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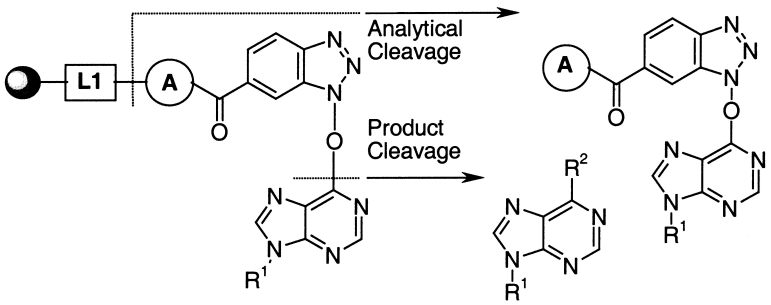

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Solid-Phase Development of a 1-Hydroxybenzotriazole Linker for Heterocycle Synthesis Using Analytical Constructs

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The development of a 1-hydroxybenzotriazole linker for the synthesis of heterocyclic derivatives is described, utilizing analytical construct methodology to facilitate the analysis of resin samples. A UV-chromophore-containing analytical construct enabled the accurate determination of resin loading and the automated monitoring of key reactions using only small quantities of resin. The syntheses of an array of isoxazole derivatives are reported.

Introduction

Solid-phase organic synthesis[1] has now become well established as one of the synthetic tools[2] available to chemists for the parallel synthesis of compound libraries. Although resin-based chemistry offers many practical advantages over conventional solution-phase methods, effective monitoring of reactions conducted on the support remains problematic because developments toward general and rapid methods of analysis[3] have not kept pace with other advances in the field. In an effort to overcome these difficulties, we and others have developed a series of analytical construct resins[4] that greatly simplify the analysis of solid-phase reaction products. Such systems (Figure 1) exploit two orthogonal linkers, allowing both conventional cleavage to release the target molecule and cleavage in an analytical sense. The latter cleavage method releases an "analytical fragment" in which the target molecule is labeled with a species that enhances analysis, facilitating product detection from very small quantities of resin. The analytical enhancer incorporates a mass spectral sensitizing group and an isotopic label, typically a 1:1 mixture of hydrogen and deuterium isotopes (mass spectral fingerprint), for rapid identification of reaction products by liquid chromatography−mass spectrometry (LCMS). Recently, we reported analytical constructs that also include an anthracene moiety, enabling direct relative quantification of resin-derived products by HPLC at a wavelength remote from extraneous components (386 nm).[5]

Although we have shown that analytical constructs are useful for following relatively simple solid-phase reactions, we were interested in extending this technology to chemistry where conventional analysis, either by linker cleavage followed by LCMS of the released fragment or by on-bead methods, would be difficult or could give ambiguous results. In particular, applying analytical construct methodology to the development of novel linker systems would allow rapid and quantitative assessment of linker loading as well as detection of any byproducts that, for example, may result in incomplete cleavage of the linker. In addition, the technique lends itself to the investigation of resin-bound activating groups, facilitating the study of potentially labile resin-bound species.

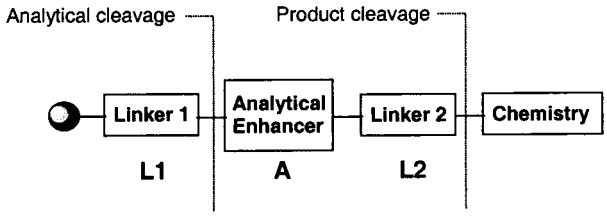

Figure 1. Schematic representation of an analytical construct. Cleavage at linker 2 (L2) releases the substrate. Alternatively, cleavage at linker 1 (L1) releases the substrate bound to an analytical enhancer (A) that facilitates characterization by HPLC−MS.

The commonly used additive for acylation reactions, 1-hydroxybenzotriazole (HOBt),[6] has recently been reported by our colleagues[7] as a catalyst for the substitution of chloropurines with amines and anilines. We were interested in applying our analytical construct technology to a study of the known HOBt linker, which has been previously exploited as a supported reagent for the synthesis of amides,[8] carbamates,[9] and esters,[10] for the immobilization of chloropurines, enabling monitoring of further on-resin reactions and the subsequent displacement from the resin by amines.

In designing the analytical construct for this application, we were restricted by the chemistry of the HOBt−purine conjugate. The analytical constructs that we have previously reported[4] have incorporated an amine-releasing linker as linker 1. This ensures that the analytical fragment will be highly sensitized in ESI-MS, positive mode, allowing clear

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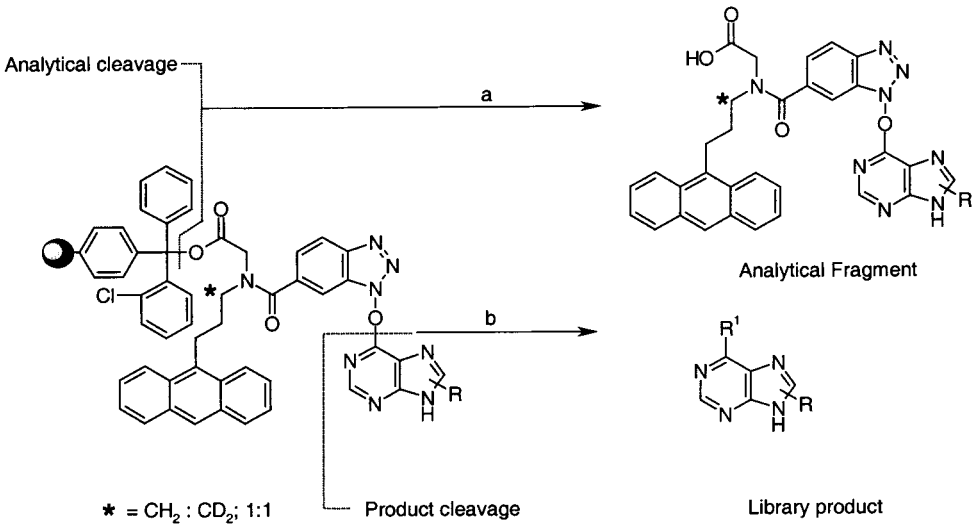
Scheme 1. Analytical Construct Features[a]



[a] Reagents and conditions: (a) HFIP/CH_2Cl_2 (1:4), 2 min, room temp; (b) primary amines, secondary amines, or anilines, CH_2Cl_2, 20 h, room temp. The construct contains the anthracene moiety for facile HPLC monitoring and a 1:1 mixture of hydrogen and deuterium isotopes (MS fingerprint). Analytical cleavage under very mild conditions (path a) releases a carboxylic acid, improving the ionization properties in ESI-MS, negative mode. Displacement with amines (path b) releases the target library product.

visualization of the MS signals from a single resin bead. Because the HOBt−purine bond is susceptible to cleavage by nucleophiles and strong acid, we were not able to employ our established analytical constructs for this purpose. To circumvent these difficulties, the analytical construct chosen for the chemistry (Scheme 1) comprised a chlorotrityl linker[11] as linker 1, allowing release of a carboxylic acid that would enhance the ionization properties of the resultant analytical fragment in ESI-MS, negative mode. Although the MS sensitization in ESI-MS negative mode is not as strong as in the positive mode,[12] we anticipated the level of sensitization would be sufficient to observe clear signals in the mass spectrum for the cleaved analytical fragments. Additionally, cleavage of the chlorotrityl linker with hexafluoroisopropanol[13] (HFIP) facilitates rapid linker scission without fragmenting the sensitive HOBt−purine bond. An isotopically labeled anthracene propyl group served as the MS fingerprint and UV chromophore.

