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Finger loop inhibitors of the HCV NS5b polymerase. Part II. Optimization of tetracyclic indole-based macrocycle leading to the discovery of TMC647055

Sandrine Vendeville *, Tse-I. Lin, Lili Hu, Abdellah Tahri, David McGowan, Maxwell D. Cummings, Katie Amssoms, Maxime Canard, Stefaan Last, Iris Van den Steen, Benoit Devogelaere, Marie-Claude Rouan, Leen Vijgen, Jan Martin Berke, Pascale Dehertogh, Els Fransen, Erna Cleiren, Liesbet van der Helm, Gregory Fanning, Kristof Van Emelen, Origène Nyanguile, Kenny Simmen, Pierre Raboisson

Janssen Infectious Diseases BVBA, 30 Turnhoutseweg, B-2340 Beerse, Belgium

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ABSTRACT

Optimization of a novel series of macrocyclic indole-based inhibitors of the HCV NS5b polymerase targeting the finger loop domain led to the discovery of lead compounds exhibiting improved potency in cellular assays and superior pharmacokinetic profile. Further lead optimization performed on the most promising unsaturated-bridged subseries provided the clinical candidate 27-cyclohexyl-12,13,16,17-tetrahydro-22-methoxy-11,17-dimethyl-10,10-dioxide-2,19-methano-3,7:4,1-dimetheno-1*H*,11*H*-14,10,2,9,11,17-benzoxathiatetraazacyclo docosine-8,18(9*H*,15*H*)-dione, TMC647055 (compound **18a**). This non-zwitterionic 17-membered ring macrocycle combines nanomolar cellular potency (EC_{50} of 82 nM) with minimal associated cell toxicity (CC_{50} >20 μM) and promising pharmacokinetic profiles in rats and dogs. TMC647055 is currently being evaluated in the clinic.

An estimated 3% of the worldwide population is infected by Hepatitis C virus (HCV), a major cause of acute hepatitis and chronic liver disease, ultimately leading to cirrhosis, liver failure, and hepatocellular carcinoma.[1,2] The current standard of care treatment, incorporating ribavirin and PEG-interferon alpha, suffers from several drawbacks including limited efficacy, treatment related side-effects and long treatment period, especially in patients infected by genotype 1 virus.[3,4] In the search for novel HCV direct antiviral agents (DAA), inhibition of the NS5b RNA-dependant RNA-polymerase is of particular interest as this enzyme was shown to be essential for viral replication[5,6] and has no mammalian counterpart.

Several classes of nucleoside and non nucleoside inhibitors,[7,8] targeting the different allosteric sites NNI-1 to 4, have demonstrated efficacy in clinical trials.[9–12] The so-called thumb domain I or finger loop region[13] is an especially attractive target, as compounds targeting this site enable a broad genotypic coverage. Several classes of indole-based inhibitors targeting the NNI-1 site have been discovered and optimized,[14–19] with a particular focus on zwitterionic structures, such as compounds **1**[20] and **2**[21] (Fig. 1). We have previously reported our strategy towards a new series of macrocyclic indole-based compounds, leading to the discovery of potent, bioavailable, and non zwitterionic inhibitors, as exemplified by compound **3** (Fig. 1).[22]

Here we report our lead optimization of a novel series of macrocyclic inhibitors which have been further rigidified with the introduction of a bridge between the indole ring and its C2 phenyl substituent. Indeed, we hypothesized that this approach could eventually improve the drug-like properties of our lead series by (i) increasing the potency by bringing the torsion angle between the phenyl and indole moiety in a pre-bound conformation of 46° as previously determined by X-ray crystallography,[18] (ii) improving the metabolic stability by increasing the overall rigidity of the molecule, which becomes less accessible to cytochromes and (iii) balancing the lipophilicity of the cyclohexylindole moiety by introducing polar functions in the macrocycle. This lead optimization effort culminated with the identification of the clinical candidate TMC647055 (**18a**).

The synthesis of the macrocyclic indole derivatives **18a–k**, **26a** and **27a** (Tables 1 and 2) was performed using either the unsaturated acids **8a–d** (Scheme 1) or the cyclopropyl acids **13a,b** (Scheme 2) as starting materials. The cinnamic acid analogs **8a–d** were readily prepared from the 2-bromoindole derivative **4**[23] following the procedures outlined in Scheme 1.

Activation of **4**[23] with pinacolborane followed by the reaction of the so-formed boronic ester **5** with the substituted 2-bromobenzaldehydes in presence of palladium acetate afforded the

* Corresponding author.
E-mail address: svendev1@its.jnj.com (S. Vendeville).

