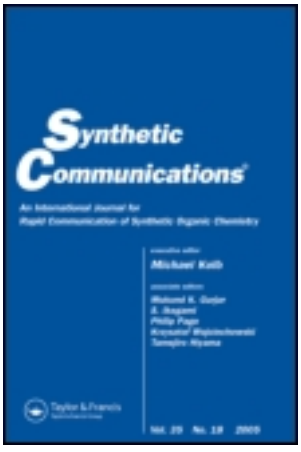

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Efficient Preparation of ((3-Chloro-2-fluoro-phenyl)-[7-methoxy-8-(3-mor for In-Vivo Study

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Efficient Preparation of ((3-Chloro-2-fluoro-phenyl)-[7-methoxy-8-(3-morpholin-4-yl-propoxy)-10,11-dihydro-5-oxa-2,4,11-triaza-dibenzo(a,d)cyclohepten-1-yl]-amine) for In-Vivo Study

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Abstract: An improved route for the preparation of highly functionalized 5,6-dihydro-pyrimido[4,5-b][1,4]oxazepine **1a** in multigram quantities was developed. This new methodology was highlighted by the proper methoxy disposition via a regioselective methylation of 2,4,5-trihydroxy-benzaldehyde followed by a magnesium sulfate–promoted cyclization.

Keywords: Oxazepine, EGFR

INTRODUCTION

Recently, the 5,6-dihydro-pyrimido[4,5-b][1,4]oxazepines **1** were described by us as potent EGFR inhibitors.[1] Additional attractive features of this scaffold also include its good PK and kinase selectivity profile. Our

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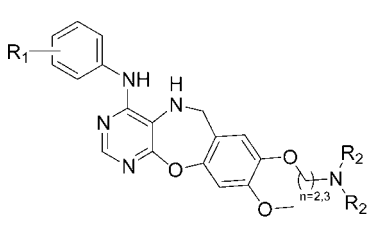
continued interests in this field required the preparation of multigram quantities of compound **1a** for preclinical studies.



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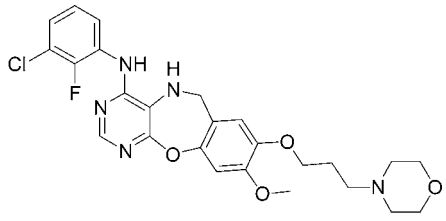


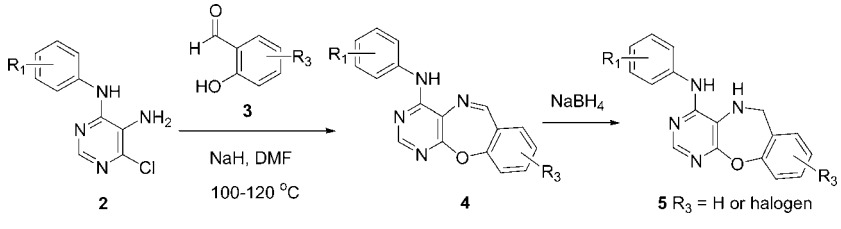
1a

Prior to our work, there was only one reported synthesis of the 5,6-dihydropyrimido[4,5-b][1,4]oxazepines **5**,[2] with R_3 being limited to hydrogen or halogen (Scheme 1). Although this route was suitable for our early-phase SAR study, it soon became obvious to us that the much more complicated substitution pattern on **1a** necessitated modifications of the reported synthetic routes and conditions. In this work, we report an improved synthesis of the oxazepines **1** that led to the preparation of multigram quantities of **1a**.

