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Synthesis of spirofuranopyrimidine–piperidines

Etzer Darout *, Kim F. McClure, Vincent Mascitti

CVMED Chemistry, Pfizer Worldwide Research & Development, Groton Laboratories, Eastern Point Rd, Groton, CT 06340, USA

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ABSTRACT

A concise synthesis of spirofuranopyrimidines is described and relies on the addition of isopropyl 4-oxopiperidine-1-carboxylate to a pyrimidine dianion. The diol intermediate formed is subjected to cycloetherification conditions leading to an unprecedented heterocyclic template.

1. Introduction

The application of benzo-spiropiperidines in drug discovery programs is particularly prevalent for targets with endogenous peptide ligands.[1–4] While the circumstances for its use varies, the ring system offers a defined way of arranging two contiguous rings in an orthogonal manner, and in specific cases, this can be viewed as a mimic for a phenylalanine residue.[5] Our interest in these spirocyclic systems stems from our goal of conformationally restricting reported ligands of the G-protein coupled receptor 119 (GPR119) (see Fig. 1).[6,7] Our ongoing desire to better understand the structure–activity relationship led us to target compounds generalized by **3**. Previously, we described related attempts to make spirocyclic analogs with an oxospiropyrazole core;[8] however, the poor pharmacology observed with these compounds motivated us to preserve the central pyrimidine from the model compounds **1** and **2** and to evaluate other modes of spirocyclization. While related spiropiperidines have been applied to neuropeptide Y (NPY),[1] melanocortin,[2] and ghrelin,[3,4,9,10] the incorporation of a fused pyrimidine would require the development of a new synthesis. Herein we report the synthesis of this heretofore unknown spirocyclic system via a two-step *C,O*-dianion addition/cycloetherification sequence.

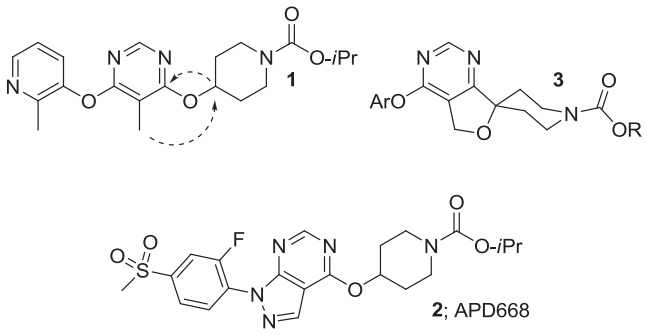

Fig. 1. Spirofuranpyrimidine–piperidine as constrained GPR119 analogs.

2. Results and discussions

We first envisioned the construction of the spirofused scaffold **4** via a strategy involving a late stage 5-*exo* cycloetherification from hydroxymethyl pyrimidine precursor **5** via electrophilic activation of the olefin[11] (Scheme 1). In the cycloetherification of γ-hydroxy olefins, 5-*exo* cyclization is generally preferred over the 6-*endo* mode absent any overriding stereoelectonic and steric effects.[12,13] Intermediate **5** would arise from a Suzuki cross-coupling reaction of boronate **7**[14] with a suitable chloropyrimidine derivative **6**.

Readily available dichloropyrimidine **8** was identified as a suitable cross-coupling partner for this strategy. Suzuki cross-coupling reaction of **8** with commercially available boronate ester **7** yielded the desired pyrimidine derivative **9** in moderate yield. However, attempts to activate the piperidine olefin to effect cycloetherification to the spirofuran **10** were unsuccessful. Iodination[2] and platinum-catalyzed hydroalkoxylation[15] under both mild and forcing conditions resulted in recovery of the alcohol **9** (Scheme 2).

* Corresponding author. E-mail address: Etzer.Darout@pfizer.com (E. Darout).