Results and Discussion

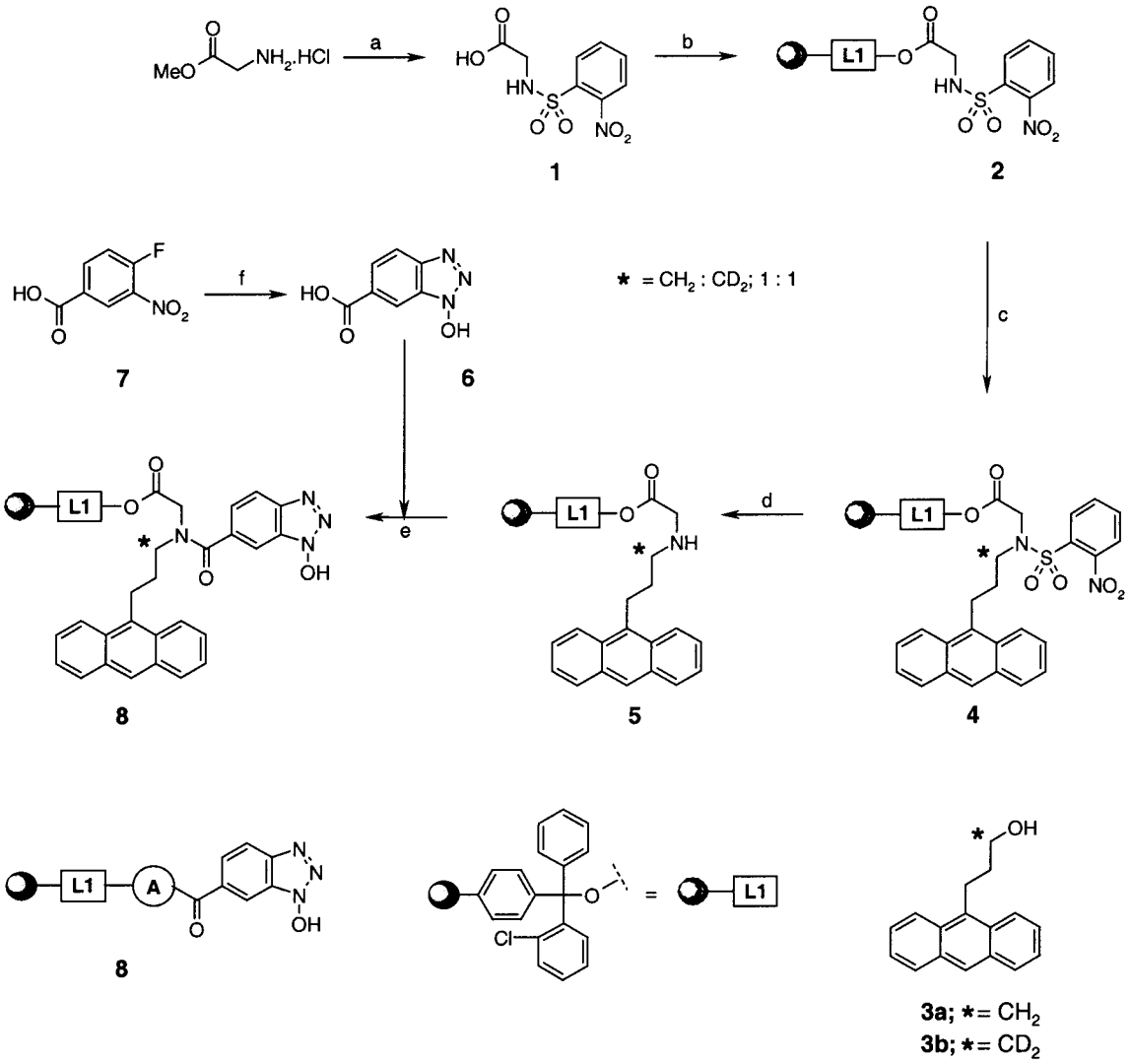
The synthesis of the analytical construct is shown in Scheme 2. The reaction of glycine methyl ester with *o*-nitrobenzenesulfonyl chloride followed by ester hydrolysis afforded **1**, which was then loaded onto chlorotrityl chloride resin to give **2** in 96% yield.[14] Direct preparation of **2** from Fmoc−glycine on the solid phase resulted in formation of the corresponding disulfonated glycine adduct as the major product after even short reaction times. The chromophoric group incorporating the MS fingerprint was introduced by Fukuyama−Mitsunobu[15] alkylation of the sulfonamide with a 1:1 mixture of the anthracene propanols[5] **3a** and **3b** to give **4** in 98% yield by weight and in 96% purity[16] as determined by HPLC of the cleaved fragment. Deprotection of **4** using a solution of sodium thiophenolate in DMF buffered with thiophenol gave smooth, quantitative conversion to the required secondary amine **5**.

Coupling of 6-carboxy-1-hydroxybenzotriazole **6**,[17] which was prepared in one step from the fluoronitrobenzene **7** in quantitative yield, to resin **5** was achieved using diisopropylcarbodiimide (DIC) in the presence of DMAP to give the analytical construct−HOBt linker conjugate **8**. The preparations of compounds **4**, **5**, and **8** were monitored by cleavage at the chlorotrityl linker (linker 1). Cleavage following the coupling of the HOBt linker to resin **5** indicated the presence of oligomeric HOBt esters. These byproducts were conveniently cleaved by treatment of the resin with a solution of benzylamine in dichloromethane.

The resin loading was determined by exploiting the quantitative cleavage of the chlorotrityl linker, employing a 20% solution of HFIP in dichloromethane containing **3a**[5] as an internal standard. HPLC quantification of the peak areas of both the resulting analytical fragment and **3a** at 386 nm gave the loading as 0.48 mmol g^{-1}. The functional activity of the resin was also determined by reaction of **8** with benzoyl chloride in dichloromethane in the presence of DIEA followed by displacement of the resin-bound active ester with the volatile 2-fluorobenzylamine after rigorous washing of the resin. The quantity of the amide produced was assessed by ^{1}H NMR using *p*-nitrophenol as an external standard.[18] The loading figure thus obtained was 0.33 mmol g^{-1}, 70% of the value obtained using the analytical construct. This difference could be attributed to partial hydrolysis of the HOBt active ester during the resin washing steps. However, the results obtained fall within the range found by previous workers.[8]

To exemplify the utility of construct **8** in heterocycle synthesis, we chose to investigate the preparation of a small array of model compounds that contained a 6-substituted purine and an isoxazole[19] as a model for future library synthesis. The N-substituted purine **9b**, required for the study, was conveniently prepared (Scheme 3) by alkylation of commercially available 6-chloropurine, giving a mixture of regioisomers, which could be separated by flash chromatography. The regiochemistry of the product was confirmed by X-ray crystallography.

