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

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Biomimetic total syntheses of glyantrypine, fumiquinazoline F, fumiquinazoline G, and fiscalin B were achieved in four steps from tryptophan methyl ester. In the key step, the anthranilamide residue in a linear tripeptide is dehydrated to a benzoxazine by reaction with triphenylphosphine, iodine, and a tertiary amine. The benzoxazines subsequently undergo rearrangement to the natural products via an amidine intermediate. This dehydrative oxazine to quinazoline route is applicable to a broad range of *N*-acylanthranilamides, including sterically hindered cases.

The elements of anthranilic acid and tryptophan are incorporated into a variety of fungal quinazoline metabolites,[2] many of which display significant biological activity. Recently, four examples were isolated in which the quinazoline skeleton is fused onto a third amino acid in diketopiperazine-like fashion: glyantrypine (**1**, Figure 1) from *Aspergillus clavatus*,[3] fumiquinazolines F (**2**) and G (**3**) from *Aspergillus fumigatus*,[4] and fiscalin B (**4**) from *Neosartorya fischeri* and *Corynascus setosus*.[5]

We were interested in a concise synthetic route to the tricyclic core of these alkaloids, which may be viewed as one of Nature's solutions for the display of amino acid side-chains in a peptidomimetic scaffold. The fumiquinazolines are cytotoxic against the P388 leukemia cell line, while fiscalin B is a substance P antagonist, suggesting that analogues based on this template might result in novel biologically active compounds. Furthermore, a synthesis of these natural products would also pave the way toward more complex members in this series, which feature further oxidative transformations of the indole and quinazoline rings. Here, we describe our efforts[6] culminating in the total synthesis of **1**−**4**. Our route has also been translated[7] to solid-phase conditions for the parallel array synthesis of analogues.

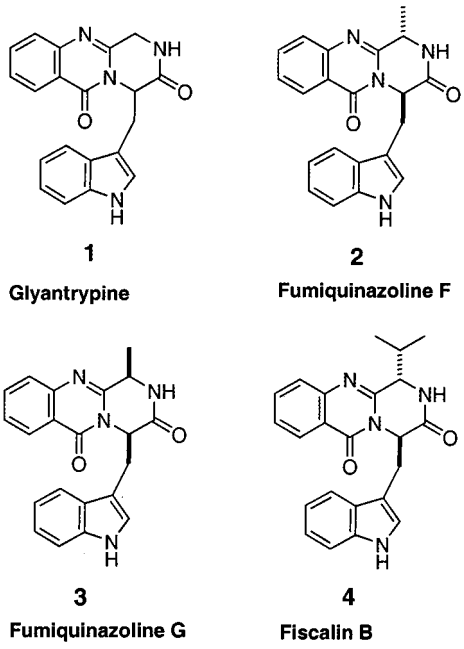

Figure 1.

Results and Discussion

Our retrosynthesis of fumiquinazoline G was based on a possibly biomimetic dehydration of tripeptide **5** (Figure 2). While the regioselectivity was open to question, we believed it would occur in the desired sense due to the differential bias imparted by the anthranilate. Thus, only one amide NH involves an aniline instead of an aliphatic amine, and similarly only one amide involves a benzoic acid instead of an aliphatic carboxylate. Another retrosynthetic candidate was **6**, which differs from **5** in the timing of ring formation: quinazoline dehydration first, followed by diketopiperazine-like cyclization. This alternative appeared synthetically more tractable. In addition, this route proceeds via two six-membered ring closures, rather than an entropically more demanding macrocyclic intermediate as in **5**. Soon after we had set the synthesis of linear tripeptide **6** as our immediate goal, a total

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(1) Abbreviations: Ala = Alanine, EDC = 1-ethyl-3-(3-(diethylamino)-propyl)carbodiimide·HCl, Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl, Gly = glycine, Phe = phenylalanine, PyBrOP = bromo-tris-pyrrolidinophosphonium hexafluorophosphate, Trp = tryptophan, Val = valine.

(2) For recent reviews, see (a) Michael, J. P. *Nat. Prod. Rep.* **1998**, *15*, 595−606. (b) Johne, S. In *Rodd's Chemistry of Carbon Compounds (Supplements to the 2nd edition)*; Ansell, M. F., Ed.; Elsevier: Amsterdam, 1995; Vol. IV I/J, pp 223−240.

(3) Penn, J.; Mantle, P. G.; Bilton, J. N.; Sheppard, R. N. *J. Chem. Soc., Perkin Trans 1* **1992**, 1495−1496.

(4) (a) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621−1624. (b) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345−2353.

(5) (a) Wong, S.-M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545−553. (b) Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1843−1848.

(6) (a) Communication: Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432−2433. (b) Portions of this work were presented by H. Wang at the 12th International Conference on Organic Synthesis, Venezia, Italy, Jun 28−Jul 2, 1998.

(7) Wang, H.; Ganesan, A. *J. Comb. Chem.* **2000**, *2*, in press.

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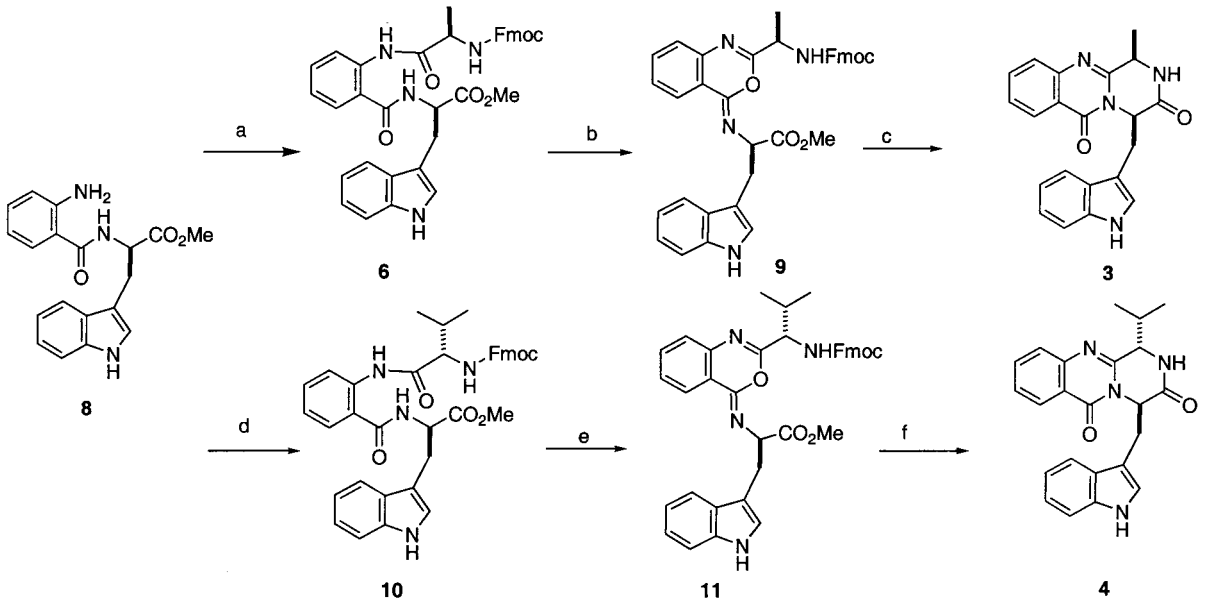
Scheme 1[a]



[a] Reagents and conditions: (a) Fmoc-D-Ala-Cl (1.2 equiv), CH_2Cl_2/aq Na_2CO_3, rt, 1 h, 86%; (b) Ph_3P (5.0 equiv), I_2 (4.9 equiv), EtN(*i*-Pr)$_2$ (10.1 equiv), rt, 2.5 h, 65%; (c) (i) 20% piperidine in CH_2Cl_2, rt, 12 min; (ii) MeCN, reflux 1.5 h, 78.5%; (d) Fmoc-L-Val-Cl (1.4 equiv), CH_2Cl_2/aq Na_2CO_3, rt, 2 h, 90%; (e) Ph_3P (5.0 equiv), I_2 (4.9 equiv), EtN(*i*-Pr)$_2$ (10.4 equiv), rt, 8 h, 82%; (f) (i) 20% piperidine in CH_2Cl_2, rt, 12 min; (ii) MeCN, DMAP (1.3 equiv), reflux 19 h, 72%.

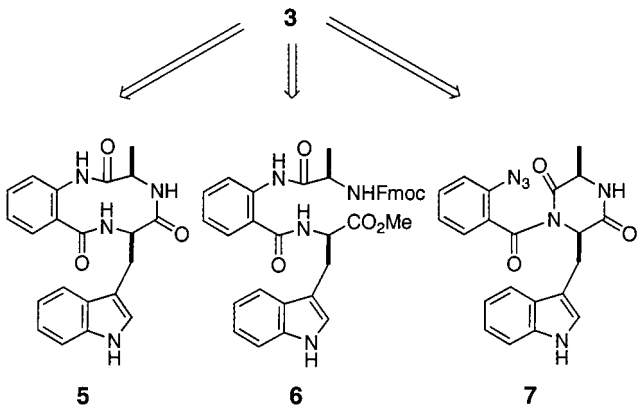


Figure 2.

synthesis of *ent*-fumiquinazoline G was reported[8] which involved disconnection to **7**, i.e., annulation of the quinazoline onto a diketopiperazine. In practice, the aza-Wittig reaction used required significant protecting group manipulation, and the overall synthesis takes 12 steps from Cbz-L-tryptophan.

The direct coupling of D-tryptophan methyl ester[9] with anthranilic acid mediated by EDC[10] gave dipeptide **8** in 93% yield (Scheme 1).[11] Condensation of **8** and Fmoc-D-alanine with PyBroP as acylating agent occurred in only 35% yield; instead, use of the more reactive Fmoc-D-alanine acid chloride[12] under two-phase Schotten−Baumann conditions proceeded smoothly to yield **6**. Previous protocols[13] for the transformation of linear peptides such as **6** to quinazolines are highly susceptible to steric hindrance around the cyclizing amide groups and unlikely to work with our compound.[14] Thus, we anticipated having to survey a broad range of dehydrating reagents. In the event, this proved to be unnecessary. Our first trial was a Ph_3P/I_2/tertiary amine combination recently used by Wipf[15] to dehydrate β-keto amides to oxazoles. Since the acidity of our anthranilamide would approximate a ketone, we tested these conditions with our substrate. Provided a large excess of reagents was used, a major product was obtained in good yield (later identified as oxazine **9**, vide infra), which upon treatment with 20% piperidine in dichloromethane afforded the natural product (−)-fumiquinazoline G (**3**). In addition, a small amount (5%) of the trans epimer (i.e., fumiquinazoline F, **2**) was obtained. The optical activity of this material was almost zero, indicating that either chiral center is equally capable of epimerization. The extent of formation of **2** places an upper limit for a single epimerization event, while the probability of both centers racemizing simultaneously to contaminate **3** with its enantiomer is significantly lower.[16]

For the synthesis of fiscalin B, we coupled **8** with Fmoc-L-valine acid chloride to yield tripeptide **10**. Following Ph_3P/I_2 dehydration to oxazine **11** and Fmoc deprotection by piperidine, an analogous cyclization to the natural product did not occur at room temperature, either in solution or during silica purification. The solvent was

(8) He, F.; Snider, B. B. *Synlett* **1997**, 483−484.

(9) In our initial studies, we used the cheaper L-amino acids, leading to the total synthesis of *ent*-fumiquinazoline G, which is summarized in the Experimental Section.

(10) (a) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742−5743. (b) Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240−1256.

(11) Alternatively, tryptophan methyl ester was refluxed with isatoic anhydride in 1,2-dichloroethane to give **8** in 93% yield.

(12) Carpino, L. A.; Cohen, B. J.; Stephens, K. E., Jr.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732−3734.

