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Practical Synthesis of Roscovitine and CR8

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Abstract:

Roscovitine and CR8 are potent inhibitors of cyclin-dependent kinases. A scalable synthesis of both inhibitors is described. In the case of CR8, the biarylmethylamine moiety was obtained as a stable and high-purity salt.

1. Introduction

Abnormalities in protein phosphorylation have been observed in numerous major human diseases,[1] strongly encouraging the search for pharmacological inhibitors of protein kinases.[2] The 2,6,9-trisubstituted purines were among the first low-molecular weight inhibitors of cyclin-dependent kinases (CDKs).[3] One of these, (*R*)-roscovitine, **10a** (CYC202, Seliciclib), has now reached clinical phase 2 trials against nonsmall cell lung cancer and nasopharyngeal cancer.[4] In this context we have pursued an intensive search for improved analogues of roscovitine, taking into account their ability to interact with CDKs (guided by the CDK2/ and CDK5/roscovitine crystal structures), to maintain high kinase selectivity, and to induce cell death at lower concentrations. In this study,[5] CR8, **10b**, was identified as a highly efficacious agent, 25−50 times more potent than (*R*)-roscovitine at inducing apoptotic cell death and its accompanying biochemical events and therefore suitable for preclinical development.[6] We herein describe a protocol for a scalable synthesis of roscovitine and CR8 (Scheme 1).

2. Results and Discussion

We first focussed our work on the production of roscovitine. Roscovitine can be prepared in a simple three-step procedure (Scheme 1). In the last step, a chromatographic purification of roscovitine is required.[7] The three-step procedure has been optimized with the goal of avoiding any chromatographic isolation of either the intermediates or the target compound. In the first step, 2,6-dichloropurine **7**, was converted into 6-benzylaminopurine **8a**, upon heating with benzylamine in *n*-butanol. Alkylation of **8a** was regioselectively accomplished in the usual way upon treatment with isopropylbromide in the presence of K_2CO_3.[5] Amination with (*R*)-2-aminobutanol was then performed. However, in this last step, the isolation of the material was plagued by the formation of side compounds (which had lower R_f than **10a** in thin-layer chromatography (TLC)). The key feature affecting the reaction's outcome based on an in-depth study appeared to be the quantity of (*R*)-2-aminobutanol. The best compromise between reaction rate and isolated yield was obtained with 8 mol equiv. In the optimized conditions, **10a** was purified by crystallization without the need of chromatographic purification. Indeed, the reaction proceeded faster to completion with 10 mol equiv. However, the isolated yield was diminished (65% instead of 89%).

In the case of CR8, **10b**, a practical route to the key building block **6** had to be secured. Commercially available 4-pyridylbenzaldehyde, **1**, was converted into the oxime **2** using hydroxylamine hydrochloride and AcONa in EtOH at rt. Reduction of **2** was first performed using $LiAlH_4$ in THF. TLC of the crude reaction mixture showed four to five spots less polar than that for the targeted amine **3**. When this crude amine

