Synthesis of Bicyclic Pyrimidine Derivatives as ATP Analogues

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A highly efficient and general solid-phase synthesis of bicyclic pyrimidine derivatives that target purine dependent proteins is reported. The synthesis of the key intermediate, 4,6-disubstituted-5-amino-pyrimidine, involved reduction of the corresponding nitro derivatives using 1,1′-dioctyl-viologen in a triphasic milieu. The mild reduction conditions enable the use of any acid labile solid support as well as a wide range of combinatorial substituents, thus enabling the synthesis of large libraries of highly diverse bicyclic pyrimidines. Alternative reduction conditions with tin(II) chloride and structure−reactivity studies are discussed as well.

Introduction

Purines and pyrimidines are involved in a large number of biological processes. The purine scaffold is a component of guanine and adenine and therefore appears in nucleic acids and cofactors that play an essential role in the modulation of protein function and signal transduction. It has been found that at least 10% of the proteins encoded in the yeast genome appear to be dependent on biomolecules that contain the purine scaffold.[1] DNA and RNA polymerases, ATPase and GTPase, adenosine receptors, biosynthetic and metabolic enzymes, kinases, and other ATP-dependent proteins such as heat shock proteins are all potential targets for therapeutic intervention. DHFR inhibitors that include pyrimidines have antiviral, antifungal, antiprotozoan, and anticancer activity. Adenosine and xanthine analogues have been shown to have adenosine receptor agonist and antagonist properties, which may be relevant in cardiovascular and CNS therapy.[2]

A number of methods have been reported for the synthesis of 2,6,9-trisubstituted purines starting from 2,6-dihalogenated purines in solution,[3,4] on solid phase,[1,5] and a combination thereof.[6] This strategy enables the synthesis of the purine scaffold but not that of related ring systems. 6-aminopurine derivatives (**1**−**3**, Figure 1) have been synthesized on solid phase using Rink resin starting from 4,6-dichloro-5-nitropyrimidine.[7] No 6-substituted analogues other than the 6-amino group were enabled by this synthetic methodology (Figure 2). The reduction of the 5-nitro group was reported to be particularly difficult. A number of methods at wide ranges of temperatures were investigated and only a mixture of $LiAlH_4$ and $AlCl_3$ was found to reduce the 4,6-dialkylamino-5-nitropyrimidines to their corresponding 5-amino derivatives. The reported synthesis does not permit the

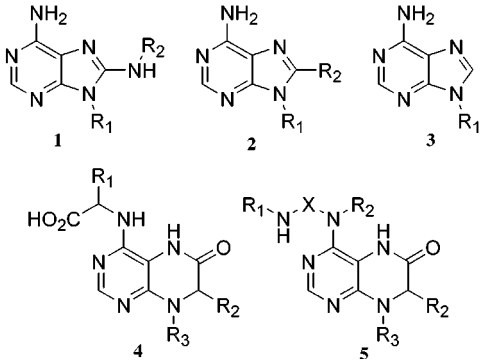

Figure 1. Related scaffolds from literature.

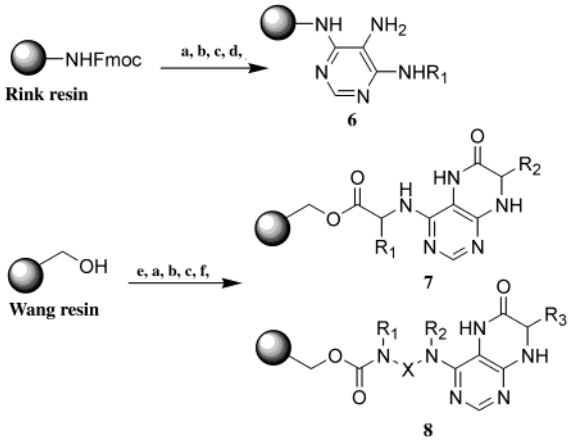

Figure 2. Synthetic routes to related scaffolds. (a) piperidine/DMF; (b) 4,6-dichloro-5-nitropyrimidine/DIPEA/DMF; (c) amine/DIPEA/DMF; (d) $LiAlH_4/AlCl_3$/THF; (e) $FmocNHCHRCO_2H$/DIC/DMAP/DMF; (f) $SnCl_2$/EtOH/DMF (70 °C).

* To whom correspondence should be addressed.

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Table 1. Reduction Tests with Tin(II) Chloride

entry	resin	R_1[a]	R_2[a]	yield, %	purity, %[b]	MS
16a	Rink	NH_2	p-Me-benzylamine	95+	95	326
16b	Rink	NH_2	o-anisidine	60[b]	90	328
16c	Rink	NH_2	cyclohexylamine	95+	95	304
16d	Rink	NH_2	3-Fluoroaniline	95+	95	316
16e[c]	Rink	alanine	*p*-Me-benzylamine	90	95	284
16f	Wang	*p*-carboxybenzylamine	p-Me-benzylamine	70[d]	90	364/460
16g	Wang	*β*-alanine	*p*-Me-benzylamine	95+	90	302/398
16h	Br−Wang	*p*-Me-phenethylamine	*p*-Me-benzylamine	0	N/A	N/A
16h	formyl	*p*-Me-phenethylamine	*p*-Me-benzylamine	0	N/A	N/A
16i	formyl	benzylamine	*p*-Me-benzylamine	0	N/A	N/A
17a	Rink	NH_2	alanine methyl ester	95+	95	180
17b	Wang	alanine	*p*-Me-benzylamine	0	N/A	N/A