(13) For example, see: (a) Büchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084−5086. (b) Ohnuma, T.; Kimura, Y.; Ban, Y. *Tetrahedron Lett.* **1981**, *22*, 4969−4972. (c) Nakagawa, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc.* **1983**, *105*, 3709−3710.

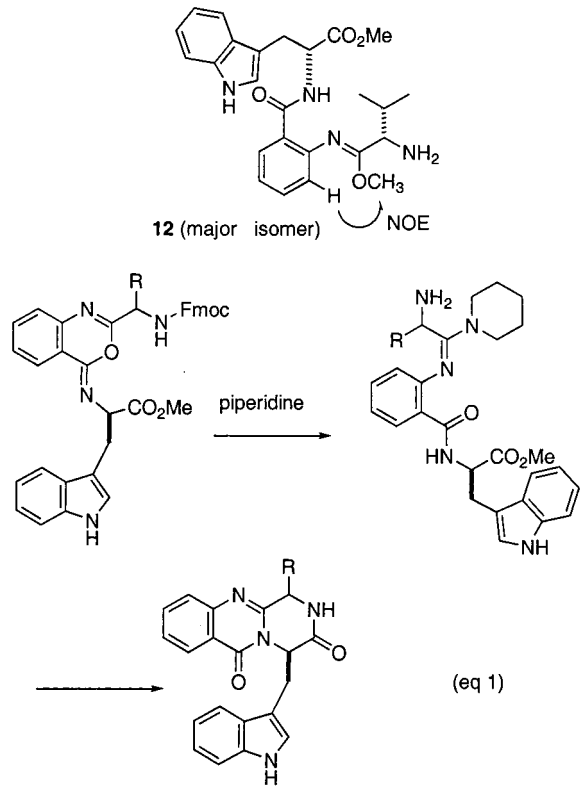
(14) He and Snider (ref 8) were unsuccessful with such reactions on a similar peptide, although details are not given.

(15) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.

(16) We did not observe any enantiomer by NMR analysis with chiral lanthanide shift reagents (detection limit of 2% from control experiments).

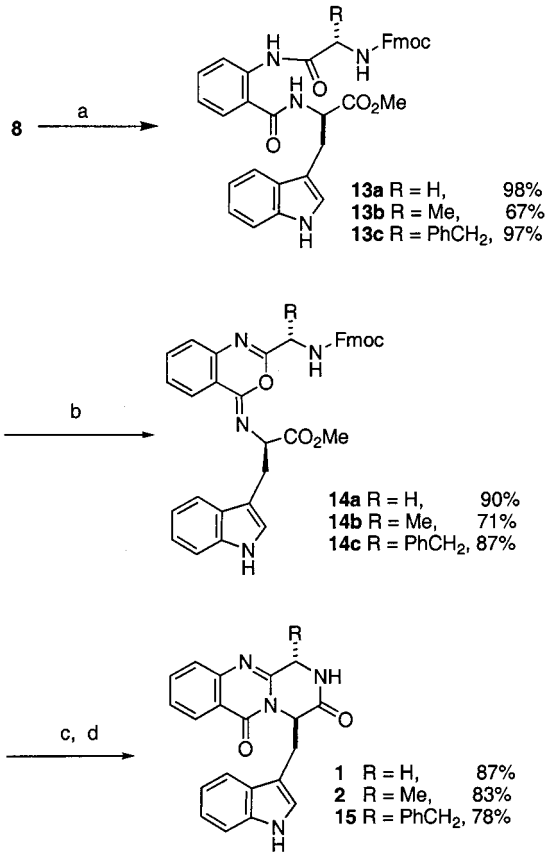
evaporated off, and the residues were washed with hexanes to remove the dibenzofulvene−piperidine adduct. Refluxing the residue overnight in toluene/triethylamine (40:1) gave 36% of fiscalin B (**4**). The yield was significantly improved by switching to a more polar solvent: refluxing in acetonitrile with DMAP for 19 h afforded fiscalin B in 72% yield (49% overall for the four steps from D-tryptophan methyl ester).

In these sequences, we originally believed the Ph_3P/I_2/tertiary amine dehydration of **6** and **10** resulted in a quinazoline, while the subsequent piperidine treatment would release a free amine which cyclizes to the natural product. However, in the fiscalin B series, there were significant differences in ^{15}N chemical shift between **11** and model quinazolines. Attempted silica purification after Fmoc deprotection yielded only linear tripeptide **10** with the Fmoc group removed, while refluxing the crude material in methanol with 1.3 equiv of DMAP for 60 h gave 23% of a ring-opened methanol adduct identified as imino ether **12** as well as 40% of fiscalin B. All these results are consistent with the Ph_3P/I_2/tertiary amine dehydration producing a relatively unstable oxazine as in an earlier publication[17] by Mazurkiewicz. Meanwhile, both the Snider and Hart groups have independently repeated[18] our quinazoline synthesis, and Snider has demonstrated the mechanism (eq 1) for the conversion of the initially formed oxazine to the quinazoline upon piperidine treatment.



Our choice of the Fmoc protecting group was based on its extensive use in solution- and solid-phase peptide synthesis and the ease of formation of stable amino acid chlorides, as well as our past experience[19] in diketopiperazine cyclizations. With hindsight, this selection turned out to be crucial for success, as only a deprotection scheme using a nucleophilic amine would have caused ring-opening of the oxazine to the amidine. The oxazine−quinazoline rearrangement was mediated by silica in Snider's case, and a trimethylaluminum−thiophenolate complex in Hart's. We find that heating[20] of the piperidine amidine is sufficient to effect this reaction, as in the fiscalin B synthesis described above. The synthesis of fumiquinazoline G (**3**) was also repeated with thermal cyclization for the last step. Refluxing the crude amidine in acetonitrile for 1.5 h with DMAP resulted in almost complete conversion to **3**. We then found that the addition of DMAP was not required; refluxing in acetonitrile alone for 1.5 h afforded **3** in 78.5% yield, together with 4.7% of racemized **2**. Similarly, we have also synthesized the natural products (−)-glyantrypine[21] (**1**), fumiquinazoline F[22] (**2**), and an unnatural analogue **15** with a phenylalanine side-chain (Scheme 2). Overall yields for **1**, **2**, and **15** from D-tryptophan methyl ester were 71, 37, and 61% respectively.

Scheme 2[a]



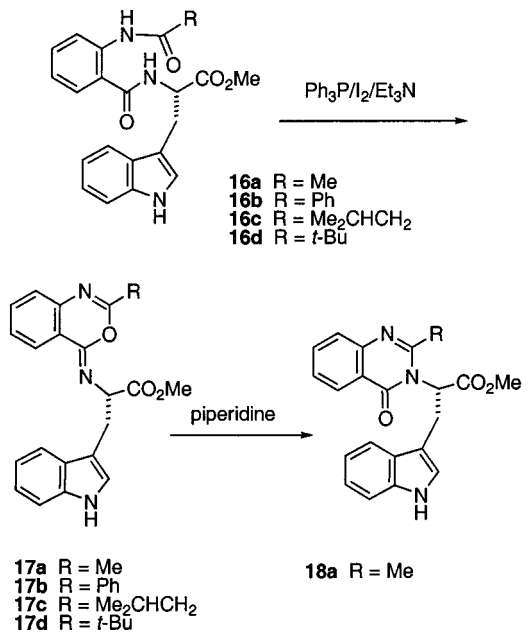
[a] Reagents and conditions: (a) Fmoc-NH(R)CHCOCl, CH_2Cl_2/aq Na_2CO_3, rt; (b) Ph_3P, I_2, $EtN(i\text{-}Pr)_2$, rt; (c) 20% piperidine in CH_2Cl_2, rt; (d) MeCN, reflux.

Our oxazine−quinazoline synthesis was also tested with simple amides **16a**−**d** (Scheme 3). With oxazine **17a**,

(17) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973−980.
(18) (a) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397−1399. (b) Hart, D. J.; Magomedov, N. *Tetrahedron Lett.* **1999**, *40*, 5429−5432.
(19) (a) Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1997**, *38*, 4327−4328. (b) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647−1649.

(20) Although we use a neutral solvent, it is possible that the reaction is catalyzed by the piperidine byproduct released.
(21) The absolute configuration of the natural product was not assigned, and we were unable to obtain a sample.
(22) For both fumiquinazoline F and fiscalin B, the melting point and optical rotation for our synthetic material is significantly higher than reported for the natural product, probably reflecting the difficulty of purifying the limited amount isolated and obtaining accurate measurements.

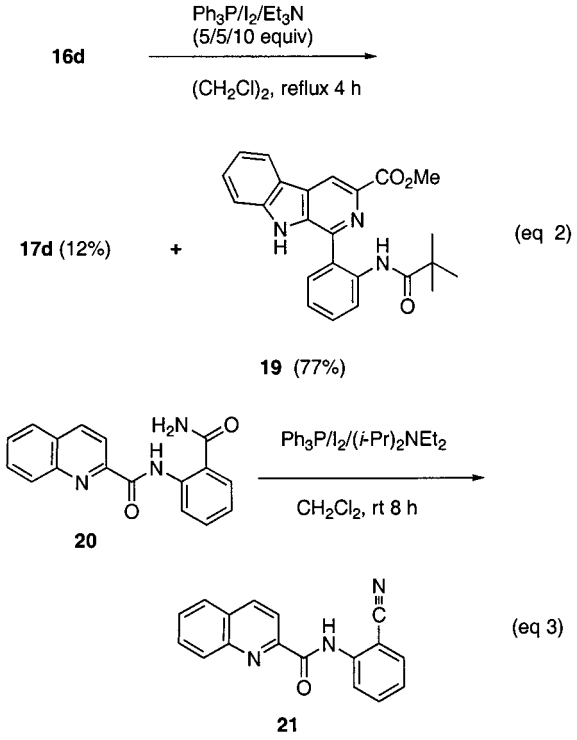
Scheme 3



piperidine treatment gave a mixture of piperidine amidine, quinazoline **18a**, and decomposition back to acetamide **16a** in a 86:8:6 ratio. Refluxing this crude mixture in 1:1 acetonitrile/1,2-dichloroethane for 15 h resulted in 93% yield of quinazoline **18a**, with 5% of acetamide **16a** recovered. Instead, reaction of the crude mixture under Snider-type conditions (silica, EtOAc/CH_2Cl_2/MeOH 67:20:13, rt 15 h) only gave a 61:33:6 mixture of amidine, **18a**, and **16a**, respectively.

Only the extremely hindered pivalamide **16d** did not provide a satisfactory yield of oxazine **17d** with our usual Ph_3P/I_2 protocol at room temperature. Carrying out the reaction in refluxing dichloroethane resulted in formation of a fluorescent compound, identified as β-carboline **19** (eq 2). Under these harsher conditions, Bischler–Napieralski-like electrophilic substitution of the indole apparently becomes the major pathway, and the resulting dihydro-β-carboline further aromatized to **19**. The only other limitation we have encountered in our oxazine-forming reaction is with primary amides. In a projected synthesis of luotonin A (eq 3), treatment of diamide **20**[23] under our dehydrating conditions yielded nitrile **21**. The ability of Ph_3P/I_2 combinations to dehydrate primary amides to nitriles is precedented,[24] and is presumably too facile for the oxazine cyclization[25] to compete.

We screened our quinazolines in filter disk antibacterial (tested strains: *Staphylococcus aureus* S1, *Escherichia coli* 15153, and *Pesudomonas aeruginosa* 9027) and antifungal (tested strain: *Candida albicans* 1060) assays, but they did not display any activity. Glyantrypine (**1**), fiscalin B (**4**), and analogue **15** were submitted to the National Cancer Institute's 60-cell line in vitro antitumor assay. The mean panel IC_{50} values were respectively >100 μM, 19 μM, and 15 μM. These results imply that a large substituent on the quinazoline ring is beneficial for



activity and also show that fiscalin B, previously reported only as a substance P antagonist, has cytotoxic activity.

