Accepted Manuscript

Functionalized Triazines as Potent HCV Entry Inhibitors

Eric S. Mull, Li-Qiang Sun, Qian Zhao, Betsy Eggers, Kevin Pokornowski, Guangzhi Zhai, Ramkumar Rajamani, Susan Jenkins, Melissa Kramer, Ying-Kai Wang, Hua Fang, Daniel Tenney, Carl J. Baldick, Mark I. Cockett, Nicholas A. Meanwell, Paul M. Scola

PII: S0960-894X(16)31304-X
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.12.038
Reference: BMCL 24527

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 2 November 2016
Revised Date: 13 December 2016
Accepted Date: 14 December 2016

Please cite this article as: Mull, E.S., Sun, L-Q., Zhao, Q., Eggers, B., Pokornowski, K., Zhai, G., Rajamani, R., Jenkins, S., Kramer, M., Wang, Y-K., Fang, H., Tenney, D., Baldick, C.J., Cockett, M.I., Meanwell, N.A., Scola, P.M., Functionalized Triazines as Potent HCV Entry Inhibitors, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.12.038

Functionalized Triazines as Potent HCV Entry Inhibitors

Eric S. Mull*[a], Li-Qiang Sun*[a], Qian Zhao[a], Betsy Eggers[b], Kevin Pokornowski[b], Guangzhi Zhai[b], Ramkumar Rajamani[c], Susan Jenkins[d], Melissa Kramer[d], Ying-Kai Wang[e], Hua Fang[e], Daniel Tenney[b], Carl J. Baldick[b], Mark I. Cockett[b], Nicholas A. Meanwell[a], Paul M. Scola[a]

[a]Department of Discovery Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT, 06492.

[b]Department of Virology Discovery Biology, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT, 06492.

[c]Department of Computer-Assisted Drug Design, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT, 06492

[d]Department of Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT, 06492.

[e]Department of Lead Evaluation, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT, 06492.

KEYWORDS: Hepatitis C virus, entry inhibitor, acyl sulfonamide, triazine

ABSTRACT: A series of potent and novel acylsulfonamide-bearing triazines were synthesized and the structure-activity relationships (SARs) as HCV entry inhibitors were evaluated. This acylsulfonamide series was derived from an early lead, 4-(4-(1-(4-chlorophenyl)cyclopropylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylamino)benzoic acid wherein the carboxylic acid was replaced with an acylsulfonamide moiety. This structural modification provided a class of compounds which projected an additional vector off the terminus of the acylsulfonamide functionality as a means to drive activity. This effort led to the discovery of potent analogues within this series that demonstrated sub-nanomolar EC_{50} values in the HCV pseudotype particle (HCVpp) assay.

Hepatitis C Virus (HCV) infection is predominantly a chronic viral disease of the liver affecting more than 170 million people worldwide with 4 to 5 million cases in the U.S. alone.[1-3] For just over a decade, the optimal care for patients chronically infected with HCV was a combination of PEGylated α-interferon (PEG-IFN) with ribavirin (RBV), neither of which are specific HCV antiviral agents.[4] The first wave of direct acting antiviral (DAA) agents that were approved, telaprevir and boceprevir, were combined with PEG-IFN/RBV and provided a genotype-1 drug regimens with improved efficacy.[5,6] These regimens offered sustained viral response (SVR) rates for genotype-1 patients naïve to therapy of up to 75%.[7] Notably, these treatments required PEG-IFN and RBV for efficacy but added to the burden of tolerability issues.[7] This provided an impetus for the discovery of interferon-free DAA cocktails with potentially improved tolerability profiles and shorter durations of treatment. These regimens consist of combinations of drugs which target the virus at multiple points in its life cycle to overcome the emergence of resistance. Prominent FDA-approved combinations include Harvoni®, a combination of sofosbuvir and ledipasvir; Viekira Pak®, which combines ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir; Zepatier™, a combination of elbasvir and grazoprevir; and Epclusa®, a fixed dose combination of sofosbuvir and velpatasvir.[8]

