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Inhibition of hepatitis C virus NS5A by fluoro-olefin based γ-turn mimetics

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ABSTRACT

The HCV non-structural protein NS5A has been established as a viable target for the development of direct acting antiviral therapy. From computational modeling studies strong intra-molecular hydrogen bonds were found to be a common structural moiety within known NS5A inhibitors that have low pico-molar replicon potency. Efforts to reproduce these γ-turn-like substructures provided a novel NS5A inhibitor based on a fluoro-olefin isostere. This fluoro-olefin containing inhibitor exhibited picomolar activity (EC_{50} = 79 pM) against HCV genotype 1b replicon without measurable cytotoxicity. This level of activity is comparable to the natural peptide-based inhibitors currently under clinic evaluation, and demonstrates that a peptidomimetic approach can serve as a useful strategy to produce potent and structurally unique inhibitors of HCV NS5A.

Chronic hepatitis C virus (HCV) infection afflicts approximately 160 million people worldwide and is the leading cause of liver cirrhosis and hepatocellular carcinoma in the US.[1] Among first generation direct acting antivirals (DAAs), two NS3/4a protease inhibitors, telaprevir and boceprevir, in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) have been approved for the treatment of HCV infection in mid-2011.[2] Both of these combination treatments have shown improved sustained virological response (SVR) and reduced treatment duration compared to PEG-IFN/RBV. However, they are limited to treating only genotype 1 patients, still require PEG-IFN/RBV adjunct therapy and bring with them additional side effects which require further medical attention.[3] Therefore, the search continues for novel agents with complementary mechanisms of action that can be combined with existing or future DAA therapies and that have improved safety profiles over existing therapy.[4]

The NS5A inhibitor, BMS-790052 (daclatasvir, **1**) has recently been reported to produce promising clinical outcomes among HCV infected patients.[5] Consequently remarkable interest within the pharmaceutical community has been focused on related NS5A inhibitors.[6] Currently known development candidates in this series include BMS-790052, & BMS-824393, GS-5885, PPI-461, PPI-437, PPI-668, & PPI-833, ABT-267, EDP-239, ACH-2928 & ACH-3102, GSK-2336805, MK-4882, and IDX-719. Although the exact structures of many of these agents are undisclosed, a majority of the efforts described in recent patent applications concentrate on simple modifications of the central linker, and the two pyrrolidine (B,B′) units (Fig. 1).[7]

A general structural feature found in the known NS5A inhibitors having low pico-molar replicon potency is a peptide substructure containing multiple functional groups which can act as hydrogen bond donors or acceptors. In order to better understand if these chemical features conferred an energetically favored three dimensional shape which could be correlated to potency, we applied the following molecular modeling approach to all of the compounds. Conformers were generated using torsional sampling (MCMM)[8] followed by energy minimization to a convergence gradient of 0.001 using MMFFs with a distance dependent dielectric of 2r.[9] An RMSD of 0.25 and a 12 or 20 kcal/mol energy window were used as criterion to limit the number of conformers output with an upper limit of 1000 being possible. Of the 297 conformers generated for compound **1** within the range of 88–108 kcal/mol (Fig. 2), the 12 lowest energy conformers were observed to make internal hydrogen bonds between the valine C=O and imidazole N–H (distance = 2.22 Å) on both sides of the dimer. The observed lowest energy conformations were similar to γ-turns typically found in polypeptide structures: the γ-turn is a three amino acid residue turn which contains a seven-membered ring constructed by the hydrogen bond between the carbonyl C=O of the *i*th residue and the amide N–H of the *i* + 2 residue.[10]

We envisaged that the intra-molecular hydrogen bonds within the NS5A inhibitor structure might play a crucial role in holding the molecule in an optimized binding conformation. As an effort to both verify our hypothesis and to discover a novel inhibitor

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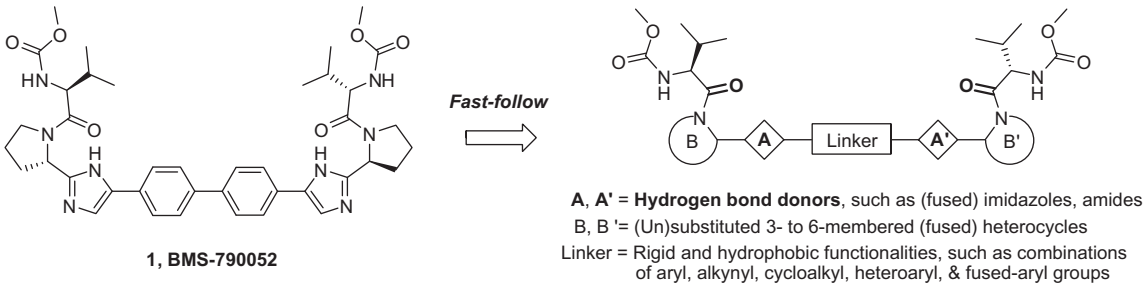


