Supplementary Materials for

Alkyl Sulfinates: Radical Precursors Enabling Drug Discovery

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Patented Processes using Alkyl Sulfinates and Therapeutic Derivatives Synthesized

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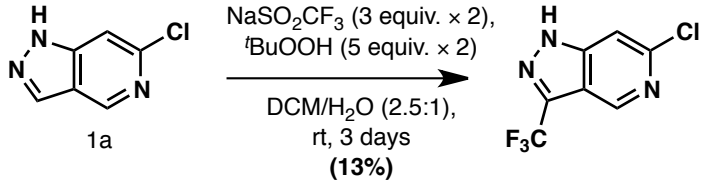
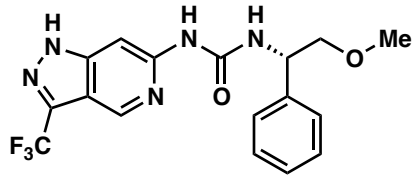
Patents from 2013

1. WO 2013063214, Applicant: Merck Sharp & Dohme Corp.

Lim, J.; Kelley, E. H.; Methot, J. L.; Zhou, H.; Petrocchi, A.; Mansoor, U. F.; Fischer, C.; O'Boyle, B. M.; Guerin, D. J.; Bienstock, C. E.; Bo C. W.; Daniels, M. H.; Falcone, D.; Ferguson, R. D., II; Fevrier, S.; Huang, X.; Lipford, K. A.; Sloman, D. L.; Wilson, K.; Zhou, W.; Witter, Maletic, M. M.; Siliphaivanh, P. Novel Compounds That Are ERK Inhibitors. WO 2013063214 A1, May 2, 2013.

pp. 149, Example 167, Step 1



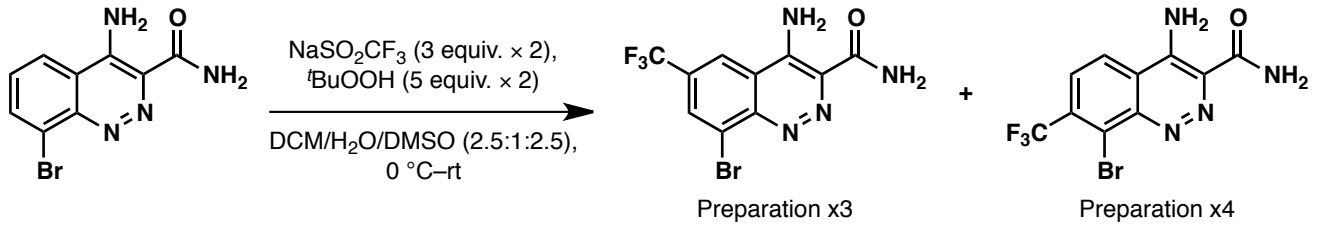


pp. 149, Example 167

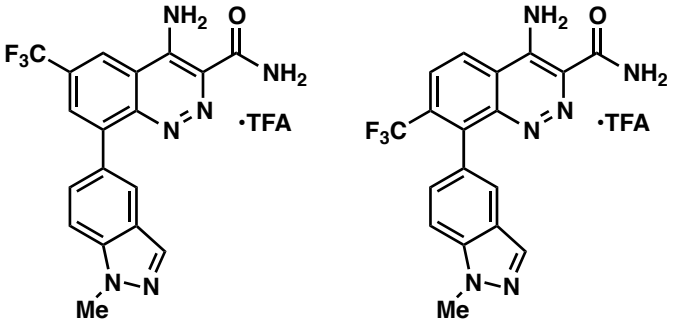
2. WO 2013148603, Applicant: Takeda Pharmaceutical Company Limited

Lawson, J. D.; Sabat, M.; Smith, C.; Wang, H.; Chen, Y. K.; Kanouni, T. Cinnoline Derivatives as BKT Inhibitors. WO 2013148603 October 3, 2013.

pp. 38, Preparations x3 and x4



Preparation x3 Preparation x4

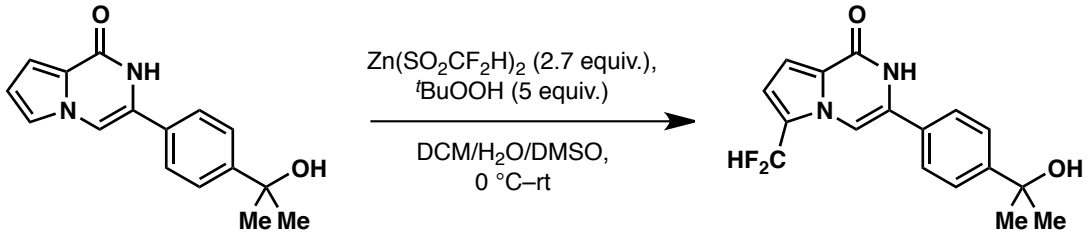


pp. 66, Example 34 pp. 66, Example 35

3. WO 2013143663, Applicant: Merck Patent GmbH

Dorsch, D.; Buchstaller, H. -P.; Moinet, G.; Wegener, A. Bicyclic Pyrazinone Derivatives. WO 2013143663 A1, October 3, 2013. (Reaction conditions adapted from, *J. Am. Chem. Soc.* **2012,** *134*, 1494-1497.)

pp. 110, Example 29, Synthesis of A96



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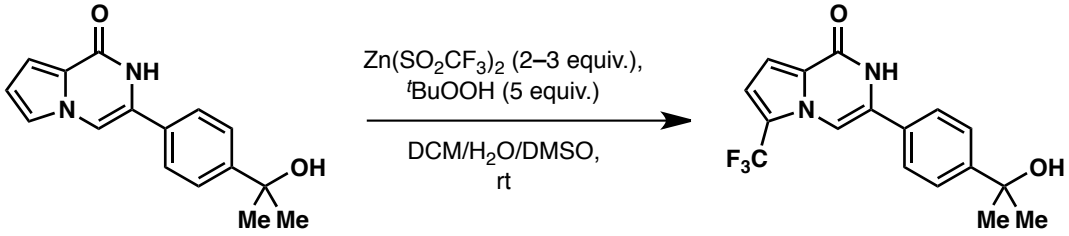

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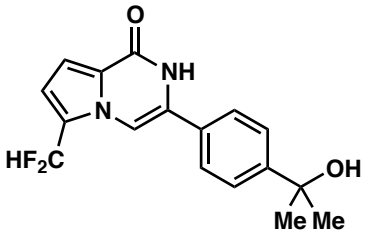

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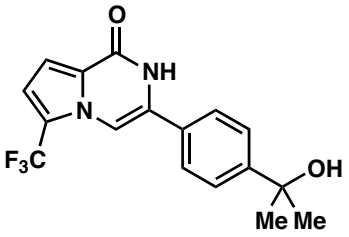


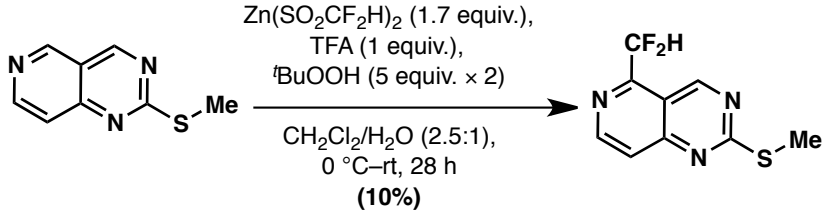
pp. 112, A97

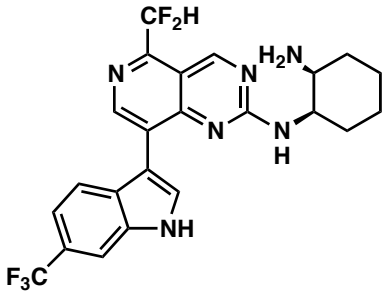
Patents from 2014

1. WO 2014023385, Applicant: Merck Patent GmbH

Burgdorf, L.; Kuhn, D.; Ross, T.; Deutsch, C. Pyridopyrimidine Derivatives as Protein Kinase Inhibitors. WO 2014023385 A1, February 13, 2014.

pp. 141, Example 82, Step 1





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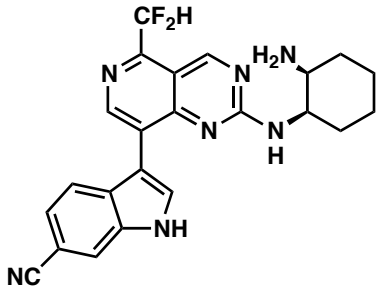

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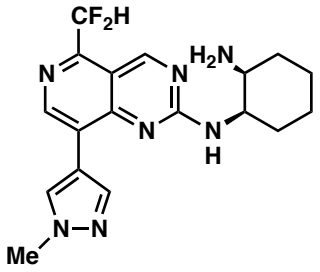

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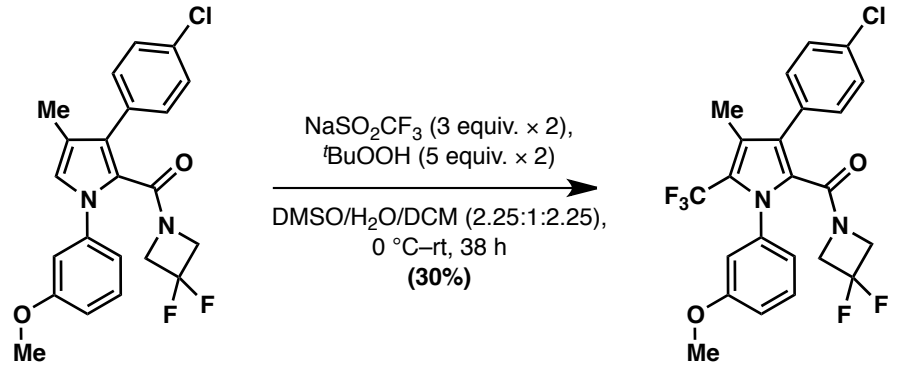
2. WO 2014032801, Applicant: Grunenthal GmbH

Schunk, S.; Reich, M.; Steinhagen, H.; Damann, N.; Skone, P.; Hamlyn, R.; Kirby, R.; Rogers, M.; Sutton, K. Fluoromethyl-Substituted Pyr
Caboxamindes. WO 2014032801 A1, March 6, 2014.

pp. 151, Synthesis of Example SC-32, Step 4



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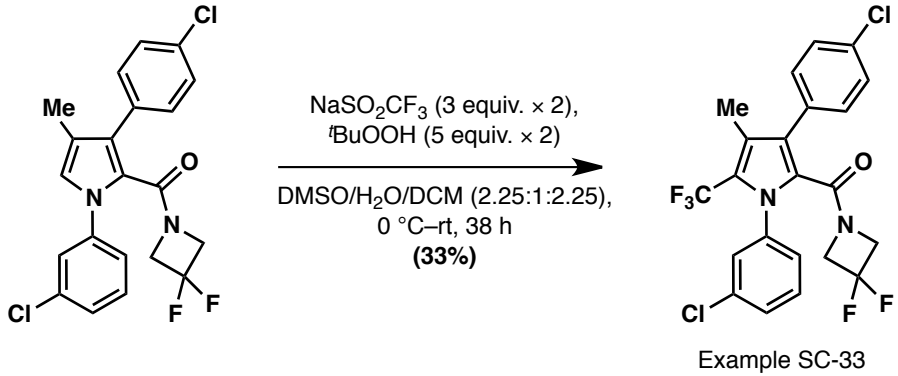

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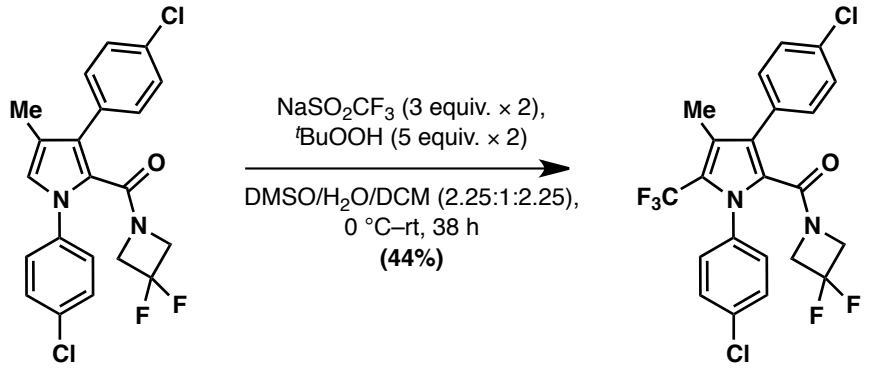

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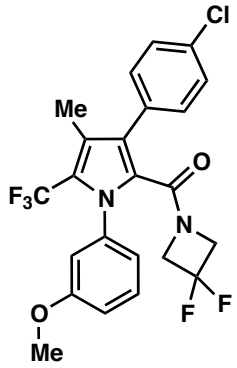

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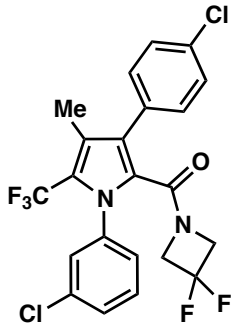

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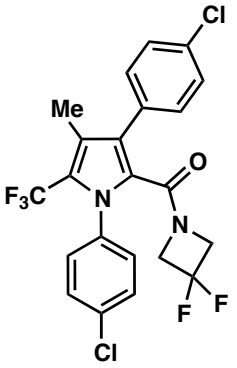

pp. 153–154, Example SC-44

3. WO 2014052563, Applicant: Merck Sharp & Dohme Corp.

Wilson, K. J.; Witter, D. J.; Siliphaivanh, P.; Lipford, K.; Sloman, D.; Falcone, D.; O'Boyle, B.; Mansoor, U. F.; Lim, J.; Methot, J. L.; Boy C.; Chen, L.; Daniels, M. H.; Fevrier, S.; Huang, X.; Kurukulasuriya, R.; Tong, L.; Zhou, W.; Kozlowski, J.; Maletic, M. M.; Shinkre, B. Thatai, J. T.; Bakshi, R. K.; Karunakaran, G. B. Novel Compounds That Are ERK Inhibitors. WO 2014052563 A2, April 3, 2014.

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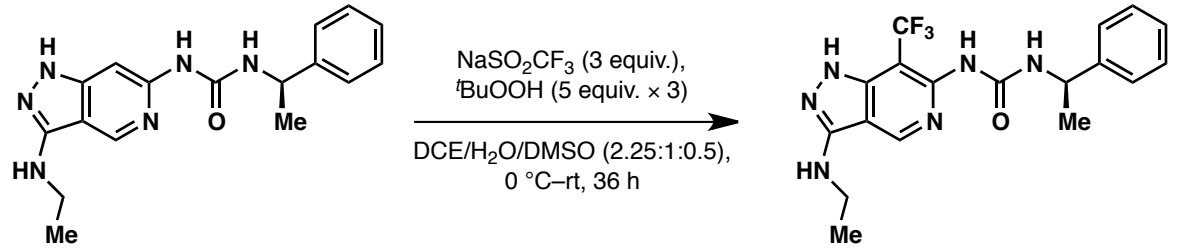

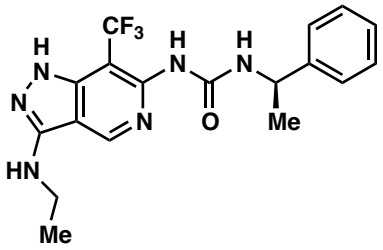

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4. WO 2014057078, Applicant: H. Lundbeck A/S, Den.

Kilburn, J. P.; Rasmussen, L. K.; Jessing, M.; Eldemenky, E. M.; Chen, B.; Jiang, Y.; Hopper, A. T. Benzamides. WO 2014057078 A1, April 2014.

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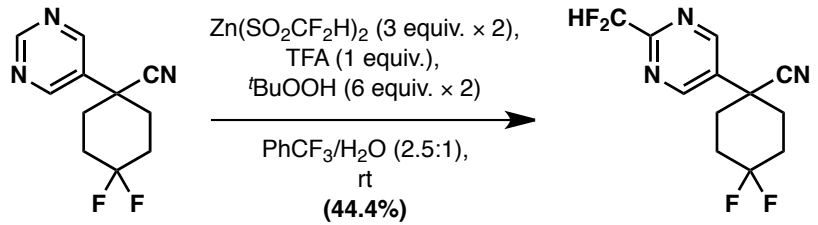

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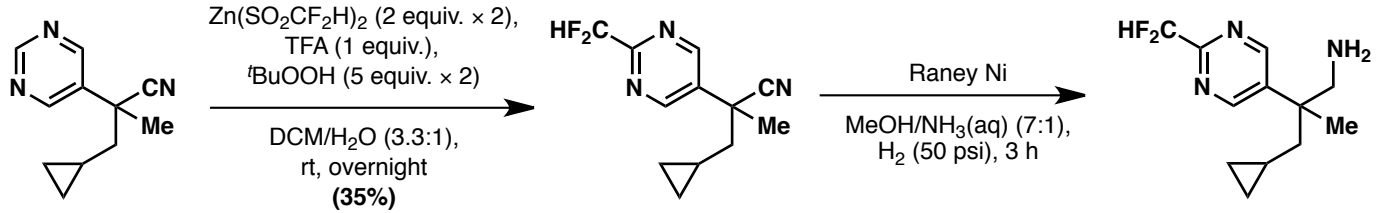

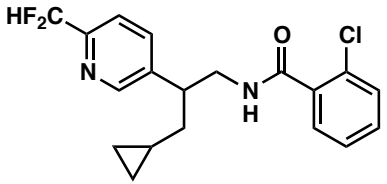

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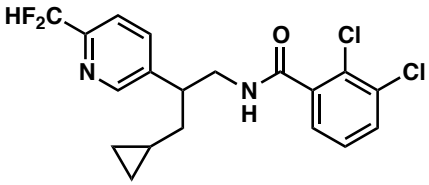

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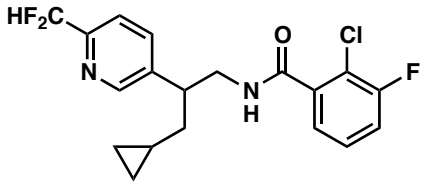

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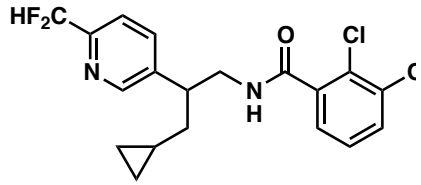

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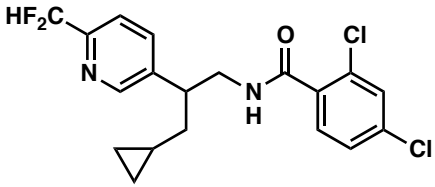

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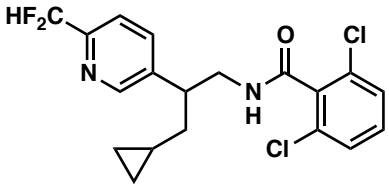

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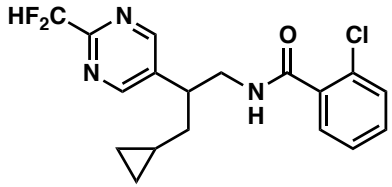

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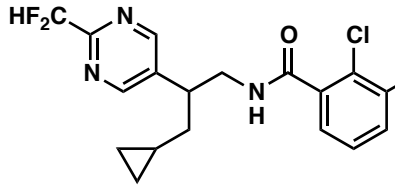

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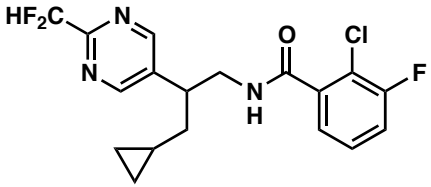

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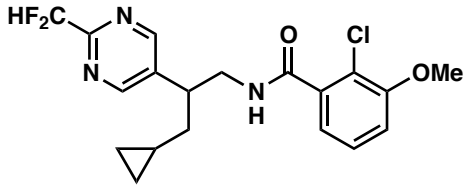

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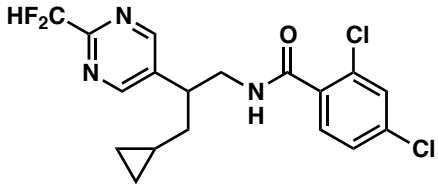

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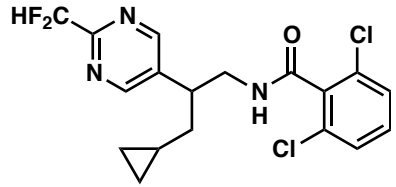

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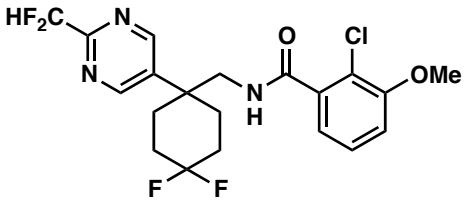

