Pergamon

Tetrahedron Letters 42 (2001) 2771–2773

TETRAHEDRON LETTERS

Novel solid-phase preparation of 2,6,9-trisubstituted purines for combinatorial library generation

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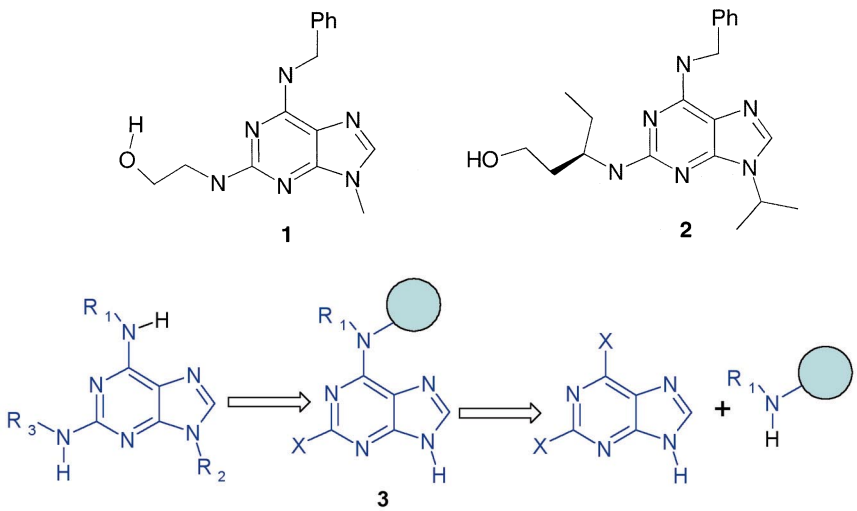
Received 6 February 2001; revised 20 February 2001; accepted 23 February 2001

Abstract—A novel procedure for the preparation of 2,6,9-trisubstituted purine libraries has been developed.

The purine ring is a critical structural element in several effector molecules (such as agonists, antagonists and substrates) that play a key role in numerous cellular processes.[1–4] An example of such an inhibitor is Olomoucine (**1**), which exhibits a moderate activity (IC_{50} = 7 μM) towards cdk-2. Despite this moderate activity, the 2,6,9-trisubstituted purine is an ideal scaffold for the generation of kinase inhibitor libraries. Consequently, combinatorial libraries on this template should facilitate the identification of important pharmacological agents. There have been several publications dedicated to chemistry leading to such libraries.[5–7] Our principal goal has been to use combinatorial chemistry to increase the affinity and selectivity of this class of compounds, such as Olomoucine (**1**) and Roscovitine (**2**), by simultaneous introduction of diversity at the 2-, 6- and 9-positions of the purine ring. The solid-phase strategies described in the literature thus far only allow one to vary two diversity elements at a time. Here, we describe a procedure that facilitates the preparation of combinatorial libraries in which all the three substituents of the Olomoucine class of inhibitors can be independently varied. This offers an opportunity to study the cumulative affects of the diverse substituents on the affinity and selectivity towards various kinases.

We envisioned a procedure where a resin-bound amine or aniline can be reacted with a dihalo purine, which



Scheme 1.

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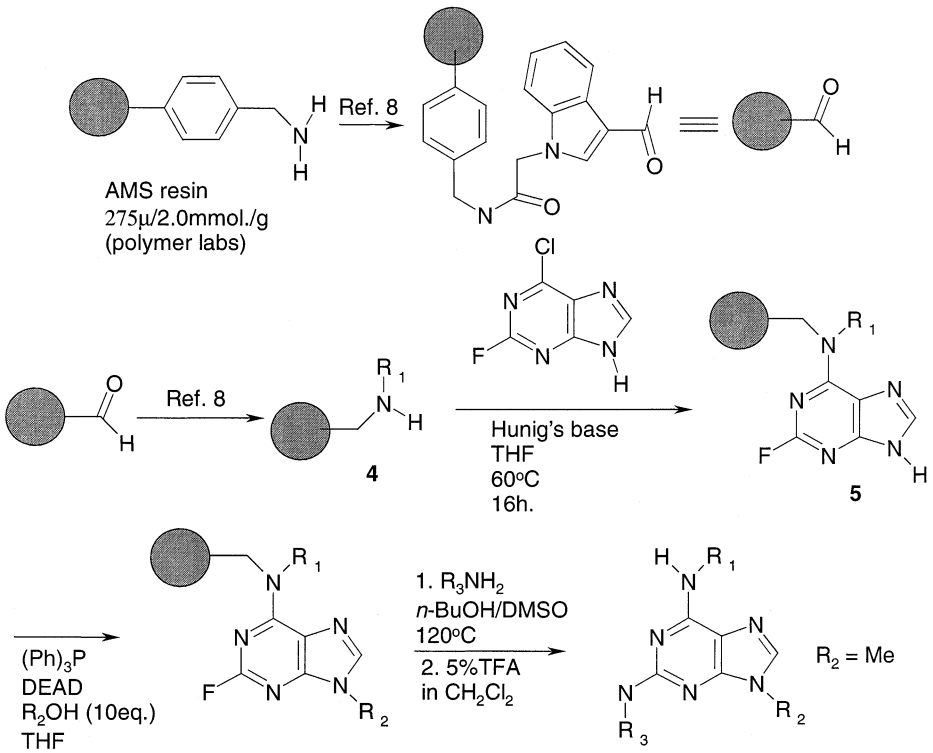
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00328-8