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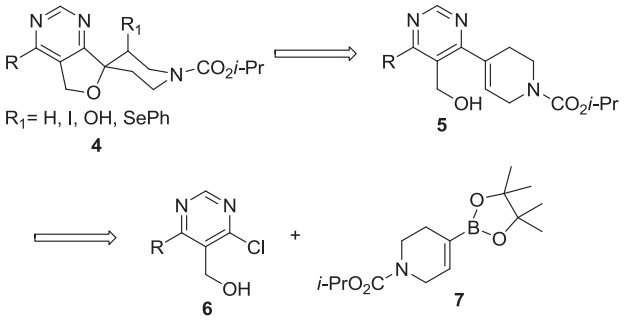
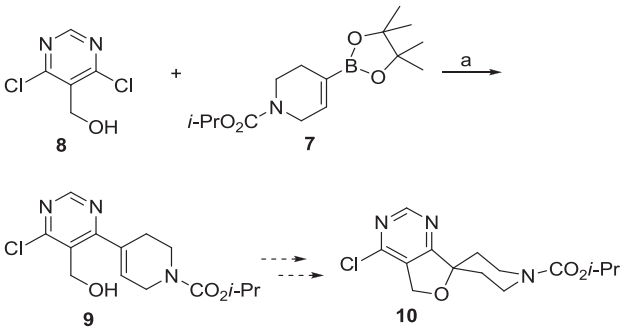


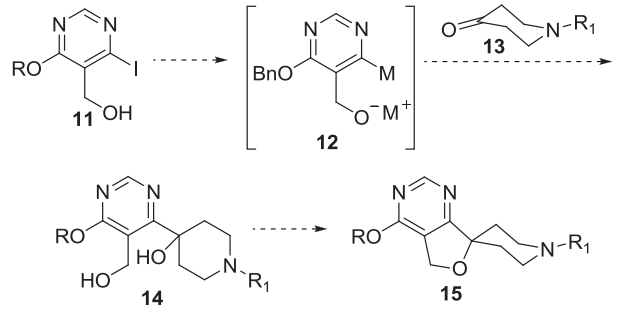
Scheme 1. Retrosynthetic scheme to initial spirocyclization attempt.



Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_4$, 2 M Na_2CO_3, 1,4-dioxane, 140 °C, microwave, 40%.

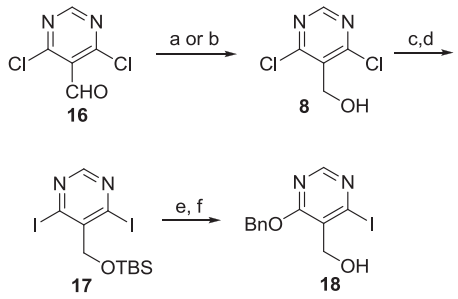
Given, these results an alternative approach was explored to arrive at the desired spirocyclic core.

The synthesis of spiro[isobenzofuran-1(3*H*),4′-piperidines] have been previously reported and were accessed via carboxylate dianion addition to piperidinones.[9] The *C*,*O*-dianion described was derived from 2-bromobenzoic acid. The dianion strategy increases the ease of generating and controlling the dilithio species and eliminates the need for a hydroxymethyl protecting group. Since this approach offered elements of practicality, we decided to explore a *C*,*O*-dianion strategy in the unprecedented context of a substituted 4-iodo-5-hydroxymethyl pyrimidine **11** as precursor (Scheme 3). We hypothesized that generation of dianion **12** from **11**, followed by nucleophilic addition of **12** to **13** would provide **14**, which upon cycloetherification would lead to the desired spiropyrimidine core **15**.



Scheme 3. Dianion addition precursors and spirofused derivatives.

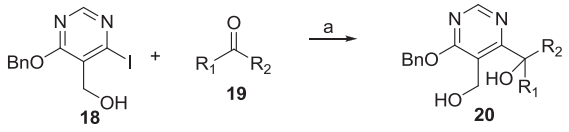
As shown in Scheme 4, an efficient route to gram quantities of hydroxymethyl pyrimidine **18** was achieved in five steps and included only one chromatographic purification step. The sequence begins with reduction of commercially available dichloropyrimidine aldehyde **16**. While treatment of **16** with sodium borohydride provided the expected alcohol **8** in moderate yield after column chromatography, DIBAL–H reduction cleanly provided the dichloropyrimidine alcohol in very good yield following aqueous workup. Iodination[16] of **8**, followed by silylation provided the silylether derivative **17**. The benzyl ether was introduced via an S_NAr reaction and subsequent desilylation of the resulting intermediate provided the hydroxymethyl pyrimidine **18** in 39% overall yield.