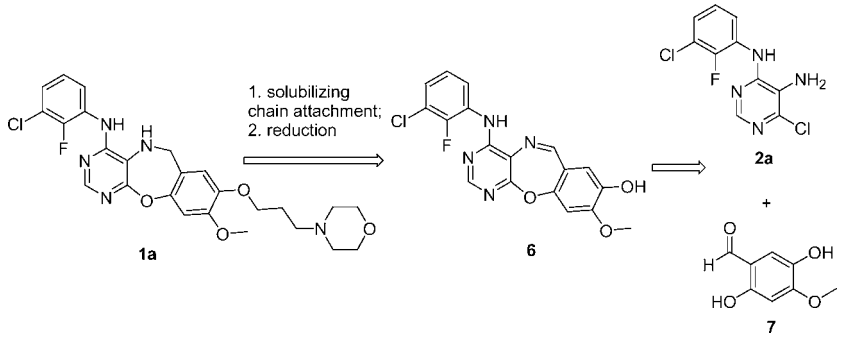
RESULTS AND DISCUSSION

A simple retrosynthetic analysis revealed that the morpholine-containing solubilizing chain in **1a** could be introduced in the later steps of the synthesis (Scheme 2). Furthermore, the preparation of the key intermediate **6** required condensation between the readily available pyrimidine **2a** and the benzaldehyde **7** with the desired hydroxy and methoxy disposition.

The preparation of the two coupling precursors **2a** and **7** were shown in Scheme 3. Chloride substitution on **8** with the corresponding aniline afforded **2a** in a 68% yield. Although there was one report on the selective alkylation of 2,4-dihydroxybenzaldehyde under basic conditions,[3] the selective methylation of 2,4,5-trihydroxy-benzaldehyde **9** was not straightforward. Optimized methylation conditions required cesium carbonate, as base, and DMF, as solvent, that led to **7** in a 53% yield and excellent purity after simple workup. It is noteworthy to point out that potassium carbonate as



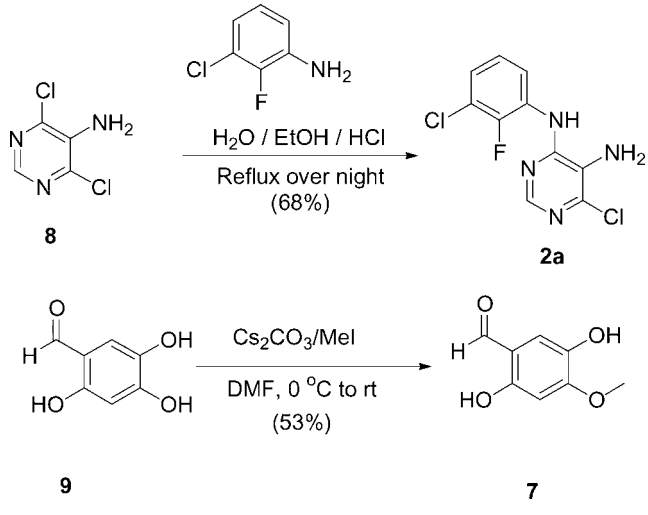
Scheme 1.



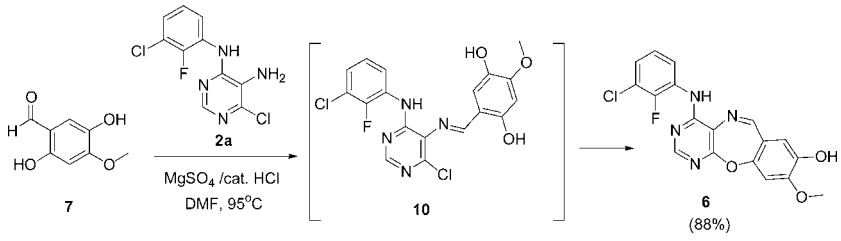
Scheme 2.

base gave **7** in only 20–30% yields. The observed high regioselectivity in the methylation step might be caused by a cesium-mediated chelation effect between the aldehyde and the 2-hydroxy moieties in **9**.

With both **2a** and **7** in hand, we then shift our attention to the coupling reaction between them (Scheme 4). A brief survey of conditions indicated that the imine formation step was crucial for the cyclization to proceed, as magnesium sulfate as additive in the presence of catalytic amount of HCl afforded **6** in a 88% yield, and also with acceptable purity after simple workup, followed by filtration and wash of the solid formed. On the other hand, when only sodium hydride was used as additive, **6** was obtained in a 70% yield and in less purity. Only decomposition occurred when the condensation was carried out without any additives.