[a] R_1 is site at resin; R_2 is from amine replacing the second chlorine. [b] Some 5-aminopyrimidines form the corresponding 5-trifluoroacetamide during cleavage. For these samples, HPLC purity was assessed as a combination of both products. [c] Product was found to be the corresponding piperazinone analog. [d] These entries were stirred (magnetic) therefore loss of some beads is expected due to crushed resin.

inclusion of building blocks that contain functional groups that are labile under these harsh conditions. The products were also of low purity due to inorganic contaminants derived from the reducing cocktail. Substituted pyrimidines have also been prepared by de novo synthesis of the pyrimidine ring[8] or from the pyrimidine core itself.[9] Following the completion of experiments in our laboratory, a synthesis of dihydropteridinones (**4** and **5**, Figure 1) starting from 4,6-dichloro-5-nitropyrimidine was reported.[10] Either amino acids were attached to Wang resin or diamines were linked to the Wang resin via a carbamate linker (Figure 2). Reduction of the nitro group could be effected with $SnCl_2$ at 70 °C, a finding that is in contrast to the results reported earlier.[7] The published methodology yielded high purities but low yields for several entries with amino acid building blocks and limited diversity elements at the 6-position due to a need for linkage to the resin at this position.

We report herein a synthetic route to substituted bicyclic pyrimidine (and ATP) analogues such as dihydropteridinones, pyrimidoimidazolones, and 6,8-diaminopurines starting from 4,6-dichloro-5-nitropyrimidine. The key step is a mild reduction of the nitro group with catalytic 1,1′-dioctyl-viologen in a mixture of water and dichloromethane. Results and limitations for incorporating diversity elements with different solid supports are discussed, as are our findings for reduction conditions with $SnCl_2$. The above reducing conditions enable the use of all acid-sensitive solid-support types and therefore greatly enhance the diversity of combinatorial libraries that can be synthesized against a wide range of therapeutic targets. The key 5-amino intermediate opens an avenue to the synthesis of other diverse scaffolds as well.

Results and Discussion

To begin this study we set out to investigate the reduction of the 5-nitropyrimidine moiety under various conditions. Despite the lack of reduction reported[7] with tin(II) chloride, our earlier success in the synthesis of unrelated scaffolds using this simple reducing agent prompted us to subject the 4-(*p*-methylbenzyl) derivative (**16a**, Table 1) on Rink resin to $SnCl_2$ in various solvents. No reduction was observed at 25 °C, but complete reduction took place at temperatures above 45 °C. Since acid-sensitive resins are prone to premature cleavage at low pH environments, we opted for 2 N $SnCl_2$ in NMP at 50 °C for 24 h as an initial method. Indeed, at or above 70 °C, the product was lost during reduction when Rink resin was used. The Wang ester type linkage (**16f**,**g**) and other Rink attached derivatives (**16b**−**d**) were found to be compatible with the standard conditions, but no product was obtained when α-amino acids were attached as esters to Wang resin (**17b**). As expected, the piperazinone ring is closed in situ when reduction occurs (**17a**) resulting in loss of the resin-bound compound. The same phenomenon is likely to be responsible for the lower yields reported when both pyrimidine substituents are amino acid esters[10] (Figure 3).

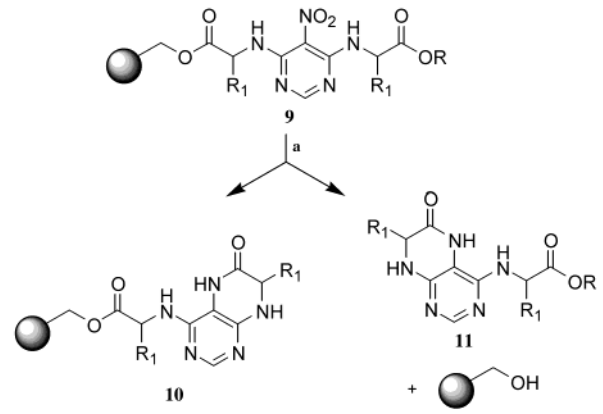

Figure 3. Scheme for premature cleavage of products with amino acid esters. (a) Reduction.

When a *β*-amino acid was attached in a similar manner, the 5-amino derivative was obtained in a good yield (**16g**). The closure to the seven-membered ring system by the *β*-amino acid ester is kinetically unfavorable compared to that of the six-membered ring created by the α-amino acid esters. Interestingly, when alanine was attached to Rink resin (**16e**), the reduced amine was not cleaved during reduction but gave the ring-closed piperazinone upon cleavage in good yield and purity.