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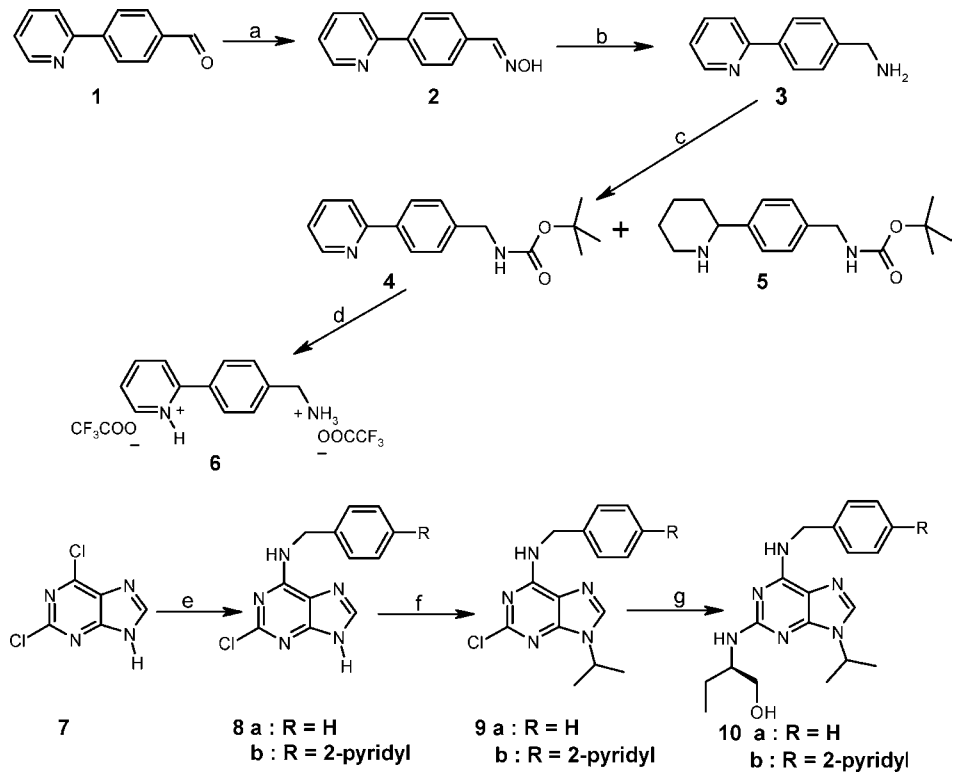
Scheme 1[a]



[a] Reagents and conditions: a) $NH_2OH \cdot HCl$, NaOAc; b) H_2 Pd/C, or $LiAlH_4$,THF; c) Boc_2O, NEt_3; d) CH_2Cl_2, TFA; e) benzylamines, BuOH, 110°C; f) 2-bromopropane, K_2CO_3, DMSO, 18−20 °C; g) (*R*)-2-aminobutan-1-ol, heat, 160°C.

was reacted in the next step, compound **7b** was isolated in moderate yield. Several attempts to purify **3** as salts were unsuccessful. Hydrogenation of **2** was then investigated. Although the TLC of the mixture looked clean, the NMR spectrum of the crude amine showed a 6:1 mixture of the desired amine **3** and an impurity. In order to identify this side product, the crude reaction mixture was submitted to protection with di-*tert*butyldicarbonate. Interestingly, the Boc protected derivative **4**, crystallized easily from Et_2O, and acylated impurity **5** was well rejected in the mother liquors. The bis-trifluoroacetate was not hygroscopic and could be kept at rt for at least six months. Compound **5** was identified as a piperidine derivative. The hydrogenation conditions were investigated in detail (reaction time, temperature, pressure, solvent). In particular, the influence of pressure on yield and selectivity was measured in the range of 1−10 atm. The reaction rate was low below 3 atm. Noticeable amounts of the piperidine derivative (12−15%) were formed at 10 atm. Under optimized conditions (5 atm, 18−24 h reaction time) some over-reduction could not be completely avoided, leading to 3−5% **5** in the crude reaction mixture after acylation. The acylated derivative, **4**, was converted into the bis-trifluoroacetate salt **6** which was isolated in good overall yield (80−85% from the aldehyde) and purity (>98%). The bis-trifluoroacetate **6** was not hygroscopic and could be stored at rt for at least 6 months. Condensation of **6** with 2,6-dichloropurine was performed in the presence of 4 molar equiv of NEt_3. The last two synthetic steps were achieved using the same conditions for the synthesis of roscovitine to afford CR8 in 72−76% overall yield.

Interestingly, the piperidine **5** had been previously incorporated in other series of active compounds.[8] Therefore, a selective route to this compound was investigated. The monoprotected piperidine **5** was easily obtained upon adding 1 molar equiv of AcOH in the hydrogenation medium.