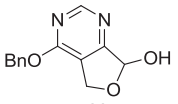
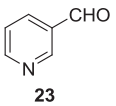
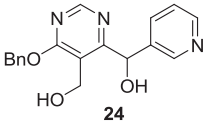
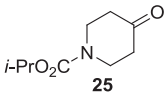
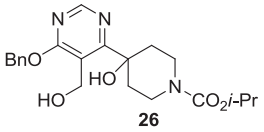


Scheme 4. Reagents and conditions: (a) $NaBH_4$, EtOH/THF, −15 °C, 30 min, 40%; (b) DIBAL–H, THF/toluene, −78 °C, 45 min, 81%; (c) Hydriodic acid (57% aq solution), room temperature, 1 h, 98%; (d) TBS–Cl, Imid., DMF, room temperature, 15 h, 81%; (e) sodium benzyloxide, BnOH, THF, 0 °C to room temperature, 14 h; (f) TBAF, THF, 0 °C to room temperature, 15 h, 61% (two steps).

With **18** in hand, we began to investigate its utility as a *C*,*O*-dianion nucleophile (see Table 1). Treatment of **18** with 0.9 equiv of Turbo Grignard (isopropylmagnesium chloride complexed with lithium chloride) at −78 °C for 30 min, followed by a methanol quench, resulted in unchanged starting material by TLC and UPLC analysis. However when **18** was treated at −40 °Cwith a stoichiometric amount of Grignard reagent, there was evidence of the *des*-iodo product by both TLC and UPLC. This suggests that at higher temperatures, metal–halogen exchange competes with deprotonation.[17,18] To avoid using a large excess of Turbo Grignard, methylmagnesium bromide was first used for the deprotonation of **18**. Turbo Grignard was then used to accomplish the metal–iodine exchange. Results from the various conditions explored are exemplified in Table 1. Treatment of the *C*,*O*-dianion of pyrimidine **18**, formed from deprotonation and subsequent metal–iodine

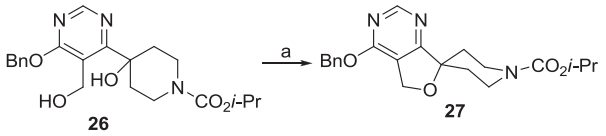
Table 1
Results of reactions of pyrimidine derivative **13** with carbonyl electrophiles



Nucleophile	Electrophile	Product	Yield (%)
18	 **21**	 **22**	75
18	 **23**	 **24**	70
18	 **25**	 **26**	57

Conditions: (a) MeMgBr, THF, −50 °C, 15–25 min; then *i*-PrMgCl·LiCl, −50 °C to 0 °C; then addition of carbonyl electrophile.

exchange, with excess *N*,*N*-dimethylformamide, gave the fused bicyclic hemiacetal derivative **22** in good yield. Likewise, addition of nicotinaldehyde to a solution of the dianion gave the bicyclic diol **24** in good yield. A true test of this methodology involved the reaction of the dianion with oxopiperidine **25**, which gratifyingly resulted in the desired diol **26** in moderate yield. After exploring various options, cycloetherification of diol **26** was successfully executed in a one-pot tosylation, nucleophilic displacement in good yield (Scheme 5).[19]



26 27

Scheme 5. Reagents and conditions: (a) NaHMDS (2 equiv), THF, 0 °C; TsCl 30 min, 74%.

In conclusion, the expedient synthesis of pyrimidine **18** was successfully achieved in five steps, and several electrophiles were used to establish its utility as a *C*,*O*-dianion precursor. The formation of the dianion was achieved with a two-base system to allow deprotonation prior to metal–iodine exchange. This strategy efficiently generated the dianion and avoided the use of a protecting group on the pyrimidine C-5-hydroxymethyl. Subsequent addition of electrophiles to the in situ generated dianion led to the synthesis of a complex spirofuranopyrimidine–piperidine core. To our knowledge, this is the first example of a *C*,*O*-dianion strategy wherein hydroxypyrimidine is used as a nucleophile. This methodology has led to a rapid, practical, and scalable synthesis of the spiropyrimidine piperidine motif that can potentially be applied to other medicinal chemistry programs.

