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Pilot-Scale Synthesis of a Novel Non-Xanthine Adenosine A_1 Receptor Antagonist. 1,3-Dipolar Cycloaddition of Pyridine *N*-Imine to an Acetylene

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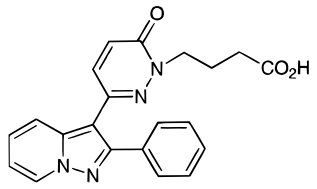
Abstract:

Adenosine A_1 receptor antagonist, FK838, has been synthesized in 44% overall yield by a five-step sequence which is operationally straightforward and readily carried out on a large scale. Investigations into the 1,3-dipolar cycloaddition process that afforded a pyrazolo[1,5-*a*]pyridine derivative are also described. Process improvements and optimization of each step permitted elimination of column chromatography, resulting in a practical and cost-effective synthesis of FK838. These methods were successfully scaled up in a pharmaceutical pilot plant to give bulk drug used in clinical trials.

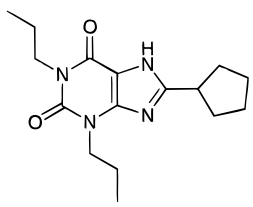
Introduction

In recent years the pharmacological usefulness of adenosine A_1 receptor antagonists for the regulation of renal function have been described.[1] The discovery of DPCPX, **2**,[2] and Bay n 1468, **3**,[3] which have renal vasodilator effects, prompted us to turn attention to the discovery of new types of nonxanthine adenosine A_1 antagonists and led to the novel and selective antagonist FK838 (3-[2-phenylpyrazolo[1,5-*a*]pyridin-3-yl]-1(6*H*)-pyridazine-6-one butyric acid), **1**, which has potent diuretic and anti-hypertensive effects, useful for the regulation of renal function (see Figure 1 for structures).[4]

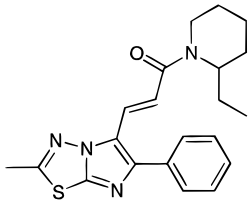
For complete biological evaluation, we required large quantities of compound **1** for in vitro and in vivo study of efficacy and pharmacokinetics. Akahane *et al.* prepared **7** via the synthetic route shown in Scheme 1.[5,6] Despite the usefulness of this preparative method on a small scale, a number of shortcomings remained when viewed from the standpoint of large-scale manufacturability. For example, decarboxylation of the ester (**6**) required severe conditions such as long reaction times (16 h) at 80 °C in polyphosphoric acid[7] or requiring highly corrosive 47% HBr.[5] As a result,



FK838, **1**



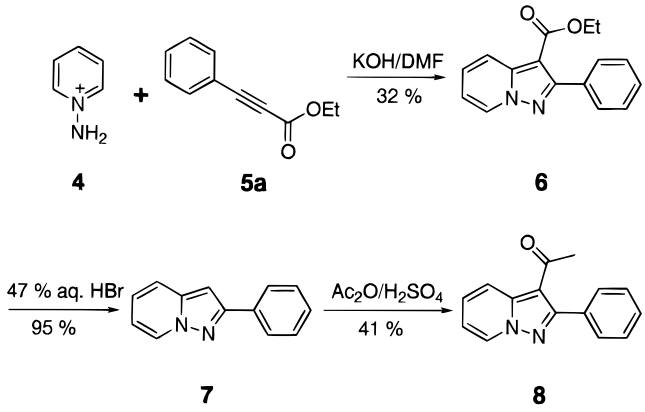
DPCPX, **2**



Bay n 1468, **3**

Figure 1. **Structure of adenosine A_1 receptor antagonists**

Scheme 1. **Original route to 8 (route A)**



despite many efforts, the obtained **7** was contaminated with several undesired byproducts that were difficult to remove, except by chromatographic purification. The low yield (32%) in the 1,3-dipolar cycloaddition was also problematic and not compatible with inexpensive synthesis. In addition, decarboxylation and subsequent re-acylation in a synthetic process leads to a prolonged and inherently inefficient procedure. To develop a more inexpensive, direct, and practical synthesis of the pyrazolopyridine (**8**) amenable to a large scale, we investigated the 1,3-dipolar cycloaddition of *N*-imine to acetynyl ketones. Herein, we report the results of these endeavours and the optimization of the methods that afforded **1** in large quantities.