Internal efforts led to the discovery of daclatasvir (BMS-790052, **1**)[9], a NS5A replication complex inhibitor, asunaprevir (BMS-650032, **2**),[10] a NS3 protease inhibitor, and the non-nucleoside NS5B polymerase inhibitor beclabuvir (BMS-791325, **3**)[11]. The combination of asunaprevir with daclatasvir was the first DAA regimen to demonstrate that a chronic HCV infection could be cured without the use of PEG-IFN/RBV and became the first all-oral, interferon- and ribavirin-free regimen marketed for the treatment of individuals with genotype-1b chronic hepatitis C infection when it was approved in Japan in July of 2014.[12-17] The triple combination of daclatasvir, asunaprevir, and beclabuvir has proven effective for the treatment of individuals infected with genotype-1b and genotype-1a viruses with the latter a more challenging patient population to treat with direct-acting antiviral agents (DAAs).[18,19]

In addition to focusing on life cycle targets of HCV, a complementary approach was taken that targeted interfering with viral entry into the host cell. This strategy has been adopted in HIV-1 therapy[20] and with respect to HCV there have been reports of agents targeting entry through various stages and mechanisms of action.[21-27]

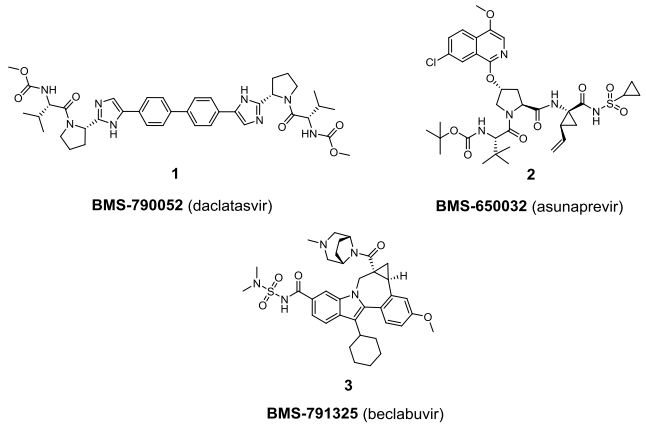


Figure 1: Internal research discoveries at Bristol-Myers Squibb

We[28] and others[29] have previously reported on the discovery of triazine-based small molecule HCV entry inhibitors. These inhibitors were identified in high throughput (HTS) screening campaigns using an HCV pseudotype particle assay (HCVpp). HCVpp, consisting of lentiviral particles engineered to contain

the HCV envelope proteins E1 and E2, are a validated system for studying the early steps of HCV entry.[28] Our initial triazine HTS hit **4** (Fig. 2) exhibited modest potency toward genotypes 1a and 1b but poor rat microsomal stability and PAMPA permeability. SARs borne out of exploration of the substituents on the triazine core led to the identification of the early lead compound **5**, which showed an improvement in genotype 1a potency along with a more favorable microsomal stability profile. In an effort to further advance this triazine series with respect to potency and drug-like properties, SARs were explored at the terminus of each aryl group. Described herein are our efforts to replace the carboxyl moiety with groups that expand the binding silhouette in this series. It should be noted that acylsulfonamides were selected as the functional group with which to explore this seam of SARs, viewed as promising since the acidity

