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Extraction, Hemisynthesis, and Synthesis of Canthin-6-one Analogues. Evaluation of Their Antifungal Activities

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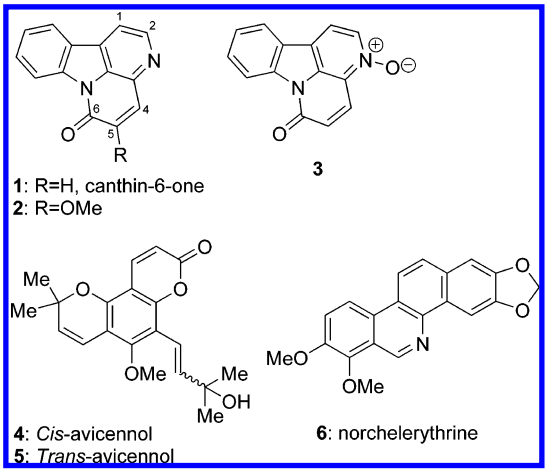
Zanthoxylum chiloperone var. *angustifolium* was investigated. Alkaloids **1**−**3** from the canthin-6-one series were characterized. Derivatives **7**−**28** were prepared by hemisynthesis or total synthesis. All compounds were tested for in vitro antifungal activities against five pathogenic fungal strains. Analogues of canthin-6-one did not show better antifungal activities.

The canthin-6-one alkaloids are a subclass of β-carboline alkaloids with an additional D-ring. Canthin-6-one **1** was first isolated in 1952 by Haynes et al. from Australian *Pentaceras australis* (Rutaceae).[1,2] Since then, more than forty members of this class of alkaloids have been reported from several plants primarily of the Rutaceae[2,3] and Simaroubaceae[2,4] families, but also from Malvaceae,[2] Amaranthaceae,[2] Caryophyllaceae,[2,5] Zygophyllaceae,[6] and recently from fungi (*Boletus curtisii* Berk.).[7] Several of these alkaloids have been bioassayed and show interesting pharmacological activities.[2,8,9] Canthin-6-one and some derivatives isolated from *Zanthoxylum chiloperone* var. *angustifolium* displayed interesting antifungal activities.[3b,10] We wanted to further investigate these observations by screening additional natural canthin-6-ones and also hemisynthetic and synthetic analogues of **1**.



Results and Discussion

Silica gel chromatography of the CH_2Cl_2 extract of air-dried and ground bark material of *Zanthoxylum chiloperone* var. *angustifolium* Engl. (Rutaceae) yielded three known alkaloids (canthin-6-one **1**, 5-methoxycanthin-6-one (**2**), and canthin-6-one *N*-oxide (**3**)). Two other compounds were also isolated. Compounds **4** and **5** were *cis*-avicennol and *trans*-avicennol, two pyranocoumarins previously isolated from other species of *Zanthoxylum* such as *Z. elephantiasis* Macfad.[11] Norchelerythrine (**6**) was also characterized from this extract.[12]

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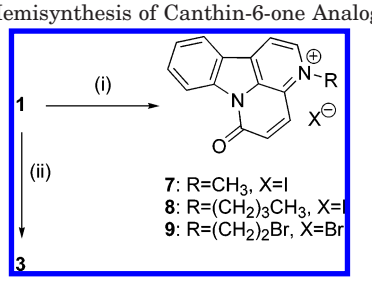
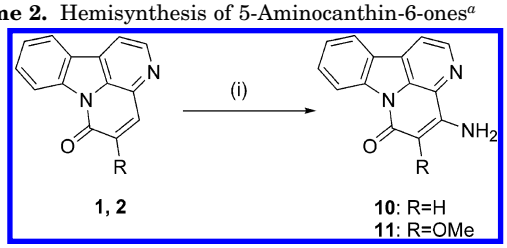
Scheme 1. Hemisynthesis of Canthin-6-one Analogues[a]



[a] Reagents and conditions: (i) RX (excess), rt (**7**: 50%; **8**: 50%; **9**: 50%); (ii) *m*CPBA (3 equiv), CH_2Cl_2, rt, 18 h (75%).

Scheme 2. Hemisynthesis of 5-Aminocanthin-6-ones[a]



[a] Reagents and conditions: NaN_3 (15 equiv), $ZnBr_2$ (15 equiv), H_2O/DMF, reflux, 48 h (**10**: 70%; **11**: 40%).

Our efforts were first directed to exploring the possibilities of chemical modifications starting from natural **1**. A few analogues were prepared using simple reactions (Scheme 1). A series of *N*-3 alkyl derivatives were prepared by reacting **1** with excess haloalkanes. In these conditions, water-soluble **7**−**9**, bearing respectively a methyl, an *n*-propyl, and a bromoethane moiety, were obtained in 50% yield. Larger amounts of canthin-6-one *N*-oxide (**3**) for needed biological assays were also prepared by oxidation of **1** with *meta*-chloroperbenzoic acid in CH_2Cl_2 or alternatively with hydrogen peroxide in acetic acid, affording **3** in 75% yield. An original amination reaction, involving sodium azide and a zinc salt, was also exploited toward the synthesis of two 4-aminated analogues (**10**, **11**) from respectively **1** and **2** (Scheme 2).[13]

Our interest in canthin-6-one and analogues for extended biological assays has taken us to search for a flexible and low-cost method of preparation,[14] using tryptamines as starting materials. The retrosynthetic analysis for the construction of their basic framework is depicted in Figure 1. The key step in our synthesis is to access an appropriately substituted *β*-carboline precursor promoted by a Bischler−Napieralski cyclization. Thus, total synthesis of canthin-6-one and analogues is depicted in Scheme 3. Exposure of tryptamines **12a**−**d** to succinic anhydride in CH_2Cl_2 at room temperature afforded the corresponding amides **13a**−**d**. Esterification of the latter with catalytic Amberlyst H-15 in MeOH afforded methyl esters **14a**−**d** in almost quantitative yields over the two steps. Treatment of amides **14a**−**d** in the Bischler−Napieralski conditions using $POCl_3$ afforded cyclization to produce imines **15a**−**d**.[15] Reaction conditions of this crucial step, especially in terms of solvent and temperature, were extensively studied. The best conditions appeared to be the use of 3 equiv of $POCl_3$ in refluxing benzene for 2 h;[16] other conditions resulted in substantial decomposition with little or no

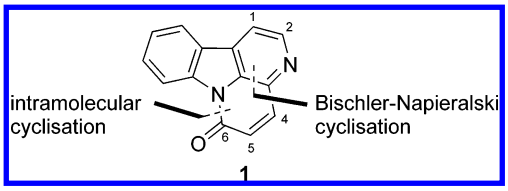
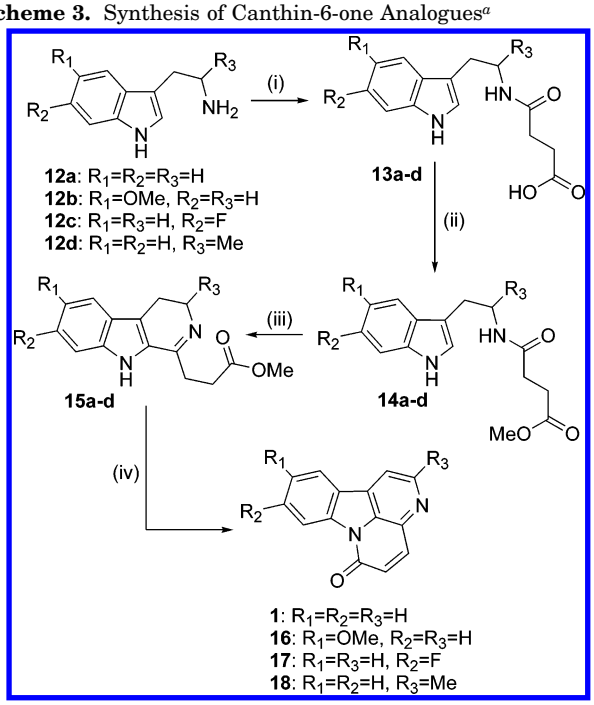


Figure 1. Synthetic approach for **1**.