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Scheme 2. **New synthetic route to 8 (route B)**

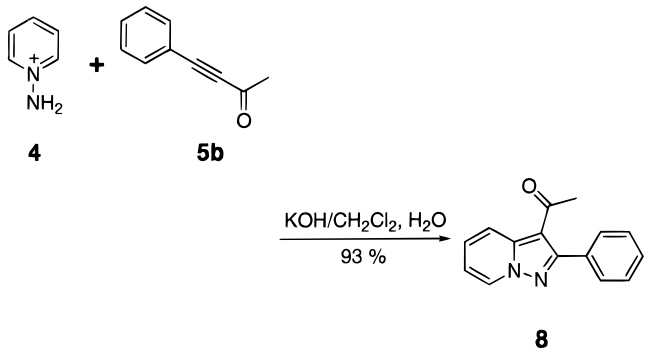

Table 1. **1.3-Dipolar cycloaddition of the *N*-imine (4) with the alkyne (5b)**

entry	equiv of **4**	solvent	additive (equiv)	yield (%)[a]
1[b]	1.5	DMSO	none	67
2[c]	1.7	DMSO	none	83
3[d]	1.2	CH_2Cl_2/H_2O[e]	none	62
4[d]	1.7	CH_2Cl_2/H_2O[e]	$BnEt_3NCl$ (0.1)	84
5[d]	2.0	CH_2Cl_2/H_2O[e]	$BnEt_3NCl$ (0.1)	96
6[d]	2.0	CH_2Cl_2/H_2O[e]	none	98

[a] Yield was determined by quantitative HPLC. [b] In the presence of granulated KOH (1.8 equiv). [c] In the presence of granulated KOH (0.5 equiv) and granulated K_2CO_3 (1.5 equiv). [d] In the presence of KOH (2.5 equiv). [e] Volume ratio of CH_2Cl_2/H_2O = 1:1.

Results and Discussion

The alkyne (**5b**) can be purchased from the Aldrich Chemical Co.; however, the required quantity (>100 kg) was so large that it was synthesized as described earlier.[8] We investigated 1,3-dipolar cycloaddition of the *N*-imine (**4**) with the alkyne (**5b**) with a view to developing a simple preparation of the pyrazolopyridine (**8**) according to the methods reported by Anderson (Scheme 2).[7] In early experiments, the yield was low, but further investigations revealed the characteristic features of this reaction. According to our results, even using excess amounts of the *N*-imine (**4**), the alkyne (**5b**) remained, along with several byproducts, and the amount of the *N*-imine (**4**) was crucial in securing high yields (Table 1). Concerning the mechanism of the 1,3-dipolar cycloaddition of *N*-imine to acetylenes, it is not well-known, but it has been pointed out by Huisgen that there must be an oxidative step.[9] However, even without oxidizing agent, only the oxidized product the pyrazolopyridine (**8**) could be obtained. Krischke reported that acetylenes might play a role as an oxidizing agent,[10] but this hypothesis goes against our experimental results. In effect, complete consumption of the alkyne (**5b**) required excess amounts of the *N*-imine (**4**) to afford the pyrazolopyridine (**8**) quantitatively. To optimize the reaction conditions, we investigated in greater detail the amount of the *N*-imine (**4**) required to allow complete starting material consumption, and this proved to be 2 molar equivalents relative to the alkyne (**5b**). Furthermore, as shown in Table 1, the yield of the pyrazolopyridine (**8**) was about half the molar equivalent of the *N*-imine (**4**), unrelated to the reaction system. The reason 2 molar equivalents of the *N*-imine (**4**) were required is not known at this point, but our best speculation is that the excess *N*-imine (**4**) played the role of oxidizing agent, leading to *N*-amino dihydropyridines, which are presumably so unstable that they readily decomposed to byproducts.

