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Syntheses of metabolites of ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (TAK-603)

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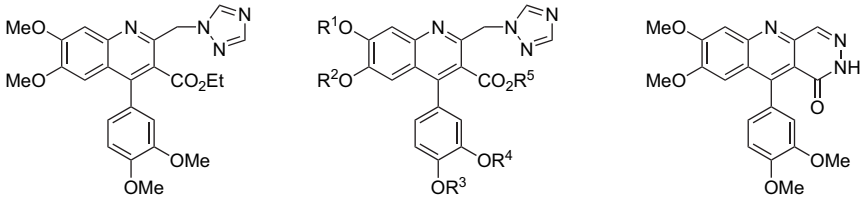
Abstract—Convenient and efficient syntheses of ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (**1d**) and 10-(3,4-dimethoxyphenyl)-7,8-dimethoxy-2*H*-pyridazino[4,5-*b*]quinolin-1-one (**1e**), metabolites of TAK-603 (**1**), have been achieved. Use of the methanesulfonyl as a protective group of the phenolic hydroxy for Friedel–Crafts reaction enabled a new simpler synthetic route of **1d** in high yield. Chloromethyl derivative (**23**) was converted to formyl derivative (**32**) using the Kröhnke reaction, followed by cyclization with hydrazine, which formed a novel compound **1e**.

1. Introduction

Ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (TAK-603, **1**, Fig. 1) was found to be a disease-modifying antirheumatic drug.[1] In pre-clinical and clinical studies, the metabolic mechanism and reaction of TAK-603 (**1**) have been studied in several animal species and humans.[1c,2] Analytical evaluation using liquid chromatography–mass spectrometry (LC–MS) and/or liquid chromatography–NMR (LC–NMR) suggested that **1a**–**d** existed in rat bile and **1a**,**d**,**e** (Fig. 1) existed in human serum.

Among them, the syntheses of four metabolites (**1a**–**d**, Fig. 1) have been reported.[1c] The carboxylic acid derivative (**1a**) was prepared easily by alkaline hydrolysis of **1**. The mono-demethylated compounds (**1b**–**d**) were synthesized by using the isopropyl as a protective group of the phenolic hydroxy as shown in Scheme 1. The pyridazinoquinolinone compound (**1e**) was a new metabolite. Prompt and rational synthesis of **1d** and **1e** was required for an urgent request for the toxicological studies.

Here, we wish to report the highly efficient synthesis of **1d** using methanesulfonyl as a protective group of the phenolic



1: TAK-603

1a: R^1=R^2=R^3=R^4=Me, R^5=H
1b: R^1=H, R^2=R^3=R^4=Me, R^5=Et
1c: R^3=H, R^1=R^2=R^4=Me, R^5=Et
1d: R^4=H, R^1=R^2=R^3=Me, R^5=Et

1e

Figure 1.

Keywords: TAK-603; Metabolite; Methanesulfonyl group; Friedel–Crafts reaction; Pyridazinoquinolinone; Kröhnke reaction.
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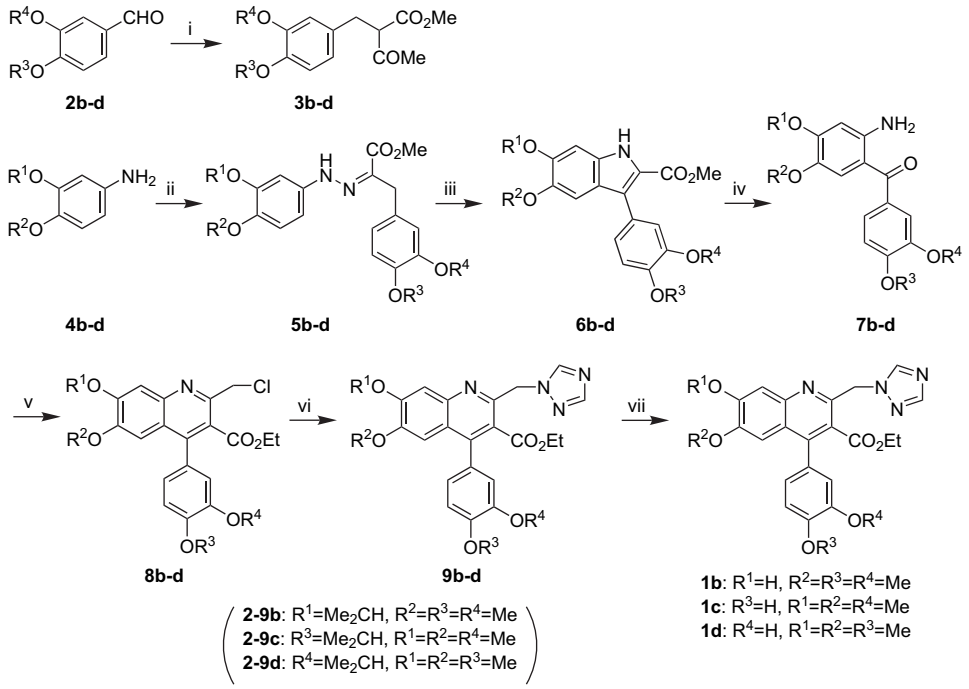


Scheme 1. Reagents and conditions: (i) (1) $MeCOCH_2CO_2Me$, piperidine, AcOH/toluene, then silica gel chromatography, (2) H_2, Pd–C/THF–EtOH; (ii) (1) $NaNO_2$, concd HCl/acetone–H_2O, (2) **3**, NaOAc, (3) KOH/MeOH; (iii) H_2SO_4/MeOH; (iv) (1) CrO_3/AcOH–H_2O, (2) KOH/H_2O; (v) $ClCH_2COCH_2CO_2Et$, H_2SO_4/AcOH, then silica gel chromatography; (vi) 1*H*-1,2,4-triazole, NaH, DMF, then silica gel chromatography; (vii) $TiCl_4/CH_2Cl_2$, then silica gel chromatography.

hydroxy by applying a Friedel–Crafts reaction. We also wish to demonstrate the synthetic route of the novel pyridazinoquinolinone metabolite (**1e**).