Scheme 3. Synthesis of Canthin-6-one Analogues[a]



[a] Reagents and conditions: (i) succinic anhydride (1.1 equiv), CH_2Cl_2, rt, 18 h (**13a**: 98%, **13b**: 99%, **13c**: 98%, **13d**: 98%); (ii) Amberlyst 15 (20% w/w), MeOH, reflux, 18 h (**14a**: 98%, **14b**: 98%, **14c**: 98%, **14d**: 98%); (iii) $POCl_3$ (3 equiv), C_6H_6, reflux, 1 h; and then (iv) DBU (3 equiv), CH_2Cl_2, rt, 18 h (**1**: 80%, **16**: 70%, **17**: 80%, **18**: 20% in two steps).

formation of the desired compounds. With our key intermediates in hand, the final step, i.e., the intramolecular cyclization, was accomplished by exposure of imines **15a**−**d** (which were normally not isolated) to a strong hindered base such as diazabicycloundecene (DBU) in CH_2Cl_2 at room temperature, which led directly to canthin-6-ones **1** and **16**−**18** in good overall yields (60% overall yield for **1**). Interestingly, complete oxidation (i.e., C-1/C-2 and C-4/C-5 bonds) of the tetracyclic structures occurred spontaneously probably by contact with air, and no intermediates could be isolated. Some points to be stressed are the following. Attempts to circumvent the esterification step were disappointing, resulting, however, in the final isolation of **1** but with a 3-fold decreased overall yield. Imines **15a**−**d** appeared to be quite unstable, and their purification remained problematic; rapid filtration of the crude reaction mixture over silica gel was chosen as a good compromise between purity and yield. In the case of **1** we were able to fully characterize the imine intermediate **15a** (see Experimental Section).

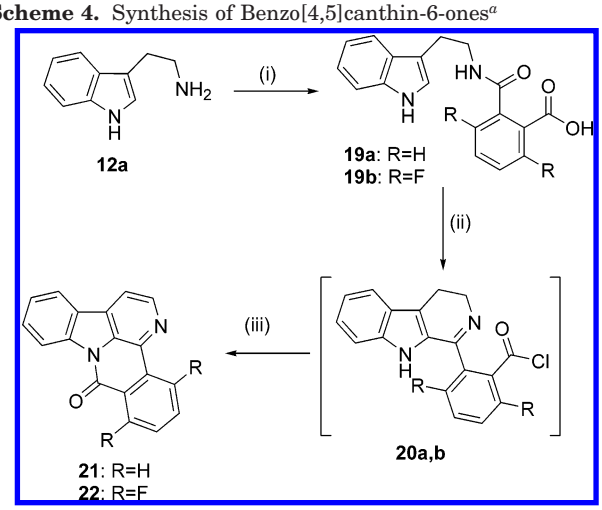
To further explore the scope of our synthetic strategy, benzo[*e*]canthin-6-one (**21**) was targeted as well as **22**, a difluoro analogue. Tryptamine was reacted with phthalic anhydrides as depicted in Scheme 4 to afford the corresponding amides **19a**,**b** in quantitative yield. This time no esterification step was required: **19a**,**b** were directly treated with $POCl_3$ in benzene, leading probably to benzoyl chlorides **20a**,**b**, which were not isolated, but were directly exposed to DBU in CH_2Cl_2 at room temperature, affording **21**[17] and **22**. As observed in the case of **1** and **16**−**18**, oxidation of the C-1/C-2 bond occurred spontaneously. Two other 4,5-substituted derivatives were prepared according to the same process. Compounds **25** and **28**, with respectively a cyclohexane ring and a pyrazine, were obtained but in modest yields (Scheme 5).

Compounds were tested for their antifungal activities against selected fungi. The results are presented in Table 1. Ketoconazole has MIC values that are about one-third

Table 1. Antifungal Screening of Canthin-6-one Analogues

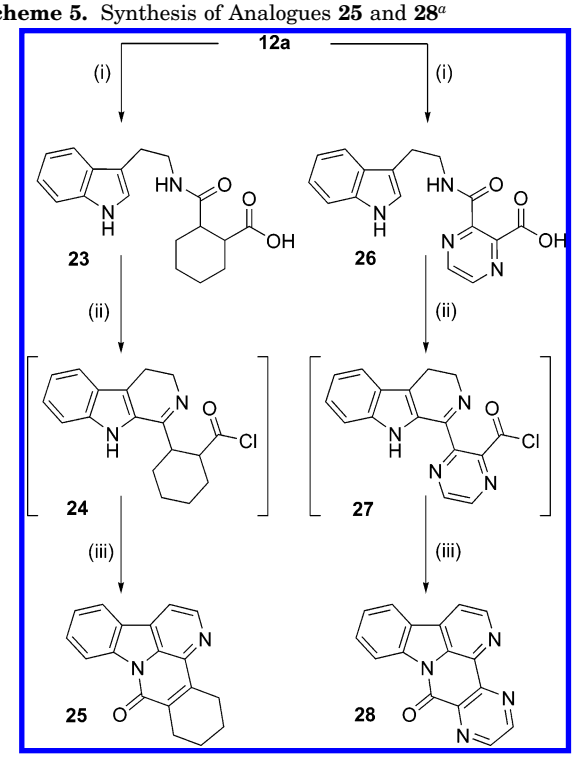
	MIC (μM L^{-1})				
compound	*Candida albicans*	*Cryptococcus neoformans*	*Saccharomyces cerevisae*	*Trychophyton mentagrophytes*	*Aspergillus fumigatus*
1	56.8	14.2	14.2	7.1	14.2
2	>200	50.0	50.0	6.3	50.0
3	>200	>200	53.0	>200	>200
4	146.0	>200	>200	nt	>200
5	146.0	>200	>200	nt	>200
8	124.0	>200	124.0	>200	>200
9	>200	>200	7.7	>200	>200
10	53.2	106.0	53.2	106.0	>200
16	100.0	200.0	50.0	>200	>200
17	13.1	13.1	13.1	nt	13.1
18	>200	>200	>200	nt	nt
ketoconazole	2.9	5.9	5.9	23.5	94.2

Scheme 4. Synthesis of Benzo[4,5]canthin-6-ones[a]



[a] Reagents and conditions: (i) anhydride (1.1 equiv), CH_2Cl_2, rt, 18 h (**19a**: 98%, **19b**: 98%); (ii) $POCl_3$ (3 equiv), C_6H_6, reflux, 1 h; and then (iii) DBU (3 equiv), CH_2Cl_2, rt, 18 h (**21**: 80%, **22**: 50%).

Scheme 5. Synthesis of Analogues **25** and **28**[a]



[a] Reagents and conditions: (i) anhydride (1.1 equiv), CH_2Cl_2, rt, 18 h (**19a**: 98%, **19b**: 98%); (ii) $POCl_3$ (3 equiv), C_6H_6, reflux, 1 h; and then (iii) DBU (3 equiv), CH_2Cl_2, rt, 18 h (**25**: 50%, **28**: 50%).