Table 2. **Effect of solvents on cycloaddition of the *N*-imine (4) with the alkyne (5b)[a]**

solvent	equiv of KOH	equiv of **4**	yield (%)[b]
CH_2Cl_2	2.5	2.0	98
CH_2Cl_2	3.6	2.9	100
PhMe	3.6	2.9	83
THF	3.6	2.9	0
isopropyl ether	3.6	2.9	0
AcOEt	3.6	2.9	5
$PhCH_2OH$	3.6	2.9	79
PhCl	3.6	2.9	97
MIBK	3.6	2.9	100
MIBK	2.5	2.0	96
MEK	2.5	2.0	97

[a] Reactions were conducted in a mixture of organic solvent and water (1:1) at room temperature. [b] Yield was determined by quantitative HPLC.

Despite these excellent results, traces of byproducts made the purification procedure tedious. In effect, the pyrazolopyridine (**8**) could not be purified to meet acceptable limits of purity (>98%) except using column chromatography, which required large quantities of solvent. Since it was found that the presumed *N*-amino dihydropyridines (the likely byproducts) were soluble in water and the desired product was selectively extracted in organic solvents, we attempted this reaction in a two-phase solvent system. Several solvents were examined for this reaction, and the results are summarized in Table 2. In toluene or benzyl alcohol, the reaction did not proceed to completion, and the reactions in THF, isopropyl ether, or ethyl acetate proceeded sluggishly. Chlorobenzene gave a good result in terms of yield, but also resulted in a dark colored product. The most favorable results were obtained by using methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), and methylene chloride. From the standpoint of the isolation of the pyrazolopyridine (**8**) on a large scale, methylene chloride was selected. In effect, the pyrazolopyridine (**8**) was allowed to selectively precipitate from 2-propanol (bp 82 °C), with which methylene chloride (bp 39 °C) was readily exchanged by distillation. On the other hand, MEK (bp 79 °C) or MIBK (bp 116 °C) required tedious solvent exchange procedures.

At first, we envisaged that a phase-transfer catalyst would be required to accelerate the reaction to afford the pyrazolopyridine (**8**) in high yield. However, there were no differences in reaction speeds or yields, irrespective of the presence of phase-transfer catalyst. We speculated that the unexpected high reaction speed was due to the high reactivity of the *N*-imine (**4**) or that the *N*-imine (**4**) was dimerized,[11] which then allowed a smooth partition into the organic phase (Scheme 3). As a result of these findings and adoption of a