Figure 1. Current HCV NS5A inhibitors.[6a]

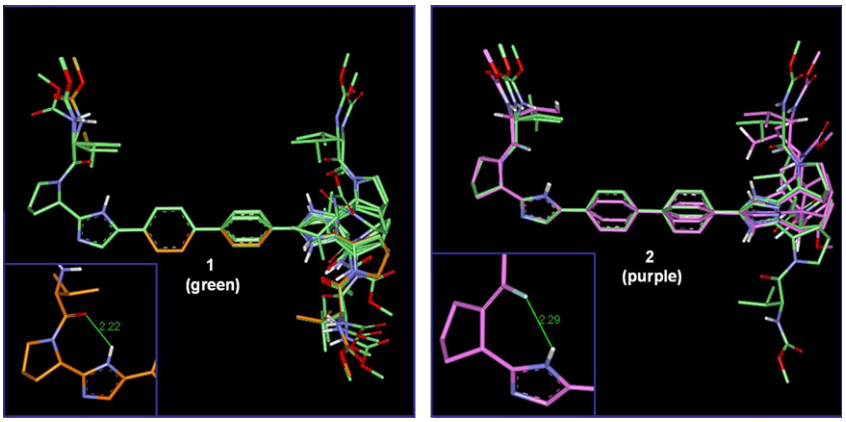


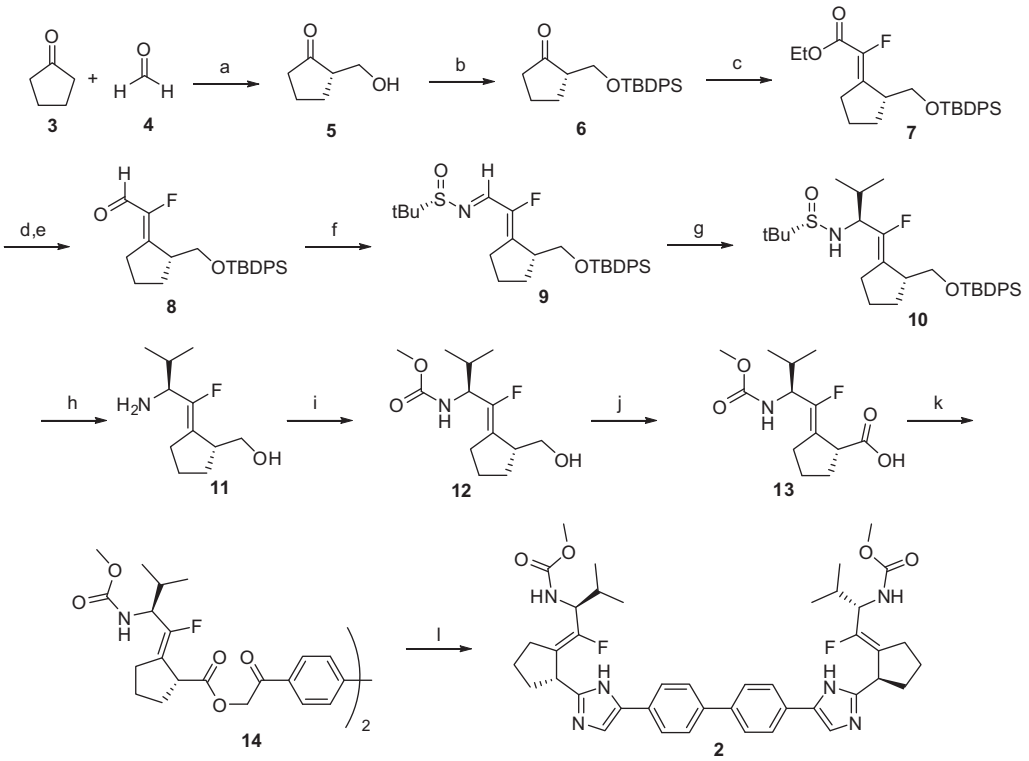
Figure 2. Energy-minimized structures of HCV NS5A inhibitors.

