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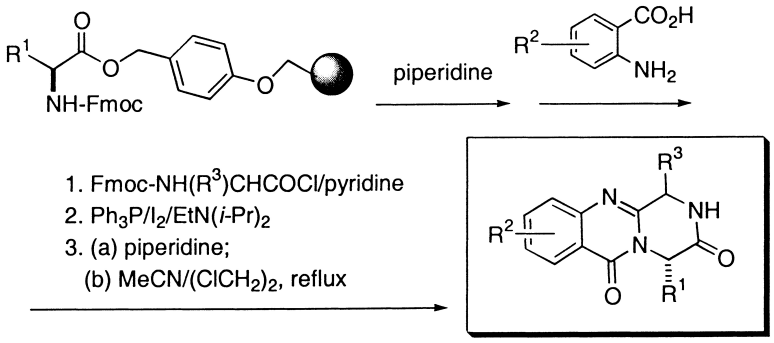

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Total Synthesis of the Fumiquinazoline Alkaloids: Solid-Phase Studies[1]

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We have previously described an efficient four-step synthesis of the fumiquinazoline alkaloids (Wang, H.; Ganesan, A. *J. Org. Chem*. **1998**, *63*, 2432−2433). Here, we demonstrate that this route is readily adaptable to combinatorial synthesis on solid phase. Linear tripeptides containing a central anthranilate unit were assembled on the Wang resin and subjected to dehydration and cyclative release to yield the pyrazino[2,1-*b*]quinazoline-3,6-diones in high purity. To demonstrate the scope of this protocol, a small library [ca. 20 compounds] of unnatural analogues was prepared by parallel synthesis.

Natural products represent promising templates for combinatorial chemistry, as they have been evolutionarily selected for their ability to display chemical information in three-dimensional space. Libraries built around such scaffolds thus have potential for both lead discovery [against targets unrelated to the original activity of the natural product] *and* lead optimization [analogues with improved properties over the natural product]. We have recently been applying[2] this principle to devise concise and modular alkaloid syntheses which are suitable for combinatorial applications. Here, we describe the adaptation of our four-step solution-phase total synthesis[3] of the fumiquinazoline alkaloids to solid-phase conditions, which in recent years[4] has emerged as a powerful means for parallel array synthesis.

Results and Discussion

For our first solid-phase studies, we targeted the total synthesis of (+)-glyantrypine, the simplest of these natural products. Commercially available Wang resin loaded with Fmoc-L-Trp **1** was deprotected and coupled with anthranilic acid in the presence of EDC as activating agent (Scheme 1). These conditions were based on those reported[5] by the Ellman group. The next step was acylation of aniline **2**, for which we had used an Fmoc-amino acid chloride under two-phase Schotten−Baumann conditions in our solution-phase work. Carpino has explored[6] solid-phase peptide couplings with Fmoc-amino acid chlorides, although one limitation was formation of an unreactive oxazolone. In recent[7] solid-phase acylations of 2-aminobenzophenones and anthranilates, the Ellman group used the more reactive Fmoc-amino acid fluorides and the hindered base 2,6-di-*tert*-butyl-4-methylpyridine. We preferred to continue using the amino acid chlorides, for reasons of ease of preparation, expense, and stability (the crystalline Fmoc-amino acid chlorides can be stored indefinitely under refrigeration, and we have used them several months after preparation). A large excess was used in order to compensate for any oxazolone formation, which was also suppressed by using pyridine as a relatively weak base. On the basis of quantification of the dibenzofulvene-piperidine adduct produced upon later deprotection of the Fmoc group, we estimated a yield of 68% for the acylation.

The next step was the key dehydrative cyclization of linear tripeptide **3**. In solution phase, this was done with 5 equiv of triphenylphosphine, although at least 1 equiv was recovered after the reaction. To ensure complete conversion, 10 equiv was used in solid-phase. The final reaction was piperidine mediated deprotection of the Fmoc group and rearrangement of oxazine **4** to amidine carboxamide **5**. After washing, the resin was refluxed in acetonitrile to induce cyclative cleavage of (+)-glyantrypine **6**. The only observable impurities in the ^{1}H NMR spectrum were derived from the byproduct, piperidine. Chromatographic purification afforded (+)-glyantrypine in 51% overall yield for the four steps, based on the loading of Wang resin. The optical rotation (+537) of this material was in fact slightly higher than the enantiomer we prepared by solution-phase methods (−522), indicating that the amino acid chirality is preserved during the solid-phase reactions.

The above natural product synthesis nicely illustrates the favorable features of our route for solid-phase conditions. The first two steps involve peptide couplings—the reaction for which solid-phase synthesis was first developed and which proceeds in almost quantitative yield for a variety of amino acids. The dehydration of the linear tripeptide requires a large excess of triphenylphosphine, iodine, and triethylamine—reagents which are readily removed by simple filtration on solid phase. The ester functionality undergoing cyclization in the final step was chosen as the position for solid-phase attachment, resulting in self-cleavage[8] from the resin. Furthermore, as only the desired penultimate precursor

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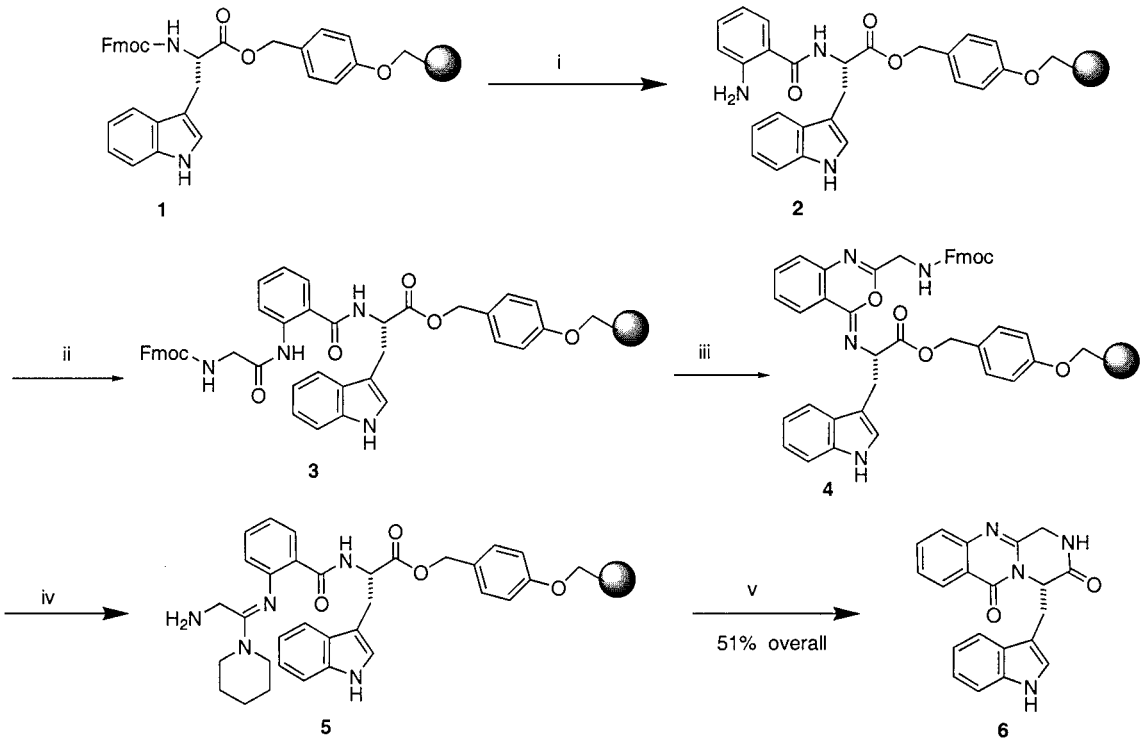
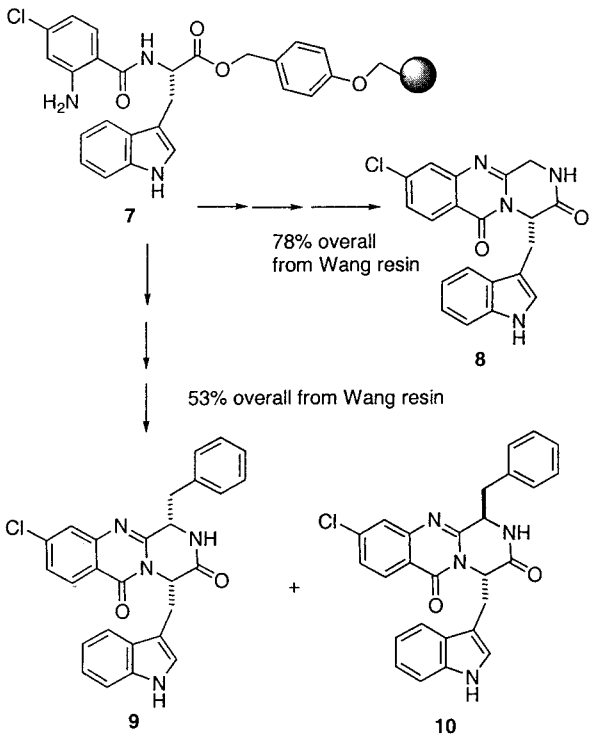
Scheme 1[a]



