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Inhibitors of hepatitis C virus NS3/4A: α-Ketoamide based macrocyclic inhibitors

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ABSTRACT

A novel series of hepatitis C virus (HCV) NS3/4A protease inhibitors bearing a P2-P4 macrocycle and a P1-P1′ α-ketoamide serine trap is reported. The NS3 protease, which is essential for viral replication, is considered one of the most attractive targets for developing novel anti-HCV therapies. The optimization of both the macrocycle and the warhead portions led to the discovery of compounds **8b** and **8g** with a good activity both in the enzyme as well as in the cell based (replicon) assays with favorable PK profile in a preclinical species.

Hepatitis C virus (HCV) is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons, 3% of the world's population, are chronically infected with HCV and 3–4 million people are newly infected each year.[1] A significant fraction of these develop serious liver disease including cirrhosis and hepatocellular carcinoma.[2] No vaccine is currently available to prevent hepatitis C, while the current standard of care—pegylated interferon-α in combination with ribavirin—is poorly tolerated and not highly efficacious, particularly in patients infected with HCV genotypes 1 and 4–6.[3] Consequently, there is an intense interest in the development of orally active, small-molecule inhibitors of HCV replication that may offer enhanced efficacy and less adverse effects.

Following the successful paradigm established for HIV, initial efforts to develop HCV-directed antiviral agents have focused on inhibition of essential virally-encoded enzymes.[4] Among these, the serine protease NS3 is one of the validated targets that plays an essential role in the viral replication cycle.[5] The HCV NS3 protein is noncovalently associated with the viral protein NS4A in a heterodimeric complex (NS3/4A) responsible for the proteolytic cleavage of the viral polyprotein into its components and it is, therefore, essential in the process of HCV replication.[6]

Currently there are several NS3/4A protease inhibitors in clinical trials, which can be divided into two main classes: (i) the covalent reversible α-ketoamide serine trap inhibitors, represented by VX-950 (**1**: telaprevir, Fig. 1)[7] and SCH 503034 (**2**: boceprevir)[8] and (ii) the non-covalent reversible macrocyclic inhibitors exemplified by the prototypical compound, now discontinued, BILN-2061 (**3**: ciluprevir)[9] and the more recent ITMN-191 (phase Ib)[10] and TMC435350 (phase IIa).[11] Telaprevir (**1**) and boceprevir (**2**) are the most advanced inhibitors, and both recently entered phase III clinical trials.[12]

A new series of structurally distinct NS3/4A inhibitors bearing a P2-P4 macrocyclization was recently reported by our colleagues[13] and, the most advanced compound is MK-7009 (**4,** Fig. 2) currently in phase II with POC achieved.[14]

In this Letter, we report our efforts to evaluate the NS3/4A inhibition ability of a hybrid series of molecules designed by the

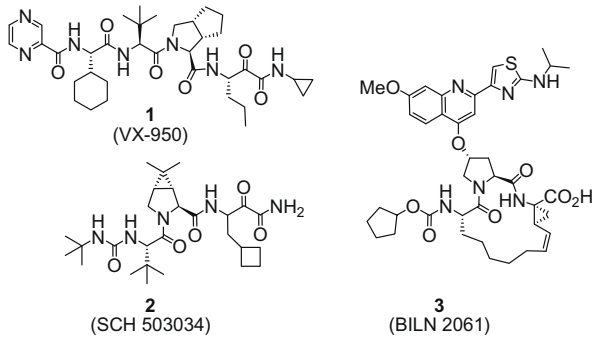

Figure 1. NS3/4A protease reference inhibitors.

