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Solid-phase synthesis of pyrido[2,3-*d*]pyrimidin-7-ones

Mauro Angiolini, Domenico Fusar Bassini, Markus Gude[†] and Maria Menichincheri[*]

Discovery Oncology, Nerviano Medical Sciences, viale Pasteur 10, 20014 Nerviano, Italy

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Abstract—A novel solid-phase method for the synthesis of 4-methyl-pyrido[2,3-*d*]pyrimidin-7-one compounds with two diversity points is described. The polymer supported methylsulfonyl derivatives $\mathbf{A_3}$, achieved by coupling compound **G** with different resin-bound amines $\mathbf{A_1}$ followed by oxidation with MCPBA, are substituted with several amines R_1R_2NH. Final cleavage affords 126 compounds having formula **H** in good yield and purity.

In drug discovery combinatorial chemistry based on pharmacophoric scaffolds is a promising approach towards new bioactive entities. In this respect, pyrido-[2,3-*d*]pyrimidin-7-ones having structure **1** represent an attractive heterocyclic class due to their biological effects in particular as kinase inhibitors (Fig. 1).[1–6]

Thus, in the effort to identify new active compounds we envisaged the opportunity to design a chemical library of potential biological interest based on structure **2** (Fig. 1). As for our knowledge, solid-phase expansion of such heterocyclic series is scarcely documented in the literature. So we undertook a synthetic study for the development of a solid supported methodology with the aim to synthesize a 4-methyl-pyrido[2,3-*d*]pyrimidin-7-one based library with two diversity points, one at position 2 and the other at *para* position of the phenyl ring present on the scaffold.

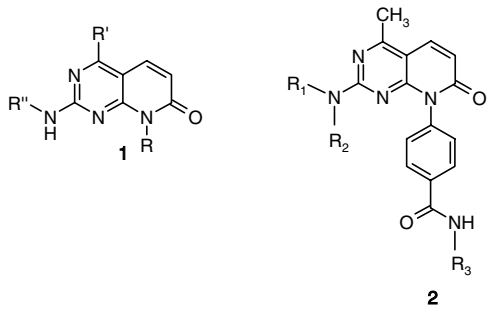

Figure 1.

The retrosynthetic route is reported in Scheme 1 where the aryl amidic moiety is first introduced with the use of a solid supported amine $\mathbf{A_1}$. The amine at position 2 is derived from a nucleophilic displacement of a methylsulfone. The final compounds of general formula **2** are easily released from the resin under acidic conditions with trifluoroacetic acid (Scheme 1).

As the first step a synthetic route to 4-methyl-pyrido-[2,3-*d*]pyrimidin-7-one scaffold **D**, a key intermediate both for solution and solid-phase methods, was developed according to Scheme 2. Thus condensation between the commercially available diethyl ethylidene malonate **A** with *S*-methyl-isothiourea followed by oxidation with NBS smoothly affords compound **B**. Treatment of **B** with $POCl_3$ and nucleophilic aromatic substitution at position 6 with *tert*-butyl-4-aminobenzoate gives the pyrimidine derivative **C** in good yield. Selective reduction of the ethyl ester **C** followed by oxidation with MnO_2 affords the aldehyde, which in turn undergoes Horner–Emmons olefination and final intramolecular cyclization gives scaffold **D**. This route is amenable to large scale synthesis (20 g). Oxidation of **D** with MCPBA gives the methylsulfone moiety, which provides the template for investigating the solution-phase nucleophilic substitution at position 2 with different amines.[7]

A model case is reported in Scheme 2 where a 2.5-fold excess of *N*-phenylpiperazine is refluxed in dioxane with

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* Corresponding author. Tel.: +39 0331 581928; fax: +39 0331 581757; e-mail: maria.menichincheri@nervianoms.com
† Present address: Actelion AG, Allschwil, Switzerland.