[a] Reagents: (i) (a) piperidine; (b) anthranilic acid (10 equiv), EDC (12 equiv); (ii) Fmoc-Gly-Cl (7 equiv), pyridine (15 equiv); (iii) $Ph_3P/I_2/EtN(i\text{-}Pr)_2$ (11/11/22 equiv); (iv) piperidine; (v) $MeCN/ClCH_2CH_2Cl$ (1:1), reflux overnight.

Scheme 2

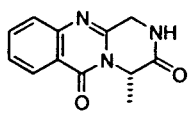
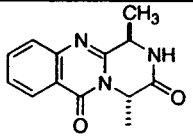
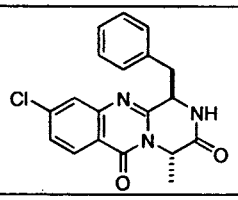
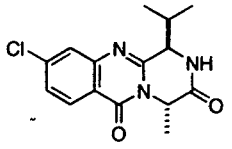
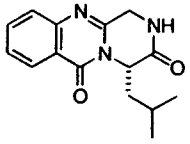
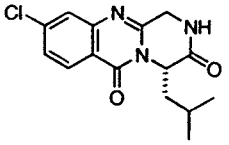
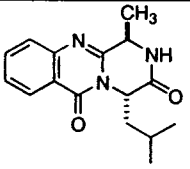
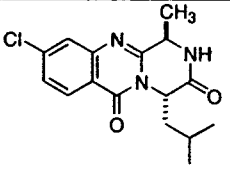
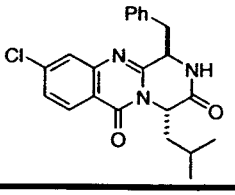


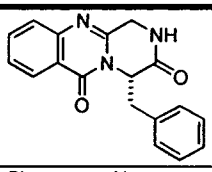
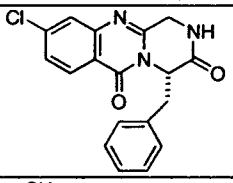
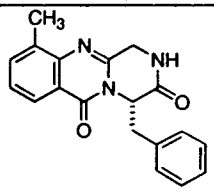
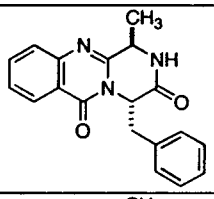
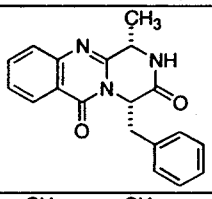
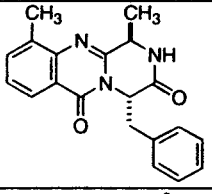
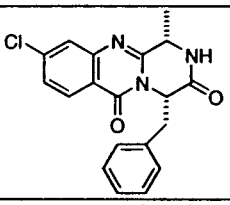
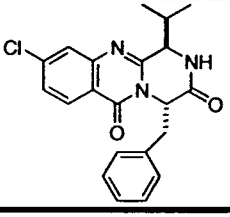
can undergo this facile cyclization, the product is free of any other resin-bound synthetic intermediates or impurities.

The feasibility of using substituted anthranilic acids was tested by repeating the synthesis using 4-chloroanthranilic acid (Scheme 2). The acylation of **7** with Fmoc-Gly-Cl was quantitative, according to determination of Fmoc release. The final cyclative release (refluxing acetonitrile, 2 h) afforded 9-chloro-glyantrypine **8** in 78% overall yield. A further 4% was recovered by repeating the refluxing for 6 h. A more demanding example occurred when we substituted Fmoc-L-PheCl for Fmoc-GlyCl in this sequence, as the final product would contain two bulky side chains (Trp and Phe) in a sterically less favorable *cis* configuration. In the event, the final cyclative release was slower than in the glyantrypine cases. After refluxing for 2 h in acetonitrile, only 28% of product was obtained; further refluxing for 6 h resulted in an additional 26%. Besides the desired product **9** (40%), we also obtained **10** (13%). We believe the formation of *trans* diastereomer **10** predominantly occurs during the final cyclative resin cleavage, as solution-phase studies indicate a maximum of only 5−10% racemization during the amino acid peptide couplings. Epimerization of the resin-bound amidine intermediate or of free *cis* **9** in solution may both be contributing to this process. Treatment of pure **9** in refluxing acetonitrile overnight, for example, resulted in approximately 25% epimerization to **10**. In the solid-phase reactions, this process may be accelerated by the piperidine byproduct.

A small array of unnatural fumiquinazoline hybrids was then prepared by discrete synthesis to further examine the scope and generality of the solid-phase route. We replaced the starting L-Trp loaded resin with L-Ala, L-Leu, and L-Phe. These were then acylated with a set of five anthranilic acids, followed by a final coupling with either D or L amino acid chlorides (resulting in *trans* or *cis* quinazoline products, respectively). Following cyclative cleavage, the purity of the crude products was evaluated by both HPLC with UV detection and by ^1H NMR with an internal standard (Table 1). The former method tends to overestimate compound purity, as the piperidine byproduct is non-UV active, while

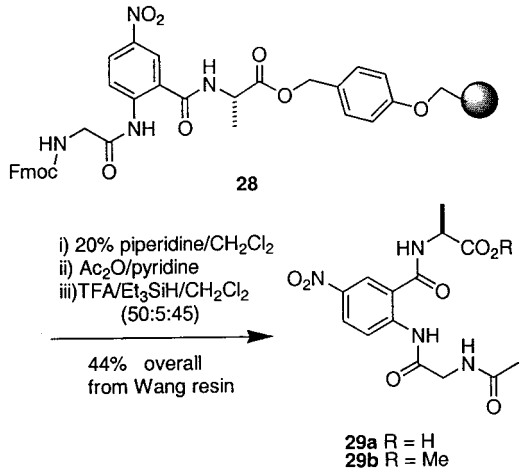
Table 1. Examples of Pyrazino[2,1-*b*]quinazoline-3,6-diones Prepared on Solid Phase

Compound / Structure	Crude material		Isolated Yield (%)[c]
	Yield (%)[a]	Purity (%)[b]	
11 	42	88	49
12 	81[d]	78	37 +8(*cis* isomer)
13 	76[d]	82	53 +4 (*cis* isomer)
14 	17	90	24
15 	90[d]	95	53
16 	88[d]	96	58
17 	64	89	45
18 	80[d]	74	52
19 	54	95	40 +4(*cis* isomer

Compound / Structure	Crude material		Isolated Yield (%)[c]
	Yield (%)[a]	Purity (%)[b]	
20 	44	89	54
21 	52	94	67
22 	55	98	64
23 	67	91	63
24 	57	75	46 +10 (*trans* isomer)
25 	24	93	23
26 	52	81	43 +6 (*trans* isomer)
27 	76[d]	82	53 +4(*cis* isomer)

[a] By quantitative ^{1}H NMR with an internal standard (hexamethyldisiloxane)
[b] By HPLC with UV diode array detection at 210 nm.
[c] After purification by preparative TLC.
[d] Due to a calibration error, the yield is an overestimate.