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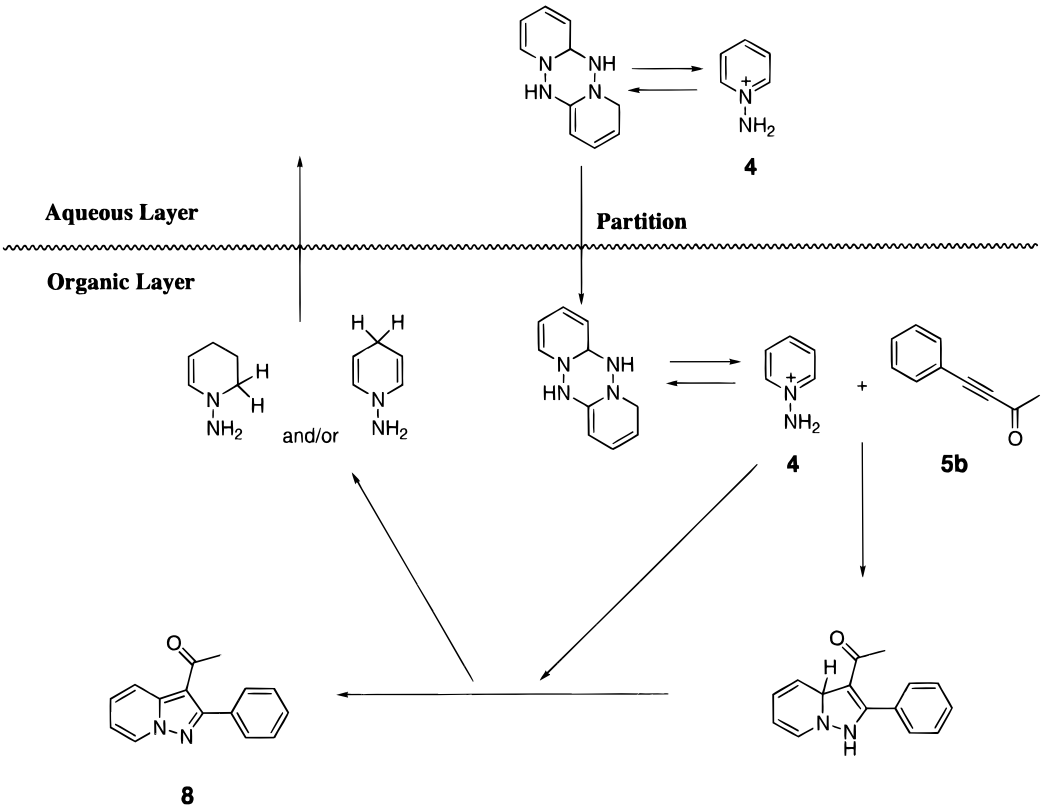
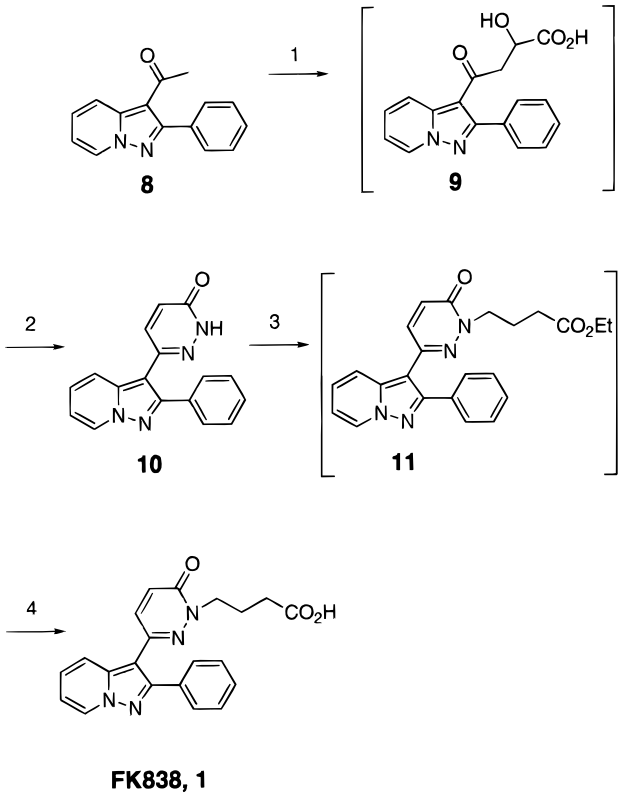
Scheme 3. **Mechanism of 1,3-dipolar cycloaddition**



Scheme 4. **Synthetic route to 1 from 8**[a]



[a] Reagents and conditions: 1. $HCOCO_2H \cdot 2H_2O$/AcOH, DME, AcOEt; 2. $NH_2NH_2 \cdot H_2O$/DMAc; 3. $Br(CH_2)_3CO_2Et/[C_6H_5CH_2N(C_2H_5)_3]Cl$, DME, MeOH; 4. $NaOH/H_2O$.

two-phase system, the reaction allowed complete consumption of the alkyne (**5b**), and simple exchange of methylene chloride in the system for 2-propanol led to the pyrazolopyridine (**8**) in excellent yields and purity.

Table 3. **Effect of additives on Aldol condensation of the pyrazolopyridine (8) with glyoxalic acid**[a]

entry	equiv of $HCOCO_2H$	additive (equiv)	time (h)	yield (%)[b]
1	2.0	none	16	56
2	3.8	none	3.5	45
3	2.0	AcOH (1.0)	6	65
4	2.0	AcOH (3.0)	8	59
5	2.0	HCO_2H (1.0)	9	52
6	2.0	$CH_2(CO_2H)_2$ (1.0)	6	46
7	2.0	$(CO_2H)_2$ (1.0)	3	50
8	2.0	$CH_3CH_2CO_2H$ (1.0)	7	45
9	2.0	$PhCO_2H$ (1.0)	3	49
10	2.0	citric acid (1.0)	4	54

[a] Reactions were conducted in 1,2-dimethoxyethane at 90−95 °C. [b] Yield was determined by HPLC.

