

A new efficient synthesis of *N*-(2-(2-(3-methoxy-4-(oxazol-5-yl)phenylamino)oxazol-5-yl)phenyl)-*N*-methyl-2-morpholinoacetamide (BMS-337197), a novel IMPDH inhibitor

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Dedicated to Professor Madeleine M. Joullie on her 80th birthday

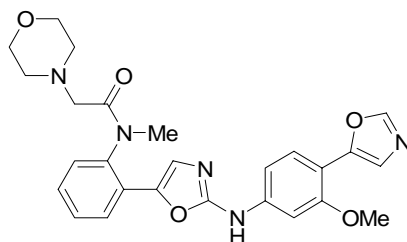
Abstract

A new, efficient method has been developed for the synthesis of BMS-337197, a novel IMPDH inhibitor. The new method uses the readily available 2-bromo-1-(2-nitrophenyl)ethanone as a starting reagent and provides BMS-337197 in 9 steps in 55% overall yield on a multigram scale.

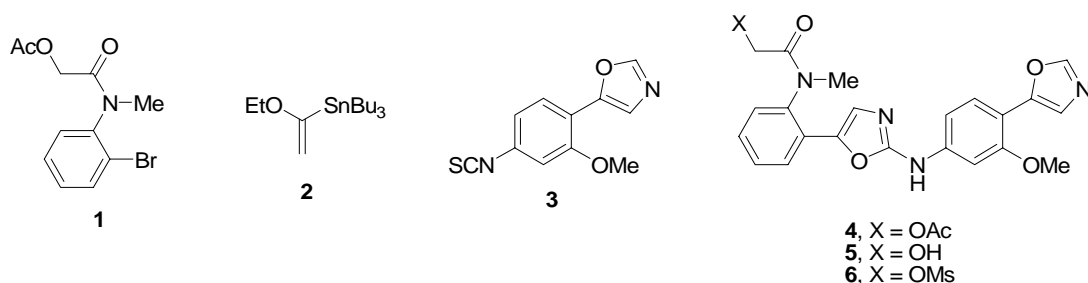
Keywords: 2-Aminooxazole, α -azidoketone, isothiocyanate, cyclization, IMPDH inhibitor

Introduction

Inosine monophosphate dehydrogenase (IMPDH) is a key enzyme that catalyzes the nicotinamide adenosine dinucleotide (NAD) dependent conversion of inosine 5'-monophosphate (IMP) to xanthosine 5'-monophosphate (XMP).¹ Due to its important role in the *de novo* synthesis of purine nucleotides, IMPDH is an attractive target for immunosuppressive, anticancer, and antiviral therapies.² In the course of a program to identify novel IMPDH inhibitors, we discovered that *N*-(2-(2-(3-methoxy-4-(oxazol-5-yl)phenylamino)oxazol-5-yl)phenyl)-*N*-methyl-2-morpholinoacetamide (BMS-337197) is a potent uncompetitive inhibitor of IMPDH II enzyme ($IC_{50} = 16$ nM, $K_i = 3.2$ nM, IMPDH I $IC_{50} = 120$ nM). BMS-337197 also has an IC_{50} of 520 nM in a CEM T-cell proliferation assay³ and inhibited the proliferation of normal human PBMCs stimulated with anti-CD3 and anti-CD28, with an IC_{50} of 130 nM. Furthermore, BMS-337197 showed excellent *in vivo* activity in the inhibition of antibody production in mice and in the adjuvant induced arthritis model in rats.³