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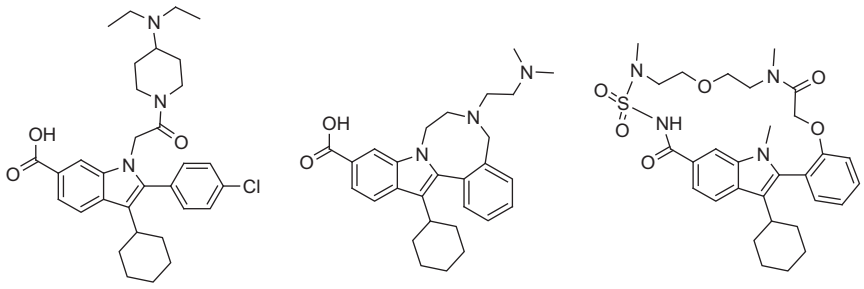


1
EC_{50} = 127 nM

2
EC_{50} = 140 nM

3
EC_{50} = 190 nM

Figure 1. Finger loop inhibitors of NS5b polymerase.

Table 1
Effect of the type of bridge on potency in cellular HCV assays, metabolic stability and rat PK parameters

No.	EC_{50} (nM)	RLM[b]	HLM[b]	In vivo rat PK parameters[a]			
				Cl[c] (L/h/kg)	[Liver][d] (ng/mL)	L/P[e]	*F* (%)[f]
3	190	50	65	7.7	1717	64	21
18a	82	30	35	3.2	7807	46	>66
26a	40	72	95	5.2	3200	38	51
27a	800	nd	nd	—	—	—	—
25a	79	42	63	3.2	898	22	15
25b	3830	nd	nd	—	—	—	–

[a] Vehicle iv (2 mpk) PEG400/saline 70/30; po (10 mpk) PEG400/2% vitE-TPGS; $n = 3$.
[b] RLM and HLM: resp. rat and human liver microsomes stability expressed as % of compound metabolized after 15 min at a concentration of 5 μM.
[c] Plasma clearance.
[d] Liver concentrations after oral administration 7 h post-dosing.
[e] Liver/plasma ratio after oral administration 7 h post-dosing.
[f] Oral bioavailability.

corresponding aldehydes **6a**–**b**, which were subsequently reacted with methyl 2-(dimethoxyphosphoryl)acetate in presence of cesium carbonate to afford the corresponding esters **7a**–**b** in high yields (72–94%). Alternatively, aldehydes **6c–d** could be obtained via a one step procedure by reacting the bromoindole derivative **4** with commercially available 2-formyl-4 or 5-Cl-phenylboronic acids, in the presence of potassium carbonate. The acid intermediates **8a**–**d** were obtained by saponification of the corresponding esters **7a**–**d** in almost quantitative yields.

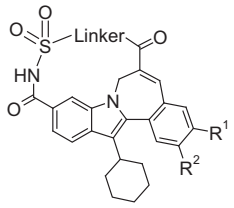
Alternatively, the ester **7a** was reacted with trimethylsulfoxonium iodide in presence of sodium hydride to give the cyclopropyl ester **9**, which was saponified to the corresponding acid **10** in 93% yield as shown in Scheme 2. The enantiomerically pure carboxylic acids **13a** and **13b** were obtained via the transformation of the racemic mixture of **10** into the pair of diastereoisomers **12a** and **12b**, using (*S*)-4-benzyl-2-oxazolidinone as chiral auxiliary followed by a separation by column chromatography and the subsequent removal of the chiral auxiliary under basic conditions in quantitative yields.

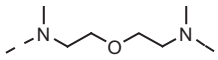
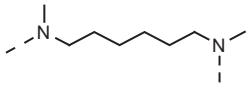
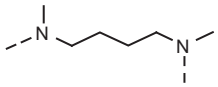
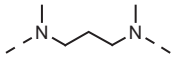
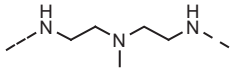
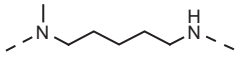
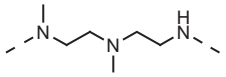
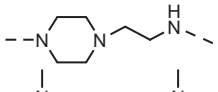
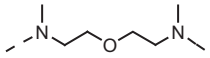
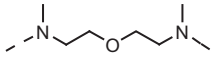
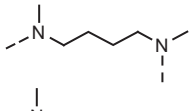
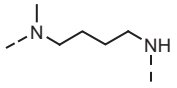
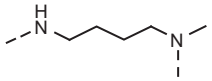
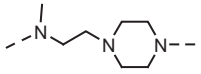
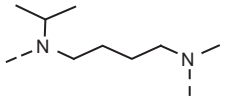
Starting from the mono-protected indole derivatives **8a–d** and **13a**,**b** two routes were used to introduce the linkers as shown in Schemes 3 and 4. The first route (Scheme 3) allowed the introduction of the bis-amino linker on the carboxylic acids **8a**–**d** using either mono-protected bis-amines **14f–h** or symmetrical unprotected bis-amines **14a–e** to afford the amides **15a**–**k** in good yields (>80%). The formation of dimers with the unprotected bis-amines **14a–e** was minimal when an excess of amine was used in diluted conditions. After a deprotection step, with thiophenol in the presence of cesium carbonate in dimethylformamide or trifluoroacetic acid in dichloromethane to remove, respectively, the nosyl or the Boc protecting group, intermediates **15a–k** were refluxed in dioxane with an excess of sulfamide to provide intermediates **16a–k** in moderate to good yields (50–90%). Finally, after the deprotection of the *tert*-butylester, the macrocyclisation was achieved by a tandem of reactions involving the activation of the carboxylic acid in the presence of CDI, followed by subsequent intramolecular nucleophilic attack of the sulfamide moiety in presence of DBU resulting in the target compounds **18a–k**. Similarly, this route was applied to the cyclopropyl carboxylic acids **13a** and **13b**, to provide compounds **26a** and **27a**, respectively.