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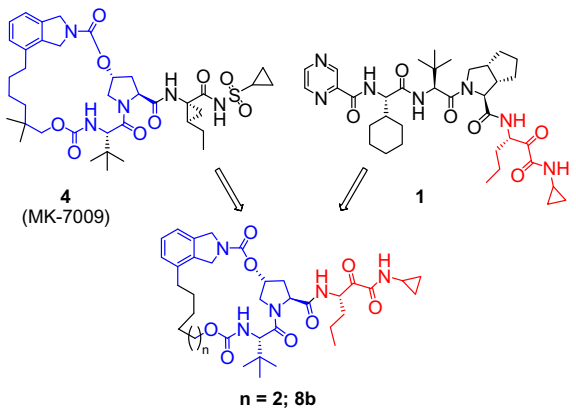
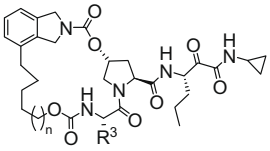


Figure 2. Strategy leading to the discovery of **8b**.

combination of the P2-P4 macrocycle portion of MK-7009 (**4**, in blue in Fig. 2) and the P1-P1′ warhead of the VX-950 (**1**, in red in Fig. 2) inhibitor.

An initial effort was aimed at determinining the best macrocycle size and the optimal P3 residue. Driven by our recent results in the field, attention was focused on 19- and 20-member macrocycles.[13] As shown in Table 1, the coupling of a P2-P4 19-member macrocycle moiety with the VX-950 **(1)** P1-P1′ warhead resulted in compound **8a** that showed similar enzymatic potency (K_i = 83 nM vs K_i = 110 nM for VX-950)[15] and improved activity in the cell based assay (EC_{50} = 600 nM vs EC_{50} = 1600 nM for VX-950).[16] An incremental lengthening of the linker afforded a further enhancement of both the enzymatic and the cell based replicon activity (**8b**; K_i = 57 nM; EC_{50} = 380 nM) compared to VX-950 (**1**). Replacement of the *t*-Leu residue of **8b** with one of the best known P3 residues previously identified, the *c*-pentyl, gave **8c** that resulted in a reduction of both the enzymatic inhibition and the cell based replicon activity (Table 1). Compound **8b** was then selected for the exploration of the P′ region.

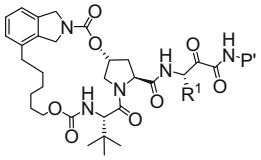
Table 1
Effect of the macrocycle size and P3 substitution on enzymatic and cellular potencies



Compd	*n*	R^3	**1b**	**1b** replicon[a]
			K_i[b] (nM)	EC_{50}[c] (nM)
VX-950 (**1**)	—	—	110	1600[d]
SCH 503034 (**2**)	—	—	35	200[e]
8a	1		83	600
8b	2		57	380
8c	2		95	670

[a] On the basis of the CC_{50} values determined for all the inhibitors listed in Tables 1 and 2 (mostly > 50–100 μM), none of these compounds was considered as cytotoxic.
[b] Inhibition of the full-length HCV NS3/4A protease measured by the inhibiton constants (K_i values);[15] K_i and EC_{50} values are the average of at least three independent determinations, standard deviation ± 10%.
[c] Inhibition of HCV replication in Huh-7 cell expressing a stably-replicating subgenomic HCV RNA; compounds were incubated at 37 °C for 96 h in the presence of 10% FCS.[16,17]
[d] In house data; the literature data (from Ref. 7) is: EC_{50} = 354 nM ± 35 nM obtained after 48 h incubation in the presence of 2% FBS.
[e] Data from Ref. 8b, obtained after 72 h incubation in the presence of 5% FBS.

Table 2
P1-P1′ optimisation



Compd	R^1	P′	**1b**	**1b** Replicon*
			K_i* (nM)	EC_{50}* (nM)
8b			57	380
8d			140	940
8e			78	1050
8f			66	520
8g			71	550
8h			242	1320
8i			140	>500
8j			176	790
8k			~2400	>12,500
8l			>2900	>6250

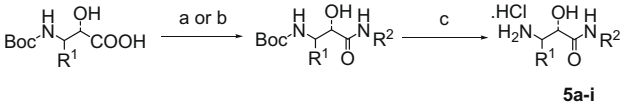
* See note a, b and c in Table 1.

