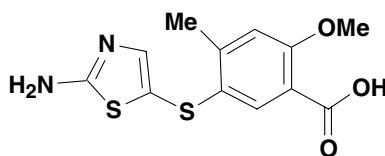


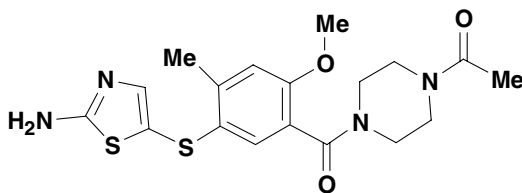
Synthesis of BMS-509744

A. [3-[(2-Aminothiazol-5-yl)thio]-4-methyl-6-methoxy]benzoic acid



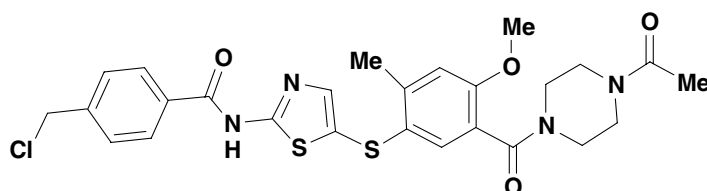
A 4.37 M solution of sodium methoxide in methanol (33.7 mL, 147.3 mmol) was added dropwise to a stirred suspension of 2-amino-5-bromothiazole hydrobromide (9.96 g, 38.3 mmol) and 3-carboxy-4-methoxy-6-methyl-thiophenol (5.84 g, 27.5 mmol) in methanol (95 mL) at 0-5 °C under argon. The cooling bath was removed and the solution was stirred at rt. for 1 h. The mixture was cooled to 0 °C and acidified with a 4 M solution of hydrogen chloride in dioxane (37 mL, 148 mmol). Supplemental hydrogen chloride in dioxane was added slowly to adjust the pH to 2. Precipitated salts were filtered and washed with methanol. The filtrate was concentrated under reduced pressure and the residual solid was washed with water (2 x 15 mL). The solid was dried in vacuo, and triturated with ether to obtain the carboxylic acid (8.52 g, 87%) as a tan solid.

B. 5-[[[3-[(4-Acetylpiperazin-1-yl)carbonyl]-4-methyl-6-methoxy]phenyl]thio]-2-amino-thiazole



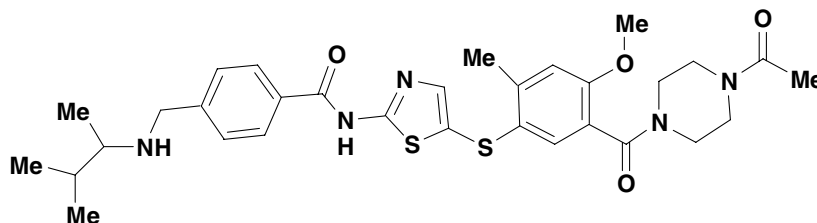
A suspension of [3-[(2-aminothiazol-5-yl)thio]-4-methyl-6-methoxy]benzoic acid (4 g, 12 mmol), N-acetylpiperazine (6.15 g, 48 mmol), ethyl-3-(3-dimethylamino)propyl carbodiimide hydrochloride (4.6 g, 24 mmol), 1-hydroxy-7-azabenzotriazole (1.96 g, 14.4 mmol) and diisopropylethylamine (8.3 mL, 48 mmol) in THF (100 mL) and DMF (12 mL) was heated to 64 °C for 2.75 h. The mixture was cooled to rt. and concentrated in vacuo. The residue was dissolved in dichloromethane and washed with water (50 mL) and 1 N aq. HCl solution (4 x 100 mL). The aqueous layers were combined, brought to slightly alkaline pH using 1 N aq. NaOH solution and extracted with dichloromethane (6 x 70 mL). The dichloromethane extracts were combined, dried (Na₂SO₄), filtered, and concentrated. The residue was triturated with ether (90 mL) to obtain the carboxamide (3.8 g, 78%) as a light tan solid.