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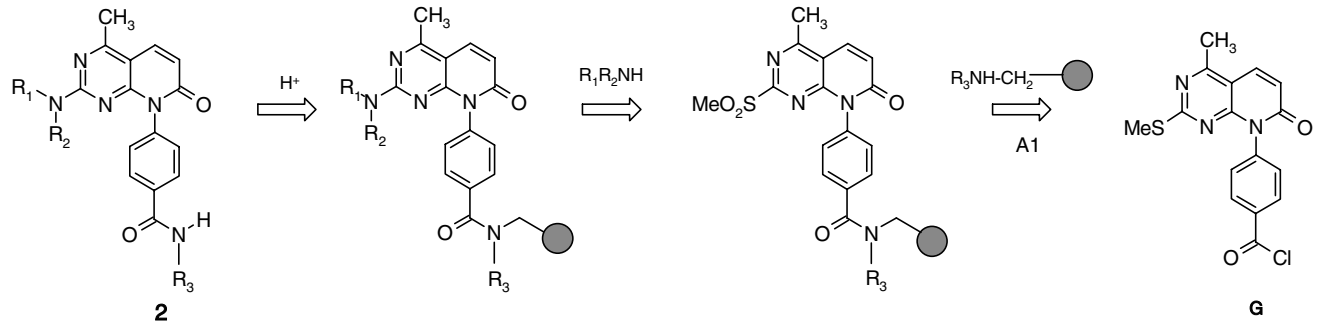
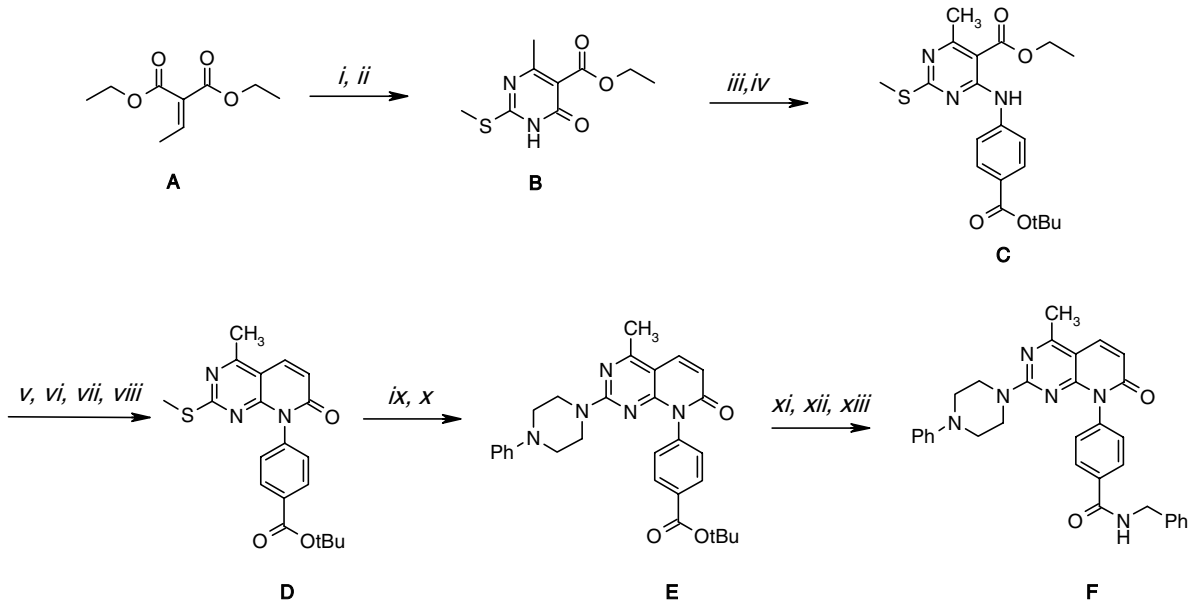


Scheme 1.

