

# The Discovery and Early Development of the HCV NS3 Protease Inhibitor BMS-605339

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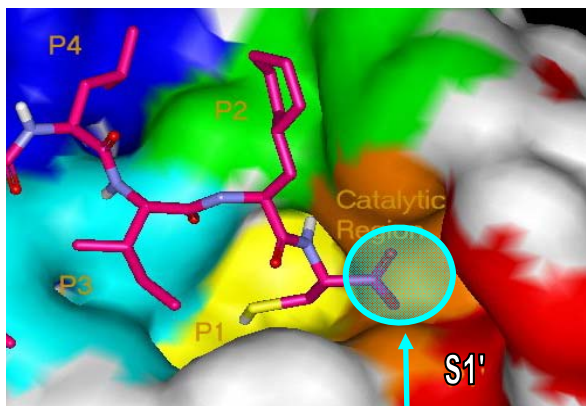
HEP DART 2009

frontiers in drug development for viral hepatitis

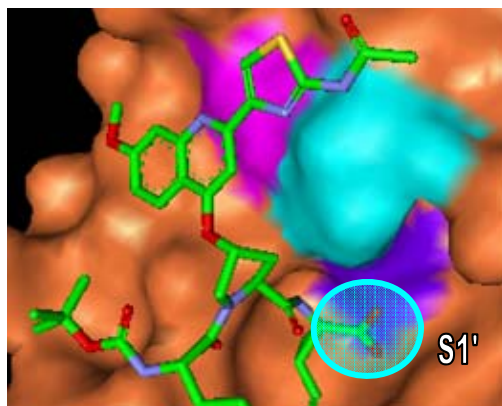


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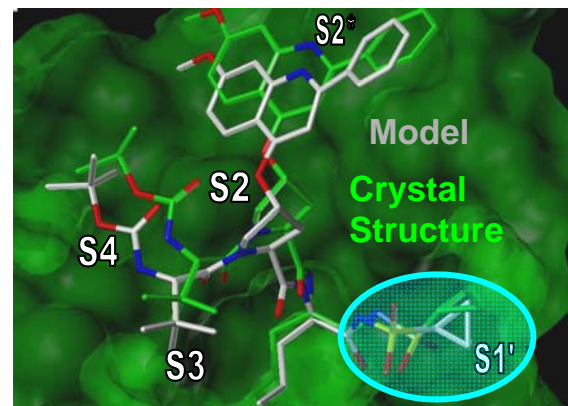
# Design of the P1` Acylsulfonamide Moiety



Unusual acid binding motif with salt bridge to protonated catalytic H57



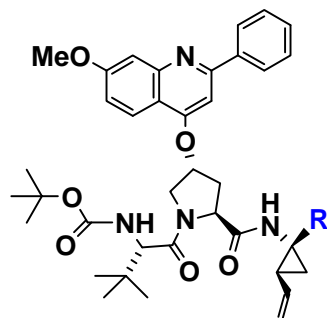
BI chemotype



Acylsulfonamide model / X-ray structure

- Hexapeptide product inhibitor structure used to design acid isostere
  - Allows access to S1` pocket
- BI tripeptide mimetic disclosed early 2000
  - Shares same acid binding motif
- BI inhibitor used as template to design acylsulfonamide motif
  - Crystal structure confirmed model

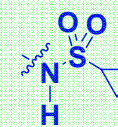
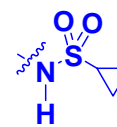
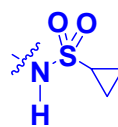
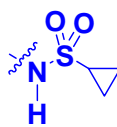
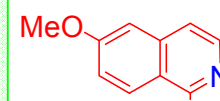
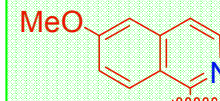
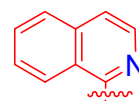
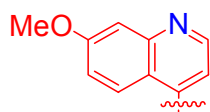
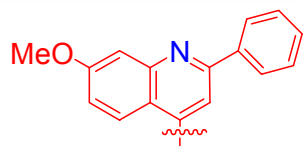
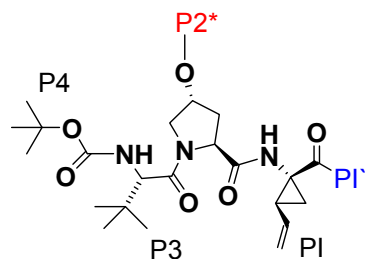
# Potent P1` Acylsulfonamide Inhibitors of the NS3 Protease Rapidly Identified