2. Results and discussion

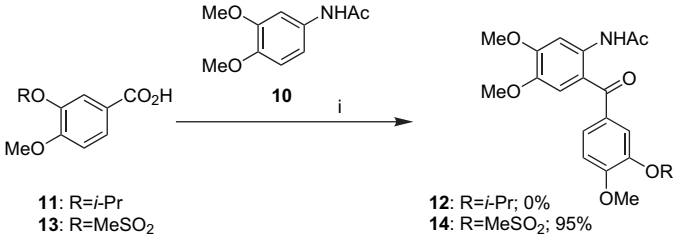
2.1. Alternative synthesis of ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (1d)

In an early report,[1c] the synthetic process of **1d** involved several drawbacks from the standpoint of large scale preparation, for example, indole cyclization–cleavage–quinoline cyclization sequence, repeated tedious chromatographic methods, and low yield (overall 3%). To avoid these problems, we tried to adopt a synthetic process that uses a Friedel–Crafts reaction, which includes a basic problem where most of the protective groups of the phenolic hydroxy are vulnerable in the reaction conditions. Actually, using the isopropyl as a protective group of the phenolic hydroxy did not afford a Friedel–Crafts acylated compound (**12**) but gave a complex mixture as shown in Scheme 2.

Generally, an aryl methane- or toluenesulfonate ester is stable under the acidic conditions used for the nitration of an aromatic ring (HNO_3/AcOH),[3] and to the high temperatures (200–250 °C) of the Ullman reaction. Also, few reports[3] have shown whether an aryl methanesulfonate ester is stable under the condition of a Friedel–Crafts reaction. So we studied using methanesulfonyl as a protective group of the phenolic hydroxy of **1d**.

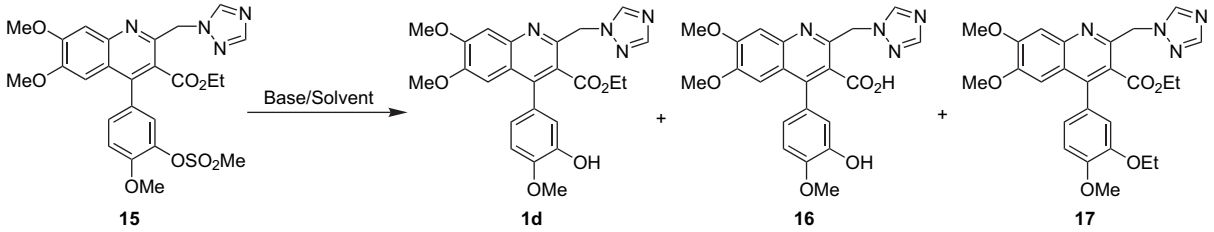
Thus, 3-mesyloxy-4-methoxybenzoic acid (**13**) reacted with *N*-(3,4-dimethoxyphenyl)acetamide (**10**) under Friedel–Crafts reaction conditions to give a benzophenone product (**14**) in 95% yield with high quality.

Initial trial using sodium hydroxide as a base reagent gave **1d** in moderate yield; however, a lot of carboxylic acid (**16**) was produced as a by-product as shown in Table 1, entries 1 and 2. Use of sodium carbonate or potassium carbonate produced a disappointing result (entries 3 and 4). Highly chemoselective deprotection of methanesulfonyl ester against ethyl ester was successfully performed using cesium carbonate in ethanol (entry 5), according to the reported method,[4] where the selective cleavage of acylphenol using



Scheme 2. Reagents and conditions: (i) $SnCl_4$, $POCl_3$, CH_2ClCH_2Cl, reflux.

Table 1. Deprotection of methanesulfonyl as a protective group of the phenolic hydroxy



15 **1d** **16** **17**

Entry	Base	Solvent	Ratio by HPLC[a]			
			15	**1d**	**16**	**17**
1	NaOH	EtOH–H_2O	0.1	67	24	9
2	NaOH	MeCN–H_2O	3	77	20	ND
3	Na_2CO_3	EtOH	91	5	ND	0.5
4	K_2CO_3	EtOH	26	47	ND	22
5	Cs_2CO_3	EtOH	ND[b]	88	ND	6
6	Cs_2CO_3	MeCN	88	6	ND	ND
7	Cs_2CO_3	THF	90	5	ND	ND
8	Cs_2CO_3	H_2O	97	0.3	ND	ND

[a] Determined at 254 nm.
[b] ND=not detected.