The first moiety studied was the ring-size in the P′ ketoamide contained in **8b**. Towards this end, cyclobutyl and cyclopentyl were incorporated (as P1′) to yield **8d** and **8e** (Table 2). When compared to **8b**, both compounds showed a decreased activity in the enzymatic assay and in the replicon assay (**8d**: K_i = 140 nM, EC_{50} = 940 nM; **8e:** K_i = 78 nM, EC_{50} 1050 nM). Moving from cyclic to acyclic derivatives, the (±)-*sec*-butyl α-ketoamide **8f** retained the enzymatic activity (K_i = 66 nM) but exhibited a 1.4-fold reduced replicon activity when compared to **8b** (EC_{50} = 520 nM vs 380 nM for **8f** and **8b**, respectively). A similar shift in replicon activity was obtained when the cyclopropyl moiety was replaced with the allyl group yielding **8g.** When compared with **8b**, the newly synthesized inhibitor exhibited similar enzyme activity (K_i = 71 nM vs 57 nM for **8g** and **8b**, respectively) and a 1.4-fold shift in the replicon assay (EC_{50} = 550 nM vs 380 nM for **8g** and **8b**, respectively). When benzyl **8h**, (±)-1-phenylethyl **8i** and 2-pyridylmethyl **8j** were introduced in place of the cyclopropyl amide moiety of 8**b**, a reduced potency was observed, the three

Table 3
Liver levels and pharmacokinetic profile of **8b** and **8d**[a]

Compd	C_{max} (μM)	Plasma AUC 0–∞ (μM h)	4 h liver Concn[b] (μM)	F (%)
1 (VX-950)[c]	0.63	1.54[d]	0.81[e]	34.8
2 (SCH 503034)[c]	0.13	0.21[c]	NA[f]	3.5
8b	0.02	0.08	0.17	10
8g	0.16	0.58	0.48	ND[g]

[a] Compounds dosed at 5 mg/kg P.O. in PEG 400; data are geometric means from 3 animals, standard deviation ± 10%.
[b] It is assumed that density of liver tissue is 1 g/mL.
[c] Data adapted from Ref. 19.
[d] 0–8 h.
[e] Measured at 8 h; data adapted from Ref. 7.
[f] NA = not available.
[g] ND = not done.



cpd#	R^1	R^2	Yield (%)
5a	(S)-Nva	*c*-Pr	72
5b	(S)-Nva	*c*-Bu	70
5c	(S)-Nva	*c*-Pent	72
5d	(S)-Nva	(±)-*sec*-Bu	63
5e	(S)-Nva	allyl	80
5f	(S)-Nva	CH_2Ph	60
5g	(S)-Nva	(±)-$CH(CH_3)Bn$	75
5h	(S)-Nva	CH_2Pyr	59
5i	(R/S)-diFAbu	(±)-*sec*-Bu	77

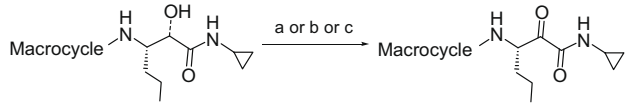
Scheme 1. Synthesis of the key α-hydroxyamides **5a–i**. Reagents and conditions: (a) HOBt, EDC, DIPEA, DMF, R–NH_2; (b) HATU, DIPEA, DMF, R–NH_2; (c) 4 M HCl, dioxane.

compounds exhibited a substantial reduction in both the enzymatic (2.5–4-fold) and cell based activity (up to fourfold) when compared with the best compound of the series.

The SAR then moved on the critical moiety represented by the P1 fragment. In particular the Norvaline (Nva) was replaced by the 2-amino-4,4-difluorobutyric acid (difluoroAbu), an amino acid that was designed and successfully implemented in our laboratory as a unique replacement of the natural cysteine residue (as P1) in the substrate-, product-like and α-ketoacid inhibitors of NS3/4A.[18] This replacement was applied to the α-ketoamide series, and resulted in compounds **8k** and **8l** (obtained as a mixture of diastereoisomers) that showed a significant loss of both the enzymatic activity (**8k**: $K_i \sim 2400$ nM; **8l**: $K_i > 2900$ nM) and the cell based activity (EC_{50} in the μM range).

