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Practical Preparation of a 1,3,5-Trisubstituted Pyridazin-4(1*H*)-one Using Selective C_1 Unit Insertion and Cyclization

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Supporting Information

ABSTRACT: A novel and practical preparation of the selective phosphodiesterase 10A (PDE10A) inhibitor **1** having the core moiety of a 1,3,5-trisubstituted pyridazin-4(1*H*)-one has been achieved. The facile preparation of **1** in 42% overall yield involves the following key features: (1) the finding that filling the headspace of the reaction vessel with Ar gas and controlling the flow rate of the gas were found to be important to complete the substitution of an aryl iodide with pyrazole; (2) synthesis of a 3-acetyl-5-methoxy-substituted pyridazin-4(1*H*)-one via regioselective dimethylaminomethylenation of a diazo compound and simultaneous cyclization; and (3) regioselective ring formation of a 1,5-disubstituted pyrazole through reaction of a dimethylaminomethylene group with phenylhydrazine. In addition, an alternative synthesis of **1** via selective alkylation of 1-phenylpyrazole has been discovered.

KEYWORDS: *1,3,5-trisubstituted pyridazin-4(1H)-one, regioselective C_1 insertion, regioselective ring formation, PDE10A inhibitor*

INTRODUCTION

Phosphodiesterase 10A (PDE10A) is one of a superfamily of enzymes that is predominantly expressed in dopaminoreceptive medium spiny neurons of the striatum, and PDE10A inhibitors are expected to be therapeutic agents for neurological disorders. Compound **1** (TAK-063), showing selective inhibition of PDE10A, was identified by Takeda Pharmaceutical Company Limited (Scheme 1).[1,2]

The medicinal chemistry synthesis of **1** is shown in Scheme 1.[2a] Diazonium formation of aniline **2** with $NaNO_2$ followed by the reaction with β-keto ester **3** provided diazo compound **4**. Pyridazin-4(1*H*)-one ester **5** was obtained by C_1 insertion of **4** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (used as a solvent) and simultaneous cyclization.[3] The ester group of **5** was converted into the acetyl group in two steps to give pyridazin-4(1*H*)-one ketone **6**. After dimethylaminomethylenation of **6**, pyridazin-4(1*H*)-one pyrazole **8** was derived by cyclization with phenylhydrazine. Finally, the coupling reaction of **8** with pyrazole in the presence of Cu_2O and salicylaldoxime afforded **1**. In order to support the clinical and toxicological studies, a practical preparation of **1** on a scale of tens of kilograms was required.

RESULTS AND DISCUSSION

Our synthetic strategy to obtain **1** is described in Scheme 2. In medicinal synthesis, five steps were required to establish the 3-(1-phenyl-1*H*-pyrazol-5-yl)pyridazin-4(1*H*)-one moiety **D** from **A** in low yield (route A). To reduce the number of reaction steps needed to produce **1**, we envisioned two alternative routes. One was that 1-phenylpyrazole (**9**) would be converted to **1** through selective alkylation of the 5-lithiated pyrazole moiety (route B).[4] The other was that the cyclization of 3-(2-substituted hydrazinylidene)-1-methoxypentane-2,4-dione **B** with DMFDMA could be transformed to **C** in only one step, which would then lead to **D** (route C). This route was expected to require the discovery of two regioselective formations for the pyridazine and pyrazole rings.

Preparation of 1 from 9 (Route B). First, the transformation to **1** using **9** as the starting material (route B) was conducted as shown in Scheme 3. Reaction of the lithiated compound derived from **9** using 1.5 equiv of *n*-BuLi at −70 °C was carried out with epoxide **10** at 25 °C to synthesize regioselectively **11** as an oily compound in 57% yield, whereas the reaction did not proceed at −70 °C (Table 1, run 1).[4] Increasing the amount of *n*-BuLi to 4.0 equiv increased the yield to 77%, but **9** was incompletely consumed (run 2). When the lithiation was conducted at 0 or −30 °C, the yield decreased (runs 3 and 4). It was thought from these results that the lithiated compound was more stable at −70 °C than at −30 or 0 °C. Thus, both the lithiation and the alkylation were performed at −70 °C in the presence of an additive. When $BF_3{\cdot}OEt_2$ (1.5 equiv) was added for the alkylation, it was necessary to raise the reaction temperature to −20 °C for the reaction to proceed (run 5). On the other hand, the addition of hexamethylphosphoramide (HMPA) (2% v/w) or *t*-BuOK (1.5 equiv) allowed the reaction to proceed at −70 °C (runs 6 and 7). Interestingly, increasing the amounts of *n*-BuLi and *t*-BuOK improved the conversion of **9**, affording **11** in 90% isolated yield (run 8).[5] A variety of oxidation conditions were screened for **11**. In the case of $SO_3{\cdot}$pyridine as the oxidant, **11** was completely consumed, but ketone **12** was not detected.[6] Also, the system of Me-AZADO/NaOCl[7] and the combination of *N*-*tert*-butylphenylsulfenamide/*N*-chlorosuccinimide/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) did not produce **12**, and **11** mainly remained.[8] On the other hand, Swern oxidation

