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One-Pot Directed Alkylation/Deprotection Strategy for the Synthesis of Substituted Pyrrole[3,4-*d*]pyridazinones

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In the course of a structure–activity relationship study of pyrrole[3,4-*d*]pyridazinones, we optimized conditions for a one-pot directed lithiation/alkylation reaction that also promoted in situ cleavage of a *tert*-butoxycarbonyl (Boc) protecting group on the pyrrole ring. The efficiency of the process gave access to a number of substituted analogs of interest as possible antitumor agents.

Introduction

Inhibition of the monocarboxylate transporters, particularly isoforms MCT1[1] and MCT4,[2] is a promising strategy for thwarting tumor growth,[3] particularly poorly-treated hypoxic tumors.[4,5] AstraZeneca's MCT1 inhibitor **1** (Figure 1) has shown early clinical promise[6] in tumors with high levels of MCT1 expression.[7,8] The substituted pyrrole[3,4-*d*]pyridazin-1-one **2** is also highly potent,[9–11] as are structurally related compounds from other labs,[12] including our own.[13] As part of an effort to study the consequences of MCT1 inhibition, we wished to prepare analogs of compound **2** that retain a hydroxy-containing side-chain, shown by us[13] and by Bantick et al. to be essential for activity.[14]

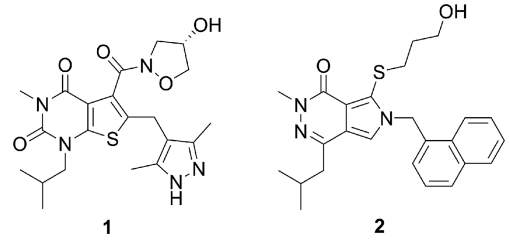
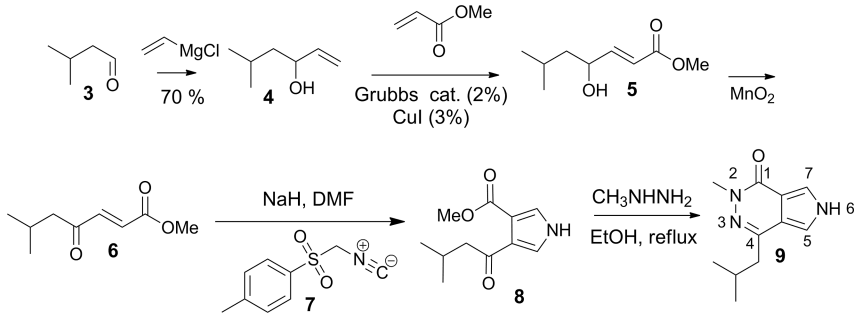


Figure 1. Structures of potent AstraZeneca MCT1 inhibitors.

Recently, we reported a Grubbs cross-metathesis strategy to prepare keto ester **6**, which is used for the synthesis of substituted pyrrole[3,4-*d*]pyridazin-1-one **9**, the core scaffold of inhibitor **2** (Scheme 1).[15] In that report, we also



Scheme 1. Synthesis of keto ester **6** and fused pyrrole **9**.

discussed previous synthetic strategies for the preparation of this fused ring system.[15]

Results and Discussion

We wanted to install side-chains at N-6 and C-7 of the pyrrole ring of core structure **9**, or a precursor, to mimic or

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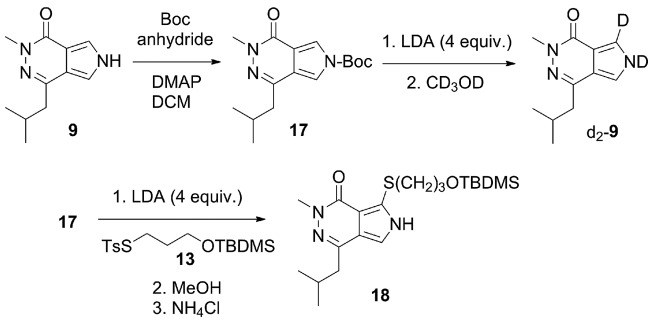
duplicate the corresponding side-chains of inhibitors **1** and **2**. As an example, *N*-alkylation of ester **8** with bromide **10** (Scheme 2) followed by methylhydrazine-promoted ring closure gave substituted pyrrole[3,4-*d*]pyridazin-1-one **12**. To our surprise, however, attempted direct lithiation of **12** was unsuccessful, resulting instead in deprotonation at the benzylic-like carbon to give, after quenching with an excess of thiotosylate **13**,[16] dithiane-containing derivative **14**. In the ^{1}H NMR spectrum of **14**, it was apparent that the *N*-CH_2 protons that resonated at δ = 5.85 ppm for compound **12** were absent, and also that five rather than four aromatic protons were present. The protons for the S–CH_2–CH_2–CH_2–OTBDMS side-chain were also doubled in number relative to what was expected for the desired *N*-alkylated pyrrole[3,4-*d*]pyridazin-1-one (i.e., **15**). Desilylated diol **16** was readily purified and fully characterized to confirm the assigned structure. The CH_2 deprotonation observed for fused pyrrole **12** had not been seen when similar reaction conditions were used during the synthesis of naphthyl-substituted analog **2**. The greater electron-withdrawing ability of the chloropyridyl group relative to that of a naphthylmethyl group was apparently a complicating factor, and so a change in tactics was required. We felt that an appropriate protecting group at the pyrrole N-6 would direct C-7 lithiation[17] and subsequent alkylation. N-5 deprotection and alkylation would then be used to install the chloropyridylmethyl group of the target pyrrole[3,4-*d*]pyridazin-1-one (i.e., **15**).

We found that a *tert*-butoxycarbonyl (Boc) group did indeed direct *o*-lithiation: Boc-protected pyrrole[3,4-*d*]pyridazin-1-one **17** underwent LDA-promoted metalation, as shown by deuterium incorporation upon quenching with CD_3OD, which was confirmed by ^{1}H NMR spectroscopic analysis of the resulting product (Scheme 3). Surprisingly, however, the Boc group was also cleanly removed during the reaction, or more probably in the work-up. Having established the possibility of conducting *o*-lithiation, the sulfur-containing side-chain was incorporated using thiotosylate **13**. Once again, the Boc group was cleanly removed following a methanol quench to give thioether **18** with an unprotected pyrrole group. It is likely that in such reactions, the CH_3OLi that is formed during the work-up prompts the Boc removal. Although the Boc group is normally base-stable, alkoxides have been used for the removal of Boc groups from pyrroles.[18] The one-pot alkylation/deprotection method was robust, and good results (yields of 57–63%) were obtained upon scale-up for multigram synthesis of thioether **18** (Table 1).

