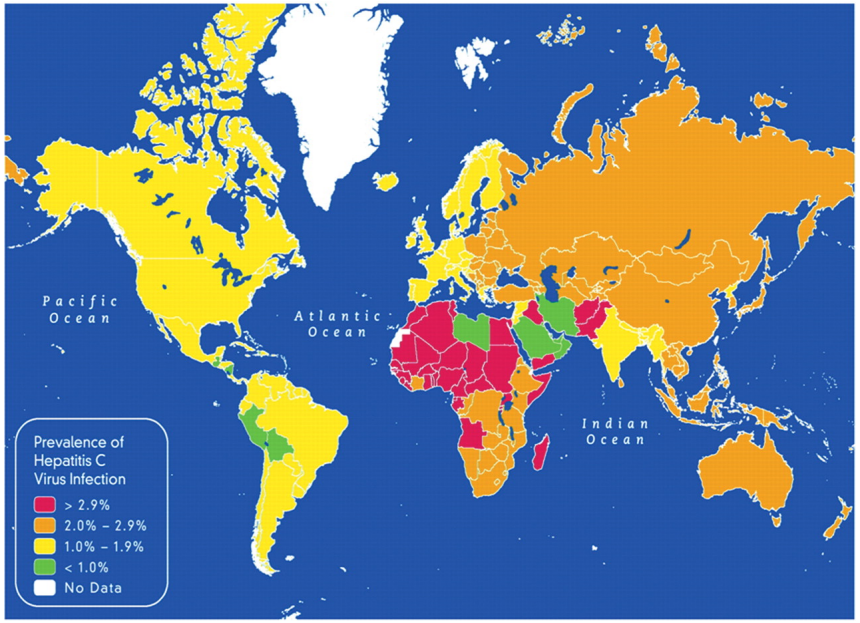
Discovery and Development of Small Molecule Hepatitis C Treatments

- 170 million Hepatitis C (HCV) cases worldwide
  - 60% of these are genotype 1
- 15-30% liver cirrhosis within 20 years
- Responsible for 500,000 deaths annually
- Modern small molecule treatments have ~90% cure rate.
- Bloodborn infection
- Major Targets: NS3, NS4A, NS5A

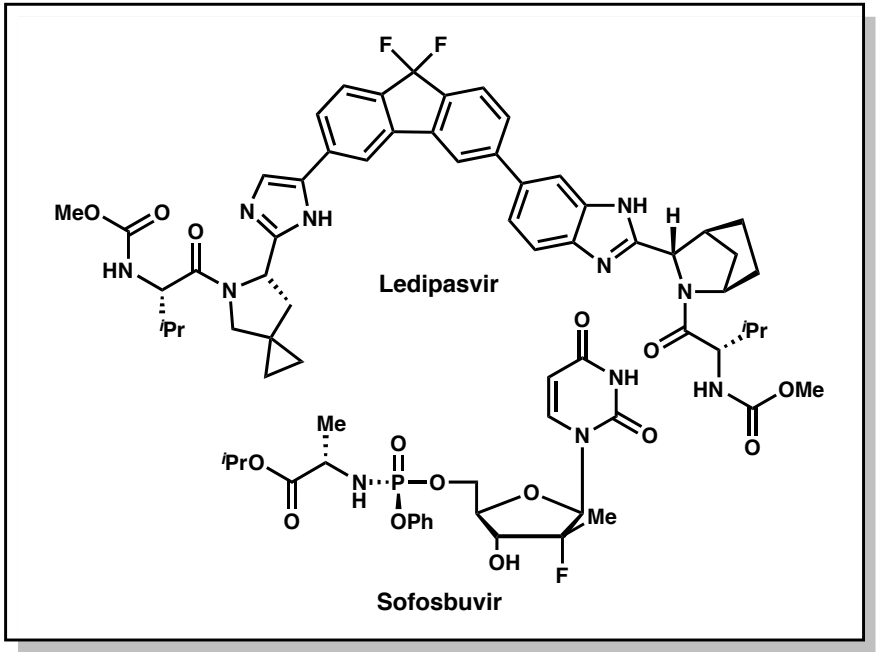


Pharma: the major players

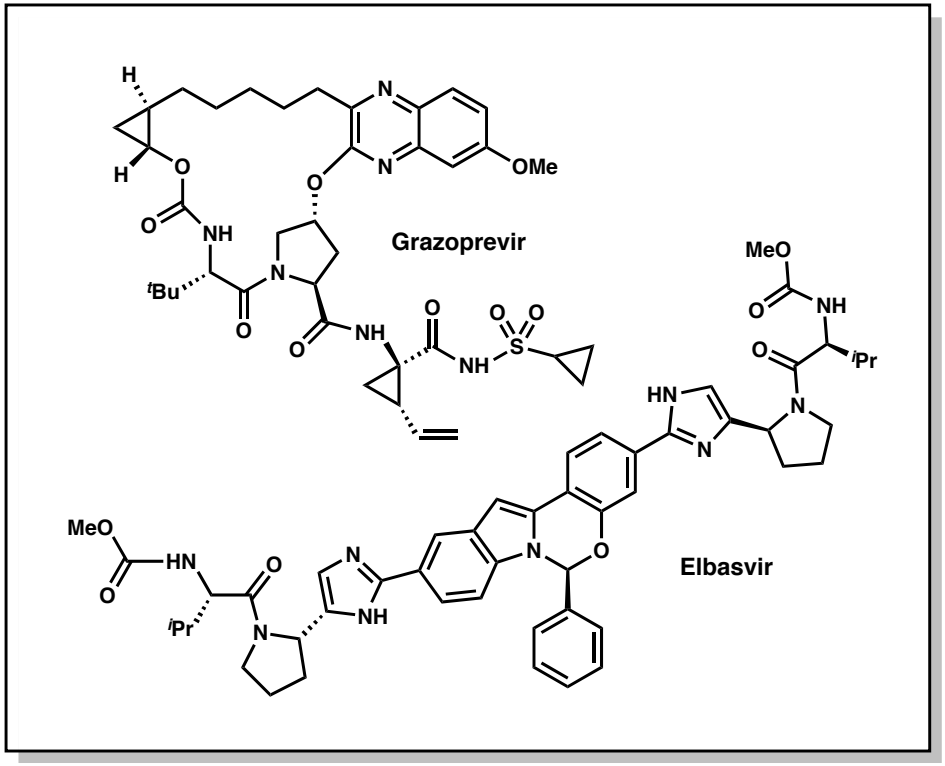
- **Simprevir, Johnson and Johnson (2013)** genotype 1
- Sofosbuvir, Gilead (+Merck patent dispute) (2013) genotype 1,2
- **Harvoni, Gilead (2014)** genotype 1,4,5,6
- Viekira Pak, AbbVie (2014) genotype 1
- Technivie, AbbVie (2015) genotype 4
- Daclatasvir, BMS (2015) genotype 3
- **Zepatier, Merck (2016**) genotype 1,4