Several complications were foreseen in direct scale-up of the initial methods used in the next step: the Aldol condensation reaction of the pyrazolopyridine (**8**) with glyoxalic acid (Scheme 4). On a laboratory scale, the reaction was conducted in the presence of 2.0 equiv of glyoxalic acid over 16 h at 90−95 °C to afford **9** in 56% yield. To improve productivity and shorten the reaction time, our program began by investigating the optimized amount of glyoxalic acid. The results are summarized in Table 3. Excess use of glyoxalic acid led to enhancement of not only the reaction speed but also decomposition of products, resulting in inferior yield (Table 3, entry 2). Next, we investigated the effect of various acid catalysts. As shown in Table 3, reaction proceeded in

Table 4. **Effect of additives on alkylation of the pyridazone (10)[a]**

entry	solvent	additive (equiv)	yield (%)[b]
1[c]	DMF	none	91
2	DME	Triton B (1.1)	89
3[d]	DME/EtOH	^{n}Bu$_4$NBr (0.1)	93
4[e]	DME/MeOH	^{n}Bu$_4$NBr (0.1)	94
5[e]	DME/MeOH	BnEt$_3$NCl (0.1)	94

[a] Reactions were conducted at 35−45 °C. [b] Isolated yield of **1**. [c] In the presence of NaH (1.3 equiv). [d] In the presence of granulated KOH (1.3 equiv) and granulated K_2CO_3 (1.3 equiv). [e] In the presence of granulated K_2CO_3 (2.0 equiv).

good yield and was accelerated by one molar equivalent of acid. The most favorable result was obtained using acetic acid (Table 3, entry 3). In another approach, ethyl glyoxalate in the presence of acid catalyst was examined, since the glyoxalic acid used in our system contained 1 molar equivalent of water, which may have a detrimental influence. Slight improvement in the yield (5−10%) was noted, but to our disappointment, no desired product was obtained in the subsequent step. The nature of this side reaction was not examined, but the possibility that coupling of hydrazine with the ester moiety before cyclization could occur appeared to be most likely.

Despite establishing optimized reaction conditions as described above, further problems were encountered during workup procedures. The reaction involved several byproducts with about 20% of the unreacted pyrazolopyridine (**8**), and tedious purification procedures were required to meet acceptable limits of purity. During extensive investigation, it was found that only starting material the pyrazolopyridine (**8**) dissolved in the organic phase upon extraction of the reaction mixture at pH = 7.0. In effect, after separation of the layers, the organic layer was concentrated and treated with 2-propanol to afford the pyrazolopyridine (**8**) of the same quality (98% chemical purity) as the starting material. Adoption of this method allowed recovery of about 16% of the unreacted pyrazolopyridine (**8**), which could be directly reused in this step. To the aqueous layer was subsequently added ethyl acetate, followed by adjusting the pH to 2.0−2.2, and only **9** was selectively extracted in the organic layer. The organic layer was then successively exchanged for *N*,*N*-dimethylacetamide (DMA) by distillation, followed by addition of 80% hydrazine monohydrate in water. The subsequent reaction then proceeded smoothly at 105−110 °C to afford the pyridazone (**10**) in high quality after addition of water and filtration.

In early studies on a laboratory scale, the pyridazone (**10**) could be effectively coupled with ethyl 4-bromo-*n*-butyrate using NaH in DMF (Table 4, entry 1). However, the known instability of NaH−DMF mixtures precluded any development of a large scale process.[12] In the course of further study, it was found that Triton B led to the product cleanly in excellent yield (Table 4, entry 2). Since use of stoichiometric amounts of Triton B was not feasible economically, it was necessary to investigate alternative systems. Whilst the reaction proceeded sluggishly without additives, good yields were obtained by addition of MeOH in the presence of granulated K_2CO_3 and a catalytic amount of ^{n}Bu$_4$NBr or BnEt$_3$NCl. Thus, the final method used a mixture of DME and MeOH in the presence of BnEt$_3$NCl and was suitable for large-scale synthesis after considering economics and chemical hazard issues, especially compared to Triton B or NaH−DMF mixtures.

The final ester hydrolysis was smoothly conducted simply by addition of NaOH in water without isolation of the precursor ester (**11**). After reaction completion, addition of water allowed extraction of **1** into the aqueous layer. By this sequence, byproducts were selectively removed in the organic layer. To the separated aqueous layer was carefully added 17.5% hydrochloric acid (caution! evolution of carbon dioxide) to adjust the pH to 0.5−1.0. The resulting precipitate was then filtered and dried under reduced pressure to afford crude **1** as a yellowish solid. Purified **1** was obtained by treatment with activated carbon and recrystallization from a mixture of 2-propanol and water.