**BMS-337197**

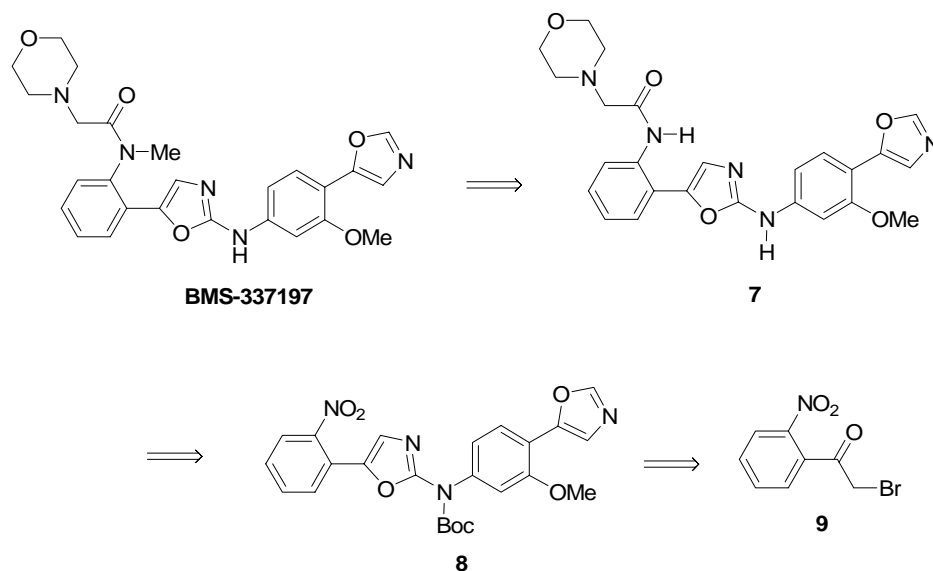
BMS-337197 was originally prepared via a 9 step sequence starting from 2-bromoaniline.³ This synthesis is highlighted by construction of the center oxazole ring *via* a Stille coupling of a functionalized bromide **1** with tributyl(1-ethoxyvinyl)stannane **2** followed by electrophilic bromination, azide substitution and cyclization with isothiocyanate **3** to give the advanced intermediate **4**. Acetate **4** was hydrolyzed to alcohol **5** which was then activated as a mesylate **6**. The morpholino moiety was finally installed by displacement of the mesyl group by excess morpholine to afford BMS-337197 in 18% overall yield. While this approach was successfully used to prepare enough material for the initial biological studies, it was not practical for scale-up to support more advanced evaluation of the compound, due to the limited availability and toxicity of the vinyl tin reagent **2** and the need for chromatographic separations of various intermediates and final product. Herein, we report a new, efficient method amenable to the large scale synthesis of BMS-337197 in which the substituted acetamide is introduced after formation of the oxazole.