Summary

Dehydration of anthranilamides features in a number of secondary metabolite biosynthetic pathways, such as the fumiquinazolines as well as compounds like the cholecystokinin antagonist asperlicin and the multidrug-resistance reversing agent ardeemin. For the first time, we have devised a general and mild procedure with simple reagents for accomplishing such dehydrations via oxazine intermediates. The power of this approach has resulted in biomimetic total syntheses of **1**–**4** which are nearly ideal in terms of step efficiency. It is difficult to imagine assembling a linear tripeptide and performing two intramolecular cyclizations in less than the four chemical operations we have taken. Two other groups have already incorporated our methodology for their own synthetic targets.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification, except for CH_2Cl_2, which was distilled from CaH_2. TLC was carried out on precoated plates: analytical (Merck Kieselgel 60 F_{254}), spots visualized with UV light and iodine vapor; preparative-scale (Aldrich, silica, 1 mm thick). Flash column chromatography was performed with silica (Merck EM9385, 230–400 mesh). Melting points were taken on a Büchi 535 melting point apparatus (capillary method) and are uncorrected. ^1H and ^{13}C NMR were recorded at 400 or 300 and at 100 or 75 MHz, respectively, in $CDCl_3$ unless otherwise mentioned. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane, ^{15}N chemical shifts are calibrated with 80% $MeNO_2$ in $CDCl_3$ as 380.2 ppm. Protons were assigned according to COSY, HMQC, and/or 1D-NOE experiments; coupling constant (J) is reported in hertz. Carbons were assigned according to DEPT and/or HMQC experiments and multiplicity was represented as s = quaternary C, d = CH, t = CH_2 and q = CH_3. For the

(23) Prepared in 90% yield by acylation of anthranilamide with quinaldic acid chloride [prepared from the acid (1 equiv) and $SOCl_2$)] in the presence of Et_3N (2.6 equiv) in CH_2Cl_2.

(24) Rauter, A. P.; Fernandes, A. C.; Figueiredo, J. A. *J. Carbohydr. Chem.* **1998**, *17*, 1037–1045.

(25) For our successful synthesis of luotonin A by another approach, see: Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097–9098.

mass spectra data, *a* and *b* represent mass fragments in case of $a + b$ = molecular weight.

***N*-(2-Aminobenzoyl)-D-tryptophan Methyl Ester (8).** To a mixture of D-tryptophan methyl ester (1.44 g, 6.60 mmol) and EDC (2.99 g, 15.6 mmol) in acetonitrile (70 mL) was added anthranilic acid (1.82 g, 13.2 mmol) in 10 portions over 75 min at room temperature with stirring. After being stirred for an additional 100 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2/aqueous Na_2CO_3, extracted with CH_2Cl_2 (×3), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (eluant 1% MeOH in CH_2Cl_2) to yield **8** as a white solid (2.07 g, 93%): mp 136−137 °C; IR ν_{max} (KBr) 1745, 1727, 1645, 1611, 1582 cm^{-1}; ^1H NMR δ 8.12 (br s, 1H, D_2O exchangeable), 7.57 (d, 1H, J = 7.9), 7.36 (d, 1H, J = 8.0), 7.21−7.15 (m, 3H), 7.10 (t, 1H, J = 7.4), 7.02 (d, 1H, J = 2.3), 6.65 (dd, 1H, J = 8.5, 1.1), 6.59 (br d, 1H, J = 8.4, D_2O exchangeable), 6.56 (t, 1H, J = 7.5), 5.08 (dd, 1H, J = 12.9, 5.3), 3.72 (s, 3H), 3.43 (d, 2H, J = 5.4); ^{13}C NMR δ (CD_3OD) 174.5, 171.6, 150.2, 138.0 (s), 133.34 (d), 129.2 (d), 128.7 (s), 124.4, 122.5, 119.9, 119.2, 118.1, 117.3 (d), 117.1 (s), 112.4 (d), 110.9 (s), 55.1, 52.7, 28.2.

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-D-alanyl-2-aminobenzoyl-D-tryptophan Methyl Ester (6).** To a solution of compound **8** (0.368 g, 1.09 mmol) in dry CH_2Cl_2 (30 mL) was added Fmoc-D-Ala-Cl[12] (0.462 g, 1.34 mmol). The mixture was stirred for 4 min, followed by addition of aqueous Na_2CO_3 (1 M, 20 mL, 20 mmol). After being stirred for a total of 1 h, the mixture was extracted with CH_2Cl_2 (×4), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (eluant 0% to 10% MeOH in CH_2Cl_2) to give **6** as a white solid (0.591 g, 86%): mp 192−194 °C (dec); $[\alpha]^{30}_D$ = +57.3 (*c* 0.49, MeOH); IR ν_{max} ($CHCl_3$) 3477, 3432, 1726, 1692, 1588 cm^{-1}; ^1H NMR δ 11.48 (br s, 1H), 8.58 (d, 1H, J = 8.4), 8.13 (br s, 1H), 7.76 (br d, 2H, J = 7.5), 7.66 (br d, 1H, J = 7.1), 7.59 (br t, 1H, J = 7.4), 7.49−7.26 (m, 8H), 7.17 (t, 1H, J = 7.2), 7.06 (t, 1H, J = 7.6), 7.00 (t, 1H, J = 7.7), 6.96 (br s, 1H), 6.71 (br d, 1H, J = 7.6), 5.55 (d, 1H, J = 6.8), 5.03 (dt, 1H, J = 7.6, 5.3), 4.44 (m, 2H), 4.36 (m, 1H), 4.26 (t, 1H, J = 7.0), 3.73 (s, 3H), 3.40 (dd, 1H, J = 15.3, 5.8), 3.34 (dd, 1H, J = 15.3, 5.3), 1.53 (d, 3H, J = 7.0); ^{13}C NMR ($CDCl_3/CD_3OD$, 6:1) δ 172.7, 172.2, 168.8, 156.6, 144.2, 143.8, 141.4, 138.6, 136.4, 132.8, 127.8, 127.5, 127.4, 127.2, 125.4, 125.3, 123.6, 123.4, 123.3, 122.1, 121.6, 120.9, 120.0, 119.5, 118.3, 111.7, 109.2, 67.3, 53.6, 52.7, 52.2, 47.3, 27.3, 18.4; MS (EI) *m*/*z* (relative intensity %) 408 ([M + H − Fmoc]$^+$, 5), 130 (100). Anal. Calcd for $C_{37}H_{34}N_4O_6$: C, 70.46; H, 5.43; N, 8.88. Found: C, 70.19; H, 5.46; N, 8.84.

***N*-{2-[(*R*)-1-*N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-aminoethyl]-4*H*-3,1-benzoxazin-4-ylidene}-D-tryptophan Methyl Ester (9).** To a solution of compound **6** (0.179 g, 0.284 mmol) in CH_2Cl_2 (15 mL) were added Ph_3P (0.370 g, 1.41 mmol), I_2 (0.352 g, 1.39 mmol), and *N*,*N*-diisopropylethylamine (0.50 mL, 2.87 mmol). The reaction mixture was stirred at room temperature for 2.5 h, quenched with aqueous Na_2CO_3, and extracted with CH_2Cl_2 (×3), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (40−50% AcOEt/hexanes with 2% Et_3N) to give **9** as a white solid (0.113 g, 65%): mp 199−200 °C; $[\alpha]^{30}_D$ = +121 (*c* 0.22, $CHCl_3$); IR ν_{max} (KBr) 1719, 1692, 1642 cm^{-1}; ^1H NMR δ 8.20 (d, 1H, J = 7.6), 7.76 (br d, 3H, J = 7.4), 7.67 (br d, 1H, J = 7.7), 7.61 (br t, 2H, J = 7.3), 7.54 (td, 1H, J = 7.7, 1.5), 7.40−7.26 (m, 6H), 7.18 (br d, 1H, J = 7.8), 7.09 (t, 1H, J = 7.6), 7.03 (t, 1H, J = 7.6), 6.99 (br s, 1H), 5.31 (d, 1H, J = 6.8), 4.88 (dd, 1H, J = 8.4, 5.0), 4.50−4.35 (m, 3H), 4.22 (t, 1H, J = 6.5), 3.71 (s, 3H), 3.47 (dd, 1H, J = 14.2, 4.8), 3.25 (dd, 1H, J = 14.3, 8.5), 1.13 (d, 3H, J = 6.7); ^{13}C NMR (DMSO-d_6) δ (at least two rotamers) 174.0, 171.9, 165.9, 160.2, 155.7, 147.1, 143.7, 142.6, 141.1, 139.4, 137.4, 136.1, 136.0, 133.7, 133.1, 131.0, 129.9, 128.8, 128.3, 127.6,127.4, 127.3, 127.0, 126.0, 125.6, 125.2, 125.1, 123.7, 123.6, 121.3, 120.9, 120.8, 120.1, 120.0, 118.7, 118.5, 118.4, 118.2, 118.0, 111.4. 110.3, 110.0, 65.7, 59.3, 52.3, 51.7, 49.0, 46.6, 29.0, 26.7, 17.3. Anal. Calcd for $C_{37}H_{32}N_4O_5$: C, 72.53; H, 5.26; N, 9.14. Found: C, 72.30; H, 5.16; N, 9.01.

(1*R*,4*R*)-4-(1*H*-Indol-3-ylmethyl)-1-methyl-2*H*-pyrazino-[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (3, fumiquinazoline G). Oxazine **9** (113 mg, 0.184 mmol) was treated with CH_2Cl_2 (4.0 mL) and piperidine (1.0 mL) at room temperature for 12 min, followed by solvent evaporation. The vacuum-dried crude residue was dissolved in MeCN (10 mL) and refluxed for 2 h (after 1 h, TLC showed no amine left). The reaction mixture was purified by preparative TLC (AcOEt: MeOH: CH_2Cl_2 = 50:5:45) to afford **3** (51.8 mg, 78.5%) and epimer **2** (3.1 mg, 4.7%). **3**: mp 158 °C; $[\alpha]^{26}_D$ = −456 (*c* 0.585, $CHCl_3$) [lit.[4b] mp. 119−121 °C; $[\alpha]_D$ = −462.8 (*c* 0.62, $CHCl_3$)]; IR ν_{max} ($CHCl_3$) 3476, 3396, 1682, 1595 cm^{-1}; ^1H NMR δ 8.39 (dd, 1H, J = 7.8, 1.6), 8.01 (br s, 1H), 7.79 (td, 1H, J = 7.7, 1.5), 7.57 (d, 1H, J = 8.3), 7.54 (td, 1H, J = 8.1, 1.0), 7.29 (dd, 1H, J = 11.5, 7.7), 7.10 (td, 1H, J = 7.2, 1.1), 6.87 (td, 1H, J = 7.2, 1.1), 6.74 (d, 1H, J = 2.4), 5.97 (br s, 1H), 5.57 (dd, 1H, J = 5.1, 3.4), 4.46 (qd, 1H, J = 7.0, 2.9), 3.81 (dd. 1H, J = 15.0, 5.2), 3.74 (dd, J = 15.0, 3.3), 0.53(d, 3H, J = 7.0); ^{13}C NMR δ 167.4, 161.0, 151.2, 147.2, 135.8, 134.8, 127.9, 126.9, 126.8, 123.7, 122.3, 120.1, 119.9, 118.6, 111.1, 109.4, 56.9, 27.1, 22.8; MS (EI) *m*/*z* (relative intensity %) 358 (M^+, 56), 229 (*a* + H, 49), 130 (*b*, 100); HRMS (EI) calcd for $C_{21}H_{18}N_4O_2$: 358.1430; found: 358.1415. Epimer **2**: $[\alpha]^{30}_D$ = −2.4 (*c* 0.15, $CHCl_3$), its NMR spectra were identical to those of fumiquinazoline F.[4b]