Two different compounds (**8b** and **8g**) with a good in vitro potency profile, were selected for further evaluate of their properties in vivo. To this end, compounds **8b** and **8g** were dosed orally to male Wistar rats at 5 mg/kg and results compared with reported data for compounds **1** and **2** (Table 3).[19] After oral administration, both compounds **8b** and **8g** showed low plasma exposure (barely detectable for **8b**). The oral bioavailability F (%) of **8b** was slightly higher than the reported value for SCH 503034 (**2**) (F% = 10 vs 3.5 for **8b** and **2**, respectively) but significantly lower than the reported value for VX-950 (**1**) (F% = 34.8). The plasma exposure and Cmax of **8g** were favorable with respect to **2**, and poorer in comparison to **1**. It is interesting to note that the liver level of **8g** is not significantly less than VX-950 (**1**) in spite of the fact that the AUC is three fold lower than **1**.

Representative synthetic routes employed for the preparation of the key α-hydroxy-β-aminoamide intermediates **5a–i** and the HCV protease inhibitors **8a–l** are outlined in Schemes 1 and 2. The P1-P1′ α-hydroxy-β-aminoamide residues **5a–i** (Scheme 1) were prepared starting from the L-norvaline or (±)-4,4-difluoro-2-aminobutyric acid (difluoroAbu)-based hydroxyl acids[20] through an



Scheme 3. Alternative oxidations. Reagents and conditions: (a) TEMPO, BAIB, DCM, rt to 40 °C;[23] (b) MnO_2, acetone, rt to reflux;[24] (c) PS-2-iodylbenzamide, DCM, rt to 40 °C, 72 h.[25]

HATU- or EDC-mediated amide coupling followed by the HCl-mediated removal of the Boc protection (Scheme 1).

The key macrocycles **6a–c** (Scheme 2) were obtained in turn starting from acyclic precursors using an high yielding ring closing metathesis (RCM) performed according to the published patent literature.[21] Subsequently, Pd on charcoal catalyzed hydrogenation of the styryl olefin followed by the hydrolysis of the proline ester, using standard basic conditions (LiOH/THF), provided the acids **7a–c** that were coupled with the α-hydroxy-β-aminoamide P1-P1′ residues (**5a–i**) using a TBTU-mediated peptide coupling to lead to diastereomeric mixtures of the corresponding macrocyclic hydroxyamides. In a final step, oxidation of the latter with the Dess–Martin periodinane[22] afforded the desired α-ketoamides macrocycles **8a–l**.

The moderate yields obtained in the oxidation step led us to consider alternatives to the Dess–Martin protocol. A summary of different approaches tried is reported in the Scheme 3. None of them resulted in a clear improvement of the synthetic yield and all were discarded in favour of the already in place Dess–Martin procedure.

The structures and purity of the final products **8a–l**, obtained after HPLC purification as powders via lyophilization, were confirmed on the basis of their proton NMR, HPLC–MS traces and HRMS.[26]

In conclusion, we have prepared a new series of HCV NS3/4A inhibitors designed as hybrids of the slowly reversible serine trap P1-P1′ α-ketoamide warhead contained in the VX-950 (**1**) with the P2-P4 portion of our recently disclosed reversible macrocyclic inhibitor MK-7009 (**4**). Two compounds **8b, 8g** showed improved in vitro activity when compared to the clinical candidate VX-950 (**1**). In particular, compound **8b** showed a >4-fold increase of the inhibition in the cell based replicon assay. Compound **8b** showed a comparable level of inhibition also with the other clinical candidate SCH 503034 (**2**). Unfortunately **8b** showed an inferior PK profile in rat with respect to VX-950 (**1**) although it was comparable with SCH 503034 (**2**) and **8g** showed similar exposure and liver level with respect to both VX-950 and SCH 503034. Encouraged by the preliminary results a further evaluation of the series is ongoing.