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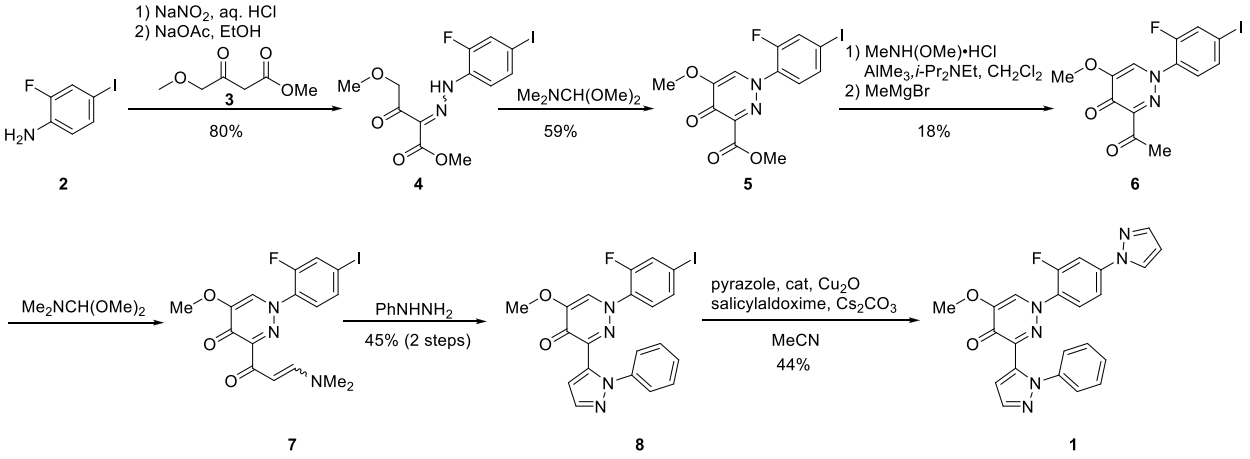
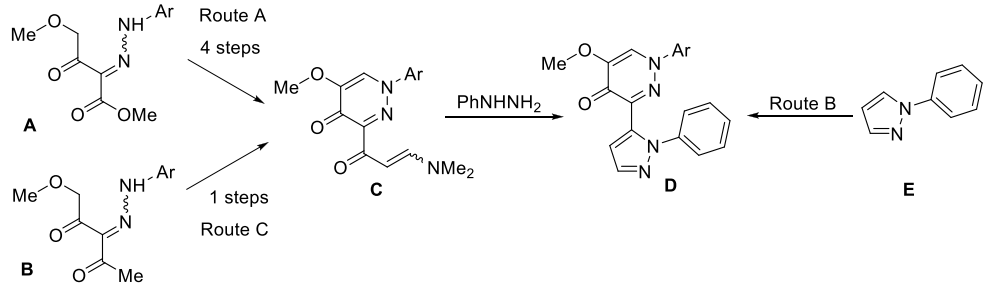
Scheme 1. Medicinal Chemistry Synthesis of 1



Scheme 2. Our Synthetic Strategy for 1



Scheme 3. Synthesis of 1 from 1-Phenylpyrazole (9)

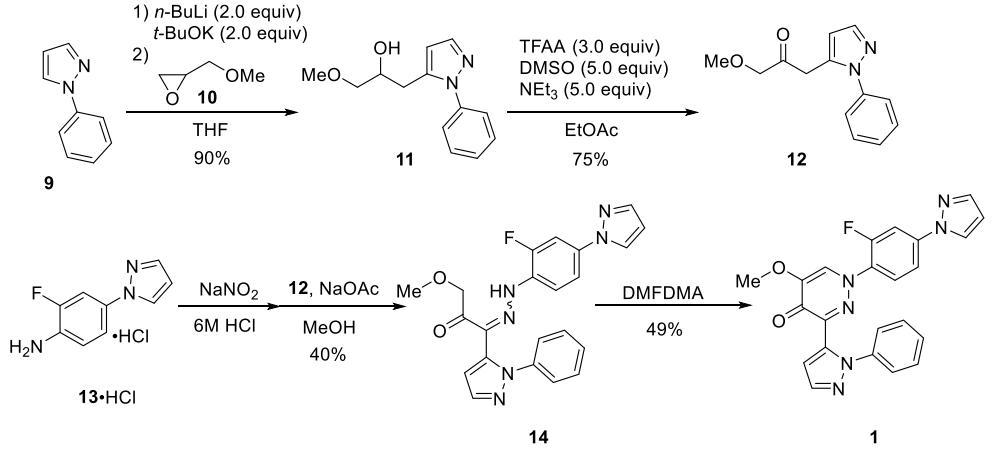


Table 1. Regioselective Alkylation of 9 with 10

run	equiv of *n*-BuLi	temp 1[a] (°C)	additive	temp 2[b] (°C)	ratio of products (%)[c]		isolated yield of **11** (%)
					9	**11**	
1	1.5	−70	–	25	55.0	39.7	57
2	4.0	−70	–	25	31.4	62.0	77
3	1.5	0	–	25	76.9	18.7	–
4	1.5	−30	–	25	65.2	29.6	–
5	1.5	−70	BF_3·OEt (1.5 equiv)	−20	58.2	12.9	–
6	1.5	−70	HMPA (2% v/w)	−70	66.6	28.6	–
7	1.5	−70	*t*-BuOK (1.5 equiv)	−70	51.1	40.5	–
8	2.0	−70	*t*-BuOK (2.0 equiv)	−70	6.9	82.5	90

[a]Temperature at lithiation. [b]Temperature at alkyation. [c]Liquid chromatography area percent (LCAP) of the reaction mixture.

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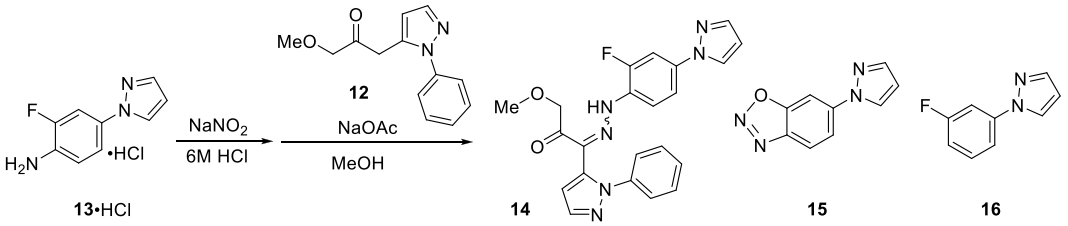
Table 2. Optimization of the Coupling Reaction of 12 with the Diazonium Salt Derived from 13·HCl



run	equiv of 13·HCl	base (equiv)	ratio of products (%)[a] 14	15	16	assay yield of 14[b] (%)
1	1.0	NaOAc (6.0)	59.2	11.9	9.7	51
2	1.2	NaOAc (7.2)	71.9	6.2	10.3	68
3	1.5	NaOAc (9.0)	58.5	4.5	13.0	64
4	1.2	NaOAc (3.0)	62.5	6.8	19.2	61
5	1.2	Na_2CO_3 (7.2)	34.1	9.9	26.7	25

[a]LCAP of the reaction mixture. [b]Determined by HPLC using an external standard.

