Microwave-Assisted, Solvent-Free Synthesis of Several Quinazoline Alkaloid Frameworks

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This paper is dedicated to Professor George A. Olah, on the occasion of his 80th birthday.

Abstract: Microwave irradiation leads to a considerable improvement of the cyclocondensation between anthranilic acid and lactim ethers derived from piperazine-2,5-diones in terms of reaction times, yields, and stereocenter integrity. This reaction has been used to prepare some derivatives of the pyrazino[2,1-*b*]quinazoline-3,6-dione system present in many quinazoline alkaloids. It could also be applied to the synthesis of compounds containing the complete hexacyclic ring system of the anti-MDR natural product *N*-acetylardeemin, and other comprising the pentacyclic framework of circumdatin E. The microwave-assisted reaction was also much better than the thermal one when applied to a bis-lactim ether, leading to the corresponding pentacyclic pyrazino[2,1-*b*:5,4-*b*′]diquinazoline-8,16-dione in excellent yield.

Key words: microwave irradiation, lactim ether, alkaloids, antitumor agents, heterocycles

About 150 naturally occurring alkaloids contain a quinazolin-4-one structural fragment. These quinazoline alkaloids[1] have been isolated from a variety of natural sources, including fungi, marine organisms, and higher plants, and the structures of some representative examples, including luotonin A,[2] fiscalin B,[3] *N*-acetylardeemin,[4] spiroquinazoline,[5] and circumdatin E[6] are shown in Figure 1. These compounds have attracted much attention from synthetic chemists prompted by their challenging structures and interesting pharmacological properties, which include, among others, antitumor activity and inhibition of topoisomerase I by the luotonins,[7] inhibition of multidrug resistance[8] to antitumor drugs (MDR)[4b,9] and immunosuppression[10] by the ardeemins, and finally competitive inhibition of the binding of substance P to the human NK-1 receptor by spiroquinazoline.[5]

Extensive synthetic efforts have been devoted to the preparation of quinazoline alkaloids and their analogues.[1,11–13] The creation of the pyrazino[2,1-*b*]quinazoline-3,6-dione fragment has relied on two strategies: a five-step sequence starting from Fmoc-protected amino acids based on the cyclization of *N*-aminoacylanthranylamides[14] via a benzo[*d*]oxazine intermediate;[15] alternatively the Eguchi protocol comprises four steps and starts from *N*-Boc-protected amino acids that are transformed into piperazine-2,5-diones, which are submitted to acylation with 2-azidobenzoyl chloride followed by a domino Staudinger–aza-Wittig process.[16] Although this method has the advantage of starting from inexpensive starting materials and has been widely employed, it has some drawbacks. Thus, when both NH groups of the piperazinedione system are free, the acylation step is often troublesome and it is difficult to avoid diacylation. An additional problem arises from the generation of a phosphine oxide as a side product, which leads to tedious chromatographic procedures. For these reasons, we decided to investigate an alternative procedure related to the von Niementowski quinazoline

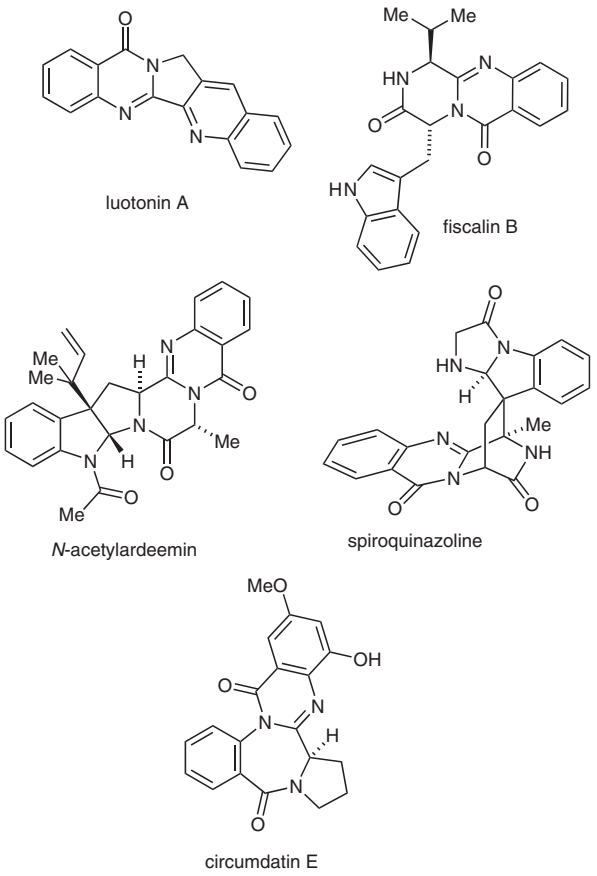

Figure 1 The structure of some representative quinazoline alkaloids.

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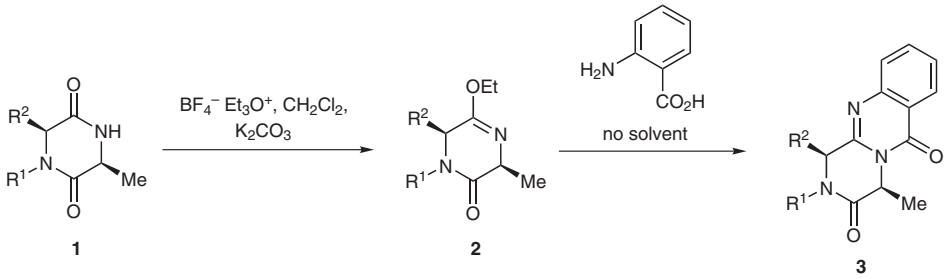
synthesis and based on the direct cyclocondensation of lactim ethers derived from piperazinediones with anthranilic acid.[17] Although the cyclocondensation step normally proceeds in low yield and sometimes leads to epimerization of stereocenters adjacent to carbonyl groups,[17,18] we considered this reaction a good candidate for optimization by microwave irradiation under solvent-free conditions,[19,20] and sought to study its application to the synthesis of representative quinazolin-4-one compounds structurally related to the above-mentioned natural frameworks. We now report in full[21] our studies on this subject.