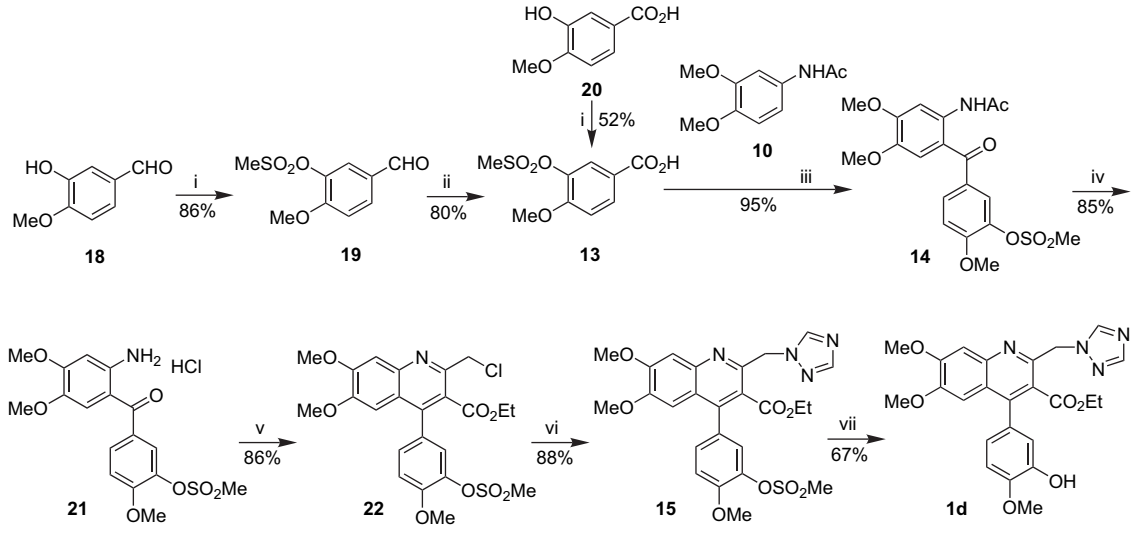
cesium carbonate without the cleavage of arylester was undertaken. Finally, under the identical reaction conditions according to entry 5 of Table 1, the ethoxybenzene by-product (**17**) was easily removed by precipitation after treatment with sodium hydroxide solution.

Compared with the early report,[1c] the present method, utilizing the synthetic method[5] of TAK-603 (**1**), for the synthesis of **1d** has a remarkable advantage in yield (3→32%) with only one chromatographic method as shown in Scheme 3.

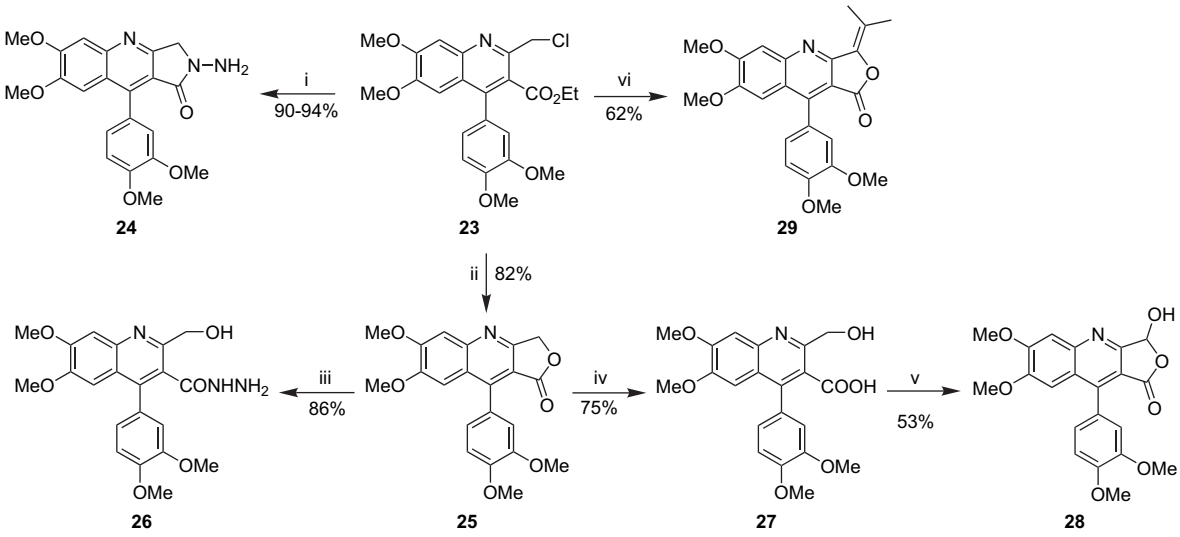
2.2. Novel synthetic route of 10-(3,4-dimethoxyphenyl)-7,8-dimethoxy-2*H*-pyridazino[4,5-*b*]quinolin-1-one (1e)

The intermediate (**23**)[5] of TAK-603 (**1**) seems to be a promising candidate for the synthesis of **1e**. At first, in order to obtain **1e**, we tried **23** to cyclize with hydrazine directly,[6] but only the lactam compound (**24**) was obtained, which cyclized as a five-member ring in 90–94% yield, as shown in Scheme 4.

This result indicated that six-member ring cyclization was more difficult than five-member ring cyclization. Using this five-member ring **24**, we studied ring expansion using silica gel,[7] but the reaction did not occur. Then, **23** was treated with dimethyl sulfoxide to obtain lactone compound (**25**), which was cyclized as a five-member ring in 82% yield. Treatment of **25** with hydrazine resulted in cleavage of the lactone ring and hydrazide compound (**26**) was obtained in 86% yield. The study of the oxidation (MnO_2, PDC, SO_3Py–DMSO) of **26** to formyl compound failed and **26** was cyclized again to obtain **25**.



Scheme 3. Reagents and conditions: (i) $MeSO_2Cl$, Et_3N, THF, 0 °C; (ii) CrO_3, AcOH; (iii) $SnCl_4$, $POCl_3$, CH_2ClCH_2Cl, reflux; (iv) concd HCl, EtOH, reflux; (v) ethyl 4-chloroacetoacetate, EtOH, reflux; (vi) 1*H*-1,2,4-triazole, K_2CO_3, DMF, then silica gel chromatography; (vii) Cs_2CO_3, EtOH, reflux.



