A Modified Synthesis of Iodoazidoaryl Prazosin

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Supporting Information

All the compounds are known from the previously reported route.²³

4,5-Dimethoxyl-2-aminobenzoic Acid (2). A mixture of 4,5-Dimethoxy-2-nitro benzoic acid **1** (5 g, 22 mmol) and 10% Raney nickel in 25 mL of 2-propanol was heated at 45 °C in H₂ atmosphere (80 bar). After 5 h, the reaction mixture was filtered, dried under vacuum and recrystallized from EtOH to obtain 3.15 g of **2** (72 %). *R_f* = 0.738 (50% MeOH/CH₂Cl₂); m.p. 172 °C. ¹H NMR (DMSO D₆, 200 MHz) δ 8.01-8.05 (b, 1 H), 7.15 (s, 2 H), 6.38 (s, 2 H), 3.84 (s, 3 H), 3.62 (s, 3 H). ¹³C NMR (DMSO D₆, 50 MHz) δ 147.6, 106.7, 106.4, 160.0, 105.7, 105.3, 105.2, 56.5, 56.1.

6,7-Dimethoxy-2,4-quinazoline-dione (3). A solution of sodium cyanate (2.4 g, 36.9 mmol) in H₂O (10 mL) was slowly added to a stirred suspension of **2** (2.48 g, 15 mmol) in a mixture of water (90 mL) and glacial AcOH (1.5 mL) at 35 °C. The reaction mixture was further stirred for 30 min. Sodium hydroxide (26.6 g, 0.67 mol) was then added in small proportions to the suspension to give a colorless precipitate. After cooling to rt, the pH of the suspension was adjusted to pH 4 with concentrated HCl. The precipitate was filtered, washed thoroughly with water and dried at 100 °C to obtain 3.2 g of **3** (97%). *R_f* = 0.732 (20% MeOH in CH₂Cl₂); mp 278 °C; ¹H NMR (DMSO D₆,

200 MHz) δ 7.24 (s, 1 H), 7.04 (s, 1 H), 6.98 (s, 2 H, amino-H), 3.94 (s, 3 H), 3.86 (s, 3 H). ^{13}C NMR (DMSO D_6 , 50 MHz) δ 168.5, 164.5, 106.9, 106.7, 160.3, 105.7, 105.3, 105.2, 57.5, 56.7.

2,4-Dichloro-6,7-Dimethoxyquinazoline (4). A mixture of **3** (3.34 g, 15.05 mmol), 10 ml (0.107 mol) of POCl_3 and 1 mL (12.8 mmol) of N,N-dimethylaniline was refluxed for 4.5 h, cooled, and allowed to stir overnight at rt. The mixture was then added to 70 mL of ice water, and the resultant precipitate was filtered, washed with water and dried to obtain 2.67 g of **4** (68%). R_f = 0.573 (20% MeOH in CH_2Cl_2); mp 156 °C; ^1H NMR (DMSO D_6 , 200 MHz) δ 7.21 (s, 1 H), 7.18 (s, 1 H), 3.96 (d, 6 H). ^{13}C NMR (DMSO D_6 , 50 MHz) δ 168.7, 164.5, 108.7, 108.4, 108.0, 107.7, 107.3, 107.2, 58.5, 56.1.

2-chloro-4-amino-6,7-dimethoxyquinazoline (5). A solution of **4** (15 g, 8 mmol) in 400 mL of THF, was saturated with anhydrous NH_3 , and stirred for 44 h at rt. The precipitate that was formed was collected and recrystallized from MeOH, to obtain 9.51g (68% yield) of **5**, R_f = 0.52 (20% MeOH/ CH_2Cl_2) mp 301 °C, ^1H NMR (DMSO D_6 , 200 MHz) δ 7.95 - 8.05 (b 2H), 7.61 (s, 1 H), 7.05 (s, 1 H), 3.91 (s, 3 H), 3.85 (s, 3 H). ^{13}C NMR (DMSO D_6 , 50 MHz) δ 152.1, 145.7, 106.7, 106.1, 105.8, 104.7, 104.3, 104.2, 58.5, 56.1.

[4 -(Piperazine-1-carbonyl)-phenyl]-carbamic acid *tert*-butyl ester (7). 1,1-Carbonyldiimidazole (0.867 g, 5.34 mmol) of was added to Boc-protected p-amino benzoic acid (1.0 g, 4.22 mmol) in 10 mL of DMF and stirred at rt for 1 h. Anhydrous piperazine (0.963 g, 11.12 mmol) was then added to this solution and the reaction mixture was stirred at rt overnight. A white precipitate formed which was washed with cold water and dried under vacuum to obtain 0.650 g (51%) of the title compound **7**. R_f 0.40 (30% CH_3OH in CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz) δ 7.40 (m, 4H), 6.65 (s, 1H), 3.60 (b, 4H), 2.83 (b, 4H), 1.44 (s, 9H). MS (EI^+) 305 (M, 100).

