

## Supplemental Methods

### Synthesis of the Methyl Ester of DAS534

A solution of 4-amino-3,6-dichloropyridine-2-carboxylic acid (1.1 kg, 5.31 mol) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis(tetrafluoroborate) (2.1 kg, 5.93 mol) in water (6 L) was warmed to 65°C for six hours. After cooling to ambient temperature, the reaction mixture was stirred an additional eighteen hours. The solution was concentrated and the resulting solid washed with 6 N hydrochloric acid (5 x 1 L) and dried to give 4-amino-3,6-dichloro-5-fluoropyridine-2-carboxylic acid (757 g, 3.53 mol, 58% purity). This crude material was added to methanol (3 L) which had been saturated with anhydrous HCl and the reaction mixture was warmed to 45°C for two hours. The solution was added with vigorous stirring to ice water (4 L) and the resulting solid collected. The crude ester was dissolved in ethyl acetate (1 L) and washed with saturated sodium bicarbonate solution (2 x 1 L), dried, and concentrated. The resulting solid was recrystallized from ethyl acetate/hexanes to give methyl 4-amino-3,6-dichloro-5-fluoropyridine-2-carboxylate; 402.5 g, 1.67 mol, melting point (mp) 128-131°C. A solution of 2-(4-chlorophenyl)-[1,3,2] dioxaborinane (75.7 g, 0.38 mol), cesium fluoride (55.3g, 0.36 mole), 1,4-bis(diphenylphosphino)butane (15.5 g, 0.04 mol), methyl 4-amino-3,6-dichloro-5-fluoropyridine-2-carboxylate (91.0 g, 0.36 mol) in acetonitrile (750 mL) was sparged for thirty minutes with nitrogen. Palladium acetate (8.1 g, 0.04 mol) was added and the reaction mixture heated under reflux for three hours. After cooling water (200 mL) was added and the mixture extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with brine (100 mL), dried (NaSO<sub>4</sub>), and concentrated. The residue was purified by column chromatography (33 percent ethyl acetate in hexane) to give the methyl ester of DAS534, methyl 4-amino-3-chloro-6-(4-chlorophenyl)-5-fluoro-pyridine-2-carboxylate (88.8 g, 0.28 mol), mp 233-236°C.

### Synthesis of DAS534 (4-amino-3-chloro-6-(4-chlorophenyl)-5-fluoro-pyridine-2-carboxylic acid)

Methyl 4-amino-3-chloro-6-(4-chlorophenyl)-5-fluoro-pyridine-2-carboxylate (50.0 g, 0.15 mol) was heated at reflux in methanol (100 mL) and 2N sodium hydroxide (125 mL) for two hours. The reaction mixture was partially concentrated and then acidified with concentrated HCl. The solid was collected and dried to give DAS534, 4-amino-3-chloro-6-(4-chlorophenyl)-5-fluoro-pyridine-2-carboxylic acid (44.5 g, 0.16 mol) mp 164-165°C.