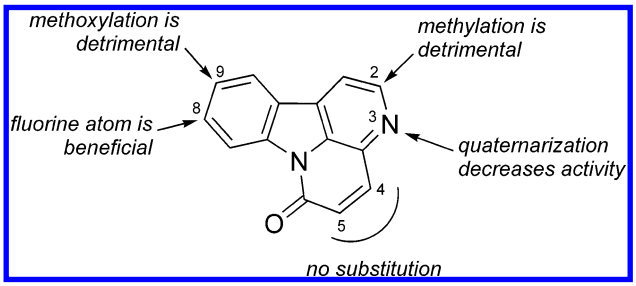


Figure 2. Structure−activity relationships for antifungal activity.

of those of **1** against *Aspergillus fumigatus* and *Trichophyton mentagrophytes* var. *interdigitale*. Against *Cryptococcus neoformans* and *Saccharomyces cerevisiae*, the MIC of ketoconazole was more than double compared to **1**. Against *Candida albicans*, **1** showed only moderate activity (MIC: 56.8 μM) compared to ketoconazole (MIC: 2.9 μM). The 5-methoxy analogue **2** was less active against *T. mentagophytes*, and N_3-substituted derivatives were not active. Concerning substitutions on the canthine skeleton: compound **17** was the most interesting, with conserved or increased activity. The presence of a methyl or a methoxy respectively at positions **2** and **9** appeared to be detrimental.

Structure−activity relationships for the antifungal activity still remain unclear. All compounds possessing substitutions at the 4 and 5 positions showed decreased activity. Hence, a free double bond at this position is more or less essential for the antifungal activity. Structure−activity relationships are depicted in Figure 2. When tested for antifungal ability, no activity was detected for any of the synthetic intermediates.

In conclusion, the methodology presented herein represents a convenient entry into functionalized canthin-6-one alkaloids. Access to hemisynthetic molecules was possible in one step from natural canthinones. Concerning total synthesis, the sequences of reactions described above provide efficient synthetic routes to canthin-6-one and other canthinone derivatives in three or four steps and satisfactory to very good overall yields (60% for the preparation of **1**) with an original DBU-mediated cyclization followed by spontaneous aromatization. The procedures are easily suitable for scale-up. The canthinone derivatives described in this study did not exhibit improved antifungal activity compared to canthin-6-one **1**.

Experimental Section

General Experimental Procedures. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated. All reactions were carried out under an argon atmosphere. Reactions were monitored by TLC

carried out on Merck Kieselgel silica gel plates (60F-254) using UV light as visualizing agent, and sulfuric vanillin or Dragendorff reagent and heat was used as developing agent. Merck Kieselgel silica gel (60, particle size 40−63 μm) was used for flash chromatography. NMR spectra were recorded on a AR 200 P or a AM-400 Bruker spectrometer and calibrated using undeuterated solvent as an internal reference. IR spectra were recorded on a Vector 22 Bruker spectrometer, and values are reported in cm^{-1} units. Mass spectra were recorded at "Laboratoire de Spectrométrie de Masse", ICSN, Gif-sur-Yvette, France.

Plant Material. Stem bark of *Zanthoxylum chiloperone* var. *angustifolium* Engl. was collected by Alain Fournet, in Paraguay near Piribebuy, Department of Cordillera, and identified by N. Soria (Department of Botany, National University of Asuncion, Paraguay). A voucher specimen (AF 917) has been deposited at the Herbarium of Chemical Sciences Faculty, Asuncion, Paraguay.

Extraction and Isolation. Powdered, dried stem bark of *Z. chiloperone* var. *angustifolium* (1.5 kg) was basified with ammonia, extracted in a Soxhlet apparatus separately, and successively with CH_2Cl_2 and MeOH for 3 days to afford 28 and 35 g of crude extracts. All extracts were evaluated for antifungal activity, and the CH_2Cl_2 extract showed strong antifungal activity.

Therefore, the CH_2Cl_2 extract was subjected to silica gel flash column chromatography, eluted with CH_2Cl_2/ethyl acetate (8:2), to obtain 30 fractions. Fractions 2−5 were combined and rechromatographed (cyclohexane/CH_2Cl_2/AcOEt, 60:35:5) to give in the order of elution **6** (5 mg), **4** (110 mg), and **5** (30 mg). Fractions 14−24 were combined to provide **1** (1.1 g), as white needles after recrystallization from acetone. Fractions 24−28 were combined and rechromatographed (AcOEt/CH_2Cl_2/MeOH, 8:1:1) to give **2** (150 mg) and then **3** (10 mg).

Canthin-6-one *N*-Oxide (3). Canthin-6-one **1** (50 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (35 mL), and the system was cooled to 5 °C. *m*-CPBA (3 equiv) was added, and the solution was then stirred at room temperature for 18 h. The reaction was quenched with H_2O, and organic fractions were washed successively with an aqueous saturated solution of $NaHCO_3$ (5 × 40 mL) and then a saturated NaCl solution (2 × 30 mL). The organic fraction was dried over Na_2SO_4, solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **3** as a yellow powder (40 mg, 75%). **3**: yellow powder, mp 243−245 °C; IR (film, CH_2Cl_2) ν_{max} 1677, 1432, 1329, 1299, 1140, 826, 779, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (1H, d, J = 8.0 Hz, H-8), 8.38 (1H, d, J = 10.0 Hz, H-4), 8.34 (1H, d, J = 6.6 Hz, H-2), 7.99 (1H, d, J = 8.0 Hz, H-11), 7.82 (1H, d, J = 6.6 Hz, H-1), 7.64 (1H, t, J = 8.0 Hz, H-9), 7.53 (1H, t, J = 8.0 Hz, H-10), 6.92 (1H, d, J = 10.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0 (C-7a), 134.0 (C-3b), 133.0 (C-4), 132.1 (C-11b), 130.0 (C-9), 129.6 (C-10), 129.1 (C-3a), 128.4 (C-2), 126.3 (C-5), 123.7(C-11a), 121.8 (C-11), 117.7 (C-8), 117.4 (C-1); ESIMS *m/z* 237 $[M + H]^+$.

***N*$_3$-Methylcanthin-6-one, Iodide Salt (7).** Canthin-6-one **1** (50 mg, 0.22 mmol) was dissolved in CH_3I (3 mL). The mixture was then stirred at room temperature for 48 h. The precipitate was filtered and washed with CH_2Cl_2 (40 mg, 50%). **7**: orange powder, mp 238−241 °C; IR (film, CH_2Cl_2) ν_{max} 1684, 1655, 1448, 1340, 1142, 815, 787, 766 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.18 (1H, d, J = 6.3 Hz, H-2), 8.90 (1H, d, J = 6.3 Hz, H-1), 8.57 (3H, m, H-8, H-4, H-11), 7.96 (1H, t, J = 7.8 Hz, H-9), 7.73 (1H, t, J = 7.8 Hz, H-10), 7.41 (1H, d, J = 10.0 Hz, H-5), 4.64 (3H, s, −Me); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 158.0 (C-6), 142.7 (C-2), 141.4 (C-7a), 136.1 (C11-b), 134.7 (C-9), 133.7 (C-5), 133.3 (C-3b), 130.2 (C-3a), 130.2 (C-4), 127.4 (C-10), 125.7 (C-11), 122.5 (C-11a), 119.1 (C-1), 116.8 (C-8), 44.3 (N-Me); ESIMS *m/z* 235 $[M]^+$; HRESIMS *m/z* 235.2602 (calcd for $C_{15}H_{11}N_2O$, 235.2615).