Scheme 4. Alternative Route to 1 from Diketone 19

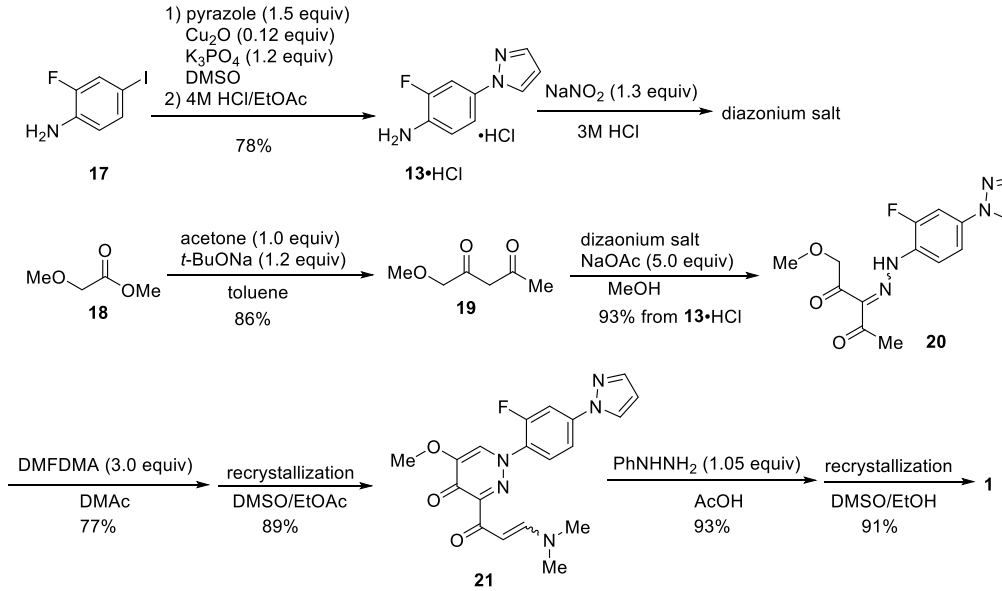


Table 3. Optimization of the Coupling Reaction of 17 with Pyrazole

run	solvent	base (equiv)	equiv of Cu_2O	time (h)	ratio of products (%)[a] 13	17	yield of 13·HCl (%)
1	DMF	Cs_2CO_3 (1.2)	0.3	9	89.6	2.2	–
2	DMSO	Cs_2CO_3 (1.2)	0.12	4	93.5	0.7	77
3	DMAc	Cs_2CO_3 (1.2)	0.12	6	93.5	1.5	–
4	DMSO	K_3PO_4 (1.2)	0.12	5	93.2	0.5	77
5	DMSO	K_2CO_3 (1.2)	0.12	6	79.8	12.4	–
6	DMSO	DBU (1.2)	0.12	6	59.3	34.9	–

[a]LCAP of the reaction mixture.

of **11** using trifluoroacetic anhydride (TFAA)/dimethyl sulfoxide (DMSO)/NEt_3 in EtOAc was carried out to give **12** as an oily product in 75% yield after chromatographic purification.[9]

The diazonium salt derived from 1.0 equiv of **13**·HCl (described below) using $NaNO_2$ was reacted with **12** in the presence of 6.0 equiv of NaOAc to give a complex mixture including **14** in 51% assay yield along with **15** and **16** as estimated by LC/MS (Table 2, run 1). While an increase in the amount of **13**·HCl to 1.2 equiv to consume **12** improved the yield to 68%, the use of 1.5 equiv of **13**·HCl did not increase the yield (runs 2 and 3). Although the amount of NaOAc was decreased to 3.0 equiv and Na_2CO_3 was used in order to avoid conversion of the F group into OH, the yield of **14** was not improved (runs 4 and 5). Compound **14** was purified by silica gel chromatography and reacted with 1.5 equiv of DMFDMA for 2 h at 80 °C. After completion of the reaction, water was added to the resulting reaction mixture to

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Table 4. Effect of the Headspace Volume on the Reaction Rate

run	mass of **17** used (g)	approximate headspace volume (L)	gas	time (h)	ratio of products (%)[a]		yield of **13**·HCl (%)
					13	**17**	
1	10	0.12	N_2 flow	5	93.8	0.3	–
2	10	0.92	N_2 flow	7	88.5	6.4	–
3	50	0.10	N_2 flow	4	92.8	0.6	78
4	50	2.6	N_2 flow	7	92.8	1.1	–
5	50	2.6	N_2 balloon	5	83.2	11.0	–
6	50	2.6	N_2 bubbling	4	94.0	0.5	76
7	50	2.6	Ar flow	5	92.9	0.9	76

[a]LCAP.

Table 5. Optimization of the Flow Rate of Ar Per Headspace Volume

run	mass of **17** used (g)	approximate headspace volume (L)	flow rate of Ar per headspace volume (mL min^{-1} L^{-1})	residual ratio of **17** (%)[a]				
				2 h	3 h	4 h	5 h	6 h
1	50	2.6	89	13.8	6.1	3.0	1.6	0.8
2	50	2.6	133	9.3	4.3	1.7	0.9	–
3	10	0.92	133	10.0	3.4	1.6	0.7	–
4	200	3.4	133	8.0	3.5	1.4	0.5	–
5	39500	100	133	–	–	–	2.5	1.0

[a]LCAP.

crystallize **1** in 49% yield. Thus, a four-step synthesis of **1** was discovered, but it was thought that route B would be difficult to apply for a large-scale preparation because three chromatographic purifications were required.

Preparation of 13·HCl. The preparation of **1** according to the planned route C was performed as shown in Scheme 4. Compound **17** was reacted with pyrazole (1.5 equiv), Cu_2O (0.3 equiv), and Cs_2CO_3 (1.2 equiv) in DMF at 100 °C for 9 h under a N_2 atmosphere to give **13** (Table 3, run 1).[10] When DMF was changed to DMSO or *N*,*N*-dimethylacetamide (DMAc), the reaction time was reduced to 4 or 6 h in the presence 0.12 equiv of Cu_2O (runs 2 and 3). While K_3PO_4 in DMSO gave **13** in 77% yield after 5 h, K_2CO_3 or DBU prolonged the reaction time (runs 4, 5, and 6). From these results, it was found that K_3PO_4 as the base and DMSO as the solvent were the best combination.