Alternatively, the target macrocyclic indoles **24a**–**d** were prepared from the corresponding mono-Boc protected bis-amines **20a**–**d** as depicted in Scheme 4. Deprotection of the *tert*-butyl ester **7a** in presence of trifluoroacetic acid followed by the introduction of the sulfonamides **21a**–**d**, which were readily accessible via a one step synthesis from the corresponding amines **20a**–**d**, afforded the open intermediates **22a**–**d** in 53–68% yield. The ester and Boc protecting groups were successively cleaved by saponification and treatment with TFA, respectively, leading to the acidamino derivatives **23a**–**d**, which were subsequently macrocyclized to the target products **24a**–**d** using a CDI/DBU standard procedure. Eventually, the pure enantiomers possessing a saturated bridge **25a** and **25b** (Scheme 5), were synthesized by catalytic hydrogenation of the olefin bridge of compound **18a**, resulting in a mixture of enantiomers which were separated by chiral SFC.

Anti-HCV activities (EC_{50}) of final macrocyclic compounds were determined in the Huh-7 replicon cell line containing the subgenomic bicistronic HCV genotype **1b** replicon clone ET with a luciferase read out and compared with the cytotoxicity measured in MT4 and Huh-7 cell lines[24] (see Tables 1 and 2). None of the compounds showed significant cytotoxicity, with selectivity indexes range from 70 to over 400. In addition to potency and selectivity index, metabolic stability and in vivo rat PK parameters were also measured

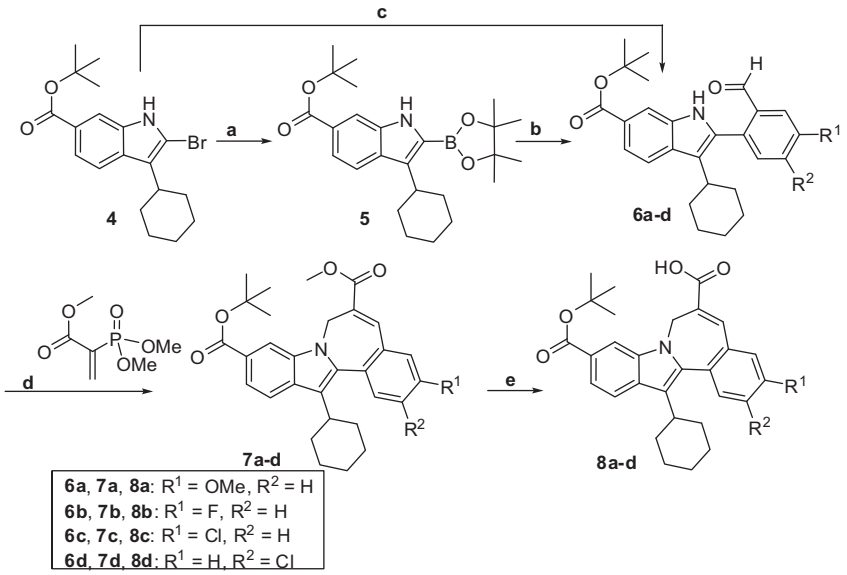
Table 2
Effect of the linker and phenyl substitution on potency and metabolic stability in the unsaturated-bridged series



