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Suzuki-type Pd(0) coupling reactions in the synthesis of 2-arylpurines as Cdk inhibitors

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Abstract—A new series of 2-aryl-substituted purine derivatives has been synthesized by Suzuki Pd(0) coupling reactions. Moderate in vitro inhibitory activity against Cdk1 and Cdk5 was observed. These compounds are inactive against GSK3.

2,6,9-Trisubstituted purines have been extensively studied as cyclin dependent kinase (Cdk) inhibitors (**1**–**3**).[1] As a consequence considerable effort has been made to develop strategies for the solution-phase and the solid-phase synthesis of trisubstituted purine libraries.[1a,d,2] This effort has been further kindled by the influx of results from the screening of purine derivatives against a wide panel of therapeutically relevant protein targets. Indeed 2,6,9-trisubstituted purines find potential therapeutic application as inhibitors of microtubule assembly,[3] Src and c-Kit (**4**),[4] p38α MAP kinase (**5**),[5] sulfotransferases,[6] phosphodiesterase,[7] and adenosine receptor antagonists.[8] It is thus of interest to continue the development of methodology for the synthesis of polyfunctionalized purines, and in particular processes permitting C–C bond formation at C-2 and C-6. Exploration in this direction has led to the development of the C-2 acetylenyl purine compounds **3a**,**b** as Cdk1 inhibitors,[1d,2c] and more recently to the exciting discovery of compounds **4**[4] and **5**[5] (Fig. 1).

In this communication, we describe the synthesis of a series of 2-aryl-substituted purines using very efficient Pd(0) Suzuki coupling conditions,[5,9] and the evaluation of these compounds as Cdk1/cyclinB, Cdk5/p25, and GSK-3β inhibitors. As a wide range of substituents on the (hetero)aryl moiety are tolerated in Suzuki couplings, this reaction has considerable potential for application to the construction of polyfunctionalized purine libraries.

Purine based Cdk inhibitors often contain an anilino or benzylamino-type substituent at C-6. However, for the present study it was of interest to test compounds possessing a 2-methoxyethylamino substituent at C-6 (see Ref. 10) in combination with different aryl motifs at C-2. A hidden reason behind the choice of this C-6 amine motif is the option to eventually incorporate it into a linker arm for solid-phase synthesis of trisubstituted purines using Suzuki reaction methodology.

Intermediate **7** was readily prepared by reaction of 6-chloro-2-iodopurine **6** with 2-methoxyethylamine in hot EtOH for two days (90% yield) (Scheme 1). As little was known concerning the Pd(0) coupling reaction of 2-iodopurines bearing an electron-donating amino group at C-6,[2f,9] different conditions were explored to optimize the coupling of **7** with 4-formylphenylboronic acid to give compound **8**. In the reaction using either $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ as catalyst (5 mol %), K_2CO_3 as base (1.25 equiv), 1.5 equiv of the boronic acid, and DMF as solvent (120 °C, 16–48 h) the yield of **8** was poor (<20%). Moderate improvements in product yield (30–55%) using these catalysts were obtained on changing the solvent to THF–H_2O (4/1) (80 °C, 3–18 h). Optimum yields (70-77%) were obtained at higher temperature (100 °C) using dioxane–H_2O (4/1) as the solvent mixture, a larger excess of potassium carbonate base (5 equiv) and $Pd(PPh_3)_4$ as the catalyst (5 mol %).

Keywords: Purine; Cdk; Inhibitors; Suzuki cross-coupling.
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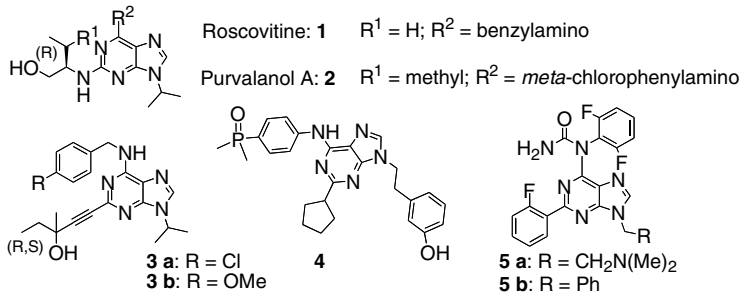
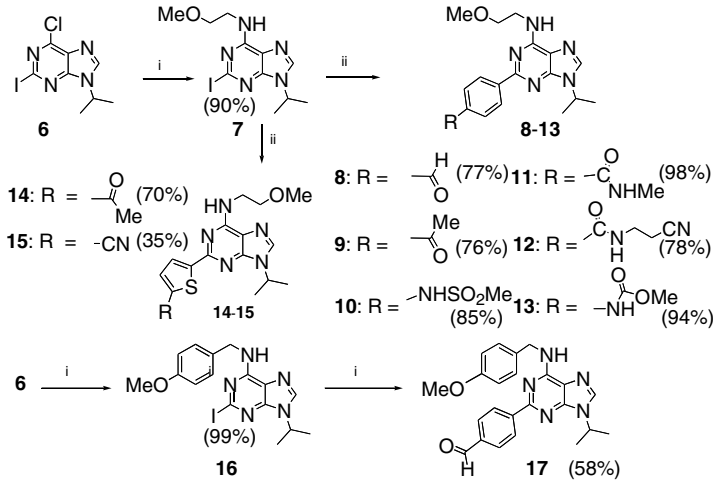