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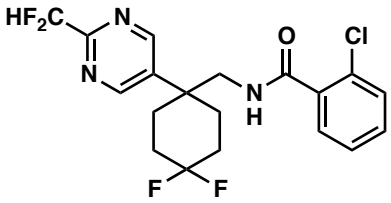

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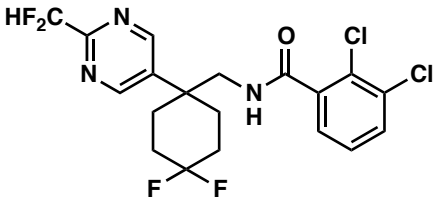

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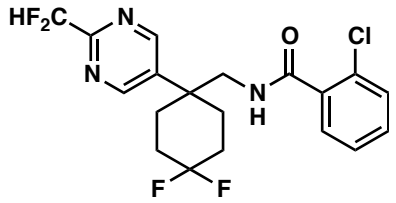

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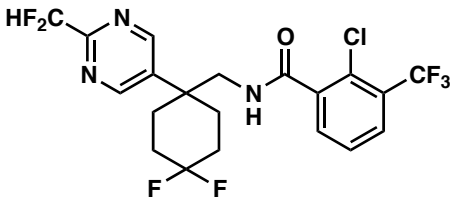

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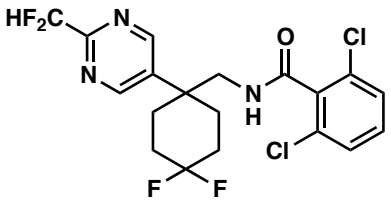

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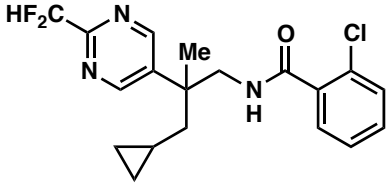

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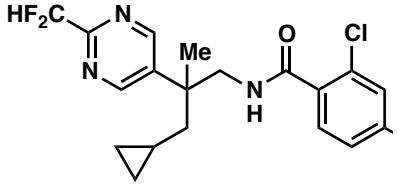

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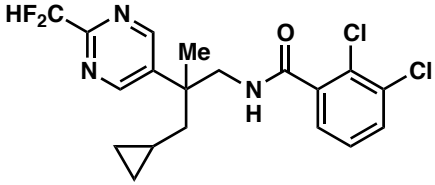

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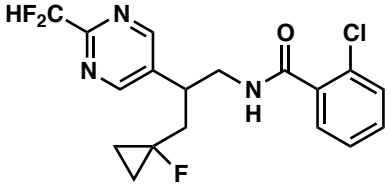

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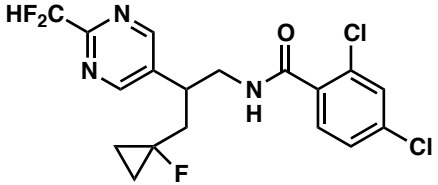

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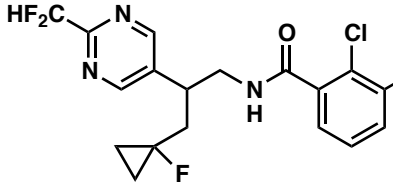

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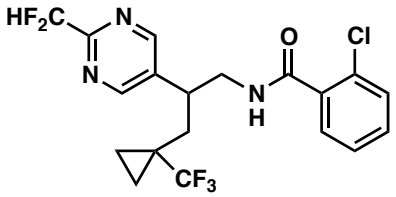

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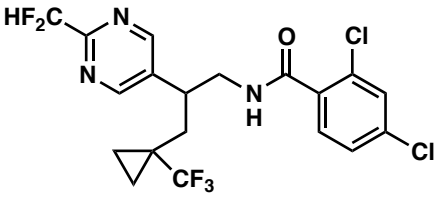

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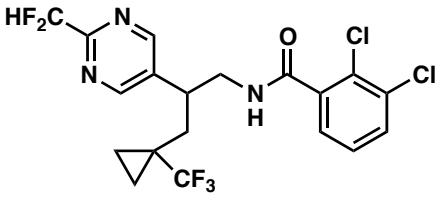
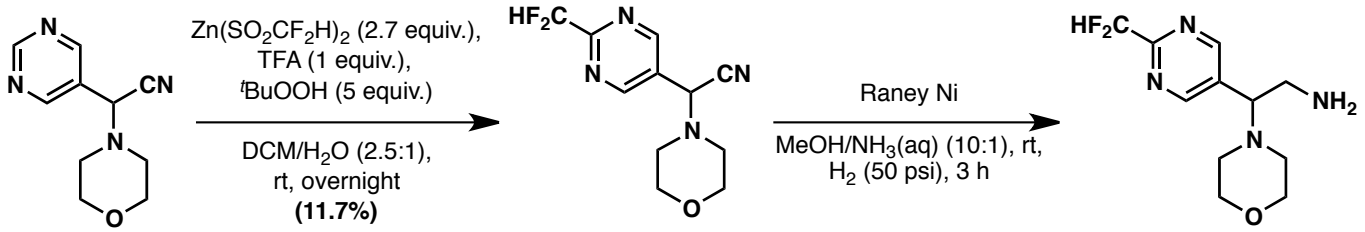


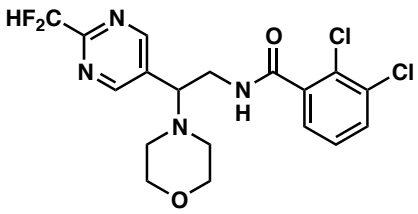
pp. 184, Examples 4s5 and 4t5

5. WO 2014057080, Applicant: H. Lundbeck A/S, Den.

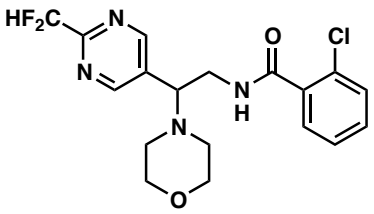
Kilburn, J. P.; Rasmussen, L. K.; Jessing, M.; Eldemenky, E. M.; Chen, B.; Jiang, Y. Cyclic Amines. WO 2014057080 A2, April 17, 2014.

pp. 21

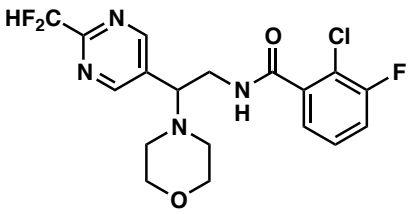




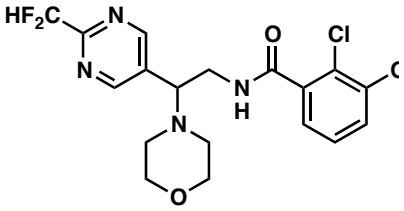
pp. 79, Examples 3v3 and 3x3



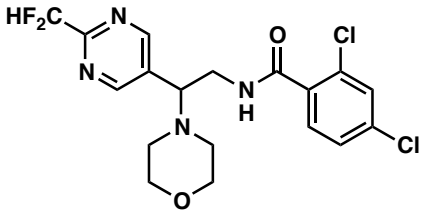
pp. 79-80, Examples 3y3 and 3z3



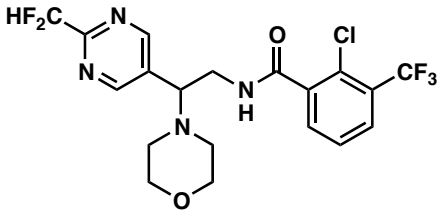
pp. 80, Examples 3a4 and 3b4



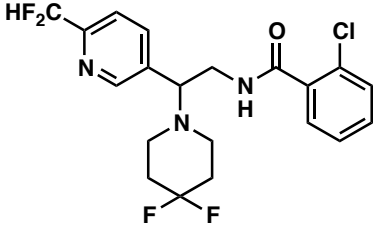
pp. 97, Examples 3i6 and 3j6



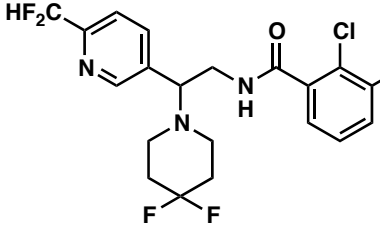
pp. 97, Examples 3k6 and 3l6



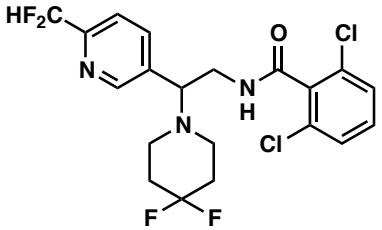
pp. 98, Examples 3m6 and 3n6



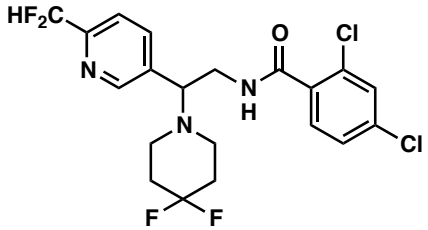
pp. 90, Examples 3j5 and 3k5



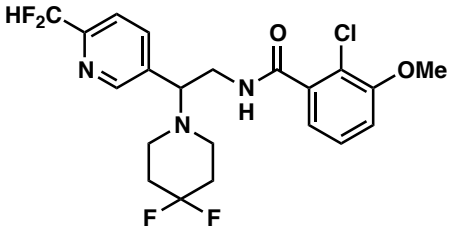
pp. 90-91, Examples 3l5 and



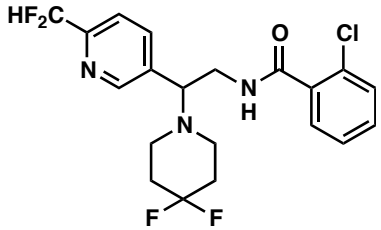
pp. 91, Examples 3n5 and 3o5



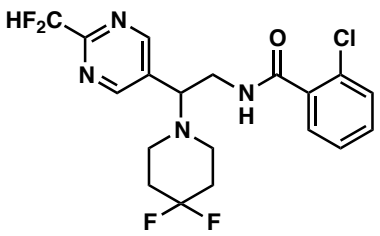
pp. 92, Examples 3p5 and 3q5



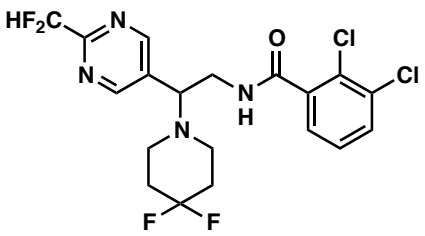
pp. 92, Examples 3r5 and 3s5



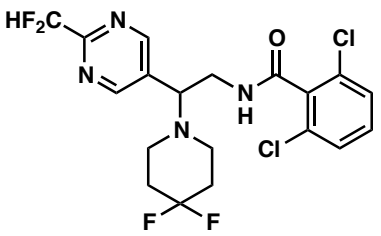
pp. 93, Examples 3t5 and 3u



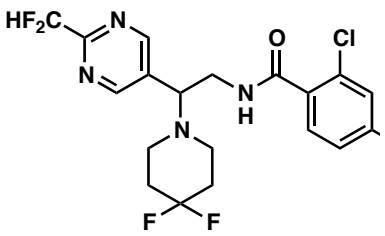
pp. 93–94, Examples 3v5 and 3x5



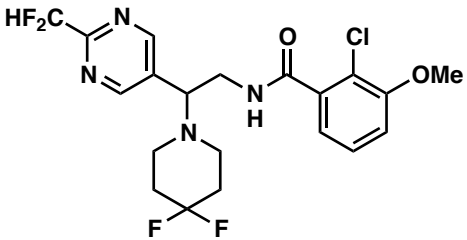
pp. 94, Examples 3y5 and 3z5



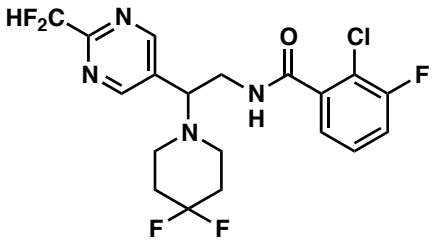
pp. 95, Examples 3a6 and 3b6



pp. 95, Examples 3c6 and 3d6



pp. 97, Examples 3e6 and 3f6

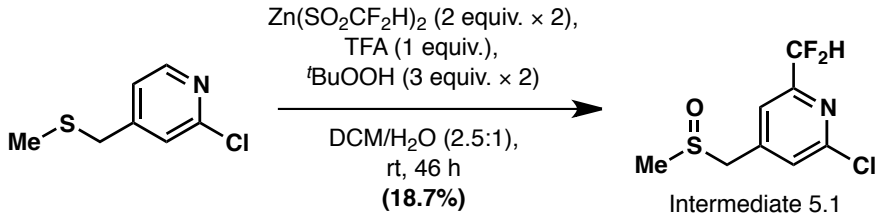


pp. 97–98, Examples 3g6 and 3h6

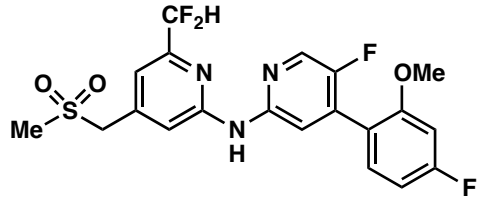
6. WO 2014060375, Applicant: Bayer Pharma Aktiengesellschaft.

Luecking, U.; Boehnke, N.; Scholz, A.; Lienau, P.; Siemeister, G.; Boemer, U.; Kosemund, D.; Bohlmann, 5-Fluoro-*N*-(pyridin-2-yl)pyridin-2-amine Derivatives Containing a Sulfone Group. WO 2014060375 A2, April 24, 2014.

pp. 82, Example 5, Preparation of Intermediate 5.1



Intermediate 5.1

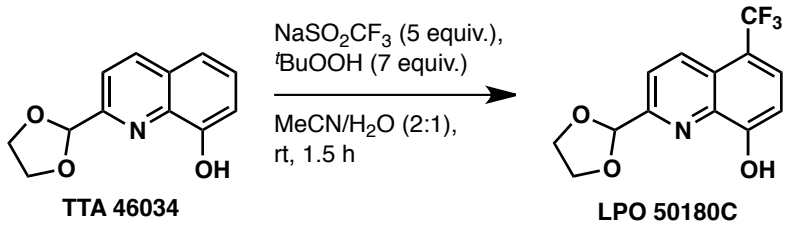


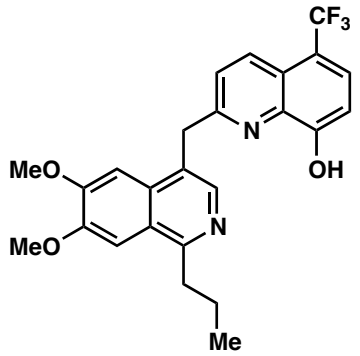
pp. 82, Example 5

7. WO 2014071044, Applicant: Allergan, Inc.; ExonHit Therapeutics

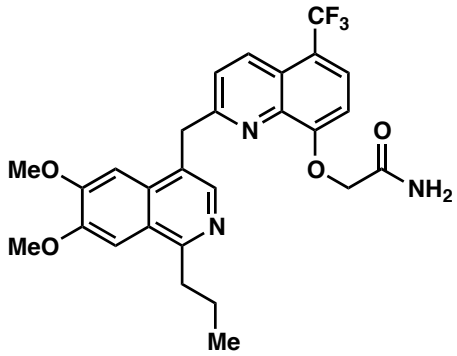
Leblond, B.; Beausoleil, E.; Casagrande, A. -S.; Desire, L. J. R.; Pando, M. P.; Donello, J. E.; Yang, R.; Taverne, T.; Chauvignac, C. Substitu 6,7-Dialkoxy-3-isoquinolinol Derivatives as Inhibitors of Phosphodiesterase 10 (PDE10A). WO 2014071044 A1, May 8, 2014.

pp. 93, Table 6, Procedure N (a); pp. 96 Preparation of Compound LPO 50180C





pp. 123, Table 7, Compound 132

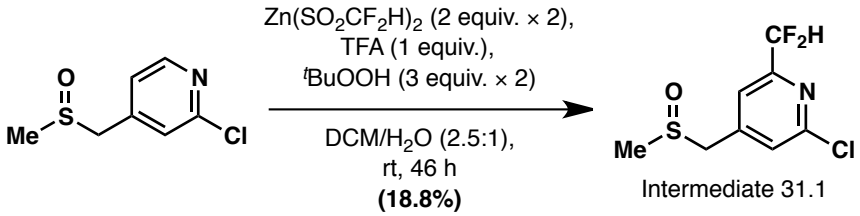


pp. 123, Table 7, Compound 133

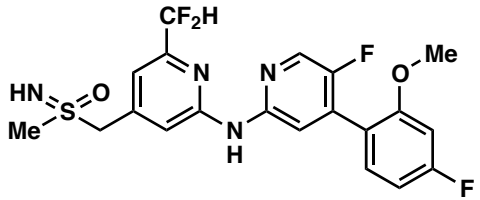
8. WO 2014076091, Applicant: Bayer Pharma Aktiengesellschaft

Luecking, U.; Boehnke, N.; Scholz, A.; Lienau, P.; Siemeister, G.; Boemer, U. Kosemund, D. Bohlmann, 5-Fluoro-*N*-(pyridin-2-yl)pyridin-2-amine Derivatives Containing a Sulfoxamine Group. WO 2014076091 A1, May 22, 2014.

pp. 153, Preparation of Intermediate 31.1



Intermediate 31.1

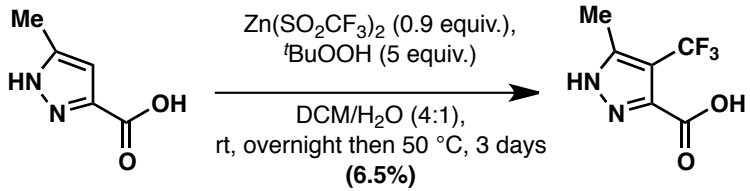


pp. 162, Table 2, Example 31

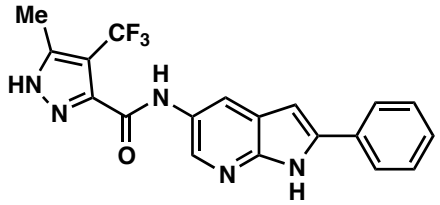
9. WO 2014100620, Applicant: Plexxikon Inc.

Wu, G.; Chan, K.; Ewing, T.; Ibrahim, P. N.; Lin, J.; Nespi, M.; Spevak, W.; Zhang, Y. Compounds and Methods for Kinase Modulation Indications Therefor. WO 2014100620 A2, June 26, 2014.

pp. 166, Example 25

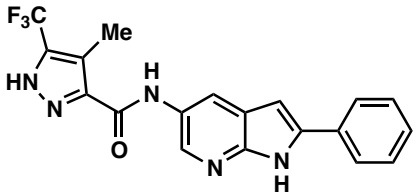


143 145

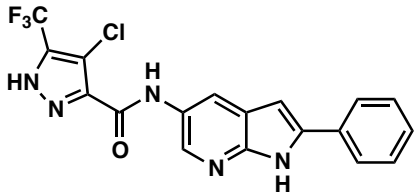


pp. 166, P-2190

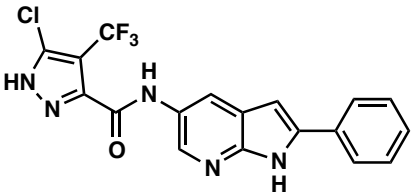
According to text on p. 166 of the patent, these compounds were prepared analogously with the requisite sufinate:



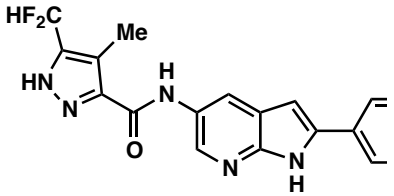
pp. 191, Table 2, P-2231



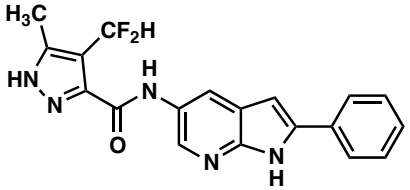
pp. 191, Table 2, P-2232



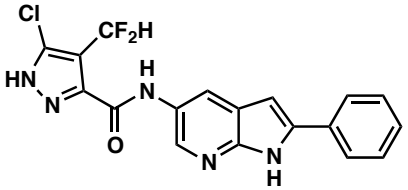
pp. 191, Table 2, P-2233



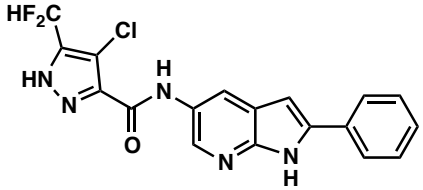
pp. 191, Table 2, P-2234



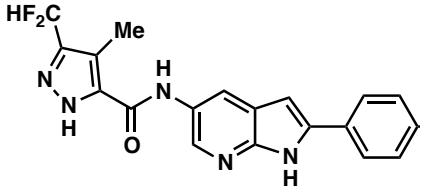
pp. 191, Table 2, P-2235



pp. 191, Table 2, P-2236



pp. 191, Table 2, P-2237

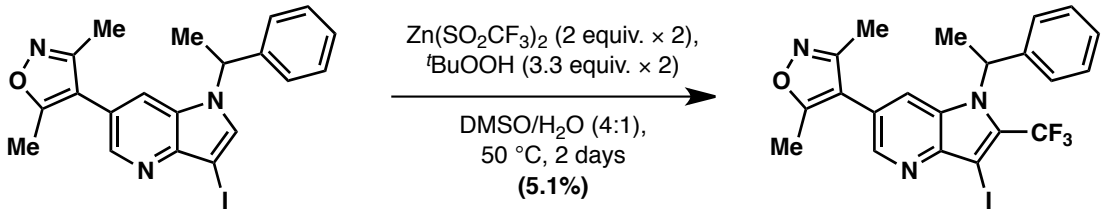


pp. 196, Table 3, P-2287

10. WO 2014145051, Applicant: Plexxikon Inc.

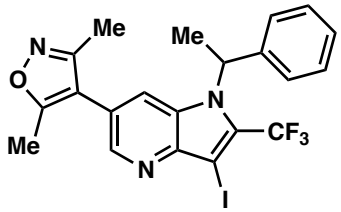
Zhang, J.; Buell, J.; Chan, K.; Ibrahim, P. N.; Lin, J.; Pham, P.; Shi, S.; Spevak, W.; Wu, G.; Wu, J. Heterocyclic Compounds and Uses Ther WO 2014145051 A1, September 18, 2014.

pp. 153, Example 38

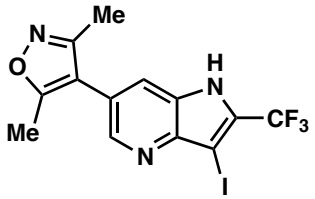


P-0224

P-0245



pp. 153, P-0245



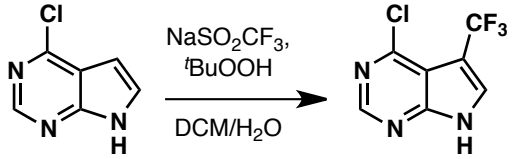
pp. 154, P-0225

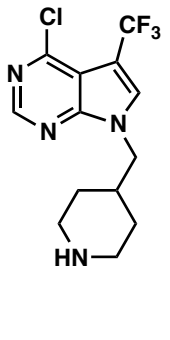
11. WO 2014145576, Applicant: Northwestern University

Schiltz, G. E.; Scheidt, K. A.; Rosen, S. T.; Krett, N. L. Substituted Pyrrolo(2,3-*d*)pyrimidines for the Treatment of Cancer. WO 2014145576 September 18, 2014.