When the acid-sensitive formyl (**16h**,**i**) or Bromo-Wang (**16h**) functionalized linkers were subjected to our best method with tin(II) chloride, no product was obtained in subsequent cleavage. We hypothesize that these linkers

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are too acid sensitive to remain intact throughout the inherently acidic reduction step at elevated temperatures. At room temperature, the unreacted nitro derivatives were recovered in every case. We were unable to optimize the tin(II) chloride method to effect the reduction on the formyl and Bromo-Wang linkers; thus, an alternative method was sought. A literature search revealed a highly selective but less-cited method for the reduction of aromatic nitro groups. A catalytic amount of an electron-transfer reagent, 1,1′-di-*N*-octyl-4,4′-bipyridinium dibromide (1,1′-dioctyl viologen) turned over by sodium dithionate under phase-transfer conditions has been shown to effect the reduction of simple aromatic nitro groups with very high yield and purity.[11,12] It remained to be seen whether the system could be applied to the reduction of the problematic 4,6-dialkylamino-5-nitropyrimidine moiety, and to solid-phase chemistry in general.[13]

Our initial attempts with the viologen system were unsuccessful: no reaction was observed with revolving shaking in a polypropylene vessel; however, our test compound attached to Rink resin was completely reduced with *vigorous horizontal shaking* in a glass vial. Similarly, good results were obtained with the use of magnetic stirring; however, the resin became pulverized and was then difficult to filter and wash. Some viologen-related contamination was also present in the cleaved product, indicating ineffective wash with our standard washing cycle (DMF, IPA, DCM). These byproducts were removed by rapid chromatography through a silica plug in the published solution-phase method.[11] Finally, all byproducts could be removed on solid phase by an exhaustive rinse procedure that employed five wash steps (DCM−1% AcOH/H_2O, ethyl acetate−H_2O, acetone, IPA, DCM).

The viologen-mediated reduction method was applied to the formyl and Wang resins as well, and high yields and purities were attained. The pH during reduction is kept slightly basic by the potassium carbonate; thus, all acid-sensitive resin types are likely to be compatible with this method. No reduction was observed without either the dioctyl viologen or sodium dithionate, which is in accord with findings reported for analogous solution phase reactions.[11] As in the tin(II) chloride system, in the viologen method amino acid esters at R_1 lead to cleavage, but at R_2 give the pyrimidopiperazinone compounds as the sole products (Figure 4).

Our strategy for combinatorial library development was based on the use of the formyl linker as the primary resin source for accessing all building blocks at the 6-position in the final bicyclic analogues possessing a secondary amine (Figure 5). The NH at the 6-position in these molecules preserves some of the natural H-bonding properties of adenine and is highly conserved in most known adenine analogues.

To demonstrate the utility of our approach, diarylamines were also made starting from nitrophenols

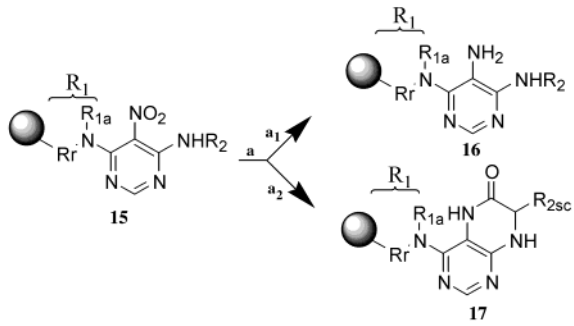

Figure 4. Products obtained by reduction with viologen. R_1, symbolizes amines attached to resin (e.g., for formyl resin, $R_r = CH_2$, R_{1a} = amine); R_{2sc}, side-chain of R_2 amino acid esters; (a) 1,1′-dioctyl viologen/DCM/K_2CO_3/$Na_2S_2O_4$/H_2O; (a_1), amines other than α-aminoesters; (a_2), α-aminoesters.

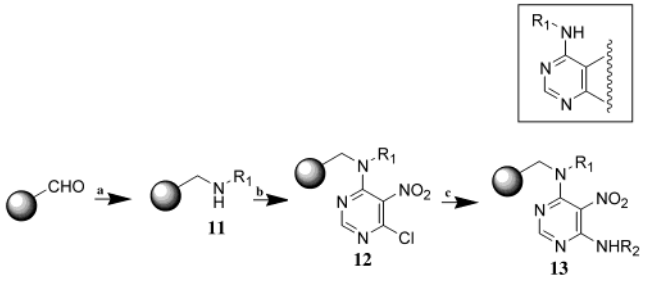

Figure 5. Synthetic strategy toward secondary 6-aminopyrimidine bicycles. (a) reductive amination; (b) 4,6-dichloro-5-nitropyrimidine/DIPEA/NMP; (c) amine/DIPEA/NMP.

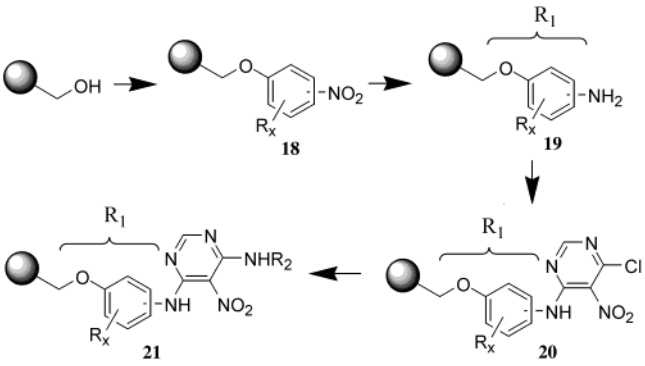

Figure 6. Synthetic scheme for synthesis starting from nitrophenols. R_X, phenol substituents.

attached to Bromo-Wang resin (Figure 6). Using the latter strategy, tertiary amines at the 6-position can also be prepared if a reductive amination step is carried out prior to nucleophilic substitution of the 4,6-dichloro-5-nitropyrimidine by the aniline. Some of the other potential solutions for accessing tertiary amines at the 6-position by various functional groups attached to different resins are depicted in Figure 7.