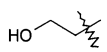
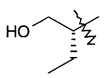
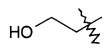
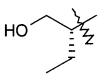
would lead to a resin-bound 6-amino-2-halopurine **3**. This reaction would lead to the introduction of the first diversity element at the C-6 of the purine. A Mitsunobu reaction or alkylation can then be carried out at N-9, followed by the displacement of the 2-halosubstituent by an amine nucleophile to afford the target molecule library[5] (Scheme 1).

The recently published indole resin seemed like an ideal choice as the solid support.[8,9] To demonstrate the viability of this synthetic protocol to prepare trisubstituted purine libraries, we chose to prepare a few analogs of Olomoucine. Aldehydes were reductively aminated onto the indole resin using the published procedure.[8] The resin-bound amine **4** was reacted with 2-fluoro-6-chloropurine[10] to cleanly afford the resin-bound purine **5**, in 95% yield.[11] This resin-bound purine **5** was *N*-alkylated smoothly under Mitsunobu conditions. The 2-amino substituent for the completion of syntheses was introduced in *n*-BuOH:DMSO (4:1) at 100°C (Scheme 2). Some of the substituents that were used in this library protocol validation are shown in Table 1. The products were efficiently cleaved with 5% TFA in CH_2Cl_2. As seen from the results in Table 1,



Scheme 2.

Table 1.

Entry	R_1	R_2	R_3	Yield (wt %)[a]	ELSD[13] yields[b]	ELSD purity
1	$PhCH_2$	Me		69	54	100
2	3,4-Dichlorobenzyl	Me		85	82	100
3	4-Methoxybenzyl	Me		96	100	100
4	4-Fluorobenzyl	Me		90	76	70

[a] Weight yields are based on 10 mg of resin.
[b] ELSD yields are normalized to entry 3. Entry 4 had 30% unreacted starting material in the second step.

the procedure is quite general and efficient for the production of trisubstituted purines.[12] Olomoucine itself was isolated in 69% yield.

In summary, we have developed an efficient solid-phase method for preparation of combinatorial libraries around the trisubstituted purine template. This method allows the independent variation of all the substituents.

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9. Indole resin was prepared using AMS resin (2 mmol/gm 450° beads) from Polymer Labs.
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11. The purine was cleaved from the resin and was identified by NMR and LC–MS.
12. Representative experimental procedure: Resin **4** (R_1 = benzyl) was prepared as described the Ref. 8. Resin **4** (0.338 mmol) was placed in a 30 ml screw cap vial with 10 ml of THF, then treated with 291 mg (1.69 mmol, 5 equiv.) of 2-fluoro-4-chloropurine and 294 μl (1.69 mmol, 5 equiv.) of diisopropylethylamine (DIPEA). The vial was sealed and shaken at 60°C for 16 h. After cooling, the resin was filtered and washed with 2×20 ml portions of MeOH, DCM, MeOH, then dried in a vacuum oven to furnish resin **5**. To resin **5** (240 mg, 0.247 mmol, 1.02 mmol/gm) in 3 ml of THF was added 655 mg of triphenylphosphine (2.50 mmol, 10 equiv.), methanol (2.50 mmol, 10 equiv.) and 197 μl of diethylazodicarboxylate (1.25 mmol, 5 equiv.) at room temperature in an 8 ml screw top vial. After shaking for 30 min, an additional 197 μl of diethylazodicarboxylate was added and shaking was continued for a further 90 min. The resin was filtered, washed with 2×3 ml portions of THF, MeOH, DCM, MeOH, and then dried in a vacuum oven to furnish resin **6**. To a suspension of resin **6** (100 mg, 0.103 mmol, 1.03 mmol/gm) in 2 ml of *n*-butanol:DMSO (4:1) in a 4 ml screw cap vial was added ethanolamine (0.500 mmol, 5 equiv.). The vial was then sealed and was shaken at 120°C for 48 h. The cooled mixture was filtered and washed with 2×1 ml portions of THF, MeOH, DCM, MeOH, and then dried in a vacuum oven to furnish resin-bound Olomoucine. The resin (105 mg) was treated with 2 ml of 5% TFA in DCM in a 4 ml screw cap vial and was shaken at room temperature for 4 h. The resin was filtered off and then washed with 10 ml of DCM. The combined filtrates were then evaporated to furnish Olomoucine (**1**).
13. ELSD (evaporative light-scattering detection) was measured using a SEDEX 75 instrument at 37°C and 3.5 bar.