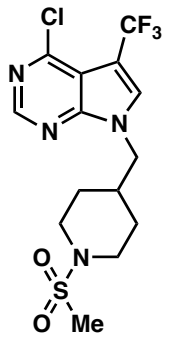
(Reaction conditions adapted from, *PNAS*, **2011,** *108*, 14411–14415.)

pp. 19, Example 38, Scheme I, Step 1

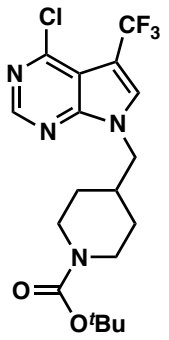




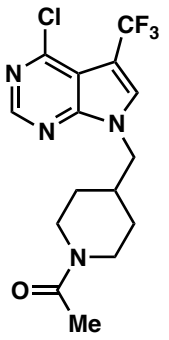
pp. 24, Table 1,
NUCC-0000381



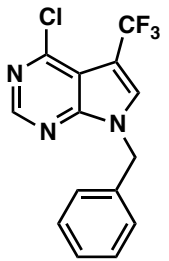
pp. 24, Table 1,
NUCC-0000383



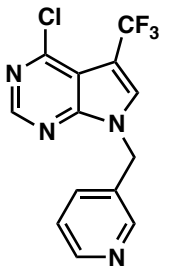
pp. 24, Table 1,
NUCC-0000357



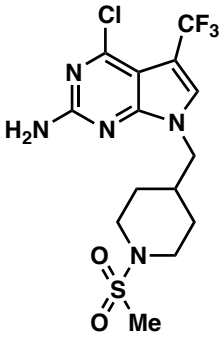
pp. 24, Table 1,
NUCC-0000383



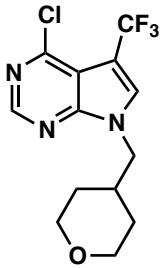
pp. 25, Table 2,
NUCC-0000315



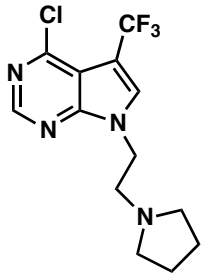
pp. 25, Table 2,
NUCC-0000326



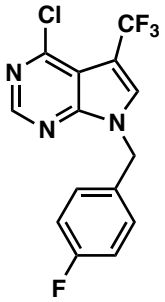
pp. 26, Table 3,
NUCC-0000576



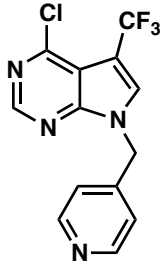
pp. 27, Table 4,
NUCC-0000329



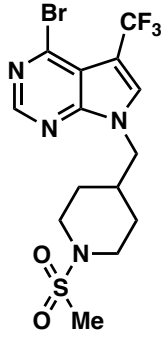
pp. 27, Table 4,
NUCC-0000358



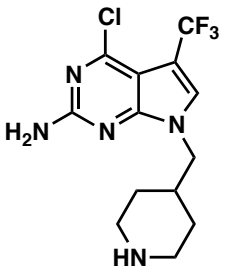
pp. 27, Table 4,
NUCC-0000325



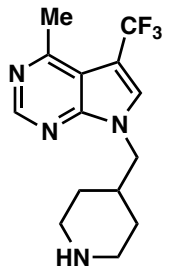
pp. 28, Table 5,
NUCC-0000327



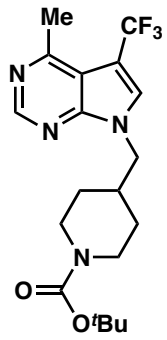
pp. 29, Table 6,
NUCC-0000598



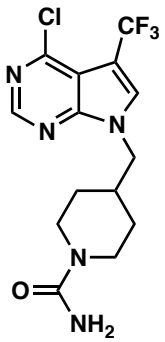
pp. 29, Table 6, NUCC-0000570



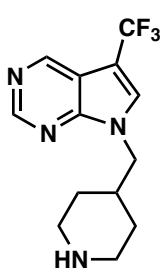
pp. 29, Table 6, NUCC-0000501



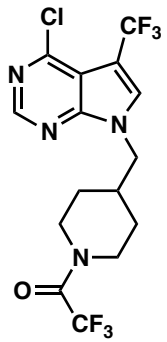
pp. 29, Table 6, NUCC-0000482



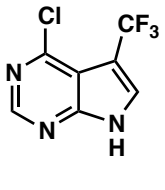
pp. 31, Table 8, NUCC-0000469



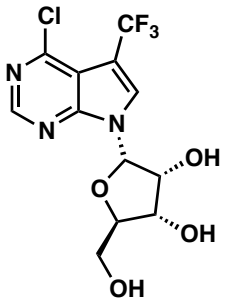
pp. 31, Table 8, NUCC-0000470



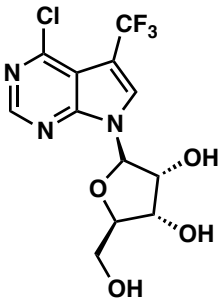
pp. 32, Table 9, NUCC-0000593



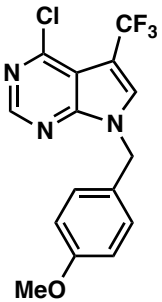
pp. 33, Table 10, NUCC-0054043



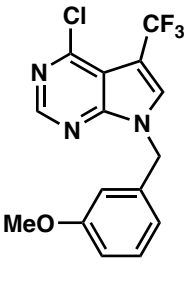
pp. 33, Table 10, NUCC-0054042



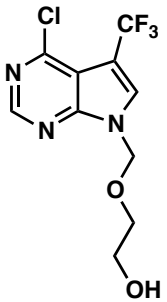
pp. 33, Table 10, NUCC-0054041



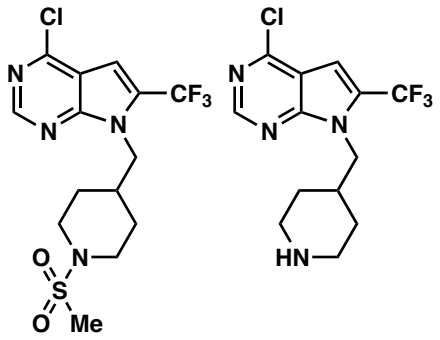
pp. 34, Table 11, NUCC-0054038



pp. 34, Table 11, NUCC-0054037



pp. 34, Table 11, NUCC-00540715



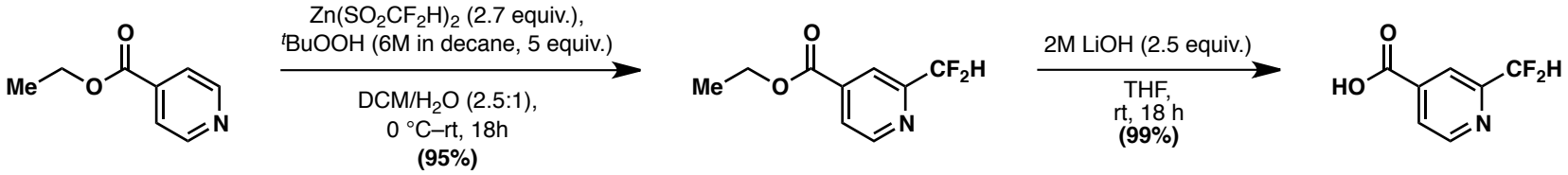
pp. 35, Table 12, NUCC-0054151

pp. 35, Table 12, NUCC-0054150

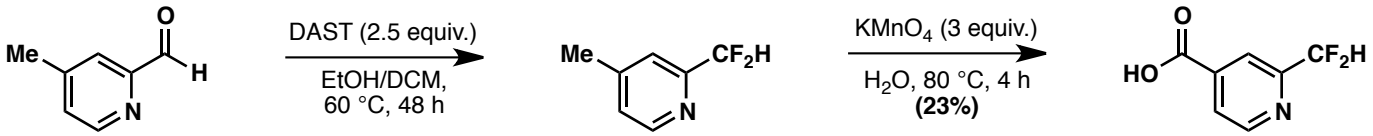
12. WO 2014151616, Applicant: Novartis AG

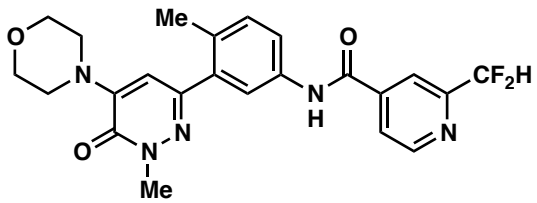
Aversa, R.; Barsanti, P. A.; Burger, M.; Dillon, M. P.; Dipesa, A.; Hu, C.; Lou, Y.; Nishiguchi, G.; Pan, Y.; Polyakov, V.; Ramurthy, S.; Ricc A.; Setti, L.; Smith, A.; Subramanian, S.; Taft, B.; Tanner, H.; Wan, L.; Yusuff, N. Biaryl Amide Compounds as Kinase Inhibitors. WO 2014151616 A1, September 25, 2014.

pp. 85, Step 1

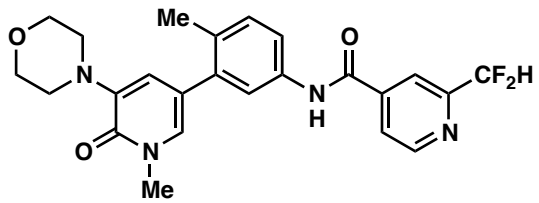


An alternative preparation is given on pp. 67.

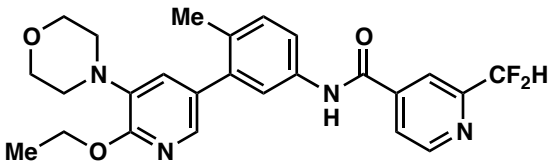




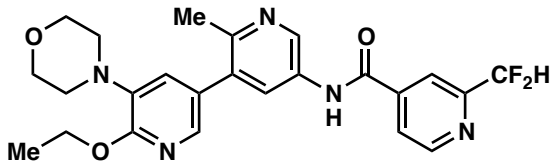
pp. 226, Example 189
pp. 458, Example 650



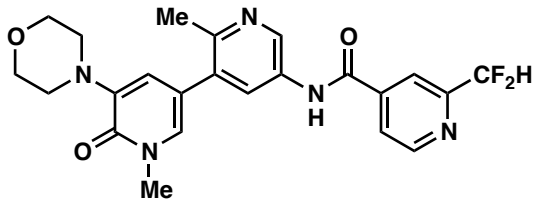
pp. 236, Example 215
pp. 306, Example 358