Results and Discussion

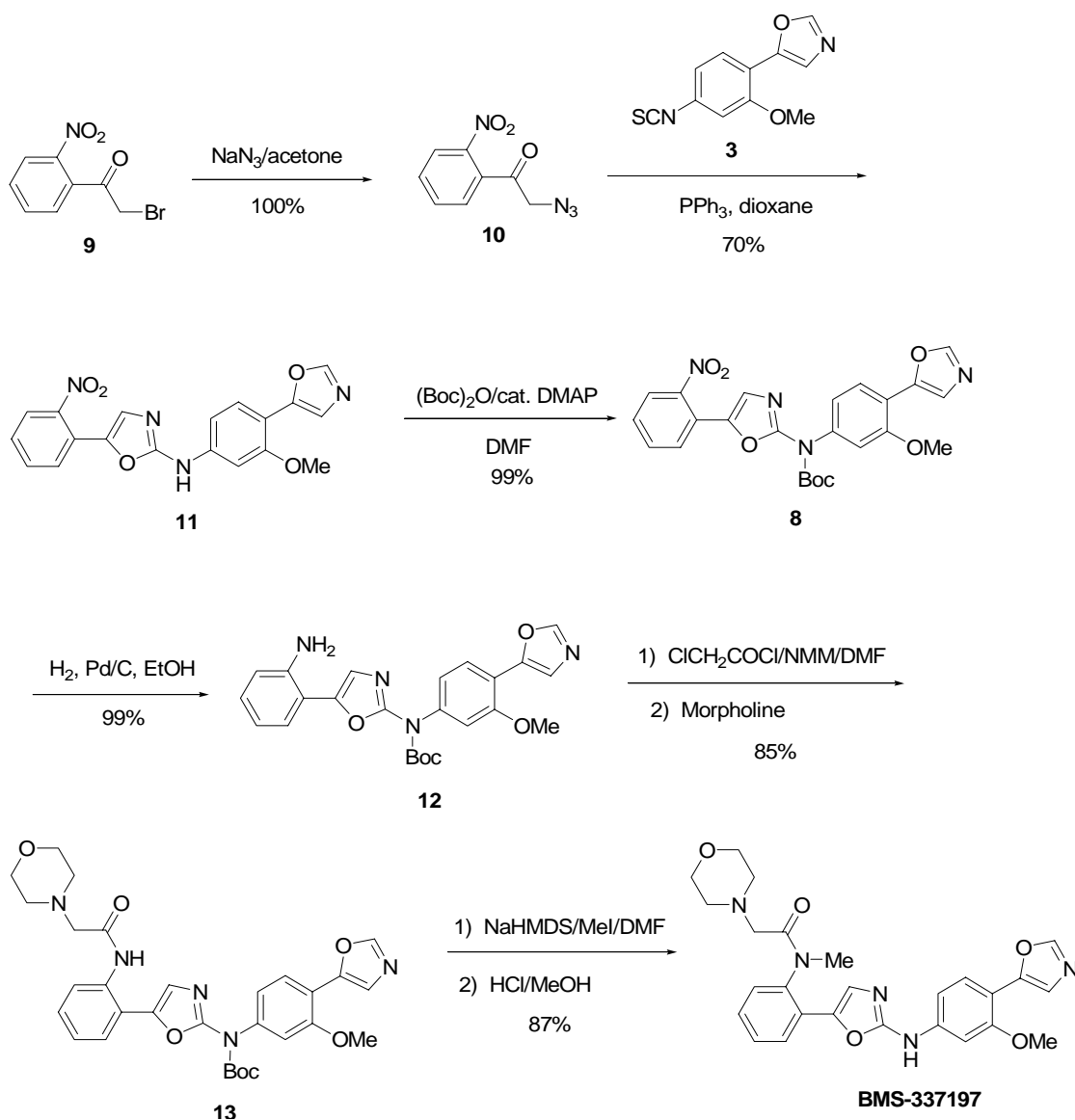
As shown in the following Scheme 1, we envisioned retrosynthetically that BMS-337197 could be constructed rapidly by a strategy involving regio- and chemoselective N-methylation of the amide nitrogen versus the oxazole amine nitrogen in molecule **7**. To achieve this, the commercially available 2-bromo-2'-nitroacetophenone **9** was selected as the starting material. The reasons for choosing **9** are multifold. Firstly, the nitro group in **9** would serve nicely as the amide nitrogen source in the final compound. Secondly, it would act as a preinstalled amide nitrogen protecting group, allowing for a facile differentiation (*via* a N-protecting group such as

Boc) of the oxazole amine nitrogen needed at the later stage of the synthesis through intermediate **8**. Thirdly, use of **9** would avoid the necessity for and handling of the expensive and toxic vinyl tin intermediate **2** in the original synthesis.



Scheme 1

Thus, treatment of **9** with sodium azide in acetone at room temperature overnight gave the α -azido ketone **10** (Scheme 2).⁴ Compound **10** was prepared previously by reaction of **9** with tetrabutylammonium azide with unspecified yield.⁵ Using sodium azide in acetone under the current conditions, the desired product **10** was isolated in quantitative yield. Triphenyl phosphine mediated cyclization of **10** with isothioisocyanate **3** in dioxane at 90 °C for 30 min smoothly afforded the desired oxazole **11** in 70% isolated yield.⁶ It should be pointed out that it is important to premix and heat the intermediate **3** and **10** in dioxane at 90 °C prior to addition of PPh₃. Mixing **3**, **10** and PPh₃ all together before heating resulted in lower yield due to formation of unknown side products. The secondary amine was next protected by treatment of **11** with Boc anhydride in the presence of a catalytic amount of dimethylaminopyridine (DMAP) in DMF at 100 °C for 4 hours and the resulting N-Boc protected intermediate **8** was then hydrogenated in ethanol (30 psi hydrogen pressure) for 3 hours to give the desired aniline **12** in 99% yield. Coupling of aniline **12** with α -chloroacetyl chloride in DMF using N-methylmorpholine as base followed by treating the resulting α -chloro amide with morpholine in one-pot afforded the corresponding α -morpholino amide **13** in 85% isolated yield. Finally, N-methylation of **13** by treatment with NaHMDS and methyl iodide in DMF and deprotection of the resulting N-methyl amide with 1 N HCl in methanol gave BMS-337197 in 87% yield.



