Bioorganic & Medicinal Chemistry Letters 19 (2009) 633–638

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of pentacyclic compounds as potent inhibitors of hepatitis C virus NS5B RNA polymerase

Jörg Habermann *, Elena Capitò, Maria del Rosario Rico Ferreira, Uwe Koch, Frank Narjes

Department of Medicinal Chemistry, IRBM "P. Angeletti" S.p.A., Merck Research Laboratories Rome, Via Pontina km 30,600, I-00040 Pomezia, Rome, Italy

ARTICLE INFO

Article history:
Received 10 November 2008
Revised 5 December 2008
Accepted 7 December 2008
Available online 13 December 2008

Keywords:
HCV
HCV NS5B polymerase inhibitor
Pauson–Khand reaction
[1,3]-Dipolar cycloaddition

ABSTRACT

We report a new series of inhibitors for hepatitis C virus NS5B RNA polymerase containing a constrained pentacyclic scaffold. Our SAR studies led to the identification of hexahydroindolo[2,1-*a*]pyrrolo[3,2-*d*][2]benzazepines exposing basic groups. The compounds displayed a high activity in the enzyme assay and displayed good activity in the cell-based (replicon) assay in the presence of serum proteins.

Hepatitis C is a viral infection of the liver and as such is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons are chronically infected with HCV and 3–4 million persons are newly infected each year. HCV is spread primarily by direct contact with human blood.[1] No vaccine is currently available to prevent hepatitis C. The front line therapy is a combination of pegylated interferon-α dosed in combination with the nucleoside analogue ribavirin. However, this treatment is often poorly tolerated and of limited success rate. Consequently, HCV continues to be a significant world health burden and remains the leading cause of liver transplantation in the United States.[2] Thus there is a need for improved therapies.

The virally encoded non-structural proteins of the hepatitis C virus are attractive targets for antiviral drug therapy. As such, the hepatitis C virus NS5B polymerase is a key enzyme necessary for the replication of the HCV gene in infected cells and has recently been the focus of many research groups.[3]

Several classes of inhibitors have been reported for this enzyme acting at the active site or one of the allosteric sites of the enzyme. A few compounds have shown antiviral effects in clinical studies (e.g., nucleoside prodrugs NM283, R-1626 and R-7128 and non-nucleoside inhibitors HCV-796, BILB-1941 and VCH-759).[4,5] We and others have previously reported benzimidazole, indole and thienopyrrole carboxylic acid derivatives as inhibitors of hepatitis C NS5B polymerase (Fig. 1).[6] These classes of compounds show selectivity for thumb domain pocket I of the enzyme.[7] A common and largely invariable structural feature of these compounds is the presence of a cyclohexyl ring and an aromatic ring attached to a heterocyclic core.

In the course of our investigations X-ray crystallography and computer modelling had indicated that the pendant *N*,*N*-dimethyl acetamide chain in **1** is directed mostly towards the solvent-exposed surface. Only to a minor extent this chain exhibits contacts with the enzyme. Thus, we deemed it possible to use this part mainly to modulate physico-chemical properties.[8]

Additionally, it is known that the enzyme contains a lipophilic pocket in close proximity to the aryl ring of the inhibitor (e.g., **3**, Fig. 2). Studies by a group from Japan Tobacco had indicated that this area might be reached by extending from *N5* of compound **3**.[9]

After our initial work in the tetracyclic indole series[10] which also indicated the beneficial effect of an exposed basic functionality we considered to reduce the rotatable bond count by locking up the side-chain in an extra ring system. In addition, we felt that the presence of an anilinic nitrogen atom in compound **3** constituted a potential liability from a drug safety point of view.[11]

Hence, we decided to move from a benzodiazepine scaffold to a benzazepine scaffold. Since our previous studies had shown that monoamines were tolerated the compounds **4–7** were designed to generically probe the concept of the fifth anellated ring. Only for **4** an activity in the cell-based assay[13] was observed which was in the range of previous tetracyclic compounds (Table 1).

In general, the intrinsic potency was largely maintained in most of the new pentacycles with the exception of the *cis*-configured pentacycle **6**, which showed a nearly 5-fold loss compared with **3**. The *trans*-anellated compound **7** was about 3.5-fold more active in terms of intrinsic potency and cell-based potency under high

* Corresponding author. Tel.: +39 06 91093851; fax: +39 06 91093225.
E-mail address: jorg_habermann@merck.com (J. Habermann).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.12.039

serum conditions than its *cis*-anellated analogue **6**. Since the binding of lead compounds and drugs to serum proteins is a ubiquitous problem modulating the availability to the target our attention turned to the serum shift.[14] We noticed that the *trans*-configured compound **7** did not exhibit any notable shift between low and high serum conditions which made this compound an interesting starting point for further evaluation. The high serum conditions may be considered a physiologically more relevant system.