Scheme 2. Synthesis of the Analytical Construct Resin[a]

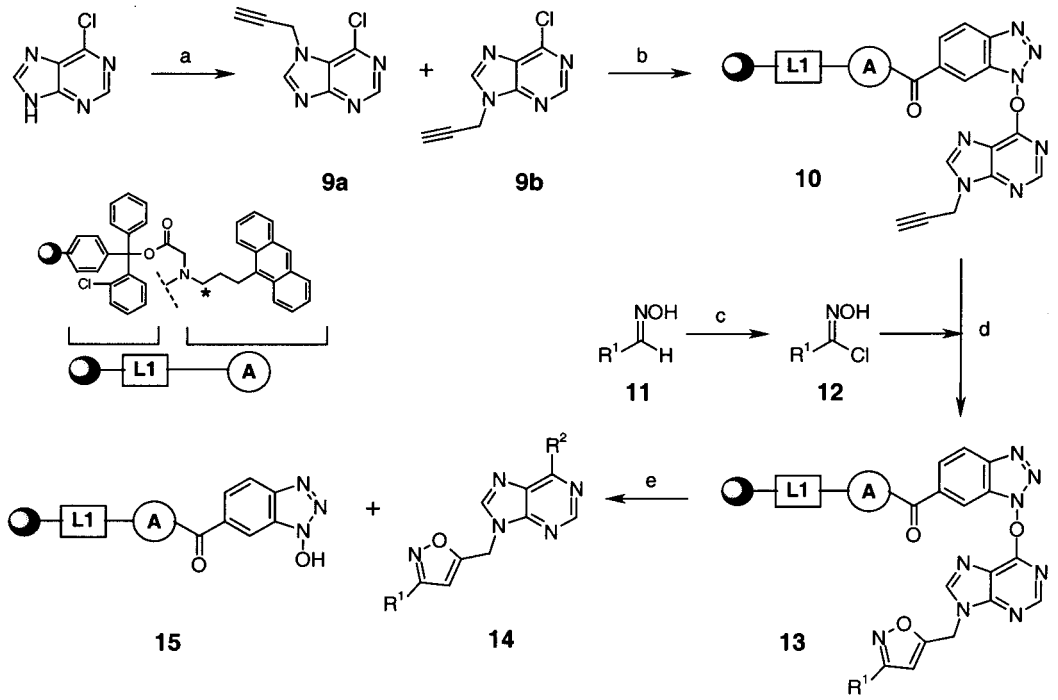


[a] Reagents and conditions: (a) (i) *o*-nitrobenzenesulfonyl chloride, DIEA, CH_2Cl_2, 16 h, room temp, 75%, (ii) aqueous sodium hydroxide (2 M, 4.6 equiv), 1,4-dioxane, MeOH, 16 h, room temp, 61%; (b) chlorotrityl chloride resin, DIEA, CH_2Cl_2, room temp, 96%; (c) **3a**/**3b** (1:1), triphenylphosphine, di-*tert*-butyl azodicarboxylate, CH_2Cl_2, room temp, 98%; (d) sodium thiophenolate, thiophenol, DMF, 2 × 15 min, room temp, quantitative; (e) (i) **6**, DIC, DMAP, CH_2Cl_2, DMF, (ii) benzylamine (10%), CH_2Cl_2, room temp, 2.5 h, 96%; (f) (i) hydrazine hydrate, EtOH, 3 h, (ii) 10% aqueous hydrochloric acid, quantitative.

The use of the analytical construct supporting the HOBt linker greatly facilitated an automated study of linker loading. Purine **9b** was allowed to react with the HOBt construct **8** in DMF in the presence of DIEA to yield the substituted resin **10** (Scheme 3). Using the Anachem SK233[20] robotic system, reaction aliquots were removed at various times and treated directly with a 20% solution of HFIP in dichloromethane. The cleaved solutions were then quenched with acetonitrile and immediately analyzed by HPLC. No washing steps were necessary because the presence of starting materials in the cleaved solutions did not affect the HPLC analysis of the analytical fragments at the wavelength being used (386 nm). In addition, the high extinction coefficient of the anthracene chromophore at 386 nm (ϵ 9000, CH_3CN) enabled the study to be carried out using small quantities of resin. Indeed, the aliquots were limited only by the ability of the robotic sampling system to handle small suspension volumes. It was found that the instrument could routinely sample 20 μL aliquots, corresponding to 2 mg of resin, from the suspension. When peak areas of the analytical fragments **8a** and **10a**, corresponding to the starting material and the product **8** and **10**, respectively, were plotted, it was possible to generate a time-course graph for the reaction (Figure 2) which indicated that the loading of the linker was 95% complete after 8 h at 25 °C. Although the reaction was monitored for a total of 72 h, the composition of the reaction mixture did not change further.

A range of commercially available aldoximes (Figure 3, chemset **11**) were chlorinated[21] with a substoichiometric quantity of *N*-chlorosuccinimide in dichloromethane to avoid overchlorination of the products at activated aromatic positions. This reaction yielded solutions containing the corresponding hydroximoyl chlorides (Scheme 3, chemset **12**). The nitrile oxides, required for the cycloaddition, were generated in situ, by addition of these solutions to suspensions of the resin-supported alkyne **10** in the presence of an excess of triethylamine. The reactions were conveniently monitored using the analytical construct, and the cyclizations of aromatic nitrile oxides were found to be complete after reaction overnight at room temperature. The formation of

Scheme 3. Isoxazole Synthesis on Analytical Construct Resin **8**[a]



[a] Reagents and conditions: (a) NaH, propargyl bromide, DMF, 1 h, 0 °C to room temp, **9a** 21%, **9b** 33%; (b) **8**, DIEA, DMF, 72 h, 25 °C, 95%; (c) *N*-chlorosuccinimide (0.7 equiv), CH_2Cl_2, 16 h, room temp; (d) **12**{*1*−*4*}, TEA, CH_2Cl_2, 20 h, 25 °C, see Experimental Section; (e) **16**{*1*−*5*}, CH_2Cl_2, 20 h, 25 °C, 20−98% (Table 1).

isoxazole **13**{*3*} was found to be only 75% complete after 20 h, but repeating the reaction with a fresh solution of **12**{*3*} after first washing the resin gave complete conversion. In all cases, analytical cleavage of approximately 1−2 mg of resin released analytical fragments, which gave the required MS doublets in ESI-MS and showed clear analytical HPLC signals at 386 nm. Monitoring the reactions using conventional on-resin techniques such as MAS ^{1}H NMR[22,23] or single-bead diffuse reflectance FTIR[24] gave inconclusive and inconsistent results for these polystyrene-based resins.

To study the displacement of the substituted purines with amines, a representative time course study for a typical amine (benzylamine) with supported purine **10** was undertaken in a way similar to that of the linker loading experiment described above. In this case, comparison of the peak areas corresponding to analytical fragments of the starting material **10** and the regenerated HOBt linker **15** at 386 nm gave an indication of the extent of linker cleavage over time (Figure 4). A 5-fold excess of benzylamine (2% in dichloromethane) at 25 °C was found to give essentially complete reaction after 8 h. To allow for potentially less nucleophilic amines and anilines, however, the aminolysis of the resins was routinely conducted over 20 h. Primary and secondary amines as well as activated anilines (chemset **16**) resulted in full release of the library products into solution.

The excess amines were removed from the final library products using polymer-supported isatoic anhydride resin,[25] and solid-phase extraction (SPE)[26] through a short pad of silica gel eluting with ethyl acetate or methanol gave the required products **14** (Table 1) in moderate to good yield and high purity. The ^{1}H NMR and high-resolution mass spectral data were satisfactory for these compounds.

The ease of reaction monitoring using the analytical construct is illustrated in Figure 5, which depicts a representative series of reactions from the loading of the HOBt linker to the displacement of the final product from the resin by aminolysis. Typically a total of 1−2 mg of resin was cleaved at L1 to release the analytical fragments and monitoring at 386 nm allowed relative quantification of any side products formed in the reaction sequence. The parent ions derived from each major peak, in ESI-MS negative mode, served to confirm the identity of the analytical fragment. Entry 2 clearly shows residual unloaded linker, whereas entry 3 indicates completion of the cycloaddition reaction, using the analytical fragment derived from **13**{*2*} as a representative example of the chemistry. On treatment with an amine, the bare linker was regenerated in >90% yield as illustrated by entry 4.

