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Discovery of fused tricyclic core containing HCV NS5A inhibitors with pan-genotype activity

Wensheng Yu [a,*], Craig A. Coburn [b], De-Yi Yang [a], Peter T. Meinke [a], Michael Wong [a], Stuart B. Rosenblum [a], Kevin X. Chen [a], George F. Njoroge [a], Lei Chen [a], Michael P. Dwyer [a], Yueheng Jiang [a], Anilkumar G. Nair [a], Oleg Selyutin [a], Ling Tong [a], Qingbei Zeng [a], Bin Zhong [c], Tao Ji [c], Bin Hu [c], Sony Agrawal [d], Ellen Xia [d], Ying Zhai [d], Rong Liu [e], Rong Kong [e], Paul Ingravallo [e], Ernest Asante-Appiah [e], Amin Nomeir [f], James Fells [g], Joseph A. Kozlowski [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, 126 E. Lincoln Avenue, Rahway, NJ 07065, USA
[b] Department of Medicinal Chemistry, Merck Research Laboratories, 770 Sumneytown Pike, West Point, PA 19486, USA
[c] WuXi AppTec, 288 Fute Zhong Road, Shanghai 200131, China
[d] Department of In Vitro Pharmacology, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[e] Department of Infectious Diseases, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[f] Department of PPDM, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[g] Department of Structural Chemistry, Merck Research Laboratories, 126 E. Lincoln Avenue, Rahway, NJ 07065, USA

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ABSTRACT

HCV NS5A inhibitors have demonstrated impressive in vitro potency profiles in HCV replicon assays and robust HCV RNA titer reduction in the clinic making them attractive components for inclusion in an all oral fixed dose combination regimen for the treatment of HCV infection. Herein, we describe research efforts that led to the discovery of a series of fused tricyclic core containing HCV NS5A inhibitors such as **24**, **39**, **40**, **43**, and **44** which have pan-genotype activity and are orally bioavailable in the rat.

Hepatitis C virus (HCV) is the leading cause of chronic liver disease and liver transplants in the developed world. The World Health Organization (WHO) estimates that approximately 3% of the world's population are infected with HCV.[1] The diversity in the virus is impressive with seven major genotypes (GT1-7) present and multiple subtypes identified for each. However, currently approximately 90% of all HCV infections are associated with genotypes 1, 2, and 3. Until 2013, treatment of the disease was focused on interferon-based therapy and was limited by both efficacy and tolerability.[2] Addition of HCV protease inhibitors, such as telaprevir or boceprevir, to the therapy improved response rates for genotype 1 patients,[3] but unfortunately left many patients without a cure, leaving open a need for improved treatment regimens. Current HCV therapy targets interferon-free, direct-acting antiviral agents (DAA) with reduced overall treatment durations, broader coverage of HCV patient sub-populations, and increased rates of sustained virologic response (SVR). Typically, these treatment regimens utilize two or more DAAs, each targeting a different mechanism of action in the life cycle of HCV. SVR rates have been dramatically improved with this approach and it continues to be an important strategy for improving clinical outcomes for HCV patients.[4,5]

The HCV NS5A protein is a multifunctional RNA binding protein essential for HCV replication.[6] NS5A encodes no known enzymatic function but has been shown to serve multiple functions at various stages of the HCV life cycle including involvement in both viral replication and virion assembly.[6] Over the past decade, NS5A has become an attractive pharmacological target and inhibitors of NS5A have become an integral part of fixed-dose combination (FDC) regimens.[7] To date, four NS5A inhibitors are available for use in clinical practice for HCV treatment: daclatasvir,[8] ledipasvir,[9] ombitasvir,[10] and elbasvir.[11]

* Corresponding author.
E-mail address: wensheng.yu@merck.com (W. Yu).

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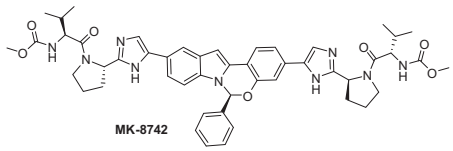


	Genotype EC_{50} (nM)				
	1a	1b	2a	3a	1a Y93H
MK-8742	0.004	0.003	0.003	0.02	2

Figure 1. MK-8742 in vitro potency profile.[11]

During our work in the development of NS5A inhibitors we noted that changes in the core structure, while holding the remainder of the molecule constant, could modulate both the wild-type HCV and mutant potency profiles.[11,12] To further interrogate this observation, we undertook an effort to study a variety of fused tricyclic cores, each possessing a different shape and length.

Using MK-8742 (Fig. 1) as a reference point for comparison, we elected to maintain the bisimidazole–proline–valine methyl carbamate unchanged and vary only the core. At the outset of this work, we were curious if a tricyclic core could impart a potency profile similar to that of the tetracyclic indole based core. Molecular modeling indicated that analogs with a fused tricyclic core have comparatively shorter spacing between the two imidazole–proline moieties compared to our tetracyclic core.[13] In addition, one could alter the attachment points of the imidazole proline moieties to the tricycle in order to perturb the spatial projection of these moieties. The ability to modulate both the length of the core and the projection of the imidazole–proline moiety into space was attractive as it allowed for considerable variation in the overall size and shape of the molecules.