***N*$_3$-Butylcanthin-6-one, Iodide Salt (8).** Canthin-6-one **1** (50 mg, 0.22 mmol) was dissolved in $CH_3(CH_2)_2I$ (3 mL). The mixture was then refluxed for 48 h. A precipitate was formed upon cooling and was filtered and washed with CH_2Cl_2 (47 mg, 50%). **8**: orange powder, mp >260 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.22 (1H, d, J = 6.3 Hz, H-2), 8.93 (1H, d, J = 6.3 Hz, H-1), 8.67 (1H, d, J = 10.0 Hz, H-4), 8.59 (1H, d, J = 8.0 Hz, H-11), 8.55 (1H, d, J = 8.0 Hz, H-8), 7.98 (1H, t, J = 8.0 Hz, H-9), 7.75 (1H, t, J = 8.0 Hz, H-10), 7.41 (1H, d, J = 10.0 Hz, H-5), 4.99 (2H, t, J = 7.5 Hz, H-α), 1.91 (2H, qu, J = 7.5 Hz, H-β), 1.37 (2H, m, J = 7.5 Hz, H-γ), 0.92 (3H, t, J = 7.5, -Me); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.4 (C-6), 142.3 (C-2), 141.0 (C-7a), 139.0 (C-11b), 134.3 (C-9), 133.7 (C-5), 133.5 (C-3b), 132.5 (C-3a), 130.0 (C-4), 126.9 (C-10), 125.6 (C-11), 122.5 (C-11a), 119.2 (C-1), 116.5 (C-8), 54.8 (C-α), 33.3 (C-β), 18.8 (C-γ), 13.3 (C-Me); ESIMS *m/z* 277 $[M]^+$; HRESIMS *m/z* 277.1339 (calcd for $C_{18}H_{17}N_2O$, 277.1341).

***N*$_3$-Bromoethylcanthin-6-one, Bromide Salt (9).** Canthin-6-one **1** (25 mg, 0.11 mmol) was dissolved in $Br(CH_2)_2Br$ (3 mL). The mixture was then refluxed for 48 h. A precipitate was formed upon cooling and was filtered and washed with CH_2Cl_2 (25 mg, 50%). **9**: green powder, mp >260 °C; IR (film, CH_2Cl_2) ν_{max} 3395, 2987, 1682, 1655, 1445, 1334, 1181, 829, 788, 758 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 8.81 (1H, d, J = 6.4 Hz, H-2), 8.41 (1H, d, J = 6.4 Hz, H-1), 8.27 (1H, d, J = 10.2 Hz, H-4), 8.16−8.06 (2H, m, H-8, H-11), 7.62 (1H, d, J = 8.0 Hz, H-9), 7.41 (1H, d, J = 8.0 Hz, H-10), 7.12 (1H, d, J = 10.2 Hz, H-5), 5.51 (2H, t, J = 5.8 Hz, H-α), 4.19 (2H, d, J = 5.8 Hz, H-β); ESIMS *m/z* 327 $[M]^+$; HRESIMS *m/z* 327.0139 (calcd for $C_{16}H_{12}N_2O$, 327.0133).

Preparation of 4-Aminocanthin-6-ones (10, 11). Canthin-6-one **1** (160 mg, 0.7 mmol) or 5-methoxycanthin-6-one (**2**) (25 mg, 0.11 mmol) was dissolved in H_2O/DMF (9:1, 5 mL). NaN_3 (15 equiv, for **1**: 10 mmol, 700 mg; for **2**: 1.65 mmol, 110 mg) and $ZnBr_2$ (15 equiv, for **1**: 10 mmol, 2.45 g, for **2**: 1.65 mmol, 370 mg) were added, and the solution was heated under reflux for 48 h. CH_2Cl_2 was added to the cooled solution, the organic layer was washed successively with H_2O (5 × 40 mL) and a saturated NaCl solution (2 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (MeOH/CH_2Cl_2, 9:1) to furnish **10** (118 mg, 70%) or **11** (12 mg, 40%).

4-Aminocanthin-6-one (10): yellow crystalline powder (CH_2Cl_2), mp 199−200 °C; IR (film, CH_2Cl_2) ν_{max} 3254, 1673, 1612, 1580, 1556, 1443, 1313, 837, 785, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.68 (1H, d, J = 5.1 Hz, H-2), 8.64 (1H, d, J = 8.0 Hz, H-8), 8.06 (1H, d, J = 8.0 Hz, H-11), 7.69 (1H, d, J = 5.1 Hz, H-1), 7.66 (1H, t, J = 8.0 Hz, H-9), 7.51 (1H, t, J = 8.0 Hz, H-10), 7.0 (1H, s, H-5), 4.98 (2H, s, −NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2 (C-6), 145.9 (C-2), 142.4 (C-4), 139.1 (C-7a), 138.8 (C-3a), 130.1 (C-9), 129.1 (C-3b), 126.4 (C-11a), 125.86 (C-11b), 125.7 (C-10), 122.5 (C-11), 116.8 (C-8), 112.0 (C-1), 106.8 (C-5); ESIMS *m/z* 236 $[M+H]^+$; HRESIMS *m/z* 236.0822 (calcd for $C_{14}H_{10}N_3O$, 236.0824).

4-Amino-5-methoxycanthin-6-one (11): yellow powder, R_f = 0.3 (CH_2Cl_2/MeOH, 85:15); IR (film, CH_2Cl_2) ν_{max} 3073, 2925, 2854, 2599, 1689, 1436, 1200, 730 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 8.43 (1H, d, J = 5.8 Hz, H-2), 8.19 (1H, d, J = 8.0 Hz, H-8), 8.10 (1H, d, J = 5.8 Hz, H-1), 7.64−7.62 (2H, m, H-9, H-11), 7.36−7.28 (1H, dt, J = 8.0, 3.2 Hz, H-10), 3.02 (3H, s, −OMe); ESIMS *m/z* 266 $[M + H]^+$; HRESIMS *m/z* 266.0934 (calcd for $C_{15}H_{12}N_3O_2$, 266.0930).

Preparation of Tryptamides 13a−d. General Procedure. The requisite tryptamine **12a** (10 mmol, 1.6 g) or **12b−d** (**12b**: 0.1 g, 0.53 mmol; **12c**: 0.1 g, 0.46 mmol; **12d**: 0.1 g, 0.57 mmol) was dissolved in dry CH_2Cl_2 (20 mL). Succinic anhydride (1.1 equiv, respectively for cases **a−d**: 1.1 g, 58 mg, 50 mg, 63 mg) was added slowly. The reaction was stirred at room temperature for 18 h. The resulting precipitate was filtered, washed with a small amount of CH_2Cl_2, and dried to furnish tryptamides **13a−d** (**13a**: 2.5 g, 98%; **13b**: 140 mg, 99%; **13c**: 130 mg, 98%; **13d**: 150 mg, 98%).

13a: yellow crystalline powder (CH_2Cl_2), mp 128−130 °C; IR (film, CH_2Cl_2) ν_{max} 3394, 3271, 2939, 1686, 1638, 1226, 1172, 833, 739, 669, 623 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.54 (1H, d, J = 8.0 Hz, H-4), 7.31 (1H, d, J = 8.0 Hz, H-7), 7.10−7.07 (2H, m, H-2, H-6), 7.0−6.99 (1H, dt, J = 8.0, 0.92 Hz, H-5), 3.45 (2H, t, J = 7.3 Hz, H-9), 2.91 (2H, t, J = 7.3 Hz, H-8), 2.56 (2H, t, J = 6.9 Hz, H-13), 2.42 (2H, t, J = 6.9 Hz,

H-12); ^{13}C NMR (CD_3OD, 50 MHz) δ 174.2 (C-14), 171.1 (C-11), (136.6 C-b), 127.6 (C−a), 122.9 (C-2), 121.2 (C-6), 118.8 (C-5), 118.5 (C-4), 112.2 (C-3), 111.7 (C-7), 40.8 (C-9), 30.5 (C-12), 29.6 (C-13), 25.5 (C-8); ESIMS *m/z* 283 [M + Na]$^+$; HRESIMS *m/z* 283.1053 (calcd for $C_{14}H_{16}N_2O_3Na$, 283.1059).