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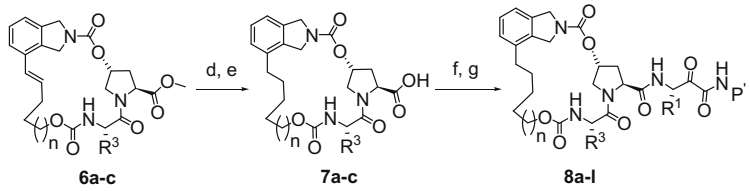

cpd#	n	R^3	R^1	P′	Yield (%)
8a	1	*t*-Bu	(S)-Nva	*c*-Pr	14
8b	2	*t*-Bu	(S)-Nva	*c*-Pr	20
8c	2	*c*-Pent	(S)-Nva	*c*-Pr	34
8d	2	*t*-Bu	(S)-Nva	*c*-Bu	21
8e	2	*t*-Bu	(S)-Nva	*c*-Pent	36
8f	2	*t*-Bu	(S)-Nva	(±)-*sec*-Bu	23
8g	2	*t*-Bu	(S)-Nva	allyl	12
8h	2	*t*-Bu	(S)-Nva	CH_2Ph	20
8i	2	*t*-Bu	(S)-Nva	(±)-$CH(CH_3)Bn$	18
8j	2	*t*-Bu	(S)-Nva	CH_2Pyr	20
8k	2	*t*-Bu	(R/S)-diFAbu	(±)-*sec*-Bu	15
8l	2	*t*-Bu	(R/S)-diFAbu	(±)-*sec*-Bu	15

Scheme 2. Synthesis of HCV protease inhibitors **8a–l**. Reagents and conditions: (d) H_2, 10% Pd/C, MeOH; 83% (**7a**), 88% (**7b**), 57% (**7c**); (e) LiOH, THF, EtOH, H_2O; (f) P1 α-hydroxy-β-aminoamides **5a–i**, TBTU, DIPEA, DMF or HATU, DIPEA, DMF; (g) Dess–Martin periodinane, Py, DCM.

NMR; Nadia Gennari and Monica Bisbocci for running the replicon assays. We also thank Michael Rowley and Nigel J. Liverton for helpful discussions.