The investigation was started by preparing a simple anthracene core, retaining the imidazoles in a 'para' or 'linear' arrangement. It was reasoned that this core should provide an overall shape and projection of the imidazoles that would mimic the tetracyclic core, but being only slightly shorter in length (based on molecular modeling,[13] anthracene is ~13% shorter than the tetracyclic core of MK-8742, Fig. 2). Preparation of **4** is illustrated in Scheme 1. 2,6-Dibromoanthracene **1** was converted to the pinacol boron diester **2** while compound **3** was prepared according to published procedures.[14,15] Suzuki coupling between **2** and **3** followed by removal of the Boc groups and installation of the (*S*)-valine methyl carbamate afforded target **4**. The chloro- or methyl-substituted anthracene analogs **10** and **11** (Table 1) were prepared according to Scheme 1 except starting with the commercially available substituted anthracene.

Efforts were then focused upon introduction of heterocycles into the anthracene core. Acridine analogs (**12**, **13**) and phenazine analog (**14**) were prepared from commercially available dibrominated starting materials using the chemistry route outlined in Scheme 1. Benzo[1,2-b:4,5-b′]difuran analog **15** was prepared according to the chemistry route shown in Scheme 2. The preparation began with benzofuran formation between phenol **5** and known pyrrolidine **6**[11] to afford benzofuran intermediate **7**. In a separate step, **7** was treated again with **6** to install a second benzofuran which was then treated with HCl to afford diamine **8**. Treatment of **8** with Moc Val **9** under HATU coupling conditions afforded **15**. Naphtho[2,1-*b*]furan analog **16** was prepared in a same manner as **15**.

Table 1 summarizes the HCV wild-type (GT1a, 1b, 2a, 3a) and mutant (GT1a Y93H) virologic profile for various tricyclic derivatives.[16] The anthracene derivative **4** was potent against the wild type virus, but its GT1a Y93H EC_{50} value was weaker and in the upper double digit nM range. Incorporation of a methyl group or chloride into the C9 position of the anthracene core (**10** and **11**) showed a comparable profile to **4** except for a 10-fold loss in activity against GT3a. Addition of a basic nitrogen, into the middle ring of anthracene (**12**), was tolerated except for a significant loss of potency toward GT1a Y93H (Table 1). A nitrile group was installed

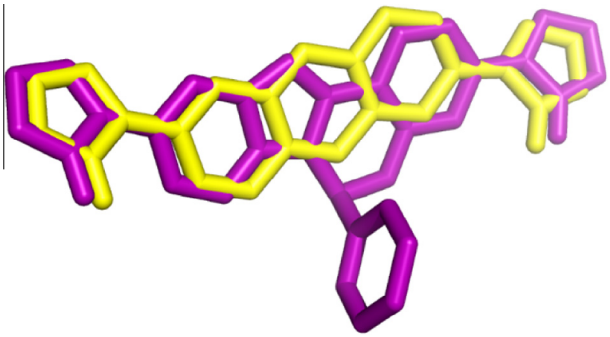
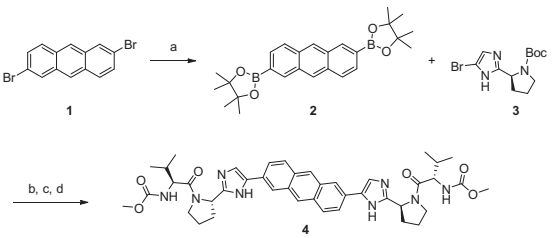
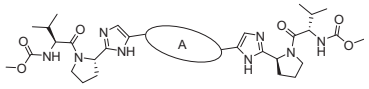


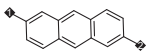
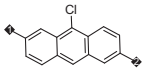
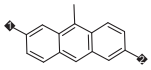
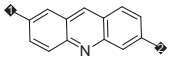
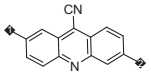
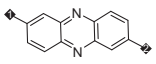
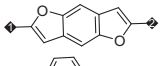
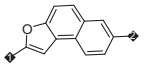
Figure 2. Overlay of anthracene-imidazole core (yellow) and MK-8742 core (purple).



Scheme 1. Preparation of **4**. Reagents and conditions: (a) Bis-pinacol diborate, Pd(dppf)Cl_2, KOAc, dioxane, 110 °C, 15 h, 73%. (b) Pd(dppf)Cl_2, Na_2CO_3, THF/H_2O (10:1), reflux, 15 h, 61%. (c) HCl, MeOH, 0.5 h, 100%. (d) (Methoxycarbonyl)-L-valine, BOP, DIPEA, DMF, 10 h, 65%.

Table 1
EC_{50} (nM) values for compounds **4**, **10**–**16**[16]



ID	A	GT-1a	GT-1b	GT-2a	GT-3a	GT-1a Y93H
4		0.006	0.001	0.005	0.06	87
10		0.05	0.003	0.01	0.6	66
11		0.02	0.005	0.005	0.5	42
12		0.05	0.01	0.04	nt	1050
13[a]		0.3	0.01	1	nt	nt
14		0.06	0.06	0.1	0.2	61
15		0.03	0.001	0.05	nt	nt
16		>10	0.01	0.3	nt	1400

nt = not tested.
[a] With 10% FBS added in the assay.