We started our study with the preparation of some derivatives **3** of the pyrazino[2,1-*b*]quinazoline-3,6-dione system, related to the fiscalins and related alkaloids (fumiquinazolines and glyantrypine).[22] Thus, treatment of the known[23] 1,3-disubstituted piperazine-2,5-diones **1** with triethyloxonium tetrafluoroborate (Meerwein's salt) in the presence of potassium carbonate[24] afforded lactim ethers **2**. As shown in Table 1, their reaction with anthranilic acid in the absence of solvent and under thermal conditions (120–140 °C for 2 h) gave the expected cyclocondensation products **3**, albeit in modest yields (16–46%). These results were considerably improved when the reactions were carried out under microwave irradiation at 600 W, with the samples introduced in an alumina bath as a heat sink. Thus, microwave irradiation was associated with a dramatic decrease in reaction time (3–5 minutes under microwave irradiation, compared to 2 h for the conventional heating conditions). Two- to threefold increases in yield were observed for **3a** (entry 1), **3b** (entry 2), and **3e** (entry 5) and smaller, but also very significant, increases in the case of the preparation of **3c** and **3d** (entries 3 and 4). Due to the presence of an adjacent carbonyl group, it was necessary to confirm the integrity of the stereocenter in the reactions summarized in Table 1 and Scheme 1, especially since, as already mentioned, several examples of epimerization processes have been described in the literature for thermal reactions.[17,18] Stereocenter inversion for microwave reactions was ruled out, within the limits of detection of this technique, by ^{1}H NMR studies of **3c** in the presence of Eu(hfc)$_3$, using racemic tricycle as a reference. Also, no epimerization was observed in the preparation of **3e**, which bears two stereocenters, either under thermal or under microwave-assisted conditions.

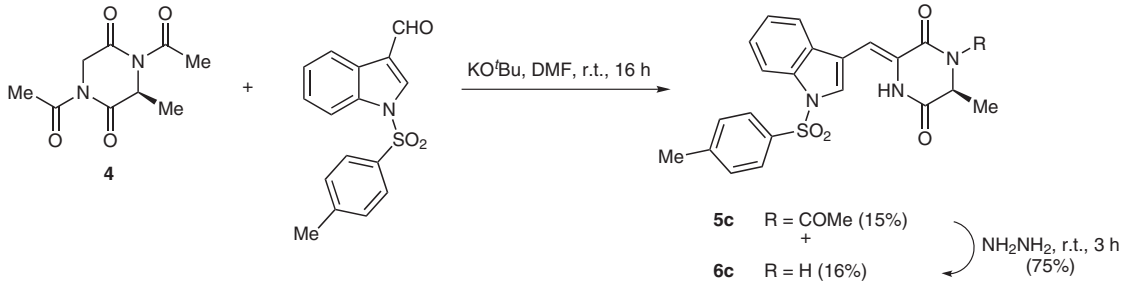
After establishing suitable microwave reaction conditions for the synthesis of the pyrazino[2,1-*b*]quinazolin-3,6-dione system, we set out for the study of more challenging examples. Lactim ethers with a conjugated, exocyclic double bond had proved in the past to be troublesome substrates for the thermal reaction with anthranilic acid.[25] Hence, we undertook the study of this case under our microwave-assisted conditions. The starting materials for this study were lactim ethers **7**, which were prepared from the corresponding piperazine-2,5-diones, two of which, **6a**,**b**, had been previously described,[25] while the preparation of **6c** is shown in Scheme 1. A base-catalyzed aldol condensation between 1,4-diacetylpiperazine-2,5-dione derivative **4** and 1-tosyl-1*H*-indole-3-carbaldehyde gave a moderate yield of a mixture of **5c** and **6c**, through a mechanism involving neighboring group assistance to the aldol reaction by the acetyl group adjacent to the reaction

Table 1 Microwave-Assisted Synthesis of Fiscalin-Related Compounds



Entry	**2**, **3**	R^1	R^2	Yield (%) of **2**	Synthesis of **3**			
					Conventional heating		Microwave irradiation	
					Conditions	Yield (%)	Conditions	Yield (%)
1	**a**	Me	H	56[17b]	120 °C, 2 h	38[17b]	600 W, 3 min	63
2	**b**	4-MeOC$_6$H$_4$	H	76	140 °C, 2 h	22[a]	600 W, 5 min	58
3	**c**	CH$_2$CH$_2$Ph	H	84	140 °C, 2 h	39	600 W, 5 min	51
4	**d**	2-naphthylmethyl	H	83	140 °C, 2 h	48	600 W, 3 min	58
5	**e**	1*H*-indol-3-ylmethyl	Me	–	140 °C, 2 h	16[b]	600 W, 6 min	48[b]

[a] This yield was mistakenly given as 40% in our preliminary report.[21]
[b] Overall yield from **1e**. The thermal reaction has been previously described.[23c]



Scheme 1

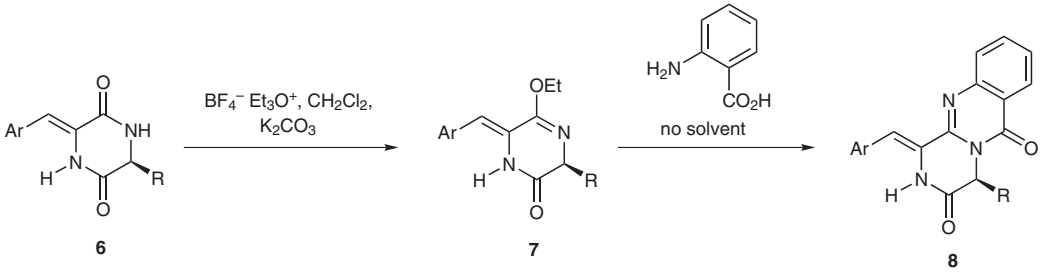
site.[25,26] Deacetylation of **5c** with hydrazine hydrate at room temperature gave an additional amount of **6c**.

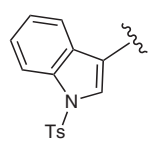
As shown in Table 2, compounds **6** were transformed into the corresponding lactim ethers **7** by exposure to Meerwein's salt. Microwave irradiation of the latter compounds in the presence of anthranilic acid led to moderate, but still much improved, yields of the desired pyrazino[2,1-*b*]quinazolines **8a–c** with regard to the results obtained under thermal conditions. In this case, the reaction required relatively long reaction times (9 min), reflecting the lowered reactivity of the lactim ether function associated with its conjugation.

