ORGANIC LETTERS

2012
Vol. 14, No. 2
556–559

Synthesis of New 4, 5-Dihydrofuranoindoles and Their Evaluation as HCV NS5B Polymerase Inhibitors

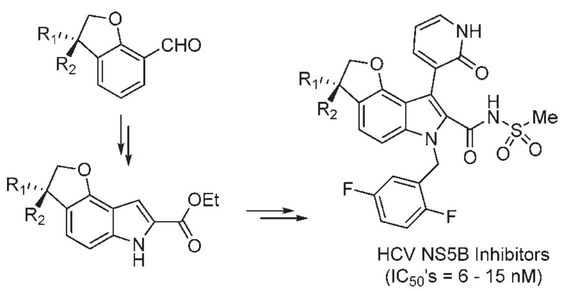
Francisco Velázquez,* Srikanth Venkatraman, Charles A. Lesburg, José Duca,‡ Stuart B. Rosenblum, Joseph A. Kozlowski, and F. George Njoroge

Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-1300, United States

francisco.velazquez@merck.com

Received November 28, 2011

ABSTRACT



The synthesis of substituted 3,4-dihydrofuranoindoles is reported. These new indole compounds were used to synthesize potent HCV NS5B inhibitors. The binding mode of the dihydrofuranoindole-derived inhibitors was established via X-ray crystallographic studies.

The indole ring system is one of the most important heterocyclic structures known in medicinal chemistry. Nature has been a continuous supplier of molecules containing indole moieties embedded in their structures.[1] More recently, numerous indole-containing molecules can trace their origins to the synthetic laboratory. A great number of indole-containing molecules have shown to possess a wide variety of biological activities such as anti-infectives, neurotransmitters, anticancer, antiinflammatory, and others.[2] Therefore, indoles are preferred molecular pharmacophores for identification of new drug candidates.[3]

As part of the efforts to identify molecules that possess antiviral activity, our research group investigated indole-based scaffolds based on structural information obtained from lead compounds bound to the active site of the hepatitis C (HCV) NS5B polymerase enzyme.[4] Based on information gathered from the indole-based lead compounds, we proposed to investigate the binding mode of new indole scaffolds containing a dihydrofuran ring fused at the 4- and 5-positions of the indole core. Although the 4,5-dihydrofuranoindole system is known in the literature,[5] it was reported as a side product in the preparation of regioisomeric 6,7-dihydrofuranoindole. Furthermore, there was no precedent for compounds having substitutions attached to the dihydrofuran ring of the proposed 4,5-dihydrofuranoindole cores. Our efforts were therefore focused on the design and execution of synthetic routes to access new dihydrofuranoindole cores in order to gather important structural information to advance our research program. In this

‡ Present address: Novartis Institutes for BioMedical Research, 100 Technology Square, Cambridge, MA 02139, United States.

(1) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497.

(2) (a) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442–453. (b) Ahmad, A.; Sakr, W. A.; Wahidur Rahman, K. M. *Curr. Drug Targets* **2010**, *11*, 652–666.

(3) Rodrigues de Sa Alves, F.; Barreiro, E. J.; Manssour Fraga, C. A. *Mini-Rev. Med. Chem* **2009**, *9*, 782–793.

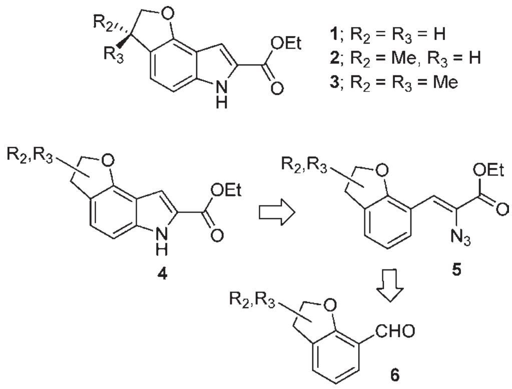
(4) Lesburg, C. A.; Cable, M. B.; Ferrari, E.; Hong, Z.; Mannarino, A. F.; Weber, P. C. *Nat. Struct. Biol.* **1999**, *6*, 937–943.

(5) Roffey, J. R.; Davidson, J. E.; Mansell, H. L.; Hamlyn, R. J.; Adams, D. R. *PCT Int. Appl.* WO 2001012602, 2001.

10.1021/ol203177g
Published on Web 01/05/2012

letter, we report our efforts in the synthesis of new dihydrofuran indole systems and their application as molecular probes.