C. N-[5-[[[3-[(4-Acetylpiperazin-1-yl)carbonyl]-4-methoxy-6-methyl]phenyl]thio]thiazol-2-yl]-4-(chloromethyl)benzamide



A solution of 5-[[[3-[(4-acetylpiperazin-1-yl)carbonyl]-4-methyl-6-methoxy]phenyl]thio]-2-aminothiazole (3.8 g, 9.35 mmol), 4-chloromethyl-benzoyl chloride (1.61 g, 8.5 mmol) and diisopropylethyl amine (2.2 mL, 12.8 mmol) in dichloromethane (105 mL) was stirred at rt. for 3 h. Supplemental 4-chloromethylbenzoyl chloride (805 mg, 4.68 mmol) was added and the solution was stirred for an additional 2.5 h. The mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution and aq. NaHCO₃ solution. The dichloromethane extract was dried (MgSO₄), filtered, and concentrated in vacuo to obtain the crude amide (4.78g, 100% yield) as a light tan solid.

D. N-[5-[[[3-[(4-Acetylpiperazin-1-yl)carbonyl]-4-methyl-6-methoxy-phenyl]thio]thiazol-2-yl]-4-(N-1,2-dimethylpropylaminomethyl)benzamide



A solution of crude N-[5-[[[3-[(4-acetylpiperazin-1-yl)carbonyl]-4-methoxy-6-methyl]phenyl]thio]thiazol-2-yl]-4-(chloromethyl)benzamide (5.75 g, 10.28 mmol) and 2-amino-3,3-dimethylbutane (4.2 g, 41.1 mmol) in methanol (140 mL) was heated to 62 °C for 16 h. Additional amine (2.7 g, 26.7 mmol) was added and heating was continued for additional 20 h. The mixture was cooled to rt. and concentrated *in vacuo*. The residue was purified using reverse phase automated preparative HPLC (conditions: YMC S10 ODS 30 x 500 mm column, 30 min gradient starting from solvent A (10% MeOH, 90% H₂O, 0.1% TFA) to solvent B (90% MeOH, 10% H₂O, 0.1% TFA), flow rate 50 mL/min, λ = 220 nm) to obtain BMS-509744 as a TFA salt (3.04 g) as an off-white solid. The solid was partitioned between EtOAc (100 mL) and satd. aq. NaHCO₃ solution (25 mL). EtOAc extract was separated and the aq. Layer was extracted with EtOAc. Combined EtOAc extract was dried (Na₂SO₄), filtered, and concentrated to obtain BMS-509744 as a free base (2.3 g, 36% overall yield in two steps, white solid); mass spectrum (M + H)⁺ = 624.29.

Synthesis of BMS-488516

Methyl 4-chloromethyl-2,3-dimethylbenzoate (2). To a solution of methyl 2,3-dimethylbenzoate (**1**) (10.1 g, 61.5 mmol) in 1,2-dichloroethane (25 mL) was added chloromethyl methyl ether (14.6 mL, 190.0 mmol), thionyl chloride (1.80 mL, 24.7 mmol), and ferric chloride (2.0 g, 12.3 mmol) at 0 °C consecutively. The resulting

mixture was heated at 55 °C for 2h before it was allowed to cool to rt, diluted with ethyl acetate, and washed with water and brine. The solution was dried over anhydrous MgSO₄. After the solvent was removed, the residue was subjected to silica gel chromatography (6% ethyl acetate/hexane) to give the desired product **2** (5.65 g, 43% yield) as a slightly yellow oil.

2-amino-5-thiocyanatothiazole (4). A mixture of 2-amino-5-bromothiazole hydrobromide (**3**) (53.0 g, 0.204 mol) and potassium thiocyanate (78.5 g, 0.808 mol) in methanol (1.4 L) was stirred at rt for 20 h. Methanol was evaporated, and to the residue was added water (180 mL). The resulting mixture was basified with 10% NaOH solution to pH 12. The precipitating product **4** (14.0 g, 44% yield) was collected by suction filtration as a brownish solid. LC/MS: (M + H)⁺ = 157.04.

