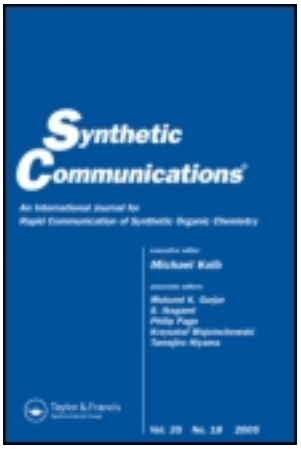

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Alternate Synthesis of Apixaban (BMS-562247), an Inhibitor of Blood Coagulation Factor Xa

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ALTERNATE SYNTHESIS OF APIXABAN (BMS-562247), AN INHIBITOR OF BLOOD COAGULATION FACTOR XA

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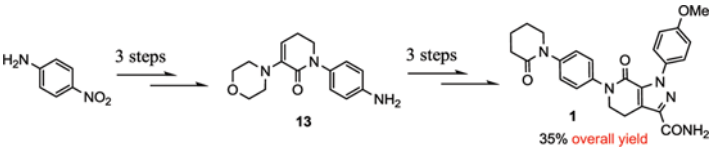
GRAPHICAL ABSTRACT



Abstract *An alternate approach to apixaban was described. The synthesis features a novel and cost-effective synthetic strategy to construct a key* N*-phenylvalerolactam intermediate* ***4*** *from 4-nitroaniline. In addition, the modified synthetic route avoids the use of expensive reagents and significantly improves reaction yields. As demonstrated practically, apixaban was successfully synthesized in overall good yield (35%).*

Keywords Apixaban; cost-effective synthetic route; inhibitor of blood coagulation factor Xa; 4-nitroaniline

INTRODUCTION

Apixaban **1**, a highly potent, selective, and orally bioavailable inhibitor of blood coagulation factor Xa (fXa), was developed in a late-stage clinic trial for the prevention and treatment of thromboembolic diseases by Bristol-Myers Squibb.[1,2] It could be marketed for the treatment of deep vein thrombosis (DVT) and venous thrombosis as a new-generation anticoagulant.[3] Moreover, it has also shown promise in treating acute coronary syndrome (ACS),[4] cerebrovascular ischemia, and cancer.[5]

Several routes for the preparation of apixaban **1** have been reported, mainly relying on the use of expensive organic iodide.[6–8] In 2003, Zhou et al.[6] disclosed two methods for its synthesis in the early stage of drug discovery (Scheme 1, routes A and B). In route A, hydrazone **3**, as a key intermediate, was prepared in two steps via the diazotization of 4-methoxyaniline followed by the Japp–Klingemann reaction with ethyl 2-chloroacetoacetate. Then it was subjected to an addition–elimination