13b: yellow crystalline powder (CH_2Cl_2), mp 101−103 °C; IR (film, CH_2Cl_2) ν_{max} 3384, 3260, 1718, 1640, 1211, 792, 638 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.20 (1H, d, J = 8.8 Hz, H-7), 7.02 (1H, d, J = 2.4 Hz, H-4), 6.97 (1H, s, H-2), 6.74 (1H, dd, J = 8.8, 2.4 Hz, H-6), 3.77 (3H, s, −OMe), 3.43 (2H, t, J = 7.2 Hz, H-9), 2.86 (2H, t, J = 7.2 Hz, H-8), 2.55 (2H, t, J = 7.0 Hz, H-13), 2.39 (2H, t, J = 7.0 Hz, H-12); ^{13}C NMR (CD_3OD, 50 MHz) δ 176.8 (C-14), 174.6 (C-11), 155.1 (C-5), 133.5 (C−b), 129.3 (C−a), 124.8 (C-2), 113.5 (C-7), 113.4 (C-3), 113.1 (C-6), 102.0 (C-4), 57.2 (−OMe), 41.6 (C-9), 32.1 (C-12), 31.0 (C-13), 26.6 (C-8); ESIMS *m/z* 313 [M + Na]$^+$; HRESIMS *m/z* 313.1166 (calcd for $C_{15}H_{18}N_2O_4Na$, 313.1164).

13c: white crystalline powder (CH_2Cl_2), mp 103−105 °C; IR (film, CH_2Cl_2) ν_{max} 3396, 2937, 1686, 1633, 1255, 1208, 1149, 950, 807 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.18 (1H, t, J = 8.0 Hz, H-4), 6.74 (1H, s, H-2), 6.69 (1H, d, J = 2.0 Hz, H-7), 6.52−6.41 (1H, dt, J = 8.0, 2.0 Hz, H-5), 3.10 (2H, t, J = 7.2 Hz, H-9), 3.0 (2H, t, J = 7.2 Hz, H-8), 2.59 (2H, t, J = 6.9 Hz, H-13), 2.09 (2H, t, J = 6.9 Hz, H-12), ^{13}C NMR (CD_3OD, 50 MHz) δ 175.6 (C-14), 175.3 (C-11), 164.3 (C-4), 159.6 (C-b), 126.4 (C−a), 124.8 (C-2), 121.1 (C-4), 114.4 (C-3), 109.1 (C-5), 99.2 (C-7), 42.2 (C-9), 32.5 (C-8), 30.6 (C-12), 27.0 (C-13); ESIMS *m/z* 301 [M + Na]$^+$; HRESIMS *m/z* 301.0963 (calcd for $C_{14}H_{15}FN_2O_3Na$, 301.0964).

13d: yellow amorphous powder; IR (film, CH_2Cl_2) ν_{max} 3387, 2926, 1711, 1618, 1532, 1338, 1231, 1168, 741 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.44 (1H, d, J = 8.0 Hz, H-4), 7.18 (1H, d, J = 8.0 Hz, H-7), 6.96−6.81 (3H, m, H-2, H-5, H-6), 4.07 (1H, q, J = 6.5 Hz, H-9), 2.83−2.58 (2H, m, H-8), 2.36 (2H, t, J = 6.0 Hz, H-13), 2.26 (2H, t, J = 6.0 Hz, H-12), 0.92 (3H, d, J = 6.5 Hz, −Me); ^{13}C NMR (CD_3OD, 50 MHz) δ 174.6 (C-14), 174.5 (C-11), 138.6 (C-b), 129.9 (C-a), 124.9 (C-2), 123.0 (C-5), 120.4 (C-6), 120.3 (C-4), 113.4 (C-3), 113.0 (C-7), 48.1 (C-9), 33.6 (C-8), 32.7 (C-12), 31.3 (C-13), 21.0 (−Me); ESIMS *m/z* 297 [M + Na]$^+$; HRESIMS *m/z* 297.12165 (calcd for $C_{15}H_{18}N_2O_3$-Na, 297.1215).

Preparation of Methyl Esters 14a−d. General Procedure. The requisite tryptamide **13a** (7.6 mmol, 2.0 g), **13b** (0.48 mmol, 140 mg), **13c** (0.45 mmol, 130 mg) or **13d** (0.55 mmol, 150 mg) was dissolved in MeOH (60 mL). Catalytic Amberlyst H-15 (20% w/w) was added, and the solution was heated under reflux for 18 h. The solvent was removed under reduced pressure. The crude product was crystallized from diisopropyl ether to furnish **14a**−**d** (**14a**: 2.0 g, 98%; **14b**: 140 mg, 98%; **14c**: 130 mg, 98%; **14d**: 150 mg, 98%).

14a: white crystalline powder (CH_2Cl_2), mp 101−102 °C; IR (film, CH_2Cl_2) ν_{max} 3336, 3282, 2862, 1721, 1651, 1538, 1258, 1221, 1188, 936, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (1H, s, −N*H*), 7.58 (1H, d, J = 7.8 Hz, H-4), 7.35 (1H, d, J = 7.8 Hz, H-7), 7.18 (1H, t, J = 7.8 Hz, H-6), 7.10 (1H, t, J = 7.8 Hz, H5), 7.04 (1H, s, H-2), 5.30 (1H, s, −*NH*), 3.64 (3H, s, −OMe), 3.57 (2H, t, J = 6.5 Hz, H-9), 2.95 (2H, t, J = 6.5 Hz, H-8), 2.63 (2H, t, J = 6.8 Hz, H-13), 2.39 (2H, t, J = 6.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.4 (C-14), 172.7 (C-11), 136.6 (C−b), 127.3 (C-a), 122.1 (C-2), 121.8 (C-6), 120.8 (C-5), 117.8 (C-4), 111.7 (C-3), 110.7 (C-7), 57.0 (−OMe), 40.0 (C-9), 29.9 (C-12), 28.7 (C-13), 24.7 (C-8); ESIMS *m/z* 297 [M + Na]$^+$; HRESIMS *m/z* 297.1216 (calcd for $C_{15}H_{18}N_2O_3Na$, 297.1215).

14b: white crystalline powder (CH_2Cl_2), mp 105−110 °C; IR (film, CH_2Cl_2) ν_{max} 3328, 2952, 2860, 1720, 1651, 1440, 1213, 860, 794, 640 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.20 (1H, d, J = 8.8 Hz, H-7), 7.02 (1H, s, H-4), 6.99 (1H, s, H-2), 6.73 (1H, d, J = 8.8 Hz, H-6), 3.78 (3H, s, Ar−OMe), 3.43 (2H, t, J = 7.0 Hz, H-9), 3.34 (3H, s, −OMe), 2.88 (2H, t, J = 7.0 Hz, H-8), 2.54 (2H, t, J = 6.0 Hz, H-13), 2.42 (2H, t, J = 6.0 Hz, H-12); ^{13}C NMR (CD_3OD, 50 MHz) δ 175.4 (C-14), 174.6 (C-11), 155.4 (C-5), 133.9 (C-b), 129.5 (C-a), 124.9 (C-2), 113.6 (C-7), 113.5 (C-3), 113.2 (C-6), 102.1 (C-4), 57.2 (Ar−OMe), 52.9 (−OMe), 42.0 (C-9), 32.1 (C-12), 30.9 (C-13), 26.8 (C-8); ESIMS *m/z* 327 [M + Na]$^+$; HRESIMS *m/z* 327.1320 (calcd for $C_{16}H_{20}N_2O_4Na$, 327.1321).