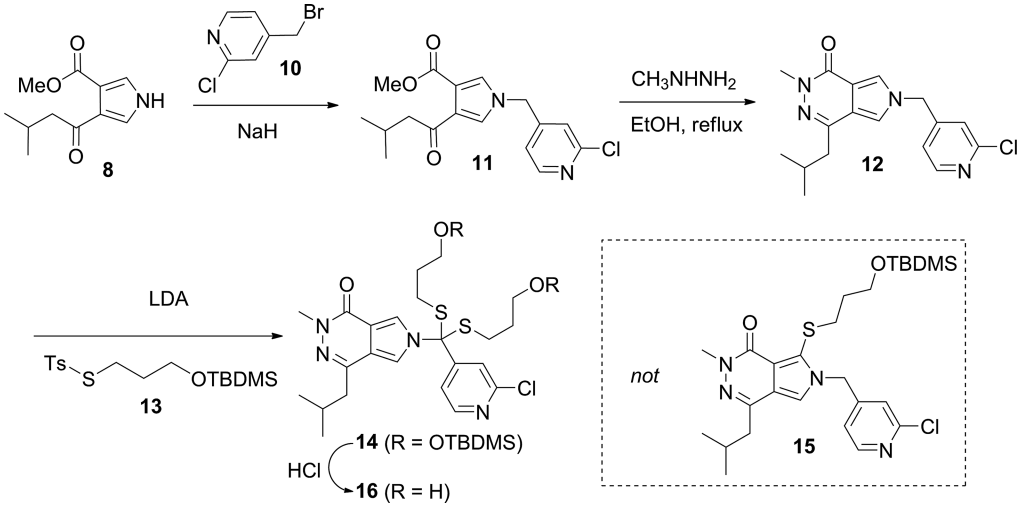


Scheme 3. Boc-directed metalation to give alkylated pyrrole **18**; DMAP = 4-(dimethylamino)pyridine, DCM = dichloromethane.

Table 1. Reaction-scale-independent efficiency of the alkylation/deprotection protocol.

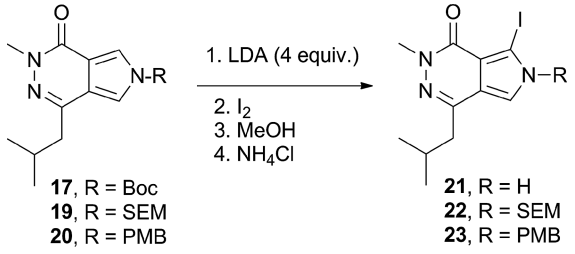
Entry	**17** [g]	Theoretical yield [g]	Actual yield of **18** [g]	Yield [%]
1	0.32	0.43	0.24	57
2	0.40	0.54	0.32	59
3	1.35	1.81	1.15	63
4	1.75	2.33	1.40	60
5	2.88	3.86	2.35	59
6	5.00	6.71	3.98	59

Other pyrrole protecting groups were also effective in directing metalation at C-7, including silylethoxymethyl (SEM) and *p*-methoxybenzyl (PMB) groups, as shown by



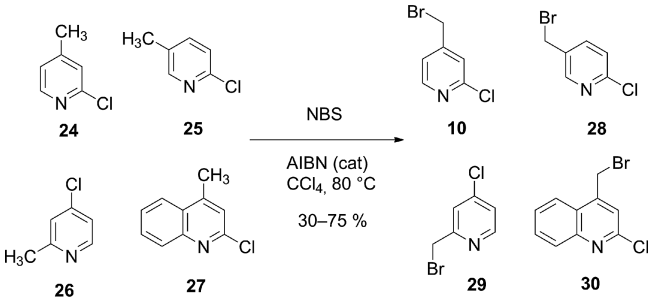
Scheme 2. Unexpected difficulties in attempts to introduce the sulfur-containing side-chain; LDA = lithium diisopropylamide; TBDMS = *tert*-butyldimethylsilyl.

quenching of electrophiles **19**–**21** with iodine, followed by MeOH/NH_4Cl work-up (Scheme 4). The facile removal of the Boc protecting group in the process, however, made Boc the preferred pyrrole protecting group in such synthetic efforts. The ready access to C-7-iodinated fused pyrroles **21**–**23** will probably give access to a wide range of analogs through transition-metal-mediated coupling reactions.



Scheme 4. Protecting-group-directed lithiation/iodination.

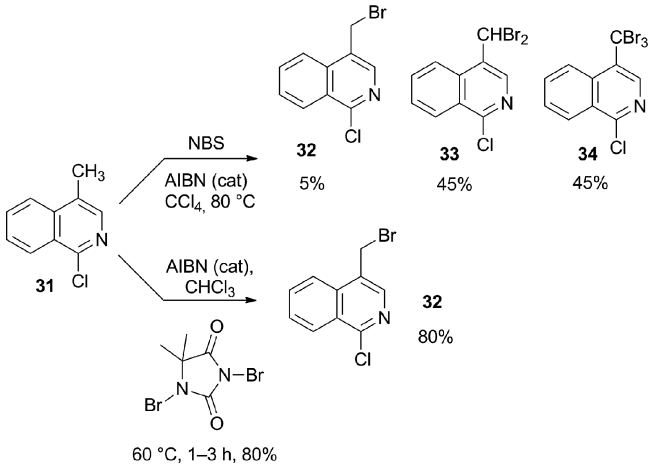
With multigram quantities of key substituted pyrrole[3,4-*d*]pyridazin-1-one **18** available, the installation of various groups at the pyrrole N-5 by direct alkylation was of interest. Bromide **10**[19] was prepared on a multigram scale cleanly but in low yield from 2-chloro-4-methylpyridine (**24**) using NBS (*N*-bromosuccinimide) with AIBN (azobisisobutyronitrile)/dibenzoyl peroxide as radical initiator in CCl_4 at 80 °C (Scheme 5). Similarly, 2-chloro-5-methylpyridine (**25**), 5-chloro-2-methylpyridine (**26**), and 2-chloro-4-methylquinoline (**27**) gave analogous bromides **28**,[20] **29**,[21] and **30**,[22] respectively, following similar protocols.



Scheme 5. Pyridyl and quinolyl bromides.

The preparation of an isoquinoline analog using the 4-methyl isoquinoline substrate (i.e., **31**)[23] was more problematic, as the desired bromide (i.e., **32**) was contaminated with much larger amounts of dibromide **33**, tribromide **34**, and unreacted starting material. This mixture was difficult to separate, and thus the formation of a mixture was undesirable, even if the efficiency of the conversion to monobromide **32** could be improved. However, the use of the less commonly-used reagent 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave monobrominated isoquinoline **32** in 80% yield (Scheme 6).