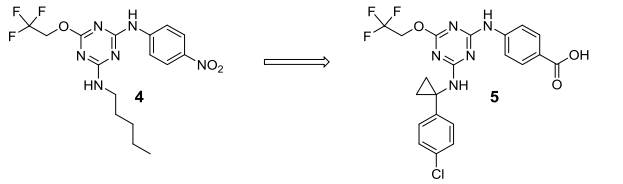


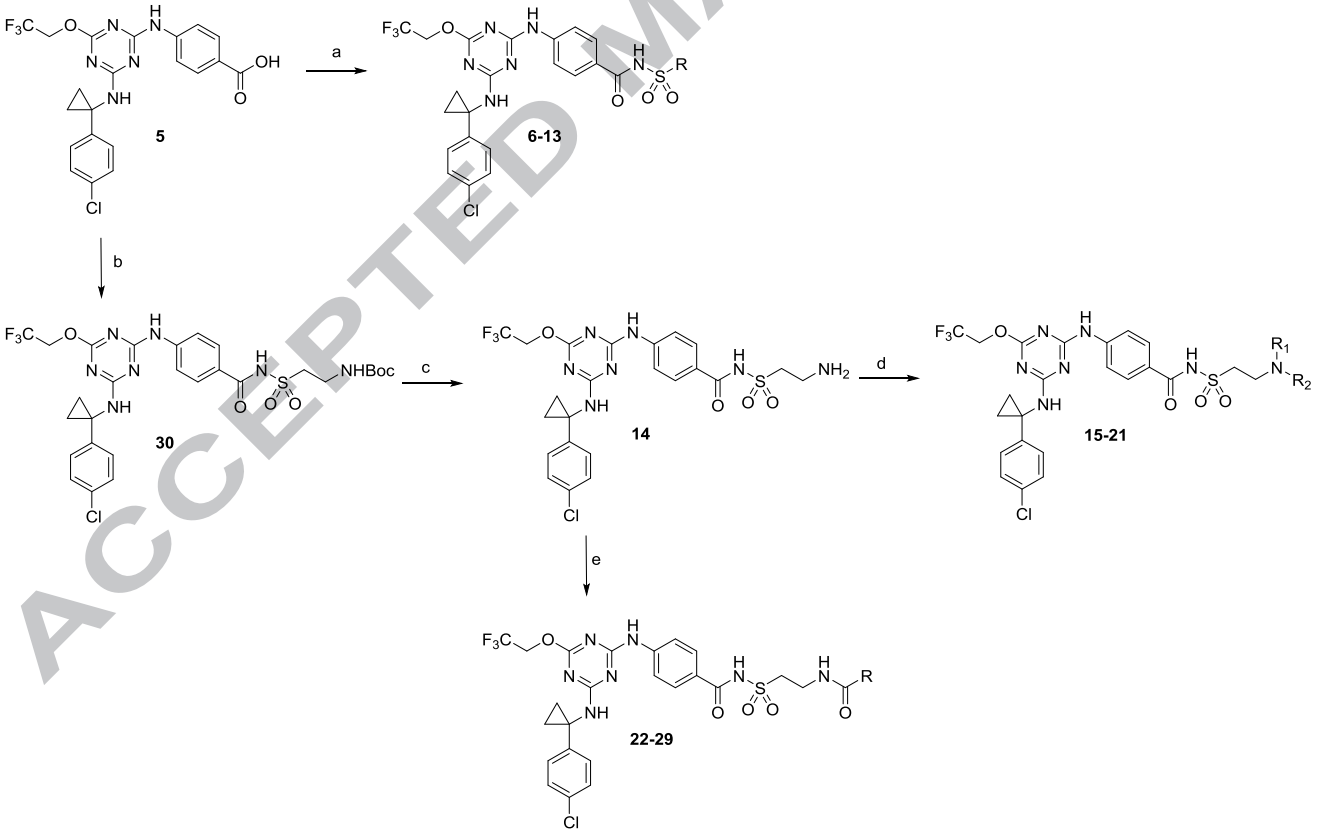
Figure 2. Structure of HTS hit and early lead. [a]Parallel artificial membrane assay (PAMPA).

found in the parent acid series would be preserved while further interactions with the target could be explored by modifications to the terminus of this functionality. In the event, a number of compounds from this novel chemotype displayed enhanced inhibitory activity toward genotype 1a and 1b virus infectivity when compared to **5** and the details of these findings are described herein.

The synthesis of lead **5** was previously disclosed.[30] The general synthetic routes to the series of analogs discussed in Table 1 and Table 2 are shown in Scheme 1. Compound **5** was elaborated by coupling of the acid moiety with a subset of alkyl sulfonamides mediated by EDC to form acylsulfonamides **6-13**. Similarly, compound **5** was coupled with *tert*-butyl (2-sulfamoylethyl)carbamate using PyBOP as a coupling agent to form **30** followed by Boc deprotection with HCl in dioxane to afford **14** in excellent yield.

Compound **14** was further modified by reductive amination to form substituted amines **15-16** and **19-21**. Cyclic amines **17-18** were prepared from **14** by di-alkylation. In addition to amine analogs **15-21**, compound **14** was also converted to a series of amides by reaction with either an acid chloride to give **22** or by peptide coupling with carboxylic acids to afford **23-24**, to ureas **25-27** by reaction with isocyanates and, finally, to carbamates **28-29** by reaction with chloroformates.

As noted, exploration of SARs of the triazine lead **5** focused on replacement of carboxylic acid functionality with a variety of acylsulfonamides (Table 1). Interestingly, simple acylsulfonamides proved to be more active than the parent acid **5**.