The 4,6-disubstituted-5-aminopyrimidines are particularly versatile precursors to a wide variety of bicyclic derivatives of the purine scaffold. In this report, we demonstrate the synthesis of three of many possible templates: dihydropteridinones, pyrimidoimidazolones, and 6,8-diaminopurines (Table 2). Dihydropteridinones were obtained if at least one of the substituents of the pyrimidine ring was an amino acid ester (**23a**−**d**, Figure 8). In our laboratory, a number of different esters have been employed successfully in this reaction including methyl, ethyl, *tert*-butyl, and benzyl (data not shown).

(11) Park, K. K.; Oh, C. H.; Joung, W. K. Sodium Dithionate Reduction of Nitroarenes Using Viologen as an Electron Phase-Transfer Catalyst. *Tetrahedron Lett.* **1993**, *34*, 7445−7446.

(12) Park, K. K.; Oh, C. H.; Sim, W.-J. Chemoselective Reduction of Nitroarenes and Nitroalkanes by Sodium Dithionate Using Octyl viologen as an Electron-Transfer Catalyst. *J. Org. Chem.* **1995**, *60*, 6202−6204.

(13) After completion of this work, a report on the reduction of the aryl nitro moiety with $Na_2S_2O_4$ and viologen on solid support was published; however, no reduction of the difficult pyrimidine system was investigated. Scheuerman, R. A.; Tumelty, D. The Reduction of Aromatic Nitro Groups on Solid Supports Using Sodium Hydrosulfite ($Na_2S_2O_4$). *Tetrahedron Lett.* **2000**, *41*, 6531−6535.

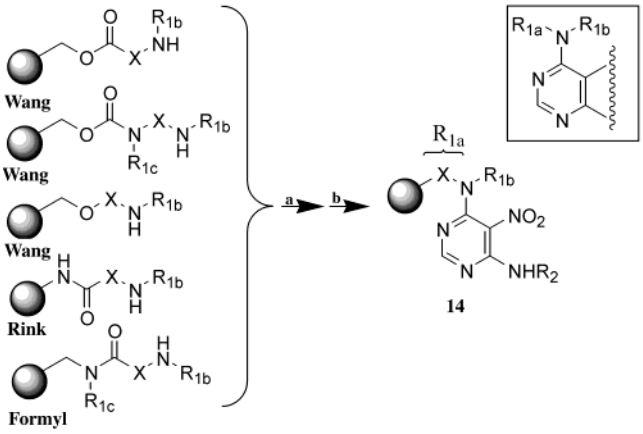

Figure 7. Potential synthetic strategy toward tertiary 6-aminopyrimidine bicycles. (a) 4,6-Dichloro-5-nitropyrimidine/DIPEA/NMP; (b) amine/DIPEA/NMP.

Pyrimidoimidazolones were readily gained by cyclization with disuccinimidyl carbonate at elevated temperatures, a modification of the method published[14] for the synthesis of benzimidazolones (**25a**−**e**, Figure 8). Addition of isothiocyanates to the 5-amino moiety results in thioureas that furnish 6,8-diaminopurines upon treatment with dehydrating agents such as DIC (**26a**−**r**, Figure 8). It is noteworthy that when both the 4- and the 6-substituent are secondary amines, cyclization can take place in two ways to yield isomeric bicycles (Figure 9). In our experience, both isomers are obtained equally in such cases (**26q**,**r** and Figure 10).

For compounds prepared with the formyl linker, an appreciable amount (0−30% depending on the amine building block used in reductive amination) of a nitroso side-product was detected by NMR and LC-MS (Figure 11). In many cases the ELSD-HPLC trace of these samples, however, showed no peaks other than the desired product. The commercial 4,6-dichloro-5-nitropyrimidine is available from a number of vendors. While the commercial material (∼75% pure by NMR) appears to be adequate for the synthesis of the title compounds, some oxidated impurities, in our hypothesis, may lead to side reactions, especially when excess amounts are used in solid-phase reactions. To remove the byproducts, we developed a simple purification method before the reduction step. It has been known that tertiary amines formed on the formyl linker are readily cleaved as tertiary amides by acylating agents.[15] Thus, 1 equiv of *o*-toluoyl chloride and DIPEA were added to the resin in dichloromethane before reduction to cleave all nitroso side-products. No significant amount of the desired intermediate was cleaved off the resin or acylated by this procedure. As a result of the above purification method, the purity of the final products can greatly be enhanced at the expense of the yield (Table 2). It should be noted that reaction requiring excess isothiocyanates for the synthesis of 6,8-diaminopurines gave rise to similar cleavage of the nitroso amines.