Figure 1. Purine derivatives with potent inhibitory activities against Cdk (**1**–**3**), Src (**4**), and MAPK (**5**).



Scheme 1. Preparation of 2,6,9-trisubstituted purines. Reagents and conditions: (i) **6** (1 g, 3.1 mmol), NEt_3 (0.43 ml, 3.1 mmol), amine (6.2 mmol) in abs EtOH (60 ml), 60 °C, 2 days; (ii) **7** or **16** (0.5 g, 1.38 mmol), boronic acid (1.5 equiv), K_2CO_3 (0.95 g, 6.9 mmol), $Pd(PPh_3)_4$ (80 mg, 0.07 mmol), degassed H_2O (3 ml), degassed dioxane (12 ml), 100 °C, 2–5 h.

These conditions were subsequently used to prepare the 2-aryl substituted purine derivatives **8**–**13** from **7** (76–98% yields). The cross-coupling of **7** with 5-acetylthiophene-2-boronic acid and 5-cyanothiophene-2-boronic acid to give compounds **14** and **15** was similarly studied. However, for the synthesis of **15**, the reaction did not go to completion, even by using 4 equiv of 5-cyanothiophene-2-boronic acid and prolonged reaction time. For comparison purposes, the purine derivative **17** (58%) was also prepared by reaction of the 6-benzylamino-substituted purine **16** with 4-formylphenylboronic acid.[11]

The 2-(hetero)aryl-substituted purines **8** to **15** are moderate (IC_{50} = 1.4–4.9 μM) inhibitors of Cdk1 and Cdk5 (Table 1). These molecules are slightly more active than the archetypical Cdk inhibitor olomoucine (IC_{50} = 7 μM), but much less so than for the related 2,6,9-trisubstituted purines roscovitine and purvalanol A (IC_{50} = 0.45 and 0.004 μM, respectively), and the acetylene based Cdk inhibitor **3a** (Table 1).[1d] Compounds **8** and **17** were nearly equipotent in their activity, and both compounds were about five times less active than the acetylene derivative **3b**. As found for the related 2,6,9-trisubstituted purines roscovitine and purvalanol, no inhibition of GSK3 was observed (competing GSK-3β inhibition is frequently observed for non-purine based inhibitors of Cdk1/cyclin B).[12] No rationale for this specificity with respect to Cdk for purine inhibitors has been proposed to date.

Table 1. Enzymatic (IC_{50} in μM) evaluation of the compounds on Cdk1, Cdk5, and GSK3, as described[13]

Compound	Cdk1/cyclin B	Cdk5/p25	GSK-3β
8[11]	1.4	1.4	>100
9	2.5	2.8	>100
10[11]	2.3	3	>100
11	3.1	1.8	>100
12	4.2	3.4	>100
13	4.4	4	>100
14[11]	3.2	4.9	>100
15	2.3	2.2	>100
17	1.5	1.3	>100
3a[1d]	0.06	nd	nd
3b[1d]	0.23	nd	nd

nd, not determined.

It is known[10] that the presence of a phenyl (or benzyl) substituent at C-6 is not necessary for anti-Cdk activity and that short linear substituents at C-6, such as the methoxyethylamino group in purine **8**, confer about the same inhibitory activity (compare **8** and **17**). In addition, the presence of a phenyl group at C-2 is not detrimental to the inhibitory activity, although all the

para-substituted phenyl derivatives at C-2 display the same order of activity against Cdk 1 and 5.

These results are encouraging, suggesting that the Suzuki cross-coupling reaction can be used to construct new more active Cdk inhibitors. In particular, it will be interesting to screen the anti-Cdk activity of other C-2 *meta*- or *ortho*-substituted (hetero)aryl purine derivatives. Taking into consideration the potent activities revealed for the purines **4** and **5**, 2-(hetero)aryl-substituted purines may also display activity against other protein targets.