Scheme 2

In summary, a new efficient method has been developed for the synthesis of BMS-337197, a novel IMPDH inhibitor. The new method uses the commercially readily available 2-bromo-1-(2-nitrophenyl)ethanone and provides BMS-337197 in 9 steps in 55% overall yield.

Experimental Section

General Procedures. Proton and carbon-13 NMR spectra were recorded with a Bruker DRX-400 spectrometer using CDCl_3 or DMSO-d_6 as solvent and TMS as internal standard. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for proton NMR, and CDCl_3 (77.0

ppm) for carbon-13 NMR. High resolution mass spectra were measured on Waters LCT instruments. 2-Bromo-2'-nitroacetophenone was purchased from Aldrich. All other reagents and solvents were commercial products and were used as received unless otherwise noted. All reactions were monitored by HPLC using a Shimadzu LC-10AS system and YMS ODS-A S5 4.6x50mm column with linear gradient system of H₂O-MeOH-H₃PO₄ 90:10:0.2 to 10:90:0.2 over 4 min. and at a flow rate of 4 mL/min. All compounds were of >99% purity by analytical HPLC analyses. Melting points are uncorrected.

2-Azido-1-(2-nitrophenyl)ethanone (10). A mixture of 2-bromo-2'-nitroacetophenone **9** (30.21 g, 123.8 mmol), sodium azide (24.34 g, 374.4 mmol) in acetone (440 mL) was stirred under nitrogen at room temperature for 16 h. The mixture was filtered to remove inorganic salts and the filtrate was concentrated carefully under reduced pressure at 0 °C. To the residue was added methylene chloride (440 mL). The mixture was stirred for 15 min and the fine powdery inorganic precipitate formed was filtered off. The filtrate was concentrated carefully under reduced pressure at 0 °C to give 2-azido-1-(2-nitrophenyl)ethanone **10** (25.5 g, 100% yield), which was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24 (d, *J*=8.2Hz, 1H), 7.93 (t, *J*=7.6Hz, 1H), 7.81 (m, 2H), 4.67 (s, 2H); ¹³C NMR (400 MHz, DMSO-*d*₆) δ 197.65, 145.94, 135.18, 133.97, 132.47, 128.67, 124.87, 57.18. MS calcd for C₈H₆N₄NaO₃ [M+Na] 229.0338, found 229.0330. Anal. HPLC tr = 1.99 min.

N-(3-Methoxy-4-(oxazol-5-yl)phenyl)-5-(2-nitrophenyl)oxazol-2-amine (11). A mixture of azide **10** (8.52 g, 42 mmol), isothiocyanate **3** (9.58 g, 42 mmol) in 1,4-dioxane (170 mL) was heated to 90 °C. Triphenylphosphine (11.00 g, 42 mmol) was added into the solution at 90 °C during a period of 2 min and the resulted mixture was stirred at 90 °C for 30 min. The solution was cooled to room temperature. The precipitate was collected by filtration, washed with dioxane, and dried to give oxazole **11** as a white solid (11.20 g, 70% yield). mp 250-251 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.70 (s, 1H), 8.37 (s, 1H), 7.97 (d, *J*=7.5 Hz, 1H), 7.84 (m, 2H), 7.66 (d, *J*=8.5 Hz, 1H), 7.60 (m, 2H), 7.51 (s, 1H), 7.43 (s, 1H), 7.30 (dd, *J*=1.8, 6.7 Hz, 1H), 3.95 (s, 3H); ¹³C NMR (400MHz, DMSO-*d*₆) δ 157.45, 156.37, 150.59, 147.60, 146.24, 140.68, 139.60, 133.37, 129.33, 128.71, 127.28, 124.82, 123.73, 121.14, 110.17, 109.54, 100.54, 55.85. MS calcd for C₁₉H₁₅N₄O₅ [M+H] 379.1042, found 379.1042. Anal. HPLC tr = 3.51 min.