3. Experimental section

3.1. General

*3.1.1. (4,6-Dichloropyrimidin-5-yl)methanol (**8**). Procedure A*: To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (500 mg, 2.82 mmol) in 1:1 THF/EtOH (23 mL) at −15 °C (MeOH/ice) was added $NaBH_4$. After 30 min, the reaction was once again cooled to −15 °C, followed by dropwise addition of 2 M HCl in diethyl ether until all the bubbling had ceased. The reaction mixture was concentrated and adsorbed onto silica. The solid residue was loaded and purified by flash column chromatography (ISCO combiflash) using a gradient elution of 0–4% MeOH/DCM to give 240 mg (47%) of the title compound as a white solid.

Procedure B: To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (4000 mg, 22.6 mmol) in THF (100 mL) at −78 °C was added dropwise a solution of DIBAL (15.8 mL of 1.5 M solution in toluene) over 15 min. After an additional 30 min at −78 °C, a saturated aqueous solution of Rochelle's salt (50 mL) was added and the dry ice/acetone bath was removed. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. At this point, the layers were separated and the organic phase was dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to give 3.25 g (81%) of the title compound as a white solid, mp 88–90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.36 (br s, 1H), 4.97 (s, 2H), 8.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 59.6, 130.8, 157.6, 162.7; HRMS (ESI) MH^+, found 178.9775. $C_5H_4Cl_2N_2O$ requires 177.9701.

*3.1.2. Isopropyl 4-(6-chloro-5-(hydroxymethyl)pyrimidin-4-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**9**).* To a 5 mL microwave vial equipped with a stir bar were added (4,6-dichloropyrimidin-5-yl) methanol (50 mg, 0.28 mmol), isopropyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (82 mg, 0.29 mmol), 1.4-dioxane (1.40 mL), and 2 M Na_2CO_3 (0.35 mL). The heterogeneous mixture was degassed by bubbling nitrogen through the mixture. After 10 min, $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) was added and the reaction mixture was degassed for another 5 min. The reaction vessel was capped and irradiated at 140 °C in the microwave for 30 min. After cooling, the vial was vented to relieve the pressure. The mixture was concentrated to dryness and purified by flash column chromatography with an isocratic elution of 40% EtOAc/heptane to give 35 mg (40%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=6.35 Hz, 6H), 2.59–2.73 (m, 3H), 3.70, (appt t, *J*=5.60 Hz, 2H), 4.18, (appt d, *J*=2.45 Hz, 2H), 4.79, (d, *J*=5.60 Hz, 2H), 4.97, (sep, *J*=6.35 Hz, 1H), 6.33, (br s, 1H), 8.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 21.3, 26.6, 30.9, 42.4, 58.2, 67.9, 127.5, 154.2, 156.0, 162.1, 167.9, 180.5; HRMS (ESI) MH^+, found 311.1105. $C_{14}H_{18}ClN_3O_3$ requires 311.1037.

3.1.3. (4,6-Diiodopyrimidin-5-yl)methanol. Hydriodic acid (250 mL of 57% aq solution) was added to (4,6-dichloropyrimidin-5-yl) methanol (20.5 g, 0.12 mol) at ambient temperature. The mixture was stirred for 1 h during which time a yellow solid precipitated out of the orange-brown solution. The mixture was diluted with water, cooled to 0 °C, and filtered. The solid was collected and dried to give 40 g (98%) of the title compound as a yellow solid, mp 98–103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.50 (s, 1H), 4.69 (s, 2H), 8.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 70.2, 135.7, 143.3, 157.9; HRMS (ESI) MH^+, found 362.8492. $C_5H_4I_2N_2O$ requires 361.8413.

*3.1.4. 5-((tert-Butyldimethylsilyloxy)methyl)-4,6-diiodopyrimidine (**17**).* To a mixture of (4,6-diiodopyrimidin-5-yl)methanol (40.0 g, 0.11 mol) in DMF (553 mL) were added TBS–Cl (38 g, 0.25 mol) and imidazole (19 g, 0.28 mmol). After 15 h, the reaction mixture was concentrated under reduced pressure to remove all of the DMF. The resulting viscous amber oil was dissolved in DMSO (50 mL) and added to a 500 mL separatory funnel. The material was extracted from DMSO with heptane (200 mL×5). The combined heptane layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give 42.4 g (81%) of the title compound as a white solid, mp 70–73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.23 (s, 6H), 0.98 (s, 9H), 4.93 (s, 2H), 8.31 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 0.00, 23.7, 31.0, 76.8, 138.3, 147.5, 161.8; HRMS (ESI) MH^+, found 475.9357. $C_{11}H_{18}I_2N_2OSi$ requires 475.9278.