Conclusion

In summary, we have exploited analytical construct methodology to facilitate the development of an HOBt linker for heterocycle synthesis, illustrating the approach by the preparation of a small array of isoxazole derivatives on the construct resin. This library served to exemplify the use of analytical constructs when applied to the monitoring of solid-phase reactions supported on a very sensitive linker. In addition, the combination of the highly acid labile chlorotrityl linker and the anthracene chromophore in the analytical construct **8** enabled the accurate determination of resin loading and the automated monitoring of key reactions to be performed on small quantities of material without the need for resin washing steps. Further work to exploit analytical constructs for the *automated* study of reaction kinetics is in progress and will be reported in due course.

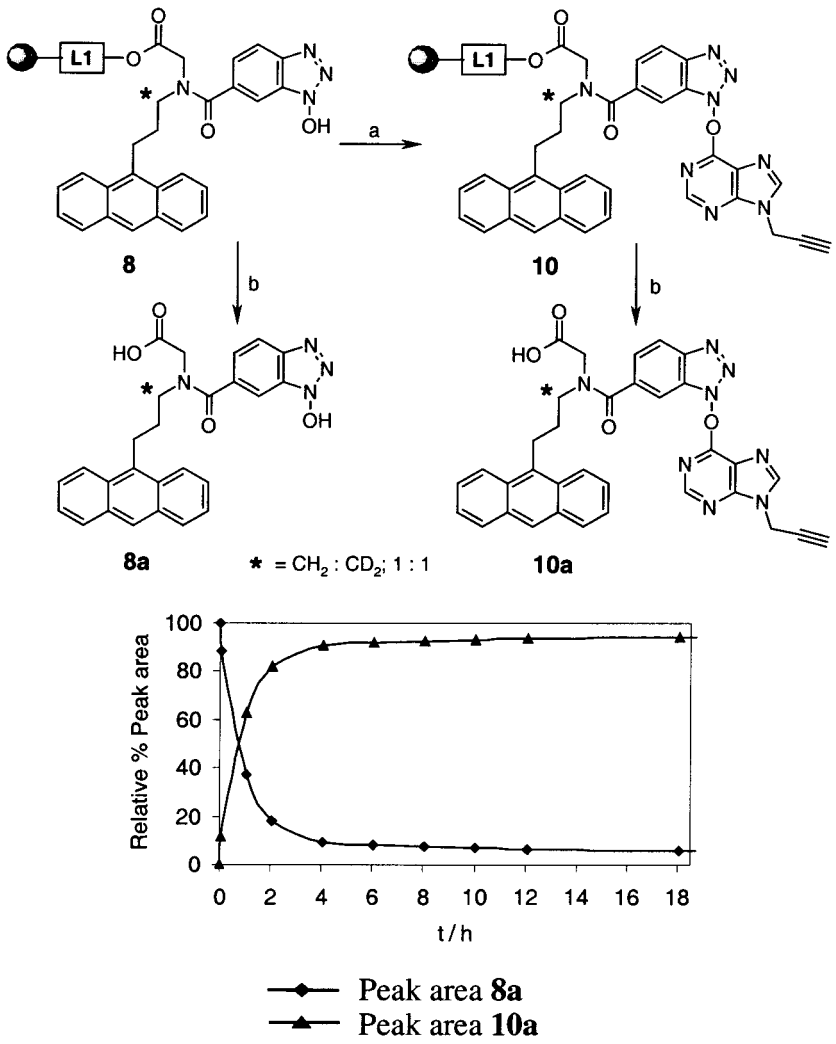


Figure 2. Time course for the immobilization of **9** onto **8**. Reagents and conditions are the following: (a) **9**, DIEA, DMF, 25 °C; (b) 20% HFIP/DCM, 2 min. HPLC peak areas at 386 nm of the analytical fragments **8a** (◆) and **10a** (▲) are derived from those of **8** and **10**, respectively.

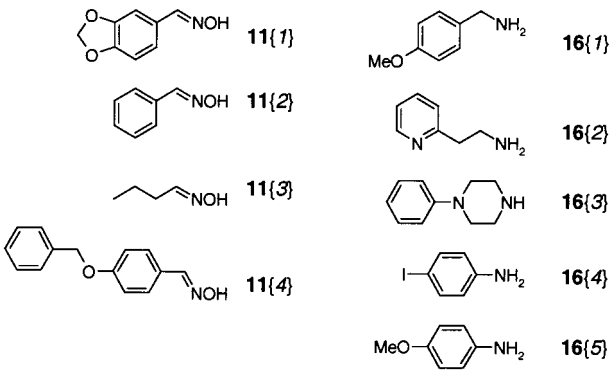


Figure 3. Diversity reagents **11**{*1*−*4*} and **16**{*1*−*5*}.

Experimental Section

General. All starting materials, reagents, and solvents were commercially available and used as received without further purification. 2-Chlorotrityl chloride resin was purchased from Calbiochem-Novabiochem. Thin-layer chromatography (TLC) was performed on CamLab SilG/UV254 precoated plates. Flash chromatography was carried out on a Merck-Kieselgel 60 (0.040−0.063 mm) under a pressure of nitrogen. Infrared spectra were recorded on a Bio-Rad Win-IR spectrometer by diffuse reflectance on KBr. FTIR microspectroscopy of resin beads was performed with a Perkin-Elmer AutoIMAGE microscope. All ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM-400 spectrometer. The chemical shifts are in δ units relative to TMS ($\delta = 0$) as the internal standard. Multiplicities are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; and br, broad; and coupling constants (J values) are quoted in hertz. LCMS analyses were performed on a Hewlett-Packard HP 1050 instrument (diode array detection) and a Micromass Platform I (8084) mass spectrometer using electrospray ionization in +ve and −ve mode. High-resolution spectra were recorded on a VG Autospec running positive or negative electrospray. Microanalyses were performed by Butterworths Laboratories, Ltd., Teddington, Middlesex. HPLC was run on a Hewlett-Packard 1050 instrument using a Supelco, Supelcosil ABZ+PLUS column (3.3 cm, 4.6 mm Φ, 3 μm). The method was the following. Eluent A: water, 0.1% TFA. Eluent B: acetonitrile 95%, water 5%, TFA 0.05%. Gradient: 10−95% eluant B in eluant A (1 mL min^{-1}) over 8 min Detection: UV (diode array 215, 230, 254, 386 nm). Melting points were performed on a Mettler FP5 automatic melting point apparatus in open tubes heated from 50 °C at 2 °C min^{-1}

