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SOLID-PHASE SYNTHESIS OF 2-(4-CARBAMOYLPYRAZOLYL)-4-ALKYLAMINO-6-AMINOPYRIMIDINE DERIVATIVES

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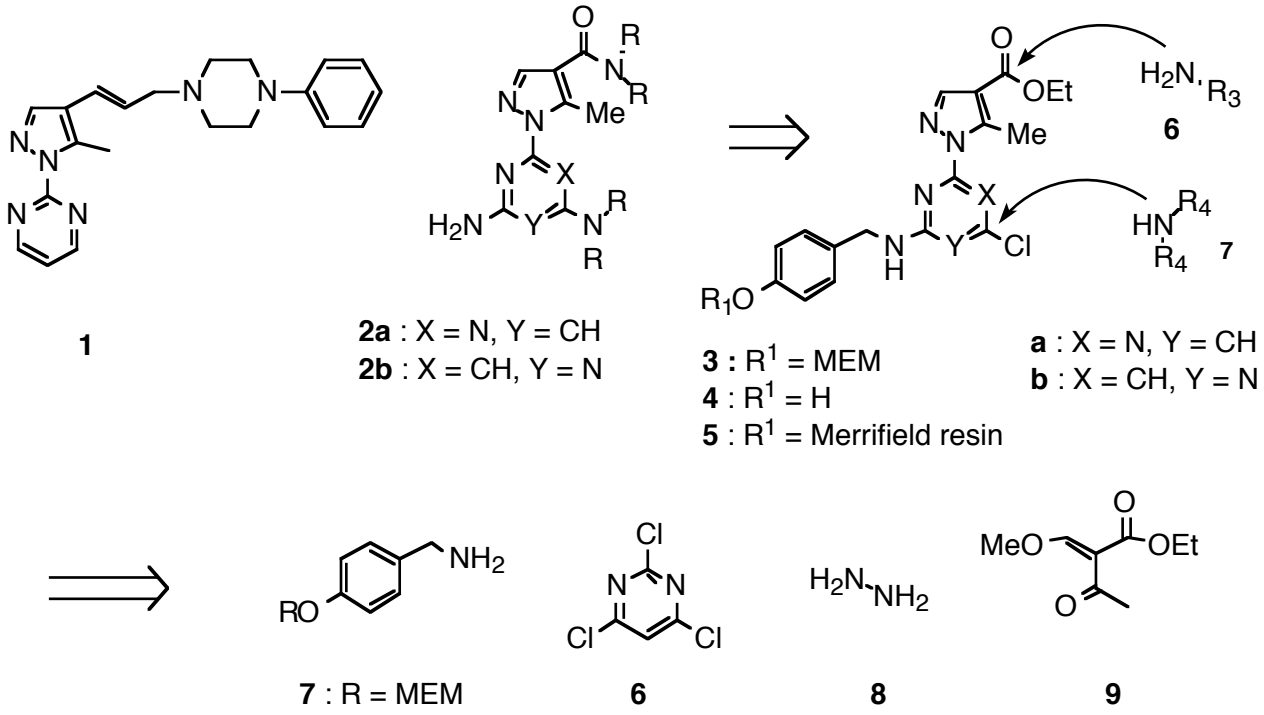
Abstract- A solid-phase synthesis of 2-(1-pyrazolyl)pyrimidine derivatives is described. The developed methodology allows the construction of a library of 2-(1-pyrazolyl)pyrimidine.

Combinatorial chemistry has been shown to be an important tool that aids in the discovery of new drug leads and allows for the optimization of lead compounds.[1] Aromatic compounds involved two and more heteoatoms such as pyrazole, pyrimidine, and purine are expected to be promising candidates for medicine because they can interact with many types of proteins through hydrogen bonds. A solid-phase methodology has proved an effective way to rapidly assemble a diverse collection of heteroaromatic derivatives because of the ease of work-up and purification.[2] We have already reported the solid-phase syntheses of small molecule libraries such as Vitamin D_3, oligosaccharides, and morphinan derivatives.[3] We now report the solid-phase synthesis of substituted 2-(1-pyrazoyl)pyrimidine with an amide side chain along with a small library of analogues.