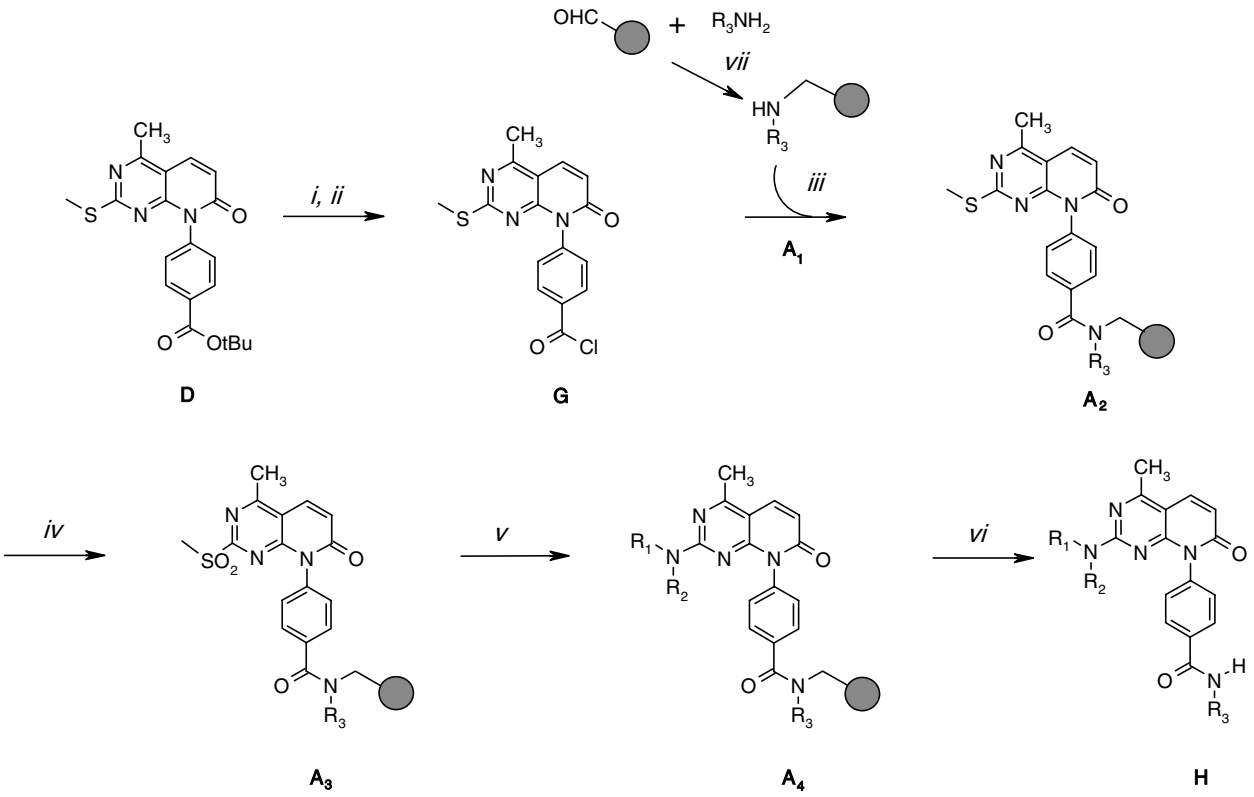


Scheme 2. Reagents and conditions: (i) *S*-methyl isothiourea, TEA, anhydrous ethanol, reflux, 3 h, 55%; (ii) anhydrous K_2CO_3, benzoyl peroxide, NBS, anhydrous dioxane, 90 °C, 3 h, 92%; (iii) $POCl_3$, reflux, 2 h, 50%; (iv) *tert*-butyl 4-aminobenzoate (2 equiv), DIPEA, dioxane, reflux, 72 h, 81%; (v) $NaBH_4$, anhydrous ethanol, 45 °C, 4 h, 82%; (vi) MnO_2, CH_2Cl_2, rt, overnight, 70%; (vii) $Ph_3PCHCOOEt$, anhydrous THF, reflux, 2.5 h, 94%; (viii) DIPEA/DBU (10:1 v/v), reflux, 30 h, 71%; (ix) MCPBA, CH_2Cl_2, rt, 1.5 h, 87%; (x) 4-phenylpiperazine (2.5 equiv), dioxane, reflux, 0.5 h, 87%; (xi) TFA, CH_2Cl_2, rt, 8 h, 95%; (xii) oxalyl chloride, anhydrous DMF, CH_2Cl_2, rt, 2 h, 95%; (xiii) benzylamine, TEA, CH_2Cl_2, rt, 78%.

the sulfone for half an hour to give compound **E** in good yield. These conditions proved to be optimal not only for primary and secondary aliphatic amines but also the less reactive aromatic amines such as ethyl *para*-aminobenzoate. Finally **E** is readily converted into the corresponding acid chloride and coupled with benzyl amine to afford **F**. The reaction sequence depicted in Scheme 2 involves a reverse addition order of amine R_1R_2NH and R_3NH_2 on the scaffold with respect to the solid-phase.