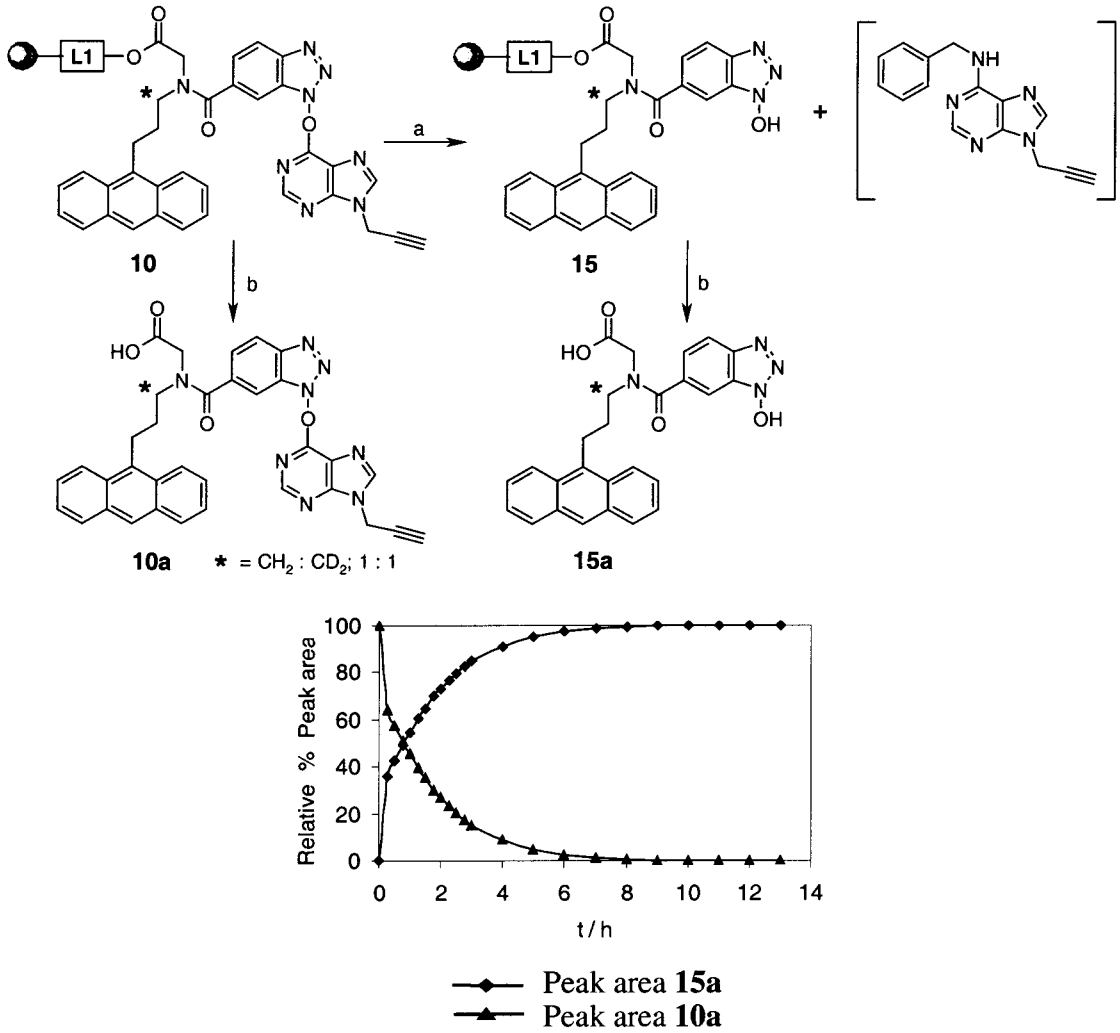
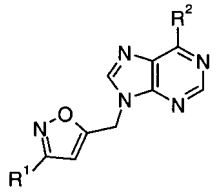


Figure 4. Time course for the displacement of **10** with benzylamine. Reagents and conditions are the following: (a) 2% $PhCH_2NH_2$ in CH_2Cl_2, 25 °C; (b) HFIP/CH_2Cl_2 (1:4), 2 min, room temperature. HPLC peak areas at 386 nm of the analytical fragments **15a** (◆) and **10a** (▲) are derived from those of **15** and **10**, respectively.

Table 1. Yields and Purities of Final Compounds **14** after Displacement from Resin



entry	no.{R^1,R^2}[a]	yield,[b] %	HPLC purity, %
1	**14**{*1,1*}	98	93
2	**14**{*2,1*}	61	97
3	**14**{*3,1*}	43	>98
4	**14**{*4,1*}	20[c]	97
5	**14**{*4,2*}	67	>98
6	**14**{*4,3*}	58	97
7	**14**{*4,4*}	49[b]	>95[d]
8	**14**{*4,5*}	72	71

[a] R^1 derived from diversity reagents **11**{*1*−*4*}, R^2 derived from diversity reagents **16**{*1*−*5*} (Figure 3). [b] Yield determined by quantification by ^{1}H NMR against *p*-nitrophenol as an external standard, based on measured resin loading from **8**. [c] The sample was purified by preparative HPLC. [d] Sample purity is >95% by ^{1}H NMR.

and are uncorrected. Analytical cleavage of resins was performed by incubation of resin samples (approximately 2 mg) with a 20% solution of HFIP in CH_2Cl_2 (10 μL) for 2 min and then dilution with HPLC eluent B (70 μL). The resultant solutions were analyzed by HPLC and LCMS.

{**[(2-Nitrophenyl)sulfonyl]amino**}**acetic Acid (1).** To a solution of glycine methyl ester hydrochloride (1.88 g, 15.00 mmol) and DIEA (5.23 mL, 30.00 mmol) in CH_2Cl_2 (50 mL) was added a solution of *o*-nitrobenzenesulfonyl chloride (3.10 g, 14.00 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred for 16 h. Then it was diluted with CH_2Cl_2 (100 mL), washed with dilute hydrochloric acid (10%, 2 × 50 mL) and water (2 × 50 mL), dried ($MgSO_4$), and then evaporated to a semicrystalline orange solid (3.56 g). Recrystallization from 2-propanol gave methyl {[(2-nitrophenyl)sulfonyl]amino}acetate as white needles (3.12 g, 75%). Mp 112.1 °C; R_f 0.38 [EtOAc/hexane (1:1)]. Found: C, 39.27; H, 3.65; N, 10.03; S, 11.95%. $C_9H_{10}N_2O_6S$ requires C, 39.42; H, 3.68; N, 10.21; S, 11.69%. ν_{max} (cm^{-1}): 3345, 1745, 1542, 1348, 1404. δ_H ($CDCl_3$): 8.08 (m, 1 H), 7.92 (m, 1 H), 7.73 (m, 2 H,), 6.03 (m, 1 H), 4.00 (d, 2 H, J = 6 Hz), 3.60 (s, 3 H). δ_C ($CDCl_3$): 169.9, 148.6, 134.8, 134.6, 133.8, 131.5, 126.5, 53.4, 45.6. LCMS: (electrospray +ve) *m*/*z* 275 $(MH)^+$. HPLC: 3.34 min, 98% (254 nm).

To a solution of methyl {[(2-nitrophenyl)sulfonyl]amino}-acetate (939 mg, 3.42 mmol) in MeOH (12 mL) and 1,4-dioxane (6 mL) was added aqueous sodium hydroxide solution (2 M, 1.88 mL, 3.76 mmol). After 16 h the reaction mixture was treated with an additional quantity of sodium hydroxide solution (2 M, 1.88 mL, 3.76 mmol) and stirring