class, a number of structural motifs that could potentially reproduce the γ-turn were evaluated computationally. Among them, the fluoro-olefin based proline analogue **2** was predicted to effectively mimic the γ-turn. Analog **2** was shown to generate low energy conformers that are internally hydrogen-bonded between the fluoro-olefin =C–F and imidazole N–H (distance = 2.29 Å) on both sides of the dimer. This fluoroalkene isostere maintain steric and electronic character similar to a peptide bond,[11] and has been previously employed in thermolysin inhibitor,[12] cyclophilin A inhibitors,[13] dipeptidyl peptidase IV inhibitors,[14] neuropeptide substance P analogs,[15] and human parathyroid hormone analogs.[16] If the peptidomimetic substructure is able to maintains the desired inhibitor conformation and demonstrate potent inhibition of HCV replication, a new approach to the development of novel NS5A inhibitors with a distinctive structural feature is possible. Therefore, we decided to prepare the fluoro-olefin based structures and study their anti-HCV activities.

The synthesis of Leu-*trans*-Pro mimetic **2** was initiated with stereoselective organocatalytic aldol reaction of cyclopentanone where it was treated with L-threonine and aqueous formaldehyde (Scheme 1).[17] After silyl protection of the hydroxyl group, ketone **6** was obtained in 55% yield and its enantiomeric excess (ee) was determined to be 60% by chiral SFC. Then, the Horner-Emmons reaction of the cyclopentanone and ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate provided (*Z*)-fluoro-olefin **7**, which was easily separated from the (*E*)-isomer by regular column chromatography.[18] A two-step sequence which included DIBALH reduction and a Dess–Martin oxidation afforded α-fluoro-α,β-unsaturated aldehyde **8.** An Ellman's sulfinyl imine was subsequently constructed using (*S*)-*tert*-butanesulfinamide and titanium(IV) ethoxide.[19] Diastereoselective addition of isopropyl lithium to β-fluoroimine **9** (dr 3:1) established the L-Leu moiety in a similar fashion as the previously reported example.[20] The sulfinyl group of compound **10** and the silyl protecting group were readily removed under acidic conditions. Introduction of the methyl carbamate functionality to amine **11** provided a crystalline solid, urethane **12**, of which regio- and absolute stereochemistries were unambiguously verified by a single crystal X-ray structure (Fig. 3, CCDC 866508). Jones oxidation of the primary alcohol **12** yielded carboxylic acid **13**,[14a] which was then reacted with symmetric 1,1′-([1,1′-biphenyl]-4,4′-diyl)bis(2-bromoethanone) to give dimeric ester **14**. Finally, the two ketoester groups of **14** were cyclized upon microwave irradiation for 30 min at 155 °C in the presence of excess ammonium acetate, thus providing the bis-imidazolic fluoro-olefin **2**.

Separately, fluoro-olefin **23** which does not include the neighboring cyclopentane rings (Leu-NMe-trans-Ala mimic) was also prepared. Unlike proline analog **2**, *N*-methylalanine analog **23** contains a freely rotatable σ-bond next to the fluoro-olefin and therefore, is less likely to induce the γ-turn sub-structure anticipated for analog **2**. By examining the biological activities of the two fluoro-olefin analogs **2** and **23**, we hoped to determine whether the γ-turn predicted for **2** is actually an important NS5A inhibitory conformational element. The synthesis of flouro-olefin **22** started from commercially available (*S*)-methyl 3-hydroxy-2-methylpropanoate **15** (Scheme 2). First, the alcohol was protected with a TBDPS group to give silyl ether **16** and a Weinreb amide was introduce to the ester moiety. Methyl Grignard reagent was subsequently reacted with the Weinreb amide **17** at −10 °C to provide ketone **18** in excellent yield. Unlike the previous example of cyclopentanone **6**, the Horner-Emmons reaction of methyl ketone **18** with ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate gave (*Z*)-olefin **19** as a minor regioisomer in a 1:1.5 ratio. The remainder of the synthesis mirrored that used to prepare compound **2**, and gave alanine mimetic **23** in 6.5% overall yield.