*3.1.5. (4-(Benzyloxy)-6-iodopyrimidin-5-yl)methanol (**18**).* To a solution of 5-((*tert*-butyldimethylsilyloxy)methyl)-4,6-diiodopyrimidine (40.8 g, 85.8 mmol) in THF (430 mL) was added 1 M benzyloxide in benzyl alcohol (prepared from 1.97 g of sodium and benzyl alcohol 85 mL) at 0 °C. The reaction mixture was allowed to stir for 14 h. Most of the benzyl alcohol was removed by distillation under high vacuum with a bath temperature 80–100 °C. The crude residue was dissolved in THF (200 mL) and TBAF (129 mL of 1 M TBAF in THF) was added at 0 °C. After 5 min, the ice bath was removed and the reaction mixture was allowed to stir for 15 h. The reaction mixture was concentrated and purified by flash column chromatography using a 330 g ISCO column with an eluant of 40% EtOAc/heptane to give 18 g (61%) of the title compound as a white solid, mp 89–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.23 (br s, 1H), 4.78 (s, 2H), 5.50 (s, 2H), 7.26–7.45 (m, 5H), 8.38 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 63.2, 69.5, 125.8, 128.5, 129.0, 133.8, 135.6, 157.3, 166.0; HRMS (ESI) MH^+, found 341.9916. $C_{12}H_{11}IN_2O_2$ requires 341.9865.

*3.1.6. 4-(Benzyloxy)-5,7-dihydrofuro[3,4-d]pyrimidin-7-ol (**22**).* To a solution of (4-(benzyloxy)-6-iodopyrimidin-5-yl)methanol (300 mg, 0.877 mmol) in THF (4.38 mL) at −50 °C was added of 3 M

methylmagnesium bromide (0.292 mL, 0.877 mmol, 3 M in diethyl ether). After 15 min, isopropylmagnesium chloride/lithium chloride (1.36 mL, 1.8 mmol, 1.3 M solution in THF) was added. After 5 min, the CH_3CN bath was removed and replaced with an ice bath. The reaction was allowed to stir until metal–halogen exchange was complete by TLC analysis (indicated by hydro-deiodination product (50% EtOAc/heptane)). DMF (1 mL, 10 mmol) was added and the reaction mixture stirred for 16 h. The reaction was quenched with satd NH_4Cl and the layers were separated. The aqueous layer was extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated. Purification of the crude by flash column chromatography with 30% EtOAc/heptane gave the title compound (160 mg (75%)) as a white foam. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.03 (d, J=13.5 Hz, 1H), 5.24 (dd, J=2.7, 13.5 Hz, 1H), 5.54 (s, 2H), 6.51 (d, J=2.45 Hz, 1H), 7.35–7.46 (m, 5H), 8.81 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 68.4, 68.9, 99.2, 117.5, 128.6, 128.8, 128.9, 135.7, 158.9, 164.8, 168.7; HRMS (ESI) MH^+, found 244.0905. $C_{13}H_{12}N_2O_3$ requires 244.0848.

*3.1.7. (6-(Benzyloxy)-5-(hydroxymethyl)pyrimidin-4-yl)(pyridin-3-yl)methanol (**24**).* To a solution of 4-(benzyloxy)-6-iodopyrimidin-5-yl)methanol (300 mg, 0.877 mmol) in THF (4.40 mL) at −50 °C was added methylmagnesium bromide (0.292 mL, 0.877 mmol of 3 M solution in diethyl ether. After 20 min, isopropylmagnesium chloride/lithium chloride (1.36 mL, 1.8 mmol of 1.3 M solution in THF) was added. After 5 min, the CH_3CN bath was removed and replaced with an ice bath. The reaction mixture was allowed to stir for 30 min. At this point a mixture of nicotinaldehyde (188 mg, 1.75 mmol) in THF (1 mL) was added dropwise followed by a 0.5 mL rinse. The solution was allowed to stir overnight. The reaction was quenched with satd NH_4Cl and the layers were separated. The aqueous layer was extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the crude with EtOAc as the eluant gave the title compound 200 mg (70%) as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 4.58–4.70 (m, 2H), 5.48 (dd, J=12.2, 18.8 Hz, 2H), 6.10 (s, 1H), 7.20–7.45 (m, 6H), 7.73 (d, J=7.85 Hz, 1H), 8.43 (appt d, J=3.70 Hz, 1H), 8.57 (s, 1H), 8.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 53.6, 67.9, 69.3, 116.2, 122.7, 127.1, 127.4, 127.6, 134.1, 134.7, 136.8, 147.2, 147.7, 155.5, 165.4, 166.6; HRMS (ESI) MH^+, found 323.2203. $C_{18}H_{17}N_3O_3$ requires 323.1270.