Structure−reactivity relationships at the site introduced by reductive amination (R_1) (Table 2) reveal that α-disubstituted amines are well tolerated with high purity, but that α-trisubstituted amines (**26n**) are too hindered for subsequent nucleophilic substitution with dichloronitropyrimidine. Both electron-deficient (**23c**) and ortho-substituted anilines (**26f**) are well tolerated at R_1, giving rise to products of high purity.

Nucleophilic displacement of the second, less-reactive chlorine at R_2 is brought to completion with α-disubstituted amines and anilines of nucleophilicity higher or equal to aniline (**25b**, **26m**). Reaction at R_2 remains incomplete with α-trisubstituted amines (**26o**) or electron-deficient anilines at ambient temperature.

Clean ring-closure with isothiocyanates at R_3 was found for unhindered aromatic and benzylic isothiocyanates. Aromatic isothiocyanates possessing bulky ortho-substituents (**26i**) may give rise to a small amount of a DIC adduct (observed mass equals the molecular weight of the key aminopyrimidine intermediate plus DIC), because thiourea formation cannot proceed to completion before DIC is added (see experimental details). In general, aliphatic isothiocyanates yield the desired products albeit with less purity (**26j**, 80%).

The strategy described herein has been utilized in our laboratories to generate large combinatorial libraries with the split and pool technique for our affinity-based screening platform, Automated Ligand Identification System (ALIS).[16] Hit-rates and activity data acquired in screening of this compound file against ATP-dependent and miscellaneous other targets will be detailed when they become available.

Conclusion

We have developed a versatile strategy for the solid-phase synthesis of diverse bicyclic pyrimidines as purine analogues. All substitution types are enabled by the method excluding compounds containing a secondary amine building block with no resin handle at the 4-position *and* an amine with no resin handle at the 6-position of the pyrimidine intermediate. All analogues were obtained with good yields and purities. Additional results of an ongoing effort in our laboratory to develop solid-phase methodologies for the synthesis of other fused ring systems based on the key pyrimidine intermediate will be reported elsewhere.

Experimental Section

Rink AM, Wang, Bromo-Wang and 4-(4-Formyl-3-methoxyphenoxy)butyryl AM ("formyl") resins were purchased from Novabiochem. 4,6-Dichloro-5-nitropyrimidine was purchased from Aldrich, Sigma and Research Plus, Inc. The substance obtained from Sigma and Research Plus, Inc. was found about 75% pure by ^{1}HNMR, and the one originated from Aldrich was about 50% pure by the same technique. Amines and isothiocyanates were purchased from various vendors and were verified to be 95+% pure by ^{1}HNMR before use. All NMR spectra were taken with a 300 MHz Brucker NMR spectrometer. HPLC analyses were performed with either a Biocad (Perceptive Biosystems) or HP-1100 Binary HPLC instruments. MS spectra were recorded in positive electrospray mode with a QTOF Tandem MS-MS mass spectrometer (Micromass). Reactions (excluding the reductive amination and the viologen reduction steps) at ambient temperature were carried out in fritted polypropylene vessels (Orochem Technologies), and were agitated by a revolving shaker (VWR). Reactions at

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(15) Miller, M. W.; Vice, S. F.; McCombie, S. W. Mild N-Dealkylation of Tertiary Benzylic Amines With Acid Chlorides: Application to Solid-Phase Chemistry. *Tetrahedron Lett.* **1998**, *39*, 3429−3432.

(16) For further information on the ALIS screening platform, please go to www.neogenesis.com.

Table 2. Selected Bicyclic Pyrimidine Derivative

entry	resin	R_1[a]	R_2[a]	R_3[a]	yield, %	purity, %	MS
23a	formyl	3-(1-morpholino)propylamine	lysine(Boc)-OMe	N/A	90	95+	364
23b	formyl	3-benzyloxyaniline	valine-OMe	N/A	60	90	390
23c	formyl	4-chloroaniline	glutamic acid(OMe)-OMe	N/A	50	95+	362
23d	formyl	3-(1-morpholino)propylamine	threonine(OtBu)-OMe	N/A	50	95+	337
25a	Rink	alanine	*p*-Me-benzylamine	N/A	70	90	327
25b	Br-Wang	3-Nitrophenol	3-fluoroaniline	N/A	75	90	338
25c	formyl	*p*-Me-benzylamine	2-aminoindane	N/A	70	95+	372
25d	Rink	NH_2	p-Me-benzylamine	N/A	95	95	256
25e	Rink	NH_2	cyclohexylamine	N/A	95	90	234
26a	formyl	cyclohexylamine	*p*-Me-benzylamine	3,4-methylenedioxyphenylSCN	70	95+	457
26b	formyl	*N*-aminopropylimidazole	*p*-Me-benzylamine	3,4-methylenedioxyphenylSCN	50	95	483
26c	formyl	*trans*-2-benzyloxycyclopropylamine	*p*-Me-benzylamine	3,4-methylenedioxyphenylSCN	70	95+	549
26d	formyl	Boc-lysine-OMe	*p*-Me-benzylamine	3,4-methylenedioxyphenylSCN	70	95+	518
26e	formyl	4-(1,2,4-triazolyl)phenylamine	*p*-Me-benzylamine	3,4-methylenedioxyphenylSCN	45	95+	518
26f	formyl	*o*-anisidine	phenethylamine	4-phenoxyphenylSCN	70	95+	529
26g	formyl	benzylamine	*p*-Me-benzylamine	3-fluorophenylSCN	85	95	439
26h	formyl	benzylamine	*p*-Me-benzylamine	4-methoxybenzylSCN	85	95	465
26i	formyl	benzylamine	*p*-Me-benzylamine	2-biphenylSCN	50	80	497
26j	formyl	benzylamine	*p*-Me-benzylamine	γ-butyrolactone-2-SCN	85	80	429
26k	formyl	benzylamine	4-amino-1-ethylcarboxypiperidine	2-naphthylSCN	70	90	522
26l	formyl	benzylamine	*trans*-2-benzyloxycyclopropylamine	2-naphthylSCN	75	90	541
26m	formyl	benzylamine	4-phenoxyaniline	2-naphthylSCN	75	95	535
26n	formyl	*p*-F-α-dimethylphenethylamine	p-Me-benzylamine	2-naphthylSCN	0	N/A	N/A
26o	formyl	benzylamine	*p*-F-α-dimethylphenethylamine	2-naphthylSCN	50	45	517
26p	formyl	benzylamine	*N*-(3-aminopropyl)imidazole	2-naphthylSCN	45	40	475
26q	Br-Wang	3-nitrophenol	3-fluoroaniline	4-phenoxyphenylSCN	70	90	505
26r	Br-Wang	5-fluoro-2-nitrophenol	phenethylamine	4-phenoxyphenylSCN	80	90	533