Scheme 1. Reagents and conditions: (a) sulfonamide or sulfamide, EDC, DMAP, DIEA, DMF, RT, 16 h; (b) *tert*-butyl 2-sulfamoylethylcarbamate, PyBOP, DIEA, DCM, RT, 72 h; (c) 4N HCl in dioxane, 1 h; (d) diiodo or dibromo alkane, K_2CO_3, ACN, 65 °C, 16 h or RCHO, $NaBH(O_2CCH_3)_3$, AcOH, DCM, RT, 4 h; (e) RCOCl, ROCOCl, or RNCO, DIEA, DCM, RT, 0.25 h or RCOOH, PyBOP, DIEA, DCM, RT, 16 h.

For example acylmethylsulfonamide **6**, acylethysulfonamide **7** and acylcyclopropylsulfonamide **8** afforded a 2- to 6-fold increase in potency in the HCVpp GT-1a assay with a 2-fold enhancement in activity against HCVpp-GT1b. However, this potency advantage was lost with isopropylsulfonamide **9** and N,N-dimethylsulfamide **10** as these analogues had activity similar to **5**. Since a crystal structure of compounds from this chemical series bound to the target was not available, these SARs were not directly interpretable. This initial data set was built upon by the construction of the phenylsulfonamide derivative **11** which exhibited 3-fold enhanced potency against HCVpp-GT1a and HCVpp-GT1b. Interestingly, further modification of the phenyl moiety in **11**, providing **12** and **13**, resulted in a decrease in GT-1a inhibitory potency while having a negligible impact on GT-1b inhibitory activity in comparison with corresponding parent compound **11**.

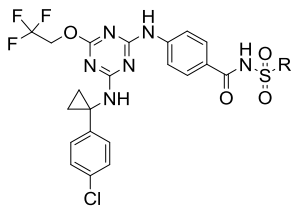
We next turned to furthering the activity gains observed for acylsulfonamide analogues bearing linear aliphatic side chains (compounds **6** and **7**) by building in additional functionality at the terminus of the alkyl group. To that end, the set of *beta*-substituted ethyl acylsulfonamides **14-30** was prepared as shown in Table 2. Substantial activity gains were realized in this series while the *in vitro* metabolic stability profile of these compounds was similarly favorable. For example, the introduction of an amine to the terminus of the acylsulfonamide group in **7** provided compound **14**. This analogue demonstrated a 3-fold increase in potency in the HCVpp GT-1a assay, while maintaining GT-1b activity comparable to the parent **7**. Interestingly, PAMPA permeability values for **14** were improved over the parent analogue **7**, a somewhat surprising result given that **14** is zwitterionic in nature. The microsomal stability for **14** was excellent and consistent with the introduction of additional polarity to the molecule when compared to **7**.

The favorable profile observed with compound **14** catalyzed a more in-depth evaluation of amine derivatives. To that end, the acylsulfonamide analogues **15-18** bearing secondary amine moieties were prepared. The inhibitory activity profile of this class was excellent and a substantial improvement over simple amine **14**. Optimal activity was found with the more lipophilic amines **15-17**, wherein half-maximal HCVpp inhibitory values of less than 10 nM were observed for both the 1a and 1b genotypes. The more active of these analogues, compound **16**, was only slightly more active versus GT-1a when compared to **14**; however, **16** was some 50-fold more active than **14** against GT-1b. A slight erosion in activity was observed by introduction of the more polar morpholino group in **18**, suggestive of the importance of van der Waals interactions as a means to drive activity in this region of the target protein. Compounds **15-18** exhibited poor to moderate PAMPA permeability, but it is of particular interest to note that these compounds showed a trend toward increased PAMPA permeability values when the lipophilicity of these substituents was increased.

Primary amine derivatives were also explored and further activity gains realized. For example, isopropylamine **19** and neopentylamine **20** were both active in GT-1a and GT-1b HCVpp assays with EC_{50} values of less than 1 nM. Interestingly, the activity of amine **20** was essentially equal against GT-1a and GT-1b in this assay with values of 0.78 nM and 0.72 nM, respectively. In addition, compound **20** exhibited a promising PAMPA value of 651 nm/s, a notable improvement compared to the progenitor **14**. Encouraged by the potency and *in vitro* ADME profile of **20** (90% remaining in RLM after 10 minutes) this compound was selected for *in vivo* dosing to rats to benchmark the pharmacokinetic properties of this series. Somewhat surprisingly, **20** was apparently not absorbed after oral dosing as the compound was not detectable in plasma (Table 3). The IV kinetics for **20** were more favorable, with moderate clearance and a modest half-life observed. While additional studies were required to provide a clear understanding of the poor absorption properties of **20**, we reasoned that transporters were possibly playing a role and turned to resolving this issue with additional analogue synthesis around progenitor **14**.