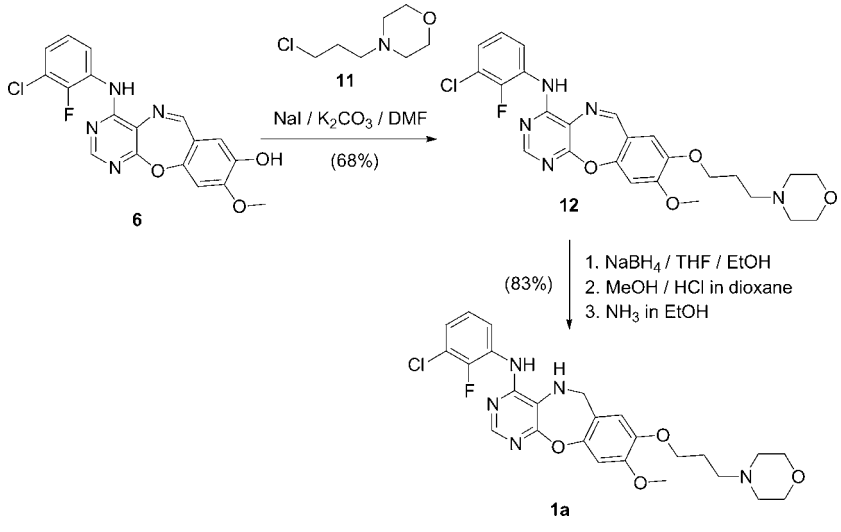
Scheme 3.



Scheme 4.

Phenol **6** was then treated with 4-(3-chloro-propyl)-morpholine **11**[4] in the presence of sodium iodide and potassium carbonate to afford **12** in a 68% yield after chromatography (Scheme 5). Although the imine in **12** was reduced readily with sodium borohydride to afford the crude **1a**, the workup conditions proved to be crucial to the yield of **1a** because of a formed boron complex. The optimized workup conditions used a combination of HCl (1,4-dioxane solution) quenching, NH_3 (ethanol solution) neutralization, and recrystallization, followed by column chromatography to afford **1a** in 83% yield.

In summary, an improved route for the preparation of highly functionalized 5,6-dihydro-pyrimido[4,5-b][1,4]oxazepine **1a** in multigram quantities was developed. This new route was highlighted by the proper methoxy disposition via a regioselective methylation of 2,4,5-trihydroxy-benzaldehyde **9**, followed by a magnesium sulfate–promoted cyclization.



Scheme 5.

EXPERIMENTAL

General

Unless stated otherwise, temperatures are given in degrees Celsius (°C); procedures carried out at room or ambient temperature are carried out at a temperature in the range of about 18°C to about 25°C; organic solutions were dried over anhydrous sodium sulfate; and evaporation of solvent was performed using a rotary evaporator under reduced pressure (600–4000 Pascals 4.5–30 mm Hg) with a bath temperature of up to 60°C. The final products were characterized using nuclear magnetic resonance (NMR) spectra and mass spectra. Elemental analysis was performed when possible. When present, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz with perdeuterio dimethyl sulfoxide (DMSO-d_6) as solvent unless otherwise indicated. Chemical symbols have their usual meanings and SI units and symbols are used.

6-Chloro-N-4-(3-chloro-2-fluoro-phenyl)-pyrimidine-4,5-diamine (2a)

In a 50-mL, round-bottomed flask were placed 5-amino-4, 6-dichloropyrimidine (4.0 g, 0.0246 mol), 2-fluoro-3-chloroaniline (3.2 g, 0.022 mol) in a mixed solvent of water (60 mL), ethanol (10 mL), and concentrated aq. hydrochloric acid (1 mL). The solution was refluxed overnight and cooled to rt, and the solid formed was filtered. The solid collected was washed with water and diethyl ether and then stirred in a 1:1 (v/v) biphase solution of EtOAc and saturated aq. $NaHCO_3$ for 1 h. The layers were then separated, and the organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine and then dried over Na_2SO_4. Filtration of Na_2SO_4 followed by concentration under vacuum afforded **2a** as an orange solid (4.12 g, 68%). ^{1}H NMR (DMSO) δ 8.65 (s, 1H), 7.81 (s, 1H), 7.59–7.54 (dt, 1H), 7.40–7.35 (dt, 1H), 7.25–7.19 (t, 1H), 5.44 (s, 2H, $ArNH_2$). MS m/z: 274(M^{+2}). Calculated for $C_{10}H_7Cl_2FN_4$: 272.

