Simple and Efficient Synthesis of 3,4-Dihydro-2-pyridones via Novel Solid-Supported Aza-Annulation

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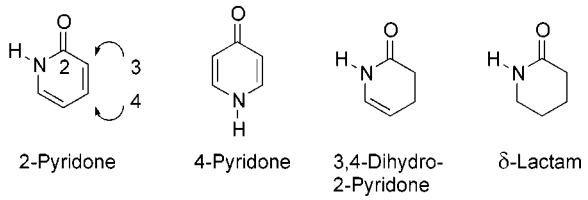
A diverse array of 3,4-dihydro-2-pyridones **13** were produced utilizing the unique properties of solid-supported reactions to both drive the reactions to completion and isolate the desired products. The pyridones were synthesized in high purity by a simple sequence of novel steps commencing from an acetophenone-functionalized resin. The *para*-substituted acetophenone **9** could be anchored to the resin through either a sulfonamide or a carboxamide linkage. The sulfonamide resin **9a**, which gave the best results, was treated with several aryl aldehydes and ethoxide to give a variety of chalcones **10a**−**k** in excellent yield (82−99%) upon TFA cleavage. Addition of either methyl or allyl malonate and DBU to **10a**−**k** afforded smoothly the Michael adducts **11a**−**j** (70−99%) which were subsequently cyclized in one step employing acetic acid as a catalyst and several diverse amines to give pure 3,4-dihydro-2-pyridones **13a**−**p** in moderate to excellent yields (30−98%).

Introduction

Although the number of individual organic reactions available for use in solid-phase applications has grown considerably in the past few years, the process of refining these transformations for the stepwise synthesis of structurally or medicinally interesting compounds is still in its infancy.[1] While the utility of solution-phase chemistry toward this end is evident, the emerging techniques of solid-phase chemistry also suggest many advantages which could be exploited synthetically. The main benefit gained by immobilizing the evolving target molecules is the ability to use large excesses of reagents while retaining the ability to quickly recover the desired products. Thus, the efficiency of a synthesis is increased both by driving reactions to completion and by simplifying the requisite workups. Hopefully then solid-phase techniques will lead to novel compounds of high purity and yield which would be difficult to access by any other approach.

As part of our continuing work to develop diverse combinatorial libraries of small nonpeptidic molecules, we envisioned structures generally related to the pyridones (Scheme 1) as both amenable to solid-phase synthesis and having attributes most likely to furnish lead medicinal compounds.[2] An attractive compound should possess a high density of diversity points attached

Scheme 1



to a compact molecular scaffold conceptually like **1** in Scheme 2. The diversity should be displayed in proximity to the compound core to help minimize the molecular weight, binding surface, and the number of binding conformers. Ideally the synthesis should utilize simple, easily available building blocks as diversity elements. This not only minimizes the cost of producing a large library of compounds but also allows for the greatest choice of different components to cover diversity space. Additionally, a modular synthetic design gives the library chemistry much more versatility. For example, a library similar in design to **1** could act as a synthon to be further elaborated by some simple modifications.[3] This would effectively yield several, albeit related, libraries **2** expediently from one general template.

The 2- and 4-pyridones and their derivatives exemplify most of the qualities we were looking for in a new library. These six-membered nitrogen-containing heterocycles, either unsaturated (pyridones) or in their reduced forms (dihydropyridones and δ-lactams), have a long history of

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‡ Medicinal Chemistry Department, Exelixis Inc., So. San Francisco, CA.

(1) For recent reviews of solid-phase chemistry, see: (a) James, I. W. *Tetrahedron* **1999**, *55*, 4855−4946. (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385−15443. (c) Corbett, J. W. *Org. Prep. Proced. Int.* **1998**, *30*, 489−550. (d) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643−5678. (e) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (f) Ellman, J.; Thompson, L. A. *Chem. Rev.* **1996**, *96*, 555−600. (g) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. (h) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135−8173. (i) Also, see ref 2.

(2) (a) Nuss, J. M.; Desai, M. C.; Zuckermann, R. N.; Singh, R.; Renhowe, P. A.; Goff, D. A.; Chinn, J. P.; Wang, L.; Dorr, H.; Brown, E. G.; Subramanian, S. *Pure Appl. Chem.* **1997**, *62*, 26−37. (b) Desai, M. C.; Zuckermann, R. N.; Moos, W. H. *Drug Dev. Res.* **1995**, *33*, 174−188.

(3) For more details on concepts of a "library from a library", see: (a) Kiely, J. S.; Dorner, B.; Ostresh, J. M.; Dooley, C.; Houghten, R. A. *High Throughput Screening* **1997**, 155−166. (b) Ostrech, J. M.; Husar, G. M.; Blondelle, S. E.; Dorner, B.; Weber, P. A.; Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11138−11142. (c) For a further discussion of library modifications, see ref 2.

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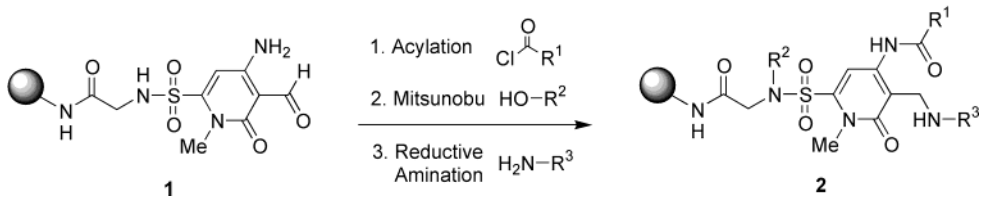
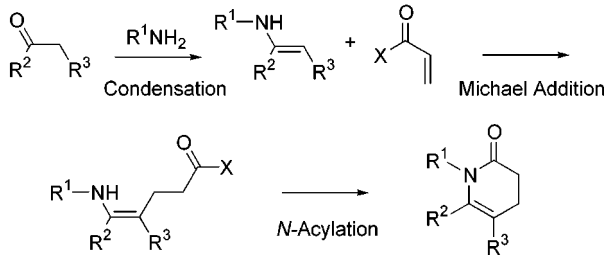
Scheme 2



Scheme 3

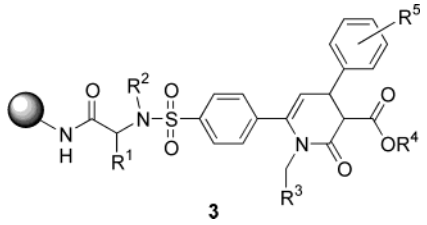


medicinal applications such as antimicrobial,[4] antitumor,[5] antiviral,[6] antifungal,[7] antihypertensive,[8] and many more and are therefore likely to be bioavailable as a group. Their construction has been extensively documented in the literature, and most routes should be compatible with solid-phase methods.[9] In this study, we focused on 3,4-dihydro-2-pyridones, which are usually constructed from a combination of three steps (Scheme 3): (1) a condensation; (2) a conjugate addition; and (3) an N-acylation. The order of the steps is entirely dependent on the building blocks used, but the final step is usually an aza-annulation.

Since pyridones can be assembled from a range of starting materials, ring substituents can be constructed in many different regiochemistries and with a great variety of functionalization. In this paper we describe a unique application of these steps leading to a novel pyridone synthesis. The route takes advantage of simple, readily available components and reactions which are driven by excess reagents. The 3,4-dihydro-2-pyridones can then be further elaborated by reduction to δ-lactams,[10] oxidation to 2-pyridones,[11] or extension of various built-in functionalities (e.g., Mitsunobu, Suzuki, or acylation reactions) giving further dimension to the parent library.

Results and Discussion

A thorough examination of literature procedures for generating different pyridones indicated that the order of the synthetic steps was not as important as bringing together the proper elements which would lead to the aza-annulation. Although many methods are available, typically the cyclization proceeds through either the N-acylation of an imine or enamine or the condensation of an amide with an aldehyde or ketone giving a six-membered ring.[9] While the variety of routes leads to greater flexibility in choosing reaction components, it may also raise issues of regiochemical control in the products. For example, regioisomers will result if an intermediate can cyclize through more than one possible six-membered ring. Also depending on the substitution of the reagents, there may be competition between five- vs six-membered annulations. Aware of the pitfalls, we decided to explore a method which would yield 2-pyridones with unambiguous regiochemistry while allowing for the greatest possible diversity and synthetic versatility. Thus, we envisioned building compounds generally resembling the structure **3** which incorporates five sites where diversity can be easily introduced.



3

Since imines and enamines are known to undergo aza-annulation with esters to yield 2-pyridones,[12] we expected that an intermediate **4** (Scheme 4) containing an imine and a malonate diester moiety would provide scaffolds such as **3**. While 1,5-dicarbonyl fragments have found utility in the synthesis of pyridines, there are few reports of acyclic 5-oxo-pentanoic esters annulating in the presence of a nitrogen equivalent to give 2-pyridones.[13] Several advantages are gained by utilizing this type of N-acylation. For example, since imines of aryl ketones

(4) Examples of biological activity can be seen in DNA gyrase inhibitors such as Ciprofloxacin, Tosufloxacin, and their derivatives.

(5) Examples of biological activity can be seen in Camptothecine and its derivatives.

(6) Examples of biological activity can be seen in compounds such as Warner−Lambert's 3N-3DU (3-nitro-3-deazauridine) a DNA directed DNA polymerase inhibitor.

(7) Examples of biological activity can be seen in compounds such as Procter & Gamble's EU-3795 (1-(3,4-dichlorobenzyl)-hexahydro-2,3-dioxo-4-pyridinecarboxylate).

(8) Examples of biological activity can be seen in Johnson & Johnson's RWJ-46458 (2-carbethoxymethylidene-4-methyl-4-ethyl-2-[4-(2′-tetrazolo)-phenyl]benzylpiperidin-6-one), an angiotensin II antagonist.

(9) Stille, J. R.; Barta, N. S. *Studies in Natural Products Chemistry*; Elsevier Science: Amsterdam, 1996; Vol. 18, pp 315−389.

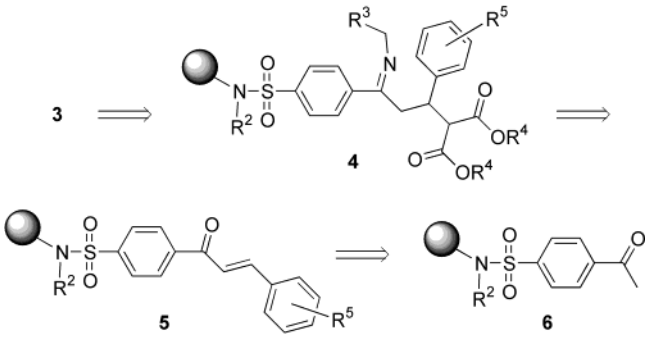
(10) (a) Jones, C. D.; Audia, J. E.; Lawhorn, D. E.; McQuaid, L. A.; Neubauer, B. L.; Pike, A. J.; Pennington, P. A.; Stamm, N. B.; Toomey, R. E.; Hirsch, K. S. *J. Med. Chem.* **1993**, *36*, 421−423. (b) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 8197−8200. (c) Bhattacharjya, A.; Bhattacharjya, P. K.; Pakrashi, S. C. *Heterocycles* **1983**, *20*, 2397−2400. (d) Kametani, T.; Terasawa, H.; Ihara, M.; Fukumoto, K. *Heterocycles* **1977**, *6*, 37−41.