R				
GT 1a IC <sub>50</sub> (nM)	54	19	1	1
GT 1b EC <sub>50</sub> (nM)	550	97	4	16

- Cyclopropyl acylsulfonamide optimal for potency
  - >50-fold increase in intrinsic potency against a GT 1a BMS strain
  - >100-fold increase in activity against a GT 1b replicon

# BMS-605339 Identified Through Lead Optimization of the P2\* Moiety



1a IC <sub>50</sub> (nM)	1	5	6	2	247	
1b Replicon EC <sub>50</sub> (nM)	4	12	12	3	2000	
Rat PK (4 h)	AUC (nM.h)	76	15	760	10,710	<1
	Liver level (nM)	9,940	870	41,060	90,650	3890

- Elevated liver levels but low plasma exposure
- P2\* isoquinolines demonstrated a significant increase in exposure
- Exposure advantage not observed in the carboxylic acid series
- BMS-605339 profiled further

# Preclinical Pharmacology Properties of BMS-605339

Assay		BMS-605339
Enzyme IC <sub>50</sub> (nM)	HCV NS3/4A (1a)	2
	HCV NS3/4A (1b)	0.7
	Human Elastase	>100000
Replicon EC <sub>50</sub> (nM)	HCV 1a	8
	HCV 1b	3
	BVDV	34000

GT 1a NS3 Protease Variant	Fold Change in `339 EC <sub>50</sub> over WT	GT 1b NS3 Protease Variant	Fold Change in `339 EC <sub>50</sub> over WT
N77S	16	D168C	41
R155K	12	D168E	25
D168E	56	D168V	165
D168S	21	D168Y	141

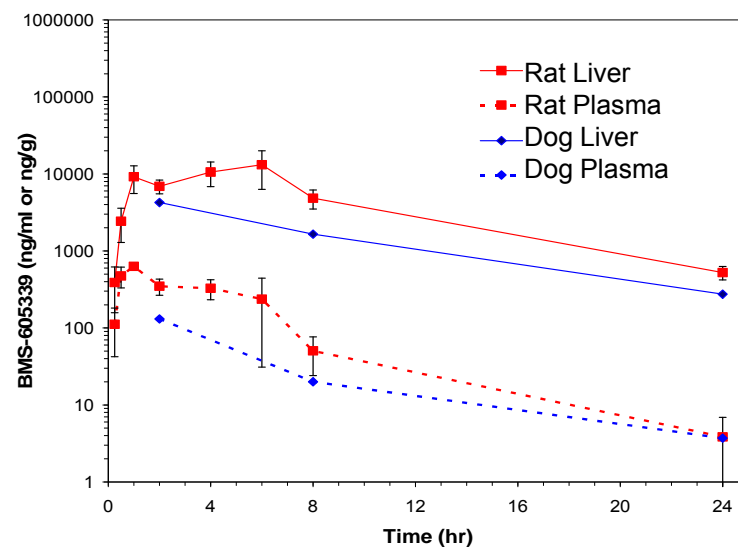
Variants with >10-fold loss in susceptibility

	IFN $\alpha$	NS4B Inhibitor	NS5A Inhibitor	NS5B Inhibitor
BMS-605339	Synergistic	Additive/ Synergistic	Additive/ Synergistic	Additive

- Potent and selective inhibitor of NS3 protease activity and HCV replication
- Predominant GT 1a or 1b resistance substitutions at NS3-R155 or -D168
- Novel substitution (1a-NS3-N77S) detected in GT 1a replicon
- Holds promise as part of a combination regimen