The coupling reaction of **17** with pyrazole under these reaction conditions showed that the reaction time differed depending on the reaction scale. As a result of investigation, it was found that the reaction time was longer for larger volumes of headspace, though the same amounts of **17**, pyrazole, Cu_2O, K_3PO_4, and DMSO were used under the same rate of N_2 flow (Table 4, runs 1 vs 2 and 3 vs 4). On the other hand, the reaction rate decreased remarkably when a N_2 balloon was used (run 5). Also, both bubbling of N_2 and an Ar flow improved the reaction rate to reduce the reaction time (runs 6 and 7). From these results, it was presumed that efficient replacement of the gas in the reaction vessel with an inert gas during the reaction accelerated the reaction rate. As a purpose-built facility would be required to apply the bubbling of N_2 in a large-scale preparation, the conditions under a flow of Ar were selected and optimized (Table 5). When the flow rate of Ar per headspace volume was set up as 89 mL min^{-1} L^{-1}, the reaction time for amidation was 6 h (run 1). Increasing the rate to 133mL min^{-1} L^{-1} reduced the reaction time to 5 h in the case of a different headspace volume and scale (runs 2–4). Thus, these conditions were thought to be the best for large-scale preparation. At the scale of 39.5 kg of **17**, the reaction was completed in 6 h under these conditions (Table 5, run 5). After the reaction, **13** was extracted with EtOAc followed by washing with an aqueous citric acid solution. Subsequently, the EtOAc extract was treated with zeolite to remove any tarlike products and then washed with both an aqueous NH_4OH solution and aqueous NH_4Cl solution. Then 4 M HCl/EtOAc containing the same amount of HCl as the assayed amount of **13** in the organic solution was added to crystallize **13**·HCl (99.8% purity, LCAP) in 78% yield (Scheme 4).

Preparation of 20. A solution of **18** (1.0 equiv) and acetone (1.3 equiv) was added dropwise to a suspension of *t*-BuONa (1.7 equiv) in tetrahydrofuran (THF) at room temperature, and the reaction mixture was stirred for 18 h to precipitate the sodium salt of **19**, which was collected by filtration in 57% yield. However, **19** was used as an aqueous solution in the reaction with the diazonium salt formed from **13** because the sodium salt showed high hygroscopicity and poor filterability. To enable efficient extraction into the aqueous layer, the reaction solvent was changed to toluene. After the reaction in toluene, aqueous HCl was added to the reaction mixture to adjust it to pH 10, and **19** was obtained in 57% assay yield. Alternatively, the reaction mixture was added to aqueous HCl followed by adjustment with aqueous NaOH to pH 10, which gave an assay yield of 65%. It was thought that **19** decomposed to byproducts under the aqueous strongly basic conditions. In addition, as a result of optimizing the amounts of the reagents, the reaction using acetone (1.0 equiv) and *t*-BuONa (1.2 equiv) provided **19** in 74% assay yield. The optimal conditions were successfully scaled up to the kilogram scale using 23.8 kg of **18** to afford a 10.5 % w/w aqueous solution of **19** in 86% assay yield. This solution was used in the next reaction without further purification. Separately, 27.0 kg of **13**·HCl was reacted with $NaNO_2$ in 3 M HCl for 1 h to give the diazonium salt, which was reacted with 1.44 equiv of **19** in the presence of NaOAc in MeOH, followed by filtration to give **20** (98.8% purity, LCAP) in 93% yield.

Preparation of 21. The reaction of **20** with 3.0 equiv of DMFDMA was carried out in DMAc as the solvent for 2 h at

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80 °C to provide the target product **21** regioselectively in 85% LCAP purity, and the undesired product **22** (Figure 1) was

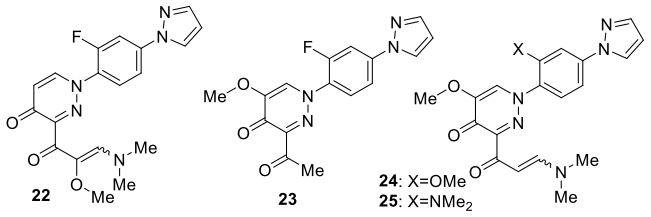


Figure 1. Estimated impurities in the ring formation to obtain **21**.

obtained in 5% LCAP purity. The ^{1}H NMR spectrum of **20** in DMSO-d_6 indicated that **20** existed as a 1:1 mixture of *E* and *Z* isomers. It was presumed that the reaction of **20** with DMFDMA proceeded preferentially at the position α to the carbonyl group possessing a methoxymethyl group because of the inductive effect of the methoxy group and that the resulting structure cyclized to form 3-acetyl-5-methoxypyridazin-4(1*H*)-one, followed by a second dimethylaminomethylenation of the acetyl group with DMFDMA, accompanying *E*/*Z* isomerization. The addition of EtOAc to the reaction mixture led to crystallization of **21**, and subsequent filtration afforded **21** (99.0% purity, LCAP) in 74% yield, resulting in the complete removal of **22** to the mother liquor, although **23**, **24**, and **25** (estimated by LC/MS) remained in the crystals of **21**. The reaction temperature was changed to 60 °C to suppress the production of byproducts while maintaining the conversion of **21**. On the basis of these experimental results, the reaction of 74.7 kg of **20** with DMFDMA was conducted, followed by addition of EtOAc, filtration of crystals, and washing with EtOAc to give crude **21** in 77% yield. Recrystallization of 68.7 kg of crude **21** from DMSO/EtOAc afforded 61.2 kg of pure **21** (99.6% purity, LCAP) in 89% yield. The remaining amounts of **23**, **24**, and **25** were all less than 0.05% (LCAP).