Scheme 1. New 4,5-Fused Dihydrofurano Indole Systems and Proposed Retrosynthetic Analysis for Their Synthesis



The 4,5-fused dihydrofuranoindole based compounds **1**−**3** (Scheme 1) were deemed important probes that would provide valuable structural information about the manner in which these molecules bind to the active site of the HCV NS5B polymerase enzyme. We postulated a synthetic approach based on the Hemetsberger−Knittel indole synthesis for their preparation.[6] A general retrosynthetic analysis for indoles **1**−**3** is outlined in Scheme 1. We proposed to assemble the desired dihydrofuran indole systems via C−H insertion of a nitrene formed from a vinyl azido intermediate such as **5**. The required vinyl azido intermediate **5** could be obtained from condensation of dihydrobenzofuran carboxaldehyde **6** and ethyl azido acetate. Aldehyde intermediates of type **6** were also unknown in the literature and synthetic routes for their preparation had to be devised as well.

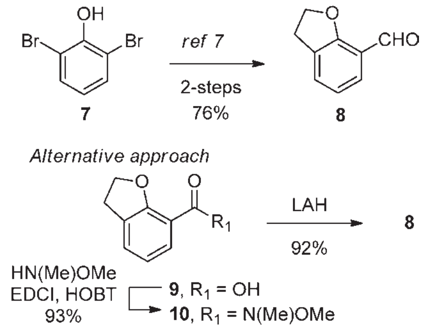
A. Synthesis of Dihydrobenzofuran Carboxaldehydes and Assembly of Indole Cores. The synthesis of dihydrofuranoindole **1** commenced with preparation of aldehyde **8** (Scheme 2).[7] A one-pot, two-step approach previously described by Spoors using 2,6-dibromophenol (**7**) as starting material was reported to deliver **8** in 76% yield. The first step of this one-pot transformation is based on a modified Parham cyclization.[8] An alternative two-step approach was used in our laboratory to obtain **8** in slightly higher yield (85% overall). Commercially available dihydrobenzofuran-7-carboxylic acid (**9**) was converted into Weinreb amide **10** followed by lithium aluminum hydride reduction to deliver **8** in high yield.

(6) (a) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1970**, *101*, 161–165. (b) Knittel, D.; Hemetsberger, H.; Leipert, R.; Weidmann, H. *Tetrahedron Lett.* **1970**, *17*, 1459–1462.

(7) Plotkin, M.; Chen, S.; Spoors, P. G. *Tetrahedron Lett.* **2000**, *41*, 2269–2273.

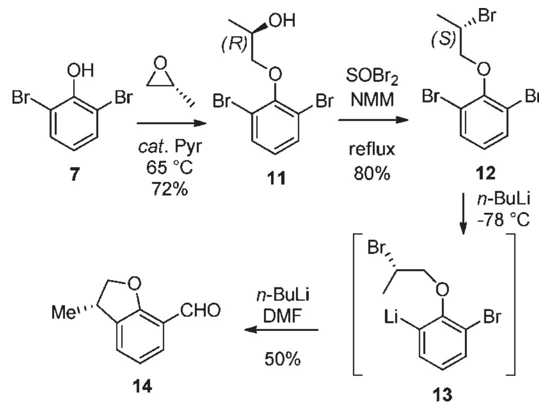
(8) Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 1384–1388.

Scheme 2. Synthesis of Dihydrobenzofuran-7-carboxaldehyde **8**



The synthesis of previously unknown aldehyde **14** was accomplished using an approach similar to that employed by Spoors and co-workers for preparation of **8**. We extended the utility of this approach to form the required stereogenic center present in **14** during the cyclization step.

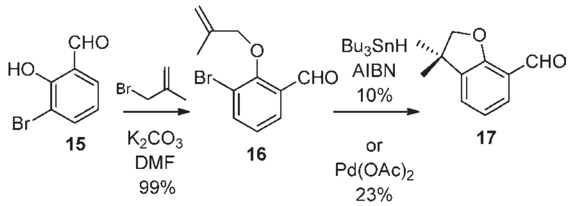
Scheme 3. Synthesis of (*S*)-3-Methyldihydrobenzofuran-7-carboxaldehyde **14**



Thus, synthesis of **14** began with preparation of the optically active alcohol **11** from 2,6-dibromophenol (**7**) as outlined in Scheme 3. Having an efficient method to obtain **11** was very important because the Parham cyclization would depend on the absolute configuration of the stereogenic center in **11** to install the 3′-methyl with complete stereocontrol during the intramolecular S_N2 process. Different approaches for synthesis of **11** were considered including the asymmetric reduction of a ketone precursor or the enantioselective addition of a methyl nucleophile to an aldehyde. Ultimately, a simpler methodology was devised using the regioselective opening of (*R*)-2-methyloxirane to obtain alcohol **11** in excellent yield with the required *R*-configuration at the stereogenic center. Conversion of **11** into bromide **12** delivered the substrate needed for the critical cyclization step.