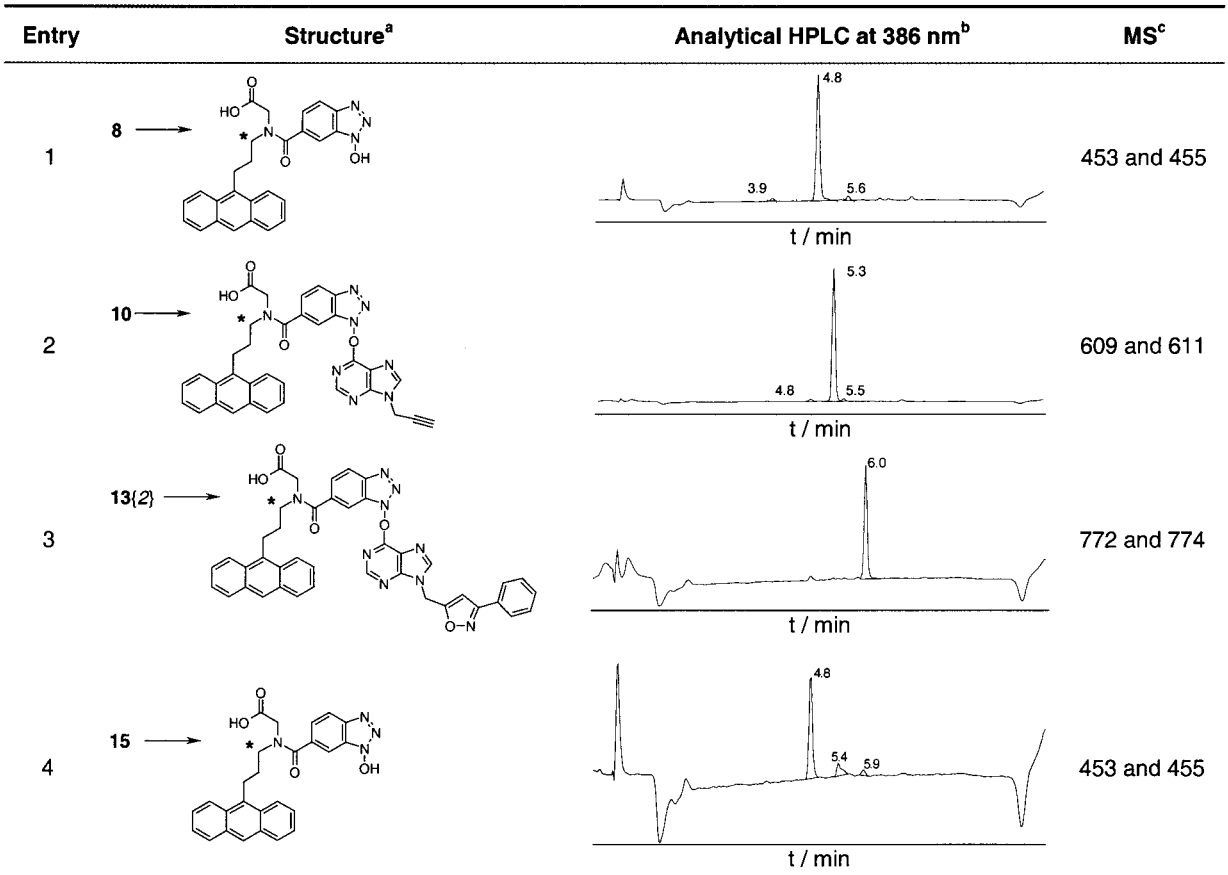


Figure 5. Analytical cleavage of resins **8** and **10**, showing the analytical fragments for the parent linker and the immobilization of the propargyl purine **9**. The analytical fragments derived from **13**{*2*} and from the regenerated linker resin **15** are shown as representative examples of the chemistry. In the figure, the footnotes are defined as follows: (a) ∗represents CH_2/CD_2, 1:1; (b) relative absorbance is at 386 nm (scale not indicated); (c) ESI-MS ions are detected for the major component, negative mode (Micromass Platform LCMS).

continued for 16 h. The reaction mixture was treated with hydrochloric acid (10%, 50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (25 mL) and saturated brine (25 mL) and then dried ($MgSO_4$), filtered, and evaporated to a yellow solid. Recrystallization from methyl *tert*-butyl ether and hexane gave the title compound as cream crystals (546 mg, 61% from methyl {[(2-nitrophenyl)sulfonyl]amino}acetate). Mp 160.4 °C Found: C, 36.70; H, 3.31; N, 10.41; S, 12.36%. $C_8H_8N_2O_6S$ requires C, 36.93; H, 3.10; N, 10.76; S, 12.32%. ν_{max} (cm^{-1}): 3325, 2877, 1720, 1542, 1353, 1395. δ_H (DMSO-d_6): 12.71 (s, 1 H), 8.39 (t, 1 H, $J = 6$ Hz), 8.0 (m, 1 H), 7.93 (m, 1 H), 7.82 (m, 2 H), 3.73 (d, 2 H, $J = 6$ Hz). δ_C (DMSO-d_6): 170.6, 147.7, 134.3, 133.8, 133.0, 130.0, 124.6, 44.3. LCMS: (electrospray +ve) *m*/*z* 282 $(MNa)^+$; (electrospray −ve), *m*/*z* 259 $(M - H)^-$. HPLC: 2.84 min, 96% (254 nm).

Coupling of {[(2-Nitrophenyl)sulfonyl]amino}acetic Acid (1) to Chlorotrityl Resin. To a suspension of chlorotrityl chloride resin (5.04 g, 6.35 mmol) and DIEA (2.22 mL 12.70 mmol) in dry CH_2Cl_2 (50 mL) was added a solution of **1** (2.83 g, 10.87 mmol) and DIEA (2.22 mL 12.70 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was agitated for 70 h and filtered, and the resin was washed with CH_2Cl_2 (1 × 10 mL), CH_2Cl_2 (17), MeOH (2), DIEA (1) (4 × 5 mL), DMF (5 × 10 mL), CH_2Cl_2 (5 × 10 mL), and ether (5 × 10 mL) and then dried in vacuo to give resin **2** (1.01 g, 96%). Analytical cleavage, LCMS: (electrospray +ve), *m*/*z* 283 $(MNa)^+$; (electrospray −ve), *m*/*z* 259 $(M - H)^-$. HPLC: 2.18 min, 97% (215 nm).

Resin-Bound Mixture (1:1 Ratio) of {[3-(9-Anthryl)-propyl][(2-nitrophenyl)sulfonyl]amino}acetic Acid and {[3-(9-Anthryl)-1-d_2-propyl][(2-nitrophenyl)sulfonyl]amino}acetic Acid (4). To a suspension of **2** (984 mg, 0.935 mmol), 3-(9-anthryl)propan-1-ol (221 mg, 0.935 mmol), 3-(9-anthryl)propan-1-d_2-ol (223 mg, 0.935 mmol), and triphenylphosphine (490.5 mg, 1.874 mmol) in dry CH_2Cl_2 (5 mL) under N_2 was added a solution of di-*tert*-butyl azodicarboxylate (430 mg, 1.87 mmol) in dry CH_2Cl_2 (7 mL) over 15 min. The reaction mixture was agitated for 26 h, filtered, and washed with CH_2Cl_2 (2 × 10 mL), DMF (5 × 10 mL), THF (5 × 10 mL), CH_2Cl_2 (5 × 10 mL), and ether (5 × 10 mL) and then dried in vacuo to give the title resin as an orange solid (1.15 g, 98%). Analytical cleavage, LCMS: (electrospray +ve), *m*/*z* 479 and 481 $(MH)^+$. HPLC: 6.65 min, 100% (386 nm).

Resin-Bound Mixture (1:1 Ratio) of {[3-(9-Anthryl)-propyl]amino}acetic Acid and {[3-(9-Anthryl)-1-d_2-propyl]-amino}acetic Acid (5). To a suspension of resin **4** (823 mg, 0.54 mmol) in DMF (10 mL) was added a solution of sodium thiophenolate (1.41 g, 10.70 mmol) and thiophenol (277 μL, 2.7 mmol) in DMF (10 mL). The reaction mixture was

agitated for 15 min, filtered, and washed with DMF (3 × 10 mL). The procedure was repeated, and the resin was washed with DMF (5 × 10 mL), THF (3 × 10 mL), CH_2Cl_2 (5 × 10 mL), and ether (5 × 10 mL). The resin was dried in vacuo to give the title resin (701 mg, quantitative) as a yellow solid. Analytical cleavage, LCMS: (electrospray +ve), *m*/*z* 294 and 296 $(MH)^+$. HPLC: 3.85 min, 100% (386 nm).