Scheme 4. Reagents and conditions: (i) NH_2NH_2, EtOH, reflux; (ii) DMSO, reflux; (iii) NH_2NH_2, EtOH, reflux; (iv) NaOEt, EtOH, reflux; (v) MnO_2, DMF, 100 °C; (vi) 2-nitropropane, NaOEt, EtOH, DMSO, 50 °C.

Treatment of **25** with sodium ethoxide resulted in lactone ring cleavage to give carboxylic compound (**27**) in 75% yield. MnO_2-oxidation of **27** gave lactol (**28**) in 53% yield. The desired reaction of **28** with hydrazine, however, did not proceed.

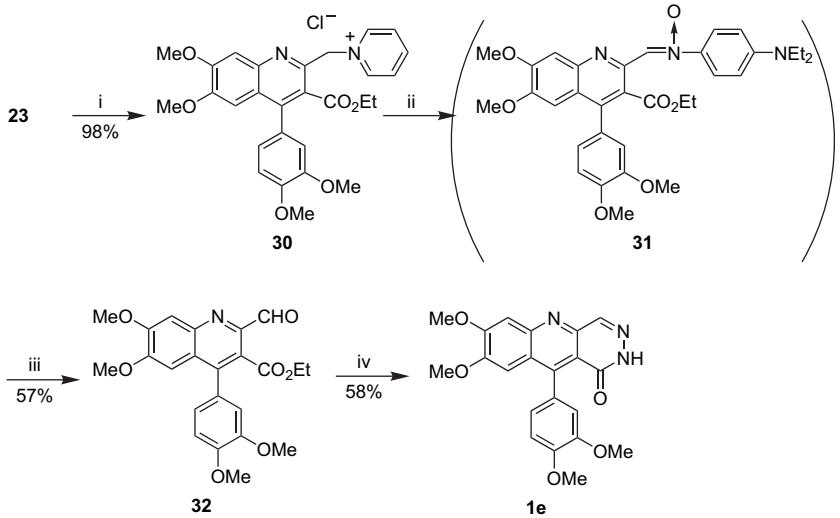
These unsuccessful results prompted us to change the synthetic strategy, that is, the stepwise route via a formyl derivative (**32**). Treatment of **23** with 2-nitropropane and sodium ethoxide [8] gave propylidene-lactone compound (**29**) in 62% yield. The application of Sommelet aldehyde synthesis (hexamethylenetetramine in acetic acid) [9] to **23** gave a complex mixture.

The failure of these formylations turned our attention on the application of a Kröhnke reaction. [10] The Kröhnke reaction was the conversion reaction from the chloromethylene moiety to the formyl moiety via a nitrone intermediate. At the first step, pyridinium salt (**30**) was obtained in 98% yield from the reaction of **23** and pyridine. Then nitrone compound (**31**) was derived from **30** by reaction with 4-nitroso-*N*,*N*-diethylaniline and sodium hydroxide in ethanol. After treatment with hydrochloric acid without isolation of **31**, formyl compound (**32**) was isolated in 57% yield as stable crystals for the first time. Finally, cyclization of **32** with hydrazine under ethanol reflux conditions gave the metabolite **1e** in 58% yield as shown in Scheme 5.

The analytical data of **1e** were in perfect agreement with the sample of human serum using liquid chromatography–mass spectrometry (LC–MS) and liquid chromatography–NMR (LC–NMR).

3. Conclusion

In summary, we have described convenient and efficient synthetic routes of ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (**1d**) and 10-(3,4-dimethoxyphenyl)-7,8-dimethoxy-2*H*-pyridazino[4,5-*b*]quinolin-1-one (**1e**), metabolites of TAK-603 (**1**). In particular, using methanesulfonyl as a protective group of the phenolic hydroxy enabled Friedel–Crafts



Scheme 5. Reagents and conditions: (i) pyridine, 100 °C; (ii) 4-nitroso-*N*,*N*-diethylaniline, NaOH, EtOH–H_2O, 100 °C; (iii) HCl; (iv) NH_2NH_2, EtOH, reflux.

reaction, and a new simpler synthetic route of **1d** was established. Also, using Kröhnke reaction as a conversion reaction from chloromethyl derivative to formyl derivative enabled us to obtain a novel compound **1e**.

4. Experimental

4.1. General

Melting points were determined based on differential scanning calorimetry (DSC). Infrared spectra were recorded on a Horiba FT-210 spectrophotometer. NMR spectra were recorded on a Bruker DPX300 spectrometer. ^{1}H and ^{13}C chemical shifts were referenced to the internal deuterated solvent or tetramethylsilane. Column chromatography was performed with a Wakogel C-200 (75–150 μm) system. HPLC was performed on an YMC-Pack ODS-A302 column (150 mm×4.6 mm i.d.) with 20 mM aqueous KH_2PO_4 solution–MeCN (55:45) at 25 °C. Detection was effected with a Shimadzu SPD-6A UV spectrophotometric detector at 254 nm. Mass spectra and elemental analysis were analyzed by Takeda Analytical Research Laboratories, Ltd. All commercial chemicals and solvents used were of reagent grade and were used without further purification.

4.2. 3-Mesyloxy-4-methoxybenzaldehyde (19)

To a solution of isovanillin (**18**; 7.61 g, 50 mmol) in THF (76 mL) at 0 °C were added triethylamine (20.24 g, 200 mmol) and methanesulfonyl chloride (8.59 g, 75 mmol), and the mixture was stirred for 15 min. AcOEt (76 mL) was poured into the reaction mixture, and washed with 1 N HCl (150 mL, 75 mL), dried ($MgSO_4$), and concentrated in vacuo. To the residue was added IPE (50 mL), and the resulting precipitates were collected by filtration, washed with IPE (20 mL), and dried in vacuo to give **19** (9.92 g, 86.2%) as a white crystalline powder; t_R: 3.0 (**18**), 4.5 (**19**); mp 87.3 °C (lit.[11] 87–89 °C); IR (KBr): 1693.6, 1367.6, 1280.8, 1176.6, 1103.3, 821.7 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.24 (s, 3H), 4.00 (s, 3H), 7.15 (d, J=8.0 Hz, 1H), 7.82 (d, J=1.8 Hz, 1H), 7.85 (dd, J=8.2, 1.8 Hz, 1H), 9.89 (s, 1H); MS (FAB): m/z 231 $[M+H]^+$.

