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Novel Flavaglines Displaying Improved Cytotoxicity

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Novel flavagline analogues were synthesized and examined with respect to their cytotoxicity. Structural features critical to the potential of this class of anticancer natural products were unraveled. We demonstrated, in particular, that the introduction of substituants at C-2 has a deleterious effect on multidrug resistance. Replacement of the hydroxy at C-1 by an aminoformyl with the opposite configuration enhances the cytotoxicity and led to a compound that reduces tumors growth in an allograft model at nontoxic doses.

Introduction

The flavaglines are a family of plant natural products that display unique anticancer properties.[1,2] These cyclopenta[*b*]-benzofurans inhibit the proliferation of tumor cells in a low nanomolar range without displaying any significant toxicity on normal cells such as endothelial and epithelial cells,[3,4] normal peripheral blood lymphocytes, bone marrow stem cells,[5] and cardiomyocytes.[6] Moreover, these compounds do not display any sign of toxicity in mice.[6−8] The molecular target of flavaglines is still unknown, but Pelletier and colleagues demonstrated that these compounds inhibit the activity of the eukaryotic translation initiation factor 4A (eIF4A[a]), which is necessary to the cap-dependent synthesis of proteins involved in oncogenesis, angiogenesis, and chemoresistance.[8,9] We have recently shown that flavaglines induce apoptosis of HL60 and HeLa cells through *apoptosis inducing factor* (AIF) and caspase-12, independently of caspases-7, -8, and -9, suggesting that these anticancer agents would retain their activity in cells refractory to activation of these caspases.[6] Considering that drug resistance and side effects are the two major obstacles limiting the efficacy of cancer chemotherapy, these data reinforce the view that flavaglines hold considerable promises in the treatment of cancers. During this study, we identified FL3 (**1a**) as the first synthetic flavagline that inhibits cell proliferation and viability ($IC_{50} \approx 1$ nM) at lower doses than did the parent compound, rocaglaol (**2**) (Figure 1). Compound **1a** enhanced doxorubicin cytotoxicity in HepG2 cells and retained its potency against adriamycin-resistant cell lines without inducing cardiomyocyte toxicity. In the course of our structure−activity relationship (SAR) of rocaglaol, we have established that replacement of the methoxy group in position 4′ by a bromine atom (Figure 1, R = Br) improved cytotoxicity, while its deletion (R = H) decreased potency more than 3 orders of magnitude, suggesting a preference for a hydrophobic substituent in this para position. Introduction of a methoxy in position 4″ on the other phenyl moiety was detrimental for cytotoxicity. Altogether, these observations prompted us to pursue our study on the structural requirements of flavaglines for their cytotoxicity and to examine, in particular, the effects of substituants at C-1, C-2, C-8, and C4′.

Chemical Synthesis. Flavaglines were first synthesized according to the biomimetic approach developed by John Porco (Scheme 1).[10,11] Photocycloaddition [3 + 2] of hydroxyflavone **3** with methyl cinnamate, followed by an acyloin rearrangement, gave a mixture of inseparable diastereomers **5**. Saponification, decarboxylation, reduction by $Me_4NBH(OAc)_3$, and HPLC purification afforded the expected racemic rocaglaol analogues **1b**. Methyl rocaglate analogues **6** were prepared by $Me_4NBH(OAc)_3$-mediated reduction of ketoesters **5** followed by HPLC purification (the synthesis of **6a** and **6b** has been reported, but their biological activities were not examined).[6] Amides **7**−**9** were prepared by EDCI/HOBt activation after saponification of esters **6**. Alternatively, the dimethylamide functionality of **7b** was directly installed into photoadduct **11** by performing the irradiation with dimethylcinnamamide **10**.