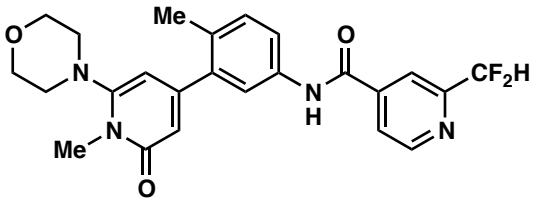
pp. 245, Example 237



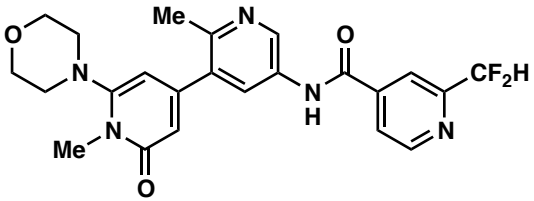
pp. 250, Example 247



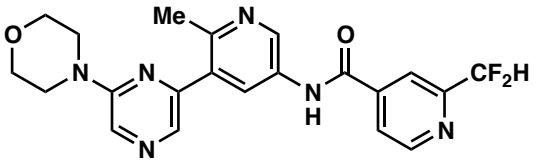
pp. 318, Example 392



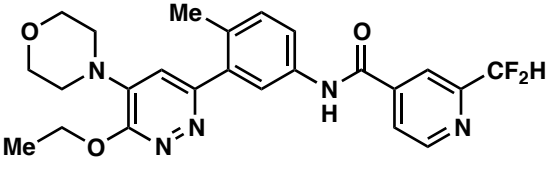
pp. 363, Example 486



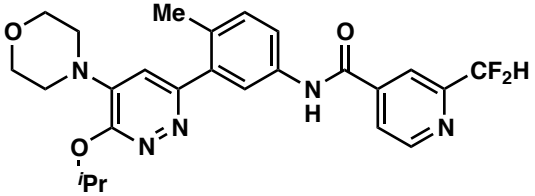
pp. 372, Example 508



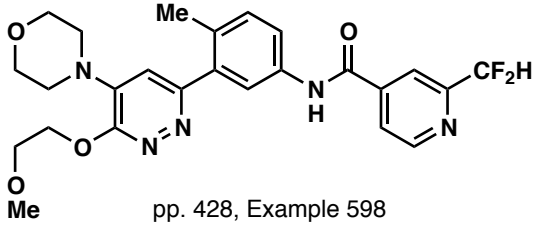
pp. 389, Example 535



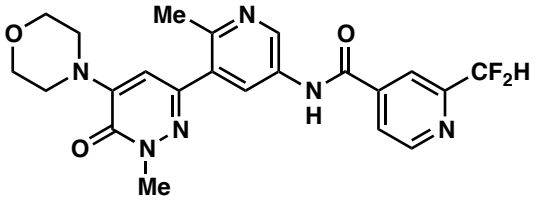
pp. 408, Example 562



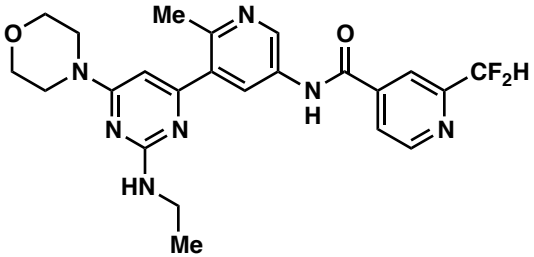
pp. 426, Example 593



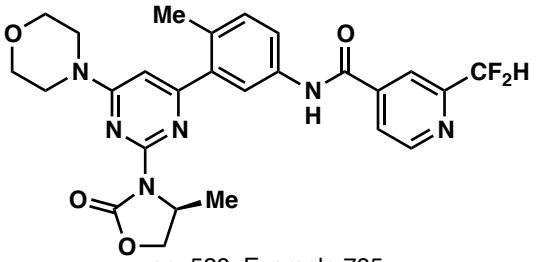
pp. 428, Example 598



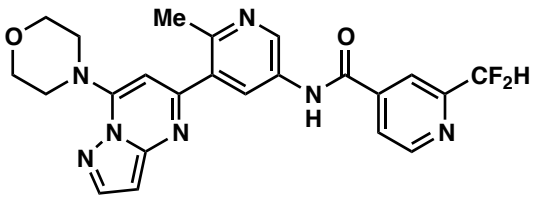
pp. 475, Example 680



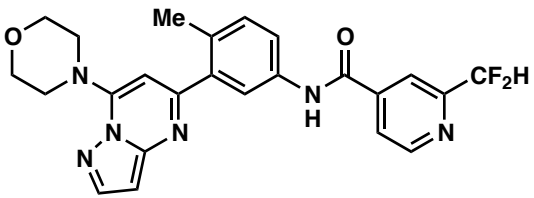
pp. 492, Example 721



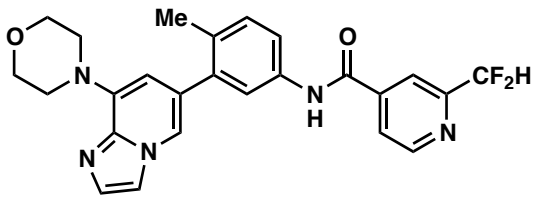
pp. 528, Example 785



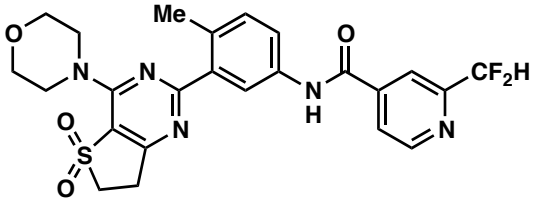
pp. 538, Example 803



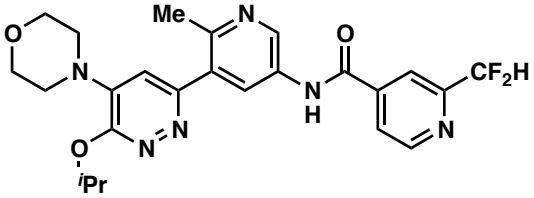
pp. 539, Example 805



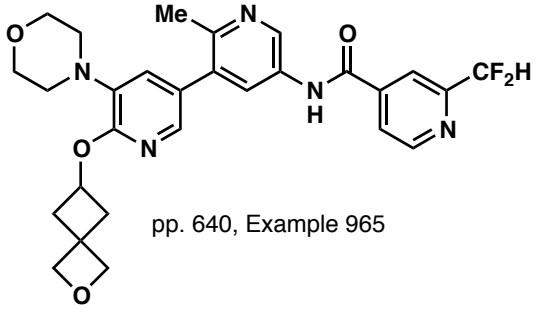
pp. 576, Example 850



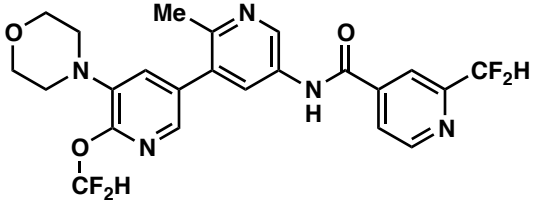
pp. 580, Example 856



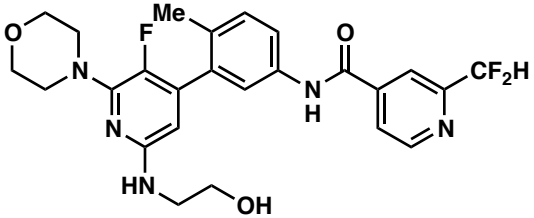
pp. 611, Example 913



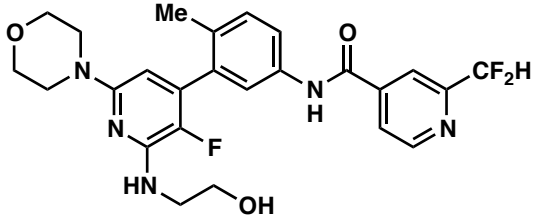
pp. 640, Example 965



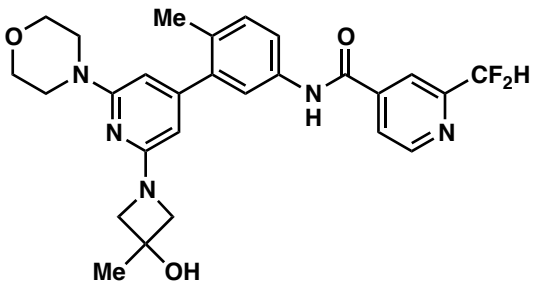
pp. 649, Example 982



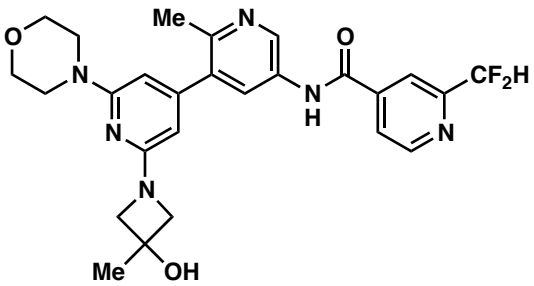
pp. 666, Example 1009



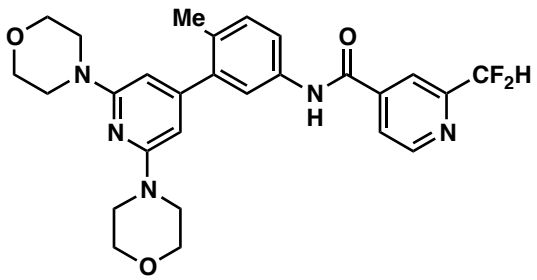
pp. 669, Example 1016



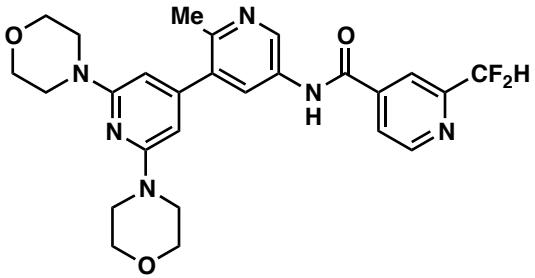
pp. 699, Example 1072



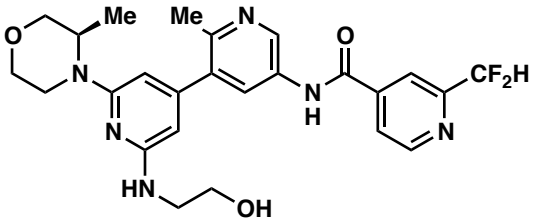
pp. 714, Example 1103



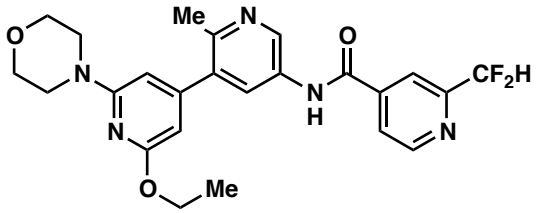
pp. 720, Example 1115



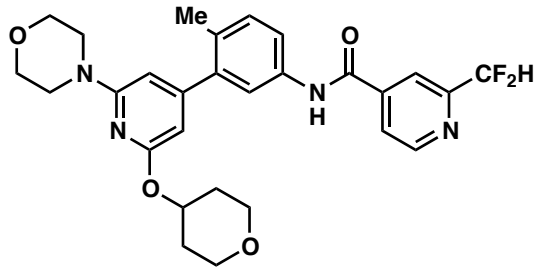
pp. 723, Example 1122



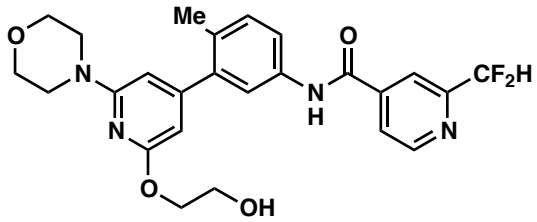
pp. 732, Example 1141



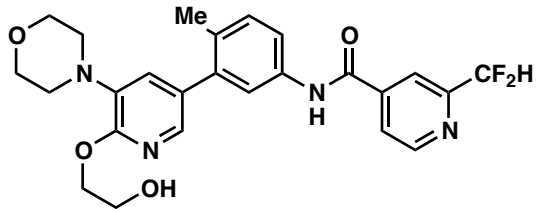
pp. 735, Example 1146



pp. 737, Example 1151



pp. 743, Example 1160

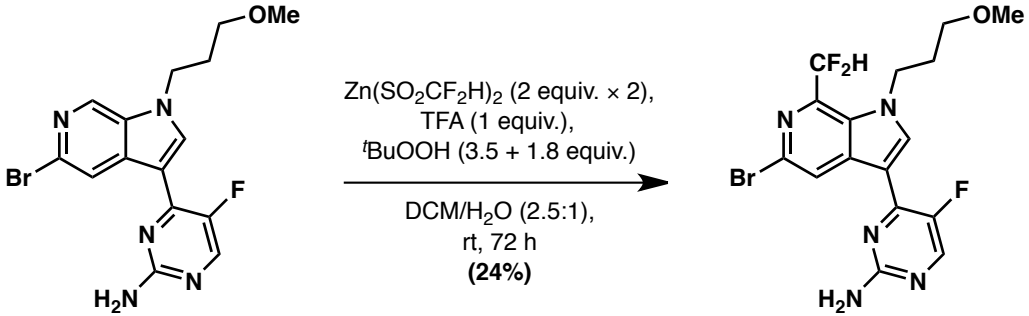


pp. 757, Table A, Example 1202

13. WO 2014174021, Applicant: Janssen Pharmaceutica NV

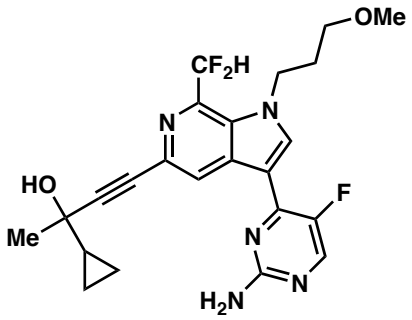
Hynd, G.; Price, S.; Kulagowski, J.; MacLeod, C.; Mann, S. E.; Panchal, T. A.; Tisselli, P.; Montana, J. 3-(2-Aminopyrimidin-4-yl)-5-(3-ylhydroxypropynyl)-1*H*-pyrrolo[2,3,-*c*]pyridine Derivatives as NIK Inhibitors for the Treatment of Can Patent no. WO 2014174021 A1, October 30, 2014.

pp. 152, Example A27, Preparation of Intermediate 145



Intermediate 101

Intermediate 145

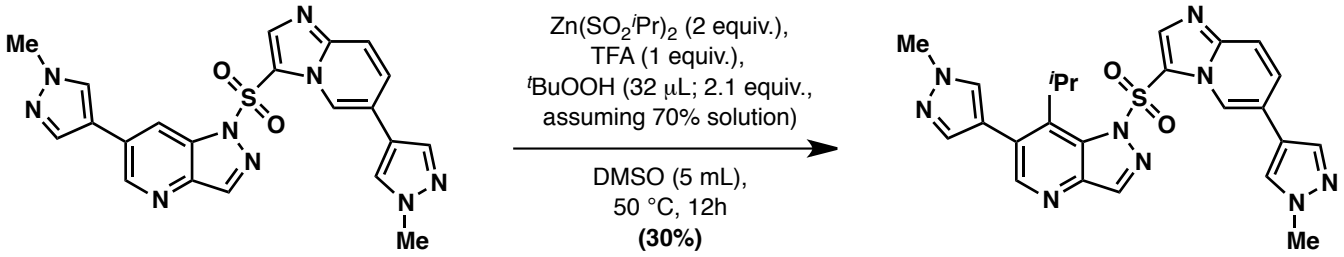


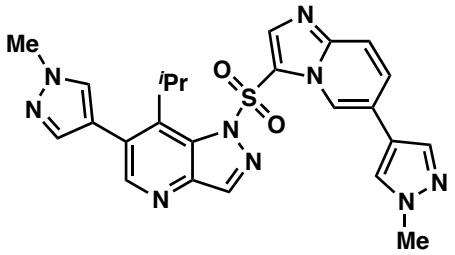
pp. 176, Table 22, Compound 96

14. WO 2014201857, Applicant: Shanghai Institute of Material Medica CAS

Shen, J.; Geng, M.; Ding, J.; Xiong, B.; Ai, J.; Ma, Y.; Wang, X.; Peng, X.; Chen, Y.; Chen, D.; Meng, T.; Ma, L.; Ji, Y. Five-Membe Heterocyclic Pyridine Compounds and Preparation Method and Use Thereof. WO 2014201857 A1, December 24, 2014.

pp. 78, Example 103





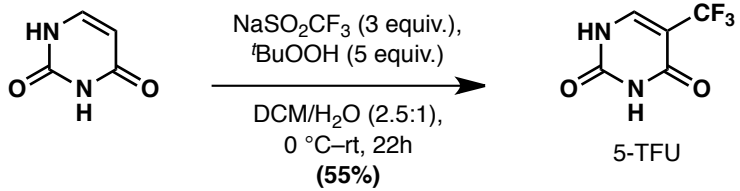
pp. 78, Example 103

15. US 20140135497, Applicant: Boehringer Ingelheim International GmbH

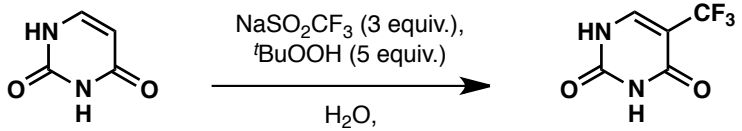
Liu, L.; Akalay, D.; Dong, W.; Feng, J.; Hemp, C. W.; Lu, J.; Xie, L.; Yang, J. Synthesis of 2,4-Dichloro-5-trifluoromethyl-pyrimidine. US 20140135497 A1, May 15, 2014.

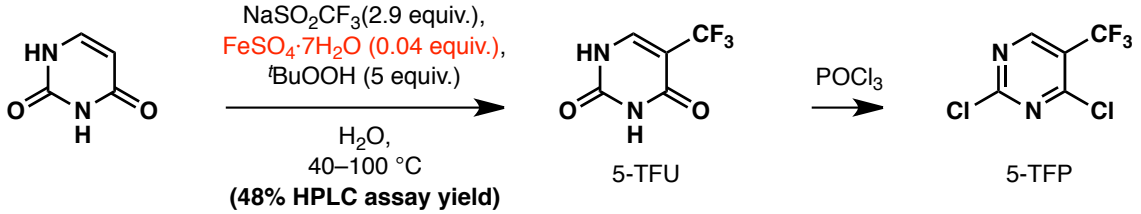
(Reaction conditions adapted from, *PNAS*, **2011,** *108*, 14411–14415.)

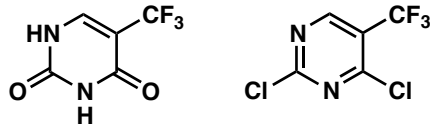
pp. 2, Scheme 4. Langlois reagent protocol, standard procedure



Scheme 5. Methods according to the invention







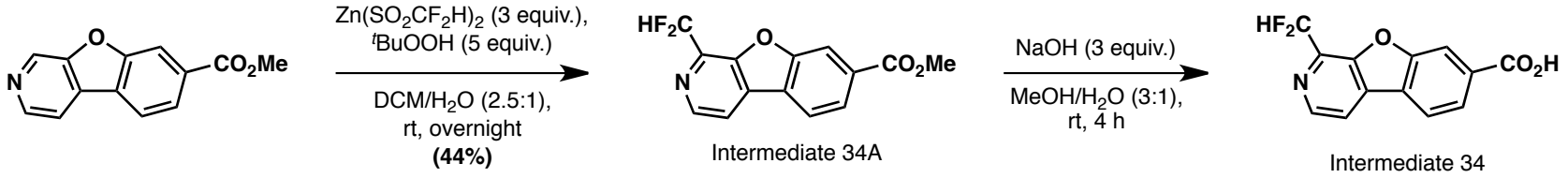
pp. 2, 5-TFU pp. 2, 5-TFP

Patents from 2015

1. WO 2015002915, Applicant: Bristol-Myers Squibb Company

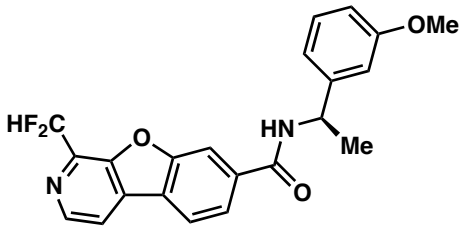
Quan, M. L.; Hu, Z.; Wang, C.; Patil, S. Tricyclic Pyridocaboxamide Derivatives as ROCK Inhibitors. WO 2015002915 A1, January 8, 2015

pp. 325, Intermediate 34A

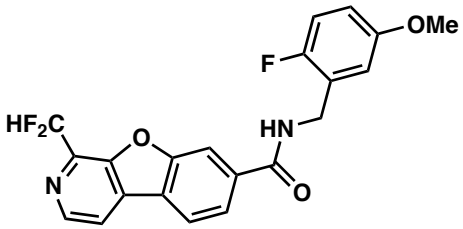


Intermediate 34A

Intermediate 34



pp. 345, Table XIV, Example XIV-36
pp. 355, Table XV, Example XV-15

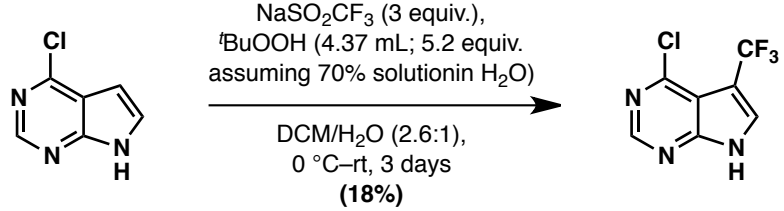


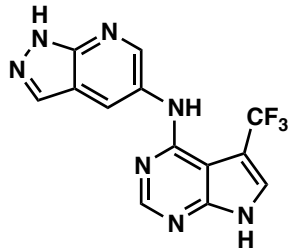
pp. 355, Table XV, Example XV-16

2. WO 2015004024, Applicant: Bayer Pharma AG

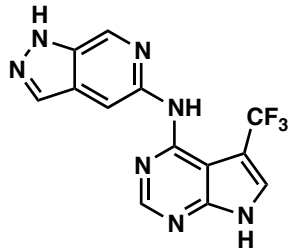
Klar, U.; Wortmann, L.; Kettschau, G.; Graham, K.; Richter, A.; Lienau, P.; Puehler, F.; Petersen, K.; Siegel, F.; Sülzle, D. Substitu Pyrazolo-Pyridinamines. WO 2015004024 A1, January 15, 2015.

pp. 76, Example 15a





pp. 76, Example 15

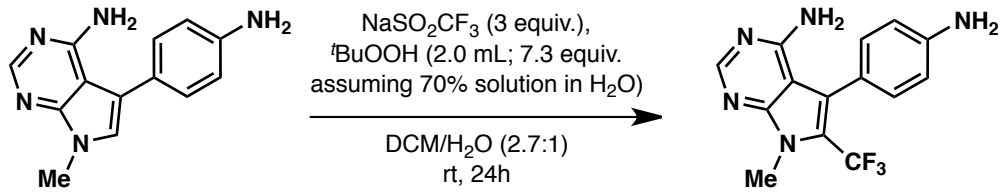


pp. 77, Example 16

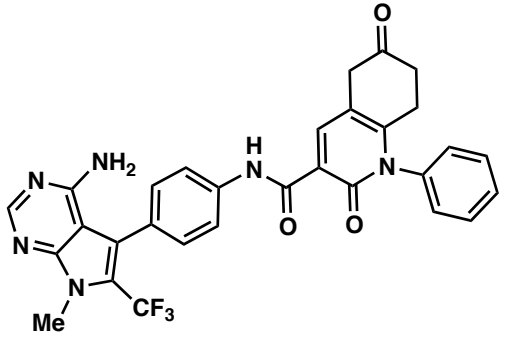
3. WO 2015068767, Applicant: Ono Pharmaceutical Co., Ltd.

Inukai, T.; Takeuchi, J.; Yasuhiro, T.; Wolf, M. A.; Pawal, V. D.; Chakrabarti, A.; Chittimalla, S. K. Pyrrolo Pyrimidine Derivative. WO 2015068767 A1, May 14, 2015.

pp. 141 Example 128



Example 3 Example 128

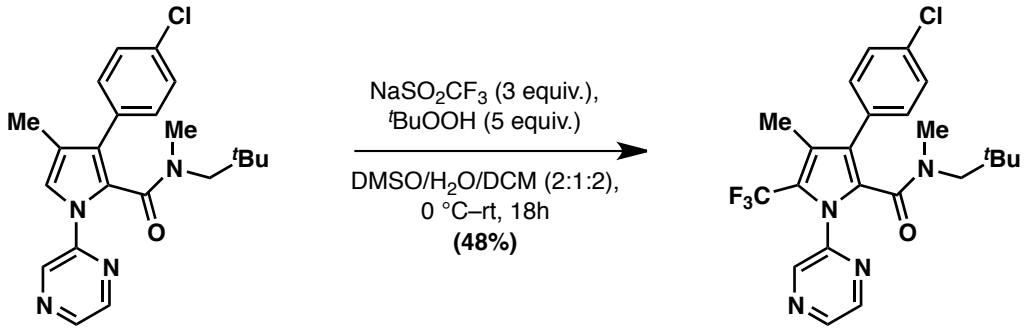


pp. 48, Example 129

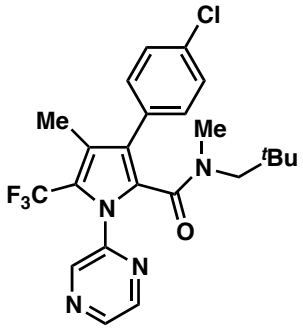
4. WO 2015090599, Applicant: Grunenthal GmbH

Reich, M.; Schunk, S.; Jakob, F.; Steinhagen, H.; Damann, N.; Haurand, M.; Hamlyn, R.; Rogers, M.; Sutton, K. Fluoromethyl-Substitu Pyrrole Carboxamides IV. WO 2015090599 A1, June 25, 2015.