14c: white crystalline powder (CH_2Cl_2), mp 124−126 °C; IR (film, CH_2Cl_2) ν_{max} 2925, 2360, 2341, 1727, 1626, 1250, 1203, 1040, 802 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.49−7.45 (1H, m, H-4), 7.02 (1H, s, H-2), 7.01 (1H, dd, J = 10.0, 2.0 Hz, H-7), 6.79−6.74 (1H, m, H-5), 3.44 (2H, t, J = 7.3 Hz, H-9), 3.34 (3H, s, −OMe), 2.89 (2H, t, J = 7.3 Hz, H-8), 2.56 (2H, t, J = 6.9 Hz, H-13), 2.44 (2H, t, J = 6.9 Hz, H-12); ^{13}C NMR (CD_3-OD, 50 MHz) δ 175.1 (C-14), 174.0 (C-11), 160.5 (C-6), 158.0 (C-b), 126.2 (C-a), 124.6 (C-2), 120.9 (C-4), 112.5 (C-3), 109.0 (C-5), 99.2 (C-7), 52.9 (−OMe), 42.2 (C-9), 32.2 (C-8), 31.0 (C-12), 26.9 (C-13); ESIMS *m/z* 315 [M + Na]$^+$; HRESIMS *m/z* 315.1125 (calcd for $C_{15}H_{17}FN_2O_3Na$, 315.1121).

14d: white amorphous powder; IR (film, CH_2Cl_2) ν_{max} 2361, 1732, 1650, 1456, 1265, 1167, 733, 702 cm^{-1}; ^{1}H NMR (CD_3-OD, 400 MHz) δ 7.57 (1H, d, J = 8.0 Hz, H-4), 7.30 (1H, d, J = 8.0 Hz, H-7), 6.07−7.96 (3H, m, H-2, H-5, H-6), 4.19 (1H, q, J = 6.6 Hz, H-9), 3.30 (3H, s, −OMe), 2.77−2.83 (2H, m, H-8), 2.53 (2H, t, J = 6.0 Hz, H-13), 2.39 (2H, t, J = 6.0 Hz, H-12), 1.11 (3H, d, J = 6.6 Hz, −Me); ^{13}C NMR (CD_3OD, 50 MHz) δ 174.7 (C-14), 174.5 (C-11), 137.4 (C-b), 128.9 (C-a), 124.1 (C-2), 122.4 (C-5), 119.9 (C-6), 119.6 (C-4), 112.3 (C-3), 112.3 (C-7), 52.7 (−OMe), 47.0 (C-9), 32.7 (C-8), 31.8 (C-12), 30.3 (C-13), 20.8 (C-Me); ESIMS *m/z* 311 [M + Na]$^+$; HRESIMS *m/z* 311.1370 (calcd for $C_{16}H_{20}N_2O_3Na$, 311.1372).

Preparation of Imines 15a−d. General Procedure. The requisite ester **14a** (0.91 mmol, 250 mg), **14b** (0.46 mmol, 140 mg), **14c** (0.41 mmol, 120 mg), or **14d** (0.52 mmol, 150 mg) was dissolved in benzene (10 mL, CAUTION). The solution was cooled to 5 °C. $POCl_3$ (3 equiv, for **14a**: 420 mg, 2.73 mmol; **14b**: 210 mg, 1.38 mmol; **14c**: 190 mg, 1.23 mmol; **14d**: 190 mg, 1.23 mmol) was added dropwise, and the solution was heated under reflux for 1 h and then cooled to room temperature. Solvents were removed under reduced pressure to furnish imines **15a**−**d** (**15a**: 140 mg, 60%; **15b**: 90 mg, 60%; **15c**: 70 g, 55%; **15d**: 60 mg, 40%), which were used in the next reaction without further purification due to instability. **15a** was purified by a rapid flash chromatography (CH_2Cl_2/MeOH, 95:5).

15a: unstable brown oil; IR (film, CH_2Cl_2) ν_{max} 2850, 1698, 1632, 1182, 1040, 748 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.90 (1H, s, −N*H*), 7.69 (1H, d, J = 8.0 Hz, H-5), 7.49 (1H, d, J = 8.0 Hz, H-8), 7.45 (1H, t, J = 8.0, H-7), 7.15 (1H, t, J = 8.0 Hz, H-6), 3.89 (2H, t, J = 8.7 Hz, H-3), 3.65 (5H, m, H-1′, −OMe), 3.27 (2H, t, J = 8.7 Hz, H-4), 2.91 (2H, t, J = 7.0 Hz, H-2′); ^{13}C NMR (CD_3OD, 50 MHz) δ 172.5 (C-3′), 169.0 (C-d), 142.6 (C-c), 129.9 (C-7), 126.2 (C-b), 125.1 (C-a), 122.5 (C-5), 122.3 (C-6), 113.8 (C-8), 52.1 (−OMe), 43.2 (C-1′), 31.1 (C-4), 28.3 (C-3), 19.5 (C-2′); ESIMS *m/z* 257 [M + H]$^+$.

Preparation of Canthin-6-ones (1, 16−18). General Procedure. The requisite imine **15a** (0.51 mmol, 130 mg), **15b** (0.31 mmol, 90 mg), **15c** (0.25 mmol, 70 mg), or **15d** (0.11 mmol, 30 mg) was dissolved in CH_2Cl_2 (30 mL). DBU (3 equiv, respectively for **a**−**d**: 230 mg, 140 mg, 115 mg, 50 mg) was added, and the solution was then stirred at room temperature for 18 h. The reaction was quenched with H_2O (10 mL), and the organic fraction was washed successively with H_2O (5 × 40 mL) and a saturated NaCl solution (2 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The mixture was purified by flash chromatography (CH_2Cl_2/MeOH, 99.5:0.5) to furnish canthin-6-ones **1** and **16**−**18** (**1**: 100 mg, 80%; **16**: 60 mg, 70%; **17**: 50 mg, 80%; **18**: 4 mg, 20%).

Canthin-6-one (1): yellow crystalline powder (CH_2Cl_2), mp 161−163 °C; IR (film, CH_2Cl_2) ν_{max} 1673, 1434, 1141, 841, 793, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70 (1H, d, J = 5.0 Hz, H-2), 8.50 (1H, d, J = 8.0 Hz, H-8), 7.98 (1H, d, J = 8.0 Hz, H-11), 7.90 (1H, d, J = 9.8 Hz, H-4), 7.80 (1H, d, J = 5.0 Hz, H-1), 7.59 (1H, t, J = 8.0 Hz, H-9), 7.42 (1H, t, J = 8.0 Hz, H-10), 6.88 (1H, d, J = 9.8 Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2 (C-6), 145.6 (C-2), 139.3 (C-4), 139.1 (C-7a), 135.9 (C-3a), 131.7 (C-3b), 130.6 (C-9), 129.9 (C-11b), 128.7 (C-5), 125.4 (C-10), 124.1 (C-11a), 122.4 (C-11), 117.0 (C-8), 116.1 (C-1); ESIMS *m/z* 243 [M + Na]$^+$.

10-Methoxycanthin-6-one (16): yellow crystalline powder (CH_2Cl_2), mp 203−205 °C; IR (film, CH_2Cl_2) ν_{max} 2924, 2359, 1672, 1302, 1222, 1001, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.81 (1H, d, J = 5.0 Hz, H-2), 8.55 (1H, d, J = 9.0 Hz, H-8), 8.05 (1H, d, J = 9.8 Hz, H-4), 7.96 (1H, d, J = 5.0 Hz, H-1), 7.57 (1H, d, J = 2.1 Hz, H-11), 7.27 (1H, dd, J = 9.0, 2.1 Hz, H-9), 6.98 (1H, d, J = 9.8 Hz, H-5), 3.96 (3H, s, −OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2 (C-6), 158.1 (C-10), 145.0 (C-2), 138.7 (C-4), 136.0 (C-3a), 133.8 (C-7a), 132.5 (C-3b), 131.0 (C-11b), 129.4 (C-5), 125.8 (C-11a), 118.3 (C-9), 118.1 (C-8), 116.4 (C-1), 106.7 (C-11), 56.0 (−OMe); ESIMS *m/z* 251 $[M + H]^+$; HRESIMS *m/z* 251.0825 (calcd for $C_{15}H_{11}N_2O_2$, 251.0821).