amfar.org
hcvadvocate.org

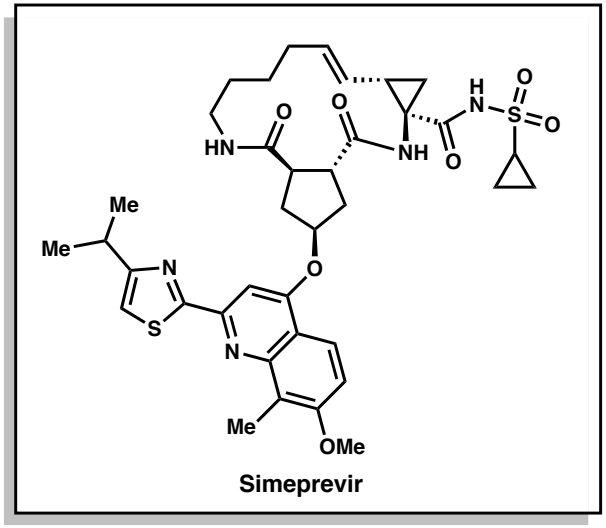
The Molecules



Harvoni, Gilead

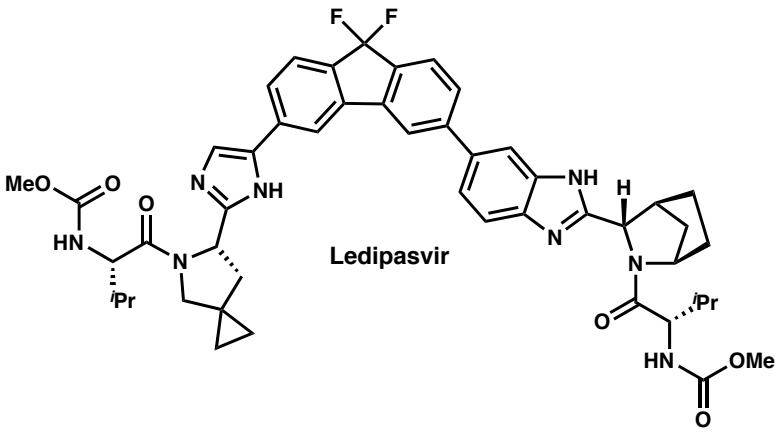


Zepatir, Merck



Olysio, Janssen Pharmeceutica

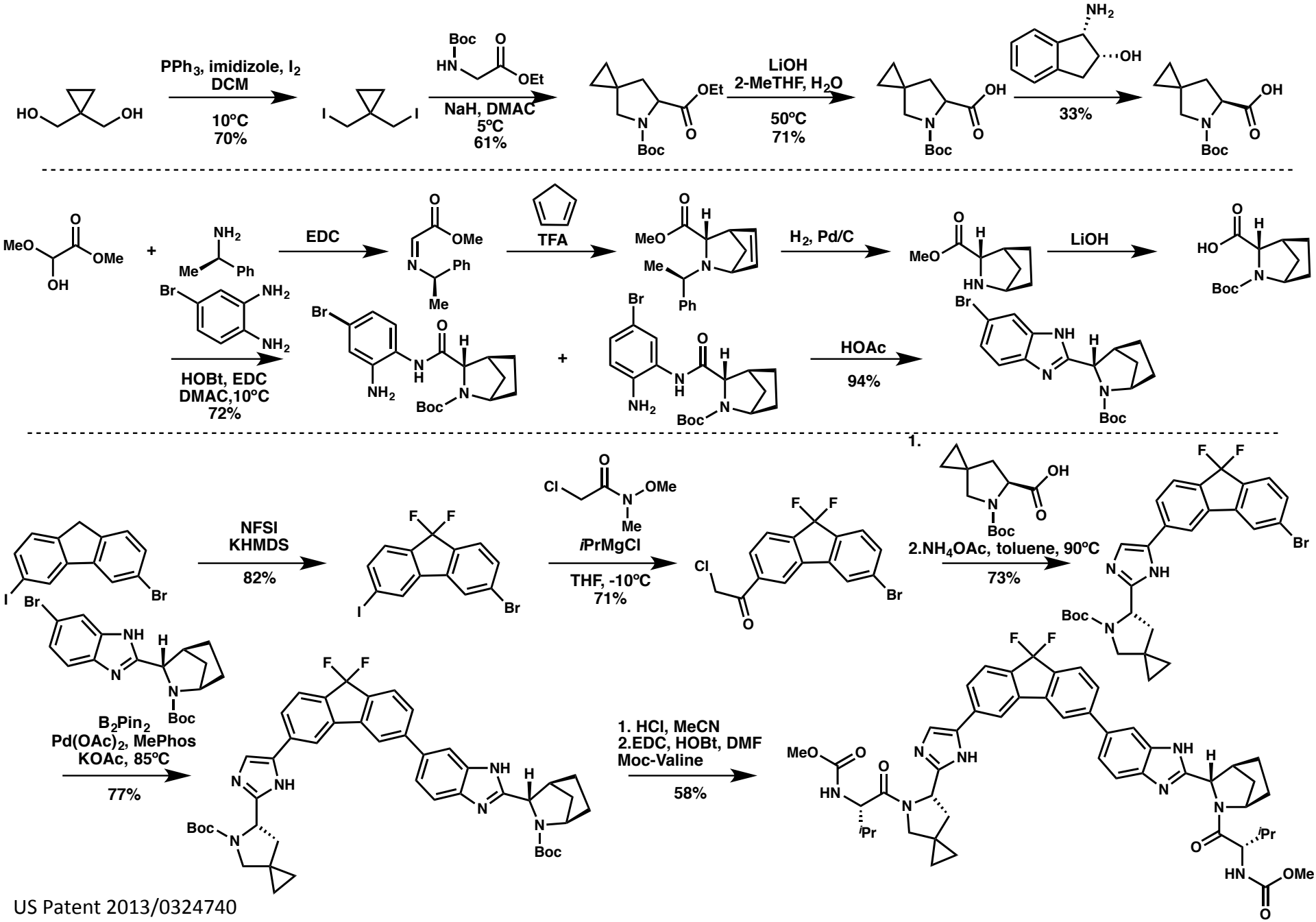
GILEAD



Ledipasvir

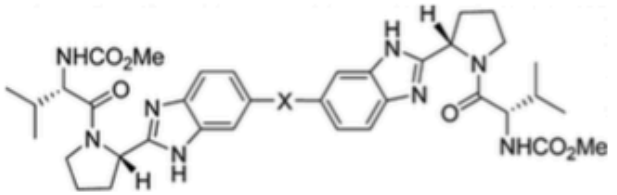
- Combination treatment with sofosbuvir (NS5B inhibitor)
- Approved 2014
- Average cost of course of treatment: $84,000
- Cost per pill: $1,125
- NS5A inhibitor
- 94-99% cure rate for genotype 1 HCV

Ledipasvir: Medicinal Chemistry Route



US Patent 2013/0324740

Table 1. In Vitro Activity[a]