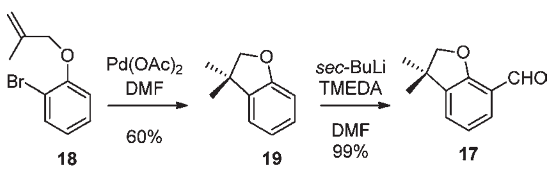
Treatment of **12** with 1 equiv of *n*-BuLi at −78 °C triggered a 5-*exo*-tet cyclization which occurred with inversion of configuration at the stereogenic center to assemble the (*S*)-3-methyl dihydrobenzofuran core. Addition of a second equivalent of *n*-BuLi followed by DMF delivered the desired aldehyde **14**. This one-pot procedure allowed preparation this valuable intermediate in large quantities.

Scheme 4. Initial Attempts for the Synthesis of 3,3-Dimethyldihydrobenzofuran-7-carboxaldehyde **17**



Different methods were investigated for the synthesis of previously unknown aldehyde **17**. The first attempt involved the free radical cyclization of **16** which was prepared in quantitative yield from 2-hydroxy-3-bromobenzaldehyde (**15**) (Scheme 4). As expected, the reaction gave the desired cyclization product **17** via a 5-*exo*-trig cyclization process but the yield was disappointingly poor (10%). We then investigated an alternative approach using palladium to promote the cyclization. Once again, the desired product **17** was obtained in suboptimal yield (23%).

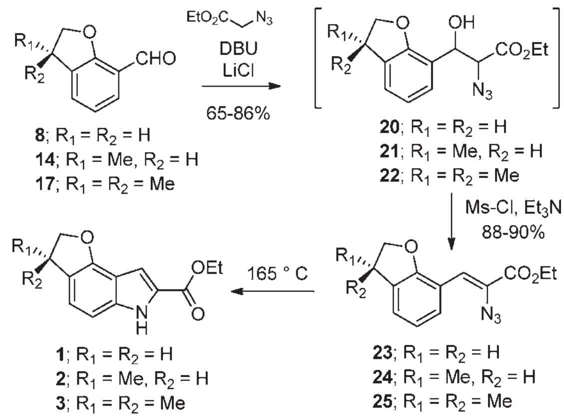
Scheme 5. Synthesis of 3,3-Dimethyldihydrobenzofuran-7-carboxaldehyde **17**



At this point, we were concerned about the possibility that the aldehyde moiety of **16** was unfavorably interfering in the reaction. Therefore, we investigated the cyclization of **18** (prepared from 2-bromophenol) with the assumption that the aldehyde moiety could be introduced at a later stage (Scheme 5). Thus, palladium-catalyzed cyclization of **18** gave the desired 3,3-dimethyldihydrobenzofuran (**19**) in 60% yield. Deprotonation of **19** with *sec*-BuLi in the presence of TMEDA followed by addition of DMF gave aldehyde **17** in quantitative yield.

Having on hand the required aldehydes **8**, **14**, and **17**, we proceeded to convert them into the required 3′-substituted dihydrofuranoindoles. The initial attempts involved the condensation of the aldehydes with ethyl azido acetate in the presence of sodium methoxide as previously described in the literature (method A).[9] Although this methodology delivered the desired vinylazido compounds **23** − **25** (as methyl esters), it suffered from low yields and extended reaction times. In order to solve this problem, a two-step approach for this synthetic transformation was investigated (method B). First, aldehydes **8** and **17** were reacted with ethyl azido acetate in the presence of DBU and lithium chloride to obtain the azidohydroxy intermediates **20** and **22** in good yields (65−86%). The azidohydroxy intermediates were then converted to their corresponding mesylate derivatives followed by an in situ β-elimination to give the vinylazido intermediates **23** and **25** in excellent yields (Scheme 6).

Scheme 6. Hemetsberger−Knittel Synthesis of 3′-Substituted Dihydrofuranoindoles



The final assembly of the dihydrofurano indoles **1**−**3** was expected to occur from vinylazido intermediates **23**−**25** under Hemetsberger−Knittel conditions. Recent work has been reported in the development of new rhodium based catalysts to promote the C−H insertion at lower temperatures.[10] In our research, we found that these catalysts would partially convert the vinylazido intermediates to the required dihydrofurano indoles. On the other hand, the thermally promoted process gave the desired dihydrofuranoindoles **1**, **2**, and **3** in moderate yields (42, 20, and 37%, respectively).

(9) For selected examples, see: (a) Chezal, J.-M.; Paeshuyse, J.; Gaumet, V.; Canitrot, D.; Maisonial, A.; Lartigue, C.; Gueiffier, A.; Moreau, E.; Teulade, J.-C.; Chavignon, O.; Neyts, J. *Eur. J. Med. Chem.* **2010**, *45*, 2044–2047. (b) Henn, L.; Hickey, D. M. V.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189–2196. (c) Roy, P.; Boisvert, M.; Leblanc, Y. *Org. Synth.* **2007**, *84*, 262–271.

(10) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500–7501.