Additionally, ease of synthetic accessibility and the possibility to reach out to the hydrophobic patch led to the choice of scaffolds **6** and **7** as starting points for further evaluation (Table 2).

We were able to gain potency by exchanging the *N*-methyl substituent of **7** with a *N*,*N*-dimethylaminoethyl side-chain. This change from a monoamine system to the diamino system represented by **8a** significantly improved both intrinsic and cell-based activity with respect to **2** and **3**.

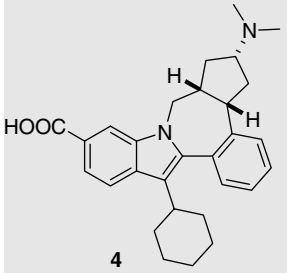
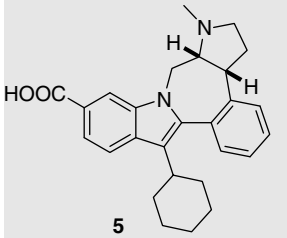
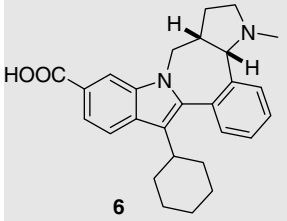
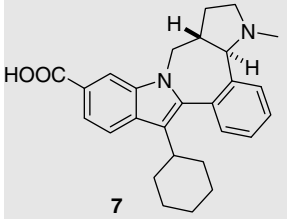
A minor improvement in intrinsic activity was observed when increasing the lipophilic character of the pendant side-chain by replacing the *N*,*N*-dimethylamino ethyl group with a piperidin-1-yl ethyl moiety (**8c** vs **8a**). However, this gain was achieved at the cost of cell-based potency in 50% NHS. We hypothesised that this is most likely due to diminished cell-penetration of **8c** since the human plasma protein binding is virtually identical for both compounds (91.5% vs 92%). We have not been able to establish a clear correlation between this empirical finding and calculated physico-chemical properties (*c*Log*D*, pK_a, PSA) but in most cases a higher *c*Log*D* (e.g., **8c**: *c*Log$D_{7.4}$ = 5.76 vs **8a**: *c*Log$D_{7.4}$ = 4.5) correlated with a higher serum shift.[15] Elongation of the pendant side-chain (**8d**, **8e**) was permitted in terms of intrinsic potency, but did not lead to a substantial gain in cell-based activity. Various amidic substitutions (**8f–k**) were tolerated in terms of activity in the biochemical assay but led in most cases to poorer cell-based activity when compared with the basic amine substituents.

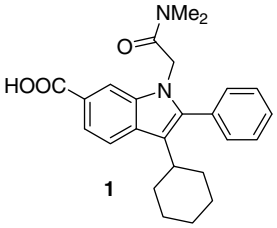
Thus, our attention turned to the modification of the benzazepine aryl moiety. In related compounds of earlier studies, the introduction of a *para*-methoxy substituent had proven beneficial, so we attempted the same modification in the new *trans*-series. The resulting compound **8b** showed improved intrinsic activity paired with a low shift (2.5-fold) for the cell-based assay between 10% FCS and 50% NHS.

For comparison the *cis*-derivatives **9** were prepared. While in general showing appreciable intrinsic activity, the cell-based activity was insufficient since no substantial gain over previously described compounds was observed. For example, with compound **9a** we noticed that while the intrinsic activity on the isolated NS5B enzyme remained nearly invaried a nearly 8-fold loss in cell-based activity against its *trans*-analogue **8a** could be observed.

Due to the interesting activity level reached with the racemic compound **8b** we decided to separate it into the two enantiomers **10** and **11**. We found that the activity largely resides only in one of the two enantiomers, while the second is nearly inactive. The large difference in activity between the two enantiomers **10** and **11** prompted us to investigate this behaviour in detail.

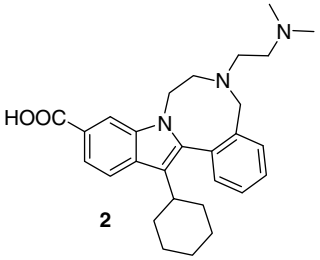
Table 1
Monoamine pentacyclic series—variation of the scaffold[12]

Compound	NS5B IC_{50} (nM)	Replicon 10% FCS EC_{50} (nM)	Replicon 50% NHS EC_{50} (nM)	Approx. serum shift
 **4**	30	130	890	7
 **5**	20	1200	3800	3
 **6**	140	770	2540	3
 **7**	40	830	700	1