In summary, the synthesis of both CDK inhibitors could be performed at a 30−50 g scale without relying on time-consuming and costly chromatography purification steps. In the particular case of CR8, the presented procedure circumvents the low solubility of biaryls.[9] Biarylamines, being privileged pharmacophore structures, are part of numerous biologically active products;[10] therefore, the herein reported simple procedure could find other applications.

Experimental Section

Melting points were determined on a Kofler hot-stage (Reichert) and are uncorrected. NMR spectra were recorded on Bruker Avance 400 MHz (100 MHz for ^{13}C NMR). Chemical shifts are given in ppm downfield of tetramethylsilane (TMS) used as an internal standard. Reactions were monitored

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by TLC using Merk silica gel 60F-254 thin layer plates. Column chromatography was carried out on SDS Chromagel 60 ACC, 40−63 μm. The HPLC analyses were carried out on a system consisting of a Waters 600 system controller, a Jones chromatography heater−chiller oven and a Waters 994 photodiode array detector.

4-(2-Pyridyl)benzaldehyde Oxime (2). To a solution of **1** (36.6 g, 0.2 mol) in 50 mL of EtOH and 20 mL of H_2O were added hydroxylamine hydrochloride (15.27, 0.21 mol) and AcONa, $3H_2O$ (29.90 g, 0.21 mol). The resulting slurry was stirred for 12 h at rt. The mixture was concentrated to dryness, and the resulting solid was washed with H_2O (2 × 5 mL) and EtOH, (1 × 5 mL). Yield 97%, mp 138−139 °C: ^{1}H NMR ($CDCl_3$): δ 7.16 (m, 1H, $H_{pyridyl}$), 7.60 (d, J = 8.08 Hz 2H, H_{phenyl}), 7.67 (m, 2H, $H_{pyridyl}$), 7.91 (d, J = 8.08 Hz, 2H, H_{phenyl}), 8.08 (s, 1H, H−C=N), 8.61 (d, J = 3.28 Hz, 1H, $H_{pyridyl}$), 10.70 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 119.45, 121.49, 125.60, 125.95, 128.98, 132.60, 136.02, 138.74, 147.08, 148.54.

***tert*-Butyloxycarbonyl-4-(2-pyridyl)phenylmethylamine (4).** To a solution of **2** (19.8 g, 0.1 mol) in 200 mL of EtOH was added 1 g of 10% Pd/C, and the suspension was submitted to hydrogenation at 5 atm for 18 h at rt. The catalyst was filtered on celite and washed with EtOH (2 × 20 mL). The solution was concentrated in vacuo, and the resulting viscous oil, **3**, was used in the next step without any purification. The crude amine, **3**, was dissolved in 150 mL of THF. The solution was cooled to 0 °C; NEt_3 (17 mL, 0.11 mol) and di*tert*-butyldicarbonate, $(Boc)_2O$ (24 g, 0.11 mol) were added. The resulting solution was stirred at rt for 4 h. The mixture was concentrated in vacuo and triturated with 30 mL of Et_2O. The resulting solid was washed with Et_2O (2 × 10 mL). Yield: 89%, mp 87−89 °C. ^{1}H NMR ($CDCl_3$): δ 1.47(s, 9H, $C(CH_3)_3$), 4.37(d, 2H J = 5.3 Hz, CH_2), 4.93 (br, 1H, NH), 7.22 (m, 1H, $H_{pyridyl}$), 7.38 (d, J = 8.08 Hz, 2H, H_{phenyl}), 7.73 (m, 2H, $H_{pyridyl}$), 7.95 (d, 2H, H_{phenyl}), 8.68 (d, J = 4.08 Hz, 1H, $H_{pyridyl}$). ^{13}C NMR ($CDCl_3$): δ 28.25, 44.15, 78.86, 120.05, 121.95, 126.87, 127.38, 136.59, 138.29, 139.65, 149.53, 155.49, 156.69. Anal. ($C_{17}H_{20}N_2O_2$) Calc: C, 71.81; H, 7.09; N, 9.85; found: C, 71.45; H, 6.98; N, 9.66.