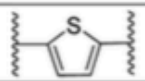
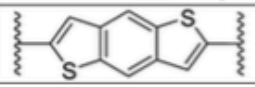
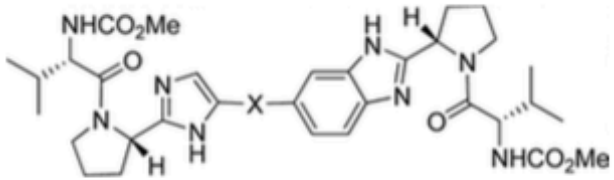
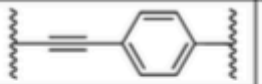
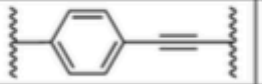
compd	X	EC_{50} (1a, nM)[b]	EC_{50} (1b, nM)
16	bond	> 44[c]	35
17		> 44[c]	0.14
18		11	0.026
19		1.7	0.01
22		0.50	0.009
23		3.7	0.044
20		0.11	0.004
21		0.20	0.016

Table 2. In Vitro Activity[a]



compd	X	EC_{50} (1a, nM)[b]	EC_{50} (1b, nM)
24		> 44[c]	0.30
25		0.071	0.007
26		2.5	0.016
27		0.38	0.011
28		0.20	0.003
29		0.17	0.007

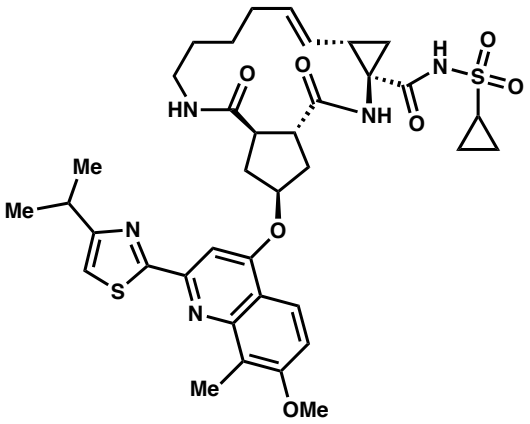
species	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (hr)	MRT (hr)[b]	%F
rat	0.43 ± 0.04	2.66 ± 0.13	4.67 ± 0.56	6.19 ± 0.28	32.5 ± 6.7
dog	0.13 ± 0.02	1.19 ± 0.13	7.41 ± 0.80	9.20 ± 1.35	53.0 ± 12.4
cyno	0.17 ± 0.00	2.15 ± 0.42	10.3 ± 1.2	12.9 ± 2.1	41.1 ± 3.6

[a]All parameters except for %F are from IV dosing. See the Experimental Section for detailed assay protocols. Intravenous doses were 1.0, 0.2, and 0.5 mg/kg of body weight in the rat, dog and monkey, respectively. Oral doses were 2, 0.5, and 1.0 mg/kg in the rat, dog and monkey, respectively. [b]Mean residence time.

J. Med. Chem. **2014**, *57,* 2033-2046.

Simprevir

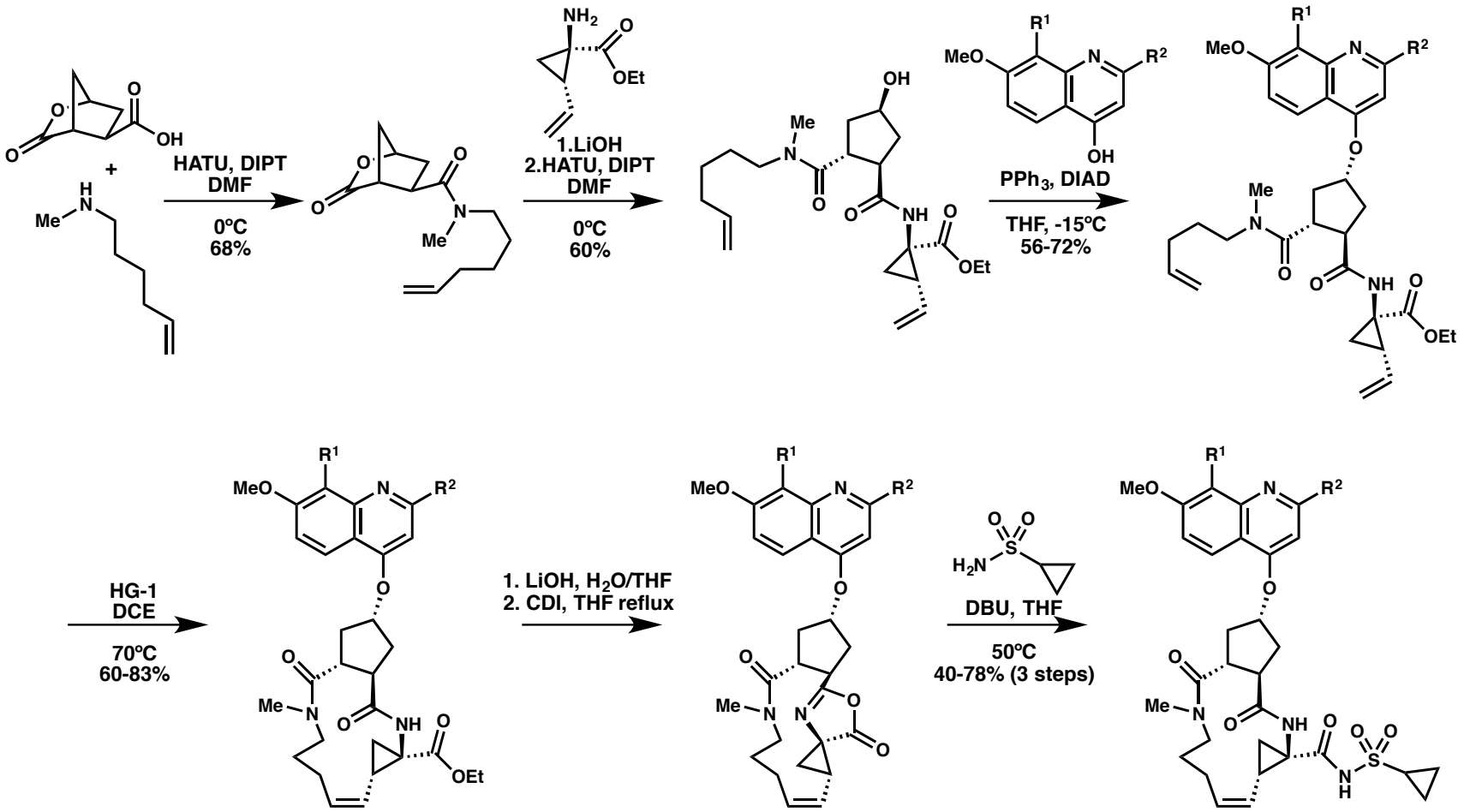
janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson



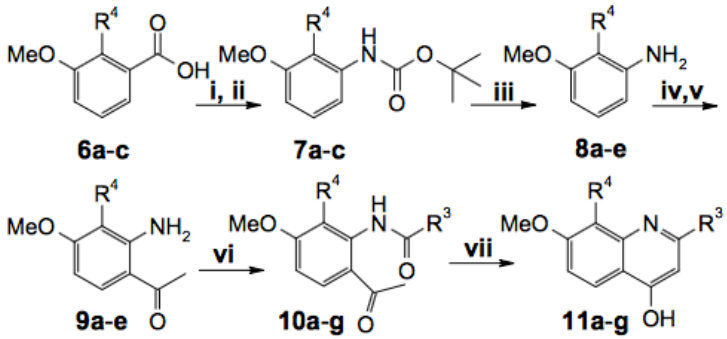
Simeprevir

- Combination treatment with sofosbuvir
- Approved 2014
- Average cost of course of treatment: $66,360
- Cost per pill: $790
- NS3/4A inhibitor
- 90% cure rate for genotype 1 HCV