Preparation of 1. The formation of the pyrazole ring by reaction of **21** with phenylhydrazine was conducted to give **1** (Table 6).[11] When 1.06 equiv of phenylhydrazine was used, the reaction was completed in 18 h at room temperature in 19:1 EtOH/TFA to achieve the regioselective cyclization with an 89:1 ratio of **1** to the isomer **26**. Addition of water to the reaction mixture gave crystals of **1** in 85% yield (run 1). While **26** was removed in the mother liquor, most of **23** remained in the crystals. Increasing the amount of phenylhydrazine to 2.0 equiv reduced the reaction time and improved the regioselectivity, but **23** still remained after crystallization from EtOH/TFA/water (run 2). Although the use of AcOH as a solvent led to slightly increased amount of **26**, pure **1** was obtained because **26** and **23** were eliminated by crystallization from AcOH/H_2O (run 3). Thus, these conditions were applied to the cyclization reaction using 30.0 kg of **21** to give crude **1** in 93% yield, which was recrystallized from DMSO/EtOH to afford 28.4 kg of pure **1** (more than 99.9% purity, LCAP) in 91% yield. Also, the residual amount of phenylhydrazine, which is strictly controlled as a mutagenic impurity, was not more than 10 ppm.

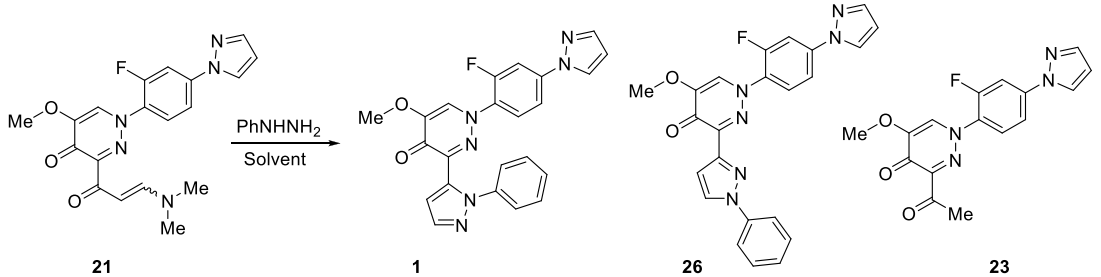
CONCLUSION

A practical synthesis of **1** by a novel route was developed. The diketone **19** obtained from acetone and methyl 2-methoxyacetate (**18**) provided an *E*/*Z* mixture of diazo compound **20** upon reaction with the diazonium salt derived from **13**. Dimethylaminomethylenation of **20** with DMFDMA proceeded preferentially at the methylene position followed by cyclization and subsequent C_1 insertion to afford **21**. Treatment of **21** with phenylhydrazine prompted a regioselective cyclization to form the 1,5-disubstituted pyrazole ring, affording **1**. These regioselective transformations led to the minimization of byproducts in each process and enabled facile isolation of the pure product in good yield without the need for cumbersome purification procedures such as column chromatography, and they were successfully scaled up to a multikilogram scale. In addition, we have discovered an alternative synthesis of **1** using a selective alkylation at the 5-position of 1-phenylpyrazole as the key reaction.

EXPERIMENTAL SECTION

General. All chemicals were purchased from commercial suppliers and used without further purification. Melting points were measured on a Stanford Research Systems OptiMelt MPA 100 instrument. NMR spectra were taken on a Bruker AVANCE 600 (600 MHz) NMR spectrometer with tetramethylsilane as the internal standard. High-resolution mass spectrometry (HRMS) data were obtained on a Shimadzu Prominence UFLC system with a Thermo Fisher

Table 6. Optimization of the Pyrazole Ring Formation by Reaction of 21 with Phenylhydrazine



run	equiv of $PhNHNH_2$	solvent (v/w)	conditions	ratio of products (%)[a] 1	26	23	yield of 1 (%)
1	1.06	EtOH/TFA (19:1)	rt, 18 h	89 (96.6)	1 (0.2)	3 (2.2)	85
2	2.0	EtOH/TFA (19:1)	rt, 3.5 h	92 (96.6)	1 (0.1)	1 (0.7)	94
3	1.05	AcOH (7.5)	rt, 3 h	94 (99.1)	3 (0.2)	1 (n.d.)	91

[a]LCAP of the reaction mixture. Values in parentheses are LCAPs of crystal **1**.

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LTQ Orbitrap Discovery system. IR spectra were recorded on a Thermo Electron FT-IR Nicolet 4700 (ATR) spectrometer. Mass spectral analyses were carried out at Takeda Analytical Research Laboratories, Ltd. LC/MS analyses were conducted using a Thermo Finnigan TSQ 7000 system.

The following HPLC conditions were used: (A) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous KH_2PO_4 (50:50) at a flow rate of 1.0 mL/min; column temperature of 30 °C. (B) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous KH_2PO_4 (pH 7.0 by 8 N NaOH) (70:30) at a flow rate of 1.0 mL/min; column temperature of 30 °C. (C) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous $AcONH_4$ (pH 4.6 by AcOH) (70:30) at a flow rate of 1.0 mL/min; column temperature of 30 °C. (D) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous $AcONH_4$ (65:35) at a flow rate of 0.9 mL/min; column temperatureof 25 °C. Purities were determined by HPLC and presented as the area percentage of the compound peak relative to the total area of all the peaks integrated.

1-Methoxy-3-(1-phenyl-1*H*-pyrazol-5-yl)propan-2-ol (11). To a solution of 1-phenylpyazole (**9**) (500 mg, 3.47 mmol) in THF (15 mL) at −70 °C were added *t*-BuOK (777 mg, 6.94 mmol) and *n*-BuLi (1.6 M in hexane, 4.34 mL, 6.94 mmol). The resulting mixture was stirred at −70 °C for 1 h. To the solution was added **10** (1.22 g, 13.88 mmol), and the resulting mixture was stirred at −70 °C for 1 h. The reaction was quenched by the addition of 1 M HCl (7 mL). The mixture was extracted with EtOAc (30 mL). The separated organic layer was concentrated in vacuo. The resulting residue was purified by silica gel to afford **11** (724 mg, 90%) as a yellow oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.67 (dd, J = 15.5, 8.3 Hz, 1H), 2.83 (dd, J = 15.5, 4.5 Hz, 1H), 3.15−3.24 (m, 5H), 3.79−3.85 (m, 1H), 4.97 (d, J = 5.3 Hz, 1H), 6.37 (d, J = 1.5 Hz, 1H), 7.42−7.47 (m, 1H), 7.47−7.54 (m, 4H), 7.58 (d, J = 1.5 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 30.4, 58.3, 68.3, 76.1, 106.4, 125.3, 127.7, 129.0, 139.5, 139.7, 140.7; IR (ATR) 419, 698, 770, 928, 1015, 1072, 1124, 1200, 1396, 1456, 1501, 1599, 2891, 3337 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_2$ 233.1290, found 233.1281.