The results obtained in the application of our methodology to the synthesis of compounds containing the complete ardeemin framework is summarized in Scheme 2. While the thermal reaction of anthranilic acid with lactim ether **9**, containing the tetracyclic ABCD ardeemin fragment, required melting both compounds together at 140 °C for six hours and gave **10** in 44% yield,[18] we found that the same transformation could be carried out in only three minutes and in 58% yield by microwave irradiation. Similarly, treatment of the known tetracyclic ardeemin fragment **11**[18] with anthranilic acid at 600 W for three minutes gave a 6:1 mixture of the diastereomeric deprenylardeemins **12** and **13**, in 48% overall yield, where the cyclocondensation is accompanied by partial epimerization of the tryptophan stereocenter. Besides the improved yield and shorter reaction time, this result was also better in terms of stereochemical integrity than the one obtained under conventional conditions, which led to a 34% overall yield of a 7:2:1 mixture of three compounds, namely **12**, retaining the configuration of the starting material, **13**, epimerized at the tryptophan stereocenter and **14**, epimerized at both the tryptophan and alanine stereocenters.[18] This result again showcases the mildness and higher efficiency of the microwave-assisted conditions in comparison with the traditional, thermal conditions.

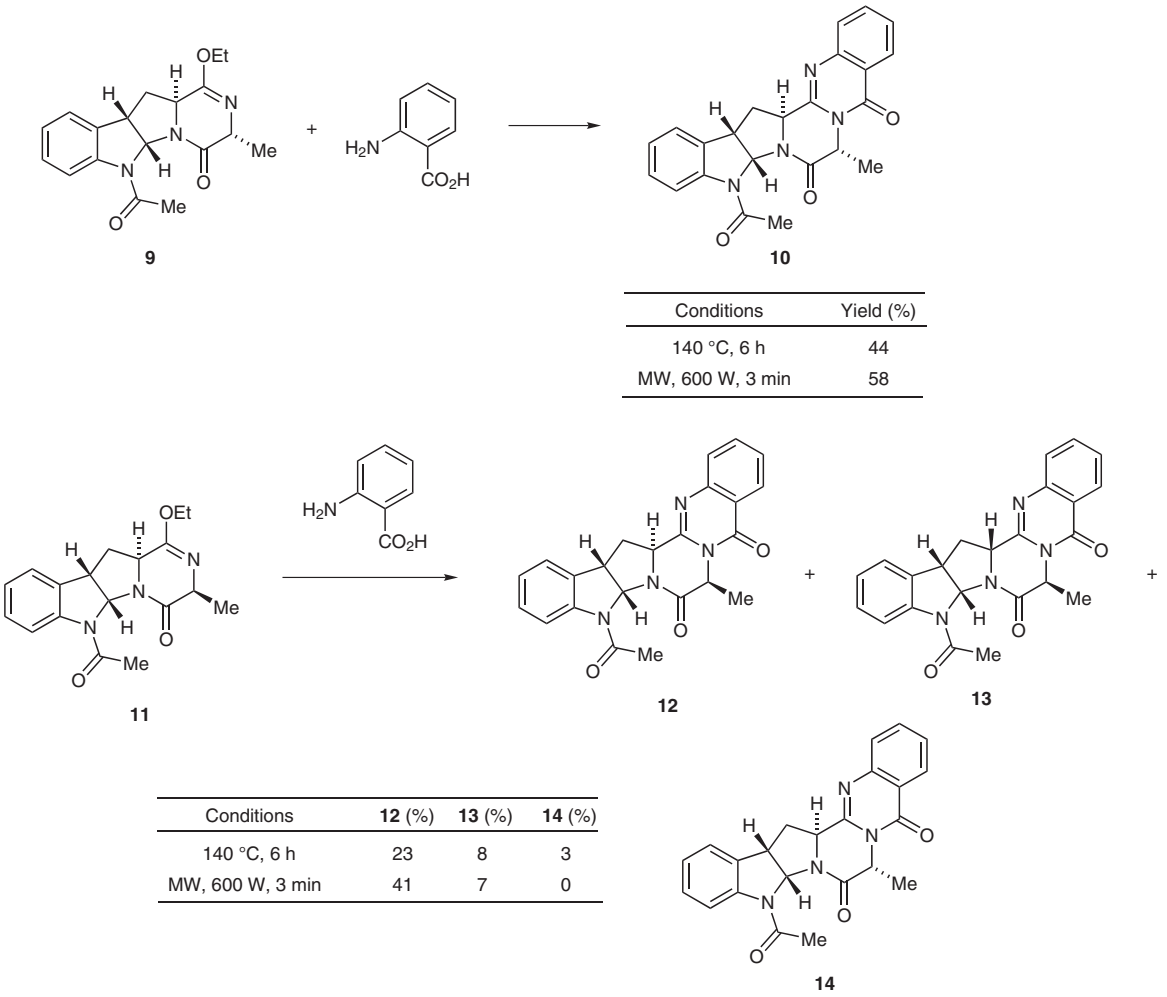
In a further development, we showed that the microwave-assisted synthesis could also be applied to the preparation of compounds where the quinazolinone moiety is fused to a seven-membered ring,[27] as shown by the one-step transformation of the known lactim ether **15**[28] into pentacyclic

Table 2 Microwave-Assisted Synthesis of Fiscalin-Related Compounds Bearing an Arylmethylene Chain



Entry	**6**, **7**, **8**	Ar	R	Yield (%) of **7**	Synthesis of **8**			
					Conventional heating		Microwave irradiation	
					Conditions	Yield (%)	Conditions	Yield (%)
1	**a**	4-$MeOC_6H_4$	Me	65[24]	120 °C, 2 h	15[25]	600 W, 9 min	26
2	**b**	4-$MeOC_6H_4$	*i*-Pr	–	not assayed	–	600 W, 9 min	25[a]
3	**c**		Me	86	not assayed	–	600 W, 9 min	19

[a] Overall yield from **6b**.