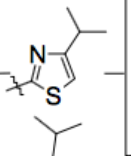
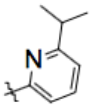
Simprevir: Medicinal Chemistry Route



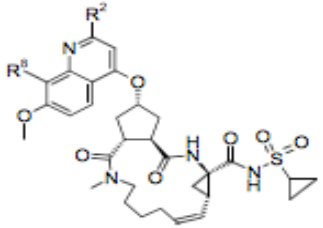
Bioorg. Med. Chem. Lett. **2008,** *18, 4853.*

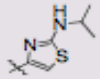
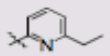


Cpd#	R^4:
6a-9a:	Me
6b-9b:	F
6c-9c:	Cl
8d, 9d:	H
8e, 9e	Et

Cpd#	R^3:	R^4:
10a, 11a		H
10b, 11b		H
10c, 11c		Me
10d, 11d		Et
10e, 11e		F
10f, 11f		Cl
10g, 11g		H

Scheme 1. Reactions and conditions: (i) TEA, diphenylphosphorylazide (dppa), toluene, 100 °C; (ii) *tert*-BuOH, toluene, 100 °C; (iii) TFA, CH_2Cl_2, 20 °C; (iv) BCl_3, xylene, 0 °C; (v) CH_3CN, $AlCl_3$, CH_2Cl_2, 0–70 °C; (vi) R^3COCl, dioxane, rt; (vii) *tert*-BuOK, *tert*-BuOH, 100 °C.

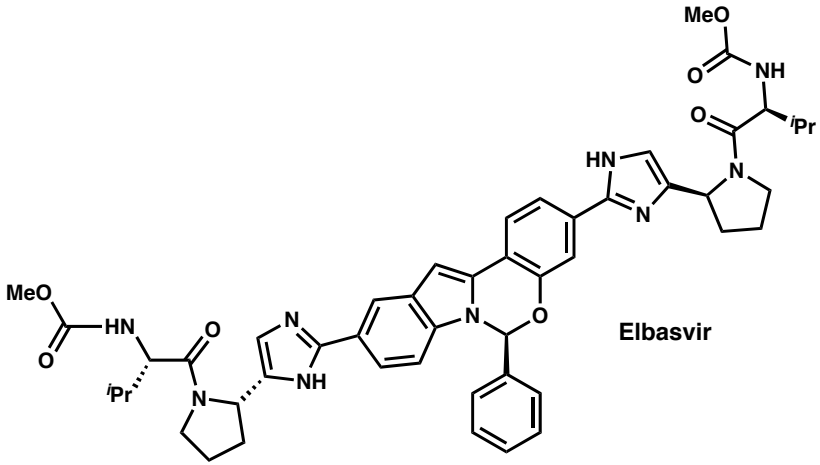


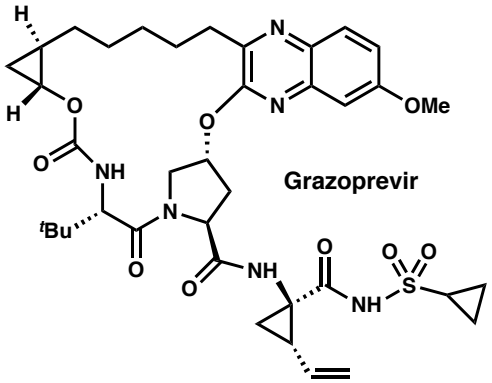
Compound	R^2	R^8	NS3/4A K_i[a] (nM)	HUH7-Rep EC_{50}[b] (nM)	Cl_{int}[c] (μL/min/mg)	P_{app} A–B[d] (cm/s x 10^{-6})
5		H	0.41	9	46	3.8
37		H	1.4	17	15	1.4
32a		H	0.20	11	38	1.6
32b		H	0.84	17	16	13
32c		Me	0.36	7.8	<6	8.4
32d		Et	3.1	66	–	–
32e		F	0.55	57	–	–
32f		Cl	0.10	2.9	9.0	5.8
32g		Me	0.16	9.7	<6	15
32h		Me	0.30	6.8	<6	12

[a] Inhibition of the full-length HCV NS3/4A protease[20] measured by the inhibition constants (K_i values).[23]
[b] Inhibition of HCV replication in Huh-7-Rep cells (luciferase assay) for macrocyclic inhibitors **32a–h** and **37** measured by 50% effective concentration (EC_{50}).[22]
[c] Intrinsic clearance in human liver microsomes (HLM).
[d] A–B apparent permeability coefficient (P_{app}) measured in Caco-2 cells.

Bioorg. Med. Chem. Lett. **2008,** *18, 4853.*

MERCK





- Approved January 2016
- Average cost of course of treatment: $54,600
- Cost per pill: $650
- NS3/4A inhibitor (grazoprevir), NS5A (elbasvir)
- 92-97% cure rate for genotype 1 and 4 HCV