1-Methoxy-3-(1-phenyl-1*H*-pyrazol-5-yl)propan-2-one (12). To a solution of DMSO (1.68 g, 21.6 mmol) and **11** (1.0 g, 4.31 mmol) in THF (20 mL) was added TFAA (1.80 mL, 12.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. To the mixture was added NEt_3 (2.18 g, 21.6 mmol), and the resulting mixture was stirred at rt for 1 h. The reaction was quenched by the addition of 10% aqueous Na_2CO_3. The mixture was extracted with EtOAc. The separated organic layer was concentrated in vacuo. The resulting residue was purified by silica gel to afford **12** (738.9 mg, 75%) as a yellow oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.18 (s, 3H), 3.97 (s, 2H), 4.04 (s, 2H), 6.37 (d, J = 1.9 Hz, 1H), 7.37−7.46 (m, 3H), 7.48−7.55 (m, 2H), 7.62 (d, J = 1.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 35.8, 58.3, 76.3, 108.0, 124.7, 127.8, 129.1, 135.6, 139.4, 139.5, 203.6; IR (ATR) 698, 770, 926, 1105, 1396, 1501, 1597, 1719, 1732, 2824, 2988 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_2$ 231.1134, found 231.1127.

1-(2-(2-Fluoro-4-(1*H*-pyrazol-1-yl)phenyl)-hydrazineylidene)-3-methoxy-1-(1-phenyl-1*H*-pyrazol-5-yl)propan-2-one (14). To a mixture of **13**·HCl (139 mg, 0.651 mmol) in 3 M HCl (1.12 mL) at 0 °C was added a solution of $NaNO_2$ (67.4 mg, 0.977 mmol) in water (0.2 mL). The reaction mixture was stirred for 2 h. The resulting mixture was added to a mixture of **12** (150 mg, 0.651 mmol) and NaOAc (320 mg, 3.91 mmol) in MeOH (1.4 mL). The reaction mixture was stirred for 1 h at 0 °C. After the resultant mixture was diluted with EtOAc, the organic layer was washed with water. The organic layer was concentrated in vacuo. The resulting residue was purified by silica gel to afford **14** (110 mg, 40%) as a yellow solid. Mp 122−125 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.12 (s, 3H), 4.65 (br s, 2H), 6.56 (s, 1H), 6.71−6.77 (m, 1H), 7.32−7.51 (m, 5H), 7.69−7.82 (m, 4H), 7.90 (d, J = 1.5 Hz, 1H), 8.51 (d, J = 2.6 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 58.2, 72.9, 106.6 (d, J = 24.2 Hz), 108.0, 109.4, 114.7 (d, J = 3.0 Hz), 118.23, 118.24, 122.9, 127.5, 127.8, 129.1, 130.3, 133.3, 135.4 (d, J = 9.1 Hz), 139.9, 140.4, 141.1, 151.1 (d, J = 244.6 Hz), 192.3; IR (ATR) 434, 478, 654, 694, 752, 768, 812, 928, 995, 1045, 1103, 1234, 1501, 1508, 1528, 1558, 1686, 3138, 3316 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{22}H_{20}FN_6O_2$ 419.1632, found 419.1624.

1-(2-Fluoro-4-(1*H*-pyrazol-1-yl)phenyl)-5-methoxy-3-(1-phenyl-1*H*-pyrazol-5-yl)pyridazin-4(1*H*)-one (1). To a mixture of **14** (100 mg, 0.239 mmol) in DMAc (1 mL) was added *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) (42.7 mg, 0.359 mmol) at rt. The mixture was stirred for 2 h at 75−85 °C. Water (1.5 mL) was added dropwise to the solution, and the resulting mixture was stirred at 25 °C. The resulting precipitates were collected by filtration, washed with water, and dried at 40 °C in vacuo to give **1** (50 mg, 49%).

2-Fluoro-4-(1*H*-pyrazol-1-yl)aniline Hydrochloride (13·HCl). DMSO (304.2 kg), **17** (39.5 kg, 166.7 mol), pyrazole (17.0 kg, 249.7 mol), and K_3PO_4 (46.2 kg, 92%, 200.0 mol) were charged to a reaction vessel at 20−50 °C under an argon atmosphere. The reaction vessel was evacuated and backfilled with argon, and this procedure was repeated. After Cu_2O (2.86 kg, 20.0 mol) and DMSO (43.5 kg) were added to the reaction vessel at 20−30 °C, the reaction vessel was again evacuated and backfilled with argon, and this procedure was repeated. The reaction mixture was stirred for 8 h at 95−105 °C under an argon flow (13.3 L/min). After the mixture was cooled to 20−30 °C and moved to a 2000 L vessel, water (390 kg) was added at 25−45 °C, and the mixture was stirred for 0.5 h at 35−45 °C. EtOAc (426.6 kg) and 10% w/w aqueous citric acid solution (409.9 kg) were added at 35−45 °C, and the mixture was stirred for 0.5 h at the same temperature. After the mixture was cooled to 20−30 °C, the two layers were separated. Zeolite (2.0 kg) was added to the organic solution. Insoluble matter was removed by filtration and rinsed with EtOAc (35.6 kg). The combined filtrate was washed with a mixture of 12% w/w aqueous NH_4OH solution (186.8 kg) and 20% w/w aqueous NH_4Cl solution (208.7 kg), a mixture of 6% w/w aqueous NH_4OH solution (191.5 kg) and 20% w/w aqueous NH_4Cl solution (208.7 kg), 10% w/w aqueous NH_4Cl solution (406.3 kg), and water (395.0 kg). The assay yield of **13** was 91.6% (152.7 mol). HCl/EtOAc (4 M, 34.0 kg, 156.7 mol) was added to the organic solution, and the mixture was stirred for 2.5 h at 20−30 °C. The resultant precipitate was collected by filtration, washed with EtOAc (142.2 kg), and dried in vacuo at 50 °C to give **13**·HCl (gross 27.9 kg, content 99.8%, net 27.9 kg, 99.8 area % (HPLC conditions A), 78% yield) as a bluish solid. Mp 215−218 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.57 (t, J = 2.1 Hz, 1H), 7.51 (t, J = 8.7 Hz, 1H),