4.3. 3-Mesyloxy-4-methoxybenzoic acid (13; using 19)

To a solution of **19** (0.46 g, 2 mmol) in AcOH (2.3 mL) was added an aqueous solution (0.6 mL) of chromic acid (0.60 g, 6 mmol), and the mixture was stirred for 20 h. After the mixture was cooled, water (4.6 mL) was added and the resulting precipitates were collected by filtration, washed with water (4.6 mL×2) and EtOH (4.6 mL), and dried in vacuo to give **13** (0.44 g, 89.8%) as a white crystalline powder; t_R: 4.5 (**19**), 2.4 (**13**); mp 232.0 °C (lit.[11] 226–227 °C); IR (KBr): 1674.3, 1363.8, 1288.5, 1167.0, 825.6 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.34 (s, 3H), 3.95 (s, 3H), 7.29 (d, J=8.8 Hz, 1H), 7.80 (d, J=2.2 Hz, 1H), 7.95 (dd, J=8.8, 2.2 Hz, 1H); MS (FAB): m/z 247 $[M+H]^+$.

4.4. 3-Mesyloxy-4-methoxybenzoic acid (13; using 3-hydroxy-4-methoxybenzoic acid 20)

To a suspension of **20** (8.41 g, 50 mmol) in THF (200 mL) at 0 °C were added methanesulfonyl chloride (11.46 g, 100 mmol) and triethylamine (20.24 g, 200 mmol), and the mixture was stirred for 15 min. AcOEt (200 mL) was poured into the reaction mixture, and washed with 1 N HCl (200 mL×2), dried ($MgSO_4$), and concentrated in vacuo. To the residue was added AcOEt–IPE (1:2, 100 mL), and the resulting precipitates were collected by filtration, washed with AcOEt–IPE (1:2, 50 mL), and dried in vacuo to give **13** (6.40 g, 52.0%) as a white crystalline powder.

4.5. 2-Acetoamino-3′-mesyloxy-4,4′,5-trimethoxybenzophenone (14)

To a suspension of *N*-acetyl-3,4-dimethoxyaniline (**10**; 3.90 g, 20 mmol) and **13** in 1,2-dichloroethane (54 mL) were added phosphoryl chloride (10.25 mL) and tin chloride (4.63 mL), and the mixture was refluxed for 7 h. After cooling, dichloromethane (100 mL) was poured into the reaction mixture, and washed with water (100 mL) and 1 N NaOH (100 mL), dried ($MgSO_4$), and concentrated in vacuo. To the residue was added AcOEt–IPE (1:9, 50 mL), and the resulting precipitates were collected by filtration, washed with AcOEt–IPE (1:9, 50 mL×2), and dried in vacuo to give **14** (8.01 g, 94.5%) as a pale yellow crystalline powder; t_R: 2.4 (**13**), 5.1 (**10**), 5.5 (**14**); mp 179.2 °C; IR (KBr): 1685.9, 1604.9, 1514.2, 1367.6, 1277.0, 1128.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 3.26 (s, 3H), 3.79 (s, 3H), 4.00 (s, 6H), 7.06 (s, 1H), 7.12 (d, J=8.4 Hz, 1H), 7.68 (d, J=2.2 Hz, 1H), 7.74 (dd, J=8.4, 2.2 Hz, 1H), 8.41 (s, 1H), 11.12 (s, 1H); MS (FAB): m/z 424 $[M+H]^+$; Anal. Calcd for $C_{19}H_{21}NO_8S\cdot 0.5H_2O$: C, 52.77; H, 5.13; N, 3.24. Found: C, 52.70; H, 4.96; N, 3.44.

4.6. 2-Amino-3′-mesyloxy-4,4′,5-trimethoxybenzophenone hydrochloride (21)

To a suspension of **14** (5.08 g, 12 mmol) in EtOH (51 mL) was added concd HCl (10.2 mL), and the mixture was refluxed for 2 h. After stirring at 0 °C for 30 min, the resulting precipitates were collected by filtration, washed with EtOH (15 mL), and dried in vacuo to give **21** (4.25 g, 84.8%) as a pale yellow crystalline powder; t_R: 5.5 (**14**), 6.4 (**21**); mp 158.9 °C; IR (KBr): 2841.4, 1514.2, 1359.9, 1280.8, 1222.9, 1120.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.23 (s, 3H), 3.72 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 5.11 (br s, 2H), 6.21 (s, 1H), 6.96 (s, 1H), 7.09 (d, J=8.4 Hz, 1H), 7.62 (d, J=2.2 Hz, 1H), 7.68 (dd, J=8.4, 2.2 Hz, 1H); MS (FAB): m/z 382 $[M+H]^+$; Anal. Calcd for $C_{17}H_{20}ClNO_7S\cdot 0.6H_2O$: C, 47.63; H, 4.98; N, 3.27. Found: C, 47.59; H, 4.80; N, 3.23.