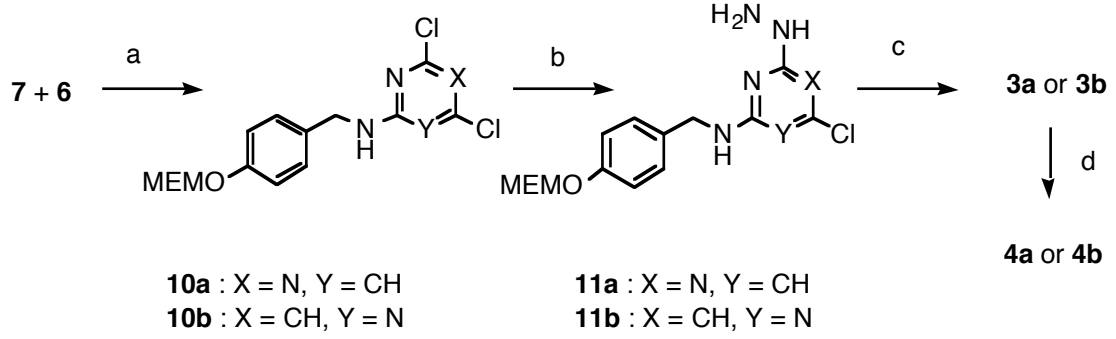
2-(1-Pyrazolyl)pyrimidine (**1**) with an allyl piperazine at the 4-position of pyrazole, exhibits *in vitro* cytotoxic activity against some tumor cell lines and *in vivo* activity against a solid tumor Meth A mouse fibrosarcoma.[4] The pyrazolylpyrimidine moiety has been shown to be essential for the antitumor activity.[4]

In order to develop new antitumor agents, we planed to synthesize a library of 2- or 4-(1-pyrazolyl)pyrimidine derivatives (**2a**) or (**2b**) with diamino groups in pyrimidine and an amide side chain at C4 position of pyrazole. Our strategy for the solid-phase synthesis of the amide derivatives (**2a**) and (**2b**) (Scheme 1) involves introduction of the two side chains by amination of solid-supported chloropyrimidine (**5a**) and (**5b**)**,** followed by amidation of remaining ester group. *p*-Hydroxylbenzylamino group was selected as the linker because the final products would be stable to acidic coniditions. Immobilization of the key intermediates (**5a** and **5b**) would be achieved by *O*-alkylation of a phenol in **4a** and **4b** with Merrifield resin. The reaction scheme for synthesis of pymidines (**4a**) and (**4b**) involves sequential selective amination of trichloropyrimidine (**6**) with amine (**7**) and hydrazine (**8**), followed by annulation of pyrazole ring with β-keto ester (**9**).[5]



Scheme 1. Design and strategy for the solid phase synthesis of new pyrimidine derivatives

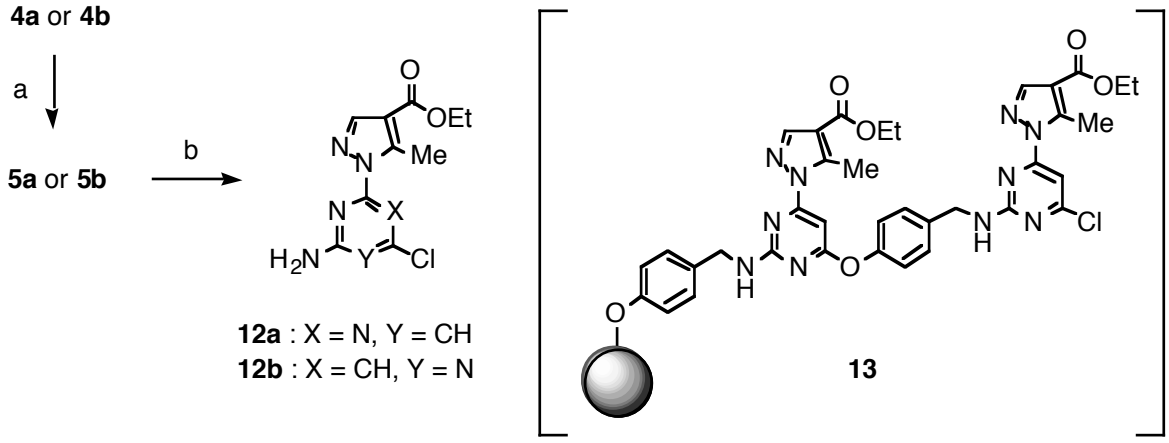
Preparation of chloropyrimidines (**4a**) and (**4b**) (Scheme 2) from 2,4,6-trichloropyrimidine (**6**) with *p*-alkoxybenzylamine (**7**) at 0 °C provides two regio-isommers (**10a**)[6] and (**10b**)[7] in 53 and 28% yields. Substitution of **10a** and **10b** with hydrazine (**8**) provided the corresponding monochloropyrimidine (**11a**) and (**11b**). Treatment of hydrazines (**11a**) and (**11b**) with ethyl 2-ethoxymethyleneacetoacetate (**9**) gives pyrazoylpyrimidines (**3a**) and (**3b**) in 85 and 87% yields, respectively. Removal of MEM group under acidic conditions afforded corresponding phenols (**4a**)[9] and (**4b**)[10] in 90 and 87% yields.