Scheme 3



NMR yields correlate fairly well to those obtained after chromatographic purification. The desired compound was the major product in all cases. All *cis* quinazolines were accompanied by the *trans* diastereomer, while some epimerization was also observed with a few of the *trans* quinazolines. In general, the results indicate that our solid-phase synthesis is an efficient means of preparing combinatorial libraries with the fumiquinazoline peptidomimetic scaffold.

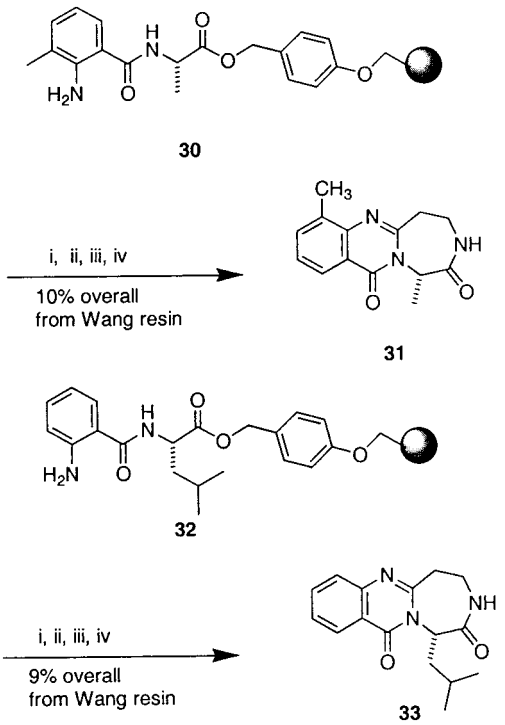
A notable exception was the lack of product formation when 5-nitroanthranilic acid was used. For example, resin-bound tripeptide **28** (Scheme 3) was treated with 3.5 equiv of dehydrating agents, but no quinazoline was detected upon cyclative cleavage. Acylation, followed by acidic cleavage yielded tripeptide **29**, indicating that the peptide coupling reactions were not at fault (**29** was isolated as a mixture of the free carboxylic acid and the methyl ester, due to the methanol solvent used). When **28** was reacted with larger amounts (8 equiv) of dehydrating agent, the resin turned dark brown, and no identifiable products were observed in the supernatant either during the reaction or after cleavage. These results suggest that the nitro functional group can cause problems in the dehydrative cyclization.

We have also examined the formation of seven-membered ring products from linear tripeptides (Scheme 4). For example, resins **30** and **32** were acylated with Fmoc-β-Ala-Cl rather than an α-amino acid. Following dehydration and cyclative cleavage, small amounts of the desired [1,4]-diazepinoquinazolones **31** and **33**, respectively, were isolated. It is possible that cyclization would be favored by more rigid and constrained β-amino acids, although we have not explored this further.

Summary

We have demonstrated a concise solid-phase entry to the pyrazino[2,1-*b*]quinazoline-3,6-dione scaffold. The procedure, while amenable to synthesis of the natural products, is also suitable for the rapid preparation of unnatural peptidomimetics with this ring skeleton. Due to the nature of the final cyclative resin cleavage, the quinazolines are formed in high purity. In the case of 3,6-*cis* substituted quinazolines, some epimerization occurs to the *trans* diastereomer.

Scheme 4[a]



[a] Reagents: (i) $FmocNHCH_2CH_2COCl$/pyridine; (ii) $Ph_3P/I_2/EtN(i\text{-}Pr)_2$; (iii) 20% piperidine in CH_2Cl_2; (iv) $MeCN/ClCH_2CH_2Cl$ (1:1), reflux overnight.

Experimental Section

For general experimental details, see ref 3a. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. (Coupling constants (*J*) were recorded in hertz.) Fmoc-L-amino acid Wang resins were purchased from Calbiochem-Novabiochem Corp. Hexamethyldisiloxane was used as internal reference in the calculation of yield by ^1H NMR. Due to its very close chemical shift (0.0656 and 1.945 ppm in $CDCl_3$ for ^1H and ^{13}C, respectively) to TMS and long relaxation time (T1), special care must be taken. Long relaxation times (D1, 25 s >5*T1) with 90° pulse and TMS-free solvent (to avoid extra hexamethyldisiloxane from TMS source) were used in quantitative experiments. Analytical HPLC was performed on a Hewlett-Packard 1050Ti series equipped with a diode array detector, using a C_{18} column (ODS Hypersil, 5μm, 4.6 × 250 mm, flow rate: 1.00 mL/min). Eluant solvent system A: methanol/water 70:30 to 100:0 eluant linear gradient over 20 min, then 100% methanol for additional 5 min; solvent system B: methanol/water 60:40 to 80:20 eluant linear gradient over 15 min, then 80:20 to 100:0 linear gradient over 5 min, finally 100% methanol for additional 5 min. Purities of all compounds were estimated from integrated peak areas of HPLC chromatographs generated at 210 nm and expressed as percentages (solvent system A or B, retention time). Isolated yield means the crude material cleaved from resin was purified by preparative TLC (Aldrich, 1 mm thickness) and the yield calculated based on the loading of starting resin. Workup for solid-phase reactions refers to filtration, washing of the resin [CH_2Cl_2 (×6), 10% MeOH/CH_2Cl_2 (×5), and MeOH (×5)], and drying before use in the next reaction.

***N*-(2-Aminobenzoyl)-L-tryptophan-Wang Resin (2).** Fmoc-L-Trp-Wang resin (**1,** loading 0.4−0.6 mmol/g) was deprotected with 20% piperidine in CH_2Cl_2. The resin loading was calculated based on quantification of the isolated dibenzofulvene-piperidine adduct. A suspension of Trp-Wang resin (0.449 g, 0.503 mmol/g, 0.226 mmol) and DMF (5 mL) was stirred for 20 min in a 50 mL flask. Then EDC (0.526 g, 2.743 mmol, 12.2 equiv) was added, followed by anthranilic acid (0.311 g, 2.26 mmol, 10.0 equiv) in five portions over 2.5 h. The mixture was stirred for an additional 16.5 h (total 19 h) at room temperature. The resin was washed with DMF (×5) and worked up to give 0.479 g of **1** with a new loading of 0.47 mmol/g.

(4*S*)-4-(1*H*-Indol-3-ylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (6). To a mixture of **2** (0.210 g, loading 0.47 mmol/g, 0.099 mmol), CH_2Cl_2 (2.5 mL), and pyridine (0.12 mL, 1.48 mmol, 15.0 equiv) was added solid Fmoc-Gly-Cl (0.220 g, 0.70 mmol, 7.0 equiv). The reaction mixture was shaken at room temperature for 3.5 h, then quenched with aqueous Na_2CO_3 (0.5 M, 2.5 mL), filtered, and washed to give **3**. Resin **3** (0.099 mmol) was reacted with a solution of $Ph_3P/I_2/NEt(i\text{-}Pr)_2$ in CH_2Cl_2 (11, 11, 22 equiv) at room temperature for 14.5 h and then worked up to give **4**. The dark resin **4** was deprotected with piperidine (0.5 mL) in CH_2Cl_2 (2 mL) for 20 min and then worked up to give resin **5** and dibenzofulvene-piperidine adducts (68%, isolated yield). The resin **5** was refluxed in MeCN for 2 h to give crude **6** [mass recovery, 25.3 mg, 74%, HPLC purity 89.9% (A, 4.03 min)] which was further purified by preparative TLC (5% MeOH /CH_2Cl_2) to give (+)-glyantrypine **6** (17.4 mg, 51%): $[\alpha]_D^{30} = +537$ (*c* 0.20, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3476, 3329, 1686, 1605 cm^{-1}; ^1H and ^{13}C NMR spectra were identical to those of (−)-glyantrypine[3b]; MS (ES, positive mode) *m*/*z* 345.3 ($[M + H]^+$).