We previously described that the reduction of the ketone **12** by $Me_4NBH(OAc)_3$ provided stereospecifically **1a** (Scheme 2).[6] Surprisingly, we found that the use of $NaBH_4$ afforded stereospecifically the other epimer **13**, which is in sharp contrast to the reported unselective reduction of a similar compound with this reagent.[7] Standard esterification afforded **14** and **15**. Reduction of the oxime methyl ether **16** with borane afforded amines **17a** and **17b** in a 3:7 ratio, which were acylated to afford **18**−**20**.

Evaluation of Biological Activities. The in vitro cytotoxicity of these new flavaglines thus synthesized was evaluated on a variety of human cancer cell lines from nasopharynx (KB), neutrophil (HL60 and HL60R), colon (HCT116), breast (MDA435 and MDA231), ovary (OV3), and prostate (PC3)-derived neoplasms by the MTS assay after a 72 h

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[a] Abbreviations: AIF, apoptosis inducing factor; eIF4A, eukaryotic translation initiation factor 4A; MDR, multidrug resistance; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenol)-2-(4-sulfophenyl)-2*H*-tetrazolium.

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treatment. Results are summarized in Table 1, with the values of taxotere, doxorubicine, and vinblastine shown for comparison. We started our SAR investigation by introducing an ester or amide moiety on position 2 to **1a**. Methyl ester **6a** exhibited a slightly reduced cytotoxicity than did compound **1a**. On the opposite, introduction of a tertiary amide (**7a**) significantly enhanced cytotoxicity. This effect was more pronounced with secondary amide **8a** and primary amide **9a** on most cell lines. However, both **8a** and **9a** were less active that reference compound **1a** on HL60R cells, which have developed resistance to chemotherapy by overexpressing the P-glycoprotein (P-gp), a plasma membrane protein encoded by the multidrug resistance (MDR1) gene.

Next, we examined the requirement of the 8-methoxy group for activity. 8-Demethoxy compounds **1b** and **6**−**8b** were significantly less active (ED_{50} 4−20 times higher) than cognate compounds **1a** and **6**−**8a**, indicating a preference but not an absolute requirement of a methoxy group in position 8 for cytotoxicity. In this 8-demethoxy series, the introduction of an amide at C-2 diminished also the cytotoxicity on HL60R.

Replacement of the bromine in 4′-position of **6a** by a methoxy (**6c**) was detrimental to the cytotoxicity activity, as it was previously observed with **1a** and rocaglaol (**2**).[6]

Because amides and esters at C-3 have a deleterious effect on multidrug resistance, we pursued our study with compounds unsubstituted in this position. Naturally occurring formate esters of flavaglines have been described to be cytotoxic in vitro,[8,12−14] suggesting that the hydroxy in position 1 could be replaced by another functionality. Evaluation of the synthetic esters **14**, amides **18**−**19**, sulfonamide **20**, and their epimers allowed to probe the substituent effect in this position (Table 2). Introduction of a formic ester (compound **14a**) was slightly detrimental to cytoxicity. Esterification by a bulkier acetyl or propionyl moiety (**14b** and **14c**) or replacement by a formamide or acetamide moiety (**18a** and **19a**) was even more detrimental. Replacement of the 1-hydroxy by a ketone (**12**) increased by almost two orders the IC_{50}. Surprisingly, inverting the configuration of this alcohol did not modify significantly the cytotoxicity (compare **13** with reference compound **1a**). Again, formylation of this epimer (**15**) slightly decreased its potency, but to our utter delight we were surprised to notice that epi-formamide **18b** was equipotent to reference compound **1a**. Epi-acetamide derivative **19b** was slightly less cytotoxic, suggesting a limited steric tolerance in the region of the amide. Introduction of a sulfonamide (**20**) was more detrimental.