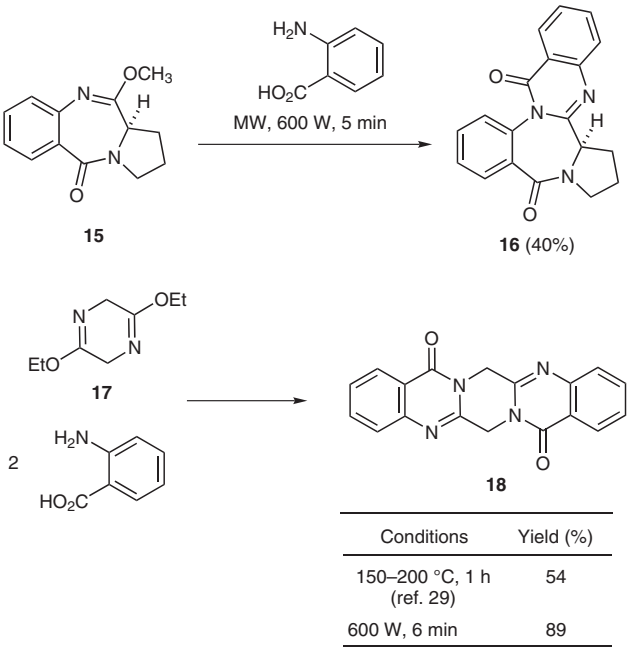


Scheme 2

compound **16** in 40% yield, which contains the complete framework of circumdatin E (Scheme 3). Although this yield is moderate, it is noteworthy that alternative methods for circumdatin synthesis often give poor yields or product mixtures.[29]

As a final check of the versatility of our method, we studied its application to a double von Niementowski-type cyclocondensation from bis-lactim ether **17**. We found that microwave irradiation provides an excellent entry to the linear pentacyclic framework of **18**, which was isolated in 89% yield compared to a 54% yield in the literature[30] for a similar reaction at 150–200 °C (Scheme 3).

In conclusion, we have shown that microwave irradiation significantly improves the reaction of lactim ethers with anthranilic acid. This reaction provides a useful alternative to existing methods for the preparation of complex heterocyclic frameworks related to the quinazoline alkaloids.



Scheme 3

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by TLC [aluminum plates coated with silica gel with fluorescent indicator (SDS CCM221254)]. Separations by flash chromatography were performed on silica gel (SDS 60 ACC

40–63 μm). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds examined as films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Polarimetric measurements were carried out on a Perkin Elmer 240 polarimeter operating at the emission wavelength of a Na lamp; concentrations for these measurements are given in g/100 mL. Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer. Microwave-assisted reactions were performed in a Moulinex domestic microwave oven. The reactants were thoroughly mixed and placed in a round-bottomed flask, which was completely submerged in alumina, contained in a beaker. The reaction was irradiated at 600 W for up to 9 × 1 min periods (see individual reactions), with 1 min cooling intervals between each pulse. The temperatures of the alumina at the end of each of these irradiation periods were 110 °C, 128 °C, 143 °C, 153 °C, 161 °C, 163 °C, 165 °C, 166 °C, and 167 °C, respectively.

5-Ethoxy-3-methyl-3,6-dihydropyrazine-2(1*H*)-ones 2; General Procedure

Triethyloxonium tetrafluoroborate (3.5 equiv) was added to a soln of **1**[23] (1 g, 1 equiv) in CH_2Cl_2 (50 mL) in the presence of anhyd Na_2CO_3 (1.3 g) and the mixture was stirred at r.t. under argon for 24 h. The mixture was then poured onto crushed ice, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to yield the crude compound, which could be used for the next reaction with no further purification. For analytical purposes, samples could be purified by column chromatography (silica gel, CH_2Cl_2). Compound **2a**[17] is known in the literature and **2e** was not isolated. Data for **2b–d** are given.

(3*S*)-5-Ethoxy-1-(4-methoxybenzyl)-3-methyl-3,6-dihydropyrazin-2(1*H*)-one (2b)

Following the general procedure for **2** using **1b** (1 g, 4.03 mmol) and triethyloxonium tetrafluoroborate (2.68 g, 14.1 mmol) gave **2b** (0.84 g, 76%) as an oil.

$[\alpha]_D^{25}$ +3.7 (*c* 0.29, $CHCl_3$).

IR (NaCl): 2975, 1700, 1653, 1512, 1489 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.8 Hz, 2 H, H2′, H6′), 6.83 (d, *J* = 8.8 Hz, 2 H, H3′, H5′), 4.51 (d, *J* = 14.3 Hz, 1 H, Ar-CH_2N), 4.47 (d, *J* = 14.3 Hz, 1 H, Ar-CH_2N), 4.20–4.00 (m, 3 H, OC*H*$_2$CH$_3$, H3), 3.80 (s, 3 H, OCH_3), 3.77 (d, *J* = 16.9 Hz, 1 H, H6), 3.67 (d, *J* = 16.9 Hz, 1 H, H6), 1.42 (d, *J* = 7.3 Hz, 3 H, C3-CH_3), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.91 (C2), 159.40 (C5), 156.72 (C4′), 129.81 (C3′, C5′), 127.9 (C1′), 114.3 (C2′, C6′), 61.6 (O*C*H$_2$CH$_3$), 55.5, 55.4 (CH_3O, C3), 48.6, 45.5 (C6, Ar-CH_2N), 21.3 (C3-*C*H$_3$), 14.2 (OCH_2CH_3).

Anal. Calcd for $C_{15}H_{20}N_2O_3$ (276): C, 65.20; H, 7.30; N, 10.14. Found: C, 65.14; H, 6.94; N, 9.81.

(3*S*)-5-Ethoxy-3-methyl-1-phenethyl-3,6-dihydropyrazin-2(1*H*)-one (2c)

Following the general procedure for **2** using **1c** (1 g, 4.31 mmol) and triethyloxonium tetrafluoroborate (2.87 g, 15.1 mmol) gave **2c** (0.94 g, 84%) as a syrup.

$[\alpha]_D^{25}$ –2.5 (*c* 0.11, $CHCl_3$).