To that end, amide, carbamate and urea derivatives of amine **14** were explored. The SARs within each of these functional classes with respect to HCVpp inhibitory activity was consistent with that observed in the amine series wherein activity increased with increasing lipophilicity of the terminal alkyl group. This SAR point was most compelling in the urea series with the *tert*-butyl analogue **27** some 10-fold more active than the simple methyl derivative **25**. Nonetheless, these three amide-derived series proved less potent than the most potent amines. Moreover, while the microsomal stabilities of compounds **22-30** were favorable, the PAMPA values for this set of analogues was poor. It was hypothesized that the polarity associated with the addition of a H-bond donor in the case of compounds **22-24** as well as **28-30**, and two H-bond donors with respect to **25-27** limit the permeability in these classes of compounds.

Table 1. Antiviral Activities of compounds **5-13**

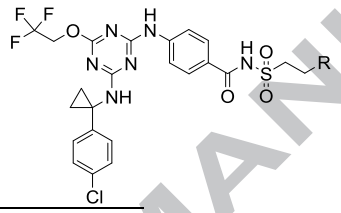


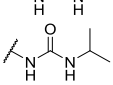
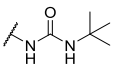
Compd	R	GT-1a EC_{50} (nM)	GT-1b EC_{50} (nM)	HLM/RLM Stability (% remaining after 10 minutes)[a]	PAMPA (nm/s)[b]
5		36	224	89/99	59
6	Me	6.1	114	100/85	11

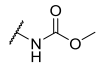
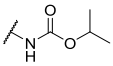
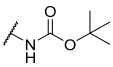
7	Et	12.2	165	100/85	28
8	*c*-Pr	14.5	108	100/85	
9	*i*-Pr	32	253	100/96	31
10	Me_2N	39.6	283	86/76	
11	Ph	13.4	73.6	100/100	182
12	2-Me-Ph	54.6	91.1	100/100	265
13	4-F-Ph	25.8	52.7	100/99	193

[a]Metabolic stability in human liver microsomes (HLM) and rat liver microsomes (RLM) values are percentage remaining after 10 minutes of incubation. [b]PAMPA values were determined at pH 7.4.

Table 2. Antiviral Activities of compounds **7**, **14-30**



Compd	R	GT-1a EC_{50} (nM)	GT-1b EC_{50} (nM)	HLM/RLM Stability (% remaining after 10 minutes)[a]	PAMPA (nm/s)[b]
7	H	12.2	165		28
14	H_2N	4.2	147	100/100	153
15	Me_2N	3.2	8.9	89/100	45
16	Et_2N	1.8	3.4	99/98	73
17		1.3	6.1	96/98	124
18		17	26	78/97	35
19	*i*-PrNH	0.40	0.87	89/100	45
20	*t*-$BuCH_2NH$	0.78	0.72	89/90	651
21	BnNH	3.6	6.0	99/100	49
22		8.5	26.7	95/100	7
23		18.5	26.3	86/84	13
24		12.9	20.1	90/aa	1
25		13.3	23.6	97/100	40
26		4.3	4.3	100/97	45
27		3.2	2.0	96/93	49

28		5.3	13.9	90/100	39
29		1.8	2.6	100/73	71
30		2.2	2.2	92/93	111

[a]Metabolic stability in human liver microsomes (HLM) and rat liver microsomes (RLM) values are percentage remaining after 10 minutes of incubation. [b]PAMPA values were determined at pH 7.4.

In conclusion, replacement of the carboxylic acid group in compound **5** with an acylsulfonamide moiety led to the discovery of a series of compounds which showed exquisite potency with EC_{50} values of less than 1 nM in the HCVpp assay against genotypes 1a and 1b. This level of activity represented an increase in potency compared to the parent carboxylic acid of up to 15-fold for genotype 1a and up to 200-fold versus genotype 1b. Activity was derived, in part, by lipophilic groups at the β-position of the acylsulfonamide group, suggesting that van der Waals forces were playing a critical role in securing potency. While the *in vitro* microsomal stability of compounds in this chemical class was excellent, the PK profile of representative compound **20** was poor since no oral absorption was observed. This series demonstrated the utility of the triazine chemotype in securing excellent potency and encouraged additional efforts within this series to expand genotype coverage and improve pharmacokinetic parameters, which will be described in due course.