# Preclinical Pharmacology Properties of BMS-605339

PK Parameters	Mouse	Rat	Dog	Monkey
IV Dose (mg/kg)	4.4	4	2	1
Clearance (mL/min/kg)	47	5.9	18	17
$T_{1/2}$ (h)	1.6	3.4	0.9	0.8
PO Dose (mg/kg)	30	20	3	3
$AUC_{0-n}$ ( $\mu$ M.h)	1.7	14.1	2.2	0.03
F (%)	11	22	51	0.5



- Variable clearance and plasma exposure across species
  - Extensive metabolism in monkey
- High liver exposure over 24 hours across species
  - Detected in spleen and heart at same levels as in plasma
  - Main route of elimination was via bile

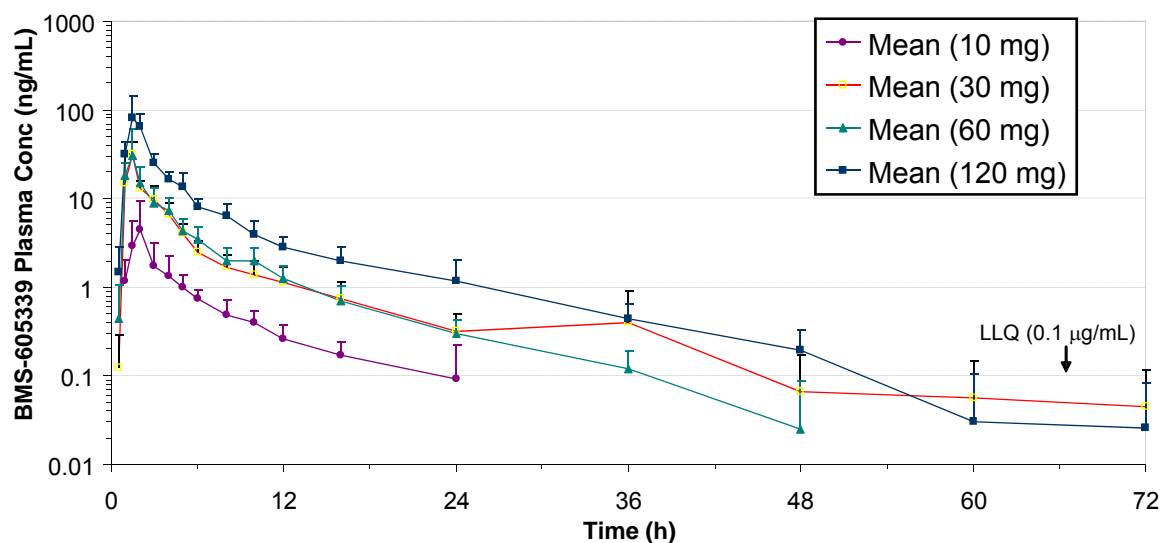
# Preclinical Toxicology of BMS-605339

Species (Study)	Dose (mg/kg/day)	Mean C <sub>max</sub> (μM)	Mean AUC (μM.h)	Effects
Rat (1-Month)	300	86	247	NOEL
		161	490	
Dog (1-Month)	60 (30, BID)	34	113	NOEL
		56	231	
Dog (Telemetry)	30 (15, BID)	≤12	ND	NOAEL