IR (NaCl): 3027, 2978, 1698, 1653, 1493 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 5 H, Ar-H), 4.12–4.03 (m, 3 H, OC*H*$_2$CH$_3$, H3), 3.77–3.60 (m, 3 H, H6, PhCH$_2$C*H*$_2$N), 3.49–3.39 (m, 1 H, PhCH$_2$C*H*$_2$N), 2.87 (t, *J* = 7.7 Hz, 2 H, PhC*H*$_2$CH$_2$N), 1.33 (d, *J* = 7.2 Hz, 3 H, C3-CH_3), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.1 (C2), 160.0 (C5), 138.5 (C1′), 128.8, 128.7, 126.7, 61.6 (O*C*H$_2$CH$_3$), 55.6 (C3), 48.1 (C6), 47.3 (PhCH$_2$*C*H$_2$N), 33.3 (Ph*C*H$_2$CH$_2$N), 20.9 (C3-*C*H$_3$), 14.2 (OCH_2CH_3).

Anal. Calcd for $C_{15}H_{20}N_2O_2$ (260): C, 69.20; H, 7.74; N, 10.76. Found: C, 68.80; H, 7.31; N, 11.02.

(3*S*)-5-Ethoxy-3-methyl-1-(2-naphthylmethyl)-3,6-dihydropyrazin-2(1*H*)-one (2d)

Following the general procedure for **2** using **1d** (1 g, 3.73 mmol) and triethyloxonium tetrafluoroborate (2.48 g, 13.05 mmol) gave **2d** (0.92 g, 83%) as an oil.

IR (NaCl): 3054, 2977, 1698, 1655, 1488 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.82–7.23 (m, 7 H, Ar-H), 4.76–4.70 (AB system, *J* = 14.5 Hz, 2 H, naphthyl-CH_2N), 4.30–4.00 (m, 3 H, OC*H*$_2$CH$_3$, H3), 3.97 (d, *J* = 16.9 Hz, 1 H, C6), 3.73 (d, *J* = 16.9 Hz, 1 H, C6), 1.47 (d, *J* = 7.2 Hz, 3 H, C3-CH_3), 1.20 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.9 (C2), 156.5 (C5), 133.1, 132.8, 128.8, 127.6, 127.3, 126.3, 126.1, 125.9, 61.3 (O*C*H$_2$CH$_3$), 55.4 (C3), 49.2 (C6), 45.5 (naphthyl-*C*H$_2$N), 21.1 (C3-*C*H$_3$), 14.1 (OCH_2CH_3).

Anal. Calcd for $C_{18}H_{20}N_2O_2$ (296): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.45; H, 6.70; N, 9.13.

Pyrazinoquinazolines 3; General Procedures

Conventional Heating; Method A

A mixture of **2** (1 equiv) and anthranilic acid (2.2 equiv) was heated at 140 °C for 2 h under argon. After cooling, the mixture was treated with 25% NH_4OH soln and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated to give crude product that was purified by column chromatography (silica gel, CH_2Cl_2). Compounds **3a**[17] and **3e**[23c] are known in the literature. Data for **3b–d** are given.

Microwave-Assisted Conditions; Method B

A 10-mL flask containing a mixture of **2** (1 equiv) and anthranilic acid (1.1 equiv) was completely submerged in alumina, contained in a beaker, and irradiated for 1 min at 600 W in a domestic microwave oven. The reaction was left to cool for 1 min and submitted to 2 additional irradiation–cooling cycles. The solid thus obtained was chromatographed (silica gel, petroleum ether–EtOAc gradients) to yield **3**.

(4*S*)-2,4-Dimethyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (3a)

Following the general procedure for **3**, method A (literature procedure[17]) gave **3a** in 38% yield; method B using **2a**[17] (100 mg, 0.59 mmol) and anthranilic acid (88 mg, 0.65 mmol) gave **3a** (90 mg, 63%) as a white solid.

(4*S*)-2-(4-Methoxybenzyl)-4-methyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (3b)

Following the general procedure for **3**, method A using **2b** (300 mg, 1.08 mmol) and anthranilic acid (340 mg, 2.42 mmol) gave **3b** (80 mg, 22%) as a colorless syrup; method B using **2b** (195 mg, 0.71 mmol) and anthranilic acid (116 mg, 0.85 mmol) gave **3b** (143 mg, 58%) as a colorless syrup.

$[\alpha]_D^{25}$ –56.14 (*c* 0.34, CH_2Cl_2).

IR (KBr): δ = 2947, 1675, 1607, 1555, 1508, 1472 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8 Hz, 1 H, H7), 7.74 (t, *J* = 7.2 Hz, 1 H, H9), 7.54 (d, *J* = 8.0 Hz, 1 H, H10), 7.46 (t, *J* = 8.0 Hz, 1 H, H8), 7.21 (d, *J* = 6.8 Hz, 2 H, H2′, H6′), 6.85 (d, *J* = 6.8 Hz, 2 H, H3′, H5′), 5.50 (q, *J* = 7.2 Hz, 1 H, H4), 4.81 (d, *J* = 14.4 Hz, 1 H, Ar-CH_2N), 4.47 (d, *J* = 14.4 Hz, 1 H, Ar-CH_2N), 4.44 (d, *J* = 16.9 Hz, 1 H, C1), 4.33 (d, *J* = 16.9 Hz, 1 H, H1), 3.77 (s, 3 H, OCH_3), 1.57 (d, *J* = 7.2 Hz, 3 H, C4-CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.45 (C3), 159.7 (C6), 151.1 (C4′), 148.1 (C11a), 147.2 (C10a), 134.9, 129.9, 129.4, 127.4, 127.3, 127.2, 127.0, 120.6, 115.2, 114.6, 55.4 (CH_3O), 52.2 (C4), 49.2 (Ar-CH_2-N), 49.1 (C1), 17.2 (CH_3).

Anal. Calcd for $C_{20}H_{19}N_3O_3$ (349): C, 68.75; H, 5.48; N, 12.03. Found: C, 68.46; H, 6.01; N, 11.89.

(4*S*)-4-Methyl-2-phenethyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (3c)

Following the general procedure for **3**, method A using **2c** (90 mg, 3.46 mmol) and anthranilic acid (1.09 g, 7.95 mmol) gave **3c** (450 mg, 39%) as a white solid; method B using **2c** (290 mg, 1.11 mmol) and anthranilic acid (193 mg, 1.41 mmol) gave **3c** (190 mg, 51%) as a colorless syrup; mp 106–08 °C.

$[\alpha]_D^{25}$ +59.64 (*c* 0.34, CH_2Cl_2).