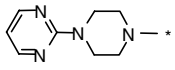
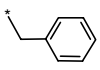
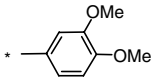
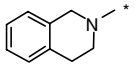
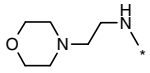
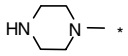
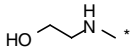
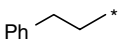
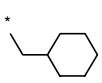
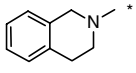
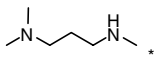
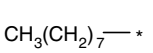
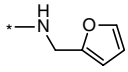
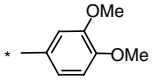
The solid-phase route is reported in Scheme 3 where the intermediate **D** previously described is converted in good yield into the corresponding chloride **G** after deprotection with trifluoroacetic acid and activation with oxalyl chloride. Then the intermediate **G** is coupled to the resin-bound amine $\mathbf{A_1}$, prepared by reductive amination with $NaBH(AcO)_3$ of the selected amines R_3NH_2 (see Table 1 both for residues R_3 and for R_1R_2N) condensed with a formyl resin [4-(4-formyl-3-methoxyphenoxy)butyrylaminomethyl resin]. Oxidation of the polymer-supported intermediate $\mathbf{A_2}$ with MCPBA affords sulfone $\mathbf{A_3}$, which is then subjected to aromatic substitution at 60 °C in THF using 6 equiv of different amines R_1R_2NH. Final release of intermediate $\mathbf{A_4}$ from the solid support under acidic conditions with trifluroacetic acid completes the preparation of the library. Thus 16 different amines were selected for nucleophilic substitution at position 2 of the scaffold $\mathbf{A_3}$ bearing nine diverse residues R_3. This achieves 126 final compounds having general formula **H**, with overall yields ranging from 50% to 80% and good purity. All the compounds were characterized by HPLC-MS and ^1H NMR technique. A representative selection of 10 different final compounds is reported in Table 1 with their HPLC-MS purity and yields.[8,9]

In conclusion we have developed a useful methodology to prepare in a scalable way a pyrido[2,3-*d*]pyrimidin-7-one scaffold and to build on solid-phase a library of 126 compounds with double diversity.



Scheme 3. Reagents and conditions: (i) TFA, CH_2Cl_2, rt, 2 h, 95%; (ii) oxalyl chloride, anhydrous DMF, CH_2Cl_2, rt, 2 h, 95%; (iii) $\mathbf{A_1}$ (R_3NH-Y-Pol), CH_2Cl_2, TEA (10 equiv), rt, overnight; (iv) MCPBA, CH_2Cl_2, rt, 1.5 h; (v) R_1R_2NH 6 equiv, TEA 6 equiv, THF, 60 °C, 1 h; (vi) TFA/CH_2Cl_2 (50%, v/v), rt, 1.25 h; (vii) R_3NH_2, THF/CH_2Cl_2 (4:1, v/v), AcOH, $NaBH(OAc)_3$, rt, overnight.

Table 1. Pyrido[2,3-*d*]pyrimidin-7-ones **H** produced via Scheme 3

Product	R_1R_2N	R_3	Yield (%)[a]	Purity (%)[b]
$\mathbf{H_1}$			50	90
$\mathbf{H_2}$			55	80
$\mathbf{H_3}$			74	90
$\mathbf{H_4}$			60	62
$\mathbf{H_5}$			78	90
$\mathbf{H_6}$			65	80
$\mathbf{H_7}$			60	70
$\mathbf{H_8}$			57	90
$\mathbf{H_9}$			67	54
$\mathbf{H_{10}}$			75	90

[a] Four-step overall yields from **G**.

[b] All the crude products purities are calculated by HPLC-MS at $\lambda = 254$ nm.