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References and notes

1. (a) Gray, N. S.; Wodicka, L.; Thunnissen, A. M. W. H.; Norman, T. C.; Kwon, S. J.; Espinoza, F. H.; Morgan, D. O.; Barnes, G.; LeClerc, S.; Meijer, L.; Kim, S. H.; Lockhart, D. J.; Schultz, P. G. *Science* **1998**, *281*, 533; (b) Knockaert, M.; Greengard, P.; Meijer, L. *Trends Pharmacol. Sci.* **2002**, *23*, 417; (c) Krystof, V.; Lenobel, R.; Havlicek, L.; Kuzma, M.; Strnad, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3283; (d) Legraverend, M.; Tunnah, P.; Noble, M.; Ducrot, P.; Ludwig, O.; Grierson, D. S.; Leost, M.; Meijer, L.; Endicott, J. *J. Med. Chem.* **2000**, *43*, 1282; (f) Meijer, L.; Raymond, E. *Acc. Chem. Res.* **2003**, *36*, 417.
2. (a) Chang, Y. T.; Gray, N. S.; Rosiana, G. R.; Sutherlin, D. P.; Kwon, S.; Norman, T. C.; Sarohia, R.; Leost, M.; Meijer, L.; Schultz, P. G. *Chem. Biol.* **1999**, *6*, 361; (b) Liu, J.; Dang, Q.; Wei, Z.; Zhang, H.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 627; (c) Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron* **2002**, *58*, 7911; (d) Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8169; (e) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594; (f) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *Tetrahedron Lett.* **2001**, *42*, 8751.
3. Wignall, S. M.; Gray, N. S.; Chang, Y.-T.; Juarez, L.; Jacob, R.; Al Burlingame; Schultz, P. G.; Heald, R. *Chem. Biol.* **2004**, *11*, 135.
4. Corbin, A. S.; Demehri, S.; Griswold, I. J.; Wang, Y.; Metcalf, C. A., III; Sundaramoorthi, R.; Shakespeare, W. C.; Snodgrass, J.; Wardwell, S.; Dalgarno, D.; Iuliucci, J.; Sawyer, T. K.; Heinrich, M. C.; Druker, B. J.; Deininger, M. W. N. *Blood* **2005**, *106*, 227.
5. Wan, Z.; Boehm, J. C.; Bower, M. J.; Kassis, S.; Lee, J. C.; Zhao, B.; Adams, J. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1191.
6. Chapman, E.; Ding, S.; Schultz, P. G.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, 14524.
7. Pitts, W. J.; Vaccaro, W.; Huynh, T.; Leftheris, K.; Roberge, J. Y.; Barbosa, J.; Guo, J.; Brown, B.; Watson, A.; Donaldson, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2955.
8. Hockemeyer, J.; Burbiel, J. C.; Müller, C. E. *J. Org. Chem.* **2004**, *69*, 3308.
9. (a) Hocek, M.; Hocková, D.; Dvofiáková, H. *Synthesis* **2004**, 889; (b) Hocek, M. *Eur. J. Org. Chem.* **2003**, 245; (c) Hocek, M.; Dvorakova, H. *J. Org. Chem.* **2003**, *68*, 5773; (d) Havelkova, M.; Dvorak, D.; Hocek, M. *Synthesis* **2001**, 1704; (e) Hocek, M.; Holy, A.; Votruba, I.; Dvorakova, H. *J. Med. Chem.* **2000**, *43*, 1817.
10. Hoechst Marion Roussel, Inc. WO 99/43675, 1999.