(11) (a) Beholz, L. G.; Benovsky, P.; Ward, D. L.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1997**, *62*, 1033−1042. (b) El-Rayyes, N. R.; Al-Hajjar, F. H. *J. Heterocycl. Chem.* **1984**, *21*, 1473−1477. (c) Krauze, A.; Liepins, E.; Kalme, Z.; Pelcers, J.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1984**, 11, 1504−1508. (d) Al-Hajjar, F. H.; Jarrar, A. A. *J. Heterocycl. Chem.* **1980**, *17*, 1521−1525.

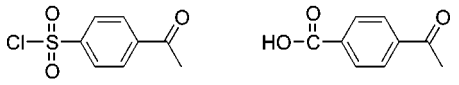
(12) (a) Ochiai, E.; Ito, Y. *Chem. Ber.* **1941**, *74*, 1111−4. (b) Knoevenagel, E.; Fries, A. *Chem. Ber.* **1898**, *31*, 761. (c) Also see ref 10d.

(13) (a) Nuss, J. M.; Harrison, S. D.; Ring, D. B.; Boyce, R. S.; Brown, S. P.; Goff, D.; Johnson, K.; Pfister, K. B.; Ramurthy, Savithry; Renhowe, P. A.; Seely, L.; Subramanian, S.; Wagman, A. S.; Zhou, X. A. PCT Int. Appl. WO 9965897 A1 19991223, 1999, 262 pp. (b) Rao, H. Surya Prakash; Bharathi, B. *Indian J. Heterocycl. Chem.* **1996**, *5*, 265−268. (c) Cook, P. D.; Day, R. T.; Robins, R. K. *J. Heterocycl. Chem.* **1977**, *14*, 1295−1298. (d) Banerjee, D. K.; Sengupta, P.; Das Gupta, S. K. *J. Org. Chem.* **1954**, *19*, 1516−1522.

Scheme 4



Scheme 5



are readily formed, many substituents may be introduced at R^3 depending on the variety of available amines.[14] Also, the regiochemistry of the cyclization is not an issue since the substituent at R^4 originates from a symmetrical diester. The ketone precursors of **4** arise from conjugate addition of a malonate diester to a chalcone (or an α,β-unsaturated ketone) **5**. The chalcones **5** are easily generated by Aldol condensation of any aryl aldehyde with a resin-bound acetophenone **6** imparting the diversity at R^5. The *para*-substituted acetophenone may be attached to any free amine or other nucleophile on resin. If the resin is preloaded with an amino acid or other functionalized amine, this would furnish the first point of diversity R^1 in the synthesis of **3**. Introduction of diversity at R^2 could come from Mitsunobu alkylation of a sulfonamide, reductive amination, or incorporation of an amino acid equivalent. Thus, late introduction of the amine component and annulation with a symmetrical diester supply highly substituted and regiocontrolled 3,4-dihydro-2-pyridones **3** by a novel route.

The point of attachment between the pyridone and the resin was mostly dictated by the chemistry of the synthesis. Theoretically, any of the components could have been immobilized, but to best exploit the benefits of solid phase chemistry, the acetophenone was chosen. This grants each of the succeeding steps the advantage of utilizing large excesses of simple readily available reagents. For this initial report, two *para*-substituted acetophenones **7a,b** (Scheme 5) were used to N-acylate either Rink resin directly or an amino-acid-loaded resin.

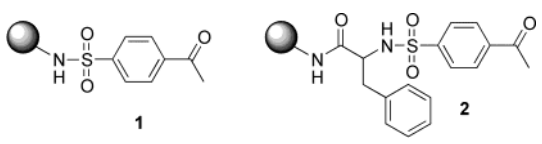
After standard Fmoc deprotection, the amine-functionalized resin **8** was reacted smoothly with the appropriate reagent **7a** or **7b**. Dissolved in CH_2Cl_2/pyridine, **7a** reacted to give a sulfonamide with the Rink resin. The amide linkage was obtained by coupling the free acid **7b** to the resin using PyBOP and HOBT in DMF (Scheme 6).[15] The acid chloride of **7b** also coupled to the resin smoothly with Hünig's base in THF, but it was found more convenient to use the available free acid. TFA hydrolysis of 100 mg of resin gave a quantitative yield of **9a,b** based on the loading capacity of the commercial Rink resin (0.50 mmol/g). Throughout the text, all description of the yields and purity of the on-resin-synthesized compounds refers to the characterization of resin-free material obtained after acid cleavage using TFA. While the linkage differentiates the products **9a,b** slightly, the sulfonamide moiety is amenable to further modification by Mitsunobu reaction.[16] Of course, acetophenones of virtually any substitution pattern should be workable in this scheme.

The chalcones were generated by procedures similar to those reported for Wang resin-anchored material.[17] Aryl aldehydes **14a**−**n** were found to react cleanly (purity >95%) giving α,β-unsaturated ketones **10a**−**n** after 0.5 h under conditions of excess aldehyde (10 equiv) and ethoxide (2 equiv) in THF. Alternately, amide-linked acetophenones **9b** were converted to chalcones **10l**−**n** using LiHMDS (4 equiv) and aryl aldehydes **14a,d,l** (30 equiv) in THF. The sulfonamide resin-bound acetophenone **9a** could be reacted with a variety of strong bases. Sodium ethoxide gave the most reproducible results due to its solubility in THF. Unfortunately, sodium and potassium alkoxide and amine bases resulted in low mass recovery of products using the amide-linked acetophenone **9b**. Possibly, Na^+ and K^+ bases resulted in the cleavage of **9a** in situ with subsequent loss of material during the resin wash workup.[18] LiHMDS was chosen for acetophenone **9b** because only this base gave good yields of pure product. The Li^+ base was sufficiently basic and soluble enough to yield Aldol products without causing deleterious side reactions. Bases other than alkoxides (NaOH, $NaHCO_3$, DBU, TEA, $NaNH_2$, etc.) did not yield products. The best Aldol results were achieved by treating the dry resin **9a,b** with an aryl aldehyde followed by addition of a resin-swelling solvent. Presumably, this helps to infuse the aldehydes evenly throughout the resin giving consistent results even on a large multiple gram scale. Base initiates the reaction, which is usually complete in less than 2 h in the case of **9a**. The reaction time and purity of the chalcone products are dependent on the nature of the aldehyde, the linker, and the base. The amide linked **9b** typically reacted to completion in 20−30 min. Electrophilic aryl aldehydes tend to react quickly but give side products if reacted too

(14) Desai, M. C.; Nuss, J. M.; Spear, K. L.; Singh, R.; Renhowe, P. A.; Brown, E. G.; Richter, L.; Scott, B. O. PCT Int. Appl. WO 9640201 A1 19961219, 1996, 100 pp.

(15) The coupling of **7a,b** to amine-functionalized resins proceeded smoothly using the standard conditions. Reaction of **7a,b** with a phenylalanine-loaded resin gave the expected products in high purity and yield. The elaboration of the Phe-linked acetophenone to a 3,4-dihydro-2-pyridone was accomplished without incident using the procedures described in this report.

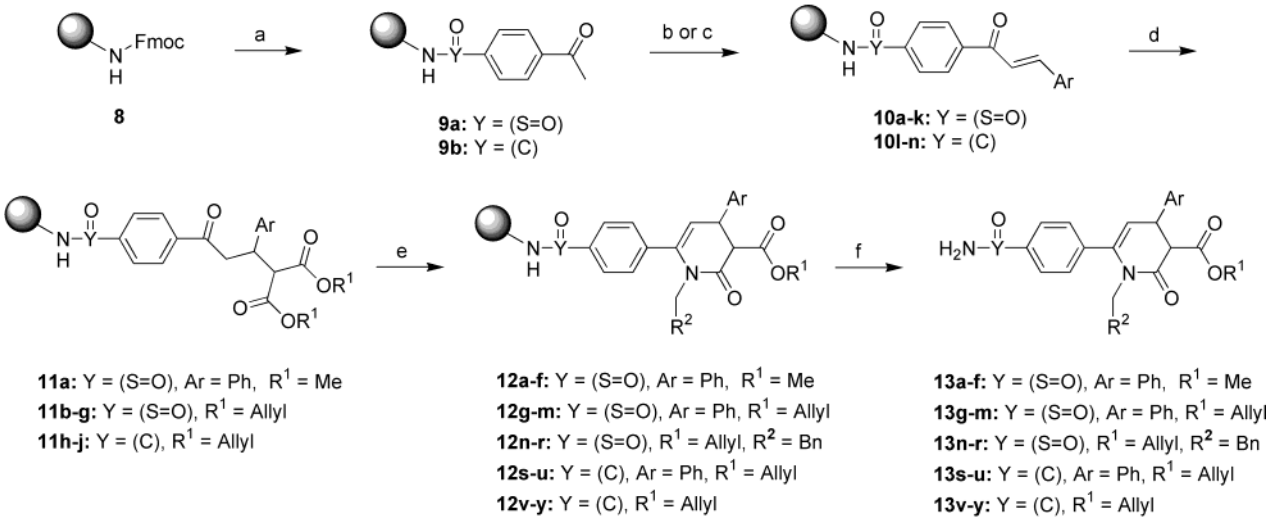
(16) Mitsunobu reactions were carried out on resin-bound substrates exemplified by **1** and **2** below. Reactions were typically run at room temperature with 10 equiv of each reagent to 1 equiv of resin based on the expected loading capacity. DEAD was added to a cooled solution (0 °C) of alcohol and triphenylphosphine in anhydrous THF (about 1 mL to 50 mg of resin). This solution was added to dry resin. Substrate **1** did not undergo Mitsunobu reaction easily. Only small alcohols such as MeOH and EtOH reached completion after 12 h with **1**. This may be due to the steric environment of the Rink-linker. Substrate **2** was a willing partner in Mitsunobu reactions using primary and benzylic alcohols. Reactions with **2** usually gave pure products. No starting material was observed after 12 h. Further details will be published elsewhere.



(17) Hollinshead, S. P. *Tetrahedron Lett.* **1996**, *37*, 9157−9160.

(18) No acid, amide, or chalcone products were found upon examination of the resin wash solvents. Only strong Na^+ and K^+ alkoxide bases caused this poor mass recovery. It is possible that the material was trapped within the resin, although very little material was obtained even after TFA resin cleavage.

Scheme 6



Reagents and conditions: (a) 1. Piperdine, DMF, rt; 2. **7a**, pyridine, DMAP, CH_2Cl_2, rt. or **7b**, PyBOP, HOBT, DMF, rt. (b) **14a-k**, EtONa , THF, rt. (c) **14a**,**d**,**l**, LiHMDS, THF, rt. (d) **15a**,**b**, DBU, THF, rt or 50 °C. (e) **16a-g**, AcOH, EtOH, toluene, 3 Å mol. sieve, 70 °C. (f) TFA/CH_2Cl_2 (1:8), rt.

long. Active aldehydes **14b,c,e,f** in Table 1 were complete after 30 min, whereas the other examples (**14d,i,j**) gave pure products after 5 h. The isolated chalcones were primarily of trans stereochemistry, although the amide-linked chalcones **10m and n** gave 30% and 20% cis isomers, respectively. The amide-linked chalcones were also prone to TFA-catalyzed dimerization.[19] This dimerization only occurred while lyophilizing the pure products in the presence of TFA after cleavage. When the chalcones **10m,n** were quickly concentrated to dryness and stripped of TFA in vacuo, no dimerization side products were observed. All attempts to perform Aldol condensations on **9a** with aliphatic aldehydes or aryl aldehydes containing acidic protons, such as phenols or acids, resulted in the recovery of starting material.