4.7. Ethyl 2-chloromethyl-4-(3-mesyloxy-4-methoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (22)

To a suspension of **21** (4.17 g, 10 mmol) in EtOH (42 mL) was added ethyl chloroacetoacetate (2.14 g, 13 mmol), and the mixture was refluxed for 2 h. Water (14 mL) and triethylamine (1.06 g, 10.5 mmol) were added and the resulting mixture was stirred for 30 min at 0 °C. The resulting precipitates were collected by filtration, washed with water–EtOH (1:3, 25 mL×2), EtOH (10 mL), and dried in vacuo to give **22** (4.38 g, 85.9%) as a pale yellow crystalline powder; t_R: 6.4 (**21**), 24.6 (**22**); mp 168.4 °C; IR (KBr): 1716.8, 1504.6, 1367.6, 1251.9, 1230.7 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 1.05 (t, J=7.4 Hz, 3H), 3.28 (s, 3H), 3.84 (s, 3H), 4.00 (s, 3H), 4.06 (s, 3H), 4.12 (q, J=7.2 Hz, 2H), 4.89 (d, J=11.4 Hz, 1H), 5.05 (d, J=11.4 Hz, 1H), 6.91 (s, 1H), 7.14 (d, J=8.4 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.40 (d, J=2.2 Hz, 1H), 7.46 (s, 1H); MS (FAB): m/z 510 $[M+H]^+$; Anal. Calcd for $C_{23}H_{24}ClNO_8S$: C, 54.17; H, 4.74; N, 2.75. Found: C, 54.09; H, 4.66; N, 2.70.

4.8. Ethyl 4-(3-mesyloxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (15)

To a solution of **22** (4.08 g, 8 mmol) in DMF (41 mL) were added 1*H*-1,2,4-triazole (0.61 g, 8.8 mmol) and potassium carbonate (3.32 g, 24 mmol), and the mixture was stirred for 4 h. After cooling, water (80 mL) and EtOH (40 mL) were added and the resulting precipitates were collected by filtration, washed with EtOH (15 mL×2), and dried in vacuo to give crude **15** (3.42 g, 78.8%) as a pale yellow crystalline powder. The mother solution was extracted with AcOEt (80 mL), and the organic extract was washed with water (80 mL) and saturated NaCl solution (80 mL), dried ($MgSO_4$), and concentrated in vacuo. To the residue was added EtOH (40 mL), and the resulting precipitates were collected by filtration, washed with EtOH (15 mL×2), and dried in vacuo to give recovered **15** (0.58 g, 13.4%) as a pale yellow crystalline powder. Both crude **15** and recovered **15** were purified together by chromatography on silica gel to give **15** (3.83 g, 88.2%) as a pale yellow crystalline powder; t_R: 24.6 (**22**), 7.1 (**15**); mp 171.9 °C; IR (KBr): 1714.8, 1504.6, 1431.3, 1367.6, 1230.7, 1209.4, 1174.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J=7.0 Hz, 3H), 3.27 (s, 3H), 3.83 (s, 3H), 3.99 (s, 3H), 4.00 (q, J=7.0 Hz, 2H), 4.05 (s, 3H), 5.69 (d, J=14.8 Hz, 1H), 5.80 (d, J=14.8 Hz, 1H), 6.89 (s, 1H), 7.12 (d, J=8.4 Hz, 1H), 7.25 (dd, J=8.4, 2.2 Hz, 1H), 7.37 (d, J=1.8 Hz, 1H), 7.41 (s, 1H), 7.94 (s, 1H), 8.28 (s, 1H); MS (FAB): m/z 542 $[M+H]^+$; Anal. Calcd. for $C_{25}H_{26}N_4O_8S\cdot 0.3H_2O$: C, 54.80; H, 4.89; N, 10.22. Found: C, 54.76; H, 4.90; N, 9.94.

4.9. Ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (1d)

To a suspension of **15** (25.0 g, 46.1 mmol) in EtOH (2.5 L) was added cesium carbonate (60.1 g, 184 mmol), and the mixture was refluxed for 30 min. After cooling and concentration, 1 N NaOH (700 mL) was poured into the residue at 0 °C and the resulting precipitates were removed by filtration. The mother solution was extracted with AcOEt (700 mL), and the aqueous solution was adjusted to pH 7 with 1 N HCl (180 mL) and stirred at 0 °C for 30 min. The resulting precipitates were collected by filtration, washed with water (200 mL) and EtOH (50 mL), and the resulting crude powder was recrystallized from 95% EtOH (1.5 L) to give **1d** (14.3 g, 67.0%) as a white crystalline powder; t_R: 7.1 (**15**), 4.5 (**1d**); mp 233.6 °C; IR (KBr): 2978.4, 1714.8, 1504.6, 1429.3, 1211.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J=7.2 Hz, 3H), 3.80 (s, 3H), 3.96 (s, 3H), 3.98 (q, J=7.2 Hz, 2H), 4.04 (s, 3H), 5.73 (s, 2H), 6.37 (s, 1H), 6.80 (d, J=8.2 Hz, 1H), 6.98–6.93 (3H, m), 7.40 (s, 1H), 7.94 (s, 1H), 8.30 (s, 1H); MS (FAB): m/z 465 $[M+H]^+$; Anal. Calcd for $C_{24}H_{24}N_4O_6$: C, 62.06; H, 5.21; N, 12.06, Found: C, 62.08; H, 5.23; N, 12.05.