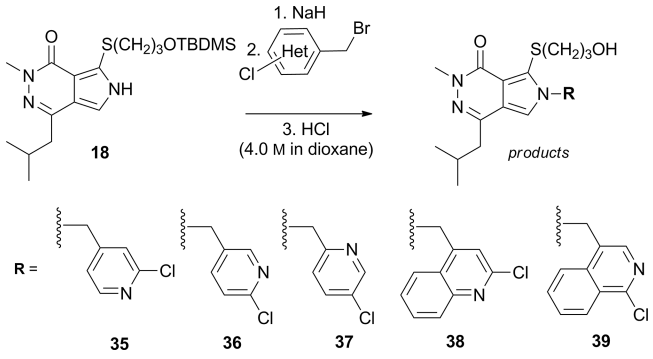
DBDMH was further used for the monobromination of a variety of methyl-substituted quinolines.[24] The mild conditions and the higher selectivity for monobromination compared to the traditional NBS/AIBN/CCl_4 method makes the use of DBDMH preferable and perhaps generally



Scheme 6. Isoquinoline bromide **32**.

useful in the monobromination of methyl-substituted pyridines and their ring-fused analogs.

Each of the bromides from Schemes 5 and 6 was then used in the efficient alkylation of pyrrole **18**, using NaH in DMF followed by acidic desilylation (Scheme 7). The resulting products (i.e., **35**–**39**) were then purified by preparative HPLC. The biological evaluation of these compounds and their substituted analogs will be the subject of future reports from our laboratories. We feel that the efficient one-pot pyrrole metalation/alkylation/deprotection and DBDMH-promoted monobromination procedures will be of general use in the preparation and study of related heterocycles.



Scheme 7. Synthesis of substituted pyrrole[3,4-*d*]pyridazin-1-ones **35**–**39**.

Experimental Section

General Remarks: All reagents and solvents were obtained from commercial suppliers, and were used as supplied. NMR spectra were recorded with a 400 MHz spectrometer (^1H, 400 MHz; ^{13}C, 100 MHz) at 25 °C. Chemical shifts are reported in ppm (δ) referenced to residual NMR solvent, and coupling constants (J) are given in Hertz. FTIR spectra were recorded as neat oils or solids. HRMS samples were analyzed with a TOF analyzer using the electrospray (ESI) ionization method. All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and HRMS. For known compounds, appropriate references are cited,

and ^{1}H NMR spectra are given in the Supporting Information. Flash column chromatography was carried out using RediSep® columns (60 Å mesh) with a Combiflash Rf® instrument from Teledyne Isco, Inc. All reactions were monitored using TLC and LCMS (conducted using an HPLC coupled with an ion-trap mass spectrometer system, from Thermo-Fisher, Inc.). Wherever necessary, reactions were carried out under an argon atmosphere. LDA was freshly prepared before each use. Methyl acrylate, isovaleraldehyde, and TOSMIC (toluenesulfonylmethyl isocyanide) acid **7** were obtained from commercial suppliers, as were compounds **24**–**27**. Substituted isoquinoline **31** was synthesized by a literature procedure.[23]

Methyl 4-(3-Methylbutanoyl)-1*H*-pyrrole-3-carboxylate (8): A dry 500 mL three-necked flask fitted with a condenser and addition funnel and containing a stirrer bar was put under argon and cooled to 0 °C. NaH (14.2 g, 352.5 mmol) and DMF (100 mL) were added. Olefin **6** (30 g, 176 mmol) and TOSMIC acid **7** (35 g, 176 mmol) were added to a separate flask containing DMF (100 mL). The resulting solution was then added to the NaH/DMF solution dropwise using an addition funnel, over a period of 45 min. The reaction mixture was allowed to warm to room temperature overnight. Saturated NH_4Cl was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, followed by brine, then it was dried with Na_2SO_4, and concentrated. The resulting oily solid was purified by flash chromatography (ethyl acetate/hexanes, 2:1). The fractions corresponding to desired product were isolated, combined, and concentrated to give **8** (11 g, 31%) as an orange-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (br. s, 1 H), 7.39 (s, 1 H), 7.29 (s, 1 H), 3.84 (s, 3 H), 2.79 (d, J = 7.0 Hz, 2 H), 2.28–2.20 (m, 1 H), 0.97 (d, J = 7.0 Hz, 6 H) ppm.

4-Isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (9): Ethanol (50 mL) and compound **8** (1.48 g, 7.07 mmol) were added to a 200 mL round-bottomed flask containing a stirrer bar. Methyl hydrazine (1.6 g, 1.9 mL, 35.4 mmol) was added, and then the reaction mixture was heated at reflux for 16 h. The completion of the reaction was confirmed by LCMS (m/z = 410.8), then the solution was cooled to room temperature and quenched by the addition of satd. aq. NH_4Cl solution (25 mL). This mixture was extracted with ethyl acetate (3× 40 mL), and the combined organic layers were washed with water (2× 50 mL), and brine (50 mL), dried with Na_2SO_4, and concentrated to give **9** (1.27 g, 87%) as a dark brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.25 (br. s, 1 H), 7.55 (s, 1 H), 7.27 (merged with $CDCl_3$ signal) (s, 1 H), 3.79 (s, 3 H), 2.63 (d, J = 7.4 Hz, 2 H), 2.23–2.13 (septet, 1 H), 0.98 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 145.6, 120.2, 116.5, 115.6, 42.5, 38.0, 28.0, 22.7 ppm. IR (neat): $\tilde{\nu}$ = 3164.9 (br), 2956.8, 2865.9, 1777.9, 1729.7, 1630.7, 1582.7, 1523.8, 1464.8, 1367.7, 1250.8, 1167.8, 1094.8, 1069.8, 880.9, 763.7, 698.8 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{11}H_{16}N_3O$ [M + H]$^+$ 206.1293; found 206.1286.

Methyl 1-[(2-Chloropyridin-4-yl)methyl]-4-(3-methylbutanoyl)-1*H*-pyrrole-3-carboxylate (11): Pale brown oil (1.01 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, J = 3.9 Hz, 1 H), 7.25 (d, J = 2.5 Hz, 1 H), 7.14 (d, J = 2.5 Hz, 1 H), 7.07 (br. s, 1 H), 6.95 (d, J = 4.0 Hz, 1 H), 5.08 (s, 2 H), 3.84 (s, 3 H), 2.81 (d, J = 6.9 Hz, 2 H), 2.26–2.18 (m, 1 H), 0.97 (d, J = 6.7 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 163.9, 152.6, 150.9, 147.9, 128.3, 127.6, 126.7, 122.2, 120.2, 115.8, 52.2, 51.6, 51.2, 25.3, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 3155.9, 2956.8, 2870.9, 1724.5, 1667.5, 1594.6, 1551.7, 1535.6, 1466.7, 1438.6, 1385.5, 1366.7, 1292.6, 1249.5, 1212.6, 1169.4, 1123.6, 1087.4, 1002.6, 990.7, 935.6, 874.8, 839.6, 813.6, 764.6, 714.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{20}N_2O_3Cl$ [M + H]$^+$ 335.1162; found 335.0941.