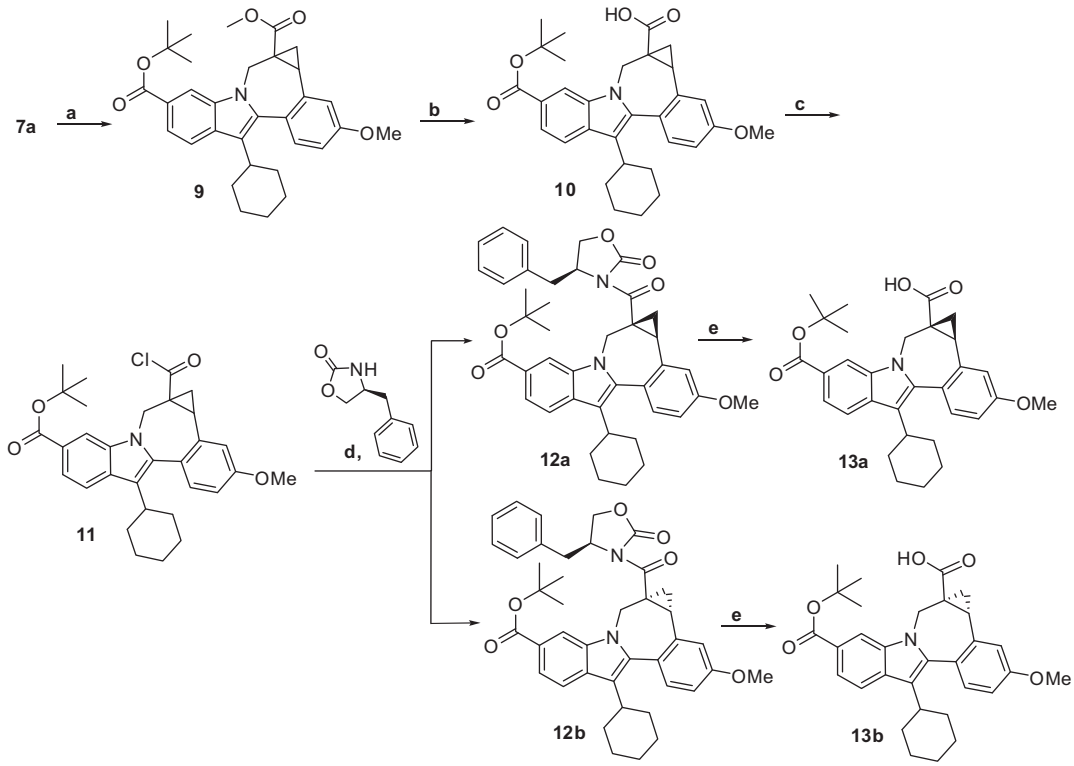
No.	R^1	R^2	Linker	EC_{50} (nM)	SI[a]	RLM[b]	HLM[b]
18a	OMe	H		82	>300	30	35
18b	OMe	H		160	150	46	99
18c	OMe	H		82	>330	26	56
18d	OMe	H		680	72	28	18
18e	OMe	H		470	>68	23	7
18f	OMe	H		130	>400	27	32
18g	OMe	H		550	>58		
18h	OMe	H		860	>40	16	10
18i	Cl	H		280	150	22	16
18j	F	H		72	>250	37	38
18k	H	Cl		14,480	>2	30	29
24a	OMe	H		912	>40	13	20
24b	OMe	H		550	>58	25	27
24c	OMe	H		180	>170	17	26
24d	OMe	H		330	>100	12	80

[a] SI (selectivity index) in Huh-7 cells (CC_{50}/EC_{50}).
[b] RLM and HLM: resp. rat and human liver microsomes stability expressed as% of compound metabolized after 15 min at a concentration of 5 μM.

and used to prioritize the different subseries, characterized by a different bridge. Thus, a first series of analogs having the same linker in common and only differing by their bridge, namely an unsaturated bridge for compound **18a**, a cyclopropyl bridge for diastereoisomers **26a** and **27a** and a saturated bridge for enantiomers **25a** and **25b**, was synthesized and evaluated in vitro (EC_{50}, RLM and HLM) and in vivo after a single iv and oral administration of 2 and 10 mg/kg of macrocyclic compound, respectively (Table 1). The introduction of a bridge was beneficial for potency, whatever the type of bridge used (compare **18a**, **26a** and **25a** with **3**). Indeed, more than a two fold increase in replicon inhibition was measured with the new macrocycles compared with our first generation macrocycle **3**, resulting in very potent inhibitors. Of note, the anti-HCV activity observed with **26a** and **25a** was highly enantiospecific, with a reduction of 20- and 48-fold in potency for the (*S*)-enantiomers **27a** and **25b**, respectively. Compound **18a** and active enantiomers **26a** and **25a** were further evaluated for rat PK analysis. The plasma kinetics, oral bioavailability together with liver tissue distribution in male Sprague–Dawley rats were determined after a single oral administration of 10 mg/kg of the dosed compounds using PEG400 2% vitamin E-TPGS as vehicle. These data were analyzed and compared with those obtained after a single intravenous (iv) administration of 2 mg/kg in PEG400/saline, 70:30. These results are reported in Table 1.