2,5-Dihydroxy-4-methoxy-benzaldehyde (7)

Anhydrous DMF (60 mL) was slowly added to a magnetically stirred one-necked, 250-mL flask with 2,4,5-trihydroxy-benzaldehyde (15.4 g, 0.10 mol) and Cs_2CO_3 (42.36 g, 0.13 mol) at room temperature. Gas (CO_2) evolved rapidly from the reaction. After stirring at rt for half an hour, the flask was placed in an ice bath, and CH_3I (21.3 g, 0.15 mol) was added slowly.

The reaction was then stirred at rt for overnight. Concentrated HCl was then added dropwise until pH = 1. Then EtOAc (50 mL) was added, and the mixture was stirred for 0.5 h. Pure **7** (8.83 g, 53%) was obtained as a brown solid by filtration of the precipitation, followed by washing with water (50 mL × 3) and methanol (30 mL × 3). Mp: 193.2–195.1 °C; ^{1}H NMR (DMSO) δ 10.50 (s, 1H), 9.95 (s, 1H), 8.88 (s, 1H), 6.99 (s, 1H), 6.50 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (DMSO) δ 190.92, 156.47, 155.62, 139.89, 114.41, 113.94, 100.11, 55.76. Anal. calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80; found: C, 56.85; H, 4.73.

1-(3-Chloro-2-fluoro-phenylamino)-7-methoxy-5-oxa-2,4,11-triaza dibenzo[a,d]cyclohepten-8-ol (6)

2a (2.73 g, 0.01 mol), **7** (1.68 g, 0.01 mol), $MgSO_4$ (3.6 g) were pleaced in a 50-mL tube in anhydrous DMF (20 mL). Concentrated HCl (aq., 3 drops) was added, and the tube was then sealed. The suspension was heated to 95 °C overnight and poured into water. The solid formed was filtered and washed with methanol (5 mL × 3) to give **6** (3.41 g, 88%) as a brown solid. ^{1}H NMR (DMSO) δ 9.46 (s, 1H), 9.10 (s, 1H), 8.49 (s, 1H), 8.23 (s, 1H), 7.73 (m, 1H), 7.39 (m, 1H), 7.23 (m, 1H), 6.96 (s, 1H), 6.84 (s, 1H), 3.86 (s, 3H); MS m/z: 386.97(M^{+1}), 388.86; calculated for $C_{18}H_{12}ClFN_4O_3$: 386.06

4-(3-Chloro-propyl)-morpholine (11)

1-Bromo-3-chloro-propane (20 g, 0.127 mol) to a magnetically stirred one-necked, 250-mL flask with toluene (100 mL) at 75 °C were added and morpholine (24.4 g, 0.28 mol). The solution was stirred at 75°C for 4 h. The reaction was then filtered to remove the precipitation, and the filtrate was concentrated under vacuum to afford crude **11**. Column chromatography (CH_2Cl_2:CH_3OH=20 : 1) afforded pure **11** as a colorless liquid (15.56 g, 75%). ^{1}H NMR ($CDCl_3$) δ 3.77–3.74 (m, 4H), 3.66 (t, J = 6.6 Hz, 2H), 2.55–2.47 (m, 6H), 2.04–1.95 (m, 2H).

(3-Chloro-2-fluoro-phenyl)-[7-methoxy-8-(3-morpholin-4-yl-propoxy)-5-oxa-2,4,11-triaza-dibenzo[a,d]cyclohepten-1-yl]-amine (12)

6 (10.5 g, 0.027 mol), **11** (6.2 g, 0.038 mol), NaI (0.21 g, 0.0014 mol), K_2CO_3 (11.2 g, 0.081 mol) in anhydrous DMF (125 mL) were placed in a 250 mL flask. The mixture was heated to 7°C overnight. The mixture was then filtered and the filtrate was poured into ethyl acetate (150 mL). The organic