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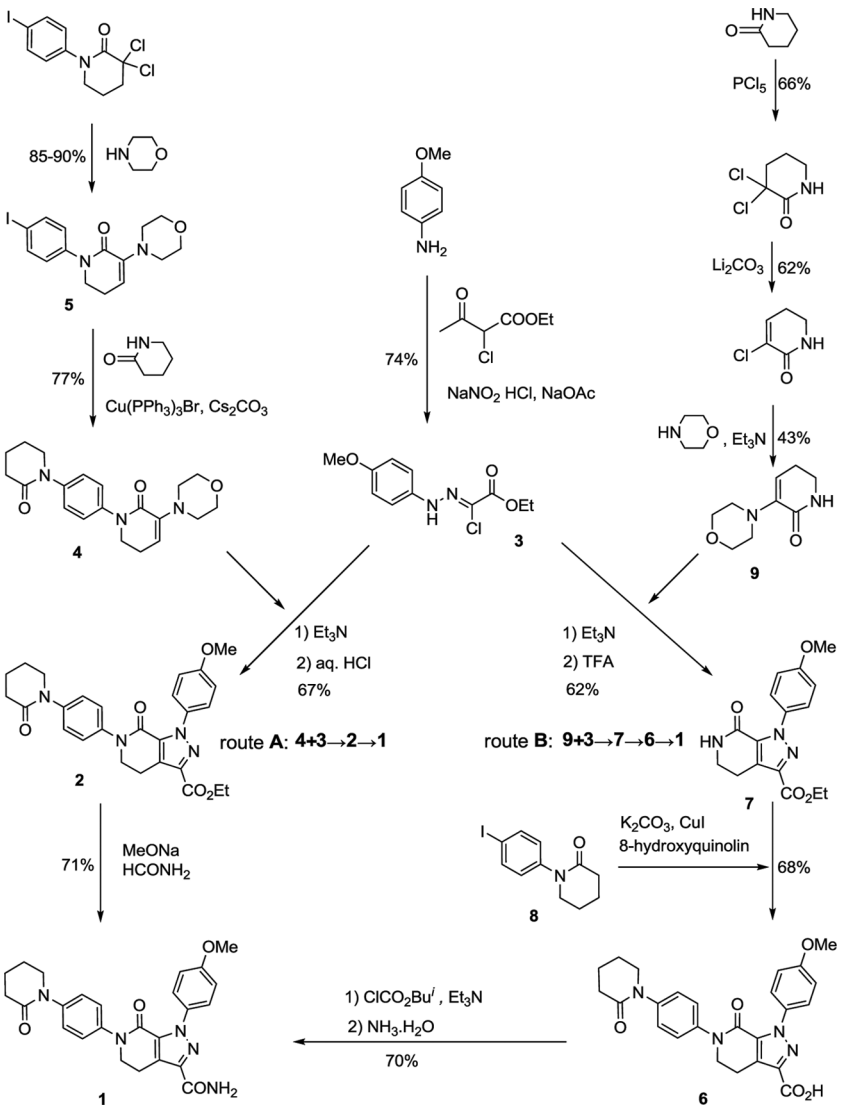
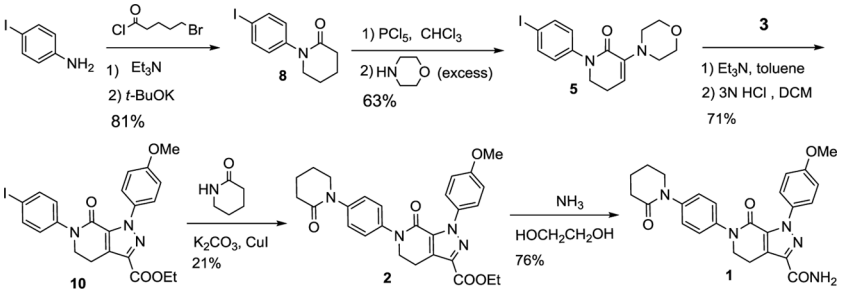


Scheme 1. Reported synthetic approaches to apixaban.[6]

sequence with *N*-phenylvalerolactam **4** to give pyrazolecarboxylate **2**. Finally, aminolysis of **2** with 10 equivalents of formamide and sodium methoxide led to target **1**. *N*-Phenylvalerolactam **4** was synthesized through an Ullmann reaction with iodide **5** in 77% yield but organic cuprous compound $Cu(PPh_3)_3Br$ as catalyst was required. In route B, pyrazolecarboxylic acid **6** reacted with isobutyl chloroformate to afford a mixed anhydride, followed by aminolysis with ammonia to produce **1**. In a similar manner, reaction of enamine **9** with key intermediate **3** through an addition–elimination sequence gave rise to pyrazololactam **7**, which subsequently underwent an Ullmann coupling with organic iodide **8** in the presence of cuprous iodide to



Scheme 2. Reported synthetic route to apixaban.[7]

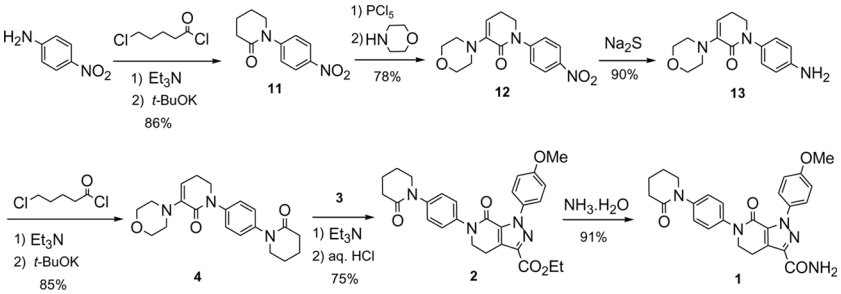
generate **6** in 68% yield. These two related methods have severe drawbacks, limiting the large-scale synthesis of **1**: (a) the use of expensive iodides, (b) the Ullmann reactions involving expensive auxiliaries, and (c) improvable yields (62% to 67%) of addition–elimination.