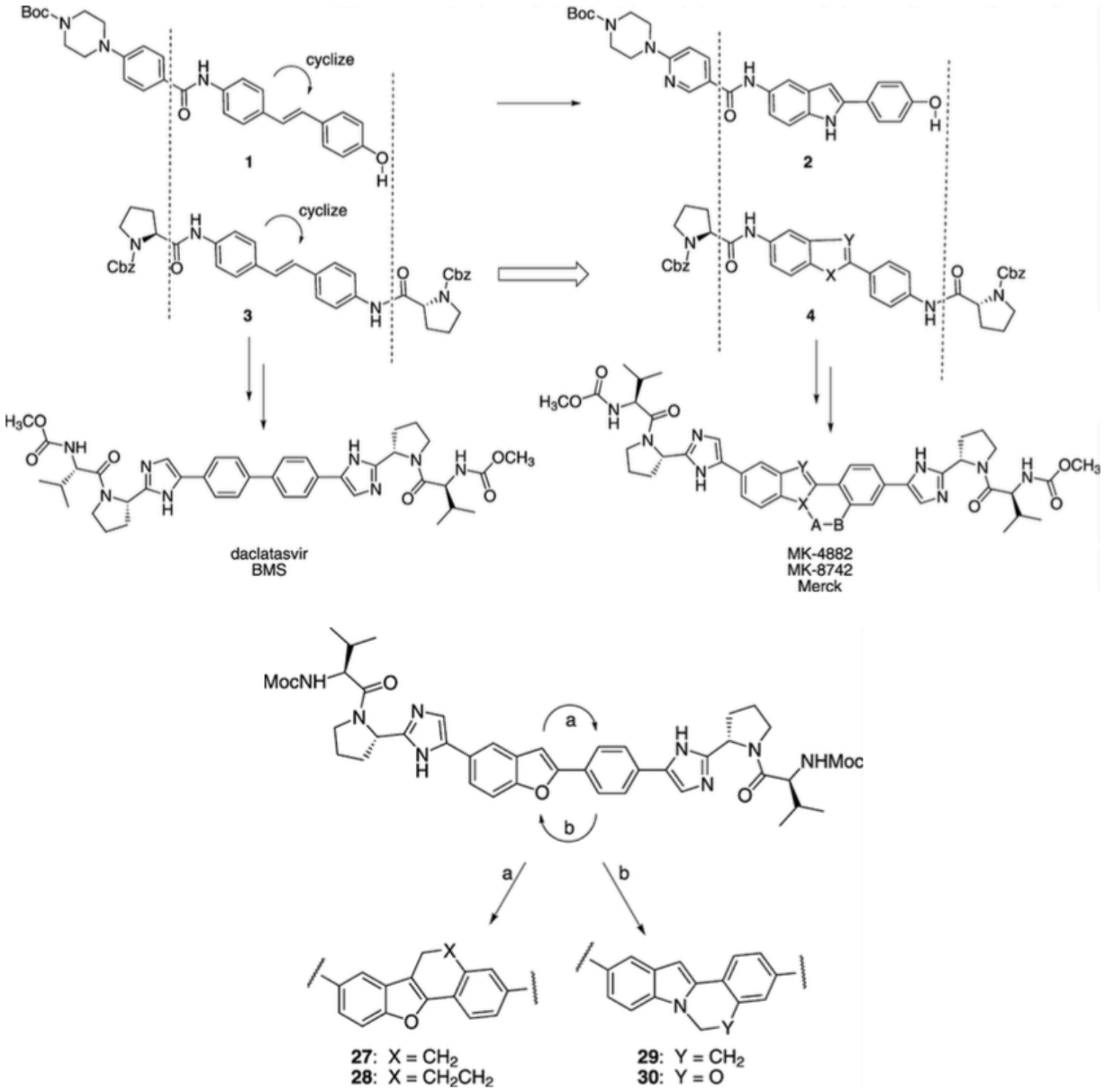
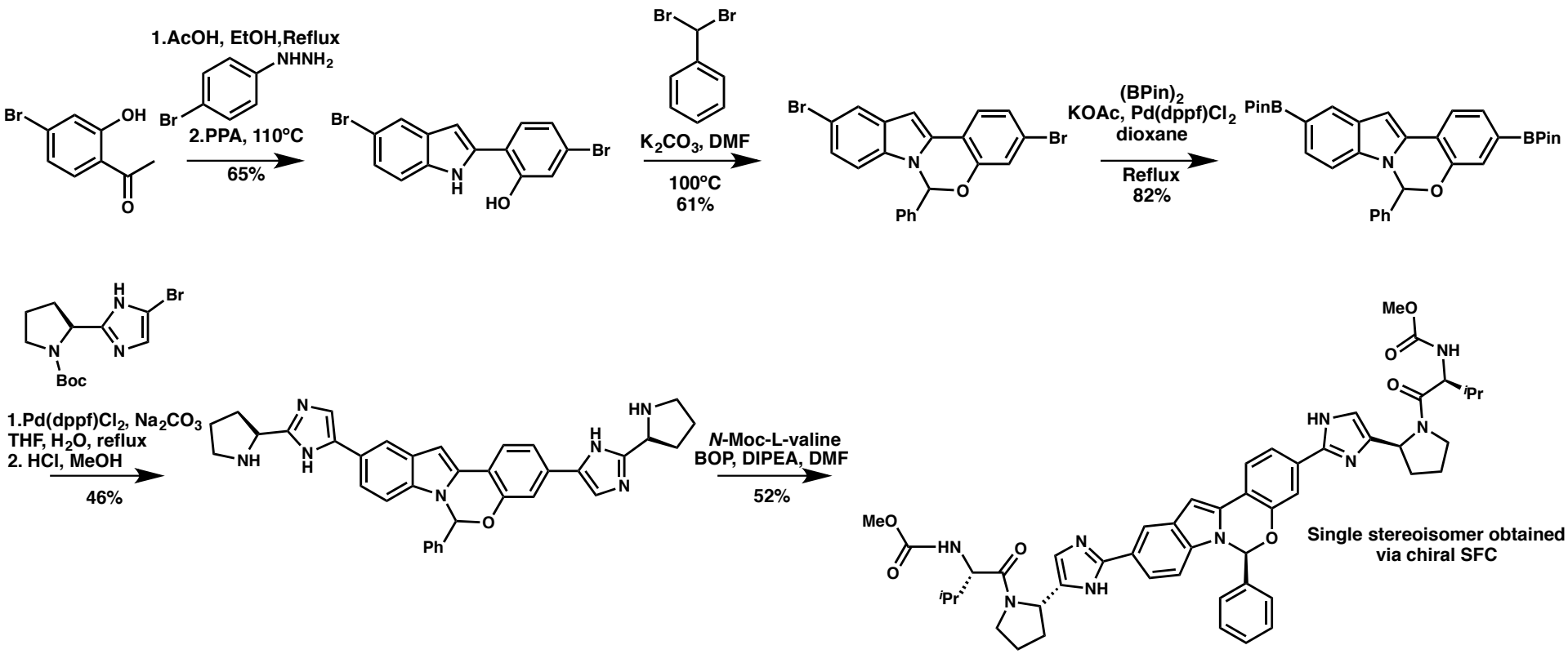


Figure 4. Design strategy for second-generation NS5A inhibitors.

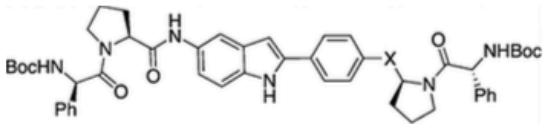
ChemMedChem, **2013**, *8*, 1930.

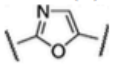
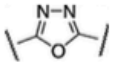
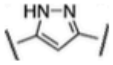
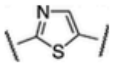
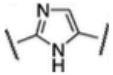
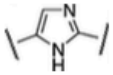
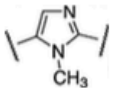
Elbasvir: Medicinal Chemistry Route



ChemMedChem, **2013**, *8*, 1930.

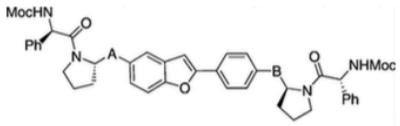
Table 2. Amide isosteres.



Compd	X	Genotype, EC_{50} [nM][a] 1b	2a	1a
8	–NHC(O)–	0.004	0.05	70
9		0.44	500	>266
10		0.09	86	>266
11		0.016	1.3	47
12		0.2	26	>266
13		0.01	0.07	3
14		0.01	0.015	0.17
15		0.06	>266	150

[a] $n=3$

Table 3. Imidazole SAR.



Compd	Substituent[a] A	B	Genotype, EC_{50} [nM][b] 1b	2a	1a	C_{max} [μM][c]
16	–(O)CHN–	–NHC(O)–	0.01	0.01	27	0.03
17	imidazole	–NHC(O)–	0.002	0.004	2	0.01
18	–(O)CHN–	imidazole	0.006	0.002	0.3	0.03
19	imidazole	imidazole	0.004	0.004	0.015	0.02

[a] Imidazole = 2-prolyl-substituted imidazole. [b] $n \geq 3$. [c] Peak plasma concentration following 10 mg kg^{-1} p.o. dose in 10% Tween to fasted male Sprague–Dawley rats (average of $n=2$).