6-[(2-Chloropyridin-4-yl)methyl]-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (12): White solid (0.401 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, J = 4.9 Hz, 1 H), 7.53 (d, J = 2.5 Hz, 1 H), 7.04 (br. s, 1 H), 7.02 (s, 1 H), 6.92 (d, J = 4.0 Hz, 1 H), 5.31 (s, 2 H), 3.75 (s, 3 H), 2.59 (d, J = 7.4 Hz, 2 H), 2.20–2.10 (m, 1 H), 0.99 (d, J = 6.7 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 152.6, 150.5, 148.1, 143.7, 122.1, 121.6, 120.1, 119.9, 117.3, 115.6, 53.0, 42.4, 37.9, 27.9, 22.7 ppm. IR (neat): $\tilde{\nu}$ = 3097.9, 3052.9, 2954.8, 1645.6, 1595.8, 1582.8, 1550.8, 1534.8, 1465.8, 1451.8, 1391.8, 1335.8, 1149.9, 1123.8, 1088.8, 996.8, 974.9, 876.8, 828.8, 774.8, 757.8, 719.9, 691.8, 670.8 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{20}N_4OCl$ [M + H]$^+$ 331.1326; found 331.1317.

6-[9-(2-Chloropyridin-4-yl)-2,2,3,3,15,15,16,16-octamethyl-4,14-dioxa-8,10-dithia-3,15-disilaheptadecan-9-yl]-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (14) and 6-{(2-Chloropyridin-4-yl)bis[(3-hydroxypropyl)thio]methyl}-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (16): THF (anhydrous; 25 mL), **12** (0.390 g, 1.16 mmol), and thiotosylate **13** (0.840 g, 2.33 mmol) were added to a dry 250 mL round-bottomed flask containing a stirrer bar under argon. The reaction mixture was then cooled to –78 °C. Under a positive argon flow, LDA (0.5 M solution in THF; 4.7 mL, 2.33 mmol) was added over 10 min, and the reaction mixture was stirred overnight. After TLC showed that the reaction was complete, satd. aq. NH_4Cl solution was added to quench the reaction. The resulting mixture was extracted with ethyl acetate (3× 25 mL), and the combined organic layers were washed with water (3× 25 mL), and brine (50 mL), dried with Na_2SO_4, filtered, and concentrated. The resulting crude oil was purified by flash chromatography (hexane/ethyl acetate, 1:1) to give dithiane bis-TBDMS ether **14** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 4.7 Hz, 1 H), 7.68 (s, 1 H), 7.20 (s, 1 H), 7.08 (s, 1 H), 6.94 (d, J = 5.4 Hz, 1 H), 3.74 (s, 3 H), 3.66 (br. t, J = 5.5 Hz, 2 H), 3.57 (t, J = 6.0 Hz, 2 H), 3.05 (t, J = 7.3 Hz, 2 H), 2.67–2.54 (m, 4 H), 2.20–2.09 (m, 1 H), 1.78–1.58 (m, 2 H), 1.00 (dd, J = 3.3, 6.6 Hz, 6 H), 0.86 (s, 9 H), 0.84 (s, 9 H), 0.03 (s, 6 H), 0.00 (s, 6 H) ppm.

This material was dissolved in THF (5 mL), and HCl (4 M in dioxane; 2 mL) was added. The resulting mixture was stirred for 1 h. The deprotection of the silyl groups was confirmed by TLC and LCMS, then the solvents were evaporated. The crude product was purified by preparative HPLC to give diol **16** (0.301 g, 53%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 8.3 Hz, 1 H), 7.92 (s, 1 H), 7.23 (s, 1 H), 7.08 (s, 1 H), 6.95 (obscured d, 1 H), 3.80–3.74 (m, 2 H), 3.67 (s, 3 H), 3.66–3.62 (obscured m, 2 H), 3.06–2.99 (m, 1 H), 2.72–2.62 (m, 2 H), 2.58 (obscured d, 2 H), 2.18–2.08 (m, 1 H), 1.84–1.75 (m, 2 H), 1.73–1.64 (m, 2 H), 0.97 (dd, J = 6.6, 2.76 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 152.2, 145.9, 126.0, 123.7, 123.7, 123.4, 121.9, 117.8, 64.5, 62.6, 61.4, 43.5, 40.0, 37.4, 33.7, 32.7, 31.1, 29.8, 29.6, 24.3, 24.3, 24.2 ppm. IR (neat): $\tilde{\nu}$ = 3381.8, 2953.8, 2869.8, 1633.5, 1585.5, 1546.7, 1491.7, 1463.7, 1421.7, 1374.6, 1348.5, 1286.7, 1261.7, 1238.7, 1202.5, 1160.6, 1125.7, 1087.7, 1052.5, 998.6, 971.7, 907.7, 881.7, 785.6, 736.6, 719.6, 670.6, 695.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{23}H_{32}N_4O_3ClS_2$ [M + H]$^+$ 511.1082; found 511.1579.

***tert*-Butyl 4-Isobutyl-2-methyl-1-oxo-1,2-dihydro-6*H*-pyrrolo[3,4-*d*]pyridazine-6-carboxylate (17):** CH_2Cl_2 (20 mL) and **9** (0.129 g, 0.63 mmol) were added to a dry 100 mL flask containing a stirrer bar. Boc anhydride (0.150 g, 0.69 mmol) and a catalytic amount of 4-dimethylaminopyridine (0.015 g, 0.125 mmol) were added, and

the mixture was stirred for 30 min. After TLC showed that the reaction was complete, the solution was concentrated, and the residue was dissolved in ethyl acetate. This solution was washed with satd. aq. NH_4Cl solution, water (2× 20 mL), and brine (25 mL), then dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 1:1) to give pure **17** (0.185 g, 98%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 2.0 Hz, 1 H), 7.56 (d, J = 2.0 Hz, 1 H), 3.70 (s, 3 H), 2.56 (d, J = 7.0 Hz, 2 H), 2.20–2.11 (septet, 1 H), 0.97 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 148.0, 144.2, 121.3, 118.6, 117.7, 114.3, 86.6, 42.2, 37.8, 27.8, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 3411.9, 2963.8, 2870.9, 1746.6, 1659.6, 1595.8, 1522.8, 1476.8, 1459.8, 1389.7, 1369.7, 1335.8, 1351.8, 1319.8, 1290.7, 1273.5, 1257.6, 1144.5, 1101.6, 1081.7, 986.6, 840.7, 768.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{24}N_3O_3$ $[M + H]^+$ 306.1814; found 306.1818.

[D_2]-9: Anhydrous THF (20 mL) and **17** (0.025 g, 0.087 mmol) were added to a dry 25 mL flask containing a stirrer bar under argon. The solution was cooled to –78 °C, and LDA (0.5 M solution in THF; 0.33 mL) was added. The mixture was stirred at –78 °C for 2 h. The reaction was quenched with CD_3OD (0.3 mL), and the solution was stirred for 30 min, and then concentrated. The crude product was analyzed by ^1H NMR spectroscopy. Since this compound was made only to test the ability of LDA to deprotonate **17**, the yield was not determined, and the product was characterized only by ^1H NMR spectroscopy and LCMS. ^1H NMR (400 MHz, CD_2Cl_2): δ = 9.93 (br. s, 1 H), 7.16 (d, J = 2.8 Hz, 1 H), 3.65 (s, 1 H), 2.56 (d, J = 7.0 Hz, 2 H), 2.18–2.07 (septet, 1 H), 0.94 (d, J = 6.6 Hz, 6 H) ppm. The disappearance of the aromatic proton and Boc group indicate the incorporation of deuterium and the loss of the Boc group, respectively.