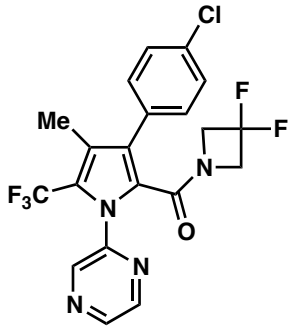
pp. 68, Example 049, Step 4



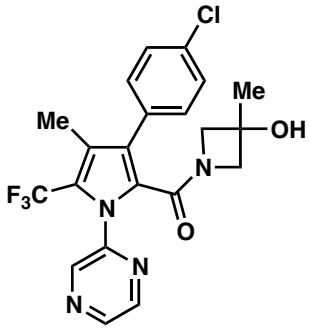
Example 049



pp. 64, Example 049



pp. 65, Example 050

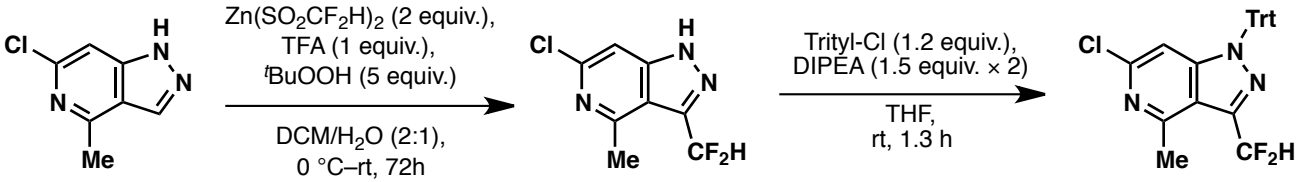


pp. 65, Example 051

5. WO 2015094929, Applicant: Merck Sharp & Dohme Corp.

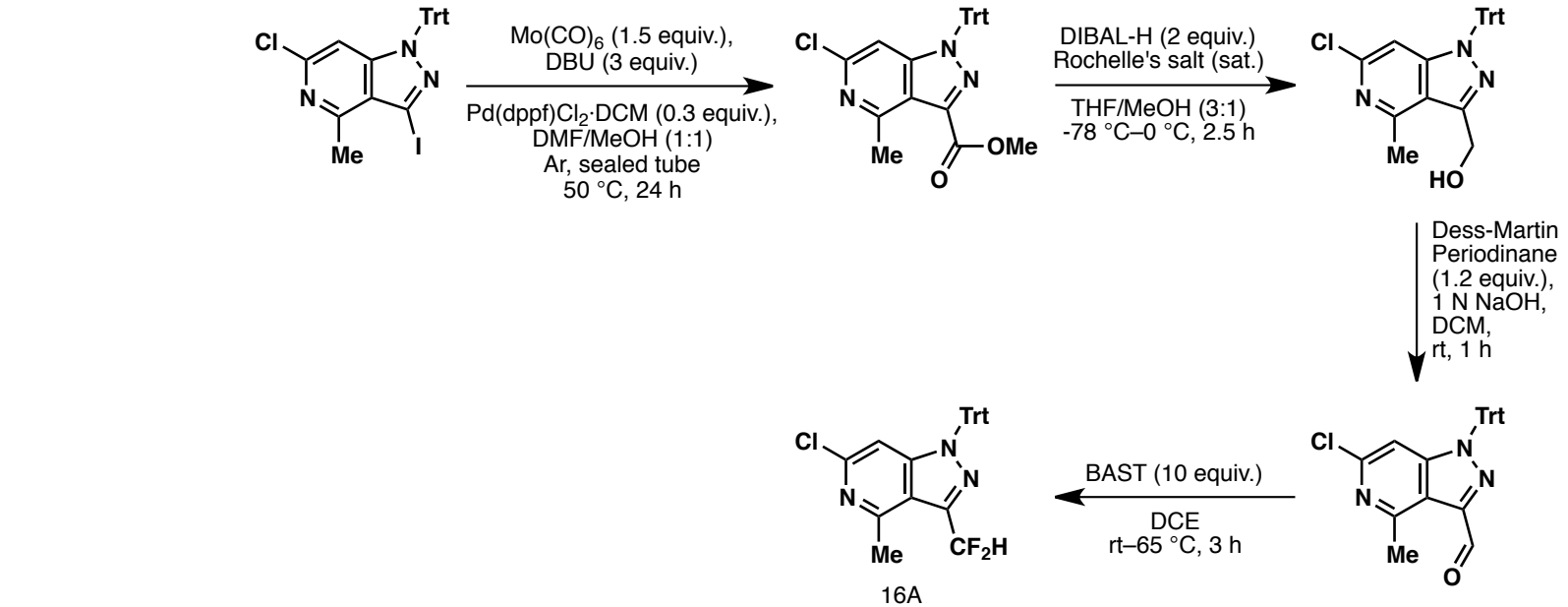
Lipford, K.; Falcone, D.; Sloman, D. L.; Witter, D. J. ERK Inhibitors. WO 2015094929 A1, June 25, 2015.

pp. 68, Scheme B, Step 1

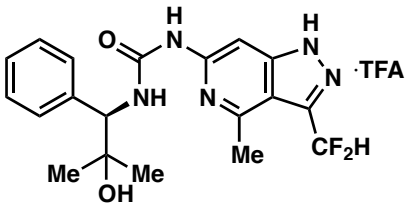


16A

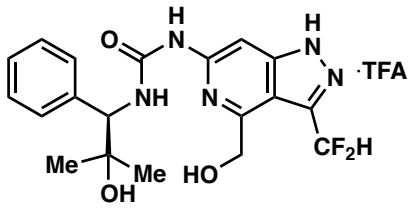
Alternative preparation on pp. 67, Scheme A



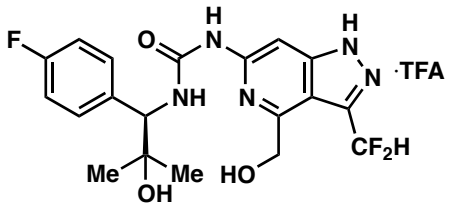
16A



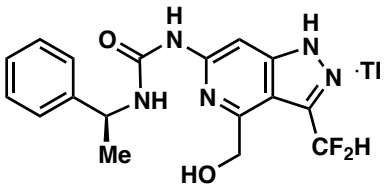
pp. 86, Example 21



pp. 87, Example 22



pp. 89, Table 5, Example 23

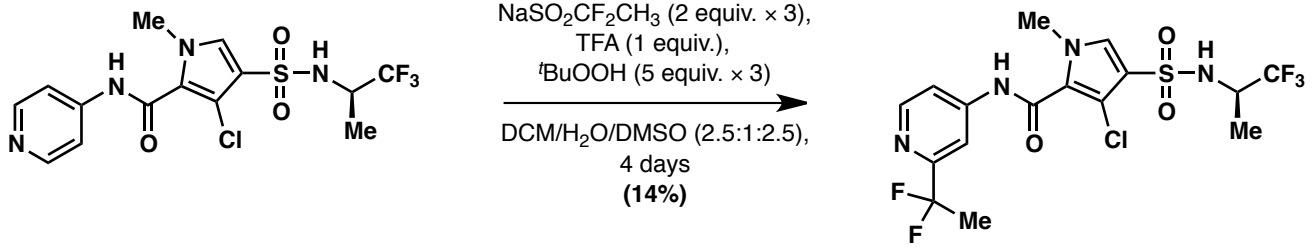


pp. 89, Table 5, Example 24

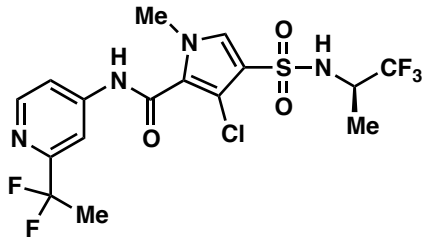
6. WO 2015118057, Applicant: Janssen Sciences Ireland UC

Vandyck, K.; Hache, G. Y. P.; Last, S. J.; Rombouts, G.; Verschueren, W. G.; Raboisson, P. J. -M. B. Sulphamoylpyrrolamide Derivatives the Use Thereof as Medicaments for the Treatment of Hepatitis B. WO 2015118057 A1, August 13, 2015.

pp. 120, Compound 182



Compound 16 Compound 182



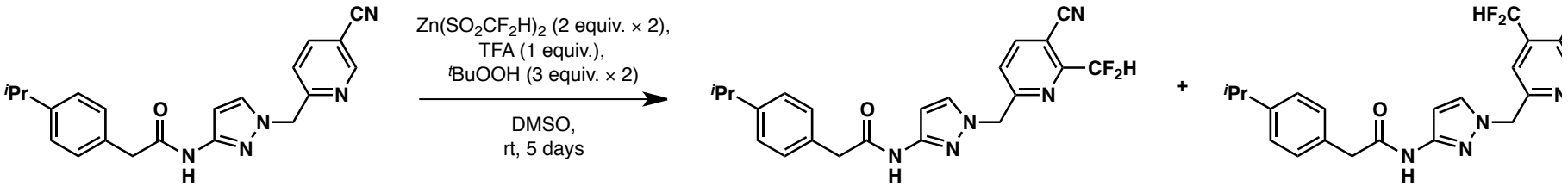
Compound 182

7. WO 2015186056, Applicant: Actelion Pharmaceuticals Ltd.

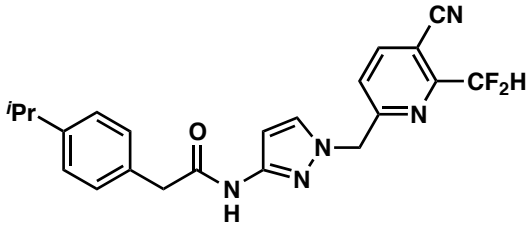
Siegrist, R.; Heidmann, B.; Stamm, S.; Gatfield, J.; Bezencon, O. Pyrazole Compounds and Their Use as T-Type Calcium Channel Blockers.

WO 2015186056 A1, December 10, 2015.

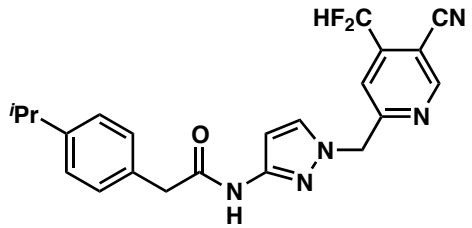
pp. 131, Examples 385 and 386



Example 71 Example 385 Example 386



pp. 131, Example 385

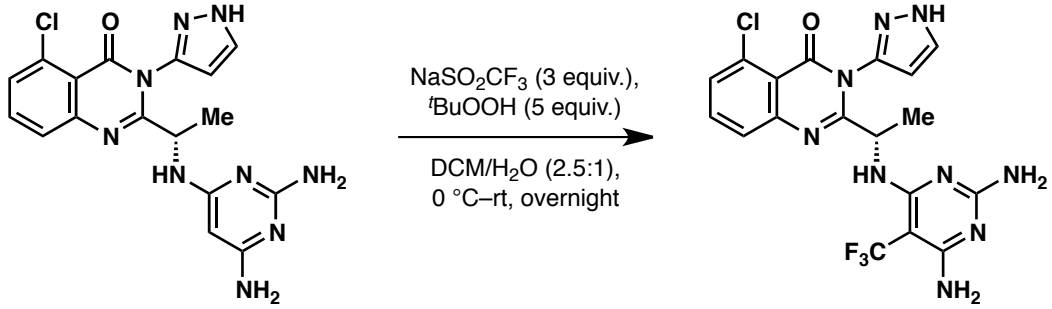


pp. 131, Example 386

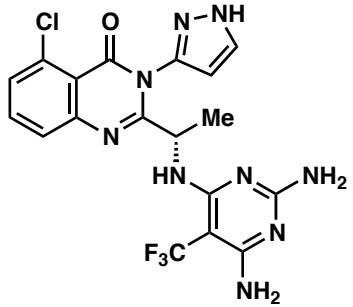
8. WO 2015191743, Applicant: Gilead Sciences, Inc.

Evarts, J.; Kaplan, J.; Patel, L.; Perreault, S.; Phillips, B. W.; Phillips, G.; Treiberg, J. A.; Yeung, S. C. Quinazolinone Derivatives Phosphatidylinositol 3-Kinase Inhibitors. WO 2015191743 A1, December 17, 2015.

pp. 151, Compound 201



Compound 201



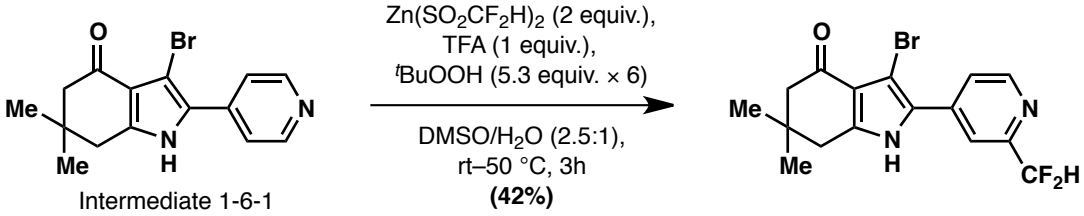
pp. 151, Compound 201

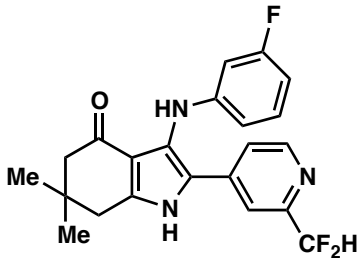
9. WO 2015193339, Applicant: Bayer Pharma Aktiengesellschaft

Graham, K.; Klar, U.; Briem, H.; Hitchcock, M.; Bärfacker, L.; Eis, K.; Schulze, V.; Siemeister, G.; Bone, W.; Schröder, J.; Holton, S.; Lier

P.; Tempel, R.; Sonnenschein, H.; Bálint, J.; Graubaum, H. 3-Amino-1,5,6,7-tetrahydro-4*H*-indol-4-ones. WO 2015193339 A1, December 2015.

pp. 426–427, Example 402



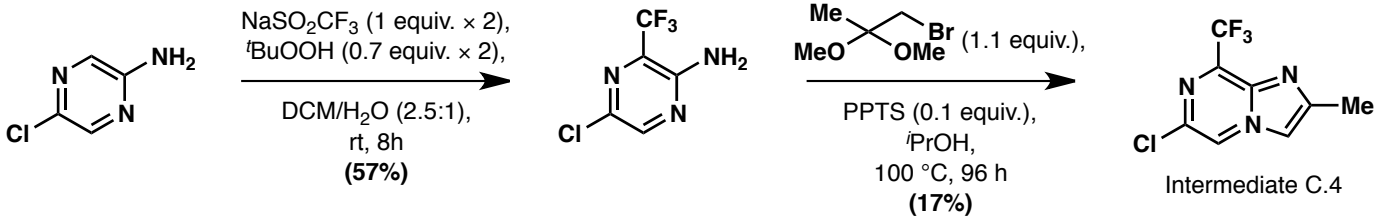


pp. 426 and 427, Example 402

10. WO 2015197503, Applicant: Hoffmann-La Roche Inc.

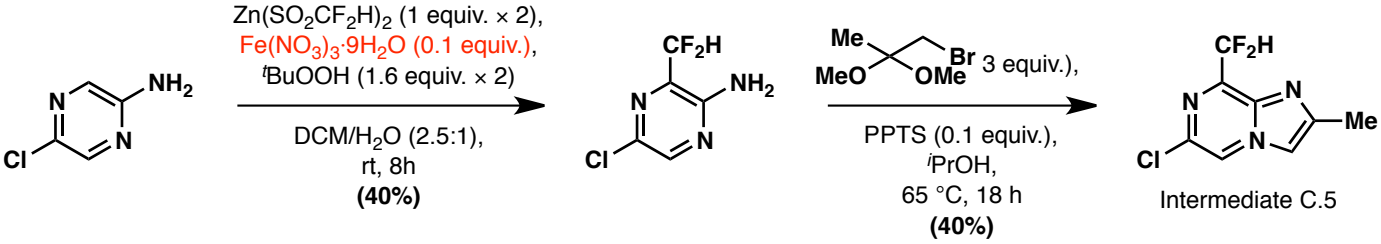
Green, L.; Pinard, E.; Ratni, H.; Williamson, P. Imidazo[1,2-*a*]pyrazin-1-yl)benzamide Compounds for Treating Spinal Muscular Atrophy. W 2015197503 A1, December 30, 2015.

pp. 50, Synthesis of Intermediate C.4, Step A

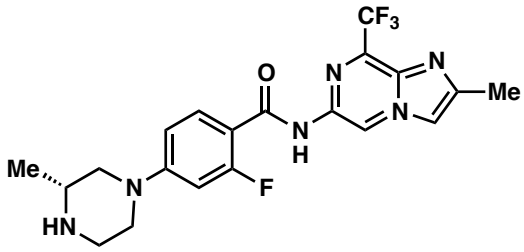


Intermediate C.4

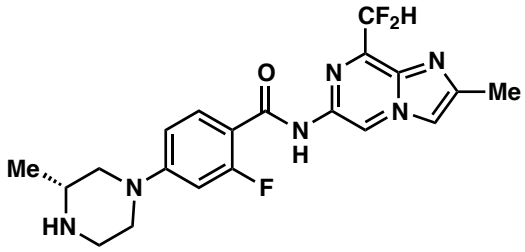
pp. 51, Synthesis of Intermediate C.5, Step A



Intermediate C.5



pp. 68, Example 43

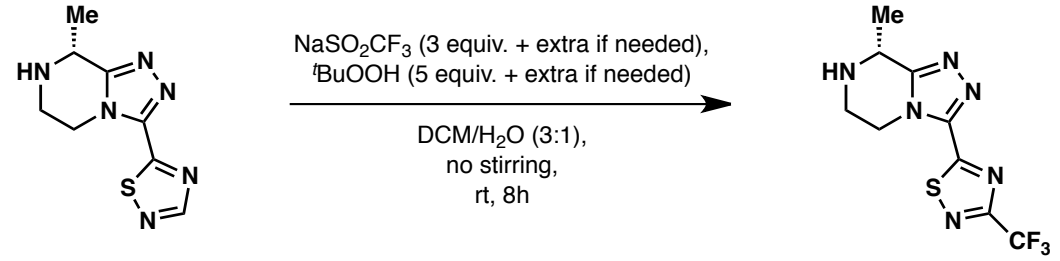


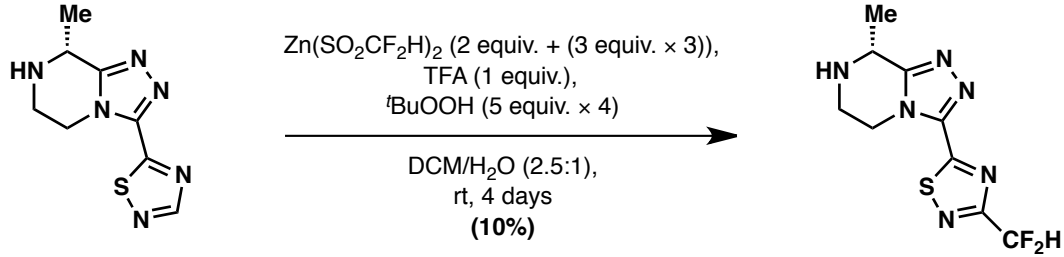
pp. 68, Example 44

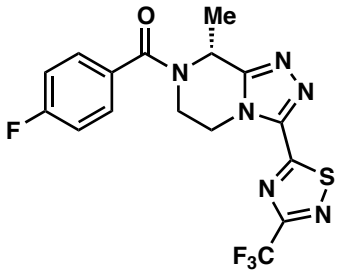
11. US 20150232471, Euroscreen SA

Hoveyda, H.; Dutheuil, G.; Fraser, G. Novel *N*-Acyl-(3-substituted)-(8-substituted)-5,6-dihydro-[1,2,4]-triazolo-[4,3-*a*]pyrazines as Selective NK-3 Receptor Antagonists, Pharmaceutical Composition, Methods for Use in NK-3 Receptor-Mediated Disorders. US 20150232471 A1, August 20, 2015.

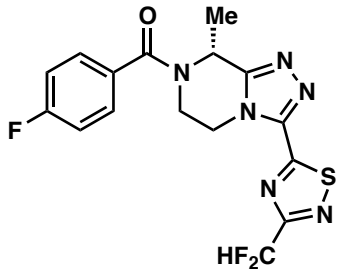
pp. 35, II.6. Optional Conversion of $R^{5'}$ to R^5 in Triazolopiperazine G.







pp. 16, Table 1, Compound 41

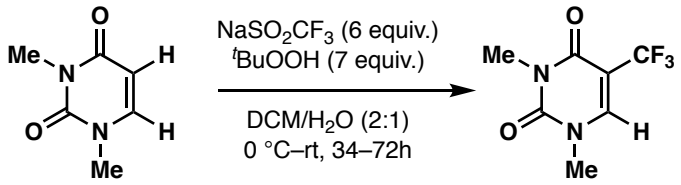


pp. 16, Table 1, Compound 42

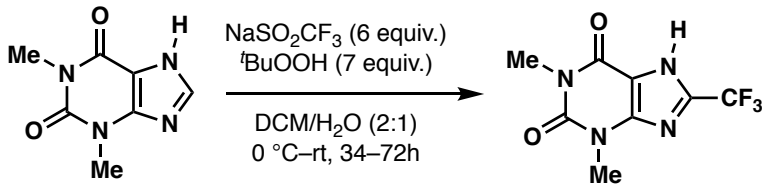
12. WO 2015106624, Applicant: West China Hospital of Sichuan University

Huang, W. Preparation of 2,4-(1*H*,3*H*)-Pyrimidinedione Derivatives. WO 2015106624 A1, July 23, 2015.

pp. 15, Compound 56



Synthesis of compound 86

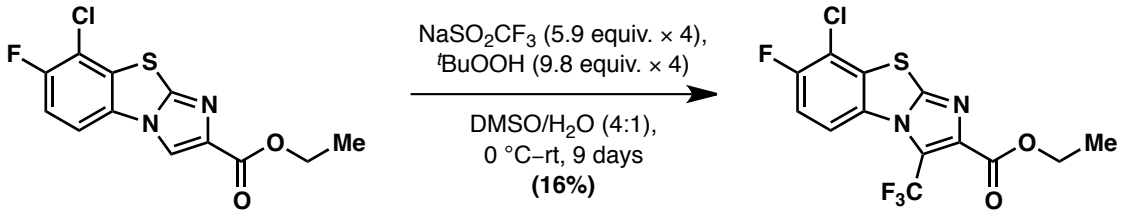


Patents from 2016

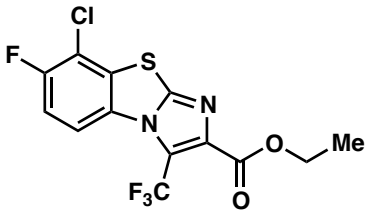
1. WO 2016042172, Applicant: Active Biotech AB

Wellmar, U.; East, S.; Bainbridge, M.; MacKinnon, C.; Carr, J.; Hargrave, J. Imidazo[2,1-*b*]thiazole and 5,6-Dihydroimidazo[2,1-*b*]thiazole Derivatives Useful as S100-Inhibitors. WO 2016042172 A1, March 24, 2016.