IR (KBr): δ = 3428, 2979, 1682, 1667, 1598 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8 Hz, 1 H, H7), 7.74 (t, *J* = 8.4 Hz, 1 H, H9), 7.55 (d, *J* = 8.1 Hz, 1 H, H10), 7.47 (t, *J* = 7.1 Hz, 1 H, H8), 7.22–7.09 (m, 5 H, Ph), 5.41 (q, *J* = 7.2 Hz, 1 H, H4), 4.32 (d, *J* = 16.7 Hz, 1 H, H1), 4.14 (d, *J* = 16.7 Hz, 1 H, H1), 4.12 (m, 1 H, $PhCH_2CH_2N$), 3.51 (m, 1 H, $PhCH_2CH_2N$), 3.01–2.91 (m, 2 H, $PhCH_2CH_2N$), 1.47 (d, *J* = 7.2 Hz, 3 H, C4-CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.4 (C3), 160.0 (C6), 148.0 (C11a), 147.2 (C10a), 138.0, 134.9, 128.9, 128.9, 127.4, 127.1, 127.0, 126.9, 120.5, 52.3 (C4), 51.1 ($PhCH_2CH_2N$), 48.7 (C1), 33.7 ($PhCH_2CH_2N$), 16.8 (CH_3).

Anal. Calcd for $C_{20}H_{19}N_3O_2$ (333): C, 72.05; H, 5.74; N, 12.60. Found: C, 72.31; H, 6.06; N, 12.95.

(4*S*)-4-Methyl-2-(2-naphthylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (3d)

Following the general procedure for **3**, method A using **2d** (0.30 g, 1.01 mmol) and anthranilic acid (0.31 g, 2.26 mmol) gave **3d** (0.18 g, 48%) as a white solid. Method B using **2d** (166 mg, 0.56 mmol) and anthranilic acid (95 mg, 0.70 mmol) gave **3d** (121 mg, 58%) as a white solid; mp 140–42 °C.

IR (KBr): 3428, 2979, 1682, 1667, 1598 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.9 Hz, 1 H, H7), 7.89–7.67 (m, 5 H Ar), 7.54–7.36 (m, 5 H, Ar), 5.55 (q, *J* = 7.2 Hz, 1 H, H4), 5.02 (d, *J* = 14.4 Hz, 1 H, ArCH_2N), 4.69 (d, *J* = 14.4 Hz, 1 H, ArCH_2N), 4.47 (d, *J* = 16.9, 1 H, H1), 4.36 (d, *J* = 16.9, 1 H, H1), 1.60 (d, *J* = 7.2 Hz, 3 H, C4-CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.5 (C3), 160.0 (C6), 151.1 (C2′), 148.1 (C11a), 147.2 (C10a), 136.3, 134.8, 127.3, 127.2, 126.9, 126.9, 122.4, 122.2, 120.5, 119.7, 118.5, 112.3, 111.4, 52.3 (C4), 51.1 (Ar-CH_2-N), 48.2 (C1), 16.8 (C4-CH_3).

Anal. Calcd for $C_{23}H_{19}N_3O_2$ (369): C, 74.78; H, 5.18; N, 11.37. Found: C, 75.19; H, 5.49; N, 11.08.

(1*S*,4*S*)-2-(1*H*-Indol-3-ylmethyl)-1,4-dimethyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (3e)

Method A: This procedure has been previously described[23c] and was used to give **3e** in 16% overall yield from **1e**. Method B: Following the general procedure for **2**, **1e**[23c] (100 mg, 0.37 mmol) was treated with triethyloxonium tetrafluoroborate (246 mg, 1.29 mmol). The crude **2e** thus obtained was mixed with anthranilic acid (66 mg, 0.48 mmol). After cooling, the mixture was subjected to column chromatography (silica gel) to afford **3e**[23c] (66 mg, 48%) as a white solid.

6-Methyl-3-[(1-tosyl-1*H*-indol-3-yl)methylene]piperazine-2,5-diones 5c and 6c

To a cooled (0 °C), stirred soln of (3*S*)-1,4-diacetyl-3-methylpiperazine-2,5-dione (**4**,[25] 488 mg, 2.3 mmol) and 1-tosyl-1*H*-indole-3-carbaldehyde (1 g, 3.4 mmol) in anhyd DMF (5 mL), maintained under argon, was added dropwise *t*-BuOK (1 M in *t*-BuOH; 2.4 mL, 2.4 mmol). The soln was stirred at r.t. for 16 h, neutralized with AcOH and poured onto ice (25–50 g), giving a precipitate which was filtered. The filtrate was extracted with EtOAc (3 × 50 mL), which was dried (Na_2SO_4) and evaporated. The residue was mixed with the precipitate initially obtained and this mixture was purified by column chromatography (silica gel, petroleum ether–EtOAc, gradient starting from 5:1) to give **5c** (153 mg, 15%) and **6c** (152 mg, 16%).

(6*S*,3*Z*)-1-Acetyl-6-methyl-3-[(1-tosyl-1*H*-indol-3-yl)methylene]piperazine-2,5-dione (5c)

Mp 211–213 °C.

$[\alpha]_D^{25}$ –3.8 (*c* 0.13, $CHCl_3$).

IR (KBr): 3083, 1693, 1380, 1175 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.91 (s, 1 H, H4), 8.00 (d, *J* = 8.0 Hz, 1 H, H7′), 7.89 (s, 1 H, H2′), 7.83 (d, *J* = 8.4 Hz, 2 H, H2″, H6″), 7.61 (d, *J* = 7.1 Hz, 1 H, H4′), 7.41–7.24 (m, 5 H, H5′, H6′, H3″, H5″, Hα), 5.19 (q, *J* = 7.1 Hz, 1 H, H6), 2.59 (s, 3 H, $COCH_3$), 2.35 (s, 3 H, $C_6H_4CH_3$), 1.21 (d, *J* = 6.9 Hz, 3 H, C6-CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.0 ($COCH_3$), 167.5 (C5), 160.8 (C2), 145.8 (C1″), 134.8 (C7a′), 134.7 (C4″), 130.3 (C3″, C5″), 129.4 (C3a′), 127.2 (C2″, C6″), 126.1 (C2′), 125.8 (C3), 125.5 and 124.2 (C4′ and C5′), 119.7 (C6′), 114.7 (C3′), 113.9 (C7′), 110.7 (Cα), 53.0 (C6), 27.0 ($COCH_3$), 21.8 ($C_6H_4CH_3$), 19.9 (C6-CH_3).