7-({3-[(*tert*-Butyldimethylsilyl)oxy]propyl}thio)-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (18): Anhydrous THF (75 mL), **17** (0.405 g, 1.33 mmol), and **13** (0.955 g, 2.65 mmol) were added to a dry 250 mL flask containing a stirrer bar under argon. The solution was cooled to –78 °C, and then LDA (0.5 M solution in THF; 8.0 mL, 3 equiv.) was added dropwise over 10 min. This mixture was kept at –78 °C for 4 h, and then it was warmed to room temperature over 2 h. Then MeOH (10 mL) was added. After 30 min, saturated aq. NH_4Cl (30 mL) was added, and the mixture was transferred to a separatory funnel and extracted with ethyl acetate. The organic layer was washed with water (3× 25 mL), and brine (25 mL), dried with Na_2SO_4, and then concentrated. The crude solid was purified by flash chromatography (hexanes/ethyl acetate, 1:1) to give compound **18** (0.32 g, 63%) as a pale brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.45 (br. s, 1 H), 7.05 (d, J = 2.8 Hz, 1 H), 3.79 (t, J = 5.8 Hz, 1 H), 3.71 (s, 3 H), 3.13 (t, J = 7.3 Hz, 2 H), 2.55 (d, J = 7.4 Hz, 2 H), 2.18–2.08 (septet, 1 H), 1.80 (pentet, 2 H), 0.97 (d, J = 6.6 Hz, 6 H), 0.90 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 144.0, 123.2, 121.8, 115.8, 112.6, 61.1, 42.1, 37.7, 32.9, 32.4, 27.9, 25.9, 22.7, 18.3, –5.2 ppm. IR (neat): $\tilde{\nu}$ = 3128.8, 2953.7, 2928.7, 2856.7, 1621.5, 1579.6, 1502.7, 1462.7, 1439.8, 1342.6, 1253.7, 1096.5, 1062.7, 1005.7, 939.7, 832.4, 772.4, 697.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{36}N_3O_2SSi$ $[M + H]^+$ 410.2297; found 410.2281.

General Procedure for NBS-Promoted Bromination Reactions: CCl_4, the methyl-substituted heterocycle (1 equiv.), AIBN (0.03 equiv.), and *N*-bromosuccinimide (1.1 equiv.) were added to a dry round-bottomed flask containing a stirrer bar under argon. The reaction mixture was heated at reflux overnight. After TLC and LCMS analysis showed full conversion, the mixture was cooled to room temperature. The insoluble solids were removed by filtration, and the filtrate was concentrated. The resulting crude oil was purified by flash chromatography (hexane/ethyl acetate, 9:1) to give the desired brominated products, which were analyzed by LCMS and ^1H NMR spectroscopy.

4-(Bromomethyl)-2-chloropyridine (10):[19] Dark oil (2.2 g, 21%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 5.1 Hz, 1 H), 7.34 (s, 1 H), 7.22 (d, J = 5.1 Hz, 1 H), 4.35 (s, 2 H) ppm.

5-(Bromomethyl)-2-chloropyridine (28):[20] Pale yellow solid (5.1 g, 62%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 7.72 (dd, J = 8.2, 2.6 Hz, 1 H), 7.35 (d, J = 8.2 Hz, 1 H), 4.46 (s, 2 H) ppm.

2-(Bromomethyl)-4-chloropyridine (29):[21] Buff solid (0.55 g, 76%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, J = 5.3 Hz, 1 H), 7.47 (s, 1 H), 7.24 (dd, J = 5.4, 2.0 Hz, 1 H), 4.52 (s, 2 H) ppm.

4-(Bromomethyl)-2-chloroquinoline (30):[22] White solid (3.47 g, 60%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.5 Hz, 2 H), 7.74 (t, J = 8.3 Hz, 1 H), 7.63 (t, J = 8.4 Hz, 1 H), 7.39 (s, 1 H), 4.74 (s, 2 H) ppm.

DBDMH-Mediated Bromination Procedure, 4-(Bromomethyl)-1-chloroisoquinoline (32): $CHCl_3$ (30 mL) and 1-chloro-4-methylisoquinoline (**31**; 0.501 g, 2.81 mmol) were added to a 100 mL dry round-bottomed flask containing a stirrer bar under argon. DBDMH (0.804 g, 2.81 mmol) and AIBN (0.03 equiv.) were then added to the mixture. The flask was fitted with a reflux condenser. The mixture was stirred at room temperature for 2 h, and then heated to 60 °C for 12 h. After this time, TLC and LCMS analysis showed full conversion. The mixture was cooled, filtered, and concentrated. The resulting crude oil was purified by flash chromatography (hexane/ethyl acetate, 9:1) to give compound **32** (0.58 g, 80%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, J = 8.5 Hz, 1 H), 8.37 (s, 1 H), 8.18 (d, J = 8.5 Hz, 1 H), 7.95 (t, J = 8.3 Hz, 1 H), 7.80 (t, J = 8.2 Hz, 1 H), 4.88 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 137.3, 134.2, 131.1, 129.1, 127.4, 126.8, 125.6, 120.7, 69.7 ppm. IR (neat): $\tilde{\nu}$ = 3002.8 (s), 2308.8 (s), 1956.8, 1648.7, 1626.7, 1613.7, 1578.7, 1554.7, 1503.7, 1441.7, 1370.7, 1338.7, 1309.6, 1288.7, 1274.7, 1253.7, 1207.6, 1137.7, 961.5, 913.7, 876.7, 779.6, 761.4, 710.6, 663.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{10}H_8NClBr$ $[M + H]^+$ 255.9529; found 255.9501.