In 2007, Pinto et al.[7] reported a similar strategy for the synthesis of **1** (Scheme 2). However, only 21% yield was obtained in the key Ullmann coupling reaction of cycloadduct **10** with δ-valerolactam. More recently Gant et al.[8] disclosed a similar pathway for **1**, and only a slight improvement of the Ullmann reaction (29% yield) was observed. Accordingly, these synthetic methods cannot meet the demand of a large-scale preparation of **1** in terms of cost and hazard generation.

As part of the process of bringing a new active pharmaceutical ingredient (API) to market, it often requires use of an alternative synthetic strategy to the initial medicinal chemistry approach. Herein, we report a dramatically improved method for the preparation of **1** from the cheap 4-nitroaniline and 5-chlorovaleryl chloride as starting materials in an overall yield of 35%. The method eliminates the use of Cu(I)-meditated low-yielding Ullmann coupling reactions. Therefore, the strategy has displayed its practical application potential.

RESULTS AND DISCUSSION

In the synthesis of apixaban **1**, the key is to construct the pyrazololactams skeleton. To achieve the structure efficiently, we developed an alternative approach by forming two δ-valerolactam rings in **11** and **4**, respectively (Scheme 3).



Scheme 3. Alternate route to the synthesis of apixaban.

Initially, 5-chlorovaleryl chloride, instead of expensive 5-bromovaleryl chloride, and 4-nitroaniline were carried out in a one-pot acylation/cyclization sequence to offer lactam **11** in 86% yield. Triethylamine was employed as an acid scavenger in the acylation reaction and then potassium *tert*-butoxide as a strong condensing agent in the subsequent cyclization.

Enamine **12** was obtained in a ''one-pot'' procedure by the chlorination of **11** with phosphorus pentachloride, followed by the condensation–elimination process with excessive morpholine in 78% yield. Reduction of **12** with sodium sulfide[9,10] gave the corresponding aniline **13** in good yield (90%). In a similar manner, the second acylation/cyclization was realized between **13** and 5-chlorovaleryl chloride to furnish the key intermediate **4** in 85% yield for the two steps.

Finally, the addition–elimination of the resulting *N*-phenylvalerolactam **4** with hydrazone **3** via a [3 + 2] cycloaddition reaction gave rise to **2** and the requisite skeleton was assembled. However, under the reported reaction conditions, moderate yields (62% to 67%) were obtained while requiring long reaction time and lower reproducibility.[6–8] We found that the use of potassium iodide as catalyst could significantly improved the reaction yield (75%) with shortened reaction time and good reproducibility. Thus, the cyclization of **4** and **3** was smoothly conducted in ethyl acetate in the presence of excess triethylamine and a catalytic amount of potassium iodide under reflux for 6 h, and then 4.0 N hydrochloric acid was added to the resulting mixture to pH 2.5-3.5. It was stirred at room temperature for 2 h to afford **2**. Aminolysis of **2** in methanolic ammonia solution produced the target product **1** in 91% yield in an autoclave at 65 °C.

In summary, a significantly improved strategy has been developed for the synthesis of inhibitor of blood coagulation fXa **1**. The described synthesis features the elimination of expensive chemicals, rare auxiliaries, and inefficient Ullmann reaction. In addition, the new route has better yields, which is of particular interest for potential large-scale syntheses.

EXPERIMENTAL

NMR spectra were recorded on a Bruker spectrometer at 500 and 125 MHz, for ^{1}H and ^{13}C, respectively, and the chemical shifts were reported as δ values in parts per million relative to tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were obtained using a Nicolet 6700 IR spectrometer. Mass spectra were recorded on Micromass GCTTM gas chromatograph–mass spectrometer or a QSTAR Pulsar I LC/TOF MS mass spectrometer. Melting points were recorded on open capillaries and are uncorrected. All solvents and reagents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) was performed on silica-gel plates (HF254), and TLC visualizations were performed with I_2 vapor and ultraviolet (UV) light.