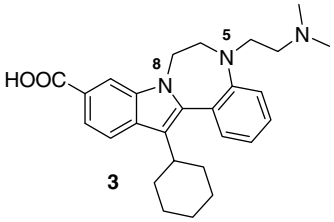
1

IC_{50} 430 nM
EC_{50} (10% FCS) 1540 nM
EC_{50} (50% NHS) 9850 nM



2

IC_{50} 27 nM
EC_{50} (10% FCS) 140 nM
EC_{50} (50% NHS) 850 nM

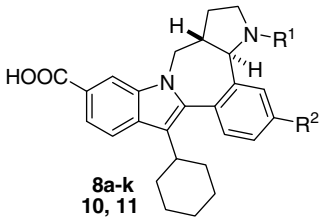


3

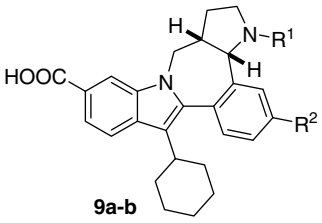
IC_{50} 28 nM
EC_{50} (10% FCS) 130 nM
EC_{50} (50% NHS) 360 nM

Figure 1. Examples of HCV NS5B inhibitors from previous work.

Table 2
SAR in the pentacyclic series



8a-k
10, 11



9a-b

Compound	R^1	R^2	NS5B IC_{50} (nM)	Replicon 10% FCS EC_{50} (nM)	Replicon 50% NHS EC_{50} (nM)
8a	$CH_2CH_2NMe_2$	H	20	32	98
9a	$CH_2CH_2NMe_2$	H	30	260	620
8b	$CH_2CH_2NMe_2$	OMe	8	25	63
9b	$CH_2CH_2NMe_2$	OMe	21	150	270
8c	CH_2CH_2pip	H	11	40	220
8d	$CH_2CH_2CH_2NMe_2$	H	24	58	80
8e	$CH_2CH_2CH_2$pip	H	11	53	110
8f	$C(=O)NHCH_2CH_2NMe_2$	H	24	630	480
8g	$CH_2C(=O)NMe_2$	H	17	78	96
8h	$C(=O)CH_2NMe_2$	H	31	170	210
8i	$C(=O)CH_2NMe_2$	OMe	23	32	110
8k	$C(=O)OCH_2CH_2NMe_2$	OMe	21	180	225
10*	$CH_2CH_2NMe_2$	OMe	312	>1000	>1000
11*	$CH_2CH_2NMe_2$	OMe	4	29	49

* Separated enantiomers of **8b**.

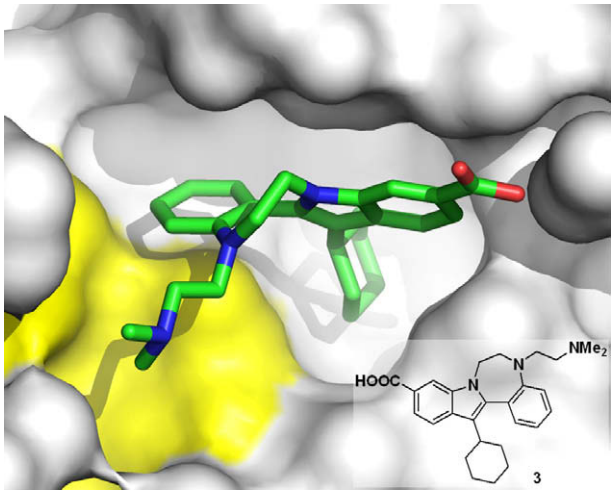


Figure 2. Hydrophobic patch (yellow) in proximity to allosteric site 1.

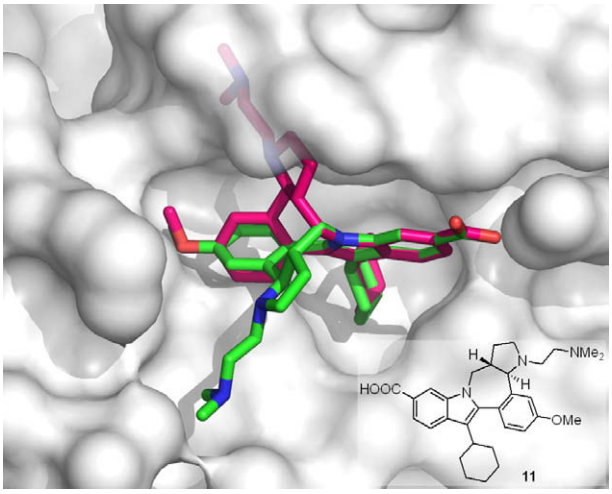


Figure 3. Modelling study explaining the difference in activity of the two *trans*-enantiomers **10** (red) and **11** (green).