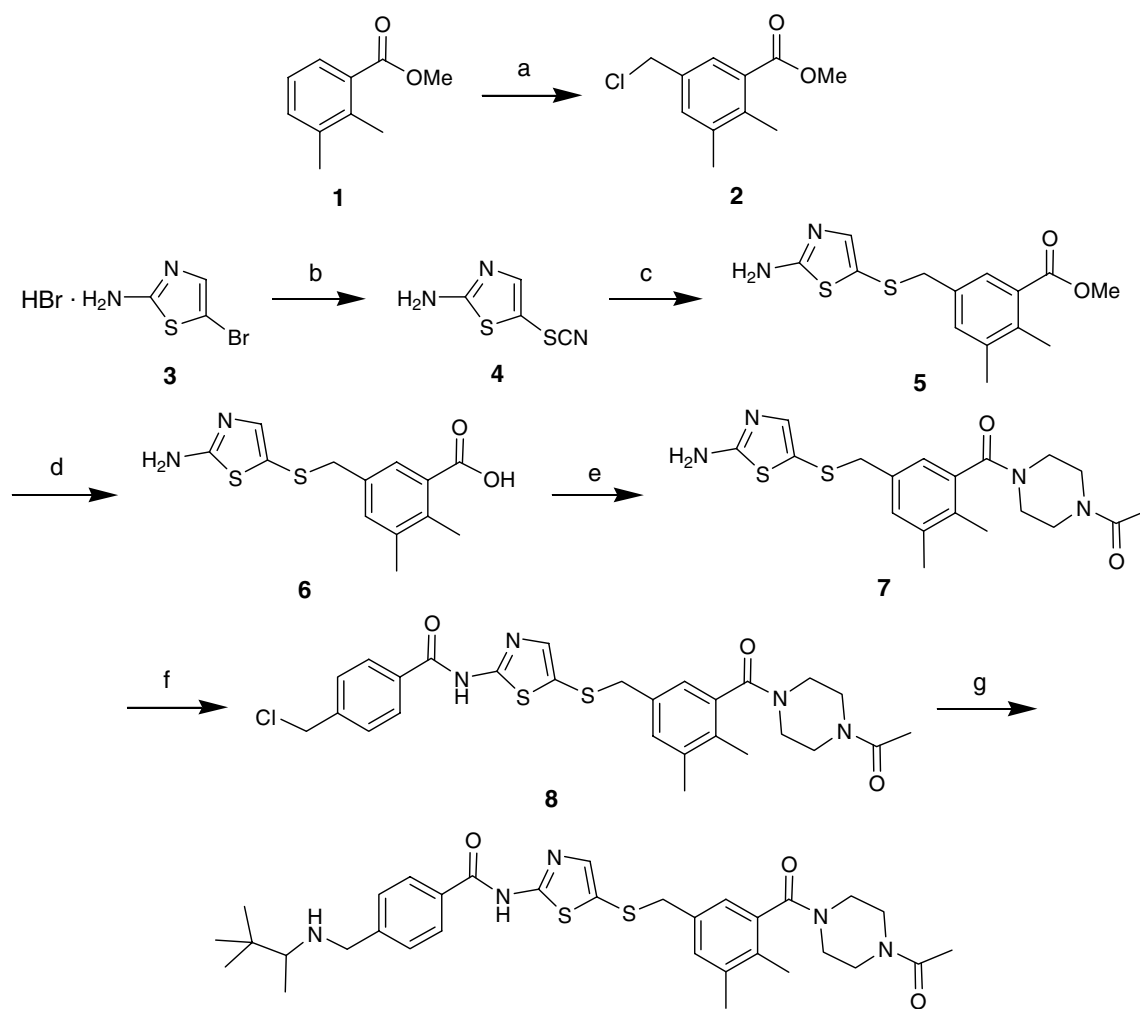
2-Amino-5-[[5-carbomethoxy-3,4-dimethyl)benzyl]thio]thiazole (5). To a solution of **4** (3.55 g, 22.6 mmol) in absolute ethanol (180 mL) was added sodium borohydride (1.70 g, 45.2 mmol) in portions at 0 °C. The resulting mixture was stirred at 0-5 °C for 2 h before acetone (20 mL, 272 mmol) was added and the stirring was continued for another 10 min. Then, to the mixture was added a solution of **2** (5.65 g, 26.6 mmol) in absolute ethanol (10 mL). The mixture was stirred at for 16 h. The solvent was evaporated under vacuum. The residue was diluted with ethyl acetate, washed with brine, and dried over anhydrous MgSO₄. Purification by silica gel chromatography provided **5** (6.07 g, 87% yield) as brownish solid. LC/MS: (M + H)⁺ = 309.17