Michael addition of malonate diesters **15a,b** to chalcones **10a**−**f,l**−**n** furnished a range of useful 1,5-dicarbonyl intermediates **11a**−**j** in excellent isolated yields and good purity (85−99%) (see Table 1). With the malonates **15a,b**, the base of choice was DBU. Weaker bases gave no reaction while stronger bases such as alkoxides or hydrides gave inconsistent or messy results. The rate of the 1,4-addition was dependent on the electronic nature of the chalcones. Michael reaction with **10b,c** led to clean products within 1 h, unlike examples **10a,e,f** which took 5−8 h to reach completion.[20]

The resin-bound amide chalcones **10l**−**n** were notably less reactive toward diallyl malonate taking up to 12 h to react completely. Unlike the sulfonamides, the amide-linked Michael adduct **11h** gave several side products when exposed to the cleavage conditions.[21] As with the acid cleavage of the amide chalcones, the side products were not seen in subsequent steps. Since α,β-unsaturated ketones will undergo conjugate addition with many nucleophiles under mild homogeneous conditions, this route should be easily extended to a variety of heterocycles derived from 1,5-dicarbonyls aside from pyridones and dihydropyridones, such as pyridines,[22] 2-pyrones,[23] 4-pyrans,[24] and 1,2-diazepines.[25] The starting chalcones are also useful building blocks since they are willing

(19) Chalcones are known to undergo Diels−Alder cyclizations under various conditions giving substituted 3,4-dihydro-2H-pyrans. In this case, cyclization products of **10l**−**n** gave distinct doublets in the ^{1}H NMR (acetone-d_6, 300 MHz) at 5.4 and 6.1 ppm (J = 6 Hz). See: (a) Nicolaides, D. N.; Adamopoulos, S. G.; Hatzigrigoriou, E. J.; Litinas, K. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, *12*, 3159−3164. (b) Abdel Megeid, F. M. E.; Bose, A. K.; Elkaschef, A. F.; Elsayed, A. S.; Mokhtar, K. E.; Sharma, S. D. *Indian J. Chem.* **1975**, *13*, 482−484. (c) Landberg, B. E.; Lown, J. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *14*, 1326−1333.

(20) If left too long, **10b,c** gave side products. Also, the best results were obtained when the dry resin was first soaked with neat malonate diester.

(21) The side products were cyclized enol lactone and the related decarboxylated ring. Longer exposure to TFA or heating caused the amounts of side products to increase. These side products did not lead to reduced yields in further steps and were only seen in the unadorned benzaldehyde adduct **11h**.

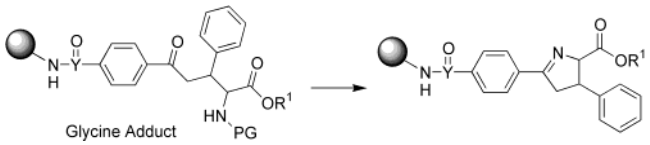
(22) (a) Chamchoumis, C.; Potvin, P. G. *J. Chem. Res., Synop.* **1998**, *4*, 180−181, 870−875. (b) Kim, H. Y.; Kim, S. H.; Nam, G.; Son, H.; Park, Tae J.; Lee, S. J.; Kang, J.; Chi, D. Y.; Kim, J. H. *Heterocycles* **1998**, *48*, 1237−1248.

(23) Gong, Y. D.; Tanaka, H.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2181−2185.

(24) Arimoto, H.; Yokoyama, R.; Nakamura, K.; Okumura, Y.; Uemura, D. *Tetrahedron* **1996**, *52*, 13901−13908.

(25) Somogyi, G.; Botka, P.; Hamori, T.; Koroesi, J.; Kiss, C.; Balogh, T.; Bidlo, M.; Horvath, G.; Simay, A.; et al. British U.K. Patent Application 1992, 25 pp.

(26) Reaction of glycine equivalents with **10a**−**n** gave almost exclusively the internally cyclized product resulting from the condensation of the glycine nitrogen with the acetyl carbonyl with concomitant nitrogen deprotection. This is an interesting scaffold as well, and it has been further explored for library production.



The Meldrum's acid adduct was stable until exposed to base and may have undergone a retro-Aldol reaction.

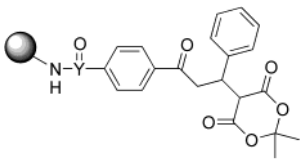
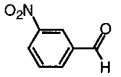
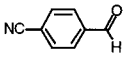
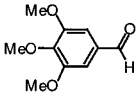
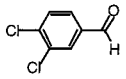
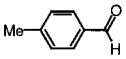
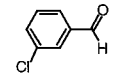
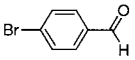


Table 1. Aldol Condensation of Aryl Aldehydes 14a–l with Acetophenone-Functionalized Resins 9a,b and Subsequent Addition of Malonate Diesters 15a,b to Chalcone Resins 10a–n

entry	starting resin	(#)[a]	aromatic aldehyde	chalcone	yield (%)[b]	malonate diester	Michael adduct	yield (%)[b]
1	**9a**	**14a**		**10a**	**94**[b]	**15a**	**11a**	**98**[b]
2	**9a**	**14a**		**10a**	**94**[b]	**15b**	**11b**	**81**[b]
3	**9a**	**14b**		**10b**	**93**[b]	**15b**	**11c**	**86**[b]
4	**9a**	**14c**		**10c**	**84**[b]	**15b**	**11d**	**88**[b]
5	**9a**	**14d**		**10d**	**99**[b]	**15b**	**11e**	**99**[b]
6	**9a**	**14e**		**10e**	**96**[b]	**15b**	**11f**	**90**[b]
7	**9a**	**14f**		**10f**	**94**[b]	**15b**	**11g**	**86**[b]
8	**9a**	**14g**		**10g**	**95**[c]			
9	**9a**	**14h**		**10h**	**89**[c]			
10	**9a**	**14i**		**10i**	**99**[c]			
11	**9a**	**14j**		**10j**	**82**[c]			
12	**9a**	**14k**		**10k**	**99**[c]			
13	**9b**	**14a**		**10l**	**98**[b]	**15b**	**11h**	**70**[b]
14	**9b**	**14d**		**10m**	**96**[b]	**15b**	**11i**	**95**[b]
15	**9b**	**14l**		**10n**	**90**[b]	**15b**	**11j**	**81**[b]

[a] Number corresponds to the aromatic aldehyde structure in the next column. [b] Yield refers to isolated products after cleavage from the resin. [c] Yield was determined after cleavage from the resin by analytical HPLC at 220 nm and checked by LCMS.

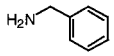
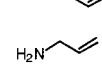
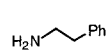
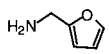
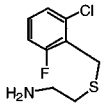
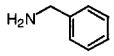
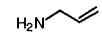
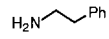
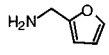
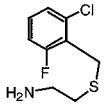
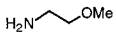
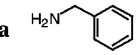
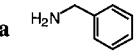
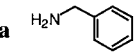
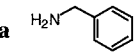
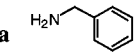
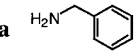
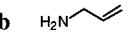
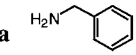
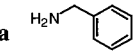
partners in conjugate additions, annulations, and Diels–Alder reactions. While malonate diesters underwent facile reaction with **10a–n**, other nucleophiles such as glycine equivalents, aryl acetates, Meldrum's acid, and nitro alkanes also gave products easily. Unfortunately, the glycine equivalents and Meldrum's acid adduct gave deleterious side reactions making them unsuitable for pyridone construction.[26] Cyanoacetate also afforded poor results giving polymeric material when exposed to the typical conditions of excess nucleophile (25 equiv) and DBU (3 equiv) in THF. One advantage of employing malonates over other nucleophiles is that the Michael adducts **11a–j** are symmetrical about the malonate methine. This eliminates issues of unexpected reactivity and uncertain stereochemistry.

The aza-annulation of Michael adducts **11a–j** was carried out with an excess of amine **16a–g** (10 equiv) and a proton source such as acetic acid (see Table 2). To drive the condensation to completion, a fairly large volume of anhydrous toluene (5 mL/100 mg resin) was used in conjunction with 3 or 4 Å molecular sieves. The amine first yielded the corresponding imine **4,** which cyclized by attacking one of the malonate esters.[27] The N-acylation was facile only at temperatures above 70 °C. The progress of the reaction was monitored by HPLC over a 48–72 h period by following the consumption of the starting material and intermediate imine. Without the molecular sieves, the aza-annulation would still yield clean products but take much longer. Some acetic acid amine salts, such as the salt of phenylalanine ethyl ester, were insoluble in toluene and gave no reaction. To increase the amount of amine salts in solution, excess AcOH or EtOH could be added. Several methods were explored to overcome this difficulty either by catalyzing the cyclization or by using forcing conditions such as trimethylorthoformate, thionyl chloride, $BF_3 \cdot Et_2O$, Yb^{III} triflate, or two-step processes.

Unfortunately, none of these efforts gave promising results. However, the general conditions did furnish

(27) The intermediate imine **4** was identified by LCMS from cleaved resin of incompletely reacted material.

Table 2. Aza-Annulation of Michael Adducts 11a−j with Amines 16a−g Giving 3,4-Dihydro-2-pyridones 13a−y

entry	starting resin	(#)[a]	primary amine	pyridone, yield (#,%)[b]
1	**11a**	**16a**		**13a, 86**
2	**11a**	**16b**		**13b, 75**
3	**11a**	**16c**		**13c, 83**
4	**11a**	**16d**		**13d, 34**
5	**11a**	**16e**		**13e, 98**
6	**11a**	**16f**	NH_4OAc	**13f, 90**
7	**11b**	**16a**		**13g, 87**
8	**11b**	**16b**		**13h, 53**
9	**11b**	**16c**		**13i, 97**
10	**11b**	**16d**		**13j, 73**
11	**11b**	**16e**		**13k, 91**
12	**11b**	**16f**	NH_4OAc	**13l, 68**
13	**11b**	**16g**		**13m, 92**
14	**11c**	**16a**		**13n, 50**
15	**11d**	**16a**		**13o, 69**
16	**11e**	**16a**		**13p, 93**
17	**11f**	**16a**		**13q, 57**
18	**11g**	**16a**		**13r, 59**
19	**11h**	**16a**		**13s, 30**
20	**11h**	**16b**		**13t, 40**
21	**11h**	**16f**	NH_4OAc	**13u, 93**
22	**11i**	**16a**		**13v, 72**
23	**11i**	**16f**	NH_4OAc	**13w, 91**[c]
24	**11j**	**16a**		**13x, 58**
25	**11j**	**16f**	NH_4OAc	**13y, 75**

[a] Number corresponds to the primary amine structure in the next column. [b] Yield refers to isolated products after cleavage from the resin. [c] Total yield of isomers and transesterified ethyl ester side product after cleavage from the resin. Approximately 1:1 allyl ester to ethyl ester.

products with most primary amines **16a−g** in good purity (85−97%) with the exception of tetrahydrofurfurylamine, which seemed to decompose. Anilines, secondary amines, branched amines, and hydrazines did not easily form products.