(1*S*,4*S*)-4-(1*H*-Indol-3-ylmethyl)-1-methyl-2*H*-pyrazino-[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione [*ent*-3, (+)-fumiquinazoline G]. *ent*-**9** was prepared in a similar manner as that for **9**. *ent*-**9** was treated with 20% piperidine in CH_2Cl_2 and then the residue purified by preparative TLC to give *ent*-**3** (75%) and epimer *ent*-**2** (6%). *ent*-**3**: $[\alpha]^{26}_D$ = +440 (*c* 0.425, $CHCl_3$) (lit.[8] $[\alpha]_D$ = +446). Epimer *ent*-**2**: $[\alpha]^{30}_D$ = +87.8 (*c* 0.115, $CHCl_3$). The NMR spectra of *ent*-**3** and *ent*-**2** were identical to those of fumiquinazoline G and F, respectively.[4b]

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-L-valyl-2-aminobenzoyl-D-tryptophan Methyl Ester (10).** Following the procedure given for **6**, compound **8** (0.363 g, 1.08 mmol) was reacted with Fmoc-L-Val-Cl (0.532 g, 1.46 mmol) for 2 h to yield **10** as a white solid (0.641 g, 90%): mp 197 °C (dec); $[\alpha]^{30}_D$ = −11.8 (*c* 0.34, $CHCl_3$); IR ν_{max} ($CHCl_3$) 1726, 1695, 1588 cm^{-1}; ^1H NMR δ 11.02 (br s, 1H), 8.55 (br d, 2H, J = 7.8), 7.77 (d, 2H, J = 7.4), 7.67 (br d, 1H, J = 7.4), 7.62 (br d, 1H, J = 7.5), 7.55−7.27 (m, 8H), 7.15 (t, 1H, J = 7.6), 7.05 (t, 1H, J = 7.2), 7.01(t, 1H, J = 7.0), 6.99 (br s, 1H), 6.68 (d, 1H, J = 8.2), 5.54 (d, 1H, J = 8.8), 5.09 (dt, 1H, J = 7.3, 4.9), 4.46−4.43 (m, 2H), 4.27 (t, 1H, J = 7.1), 4.19 (dd, 1H, J = 8.7, 5.5), 3.74 (s, 3H), 3.46 (dd, 1H, J = 14.9, 4.5), 3.22 (dd, 1H, J = 14.8, 6.9), 2.20 (m, 1H), 1.02 (d, 3H, J = 6.8,), 0.97 (d, 3H, J = 6.9); ^{13}C NMR δ ($CDCl_3/CD_3OD$, 6:1) 172.4, 170.6, 168.5, 156.9, 144.1, 143.8, 141.4, 138.4, 136.4, 136.3, 132.7, 127.8, 127.5, 127.2, 125.2, 123.5, 123.2, 123.1, 122.1, 121.4, 120.8, 120.0, 119.5, 118.3, 111.5, 109.4, 67.2, 61.6, 53.3, 52.6, 47.3, 31.2, 27.8, 19.7, 17.7; MS (EI) *m*/*z* (relative intensity %) 436 ([M + H − Fmoc]$^+$, 0.9), 178 (100), 130 (99). Anal. Calcd for $C_{39}H_{38}N_4O_6$: C, 71.11; H, 5.81; N, 8.51. Found: C, 70.72; H, 5.72; N, 8.35.

***N*-{2-[(*S*)-1-*N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino-2-methylpropyl]-4*H*-3,1-benzoxazin-4-ylidene}-D-tryptophan Methyl Ester (11).** To a solution of compound **10** (0.362 g, 0.550 mmol) in CH_2Cl_2 (20 mL) were added Ph_3P (0.715 g, 2.73 mmol), I_2 (0.677 g, 2.67 mmol), and *N*,*N*-diisopropylethylamine (1.00 mL, 5.74 mmol). The reaction mixture was stirred at room temperature for 8.2 h and quenched with aqueous Na_2CO_3, extracted with CH_2Cl_2 (×3), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (eluant 30% to 50% AcOEt/hexanes with 2% Et_3N) to give **11** as a white solid (0.290 g, 82%) which was crystallized from CH_2Cl_2/hexanes to yield colorless needles: mp 129 °C (dec); $[\alpha]^{30}_D$ = +78.0 (*c* 0.64, MeOH); IR ν_{max} ($CHCl_3$) 1725, 1681, 1649, 1608 cm^{-1}; ^1H NMR δ 8.18 (d, 1H, J = 7.7), 8.09 (br s, 1H), 7.77 (br d, 2H, J = 7.3), 7.70−7.60 (m, 3H), 7.53(t, 1H, J = 7.5), 7.45−7.20 (m, 7H), 7.11(t, 1H, J = 7.1), 7.07 (br s, 1H), 7.02 (t, 1H, J = 7.2), 5.40 (d, 1H, J = 9.2), 4.85 (dd, 1H, J = 8.2, 4.7), 4.45 (br d, 2H, J = 7.0), 4.26 (t, 1H, J = 6.8), 4.02 (dd, 1H, J = 9.0, 5.2), 3.69 (s, 3H), 3.48 (dd, 1H, J = 14.3, 4.7), 3.26 (dd, 1H, J = 14.2, 8.6), 1.95 (m, 1H), 0.87 (d, 3H, J = 6.6), 0.79 (d, 3H, J = 6.7); ^{13}C

NMR δ 172.9, 158.3, 156.3, 147.7, 143.9, 143.8, 141.3, 141.0, 136.1, 133.3, 128.2, 127.7, 127.5, 127.1, 126.2, 125.1, 122.8, 122.0, 120.0, 119.2, 118.8, 112.3, 111.3, 66.9, 60.2, 57.9, 52.2, 47.3, 31.4, 29.6, 19.1, 17.3; ^{1}H−^{15}N HMBC: three nitrogens were identified at δ 82.0 (Fmoc-NH), 225.0 and 224.7 (Trp-N=; MS (EI) *m/z* (relative intensity %) 640 (M^+, 0.6), 511 (*a* + H, 2), 130 (*b*, 96). Anal. Calcd for $C_{39}H_{38}N_4O_6\cdot H_2O$: C, 71.11; H, 5.81; N, 8.51. Found: C, 70.81; H, 5.48; N, 8.31.

(1*S*,4*R*)-4-(1*H*-Indol-3-ylmethyl)-1-isopropyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (4, fiscalin B). Compound **11** (115 mg, 0.179 mmol) was dissolved in CH_2Cl_2 (3.2 mL), followed by addition of piperidine (0.8 mL), and stirred at room temperature for 12 min. The resulting solution was concentrated under reduced pressure to provide a white residue which was triturated with hexanes (×1), CH_2Cl_2/PhMe (×1), and hexanes (×1). The residue was dissolved in acetonitrile (10 mL) and refluxed for 18.7 h in the presence of DMAP (28 mg, 0.23 mmol). The reaction mixture was concentrated and purified by preparative TLC (MeOH/CH_2Cl_2/EtOAc = 2.5:47.5:50) to yield **4** as pale yellow crystals (50 mg, 72%): mp 176.5−178.5 °C; $[\alpha]^{30}_D$ = −609 (*c* 0.59, $CHCl_3$), $[\alpha]^{26}_D$ = −504 (*c* 0.64, MeOH) [lit.[5b] mp 164.5−170.5 °C; $[\alpha]^{21.5}_D$ = −124 (*c* 0.021, MeOH)]; IR ν_{max} ($CHCl_3$) 3475, 3401, 1682, 1596 cm^{-1}; ^{1}H NMR δ 8.38 (d, 1H, *J* = 8.0), 8.01 (br s, 1H), 7.77 (ddd, 1H, *J* = 8.3, 7.0, 1.4), 7.56 (d, 1H, *J* = 8.2), 7.53 (t, 1H, *J* = 7.9), 7.45 (d, 1H, *J* = 8.1), 7.29 (d, 1H, *J* = 8.2), 7.13 (t, 1H, *J* = 7.8), 6.94 (t, 1H, *J* = 7.8), 6.60 (d, 1H, *J* = 2.2), 5.67 (dd, 1H, *J* = 4.8, 2.5), 5.57 (br s, 1H), 3.74 (dd, 1H, *J* = 15.0, 2.8), 3.65 (dd, 1H, *J* = 15.0, 5.3), 2.69 (d, 1H, *J* = 2.3), 2.63 (m, 1H), 0.65 (d, 3H, *J* = 6.6), 0.63 (d, 3H, *J* = 7.0); ^{13}C NMR δ 169.5, 160.9, 150.3,147.1, 136.1, 134.7, 127.3, 127.2, 127.0, 126.9, 123.6, 122.6, 120.2, 120.0, 118.7, 111.1, 109.4, 58.2, 56.8, 29.5, 27.4, 18.8, 14.8; ^{1}H−^{15}N HSQC and HMBC: four nitrogens were identified at δ 110.5 (Val-NH), 124.5 (indole NH), 165.9 (Trp-N) and 232.6 (Ar−N=); MS (EI) *m/z* (relative intensity %) 386 (M^+, 56), 257 (*a* + H, 31), 130 (*b*, 100); HRMS (EI) calcd for $C_{23}H_{22}N_4O_2$: 386.1743; found: 386.1731.

***(S)*-2-[(2-Amino-1-methoxy-3-methylbutylidene)amino]-benzoyl-D-tryptophan Methyl Ester (12).** Oxazine **11** (104 mg, 0.163 mmol) was treated with CH_2Cl_2 (3.2 mL) and piperidine (0.8 mL) at room temperature for 12 min and then evaporated to dryness. The vacuum-dried crude residue was dissolved in MeOH (10 mL) and DMAP (26.6 mg, 0.218 mmol) and heated at reflux for 60 h. The reaction mixture was purified by preparative TLC (AcOEt:MeOH:CH_2Cl_2 = 42:3:55) to give **4** (26 mg, 42%) and a major byproduct **12** (17 mg, 23%). **12**: ^{1}H NMR δ 8.74 (d, 1H, *J* = 8.4, CONH), 8.20 (br s, 1H, indole NH), 8.15 (dd, 1H, *J* = 7.8, 1.3), 7.49 (d, 1H, *J* = 8.1), 7.37 (t, 1H, *J* = 7.4), 7.29 (d, 1H, *J* = 8.2), 7.17 (t, 1H, *J* = 7.7), 7.13 (t, 1H, *J* = 8.2), 7.02 (t, 1H, *J* = 7.5), 6.99 (br s, 1H), 6.70 (d, 1H, *J* = 7.9), 5.28 (dt, 1H, *J* = 8.7, 5.1), 3.63 (s, 3H, CO_2CH_3), 3.41 (dd, 1H, *J* = 14.7, 4.9, Trp-CH_2), 3.33 (s, 3H, OCH_3), 3.32 (dd, 1H, *J* = 14.7, 5.7, Trp-CH_2), 3.13 (d, 1H, *J* = 8.4, Val-CHN), 1.66 (m, 1H, Val-CH), 0.79 (s, 3H, Me), 0.67 (s, 3H, Me); ^{13}C NMR δ 172.5 (CO_2Me), 166.2 (−N=CO), 165.9 (CONH), 131.9 (d), 131.1 (d), 127.6 (s), 125.3 (s), 123.6, 123.1, 122.3, 122.0 119.5, 118.8, 111.0 (d), 110.2 (s), 56.2 (Val-CHN), 53.2 (CO_2**C**H_3), 53.1 (Trp-CHN), 52.1 (OMe), 32.7 (Val-CH), 28.5 (Trp-CH_2), 19.1 (q), 18.4 (q). **12** may be present as rotamers; at least two species were seen by NMR. 1D NOE for major isomer: δ 6.70 → 3.33 (OMe). ^{1}H-^{15}N HMBC: proton at δ 6.70 has correlation with nitrogen at δ 238 (-**N**=COMe); MS (ESI, positive mode) *m/z* 451.3 ([M + H]$^+$).