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{4-[4-(4-Amino-6,7-dimethoxy-4a,5-dihydro-quinazolin-2-yl)piperazine-1-carbonyl]-phenyl}-carbamic acid *tert* butyl ester (8) The reaction mixture containing *tert*-butyl alcohol (125 mL), 2-chloro-4-amino-6,7-dimethoxyquinazoline **5** (1.0 g, 4.81 mmol) and compound **7** (1.6 g, 5.30 mmol) was refluxed for 24 h. The reaction was cooled and rotary evaporated to dryness. The solid residue was chromatographed on silica gel using 10% methanol in methylene chloride as elutant to obtain 1.245 g (75%) of the desired compound **8**. R_f 0.33 (10 % CH₃OH in CH₂Cl₂). ¹H NMR (DMSO D₆, 300 MHz) 7.52 (s, 1H), 7.46 (s, 1H), 7.36 (d, 2H), 7.26 (b, 2H), 6.67 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.76 (b, 4H), 3.51(b, 4 H). MS (EI⁺) 508 (M, 100)

[4-(4-Amino-6,7-dimethoxy-quinazolin-2-yl)]-(4-amino-phenyl)-methanone. Compound **8** (280 mg, 0.550 mmol) was stirred in 11.0 mL of 4 N HCl / dioxane at 0 °C. for 2 h. The reaction was concentrated in vacuum to give a residue which was successively washed with ethyl acetate, ether and ethanol. The resulting solid was suspended in ethanol and the suspension was heated on a steam bath, cooled to rt, and filtered to obtain 203 mg (77 %) of the title compound. ¹H NMR (DMSO D₆, 300 MHz) δ 7.39 (s, 1H) 7.14 (b, 1H), 7.11 (d, 2H), 6.72 (s, 1H), 6.53 (d, 2H), 5.43 (b, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.51(b, 4 H). MS (EI⁺) 408 (M- 2HCl, 100)

2-[4-(4-Amino-3-iodobenzoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline (9) A mixture of the dichloride salt from above (500 mg, 1.03 mmol), benzyltrimethylammonium dichloroiodate (430 mg, 1.23 mmol) and CaCO₃ (278 mg, 2.78 mmol) in 11.7 mL of CH₂Cl₂ and 8.0 ml of methanol was stirred overnight at rt for 16 h. The solution was filtered, washed with saturated Na₂S₂O₃ solution and water and dried over sodium sulfate. The solid obtained was chromatographed on silica gel using 10 % methanol in methylene chloride as elutant to obtain 520 mg (80% yield) of the desired product **9**. R_f 0.36 (10 % CH₃OH in CH₂Cl₂). ¹H NMR (CDCl₃, 300 MHz) δ 7.81 (d, 1H), 7.31 (s,1H), 6.92 (s, 1H), 6.78 (s, 1 H), 5.12 (s, 2H), 4.26 (s, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 3.7-3.91 (m, 8H); HRMS: calculated for C₂₁H₂₃O₃N₆I 534.0877 found 534.0881

Iodoazidoarylprazosin Compound **9** (100 mg, 0.19 mmol) was dissolved in 10 mL of 8 N acetic acid and cooled to 0 °C. A 5 % aqueous solution of NaNO₂ was added to this solution and the

solution was stirred for 5 min. A 5 % aqueous solution of NaN_3 (0.25 mL) was then added and the reaction was allowed to warm for 5 min. The reaction was again cooled to 0 °C, neutralized with 10 % aqueous NaOH, and extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 and evaporated. The crude yellow oil was solidified by the addition of ether and evaporation in vacuo. The solid was purified by radial chromatography using 10 % methanol in dichloromethane as elutant to obtain 72 mg (65%) iodoarylprazosin. ^1H NMR (CDCl_3 , 300 MHz) δ 7.9 (d, 1 H) 7.5 (m, 1H), 7.19 (d, 1 H), 6.92 (s, 1H), 5.16 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.40 - 4.20 (m, 8H). HRMS : calculated for $\text{C}_{21}\text{H}_{21}\text{O}_3\text{N}_8\text{I}$ 560.08, Found : 560.0779. IAAP was further purified by reverse phase HPLC (C18) using 60% acetonitrile/water and a flow rate of 1.0 mL/min (5.9 min).