Table 3. Rat PK profile of compound **20**

Cl (mL/min/kg)[b]	Vss (L/kg)[c]	$t_{1/2}$ (h)[d]	PO AUC (nM*h)[e]
22.5	0.6	2.6	<LLQ[f]

[a]Respective IV/PO dosing levels: rat (2/5 mg/kg, n = 2) Vehicle: PEG-400/ethanol/solutol (92.5/5/2.5, v/v) for rat-IV/PO. [b]Pharmacokinetic clearance. [c]Volume of distribution. [d]Plasma half-life. [e]Pharmacokinetic area under curve. [f]Lower limit of quantification.

REFERENCES

(1) Hanafiah, K. M.; Groeger, J.; Flaxman, A. D.; Wiersma, S. T. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* **2013**, *57*, 1333−1342.

(2) Hajarazadeh, B.; Grebely, J.; Dore, G. J. Epidemiology and natural history of HCV infection. *Nat. Rev. Gastroenterol. Hepatol.* **2013**, *10*, 553−562.

(3) Gravitz L. Introduction: a smouldering public-health crisis. *Nature* **2011**, *474*, S2–4.

(4) Fried, M. W.; Shiffman, M. L.; Reddy, K. R.; *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.* **2002**, 347(13), 975-982.

(5) McHutchison, J. G.; Everson, G. T.; Gordon, S. C, *et al.* Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N. Engl. J. Med.* **2009**, 360(18), 1827-1838.

(6) Poordad, F.; Mccone, J. Jr.; Bacon, B. R.; *et al.* Boceprevir for untreated chronic HCV genotype 1 infection. *N. Engl. J. Med.* **2011,** 363(13), 1195-1206.

(7) Ghany, M. G; Nelson, D. R.; Strader, D. B.; Thomas, D. L. Seeff, L. B. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the study of Liver Diseases *Hepatology* **2011**, 54, 1433.

(8) Pawlotsky, J. (coordinator); et al. EASL recommendations on treatment of hepatitis C 2016. *J. Hepatol.* **2016**, http://dx.doi.org/10.1016/j.jhep.2016.09.001

(9) Belema, M.; Lopez, O. D.; Bender, J. A.; Romine, J. L.; St. Laurent, D. R.; Langley, D. R.; Lemm, J. A.; O'BoyleII, D. R.; Sun, J.; Wang, C.; Fridell, R. A.; Meanwell, N. A. Discovery and development of hepatitis C virus NS5A replication complex inhibitors. *J. Med. Chem.* **2014**, 57, 1613-1672.

(10) Scola, P. M.; Sun, L.-Q.; Wang, A. X.; Chen, J.; Sin, N.; Venables, B. L.; Sit, S.-Y.; Chen, Y.; Cocuzza, A.; Bilder, D. M.; D'Andrea, S. V.; Zheng, B.; Hewawasam, P.; Tu, Y.; Friborg, J.; Falk, P.; Hernandez, D.; Levine, S.; Chen, C.; Yu, F.; Sheaffer, A. K.; Zhai, G.; Barry, D.; Knipe, J. O.; Han, Y.-H.; Schartman, R.; Donoso, M.; Mosure, K.; Sinz, M. W.; Zvyaga, T.; Good, A. C.; Rajamani, R.; Kish, K.; Tredup, J.; Klei, H. E.; Gao, Q.; Mueller, L.; Colonno, R. J.; Grasela, D. M.; Adams, S. P.; Loy, J.; Levesque, P. C.; Sun, H.; Shi, H.; Sun, L.; Warner, W.; Li, D.; Zhu, J.; Meanwell, N. A.; McPhee, F. The discov-

ery of asunaprevir (BMS-650032), an orally efficacious NS3 protease inhibitor for the treatment of hepatitis C virus infection. *J. Med. Chem.* **2014**, *57*, 1730– 1752.