2-Amino-5-[[[(5-carbohydroxy-3,4-dimethyl)benzyl]thio]thiazole (6). A mixture of **5** (5.00 g, 16.2 mmol), methanol (200 mL), and 1 N sodium hydroxide (60 mL, 60 mmol) was heated at reflux for 5 h. Methanol was evaporated under vacuum, and the residue was neutralized with 1 N HCl to pH 6. The precipitating product **6** (4.10 g, 86% yield) was collected by suction filtration as a beige solid. LC/MS: (M + H)⁺ = 295.14.

2-Amino-5-[[[(5-N-acetylpiperazinylcarboxamido-3,4-dimethyl)benzyl]thio]thiazole (7). A mixture of **6** (0.367 g, 1.25 mmol), 1-acetylpiperazine (0.481 g, 3.75 mmol), BOP reagent (1.11 g, 2.50 mmol), 4-methylmorpholine (0.70 mL, 6.36 mmol), and *N,N*-dimethylformamide (15 mL) was heated at 50 °C for 5 h. After cooling to rt, the mixture was poured into water (50 mL). The resulting mixture was extracted with ethyl acetate (4 x 30 mL). The combined extract was washed with brine (twice) and dried over anhydrous MgSO₄. After the solvent was removed, the residue was subjected to silica gel chromatography (10% methanol/ethyl acetate) to give **7** (0.448 g, 88% yield) as a yellowish solid. LC/MS: (M + H)⁺ = 405.22.

2-(4-chloromethyl)benzamido-5-[[[(5-N-acetylpiperazinylcarboxamido-3,4-dimethyl)benzyl]thio]thiazole (8). To a solution of **7** (0.891 g, 2.20 mmol) and pyridine (3 mL) in dichloromethane (30 mL) was dropwise added 4-chloromethyl benzoyl chloride in dichloromethane (5 mL) at 0 °C. The mixture was stirred at rt for 16 h before it was diluted with ethyl acetate, washed with 1N HCl, water, and brine. The solution was dried over anhydrous MgSO₄. Evaporation of solvent under vacuum gave crude **8**, which was used in the next step without further purification.

BMS-488516. A mixture of **8** (30 mg, 0.054 mmol) and 3,3-dimethyl-2-butanamine (32 mg, 0.32 mmol) in *N,N*-dimethylformamide (0.5 mL) was heated at 55 °C for 16 h before it was diluted with methanol (1.5 mL) and subjected to preparative HPLC to give **BMS-488516** (12 mg, 30% yield) as its TFA salt. LC/MS: (M + H)⁺ = 622.33.



BMS-488516

Scheme 1. Synthesis of BMS-488516. (a). Chloromethyl methyl ether, thionyl chloride, ferric chloride, 43%; (b). Potassium thiocyanate, methanol, rt, 20 h, 44%; (c). i) Sodium borohydride, ethanol, rt, 2 h, ii) **2**, rt, 16h, 87% based on **4**; (d). 1N sodium hydroxide solution, methanol, reflux, 5 h, 86%; (e). 1-Acetylpiperazine, BOP reagent, 4-

methylmorpholine, *N,N*-dimethylformamide, 60 °C, 16 h, 88%; (f). 4-Chloromethyl benzoyl chloride, pyridine, dichloromethane, 16 h; (g). 3,3-Dimethyl-2-butanamine, 33%.

Synthesis of BMS-285047

The procedure is similar to that for BMS-488516 and is detailed in US patent publication US2004/0077695.