*3.1.8. Isopropyl 4-(6-(benzyloxy)-5-(hydroxymethyl)pyrimidin-4-yl)-4-hydroxypiperidine-1-carboxylate (**26**).* To a solution of (4-(benzyloxy)-6-iodopyrimidin-5-yl)methanol (300 mg, 0.877 mmol) in THF (4.4 mL) at −50 °C was added methylmagnesium bromide (0.292 mL, 0.877 mmol of 3 M) solution in diethyl ether. After 25 min, isopropylmagnesium chloride/lithium chloride (1.36 mL, 1.8 mmol of 1.3 M solution in THF) was added. After 5 min, the CH_3CN bath was removed and replaced with an ice bath. The reaction mixture was allowed to stir until consumption of the iodide was observed by TLC analysis (30% EtOAc/heptane). At this point a mixture of isopropyl 4-oxopiperidine-1-carboxylate (487 mg, 2.63 mmol) in THF (1 mL) was added dropwise followed by a 0.5 mL rinse. The solution was allowed to stir overnight. The reaction was quenched with satd NH_4Cl and the layers were separated. The aqueous layer was extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the filtrate concentrated. Purification of the crude with 30% EtOAc/heptane as the eluant gave the title compound as a clear oil 200 mg (57%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.25 (d, J=6.35 Hz, 6H), 1.66 (d, J=13.2 Hz, 2H), 2.24–2.29 (m, 2H), 3.15–3.25 (m, 3H), 4.00–4.13 (m, 2H), 4.86–4.95 (m, 3H), 5.11 (br s, 1H), 5.48 (s, 2H), 7.33–7.46 (m, 5H), 8.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 22.5, 37.0, 40.0, 55.5, 68.9, 69.1, 74.1, 117.6, 128.3, 128.6, 128.9, 136.2, 155.5, 155.7, 168.6, 170.9; HRMS (ESI) MH^+, found 401.2004. $C_{21}H_{27}N_3O_5$ requires 401.1951.

*3.1.9. Isopropyl 4-(benzyloxy)-5H-spiro[furo[3,4-d]pyrimidine-7,4′-piperidine]-1′-carboxylate (**27**).* To a solution of isopropyl 4-(6-(benzyloxy)-5-(hydroxymethyl)pyrimidin-4-yl)-4-hydroxypiperidine-1-carboxylate (22 mg, 0.055 mmol) in THF (0.5 mL) at 0 °C was added NaHMDS (0.121 mL, 0.121 mmol of 1 M solution in THF). After stirring for 5 min, a solution of TsCl (13 mg, 0.0660 mmol) in THF (0.5 mL) was added dropwise. After 20 min, the reaction mixture was quenched via the addition of satd NH_4Cl and brine followed. The heterogeneous mixture was poured into a separatory funnel and extracted with DCM (3×2 mL). The combined DCM layers were dried over $MgSO_4$, filtered, and the filtrate concentrated. Purification using a 4 g RediSep column with 45% EtOAc/heptane as an eluant gave 80 mg (74%) of the title compound as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm; 1.27 (d, J=6.50 Hz, 6H), 1.64–1.68 (m, 2H), 2.00 (dt, J=4.5, 13.0 Hz, 2H), 3.20–3.34 (m, 2H), 4.01–4.20 (m, 2H), 4.95 (sept, J=6.0 Hz, 1H), 5.05 (s, 21H), 5.51 (s, 2H), 7.33–7.47 (m, 5H), 8.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 22.5, 34.4, 40.2, 67.2, 68.5, 68.9, 84.3 115.7, 128.6, 128.7, 128.9, 136.1, 155.5, 158.8, 164.2, 173.6. HRMS (ESI) MH^+, found 383.1902. $C_{21}H_{25}N_3O_4$ requires 383.1845.