A modelling study[16] (Fig. 3) indicated that binding to the enzyme is compatible only with **11** (3a*S*,14b*R*, shown in green). The minimum conformation of the inactive enantiomer **10** (3a*R*,14b*S*, shown in red) does not fit into the pocket as the pendant side-chain clashes with the backbone of the enzyme.

The compounds evaluated in this study were prepared as described in Schemes 1–3.[17]

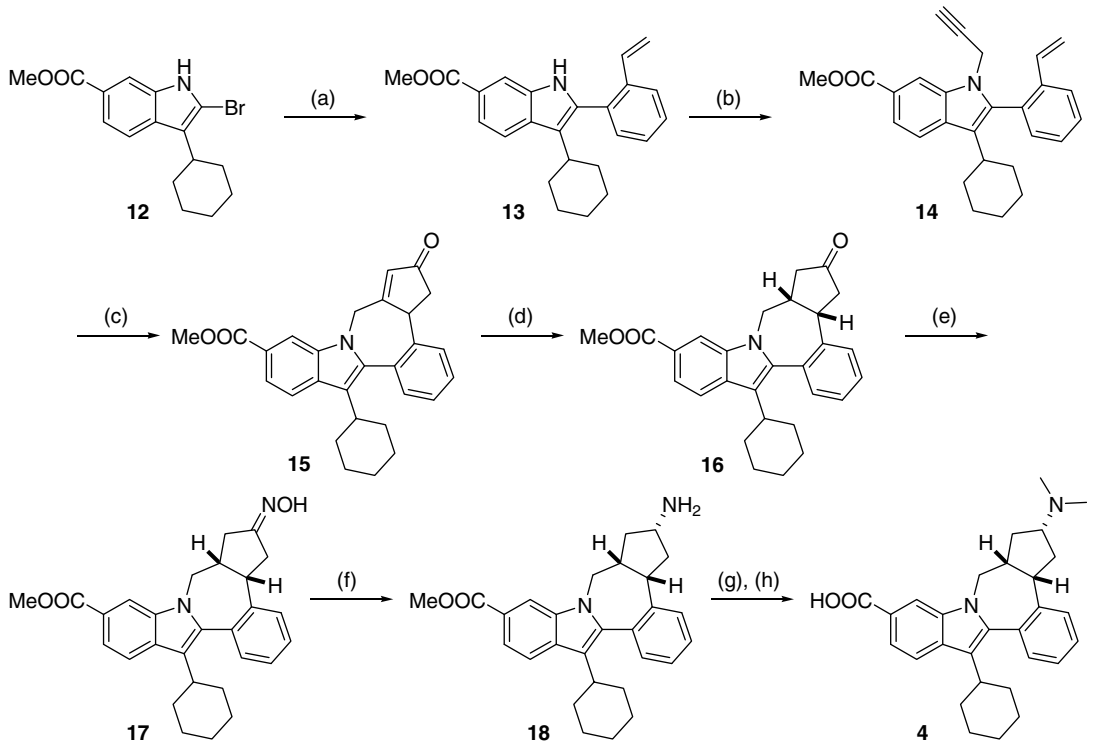
The pentacyclic indolobenzazepine **4** could be prepared by applying the Pauson–Khand reaction[18] to the vinyl/propargyl-substituted aryl indole **14** which in turn had been obtained by Suzuki reaction of bromoindole **12** with 2-vinylbenzene boronic acid followed by N-alkylation of **13** with propargylbromide (Scheme 1).

It was observed that the ring-closure reaction proceeded best using an excess of dicobalt octacarbonyl without the application of external carbon monoxide pressure. Transformation of the ketone **16** (obtained by hydrogenation of intermediate **15**) into the amine could not be achieved by direct reductive amination. Therefore, hydrogenation of the corresponding oxime **17** over platinum was carried out.[19] Reductive amination and basic hydrolysis completed the synthesis of **4**.

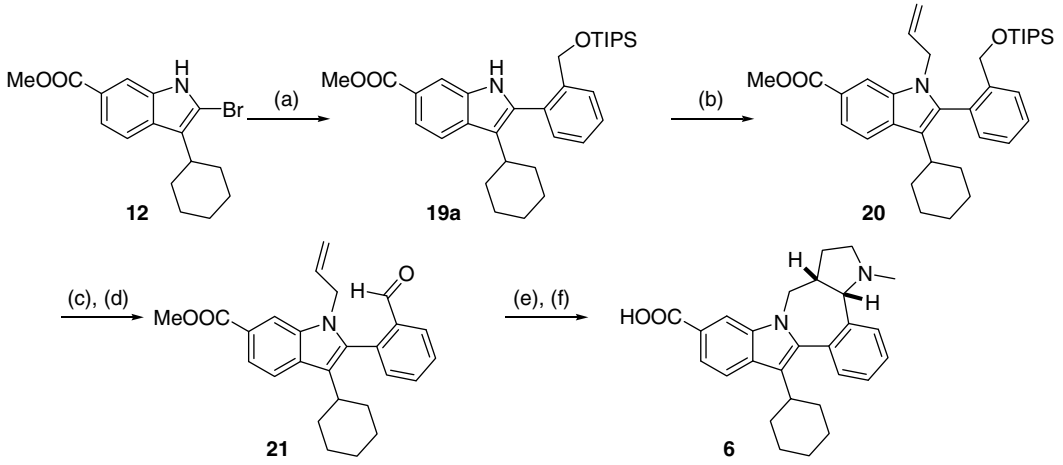
The relative stereochemical outcome of the ring-closure and the oxime reduction was confirmed by the observation of nOe's in the proton NMR.