4-Isobutyl-2-methyl-6-{[2-(trimethylsilyl)ethoxy]methyl}-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (19): Anhydrous DMF (40 mL) and NaH (0.293 g, 60%, 7.31 mmol) were added to a dry 100 mL round-bottomed flask under argon. The resulting solution was cooled to 0 °C. In a separate flask, **9** (1.021 g, 4.87 mmol) was dissolved in DMF (10 mL), and then this solution was added dropwise by cannula to the NaH/DMF mixture. The reaction mixture was stirred at 0 °C for 2 h, and then 2-(trimethylsilyl)ethoxymethyl chloride (1.067 g, 6.33 mmol) was added. After 6–10 h, LCMS analysis indicated that the reaction was complete. Saturated aq. NH_4Cl solution (10 mL) was added, and this mixture was extracted with ethyl acetate. The combined organic layers were washed with water (3× 25 mL), and brine (25 mL), dried with Na_2SO_4, and then concentrated. The crude solid was purified by flash chromatography (hexanes/ethyl acetate, 1:1) to give **19** (1.32 g, 82%) as a pale brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 2.0 Hz, 1 H), 7.13 (d, J = 2.0 Hz, 1 H), 5.41 (s, 2 H), 3.73 (s, 3 H), 3.48 (br. t, 2 H), 2.58 (d, J = 7.0 Hz, 2 H), 2.20–2.11 (septet, 1 H), 0.97 (d, J = 6.6 Hz, 6 H), 0.92 (br. t, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 145.6, 122.6, 120.6, 118.1, 116.3, 81.2, 68.4, 43.8, 39.3, 29.4, 24.1, 19.1, 0.0 ppm. IR (neat): $\tilde{\nu}$ = 3095.9, 2951.7, 2866.8, 1636.4, 1586.7, 1534.7, 1459.8, 1427.8, 1399.8, 1355.7, 1335.8, 1288.9, 1249.6, 1203.7, 1167.8, 1146.7,

1093.4, 1072.6, 1036.8, 1016.8, 997.8, 943.7, 928.7, 943.7, 928.7, 859.5, 833.4, 789.7, 748.6, 710.7, 697.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{29}N_3O_2Si$ $[M + H]^+$ 336.2101; found 336.2107.

4-Isobutyl-6-(4-methoxybenzyl)-2-methyl-2,6-dihydro-1*H*-pyrrolo-[3,4-*d*]pyridazin-1-one (20): A dry 100 mL round-bottomed flask was put under argon and cooled to 0 °C. Anhydrous DMF (50 mL), **9** (0.502 g, 2.44 mmol), K_2CO_3 (0.505 g, 3.65 mmol), *p*-methoxybenzyl chloride (0.575 g, 3.65 mmol), and tetrabutylammonium iodide (0.089 g, 0.243 mmol) were added. The reaction mixture was allowed to warm to room temperature over 12 h, after which time LCMS analysis indicated complete conversion. Saturated aq. NH_4Cl solution (10 mL) was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water (3 × 25 mL), and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude solid was purified using flash chromatography (hexanes/ethyl acetate, 1:1) to give **20** (0.69 g, 87%) as a pale brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 2.0 Hz, 1 H), 7.14 (d, J = 8.7 Hz, 2 H), 6.99 (d, J = 2.0 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 5.19 (s, 2 H), 3.82 (s, 3 H), 3.72 (s, 3 H), 2.54 (d, J = 7.0 Hz, 2 H), 2.17–2.07 (septet, 1 H), 0.97 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 159.8, 158.3, 143.9, 129.2, 127.6, 120.9, 119.4, 116.4, 115.2, 114.5, 55.4, 54.4, 42.4, 37.8, 27.9, 22.7 ppm. IR (neat): $\tilde{\nu}$ = 2955.8, 1634.7, 1581.8, 1535.9, 1515.8, 1464.8, 1347.8, 1306.9, 1285.9, 1243.7, 1209.8, 1178.8, 1151.8, 1075.8, 1041.7, 999.8, 971.9, 936.9, 831.7, 788.8, 755.8, 740.8, 695.8 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{23}N_3O_2$ $[M + H]^+$ 326.1864; found 326.1869.

General Procedure for Iodination: The protected pyrrole compound (1 equiv.), and I_2 (2 equiv.) in anhydrous THF were added to a clean dry flask containing a stirrer bar under argon. The mixture was cooled to –78 °C, and LDA (0.5 M solution in THF; 3 equiv.) was added dropwise over 10 min. The mixture kept at –78 °C for 4 h, and then it was warmed to room temperature over 15 h. MeOH (10 mL) was added, and the mixture was stirred for 30 min. Saturated aq. NH_4Cl solution (30 mL) was added, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water (3 × 25 mL), and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude solid was purified by flash chromatography to give the desired iodinated product.

7-Iodo-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (21): In this case, the Boc protecting group was found to be removed, giving compound **21** (0.627 g, 62%). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.76 (br. s, 1 H), 7.32 (s, 1 H), 3.74 (s, 3 H), 2.57 (d, J = 7.4 Hz, 2 H), 2.18–2.07 (septet, 1 H), 0.96 (d, J = 6.6 Hz, 6 H), 0.93 (obscured t, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 144.9, 123.2, 121.2, 120.4, 70.2, 68.3, 43.7, 39.2, 29.3, 24.1, 19.2, 0.0 ppm. IR (neat): $\tilde{\nu}$ = 2953.8, 1731.9, 1635.5, 1586.8, 1536.9, 1495.8, 1464.8, 1406.8, 1347.7, 1286.8, 1249.7, 1210.7, 1177.8, 1074.6, 1035.7, 1000.7, 973.8, 937.7, 915.8, 855.6, 833.3, 788.7, 758.6, 693.6, 663.7 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{11}H_{14}IN_3O$ $[M + H]^+$ 332.0264; found 332.0260.

7-Iodo-4-isobutyl-2-methyl-6-{[2-(trimethylsilyl)ethoxy]methyl}-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (22): Yield 0.728 g, 68%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H), 5.47 (s, 2 H), 3.69 (s, 3 H), 3.54 (br. t, 2 H), 2.53 (d, J = 7.0 Hz, 2 H), 2.16–2.06 (septet, 1 H), 0.97 (d, J = 6.6 Hz, 6 H), 0.92 (br. t, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 145.6, 122.6, 120.6, 118.1, 116.3, 81.2, 68.4, 43.8, 39.3, 29.4, 24.1, 19.1, 0.0 ppm. IR (neat): $\tilde{\nu}$ = 3095.9, 2951.7, 2866.8, 1636.4, 1586.7, 1534.7, 1459.8, 1427.8, 1399.8, 1355.7, 1335.8, 1288.9, 1249.6, 1203.7, 1167.8, 1146.7, 1093.4, 1072.6, 1036.8, 1016.8, 997.8, 943.7, 928.7, 943.7, 928.7, 859.5, 833.4, 789.7, 748.6, 710.7, 697.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{28}IN_3O_2Si$ $[M + H]^+$ 462.1072; found 462.1074.

7-Iodo-4-isobutyl-6-(4-methoxybenzyl)-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (23): Yield 0.451 g, 64%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1 H), 7.08 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 5.26 (s, 2 H), 3.81 (s, 3 H), 3.70 (s, 3 H), 2.49 (d, J = 7.0 Hz, 2 H), 2.13–2.03 (septet, 1 H), 0.95 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 157.6, 143.4, 128.8, 127.3, 121.8, 119.4, 118.7, 114.4, 55.3, 54.6, 42.2, 37.8, 27.8, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 2954.7, 2867.8, 1638.3, 1616.5, 1583.6, 1512.4, 1494.5, 1463.6, 1380.7, 1287.7, 1246.3, 1213.5, 1175.4, 1113.7, 1099.7, 1030.5, 997.6, 971.6, 881.8, 822.6, 759.5, 690.5 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{23}IN_3O_2$ $[M + H]^+$ 452.0833; found 452.0835.