(11) Gentles, R. G.; Ding, M. ; Bender, J. A.; Bergstrom, C. P.; Grant-Young, K.; Hewawasam, P.; Hudyma, T.; Martin, S.; Nickel, A.; Regueiro-Ren, A.; Tu, Y.; Yang, Z.; Yeung, K.; Zheng, X.; Chao, S.; Sun, J.; Beno, B. R.; Camac, D. M.; Chang, C.; Gao, M.; Morin, P. E.; Sheriff, S.; Tredup, J.; Wan, J.; Witmer, M. R.; Xie, D.; Hanumegowda, U.; Knipe, J.; Mosure, K.; Santone, K. S.; Parker, D. D.; Zhuo, X.; Lemm, J.; Liu, M.; Pelosi, L.; Rigat, K.; Voss, S.; Wang, Y.; Wang, Y.; Colonno, R. J.; Gao, M.; Roberts, S. B.; Gao, Q.; Ng, A.; Meanwell, N.; Kadow, J. F. Discovery and preclinical characterization of the cyclopropylindolobenzazepine BMS-791325, a potent allosteric inhibitor of the hepatitis C virus NS5B polymerase. *J. Med. Chem.* **2014**, *57*, 1855– 1879.

(12) Chayanna, K.; Takahashi, S.; Toyota, J.; Karino, Y.; Ikeda, K.; Ishikawa, H.; Watanabe, H.; McPhee, F.; Hughes, E.; Kumada, H. Dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protein 3 protease inhibitor, asunaprevir, in hepatitis C virus genotype 1b-infected null responders. *Hepatology* **2012**, *55*, 742–748.

(13) Pasquinelli, C.; McPhee, F.; Eley, T.; Villegas, C.; Sandy, K.; Sheridan, P.; Persson, A.; Huang, S.-P.; Hernandez, D.; Sheaffer, A. K.; Scola, P.; Marbury, T.; Lawitz, E.; Goldwater, R.; Rodriguez-Torres, M.; DeMicco, M.; Wright, D.; Charlton, M.; Kraft, W. K.; Lopez-Talavera, J.-C.; Grasela, D. M. Single- and multiple-ascending-dose studies of the NS3 protease inhibitor asunaprevir in subjects with or without chronic hepatitis C. *Antimicrob. Agents Chemother.* **2012**, *56*, 1838-1844.

(14) (a) Lok, A. S.; Gardiner, D. F.; Lawitz, E.; Martorell, C.; Everson, G. T.; Ghalib, R.; Reindollar, R.; Rustgi, V.; McPhee, F.; Wind-Rotolo, M.; Persson, A.; Zhu, K.; Dimitrova, D. I.; Eley, T.; Guo, T.; Grasela, D. M.; Pasquinelli, C. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N. Engl. J. Med.* **2012**, 219-224. (b) Suzuki, Y.; Ikeda, K.; Suzuki, F.; Toyota, J.; Karino, Y.; Chayama, K.; Kawakami, Y.; Ishikawa, H.; Watanabe, H.; Hu, W.; Eley, T.; McPhee, F.; Hughes, E.; Kumada, H. Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options *J. Hepatol*. **2013**, *58*, 655–662.

(15) Lok, A. S.; Gardiner, D. F.; Hézode, C.; Lawitz, E.J.; Bourlière, M.; Everson, G.T.; Marcellin, P.; Rodriguez-Torres, M.;Pol, S.; Serfaty, L.; Eley, T.; Huang, S.-P.; Li, J.; Wind-Rotolo, M.; Yu, F.; McPhee, F.; Grasela, D. M.; Pasquinelli, C. Randomized trial of daclatasvir and asunaprevir with or without pegIFN/RBV for hepatitis C virus genotype 1 null responders. *J Hepatol.* **2014**, *60*, 490–499.

(16) Kumada, H.; Suzuki, Y.; Ikeda, K.; Toyota, J.; Karino, Y.; Chayama, K.; Kawakami, Y.; Ido, A.; Yamamoto, K.; Takaguchi, K.; Izumi, N.; Koike, K.; Takehara, T.; Kawada, N.; Sata, M.; Miyagoshi, H.; Eley, T.; McPhee, F.; Damokosh, A.; Ishikawa, H.; Hughes, E. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* **2014**, *59*, 2083-2091.

(17) Poole R. Daclatasvir + asunaprevir: first global approval. *Drugs* **2014**, *74*, 1559-1571.

(18) Everson, G.T.; Sims, K.D.; Rodriguez-Torres, M.; Hézode, C.; Lawitz, E.; Bourlière, M.; Loustaud-Ratti, V; Rustgi, V.; Schwartz, H.; Tatum, H.; Marcellin, P.; Pol, S.; Thuluvath, P.J.; Eley, T.; Wang, X.; Huang, S.-P.; McPhee, F.; Wind-Rotolo, M.; Chung, E.; Pasquinelli, C.; Grasela, D.M.; Gardiner, D.F. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naive patients with HCV genotype 1 infection. *Gastroenterology* **2014**, *146*, 420-429.