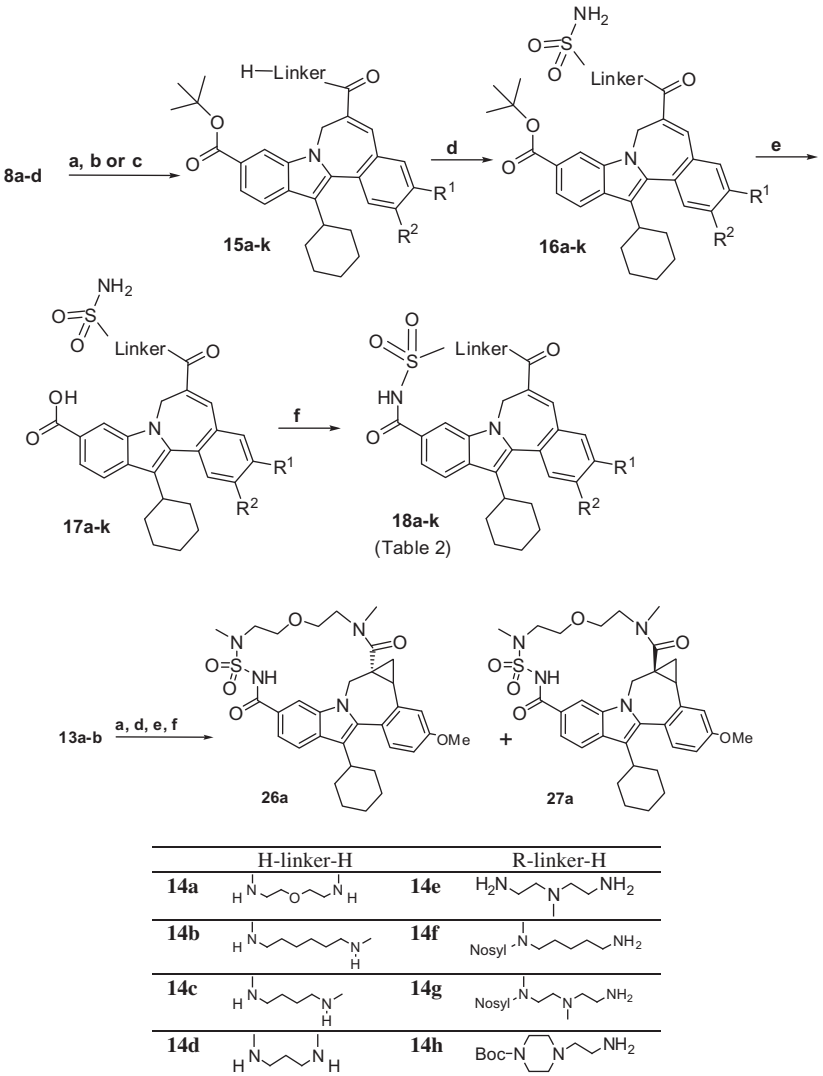


Scheme 1. Reactions and conditions: (a) (i) Pinacolborane, TEA, THF, RT; (ii) biphenyl-2-yldicyclohexylphosphine, $Pd(OAc)_2$, 80 °C; (b) 2-Br-4-(R^2)-5-(R^1)benzaldehyde 1.2 equiv (R^1 = OMe, R^2 = H and R^1 = F, R^2 = H), Na_2CO_3 3 equiv, $Pd(PPh_3)_4$ 0.05 equiv, DME/H2O 4/1, 70 °C, 1 h; (c) 2-CHO-4-(R^1)-5-(R^2)phenylboronic acid 1.2 equiv (R^1 = Cl, R^2 = H and R^1 = H, R^2 = Cl), K_2CO_3 2.4 equiv, $PdCl_2(PPh_3)_2$ 0.05 equiv, DME/H2O 4/1, 70 °C, 3 h; (d) Cs_2CO_3, DMF, 60 °C; (e) LiOH, H_2O/THF/MeOH, RT.



Scheme 2. Reactions and conditions: (a) (i) Trimethylsulfoxonium iodide, NaH, DMSO, RT; (ii) **7a**, 50 °C; (b) LiOH, H_2O/THF/MeOH, RT.; (c) $(COCl)_2$, DMF, THF, 0 °C; (d) (i) (*S*)-4-benzyl-2-oxazolidinone (1.1 equiv), *n*-BuLi (1.1 equiv), THF, −78 °C, (ii) **11**, THF, −78 °C, (iii) flash chromatography; (d) NaOH 1 N, MeOH/THF, RT.

All three compounds exhibited an improved in vivo clearance compared with compound **3**. Compounds **18a** and **25a** although having a similar clearance of 3.2 L/h/kg, exhibited marked differences after oral administration. The saturated bridged-analog **25a** resulted in reduced absorbtion compared with its unsaturated counterpart **18a** (oral bioavailability of 15% for **25a** vs >66% for **18a**), and also displayed a lower distribution to the liver (liver to plasma ratio being 22 and 46, respectively). Although the cyclopropyl bridged-analog **26a** combines a good oral bioavailability of 51% with a high liver to plasma ratio (38), its clearance was high (5.2 L/h/kg), above rat hepatic blood flow. Overall, **18a** exhibited the best PK profile with a high bioavailability of at least 66%, an acceptable plasma clearance of 3.2 L/h/kg, and a high hepatic exposure of 7807 ng/mL at 7 h post oral administration, corresponding to approximately 20 times the value of the EC_{50} measured in the presence of 40% human serum. Of note, the