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7.71 (dd, J = 8.5, 2.1 Hz, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.85 (dd, J = 11.9, 2.5 Hz, 1H), 8.53 (d, J = 2.6 Hz, 1H), 9.35 (br s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 106.5 (d, J = 24.2 Hz), 107.8, 114.7 (d, J = 3.0 Hz), 121.6, 125.2, 127.8, 135.2, 140.9, 153.1 (d, J = 243.1 Hz); IR (ATR) 461, 507, 600, 650, 762, 804, 878, 889, 914, 955, 1030, 1047, 1109, 1142, 1211, 1277, 1393, 1510, 1524, 1626, 2577, 2758, 2797, 2974 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_9H_9FN_3$ 178.0781, found 178.0775.

1-Methoxypentane-2,4-dione (19). Toluene (165.7 kg), and *t*-BuONa (26.4 kg, 274.3 mol) were charged to a reaction vessel at 20−30 °C under a nitrogen atmosphere. The suspension was stirred for 10 min at 20−30 °C and cooled to 0−10 °C. A mixture of **18** (23.8 kg, 228.6 mol) and acetone (13.3 kg, 228.6 mol) was added dropwise to the suspension at 0−10 °C, and the reaction mixture was stirred for 18 h at 20−30 °C and then cooled to 0−10 °C. HCl (2 M, 98.5 kg) was added, followed by adjustment with 2 M NaOH (70.0 kg) to pH 10.25−10.75. The two layers were separated, and 90% w/w AcOH (21.4 kg, 320.0 mol) was added to the aqueous solution to give a solution of **19** (gross 243.1 kg, content 10.5% w/w, net 25.5 kg, HPLC purity 93.7 area % (HPLC conditions B), 86% yield). This solution was used in the next reaction without further purification.

3-(2-(2-Fluoro-4-(1*H*-pyrazol-1-yl)phenyl)-hydrazineylidene)-1-methoxypentane-2,4-dione (20). HCl (3 M, 226.2 kg, 644.6 mol) and **13**·HCl (gross 27.1 kg; content 99.8% w/w, net 27.0 kg, 126.4 mol) were charged to a reaction vessel (vessel A) at 20−30 °C under a nitrogen atmosphere. A solution of $NaNO_2$ (11.3 kg, 164.3 mol) and water (27 kg) was added dropwise at 0−10 °C, and the solution was stirred for 1 h at the same temperature (solution A). A solution of **19** (gross 225.6 kg, content 10.5% w/w, net 23.7 kg, 182.1 mol), NaOAc (51.8 kg, 632.0 mol), and MeOH (405.3 kg) were charged to a reaction vessel at 20−30 °C under a nitrogen atmosphere, and the solution was stirred for 10 min at 20−30 °C and then cooled to 0−10 °C (vessel B). Solution A was added dropwise to vessel B at 0−10 °C. After MeOH (21.3 kg) was added, the mixture (1000 L) was stirred for 2 h at 20−30 °C. The mixture was separated into two volumes, 510 and 490 L. The resultant precipitate from the 510 L portion was collected by filtration, washed with water (91.8 kg) three times, and 50% v/v aqueous MeOH (24.6 kg) to give wet **20** (33.3 kg), and the resultant precipitate from the 490 L portion was collected by filtration, washed with water (88.2 kg) three times, and 50% v/v aqueous MeOH (23.7 kg) to give wet **20** (31.8 kg). The combined wet **20** was dried in vacuo at 50 °C to give **20** (37.5 kg, 98.8 area % (HPLC conditions A), 93% yield) as a yellowish solid comprising a 1:1 mixture of *E* and *Z* isomers. Mp 154−156 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.42 (s, 1.5H), 2.52 (s, 1.5H), 3.33 (s, 1.5H), 3.34 (s, 1.5H), 4.56 (s, 1H), 4.69 (s, 1H), 6.59 (s, 1H), 7.79 (s, 1H), 7.81−7.86 (m, 1H), 7.87−7.97 (m, 2H), 8.57 (d, J = 2.3 Hz, 1H), 14.51 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 26.1, 30.7, 58.41, 58.44, 73.3, 76.8, 106.2 (d, J = 24.2 Hz), 106.3 (d, J = 24.2 Hz), 108.3, 115.17 (d, J = 3.0 Hz), 115.22 (d, J = 3.0 Hz), 117.4, 117.6, 127.1 (d, J = 10.6 Hz), 127.2 (d, J = 9.1 Hz), 128.0, 133.0, 133.5, 137.22 (d, J = 9.1 Hz), 137.23 (d, J = 9.1 Hz), 141.5, 151.4 (d, J = 244.6 Hz), 151.5 (d, J = 244.6 Hz), 193.8, 196.3, 196.5, 197.0; IR (ATR) 449, 525, 600, 611, 654, 756, 789, 829, 876, 937, 949, 978, 1047, 1090, 1204, 1231, 1265, 1302, 1352, 1375, 1396, 1506, 1522, 1641, 1668, 3115 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{15}H_{16}FN_4O_3$ 319.1206, found 319.1197.