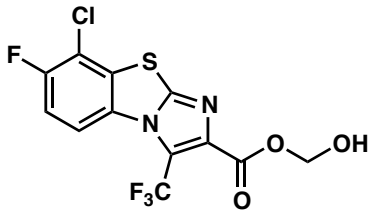
pp. 143, Example 128



Example 128



pp. 143, Example 128

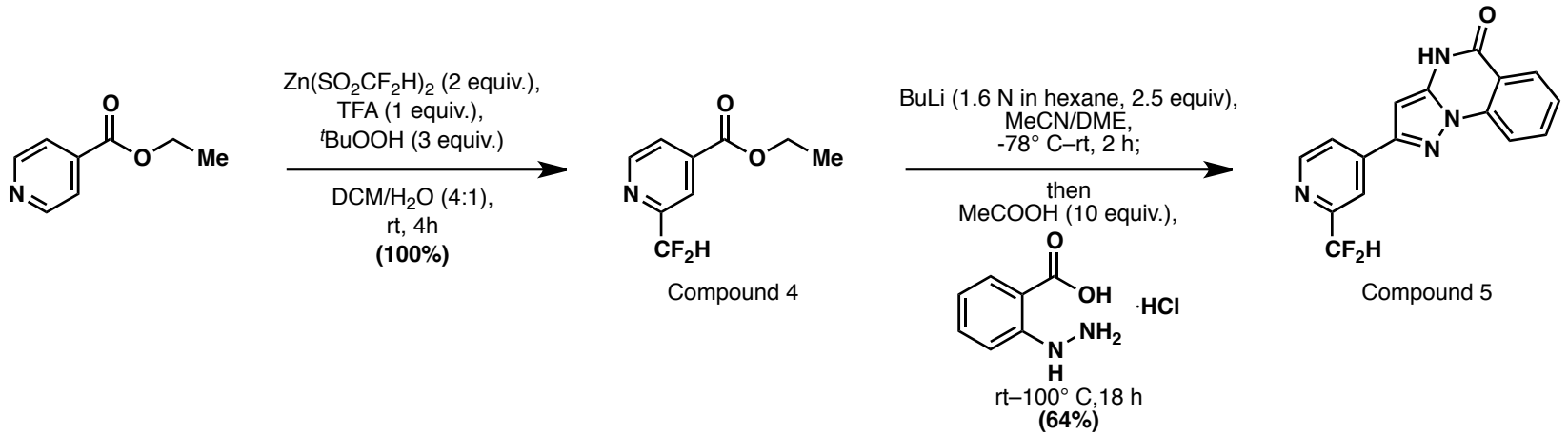


pp. 183, Example 226

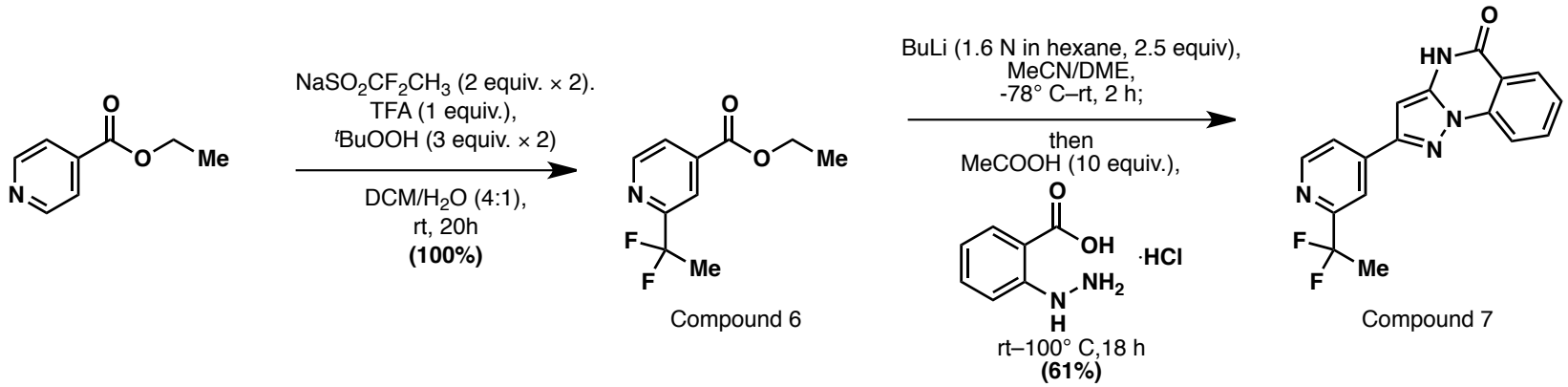
2. WO 2016046404, Applicant: Domain Therapeutics

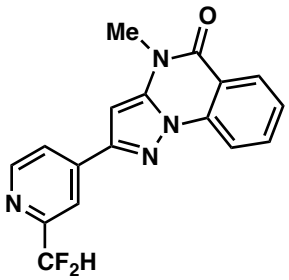
Schann, S.; Mayer, S.; Manteau, B. Substituted Pyrazoloquinazolinones and Pyrroloquinazolinones as Allosteric Modulators of Group II Metabotropic Glutamate Receptors. WO 2016046404 A1, March 31, 2016.

pp. 85, Compounds 4 and 5

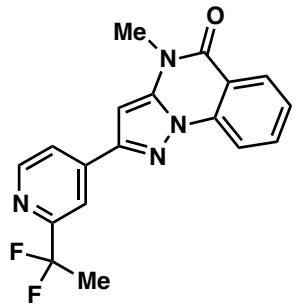


pp. 85–86, Compounds 6 and 7

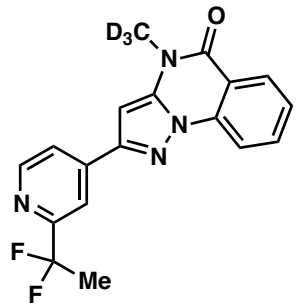




pp. 85, Example 31



pp. 86, Example 32

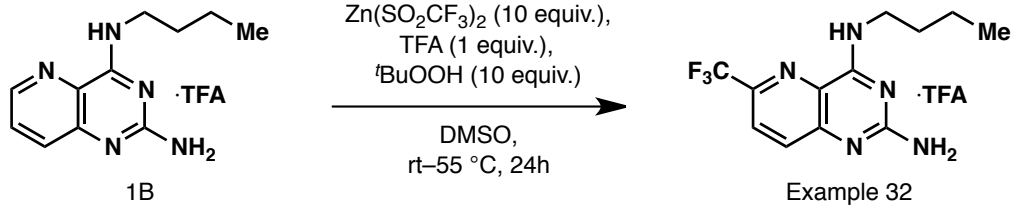


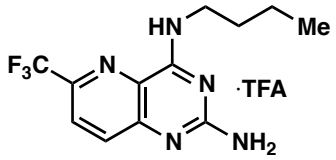
pp. 87, Example 33

3. WO 2016141092, Applicant: Gilead Sciences, Inc.

Aktoudianakis, E.; Chin, G.; Mackman, R. L.; Metobo, S. E.; Mish, M. R.; Pyun, H. -J.; Zablocki, J. Toll-like Receptor Modulating 4,6-Diamino-pyrido[3,2-*d*]pyrimidines Compounds. WO 2016141092 A1, September 9, 2016.

pp. 181, Example 32



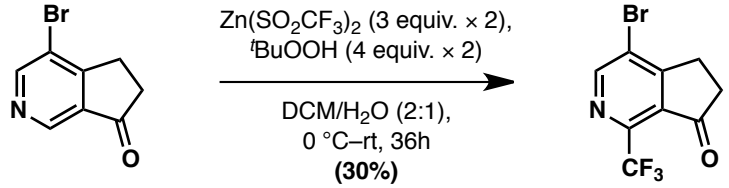


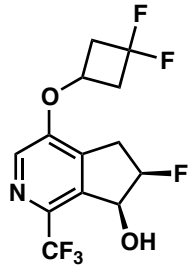
pp. 181, Example 32

4. WO 2016144826, Applicant: Peloton Therapeutics, Inc.

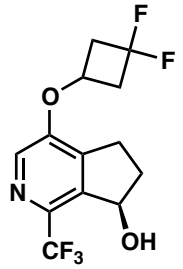
Wehn, P.; Xu, R.; Yang, H. Substituted Pyridines and Uses Thereof. WO 2016144826 A1, September 15, 2016.

pp. 105, Example 1, Step A

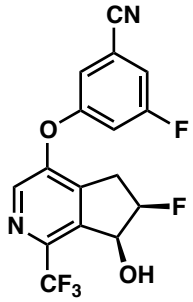




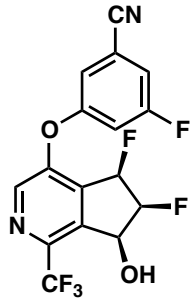
pp. 105, Example 1, Compound 1



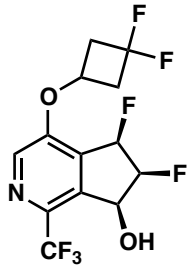
pp. 105, Example 1, Compound 2



pp. 108, Example 2, Compound 3



pp. 118, Example 6, Compound 22



pp. 126, Example 9, Compound 37

See also:

(a) **WO 2016145032, Applicant: Peloton Therapeutics, Inc.**

Josey, J. A.; Wallace, E. M.; Du, X.; Goggin, B. Compositions for Use in Treating Pulmonary Arterial Hypertension. WO 2016145032A1, September 15, 2016.

(b) **WO 2016145045, Applicant: Peloton Therapeutics, Inc.**

Josey, J. A. Compositions for Use in Treating Glioblastoma. WO 2016145045A1, September 15, 2016.

(c) **WO 2016168510, Applicant: Peloton Therapeutics, Inc.**

Josey, J. A.; Wallace, E. M.; Han, G. Combination Therapy of a HIF-2α Inhibitor and an Immunotherapeutic Agent and Uses Ther WO 2016168510A1, October 20, 2016.

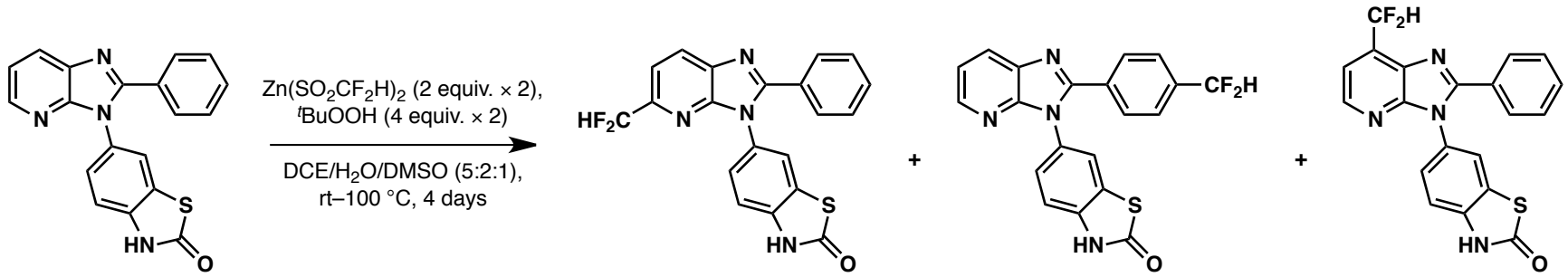
(d) **WO 2017053192, Applicant: University of Texas**

Kim, M. S.; Brugarolas, J.; Hwang, T. H.; Xie, Y. Biomarkers of Response to HIF-2α Inhibition in Cancer and Methods for the Thereof. WO 2016196910A1, March 30, 2017.

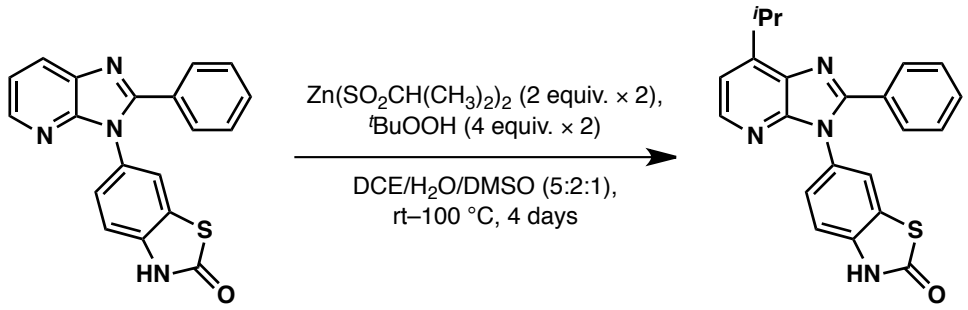
5. WO 2016176460, Applicant: Janssen Pharmaceutica NV

Berry, C. G. B.; Chen, G.; Jourdan, F. L.; Lebold, T. P.; Lin, D. W.; Pena Piñón, M. A.; Ravula, S.; Savall, B. M.; Swanson, D. M.; Wu, D.; Zhang, W.; Ameriks, M. K. Azabenzimidazoles and Their Use as AMPA Receptor Modulators. WO 2016176460 A1, November 3, 2016.

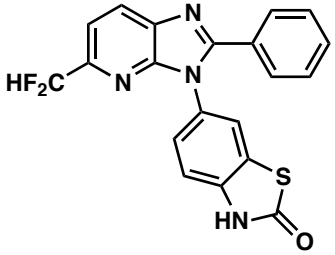
pp. 155–156, Step B, Examples 67–69



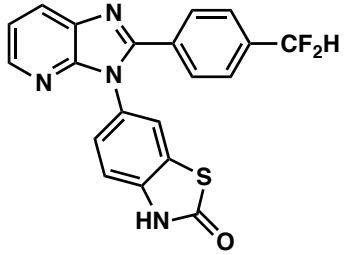
pp.157, Example 70



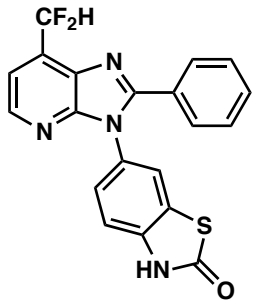
Example 70



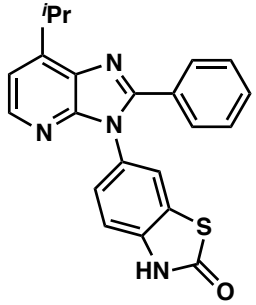
pp. 155, Example 67



pp. 156, Example 68



pp. 156, Example 69

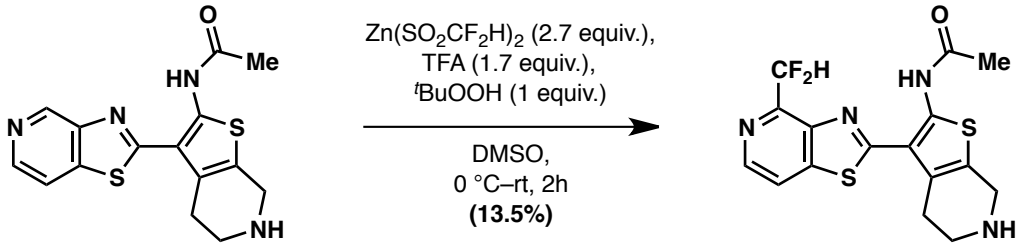


pp. 157, Example 70

6. WO 2016196910, Applicant: Syros Pharmaceuticals, Inc.

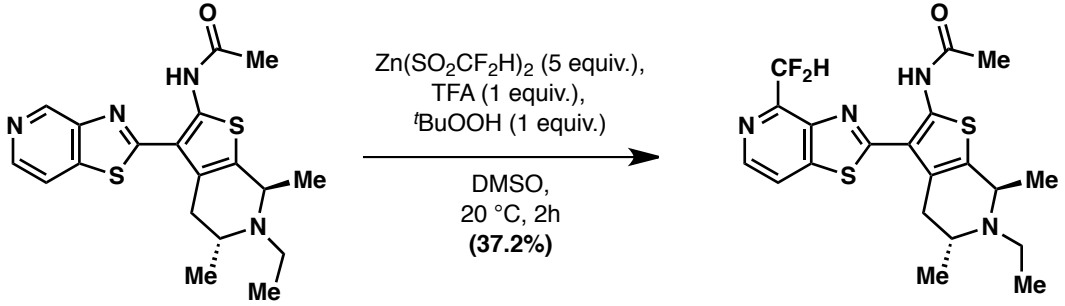
Roberts, C.; Zhang, Y.; Beaumier, F.; Lepissier, L.; Marineau, J. J.; Rahl, P.B.; Sprott, K.; Ciblat, S.; Sow, B.; Larouche-Gauther, R.; Berstle Preparation of Substituted Benzothiazoles for the Modulation of Myc Activity. WO 2016196910 A1, 2016.

pp. 97, Example 7, Compound 106

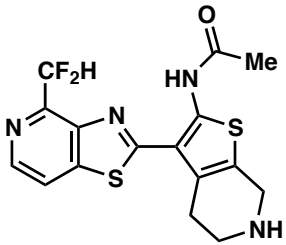


Compound 106

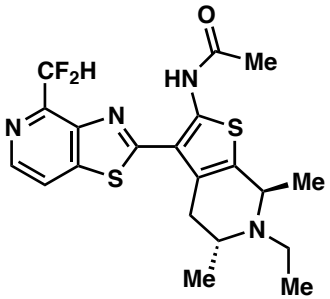
pp. 136, Compound 235



Compound 235



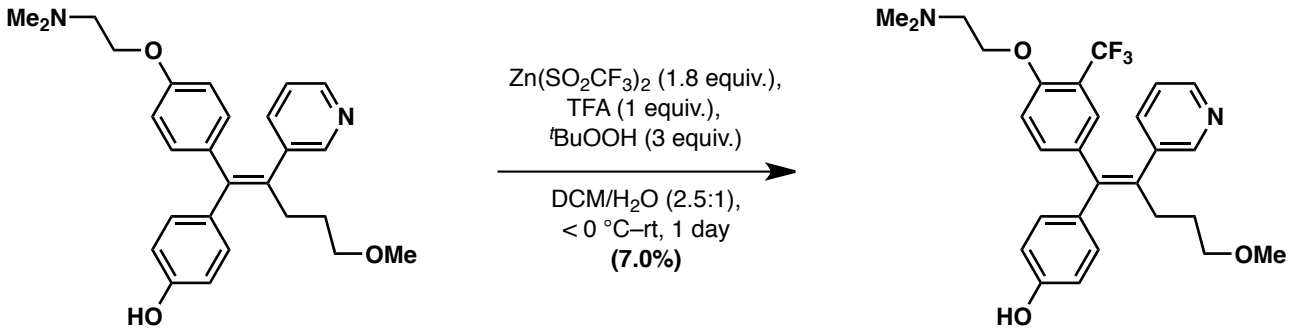
pp. 97, Example 7, Compound 106



pp. 136, Exampel 34, Compound 235

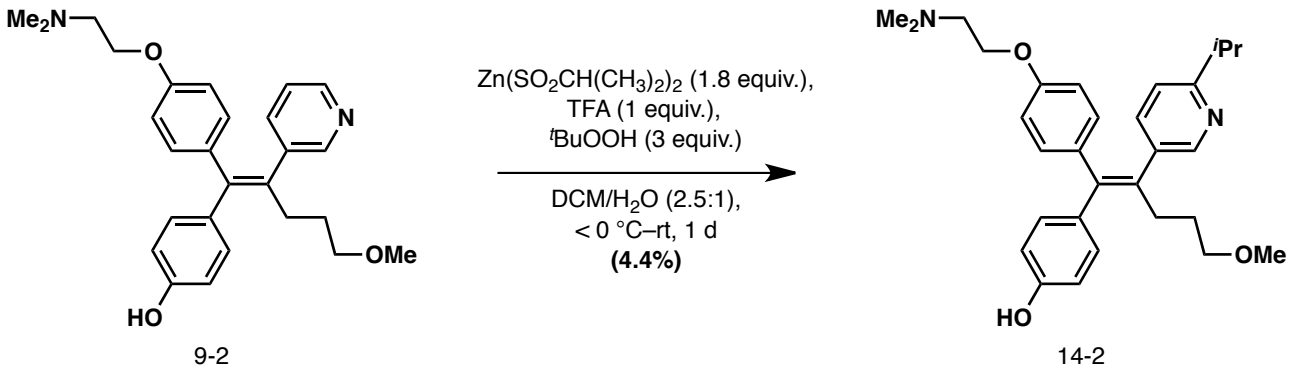
7. KR 1681041, Applicant: Kyungpook National University Hospital, S. Korea; Daegu-Gyeongbuk Medical Innovation Foundation
Lee, I. G.; Kim, S. H.; Kim, G. H.; Hwang, H. Y.; Cho, S. J.; Lim, C. Y.; Kim, J. A.; Jeon, J. H.; Yoo, E. G. Preparation of Aromatic Ring Compound Derivatives as ERRγ Deactivation Ligand. KR 1681041 B1, December 22, 2016.

pp. 13, Reaction scheme III.