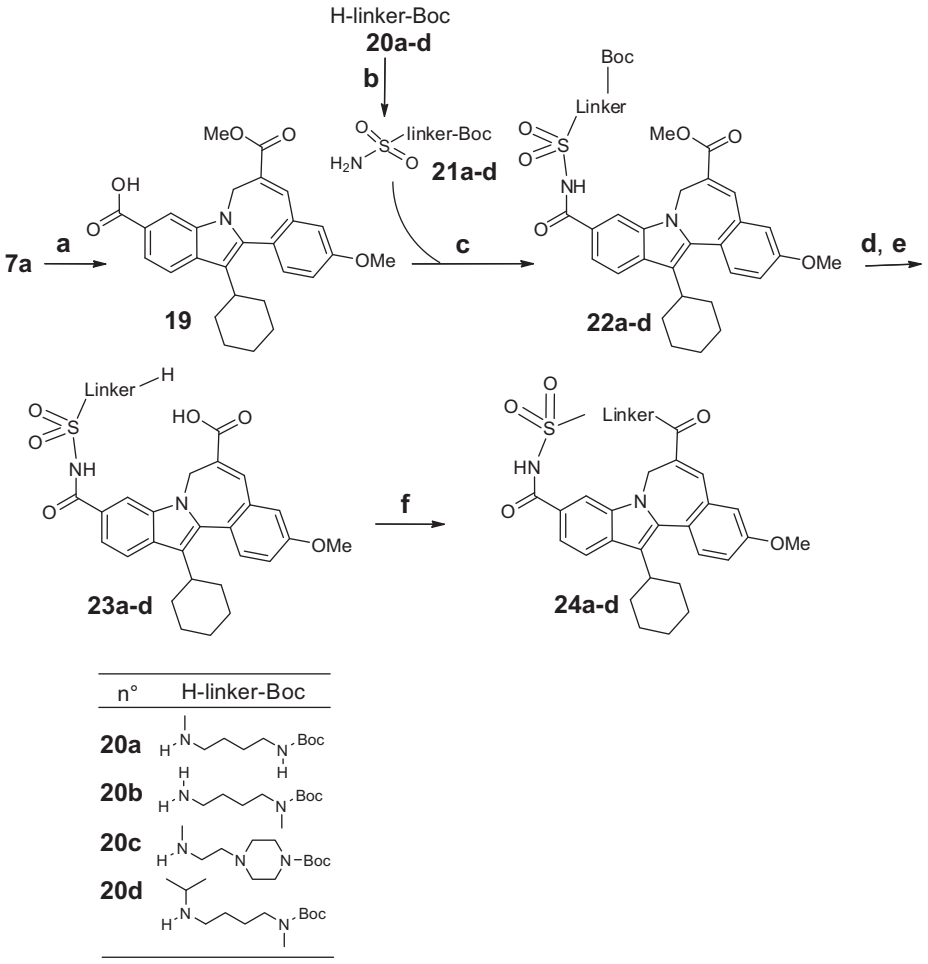


Scheme 3. Reactions and conditions: (a) **14a–e**, HATU, DIPEA,THF; (b) (i) **14f–g**, HATU, DIPEA, THF; (ii) thiophenol, Cs_2CO_3, DMF, RT (c) (i) **14h**, HATU, DIPEA, THF; (ii) TFA/DCM, (d) sulfamide, dioxane 100 °C; (e) TFA/DCM; (f) CDI, dry THF, RT, then DBU, THF.

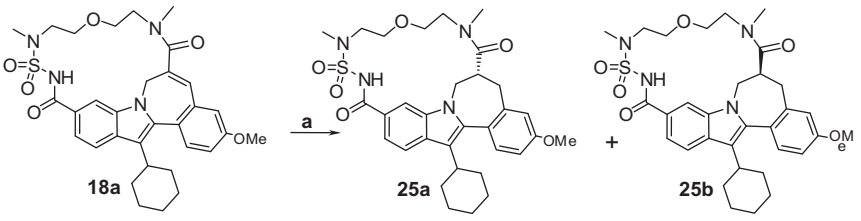
excellent distribution to the liver (L/P ratio of 46) observed with **18a** is a key parameter toward in vivo efficacy for an anti-HCV drug given that the virus replicates primarily in hepatocytes. These results prompted the selection of the unsaturated subseries for further structure–activity studies.