Anti-HCV activity of fluoro-olefins **2** and **23** was measured in a clone A replicon whole cell assay (Table 1). Inhibitor **23** based on (*Z*)-Leu-ψ[CF=C(Me)]-Ala, which displayed a less favorable



Scheme 1. Reagents and conditions: (a) 0.3 equiv L-threonine, dioxane, rt, 33%, 60% ee; (b) TBDPSCl, imidazole, DCM, rt, 55%; (c) ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate, NaH, ether, 36%, (*E*:*Z* = 1:1.2); (d) DIBALH, ether, 0 °C, 62%; (e) Dess–Martin periodinane, DCM, rt, 85%; (f) (*S*)-2-*tert*-butanesulfinamide, $Ti(OEt)_4$, DCM, rt, 63% in two steps; (g) *i*PrLi, toluene, −78 °C, 58% (dr 3:1); (h) 2 N HCl, dioxane/EtOH; (i) methylchloroformate, Et_3N, DCM/EtOH, 63% in two steps; (j) CrO_3, aq H_2SO_4, acetone, 0 °C, 61%; (k) 1,1′-([1,1′-biphenyl]-4,4′-diyl)bis(2-bromoethanone), *i*PrNEt$_2$, CH_3CN, 92%; (l) NH_4OAc, *p*-xylene, Microwave, 155 °C, 32%.

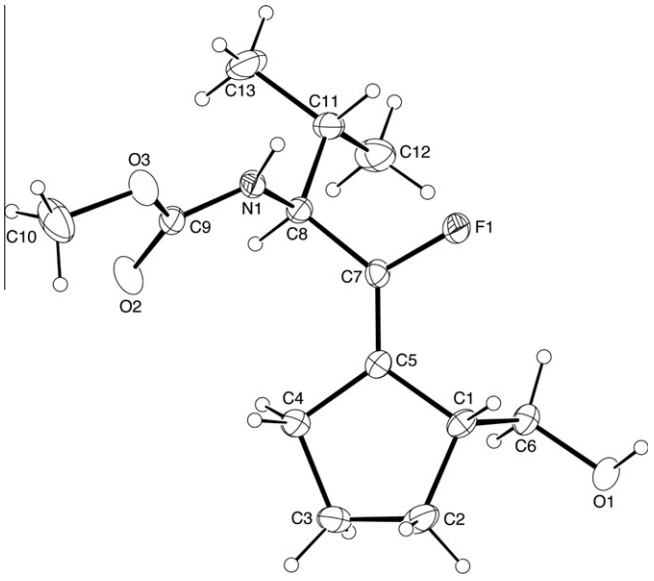
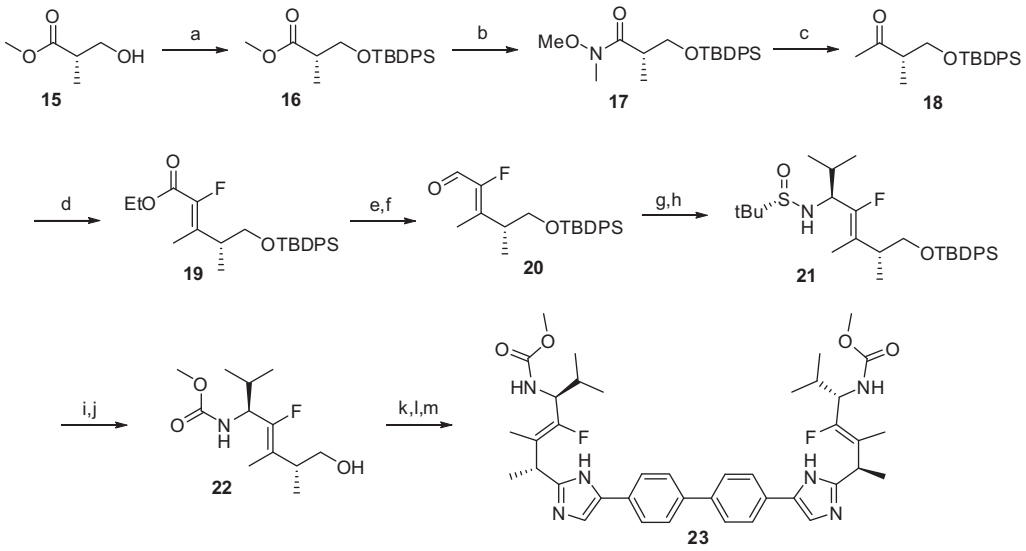