***N*-(2-Amino-4-chlorobenzoyl)-L-tryptophan-Wang Resin (7).** Following the procedure given for **2**, the deprotected L-Trp-Wang resin (0.416 g, 0.503 mmol/g, 0.209 mmol) was reacted with EDC (12.1 equiv) and 4-chloro-anthranilic acid (10.0 equiv) at room temperature for 19 h to give 0.500 g of **7** with a new loading of 0.419 mmol/g.

(4*S*)-4-(1*H*-Indol-3-ylmethyl)-9-chloro-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (8). To resin **7** (0.247 g, 0.104 mmol) in CH_2Cl_2 (2 mL) were added pyridine (3.09 M, 0.24 mL, 0.74 mmol, 7.2 equiv) followed by Fmoc-Gly-Cl (0.37 M in CH_2Cl_2, 1.4 mL, 0.52 mmol, 5.0 equiv). After the mixture was shaken for 1.5 h at room temperature, a second portion of Fmoc-Gly-Cl (0.37 M, 1.4 mL, 0.52 mmol, 5.0 equiv) was added and the resin shaken for 1 h, followed by addition of pyridine (3.09 M, 0.20 mL, 0.62 mmol, 6.0 equiv). After an additional 7.5 h (total of 10 h), workup gave a resin which was mixed with Ph_3P solution in $(CH_2Cl)_2$ (1.52 M, 1.1 mL, 1.67 mmol, 16.1 equiv), I_2 in $(CH_2Cl)_2$ (ca 0.3 M, 2.8 mL, 0.84 mmol, 8.1 equiv), and followed by $EtN(i\text{-}Pr)_2$ (0.45 mL, 24.9 equiv). After reaction at room temperature for 14.5 h, the resin was deprotected with piperidine (0.4 mL) in CH_2Cl_2 (1.6 mL) for 20 min, and the dibenzofulvene-piperidine adduct was isolated (28.2 mg, 103%). The resin was refluxed in MeCN for 2 h to give crude **8** (mass recovery, 78%). Further refluxing for 6 h gave additional crude **8** (mass recovery, 3.8%), after which refluxing for 7 h did not provide any product by TLC. All fractions were combined [mass recovery 32.0 mg, 82%, HPLC purity 93.8% (A, 5.91 min)] and purified by preparative TLC (5% MeOH/CH_2Cl_2) to give pure **8** (30.5 mg, 78%) as a solid: $[\alpha]_D^{30} = +511$ (*c* 0.27, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3475, 3407, 1689, 1600 cm^{-1}; ^1H NMR δ 8.42 (br s, 1H, indole NH), 8.29 (d, 1H, $J = 8.5$), 7.50 (d, 1H, $J = 1.8$), 7.47 (dd, 1H, $J = 8.5, 2.0$), 7.33 (d, 1H, $J = 8.1$ 0, 7.28 (d, 1H, $J = 9.0$), 7.12 (td, 1H, $J = 7.2, 0.7$), 6.90 (t, 1H, $J = 7.2$), 6.70 (d, 1H, $J = 2.2$, indole C_2-H), 6.65 (d, 1H, $J = 3.5$, CONH), 5.57 (dd, 1H, $J = 5.0, 3.0$, Trp-CHN), 3.79 (dd, 1H, $J = 17.0, 4.1$, Gly-CH_2), 3.69 (dd, 1H, $J = 15.0, 2.9$, Trp-CH_2), 3.60 (dd, 1H, $J = 15.0, 5.3$, Trp-CH_2), 2.80 (d, 1H, $J = 17.0$, Gly-CH_2); ^{13}C NMR δ 169.3, 160.0, 149.7, 148.1, 141.2, 136.0 (s), 128.4, 127.8 (d), 127.2 (s), 126.3 (d), 123.6, 122.7, 120.2 (d), 118.6 (s), 118.3 (d), 111.3 (d), 109.0 (s), 56.9 (d), 44.7 (t), 27.2 (t); MS (ESI, positive mode) *m*/*z* calcd for M + H: 379.1, found 378.9.

(1*S*,4*S*)-4-(1*H*-Indol-3-ylmethyl)-1-phenylmethyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (9) and (1*S*,4*R*)-4-(1*H*-Indol-3-ylmethyl)-1-phenylmethyl-2*H*-pyrazino-[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (10). Following the procedure given for **6**, resin **7** (0.215 g, 0.419 mmol/g, 0.090 mmol) was reacted with Fmoc-L-Phe-Cl. After dehydration and deprotection, the dibenzofulvene-piperidine adduct was isolated (21.5 mg, 91%). The resin was refluxed in MeCN for 2 h to afford crude products (mass recovery, 12.0 mg, 28%). Refluxing was repeated until no further product was cleaved: 6 h, mass recovery 11.1 mg, 26%; 7 h, mass recovery 6.2 mg, 15%; 16.5 h in MeCN−$(CH_2Cl)_2$ (1:1), almost no product. The combined crude products (mass recovery, 29.3 mg, 79%) were purified by preparative TLC (75% ethyl acetate in hexanes) to yield **9** (17.1 mg, 40%) and epimerized **10** (5.5 mg, 13%) with a total yield of 53%. Compound **9**: $[\alpha]_D^{30} = +321$ (*c* 0.26, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3475, 3384, 1684, 1591 cm^{-1}; ^1H NMR δ 8.34 (d, 1H, $J = 8.6$), 8.14 (br s, 1H, indole NH), 7.67 (d, 1H, $J = 2.0$, H-10), 7.54 (d, 1H, $J = 8.2$), 7.51 (dd, 1H, $J = 8.6, 2.0$), 7.31 (d, 1H, $J = 8.1$), 7.21 (td, 1H, $J = 7.6, 0.8$), 7.16−7.13 (m, 3H, Ph), 7.10 (td, 1H, $J = 7.5, 0.7$), 6.62 (d, 1H, $J = 2.3$), 6.35−6.32 (m, 2H, Ph), 5.58 (br d, 1H, $J = 2.0$, CONH), 5.52 (dd, 1H, $J = 4.6, 3.2$, Trp-CHN), 4.35 (dt, 1H, $J = 11.6, 2.8$, Phe-CHN), 3.83 (dd, 1H, $J = 15.1, 3.1$, Trp-CH_2), 3.77 (dd, 1H, $J = 15.1, 4.8$, Trp-CH_2), 2.96 (dd, 1H, $J = 13.1, 3.0$, Phe-CH_2), 0.56 (dd, 1H, $J = 12.8, 12.0$, Phe-CH_2); ^{13}C NMR δ 166.3, 160.3, 151.5, 148.1, 141.2, 135.8, 135.4 (s), 129.2, 128.9, 128.5 (d), 128.0 (s), 127.7, 127.3, 126.5, 123.5, 122.8, 120.5, 119.3 (d), 118.6 (s), 111.5, 109.5, 57.9, 56.8, 42.7, 26.6; MS (ESI, positive mode) *m*/*z* calcd for M + H: 469.1, found 468.9. Compound **10**: $[\alpha]_D^{30} = +655$ (*c* 0.155, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3475, 3377, 1685, 1598 cm^{-1}; ^1H NMR δ 8.32 (d, 1H, $J = 8.6$), 8.10 (br s, 1H, indole NH), 7.63 (d, 1H, $J = 1.9$), 7.51 (dd, 1H, $J = 8.6, 2.0$), 7.41 (dd, 2H, $J = 8.2, 0.8$), 7.25−7.15 (m, 4H), 6.94 (t, 1H, $J = 7.4$), 6.63 (d, 1H, $J = 2.2$), 6.50 (d, 2H, $J = 6.8$), 5.62 (dd, 1H, $J = 5.2, 2.6$, Trp-CHN), 5.35 (br s, 1H, NH), 3.75 (dd, 1H, $J = 15.0, 2.6$, Trp-CH_2), 3.63 (dd,

1H, J = 15.2, 5.5, Trp-CH_2), 3.60 (dd, 1H, J = 15.0, 3.8, Phe-CH_2), 2.94 (dd, 1H, J = 11.1, 3.6, Phe-CHN), 2.50 (dd, 1H, J = 14.7, 11.2, Phe-CH_2); ^{13}C NMR δ 169.0, 160.1, 152.3, 147.9, 141.0, 136.1, 134.8 (s), 129.2, 128.4, 128.4, 127.9, 127.4 (d), 127.1 (s), 126.9, 123.7, 122.9, 120.7, 118.9 (d), 118.8 (s), 111.1 (d), 109.6 (s), 57.4 (d), 52.9 (d), 37.9 (t), 27.2 (t); MS (ESI, positive mode) *m*/*z* calcd for M + H: 469.1, found 469.0.