1-(4-Nitrophenyl)piperidin-2-one (11)[7]

A solution of 5-chloropentanoyl chloride (12.9 mL, 15.50 g, 0.10 mol) in tetrahydrofuran (THF, 20 mL) was added below 5 °C to a solution of 4-nitroaniline (11.05 g, 0.08 mol) and triethylamine (22.5 mL, 0.16 mol) in THF (50 mL). The

mixture was stirred at room temperature under N_2 for 5 h. Potassium *tert*-butoxide (24.70 g, 0.22 mol) was added to the reaction solution in batches below 5 °C during 30 min and then stirred at room temperature for 2 h. The suspension was concentrated to dryness and redissolved in ethyl acetate (100 mL) and water (100 mL) to separate the organic phase. The aqueous phase was extracted with ethyl acetate (2 × 80 mL) and washed with water (2 × 80 mL) and brine (80 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated completely to get a yellow solid. The recrystallization of the crude product from ethyl acetate afforded **11** as a pale yellow solid. Yield: 15.13 g, 86%; mp 97–99 °C; IR (KBr, cm^{-1}): 3015 and 2958 (C-H aliphatic), 1656 (C=O stretching), 1520 (aromatic C=C), 1477, 1343 (N=O stretching), 1308 and 1168 (C-N stretching), 860 and 698 (Ar-H aromatic bending); ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ: 8.25 (d, $J = 8.8$ Hz, Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 3.73 (t, $J = 5.8$ Hz, 2H), 2.62 (t, $J = 6.5$ Hz, 2H), 1.96–2.01 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm), δ: 170.3, 150.0, 145.2, 125.9 (2C), 124.3 (2C), 50.9, 33.1, 23.4, 21.2; MS/EI $m/z = 220.1$ (M^+).

3-Morpholino-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (12)[7]

Phosphorus pentachloride (18.7 g, 0.09 mol) was slowly added to a solution of **11** (6.6 g, 0.03 mol) in chloroform (40 mL) at room temperature. The resulting mixture was heated to reflux for 3 h, poured into ice water, and extracted with chloroform (3 × 30 mL). The combined organic phase was washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to dryness. The residue was dissolved in morpholine (30 mL) and refluxed for 1 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting solid was redissolved in water, and the precipitate was filtered. The recrystallization of the filter cake from ethyl acetate afforded **12** as a yellow solid. Yield: 7.08 g, 78%; mp 158–160 °C; IR (KBr, cm^{-1}): 2814 (C-H aliphatic), 1673 (C=O stretching), 1626 (aliphatic C=C), 1591 and 1510 (aromatic C=C), 1487 (N=O stretching), 1350 (C-N stretching), 1112 (C-O stretching), 835 and 783 (Ar-H aromatic bending); ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ: 8.25 (d, $J = 8.9$ Hz, 2H), 7.60 (d, $J = 8.9$ Hz, 2H), 5.80 (t, $J = 4.1$ Hz, 1H), 3.84–4.01 (m, 6H), 2.83–2.96 (m, 4H), 2.54–2.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm), δ: 161.3, 148.4, 144.6, 143.5, 124.6 (2C), 124.1 (2C), 115.7, 66.7 (2C), 50.5 (2C), 48.3, 23.3; MS/EI $m/z = 303.1$ (M^+).

1-(4-Aminophenyl)-3-morpholino-5,6-dihydropyridin-2(1H)-one (13)

A solution of sodium sulfide nonahydrate (9.60 g, 0.04 mol) in water (20 mL) was added to a solution of **12** (6.07 g, 0.02 mol) in ethanol (60 mL). The mixture was heated to 50 °C and stirred for 4 h, cooled to room temperature, and concentrated in vacuo. The residue was added to ethyl acetate (60 mL), heated to boiling, and filtered. The filtrate was concentrated in vacuo to dryness to yield **13** as a pale yellow solid. Yield: 4.92 g, 90%; mp 180–182 °C; IR (KBr, cm^{-1}): 3428 and 3350 (N-H stretching), 2811 (C-H aliphatic), 1656 (C=O stretching), 1610 (aliphatic C=C), 1519 and 1444 (aromatic C=C), 1260 (C-N stretching), 1131 and 1117 (C-O stretching), 765 and 748 (Ar-H aromatic bending); ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ: 7.09 (d, $J = 8.4$ Hz, 2H), 6.68 (d, $J = 8.4$ Hz, 2H), 5.52–5.70 (m, 1H), 3.75–3.90 (m, 4H), 3.53–3.71 (m, 4H), 2.83–3.10 (m,

4H), 2.42–2.59 (m, 2H);^{13}C NMR (125 MHz, DMSO-d_6, ppm), δ: 160.6, 146.7, 143.1, 131.9, 126.4 (2C), 113.7, 113.5 (2C), 65.9 (2C), 49.9 (2C), 48.9, 22.9; MS/EI $m/z = 273.2$ (M^+). HRMS/EI calcd. for $C_{15}H_{19}N_3O_2$: 273.1477; found: 273.1468.