Scheme 2 exemplifies the synthesis of cis-configured compounds of type 6. Depending on the desired substitution pattern, the sequence started with a Suzuki reaction of bromoindole 12 with a 2-formyl benzene boronic acid or an aryl boronic acid bearing a protected benzylic alcohol as the precursor for the 2-formyl group. This reaction was followed by *N*-allylation.

When a protected benzyl alcohol had been used as the precursor, the alcohol was liberated and subjected to Swern oxidation. Intermediate **21** was thus set up for a [1,3]-dipolar cycloaddition. The cycloaddition was carried out with glycine or *N*-substituted



Scheme 1. Pauson–Khand reaction to form *cis*-pentacycle **4**. Reagents and conditions: (a) 2-vinylbenzene boronic acid, $PdCl_2(PPh_3)_2$, 2 M Na_2CO_3, dioxane, 110 °C, 83%; (b) NaH, propargylbromide, DMF, 84%; (c) $Co_2(CO)_8$, 4 Å MS, toluene, 110 °C, 36%; (d) Pd/C, H_2, EtOAc/iPrOH, 54%; (e) NH_2OH HCl, NaOAc, H_2O/MeOH/EtOAc, 60 °C, 83%; (f) PtO_2, H_2 (50 psi), HOAc, quant; (g) HCHO, $NaCNBH_3$, DCM, HOAc, 91%; (h) KOH, THF/MeOH/H_2O, 45 °C, 37%.



Scheme 2. [1,3]-Dipolar cycloaddition for *cis*-pentacycles. Reagents and conditions: (a) (4-methoxy-2-{[(triisopropylsilyl)oxy]methyl}phenyl) boronic acid, $PdCl_2(PPh_3)_2$, 2 M Na_2CO_3, dioxane, 110 °C, 81%; (b) NaH, allylbromide, DMF, 84%; (c) TBAF, THF, 88%; (d) $(COCl)_2$, DMSO, DCM, −70 °C, then NEt_3, 0 °C, 88%; (e) sarcosine, toluene/DMF, 110 °C, 61%; (f) KOH, MeOH/dioxane/H_2O, 59%.

derivatives of glycine (e.g., sarcosine to directly introduce R^1 = methyl) setting up a *cis*-pentacyclic system.[20] Finally, basic hydrolysis of the ester moiety gave the free acid **6**.

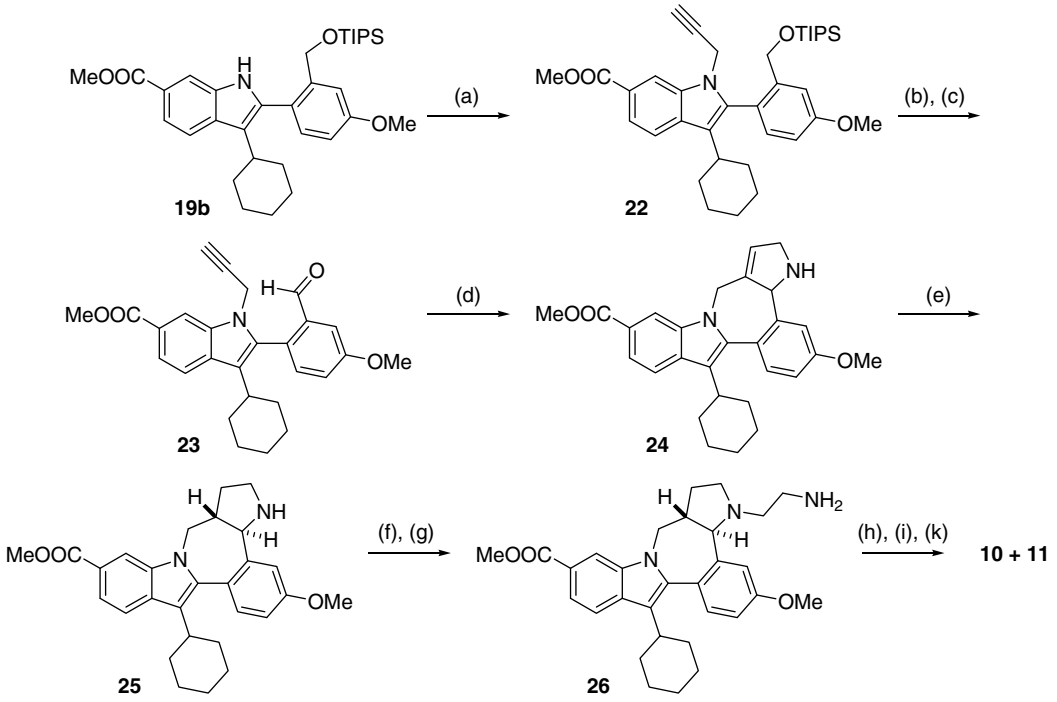
For the preparation of *trans*-pentacyclic systems a similar approach to the one described before was taken (Scheme 3). Starting from intermediate **19b** (prepared in analogy to **19a**) the indole nitrogen was propargylated to give **22**. The benzylic alcohol was liberated and oxidised to give the aldehyde **23**.