General Procedures for Solid-Phase Synthesis. Coupling of Anthranilic Acids. Fmoc-L-AA-Wang resins (AA = amino acids, Phe, Ala, Leu) were deprotected with 20% piperidine in DMF for 10 min, and the deprotection was repeated once. The deprotected resin (ca. 0.3−0.8 g, 1 equiv) and solid EDC (12 equiv) were added to a 20 mL brown glass vial, followed by addition of dry DMF (ca. 1.0−1.2 mL/mmol EDC, to swell the mixture) and sonication for a few seconds. Anthranilic acids dissolved in DMF (1 M, 3.2 equiv) were added via syringe, and the vial was shaken horizontally. Additional portions of anthranilic acids (3.4 equiv × 2) were added after 1 and 2 h, respectively (total 10 equiv). The vial was shaken at room temperature overnight (14−23 h), the resin worked up, and the loading recalculated.

Acylation with Fmoc-Amino Acid Chlorides. The above resin (ca 0.1 mmol, 1 equiv) was added to a 20 mL glass vial, followed by dry CH_2Cl_2 (ca 1 mL) and pyridine solution in CH_2Cl_2 or $(CH_2Cl)_2$ (3 M, 7 equiv). The Fmoc-amino acid chloride solution in CH_2Cl_2 or $(CH_2Cl)_2$ (5 equiv, concentrations for Gly, 0.6 M; Phe, 0.4 M, Ala, 0.6 M; Val, 0.4 M; β-Ala, 0.6 M) was injected into the vial via syringe. After being shaken for 2 h at room temperature, additional pyridine (6 equiv) and Fmoc-amino acid chloride solution (5 equiv) were added. The vial was shaken overnight (ca 18 h). The resin was filtered and washed with CH_2Cl_2, DMF, 10% MeOH/CH_2Cl_2, and MeOH.

Dehydration with Ph_3P/I_2/EtN(*i*-Pr)$_2$. Ph_3P (5.29 g, 20.2 mmol) and I_2 (4.27 g, 16.8 mmol) were added to a dry 200mL flask. Dry CH_2Cl_2 (40 mL) was added to the flask, followed by addition of EtN(*i*-*Pr*)$_2$ (7.2 mL, 41.3 mmol). The solution was stirred at room temperature for 10 min. This orange colored suspension, with fine solids, was used as a stock solution with an estimated concentration of 0.3 M in I_2, and aliquots were removed via syringe with an 18-gauge needle. The above resin (ca 0.1 mmol, 1 equiv) was added to a 20 mL glass vial. The dehydrating reagent (10 equiv of I_2) was added into the vial via syringe. The mixture was shaken overnight (ca 17 h) at room temperature. The resin was filtered through a 2 mL fritted plastic syringe and worked up.

Deprotection and Cyclization. To the above resin (ca. 0.1 mmol) in a 2 mL fritted plastic syringe was added CH_2Cl_2 (1.6 mL) and piperidine (0.4 mL). The mixture was stood vertically and occasionally shaken at room temperature for 20 min. After resin workup, the dry resin was placed into a 50 mL flask and refluxed with MeCN (5 mL) and $(CH_2Cl)_2$ (5 mL) overnight (ca. 18 h). The mixture was filtered, and the resin was washed with CH_2Cl_2, 10% MeOH/CH_2Cl_2, and MeOH. The combined filtrates were concentrated to give the crude final product. The whole or part of the crude product was dissolved in $CDCl_3$−CD_3OD with $Me_3SiOSiMe_3$ as internal standard to calculate the crude yield. About 1 mg of the crude product was dissolved in MeOH (1 mg/mL) for MS and purity determination by HPLC. The crude product was then purified by preparative TLC.

(4*S*)-4-Methyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (11). HPLC purity 88% (B, 3.53 min), NMR yield 42%, isolated yield 49%. ^{1}H NMR δ 8.29 (dd, 1H, J = 8.0, 1.4), 7.78 (ddd, 1H, J = 8.5, 7.2, 1.5), 7.65 (d, 1H, J = 8.1), 7.51 (td, 1H, J = 7.5, 1.1), 7.39 (br s, 1H, NH), 5.46 (qd, 1H, J = 7.2, 0.7, Ala-CHN), 4.69 (d, 1H, J = 16.8), 4.52 (dd, 1H, J = 16.8, 5.0), 1.66 (d, 3H, J = 7.2); ^{13}C NMR δ 170.3, 160.2, 147.6, 147.1 (s), 134.9, 127.4, 127.0, 126.9 (d), 120.4 (s), 51.8 (d), 45.0 (t), 16.9 (q); MS (ESI, positive mode) *m*/*z* calcd for M + H: 230.1, found 230.2.

(1*R*,4*S*)-1, 4-Dimethyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (12). HPLC purity 78% (B, 4.81 min), isolated yield 37% and 8% (epimer), total 45%. ^{1}H NMR δ 8.28 (ddd, 1H, J = 8.0, 1.6, 0.6), 7.77 (ddd, 1H, J = 8.4, 7.0, 1.6), 7.69 (dd, 1H, J = 8.2, 0.8), 7.50 (ddd, 1H, J = 8.2, 7.0, 1.4), 7.40 (br s, 1H, NH), 5.50 (qd, 1H, J = 7.4, 1.2), 4.74 (q, 1H, J = 6.6), 1.81 (d, 3H, J = 6.6), 1.67 (d, 3H, J = 7.3); ^{13}C NMR δ 170.4, 160.4, 150.8, 147.1 (s), 134.7, 127.6, 127.3, 126.8 (d), 120.4 (s), 52.4, 49.3, 17.52, 16.6.

(1*R*,4*S*)-9-Chloro-4-methyl-1-(phenylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (13). HPLC purity 82% (A, 9.64 min), isolated yield 53% and 4% (epimer), total 57%. ^{1}H NMR δ 8.22 (d, 1H, J = 8.6), 7.74 (d, 1H, J = 2.0), 7.48 (dd, 1H, J = 8.6, 2.0), 7.43−7.30 (m, 5H), 5.97 (br s, 1H, NH), 5.41 (q, 1H, J = 7.2), 4.81 (dd, 1H, J = 10.3, 3.7), 4.09 (dd, 1H, J = 14.5, 3.7), 2.97 (dd, 1H, J = 14.5, 10.3), 1.61 (d, 3H, J = 7.2, Ala-Me); ^{13}C NMR δ 168.9, 159.7, 151.0, 147.8, 141.0, 135.2, 129.5, 128.4, 128.1, 127.9, 127.1, 119.0, 54.1, 52.3, 37.9, 16.9; MS (ESI, positive mode) *m*/*z* calcd for M + H: 354.1, found 354.3.