***tert*-Butyloxycarbonyl-4-(2-piperidyl)benzylamine (5).** In the reduction step 1 molar equiv of CH_3COOH was added. Otherwise, the procedure was accomplished according to the method described in the preceding section. Compound **4** did not crystallize and was purified by column chromatography using CH_2Cl_2/MeOH/NEt_3 (98:2:0.1) as eluent. Yield 65%, oil. ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 9H, *tert*-Bu), 1.43−1.93 (m, 6H, $H_{piperidyl}$), 2.78 (td, 1H, J = 11.6, 3.1 Hz, $H_{piperidyl}$), 3.19 (d, 1H, J = 11.6 Hz, $H_{piperidyl}$), 3.58 (dd, 1H, J = 10.4, 2.4 Hz, $H_{piperidyl}$), 4.24 (d, 2H, J = 5.8 Hz, CH_2), 4.81 (br, 1H, NH), 7.19 (d, J = 7.5 Hz, 2H, H_{phenyl}), 7.38 (d, 2H, H_{phenyl}); ^{13}C NMR ($CDCl_3$): δ 5.2, 25.7, 28.33, 30.22, 34.8, 44.3, 47.65, 61.92, 126.85, 127.41, 137.58, 144.49, 155.83. Anal. ($C_{17}H_{26}N_2O_2$) Calc: C, 70.31; H, 9.02; N, 9.65; found: C, 70.39; H, 9.24; N, 9.48.

4-(2-Pyridyl)benzylamine Ditrifluoroacetate (6). To a cooled (0 °C) solution of **3** (18 g, 0.063 mol) in 85 mL of CH_2Cl_2 was added 85 mL of anhydrous CF_3COOH. The cooling bath was removed, and the mixture was stirred at rt for 2 h. The mixture was evaporated to dryness, and the residue was first triturated with 20 mL of cyclohexane. The cyclohexane was decanted, and 20 mL of Et_2O was added. The salt crystallized and was washed with 10 mL of Et_2O. Yield 87%, mp 165−168 °C. ^{1}H NMR ($CDCl_3$): δ 4.11(s, 2H, CH_2), 4.99 (br, 3H, NH), 7.23 (t, 1H, $H_{pyridyl}$), 7.38 (m, 2H, H_{phenyl}), 7.73 (dt, 2H, $H_{pyridyl}$), 7.94 (d, J = 7.83 Hz, 2H H_{phenyl}), 8.61 (d, J = 4.08 Hz,1H, $H_{pyridyl}$), 8.7 (br s, 3H H_3N). ^{13}C NMR (DMSO-d_6): δ 41.28, 115.42 (q, J_{C-F} = 293 Hz), 120.16, 122.41, 126.49, 128.59, 134.41, 137.40, 137.43, 148.29, 154.29, 157.77 (q, J_{C-C-F} = 35 Hz). Anal. ($C_{16}H_{14}N_2O_4F_6$) Calc: C, 46.61; H, 3.42; N, 6.79; found: 46.84; H, 3.53; N, 6.43.

Synthesis of 6-Arylmethylamino-2-chloropurines. To a solution of **1** (23 g, 0.1 mol) in 200 mL of *n*-BuOH were added the primary amine (0.12 mol) and NEt_3 (synthesis of **8a**: 22.5 mL, 0.16 mol; synthesis of **8b**: 70 mL, 0.50 mol). After 3 h heating at 110 °C, the mixture was cooled to 20 °C, and the solid was filtrated, washed with 5 mL of cold *n*-BuOH, and dried in vacuo.