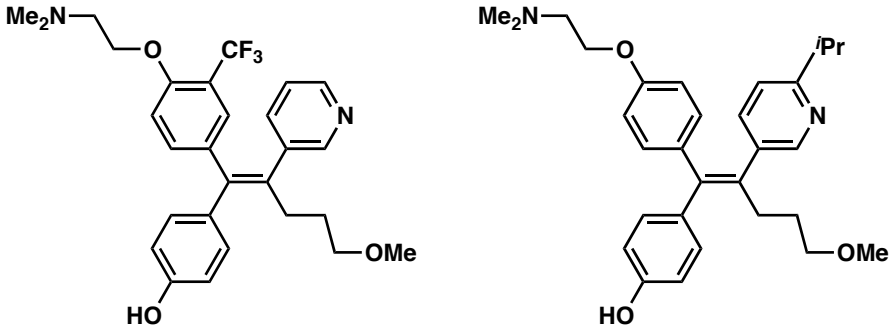


9-2

14-1



9-2 14-2



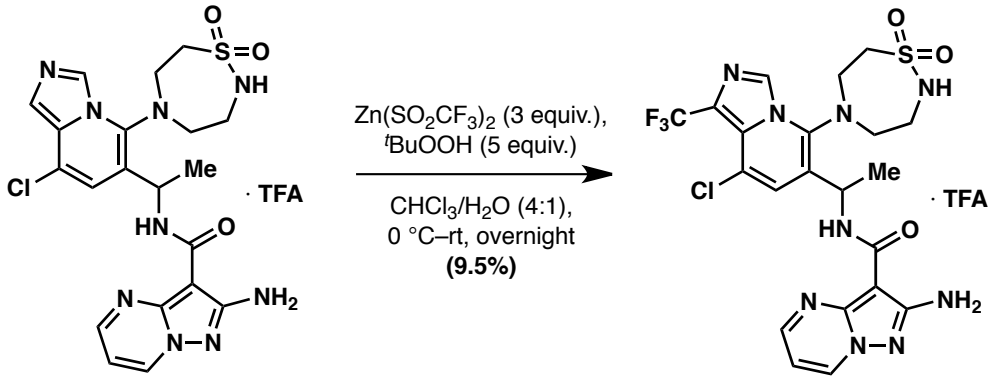
14-1 **14-2**

Patents from 2017

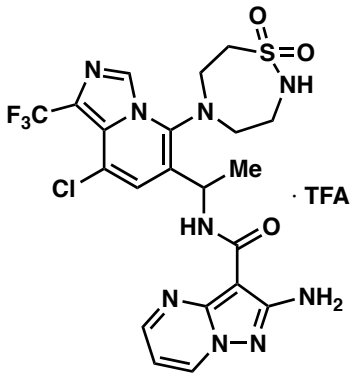
1. US 20170129899, Applicant: Incyte Corporation

Shvartsbart, A.; Shepard, S.; Combs, A. P.; Shao, L.; Falahatpisheh, N.; Zou, G.; Buesking, A.W.; Sparks, R. B.; Yue, E. W.; Jalluri. Heterocyclic Compounds as PI3K Inhibitors. US 20170129899 A1, May 11, 2017.

pp. 153, Example 159



Example 149 Example 159

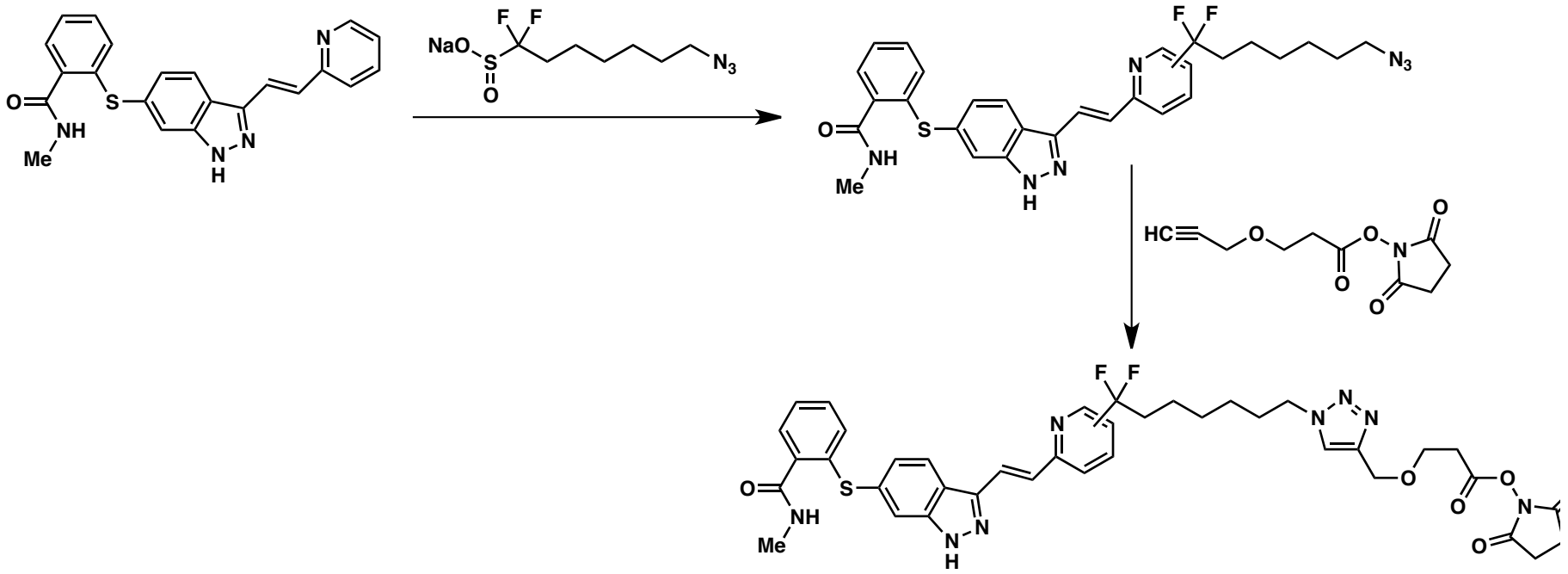


pp. 153, Example 159

2. US 20170205417, Applicant: Konica Minolta, Inc.

Aimiya, T.; Furusawa, N. Labeling Reagent Containing a Molecularly Targeted Drug. US 20170205417 A1, July 20, 2017.

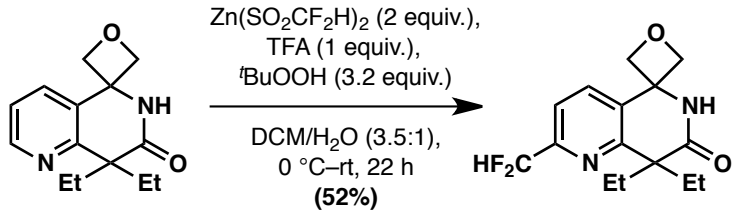
pp. 7, Synthesis Step Z-1, based on *J. Am. Chem. Soc.*, **2013**, *135* (35), 12994–12997.

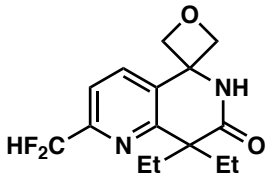


3. WO 2017139526, Applicant: Astellas Pharma Inc.; Cytokinetics, Inc.

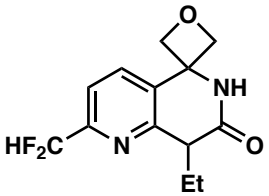
Sato, I.; Kamikubo, T.; Miura, M.; Matsushima, Y.; Tanaka, H.; Shiina, Y.; Yamaki, S.; Saito, T.; Kiyohara, H.; Ohe, M.; Mihara, K.; Morg B. P.; Malik, F.; Collibee, S. E.; Ashcraft, L.; Lu, P. -P.; Warrington, J. M.; Garard, M. Tetrahydroisoquinoline Derivatives. WO 2017139 A1, August 17, 2017.

pp. 129, Example 13

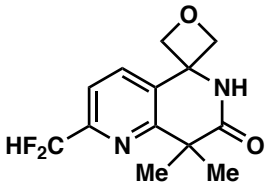




pp. 129, Example 13



pp. 154, Table 4, Example 100



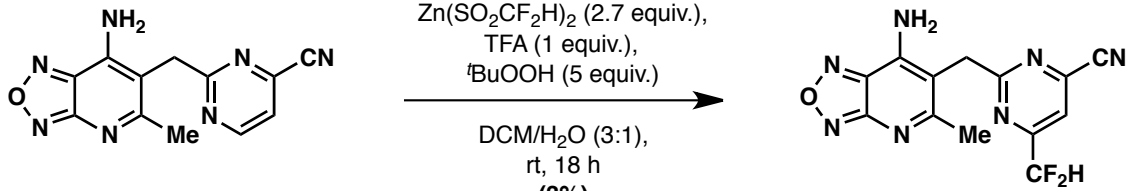
pp. 161, Table 4, Example 169

Patents from 2018

1. WO 2018024653, Applicant: Boehringer Ingelheim International GmbH

Godbout, C.; Trieselmann, T.; Vintonyak, V. Oxadiazolopyridine Derivatives for Use as Ghrelin *O*-Acyl Transferase (GOAT) Inhibitors. WC 2018024653 A1, February 8, 2018.

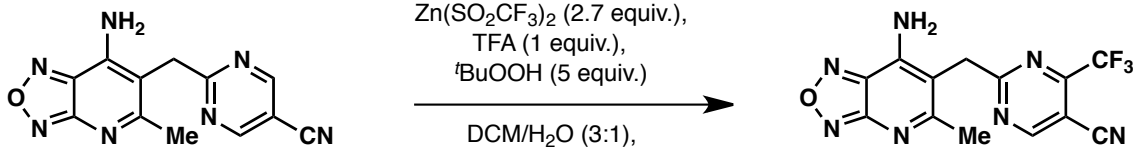
pp. 165, Example 165



Example 51

Example 165

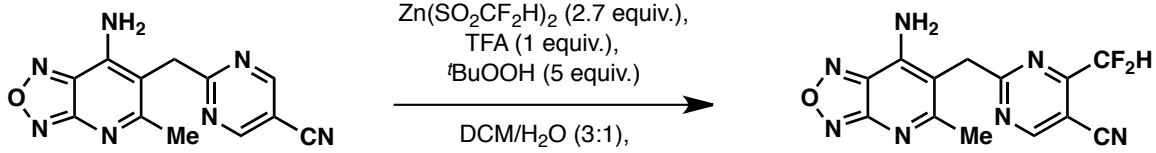
pp. 125, Example 78



Example 77

Example 78

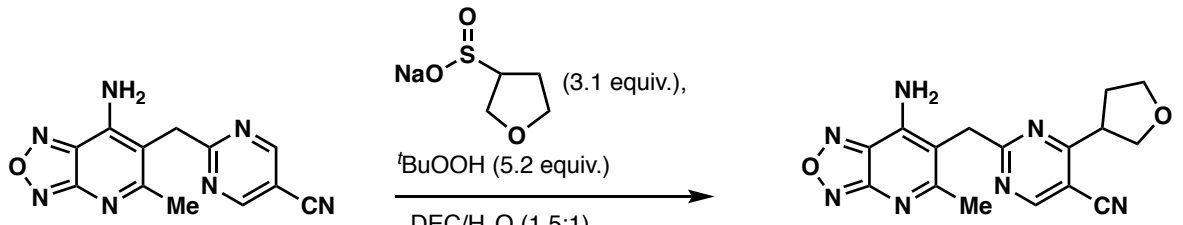
pp. 126, Example 79



Example 77

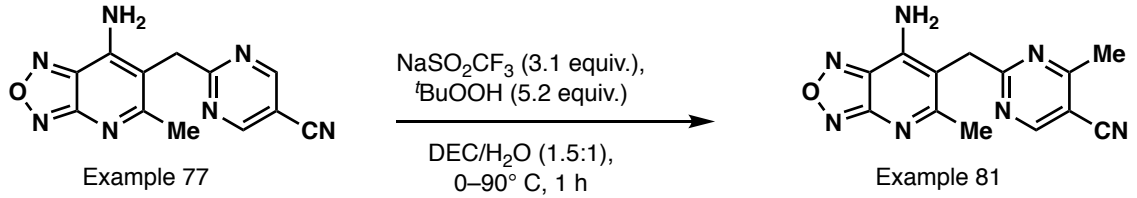
Example 79

pp. 126, Example 80



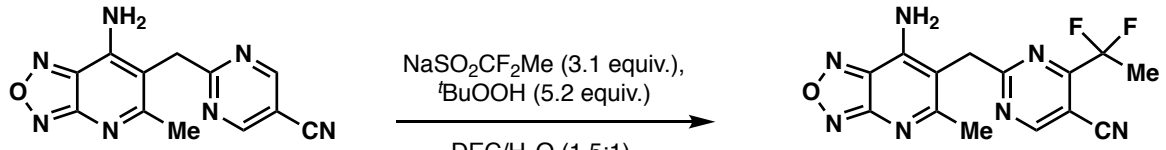
Example 77 — Example 80

pp. 127, Example 81



Example 77 — Example 81

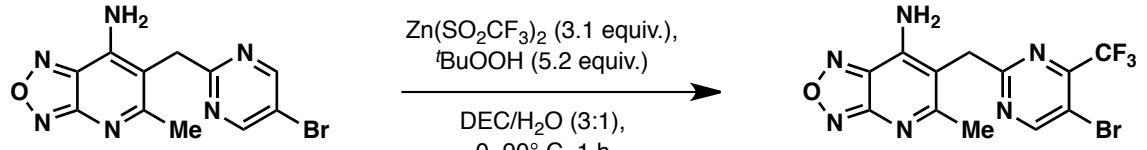
pp. 127, Example 82



Example 77

Example 82

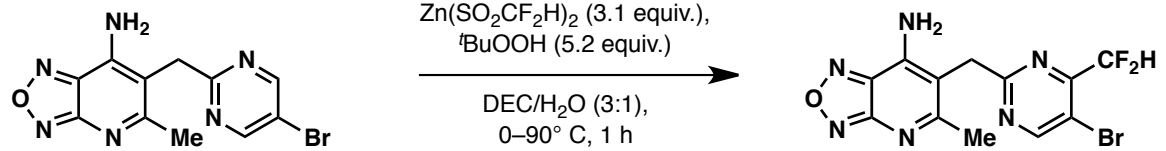
pp. 128, Example 83



Example 31

Example 83

pp. 128, Example 84



Example 77

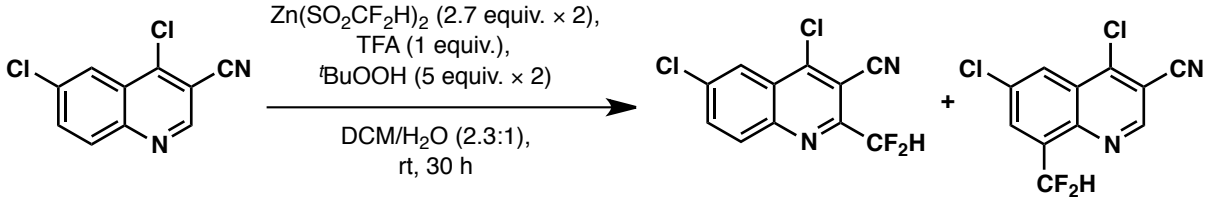
Example 84

pp. 166, Examples 166 and 167

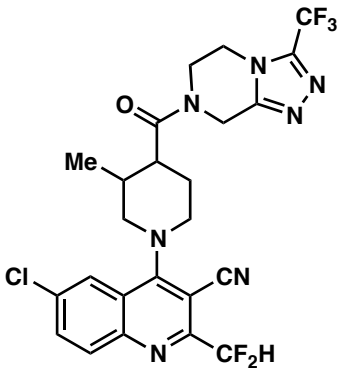
2. WO 2018034918, Applicant: Merck Sharp & Dohme Corp.

Cumming, J. N.; Dykstra, K. D.; Hruza, A.; Li, D.; Liu, H.; Tang, H.; Taoka, B. M.; Verras, A.; Walsh, S. P.; Wu, W. -L. Compounds Useful Altering the Levels of Bile Acids for the Treatment of Diabetes and Cardiometabolic Disease. WO 2018034918 A1, February 22, 2018.

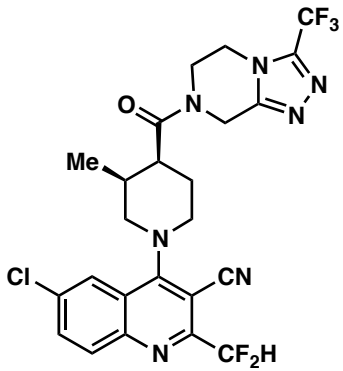
pp. 42 Intermediates 35 and 36



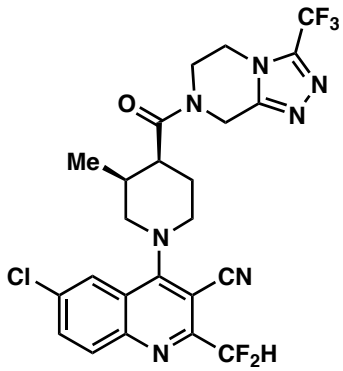
Intermediate 35 Intermediate 36



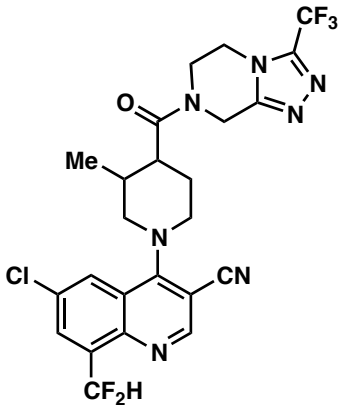
pp. 105, Example 57



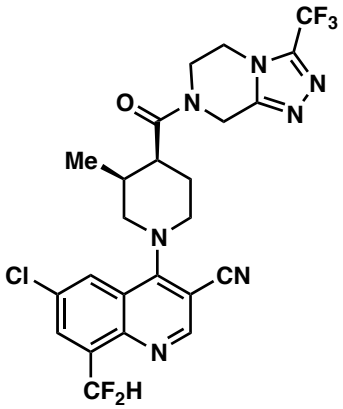
pp. 106, Example 57a



pp. 106, Example 57b



pp. 107, Table 7, Example 58

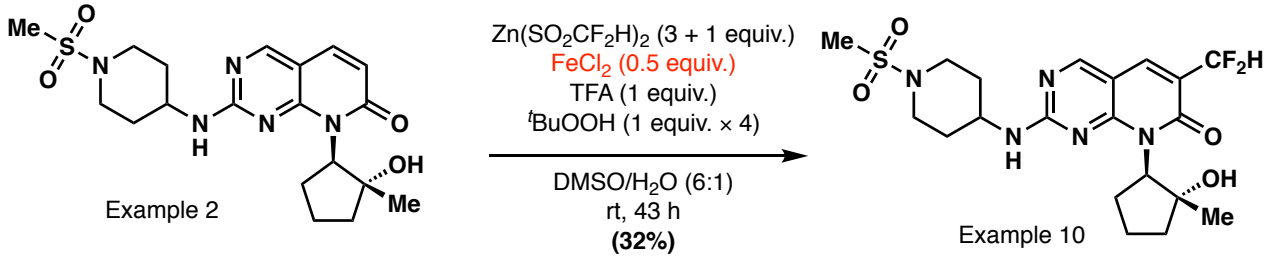


pp. 84, Table 3, Example 3

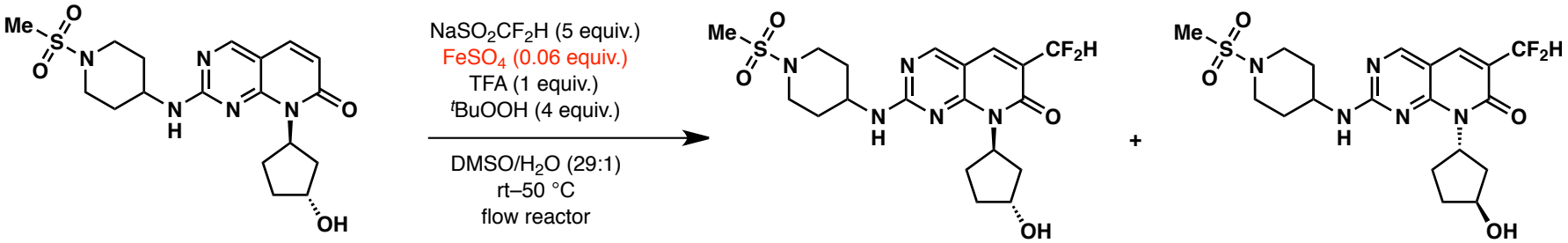
3. US 20180044344, Applicant: Pfizer Inc.