While only primary amines seemed to readily give products, the variety of amines which could be employed at this position confers a great deal of diversity to the ring. Also, depending on the substituents or protected functionality imported with the amine, this position can easily be extended by a host of augmenting reactions. Alternative structures may also be reached by simply oxidizing or reducing the parent library of 3,4-dihydro-2-pyridones to 2-pyridones or δ-lactams, respectively.[28] Of course, the methyl or allyl esters can also be deprotected to exploit the chemistry of the carboxylic acid.[29] From the exposed free carboxylic acids, a Curtius rearrangement yielded ureas and carbamates. The acid could also be decarboxylated using known procedures.[30] ^{1}H NMR revealed that of the 3,4-dihydro-2-pyridones **13a−y** isolated, the relative stereochemistry in the pyridone ring was predominately trans. Bulky aryl aldehydes gave entirely trans products while aryl aldehydes with electron-withdrawing substituents gave 20−30% of the cis isomer. The choice of amide or sulfonamide resin-linker also played a role in the purity of the products. The amide-linked pyridones typically gave a small amount of transesterification to the ethyl ester and also air-oxidized aromatic 2-pyridones.[31] They also gave more of the cis diastereomer and were in general less pure than the sulfonamide pyridones. Routinely, the reactions gave

(28) 2-Dihydropyridones, such as **13f** and **13l**, were oxidized to 2-pyridones using DDQ in toluene at room temperature. The resin is stained dark, but all of the DDQ residue is washed out using 20% AcOH/CH_2Cl_2 and 20% piperdine/DMF. Dihydropyridones with an alkyl group on nitrogen oxidized more slowly than those derived from ammonia. CAN and SeO_2 also gave good results.

(29) Methyl esters were hydrolyzed using TMSOK/CH_2Cl_2, and allyl esters were deprotected with Pd/dimethyl barbaturic acid.

(30) (a) Mosti, L.; Schenone, P.; Menozzi, G. *J. Heterocycl. Chem.* **1985**, *22*, 1503−9. (b) Pessolano, A. A.; Witzel, B. E.; Graham, P. M.; Clark, R. L.; Jones, H.; Dorn, C. P., Jr.; Carty, J.; Shen, T. Y. *J. Heterocycl. Chem.* **1985**, *22*, 265−272.

(31) The amide-linked pyridone **13w** gave the most transesterification from the allyl to ethyl ester leading to a 1:1 ratio of esters. Typically the amide-linked pyridones gave ~5% of the ethyl ester. The ethyl esters were not detected in the sulfonamide-linked pyridone series. It is possible that changing the solvent or reaction conditions might avoid the transesterification. These conditions were not optimized. The ethyl ester of **13w** was isolated and characterized: HPLC (220 nm) 25.86 min; ^{1}H NMR (DMSO-d_6, 300 MHz) 7.86 (d, J = 8.7 Hz, 2 H), 7.62 (d, J = 8.7 Hz, 2 H), 7.49 (d, J = 7.5 Hz, 2 H), 7.38−7.32 (m, 1 H), 5.59−5.54 (m, 1 H), 5.17 (dd, J = 2.7, 14.2 Hz, 1 H), 4.32 (d, J = 14.2 Hz, 1 H), 4.09−3.87 (m, 2 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) 168.24, 167.20, 166.40, 136.29, 135.65, 135.03, 134.49, 134.10, 130.14, 129.69, 127.61, 125.32, 105.81, 60.70, 50.38, 13.72; LCMS LC (220 nm) 2.57 min; MS (ES+) *m/z* 433.3 ($C_{21}H_{18}Cl_2N_2O_4$ + H requires 433.06). All of the dihydropyridones were prone to air oxidation under the annulation reaction conditions. The amide-linked pyridones were more reactive to oxidation than the sulfonamide pyridones. Dihydropyridones **13s** and **13t** gave the most oxidized side product.

clean products (>90% of both cis and trans), but filtration of the cleaved products through a plug of silica removed any undesirable polar decomposition material. Cleavage of the final products and all of the intermediates from the Rink resin was accomplished with a 10% TFA/CH_2Cl_2 solution. Typically TFA did not affect the products even after prolonged exposure.

Conclusions

While the main topic of this report is the synthesis of 3,4-dihydro-2-pyridones, we have striven to show how a versatile molecular scaffold and a modular synthetic design can cover the greatest possible diversity space while still imparting attractive and novel molecules. Diversity-extending modifications explored in this work include Mitsunobu reactions of aryl sulfonamides, deprotection of allyl esters, reactions on exposed carboxylic acids, and oxidations to fully aromatic core rings. This route provides 2-pyridones with a high density of varied substituents, regiospecific control of the arrayed elements afforded by the symmetrical malonate diester moiety, and good yields of novel aza-annulated products derived from available materials. This route not only provides an array of interesting ring motifs by solid phase methods but also provides a few useful resin-bound building blocks such as chalcones and 1,5-dicarbonyl compounds which are currently under investigation in these labs. Since the utility of solid-phase synthesis is just being realized, we can envision many new libraries evolving from extension of these intermediates and the pyridone products. The progress of these will be reported in due course.

Experimental Section

General. Unless otherwise noted, all starting materials and dry solvents were obtained from commercial suppliers and were used without further purification. Solvents were stored with 3 Å molecular sieves under dry argon. Reactions involving air and/or moisture sensitive reagents were executed under an atmosphere of dry argon, and the glassware was flame dried under vacuum. All compounds which were synthesized on resin were first cleaved under acidic (TFA) conditions, filtered to remove most polymer residue, and dried to remove solvents before undergoing physical characterization by NMR, HPLC, and LCMS. While the same number is used for both the resin-bound and the cleaved material, only resin-free material was characterized, only yields of cleaved material were reported, and every attempt was made to clearly indicate which material was being described in the text and through footnotes. Proton (^{1}H) (300 MHz), carbon (^{13}C) (75 MHz), and nuclear magnetic resonance (NMR) spectra were obtained as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm, δ) downfield relative to tetramethylsilane (TMS), which was referenced to the solvent. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated in the following manner: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Flash chromatography was performed according to the established protocol with Merck silica gel 60 (230−400 ASTM).[32] HPLC samples were run using reverse-phase analytical columns (Alltima 5u C-18, 4.6 mm × 250 mm from Alltech) and a 40 min gradient. Liquid chromatography/mass spectrometric analysis (LCMS) was performed on either a Waters Micromass Platform LCZ or a Hewlett-Packard (HP) 1100 series LC/MSD electrospray mass spectrometer with an LC module. High-resolution mass spectrometry (HRMS) was performed at UC Berkeley's mass spectrometry facility.

4-Sulfonyl Chloride Acetophenone (7a).[33] A solution of $NaNO_2$ (25 g, 0.36 mol) in H_2O (40 mL) was added dropwise over 15 min to a precooled (0 °C) solution of 4-aminoacetophenone (45 g, 0.33 mol) in concentrated aqueous HCl (115 mL) and glacial acetic acid (330 mL) while stirring vigorously and maintaining the temperature with an ice bath. The resulting mixture was removed from the ice bath and allowed to warm for 15 min giving an orange-red diazonium salt solution which was again immersed in the cold bath. Meanwhile, a blue-green solution of $CuCl_2 \cdot H_2O$ (13.6 g, 0.08 mol) in H_2O (25 mL) was added in one portion to a vigorously stirring saturated solution of SO_2 in glacial acetic acid (260 mL) at 0 °C to produce an opaque milky-green mixture. The cold sulfur dioxide mixture is carefully added to the stirred diazo solution at 0 °C resulting in a dark mixture which evolves gas. The reaction is removed from the ice bath and allowed to warm to room temperature for 2 h. When the reaction no longer evolves gas, it is filtered to remove some residual solids and the clear orange filtrate is poured into a beaker of stirred ice/H_2O (1000 mL). The thick white solid that forms is collected on a sintered glass Büchner funnel, washed with H_2O (2 × 100 mL) and hexane (3 × 200 mL), and dried overnight in vacuo. The product is recrystallized from hot hexane (∼1600 mL) and added portions of CH_2Cl_2 (∼100 mL) to yield analytically pure material (39.8 g, 55%) as white to light tan crystalline spears.

Standard Washing Method. Typically, the resin (10 g) in a reaction vessel is washed sequentially with MeOH (100 mL), DMF (100 mL), and CH_2Cl_2 (100 mL). This sequence is repeated as needed to remove all of the reagents and sequentially followed with a final wash of MeOH (100 mL) and CH_2Cl_2 (3 × 100 mL). This washing sequence was applied to the resin after every reaction step. The resin was typically dried in vacuo in preparation for the next reaction.

Rink-Resin-Coupled 4-Acetylbenzenesulfonamide (9a). Fresh dry Fmoc-protected Rink resin (10 g) was treated with a solution of 20% piperidine in DMF (80 mL) in a reaction vessel for 1 h with shaking. The deprotected Rink resin (∼0.5 mmol/g) was washed using the standard method. After the resin was allowed to dry for several hours in vacuo, a solution of 4-acetylbenzenesulfonyl chloride (**7a**) (3.28 g, 15 mmol), pyridine (2.8 mL, 35 mmol), and CH_2Cl_2 (70 mL) was added. The reaction mixture turned bright yellow after shaking for 5 min at which time DMAP (0.6 g, 5 mmol) was added in one portion. Adding the DMAP after mixing the other reagents avoided the formation of a small amount of unidentified side product. After 12 h, the reaction was drained and washed using the standard method. Cleavage of resin (100 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **9a** (11 mg, ∼quantitative) in high purity (>99%) following trituration with $CHCl_3$ and lyophilization: HPLC (220 nm) 13.72 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.15 (d, J = 9.0 Hz, 2 H), 8.03 (d, J = 9.0 Hz, 2 H), 2.64 (s, 3 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 197.1, 148.5, 140.4, 129.5, 127.1, 22.1; GCMS GC(TIC) 11.2 min; MS (EI) m/z 200, 184; LCMS LC (214 nm) 7.41 min; MS (CI+) m/z 200.1 ($C_8H_9NO_3S$ + H requires 200.04).

Rink-Resin-Coupled 4-Acetylbenzenecarboxamide (9b). Dry deprotected Rink resin (10 g) was prepared following the procedure for **9a**. PyBOP (7.8 g, 15 mmol) was added to a shaken solution of 4-acetylbenzoic acid (**7b**) (2.46 g, 15 mmol), Hunig's base (3.2 mL, 30 mmol), and HOBT (2.3 g, 15 mmol) in DMF (30 mL). After the reagents were thoroughly mixed, the solution was added to the dry Rink resin which was shaken for 3 h at room temperature. The reaction was drained and washed using the standard method. Cleavage of resin (200 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **9b** (17 mg, ∼quantitative) in high purity (>99%) following trituration with $CHCl_3$ and lyophilization: HPLC (220 nm) 11.81 min; ^{1}H NMR

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2924.

(33) Montserrat, C.; Riera, J. ES 499575 A1 19811216, 1981, 6 pp. The 4-sulfonyl chloride acetophenone **7a** can also be made from the available sodium salt of 4-acetybenzenesulfonic acid which is treated with thionyl chloride as reported: Kaltenbronn, J. S.; Haskell, T. H.; Doub, L. U.S. Patent 4,101,661, 1978, 15 pp.