2-Chloro-6-phenylmethylaminopurine (8a): yield 95%; mp > 250 °C. ^{1}H NMR (DMSO-d_6): δ 4.80 (s, 2H, CH_2), 7.45−7.70(m, 5H, H_{phenyl}), 7.91(s, 1H, H-8). (Solubility in $DMSO_{d6}$ or in CD_3OD was to low for recording a ^{13}C NMR spectrum). Anal. ($C_{12}H_{10}N_5Cl$) Calc: C, 55.50; H, 3.88; N, 26.97; found: C, 55.81; H, 3.73; N, 26.41.

2-Chloro-6-[4-(2-pyridyl)phenylmethylamino]purine (8b): yield 93%; mp > 250 °C. ^{1}H NMR (DMSO-d_6): δ 4.80 (s, 2H, CH_2), 7.20 (m, 1H, $H_{pyridyl}$), 7.45 (d, 2H, J = 8 Hz, H_{phenyl}), 7.72 (m, 2H, $H_{pyridyl}$), 7.95 (m, 3H, H_{phenyl} and H-8), 8.54 (d, 1H, J = 4.8 Hz, $H_{pyridyl}$). Anal. ($C_{17}H_{13}N_6Cl$) Calc: C, 60.63; H, 3.89; N, 24.95; found: C, 60.80; H, 3.98; N, 24.61.

Alkylation of Chloropurines 9. To a solution of **8** (0.08 mol) in DMSO (100 mL) at 18−20 °C were added K_2CO_3 (35.52 g, 0.24 mol) and 2-bromopropane (19 mL, 0.2 mol). After 5 h stirring at 18−20 °C, 2-bromopropane (4.7 mL, 0.05 mL) was added, and the stirring continued at the same temperature for 5 h. After addition of 200 mL of cold (5 °C) H_2O, the mixture was extracted with EtOAc (3 × 100 mL, and the combined organic layers were washed with brine (3 × 50 mL), dried, and dried over Na_2SO_4. Derivatives **9**, which crystallized upon concentration, were triturated once with 5 mL of 2-propanol and were collected by filtration.

2-Chloro-6-phenylmethylamino-9-iso-propylpurine (9a): yield 85%, mp 180−182 °C. ^{1}H NMR (DMSO): δ 1.58 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$), 4.90 (hept, 1H, $CH(CH_3)_2$), 6−7.25−7.50 (m, 5H, H_{phenyl}), 8.16 (s, 1H, H-8). ^{13}C NMR (DMSO): δ 21.81, 43.19, 46.04, 117.98, 126.44, 126.85, 127.67, 137.03, 137.97, 148.93, 153.03, 154.45. Anal. ($C_{15}H_{16}N_5Cl$) Calc: C, 59.70; H, 5.34; N, 23.21; found: C, 59.60; H, 5.22; N, 23.36.

2-Chloro-6-[4-(2-pyridyl)phenylmethylamino]-9-iso-propylpurine (9b): yield 86%, mp 187−189 °C. ^{1}H NMR ($CDCl_3$): δ 1.58 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$), 4.79 (hept, 1H, $CH(CH_3)_2$), 4.85 (bs, 2H, $NHCH_2$), 6.59 (bs, 1H, $NHCH_2$), 7.20−7.23 (m, 1H, $H_{pyridyl}$), 7.49 (d, 2H, J = 8 Hz, H_{phenyl}), 7.73−7.71 (m, 2H, $H_{pyridyl}$), 7.79 (s, 1H, H-8), 7.98 (d, 2H, H_{phenyl}), 8.71 (d, 1H, J = 4.8 Hz, $H_{pyridyl}$). 22.52, 44.07, 46.78, 118.72, 120.25, 122.08, 127.01, 128.04, 136.66, 137.67, 138.54,

139.02, 149.57, 154.15, 155.15, 156.67. Anal. ($C_{20}H_{19}N_6Cl$) Calc: C, 63.41; H, 5.05; N, 22.18; found: C, 63.27; H, 5.20; N, 22.35.