9-Fluorocanthin-6-one (17): yellow crystalline powder (CH_2Cl_2), mp 155−158 °C; IR (film, CH_2Cl_2) ν_{max} 2925, 2360, 1674, 1637, 1448, 1306, 1140, 843, 829, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.83 (1H, d, J = 5.0 Hz, H-2), 8.41 (1H, dd, J = 8.7, 2.2 Hz, H-8), 8.09 (2H, m, H-4, H-11), 7.96 (1H, d, J = 5.0 Hz, H-1), 7.29 (1H, dd, J = 8.7, 2.2 Hz, H-10), 6.99 (1H, d, J = 10.0 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0 (C-6), 159.8 (C-9), 145.52 (C-2), 140.0 (C-7a), 139.53 (C-4), 135.71 (C-3a), 132.1 (C-3b), 130.08 (C-11b), 129.04 (C-5), 123.95 (C-11), 120.58 (C-11a), 116.22 (C-1), 113.89 (C-10), 105.17 (C-8); ESIMS *m/z* 239 $[M + H]^+$; HRESIMS *m/z* 239.0624 (calcd for $C_{14}H_8FN_2O$, 239.0621).

2-Methylcanthin-6-one (18): yellow amorphous powder; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.71 (1H, d, J = 8.0 Hz, H-8), 8.28 (1H, s, H-1), 8.11 (1H, d, J = 8.0 Hz, H-11), 7.89 (1H, H-4), 7.74−7.66 (1H, t, J = 8.0 Hz, H-9), 7.57−7.49 (1H, t, J = 8.0 Hz, H-10), 6.49 (1H, d, J = 9.2 Hz, H-5); ESIMS *m/z* 235 $[M + H]^+$; HRESIMS *m/z* 235.0876 (calcd for $C_{15}H_{11}N_2O$, 235.0871).

Tryptamides 19a,b, 23, and 26. General Procedure. Tryptamine (for **19a**: 1.6 g, 0.01 mol; **19b**: 0.08 g, 0.5 mmol; **23**: 160 mg, 1 mmol; **26**: 1.1 mmol, 165 mg) was dissolved in dry CH_2Cl_2 (20 mL) with the requisite anhydride (1.1 equiv, phthalic anhydride: 11 mmol, 1.630 g; difluorophthalic anhydride: 0.55 mmol, 85 mg; cyclohexanedicarboxylic anhydride: 1.1 mmol, 170 mg; pyrazine dicarboxylic anhydride: 1.1 mmol, 165 mg). The reaction was stirred at room temperature for 18 h. The resulting precipitate was filtered, washed with a small amount of CH_2Cl_2, and dried to furnish **19a** (3.0 g, 98%), **19b** (170 mg, 98%), **23** (310 mg, 98%), and **26** (300 mg, 98%).

19a: yellow crystalline powder (CH_2Cl_2), mp 123−125 °C; IR (film, CH_2Cl_2) ν_{max} 3371, 1693, 1637, 1540, 1277, 1267, 730 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.90 (1H, d, J = 8.0 Hz, H-13), 7.60 (1H, d, J = 8.0 Hz, H-4), 7.52−7.41 (2H, m, H-14, H-15), 7.33−7.29 (2H, m, H-7, H-16), 7.08−7.06 (2H, m, H-2, H-6), 6.99 (1H, t, J_1 = 8.0 Hz, H-5), 3.63 (2H, t, J = 7.4 Hz, H-9), 3.06 (2H, t, J = 7.4 Hz, H-8); ^{13}C NMR (CD_3OD, 50 MHz) δ 173.3 (C-18), 170.4 (C-11), 140.5 (C-17), 138.9 (C−b), 138.9 (C-12), 133.6 (C-14), 132.9 (C-13), 132.0 (C-a), 131.9 (C-16), 131.3 (C-2), 129.6 (C-6), 124.4 (C-5), 123.1 (C-4), 120.2 (C-15), 114.2 (C-3), 113.1 (C-7), 42.8 (C-9), 26.7 (C-8); ESIMS *m/z* 331 $[M + Na]^+$; HRESIMS *m/z* 331.1057 (calcd for $C_{18}H_{16}N_2O_3Na$, 331.1059).

19b: white amorphous powder; IR (film, CH_2Cl_2) ν_{max} 3352, 2494, 1702, 1611, 1468, 1260, 830, 746 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.59 (1H, d, J = 7.7 Hz, H-4), 7.32 (1H, d, J = 7.7 Hz, H-7), 7.29−7.22 (2H, m, H-14, H-15), 7.11 (1H, s, H-2), 7.09 (1H, t, J = 7.7 Hz, H-6), 6.99 (1H, t, J = 7.7 Hz, H-5), 3.62 (2H, t, J = 7.5 Hz, H-9), 3.04 (2H, t, J = 7.5 Hz, H-8); ^{13}C NMR (CD_3OD, 50 MHz) δ 166.4 (C-11), 165.4 (C-18), 159.7 (C-12), 158.5 (C-17), 154.7 (C-13), 153.6 (C-16), 138.0 (C-b), 128.6 (C-a), 123.6 (C-2), 122.3 (C-6), 120.8 (C-14), 120.2 (C-15), 119.6 (C-5), 119.2 (C-4), 113.1 (C-3), 112.3 (C-7), 42.0 (C-9), 26.0 (C-8); ESIMS *m/z* 367 $[M + Na]^+$; HRESIMS *m/z* 367.0874 (calcd for $C_{18}H_{14}F_2N_2O_3Na$, 367.0870).

23: white crystalline powder (CH_2Cl_2), mp 98−100 °C; IR (film, CH_2Cl_2) ν_{max} 3399, 2932, 2858, 1701, 1530, 1188, 1129, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.50 (1H, s, H-1), 7.60 (1H, d, H-4), 7.37 (1H, d, H-7), 7.20 (1H, t, H-6), 7.10 (1H, t, H-5), 7.0 (1H, s, H-2), 6.0 (1H, s, −N*H*), 3.64−3.55 (2H, m, H-9), 2.99−2.91 (2H, m, H-8), 2.86 (1H, m, H-12), 2.52−2.50 (1H, m, H-17), 2.19−2.17 (1H, m, H-13), 1.81−1.73 (1H, m, H-16), 1.61−1.50 (4H, m, H-13, H-14, H-15, H-16), 1.44 (1H, m, H-14), 1.35−1.31 (1H, m, H-15); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.0 (C-18), 175.2 (C-11), 136.4 (C-b), 127.2 (C-a), 122.5 (C-2), 121.9 (C-6), 119.1 (C-5), 118.4 (C-4), 112.2 (C-3), 111.4 (C-7), 44.3 (C-17), 42.7 (C-12), 39.8 (C-9), 27.2 (C-13), 26.9 (C-8), 24.9 (C-16), 24.1 (C-15), 23.0 (C-14); ESIMS *m/z* 337 $[M + Na]^+$.

26: yellow crystalline powder (CH_2Cl_2), mp 105−107 °C; IR (film, CH_2Cl_2) ν_{max} 3052, 1726, 1531, 1359, 1094, 742 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 8.79 (1H, d, J = 2.4 Hz, H-15), 8.63 (1H, d, J = 2.4 Hz, H-14), 7.56 (1H, t, J = 8.0 Hz, H-4), 7.33 (1H, t, J = 8.0 Hz, H-7), 7.15−6.95 (3H, m, H-2, H-5, H-6), 3.68 (1H, t, J = 7.3 Hz, H-9), 3.23 (1H, t, J = 7.3 Hz, H-9), 3.13−3.04 (2H, m, H-8); ^{13}C NMR (CD_3OD, 50 MHz) δ 172.7 (C-18), 165.6 (C-11), 152.3 (C-12), 146.5 (C-17), 143.7 (C-14), 143.5 (C-15), 137.9 (C-b), 128.5 (C-a), 124.3 (C-6), 123.6 (C-5), 122.3 (C-2), 119.6 (C-4), 112.5 (C-7), 110.5 (C-3), 41.3 (C-9), 26.1 (C-8); ESIMS *m/z* 311 $[M + H]^+$.