(DMSO-d_6, 300 MHz) δ 8.02 (d, J = 8.5 Hz, 2 H), 7.98 (d, J = 8.5 Hz, 2 H), 2.62 (s, 3 H); LCMS LC (220 nm) 0.69 min; MS (ES+) m/z 164.2 ($C_9H_9NO_2$ + H requires 164.11).

General Procedure for the Preparation of Rink-Resin-Coupled 4-Sulfonamide Chalcones (10a−k). To dry Rink-bound sulfonamide acetophenone **9a** (2.5 g, ∼1.3 mmol) was added a benzaldehyde (**14a−k**) (13 mmol) followed by THF (60 mL) and then a solution of NaOEt in EtOH (2.5 mL, 0.5 M). Typically, the reaction mixture was shaken for several minutes before the base was added. After the mixture was shaken for 0.5 h, the resin was drained and washed using the standard method. Cleavage of resin (100 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **10a−k** following lyophilization.

4-((2*E*)-3-Phenylprop-2-enoyl)benzenesulfonamide (10a). HPLC (220 nm) 26.74 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.42−8.02 (m, 4 H), 7.97−7.83 (m, 4 H), 7.57−7.46 (m, 3 H), 6.82 (br s, 2 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 188.3, 147.4, 144.8, 139.7, 134.3, 130.7, 129.0, 128.9, 125.8, 121.8; LCMS LC (214 nm) 19.93 min; MS (CI+) m/z 288.1 ($C_{15}H_{13}NO_3S$ + H requires 288.07).

4-[(2*E*)-3-(3-Nitrophenyl)prop-2-enoyl]benzenesulfonamide (10b). HPLC (220 nm) 26.98 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.73 (s, 1 H), 8.41−8.26 (m, 2 H), 8.22−7.20 (m, 7 H), 6.75 (br s, 2 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 188.5, 148.1, 142.4, 140.4, 137.0, 134.9, 130.5, 129.3, 128.9, 126.6, 126.1, 124.9, 124.8, 123.0; LCMS LC (214 nm) 20.48 min; MS (CI+) m/z 333.1 ($C_{15}H_{12}N_2O_5S$ + H requires 333.06).

4-[(2*E*)-3-(4-Cyanophenyl)prop-2-enoyl]benzenesulfonamide (10c). HPLC (220 nm) 25.55 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.34 (d, J = 9.0 Hz, 2 H), 8.28−8.02 (m, 5 H), 7.98−7.81 (m, 2 H), 7.76−7.64 (m, 1 H), 6.82 (br s, 2 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 189.2, 148.7, 143.4, 141.2, 140.2, 133.5, 130.2, 130.0, 127.3, 125.9, 119.0, 114.3; LCMS LC (214 nm) 17.87 min; MS (CI+) m/z 313.1 ($C_{16}H_{12}N_2O_3S$ + H requires 313.07).

4-[(2*E*)-3-(2,6-Dichlorophenyl)prop-2-enoyl]benzenesulfonamide (10d). HPLC (220 nm) 30.92 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.26 (d, J = 9.0 Hz, 2 H), 8.08 (d, J = 9.0 Hz, 2 H), 7.91−7.78 (m, 2 H), 7.64−7.53 (m, 2 H), 7.51−7.40 (m, 1 H), 6.80 (br s, 2 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 189.3, 148.9, 140.9, 138.7, 135.6, 133.2, 131.7, 131.2, 130.0, 127.4; LCMS LC (214 nm) 22.48 min; MS (CI+) m/z 356.1 ($C_{15}H_{11}C_{l2}NO_3S$ + H requires 355.99).

4-((2*E*)-3-(2-Furyl)prop-2-enoyl)benzenesulfonamide (10e). HPLC (220 nm) 23.52 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.23 (d, J = 9.0 Hz, 2 H), 8.06 (d, J = 9.0 Hz, 2 H), 7.80 (s, 1 H), 7.78−7.59 (m, 2 H), 7.04 (s, 1 H), 6.79 (br s, 2 H), 6.65 (s, 1 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 188.9, 152.7, 148.3, 146.5, 142.0, 132.1, 129.7, 127.2, 119.9, 118.0, 113.8; LCMS LC (214 nm) 4.09 min; MS (ES+) m/z 278.1 ($C_{13}H_{11}NO_4S$ + H requires 278.05).

4-[(2*E*)-3-(3-Methyl(2-thienyl))prop-2-enoyl]benzenesulfonamide (10f). HPLC (220 nm) 27.09 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.24 (d, J = 8.0 Hz, 2 H), 8.06 (d, J = 8.0 Hz, 2 H), 8.03 (d, J = 12.0 Hz, 1 H), 7.58 (d, J = 3.0 Hz, 1 H), 7.42 (d, J = 12.0 Hz, 1 H), 7.05 (d, J = 3.0 Hz, 1 H), 6.77 (br s, 2 H), 2.44. (s, 3 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 187.7, 147.4, 143.4, 140.7, 135.7, 134.0, 131.6, 128.7, 128.3, 126.3, 119.2, 13.1; LCMS LC (214 nm) 4.61 min; MS (ES+) m/z 308.0 ($C_{14}H_{13}NO_3S2$ + H requires 308.04).

4-{(2*E*)-3-[2-(Trifluoromethoxy)phenyl]prop-2-enoyl}benzenesulfonamide (10 g). HPLC (220 nm) 31.03 min; LCMS LC (214 nm) 4.89 min; MS (ES+) m/z 371.8 ($C_{16}H_{12}F_3NO_4S$ + H requires 372.05).

4-[(2*E*)-3-(3,4,5-Trimethoxyphenyl)prop-2-enoyl]benzenesulfonamide (10h). HPLC (220 nm) 25.77 min; LCMS LC (214 nm) 4.44 min; MS (ES+) m/z 378.2 ($C_{18}H_{19}NO_6S$ + H requires 378.10).

4-[(2*E*)-3-(3,4-Dichlorophenyl)prop-2-enoyl]benzenesulfonamide (10i). HPLC (220 nm) 32.60 min; LCMS LC (214 nm) 23.75 min; MS (CI+) m/z 356.2 ($C_{15}H_{11}Cl2NO_3S$ + H requires 355.99).

4-[(2*E*)-3-(4-Methylphenyl)prop-2-enoyl]benzenesulfonamide (10j). HPLC (220 nm) 29.09 min; LCMS LC (214 nm) 4.89 min; MS (ES+) m/z 302.2 ($C_{16}H_{15}NO_3S$ + H requires 302.09).

4-[(2*E*)-3-(3-Chlorophenyl)prop-2-enoyl]benzenesulfonamide (10k). HPLC (220 nm) 29.94 min; LCMS LC (214 nm) 5.03 min; MS (ES+) m/z 322.0 ($C_{15}H_{12}ClNO_3S$ + H requires 322.03).

General Procedure for the Preparation of Rink-Resin-Coupled 4-Carboxamide Chalcones (10l−n). To dry Rink-bound carboxamide acetophenone **9b** (2.0 g, ∼1.0 mmol) was added a benzaldehyde (**14a,d,l**) (30 mmol) dissolved in THF (10 mL). After the mixture was shaken for 1 min, additional THF (15 mL) and LiHMDS (4 mL, 1M in THF) were added sequentially. After the mixture was shaken again for 0.5 h, the resin was drained and washed immediately using the standard method. Cleavage of resin (200 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **10l−n** following lyophilization.

4-((2*E*)-3-Phenylprop-2-enoyl)benzamide (10l). HPLC (220 nm) 24.84 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.24 (d, J = 8.4 Hz, 2 H), 8.08 (d, J = 8.4 Hz, 2 H), 8.04−7.94 (m, 2 H), 7.94−7.89 (m, 2 H), 7.85−7.76 (m, 1 H), 7.52−7.45 (m, 2 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 189.0, 167.2, 144.6, 139.6, 138.1, 134.6, 130.8, 129.0, 129.0, 128.5, 127.9, 127.8, 122.1; LCMS LC (220 nm) 2.45 min; MS (ES+) m/z 252.2 ($C_{16}H_{13}NO_2$ + H requires 252.11).

4-[(2*E*)-3-(2,6-Dichlorophenyl)prop-2-enoyl]benzamide (10m). HPLC (220 nm) 29.46 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.18 (d, J = 8.1 Hz, 2 H), 8.11 (d, J = 8.1 Hz, 2 H), 7.92−7.83 (m, 2 H), 7.59−7.41 (m, 2 H), 7.38−7.19 (m, 1 H); LCMS LC (220 nm) 2.75 min; MS (ES+) m/z 320.2 ($C_{16}H_{11}Cl_2NO_2$ + H requires 320.03).

4-[(2*E*)-3-(4-Bromophenyl)prop-2-enoyl]benzamide (10n). HPLC (220 nm) 29.07 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.22 (d, J = 9.0 Hz, 2 H), 8.09 (d, J = 9.0 Hz, 2 H), 8.02−7.91 (m, 1 H), 7.83 (d, J = 8.1 Hz, 2 H), 7.81−7.74 (m, 1 H), 7.67 (d, J = 8.1 Hz, 2 H); LCMS LC (220 nm) 2.73 min; MS (ES+) m/z 330.3 ($C_{16}H_{12}BrNO_2$ + H requires 330.02).

General Procedure for the Preparation of Rink-Resin-Coupled 4-Sulfonamide Dimethyl- or Diallylmalonate Adducts (11a−g). To a dry Rink-bound sulfonamide chalcone (**10a−k**) (3.0 g, ∼1.5 mmol) was added dimethylmalonate (1.7 mL, 15 mmol) (or diallylmalonate (1.7 mL, 15 mmol)) followed by THF (60 mL) and finally a solution of DBU in THF (2.5 mL, 0.6 M). After the mixture was shaken for 1 h at room temperature, the resin was drained and washed using the standard method. Cleavage of resin (100 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **11a−g** following lyophilization.

Dimethyl 2-[3-Oxo-1-phenyl-3-(4-sulfamoylphenyl)propyl]propane-1,3-dioate (11a). HPLC (220 nm) 26.44 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09−7.97 (m, 4 H), 7.33−7.12 (m, 5 H), 5.12 (br s, 2 H), 4.15 (ddd, J = 4.5, 9.0, 9.3 Hz, 1 H), 3.84 (d, J = 9.3 Hz, 1 H), 3.73 (s, 3 H, Me), 3.59 (dd, J = 4.5, 17.0 Hz, 1 H), 3.52 (s, 3 H), 3.46 (dd, J = 9.0, 17.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.4, 168.6, 167.9, 145.5, 139.8, 139.7, 128.7, 128.5, 127.8, 127.4, 126.6, 57.1, 52.8, 52.6, 42.8, 40.8; MS (ES+) m/z 419.8 ($C_{20}H_{21}NO_7S$ + H requires 420.11).