Behenna, D. C.; Chen, P.; Freeman-Cook, K. D.; Hoffman, R. L.; Jalaie, M.; Nagata, A.; Nair, S. K.; Ninkovic, S.; Ornelas, M. A.; Palmer, C Rui, E. Y. CDK2/4/6 Inhibitors. US 20180044344 A1, February 15, 2018.

pp. 57, Method E (Di- and Trifluoromethylation at C-6 After Cyclization), Example 10

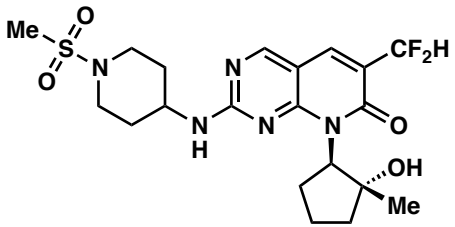


pp. 58, Examples 133 and 134

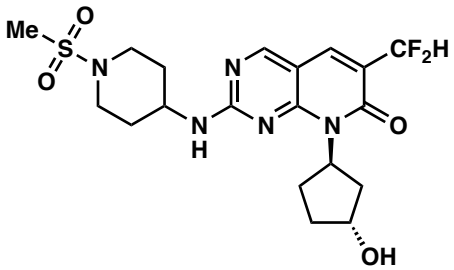


Example 133 **(15%)**

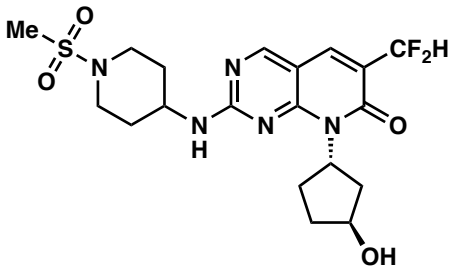
Example 134 **(14%)**



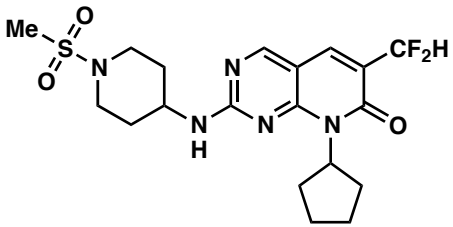
pp. 57, Example 10



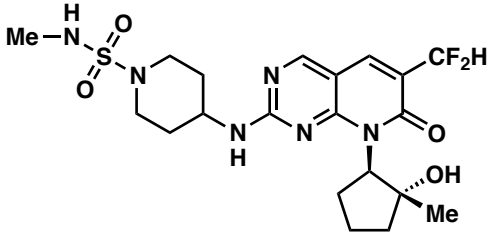
pp. 57, Example 133



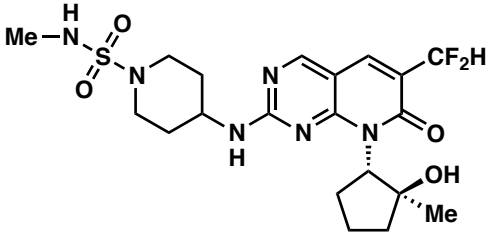
pp. 57, Example 134



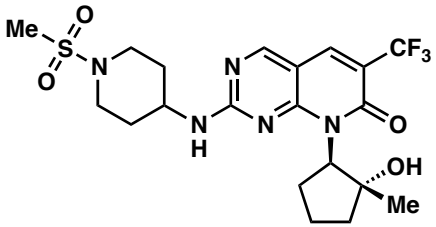
pp. 69, Table 1, Example 30



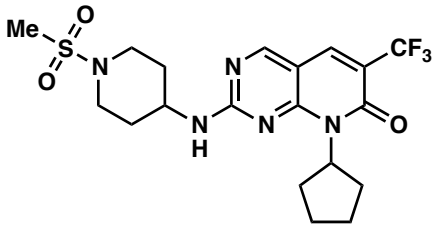
pp. 95, Table 1, Example 130



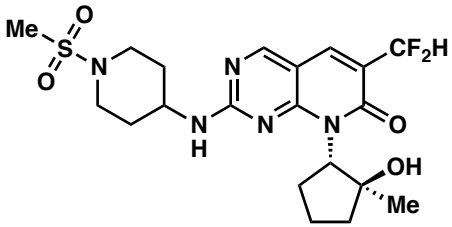
pp. 95, Table 1, Example 131



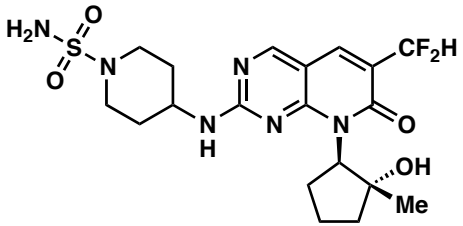
pp. 95, Table 1, Example 132



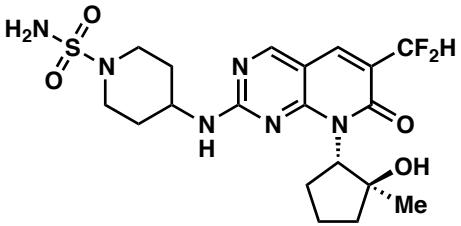
pp. 97, Table 1, Example 148



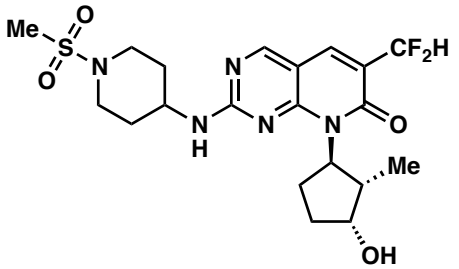
pp. 105, Table 1, Example 176



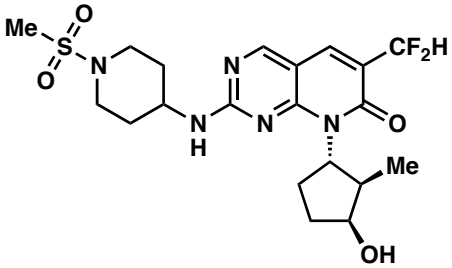
pp. 107, Table 1, Example 187



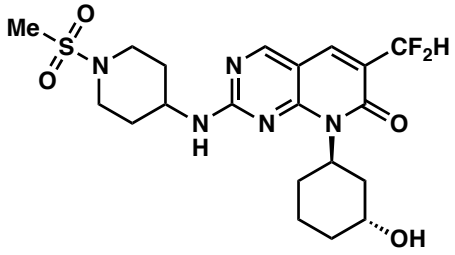
pp. 108, Table 1, Example 188



pp. 112, Table 1, Example 204



pp. 113, Table 1, Example 205

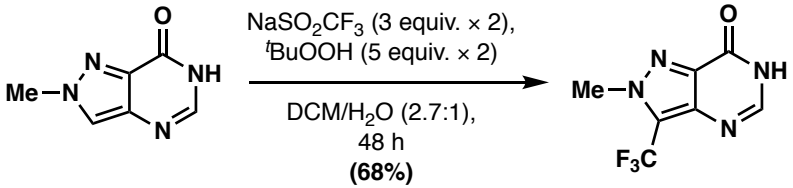


pp. 115, Table 1, Example 212

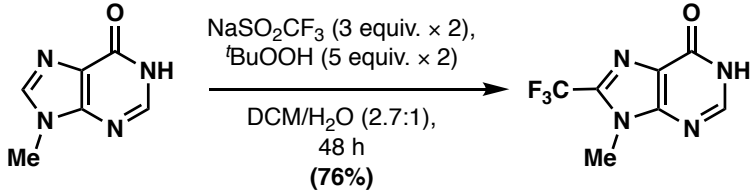
4. WO 2018073602, Applicant: Almac Discovery Limited

O'Dowd, C.; Harrison, T.; Hewitt, P.; Rountree, S.; Hugues, M.; Burkamp, F.; Jordan, L.; Helm, M.; Broccatelli, F.; Crawford, J. J.; Gazzard, Wertz, I.; Lee, W. Piperidine Derivatives as Inhibitors of Ubiquitin Specific Protease 7. WO 2018073602 A1, April 26, 2018.

pp. 76, Example 23



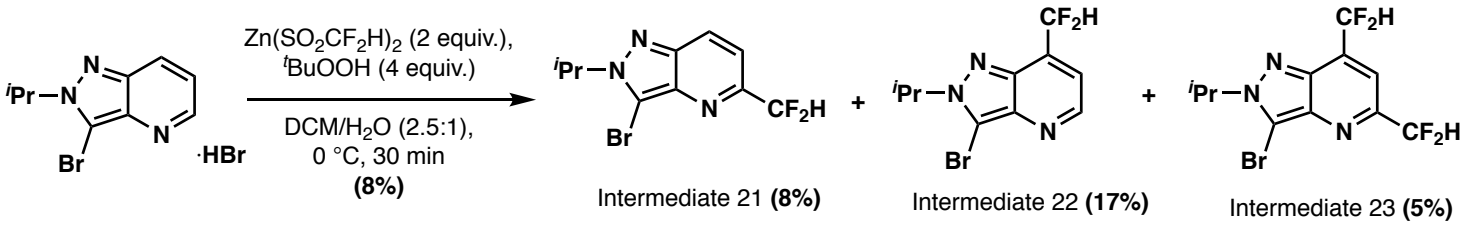
pp. 139, Example 96

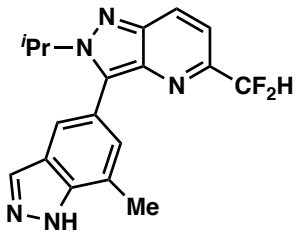


5. WO 2018080918, Applicant: Janssen Pharmaceutica NV

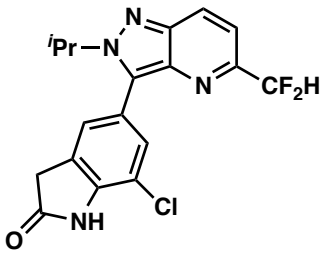
Ameriks, M. K.; Laforteza, B. N.; Savall, B. M.; Wade, W. S.; Meyer, S. T.; Gyuris, M. 3-Aryl-2*H*-pyrazolo[4,3-*b*]pyridine Compounds Their Use as AMPA Receptor Modulators. WO 2018080918 A1, May 3, 2018.

pp. 51, Intermediate 21, Step B; Intermediates 22 and 23

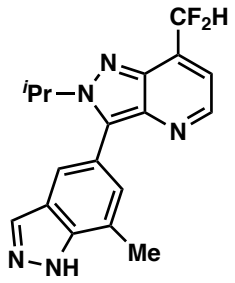




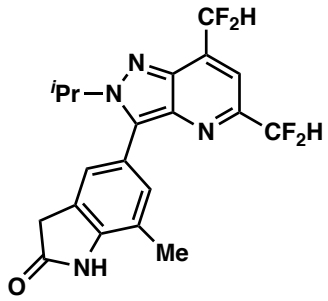
pp. 69, Example 34



pp. 70, Example 36



pp. 71, Example 38

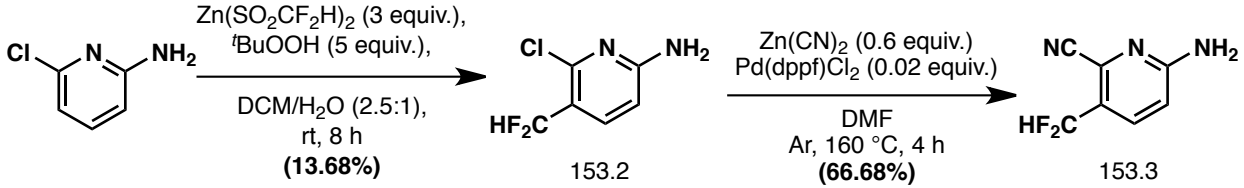


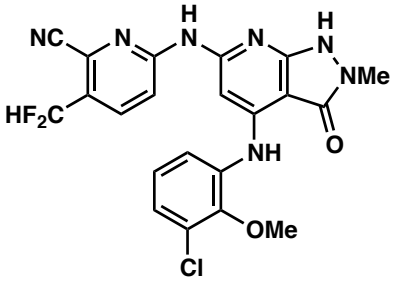
pp. 77, Example 40

6. WO 2018071794, Applicant: Nimbus Lakshmi, Inc.

Greenwood, J. R.; Harriman, G. C.; Leit de Moradei, S. M.; Masse, C. E.; Mclean, T. H.; Mondal, S. TYK2 Inhibitors and Uses Thereof. WO 2018071794 A1, April 19, 2018.

pp. 275–276, Example 153



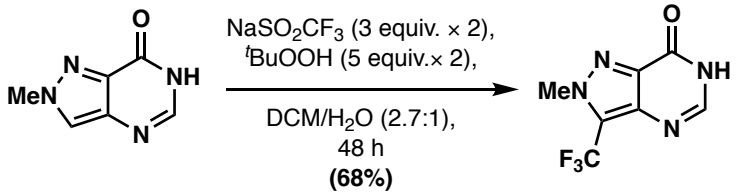


p. 276, I-156

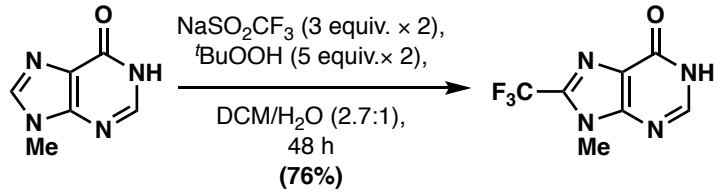
7. WO 2018073602, Applicant: Almac Discovery Limited

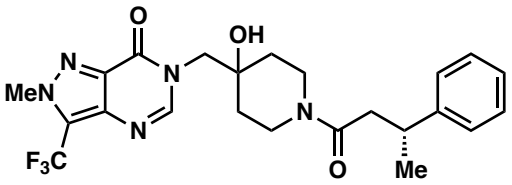
O'Dowd, C.; Harrison, T.; Hewitt, P.; Rountree, S.; Hugues, M.; Burkamp, F.; Jordan, L.; Helm, M.; Broccatelli, F.; Crawford, J. J.; Gazzard, Wertz, I.; Lee, W. Piperidine Derivatives as Inhibitors of Ubiquitin Specific Protease 7. WO 2018073602 A1, April 26, 2018.

pp. 76, Example 23, Step 1

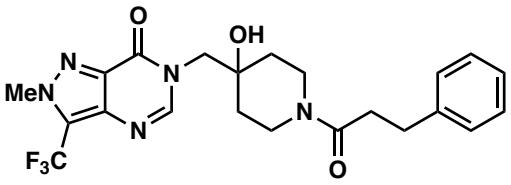


pp. 139, Example 96, Step 1

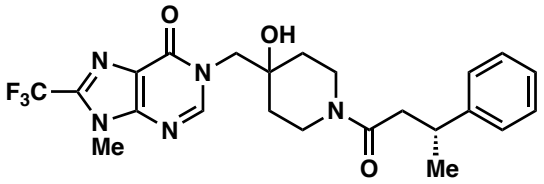




pp. 76, Example 23



pp. 87, Example 39;
pp. 138, Example 95

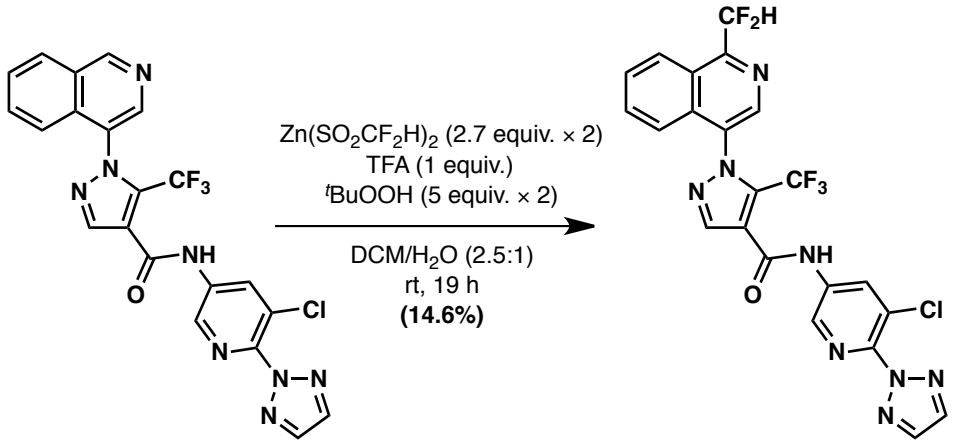


pp. 139, Example 96

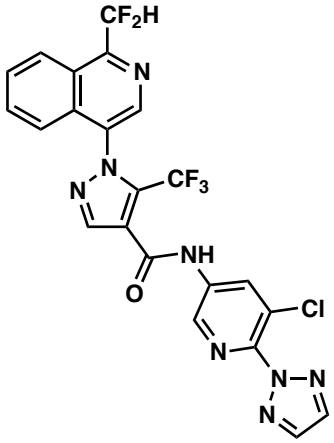
8. WO 20181190363, Applicant: Janssen Biotech, Inc.

Lu, T.; Allison, B. D.; Barbay, J. K.; Connolly, P. J.; Cummings, M. D.; Diels, G.; Edwards, J. P.; Kreutter, K. D.; Philippar, U.; Shen, Thuring, J. W. J. F.; Wu, T. Pyrazole Derivatives as MALT1 Inhibitors. WO 2018024653 A1, June 28, 2018.

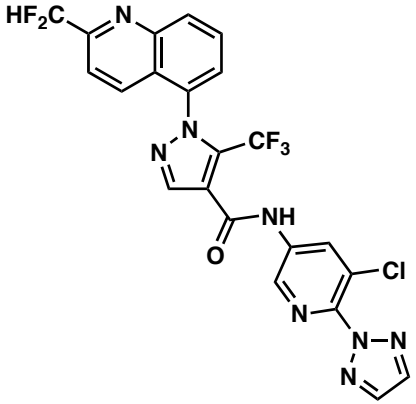
pp. 698–702, Examples 394-402



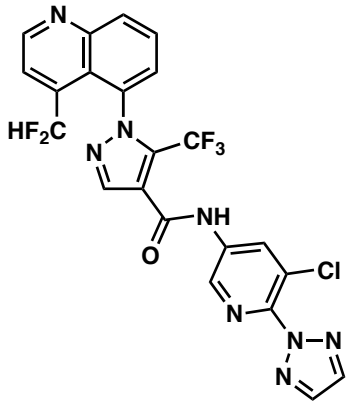
Compound 394



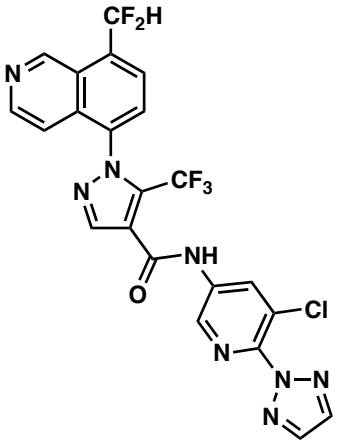
pp. 698, Compound 394



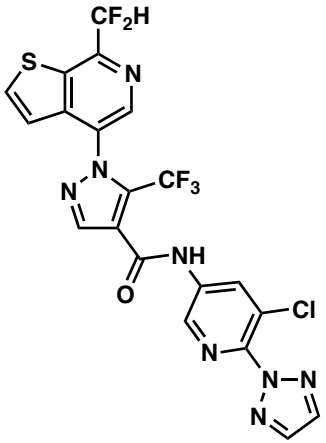
pp. 699, Compound 395



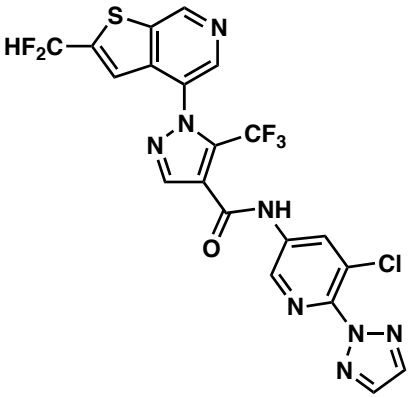
pp. 699, Compound 396



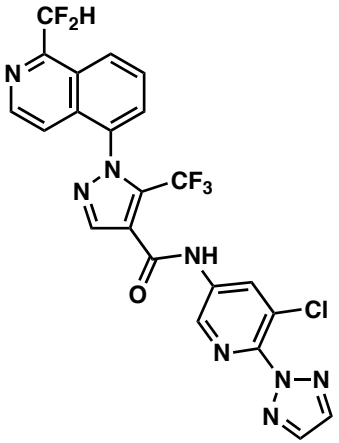
pp. 700, Compound 397



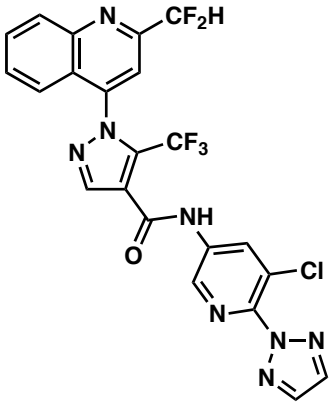
pp. 700, Compound 398



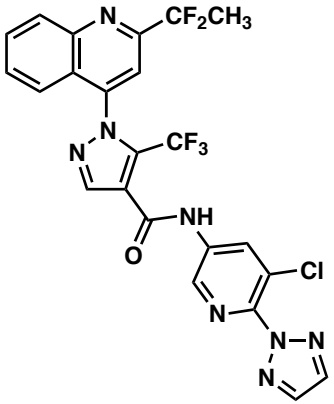
pp. 701, Compound 399



pp. 701, Compound 400



pp. 702, Compound 401



pp. 702, Compound 402