References and notes

1. World Health Organization (WHO). Fact Sheet No. 164, October 2000.
2. Liang, T. J.; Heller, T. *Gastroenterology* **2004**, *127*, S62.
3. Feld, J. J.; Hoofnagle, J. H. *Nature* **2005**, *436*, 967.
4. De Clerq, E. *Nat. Rev. Drug Disc.* **2007**, *6*, 1001.
5. De Francesco, R.; Carfì, A. *Adv. Drug Delivery Rev.* **2007**, *59*, 1242.
6. Failla, C.; Tomei, L.; De Francesco, R. *J. Virol.* **1994**, *68*, 3753.
7. Lin, C.; Kwong, A. D.; Perni, R. B. *Infect. Disorder: Drug Targets* **2006**, *6*, 3.
8. (a) Venkatraman, S.; Bogen, S. L.; Arasappan, A.; Bennet, F.; Chen, K.; Jao, E.; Liu, Y.-T.; Lovey, R.; Hendrata, S.; Huang, Y.; Pan, W.; Parekh, T.; Pinto, P.; Popov, V.; Pike, R.; Ruan, S.; Santhanam, B.; Vibulbhan, B.; Wu, W.; Yang, W.; Kong, J.; Liang, X.; Wong, J.; Liu, R.; Butkiewicz, N.; Chase, R.; Hart, A.; Agrawal, S.; Ingravallo, P.; Pichardo, J.; Kong, R.; Baroudy, B.; Malcom, B.; Guo, Z.; Prongay, A.; Madison, V.; Broske, L.; Cui, X.; Cheng, K.-C.; Hsieh, Y.; Brisson, J.-M.; Prelusky, D.; Korfmacher, W.; White, R.; Bogdanowich-Knipp, S.; Pavlovsky, A.; Bradley, P.; Saksena, A. K.; Ganguly, A.; Piwinski, J.; Girijavallabhan, V.; Njoroge, F. G. *J. Med. Chem.* **2006**, *49*, 6074; (b) Malcom, B. A.; Liu, R.; Lahser, F.; Agrawal, S.; Belanger, B.; Butkiewicz, N.; Chase, R.; Gheyas, F.; Hart, A.; Hesk, D.; Ingravallo, P.; Jiang, C.; Kong, R.; Lu, J.; Pichardo, J.; Prongay, A.; Skelton, A.; Tong, X.; Venkatraman, S.; Xia, E.; Girijavallabhan, V.; Njoroge, F. G. *Antimicrob. Agents Chemother.* **2006**, *50*, 1013.
9. BILN 2061 historically was the first clinical proof-of- concept HCV NS3/4A protease inhibitor discontinued due to cardiotoxicity issues in primates: (a) Hinrichsen, H.; Benhamou, Y.; Wedemeyer, H.; Reiser, M.; Sentjens, R. E.; Calleja, J. L.; Forns, X.; Erhardt, A.; Crönlein, J.; Chaves, R. L.; Yong, C.-L.; Nehmiz, G.; Steinmann, G. *Gastroenterology* **2004**, *127*, 1347; (b) Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P.; Bös, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagacé, L.; LaPlante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llinàs-Brunet, M. *Nature* **2003**, *426*, 186.
10. Seiwert, S. D.; Andrews, S. W.; Jiang, Y.; Serebryany, V.; Tan, H.; Kossen, K.; Rajagopalan, P. T. R.; Misialek, S.; Stevens, S. K.; Stoycheva, A.; Hong, J.; Lim, S. R.; Qin, X.; Rieger, R.; Condroski, K. R.; Zhang, H.; Do, M. G.; Lemieux, C.; Hingorani, G. P.; Hartley, D. P.; Josey, J. A.; Pan, L.; Beigelman, L.; Blatt, L. M. *Antimicrob. Agents Chemother.* **2008**, *52*, 4432.
11. (a) Raboisson, P.; De Kock, H.; Rosenquist, Å.; Nilsson, M.; Salvador-Oden, L.; Lin, T.; Roue, N.; Ivanov, V.; Wähling, H.; Wickström, K.; Hamelink, E.; Edlung, M.; Vrang, L.; Vendeville, S.; Van de Vreken, W. V.; McGowan, D.; Tahri, A.; Hu, L.; Boutton, C.; Lenz, O.; Delouvroy, F.; Pille, G.; Surleraux, D.; Wigerinck, P.; Samuelsson, B.; Simmen, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4853; (b) Manns, M. P.; Reesink, H. W.; Moreno, C.; Berg, T.; Benhamou, Y.; Horsmans, Y. J.; Dusheiko, G. M.; Flisiak, R.; Meyvisch, P.; Lenz, O.; Simmen, K.; Verloes, R. *Hepatology* **2008**, *48*, 1023A.
12. (a) New Clinical Data Support Broad Profile for Telaprevir in Patients with Genotype 1 Hepatitis C Virus (HCV) Infection, *Vertex Press release 2008, November 1st.*; (b) Boceprevir Phase II Study Showed High Rate of Sustained Response With 28- and 48- Week Regimens in Genotype 1 Treatment-Na Hepatitis C Patients, Schering-Plough Press release 2008, November 1st.