Diprop-2-enyl 2-[3-Oxo-1-phenyl-3-(4-sulfamoylphenyl)propyl]propane-1,3-dioate (11b). HPLC (220 nm) 31.35 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03−7.91 (m, 4 H), 7.28−7.15 (m, 5 H), 5.95−5.77 (m, 1 H), 5.68−5.53 (m, 1 H), 5.38−5.09 (m, 4 H), 5.27 (br s, 2 H), 4.63 (d, J = 5.6 Hz, 2 H), 4.39 (d, J = 5.6 Hz, 2 H), 4.17 (ddd, J = 4.2, 8.9, 9.3 Hz, 1 H), 3.88 (d, J = 9.3 Hz, 1 H), 3.58 (dd, J = 4.2, 17.4 Hz, 1 H), 3.46 (dd, J = 8.9, 17.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.5, 167.7, 167.1, 145.6, 139.7, 139.5, 131.1, 131.0, 128.7, 128.5, 128.0, 127.3, 126.5, 118.9, 118.6, 66.3, 66.1, 57.3, 42.9, 40.9; MS (ES+) m/z 472.3 ($C_{24}H_{25}NO_7S$ + H requires 471.15).

Diprop-2-enyl 2-[1-(3-Nitrophenyl)-3-oxo-3-(4-sulfamoylphenyl)propyl]propane-1,3-dioate (11c). HPLC (220 nm) 31.25 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (s, 1 H), 8.06 (d, J = 7.6 Hz, 1 H), 8.04−7.93 (m, 4 H), 7.69 (d, J = 7.6 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 1 H), 5.93−5.79 (m, 1 H), 5.75−5.58 (m, 1 H), 5.35−5.10 (m, 4 H), 5.23 (br s, 2 H), 4.65 (d, J = 5.6 Hz, 2 H), 4.43 (d, J = 5.6 Hz, 2 H), 4.30 (ddd, J = 4.3, 8.7, 9.3 Hz, 1 H), 3.94 (d, J = 9.3 Hz, 1 H), 3.69 (dd, J = 4.3,

17.3 Hz, 1 H), 3.58 (dd, J = 8.7, 17.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.9, 167.4, 166.9, 148.2, 146.0, 142.3, 139.3, 135.2, 131.0, 130.8, 129.5, 128.8, 126.8, 122.9, 122.5, 119.3, 66.5, 66.3, 56.6, 42.3, 40.0; LCMS LC (214 nm) 5.31 min; MS (ES+) m/z 517.1 ($C_{24}H_{24}N_2O_9S$ + H requires 517.13).

Diprop-2-enyl 2-[1-(4-Cyanophenyl)-3-oxo-3-(4-sulfamoylphenyl)propyl]propane-1,3-dioate (11d). HPLC (220 nm) 30.21 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06−7.93 (m, 4 H), 7.56 (d, J = 7.8 Hz, 2 H), 7.42 (d, J = 7.8 Hz, 2 H), 5.94−5.79 (m, 1 H), 5.73−5.59 (m, 1 H), 5.35−5.12 (m, 4 H), 5.23 (br s, 2 H), 4.65 (d, J = 5.0 Hz, 2 H), 4.43 (d, J = 5.0 Hz, 2 H), 4.30 (ddd, J = 3.1, 4.3, 9.3 Hz, 1 H), 3.90 (d, J = 9.3 Hz, 1 H), 3.65 (dd, J = 4.5, 17.7 Hz, 1 H), 3.52 (dd, J = 3.1, 17.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.9, 167.4, 166.9, 146.0, 145.6, 139.3, 132.6, 132.3, 131.0, 130.8, 129.2, 128.9, 128.7, 127.4, 126.8, 119.3, 119.2, 118.5, 111.3, 66.5, 66.3, 56.5, 42.2, 40.5; LCMS LC (214 nm) 5.14 min; MS (ES+) m/z 497.0 ($C_{25}H_{24}N_2O_7S$ + H requires 497.14).

Diprop-2-enyl 2-[1-(2,6-Dichlorophenyl)-3-oxo-3-(4-sulfamoylphenyl)propyl]propane-1,3-dioate (11e). HPLC (220 nm) 32.58 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 8.5 Hz, 2 H), 7.89 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.1 Hz, 1 H), 7.15 (d, J = 8.1 Hz, 1 H), 7.01 (d, J = 8.1 Hz, 1 H), 5.91−5.51 (m, 1 H), 5.60−5.43 (m, 1 H), 5.31−4.98 (m, 5 H), 5.19 (br s, 2 H), 4.68−4.53 (m, 2 H), 4.50 (d, J = 11.4 Hz, 1 H), 4.34−4.18 (m, 2 H), 3.80 (dd, J = 9.6, 16.4 Hz, 1 H), 3.56 (dd, J = 4.4, 16.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.4, 167.8, 166.7, 145.8, 139.4, 137.7, 134.8, 134.5, 131.1, 130.9, 129.9, 129.0, 128.9, 126.7, 119.1, 118.9, 66.5, 66.1, 53.7, 40.5, 36.7; LCMS LC (214 nm) 5.49 min; MS (ES+) m/z 540.1 ($C_{24}H_{23}Cl_2NO_7S$ + H requires 540.07).

Diprop-2-enyl 2-[1-(2-Furyl)-3-oxo-3-(4-sulfamoylphenyl)propyl]propane-1,3-dioate (11f). HPLC (220 nm) 30.07 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, J = 8.2 Hz, 2 H), 7.99 (d, J = 8.2 Hz, 2 H), 7.26 (s, 1 H), 6.26−6.19 (m, 1 H), 6.13−6.08 (m, 1 H), 5.96−5.73 (m, 2 H), 5.35−5.17 (m, 4 H), 5.05 (br s, 2 H), 4.64 (d, J = 5.5 Hz, 2 H), 4.54 (d, J = 5.5 Hz, 2 H), 4.30 (ddd, J = 5.7, 8.4, 8.4 Hz, 1 H), 3.98 (d, J = 8.4 Hz, 1 H), 3.69 (dd, J = 8.4, 17.4 Hz, 1 H), 3.58 (dd, J = 5.7, 17.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.3, 167.5, 167.3, 152.8, 145.7, 141.8, 139.7, 131.2, 128.8, 126.7, 118.9, 110.3, 107.3, 66.3, 54.9, 40.1, 34.3; LCMS LC (214 nm) 5.10 min; MS (ES+) m/z 461.8 ($C_{22}H_{23}NO_8S$ + H requires 462.12).

Diprop-2-enyl 2-[1-(3-Methyl(2-thienyl))-3-oxo-3-(4-sulfamoylphenyl)propyl]propane-1,3-dioate (11g). HPLC (220 nm) 31.92 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13−7.92 (m, 4 H), 7.04 (d, J = 5.4 Hz, 1 H), 6.67 (d, J = 5.4 Hz, 1 H), 5.97−5.81 (m, 1 H), 5.78−5.63 (m, 1 H), 5.37−5.13 (m, 4 H), 5.16 (br s, 2 H), 4.73−4.39 (m, 5 H), 3.84 (d, J = 9.3 Hz, 1 H), 3.51 (d, J = 6.9 Hz, 2 H), 2.18 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.3, 167.6, 167.1, 145.7, 139.7, 136.5, 135.4, 131.2, 129.9, 128.8, 126.7, 122.9, 119.1, 118.7, 66.4, 66.2, 57.8, 44.2, 34.3, 13.9; LCMS LC (214 nm) 5.38 min; MS (ES+) m/z 492.1 ($C_{23}H_{25}NO_7S_2$ + H requires 492.12).

General Procedure for the Preparation of Rink-Resin-Coupled 4-Carboxamide Diallylmalonate Adducts (11h−j). To dry Rink bound carboxamide chalcone **10l−n** (1.0 g, ∼0.5 mmol) was added diallylmalonate (0.9 mL, 5.0 mmol) followed by THF (10 mL) and lastly DBU (0.15 mL, 1.0 mmol). After the mixture was shaken for 8 h at 50 °C, the resin was drained and washed using the standard method. Cleavage of resin (200 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **11h−j** following lyophilization.

Diprop-2-enyl 2-[3-(4-Carbamoylphenyl)-3-oxo-1-phenylpropyl]propane-1,3-dioate (11h). HPLC (220 nm) 28.97 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.14−7.73 (m, 4 H), 7.58−7.09 (m, 5 H), 5.92−5.79 (m, 1 H), 5.61−5.45 (m, 1 H), 5.32−5.16 (m, 2 H), 5.11−4.98 (m, 2 H), 4.79−4.38 (m, 2 H), 4.29 (d, J = 5.7 Hz, 2 H), 4.08 (d, J = 10.6 Hz, 1 H), 3.97 (ddd, J = 3.9, 9.9, 10.6 Hz, 1 H), 3.69 (dd, J = 9.6, 11.1 Hz, 1 H), 3.54−3.34 (dd, J = 8.9, 17.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 167.5, 167.1, 140.4, 138.4, 132.0, 131.7, 128.9, 128.7, 128.2, 127.8, 127.6, 126.9, 118.2, 117.9, 65.7, 65.2, 56.9, 42.5, 40.7; LCMS LC (220 nm) 2.87 min; MS (ES+) m/z 436.4 ($C_{25}H_{25}NO_6$ + H requires 436.18).

Diprop-2-enyl 2-[1-(2,6-Dichlorophenyl)-3-(4-carbamoylphenyl)-3-oxopropyl]propane-1,3-dioate (11i). HPLC (220 nm) 30.61 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J = 8.4 Hz, 2 H), 7.88 (d, J = 8.4 Hz, 2 H), 7.30−7.92 (m, 2 H), 7.07 (t, J = 7.8 Hz, 1 H), 5.97−5.82 (m, 1 H), 5.66−5.52 (m, 1 H), 5.37−5.06 (m, 5 H), 4.74−4.60 (m, 2 H), 4.50 (d, J = 11.4 Hz, 1 H), 4.41−4.26 (m, 2 H), 3.89 (dd, J = 9.0, 16.5 Hz, 1 H), 3.65 (dd, J = 4.8, 16.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.8, 169.7, 167.8, 166.7, 139.3, 137.8, 136.4, 134.8, 134.7, 131.2, 131.0, 129.9, 129.0, 128.5, 127.8, 119.1, 118.8, 66.5, 66.1, 53.8, 40.4, 36.8; LCMS LC (220 nm) 1.91 min; MS (ES+) m/z 504.3 ($C_{25}H_{23}Cl_2NO_6$ + H requires 504.10).

Diprop-2-enyl 2-[1-(4-Bromophenyl)-3-(4-carbamoylphenyl)-3-oxopropyl]propane-1,3-dioate (11j). HPLC (220 nm) 31.48 min; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.04−7.96 (m, 5 H), 7.42 (d, J = 8.7 Hz, 2 H), 7.34 (d, J = 8.7 Hz, 2 H), 5.98−5.85 (m, 1 H), 5.74−5.60 (m, 1 H), 5.36−5.08 (m, 3 H), 4.73−4.59 (m, 2 H), 4.40 (dt, J = 1.2, 5.4 Hz, 2 H), 4.21−4.11 (m, 1 H), 4.06 (d, J = 10.2 Hz, 1 H), 4.75 (dd, J = 9.3, 17.4 Hz, 1 H), 3.65 (dd, J = 4.2, 17.4 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 197.0, 167.7, 167.2, 140.5, 139.1, 132.2, 132.0, 131.4, 131.0, 128.1, 128.0, 118.0, 117.8, 66.0, 65.6, 57.2, 42.7, 40.6; LCMS LC (220 nm) 3.09 min; MS (ES+) m/z 514.3 ($C_{25}H_{24}BrNO_6$ + H requires 514.09).