Conclusions

In this paper, we have a described a new, concise, and efficient synthesis of the novel non-xanthine adenosine A_1 receptor antagonist FK838 (**1**). Investigation of 1,3-dipolar cycloadditions of a pyridine *N*-imine to an acetylene, in a two phase system, allowed smooth isolation of the pyrazolopyridine (**8**) in remarkably high yield and quality compared to published procedures. It is worth emphasizing that process improvement efforts focused on safe and optimized reaction conditions for each step with a view to identifying a cost-effective production system. The described methods were successfully scaled up in a pilot plant to afford over 200 kg of FK838 (**1**) suitable for pharmaceutical and toxicological evaluation.

Experimental Section

General Procedures. Pure grade *N*-aminopyridinum iodide salt was commercially available from Ube Industry Co. 4-Phenyl-3-butyne-2-one (**5b**) was prepared by our reported method.[8] All other chemicals were obtained from the usual commercial suppliers. IR spectra were recorded on a HORIBA FT-210 spectrometer. NMR spectra were measured on a Bruker AC200P (^{1}H, 200 MHz). Chemical shifts are given in parts per million (ppm), and tetramethylsilane was used as the internal standard. Mass spectra were measured on a Hitachi Model M-80 mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyzer. HPLC analyses were performed using a YMC GEL ODS 120 Å S-7 column and a MeOH/water phase. The water component was adjusted with citric acid to pH = 2.5. Purity of each obtained product was determined by comparison with purified authentic samples using quantitative HPLC. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected.

1-Acetyl-2-phenylpyrazolo[1,5-*a*]pyridine (8). To a mixture of 4-phenyl-3-butyn-2-one (**5b**) (74.0 kg, 513 mol)

(12) Laird, T. *Chem. Ind.* **1986**, *17*, 134.

in methylene chloride (740 L) and KOH (72.0 kg, 1283 mol) in water (740 L) was added *N*-aminopyridinum iodide (**4**) (227.8 kg, 1026 mol) with stirring at 5−25 °C. After completion of addition, the resulting mixture was further stirred at 15−25 °C for 1 h, the organic layer was separated, and the aqueous layer was re-extracted with methylene chloride (370 L). The organic layers were combined and washed with water (740 L), concentrated to ∼220 L under reduced pressure, treated with 2-propanol (740 L), and again concentrated to ∼590 L under ambient conditions. To the residue was added 2-propanol (222 L), and the solution was concentrated again to ∼590 L and then treated with water (592 L), followed by heating to 50 °C in order to dissolve the precipitate. To this solution was added water (666 L), maintaining the temperature at 45−50 °C for 30 min, and stirring was then continued at ambient temperature, followed by cooling to 5 °C for 1 h. The resulting precipitate was collected and washed with a mixture of water (259 L) and 2-propanol (111 L). Drying under reduced pressure afforded 1-acetyl-2-phenylpyrazolo[1,5-*a*]pyridine (**8**) (113.1 kg, 93% yield) of 99% purity as a yellowish solid: mp 84−85 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H), 7.03 (dt, 1H, J = 6.9, 1.4 Hz), 7.45−7.62 (m, 6H), 8.45 (d, 1H, J = 8.9 Hz), 8.53 (d, 1H, J = 6.9 Hz); IR (KBr) 1648, 1619, 1540, 1498, 1410 cm^{-1}; MS (EI) *m*/*z* 237 $(M + H)^+$. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.56; H, 5.06; N, 11.81.