Table 9. MK-8742 in vitro potency profile GT1-4 and key GT1 mutants.

Genotype	$EC_{50} \pm SD$ [nM]	Genotype	$EC_{50} \pm SD$ [nM]
1a WT	0.004 ± 0.002	1b WT	0.003 ± 0.001
1a Q30H	0.03 ± 0.002	1b L28V	0.004 ± 0.001
1a Q30R	0.5 ± 0.5	1b R30Q	0.009 ± 0.003
1a L31F	0.08 ± 0.04	1b L31F	0.05 ± 0.02
1a L31V	0.5 ± 0.3	1b L31V	0.01 ± 0.01
1a Y93C	0.2 ± 0.07	1b Y93C	0.005 ± 0.001
1a Y93H	2.4 ± 1.3	1b Y93H	0.05 ± 0.03
2a WT	0.003 ± 0.001	2b (JFH)[b]	3.4 ± 2.6
3a (con1)[b]	0.03 ± 0.01	4a (con1)[b]	0.003 ± 0.001

[a] SD is calculated from $n>3$ independent experiments. [b] Chimeric replicons with indicated NS5A genotype cloned into GT1b (con1) or GT2a (JFH) background; see ref. [12] for assay details.

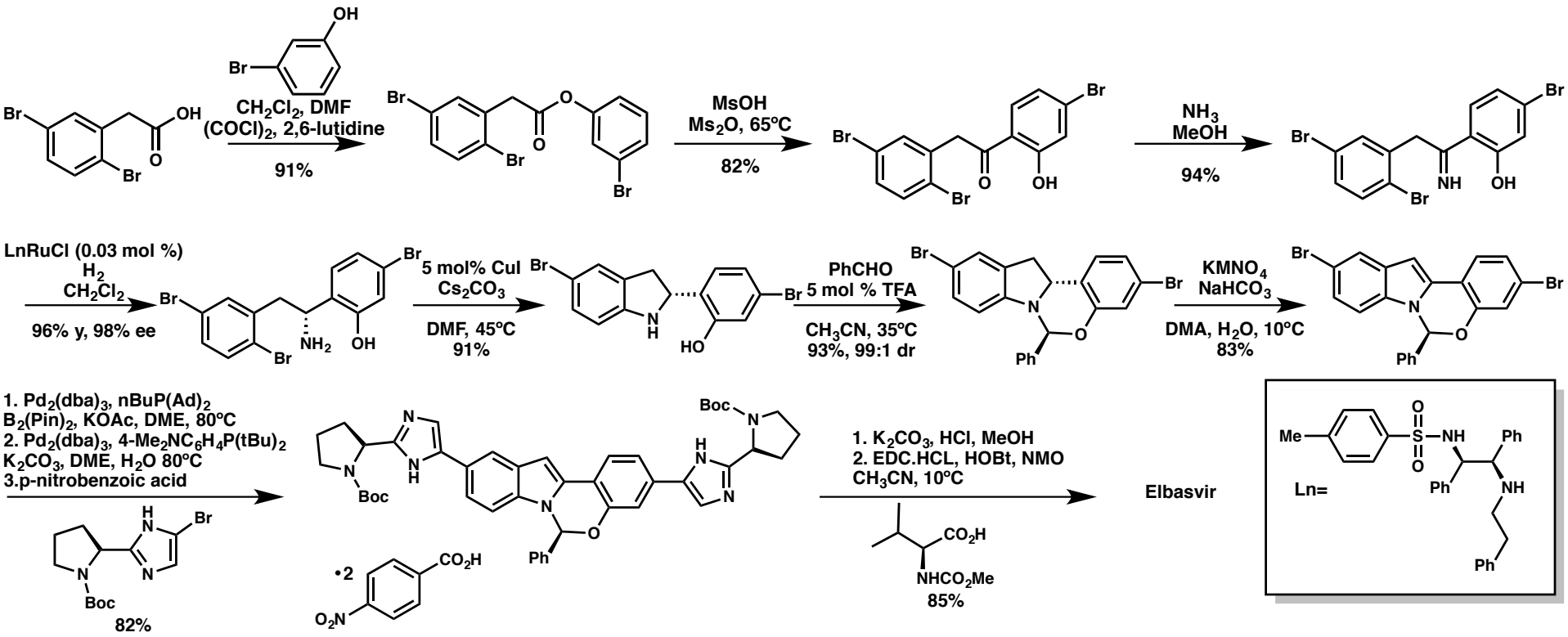
Table 10. Preclinical pharmacokinetics of MK-8742.

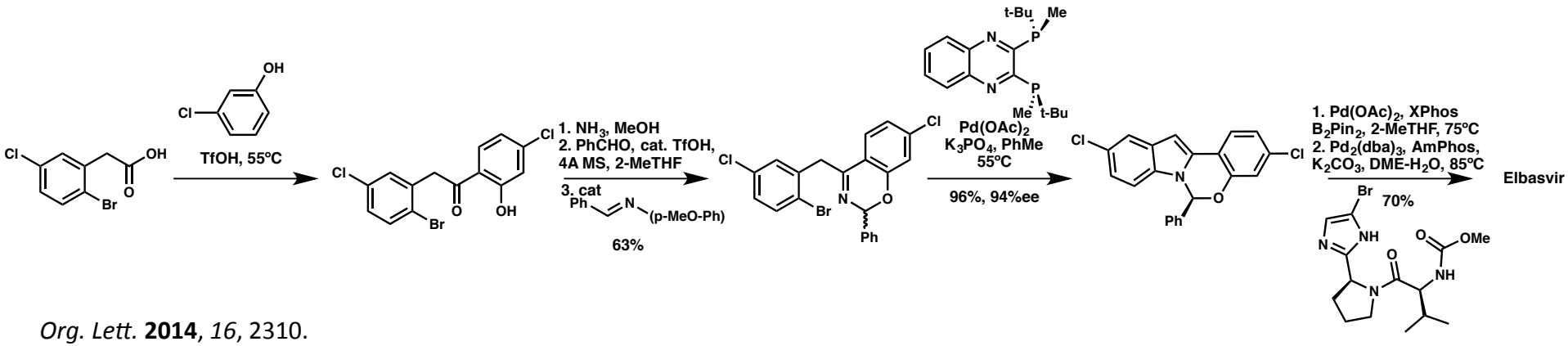
Species	Cl [mL min^{-1} kg^{-1}]	$t_{1/2}$ [h]	p.o. C_{max} [μM]	p.o. AUC [μM h^{-1}]	F [%]
rat[a]	24 ± 8.0	4.2 ± 1.0	0.36 ± 0.3	2.3 ± 1.0	~9
dog[b]	8.4 ± 2	7.7 ± 2.0	0.29 ± 0.02	1.7 ± 0.3	~35
monkey[b]	5.2 ± 0.3	16 ± 4.0	0.1 ± 0.04	1.2 ± 0.4	~17

[a] 5 mg kg^{-1} i.v. (3% DMA in 40% HPβCD; 30 mg kg^{-1} p.o. (0.4% HPMC in water). [b] 1 mg kg^{-1} i.v. (20% HPβCD; 2 mg kg^{-1} p.o. (10% T80/90% PEG400).