phase was washed with brine (100 mL × 3) and dried over $MgSO_4$. Filtration followed by concentration of the filtrate under vacuum provided crude **12**. Further purification by column chromatography (silica gel, EtOAc–hexane–CH_3OH = 5 : 5 : 1) provided pure **12** as a yellow solid (9.51 g, 68%). Mp: 126.1–128.2°C; ^{1}H NMR (DMSO) δ 9.15 (s, 1H), 8.55 (s, 1H), 8.23 (s, 1H), 7.71 (m, 1H), 7.38 (m, 1H), 7.25 (m, 2H), 6.88 (s, 1H), 4.03(t, J = 6.4 Hz, 2H), 3.86 (s, 3H), 3.57(m, 4H), 2.43–2.35 (m, 6H), 1.89 (m, 2H); ^{13}C NMR (DMSO) δ 161.83, 160.28, 158.31, 156.57, 154.53, 151.26, 150.97 (d, J_{C-F} = 246.8 Hz), 145.64, 128.25 (d, J_{C-F} = 11.3 Hz), 125.85, 124.71(d, J_{C-F} = 4.5 Hz), 124.48, 119.75 (d, J_{C-F} = 16.6 Hz), 118.12, 116.41, 114.41, 105.32, 67.40, 66.19, 56.25, 54.74, 53.34, 25.89; MS m/z: 514.18, 516.13 (M^{+1}); calculated for $C_{25}H_{25}ClFN_5O_4$: 513.16; anal. calcd for $C_{25}H_{25}ClFN_5O_4$: C, 58.42; H, 4.90; N, 13.63; found: C, 58.41; H, 4.83; N, 13.57.

(3-Chloro-2-fluoro-phenyl)-[7-methoxy-8-(3-morpholin-4-yl-propoxy)-10,11-dihydro-5-oxa-2,4,11-triaza-dibenzo[a,d] cyclohepten-1-yl]-amine (1a)

12 (11.32 g, 0.022 mol) was placed in a 250-mL flask in a mixed solvent of THF (50 mL) and EtOH (15 mL). Sodium borohydride (3.67 g, 0.097 mol) was then added, and the reaction was heated to 60 °C for 3 h. The flask was then placed in an ice bath and MeOH (30 mL) was added slowly, followed by HCl (4M in 1,4-dixane, 40 mL). The mixture was stirred at room temperature for 1.5 h and then vacuum filtrated to remove inorganic salts. The filtrate was rotatory evaporated to remove most of the solvent, and the residue was kept at −20°C overnight. The yellow solid formed was collected by vacuum filtration, followed by washing with water and diethyl ether. The yellow solid was then suspended in NH_3 ethanol solution (2M, 300 mL), and the suspension was stirred at rt for 1 h. The yellow solid was then collected by vacuum filtration, decolorized by active carbon in methanol (300 mL), and recrystallized from methanol to afford the first batch of **1a** as a light yellow solid. The mother liquor and the filtrate from the previous NH_3 neutralization step were combined and extracted with ethyl acetate. The combined organic phases were washed with brine and dried over $MgSO_4$. Filtration followed by concentration under vacuum gave a brown solid, which was purified by column chromatography (silica gel, EtOAc–Hexane–Methanol = 5 : 5 : 1) to provide a second batch of **1a** as a light yellow solid. Both batches of **1a** were combined and recrystallized from methanol (250 mL) to provide **1a** as a light yellow crystal. (9.37 g, 83%). Mp: 86.0–88.0 °C; ^{1}H NMR (DMSO) δ 8.27 (s, 1H), 7.83 (s, 1H), 7.63 (m, 1H), 7.31 (m, 1H), 7.18 (m, 1H), 7.00 (s, 1H), 6.85 (s, 1H), 5.40 (t, J = 4.8 Hz, 1H), 4.37 (d, J = 4.8 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.76 (s, 3H), 3.58–3.55(m, 4H), 2.43–2.35 (m, 6H), 1.89–1.84 (m, 2H);

^{13}C NMR (DMSO) δ 154.95, 153.44, 150.50 (d, $J_{C-F} = 246.8$ Hz), 149.40, 149.29, 146.71, 144.75, 129.33(d, $J_{C\text{-}F} = 11.3$ Hz), 124.85, 124.65(d, $J_{C-F} = 4.5$ Hz), 123.84, 123.58, 119.78 (d, $J_{c-F} = 16.6$ Hz), 117.11, 113.78, 105.62, 67.54, 66.21, 56.00, 54.82, 53.35, 45.18, 26.09; MS m/z: 516.07, 518.09 (M^{+1}); calculated for $C_{25}H_{25}ClFN_5O_4$: 515.17; anal. calcd. for $C_{25}H_{27}ClFN_5O_4$: C, 58.20; H, 5.27; N, 13.57; found: C, 57.81; H, 5.10; N, 13.51.

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