General Procedure for the Preparation of Rink-Resin-Coupled 4-Sulfonamidobenzene-2-pyridones (13a−r). To dry Rink-coupled sulfonamide malonate compounds **11a−g** (200 mg, 0.1 mmol) was added alkylamine (1.0 mmol) followed by dry toluene (10 mL). After the mixture was shaken for 1 min, glacial acetic acid (0.8 mL) was added, resulting in a white slurry which clears upon heating. Predried (flame heated under vacuum) 3 Å molecular sieves (∼0.5−1 g) were then added followed by a second addition after 24 h (∼0.25 g) of heating at 70 °C. After the mixture was shaken for 48−60 h, the resin was transferred to a large disposable plastic filter rinsing first with MeOH (2 × 10 mL) to dissolve any solid developed in the reaction and then with CH_2Cl_2 (2 × 10 mL). The resin was separated from the 3 Å molecular sieves by addition of CH_2Cl_2 allowing the floating resin to be drained away. The recovered resin is then washed using the standard method. Cleavage of resin (100 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **13a−r** following filtration through a plug of silica (eluting with EtOAc/hexane (4:6)). The crude product was approximately 90% pure directly cleaved from the resin as judged by HPLC, LCMS, and NMR.

Methyl 2-Oxo-4-phenyl-1-benzyl-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13a). HPLC (220 nm) 30.09 min; ^{1}H NMR ($CDCL_3$, 300 MHz) δ 7.89 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.28−7.09 (m, 8 H), 6.87−6.80 (m, 2 H), 5.47 (d, J = 4.8 Hz, 1 H), 4.94 (br s, 2 H), 4.77 (s, 2 H), 4.24 (dd, J = 4.8, 7.5 Hz, 1 H), 3.88 (d, J = 7.5 Hz, 1 H), 3.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 166.4, 141.9, 141.0, 139.6, 139.0, 136.3, 128.8, 128.5, 128.3, 127.9, 127.5, 127.4, 126.6, 114.9, 55.6, 52.8, 46.6, 40.6; HRMS (FAB+) m/z 477.1474 ($C_{26}H_{24}N_2O_5S$ + H requires 477.1484).

Methyl 2-Oxo-4-phenyl-1-prop-2-enyl-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13b). HPLC (220 nm) 27.55 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 7.8 Hz, 2 H), 7.48 (d, J = 7.8 Hz, 2 H), 7.37−7.23 (m, 4 H), 5.70−5.55 (m, 1 H), 5.48 (d, J = 4.5 Hz, 1 H), 5.12−4.97 (m, 1 H), 4.94 (br s, 2 H), 4.86 (d, J = 17.1 Hz, 1 H), 4.28 (dd, J = 4.5, 9.0 Hz, 1 H), 4.20 (dd, J = 5.5, 15.6 Hz, 1 H), 4.06 (dd, J = 5.5, 15.9 Hz, 1 H), 3.84 (d, J = 9.0 Hz, 1 H), 3.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 166.3, 142.2, 141.2, 139.6, 139.4, 132.2, 129.0, 128.6, 127.7, 127.5, 126.9, 126.7, 117.7, 114.7, 55.5, 52.6, 46.0, 40.8; LCMS LC (214 nm) 4.72 min; MS (ES+) m/z 427.4; HRMS (FAB+) m/z 427.1326 ($C_{22}H_{22}N_2O_5S$ + H requires 427.1327).

Methyl 2-Oxo-4-phenyl-1-(2-phenylethyl)-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13c). HPLC (220 nm) 31.16 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 8.1 Hz, 2 H), 7.39−7.12 (m, 10 H), 6.91 (s, 2 H), 5.37 (d, J = 4.6 Hz, 1 H), 4.99 (br s, 2 H), 4.14 (dd, J = 4.5, 7.6 Hz, 1 H), 4.04−3.89 (m, 1H), 3.81 (d, J = 7.6 Hz, 1 H), 3.77 (s, 3 H), 2.84−2.71 (m, 1 H), 2.70−2.57 (m, 1H); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 169.1, 166.7, 142.1, 140.9, 139.6, 137.9, 128.9, 128.9, 128.5, 128.4, 127.6, 127.5, 126.8, 126.6, 115.4, 55.5, 52.5, 45.2, 40.8, 34.4; LCMS LC (214 nm) 5.24 min; MS (ES+) *m/z* 491.0; HRMS (FAB+) *m/z* 491.1627 ($C_{27}H_{26}N_2O_5S$ + H requires 491.1640).

Methyl 1-(2-Furylmethyl)-2-oxo-4-phenyl-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13d). HPLC (220 nm) 28.39 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, *J* = 8.1 Hz, 2 H), 7.48 (d, *J* = 8.1 Hz, 2 H), 7.28−7.18 (m, 4 H), 7.10−7.03 (m, 1 H), 6.54−6.45 (m, 1 H), 6.25 (s, 1 H), 5.98−5.92 (m, 1 H), 5.49 (d, *J* = 5.4 Hz, 1 H), 4.94 (br s, 2 H), 4.92 (s, 2 H), 4.60−4.51 (m, 1 H), 4.25−4.18 (m, 1 H), 3.79 (s, 1 H), 3.74 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 166.1, 149.8, 142.0, 139.7, 139.0, 129.0, 128.6, 127.5, 127.4, 126.8, 114.5, 110.4, 109.0, 106.2, 55.7, 52.8, 40.7, 39.7, 30.9; LCMS LC (214 nm) 4.82 min; MS (ES+) *m/z* 467.2; HRMS (FAB+) *m/z* 467.1282 ($C_{24}H_{22}N_2O_6S$ + H requires 467.1276).

Methyl 1-{2-[(6-Chloro-2-fluorophenyl)methylthio]ethyl}-2-oxo-4-phenyl-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13e). HPLC (220 nm) 33.68 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.38−7.24 (m, 5 H), 7.19−7.13 (m, 2 H), 6.99−6.90 (m, 1 H), 5.51 (d, *J* = 4.5 Hz, 1 H), 4.98 (s, 2 H), 4.32 (dd, *J* = 4.5, 9.3 Hz, 1 H), 3.83 (d, *J* = 9.3 Hz, 1 H), 3.99−3.86 (m, 1 H), 3.70 (s, 3 H), 3.72−3.63 (m, 1 H), 2.68−2.56 (m, 1 H), 2.55−2.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 166.9, 142.2, 140.9, 139.5, 139.4, 129.0, 128.8, 128.4, 127.6, 127.5, 126.9, 126.8, 125.6, 115.7, 114.2, 113.9, 55.6, 52.6, 42.8, 40.7, 30.5, 26.6; LCMS LC (214 nm) 5.70 min; MS (ES+) *m/z* 588.8; HRMS (FAB+) *m/z* 589.1036 ($C_{28}H_{26}ClFN_2O_5S_2$ + H requires 589.1034).

Methyl 2-Oxo-4-phenyl-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13f). HPLC (220 nm) 20.84 min; LCMS LC (214 nm) 2.23 min; MS (ES+) *m/z* 387.1; HRMS (FAB+) *m/z* 387.1012 ($C_{19}H_{18}N_2O_5S_1$ + H requires 387.1015).

Prop-2-enyl 2-Oxo-4-phenyl-1-benzyl-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13g). HPLC (220 nm) 32.37 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.27−7.09 (m, 8 H), 6.83 (d, *J* = 4.5 Hz, 2 H), 5.92−5.77 (m, 1 H), 5.47 (d, *J* = 4.8 Hz, 1 H), 5.29 (br s, 2 H), 5.06 (s, 2 H), 4.95−4.68 (m, 2 H), 4.63−4.58 (m, 2 H), 4.25 (dd, *J* = 4.8, 7.8 Hz, 1 H), 3.84 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 166.6, 142.1, 141.2, 139.6, 139.0, 136.4, 131.4, 128.9, 128.6, 128.4, 127.9, 127.5, 126.6, 118.7, 115.0, 66.2, 55.6, 53.4, 46.6, 40.6; LCMS LC (214 nm) 5.45 min; MS (ES+) *m/z* 503.2; HRMS (FAB+) *m/z* 503.1638 ($C_{28}H_{26}N_2O_5S$ + H requires 503.1641).

Prop-2-enyl 2-Oxo-4-phenyl-6-(4-sulfamoylphenyl)-1,3,4-trihydropyridine-3-carboxylate (13l). HPLC (220 nm) 21.82 min; LCMS LC (214 nm) 2.73 min; MS (ES+) *m/z* 413.2; HRMS (FAB+) *m/z* 413.1176 ($C_{21}H_{20}N_2O_5S_1$ + H requires 413.1171).

Prop-2-enyl 4-(3-Nitrophenyl)-6-(4-sulfamoylphenyl)-2-oxo-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13n). HPLC (220 nm) 31.56 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16−7.97 (m, 3 H), 7.92 (d, *J* = 8.1 Hz, 2 H), 7.49 (m, 2 H), 7.37 (d, *J* = 8.1 Hz, 2 H), 7.24−7.11 (m, 3 H), 6.82 (d, *J* = 7.8 Hz, 1 H), 5.93−5.56 (m, 1 H), 5.47 (d, *J* = 4.8 Hz, 1 H), 5.34−5.02 (m, 3 H), 4.75 (s, 2 H), 4.73−4.57 (m, 1 H), 4.47−4.25 (m, 1 H), 3.93 (d, *J* = 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.7, 165.8, 148.3, 142.3, 141.2, 139.0, 136.1, 133.7, 131.1, 129.8, 128.7, 128.6, 128.4, 127.8, 127.6, 126.7, 126.6, 122.6, 119.2, 112.9, 66.6, 55.3, 46.8, 40.1; LCMS LC (214 nm) 4.50 min; MS (ES+) *m/z* 548.0; HRMS (FAB+) *m/z* 548.1481 ($C_{28}H_{25}N_3O_7S$ + H requires 548.1491).

Prop-2-enyl 4-(4-Cyanophenyl)-6-(4-sulfamoylphenyl)-2-oxo-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13o). HPLC (220 nm) 30.53 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11−7.96 (m, 2 H), 7.94 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 8.7 Hz, 1 H), 7.49 (d, *J* = 6.8 Hz, 2 H), 7.37 (d, *J* = 7.8 Hz, 2 H), 7.26−7.14 (m, 3 H), 6.84 (d, *J* = 6.8 Hz, 1 H), 5.93−5.58 (m, 1 H), 5.44 (d, *J* = 5.1 Hz, 1 H), 5.34−5.00 (m, 3 H), 4.88−4.41 (m, 4 H), 4.29 (dd, *J* = 12.6, 5.1 Hz, 1 H), 3.85 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.7, 165.7, 144.2, 142.3, 139.1, 136.1, 132.6, 131.1, 129.3, 128.6, 128.4, 128.3, 128.1, 127.7, 126.7, 119.1, 113.0, 66.6, 55.2, 46.7, 40.5; LCMS LC (214 nm) 4.34 min; MS (ES+) *m/z* 528.0; HRMS (FAB+) *m/z* 528.1580 ($C_{29}H_{25}N_3O_5S$ + H requires 528.1593).