Predicted human efficacious C<sub>max</sub> ~ 300 nM, AUC ~ 1 μM.h

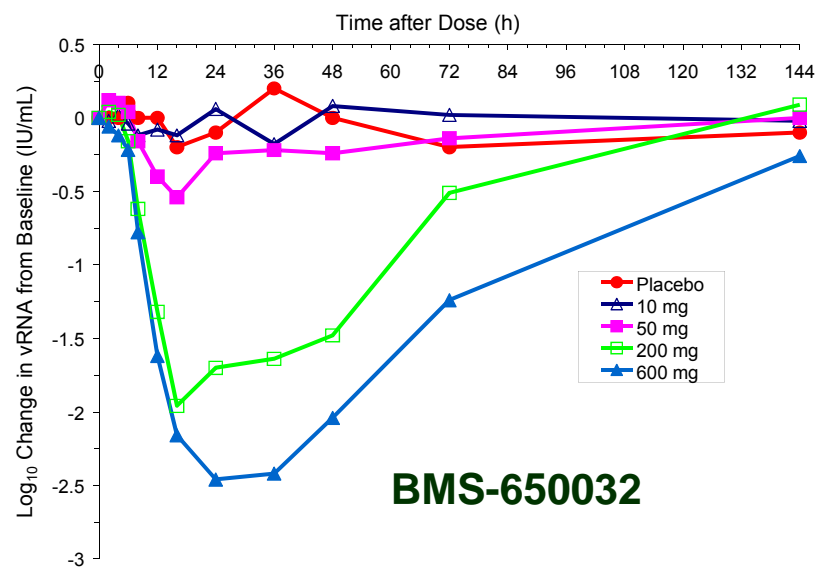
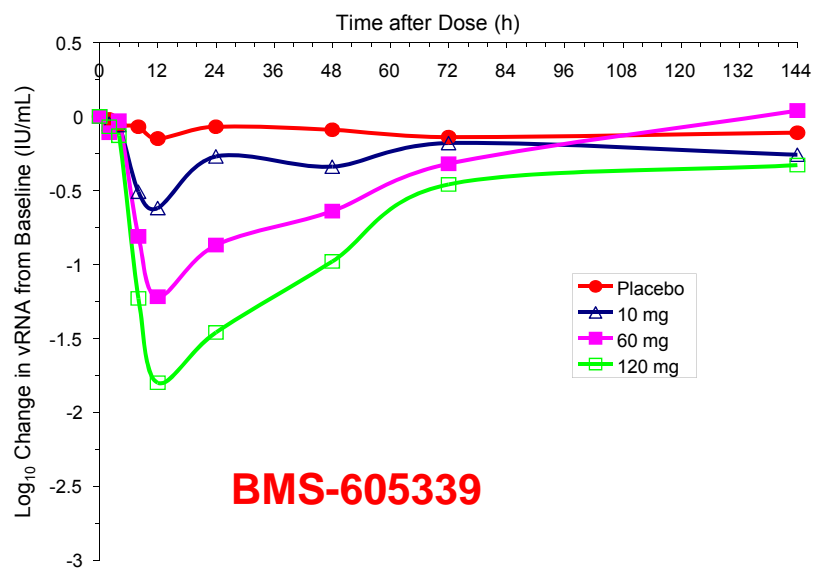
- No safety concerns identified in *in vitro* toxicity profiling assays
- Animal safety margins supported clinical development of BMS-605339

# Safety and Pharmacokinetic Properties of BMS-605339 in Normal Healthy Volunteers



- Single doses up to and including 120 mg well tolerated
  - No dose-related trends in clinical adverse events or marked lab abnormalities
- Rapid absorption with  $T_{max} \leq 2$  hours
- Plasma exposure increased with dose
  - Mean terminal half-life ~8 to 11 hours

# Single Dose Mean Viral Response in HCV GT 1 Subjects



Pasquinelli et al, AASLD, 2009

- Maximum declines in HCV RNA of -0.62 to -1.82 log<sub>10</sub> IU/mL
- More robust response with current clinical candidate BMS-650032
  - Maximum decline in HCV RNA of ~ 2.5 log<sub>10</sub> IU/mL

# Summary

- Structure-based design yielded novel P1` cyclopropyl acylsulfonamide
  - 2 orders of magnitude increase in potency versus carboxylate
- Optimization of P2\* improved PK leading to discovery of BMS-605339
  - Sustained hepatotropic distribution and biliary elimination
- BMS-605339 profile supported its evaluation in HCV-infected subjects
  - Maximum decline in HCV RNA up to 2 log<sub>10</sub> with a single 120 mg dose
  - Studies halted due to single mild asymptomatic adverse cardiovascular event
- Further lead optimization yielded current clinical candidate BMS-650032
  - Improved toxicity profile and antiviral response

# Acknowledgements

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