(1*R*,4*S*)-9-Chloro-1-(2-methylethyl)-4-methyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (14). HPLC purity 90% (B, 14.22 min), isolated yield 24%. ^{1}H NMR δ 8.21 (d, 1H, J = 8.5), 7.69 (d, 1H, J = 2.0), 7.45 (dd, 1H, J = 8.6, 2.0), 6.71 (br s, 1H, NH), 5.44 (q, 1H, J = 7.2), 4.53 (d, 1H, J = 2.3), 3.14 (m, 1H), 1.63 (d, 3H, J = 7.2, Ala-Me), 1.24 (d, 3H, J = 7.3), 0.96 (d, 3H, J = 6.8); ^{13}C NMR δ 169.9, 159.9, 150.6, 148.0, 140.9, 128.3, 127.9, 127.0, 118.8, 58.3, 51.9, 28.9, 19.4, 17.2, 15.2; MS (ESI, positive mode) *m*/*z* calcd for M + H: 306.1, found 306.4.

(4*S*)-4-(2-Methylpropyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (15). HPLC purity 95% (B, 6.89 min), isolated yield 53%. ^{1}H NMR δ 8.28 (dd, 1H, J = 8.0, 1.4), 7.77 (ddd, 1H, J = 8.5, 7.2, 1.5), 7.64 (d, 1H, J = 7.8), 7.50 (td, 1H, J = 7.6, 1.1), 7.46 (br d, 1H, J = 4.6, NH), 5.51 (dd, 1H, J = 11.0, 3.0, Leu-CHN), 4.70 (d, 1H, J = 16.9), 4.48 (dd, 1H, J = 16.9, 5.3), 1.87−1.80 (m, 2H), 1.70 (m, 1H), 1.11 (d, 3H, J = 6.3), 1.04 (d, 3H, J = 6.3); ^{13}C NMR δ 169.8, 160.4, 148.2, 147.1 (s), 134.8, 127.3, 127.0 (d), 120.4 (s), 54.2 (d), 45.1, 40.7, 25.0, 23.0, 21.9; MS (ESI, positive mode) *m*/*z* calcd for M + H: 272.1, found 272.2.

(4*S*)-4-(2-Methylpropyl)-9-chloro-2*H*-pyrazino[2,1-*b*]-quinazoline-3,6-(1*H*,4*H*)dione (16). HPLC purity 96% (B, 11.38 min), isolated yield 58%. ^{1}H NMR δ 8.20 (d, 1H, J = 8.6), 7.63 (d, 1H, J = 2.0), 7.51 (br d, 1H, J = 4.6, NH), 7.45 (dd, 1H, J = 8.6, 2.0), 7.50 (ddd, 1H, J = 8.2, 7.0, 1.4), 5.46 (dd, 1H, J = 10.8, 4.0, Leu-CHN), 4.68 (d, 1H, J = 17.0), 4.47 (dd, 1H, J = 17.0, 5.3), 1.87−1.79 (m, 2H, Leu-CH and one of the CH_2), 1.69 (m, 1H, one of the Leu-CH_2), 1.11 (d, 3H, J = 6.3), 1.03 (d, 3H, J = 6.3); ^{13}C NMR δ 169.6, 159.7, 149.5, 148.1, 141.1 (s), 128.4, 127.9, 126.6 (d), 118.8 (s), 54.2 (d), 45.1, 40.6, 25.0, 23.0, 21.9; MS (ESI, positive mode) *m*/*z* calcd for M + H: 306.1, found 306.4.

(1*R*,4*S*)-1-Methyl-4-(2-methypropyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (17). HPLC purity 89% (A, 6.03 min), isolated yield 45%. ^{1}H NMR δ 8.27 (dd, 1H, J = 8.0, 1.1), 7.76 (td, 1H, J = 7.6, 1.5), 7.69 (d, 1H, J = 7.6, 2.0), 7.50 (td, 1H, J = 7.5, 1.1), 7.25 (s, 1H, NH), 5.56 (td, 1H, J = 7.6, 1.4), 4.76 (q, 1H, J = 6.6), 1.89−1.83 (m, 2H), 1.78 (d, 3H, J = 6.6), 1.75−1.69 (m, 1H), 1.11 (d, 3H, J = 6.3), 1.04 (d, 3H, J = 6.3); ^{13}C NMR δ 169.7, 160.5, 151.3, 147.0 (s), 134.6, 127.5, 127.3, 126.9 (d), 120.4 (s), 54.8, 49.2 (d), 40.3 (t), 25.0, 23.1, 21.9, 17.4; MS (ESI, positive mode) *m*/*z* calcd for M + H: 286.2, found 286.4.

(1*R*,4*S*)-9-Chloro-1-methyl-4-(2-methylpropyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (18). HPLC yield 74% (A, 9.49 min), isolated yield 52%. ^{1}H NMR δ 8.20 (d, 1H, J = 8.6), 7.73 (d, 1H, J = 2.0), 7.45 (dd, 1H, J = 8.6, 2.0), 6.55 (s, 1H, NH), 5.53 (ddd, 1H, J = 9.4, 5.6, 1.3), 4.75 (q, 1H, J = 6.6), 1.88−1.83 (m, 2H), 1.76 (d, 3H, J = 6.6), 1.70−1.66 (m, 1H), 1.11 (d, 3H, J = 6.3), 1.03 (d, 3H, J = 6.3); ^{13}C NMR δ 168.9, 159.9, 152.6, 147.9, 140.9 (s), 128.4, 128.0, 127.1 (d), 118.9 (s), 54.9, 49.3 (d), 40.3 (t), 25.0, 23.0, 21.8, 17.4; MS (ESI, positive mode) *m*/*z* calcd for M + H: 320.1, found 320.4.

(1*R*,4*S*)-9-Chloro-1-(phenylmethyl)-4-(2-methylpropyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (19). HPLC purity 95% (A, 14.23 min), isolated yield 40% and 4% (epimer), total 44%. ^{1}HNMR δ 8.20 (d, 1H, J = 8.6), 7.74 (d, 1H, J = 1.9), 7.48 (dd, 1H, J = 8.6, 2.0), 7.44−7.31 (m, 5H, Ph), 5.87 (s, 1H, NH), 5.49 (dd, 1H, J = 7.6, 6.3, Leu-CHN), 4.82 (dd, 1H, J = 10.4, 3.8, Phe-CHN), 4.10 (dd, 1H, J = 14.5, 3.7), 2.94 (dd, 1H, J = 14.5, 10.5), 1.79 (m, 2H), 1.64 (m, 1H), 1.08 (d, 3H, J = 6.3), 0.98 (d, 1H, J = 6.3); ^{13}C NMR δ 168.2, 159.9, 151.5, 147.8, 141.0, 135.3 (s), 129.6, 129.3, 128.4, 128.1, 127.9, 127.1 (d), 119.0 (s), 54.6, 53.9 (d), 40.7 ($Me_2CH\mathbf{C}H_2$), 37.8 ($Ph\mathbf{C}H_2$), 24.9 ($Me_2\mathbf{C}H$-), 23.0 (Me), 21.8 (Me); MS (ESI, positive mode) *m*/*z* calcd for M + H: 396.2, found 396.0.

(4*S*)-4-(2-Methylethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (20). HPLC purity 89% (B, 4.41 min), NMR yield 44%, isolated yield 54%. ^{1}H NMR δ 8.36 (dd, 1H, J = 8.0, 1.2), 7.80 (ddd, 1H, J = 8.3, 7.1, 1.4), 7.60 (d, 1H, J = 8.0), 7.54 (td, 1H, J = 7.6, 1.1), 7.30 (tt, 1H, J = 7.4, 2.3), 7.23 (t like, 2H, J = 7.6), 6.99 (d like, 2H, J = 7.0), 6.98 (overlapped 1H, NH), 5.61 (t, 1H, J = 4.3), 3.94 (dd, 1H, J = 16.9, 4.3), 3.49 (d, 2H, J = 4.4, Phe-CH_2), 2.81 (d, 1H, J = 16.9); ^{13}C NMR δ 168.8, 160.5, 148.1, 147.1, 135.0, 134.8, 129.8, 129.0, 128.0, 127.2, 127.0, 126.9, 120.1, 57.0, 44.5, 37.1; MS (ESI, positive mode) *m*/*z* calcd for M + H: 306.1, found 306.4.