To the best of our knowledge, this represents the first combinatorial expansion on this versatile scaffold reported in the literature.

References and notes

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9. Typical procedure for solid-phase: Synthesis of *N*-benzyl-4-[4-methyl-7-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-7*H*-pyrido[2,3-*d*]pyrimidin-8-yl]benzamide (compound $\mathbf{H_1}$).
Preparation of polymer supported benzylamine $\mathbf{A_1}$ by reductive amination: To a suspension of 4-(4-formyl-3-methoxyphenoxy)butyrylaminomethyl resin (AMEBA resin) (500 mg, 0.40 mmol, loading 0.59 mmol/g, 100–200 mesh, 1% DVB, Novabiochem) in 5 ml of THF/DCM (4:1, v/v) benzylamine (260 μl, 2.40 mmol) and AcOH (135 μl, 2.40 mmol) were added. Shaking continued for 15 min, then $NaBH(AcO)_3$ (250 mg, 1.20 mmol) was added and shaking was continued over-night at room temperature. The completion of the reaction was confirmed by disappearance of the formyl signal via solid-phase NMR technique. The resin was washed with MeOH (2 × 1 min), DMF (2 × 1 min), DCM (1 × 1 min), MeOH (1 × 1 min) and DCM (3 × 1 min). The resin was dried at 30 °C at 10 Torr for 2 h.
Polymer supported *N*-benzyl-4-[4-methyl-7-oxo-2-methylsulfanyl-7*H*-pyrido[2,3-*d*]pyrimidin-8-yl]benzamide $\mathbf{A_2}$: To a suspension of polymer supported benzylamine $\mathbf{A_1}$ (0.40 mmol) in 15 ml of DCM and TEA (0.82 ml, 5.9 mmol), 4-[4-methyl-7-oxo-2-methylsulfanyl-7*H*-pyrido[2,3-*d*]pyrimidin-8-yl]benzoyl chloride was added and the mixture was shaken over-night at room temperature. This was then filtered and the resin was washed in the following order: DMF (3 × 1 min), DCM/MeOH (1:1, v/v, 3 × 1 min), DCM (3 × 1 min), MeOH (1 × 1 min) and DCM (3 × 1 min). The resin so achieved was dried for 2 h at 10 Torr and 30 °C.
Polymer supported *N*-benzyl-4[4-methyl-7-oxo-2-methylsulfonyl-7*H*-pyrido[2,3-*d*]pyrimidin-8-yl]benzamide $\mathbf{A_3}$: The resin $\mathbf{A_2}$ (ca. 45 mg, 0.0214 mmol) was suspended in 1 ml of DCM and treated for 1.5 h with MCPBA (14.3 mg, 0.064 mmol) at room temperature. The resin $\mathbf{A_3}$ was then washed with dioxane (2 × 1 min) and DCM (2 × 1 min).
Polymer supported *N*-benzyl-4-[4-methyl-7-oxo-2-(1-piperazinyl)-7*H*-pyrido[2,3-*d*]pyrimidin-8-yl]benzamide $\mathbf{A_4}$: To a mixture of resin $\mathbf{A_3}$ in 1 ml of THF and TEA (14 mg, 0.13 mmol) was added the respective amine (0.13 mmol) and shaking was continued for 1 h at 60 °C. The resin $\mathbf{A_4}$ was then washed with THF (2 × 1 min), DMF (3 × 1 min) and DCM (3 × 1 min).
Release of product $\mathbf{H_1}$ from the resin $\mathbf{A_4}$: Resin $\mathbf{A_4}$ was treated with a mixture of TFA/DCM (1 ml, 50% v/v) for 75 min. The resin was filtered, washed with DCM (1 × 1 min) and the combined organic layers were evaporated yielding compound $\mathbf{H_1}$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (t, 1H), 8.34 (d, 2H), 8.03 (m, 3H), 7.47 (m, 7H), 6.62 (t, 1H), 6.36 (d, 1H), 4.51 (d, 2H), 3.62 (m, 4H), 3.33 (m, 4H), 2.58 (s, 3H); LC/MS (ESI): *m*/*z* 647 (M+H).