3-(3-(Dimethylamino)acryloyl)-1-(2-fluoro-4-(1*H*-pyrazol-1-yl)phenyl)-5-methoxypyridazin-4(1*H*)-one (21). $Me_2NCH(OMe)_2$ (83.9 kg, 704.1 mol), **20** (74.7 kg, 234.7 mol), and DMAc (189.6 kg) were charged to a reaction vessel at 20−30 °C under a nitrogen atmosphere. The mixture was stirred for 3 h at 57−67 °C and cooled to 45−55 °C. EtOAc (1008.5 kg) was added dropwise at 45−55 °C, and the mixture (1500 L) was stirred for 2 h at 20−30 °C. The mixture was separated into two volumes, 850 and 650 L. The resultant precipitate from the 850 L portion was collected by filtration and washed with EtOAc (114.3 kg) to give wet crude **14** (43.4 kg), and the resultant precipitate from the 650 L portion was collected by filtration and washed with EtOAc (87.4 kg) to give wet crude **21** (32.9 kg). The combined wet crude **21** was dried in vacuo at 50 °C to give crude **21** (68.8 kg, 77% yield) as a light-brownish solid. A suspension of crude **21** (68.7 kg) and DMSO (377.9 kg) was dissolved at 80−90 °C, and the solution was cooled to 45−55 °C and stirred for 0.5 h at the same temperature. EtOAc (618.3 kg) was added dropwise over 3 h at 45−55 °C, and the mixture was stirred for 0.5 h at the same temperature. After cooling to 20−30 °C, the mixture (1050 L) was stirred for 1.5 h at the same temperature. The mixture was separated into two volumes, 520 and 530 L. The resultant precipitate from the 520 L portion was collected by filtration and washed with EtOAc (91.9 kg) to give wet **21** (31.3 kg), and the resultant precipitate from the 530 L portion was collected by filtration and washed with EtOAc (93.6 kg) to give wet **21** (32.9 kg). The combined wet **21** was dried in vacuo at 50 °C to give **21** (61.2 kg, 99.6 area % (HPLC conditions C), 89% yield) as a light-yellowish solid. Mp 225−227 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.82 (s, 3H), 3.09 (s, 3H), 3.79 (s, 3H), 5.22 (br s, 1H), 6.64 (s, 1H), 7.38 (br s, 1H), 7.81−7.88 (m, 2H), 7.92 (dd, J = 8.7, 2.3 Hz, 1H), 8.05 (dd, J = 12.1, 2.3 Hz, 1H), 8.49 (s, 1H), 8.67 (d, J = 2.6 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 36.8, 44.3, 56.1, 106.6 (d, J = 25.7 Hz), 108.8, 114.2 (d, J = 3.0 Hz), 126.3, 128.2, 128.5, 129.0 (d, J = 10.6 Hz), 140.6 (d, J = 10.6 Hz), 142.0, 154.4, 155.1 (d, J = 250.7 Hz), 161.7; IR (ATR) 436, 457, 513, 606, 629, 652, 685, 758, 814, 854, 864, 910, 966, 1028, 1042, 1063, 1117, 1202, 1321, 1364, 1439, 1514, 1568, 1597, 3123 cm^{-1}; HRMS (ESI) [M + H]$^+$ calcd for $C_{19}H_{19}FN_5O_3$ 384.1472, found 384.1460.

1-(2-Fluoro-4-(1*H*-pyrazol-1-yl)phenyl)-5-methoxy-3-(1-phenyl-1*H*-pyrazol-5-yl)pyridazin-4(1*H*)-one (1). AcOH (225 L) and **21** (30.0 kg, 78.2 mol) were charged to a reaction vessel at 20−30 °C under a nitrogen atmosphere, and the mixture was dissolved at the same temperature. Phenylhydrazine (8.88 kg, 82.1 mol) was added at 20−30 °C, and the mixture was stirred for 4.6 h at 20−30 °C. HCl (1 M, 750 mL) was added to the reaction mixture kept at 20−30 °C, and the mixture was allowed to stand overnight and then stirred for 1 h at 20−30 °C. The resultant precipitate was collected by filtration, washed with a solution of AcOH (21 L) and water (39 L) and then with EtOH (150 L), and dried in vacuo at 50 °C to give crude **1** (31.2 kg, 93% yield) as a light-yellowish solid. DMSO (280 L) and crude **1** (31.2 kg) were charged to a reaction vessel at 20−30 °C under a nitrogen atmosphere, and the mixture was dissolved at 67−68 °C. The solution was filtered with a microfiltration membrane filter and rinsed with DMSO (31 L). To the combined filtrate was added EtOH (315 L) dropwise at 60−70 °C. After cooling to 20−30

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°C, the mixture was stirred for 1 h at the same temperature. After cooling to 0−10 °C, the mixture was stirred for 1 h at the same temperature. The resultant precipitate was collected by filtration, washed with EtOH (156 L), and dried in vacuo at 50 °C to give **1** (28.4 kg, >99.9 area % (HPLC conditions D), 91% yield) as a light-yellowish solid. Mp 215−217 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.79 (s, 3H), 6.63 (s, 1H), 7.00 (d, J = 1.9 Hz, 1H), 7.18 (t, J = 8.5 Hz, 1H), 7.33−7.46 (m, 5H), 7.75 (dd, J = 8.7, 2.3 Hz, 1H), 7.80 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 1.5 Hz, 1H), 7.99 (d, J = 12.3, 2.5 Hz, 1H), 8.53 (d, J = 1.5 Hz, 1H), 8.66 (d, J = 2.6 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 56.2, 106.5 (d, J = 24.2 Hz), 108.8, 110.5, 113.9 (d, J = 3.0 Hz), 124.4, 126.0 (d, J = 3.0 Hz), 127.3, 127.5, 128.5, 128.7 (d, J = 10.6 Hz), 128.9, 134.8, 139.6, 140.6 (d, J = 9.1 Hz), 140.8, 142.0, 144.9, 149.7, 154.6 (d, J = 250.7 Hz), 161.4; IR (ATR) 447, 525, 546, 602, 652, 694, 764, 802, 912, 928, 951, 989, 1055, 1229, 1391, 1452, 1497, 1508, 1518, 1522, 1597, 1624, 3055, 3115 cm^{-1}; HRMS (ESI) $[M + H]^+$ calcd for $C_{23}H_{18}FN_6O_2$ 429.1475, found 429.1465.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00394.

^{1}H and ^{13}C NMR analyses (PDF)

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Notes

The authors declare no competing financial interest.

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