Prop-2-enyl 4-(2,6-Dichlorophenyl)-6-(4-sulfamoylphenyl)-2-oxo-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13p). HPLC (220 nm) 32.76 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06−7.95 (m, 1 H), 7.85 (d, *J* = 8.1 Hz, 2 H), 7.26 (d, *J* = 8.1 Hz, 2 H), 7.34−7.12 (m, 5 H), 6.95−6.89 (m, 2 H), 5.87−5.61 (m, 2 H), 5.42−504 (m, 3 H), 4.79 (d, *J* = 15.6 Hz, 1 H), 4.71−4.48 (m, 2 H), 4.20 (d, *J* = 15.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.7, 167.2, 141.9, 139.4, 136.5, 135.7, 134.0, 131.4, 129.4, 129.3, 128.5, 128.5, 127.4, 127.1, 126.4, 118.2, 114.9, 66.0, 51.4, 46.9, 37.7; LCMS LC (214 nm) 5.66 min; MS (ES+) *m/z* 571.0 ($C_{28}H_{24}Cl_2N_2O_5S$ + H requires 571.08).

Prop-2-enyl 4-(2-Furanyl)-6-(4-sulfamoylphenyl)-2-oxo-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13q). HPLC (220 nm) 30.65 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16−7.97 (m, 4 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.18−7.13 (m, 2 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 6.28−6.22 (m, 1 H), 5.97−5.65 (m, 1 H), 5.48 (d, *J* = 5.7 Hz, 1 H), 5.39−5.12 (m, 2 H), 4.86 (s, 2 H), 4.79−4.53 (m, 2 H), 4.40−4.28 (m, 1 H), 4.03−3.96 (m, 1 H), 3.62−3.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 166.3, 152.9, 151.4, 145.7, 142.5, 141.8, 139.6, 136.4, 131.3, 129.0, 128.9, 128.6, 127.8, 126.8, 126.6, 118.9, 111.4, 110.3, 107.3, 66.5, 54.9, 46.6, 34.6; LCMS LC (214 nm) 5.30 min; MS (ES+) *m/z* 493.0; HRMS (FAB+) *m/z* 493.1425 ($C_{26}H_{24}N_2O_6S$ + H requires 493.1433).

Prop-2-enyl4-(3-Methyl-2-thiophenyl)-6-(4-sulfamoylphenyl)-2-oxo-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13r). HPLC (220 nm) 32.76 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18−7.94 (m, 2 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.24−7.09 (m, 2 H), 7.05 (d, *J* = 5.1 Hz, 1 H), 6.98−6.88 (m, 1 H), 6.80 (d, *J* = 5.1 Hz, 1 H), 5.96−5.79 (m, 1 H), 5.43 (d, *J* = 4.8 Hz, 1 H), 5.35−5.11 (m, 2 H), 5.08−4.84 (m, 2 H), 4.72−4.38 (m, 2 H), 3.88 (d, *J* = 7.5 Hz, 1 H), 3.52 (d, *J* = 7.5 Hz, 1 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0, 166.0, 142.0, 141.1, 139.4, 136.5, 135.4, 134.3, 131.4, 130.5, 128.8, 128.3, 127.6, 127.3, 126.6, 126.4, 123.1, 122.7, 122.3, 118.6, 114.1, 66.3, 55.7, 47.5, 34.7, 14.0; LCMS LC (214 nm) 5.53 min; MS (ES+) *m/z* 523.0; HRMS (FAB+) *m/z* 523.1369 ($C_{27}H_{26}N_2O_5S_2$ + H requires 523.1361).

General Procedure for the Preparation of Rink-Resin-Coupled 4-Carboxamidobenzene-2-Pyridones (13s−y). To dry Rink-coupled carboxamide malonate compounds **11h−j** (100 mg, ∼0.05 mmol) was added a solution of alkylamine (5−6 mmol) dissolved in dry toluene (2 mL), glacial acetic acid (1 mL), and abs ethanol (1 mL). Predried (flame heated under vacuum) 4 Å molecular sieves (∼0.5 g) were then added followed by a second addition after 24 h (∼0.25 g) of heating and shaking at 80 °C. After the mixture was shaken for 48 h, the reaction was diluted with glacial acetic acid (2 mL) and abs ethanol (6 mL). The resin mixture was transferred to a large disposable plastic filter rinsing first with MeOH (2 × 10 mL) and then with CH_2Cl_2 (2 × 10 mL). The resin was separated from the 4 Å molecular sieves by addition of CH_2Cl_2 allowing the floating resin to be drained away. The recovered resin was then washed using the standard method. Cleavage of resin (100 mg) with 10% TFA in CH_2Cl_2 (4 mL) yielded **13s−y** following filtration through a plug of silica (eluting with EtOAc/hexane (1:1)).

Prop-2-enyl 6-(4-Carbamoylphenyl)-2-oxo-4-phenyl-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13s). HPLC (220 nm) 29.02 min; LCMS LC (220 nm) 2.76 min; MS (ES+) *m/z* 467.4 ($C_{29}H_{26}N_2O_4$ + H requires 467.19).

Prop-2-enyl 6-(4-Carbamoylphenyl)-2-oxo-4-phenyl-1-prop-2-enyl-1,3,4-trihydropyridine-3-carboxylate (13t). HPLC (220 nm) 28.20 min; LCMS LC (220 nm) 2.78 min; MS (ES+) *m/z* 417.4 ($C_{25}H_{24}N_2O_4$ + H requires 417.17).

Prop-2-enyl 6-(4-Carbamoylphenyl)-2-oxo-4-phenyl-1,3,4-trihydropyridine-3-carboxylate (13u). HPLC (220 nm) 24.86 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.88 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.43−7.23 (m, 5 H), 5.83−5.68 (m, 2 H), 5.62 (d, *J* = 3.6 Hz, 1 H), 5.20−5.05 (m, 2 H), 4.53 (d, *J* = 4.8 Hz, 2 H), 4.25 (dd, *J* = 3.6, 10.8 Hz, 1 H),

3.88 (d, J = 10.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 169.1, 167.9, 167.4, 141.6, 137.3, 137.1, 134.8, 132.8, 129.4, 128.4, 128.3, 127.9, 126.1, 118.0, 108.0, 65.6, 55.2, 42.3; LCMS LC (220 nm) 2.52 min; MS (ES+) m/z 377.4; HRMS (FAB+) m/z 377.1493 ($C_{22}H_{20}N_2O_4$ + H requires 377.1501).

Prop-2-enyl 4-(2,6-Dichlorophenyl)-6-(4-carbamoylphenyl)-2-oxo-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13v). HPLC (220 nm) 32.52 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.85 (d, J = 8.7 Hz, 2 H), 7.49 (d, J = 8.7 Hz, 2 H), 7.45−7.20 (m, 7 H), 7.97 (d, J = 6.3 Hz, 1 H), 5.78−5.61 (m, 2 H), 5.48 (d, J = 3.0 Hz, 1 H), 5.26−5.02 (m, 3 H), 4.78 (d, J = 14.4 Hz, 1 H), 4.62−4.38 (m, 2 H), 4.22 (d, J = 15.9 Hz, 1 H), 4.08−4.01 (m, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.5, 167.2, 166.7, 140.3, 137.3, 135.1, 134.2, 133.7, 131.9, 130.2, 129.7, 129.3, 128.8, 127.9, 126.5, 117.4, 113.2, 65.0, 51.0, 46.0, 37.3; LCMS LC (220 nm) 3.14 min; MS (ES+) m/z 535.4; HRMS (FAB+) m/z 535.1199 ($C_{29}H_{24}Cl_2N_2O_4$ + H requires 535.1191).

Prop-2-enyl 4-(2,6-Dichlorophenyl)-6-(4-carbamoylphenyl)-2-oxo-1,3,4-trihydropyridine-3-carboxylate (13w). HPLC (220 nm) 26.80 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.87 (d, J = 8.5 Hz, 2 H), 7.63 (d, J = 8.5 Hz, 2 H), 7.49 (d, J = 8.3 Hz, 2 H), 7.36−7.28 (m, 1 H), 5.78−5.60 (m, 2 H), 5.60−5.56 (m, 1 H), 5.19 (dd, J = 2.7, 14.4 Hz, 1 H), 5.12−5.08 (m, 2 H), 4.61−4.58 (m, 1 H), 4.56−4.24 (m, 2 H); LCMS LC (220 nm) 2.65 min; MS (ES+) m/z 445.3 ($C_{22}H_{18}Cl_2N_2O_4$ + H requires 445.06).

Ethyl 4-(2,6-Dichlorophenyl)-6-(4-carbamoylphenyl)-2-oxo-1,3,4-trihydropyridine-3-carboxylate (13w; Ethyl Ester). HPLC (220 nm) 25.86 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.86 (d, J = 8.7 Hz, 2 H), 7.62 (d, J = 8.7 Hz, 2 H), 7.49 (d, J = 7.5 Hz, 2 H), 7.38−7.32 (m, 1 H), 5.59−5.54 (m, 1 H), 5.17 (dd, J = 2.7, 14.2 Hz, 1 H), 4.32 (d, J = 14.2 Hz, 1 H), 4.09−3.87 (m, 2 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.2, 167.2, 166.4, 136.3, 135.7, 135.0, 134.5, 134.1, 130.1, 129.7, 127.6, 125.3, 105.8, 60.7, 50.4, 13.7; LCMS LC (220 nm) 2.57 min; MS (ES+) m/z 433.3 ($C_{21}H_{18}Cl_2N_2O_4$ + H requires 433.06).

Prop-2-enyl 4-(4-Bromophenyl)-6-(4-carbamoylphenyl)-2-oxo-1-benzyl-1,3,4-trihydropyridine-3-carboxylate (13x). HPLC (220 nm) 33.47 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.84 (d, J = 8.4 Hz, 2 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.44−7.12 (m, 8 H), 7.91−7.79 (m, 1 H), 5.84−5.74 (m, 2 H), 5.45 (d, J = 3.9 Hz, 1 H), 5.25−5.02 (m, 3 H), 4.78 (d, J = 14.2 Hz, 1 H), 4.62−4.33 (m, 2 H), 4.22−4.13 (m, 1 H), 4.07−3.96 (m, 1 H); LCMS LC (220 nm) 3.23 min; MS (ES+) m/z 545.4 ($C_{29}H_{25}BrN_2O_4$ + H requires 545.10).

Prop-2-enyl 4-(4-Bromophenyl)-6-(4-carbamoylphenyl)-2-oxo-1,3,4-trihydropyridine-3-carboxylate (13y). HPLC (220 nm) 27.96 min; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.87 (d, J = 8.1 Hz, 2 H), 7.61 (d, J = 8.1 Hz, 2 H), 7.52 (d, J = 8.1 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 2 H), 5.83−5.38 (m, 2 H), 5.58 (d, J = 3.6 Hz, 1 H), 5.39−5.11 (m, 2 H), 4.52 (d, J = 3.6 Hz, 2 H), 4.23 (dd, J = 3.6, 11.1 Hz, 1 H), 3.88 (d, J = 11.1 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.2, 167.1, 166.4, 140.3, 136.8, 136.3, 134.1, 132.1, 131.6, 130.0, 127.8, 127.6, 126.8, 125.4, 117.4, 106.7 65.0, 54.2, 41.0; LCMS LC (220 nm) 2.76 min; MS (ES+) m/z 455.1 ($C_{22}H_{19}BrN_2O_4$ + H requires 455.05).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of selected new compounds, several HPLC traces of representative compounds, and details of the HPLC and LCMS methods used. This material is available free of charge via the Internet at http://pubs.acs.org.

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