tert-Butyl 3-methoxy-4-(oxazol-5-yl)phenyl(5-(2-nitrophenyl)oxazol-2-yl)carbamate (8). To a solution of oxazole **11** (9.00 g, 23.7 mmol) in DMF (150 mL) was added *tert*-butyl dicarbonate (18.00 g, 81 mmol) and DMAP (0.1 g). The solution was stirred at 100°C for 4 h, and then diluted with EtOAc (1 L) and water (1 L) at room temperature. The organic layer was washed with water (1 L) and NaH₂PO₄ aqueous solution (1 L), concentrated under reduced pressure to give **8** as a white amorphous solid (11.34 g, 99% yield). ¹H NMR (400MHz, DMSO-*d*₆) δ 8.45 (s, 1H), 8.04 (d, *J*=8.0Hz, 1H), 7.88-7.66 (m, 5H), 7.58 (s, 1H), 7.14 (d, *J*=1.9Hz, 1H), 6.99 (dd, *J*=1.9, 6.4Hz, 1H), 3.95 (s, 3H), 1.45 (s, 9H); ¹³C NMR (400MHz, DMSO-*d*₆) δ 155.92, 154.78, 151.49, 151.41, 147.14, 146.76, 145.48, 140.02, 133.63, 131.03, 130.00, 127.05, 126.17, 125.75,

124.91, 120.44, 118.49, 115.51, 109.79, 83.77, 56.34, 27.87. MS calcd for C₂₄H₂₃N₄O₇ [M+H] 479.1567, found 479.1567. Anal. HPLC tr = 3.60 min.

***tert*-Butyl 5-(2-aminophenyl)oxazol-2-yl(3-methoxy-4-(oxazol-5-yl)phenyl)carbamate (12).**

To a solution of **8** (9.56 g, 20mmol) in EtOH (400 mL) was added 10% wet Pd/C (1.00 g) to give a black suspension, which was evacuated and flushed with hydrogen three times before being stirred under hydrogen at 30 psi for 3 h. The black suspension was evacuated and filtered through a pad of celite and concentrated to give **12** as an off-white solid (8.80 g, 99% yield). mp 143-144 °C; ¹H NMR (400MHz, DMSO-*d*₆) δ 8.45 (s, 1H), 7.74 (d, *J*=8.4Hz, 1H), 7.57 (s, 1H), 7.47 (s, 1H), 7.41 (dd, *J*=1.2, 7.7Hz, 1H), 7.22 (d, *J*=1.9Hz, 1H), 7.12 (t, *J*=6.9Hz, 1H), 7.01 (dd, *J*=1.9, 6.4Hz, 1H), 6.85 (d, *J*=8.0Hz, 1H), 6.69 (t, *J*=7.3Hz, 1H), 5.35 (s, 2H), 3.94 (s, 3H), 1.45 (s, 9H); ¹³C NMR (400 MHz, DMSO-*d*₆) δ 155.85, 152.75, 151.74, 151.48, 148.96, 146.80, 145.22, 140.39, 129.88, 126.80, 126.09, 125.65, 123.51, 118.61, 117.08, 116.92, 115.33, 111.49, 110.09, 83.40, 56.39, 28.01. MS calcd for C₂₄H₂₅N₄O₅ [M+H] 449.1825, found 449.1825. Anal. HPLC tr = 3.50 min.