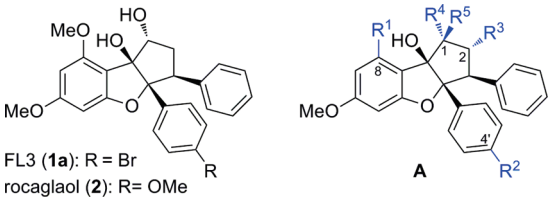
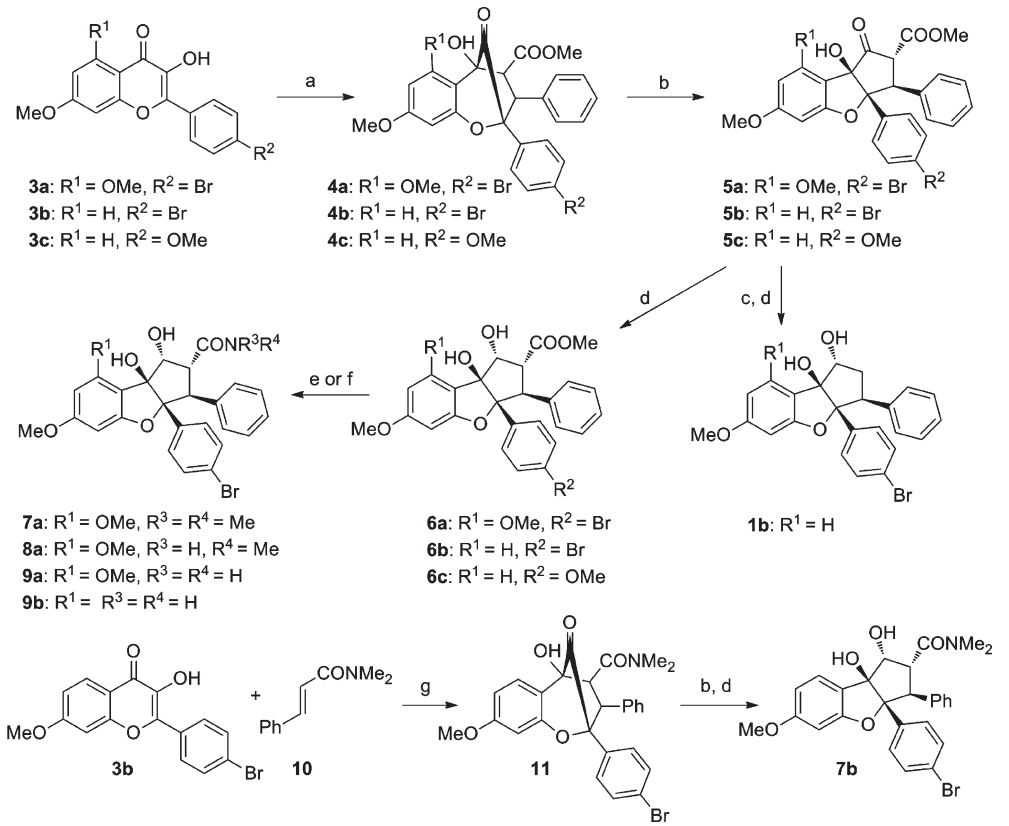


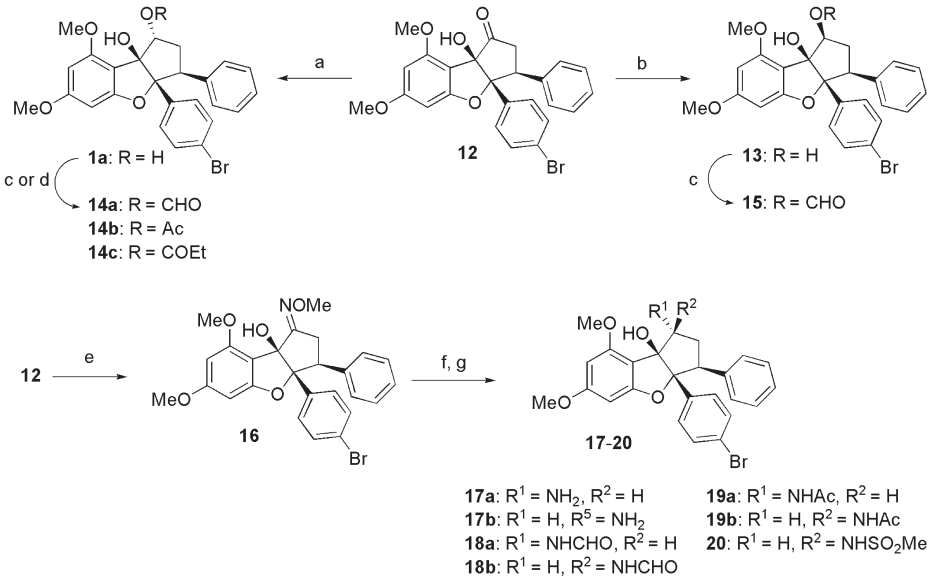
Figure 1. Structures of FL3 (**1a**), rocaglaol (**2**), and general structure of synthesized analogues (**A**).