Figure 3. ORTEP drawing of carbamate **12**.

tendency to induce a γ-turn in computational modeling, did show nano-molar in vitro activity (EC_{50} = 27.3 nM) in a genotype 1b replicon assay. However, the proline mimetic **2,** which was calculated to induce a more stable γ-turn as is seen for other NS5A inhibitors, exhibited pico-molar anti-HCV activity (EC_{50} = 79 pM) in a genotype 1b replicon assay. Thus **2** was shown to be >300-fold more potent than the acyclic analog **23** providing support for the γ-turn substructure as an important conformational motif in the binding interaction with the NS5A protein that ultimately results in the inhibition of HCV replication by this class of molecules. In addition, the (*Z*)-Leu-ψ[CF=C]-Pro based inhibitor **2** did not exhibit any cytotoxicity up to the highest concentration tested (CC_{50} >10 μM) rendering a large selectivity index. It was also observed that **2** produced significantly reduced potency against genotype 1a replicon relative to genotype 1b. This is in contrast to the result observed for **1** and consistent with the genotype activities observed for previously reported NS5A inhibitors.[6,21] Consequently, in order to achieve comparable potency across multiple genotypes further work is needed.

In 2010, Urban and co-workers, reported *ab initio* calculation of simple fluoro-olefins as peptide mimics, where the structure of (*R*,*Z*)-4-fluoro-*N*,2-dimethylpent-3-enamide (NFA) was predicted to closely resemble the structure of its natural peptide congener, (*S*)-2-acetamido-*N*-methylpropanamide (ADA).[22] However, the inter-atomic distance between the fluorine in the =C–F and the hydrogen in the N–H in NFA was calculated to be 2.407 Å, which was significantly longer than the calculated length of the γ-turn hydrogen bond (2.026 Å) in ADA. This calculated result showed that the hydrogen-bond accepting ability of the fluorine atom in a fluoro-olefin analog is less strong than that of the oxygen in a carbonyl group.[23] Comparing the fluoro-olefins **2** and **23** described here, the (*Z*)-Me-ψ[CF=CH]-Ala model (NFA) imparts significantly less conformational restriction. Consequently, our results demonstrate that by imposing appropriate conformational constraint around the putative internal hydrogen bond, even a weak hydrogen-bond-acceptor such as fluorine can stabilize a γ-turn substructure and produce effective HCV NS5A inhibitor. Further studies toward more potent NS5A inhibitors that incorporate strong internal hydrogen bonds are currently in progress.



Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, DCM, rt, 61%; (b) *N*,*O*-dimethylhydroxylamine hydrochloride, *i*PrMgCl, THF, −20 to −5 °C, 99%; (c) MeMgBr, THF, −10 °C, 99%; (d) ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate, NaH, ether, 33% (*E*:*Z* = 1.5:1); (e) DIBALH, ether, −78 °C; (f) Dess–Martin periodinane, DCM, rt, 60%; (g) (*S*)-2-*tert*-butanesulfinamide, $Ti(OEt)_4$, DCM, rt; (h) *i*PrLi, toluene, −78 °C, 50% (dr 7:3); (i) 2 N HCl, dioxane/EtOH; (j) methylchloroformate, Et_3N, DCM/EtOH, 54%; (k) CrO_3, aq H_2SO_4, acetone, 0 °C; (l) 1,1′-([1,1′-biphenyl]-4,4′-diyl)bis(2-bromoethanone), *i*PrNEt$_2$, CH_3CN; (m) NH_4OAc, *o*-xylene, microwave, 140 °C, 40%.

Table 1
HCV replicon activity and cytotoxicity

Compd	EC_{50} (nM)			CC_{50} (nM)
	GT 1B	GT 1A	GT 2A	
23	27.3	659	397	1,400
2	0.079	189	167	>10,000
1	0.009	0.050	0.063	2,800

In conclusion, a series of novel HCV NS5A inhibitors were designed and prepared where a fluoro-olefin moiety replaced the intramolecular hydrogen bonded amide group in a known class of HCV NS5A inhibitors (**1**). The fluoro-olefin based proline mimic **2** demonstrated pico-molar in vitro activity supporting the hypothesis that the γ-turn substructure is an active conformation important for the inhibition of HCV by NS5A inhibitors. Therefore, structurally distinct NS5A inhibitors with strong anti-HCV potency can be obtained via the peptidomimetic approach where the optimal molecular conformer for inhibition is reproduced.