(11) See the Supporting Information for experimental details. Also see the following references for information about structure−activity of functional groups in these compounds: Anilkumar, G.; Lesburg, C.; Selyutin, O.; Rosenblum, S.; Zeng, Q.; Jiang, Y.; Chan, T.-Y.; Pu, H.; Vaccaro, H.; Wang, L.; Bennett, F.; Chen, K.; Duca, J.; Gavalas, S.; Huang, Y.; Pinto, P.; Sannigrahi, M.; Velazquez, F.; Venkatraman, S.; Vibulbhan, B.; Agrawal, S.; Butkiewicz, N.; Feld, B.; Ferrari, E.; He, Z.; Jiang, C.; Palermo, R.; Mcmonagle, P.; Huang, H.-C.; Shih, N.-Y.; Njoroge, G.; Kozlowski, J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5336–5341.

B. Synthesis of HCV NS5B Inhibitors and Macromolecular X-ray Diffraction Studies. To exemplify the utility of the new dihydrofuranoindoles synthesized in this study, appropriate functional groups were attached to compounds **1** and **2** in order to convert them into effective HCV NS5B inhibitors.[11] Thus, acylsulfonamides **26** and **27** were obtained from **1** and **2**, respectively, and had their inhibitory activity measured,[12] Figure 1. It was determined that the 3′-methyl-substituted compound **27** (IC_{50} = 6 nM) increased the potency by 2-fold compared to the unsubstituted analogue **26** (IC_{50} = 15 nM).

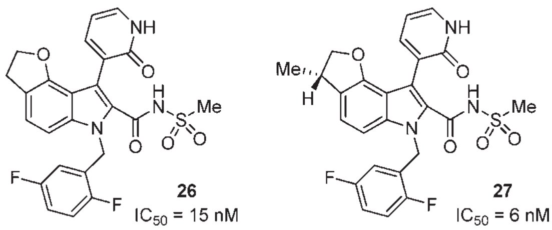


Figure 1. Enzymatic activity of dihydrofuranoindole-based HCV NS5B inhibitors **26** and **27**.

The primary goal for the preparation of these dihydrofuranoindoles was their utilization as molecular probes to investigate the mode of binding in the HCV NS5B polymerase active site. To this end, compounds **26** and **27** were soaked into preformed crystals of HCV NS5B protein.[13] The resulting structures showed how the unsubstituted inhibitor **26** (Figure 2, green color, IC_{50} = 15 nM) binds to the enzyme. Important interactions include H-bonding of the pyridone moiety with the protein backbone of Tyr-448 and Ile-447. The dihydrofuran ring of **26** rests in a hydrophobic pocket deep within the active site cavity lined in part by the side chains of Pro-197 and Met-414.

(12) Ferrari, E.; He, Z.; Palermo, R. E.; Huang, H.-C. *J. Biol. Chem.* **2008**, *283*, 33893–33901.

(13) Macromolecular crystallographic data have been deposited at the Protein Data Bank (http://www.pdb.org) with accession codes 3uph and 3upi.

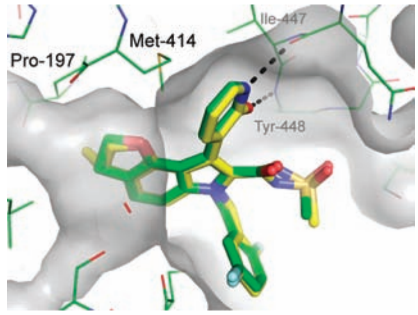


Figure 2. X-ray structures of dihydrofuranoindoles **26** (green) and **27** (yellow) bound to HCV NS5B. Hydrogen bonds to the backbone atoms of Ile-447 and Tyr-448 are shown as dots. Also labeled are residues Pro-197 and Met-414, which line the subpocket into which the 3′-methyl group of **27** protrudes. The interior surface of the HCV NS5B protein is shown in light gray. This figure was prepared using PyMOL.

The 3′-methyl-substituted dihydrofuranoindole **27** (yellow, IC_{50} = 6 nM) showed the same interactions as compound **26**. However, the 3′-methyl group projects more deeply into the hydrophobic cavity. The 2-fold increase in potency was attributed to the additional van der Waals interactions made by the 3′-methyl group.

In conclusion, a series of new dihydrofuranoindoles were synthesized as core structures for HCV NS5B polymerase inhibitors. Synthesis of the dihydrofuranoindoles required preparation of previously unknown 3-substituted dihydrobenzofuran carboxaldehydes and their conversion to dihydrofurano indoles was reported. The 3′-substituted dihydrofuranoindoles were converted to potent HCV NS5B inhibitors and used as molecular probes to obtain new information about the binding mode of our initial lead compounds in order to design inhibitors with improved potency.

Supporting Information Available. Experimental procedures, spectroscopical data, and copies of spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.