Anal. Calcd for $C_{23}H_{21}N_3O_5S$ (451): C, 61.19; H, 4.69; N, 9.31. Found: C, 60.80; H, 4.67; N, 9.07.

(3*S*,6*Z*)-3-Methyl-6-[(1-tosyl-1*H*-indol-3-yl)methylene]piperazine-2,5-dione (6c)

Mp 261–263 °C.

$[\alpha]_D^{25}$ –32.5 (*c* 0.08, DMSO).

IR (KBr): 3205, 3062, 1674, 1372, 1168 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 10.18 (br s, 1 H, H1), 8.52 (br s, 1 H, H4), 8.34 (s, 1 H, H2′), 7.98 (d, *J* = 8.3 Hz, 2 H, H2″, H6″), 7.89 (d, *J* = 7.8 Hz, 1 H, H7′), 7.66 (d, *J* = 7.9 Hz, 1 H, H4′), 7.39 (d, *J* = 8.2 Hz, 2 H, H3″, H5″), 7.32–7.28 (m, 2 H, H5′, H6′), 6.70 (s, 1 H, Hα), 4.19 (q, *J* = 7.0 Hz, 1 H, H3), 2.30 (s, 3 H, $C_6H_4CH_3$), 1.36 (d, *J* = 6.9 Hz, 3 H, C3-CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.9 (C5), 159.8 (C2), 145.6 (C1″), 133.8 (C7a′), 133.4 (C4″), 130.2 (C3″, C5″), 129.8 (C3a′), 127.4 (C2′), 126.9 (C2″, C6″), 125.7 (C3), 125.2 (C4′), 123.7 (C5′), 119.4 (C6′), 114.1 (C3′), 113.0 (C7′), 103.0 (Cα), 50.3 (C6), 21.00 ($C_6H_4CH_3$), 19.2 (C3-CH_3).

Anal. Calcd for $C_{23}H_{21}N_3O_5S$ (409): C, 61.60; H, 4.68; N, 10.26. Found: C, 61.36; H, 4.60; N, 10.10.

Formation of 6c by Deacetylation of 5c with Hydrazine Hydrate

To a soln of **5c** (0.250 g, 0.554 mmol) in DMF (5 mL), cooled to 0 °C and kept under argon, was added 80% hydrazine monohydrate (25 μL, 1.031 mmol). The mixture was stirred at r.t. for 3 h and poured onto crushed ice. **6c** (170 mg, 75%) precipitated as a white

solid that was filtered and dried overnight in vacuo in the presence of P_2O_5.

(3S,6Z)-5-Ethoxy-3-methyl-6-(1-tosyl-1*H*-indol-3-ylmethylene]piperazin-2-one (7c)

Following the general procedure for **2** using **6c** (100 mg, 0.24 mmol), triethyloxonium tetrafluoroborate (55 mg, 0.29 mmol), Na_2CO_3 (154 mg), and CH_2Cl_2 (3.5 mL), followed by chromatography (silica gel, petroleum ether–EtOAc, 4:1) gave **7c** (92 mg, 86%) as a colorless viscous oil.

IR (KBr): 3117, 1679, 1637 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.1 Hz, 2 H, H2″, H6″), 7.81 (d, *J* = 8.4 Hz, 2 H, H3″, H5″), 7.69 (s, 1 H, H2′), 7.58 (br s, 1 H, H1), 7.55–7.24 (m, 4 H, H4′, H5′, H6′, H7′), 6.51 (s, 1 H, Hα), 4.43–4.20 (m, 3 H, H3, OCH_2CH_3), 2.35 (s, 3 H, $C_6H_4CH_3$), 1.55 (d, *J* = 8.1 Hz, 3 H, C3-CH_3), 1.39 (q, *J* = 7.0 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.5 (C5), 152.3 (C2), 145.3 (C1″), 134.7 (C7a′), 134.7 (C4″), 129.9 (C3″, C5″), 129.4 (C2′), 126.8 (C2″, C6″), 125.5 (C3a′), 124.8 (C6′), 123.7 (C4′, C5′), 119.7 (C7′), 115.0 (C6), 113.7 (C3′), 99.8 (Cα), 62.0 (OCH_2CH_3), 55.8 (C3), 21.4 (OCH_2CH_3), 21.4 ($C_6H_5CH_3$), 14.1 (C3-CH_3).

Anal. Calcd for $C_{23}H_{23}N_3O_4S$ (437): C, 63.14; H, 5.30; N, 9.60. Found: C, 62.83; H, 5.45; N, 9.31.

1-(Arylmethylene)pyrazinoquinazolines 8; General Procedures

Following the general procedures for **3**, methods A and B, the microwave-assisted reactions required 9 × 1 min irradiation pulses, with intermediate 1 min cooling periods. **8a** and **8b** are known in the literature.[25]

(4*S*,1*Z*)-1-(4-Methoxybenzylidene)-4-methyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (8a)

Following the general procedure for **3**, method A, the preparation of **8a** has been previously described;[25] method B using **7a**[25] (15 mg, 0.054 mmol) and anthranilic acid (8 mg, 0.060 mmol) with 9 × 1 min irradiation gave **8a** (5 mg, 26%) as a white solid.

(4*S*,1*Z*)-4-Isopropyl-1-(4-methoxybenzylidene)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (8b)

Previously prepared using the Eguchi protocol.[25] Following the general procedures for **2** and **3**, method B using **6b** (100 mg, 0.36 mmol), triethyloxonium tetrafluoroborate (82 mg, 0.431 mmol), Na_2CO_3 (230 mg), and CH_2Cl_2 (5 mL) gave **7b** (60 mg, 54%) as a colorless oil, together with recovered starting material (30 mg, 33%). The microwave-assisted reaction between crude **7b** (16 mg, 0.058 mmol) and anthranilic acid (9 mg, 0.067 mmol) using 9 × 1 min irradiation gave **8b** (9 mg, 25% overall from **6b**) as a pale orange oil.

(4*S*,1*Z*)-4-Methyl-1-(1-tosyl-1*H*-indol-3-ylmethylene)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (8c)

Following the general procedure for **3**, method B using **7c** (90 mg, 0.206 mmol) and anthranilic acid (35 mg, 0.260 mmol) and 9 × 1 min irradiation gave **8c** (20 mg, 19%) as a white solid.