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Supplementary data

Supplementary data (experimentals and spectral data for compound **2**, **5**–**14**, and **23**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.02.051.

References and notes

1. Negro, F.; Alberti, A. *Liver Int.* **2011**, *31*, 1.
2. Pockros, P. J. *Expert Opin. Biol. Ther.* **2011**, *11*, 1611.
3. Garber, K. *Nat. Biotechnol.* **2011**, *29*, 963.
4. Sofia, M. J.; Chang, W.; Furman, P. A.; Mosley, R. T.; Ross, B. S. *J. Med. Chem.* **2012**. doi:10.1021/jm201384j.
5. (a) Nettles, R.; Chien, C.; Chung, E.; Persson, A.; Gao, M.; Belema, M.; Meanwell, N. A.; DeMicco, M. P.; Marbury, T. C.; Goldwater, R.; Northup, P.; Coumbis, J.; Kraft, W. K.; Charlton, M. R.; Lopez-Talavera, J. C.; Grasela, D. Abstract of Papers, 59th Annual Meeting of the American Association for the Study of Liver Diseases, San Francisco, CA; John Wiley & Sons Inc.: Malden, MA, 2008, Abstract LB12.; (b) Gao, M.; Nettles, R. E.; Belema, M.; Snyder, L. B.; Nguyen, V. N.; Fridell, R. A.; Serrano-Wu, M. H.; Langley, D. R.; Sun, J. H.; O'Boyle, D. R., II; Lemm, J. A.; Wang, C.; Knipe, J. O.; Chien, C.; Colonno, R. J.; Grasela, D. M.; Meanwell, N. A.; Hamann, L. G. *Nature* **2010**, *465*, 96; (c) Nettles, R. E.; Gao, M.; Bifano, M.; Chung, E.; Persson, A.; Marbury, T. C.; Goldwater, R.; DeMicco, M. P.; Rodriguez-Torres, M.; Vutikullird, A.; Fuentes, E.; Lawitz, E.; Lopez-Talavera, J. C.; Grasela, D. M. *Hepatology* **2011**, *54*, 1956.
6. (a) Meanwell, N. A.; Belema, M. *Annu. Rep. Med. Chem.* **2011**, *46*, 263; (b) Najarro, P.; Mathews, N.; Cockerill, S. In *Hepatitis C*; Tan, S.-L., He, Y., Eds.; Caister Academic Press: Norfolk, UK, 2011; pp 271–292; (c) Cordek, D. G.; Bechtel, J. T.; Maynard, A. T.; Kazmierski, W. M.; Cameron, C. E. *Drugs Future* **2011**, *36*, 691.
7. Some recent patent applications on related NS5A inhibitors: (a) Bachand, C.; Belema, M.; Deon, D. H.; Good, A. C.; Goodrich, J.; James, C. A.; Lavoie, R.; Lopez, O. D.; Martel, A.; Meanwell, N. A.; Nguyen, V. N.; Romine, J. L.; Ruediger, E. H.; Snyder, L. B.; St. Laurent, D. R.; Yang, F.; Langley, D. R.; Wang, G.; Hamann, L. G. PCT Int. Appl. WO 2008021927, 2008; (b) Guo, H.; Kato, D.; Kirschberg, T. A.; Liu, H.; Link, J. O.; Mitchell, M. L.; Parrish, J. P.; Squires, N.; Sun, J.; Taylor, J.; Bacon, E. M.; Canales, E.; Cho, A.; Cottell, J. J.; Desai, M. C.; Halcomb, R. L.; Krygowski, E. S.; Lazerwith, S. E.; Liu, Q.; Mackman, R.; Pyun, H.-J.; Saugier, J. H.; Trenkle, J. D.; Tse, W. C.; Vivian, R. W.; Schroeder, S. D.; Watkins, W. J.; Xu, L.; Yang, Z.-Y.; Kellar, T.; Sheng, X.; Clarke, M. O. H.; Chou, C.-H.; Graupe, M.; Jin, H.; Mcfadden, R.; Mish, M. R.; Metobo, S. E.; Phillips, B. W.; Venkataramani, C. PCT Int. Appl. WO 2010132601, 2010; (c) Li, L.; Zhong, M. PCT Int. Appl. WO 2010065668, 2010; (d) Degoey, D. A.; Kati, W. M.; Hutchins, C. W.; Donner, P. L.; Krueger, A. C.; Randolph, J. T.; Motter, C. E.; Nelson, L. T.; Patel, S. V.; Matulenko, M. A.; Keddy, R. G.; Jinkerson, T. K.; Soltwedel, T. N.; Hutchinson, D. K.; Flentge, C. A.; Wagner, R.; Maring, C. J.; Tufano, M. D.; Betebenner, D. A.; Rockway, T. W.; Liu, D.; Pratt, J. K.; Lavin, M. J.; Sarris, K.; Woller, K. R.; Wagaw, S. H.; Califano, J. C.; Li, W. PCT Int. Appl. WO 2010144646, 2010; (e) Or, Y. S.; Peng, X.; Ying, L.; Ce, W.; Tang, D.; Qiu, Y.-L. PCT Int. Appl. WO 2010096462, 2010; (f) Schmitz, F. U.; Rai, R.; Roberts, C. D.; Kazmierski, W.; Grimes, R. PCT Int. Appl. WO 2010062821, 2010; (g) Rosenblum, S. B.; Chen, K. X.; Kozlowski, J. A.; Njoroge, F. G.; Coburn, C. A. PCT Int. Appl. WO 2010132538, 2010; (h) Dousson, C. B.; Dukhan, D.; Parsy, C. C.; Pierra, C.; Alexandre, F.-R.; Brandt, G.; Da Costa, D.; Rahali, H.; Paparin, J.-L.; Derock, M.; Convard, T.; Surleraux, D. PCT Int. Appl. WO 2011075615, 2011.
8. Monte Carlo Multiple Minimum: (a) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379; (b) Saunders, M.; Houk, K. N.; Wu, Y. D.; Still, C. W.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.
9. (a) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 720; (b) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 730.
10. Etzkorn, F. A.; Travins, J. M. In *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; Jai Press Inc.: Stamford, CT, 1999; Vol. 2, pp 125–163.
11. (a) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151; (b) Welch, J. T. In *Fluorine and Health*; Tressaud, A., Haufe, G., Eds.; Elsevier, 2008; pp 699–735.
12. Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107.