[a] R_1 is site at resin, R_2 is from amine replacing the second chlorine, and R_3 is from isothiocyanates.

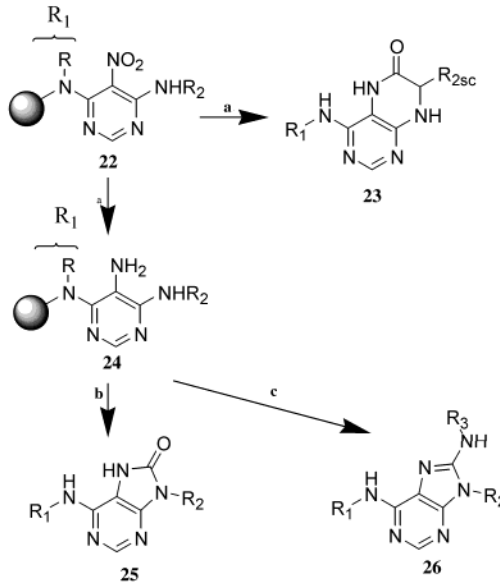


Figure 8. Bicycles from 5-nitropyrimidines (resin connection symbolizes all resin linkers used). R_{2sc}, side-chain of amino acid esters; (a) 1,1′-dioctyl viologen/DCM/K_2CO_3/$Na_2S_2O_4$/H_2O; (b) DSC/DMF/80 °C; (c) R_3SCN/DMF/DIC/80 °C.

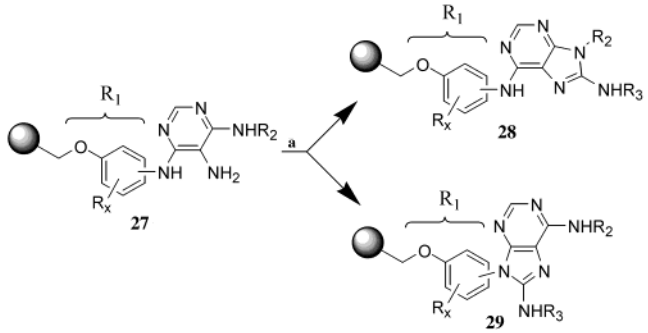


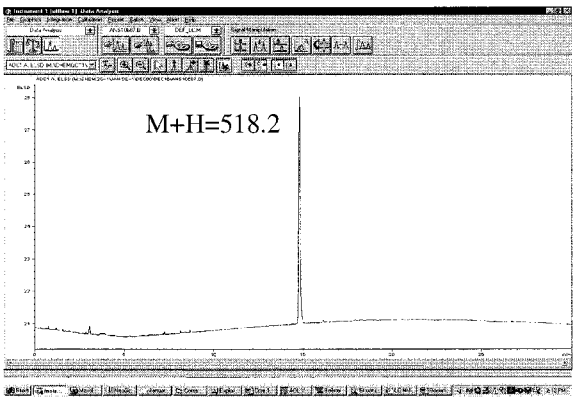
Figure 9. Possible cyclization routes to isomeric bicycles. (a) R_3SCN/DMF/DIC/80 °C.

elevated temperatures were double coupled in tightly capped 13 × 100 mm Pyrex tubes and were carried out in heating blocks (VWR) tightened on an orbital shaker. Reductive aminations were performed in 4 mL Teflon capped glass vials shaken with a revolving shaker (VWR) The viologen reductions were done in 4 mL Teflon capped glass vials shaken horizontally with a reciprocating shaker. Cleavage of products from the beads for formyl resins was effected by a dilute TFA cocktail (TFA:H_2O = 7:3) while that for Wang, Bromo-Wang and Rink resins was achieved by a concentrated TFA cocktail (TFA:H_2O = 95:5). A dilute cleavage condition was found to produce products of high purity for all batches of formyl resin, while 95% TFA led to lower purity for some (but not all) of the batches. Cleavages were carried out for 1 h at room temperature. 10% bead loss was calculated into all yields shown in Table 2 for every step that involves resin transfer. This according to our calibration is approximately the average amount lost in a single transfer of polystyrene beads.