Preparation of 21, 22, 25, and 28. General Procedure. The requisite tryptamide (**19a**: 250 mg, 0.81 mmol; **19b**: 170 mg, 0.5 mmol, **23**: 300 mg, 0.95 mmol; **26**: 0.31 mg, 0.96 mmol) was treated under Bischler−Napieralski reaction conditions as described above for **14a** ($POCl_3$: XXX equiv; for **19a**: 371 mg, 2.43 mmol; **19b**: 230 mg, 1.5 mmol; **23**: 436 mg, 2.85 mmol; **26**: 440 mg, 2.88 mmol). The crude mixture of the imine (**20a**: 140 mg; **20b**: 90 mg; **24**: 200 mg, **27**: 160 mg) was dissolved in dry CH_2Cl_2 (20 mL), and DBU (3 equiv, for **20a**: 1.4 mmol, 210 mg; **20b**: 0.83 mmol, 130 mg; **24**: 2 mmol, 310 mg; **27**: 1.6 mmol, 250 mg) was added. The mixture was then stirred at room temperature for 18 h, and the reaction was quenched with H_2O (10 mL). The organic layer was washed successively with H_2O (5 × 40 mL) and then a saturated NaCl solution (2 × 30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (CH_2Cl_2 for **21**, **22**, **25** and CH_2Cl_2/MeOH, 97:3, for **28**) to give **21** (40 mg, 80%), **22** (60 mg, 50%), **25** (110 mg, 50%), and **28** (60 mg, 50%).

Benzo[*e*]canthin-6-one (21): white crystalline powder (CH_2Cl_2), mp 228−230 °C; IR (film, CH_2Cl_2) ν_{max} 1681, 1444, 1339, 1272, 874, 756, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.81 (1H, d, J = 5.0 Hz, H-2), 8.75 (1H, m, H-8, H-12), 8.61 (1H, d, J = 8.0 Hz, H-15), 8.10 (1H, d, J = 8.0 Hz, H-11), 7.91 (1H, d, J = 5.0 Hz, H-1), 7.87 (1H, t, J = 8.0 Hz, H-13), 7.76−7.68 (2H, m, H-9, H-14), 7.51 (1H, t, J = 8.0 Hz, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4 (C-6), 144.9 (C-2), 139.4 (C-7a), 136.0 (C-5), 134.7 (C-4), 133.5 (C-13), 130.6 (C-9), 130.5 (C-11b), 130.5 (C-3b), 130.1 (C-14), 129.5 (C-3a), 129.2 (C-15), 125.3 (C-10), 124.9 (C-11a), 123.5 (C-12), 122.4 (C-11), 117.5 (C-8), 115.1 (C-1); ESIMS *m/z* 271 $[M + H]^+$; HRESIMS *m/z* 271.0873 (calcd for $C_{18}H_{11}N_2O_2$, 271.0871).

12,15-Difluoro[*e*]canthin-6-one (22): white crystalline powder (CH_2Cl_2), mp >260 °C; R_f = 0.9 (CH_2Cl_2/MeOH, 9:1); IR (film, CH_2Cl_2) ν_{max} 2361, 2341, 1693, 1479, 1336, 841, 749, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.98 (1H, d, J = 5.0 Hz, H-2), 8.79 (1H, d, J = 7.8 Hz, H-8), 8.14 (1H, d, J = 7.8 Hz, H-11), 8.0 (1H, d, J = 5.0 Hz, H-1), 7.74 (1H, t, J = 7.8 Hz, H-9), 7.63−7.57 (2H, m, H-10, H-14), 7.41 (1H, dt, J = 10.5 Hz, 1.5 Hz, H-13); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0 (C-6), 159.0 (C-15), 154.5 (C-12), 146.0 (C-2), 145.5 (C-3b), 143.5 (C-3a), 139.0 (C-7a), 131.0 (C-9), 130.5 (C-11b), 124.9 (C-11a), 122.5 (C-11), 119.0 (C-4), 118.7 (C-14), 118.5 (C-13), 118.0 (C-5), 117.0 (C-8), 115.5 (C-1); ESIMS *m/z* 329 $[M + Na]^+$; HRESIMS *m/z* 329.0505 (calcd for $C_{18}H_8F_2N_2ONa$, 329.0502).

Cyclohexyl[*e*]canthin-6-one (25): yellow crystalline powder (CH_2Cl_2), mp 201−203 °C; IR (film, CH_2Cl_2) ν_{max} 3060, 2934, 2360, 1706, 1661, 1638, 1443, 1333, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.77 (1H, d, J = 5.0 Hz, H-2), 8.65 (1H, d, J = 8.0 Hz, H-8), 8.06 (1H, d, J = 8.0 Hz, H-11), 7.87 (1H, d, J = 5.0 Hz, H-1), 7.67 (1H, 1H, t, J = 8.0 Hz, H-9), 7.48 (1H, t, J = 8.0 Hz, H-10), 3.18 (2H, s, H-12), 2.78 (2H, s, H-15), 1.92 (4H, s, H-13, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0 (C-6), 145.5 (C-5), 144.8 (C-2), 139.5 (C-7a), 136.9 (C-3a), 135.0 (C-4), 130.5 (C-9), 130.1 (C-3b), 129.8 (C-11b), 125.2 (C-10), 124.7 (C-11a), 122.5 (C-11), 117.2 (C-8), 115.3 (C-1), 24.4 (C-15), 23.9 (C-12), 22.0 (C-14), 21.3 (C-13); ESIMS *m/z* 297 $[M + Na]^+$; HRESIMS *m/z* 297.3060 (calcd for $C_{18}H_{14}N_2ONa$, 297.3063).

Pyrazine[*e*]canthin-6-one (28): brown crystalline powder (CH_2Cl_2), mp 250−253 °C; IR (film, CH_2Cl_2) ν_{max} 1699, 1430, 1355, 1276, 1146, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.15 (1H, d, J = 1.6 Hz, H-14), 9.07, (1H, d, J = 1.6 Hz, H-13), 9.02 (1H, d, J = 5.2 Hz, H-2), 8.82 (1H, d, J = 8.0 Hz, H-8), 8.15 (1H, d, J = 8.0 Hz, H-11), 8.09 (1H, d, J = 5.2 Hz, H-1), 7.78 (1H, t, J = 8.0 Hz, H-9), 7.58 (1H, t, J = 8.0 Hz, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.1 (C-6), 148.6 (C-14), 147.4 (C-5), 147.5 (C-4), 146.7 (C-13), 145.9 (C-2), 141.6 (C-3a), 139.0 (C-7a), 134.1 (C-3b), 132.1 (C-11-b), 131.4 (C-9), 126.2 (C-10), 124.7 (C-11a), 122.7 (C-11), 117.8 (C-8), 117.3 (C-1); ESIMS *m/z* 295 $[M + Na]^+$; HRESIMS *m/z* 295.0593 (calcd for $C_{16}H_8N_4ONa$, 295.0596).

Biological Assays. The antifungal activity was evaluated by a bioautographic method, and the minimal inhibitory concentrations (MIC) were estimated. Details of the assay were described previously.[10]

Microorganisms. The following microorganisms were used for the determination of the MIC: *Candida albicans* CIP (Collection de l'Institut Pasteur) 4872 (ATCC 10231 = NIH 3147); *Saccharomyces cerevisiae* CPCM (Collection de Pharmacie de Châtenay-Malabry) 116.85 (ATCC 26.01); *Cryptococcus neoformans* H99;[18] *Aspergillus fumigatus* 04-486;[18] and *Trichophyton mentagrophytes* var. *interdigitale* CPCM 06.99.

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