General Procedure for the Alkylation of Compound 18: A dry 100 mL flask containing a stirrer bar was put under argon and cooled to 0 °C. Anhydrous degassed DMF (10 mL) and NaH (0.024 g, 0.585 mmol) were added, followed by a solution of **18** (0.200 g, 0.488 mmol) in degassed DMF (5 mL). The mixture was stirred for 2 h. A solution of 2-chloro-4-bromomethyl pyridine (**10**; 0.037 g, 0.150 mmol) in degassed anhydrous DMF (5 mL) was then added dropwise to the reaction mixture, and the resulting mixture was stirred overnight during which time it was allowed to warm room temperature. After this time, LCMS and TLC analysis indicated full conversion. NH_4Cl solution was added, and the mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude solid was then dissolved in a minimal amount of THF to which was added HCl (4.0 M in dioxane, 2 mL). After 2 h, the solvents were evaporated, and the crude material was purified by preparative HPLC using a gradient combination of (methanol/acetonitrile, 1:1) and (water with 1% TFA) to give the pure product.

6-[(2-Chloropyridin-4-yl)methyl]-7-[(3-hydroxypropyl)thio]-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (35): Pale brown oil (0.024 g, 70%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 7.33 (obscured d, 1 H), 7.15 (s, 1 H), 5.52 (s, 2 H), 3.67 (s, 3 H), 3.54 (t, J = 6.1 Hz, 2 H), 2.93 (d, J = 7.2 Hz, 2 H), 2.60 (d, J = 7.3 Hz, 2 H), 2.20–2.09 (m, 1 H), 1.65–1.58 (m, 2 H), 0.96 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 152.5, 150.3, 149.0, 143.6, 124.3, 121.8, 121.6, 119.9, 118.6, 117.0, 59.4, 49.8, 46.7, 41.9, 38.3, 35.3, 30.8, 29.7, 27.9, 22.7, 22.7, 14.1, 8.7 ppm. IR (neat): $\tilde{\nu}$ = 3422.9, 2955.8, 1726.8, 1630.7, 1594.7, 1552.8, 1491.8, 1466.7, 1388.7, 1348.7, 1241.5, 1222.5, 1158.5, 1124.7, 1087.7, 1063.7, 1028.3, 876.8, 832.8, 767.7, 757.8, 716.7, 696.7 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{26}N_4O_2ClS$ $[M + H]^+$ 421.1465; found 421.1454.

6-[(6-Chloropyridin-3-yl)methyl]-7-[(3-hydroxypropyl)thio]-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (36): Buff solid (0.016 g, 48%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 4.7 Hz, 1 H), 7.73 (s, 1 H), 7.12 (s, 1 H), 6.99 (d, J = 6.3 Hz, 1 H), 5.65 (s, 2 H), 3.94 (t, J = 6.1 Hz, 2 H), 3.74 (s, 3 H), 3.08 (obscured t, 2 H), 2.55 (d, J = 6.6 Hz, 2 H), 2.15–2.08 (m, 1 H), 1.83–1.77 (m, 2 H), 0.96 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 151.5, 148.4, 143.6, 137.4, 131.2, 124.7, 123.8, 121.5, 118.5, 116.7, 59.5, 48.2, 41.9, 38.2, 35.3, 30.9, 27.8, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 3401.8, 3092.9, 2953.7, 2868.8, 1724.9, 1632.4, 1586.6, 1564.7, 1537.8, 1490.6, 1460.5, 1383.6, 1346.5, 1333.5, 1285.7, 1245.7, 1206.6, 1164.7, 1133.7, 1101.5, 1060.6, 1022.5, 998.6, 968.7, 908.7, 851.7, 832.6, 801.7, 765.6, 691.5 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{26}N_4O_2ClS$ $[M + H]^+$ 421.1465; found 421.1452.

6-[(5-Chloropyridin-2-yl)methyl]-7-[(3-hydroxypropyl)thio]-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (37): Pale brown oil (0.020 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 6.1 Hz, 1 H), 7.29 (obscured d, 2 H), 6.93 (s, 1 H), 5.61 (s, 2 H), 4.08 (t, J = 5.8 Hz, 2 H), 3.74 (s, 3 H), 3.09 (t, J = 7.5 Hz, 2 H), 2.57 (d, J = 8.4 Hz, 2 H), 2.18–2.11 (m, 1 H), 1.85–1.78 (m, 2 H), 0.97 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 154.1, 148.7, 143.8, 136.9, 131.6, 122.2, 121.3, 118.4, 117.3, 59.5, 52.3, 41.9, 38.2, 35.2, 30.8, 27.8, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 3377.8, 2927.8, 2868.8, 1723.8, 1632.5, 1580.7, 1534.8, 1491.7, 1467.6, 1367.7, 1348.6, 1286.7, 1256.7, 1211.6, 1164.7, 1108.6, 1060.6, 1013.5, 915.7, 830.7, 768.6, 693.6 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{26}N_4O_2ClS$ $[M + H]^+$ 421.1465; found 421.1454.

6-[(2-Chloroquinolin-4-yl)methyl]-7-[(3-hydroxypropyl)thio]-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (38): White solid (0.021 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.1 Hz, 1 H), 7.98 (d, J = 9.8 Hz, 1 H), 7.85 (t, J = 7.2 Hz, 1 H), 7.70 (t, J = 9 Hz, 1 H), 7.18 (s, 1 H), 6.41 (s, 1 H), 6.01 (s, 2 H), 3.90 (t, J = 6.4 Hz, 2 H), 3.79 (s, 3 H), 3.15 (t, J = 5.1 Hz, 2 H), 2.58 (d, J = 3.8 Hz, 2 H), 2.18–2.11 (m, 1 H), 1.81–1.74 (m, 2 H), 0.97 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 153.9, 150.7, 148.6, 146.7, 134.1, 132.7, 130.8, 127.4, 126.9, 125.0, 124.7, 122.1, 121.6, 120.3, 62.3, 51.0, 44.9, 41.3, 38.4, 33.8, 30.8, 25.6 ppm. IR (neat): $\tilde{\nu}$ = 3387.9, 3093.9, 2955.9, 1633.8, 1587.8, 1565.9, 1492.9, 1418.9, 1348.8, 1391.8, 1257.9, 1212.9, 1150.8, 1100.8, 1073.9, 899.9, 852.9, 755.8, 697.8 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{28}N_4O_2ClS$ $[M + H]^+$ 471.1621; found 471.1604.