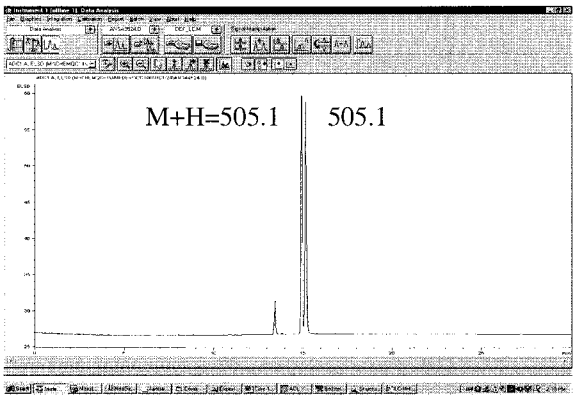
Purity of all compounds was established by HPLC, high-resolution mass spectroscopy and LC-MS. In addition, representative compounds in every product class were confirmed by ^{1}H NMR spectroscopy.

Representative Procedure for the 5-Nitropyrimidine Intermediates Starting from Rink AM Resin. Rink AM resin (0.1 mmol) was shaken with 50% piperidine in DMF (2 mL) for 30 min. The resin was filtered off and washed with DMF (4×), IPA (3×), and DCM (3×). To the resin were added NMP (1.5 mL), DIPEA (174 μL, 1.0 mmol), and 4,6-dichloro-5-nitropyrimidine (97 mg, 0.5 mmol). The mixture was shaken for 2h at room temperature. The resin was filtered and washed with DMF (3×), IPA (3×), and DCM (3×). To the resin were added NMP (1.0 mL), DIPEA (88 μL, 0.5 mmol), and amine building block (0.5 mmol). The mixture was shaken for 16h at room temperature. The resin was filtered, washed with DMF (3×), IPA (3×), and DCM (3×), and dried.

Representative Procedure for the 5-Nitropyrimidine Intermediates Starting from Rink AM Resin and Amino Acids. Rink AM resin (0.1 mmol) was shaken with 50% piperidine in DMF (2 mL) for 30 min. The resin was filtered off and washed with DMF (4×), IPA (3×), and DCM (3×). To the resin were added DMF (1.5 mL), Fmoc-protected amino acid (0.3 mmol), a mixture of TBTU (86 mg, 0.3 mmol) and



a, **26e** (Table 2)



b, **26q** (Table 2)

Figure 10. Typical HPLC profiles of crude 6,8-diaminopurines.

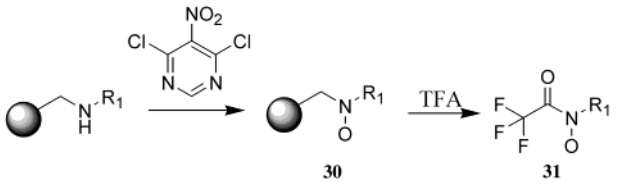


Figure 11. Proposed side reaction observed with formyl linkers.

HOBt monohydrate (46 mg, 0.3 mmol) in DMF (0.5 mL), and DIPEA (105 μL, 0.6 mmol). The mixture was shaken for 16 h at room temperature. The resin was filtered and washed with DMF (3×), IPA (3×), and DCM (3×). The resin (0.1 mmol) was then shaken with 50% piperidine in DMF (2 mL) for 30 min. The resin was filtered off and washed with DMF (4×), IPA (3×), and DCM (3×). To the resin were added NMP (1.5 mL), DIPEA (174 μL, 1.0 mmol), and 4,6-dichloro-5-nitropyrimidine (97 mg, 0.5 mmol). The mixture was shaken for 2 h at room temperature. The resin was filtered and washed with DMF (3×), IPA (3×), and DCM (3×). To the resin were added NMP (1.0 mL), DIPEA (88 μL, 0.5 mmol), and amine building block (0.5 mmol). The mixture was shaken for 16 h at room temperature. The resin was filtered, washed with DMF (3×), IPA (3×), and DCM (3×), and dried.

Representative Procedure for the 5-Nitropyrimidine Intermediates Starting from Formyl Resin. To formyl resin (0.1 mmol) in a vial were added 1% acetic acid in DMF (1.3 mL), DIPEA (30 μL, 0.172 mmol), and amine building block (0.55 mmol). The mixture was shaken for 6 h at room temperature. when $NaBH(OAc)_3$ (117 mg, 0.55 mmol) was added. The mixture was shaken for 36 h when methanol (1 mL) was added to help dissolve the borate salts. The mixture was transferred to a polypropylene vessel, and the resin was filtered and washed with MeOH (3×), DMF (3×), IPA (3×), and DCM (3×). To the resin were added NMP (1.5 mL), DIPEA (210 μL, 1.2 mmol), and 4,6-dichloro-5-nitropyrimidine (48 mg, 0.25 mmol). The mixture was shaken for 2 h at room temperature. The resin was filtered and washed with DMF (3×), IPA (3×), and DCM (3×). To the resin were added NMP (1.0 mL), DIPEA (87 μL, 0.5 mmol), and amine building block (0.5 mmol). The mixture was shaken for 16 h at room temperature. The resin was filtered, washed with DMF (3×), IPA (3×), and DCM (3×), and dried. To the resin were added DCM (1.5 mL), DIPEA (35 μL, 0.2 mmol), and o-toluoyl chloride (13 μL, 0.1 mmol). The mixture was shaken for 2 h at room temperature and filtered. The resin was washed with DCM (3×), IPA (3×), and DCM (3×).