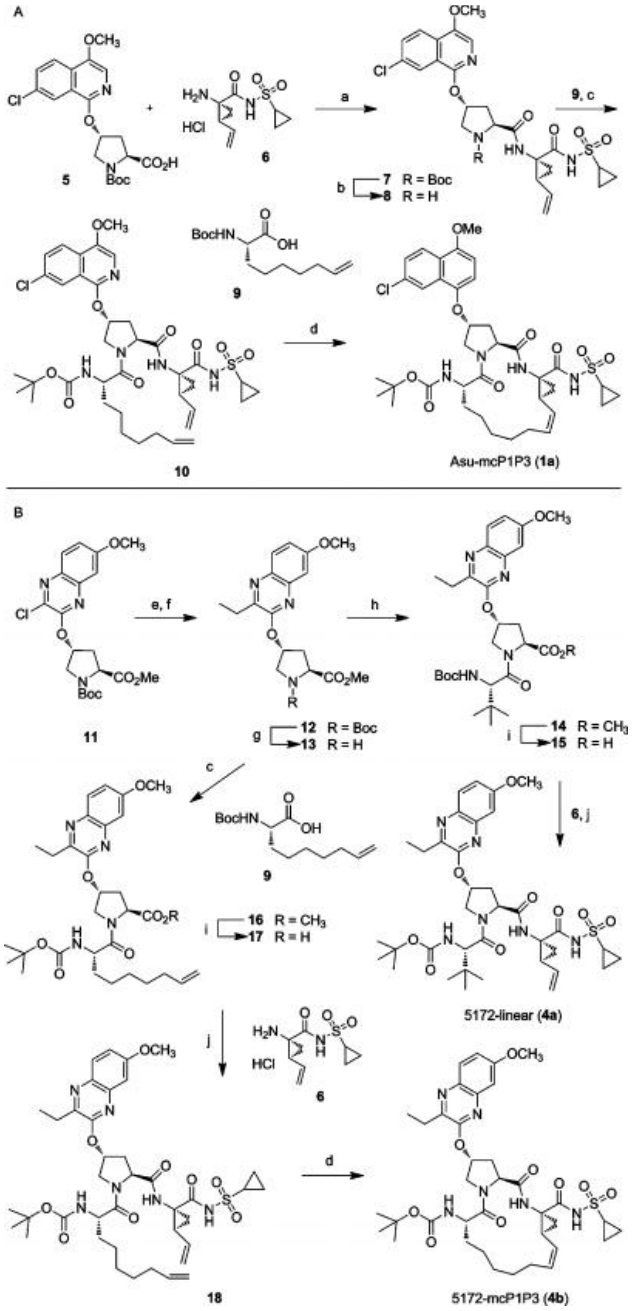
ChemMedChem, **2013**, *8*, 1930.

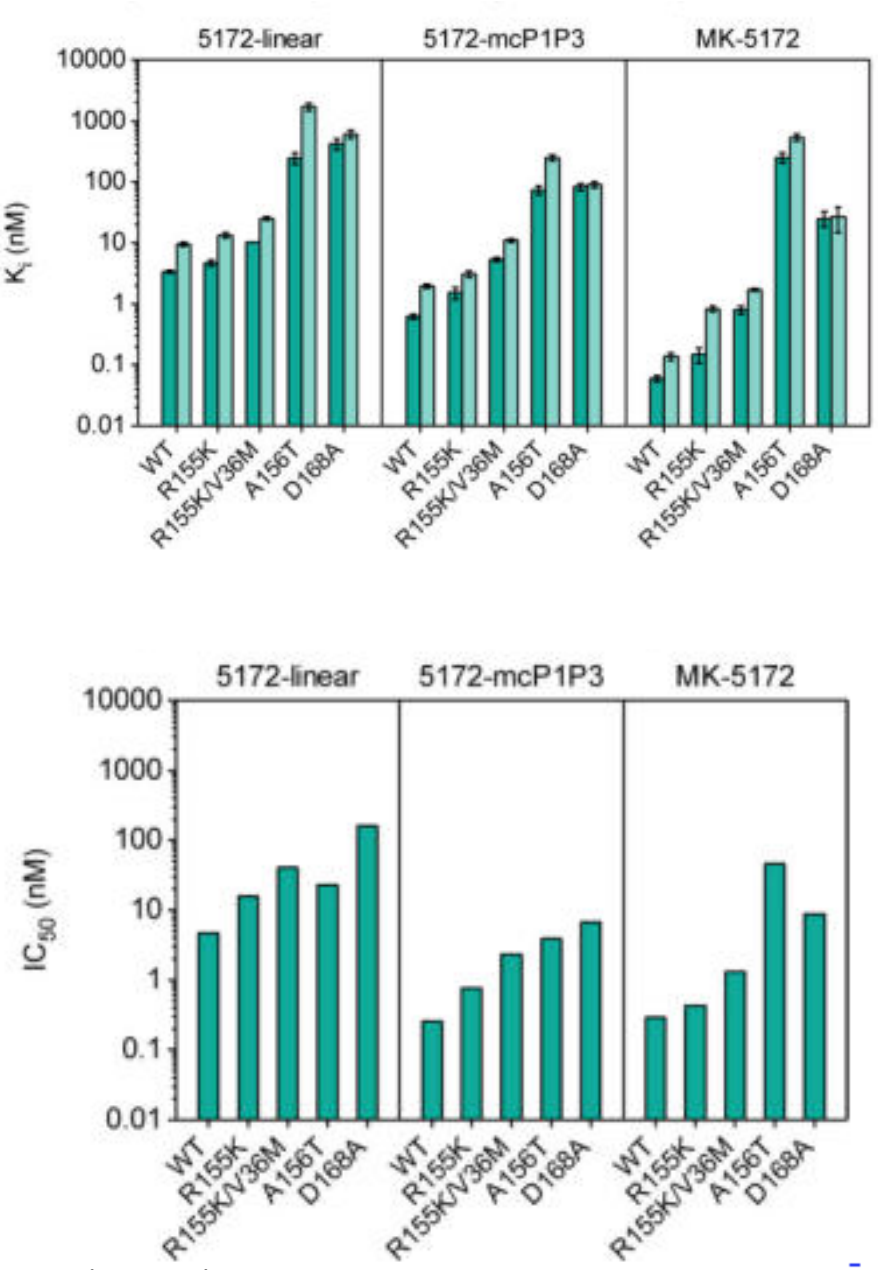
Elbasvir: Two Enatioselective Syntheses



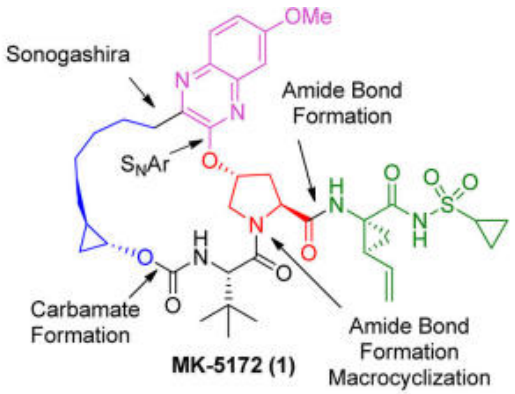


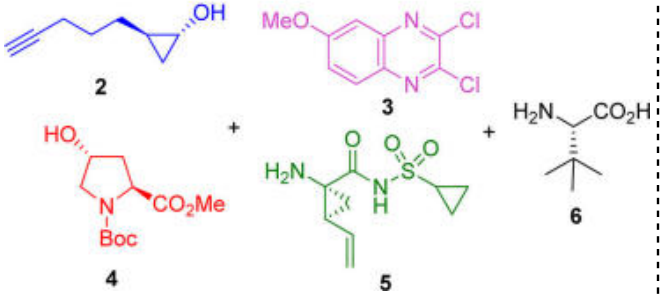
Org. Lett. **2014**, *16*, 2310.
J. Am. Chem. Soc., **2015,** 13728.

