16	0.092	0.083		>300	>300	2.8	2.1	Y	99	597.2 (H+)
D17	0.039	0.076	10.1	167		2.9	2.18	Y	97	581.3 (H+)
D18	0.28	0.22	1.3	187	>300	0.9	0.68	Y	97.8	631.3 (H+)
D19	0.063	0.076	8.6	28				Y	98	593.4 (H+)
D20	0.073	0.048	1.8	>300	62	1.8**	1.8	Y	99	578.2 (H+)
D21	0.12	0.049	0	>300	39	0	0	Y	99	593.3 (H+)
D22	0.19	0.12	3.4	73	24	3.7**	3.7	Y	99.4	577.3 (H+)
D23	0.2	0.082	1.5	95	61	0.9**	0.9	Y	98.8	593.3 (H+)
D24	0.13	0.067	2.9	112	69	2.1	1.58	Y	99.6	563.3 (H+)
D25	0.049	0.094	10	96	56	6.7	5.03	Y	96.1	564.3 (H+)
D26	0.049	0.21						Y	99	564.3 (H+)
D27	0.75	0.13		>300	44	0.9**	0.9	Y	98.4	613.3 (H+)
D28	0.22	0.078	0.2	>300	32	1	0.75	Y	95.6	613.3 (H+)

** 3 mg/kg p.o. cassette

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
E1	0.12	0.073	0	>300	250	0.8	0.6	Y	99	566.2 (H+)
E2	0.15	0.13						Y	95.1	582.3 (H+)
E3	0.044	0.15	4	123		0.2	0.15	Y	98.5	567.3 (H+)
E4	0.13	0.14						Y	96.6	583.3 (H+)
E5	0.15	0.17						Y	96.1	583.3 (H+)
E6	0.071	0.096	2.3	36				Y	98.1	597.3 (H+)
E7	0.12	0.079	1	106		0.3	0.23	Y	84	598.3 (H+)
E8	0.21	0.08	0.8	>300		0.5	0.38	Y	97.1	640.3 (H+)
E9	0.24	0.08	0.4	41				Y	97.2	612.3 (H+)
E10										
E11										
E12	0.59	0.067		>300	251	0.7	0.53	Y	95.5	610.3 (H+)
E13	0.045	0.084	12.6	96	19	1.9**	1.9	Y	99	577.2 (H+)
E14	0.09	0.1	2.7	30				Y	98.3	591.4 (H+)
E15	0.056	0.1	5.8	31				Y	99.1	591.4 (H+)
E16	0.098	0.085		>300		2.3	1.73	Y	99	611.2 (H+)
E17										
E18	0.4	0.22		>300	>300	0.3	0.23	Y	98.3	645.3 (H+)
E19										
E20	0.13	0.056	0.7	>300	89	0.9**	0.9	Y	99	592.3 (H+)
E21	0.17	0.065	0	>300	52	0	0	Y	98.7	607.3 (H+)
E22	0.11	0.12	1	64		1.6	1.2	Y	98.5	591.3 (H+)
E23										
E24	0.066	0.071	0.8	107		1.6	1.2	Y	99.2	577.3 (H+)
E25	0.039	0.16						Y	98.3	578.3 (H+)
E26										
E27										
E28										

** 3 mg/kg p.o. cassette

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
F1										
F2										
F3										
F4	0.084	0.19	0.4	56	76	0.1	0.08	Y	100	584.2 (H+)
F5										
F6										
F7										
F8										
F9										
F10										
F11										
F12	0.85	0.13		25	134	0	0	Y	95.8	609.3 (-H)
F13	0.041	0.17	0.35	79		0.2	0.15	Y	100	578.2 (H+)
F14	0.064	0.13	0.1	17	90	0	0	Y	100	592.3 (H+)
F15										
F16										
F17										
F18										
F19										
F20										
F21										
F22	0.19	0.3	0.2	8	44	0.1	0.08	Y	97.8	592.3 (H+)
F23	0.27	0.1		7	40	0	0	Y	96.7	608.3 (H+)
F24	0.052	0.13	0.3			0	0	Y	100	578.2 (H+)
F25										
F26										
F27	1.02	0.55	0	102	79	0.8**	0.8	Y	97.1	628.3 (H+)
F28	0.17	0.11	0.1	139	68	0.2	0.15	Y	98.6	628.3 (H+)