Scheme 1[a]



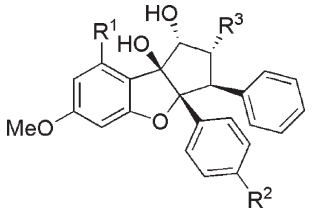
[a] Reactants and conditions: (a) hν, (*E*)-PhCH=CHCOOMe, CH_2Cl_2-MeOH, 0 °C, 15 h; (b) MeONa, MeOH, 60 °C, 20 min; (c) LiCl, H_2O, DMSO, 100 °C, 12 h; (d) $Me_4NBH(OAc)_3$, AcOH, CH_3CN; (e) (i) KOH, MeOH, 45 °C, 12 h, (ii) $Me_2NH.HCl$ or $MeNH_2.HCl$, ECDI, HOBT, DIPEA, CH_2Cl_2, rt, 12 h; (f) NH_3, MeOH, 100 °C, 36 h; (g) hν, CH_2Cl_2-MeOH, 0 °C, 15 h.

Scheme 2[a]



[a] Reactants and conditions: (a) $Me_4NBH(OAc)_3$, CH_3CN, rt, 12 h; (b) $NaBH_4$, MeOH, rt, 12 h; (c) DCC, DMAP, HCOOH, CH_2Cl_2, rt, 36 h; (d) $(RCO)_2O$, DMAP, pyr, rt, 6 h; (e) $H_2NOMe.HCl$, pyr, EtOH, 70 °C, 4 h; (f) BH_3, THF, 66 °C, 12 h; (g) HCOOEt, THF, reflux, 12 h, or Ac_2O, pyr, rt, or $MeSO_2Cl$, *N*-methylmorpholine, CH_2Cl_2, rt.

Table 1. Cytotoxicity of Flavaglines Analogues Against Human Cancer Cell Lines with R^1-R^3 variations (IC_{50}, nM)[a]



compd	R^1	R^2	R^3	HL60	HL60R	KB	HCT116	MDA231	MDA435	OV3	PC3
1a	OMe	Br	H	5.5	4.5	15	7.6	3.8	8.7	8.5	17
6a	OMe	Br	COOMe	14	14	24	18	8.7	15	21	29
7a	OMe	Br	$CONMe_2$	4.5	12	7.5	5.9	2.7	3.2	6.7	7.2
8a	OMe	Br	CONHMe	2.5	16	4.5	3.8	1.9	2.6	3.8	3.3
9a	OMe	Br	$CONH_2$	1	18	2	1.8	1.0	1.5	2.1	2.7
1b	H	Br	H	115	67	255	108	48	205	251	224
6b	H	Br	COOMe	65	44	165	96	27	65	101	174
7b	H	Br	$CONMe_2$	15	28	35	13	5.7	13	37	33
9b	H	Br	$CONH_2$	16	78	22	15	10	16	29	31
6c	H	OMe	COOMe	195	121	340	202	51	298	260	273
doxorubicine				30	990	40	22	0.047	3.5	41	186
taxotere				0.5	531	0.17	0.52	0.018	0.25	0.51	1.4
vinblastine				1.11	> 100	0.8	1.42	0.63	1.24	2.7	5.5

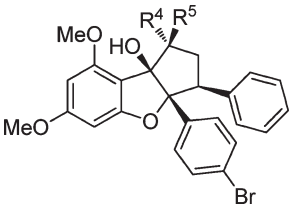
[a] Data are the average of two independent IC_{50} value determinations.