[1,3]-Dipolar ring-closure with glycine resulted in the formation of an intermediate 2,5-dihydro-1*H*-pyrrole system **24** which is prone to oxidation and thus needed to be reacted onward quickly. Hydrogenation over palladium led to the *trans*-pentacyclic system **25**.

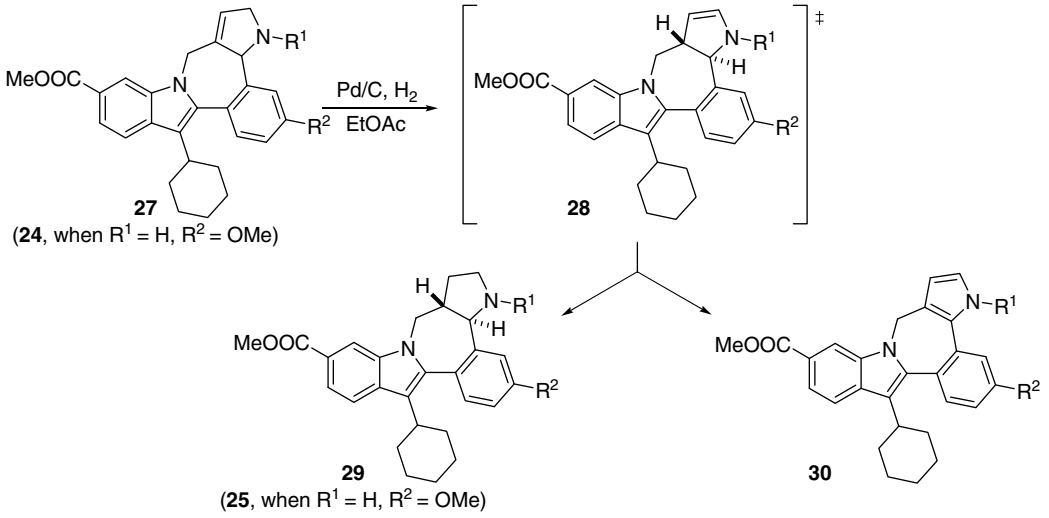
Since some formation of the corresponding pyrrole **30** during the hydrogenation process was observed, it could be speculated that the reaction proceeds *via* an intermediary (and not observed) 2,3-dihydro-1*H*-pyrrole system **28** (Scheme 4). Reductive amination of **25** with various aldehydes or acylation worked smoothly.

Using *N*-Boc-amino acetaldehyde and subsequent cleavage of the protecting group gave **26.** After reductive amination and hydrolysis of the methyl ester, the racemate **8b** was obtained and separated by SFC[21] into the single enantiomers **10** and **11**. The peak separation was complete and gave pure products of 99% enantiomeric excess.

The pyrroles **30** while maintaining intrinsic activity in the low nanomolar range lost significantly in cell-based potency, a fact



Scheme 3. Synthesis of *trans*-pentacycles. Reagents and conditions: (a) NaH, propargylbromide, DMF, 96%; (b) TBAF, THF, 64%; (c) $(COCl)_2$, DMSO, DCM, −70 °C, then NEt_3, 0 °C; (d) glycine, NEt_3, DMF, 140 °C; (e) Pd/C, H_2, EtOAc, 43% over three steps; (f) *N*-Boc-aminoacetaldehyde, MeOH, AcOH, NEt_3, $NaCNBH_3$; (g) TFA, DCM; (h) HCHO, MeOH, AcOH, $NaCNBH_3$; (i) KOH, MeOH/dioxane/H_2O; (k) separation by SFC (Chiralpak AD-H, modifier 35% *i*PrOH + 0.4% DEA, T_{col} 35 °C, p_{col} 100 bar), 12% over four steps.