11. All compounds gave satisfactory spectral data as well as elemental analyses. As a typical procedure, **8** was obtained in 77% yield from 2-iodo derivative **7**[2c] (0.5 g, 1.38 mmol), 4-formylphenyl boronic acid (311 mg, 2.07 mmol), K_2CO_3 (955 mg, 6.92 mmol), and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol), in degassed H_2O (3 ml) and degassed dioxane (12 ml) (Ar or N_2 bubbling). The reaction mixture was stirred at 100 °C for 2–5 h, with phenylboronic acid, (for 12–18 h with thiophene-2-boronic acids), and monitored by TLC, before evaporation of the solvent and extraction in CH_2Cl_2. After drying ($MgSO_4$) and evaporation, **8** was purified on silica gel column to give a white solid. Mp 147 °C. ^{1}H NMR ($CDCl_3$) δ: 10.09 (s, 1H, HCO), 8.65 (d, 2H ar bb′, J = 8.3 Hz); 7.95 (d, 2H ar aa′, J = 8.3 Hz); 7.85 (s, 1H, H8); 6.21 (br s, 1H, NH); 4.94 (sept, 1H, CH *i*PrN, J = 6.8 Hz); 4.00 (br s, 2H, CH_2N); 3.69 (t, 2H, CH_2O, J = 5.2 Hz); 3.42 (s, 3H, CH_3O); 1.66 (d, 6H, $2CH_3$ *i*Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 192.3 (CO); 157.1 (C2); 154.5 (C4); 150.0 (*C*–C2); 138.2 (C8); 136.8 (C–CHO); 129.6 (2CH Ar); 128.6 (2CH Ar); 119.6 (C5); 71.3 (CH_2O); 58.9 (CH_3O); 47.1 (CH ^{i}PrN); 40.5 (CH_2N); 22.8 ($2CH_3$ ^{i}Pr). HRMS Calcd *m*/*z*: 340.1768 [M+H]. Found *m*/*z*: 340.1773. Anal. Calcd for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.64. Found: C, 63.99; H, 6.33; N, 20.58.
Compound **10**: physical data: mp: 172 °C. ^{1}H NMR ($CDCl_3$) δ: 8.47 (d, 2H Ar oo′, J = 8.6 Hz); 7.82 (s, 1H, H8); 7.30 (d, 2H Ar mm′, J = 8.7 Hz); 6.23 (br s, 1H, NH); 4.91 (sept, 1H, CH ^{i}PrN, J = 6.8 Hz); 3.96 (br s, 2H, CH_2N); 3.68 (t, 2H, CH_2O, J = 5.3 Hz); 3.40 (s, 3H, CH_3O); 3.04 (s, 3H, CH_3SO_2); 1.64 (d, 6H, $2CH_3$ *i*Pr, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 157.8 (C2); 154.4 (C4); 150.0 (C6); 138.0 (*C*–C2); 137.6 (CH, C8);136.1 (*C*–$NHSO_2Me$); 129.6 (2CH Ar); 119.8 (2CH Ar); 118.9 (C5); 71.3 (CH_2O); 58.8 (CH_3O); 46.9 (*C*H–^{i}Pr); 40.7 (CH_2NH); 39.3 (CH_3SO_2); 22.7 ($2CH_3$ *i*Pr). HRMS Calcd *m*/*z*: 405.1703 [M+H]. Found: *m*/*z* 405.1712. Anal. Calcd for $C_{18}H_{24}N_6O_3S$: C, 53.45; H, 5.98; N, 20.78; S, 7.93. Found: C, 53.57; H, 5.95; N, 20.57; S, 7.71.
Compound **14**: mp: 159 °C. ^{1}H NMR ($CDCl_3$) δ: 7.90 (d, 1H Ar, J = 2.6 Hz); 7.81 (s, 1H, H8); 7.68 (d, 1H Ar, J = 2.6 Hz); 6.06 (br s, 1H, NH); 4.86 (sept, 1H, CH ^{i}PrN, J = 6.6 Hz); 3.93 (br s, 2H, CH_2N); 3.66 (t, 2H, CH_2O, J = 4.8 Hz); 3.41 (s, 3H, CH_3O); 2.59 (s, 3H, CH_3CO); 1.63 (d, 6H, $2CH_3$ *i*Pr, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ : 191.2 (CO); 154.3 (C2); 153.0 (C4); 150.0 (C6); 145.1 (*C*–CO); 138.1 (CH, C8); 132.9 (CH Ar); 128.6 (CH Ar); 127.5 (CH Ar); 119.6 (C5); 71.2 (CH_2O); 58.8 (CH_3O); 47.2 (CH *i*Pr); 40.3 (CH_2N); 26.8 (*C*H_3CO); 22.7 ($2CH_3$ *i*Pr). HRMS Calcd *m*/*z*: 360.1489 [M+H]. Found *m*/*z*: 360.1491. Anal. Calcd for $C_{17}H_{21}N_5O_2$ S: C, 56.80; H, 5.89; N, 19.48; S, 8.92. Found: C, 56.88; H, 5.75; N, 19.55; S, 8.75.
12. Meijer, L.; Flajolet, M.; Greengard, P. *Trends Pharmacol. Sci.* **2004**, *25*, 471.
13. Meijer, L.; Skaltsounis, A.-L.; Magiatis, P.; Polychronopoulos, P.; Knockaert, M.; Leost, M.; Ryan, X. P.; Vonica, C. A.; Brivanlou, A.; Dajani, R.; Crovace, C.; Tarricone, C.; Musacchio, A.; Roe, S. M.; Pearl, L.; Greengard, P. *Chem. Biol.* **2003**, *10*, 1255.