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-glycyl-2-aminobenzoyl-D-tryptophan Methyl Ester (13a).** Following the procedure given for **6**, compound **8** (0.330 g, 0.979 mmol) was reacted with Fmoc-Gly-Cl (0.406 g, 1.281 mmol) for 2 h to give **13a** as a white solid (0.594 g, 98%): mp 183−185 °C; $[\alpha]^{30}_D$ = −17.3 (*c* 0.23, $CHCl_3$); IR ν_{max} (KBr) 3326, 1739, 1696, 1682, 1632 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.59 (br s, 1H), 10.83 (br s, 1H), 9.04 (d, 1H, *J* = 7.5, Trp-CHNH), 8.48 (d, 1H, *J* = 8.4), 7.97 (t, 1H, *J* = 5.9, Fmoc-NH-Gly), 7.90 (d, 2H, *J* = 7.5), 7.77 (d, 1H, *J* = 7.7), 7.70 (d, 1H, *J* = 7.3), 7.69 (d, 1H, *J* = 7.4), 7.51 (t, 1H, *J* = 7.6), 7.48 (d, 1H, *J* = 7.7), 7.41 (t, 2H, *J* = 7.5), 7.32−7.26 (m, 3H), 7.15 (br s, 1H), 7.15 (t, 1H, *J* = 7.5), 7.03 (t, 1H, *J* = 7.5), 6.92 (t, 1H, *J* = 7.4), 4.66 (m, 1H, Trp-CHN), 4.30 (m, 2H, CH_2O), 4.24 (m, 1H), 3.73 (m, 2H, Gly-CH_2N), 3.54 (s, 3H, OCH_3), 3.24 (d, 2H, *J* = 8.1); ^{13}C NMR (DMSO-d_6) δ 171.9, 168.4, 168.1, 156.6, 143.8, 143.7, 140.6, 138.6, 136.0 (s), 132.2, 128.3, 127.5, 126.9, 125.1, 123.5, 122.5, 120.9, 120.0, 119.9 (d), 119.6 (s), 118.3, 117.9, 111.4 (d), 109.7 (s), 109.6 (s), 65.8 (t), 53.4 (Trp-CHN), 51.8 (q), 46.6 (d), 45.1 (Gly-CH_2N), 26.2 (t). Anal. Calcd for $C_{36}H_{32}N_4O_6\cdot 1/4H_2O$: C, 69.61; H, 5.27; N, 9.02. Found: C, 69.52; H, 5.61; N, 8.71.

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-L-alanyl-2-aminobenzoyl-D-tryptophan Methyl Ester (13b).** Following the procedure given for **6**, **8** (0.331 g, 0.98 mmol) was reacted with Fmoc-L-Ala-Cl[12] (0.496 g, 1.44 mmol) for 4.7 h to give **14b** as a white solid (0.416 g, 67%): mp 144−146 °C; $[\alpha]^{30}_D$ = −28.1 (*c* 0.26, $CHCl_3$); IR ν_{max} ($CHCl_3$) 1725, 1692, 1650, 1602, 1588 cm^{-1}; ^{1}H NMR δ 11.22 (br s, 1H, anilide NH), 8.55 (d, 1H, *J* = 8.2), 8.40 (br s, 1H, indole-NH), 7.77 (br d, 2H, *J* = 7.2), 7.70 (d, 1H, *J* = 7.3), 7.63 (d, 1H, *J* = 7.3), 7.52−7.26 (m, 8H), 7.16 (t, 1H, *J* = 7.5), 7.05 (t, 1H, *J* = 7.7), 7.01 (t, 1H, *J* = 7.2), 6.98 (br s, 1H), 6.70 (d, 1H, *J* = 7.8)), 5.50 (d, 1H, *J* = 6.8, Fmoc-NH), 5.04 (m, 1H), 4.48−4.35 (m, 3H), 4.26 (t, 1H, *J* = 7.0), 3.72(s, 3H), 3.44 (dd, 1H, *J* = 14.8, 4.7), 3.25 (dd, 1H, *J* = 14.7, 6.1), 1.49 (d, 3H, *J* = 7.0); ^{13}CNMR ($CDCl_3$−CD_3OD, v/v = 3/1) δ 172.7, 172.4, 168.9, 156.9, 144.4, 144.0, 141.5, 138.6, 136.7 (s), 132.8, 127.9 (d), 127.6 (s),127.6, 127.3, 125.6, 125.4, 123.7, 123.5, 122.0, 121.6, 120.1, 119.4, 118.4, 111.8 (d), 109.4 (s), 67.4(t), 53.7, 52.6, 52.3, 47.5, 27.7 (t), 18.2 (q). Anal. Calcd for $C_{37}H_{34}N_4O_6$: C, 70.46; H, 5.43; N, 8.88. Found: C, 70.14; H, 5.74; N, 8.67.

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-L-phenalanyl-2-aminobenzoyl-D-tryptophan Methyl Ester (13c).** Following the procedure given for **6**, **8** (0.322 g, 0.96 mmol) was reacted with Fmoc-L-Phe-Cl (0.508 g, 1.24 mmol) for 2 h to give **13c** as a white solid (0.652 g, 97%): $[\alpha]^{30}_D$ = −47.7 (*c* 0.375, $CHCl_3$); IR ν_{max} (KBr) 3422, 3317, 1741, 1702, 1686, 1656 cm^{-1}; ^{1}H NMR δ 11.24 (br s, 1H, anilide NH), 8.54 (d, 1H, *J* = 8.3), 8.36 (br s, 1H, indole NH), 7.76 (br d, 2H, *J* = 7.5), 7.60 (d, 1H, *J* = 7.5), 7.55 (d, 1H, *J* = 7.5), 7.49 (d, 1H, *J* = 8.2), 7.45 (t, 1H, *J* = 8.0), 7.39 (br t, 2H, *J* = 7.1), 7.32−7.25 (m, 6H), 7.22−7.14 (m, 4H), 7.06 (ddd, 1H, *J* = 8.0, 7.1, 0.9), 7.00 (td, 1H, *J* = 7.7, 1.1), 6.95 (br s, 1H, indole C_2-H), 6.67 (d, 1H, *J* = 7.8, Trp-CHNH), 5.45 (d, 1H, *J* = 7.8, Fmoc-NH−Phe), 5.00 (m, 1H, Trp-CHN), 4.60 (m, 1H, Phe-CHN), 4.38 (d, 2H, *J* = 7.0, CH_2O), 4.23 (t, 1H, *J* = 7.2), 3.70 (s, 3H, OCH_3), 3.40 (dd, 1H, *J* = 14.8, 4.8, Trp-CH_2), 3.25−3.22 (m, 2H), 3.12 (dd, 1H, *J* = 13.9, 7.0); ^{13}C NMR δ 172.0, 169.7, 168.0, 156.0, 144.0, 143.7, 141.3, 141.3, 138.8, 136.1, 136.1 (s), 132.8, 129.4, 128.7, 127.7 (d), 127.5 (s), 127.1, 127.0, 126.7, 123.3, 122.8, 122.3, 121.4 (d), 120.3 (s), 120.0, 119.9, 119.7, 118.4, 111.4 (d), 67.3 (CH_2O), 57.1 (Phe-CHN), 53.2 (Trp-CHN), 52.6 (q), 38.7 (Phe-CH_2), 27.9 (Trp-CH_2). Anal. Calcd for $C_{43}H_{38}N_4O_6$: C, 73.07; H, 5.42; N, 7.93. Found: C, 72.89; H, 5.79; N, 7.73.

***N*-{2-[*N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]aminomethyl]-4*H*-3,1-benzoxazin-4-ylidene}-D-tryptophan Methyl Ester (14a)**. Following the procedure given for **9**, **13a** (0.498 g, 0.807 mmol) was dehydrated at room temperature for 7 h. The residue was purified by flash chromatography (50% to 60% AcOEt/hexanes) to give **14a** as an off-white solid (0.435 g, 90%) and recovered **13a** (0.036 g, 7%). **14a**: mp 104 °C (dec); $[\alpha]^{30}_D$ = +141 (*c* 0.33, $CHCl_3$); IR ν_{max} (KBr) 3398, 3326, 1720, 1689, 1535 cm^{-1}; ^{1}H NMR δ 8.17 (d, 1H, *J* = 7.9), 7.94 (br s, 1H), 7.78 (d, 1H, *J* = 7.3), 7.64 (br t, 2H overlapped), 7.51 (t, 1H, *J* = 7.0), 7.44−7.23 (m, 9H), 7.13 (td, 1H, *J* = 6.7, 1.2), 7.05 (t, 1H, *J* = 6.3), 6.94 (d, 1H, *J* = 1.8), 5.03 (br t like, 1H), 4.91 (dd, 1H, *J* = 9.2, 4.3), 4.30 (d, 2H, *J* = 6.3), 4.24 (t, 1H, *J* = 6.4), 3.74 (s, 3H), 3.64 (dd, 1H, *J* = 18.3, 5.5), 3.48 (dd, 1H, partially overlapped, *J* = [12.2], 4.3), 3.42 (dd, 1H, partially overlapped, *J* = [17.7], 5.5), 3.17 (dd, 1H, *J* = 14.0, 9.8); ^{13}C NMR δ 172.9, 156.2, 156.0, 147.3, 143.8, 141.3, 140.9, 136.0 (s), 133.3, 128.1, 127.7 (d), 127.5 (s), 127.1, 126.3, 125.8, 125.0, 123.3, 121.9, 120.0, 119.3 (d), 119.1 (s), 118.8 (d), 111.9 (s), 111.2, 66.9 (CH_2O), 59.5 (CHN), 52.2 (OCH_3), 47.1 (d), 41.7 (CH_2N), 29.5 (t).

***N*-{2-[(*S*)-1-*N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-aminoethyl]-4*H*-3,1-benzoxazin-4-ylidene}-D-tryptophan

Methyl Ester (14b). Following the procedure given for **9**, **13b** (0.269 g, 0.425 mmol) was dehydrated for 5.5 h and the reaction mixture purified by flash chromatography (eluant 30−60% AcOEt/hexanes, no Et_3N added) to give **14b** as a white solid (0.186 g, 71%) and recovered **13b** (0.024 g, 9%). **14b**: mp124−126 °C; $[\alpha]^{30}_D = +92.0$ (*c* 0.65, MeOH); IR ν_{max} ($CHCl_3$) 1725, 1680, 1511 cm^{-1}; ^1H NMR δ 8.18 (d, 1H, *J* = 7.8), 8.00 (br s, 1H, indole-NH), 7.78 (br d, 2H, *J* = 7.2), 7.64 (br t, 3H, *J* = 8.7), 7.53 (td, 1H, *J* = 7.6, 1.3), 7.43−7.24 (m, 7H), 7.12 (t, 1H, *J* = 7.4), 7.02 (t, 1H, *J* = 7.8), 7.02 (br s, 1H), 5.32 (d, 1H, *J* = 7.7, Fmoc-NH), 4.86 (dd, 1H, *J* = 8.5, 4.5), 4.45 (br d, 2H, *J* = 7.0), 4.25 (t, 1H, *J* = 6.6), 4.11 (t, 1H, *J* = 7.0), 3.71 (s, 3H, OMe), 3.48 (dd, 1H, *J* = 14.2, 4.6), 3.24 (dd, 1H, *J* = 14.2, 8.9), 1.23 (d, 3H, *J* = 6.9); ^{13}C NMR δ 172.9, 159.2, 155.5, 147.6, 144.0, 143.8, 141.3, 141.0, 136.0 (s), 133.3, 128.2, 127.7 (d), 127.5 (s), 127.1, 126.4, 126.0, 125.1, 123.0, 122.0, 120.0, 119.3 (d), 119.1 (s), 118.8 (d), 112.2 (s), 111.2 (d), 66.8 (t), 59.8 (d), 52.2 (d), 48.6 (d), 47.2 (d), 29.6 (t), 19.2. Anal. Calcd for $C_{37}H_{32}N_4O_5 \cdot 5/4H_2O$: C, 69.96; H, 5.47; N, 8.82. Found: C, 69.88; H, 5.48; N, 8.73.