Scheme 2. : Reagents and conditions : a) K_2CO_3, DMF, 0 °C.; b) hydrazine, THF, reflux.; c) **9**. EtOH, reflux.; d) conc. HCl / MeOH / THF (1 : 5 : 5)

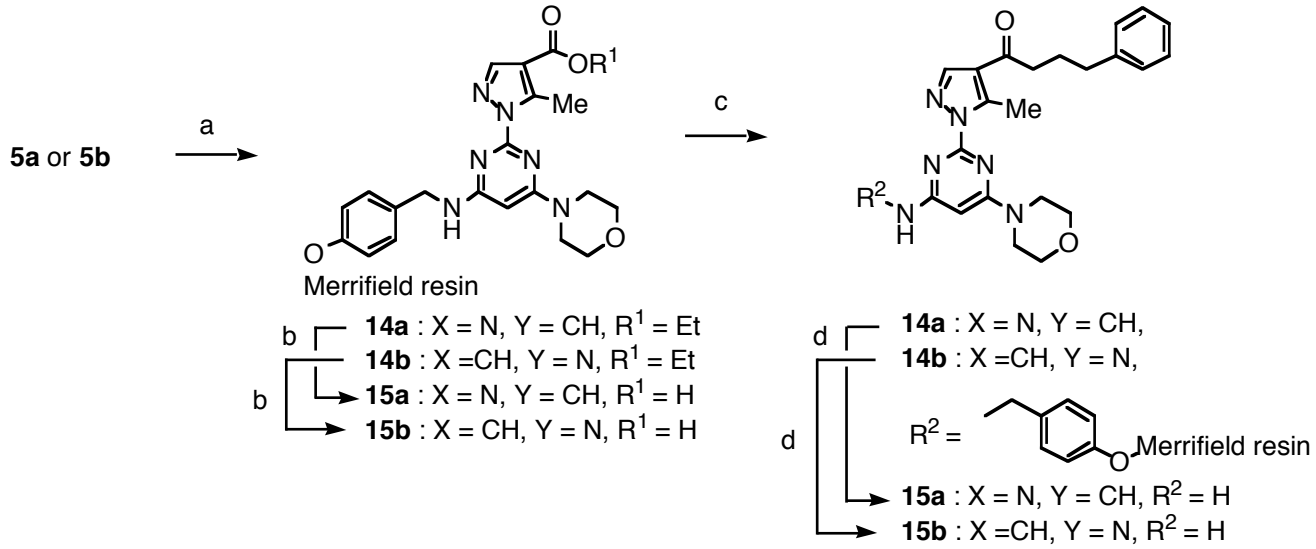
Immobilization of **4a** on solid-phase was achieved by treatment of five equivalents of **4a** in DMF with Merrifield resin (0.63 mmol/g) in the presence of *tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) to provide solid-supported pyrimidine (**5a**). In order to determine the loading of the pyrimidine (**4a**), ethyl 1-(4-amino-6-chloropyrimidin-2-yl)-5-methylpyrazole-4-carboxylate (**12a**)[5] was cleaved from the resin (**5a**) with TFA. Immobilization of **4b** under the same conditions resulted in the lower purity product of **12b** (31%). LCMS analysis of the cleaved material

suggested that dimerization by SN-Ar reaction with phenol group proceed to give **13** in 31% purity.