3-Morpholino-1-(4-(2-oxopiperidin-1-yl)phenyl)-5,6-dihydropyridin-2(1H)-one (4)[6]

A solution of 5-chloropentanoyl chloride (1.6 mL, 1.94 g, 12.5 mmol) in THF (10 mL) was added to a solution of **13** (2.73 g, 10 mmol) and triethylamine (2.8 mL, 20 mmol) in THF (75 mL) below 5 °C. The mixture was stirred at 50 °C under N_2 for 2 h. Potassium *tert*-butoxide (3.37 g, 30 mmol) was added to the reaction solution in batches below 5 °C during 30 min and then stirred at 50 °C for 8 h. The suspension was cooled to room temperature and concentrated in vacuo to dryness. The residue was dissolved in water, stirred, and then filtered. The filter cake was washed with water and dried to afford **4** as a white solid. Yield: 3.02 g, 85%; mp 204–206 °C; IR (KBr, cm^{-1}): 2965, 2852 and 2803 (C-H aliphatic), 1646 (C=O stretching), 1616 (aliphatic C=C), 1514 and 1463 (aromatic C=C), 1262 (C-N stretching), 1114, 1070 and 1050 (C-O stretching), 835 and 783 (Ar-H aromatic bending); ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ: 7.35 (d, $J = 8.5$ Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 2H), 5.66 (t, $J = 4.3$ Hz, Hz, 1H), 3.78–3.86 (m, 6H), 3.60–3.65 (m, 2H), 2.82–2.90 (m, 4H), 2.43–2.59 (m, 2H), 2.24–2.41 (m, 2H), 1.93–2.01 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm), δ: 170.8, 162.1, 144.3, 141.7, 141.5, 127.3(2C), 126.4(2C), 115.1, 67.4(2C), 52.3, 51.1(2C), 49.2, 33.5, 24.2, 24.0, 22.1; MS/EI $m/z = 355.2$ (M^+). HRMS/EI calcd. for $C_{20}H_{25}N_3O_3$: 355.1896; found: 355.1906.

(Z)-Ethyl 2-Chloro-2-(2-(4-methoxyphenyl)hydrazono)acetate (3)[4,11–13]

Hydrochloric acid (35–36%, 6 mL, 60 mmol) was added to a solution of 4-methoxyaniline (2.46 g, 20 mmol) in water (12 mL) at −5 to 0°C. A solution of sodium nitrite (1.66 g, 24 mmol) in water (8 mL) was added to the mixture dropwise below 0 °C. Then, the reaction solution was stirred for 30 min at 0 °C, followed by the addition of sodium acetate (3.28 g, 40 mmol) until pH 5–6. After that, a solution of ethyl 2-chloroacetoacetate (2.8 mL, 3.28 g, 20 mol) in methanol (30 mL) was added dropwise to the reaction mixture at 0 to 5 °C. The resulting solution was stirred at room temperature for 4 h. The solution was removed from the mixture in vacuo, and the residue was dissolved in water (10 mL) and ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic phase was washed with water (2×10 mL) and brine (2×10 mL), dried over anhydrous sodium sulfate, filtrated, and concentrated thoroughly. The recrystallization of the crude product from ethyl acetate afforded **3** as a pale yellow solid. Yield: 3.94 g, 77%; mp 106-109 °C; IR (KBr, cm^{-1}): 3465 and 3257 (N-H stretching), 2999 and 2933 (C-H aliphatic), 1709 (C=O stretching), 1519 and 1498 (aromatic C=C), 1298 and 1226 (C-N stretching), 1169 and 1083 (C-O stretching), 820 and 745 (Ar-H aromatic bending); ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ: 8.27 (s, 1H), 7.17 (d, $J = 8.9$ Hz, 2H), 6.89 (d, $J = 8.9$ Hz, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 1.40 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$,

ppm), δ: 159.8, 155.9, 135.4, 115.8 (2C), 115.0, 114.8 (2C), 62.6, 55.6, 14.3; MS/EI $m/z = 256.1(M^+)$.