***N*-{2-[(*S*)-1-*N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino2-phenylethyl]-4*H*-3,1-benzoxazin-4-ylidene}-D-tryptophan Methyl Ester (14c)**. Following the procedure given for **9**, **13c** (0.509 g, 0.720 mmol) was dehydrated for 7 h to give **14c** as an off-white solid (0.430 g, 87%) and recovered **16a** (0.016 g, 3%). **14c**: $[\alpha]^{30}_D = +38.8$ (*c* 0.34, $CHCl_3$); IR ν_{max} (KBr) 3383, 3334, 1725, 1682, 1508 cm^{-1}; ^1H NMR δ (major rotamer) 8.18 (dd, 1H, *J* = 7.9, 1.2), 8.04 (br s, 1H, indole NH), 7.78 (br d, 2H, *J* = 7.5), 7.66 (br d, 2H, *J* = 10.5), 7.61−7.58 (m, 2H), 7.50 (td, 1H, *J* = 7.7, 1.4), 7.43−7.14 (m, 11H), 7.08 (t, 1H, *J* = 7.4), 7.03 (br s, 1H), 6.95 (d, 2H, *J* = 6.0), 5.35 (d, 1H, *J* = 8.2, Fmoc-NH−Phe), 4.71 (dd, 1H, *J* = 8.6, 4.6), 4.48 (dd, 1H, *J* = 10.6, 7.2, CH_2O), 4.38 (dd, 1H, *J* = 10.6, 6.8, CH_2O), 4.29 (dt, 1H, *J* = 8.0, 5.9, Phe-CHN), 4.24 (t, 1H, *J* = 6.7, Fmoc-CH), 3.71 (s, 3H, OCH_3), 3.47 (dd, 1H, *J* = 14.2, 4.5, Trp-CH_2), 3.22 (dd, 1H, *J* = 14.2, 8.7, Trp-CH_2), 2.99 (dd, 1H, *J* = 13.8, 5.8, Phe-CH_2), 2.88 (dd, 1H, *J* = 13.7, 5.9, Phe-CH_2); there was about 20% of minor rotamer, with broad peaks: 6.80 (0.35H), 4.99 (br d, 0.21 H), 4.55 (0.47H), 2.62 (0.35H); ^{13}C NMR δ 172.9, 157.6, 155.4, 147.4, 143.7, 141.3, 140.7, 136.1, 135.5 (s), 133.3, 129.3, 128.5, 128.3, 127.7 (d), 127.5 (s), 127.0, 126.9, 126.4, 126.1, 125.1, 123.0, 122.0, 120.0, 119.3 (d), 119.0 (s), 118.8 (d), 112.0 (s), 111.3 (d), 66.8 (CH_2O), 59.9 (d), 53.5 (d), 52.2 (q), 47.2 (d), 38.63 (t), 29.54 (t).

(*R*)-4-(1*H*-indol-3-ylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (1, glyantrypine). Following the procedure given for **3**, **14a** (0.264 g, 0.441 mmol) was deprotected and then refluxed in MeCN for 2 h; after chromatography, **1** was obtained as white crystals (0.132 g, 87%): mp 159−161 °C (foam); $[\alpha]^{30}_D = -522$ (*c* 0.24, $CHCl_3$); IR ν_{max} (KBr) 3265, 1681, 1600, 1474 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.95 (br s, 1H), 8.35 (d, 1H, *J* = 4.3, CONH), 8.22 (d, 1H, *J* = 7.6), 7.83 (td, 1H, *J* = 8.0, 1.5), 7.56 (t, 1H, *J* = 7.4), 7.55 (d, 1H, *J* = 7.8), 7.33 (d, 1H, *J* = 8.1), 7.28 (d, 1H, *J* = 7.9), 7.02 (t, 1H, *J* = 7.2), 6.88 (d, 1H, *J* = 2.3), 6.79 (t, 1H, *J* = 7.5), 5.29 (t, 1H, *J* = 4.8), 3.82 (dd, 1H, *J* = 17.0, 4.5, Gly-CH_2), 3.45 (m, strongly coupled AB system, 2H, Trp-CH_2), 3.07 (d, 1H, *J* = 17.0, Gly-CH_2); ^{13}C NMR (DMSO-d_6) δ 167.6, 159.9, 149.2, 146.9, 135.9 (s), 134.6 (d), 127.1 (s), 126.6, 126.5, 126.2, 124.3, 121.2 (d), 119.8 (s), 118.6, 117.7, 111.4 (d), 107.7 (s), 56.4 (d), 43.7 (t), 26.5 (t). MS (EI) *m*/*z* (relative intensity %) 344 (M^+, 52), 215 (*a* + H, 20), 130 (*b*, 100).

(1*S*,4*R*)-4-(1*H*-Indol-3-ylmethyl)-1-methyl-2*H*-pyrazino-[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (2, fumiquinazoline F). Following the procedure given for **3**, oxazine **14b** (96.6 mg, 0.158 mmol) was deprotected and then refluxed in MeCN for 2 h. Purification by preparative TLC (AcOEt:MeOH:CH_2Cl_2 = 50:5:45) gave **2** (46.8 mg, 82.8%) and epimer **3** (2.0 mg, 3.5%). Epimer **3**: $[\alpha]^{30}_D = -7.0$ (*c* 0.10, $CHCl_3$). Synthetic **2**: mp 137 °C (foam), $[\alpha]^{30}_D = -516$ (*c* 0.74, $CHCl_3$){lit:[4b] mp. 88−90 °C, $[\alpha]_D = -411$ (*c* 1.36, $CHCl_3$)}; ^1H NMR δ 8.37 (d, 1H, *J* = 8.0), 8.19 (br s, 1H, indole-NH), 7.77 (td, 1H, *J* = 7.6, 1.2), 7.59 (d, 1H, *J* = 8.1), 7.53 (t, 1H, *J* = 7.5), 7.40 (d, 1H, *J* = 8.0), 7.30 (d, 1H, *J* = 8.2), 6.92 (t, 1H, *J* = 7.6), 6.71(d, 1H, *J* = 2.3), 6.35 (br s, 1H, NH), 5.68 (t, 1H, *J* = 4.3), 3.70 (dd, 1H, *J* = 15.3, 3.8), 3.66 (dd, *J* = 15.3, 5.6), 3.11 (q, 1H, *J* = 6.6), 1.36 (d, 3H, *J* = 6.6); ^{13}C NMR δ 169.3, 160.8, 151.7, 147.1, 136.0 (s), 134.7, 127.3, 127.1, 126.8 (d), 123.6 (s), 122.5, 120.2 (s), 120.0, 118.5, 111.2 (d), 109.4 (s), 57.5, 49.2 (d), 27.1 (t), 19.1 (q); MS (EI) *m*/*z* (relative intensity %) 358 (M^+, 78), 229 (*a* +H, 58), 130 (*b*,100); HRMS (EI) calcd. for $C_{21}H_{18}N_4O_2$: 358.1430; found: 358.1473.

(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 (15). Following the procedure given for **3**, oxazine **14c** (286 mg, 0.415 mmol) was deprotected and then refluxed in MeCN for 3 h. Purification by preparative TLC (50% AcOEt/hexanes) gave product **15** (140 mg, 78%) and *cis*-epimer (9 mg, 5%). Compound **15**: $[\alpha]^{30}_D = -623$ (*c* 0.27, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3310, 1678, 1598 cm^{-1}; ^1H NMR δ 8.39 (dd, 1H, *J* = 8.4, 1.6), 8.11 (br s, 1H, indole NH), 7.78 (td, 1H, *J* = 6.9, 1.2), 7.63 (d, 1H, *J* = 8.0), 7.56 (td, 1H, *J* = 8.1, 1.1), 7.43 (d, 1H, *J* = 8.0), 7.40 (d, 1H, *J* = 8.2), 7.24 (td, 1H, *J* = 8.1, 1.0), 7.19−7.16 (m, 3H), 6.93 (td, 1H, *J* = 7.2, 0.8), 6.62 (d, 1H, *J* = 2.1, indole C_2-H), 6.50 (br d, 1H, *J* = 7.1, 2H, Ph), 5.65 (dd, 1H, *J* = 5.3, 2.7, Trp-CHN), 5.35 (br s, 1H, amide NH), 3.75 (dd, 1H, *J* = 15.0, 2.6, Phe-CH_2), 3.65 (dd, 1H, *J* = 15.0, 5.4, Phe-CH_2), 3.62 (dd, 1H, *J* = 14.8, 3.4, Trp-CH_2), 2.97 (dd, 1H, *J* = 11.2, 3.6, Trp-CHN), 2.52 (dd, 1H, *J* = 14.7, 11.2, Trp-CH_2); ^{13}C NMR δ 169.2, 160.7, 151.0, 146.9, 136.1, 134.9 (s), 134.8, 129.1 (d), 128.4 (d), 127.3, 127.2 (d), 127.1 (s), 126.9, 123.8, 122.8, 120.6 (d), 120.3 (s), 119.0, 111.1 (d), 109.6 (s), 57.4 (Phe-CHN), 52.8 (Trp-CHN), 37.9 (Phe-CH_2), 27.2 (Trp-CH_2); MS (EI) *m*/*z* (relative intensity %) 434 (M^+, 52), 305 (*a* + H, 40), 130 (b, 100). Anal. Calcd for $C_{27}H_{22}N_4O_2 \cdot {}^1/_3H_2O$: C, 73.62; H, 5.19; N, 12.72. Found: C, 73.69; H, 5.58; N, 12.37. Cis epimer of **15**: $[\alpha]^{30}_D = -246$ (*c* 0.315, $CHCl_3$); IR ν_{max} (KBr) 3475, 3386, 1681, 1593 cm^{-1}; ^1H NMR δ 8.42 (dd, 1H, *J* = 8.0, 1.0), 8.11 (br s, 1H, indole NH), 7.83 (ddd, 1H, *J* = 8.3, 7.1, 1.4), 7.67 (d, 1H, *J* = 8.0), 7.59−7.55 (m, 2H), 7.30 (d, 1H, *J* = 8.1), 7.21 (td, 1H, *J* = 7.6, 0.9), 7.14 (dd, 2H, *J* = 5.6, 3.7), 7.10 (t, 1H, *J* = 8.0), 6.62 (d, 1H, *J* = 2.4, indole C_2-H), 6.35−6.32 (m, 2H), 5.56 (t, 1H, *J* = 4.3), 5.55 (br s, 1H, amide NH), 4.38 (dt, 1H, *J* = 11.7, 2.8), 3.84 (dd, 1H, *J* = 15.1, 3.2), 3.82 (dd, 1H, *J* = 15.2, 4.4), 3.01 (dd, 1H, *J* = 13.1, 3.0), 0.59 (dd, 1H, *J* = 12.9, 11.9); ^{13}C NMR δ 166.5, 160.9, 150.1, 147.2, 135.8, 135.6 (s), 134.9, 129.2, 128.9 (d), 128.1 (s), 127.2, 127.1, 127.0, 126.9, 123.5, 122.8, 120.5 (d), 120.2 (s), 119.5, 111.4 (d), 109.7 (s), 57.8 (d), 56.8 (d), 42.8 (t), 26.6 (t); MS (ESI, positive mode) *m*/*z* 435.2 ($[M + H]^+$).