13. (a) Liverton, N. J.; Holloway, M. K.; McCauley, J. A.; Rudd, M. T.; Butcher, J. W.; Carroll, S. S.; DiMuzio, J.; Fandozzi, C.; Gilbert, K. F.; Mao, S. –S.; McIntyre, C. J.; Nguyen, K. T.; Romano, J. J.; Stahlhut, M.; Wan, B. –L.; Olsen, D. B.; Vacca, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4607; (b) McCauley, J. A.; Rudd, M. T.; Nguyen, K. T.; McIntyre, C. J.; Romano, J. J.; Bush, K. J.; Varga, S. L.; Ross, C. W., III; Carroll, S. S.; DiMuzio, J.; Stahlhut, M. W.; Olsen, D. B.; Lyle, T. A.; Vacca, J. P.; Liverton, N. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9104.
14. McCauley, J. A.; Rudd, M. T.; McIntyre, C. J.; Nguyen, K. T.; Romano, J. J.; Butcher, J. W.; Holloway, M. K.; Wan, B.-L.; Carroll, S. S.; DiMuzio, J. M.; Graham, D. J.; Ludmerer, S. W.; Mao, S.-S.; Stahlhut, M.; Fandozzi, C.; Trainor, N.; Olsen, D. B.; Vacca, J. P.; Liverton, N. J. *Abstracts of Papers*, 235th ACS National Meeting, New Orleans, LA, United States, April 6–10, 2008; American Chemical Society: Washington, DC, 2008; MEDI-018.
15. Mao, S. –S.; DiMuzio, J.; McHale, C.; Burlein, C.; Olsen, D.; Carroll, S. S. *Anal. Biochem.* **2008**, *373*, 1.
16. Lohmann, V.; Körner, F.; Koch, J.-O.; Herian, U.; Theilmann, L.; Bartenschlager, R. *Science* **1999**, *285*, 110.
17. The protocol used was a modification of that reported in: Migliaccio, G.; Tomassini, J. E.; Carroll, S. S.; Tomei, L.; Altamura, S.; Bhat, B.; Bartholomew, L.; Bosserman, M. R.; Ceccacci, A.; Colwell, L. F.; Cortese, R.; De Francesco, R.; Eldrup, A. B.; Getty, K. L.; Hou, X. S.; LaFemina, R. L.; Ludmerer, S. W.; MacCoss, M.; McMasters, D. R.; Stahlhut, M. W.; Olsen, D. B.; Hazuda, D. J.; Flores, O. A. *J. Biol. Chem.* **2003**, *278*, 49164.
18. (a) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701; (b) Colarusso, S.; Gerlach, B.; Koch, U.; Muraglia, E.; Conte, I.; Stansfield, I.; Matassa, V. G.; Narjes, F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 705.
19. Kempf, D. J.; Klein, C.; Chen, H.-J.; Klein, L. L.; Yeung, C.; Randolph, J. T.; Lau, Y. Y.; Chovan, L. E.; Guan, Z.; Hernandez, L.; Turner, T. M.; Dandliker, P. J.; Marsh, K. C. *Antiviral Chem. Chemother.* **2007**, *18*, 163.
20. Chen, A.-H.; Lamar, J.; Yip, Y.; Victor, F.; Johnson, R. B.; Wang, Q. M.; Glass, J. I.; Heinz, B.; Colacino, J.; Guo, D.; Tebbe, M.; Munroe, J. E. *Lett. Drug Des. Discovery* **2005**, *2*, 118.
21. PCT Patent (Merck & Co./IRBM): WO/08/051477 A2, May 2, 2008.
22. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
23. The use of catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) in combination with [bis(acetoxy)iodo]benzene (BAIB) as stoichiometric oxidants, as reported in: De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974. afforded the oxidation of only one of the two hydroxyamide diastereoisomers with moderate conversion.
24. The use of manganese dioxide as an heterogeneous oxidant resulted in no reaction: Fatiadi, A. J. *Synthesis* **1976**, 65.
25. The polymer-supported 2-iodylbenzamide (IBX) resulted in a sluggish reaction with only moderate conversion: (a) Chunk, W.-J.; Kim, D.-K.; Lee, Y.-S. *Tetrahedron Lett.* **2003**, *44*, 9251; (b) Chen, J. J.; Aduda, V. *Synth. Commun.* **2007**, *37*, 3493.