3-(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazine-6-one (10). A mixture of **8** (75 kg, 317 mol), glyoxalic acid monohydrate (58.4 kg, 634 mol), and acetic acid (19.1 kg, 317 mol) in DME (dimethoxyethane, 150 L) was heated to 90−95 °C for 6 h. To this solution were then added ethyl acetate (375 L) and water (375 L). The organic layer was separated, and the aqueous layer was re-extracted by ethyl acetate (225 L). To the combined organic layer was added water (375 L) and was followed by adjusting the pH to 7.0−7.2 with 24% NaOH in water at 20−30 °C. The layers were separated, and the organic layer was concentrated to ∼75 L under reduced pressure, treated with 2-propanol (112.5 L), and again concentrated to ∼75 L under ambient conditions. The precipitate was filtered off and washed with 2-propanol (15 L). Drying under reduced pressure afforded **8** (12.0 kg, 16% recovery yield) of 98% chemical purity. To the aqueous layer was added ethyl acetate (375 L) and followed by adjusting the pH to 2.0−2.2 with 17.5% HCl in water. The layers were separated and the organic layer was concentrated to ∼150 L under reduced pressure, followed by exchange with DMA (150 L) by distillation. To the residue was added 80% hydrazine monohydrate in water (79.5 kg, 1270 mol), and the mixture was heated to 105−110 °C for 2 h and cooled to 45−50 °C. To this solution was added dropwise water (900 L), maintaining temperature at 45−50 °C, and stirring continued over 30 min at ambient temperature, followed by cooling to 0−5 °C for 1 h. The precipitate was filtered off and washed with water (225 L). Drying under reduced pressure afforded **10** (51 kg, 56% yield) of 95% purity as a yellowish solid: mp 212−214 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.85 (d, 1H, J = 9.8 Hz), 6.90 (td, 1H, J = 6.9, 1.5 Hz), 7.10 (d, 1H, J = 9.8 Hz), 7.21−7.65 (m, 6H), 8.05 (dd, 1H, J = 7.8, 1.2 Hz), 8.52 (dd, 1H, J = 7.9, 1.0 Hz), 13.05 (br s, 1H); IR (KBr) 1678, 1657, 1632, 1588, 1533 cm^{-1} ; MS (EI) *m*/*z* 289 $(M + H)^+$, 74. Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.54; H, 4.17; N, 19.53.

3-(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazine-6-one Butyric Acid (1) (FK838). To a mixture of **10** (34 kg, 118 mol), benzyltriethylammonium chloride (2.69 kg, 11.8 mol), and ethyl 4-bromo-*n*-butyrate (29.8 kg, 153 mol) in a mixture of DME (136 L) and MeOH (34 L) was added portionwise fine granulated potassium carbonate (32.6 kg, 236 mol). The reaction mixture was heated to 50−55 °C over 4 h followed by addition of NaOH (14.2 kg, 354 mol) in water (102 L) at 40 °C. Stirring was continued for 2 h, maintaining 40−45 °C. After cooling to 10 °C, to the reaction mixture was added water (340 L) and ethyl acetate (272 L). The aqueous layer was separated, washed with ethyl acetate (170 L) and treated with 17.5% hydrogen chloride in water to adjust the pH to 0.5−1.0 at 20−25 °C. The resulting mixture was further stirred at 0−5 °C for 1 h, and the precipitate was filtered off and washed with water (170 L). Drying under reduced pressure afforded crude **1** (41.5 kg, 94% yield) of 95% purity as a yellowish solid. The crude **1** (41.5 kg, 111 mol) was treated with carbon (1.24 kg) in a mixture of 2-propanol (1656 L) and water (709 L) at 80 °C. The filtrate was cooled to 0 °C, and the precipitate was filtered off and washed with a mixture of 2-propanol (138 L) and water (59 L), and successively water (197 L). Drying under reduced pressure afforded purified **1** (37.1 kg, 89% yield) of 100% purity as a yellowish solid: mp 242−243 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.96−2.10 (m, 2H), 2.34 (t, 2H, J = 6.9 Hz), 4.18 (t, 2H, J = 6.9 Hz), 6.87 (d, 1H, J = 9.6 Hz), 7.08 (td, 1H, J = 6.8, 1.4 Hz), 7.08 (d, 1H, J = 9.6 Hz), 7.39−7.64 (m, 6H), 7.97 (d, 1H, J = 8.9 Hz), 8.82 (d, 1H, J = 6.9 H), 12.17 (br s, 1H); IR (KBr) 1713, 1634, 1565, 1534, 1497 cm^{-1} ; MS (EI) *m*/*z* 375 $(M + H)^+$, 329, 289. Anal. Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.24; H, 4.78; N, 14.93.

Acknowledgment

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