***N*-[2-(Acetylamino)benzoyl]-L-tryptophan Methyl Ester (16a)**. To a solution of *ent*-**8** (133 mg, 0.393 mmol), CH_2Cl_2 (5 mL) and Et_3N (0.16 mL, 1.15 mmol) was added Ac_2O (0.074 mL, 0.78 mmol) via a syringe. After 23 h, the mixture was diluted with aqueous Na_2CO_3 and extracted with CH_2Cl_2 (×3). After workup, the residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) and gave the acetamide as a syrup (147 mg, 99%): IR ν_{max} ($CHCl_3$) 1741, 1687, 1644, 1601, 1587 cm^{-1}; ^1H NMR δ 10.92 (br s, 1H), 7.52 (d, 1H, *J* = 7.8), 7.39 (t, 1H, *J* = 7.8), 7.33 (d, 1H, *J* = 8.1), 7.25 (d, 1H, *J* = 7.4), 7.17 (t, 1H, *J* = 7.5), 7.08 (t, 1H, *J* = 7.4), 6.96 (br s, 1H, indole C_2-H), 6.92 (t, 1H, *J* = 7.5), 6.81 (d, 1H, *J* = 7.1, NH), 5.05 (dd like, 1H, *J* = 12.3, 5.4), 3.74 (s, 3H), 3.45 (dd, 1H, *J* = 15.0, 5.3), 3.41 (dd, 1H, *J* = 14.9, 5.6), 2.14 (s, 3H); ^{13}C NMR δ 172.1, 169.2, 168.5, 139.5, 136.2, 132.8, 127.5 (s), 126.9 (d), 122.9, 122.8, 122.4, 121.4, 119.8 (d), 119.65 (s), 118.4, 111.5 (d), 109.5 (s), 53.5 (d), 52.6 (q), 27.5 (t), 25.3 (q).

***N*-[2-(Benzoylamino)benzoyl]-L-tryptophan Methyl Ester (16b).** To a solution of *ent*-**8** (0.122 g, 0.361 mmol), CH_2Cl_2 (5 mL) and Et_3N (0.12 mL, 0.86 mmol) was added PhCOCl (0.063 mL, 0.54 mmol) via a syringe. The mixture was stirred at room temperature for 2 h and then diluted with aqueous Na_2CO_3 and extracted with CH_2Cl_2 (×3). After workup, the residue was treated with CH_2Cl_2/hexanes to give **16b** quantitatively as a solid: ^1H NMR δ 12.03 (br s, 1H), 8.81(d, 1H, *J* = 8.0), 8.12 (br s, 1H), 8.03 (dd, 1H, *J* = 7.9, 1.56), 7.55−7.48 (m, 5H), 7.33 (td, 2H, *J* = 7.1, 1.2), 7.19 (t, 1H, *J* = 7.1), 7.08 (t, 1H, *J* = 7.5), 7.05−7.00 (m, 2H), 6.80 (br s, 1H, *J* = 7.6), 5.15 (dt, 1H, *J* = 5.2, 2.4), 3.75 (s, 3H), 3.49 (dd, 1H, *J* = 15.0, 5.8), 3.44 (dd, 1H, *J* = 15.0, 5.5); ^{13}C NMR ($CDCl_3$/CD_3COCD_3,= 3:1) δ 172.2, 169.2, 165.4, 140.3, 136.7, 135.1, 132.9,

132.0, 128.9, 127.7, 127.6, 127.5, 123.5, 122.8, 122.0, 120.0, 118.5, 111.7, 109.7, 53.8, 52.5, 27.6.

***N*-[2-(2-Methylpropanoylamino)benzoyl]-L-tryptophan Methyl Ester (16c)**. Following the procedure given for **16b**, *ent*-**8** was acylated with Me_2CHCH_2COCl to give **16c** quantitatively: IR ν_{max} ($CHCl_3$) 1740, 1678, 1645, 1586 cm^{-1}; ^1H NMR δ 10.96(s, 1H, NH), 8.62 (d, 1H, J = 8.7), 8.26 (br s, 1H), 7.53 (d, 1H, J = 7.8), 7.43 (td, 1H, J = 7.5, 1.2), 7.36 (d, 1H, J = 8.1), 7.27−7.24 (m, 1H), 7.19 (td, 1H, J = 7.4, 1.0), 7.09 (t, 1H, J = 7.3), 6.98 (d, 1H, J = 2.0), 6.95 (t, 1H, J = 7.8), 6.74 (br d, 1H, J = 7.4), 5.07 (dt, 1H, J = 7.4, 5.2), 3.75 (s, 3H), 3.47 (dd, 1H, J = 13.9, 3.6), 3.43 (dd, 1H, J = 13.9, 4.0), 2.28−2.18 (m, 3H), 1.01 (d, 1H, J = 6.4), 1.00 (d, 1H, J = 6.5); ^{13}C NMR δ 172.0, 171.7, 168.5, 139.7, 136.2 (s), 132.8 (d), 127.5 (s), 126.8 (d), 122.9, 122.7, 122.4, 121.4, 119.8 (d), 119.6 (s), 118.4, 111.4 (d), 53.4 (CHN), 52.60 (q), 47.8 (t), 27.4 (t), 26.2 (d), 22.5 (q); MS (EI) *m*/*z* (relative intensity %) 421 (M^+, 2), 130 (100).

***N*-[2-(1,1,1-Trimethylacetylamino)benzoyl]-L-tryptophan Methyl Ester (16d)**. Following the procedure given for **16b**, *ent*-**8** was acylated with Me_3CCOCl to give **16d** quantitatively: IR ν_{max} ($CHCl_3$) 1740, 1646, 1586 cm^{-1}; ^1H NMR δ 11.23 (s, 1H, NH), 8.64 (d, 1H, J = 8.4), 8.17 (br s, 1H, indole-NH), 7.53 (d, 1H, J = 7.8), 7.43 (td, 1H, J = 7.9, 1.5), 7.36(d, 1H, J = 8.0), 7.25 (dd, 1H, J = 7.9, 1.5), 7.19 (t, 1H, J = 7.0), 7.08 (td, 1H, J = 7.2, 0.9), 6.99 (d, 1H, J = 2.3), 6.95 (td, 1H, J = 7.7, 1.0), 6.71(br d, 1H, J = 7.5, amide NH), 5.09 (dt, 1H, J = 7.5, 5.2), 3.74 (s, 3H), 3.48 (dd, 1H, J = 14.6, 5.0), 3.44 (dd, 1H, J = 14.8, 5.0), 1.32 (s, 9H, *t*-Bu); ^{13}C NMR δ 177.9, 172.0, 168.7, 139.9, 136.2 (s), 132.8 (d), 127.5 (s), 126.8, 122.9, 122.6, 122.4, 121.4 (d), 119.9 (s), 119.8, 118.5, 111.4 (d), 109.6 (s), 53.5, 52.6, 40.2 (s), 27.6 (q), 27.42 (t).

***N*-(2-Methyl-4*H*-3,1-benzoxazin-4-ylidene)-L-tryptophan Methyl Ester (17a)**. To a mixture of acetamide **16a** (102 mg, 0.268 mmol), CH_2Cl_2 (10 mL), Ph_3P (354 mg, 1.35 mmol), and I_2 (325 mg, 1.28 mmol) was added Et_3N (0.37 mL, 2.65 mmol). After being stirred at room temperature for 7 h, the reaction mixture was diluted with aqueous Na_2CO_3 and extracted with CH_2Cl_2 (×3). After workup, the residue was purified by flash chromatography (50% AcOEt/hexanes with 1% Et_3N) to give **17a** (97 mg, 99%) as a syrup: IR ν_{max} ($CHCl_3$) 1740, 1682, 1646, 1587 cm^{-1}; ^1H NMR δ 8.18 (dd, 1H, J = 7.9, 1.4), 7.98 (br s, 1H), 7.51 (td, 1H, J = 7.7, 1.7), 7.34−7.30 (m, 2H), 7.25(d, 1H, J = 7.3), 7.17 (td, 1H, J = 7.0, 1.0), 7.11 (td, 1H, J = 7.1, 1.1), 6.99 (d, 1H, J = 2.1), 4.96 (dd, 1H, J = 8.7, 4.8, Trp-CHN), 3.75 (s, 3H), 3.50 (dd, 1H, J = 14.1, 4.7), 3.19 (dd, 1H, J = 14.1, 8.8), 1.76 (s, 3H, Me); ^{13}C NMR δ 173.2 (CO_2-Me), 157.8 (Trp-N=*C*), 148.3 (Me−*C*=N), 141.8, 136.2 (s), 133.3, 127.7 (d), 127.7 (s), 126.2, 125.5, 123.3, 121.9, 119.3, 118.8 (d), 118.7 (s), 111.9 (s), 111.2 (d), 59.4 (d), 52.2 (q), 29.6 (t), 20.0 (q); $^1H-^{15}N$ HMBC: three nitrogens were identified at δ 122.2 (indole N), 223.0 (correlated with protons at δ 4.96, 3.50, and 3.19) and 224.2 (Trp-N=, correlated with protons at δ 1.76 and 7.25); MS (EI) *m*/*z* (relative intensity %) 361 (M^+, 54), 231 (*a*, 64), 130 (*b*, 100).

***N*-(2-Phenyl-4*H*-3,1-benzoxazin-4-ylidene)-L-tryptophan Methyl Ester (17b).** Following the procedure given for **17a**, **16b** was dehydrated for 1.4 h. Purification by preparative TLC (5% MeOH/CH_2Cl_2) afforded product **17b** (44 mg, 82%) and recovered **16b** (6 mg, 11%, due to decomposition of **17b**). **17b**: IR ν_{max} ($CHCl_3$) 1737, 1675, 1627, 1605 cm^{-1}; ^1H NMR δ 8.26 (dd, 1H, J = 8.0, 1.3), 7.95−7.91(m, 3H), 7.75 (dd, 1H, J = 6.7, 1.8), 7.58 (td, J = 7.7, 1.4), 7.50−7.44 (m, 3H), 7.40−7.34 (m, 3H), 7.28−7.23 (m, 1H), 7.16−7.05 (m, 3H), 5.05 (dd, 1H, J = 8.0, 5.3), 3.71 (s, 3H), 3.56 (dd, 1H, J = 14.3, 5.4), 3.34 (dd, 1H, J = 14.1, 8.0); ^{13}C NMR δ 173.2, 154.6, 148.3, 142.2, 136.1 (s), 133.3, 131.9 (d), 130.6 (s), 128.5, 127.9, 127.7 (d), 127.5 (s), 126.5, 126.4, 123.0, 121.9, 119.24 (d), 119.18 (s), 118.8 (d), 112.0 (s), 111.2 (d), 60.1, 52.1, 29.8 (t); $^1H-^{15}N$ HMBC: three nitrogens were identified at δ 121.7 (indole N), 222.6 and 223.4 (Trp-N=); MS (ESI, positive mode) *m*/*z* 424.0 ($[M + H]^+$).

***N*-[2-(2-Methylpropyl)-4*H*-3,1-benzoxazin-4-ylidene]-L-tryptophan Methyl Ester (17c)**. Following the procedure given for **17a, 16c** was dehydrated for 20 h to give **17c** quantitatively. Shorter reaction times resulted in incomplete reaction: 2 h gave **17c** (58%) and recovered **16c** (39%); 6.2 h gave **17c** (88%) and recovered **16c** (12%). **17c**: $[\alpha]^{30}_D = -175$ (*c* 1.1, $CHCl_3$); IR ν_{max} ($CHCl_3$) 1737, 1677, 1643, 1608 cm^{-1}; ^1H NMR δ 8.19 (dd, 1H, J = 9.1, 2.1), 7.95 (br s, 1H), 7.73 (d, 1H, J = 7.9), 7.52 (td, 1H, J = 7.7, 1.2), 7.36−7.25 (m, 3H), 7.17 (t, 1H, J = 6.7), 7.11 (t, 1H, J = 7.4), 7.02 (d, 1H, J = 2.0), 4.93 (dd, 1H, J = 8.6, 5.0), 3.72 (s, 3H), 3.49 (dd, 1H, J = 14.2, 4.9), 3.22 (dd, 1H, J = 14.2, 8.5), 2.04−1.85 (m, 3H), 0.86 (d, 1H, J = 6.2), 0.84 (d, 1H, J = 5.9); ^{13}C NMR δ 173.3 (CO_2-Me), 160.0 (*i*-Pr−*C*=N), 148.5 (Trp-N=*C*), 141.8, 136.2 (s), 133.3, 127.7 (d), 127.6 (s), 126.2, 125.8, 123.3, 121.8, 119.2 (d), 118.9 (s), 118.7(d), 111.8 (s), 111.3 (d), 59.5 (d), 52.1 (q), 42.9 (t), 29.7 (Trp-CH_2), 26.3 (d), 22.3 (q), 22.13(q); $^1H-^{15}N$ HMBC: three nitrogens were identified at δ 123.4 (indole N), 221.9 (Trp-*N*=) and 225.0 (*i*-Pr−*C*=N); MS (EI) *m*/*z* (relative intensity %) 403 (M^+, 4), 274 (*a* + H, 20), 130 (*b*, 100); HRMS (EI) *m*/*z* calcd for $C_{24}H_{25}N_3O_3$: 403.1896; found: 403.1884.