4.10. 2-Amino-9-(3,4-dimethoxyphenyl)-6,7-dimethoxyazolidino[3,4-*b*]quinolin-1-one (24)

To a suspension of ethyl 2-chloromethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (**23**; 0.89 g, 2 mmol) in EtOH (10 mL) was added hydrazine hydrate (0.50 g, 10 mmol), and the mixture was refluxed for 2.5 h. After cooling, the resulting precipitates were collected by filtration, washed with EtOH (5 mL), and dried in vacuo to give **24** (0.74 g, 93.7%) as a pale yellow crystalline powder; t_R: 20.0 (**23**), 3.0 (**24**); mp 265.1 °C; IR (KBr): 1695.6, 1502.7, 1249.9, 1232.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 3.90 (s, 3H), 4.00 (s, 3H), 4.08 (s, 3H), 4.37 (s, 2H), 4.66 (s, 2H), 7.00 (s, 1H), 7.06 (s, 2H), 7.16 (s, 1H), 7.48 (s, 1H); MS (FAB): m/z 396 $[M+H]^+$; Anal. Calcd for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.51; H, 5.40; N, 10.40.

4.11. 9-(3,4-Dimethoxyphenyl)-6,7-dimethoxyoxolano-[3,4-*b*]quinolin-1-one (25)

A solution of **23** (0.89 g, 2 mmol) in DMSO (10 mL) was stirred for 5.5 h at 120 °C. After cooling, water (20 mL) was added and the resulting precipitates were collected by filtration, washed with water (10 mL) and EtOH (5 mL), and dried in vacuo to give **25** (0.62 g, 81.6%) as a yellow crystalline powder; t_R: 20.0 (**23**), 5.7 (**25**); mp 238.2 °C (lit.[1d] 241–242 °C); IR (KBr): 1759.2, 1518.1, 1502.7, 1483.4, 1251.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 3.91 (s, 3H), 4.01 (s, 3H), 4.10 (s, 3H), 5.38 (s, 2H), 7.02 (s, 1H), 7.07 (s, 2H), 7.23 (s, 1H), 7.49 (s, 1H); MS (FAB): m/z 382 $[M+H]^+$.

4.12. 2-Hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carbohydrazide (26)

To a suspension of **25** (0.19 g, 0.5 mmol) in EtOH (4 mL) was added hydrazine hydrate (0.13 g, 2.5 mmol), and the mixture was refluxed for 11 h. After cooling, AcOEt (4 mL) was added and the resulting precipitates were collected by filtration, washed with AcOEt (2 mL×2), and dried in vacuo to give **26** (0.18 g, 85.7%) as an ivory crystalline powder; t_R: 5.7 (**25**), 2.2 (**26**); mp 240.9 °C; IR (KBr): 3287.0, 1657.0, 1518.1, 1504.6, 1248.0 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.70 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 3.97 (s, 3H), 4.21 (br s, 2H), 4.68 (d, J=5.6 Hz, 2H), 5.02 (t, J=5.2 Hz, 1H), 6.90 (s, 1H), 6.92 (d, J=8.4 Hz, 1H), 6.99 (s, 1H), 7.05 (d, J=8.4 Hz, 1H), 7.47 (s, 1H), 9.29 (s, 1H); MS (FAB): m/z 414 $[M+H]^+$; Anal. Calcd for $C_{21}H_{23}N_3O_6\cdot 0.3H_2O$: C, 60.22; H, 5.68; N, 10.03. Found: C, 60.13; H, 5.55; N, 10.00.

4.13. 2-Hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylic acid (27)

To a suspension of **25** (0.19 g, 0.5 mmol) in EtOH (4 mL) was added sodium ethoxide (0.14 g, 2 mmol), and the mixture was refluxed for 1 h. After cooling, 1 N HCl (3 mL) was added and the resulting precipitates were collected by filtration, washed with EtOH (4 mL), water (4 mL), and

again with EtOH (4 mL), and dried in vacuo to give **27** (0.15 g, 75.0%) as an orange crystalline powder; t_R: 5.7 (**25**), 1.7 (**27**); mp 239.3 °C; IR (KBr): 3343.0, 2548.2, 1724.5, 1500.7, 1265.4 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.76 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 4.92 (s, 2H), 6.96–7.03 (m, 3H), 7.14 (d, J=8.8 Hz, 1H), 7.79 (s, 1H); MS (FAB): m/z 400 $[M+H]^+$; HRMS Calcd: 400.1396. Found: 400.1425.

4.14. 3-Hydroxy-9-(3,4-dimethoxyphenyl)-6,7-dimethoxyoxolano[3,4-*b*]quinolin-1-one (28)

To a suspension of **27** (0.40 g, 1 mmol) in DMF (4 mL) was added manganese(IV) oxide (0.43 g, 5 mmol), and the mixture was stirred for 1 h at 100 °C. After cooling, the resulting precipitates were removed by filtration. To the mother solution was added water, and the resulting precipitates were collected by filtration, washed with water (8 mL) and EtOH (4 mL×2), and dried in vacuo to give **28** (0.21 g, 52.5%) as a pale brown crystalline powder; t_R: 1.7 (**27**), 3.7 (**28**); mp 249.9 °C; IR (KBr): 1761.1, 1506.5, 1259.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 1H), 2.92 (d, J=14.4 Hz, 1H), 3.86 (s, 3H), 3.91 (s, 3H), 4.01 (s, 3H), 4.17 (s, 3H), 6.89 (s, 1H), 6.99 (s, 1H), 7.07 (s, 1H), 7.21 (s, 1H), 7.81 (s, 1H); MS (FAB): m/z 398 $[M+H]^+$; HRMS Calcd: 398.1240. Found: 398.1264.