***tert*-Butyl 3-methoxy-4-(oxazol-5-yl)phenyl(5-(2-(2-morpholinoacetamido)phenyl)oxazol-2-yl)carbamate (13).**

To a solution of **12** (8.80 g, 20 mmol) and N-methyl-morpholine (3.48 g, 40 mmol) in DMF (80 mL) was added 2-chloroacetyl chloride (2.72 g, 24 mmol) during a period of 5min at 0 °C. The solution was stirred at 0 °C for 30 min and morpholine (1.72 g, 24 mmol) was added. The solution was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was partitioned between EtOAc(200 mL) and water (200 mL). The organic phase was washed with brine, dried over Na₂SO₄, and evaporated to dryness to give **13** as an off-white amorphous solid (9.60 g, 85% yield). ¹H NMR (400MHz, DMSO-*d*₆) δ 9.77 (s, 1H), 8.46 (s, 1H), 7.91 (d, *J*=7.9Hz, 1H), 7.75 (d, *J*=8.4Hz, 1H), 7.65 (m, 2H), 7.58 (s, 1H), 7.45 (m, 2H), 7.20 (d, *J*=1.9Hz, 1H), 7.02 (dd, *J*=2.0, 6.5Hz, 1H), 3.95 (s, 3H), 3.52 (t, *J*=1.7Hz, 4H), 3.14 (s, 2H), 2.50 (t, *J*=1.7Hz, 4H), 1.44 (s, 9H); ¹³C NMR (400MHz, DMSO-*d*₆) δ 168.75, 155.89, 154.02, 151.59, 151.51, 147.35, 146.78, 140.28, 134.44, 129.78, 127.52, 126.13, 125.71, 124.87, 120.54, 118.39, 115.38, 109.86, 83.64, 66.33, 56.39, 55.29, 53.61, 27.99. MS calcd for C₃₀H₃₄N₅O₇ [M+H] 576.2458, found 576.2458. Anal. HPLC tr = 2.85 min.

***N*-(2-(2-(3-Methoxy-4-(oxazol-5-yl)phenylamino)oxazol-5-yl)phenyl)-*N*-methyl-2-**

morpholinoacetamide (BMS-337197).

To a solution of **13** (8.64 g, 15 mmol) in DMF (80 mL) at -50 °C was added 1 N NaHMDS in THF solution (18 mL, 18 mmol) and iodomethane (2.55 g, 18 mmol). The mixture was stirred at -50 °C for 10 min and then warmed to 0 °C slowly during a period of 30 min. The reaction was quenched with water (150 mL) and EtOAc (250 mL). The organic layer was washed with NaHCO₃ aqueous solution and brine, dried over Na₂SO₄, and evaporated to dryness. The residue was dissolved in MeOH (250 mL) and 1N HCl (40 mL), and stirred at 50 °C for 10 h. The organic solvent was removed under reduced pressure and the residue was neutralized with 1 N NaOH to pH=8. The solution was extracted with EtOAc (400 mL) The organic layer was washed with brine, concentrated and then purified by recrystallization from MeOH to give **BMS-337197** as an off- white solid (6.37 g, 87% yield). mp 139-140 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.69 (s, 1H), 8.37 (s, 1H), 7.75-7.24 (m, 9H),

6.97 (s, 1H), 3.95 (s, 3H), 2.41 (m, 4H), 3.12 (s, 3H), 2.86 (dd, $J=15.2, 50.9\text{Hz}$, 2H), 2.21 (t, $J=4.5\text{Hz}$, 3H); ^{13}C NMR (400MHz, DMSO- d_6) δ 169.04, 156.51, 156.39, 150.56, 147.63, 141.19, 140.84, 138.03, 130.17, 129.30, 128.81, 126.53, 126.10, 125.51, 125.45, 123.68, 110.02, 109.48, 100.42, 66.31, 59.82, 55.86, 53.28, 35.41. MS calcd for $\text{C}_{26}\text{H}_{28}\text{N}_5\text{O}_5$ [M+H] 490.2090, found 490.2090. Anal. HPLC tr =2.76 min.

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