Scheme 3 : Reagents and conditions : a) Merrifield resin, BENP, 60 ^{o}C. ; b) TFA, reflux

Amination on solid-phase by SN-Ar reaction of **4a** was conducted. Treatment of solid-supported chloropyrimidine (**5a**) with morpholine in EtOH at reflux for 48 h provided triamino pyrimidine (**14a**). Hydrolysis of ester by potassium trimethylsilanolate in THF at reflux for 2 h provided carboxylic acid (**15a**),[11] followed by amidation with phenethylamine *via* pentafluorophenyl ester to give solid-linked amide (**16a**). Cleavage of **16a** under acidic conditions gave pyrimidine derivative (**17a**) in 81 % purity. The amination, followed by amidation on solid-phase sequence was applied to the synthesis of **17b** using **4b**. HPLC analysis of the crude products after cleavage under acidic conditions showed the desired product was obtained with an unexpected high purity (69%). This result indicates that SN-Ar reaction of phenoxypyrimidine of **13** with the amine would be carried out under the conditions.



Scheme 4. Reagent and conditions; a) morpholine, EtOH, reflux.; b) TMSOK,THF, reflux.; c) i) CF_3COPfp, pyridine, DMF.; ii) Phenethyl amine, Et_3N, DMF.; d) TFA, reflux

In order to demonstrate the feasibility of the solid-phase synthesis, we planned the synthesis of a small library of the amide derivatives using immobilized chloropyrimidine (**4a**). Thirteen amines were selected as building blocks for the library synthesis (Figure 1 and Table). The library synthesis using a reagent group **A** (4 amines) x **B** (10 amines) gave 40 compounds and analysis of all the products by

HPLC and MS revealed that all the reagents performed well in the second amidation step. All 2-(4-methoxyphenyl)ethyamine derivatives (**A-4**) were obtained in excellent purity (90-95%). However a use of other amines (**A-1**, **A-2** and **A-3**) in the first amination resulted in only moderate purity (50-90%) of the target molecules.

Figure 1. Building blocks for the small library synthesis

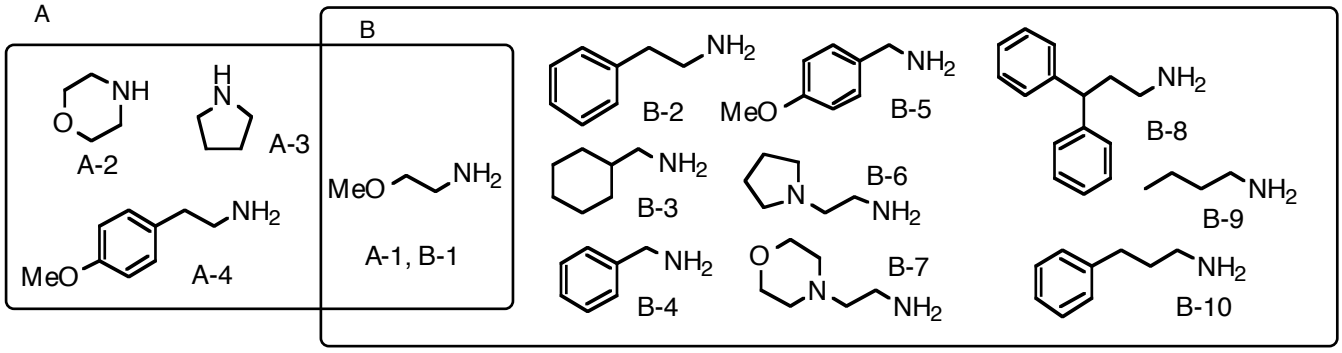


Table Purity of 2-(4-carbamoylpyrazolyl)-4-alkylamino-6-aminopyrimidine derivatives by the solid-phase synthesis using 4 X 10 amine building blocks.