(4*S*)-4-(Phenylmethyl)-9-chloro-2*H*-pyrazino[2,1-*b*]-quinazoline-3,6-(1*H*,4*H*)dione (21). HPLC purity 94% (A, 6.85 min), NMR yield 52%, isolated yield 67%. ^{1}H NMR δ 8.27 (d, 1H, J = 8.6), 7.59 (d, 1H, J = 1.9), 7.48 (dd, 1H, J = 8.6, 2.0), 7.31 (tt, 1H, J = 7.4, 2.2), 7.23 (t, 2H, J = 7.8), 7.18 (br s, 1H, NH), 6.97 (d, 2H, J = 7.0), 5.57 (t, 1H, J = 4.3, Phe-CHN), 3.93 (dd, 1H, J = 17.1, 4.3), 3.47 (d, 2H, J = 4.3), 2.79 (d, 1H, J = 17.1); ^{13}C NMR δ 168.6, 159.9, 149.5, 148.1, 141.3, 134.6, 130.0, 129.0, 128.5, 127.9, 126.6, 118.5, 57.0, 44.5, 37.0; MS (ESI, positive mode) *m*/*z* calcd for M + H: 306.1, found 306.4

(4*S*)-4-(Phenylmethyl)-10-methyl-2*H*-pyrazino[2,1-*b*]-quinazoline-3,6-(1*H*,4*H*)dione (22). HPLC purity 98% (A, 6.30 min), NMR yield 55%, isolated yield 64%. ^{1}H NMR δ 8.19 (d, 1H, J = 8.0), 7.63 (d, 1H, J = 7.2), 7.32−7.01 (m, 3H), 7.00 (d, 2H, J = 7.2), 6.96 (d, 1H, J = 3.6), 5.59 (t, 1H, J = 4.4), 3.96 (dd, 1H, J = 16.7, 4.3), 3.51 (dd, 1H, J = 13.9, 4.9, Phe-CH_2), 3.48 (dd, 1H, J = 13.9, 3.6), 2.86 (d, 1H, J = 16.7), 2.53 (s, 3H, Ar-CH_3); ^{13}C NMR δ ($CDCl_3$−CD_3O, v/v = 7/3) 168.6, 161.0, 146.8, 145.6, 135.4, 135.4, 134.4, 129.4, 128.5, 127.6, 126.5, 124.0, 120.0, 56.8 (d), 43.9 (t), 36.61 (t), 16.70 (q); MS (ESI, positive mode) *m*/*z* calcd for M + H: 320.1, found 320.5.

(1*R*,4*S*)-1-Methyl-4-(phenylmethyl)-2*H*-pyrazino[2,1-*b*]-quinazoline-3,6-(1*H*,4*H*)dione (23). HPLC purity 91% (B, 9.44 min), NMR yield 67%, isolated yield 63% and 5% (epimer), total 68%. ^{1}H NMR δ 8.34 (dd, 1H, J = 8.0, 1.2), 7.79 (ddd, 1H, J = 8.2, 7.2, 1.5), 7.65 (d, 1H, J = 7.6), 7.52 (dt, 1H, J = 7.3, 1.1), 7.28 (m, 1H), 7.24−7.20 (m, 3H), 7.05 (br s, 1H, NH), 7.00 (dd like, 2H, J = 8.4, 1.5), 5.65 (t, 1H, J = 4.6, Phe-CHN), 3.50 (dd, 1H, J = 13.9, 5.1), 3.47 (dd, 1H, J = 13.9, 3.8), 3.03 (q, 1H, J = 6.6, Ala-Me), 1.47 (d, 3H, J = 6.6, Ala-Me); ^{13}C NMR δ 168.7, 160.7, 151.5, 147.1, 135.1 (s), 134.8, 129.8, 128.9, 127.9, 127.5, 127.2, 126.9 (d), 120.1 (s), 57.7 (Phe-CHN), 49.0 (Ala-CHN), 37.0 (Phe-CH_2), 18.9 (Ala-Me); MS (ESI, positive mode) *m*/*z* calcd for M + H: 320.1, found 320.5.

(1*S*,4*S*)-1-Methyl-4-(phenylmethyl)-2*H*-pyrazino[2,1-*b*]-quinazoline-3,6-(1*H*,4*H*)dione (24). HPLC purity 75% (B, 8.60 min), NMR yield 57%, isolated yield 46% and 10% (epimer), total 56%. ^{1}H NMR δ 8.35 (ddd, 1H, J = 8.0, 1.6, 0.6), 7.79 (ddd, 1H, J = 8.0, 7.0, 1.6), 7.63 (ddd, 1H, J = 8.2, 1.1, 0.6), 7.52 (ddd, 1H, J = 8.0, 7.0, 1.2), 7.27 (br d, 1H, J = 2.5, NH), 7.27−7.20 (m, 3H), 6.96−6.94 (m, 2H), 5.51 (dd, 1H, J = 6.3, 3.5, Phe-CHN), 4.53 (qd, 1H, J = 7.1, 3.0, Ala-CHN), 3.60 (dd, 1H, J = 14.0, 5.8), 3.50 (dd, 1H, J = 14.0, 3.5), 0.76 (d, 3H, J = 7.1, Ala-Me); ^{13}C NMR δ 166.8, 160.9, 151.1, 147.2, 135.3 (s), 135.0, 130.2, 128.9, 127.7, 126.9, 126.9 (d), 120.0 (s), 57.0, 52.0, 36.9, 23.1.

(1*R*,4*S*)-1,10-Dimethyl-4-(phenylmethyl)-2*H*-pyrazino-[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (25). HPLC purity 93% (A, 8.65 min), NMR yield 24%, isolated yield 23%. ^{1}H NMR δ 8.18 (dd, 1H, J = 8.0, 0.7), 7.63 (d, 1H, J = 7.3), 7.41 (t, 1H, J = 7.6), 7.29 (m, 1H), 7.22 (t, 2H, J = 7.6), 7.01 (d, 2H, J = 7.4), 6.59 (br s, 1H, NH), 5.64 (t, 1H, J = 4.6), 3.51 (dd, 1H, J = 14.0, 5.4), 3.48 (dd, 1H, J = 14.0, 3.9), 3.04 (q, 1H, J = 6.6, Ala-CHN), 2.56 (s, 3H,

Ar-Me), 1.48 (d, 3H, $J = 6.6$, Ala-Me); ^{13}C NMR δ 168.6, 161.1, 150.0, 145.6, 136.2, 135.3, 135.2, 129.8, 128.9, 127.8, 126.8, 124.5, 120.1, 57.8, 49.0, 37.0, 18.8, 17.1; MS (ESI, positive mode) *m*/*z* calcd for M + H: 334.2, found 334.4.

(1*S*,4*S*)-9-Chloro-1-methyl-4-(phenylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (26). HPLC purity 81% (A, 8.53 min), NMR yield 52%, isolated yield 43% and 6% (epimer), total 49%. ^{1}H NMR δ 8.27 (d, 1H, $J =$ 8.5), 7.62 (d, 1H, $J = 2.0$), 7.45 (dd, 1H, $J = 8.6, 2.0$), 7.23−7.20 (m, 3H), 6.93−6.90 (m, 2H), 5.47 (dd, 1H, $J = 5.5$, 3.5, Phe-CHN), 4.51 (qd, 1H, $J = 7.0, 2.9$, Ala-CHN), 3.58 (dd, 1H, $J = 14.1, 5.6$), 3.48 (dd, 1H, $J = 14.0, 3.5$), 0.72 (d, 1H, $J = 7.0$); ^{13}C NMR ($CD_3OD-CDCl_3$) δ 166.2, 160.2, 152.9, 147.8, 141.3, 134.8 130.0, 128.8, 128.2, 127.7, 127.6, 126.1, 118.1, 56.8, 51.6, 36.5, 22.4; MS (ESI, positive mode) *m*/*z* calcd for M + H: 354.1, found 354.3.