Ethyl 1-(4-Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (2)[7]

Compound **4** (1.42 g, 4.0 mmol), triethylamine (1.7 mL, 12 mmol), and potassium iodide (0.064 g, 0.4 mmol) ware added to a solution of **3** (1.13 g, 4.4 mmol) in ethyl acetate (40 mL) at room temperature. The mixture was stirred for 6 h under reflux and then cooled to 0 °C. The resulting mixture was added dropwise with 4.0 N hydrochloric acid (5 mL, 20 mmol) and stirred at room temperature for 2 h. Thereafter, water (10 mL) was added to the mixture to separate the organic layer. The aqueous layer was extrated with ethyl acetate (3×10 mL), and then the combined organic extracts were washed with brine (2×10 mL), dried over anhydrous sodium sulfate, and concentrated to dryness. Recrystallization of the residue from ethyl acetate and drying in vacuo afforded **2** as a pale yellow solid. Yield: 1.46 g, 75%; mp 120–124 °C; IR (KBr, cm^{-1}): 2936 and 2873 (C-H aliphatic), 1711 (C=N stretching), 1658 (C=O stretching), 1609 (aliphatic C=C), 1558, 1513, 1482 and 1460 (aromatic C=C), 1325, 1302 and 1254 (C-N stretching), 1144, 1088 and 1027 (C-O stretching), 833, 802 and 765 (Ar-H aromatic bending); ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ: 7.49 (d, $J = 8.8$ Hz, 2H), 7.35 (d, $J = 8.8$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 4.48 (q, $J = 7.0$ Hz, 2H), 4.15 (t, $J = 3.2$ Hz, 2H), 3.82 (s, 3H), 3.61 (t, $J = 5.6$ Hz, 2H), 3.33 (t, $J = 6.8$ Hz, 2H), 2.57 (t, $J = 5.6$ Hz, 2H), 1.94–2.00 (m, 4H), 1.45 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm), δ: 170.8, 162.8, 160.5, 157.9, 142.1, 140.6, 139.7, 133.7, 133.2, 127.63 (2C), 127.56, 127.44 (2C), 126.9 (2C), 114.3 (2C), 61.9, 56.2, 52.3, 51.6, 33.5, 24.2, 22.2, 22.1, 15.1; MS/EI $m/z = 488.2$ (M^+).

1-(4-Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (1)[7]

To the advanced intermediate **2** (2.44 g, 5.0 mmol) was added 25% ammonia water (1.5 mL, 20 mmol) in methanol (20 mL), and the mixture was heated to 65 °C for 5 h in an autoclave of 50 mL. The resulting mixture was cooled to room temperature, poured into water (30 mL), and crystalized below 0°C. The precipitate was filtrated and dried in vacuo at 50°C to afford the desired product **1** as a pale white solid. Yield: 2.09 g, 91%; mp 171–173 °C; IR (KBr, cm^{-1}): 3448 and 3298 (N-H stretching), 2940 (C-H aliphatic), 1669 (C=N stretching), 1614 (C=O stretching), 1544 (aliphatic C=C), 1513, 1463 and 1441 (aromatic C=C), 1334, 1300 and 1254 (C-N stretching), 1146, 1111, 1090 and 1024 (C-O stretching), 835, 816, 794 and 758 (Ar-H aromatic bending); ^{1}H NMR (500 MHz, $CDCl_3$, ppm), δ: 7.48 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 6.95 (d, $J = 8.0$ Hz, Hz, 2H), 5.66 (brs, 2H), 4.12 (t, $J = 5.6$ Hz, 2H), 3.84 (s, 3H), 3.55–3.65 (m, 2H), 3.39 (t, $J = 5.6$ Hz, 2H), 2.57 (t, $J = 6.2$ Hz, 2H), 1.91–2.01 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm), δ: 170.9, 164.4, 160.5, 158.0, 142.1, 140.6 (2C), 134.0, 133.2, 127.4 (4C), 126.9 (2C), 126.5, 114.4 (2C), 56.2, 52.3, 51.8, 33.5, 24.2, 22.1, 21.9; MS/EI $m/z = 459.2$ (M^+).

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