13. Welch, J. T.; Lin, J.; Boros, L. G.; DeCorte, B.; Bergmann, K.; Gimi, R. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington D.C., 1996; pp 129–142.
14. (a) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291; (b) Lin, J.; Toscano, P. J.; Welch, J. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14020; (c) Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 207; (d) Van der Veken, P.; Kertesz, I.; Senten, K.; Haemers, A.; Augustyns, K. *Tetrahedron Lett.* **2003**, *44*, 6231; (e) Van der Veken, P.; Senten, K.; Kertesz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpe, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768; (f) Edmondson, S. D.; Wei, L.; Xu, J.; Shang, J.; Xu, S.; Pang, J.; Chaudhary, A.; Dean, D. C.; He, H.; Leiting, B.; Lyons, K. A.; Patel, R. A.; Patel, S. B.; Scapin, G.; Wu, J. K.; Beconi, M. G.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2409.
15. (a) Allmendinger, T.; Furet, P.; Hungerbuehler, E. *Tetrahedron Lett.* **1990**, *31*, 7297; (b) Allmendinger, T.; Furet, P.; Hungerbuehler, E. *Tetrahedron Lett.* **1990**, *31*, 7031.
16. Waelchli, R.; Gamse, R.; Bauer, W.; Meigel, H.; Lier, E.; Feyen, J. H. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1151.
17. Mase, N.; Inoue, A.; Nishio, M.; Takabe, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3955.
18. (*E*):(*Z*) = 1:1.2, determined by ^{19}F NMR of the crude mixture.
19. (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600; (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
20. (a) Pierry, C.; Zoute, L.; Jubault, P.; Pfund, E.; Lequeux, T.; Cahard, D.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron Lett.* **2009**, *50*, 264; (b) Pierry, C.; Cahard, D.; Couve-Bonnaire, S.; Pannecoucke, X. *Org. Biomol. Chem.* **2011**, *9*, 2378.
21. Schmitz, U.; Tan, S.-L. *Recent Pat. Anti-infect. Drug Discov.* **2008**, *3*, 77.
22. McKinney, B. E.; Urban, J. J. *J. Phys. Chem. A* **2010**, *114*, 1123.
23. Howard, J. A.; Hoy, W. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613.