Two main variations were then considered (see Table 2): the linker (length, presence of heteroatoms, substitution on the nitrogen) with the synthesis of compounds **18b–h** and **24a–d** and the substitution of the phenyl moiety (**18i–k**). Both the length of the linker and the substitution on the amines had an impact on potency and metabolic stability. The optimal macrocycle size was found to be a 16- to 17-membered ring where **18a**, **18c**, **18f** and **24c** were all potent inhibitors (EC_{50} <200 nM). Although the ring constriction led reduced potency (**18d**, EC_{50} = 680 nM) with a good human liver microsome stability (18% metab.), the ring extension had little impact on potency (**18b**, EC_{50} = 160 nM) but resulted in a dramatic loss of liver microsome stability (99% metab.). Interestingly similar effect of macrocycle ring size was observed with our previously published HCV NS3 serine protease analogs. We hypothesize that a more rigid macrocycle results in a reduced accessibility to the active site of cytochromes leading to reduced metabolism and improved stability. In particular, the removal of either methyl group on the nitrogens of the linker yielded less active compounds, although these were more stable in HLM (compare **24a** and **24b** with **18c**). Replacement of the methyl group on the sulfamide nitrogen by a bulkier isopropyl group (**24d**) also led to decreased potency (EC_{50} = 330 nM) and HLM stability (80% metab.) when compared with **18c** (EC_{50} = 82 nM, 56% metab.). This reduced activity might be explained by the steric hindrance of the isopropyl moiety which would disturb the optimal binding conformation of the acylsulfonamide moiety. Finally, introduction of a basic amine in the macrocycle resulted in compounds **18e, g, h** and **24c** which were all less potent than **18a** but were metabolically more stable. This loss of potency contrasts with the observations from other indole series, where a fivefold gain in potency was measured.[15] Analysis of the published X-ray structure suggests that a small substituent in position R^1 or R^2 would be tolerated.[18] Although a fluoro atom in R^1 (**18j**) was found equipotent compared with the lead **18a** (EC_{50} = 72 and 81 nM, respectively), the introduction of a chlorine led to **18i**, which is approximately three times less potent than the methoxy analog **18a**. The introduction of a chloro atom in R^2 position led to an almost inactive compound (**18k**, EC_{50} = 14 μM).

Based on their overall profile, **18c, f, j** and **24c** were selected and compared with the lead **18a** for their PK profile in rats (Table 3). The zwitterionic compound **24c** showed overall suboptimal PK properties: poor oral bioavailability (F = 3%) associated with extensive clearance (Cl = 9.4 L/h/kg) and low



Scheme 4. Reagents and conditions: (a) TFA/DCM, RT; (b) sulfamide, dioxane, 100 °C; (c) CDI (1.3 equiv), ACN, 60 °C then **21a–d**, DBU (1.5 equiv), 60 °C; (d) LiOH, H_2O/THF/MeOH, RT; (e) TFA/DCM, RT; (f) DIPEA, HATU, dry DMF, 0 °C then RT.



Scheme 5. Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, THF; chiral separation of enantiomers by SFC using a CHIRALCEL OD-H column.

hepatic concentration measured 7 h post dosing ([liver] = 299 ng/mL). This discrepancy between in vitro rat liver microsome stability and in vivo clearance indicates that metabolism may not be the main mechanism of clearance, but bile excretion is most probably also involved. A poor oral bioavailability (F = 6%) associated with high clearance (Cl = 4.2 L/h/kg) was also measured with the analog **18f**, although a good liver distribution was observed, leading to a very high liver to plasma ratio of 341. Somewhat more encouraging, **18c** and **18j** displayed a very similar rat PK profile compared with the lead **18a**, however with no major advantage.

Further preclinical characterizations were performed on **18a**. In dogs, **18a** also showed an acceptable PK profile, characterized by high oral bioavailability (F = 87%) and high systemic exposure (C_{max} = 10.2 μM and AUC_{0-inf} = 25.8 μM h) after single oral dosing of 10 mg/kg, combined with a moderate plasma clearance (Cl = 0.54 L/h/kg) and low volume of distribution (Vd_{ss} = 0.32 L/kg). Furthermore, and contrary to other series of indole-based

Table 3
Pharmacokinetic parameters of selected macrocyclic analogs (2 mg/kg iv, 10 mg/kg po; vehicle iv PEG400/saline 70/30; po PEG400/2% vitE-TPGS, n = 3)

No.	Cl[a] (L/h/kg)	C_{max} (ng/mL)	[Liver][b] (ng/mL)	L/P[c]	F (%)[d]
18a	3.2	440	7800	46	>66
18c	2.4	800	5000	23	76
18f	4.2	30	6317	341	6
18j	3.7	272	6560	62	52
24c	9.4	6	299	108	3

[a] Plasma clearance.
[b] Liver concentrations after oral administration at 7 h post-dosing.
[c] Liver/plasma ratio after oral administration 7 h post-dosing.
[d] Oral bioavailability.

inhibitors containing a carboxylic acid,[20,21] in vivo metabolism of compound **18a** in rats did not produce any phase two metabolites, such as undesirable reactive acyl glucuronides. Further characterization of **18a** showed a high selectivity towards other polymerases and a panel of enzymes and receptors, as well as an acceptable profile in assays measuring cytotoxicity, genotoxicity and cardiovascular effects, with little potential to cause drug–drug interaction since no major inhibition of cytochromes CYP450 has been detected.

In summary, we have described the discovery of macrocyclic bridged-indoles as very potent inhibitors of HCV replication in vitro. Modulation of the type of bridge linking the indole moiety to the C2-phenyl, the macrocycle linker, and the substitution on the phenyl ring, resulted in the discovery of promising inhibitors (e.g., **18a**, **18c** and **18j**), which combine potent activity in cellular HCV assays (EC_{50} <100 nM), encouraging pharmacokinetic properties, and acceptable profiles in a panel of preclinical assays. Taken together, these data enabled us to select **18a** (TMC647055) for further pre-clinical and clinical characterization. This HCV NS5b polymerase inhibitor is currently being evaluated in phase 2 clinical trials.