	B-1	**B-2**	**B-3**	**B-4**	**B-5**	**B-6**	**B-7**	**B-8**	**B-9**	**B-10**
A-1	85%	88%	89%	73%	82%	81%	83%	74%	90%	86%
A-2	50%	56%	57%	52%	68%	56%	68%	59%	60%	60%
A-3	68%	65%	60%	61%	60%	59%	61%	60%	68%	57%
A-4	95%	90%	92%	92%	90%	91%	92%	92%	92%	93%

The purity was determined by UV spectra in 254 nm.

In conclusion we describe the solid-phase synthesis of 2 or 4-(1-pyrazolyl)pyrimidine derivatives (**2a**) and (**2b**) having amino and amide side-chains along with a small combinatorial library of analogues of **2**. The combination of an SN-Ar reaction with amine and amidation is effective for the solid-phase synthesis of the aromatic derivatives. Biological assay of the library compounds is currently being explored.

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6. **10a**: ^{1}H-NMR ($CDCl_3$): □ 3.37 (s, 3 H), 3.55 (t, 2 H, *J* = 4.62 Hz), 3.83 (t, 2 H, *J* = 4.62 Hz), 4.45 (br, 1 H), 4.55 (m, 2 H), 5.26 (s, 2 H), 6.26 (s, 1 H), 7.02 (d, 2 H, *J* = 7.26 Hz), 7.22 (d, 2 H, *J* = 7.26 Hz); IR (KBr): 1591, 1550, 1506, 1200, 1126, 1078, 997, 968, 814, 756 cm^{-1}; ESI-MS (*m/z*): 358 $(M+H)^+$.
7. **10b**: ^{1}H-NMR ($CDCl_3$): □ 3.37 (s, 3 H), 3.55 (t, 2 H, *J* = 4.62 Hz), 3.83 (t, 2 H, *J* = 4.62 Hz), 4.45 (br, 1 H), 4.55 (m, 2 H), 5.27 (s, 2 H), 6.63 (s, 1 H), 7.05 (d, 2H, *J* = 7.26 Hz), 7.22 (d, 2 H, *J* = 7.26 Hz); IR (KBr): 1568, 1498, 1221, 1076, 1011, 976, 958, 810, 771 cm^{-1}; ESI-MS (*m/z*): 358 $(M+H)^+$.
8. Removal of benzyl group of **10a** and **10b** with TFA gave corresponding amino-dichloropyrimidine derivatives whose analytical data (^{1}H NMR and HPLC) were identical with those of 4-Amino-2,6-dichloropyrimidine and 2-amino-4,6-dichloropyrimidine purchased from AVOCADO and TCI respectively.
9. **4a**: ^{1}H-NMR ($CDCl_3$): □ 1.37 (t, 3 H, *J* = 7.26 Hz), 2.96 (s, 3 H), 4.32 (q, 2 H, *J* = 7.26 Hz), 5.3 (br, 2 H), 6.32 (s, 1 H), 6.84 (d, 2 H, *J* = 8.58 Hz), 7.08 (d, 2 H, *J* = 8.57 Hz), 8.07 (s, 1 H); IR (KBr): 1591, 1398, 1379, 1271, 1232, 1093, 839, 779 cm^{-1}; ESI-MS (*m/z*) : 388 $(M+H)^+$.
10. **4b**: ^{1}H-NMR (DMSO-d_6): □ 1.29 (t, 3 H, *J* = 6.93 Hz), 2.80 (s, 3 H), 4.25 (q, 2 H, *J* = 6.93 Hz), 4.41 (s, 2 H), 6.70 (d, 2 H, *J* = 8.25 Hz), 7.11 (d, 2 H, *J* = 8.58 Hz), 8.09 (s, 1 H), 8.55 (s, 1 H), 9.26 (s, 1 H); IR (KBr): 1583, 1527, 1392, 1267, 1184, 1092, 808, 777 cm^{-1}; ESI-MS (*m/z*) : 388 $(M+H)^+$.
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