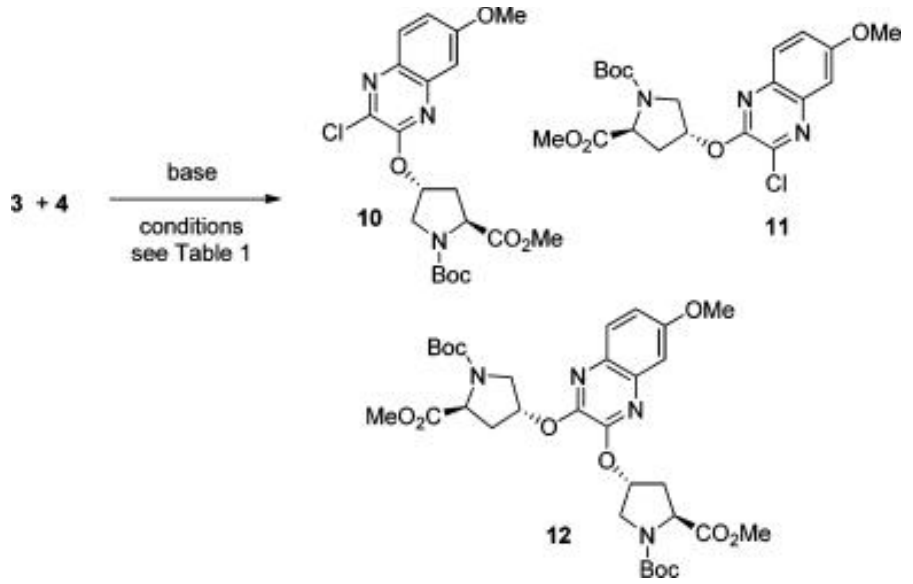


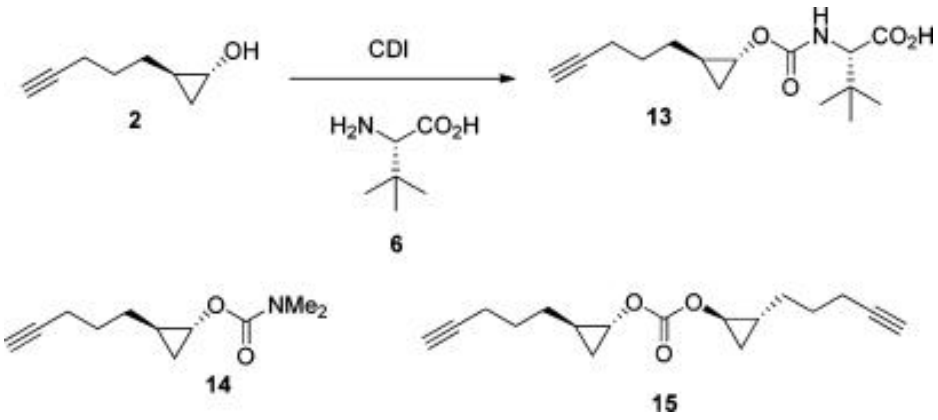


ACS Chem. Biol. **2013**, *8*, 1469.









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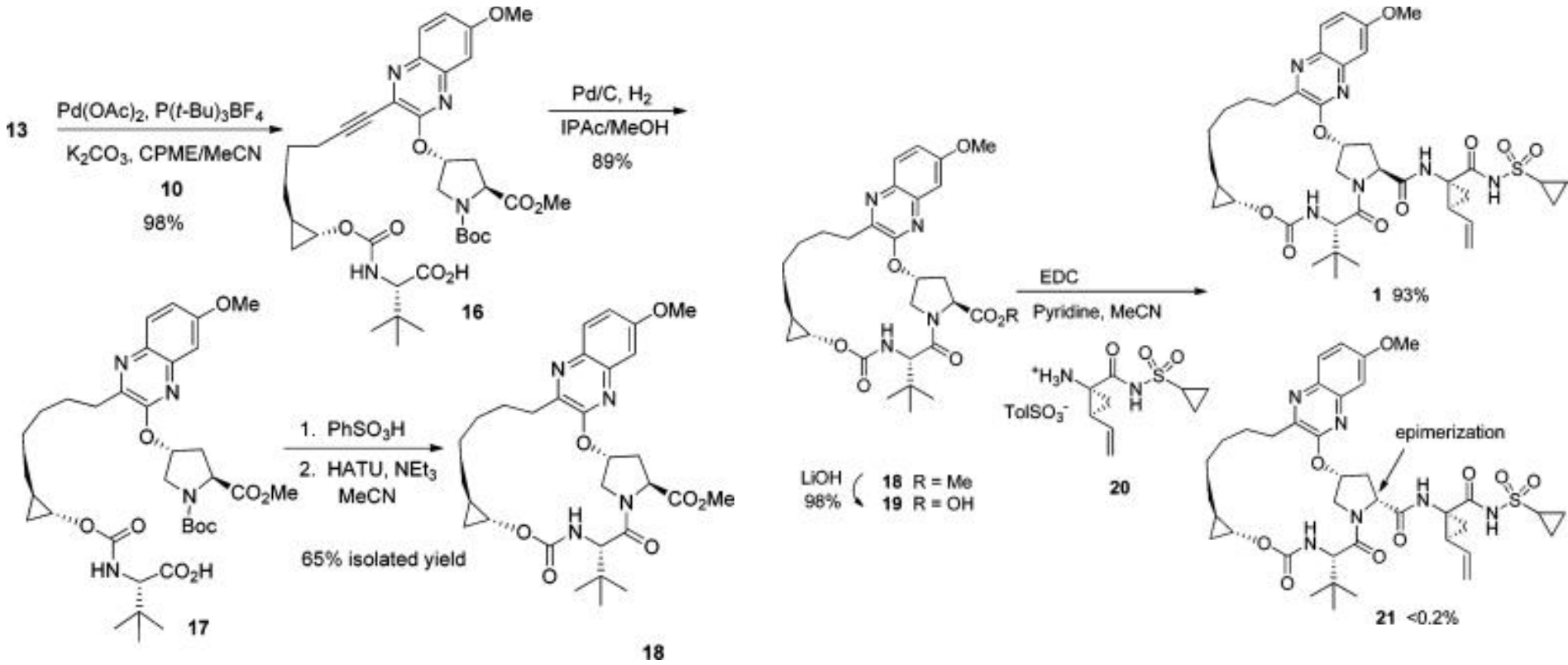

Org. Lett. **2013**, *15*, 4174.