4.15. 3-Isopropylidene-9-(3,4-dimethoxyphenyl)-6,7-dimethoxyoxolano[3,4-*b*]quinolin-1-one (29)

To a solution of **23** (0.89 g, 2 mmol) in DMSO (13 mL) were added dropwise 2-nitropropane (0.71 g, 8 mmol) and EtOH solution (7 mL) of sodium ethoxide (0.31 g, 4.5 mmol) over 20 min, and the mixture was stirred for 5 h at 50 °C. After cooling, water (20 mL) was added and the resulting precipitates were collected by filtration, washed with EtOH (10 mL), and dried in vacuo to give **29** (0.52 g, 61.9%) as a yellow crystalline powder; t_R: 20.0 (**23**), 54.2 (**29**); mp 274.2 °C; IR (KBr): 1766.9, 1506.5, 1261.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.13 (s, 3H), 2.64 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 4.00 (s, 3H), 4.11 (s, 3H), 7.01 (s, 1H), 7.06 (s, 1H), 7.07 (s, 1H), 7.16 (s, 1H), 7.50 (s, 1H); MS (FAB): m/z 422 $[M+H]^+$; Anal. Calcd for $C_{24}H_{23}NO_6 \cdot 0.1H_2O$: C, 68.11; H, 5.52; N, 3.31. Found: C, 67.92; H, 5.52; N, 3.07.

4.16. 1-(3-Ethoxycarbonyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-2-yl)methylpyridinium chloride (30)

A suspension of **23** (8.92 g, 20 mmol) and pyridine (27 mL) was stirred for 1 h at 100 °C. After cooling, AcOEt (27 mL) was added and the resulting precipitates were collected by filtration, washed with AcOEt (27 mL×2), and dried in vacuo to give **30** (10.31 g, 98.2%) as a white crystalline powder; t_R: 20.0 (**23**), 5.1 (**30**); mp 230.4 °C; IR (KBr): 3406.6, 1712.9, 1502.7, 1255.7, 1232.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.95 (t, J=7.4 Hz, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 4.02 (s, 3H), 4.15 (q, J=7.4 Hz, 2H), 6.49 (d, J=3.0 Hz, 1H), 6.86 (s, 1H), 6.88 (d, J=8.4 Hz, 1H), 7.00 (d, J=8.4 Hz, 1H), 7.21 (s, 1H), 8.21 (t, J=7.6 Hz, 2H), 8.60 (t, J=7.6 Hz, 1H), 9.55 (d, J=5.6 Hz, 2H); MS (EI): m/z 489 $[M-Cl]^+$; Anal. Calcd for $C_{28}H_{29}ClN_2O_6 \cdot 0.7H_2O$: C, 62.56; H, 5.70; N, 5.21. Found: C, 62.50; H, 5.65; N, 5.13.

4.17. Ethyl 2-formyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (32)

To a suspension of **30** (8.92 g, 17 mmol) in EtOH (45 mL) were added 4-nitroso-*N*,*N*-diethylaniline (3.49 g, 19.6 mol) and 1 N NaOH (21.3 mL), and the mixture was stirred for 17 h. Water (45 mL) was added and the resulting mixture was stirred for 2 h at 100 °C. After cooling, AcOEt (180 mL) was poured into the reaction mixture, and the organic layer was washed with water (45 mL), 1 N HCl (45 mL), and again with water (45 mL), and concentrated in vacuo. To the residue was added EtOH (30 mL), and the resulting precipitates were collected by filtration, washed with EtOH (30 mL×2) and dried in vacuo to give **32** (4.14 g, 57.3%) as a orange crystalline powder; t_R: 5.1 (**30**), 14.3 (**32**); mp 176.4 °C; IR (KBr): 1732.2, 1709.1, 1504.6, 1471.8, 1429.3, 1259.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.15 (t, J=7.2 Hz, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 4.10 (s, 3H), 4.22 (dq, J=7.2 Hz, 1.8H, 2H), 6.9–7.0 (m, 4H), 7.58 (s, 1H), 10.17 (s, 1H); MS (FAB): m/z 426 $[M+H]^+$; Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 2.75. Found: C, 64.70; H, 5.45; N, 2.70.

4.18. 10-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-2*H*-pyridazino[4,5-*b*]quinolin-1-one (1e)

To a suspension of **32** (2.98 g, 7 mmol) in EtOH (30 mL) was added hydrazine hydrate (1.75 g, 35 mmol), and the mixture was refluxed for 24 h. After cooling, the resulting precipitates were collected by filtration and washed with EtOH (20 mL×2). The resulting crystalline powder was dissolved in hot $CHCl_3$ (150 mL). After cooling, silica gel (12 g) was added to the resulting solution, and stirred for 30 min. The silica gel was filtered off and washed with $CHCl_3$–AcOEt (1:1; 400 mL) and the mother solution was concentrated in vacuo. To the residue was added AcOEt (30 mL), and the resulting precipitates were collected by filtration and washed with AcOEt (15 mL). To the resulting crystalline powder in $CHCl_3$ (150 mL) was added activated charcoal (0.15 g), and the resulting suspension was stirred for 30 min. The charcoal was filtered off and the mother solution was concentrated in vacuo. To the residue was added EtOH (50 mL), and the resulting precipitates were collected by filtration, washed with AcOEt (25 mL×2) and dried in vacuo to give **1e** (1.59 g, 57.8%) as a pale yellow crystalline powder; t_R: 14.3 (**32**), 3.8 (**1e**); mp 289.3 °C; IR (KBr): 3071.0, 2939.8, 1674.3, 1496.9, 1255.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 3.87 (s, 3H), 4.00 (s, 3H), 4.12 (s, 3H), 6.83 (d, J=1.8 Hz, 1H), 6.87 (dd, J=8.2, 1.8 Hz, 1H), 6.90 (s, 1H), 7.06 (d, J=8.2 Hz, 1H), 7.55 (s, 1H), 8.41 (s, 1H), 9.64 (s, 1H); MS (FAB): m/z 394 $[M+H]^+$; Anal. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.11; H, 4.96; N, 10.56.

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