Procedure for Palladium-Catalyzed Animation Reactions:

Using imidazolium 10 as ligand: To a flame dried flask under nitrogen were added 4-amino-6,7-dimethoxy-2-chlorolquinazoline **5** (23.9 mg, 0.1 mmol), amine nucleophile NuH (0.8 mmol), and sodium *tert*-butoxide (9.6 mg, 0.10 mmol), followed by $\text{Pd}(\text{OAc})_2$ (0.45 mg, 0.002 mmol, 2 mol %) and N,N-bis-(2,6-diisopropyl) dihydroimidazolium chloride **10** (0.85 mg, 0.002 mmol, 2 mol %) in anhydrous THF (2 mL). The resulting suspension was stirred at rt for 12 h. To the reaction mixture was added ethyl acetate (10 mL). The ethyl acetate solution was washed 3 times with aqueous brine and dried over anhydrous magnesium sulphate. The solvent was concentrated by rotary evaporation and the crude material was purified by silica gel chromatography using methanol/methylene chloride (2-10%). The known compounds **11**, with the isolated yields indicated (Table 1), were characterized by the individual data shown below.

Using tri-*tert*-butylphosphine as ligand: To a flame dried flask under nitrogen were added 4-Amino-6,7-dimethoxy-2-chlorolquinazoline **5** (23.9 mg, 0.1 mmol), amine nucleophile NuH (0.8 mmol), and sodium *tert*-butoxide (14.4 mg, 0.15 mmol), followed by $\text{Pd}(\text{OAc})_2$ (0.45 mg, 0.002 mmol, 2 mol %) and tri-*tert*-butylphosphine (0.34 mg, 0.002 mmol, 2 mol %) in anhydrous o-xylene (2 mL). The resulting suspension was stirred at reflux for 36 h. The solution was allowed to

cool and to the reaction mixture was added ethyl acetate (10 mL). The ethyl acetate solution was washed 3 times with aqueous brine and dried over anhydrous magnesium sulphate. The solvent was concentrated by rotary evaporation and the crude material was purified by silica gel chromatography using methanol/methylene chloride (2-10%). The known compounds **11**, with the isolated yields indicated (Table 1), were characterized by the individual data shown below.

Using 4,5-dehydro-10 as ligand: To a flame dried flask under nitrogen were added 4-Amino-6,7-dimethoxy-2-chloroquinazoline **5** (23.9 mg, 0.1 mmol), amine nucleophile NuH (0.8 mmol), and sodium *tert*-butoxide (9.6 mg, 0.10 mmol), followed by Pd(OAc)₂ (0.45 mg, 0.002 mmol, 2 mol %) and N,N-bis-(2,6-diisopropyl)-imidazolium chloride (0.85 mg, 0.002 mmol, 2 mol %) in anhydrous THF (2 mL). The resulting suspension was stirred at rt for 12 h. To the reaction mixture was added ethyl acetate (10 mL). The ethyl acetate solution was then washed 3 times with aqueous brine and dried over anhydrous magnesium sulphate. The solvent was concentrated by rotary evaporation and the crude material was purified by silica gel chromatography using methanol/methylene chloride (2-10%). The known compounds **11**, with the isolated yields indicated (Table 1), were characterized by the individual data shown below.

4-Amino-6, 7-dimethoxy-2-piperazinylquinazoline: *R*_f: 0.55 (DCM: MeOH: NH₄OH/ 75:23:2); ¹H NMR (DMSO) δ 7.78 (s, 1H), 7.43 (s, 1H), 7.18 (s, 1H), 6.93 (s, 1H), 5.24 (Broad, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.79-3.34 (m, 8H); ¹³C NMR (DMSO) δ 170.1 (s, 1H), 156.8 (s), 152.4 (s), 146.1 (s), 141.2 (s), 140.3 (s), 128.6 (s), 100.3 (s), 71.7 (s), 56.2 (s), 55.3 (s), 41.8 (s), 41.3 (S), 38.6 (s); MS (EI) 290.

4-Amino-6, 7-dimethoxy-2-morpholinylquinazoline: *R*_f: 0.45 (DCM: MeOH: NH₄OH/ 75:23:2); ¹H NMR (DMSO) δ 7.69 (s, 1H), 7.38 (s, 1H), 7.17 (s, 1H), 6.95 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.64-3.02(m, 8H); ¹³C NMR (DMSO) δ 178.0(s, 1H), 171.2 (s), 164.4 (s), 153.8 (s), 147.2 (s), 143.5 (s), 130.6 (s), 99.8 (s), 77.4 (s), 76.8 (s), 74.6 (s), 72.5 (s), 55.3 (s), 54.6 (S); MS (EI) 291.

4-Amino-6, 7-dimethoxy-2-imidazolinyl-quinazoline: R_f : 0.50 (DCM: MeOH: NH_4OH / 75:23:2)
 ^1H NMR (DMSO) δ 8.01 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.38 (s, 1H), 7.17 (s, 1H),
6.95 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (DMSO) δ 176.2 (s, 1H), 164.2 (s), 155.4 (s),
148.8 (s), 146.2 (s), 141.4 (s), 130.4 (s), 128.6 (s), 126.5 (s), 125.8 (s), 99.5 (s), 57.6 (s), 55.3 (s);
MS (EI) 272.