Amination by Nucleophilic Substitution of the 2-Chlorine (10). A mixture of chloropurines, **9** (0.138 mol), and (*R*)-2-aminobutan-1-ol (104.10 mL, 1.11 mol) was heated under N_2 at 160 °C for 8 h. After cooling, H_2O (100 mL) was added, and the mixture was extracted with EtOAc (4 × 100 mL). The organic layer was washed with warm (50 °C) H_2O (2 × 50 mL), dried, and evaporated until dryness. Crystallization occurred after addition of 10 mL of EtOAc. The crystals of trisubstituted purines **10** were collected by filtration.

(*R*)-2-(1-Hydroxybut-2-ylamino)-6-(benzylaminopurine)-9-isopropylpurine. Roscovitine (10a): yield 89%, mp 108−110 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (m, 3H), 1.44 (d, 6H, CH(CH_3)$_2$). 1.53 (m, 2H, CH_2CH_3), 3.57(m, C*H*NH), 3.75(m, 1H, HOC*H*), 3.84 (m,1H, HOC*H*), 4.52 (hept, J = 6.5 Hz, 1H, C*H*(CH_3)$_2$), 4.71 (bs, 2H, CH_2), 4.91 (bs, 1H), 7.28−7.30 (m, 6H).^{13}C NMR ($CDCl_3$): δ 10.84, 22.44, 22.50, 24.90, 44.24, 56.13, 68.06, 114.55, 127.16, 127.58, 128.45, 134.43, 138.90, 154.84, 159.97. Anal. ($C_{20}H_{20}N_6O$) Calc: C, 61.52; H, 6.45; N, 26.90; found: C, 61.64; H, 6.25; N, 26.64.

(*R*)-2-(1-Hydroxybut-2-ylamino)-6-[4-(2-pyridyl)phenylmethylamino]-9-iso-propylpurine. CR8 (10b): yield 92%, mp 89−93 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, J = 7.2 Hz, CH_3CH_2), 1.47 (d, 6H, J = 6.8 Hz, CH(CH_3)$_2$), 1.50−1.60 (m, 2H, CH_3CH_2), 3.56 (dd, 1H, J = 10.8 and J' = 2.8 Hz, CH_2OH), 3.75 (dd, 1H, J = 10.8 Hz, and J' = 2.4, CH_2OH), 3.79−3.85 (m, 1H, C*H*NH), 4.54 (hept, 1H, C*H*(CH_3)$_2$), 4.76 (m, 2H, NHCH_2), 4.90 (bs, 1H, CHN*H*), 6.10 (bs, 1H, N*H*CH_2), 7.16 (td, 1H, J = 5.4 and J' = 1.6 Hz, $H_{pyridyl}$), 7.41 (d, 2H, J = 8.4 Hz, H_{phenyl}), 7.45 (s, 1H, 8-H), 7.63−7.70 (m, 2H, $H_{pyridyl}$), 7.89 (d, 2H, J = 8.4 Hz, H_{phenyl}), 8.62 (d, 1H, J = 4.8 Hz, $H_{pyridyl}$). ^{13}C NMR ($CDCl_3$): δ 10.5, 22.3, 22.4, 24.1, 38.0, 45.9, 55.0, 66.8, 113.6, 120.0, 120.9, 125.5, 126.8 (×2), 127.7, 130.0, 134.1, 135.9, 137.7, 140.0, 149.1, 154.1, 156.8, 159.1. Anal. ($C_{24}H_{29}N_7O$) Calc: C, 66.80; H, 6.77; N, 22.72; found: C, 66.43; H, 6.65; N, 22.51.

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Supporting Information Available

NMR spectra of 4-(2-pyridyl)benzylamine ditrifluoroacetate (**6**), roscovitine (**10a**), and CR8 (**10b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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