26. *General procedure for the preparation of* **8b**. Step 1: a solution of **6b** (2.44 g, 4.63 mmol; prepared as described in Ref. 21) in MeOH (100 mL) was hydrogenated at 1 atm over 10% Pd/C (1.20 g) for 4 h at rt. The reaction mixture was filtered, the filtrate concentrated and crude product purified on silica gel column chromatography eluting with 10–90% ethyl acetate in petroleum ether to afford the product as a solid (2.16 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (t, J = 7.6 Hz, 1 H), 7.10 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1 H), 5.40 (s, 1H), 4.68–4.81 (m, 2H), 4.51–4.67 (m, 3H), 4.38 (d, J = 9.5 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 3.85 (dd, J = 3.5, 11.7 Hz, 1H), 3.77 (s, 3H), 3.67–3.74 (m, 1H), 3.15 (s, 1H), 2.98 (s, 1H), 2.69 (dd, J = 7.6, 14.0 Hz, 1H), 2.50–2.61 (m, 1H), 2.39–2.49 (m, 1H), 2.12–2.22 (m, 1H), 1.22–1.74 (m, 8H), 1.06 (s, 9H). LRMS (ESI) m/z calcd for $C_{28}H_{39}N_3O_7$: 530.3 $[M+H]^+$ found 530.1. Step 2: a solution of product from the previous step (2.16 g, 4.07 mmol) in THF (46 mL), EtOH (23 mL) and water (23 mL) was treated with LiOH (0.51 g, 12.22 mmol) for 30 min at 40 °C. 1 M HCl (5 mL) was added, the volatiles evaporated and the residue partitioned between water and EtOAc (2 × 100 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and solvent evaporated in vacuo to yield 2.08 g of a solid as crude **7b** product which was used with no further purification. LRMS (ESI) m/z calcd for $C_{27}H_{37}N_3O_7$: 516.3 $[M+H]^+$ found 516.1. Step 3: the solid residue from the previous step (0.100 g, 0.194 mmol) was taken up in DMF (1.0 mL) and treated with (3*S*)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-aminium chloride (**5a**, 0.065 g, 0.291 mmol; prepared as described in Ref. 20), DIPEA (0.16 mL, 9.116 mmol) and TBTU (0.093 g, 0.291 mmol). After 2 h stirring at rt, the reaction mixture was partitioned between 1 N HCl and EtOAc (2 × 25 mL). The combined organic phases were washed with 1 N HCl (2 × 10 mL), 1 M NaOH (1 × 10 mL) and brine, dried over anhydrous Na_2SO_4 and solvent removed in vacuo to yield the product (0.125 g as a mixture of diastereoisomers) as crude solid which was used with no further purification. Step 4: a solution of the hydroxyamides from the previous step (0.125 g, 0.183 mmol) in DCM (3.5 mL) was treated with pyridine (0.125 mL, 1.55 mmol) and 1,1,1-Triacetoxy-1,1- dihydro-1,2-benziodoxol-3(1H)-one (Dess–Martin periodinane, 0.155 g, 0.366 mmol) at rt. The reaction mixture was stirred at room temperature for 30 min, treated with aq ss. Na_2CO_3 and extracted with DCM (2 × 15 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and solvent removed in vacuo to yield a crude product that was purified by reverse phase HPLC (Waters Xterra® PrepMS 19x150 mm, 5 μm column; MeCN/ H_2O, 40–90% gradient in 14 min with 0.1% TFA) to give **8b** (0.025 g, 20% yield over three steps) as a white solid, after freeze-drying. ^{1}H NMR (DMSO, 400 MHz) δ 8.72 (d, J = 4.3 Hz, 1H), 8.28 (d, J = 6.7 Hz, 1H), 7.15–7.30 (m, 2H), 7.12 (d, J = 6.8 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 5.23 (s, 1H), 5.02 (br s, 1H), 4.45–4.75 (m, 5H), 4.30–4.42 (m, 1H), 4.18 (d, J = 8.6 Hz, 1H), 4.02–4.11 (m, 1H), 3.69–3.78 (m, 1H), 3.58–3.68 (m, 1H), 2.62–2.81 (m, 1H), 2.30–2.60 (m, 3H, below DMSO), 1.94–2.06 (m, 1H), 1.66–1.77 (m, 1H), 1.21–1.65 (m, 11H), 0.97 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H), 0.64–0.71 (m, 2H), 0.56–0.63 (m, 2H). HRMS (ESI) m/z calcd for $C_{36}H_{51}N_5O_8$: 682.3820 $[M+H]^+$, found: 682.3810.