6-[(1-Chloroisoquinolin-4-yl)methyl]-7-[(3-hydroxypropyl)thio]-4-isobutyl-2-methyl-2,6-dihydro-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (39): Buff solid (0.015 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, J = 8.4 Hz, 1 H), 7.90 (s, 1 H), 7.84–7.81 (m, 2 H), 7.77–7.74 (obscured m, 1 H), 6.97 (s, 1 H), 5.89 (s, 2 H), 3.93 (t, J = 5.6 Hz, 2 H), 3.72 (s, 3 H), 3.18 (t, J = 6.4 Hz, 2 H), 2.43 (d, J = 7.4 Hz, 2 H), 2.04–1.97 (m, 1 H), 1.86–1.80 (m, 2 H), 0.97 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 146.7, 144.0, 138.2, 135.3, 132.0, 130.5, 132.6, 129.6, 128.6, 126.7, 125.4, 124.3, 121.4, 119.7, 49.7, 44.7, 41.2, 38.4, 33.8, 30.7, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 3387.9, 3093.9, 2955.9, 1633.8, 1587.8, 1565.9, 1492.9, 1418.9, 1348.8, 1391.8, 1257.9, 1212.9, 1150.8, 1100.8, 1073.9, 899.9, 852.9, 755.8, 697.8 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{28}N_4O_2ClS$ $[M + H]^+$ 471.1621; found 471.1303.

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[1] S. Dhup, R. K. Dadhich, P. E. Porporato, P. Sonveaux, *Curr. Pharm. Des.* **2012**, *18*, 1319–1330.
[2] M. Gerlinger, C. R. Santos, B. Spencer-Dene, P. Martinez, D. Endesfelder, R. A. Burrell, M. Vetter, M. Jiang, R. E. Saunders, G. Kelly, K. Dykema, N. Rioux-Leclercq, G. Stamp, J. J. Patard, J. Larkin, M. Howell, C. Swanton, *J. Pathol.* **2012**, *227*, 146–156.
[3] J. R. Doherty, C. Yang, K. E. N. Scott, M. D. Cameron, M. Fallahi, W. Li, M. A. Hall, A. L. Amelio, J. K. Mishra, F. Li, M. Tortosa, H. M. Genau, R. J. Rounbehler, Y. Lu, C. V. Dang, K. G. Kumar, A. A. Butler, T. D. Bannister, A. T. Hooper, K. Unsal-Kacmaz, W. R. Roush, J. L. Cleveland, *Cancer Res.* **2014**, *74*, 908–920.
[4] S. P. Mathupala, C. B. Colen, P. Parajuli, A. E. Sloan, *J. Bioenerg. Biomembr.* **2007**, *39*, 73–77.
[5] P. Vaupel, A. Mayer, *Cancer Metastasis Rev.* **2007**, *26*, 225–239.
[6] A phase I trial of AZD3965 in patients with advanced cancer. Retrieved November 18, 2014, from http://clinicaltrials.gov/show/NCT01791595.
[7] H. Pelicano, D. S. Martin, R. H. Xu, P. Huang, *Oncogene* **2006**, *25*, 4633–4646.
[8] J. Afonso, L. L. Santos, V. Miranda-Goncalves, A. Morais, T. Amaro, A. Longatto-Filho, F. Baltazar, *Mol Carcinog* **2014**, DOI: 10.1002/mc.22222.
[9] C. M. Murray, R. Hutchinson, J. R. Bantick, G. P. Belfield, A. D. Benjamin, D. Brazma, R. V. Bundick, I. D. Cook, R. I. Craggs, S. Edwards, L. R. Evans, R. Harrison, E. Holness, A. P. Jackson, C. G. Jackson, L. P. Kingston, M. W. D. Perry, A. R. J. Ross, P. A. Rugman, S. S. Sidhu, M. Sullivan, D. A. Taylor-Fishwick, P. C. Walker, Y. M. Whitehead, D. J. Wilkinson, A. Wright, D. K. Donald, *Nat. Chem. Biol.* **2005**, *1*, 371–376.
[10] S. D. Guile, J. R. Bantick, D. R. Cheshire, M. E. Cooper, A. M. Davis, D. K. Donald, R. Evans, C. Eyssade, D. D. Ferguson, S. Hill, R. Hutchinson, A. H. Ingall, L. P. Kingston, I. Martin, B. P. Martin, R. T. Mohammed, C. Murray, M. W. D. Perry, R. H. Reynolds, P. V. Thorne, D. J. Wilkinson, J. Withnall, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2260–2265.
[11] S. D. Guile, J. R. Bantick, M. E. Cooper, D. K. Donald, C. Eyssade, A. H. Ingall, R. J. Lewis, B. P. Martin, R. T. Mohammed, T. J. Potter, R. H. Reynolds, S. A. St-Gallay, A. D. Wright, *J. Med. Chem.* **2007**, *50*, 254–263.
[12] N. Draoui, O. Schicke, A. Fernandes, X. Drozak, F. Nahra, A. Dumont, J. Douxfils, E. Hermans, J.-M. Dogne, R. Corbau, A. Marchand, P. Chaltin, P. Sonveaux, O. Feron, O. Riant, *Bioorg. Med. Chem.* **2013**, *21*, 7107–7117.
[13] H. Wang, C. Yang, J. R. Doherty, W. R. Roush, J. L. Cleveland, T. D. Bannister, *J. Med. Chem.* **2014**, *57*, 7317–7324.
[14] J. Bantick, M. Cooper, P. Thorne, M. Perry (Astra Pharmaceuticals Ltd., UK; Astra AB), WO9929695A1, **1999**.
[15] R. N. Nair, T. D. Bannister, *J. Org. Chem.* **2014**, *79*, 1467–1472.
[16] S. Hayashi, M. Furukawa, J. Yamamoto, K. Niigata, *Chem. Pharm. Bull.* **1967**, *15*, 1188–1192.
[17] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.
[18] S. J. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158–16159.
[19] Z. Ferjancic, B. Quiclet-Sire, S. Z. Zard, *Synthesis* **2008**, 2996–3008.
[20] E. Altmann, R. Beerli, M. Gerspacher, J. Renaud, S. Weiler, L. Widler (Novartis Ag, Switzerland; Novartis Pharma GmbH), WO2004056365A2, **2004**.
[21] H. M. Armstrong, L. L. Chang, R. N. Guthikonda, W. K. Hagmann, L. S. Lin, S. K. Shah (Merck & Co., Inc., USA), WO2005027837A2, **2005**.
[22] G. N. Anilkumar, F. Bennett, T.-Y. Chan, K. X. Chen, M. Sannigrahi, F. Velazquez, S. Venkatraman, Q. Zeng, J. S. Duca, C. A. Lesburg, J. A. Kozlowski, F. G. Njoroge, S. B. Rosenblum, N.-Y. Shih (Schering Corporation, USA), WO2009032124A1, **2009**.
[23] R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 5291–5294.
[24] DBDMH has also been used in the monobromination of several methyl-substituted quinolines. The method was preferable to traditional NBS brominiation in terms of both yield and selectivity; C. Wang, T. D. Bannister, unpublished results.

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