Scheme 4. Hypothesis regarding the formation of the *trans*-product during the hydrogenation.

which can be attributed to the poor solution stability of those derivatives investigated.

In conclusion, we have identified a new class of allosteric inhibitors of HCV NS5B polymerase based on a pentacyclic scaffold. Our work led to the discovery of several new scaffolds **4–7**.

While the substituent R^2 on the aryl ring helped in gaining intrinsic activity, the substituent R^1 on the pyrrolidine ring increased the cell-based potency as evidenced by the change in replicon activity. Furthermore, the ring junction (*cis*/*trans*) plays an important role in that the *trans*-pentacyclic derivatives are clearly more potent.

Finally, we were able to show that in the *trans*-pentacyclic series a clear preference for one of the two enantiomers exists. A modelling study could rationally explain this behaviour. This led to the identification of **11**, which efficiently blocks subgenomic HCV RNA replication in HUH7-cells at low nanomolar concentrations. This compound is 7-fold more potent in the biochemical assay than our starting point, the tetracyclic compound **3**. In addition, the pentacycle **11** displays a lower serum shift than **3**.

Acknowledgements

The authors thank Renzo Bazzo and Silvia Pesci for analytical support and structure confirmation by NMR, and Cecilia M. Palumbi for her assistance with the purification of some compounds and for determining the enantiomeric excess. We also thank Nadia Gennari, Monica Bisbocci and Sergio Altamura for running the biological assays.