(19) Hassanein, T.; Sims, K. D.; Bennett, M.; Gitlin, N.; Lawitz, R.; Nguyen, T.; Webster, L.; Younossi, Z.; Schwartz, H.; Thuluvath, P. J.; Zhou, H.; Rege, B.; McPhee, F.; Zhou, N.; Wind-Rotolo, M.; Chung, E.; Griffies, A.; Grasela, D. M.; Gardiner, D. F. A randomized trial of daclatasvir in combination with asunaprevir and beclabuvir in patients with chronic hepatitis C virus genotype 4 infection. *J. Hepatology* **2015**, *62*, 1204-1206.

(20) Haqqani, A. A.; Tilton, J. C. Entry inhibitors and their use in the treatment of HIV-1 infection. *Antiviral Res.* **2013**, 98, 158.

(21) Wang, H.; Wang, S.; Cheng, L.; Chen, L.; *et al.* Discovery of imidazo[1,2-α][1,8]naphthyridine derivatives as potential HCV entry inhibitor. *ACS Med. Chem. Lett.* **2015**, 6, 977-981.

(22) Bhat, R.; Adam, A. T.; Lee, J. J.; *et al.* Structure-activity studies of (-)-epigallocatechin gallate derivatives as entry inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, 24, 4162-4165.

(23) Yu, F; Wang, Q.; Zhang, Z.; Peng, Y.; *et al.* Development of oleanane-type triterpenes as a new class of HCV entry inhibitors. *J. Med. Chem.* **2013**, 56, 4300-4319.

(24) Hwang, J. Y.; Kim, H.; Park, D.; *et al.* Identification of a series of 1,3,4-trisubstituted pyrazoles as novel hepatitis C virus entry inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, 23, 6467-6473.

(25) Snyder, A. J.; Lee, H.; Zeisel, M. B.; *et al.* Small molecule scavenger receptor BI antagonists are potent HCV entry inhibitors. *J. Hepatol.* **2011**, 54, 48-55.

(26) Lupberger, J.; Zeisel, M. B.; Xiao, F.; *et al.* EGFR and EphA2 are host factors for hepatitis C virus entry and possible targets for antiviral therapy. *Nat. Med.* **2011**, 17, 589-595.

(27) Bush, C. O.; Pokrvskii, M. V.; Saito, R.; Morganelli, P.; Canales, E.; Clarke, M. O.; Lazerwith, S. E.; Golde, J.; Reid, B. G.; Babaoglu, K.; Pagratis, N.; Zhaong, W.; Delaney (IV), W. E.; Paulson, M. S.; Beran, R. K. F. A small-molecule inhibitor of hepatitis C virus infectivity. *Antimicrob. Agents Chemother.* **2014**, 58, 386-396.

(28) Baldick, C. J.; Wichroski, M. J.; Pendri, A.; Walsh, A. W.; Fang, J.; Mazzucco, C. E.; Pokoronowski, K. A.; Rose, R. E.; Eggers, B. J.; Hsu, M.; Zhai, W.; Zhai, G.; Gerritz, S. W.; Poss, M. A.; Meanwell, N. A.; Cockett, M. I.; Tenney, D. J. A novel small molecule inhibitor of hepatitis C virus entry. *PLOS One* **2010**, 6, e1001086.

(29) Coburn, G. A.; Han, A. Q.; Provoncha, K. P.; Rotshteyn, Y. Preparation of triazines and related compounds having antiviral activity for treating viral diseases and infection, including HCV, and their compositions. WO2009/091388, **2009**.

(30) Sun, L.-Q.; Mull, E.; Zhao, Q.; Wang, T.; Scola, P. M. Compounds for the treatment of Hepatitis C US8765944, **2014**.

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered

Functionalized trazines as potent HCV entry inhibitors	Leave this area blank for abstract info.

Eric S. Mull*, Li-Qiang Sun*, Qian Zhao, Betsy Eggers, Kevin Pokornowski, Guangzhi Zhai, Ramkumar Rajamani, Susan Jenkins, Melissa Kramer, Ying-Kai Wang, Hua Fang, Daniel Tenney, Carl J. Baldick, Mark I. Cockett, Nicholas A. Meanwell, Paul M. Scola