$[\alpha]_D^{25}$ –80.0 (*c* 0.02, $CHCl_3$).

IR (NaCl): 3400, 1681 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.9 Hz, 1 H, H7), 8.68 (s, 1 H, NH), 8.01 (d, *J* = 8.1 Hz, 1 H, H7′), 7.91 (t, *J* = 7.8 Hz, 1 H, H8), 7.83 (d, *J* = 8.3 Hz, 1 H, H10), 7.78 (d, *J* = 7.8 Hz, 1 H, H9), 7.67 (d, *J* = 8.0 Hz, 2 H, H2′, H6′), 7.62 (d, *J* = 6.4 Hz, 1 H, H4′), 7.45–7.31 (m, 3 H, H2′, H5′, H6′), 7.21 (s, 1 H, Hα), 7.05 (d, *J* = 8.1 Hz, 2 H, H3′, H5′), 5.52 (q, *J* = 6.7 Hz, 1 H, H4), 2.18 (s, 3 H, $C_6H_4CH_3$), 1.59 (d, *J* = 6.7 Hz, 3 H, C4-CH_3).

Anal. Calcd for $C_{28}H_{22}N_4O_4S$ (510): C, 65.87; H, 4.34; N, 10.97. Found: C, 65.50; H, 4.63; N, 10.59.

Deprenylardeemin Analogue 10

Following the general procedure for **3**, method B using **9**[31] (110 mg, 0.34 mmol) and anthranilic acid (138 mg, 1.00 mmol) gave **10**[18] (78 mg, 58%) as a white solid.

Deprenylardeemin Analogues 12 and 13

Following the general procedure for **3**, method B using **11**[31] (90 mg, 0.27 mmol) and anthranilic acid (81 mg, 0.59 mmol) gave **12**[18] (45 mg, 41%) and **13**[18] (8 mg, 7%), both as white solids.

(5b*S*)-5b,6,7,8-Tetrahydropyrrolo[2,1-*c*]quinazolino[3,2-*a*][1,4]benzodiazepin-10,16-dione (16)

Following the general procedure for **3**, method B using **15**[28] (100 mg, 0.43 mmol) and anthranilic acid (66 mg, 0.47 mmol) and 5 × 1 min irradiation gave **16** (55 mg, 40%) as a white solid; mp 239–41 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 7.8, 1.4 Hz, 1 H, H1), 8.00 (dd, *J* = 6.8, 1.6 Hz, 1 H, H11), 7.79 (dt, *J* = 6.8, 1.8 Hz, 1 H, H2), 7.71 (dd, *J* = 7.5, 0.8 Hz, 1 H, H14), 7.60–7.45 (m, 4 H, H3, H4, H12, H13), 4.54 (d, *J* = 6.2 Hz, 1 H, H5b), 3.85–3.74 (m, 1 H, H8), 3.69–3.57 (m, 1 H, H8), 3.23–3.15 (m, 1 H, H6), 2.36–1.90 (m, 3 H, H6, H7).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 164.9 (C10), 162.1 (C16), 154.0 (C10a), 146.5 (C16a), 135.2 (C2), 133.6 (C14a), 132.7 (C4a), 131.2 (C12), 130.3 (C11), 129.1 (C13), 128.7 (C3), 128.0 (C4), 128.0 (C14), 127.9 (C1), 59.3 (C5), 46.9 (C8), 27.4 (C6), 24.1 (C7).

Anal. Calcd for $C_{19}H_{15}N_3O_2$ (317): C, 71.91; H, 4.76; N, 13.24. Found: C, 71.62; H, 5.03; N, 12.99.

6,14-Dihydropyrazino[2,1-*b*:5,4-*b*′]diquinazoline-8,16-dione (18)

2,5-Diethoxy-3,6-dihydropyrazine (17)

To a suspension of piperazine-2,5-dione (1 g, 8.77 mmol) in anhyd CH_2Cl_2 (100 mL) under argon, was added triethyloxonium tetrafluoroborate (3.019 g, 15.89 mmol). The suspension was stirred at r.t. for 48 h and then poured on a buffer soln prepared from $Na_2HPO_4 \cdot 2H_2O$ (4.688 g, 26.31 mmol), $NaH_2PO_4 \cdot H_2O$ (1.21 g. 8.77 mmol), and H_2O (30 mL). The CH_2Cl_2 phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, giving **17** (956 mg, 64%) as a colorless oil that solidified upon cooling at –18 °C.[32]

IR (KBr): 1709 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 4.02 (s, 4 H, H3, H6), 4.12 (q, *J* = 7.1 Hz, 4 H, 2 OCH_2CH_3), 1.30 (t, *J* = 7.1 Hz, 6 H, 2 OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.6 (C2, C5), 61.3 (2 OCH_2CH_3), 46.9 (C3, C6), 14.6 (2 OCH_2CH_3).

Anal. Calcd for $C_8H_{14}N_2O_2$ (170): C, 56.45; H, 8.29; N, 16.46. Found: C, 56.18; H, 8.27; N, 16.22.

Three-Component Cyclocondensation of 17 with Two Equivalents of Anthranilic Acid

Following the general procedure for **3**, method B using **17** (200 mg, 1.18 mmol) and anthranilic acid (483 mg, 3.53 mmol) with 6 × 1 min irradiation pulses, and washing the mixture with Et_2O gave **18** (332 mg, 89%) as a white solid; mp >300 °C.

IR (KBr): 1689, 1607 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.9 Hz, 2 H, H4, H12), 7.87 (t, *J* = 7.1 Hz, 2 H, H3, H11), 7.71 (d, *J* = 7.6 Hz, 2 H, H1, H9), 7.57 (d, *J* = 8.0 Hz, 2 H, H2, H10), 5.31 (s, 4 H, H6, H14).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.8 (C8, C16), 149.9 (C5a, C13a), 147.4 (C4a, C12a), 135.2 (C3, C11), 127.5 (C1, C9), 127.4 (C2, C10), 126.7 (C4, C12), 120.5 (C8a, C16a), 44.8 (C6, C14).

Anal. Calcd for $C_{18}H_{12}N_4O_2$ (316): C, 68.35; H, 3.82; N, 17.71. Found: C, 68.07; H, 3.85; N, 17.46.

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