References and notes

1. a WHO, *J. Viral Hepatitis* **1999**, *6*, 35.; b Cohen, J. *Science* **1999**, *285*, 26; c WHO Factsheet No. 164: Hepatitis C, accessed 09 May 2007, http://www. who.int/mediacentre/factsheets/fs164/en/print.html.
2. Steedman, S. A.; Younossi, Z. M. *J. Clin. Gastroenterol.* **2000**, *30*, 125.
3. a Beaulieu, P. L. *Curr. Opin. Invest. Drugs* **2006**, *7*, 618. and references cited therein; b Koch, U.; Narjes, F. *Curr. Top. Med. Chem.* **2007**, *7*, 1302. and references cited therein; c De Francesco, R.; Carfi, A. *Adv. Drug Deliv. Rev.* **2007**, *59*, 1242. and references cited therein; d Beaulieu, P. L. *Curr. Opin. Invest. Drugs* **2007**, *8*, 614. and references cited therein.
4. a Toniutto, P.; Fabris, C.; Bitetto, D.; Fornasiere, E.; Rapetti, R.; Pirisi, M. *Curr. Opin. Invest. Drugs* **2007**, *8*, 150; b Kwong, A. D.; McNair, L.; Jacobson, I.; George, S. *Curr. Opin. Pharm.* **2008**, *8*, 522. and references cited therein.
5. McCown, M. F.; Rajyaguru, S.; Le Pogam, S.; Ali, S.; Jiang, W.-R.; Kang, H.; Symons, J.; Cammack, N.; Najera, I. *Antimicr. Agents Chemother.* **2008**, *52*, 1604.
6. a Beaulieu, P. L.; Boes, M.; Bousquet, Y.; DeRoy, P.; Fazal, G.; Gauthier, J.; Gillard, J.; Goulet, S.; McKercher, G.; Poupart, M.-A.; Valois, S.; Kukolj, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 967; b Harper, S.; Pacini, B.; Avolio, S.; Di Filippo, M.; Migliaccio, G.; Laufer, R.; De Francesco, R.; Rowley, M.; Narjes, F. *J. Med. Chem.* **2005**, *48*, 1314; c Ontoria, J. M.; Martin Hernando, J. I.; Malancona, S.; Attenni, B.; Stansfield, I.; Conte, I.; Ercolani, C.; Habermann, J.; Ponzi, S.; Di Filippo, M.; Koch, U.; Rowley, M.; Narjes, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4026.
7. Tomei, L.; Altamura, S.; Bartholomew, L.; Biroccio, A.; Ceccacci, A.; Pacini, L.; Narjes, F.; Gennari, N.; Bisbocci, M.; Incitti, I.; Orsatti, L.; Harper, S.; Stansfield, I.; Rowley, M.; De Francesco, R.; Migliaccio, G. *J. Virol.* **2003**, *77*, 13225.
8. Di Marco, S.; Volpari, C.; Tomei, L.; Altamura, S.; Harper, S.; Narjes, F.; Koch, U.; Rowley, M.; De Francesco, R.; Migliaccio, G.; Carfi, A. *J. Biol. Chem.* **2005**, *280*, 29765.
9. a) Ikegashira, K.; Oka, T.; Hirashima, S.; Noji, S.; Yamanaka, H.; Hara, Y.; Adachi, T.; Tsuruha, J.-I.; Doi, S.; Hase, Y.; Noguchi, T.; Ando, I.; Ogura, N.; Ikeda, S.; Hashimoto, H. *J. Med. Chem.* **2006**, *49*, 6950; b Hirashima, S.; Oka, T.; Ikegashira, K.; Noji, S.; Yamanaka, H.; Hara, Y.; Goto, H.; Mizojiri, R.; Niwa, Y.; Noguchi, T.; Ando, I.; Ikeda, S.; Hashimoto, H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3181.
10. Stansfield, I.; Ercolani, C.; Mackay, A.; Conte, I.; Pompei, M.; Koch, U.; Giuliano, C.; Rowley, M.; Narjes, F. *Accompanying paper.*.
11. Although for the compounds in question this property has not been evaluated, in some cases aromatic amines may constitute a potential risk for being mutagenic and/or carcinogenic. For some studies see: (a) Franke, R.; Gruske, A.; Giuliani, A.; Benigni, R. *Carcinogenesis* **2001**, *22*, 1561; (b) Turesky, R.J. *Drug Metab. Rev.* **2002**, *34*, 625.
12. All compounds were profiled as racemic mixture if not denoted otherwise.
13. The compounds described were assessed for intrinsic activity (IC_{50}) against the purified BK strain of NS5BΔC21 enzyme in the presence of heterogenic template RNA using a modification of the procedure described in Ref. 7. Inhibition of the replication of subgenomic HCV RNA was measured in HUH-7 cells using a modification of the procedure described in: Lohmann, V.; Körner, F.; Koch, J. -O.; Herian, U.; Theilmann, L.; Bartenschlager, R. *Science* **1999**, *285*, 110. IC_{50} and EC_{50} values are the average of at least two independent determinations. Cell-based data was obtained in the presence of 10% fetal calf serum (FCS) or 50% normal human serum (NHS).
14. a Olson, R. E.; Christ, D. D. *Annu. Rep. Med. Chem.* **1996**, *31*, 327; b Boffito, M.; Back, D. J.; Blaschke, T. F.; Rowland, M.; Bertz, R. J.; Gerber, J. G.; Miller, V. *AIDS Res. Hum. Retrovir.* **2003**, *19*, 825; c Raboisson, P.; Manthey, C. L.; Chaikin, M.; Lattanze, J.; Crysler, C.; Leonard, K.; Pan, W.; Tomczuk, B. E.; Marugán, J. J. *Eur. J. Med. Chem.* **2006**, *41*, 847.
15. Calculated physicochemical properties were determined using the ACD/Labs 8.0 package by Advanced Chemistry Development, Inc.
16. A conformational analysis was performed on the pentacyclic structures **10** and **11** in the absence of the protein. This analysis was carried out with Maestro 7.5.112 generating 10.000 conformations and using the MMFFs force field for minimisation. The indole scaffold of the global minimum conformation was superimposed onto the corresponding scaffold of the crystal structure.
17. Detailed synthesis protocols and spectroscopic data for the compounds are described in: (a) Ercolani, C.; Habermann, J.; Narjes, F.; Ponzi, S.; Rowley, M.; Stansfield, I. WO 2006046039 A2, **2006**; (b) Capitò, E.; Habermann, J.; Narjes, F.; Rico Ferreira, Maria d. R.; Stansfield, I. WO 2007129119 A1, **2007**.
18. a Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, William E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977; b Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477; c Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835; d Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224.
19. a Rausser, R.; Weber, L.; Hershberg, E. B.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 1342; b Rausser, R.; Finckenor, C. G.; Weber, L.; Hershberg, E. B.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 1346; c Secrist, J. A., III; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335; d Wrobel, J.; Dietrich, A.; Gorham, B. J.; Sestanj, K. *J. Org. Chem.* **1990**, *55*, 2694; e Beeson, C.; Dix, T. A. *J. Org. Chem.* **1992**, *57*, 4386.
20. a Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Chem. Lett.* **1986**, 973; b Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079; c Amal Raj, A.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 10293; e Subramaniyan, G.; Raghunathan, R.; Nethaji, M. *Tetrahedron* **2002**, *58*, 9075; f Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Synlett* **2003**, 947; g Poornachandran, M.; Raghunathan, R. *Tetrahedron Lett.* **2005**, *46*, 7197; h Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. and references cited therein.
21. Super-critical fluid chromatography (SFC) was performed using a Berger system equipped with a Berger ALS 719.