***N*-[2-(2,2-Dimethylethyl)-4*H*-3,1-benzoxazin-4-ylidene]-L-tryptophan Methyl Ester (17d)**. Following the procedure given for **17a**, **16d** (0.204 g, 0.450 mmol) was dehydrated for 6.1 h to give **17d** (17%) and recovered **16d** (83%). In another trial, dehydration for 73 h gave **17d** and **16d** in yields of 22% and 78% respectively. **17d**: $[\alpha]^{30}_D = -129$ (*c* 0.575, $CHCl_3$). IR ν_{max} ($CHCl_3$) 1737, 1673, 1639, 1607 cm^{-1}; ^1H NMR δ 8.19 (dd, 1H, J = 8.0, 1.2), 7.98 (br s, 1H, indole-NH), 7.72 (d, 1H, J = 7.8), 7.52 (td, 1H, J = 7.7, 1.0), 7.36−7.29 (m, 3H), 7.18−7.06 (m, 2H), 7.12 (d, 1H, J = 2.0), 4.87 (dd, 1H, J = 8.1, 5.2), 3.67 (s, 3H), 3.47 (dd, 1H, J = 14.2, 5.3), 3.32 (dd, 1H, J = 14.3, 8.0), 1.20 (s, 9H); ^{13}C NMR δ 173.1, 165.5, 142.0, 136.1 (s), 133.2, 127.7, 126.2, 126.1, 123.0, 121.8, 119.2, 119.0 (d), 112.2 (s), 111.1 (d), 59.6, 52.0, 37.8 (s), 29.8 (t), 27.4 (q); MS (EI) *m*/*z* (relative intensity %) 403 (M^+, 17), 274 ($[a + H]^+$, 70), 130 (*b*, 100); HRMS (EI) *m*/*z* calcd for $C_{24}H_{25}N_3O_3$: 403.1896; found: 403.1902.

***(S)*-2-Methyl-α-(1*H*-indol-3-ylmethyl)-4-oxo-3(4*H*)-quinazolineacetic Acid Methyl Ester (18a).** Oxazine **17a** (52.5 mg, 0.145 mmol) was treated with piperidine (0.4 mL) in CH_2Cl_2 (1.6 mL) at room temperature for 30 min. The reaction solution was evaporated to dryness, and the residue was checked by NMR. ^1H NMR showed it contained ca. 70 mol % of piperidine impurity. The major product was *N*-[2-((1-piperidinoethylidene)amino)benzoyl]-L-tryptophan methyl ester, the amidine of **17a**: ^1H NMR δ 9.73 (d, 1H, J = 8.0, CONH), 8.87 (br s, 0.78H), 8.27 (dd, 1H, J = 8.0, 0.9), 7.48 (d, 1H, J = 7.9), 7.34−7.25 (m, 2H), 7.08 (t, 1H, J = 7.2), 7.01 (td, 1H, J = 7.9, 1.1), 6.99 (td, 1H, J = 7.6, 0.9), 6.91 (s, 1H), 6.48 (dd, 1H, J = 8.0, 0.8), 6.32 (br s, 1.34H), 5.21 (dt, 1H, J = 8.0, 5.8), 3.64 (s, 3H), 3.37 (dd, 1H, J = 14.5, 5.2), 3.33 (dd, 1H, J = 14.7, 5.7), 3.13 (br s, 4H, piperidino CH_2 × 2), 1.70 (s, 3H), 1.42 (m, 2H, piperidino CH_2), 1.26 (br s, 4H, piperidino CH_2 × 2); piperidine impurity: 3.00 (t, 4H, J = 5.6), 1.77 (m, 4H), 1.58 (m, 2H); ^{13}C NMR δ 176.2 (CO_2Me), 166.8 (CONH), 157.7 (−N=CN), 150.5 (s), 136.1 (s), 131.6 (d), 130.8 (d), 127.7 (s), 124.1 (s), 123.6 (d), 123.0 (d), 121.6 (d), 121.5 (d), 119.2 (d), 118.6 (d), 111.2 (d), 110.4 (s), 53.3 (Trp-CHN), 52.1 (OCH_3), 45.4 (not observable, identified by HMQC, piperidino NCH_2 × 2), 28.1 (Trp-CH_2), 25.7 (piperidino CH_2 × 2), 24.3 (piperidino CH_2), 15.5 (Me); piperidine impurity: 45.0 (CH_2Nx2), 23.2 (CH_2 × 2), 22.8 (CH_2); 1D NOE: δ 1.70 (Me) → 6.48. $^1H-^{15}N$ HMBC: four nitrogens were identified at δ 121.6 (Trp-CO*N*H), 125.1 (indole N), 109.6 (piperidino N, correlated with methyl group at δ 1.70) and 226.0 (*N*=CN); MS (ESI, positive mode) *m*/*z* 447.1 ($[M + H]^+$).

The above crude amidine (0.069 mmol) was refluxed in MeCN/1,2-dichloroethane (5/5 mL) for 15 h to give **18a** in 93% yield. **18a**: $[\alpha]^{30}_D = -457$ (*c* 0.44, $CHCl_3$){lit,[13b] $[\alpha]^{20}_D = -555$ (*c* 0.2, acetone); IR ν_{max} (KBr) 3478, 1747, 1675, 1596 cm^{-1}; ^1H NMR δ 8.28 (dd, 1H, J = 8.0, 1.1), 8.23 (br s, 1H, NH), 7.72 (ddd, 1H, J = 8.3, 7.0, 1.4), 7.53 (d, 1H, J = 7.8), 7.51 (d, 1H, J = 7.5), 7.46 (td, 1H, J = 7.6, 1.0), 7.30 (d, 1H, J = 7.8), 7.16 (td, 1H, J = 7.6, 1.0), 7.05 (ddd, 1H, J = 7.9, 7.1, 0.9), 6.66 (d, 1H, J = 1.9), 4.90 (br s, 1H), 3.87(dd, 1H, J = 15.2, 3.8), 3.79 (s, 3H), 3.73 (dd, 1H, J = 15.1, 10.4), 1.89 (s, 3H); ^{13}C NMR δ 169.4 (CO_2Me), 161.7 (CON), 154.5 (N=CN), 147.1, 136.1 (s),

134.6 (d), 126.9 (s), 126.7, 126.6, 126.6, 123.2, 122.4 (d), 120.6 (s), 119.9, 117.8, 111.5 (d), 110.7 (s), 60.5, 52.8 (q), 23.2 (q); 1D NOE: δ 1.89 (Me) → 5.21 (Trp-CHN); $^{1}H-^{15}N$ HMBC: three nitrogens were identified at δ 124.0 (indole N), 171.6 (CO*N*), and 239.3 (*N*=C); MS (ESI, positive mode) *m*/*z* 362.4 ($[M + H]^+$).

Methyl 9*H*-1-[2-((1,1,1-Trimethyl)acetylamino)phenyl]-pyrido[3,4-*b*]indole-3-carboxylate (19). The mixture of **16d** (53 mg, 0.126 mmol), $(CH_2Cl)_2$ (4 mL), Ph_3P (164 mg, 0.625 mmol), I_2 (154 mg, 0.606 mmol), and Et_3N (0.175 mL, 1.26 mmol) was stirred at room temperature for 1 h, and TLC showed only a very small amount of product formed. The reaction mixture was heated at reflux for 4 h, and then the black solution was quenched with aqueous Na_2CO_3 and extracted with CH_2Cl_2 (×3). After workup, the residue was purified by flash chromatography (50% AcOEt/hexanes), and the desired fractions were purified by preparative TLC (2% MeOH/CH_2Cl_2) to give oxazine **17d** (6 mg, 12%) and **19** (39 mg, 77%). **19**: white solid, fluorescent under UV 365 nm; IR ν_{max} (KBr) 3237, 1731, 1664, 1518 cm^{-1}; ^{1}H NMR δ 10.96 (s, 1H, CONH), 10.66 (s, 1H, indole NH), 8.92 (s, 1H, C_4-H), 8.25 (d, 1H, J = 7.9), 8.08 (d, 1H, J = 8.2), 7.77 (d, 1H, J = 8.2), 7.74 (dd, 1H, J = 7.7, 1.4), 7.66 (td, 1H, J = 7.2, 1.0), 7.41 (td, 1H, J = 7.1, 0.7), 6.94 (td, 1H, J = 7.5, 1.1), 6.83 (td, 1H, J = 7.8, 1.4), 4.05 (s, 3H), 1.27 (s, 9H); ^{13}C NMR δ 177.5 (CONH), 166.2 (CO_2Me), 141.4, 141.3, 136.1, 135.9, 135.4, 130.5 (s), 130.0, 129.0, 128.6 (d), 126.0 (s), 123.6, 123.6, 121.8 (d), 121.7 (s), 121.1, 117.3, 112.7 (d), 52.4 (q), 39.7 (s), 27.5 (q); $^{1}H-^{15}N$ HSQC and HMBC: three nitrogens were identified at δ 119.4 (CO*N*H), 118.4 (indole *N*), and 292.8 (β-carboline −C=N−); MS (EI) *m*/*z* (relative intensity %) 401 (M^+, 28), 344 ($[M - t\text{-Bu}]^+$, 100).

***N*-(2-Cyanophenyl)quinoline-2-carboxamide (21)**. Following the procedure given for **16a**, **20** (0.207 g, 0.710 mmol) was dehydrated for 8 h. The reaction mixture was purified by preparative TLC (30% AcOEt in hexanes) to give the nitrile **21** (103 mg, 53%) as a pale yellow solid: IR ν_{max} (KBr) 3261, 2219, 1697, 1582, 1533 cm^{-1}; ^{1}H NMR δ 11.07 (s, 1H, CONH), 8.72 (d, 1H, J = 9.0), 8.33 (d, 1H, J = 8.5), 8.30 (d, 1H, J = 8.5), 8.20 (d, 1H, J = 8.5), 7.86 (d, 1H, J = 8.2), 7.76 (ddd, 1H, J = 7.5, 6.9, 1.5), 7.65−7.59 (m, 3H), 7.19 (td, 1H, J = 7.7, 1.0); ^{13}C NMR δ 162.5, 148.4, 146.2, 140.6 (s), 138.0, 134.2, 132.5, 130.5, 130.2 (d), 129.6 (s), 128.6, 127.6, 123.9, 120.2, 118.4 (d), 116.4 (CN), 102.2 (s); MS (ESI, positive mode) *m*/*z* 274.2 ($[M + H]^+$).

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Supporting Information Available: ^{1}H NMR spectra for **12**, **14c**, **15**, epimer of **15**, **16a**−**c**, **17b**, and amidine of **17a**, and ^{13}C NMR spectra for **14a**, **16d**, **17a**,**c**,**d**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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