References

1. The Global Burden of Hepatitis C Working Group (2004). J. Clin. Pharmacol. **2004**, *44*, 20.
2. Ghobrial, R. M.; Steadman, R.; Gornbein, J.; Lassman, C.; Holt, C. D.; Chen, P.; Farmer, D. G.; Yersiz, H.; Danino, N.; Collisson, E.; Baquarizo, A.; Han, S. S.; Saab, S.; Goldstein, L. I.; Donovan, J. A.; Esrason, K.; Busuttil, R. W. *Ann. Surg.* **2001**, *234*, 384.
3. Strader, D. B.; Wright, T.; Thomas, D. L.; Seeff, L. B. *Hepatology* **2004**, *39*, 1147.
4. Manns, M. P.; Foster, G. R.; Rockstroh, J. K.; Zeuzem, S.; Zoulim, F.; Houghton, M. *Nat. Rev. Drug Disc.* **2007**, *6*, 991.
5. Behrens, S.-E.; Tomei, L.; De Francesco, R. *EMBO J.* **1996**, *15*, 12.
6. Lohmann, V.; Korner, F.; Herian, U.; Bartenschlager, R. *J. Virol.* **1997**, *71*, 8416.
7. Beaulieu, P. L. *Expert Opin. Ther. Patents* **2009**, *19*, 145.
8. Koch, U.; Narjes, F. *Curr. Top. Med. Chem.* **2007**, *7*, 1302.
9. Kwong, A. D.; McNair, L.; Jacobson, I.; George, S. *Curr. Opin. Pharmacol.* **2008**, *8*, 522.
10. Toniutto, P.; Fabris, C.; Biretto, D.; Fornasiere, E.; Rapetti, R.; Pirisi, M. *Curr. Opin. Invest. Drugs* **2007**, *8*, 150.
11. Cooper, C.; Lawitz, E. J.; Ghali, P., et al *J. Hepatol.* **2009**, *51*, 39.
12. Erhardt, A.; Deterding, K.; Benhamou, Y.; Reiser, M.; Forns, X.; Pol, S.; Calleja, J. L.; Ross, S.; Spangenberg, H. C.; Garcia-Samaniego, J.; Fuchs, M.; Enriquez, J.; Wiegand, J.; Stern, J.; Wu, K.; Kukolj, G.; Marquis, M.; Beaulieu, P.; Nehmiz, G.; Jurgen, S. And BILB 1941 Study Group *Antiviral Ther.* **2009**, *14*, 23.
13. Beaulieu, P. L. *Curr. Opin. Drug Disc. Dev.* **2006**, *9*, 618.
14. Beaulieu, P. L.; Gillard, J.; Bykowski, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4987.
15. Harper, S.; Avolio, S.; Pacini, B., et al *J. Med. Chem.* **2005**, *48*, 4547.
16. Harper, S.; Avolio, S.; Pacini, B., et al *J. Med. Chem.* **2005**, *48*, 1314.
17. Stansfield, I.; Pompei, M.; Conte, I., et al *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5143.
18. (a) Ikegashira, K.; Oka, T.; Hirashima, S., et al *J. Med. Chem.* **2006**, *49*, 6950; (b) Cummings, M. D.; Lin, T.-I.; Hu, L.; Tahri, A.; McGowan, D.; Amssoms, K.; Last, S.; Devogelaere, B.; Rouan, M.-C.; Vijgen, L.; Berke, J. M.; Dehertogh, P.; Fransen, E.; Cleiren, E.; van der Helm, L.; Fanning, G.; Van Emelen, K.; Nyanguile, O.; Simmen, K.; Raboisson, P.; Vendeville, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 4637.
19. Habermann, J.; Capito, E.; FerreiraMdel, R.; Koch, U.; Narjes, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 633.
20. Giuliano, C.; Fiore, F.; Di Marco, A., et al *Xenobiotica* **2005**, *1035*, 35.
21. Stansfield, I.; Ercolani, C.; Mackay, A., et al *Bioorg. Med. Chem. Lett.* **2009**, *19*, 627.
22. For part 1, see: McGowan, D. et al. *Bioorg. Med. Chem. Lett.* 2012, http://dx.doi.org/10.1016/j.bmcl.2012.03.097.
23. Colarusso, S.; Conte, I.; Habermann, J.; Narjes, F.; Ponzi, S. WO2006029912A1.
24. Lin, T.-I.; Lenz, O.; Fanning, G.; Verbinnen, T.; Delouvroy, F.; Scholliers, A.; Vermeiren, K.; Rosenquist, Å.; Edlund, M.; Samuelsson, B.; Vrang, L.; de Kock, H.; Wigerinck, P.; Raboisson, P.; Simmen, K. *Antimicrob. Agents Chemother.* **2009**, *53*, 1377.