1-Hydroxy-1*H*-1,2,3-benzotriazole-6-carboxylic Acid (6). To a solution of 4-fluoro-3-nitrobenzoic acid (1.86 g, 10 mmol) in absolute EtOH (20 mL) was added hydrazine hydrate (7.8 mL), and the resulting dark suspension was heated at reflux for 3 h and then cooled, diluted with EtOH (30 mL), and filtered to give a cream solid that was washed with EtOH (50 mL). The solid was dissolved in water (30 mL) and then treated with aqueous hydrochloric acid (10%, 100 mL), and the resultant precipitate was filtered and dried in vacuo over P_2O_5 to give the title compound as a white solid (1.85 g, quantitative). Mp 257 °C (dec). Found: C, 43.14; H, 3.44; N, 21.72%. $C_7H_5N_3O_3 \cdot 0.9H_2O$ requires C, 43.04; H, 3.51; N, 21.51%. ν_{max} (cm^{-1}): 3500, 1692. δ_H (DMSO-d_6): 8.21 (s, 1 H), 8.05 (d, 1 H, $J = 9$ Hz), 7.90 (d, 1 H, J 9 = 9 Hz). δ_C (DMSO-d_6): 168.4, 146.3, 131.4, 129.3, 126.6, 121.1, 113.5. LCMS: (electrospray +ve), *m*/*z* 180 $(MH)^+$. HPLC: 2.38 min, 96% (230 nm).

Resin-Bound Mixture (1:1 Ratio) of {[3-(9-Anthryl)-propyl][(1-hydroxy-1*H*-1,2,3-benzotriazol-6-yl)carbonyl]-amino}acetic Acid and {[3-(9-Anthryl)-1-d_2-propyl]-[(1-hydroxy-1*H*-1,2,3-benzotriazol-6-yl)carbonyl]amino}-acetic Acid (8). To a solution of 1-hydroxy-1*H*-1,2,3-benzotriazole-6-carboxylic acid (1.85 g, 10.35 mmol) in DMF (17.5 mL) was added DIC (1.62 mL, 10.35 mmol) and a catalytic quantity of DMAP. The resulting yellow solution was added to a suspension of amino resin **5** (2.18 g, 2.07 mmol) in CH_2Cl_2 (17.5 mL). After 2.5 h, the resin was washed with DMF (5 × 20 mL) and then treated with a solution of benzylamine in CH_2Cl_2 (10%, 10 mL) for 3 h and washed with DMF (5 × 20 mL), THF (5 × 20 mL), and ether (5 × 20 mL) and then dried in vacuo to give the title resin as a yellow solid (2.42 g, 96%). Analytical cleavage, LCMS: (electrospray −ve), *m*/*z* 453 and 455 $(M - H)^-$. HPLC: 4.82 min, 91% (386 nm).

Alkylation of 6-Chloropurine. To a solution of 6-chloropurine (3.97 g, 25.66 mmol) in DMF (50 mL) at 0 °C under N_2 was added sodium hydride (60% dispersion in oil, 1.13 g, 28.25 mmol) over 5 min. The reaction mixture was stirred for 30 min and then treated with a solution of propargyl bromide in toluene (80%, 3.2 mL, 28.3 mmol). The reaction mixture was allowed to warm to room temperature over 1 h and then was quenched with water (10 mL), diluted with EtOAc (200 mL), and washed with LiCl solution (10%, 50 mL). The aqueous phase was extracted with EtOAc (50 mL), and the combined organic phases were washed with LiCl solution (10%, 2 × 50 mL), water (50 mL), and brine (50 mL) and then dried ($MgSO_4$), filtered, and evaporated to give an orange solid. Flash chromatography (EtOAc/hexane 1:2, then 1:1) gave compounds **9a** and **9b.** 6-Chloro-7-prop-2-ynyl-7*H*-purine (**9a**) (372 mg, 21%) was a white solid. Mp 131.3 °C; R_f 0.12 [EtOAc/hexane (1:1)]. Found: C, 49.63; H, 2.18; N, 29.41; Cl, 18.40%. $C_8H_5N_4Cl$ requires C, 49.89; H, 2.62; N, 29.09; Cl, 18.41%. ν_{max} (cm^{-1}): 3278, 3060, 2128, 1602, 1538. δ_H (DMSO-d_6): 8.86 (s, 1 H), 8.82 (s, 1 H), 5.36 (d, 2 H, $J = 2$ Hz), 3.63 (t, 1 H, $J = 2$ Hz). δ_C (DMSO-d_6): 163.0, 153.9, 152.2, 144.3, 124.2, 79.8, 79.6, 38.3. LCMS: (electrospray +ve), *m*/*z* 193 $(MH)^+$. HPLC: 2.32 min, 95% (230 nm).

9b was further purified by recrystallization from methyl *tert*-butyl ether and hexane to give 6-chloro-9-prop-2-ynyl-9*H*-purine as white needles (1.62 g, 33%). Mp 161.5 °C; R_f 0.35 [EtOAc/hexane (1:1)]. Found: C, 49.87; H, 2.47; N, 28.91; Cl, 18.19%. $C_8H_5N_4Cl$ requires C, 49.89; H, 2.62; N, 29.09; Cl, 18.41%. ν_{max} (cm^{-1}): 3245, 3120, 2129, 1592, 1565. δ_H (DMSO-d_6): 8.83 (s, 1 H), 8.76 (s, 1 H), 5.21 (d, 2 H, $J = 2.5$ Hz), 3.55 (t, 1 H, $J = 2.5$ Hz). δ_C (DMSO-d_6): 152.2, 151.8, 149.6, 147.2, 131.1, 77.7, 77.1, 33.6. LCMS: (electrospray +ve), *m*/*z* 193 $(MH)^+$. HPLC: 2.26 min, >99% (230 nm).

Resin-Bound Mixture (1:1 Ratio) of [[3-(9-Anthryl)-propyl]({1-[(9-prop-2-ynyl-9*H*-purin-6-yl)oxy]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)amino]acetic Acid and [[3-(9-Anthryl)-1-d_2-propyl]({1-[(9-prop-2-ynyl-9*H*-purin-6-yl)-oxy]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)amino]acetic Acid (10). To a suspension of resin **8** (1.75 g, 0.84 mmol) and DIEA (761 μL, 4.37 mmol) in DMF (10 mL) was added a solution of **9b** (809 mg, 4.2 mmol) in DMF (10 mL). The reaction mixture was shaken for 3 days, filtered, washed with DMF (5 × 10 mL), CH_2Cl_2 (5 × 10 mL), and ether (5 × 10 mL) and then dried in vacuo to give the title resin (1.765 g, 95%) as a yellow solid. Analytical cleavage, LCMS: (electrospray −ve), *m*/*z* 609 and 611 $(M - H)^-$. HPLC: 5.27 min, 91% (386 nm), 93% (230 nm).

General Method for the Preparation of Resin-Bound Isoxazoles 13 from Aldoximes 11. To a solution of the aldoxime (1.05 mmol) in CH_2Cl_2 (5 mL) was added a solution of *N*-chlorosuccinimide (98.1 mg, 0.74 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 16 h and then was added directly to the preswollen (CH_2Cl_2) propargyl resin **10** (250 mg, 0.105 mmol). Triethylamine (25 μL, 0.178 mmol) was added, and the reaction mixture was stirred for an additional 16 h. Analytical cleavage of resin aliquots indicated that reaction was complete:

compound	LCMS (electrospray −ve)	HPLC (386 nm), %
13{*1*}	772 and 774	91
13{*2*}	728 and 730	>98
13{*3*}	694 and 696	>98
13{*4*}	820 and 822	84

The resin was washed with CH_2Cl_2 (2 × 5 mL), DMF (2 × 5 mL), THF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), and ether (2 × 5 mL) and then dried in vacuo to give the resin-bound isoxazole **13**.