Representative Procedure for the 5-Nitropyrimidine Intermediates Starting from Wang Resin. Amino acid attached to Wang resin (0.1 mmol) was shaken with 50% piperidine in DMF (2 mL) for 30 min to remove the Fmoc group. The resin was filtered and washed with DMF (4×), IPA (3×), and DCM (3×). To the resin were added NMP (1.5 mL), DIPEA (174 μL, 1.0 mmol), and 4,6-dichloro-5-nitropyrimidine (97 mg, 0.5 mmol). The mixture was shaken for 2 h at room temperature. The resin was filtered and washed with DMF (3×), IPA (3×), and DCM (3×). To the resin were added NMP (1.0 mL), DIPEA (88 μL, 0.5 mmol), and amine building block (0.5 mmol). The mixture was shaken for 16 h at room temperature. The resin was filtered, washed with DMF (3×), IPA (3×), and DCM (3×), and dried.

Representative Procedure for the 5-Nitropyrimidine Intermediates Starting from Bromo-Wang Resin. To Bromo-Wang resin (0.1 mmol) in DMF (1.0 mL) were added Cs_2CO_3 (98 mg, 0.30 mmol), KI (17 mg, 0.1 mmol), and nitrophenol building block (0.5 mmol). The mixture was shaken for 16 h at 80 °C. The mixture was cooled to room temperature and the resin was transferred to a polypropylene vessel, filtered, and washed with DMF (3×), H_2O (3×), DMF (2×), IPA (3×), and DCM (3×). To the resin was added a solution of $SnCl_2$ (500 mg, 2.64 mmol) in a mixture of NMP (1.0 mL) and ethanol (50 μL), and the mixture was shaken for

16,h at room temperature. The resin was filtered and washed with DMF (3×), IPA (3×), and DCM (3×). To the resin were added NMP (1.5 mL), DIPEA (174 μL, 1.0 mmol), and 4,6-dichloro-5-nitropyrimidine (97 mg, 0.5 mmol). The mixture was shaken for 2 h at room temperature. The resin was filtered and washed with DMF (3×), IPA (3×), and DCM (3×). To the resin were added NMP (1.0 mL), DIPEA (88 μL, 0.5 mmol), and amine building block (0.5 mmol). The mixture was shaken for 16 h at room temperature. The resin was filtered, washed with DMF (3×), IPA (3×), and DCM (3×), and dried.

Representative Procedure for Reduction with $SnCl_2$. To the resin (0.1 mmol) was added a solution of $SnCl_2$ in NMP (2 N, 2.0 mL), and the mixture was shaken for 20 h at 50 °C. The mixture was transferred to a fritted polypropylene vessel, and the solvent was drained. The resin was rinsed with DMF (3×), IPA (3×), and DCM (3×).

Representative Procedure for Reduction with Viologen (and for the synthesis of dihydropteridinones). To the resin (0.1 mmol) in a vial in DCM (2 mL) was injected a mixture of K_2CO_3 (138 mg, 1.0 mmol) and $Na_2S_2O_4$ (156 mg, 0.896 mmol) in H_2O (0.8 mL). 1,1-Dioctyl-viologen dihydrobromide (20 mg, 0.037) was added, and the deep blue mixture was vigorously shaken for 20 h at room temperature. The mixture was transferred to a fritted polypropylene vessel, and the solvent was drained. The resin was rinsed with DCM−1% AcOH/H_2O (1:1, 3×), ethyl acetate−H_2O (1:1, 3×), acetone (3×), IPA (3×), and DCM (3×).

Representative Procedure for the Synthesis of Pyrimidoimidazolones. 5-Aminopyrimidine resin (obtained in reduction, 0.1 mmol) in a mixture of THF (1.1 mL) and DMF (0.4 mL) was treated with disuccinimidyl carbonate (43 mg, 0.168 mmol). The mixture was shaken for 16 h at 80 °C and then cooled to room temperature. The mixture was transferred to a polypropylene vessel, and the resin was filtered off and washed with THF (3×), DMF (3×), IPA (3×), and DCM (3×). The procedure was repeated one more time.

Representative Procedure for the Synthesis of 6,8-Diaminopurines. To 5-aminopyrimidine resin (obtained in reduction, 0.1 mmol) in DMF (1.5 mL) was added the isothiocyanate building block (1.0 mmol). The mixture was heated to 80 °C for 20−25 min (prolonged heating before DIC is added results in decreased purity of the final products), DIC (156 μL, 1.0 mmol) was injected, and the mixture was shaken for 16 h at 80 °C. The mixture was cooled to room temperature and was transferred to a polypropylene vessel, and the resin was filtered off and washed with DMF (3×), IPA (3×), and DCM (3×). The procedure was repeated one more time.

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