(1*R*,4*S*)-9-Chloro-1-(2-methylpropyl)-4-(phenylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)dione (27). HPLC purity 77% (A, 12.99 min), isolated yield 22%. ^{1}H NMR δ 8.28 (d, 1H, $J = 8.6$), 7.63 (d, 1H, $J = 2.0$), 7.49 (dd, 1H, $J = 8.6, 2.0$), 7.30−7.25 (m, 1H), 7.18 (t like, 2H, $J = 7.5$), 6.91 (dd like, 2H, $J = 8.4, 1.3$), 5.81 (br s, 1H), 5.63 (t, 1H, $J = 4.1$, Phe-CHN), 3.46 (d, 2H, $J = 4.2$, Phe-CH_2), 2.73 (quintet-*d*, 1H, $J = 7.1, 2.4$, Val-$CHMe_2$), 2.67 (d, 1H, $J =$ 2.4, Val-CHN), 0.87 (d, 3H, $J = 7.3$, Val-Me), 0.70 (d, 3H, $J = 6.7$, Val-Me); ^{13}C NMR δ 168.3, 160.3, 151.4, 148.0, 141.1, 134.8 (s), 129.9, 128.9, 128.4, 128.0, 127.9, 127.0 (d), 118.5 (s), 58.0 (Val-CHN), 57.2 (Phe-CHN), 37.2 (Phe-CH_2), 29.4 (Val-**CH**Me_2), 19.0 (Val-Me), 14.9 (Val-Me); MS (ESI, positive mode) *m*/*z* calcd for M + H: 382.1, found 382.4.

Compound 29a and 29b. The tripeptide resin **28** (0.098 mmol) was treated with dehydrating reagent [Ph_3P/I_2/EtN-(*i*-Pr)$_2$, 4/3.5/8 equiv] at room temperature for 15 h. The resin was deprotected with 20% piperidine in CH_2Cl_2 and the dibenzofulvene-piperidine adduct isolated (26.6 mg, 103.5%). The free amine was refluxed in MeCN for 6 h and only gave a very small amount of dark residue (1.9 mg). The resin was acylated with Ac_2O (0.3 mL) and pyridine (0.3 mL) in CH_2Cl_2 (1.5 mL) for 23 h and then treated with a cleavage cocktail: CH_2Cl_2 (0.9 mL), Et_3SiH (0.1 mL), and TFA (1.0 mL) for 1.5 h. The resin was washed with CH_2Cl_2/MeOH and the combined filtrates were concentrated to give a residue (38 mg) which was purified by preparative TLC (10% and 30% MeOH in CH_2Cl_2, respectively) to give acid **29a** (8.9 mg, 26%) and methyl ester **29b** (6.3 mg, 18%), 44% overall from Wang resin. Acid **29a**: ^{1}H NMR (DMSO-d_6) δ 12.2 (very broad, 1H), 8.67 (d, 1H, $J = 9.2$), 8.58 (br s, 1H, Gly-CH_2NH), 8.39 (s, 1H), 8.32 (d, 1H, $J = 9.3, 2.6$), 4.17 (m, 1H, Ala-CHN), 3.93 (m, 2H, Gly-CH_2), 1.95 (s, 3H), 1.33 (d, 3H, $J = 6.0$, Ala-CH_3); ^{13}C NMR (DMSO-d_6) δ 175.5, 170.1, 169.7, 165.1, 143.3, 141.2 (s), 126.2 (d), 124.0 (s), 123.4, 119.8 (d), 50.5 (d), 43.6 (t), 22.4, 17.6 (q); MS (ESI, positive mode) *m*/*z* calcd for [M + Na]: 375.1, found 375.1; *m*/*z* (negative mode) calcd for [M − H]: 351.0, found 351.1. Methyl ester **29b**: ^{1}H NMR (DMSO-d_6) δ 12.00 (br s, 1H, NH), 9.59 (d, 1H, $J = 6.4$, Ala-CHNH), 8.78 (d, 1H, $J =$ 9.3), 8.78 (d, 1H, $J = 2.7$), 8.65 (t, 1H, $J = 5.8$, Gly-CH_2-NH), 8.44 (dd, 1H, $J = 9.3, 2.6$), 4.49 (m, 1H, Ala-CHN), 3.84 (d, 2H, $J = 3.84$, Gly-CH_2), 1.96 (s, 3H), 1.45 (d, 3H, $J = 7.3$, Ala-CH_3); ^{13}C NMR (DMSO-d_6) δ 172.4, 170.4, 169.5, 166.5, 144.3, 141.3 (s), 127.8, 124.3, 119.8 (d), 119.0 (s), 52.0 (q), 48.5 (d), 43.8 (t), 22.2, 16.3 (q); MS (ESI, positive mode) *m*/*z* calcd for [M + Na]: 389.1, found 389.0; *m*/*z* (negative mode) calcd for [M − H]: 365.1, found 365.1.

(5*S*)-1,2-Dihydro-5,11-dimethyl[1,4]diazepino[7,1-*b*]-quinazolin-4,7-(3*H*,5*H*)dione (31). HPLC purity 92% (B, 5.11 min), isolated yield 10%. ^{1}H NMR δ 8.12 (dd, 1H, $J =$ 7.3, 0.7), 7.59 (dd, 1H, $J = 7.3, 0.7$), 7.36 (t, 1H, $J = 7.7$), 6.42 (q, 1H, $J = 7.5$), 6.38 (br s, 1H, NH), 3.63−3.59 (m, 2H, β-Ala-CH_2N), 3.54−3.46 (m, 1H), 3.36−3.31 (m, 1H), 2.59 (s, 3H, Ar-Me), 1.76 (d, 3H, $J = 7.5$, Ala-Me); ^{13}C NMR δ 171.6, 161.8, 153.5, 145.5, 135.6, 135.3, 126.8, 125.0, 120.2, 52.8 (Ala-CHN), 41.7 (β-Ala-CH_2N), 35.8 (β-Ala-CH_2), 20.4 (Ala-Me), 17.1 (Ar-Me); MS (ESI, positive mode) *m*/*z* calcd for M + H: 258.1, found 258.3.

(5*S*)-1,2-Dihydro-5-(2-methylpropyl)[1,4]diazepino[7,1-*b*]quinazolin-4,7-(3*H*,5*H*)dione (33). HPLC purity 86% (A, 4.53 min), NMR yield 8%, isolated yield 9%. ^{1}H NMR δ 8.29 (d, 1H, $J = 8.0$), 7.76 (td, 1H, $J = 7.6, 1.1$), 7.62 (d, 1H, $J = 8.1$), 7.49 (t, 1H, $J = 7.6$), 6.38 (dd, 1H, $J = 8.8$, 5.1, Leu-CHN), 6.09 (s, 1H, NH), 3.65−3.58 (m, 1H), 3.61 (s, 2H, CH_2N), 3,25 (m, 1H), 2.16 (ddd, 1H, $J = 13.9, 8.5$, 5.3), 1.88 (ddd, 1H, $J = 14.0, 8.8, 5.4$), 1.64−1.57 (m, 1H, Leu-CH), 1.05 (d, 3H, $J = 6.5$), 0.93 (d, 3H, $J = 6.6$); ^{13}C NMR δ 170.9, 161.7, 155.2, 146.9 (s), 134.8, 127.6, 127.3, 126.8 (d), 120.2 (s), 55.6 (Leu-CHN), 45.1 (leu-CH_2), 41.8 (β-Ala-CH_2N), 35.4 (β-Ala-CH_2), 25.7 (Leu-CH), 22.9 (Me), 22.2 (Me); MS (ESI, positive mode) *m*/*z* calcd for M + H: 286.2, found 286.4.

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Supporting Information Available. ^{1}H NMR spectra for **6**, **8**−**10**, **12**−**16**, **18**−**22**, **25**−**26**, **29a**−**b**, and **33** and ^{13}C NMR spectra for **9**−**11**, **17**, **23**−**24**, **27**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Abbreviations: Ala = Alanine, EDC = 1-ethyl-3-(3-(diethylamino)-propyl)carbodiimide·HCl, Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl, Gly = glycine, Leu = leucine, Phe = phenylalanine, Trp = tryptophan.

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