General Method for Amine Displacement To Give Isoxazoles 14. To the swollen (CH_2Cl_2) resin **13** (40 mg, 0.017 mmol) was added a solution of the required amine (0.17 mmol) in CH_2Cl_2 (0.4 mL). The reaction mixtures were

shaken for 16 h and then filtered, and the resin was washed with CH_2Cl_2 (2 × 1 mL), DMF (2 × 1 mL), and CH_2Cl_2 (2 × 1 mL). The combined filtrates were treated with PS-isatoic anhydride (40 mg, 0.21 mmol) for 3 h, the mixture was then filtered, the scavenger resin was washed with CH_2Cl_2 (2 × 1 mL), and the solvent was evaporated from the combined filtrates. Purification by solid-phase extraction eluting with EtOAc or MeOH gave, on evaporation, the required isoxazoles **14**.

9-{[3-(1,3-Benzodioxol-5-yl)isoxazol-5-yl]methyl}-*N*-(4-methoxybenzyl)-9*H*-purin-6-amine (14{*1,1*}). Yield 98%. δ_H (DMSO-d_6): 8.35 (bs, 1 H), 8.28 (s, 1 H), 8.20 (s, 1 H), 7.35 (m, 2 H), 7.25 (d, 2 H, J = 9 Hz), 6.98 (d, 1 H, J = 8.5 Hz), 6.89 (s, 1 H), 6.82 (d, 2 H, J = 9 Hz), 6.06 (s, 2 H), 5.61 (s, 2 H), 4.61 (bs, 2 H), 3.67 (s, 3 H). HRMS: $C_{24}H_{21}N_6O_4$ requires 457.1624; found 457.1642. HPLC: 4.11 min, 93% (254 nm).

***N*-(4-Methoxybenzyl)-9-[(3-phenylisoxazol-5-yl)methyl]-9*H*-purin-6-amine (14{*2,1*}).** Yield 61%. δ_H (DMSO-d_6): 8.35 (bs, 1 H), 8.29 (s, 1 H), 7.81 (m, 2 H), 7.45 (m, 3 H), 7.26 (d, 2 H, J = 9 Hz), 6.96 (s, 1 H), 6.82 (d, 2 H, J = 9 Hz), 5.63 (s, 2 H), 4.61 (bs, 2 H), 3.67 (s, 3 H). LCMS: (electrospray +ve), m/z 413 $(MH)^+$. HPLC: 4.09 min, 97% (254 nm).

***N*-(4-Methoxybenzyl)-9-[(3-propylisoxazol-5-yl)methyl]-9*H*-purin-6-amine (14{*3,1*}).** Yield 43%. δ_H (DMSO-d_6): 8.35 (bs, 1 H), 8.24 (s, 1 H), 8.19 (s, 1 H), 7.25 (d, 2 H, J = 9 Hz), 6.82 (d, 2 H, J = 9 Hz), 6.28 (s, 1 H), 5.52 (s, 2 H), 4.61 (bs, 2 H), 3.67 (s, 3 H), 2.50 (m, 2 H), 1.54 (m, 2 H), 0.84 (t, 3 H, J = 8 Hz). HRMS $C_{20}H_{23}N_6O_2$ requires 379.1882; found 379.1886. HPLC: 3.67 min, >98% (254 nm).

9-({3-[4-(Benzyloxy)phenyl]isoxazol-5-yl}methyl)-*N*-(4-methoxybenzyl)-9*H*-purin-6-amine (14{*4,1*}). Yield 20%. δ_H (DMSO-d_6): 8.29 (bs, 1 H), 8.28 (s, 1 H), 8.20 (bs, 1 H), 7.75 (d, 2 H, J = 9 Hz), 7.30−7.45 (m, 5 H), 7.26 (d, 2 H, J = 9 Hz), 7.08 (d, 2 H, J = 9 Hz), 6.88 (s, 1 H), 6.82 (d, 2 H, J = 9 Hz), 5.60 (s, 2 H), 5.13 (s, 2 H), 4.60 (bs, 2 H), 3.67 (s, 3 H). LCMS: (electrospray +ve), m/z 519 $(MH)^+$. HPLC: 5.07 min, 97% (254 nm).

9-({3-[4-(Benzyloxy)phenyl]isoxazol-5-yl}methyl)-*N*-(2-pyridin-2-ylethyl)-9*H*-purin-6-amine (14{*4,2*}). Yield 67%. δ_H (DMSO-d_6): 8.46−8.50 (m, 2 H), 8.26 (s, 1 H), 7.75 (d, 2 H, J = 9 Hz), 7.64−7.70 (m, 1 H), 7.16−7.46 (m, 7 H), 7.08 (d, 2 H, J = 9 Hz), 6.88 (s, 1 H), 5.61 (s, 2 H), 5.13 (s, 2 H), 2.85−3.15 (m, 4 H). HRMS $C_{29}H_{26}N_7O_2$ requires 504.2148; found 504.2153. HPLC: 3.81 min, >98% (254 nm).

9-({3-[4-(Benzyloxy)phenyl]isoxazol-5-yl}methyl)-6-(4-phenylpiperazin-1-yl)-9*H*-purine (14{*4,3*}). Yield 58%. δ_H (DMSO-d_6): 8.35 (s, 1 H), 8.27 (s, 1 H), 7.75 (d, 2 H, J = 9 Hz), 7.43 (m, 2 H), 7.36 (m, 2 H), 7.30 (m, 1 H), 7.21 (m, 2 H), 7.08 (d, 2 H, J = 9 Hz), 6.98 (m, 2 H), 6.88 (s, 1 H), 6.79 (t, 1 H, J = 8 Hz), 5.64 (s, 2 H), 5.13 (s, 2 H), 3.38 (m, 8 H). HRMS: $C_{32}H_{30}N_7O_2$ requires 544.2461; found 544.2471. HPLC: 5.57 min 97% (254 nm).

9-({3-[4-(Benzyloxy)phenyl]isoxazol-5-yl}methyl)-*N*-(4-iodophenyl)-9*H*-purin-6-amine (14{*4,4*}). Yield 49%. δ_H (DMSO-d_6): 10.05 (s, 1 H), 8.46 (s, 1 H), 8.42 (s, 1 H), 7.81 (m, 2 H), 7.75 (d, 2 H, J = 9 Hz), 7.62 (m, 2 H), 7.29−7.42 (m, 5 H), 7.08 (d, 2 H, J = 9 Hz), 6.91 (s, 1 H), 5.69 (s, 2 H), 5.13 (s, 2 H). HRMS: $C_{28}H_{21}IN_6O_2$ requires 601.0840; found 601.0849. HPLC: 5.27 min, 71% (254 nm).

9-({3-[4-(Benzyloxy)phenyl]isoxazol-5-yl}methyl)-*N*-(4-methoxyphenyl)-9*H*-purin-6-amine (14{*4,5*}). Yield 72%. δ_H (DMSO-d_6): 9.76 (s, 1 H), 8.41 (s, 1 H), 8.32 (s, 1 H), 7.75−7.79 (m, 4 H), 7.43 (m, 2 H), 7.36 (m, 2 H), 7.31 (m, 1 H), 7.08 (d, 2 H, J = 9 Hz), 6.90 (s, 1 H), 6.89 (m, 2 H), 5.67 (s, 2 H), 5.13 (s, 2 H), 3.71 (s, 3 H). HRMS $C_{29}H_{25}N_6O_3$ requires 505.1988; found 505.1993. HPLC: 5.27 min, 71% (254 nm).

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Supporting Information Available. X-ray crystallographic data for compound **9b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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