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References and notes

1. Takahashi, T.; Haga, Y.; Sakamoto, T.; Moriya, M.; Okamoto, O.; Nonoshita, K.; Shibata, T.; Suga, T.; Takahashi, H.; Hirohashi, T.; Sakuraba, A.; Gomori, A.; Iwaasa, H.; Ohe, T.; Ishihara, A.; Ishii, Y.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3511–3516.
2. Guo, L.; Ye, Z.; Liu, J.; He, S.; Bakshi, R. K.; Sebhat, I. K.; Dobbelaar, P. H.; Hong, Q.; Jian, T.; Dellureficio, J. P.; Tsou, N. N.; Ball, R. G.; Weinberg, D. H.; MacNeil, T.; Tang, R.; Tamvakopoulos, C.; Peng, Q.; Chen, H. Y.; Chen, A. S.; Martin, W. J.; MacIntyre, D. E.; Strack, A. M.; Fong, T. M.; Wyvratt, M. J.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4895–4900.
3. Nargund, R. P.; Patchett, A. A.; Bach, M. A.; Murphy, M. G.; Smith, R. G. *J. Med. Chem.* **1998**, *41*, 3103–3127.
4. Liu, J.; Jian, T.; Guo, L.; Atanasova, T.; Nargund, R. P. *Tetrahedron Lett.* **2009**, *50*, 5228–5230.
5. Patchett, A. A.; Nargund, R. P.; Tata, J. R.; Chen, M. H.; Barakat, K. J.; Johnston, D. B.; Cheng, K.; Chan, W. W.; Butler, B.; Hickey, G. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 7001–7005.
6. Jones, R. M.; Lehmann, J. WO 2007035355, 2007.
7. Semple, G.; Ren, A.; Fioravanti, B.; Pereira, G.; Calderon, I.; Choi, K.; Xiong, Y.; Shin, Y.-J.; Gharbaoui, T.; Sage, C. R.; Morgan, M.; Xing, C.; Chu, Z.-L.; Leonard, J. N.; Grottick, A. J.; Al-Shamma, H.; Liang, Y.; Demarest, K. T.; Jones, R. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3134–3141.
8. Stevens, B. D.; Darout, E.; Mascitti, V.; McClure, K. F. *Tetrahedron Lett.* **2011**, *52*, 1949–1951.
9. Marxer, A.; Rodriguez, H. R.; McKenna, J. M.; Tsai, H. M. *J. Org. Chem.* **1975**, *40*, 1427–1433.
10. Canonne, P.; Foscolos, G. B.; Belanger, D. *J. Org. Chem.* **1980**, *45*, 1828–1835.
11. Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry Part B: Reactions and Synthesis*, 5th ed.; Springer: New York, NY, **2007**, pp 289–365.
12. Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476.
13. Bravo, F.; Castillón, S. *Eur. J. Org. Chem.* **2001**, *2001*, 507–516.
14. Altenbach, R. J.; Adair, R. M.; Bettencourt, B. M.; Black, L. A.; Fix-Stenzel, S. R.; Gopalakrishnan, S. M.; Hsieh, G. C.; Liu, H.; Marsh, K. C.; McPherson, M. J.; Milicic, I.; Miller, T. R.; Vortherms, T. A.; Warrior, U.; Wetter, J. M.; Wishart, N.; Witte, D. G.; Honore, P.; Esbenshade, T. A.; Hancock, A. A.; Brioni, J. D.; Cowart, M. D. *J. Med. Chem.* **2008**, *51*, 6571–6580.
15. Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536–9537.
16. d'Alarcao, M.; Leonard, N. J. *J. Am. Chem. Soc.* **1983**, *105*, 5958–5960.
17. Gannon, M. K.; Detty, M. R. *J. Org. Chem.* **2007**, *72*, 2647–2650.
18. Gallagher, D. J.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 7984–7987.
19. Moulines, J.; Lamidey, A.-M.; Desvergnes-Breuil, V. *Synth. Commun.* **2001**, *31*, 749–758.