** 3 mg/kg p.o. cassette

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
G1										
G2	0.2	0.11		63		0	0	Y	98.5	593.3 (H+)
G3										
G4	0.11	0.15						Y	98.1	596.2 (H+)
G5										
G6										
G7										
G8										
G9										
G10										
G11										
G12										
G13	0.061	0.17						Y	97.5	590.3 (H+)
G14	0.1	0.15						Y	98.9	604.3 (H+)
G15	0.12	0.092	0.8	25				Y	99.4	604.4 (H+)
G16										
G17										
G18										
G19										
G20	0.061	0.095	0.4	62				Y	98.3	605.3 (H+)
G21										
G22	0.15	0.13						Y	98.2	604.3 (H+)
G23										
G24										
G25	0.04	0.12	0	41				Y	99.3	613.3 (Na+)
G26										
G27										
G28										

	IC50 (μM)	EC50 (μM)	Caco-2 x10-6 cm/sec	HLM T1/2 (min)	RLM T1/2 (min)	[Plasma] C1h (μM)	[Plasma] C1h normalized to 3 mpk	NMR	HPLC (%)	MS m/z
H1										
H2	0.14	0.17		204				Y	98.7	582.3 (H+)
H3										
H4	0.2	0.29						Y	94.2	583.5 (H+)
H5										
H6										
H7										
H8										
H9										
H10										
H11										
H12										
H13	0.076	0.26						Y	97.8	577.3 (H+)
H14	0.1	0.18						Y	98.5	591.4 (H+)
H15	0.13	0.16						Y	99.4	591.3 (H+)
H16										
H17										
H18										
H19										
H20	0.11	0.11	2.5	65				Y	98.8	592.3 (H+)
H21										
H22	0.17	0.18						Y	99.3	591.4 (H+)
H23										
H24										
H25	0.053	0.29						Y	98.7	578.3 (H+)
H26										
H27										
H28										

Frequency (MHz) 400.13
Solvent DMSO-d6

Beaulieu_et_al. cpd A14

Frequency (MHz) 400.13
Solvent DMSO-d6

Frequency (MHz) 400.13
Solvent DMSO-d6

Beaulieu_et_al. cpd A20

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd A22

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd A25

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B2

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B4

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B13

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B14

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B15

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B16

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B20

Frequency (MHz) 400.13

Solvent DMSO-d6

S22

Beaulieu_et_al. cpd B22

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd B25

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C1

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C2

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C3

Frequency (MHz) 400.20
Solvent DMSO-d6

Frequency (MHz) 400.13
Solvent DMSO-d6

Beaulieu_et_al. cpd C5

Frequency (MHz) 400.30

Solvent DMSO-d6

Beaulieu_et_al. cpd C6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C7

Frequency (MHz) 400.20

Solvent DMSO-d6

Beaulieu_et_al. cpd C8

Frequency (MHz) 400.20

Solvent DMSO-d6

Frequency (MHz) 400.20

Solvent DMSO-d6

Beaulieu_et_al. cpd C10

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.30
Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13
Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C15

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C16

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C18

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C20

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C21

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13
Solvent DMSO-d6

S44

Beaulieu_et_al. cpd C23

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C24

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C25

Frequency (MHz) 400.13

Solvent DMSO-d6

547

Beaulieu_et_al. cpd C27

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd C28

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd D1

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd D2

Frequency (MHz) 400.13

Solvent DMSO-d6

SSI

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd D5

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd D6

Frequency (MHz) 400.30

Solvent DMSO-d6

554

Beaulieu_et_al. cpd D7

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.30
Solvent DMSO-d6

Frequency (MHz) 400.30
Solvent DMSO-d6

Beaulieu_et_al. cpd D12

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

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Frequency (MHz) 400.13
Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd D21

Frequency (MHz) 400.13

Solvent DMSO-d6

895

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13
Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd D26

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E1

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E3

Frequency (MHz) 400.20
Solvent DMSO-d6

Beaulieu_et_al. cpd E4

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E5

Frequency (MHz) 400.20

Solvent DMSO-d6

Beaulieu_et_al. cpd E6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E7

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E8

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E9

Frequency (MHz) 400.20

Solvent DMSO-d6

Beaulieu_et_al. cpd E12

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E14

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E15

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13
Solvent DMSO-d6

Beaulieu_et_al. cpd E18

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_all. cpd E24

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd E25

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd F4

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd F13

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd F14

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd F22

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd F23

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd F27

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd F28

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd G4

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd G14

Frequency (MHz) 400.13

Solvent DMSO-d6

4015

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd G20

Frequency (MHz) 400.13

Solvent DMSO-d6

6015

Beaulieu_et_al. cpd G22

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd G25

Frequency (MHz) 400.13

Solvent DMSO-d6

S111

Beaulieu_et_al. cpd H2

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd H4

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd H13

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6

Beaulieu_et_al. cpd H20

Frequency (MHz) 400.13

Solvent DMSO-d6

S117

Frequency (MHz) 400.13

Solvent DMSO-d6

Frequency (MHz) 400.13

Solvent DMSO-d6