Central and peripheral nervous system toxicity is a common side effect of antineoplastic therapy. This prompted us to investigate whether epi-formamide **18b** is cytotoxic on neurons, which represent a type of cells that are particularly sensitive to chemotherapeutic agents.[15] Remarkably, incubation of neurons with 1 or 10 nM of **18b** for 24 h did not alter cell viability assessed by MTS assay (Supporting Information Figure S1).

The anticancer potential of **18b** was then tested on murine 3LL Lewis lung cancer. In vitro, **18b** showed a significant antiproliferative activity on 3LL cells, with an IC_{50} of 26 nM (Supporting Information Figure S2).

In vivo studies were performed on mice presenting xenografted 3LL tumors[16] using a nontoxic dose of **18b** (Figure 2). Mice with tumors $> 60\ mm^3$ were injected twice a week with **18b**. Cisplatin was also assayed for comparison (Supporting Information Figure S3). Twenty-eight days after initiation of the injection, **18b** at the dose of 10 mg/kg ip reduced tumors growth by about 33% (T/C value of 67%, Supporting Information Figure S3). Interestingly, at the dose of 25 mg/kg ip, the growth of the tumor was reduced by 65% (T/C value of 35%, Supporting Information Figure S3). Moreover, chronic administration of **18b** did not induce any visible toxicity on animals, confirming the absence of significant toxicity observed during single dose studies (Supporting Information Figure S4). These data are encouraging because flavaglines were reported to potentiate the antitumor activity

Table 2. Cytotoxicity of Flavaglines Analogues Against Human Cancer Cell Lines with R^4 and R^5 Variations (IC_{50}, nM)[a]



compd	R^4	R^5	HL60	HL60R	KB	HCT116	MDA231	MDA435	SK-OV3	PC3
14a	OCHO	H	7.0	5.1	6.9	6.8	2.9	7.0	8.1	8.2
14b	OAc	H	40		71					
14c	OCOEt	H	51		415					
18a	NHCHO	H	44		29					
19a	NHAc	H	268	361	434	543	65	526	525	382
12	=O		160		99					
13	H	OH	5.5	1.5	1.5	2.7	0.75	1.7	1.8	1.9
15	H	OCHO	89	82	124	133	67	144	195	145
18b	H	NHCHO	2.3	1.7	1.9	1.8	0.5	2.0	2.0	1.5
19b	H	NHAc	0.75	3.7	2.9	4.3	1.3	2.8	3.5	3.0
20	H	$NHSO_2Me$	17	22	24	13	1.2	34	14	22

[a] Data are the average of two independent IC_{50} value determinations.

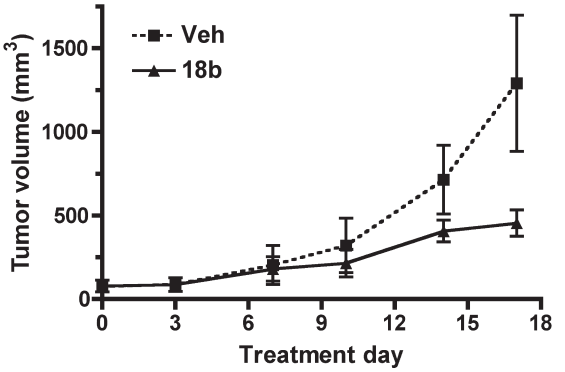


Figure 2. Antitumor activities of **18b** in a murine 3LL Lewis lung carcinoma allograft model. Treatments started when the volumes of tumors reached 60 mm^3. Compound **18b** was administered ip at 25 mg/kg ip twice a week for 17 days total. All data are expressed as mean values (n = 8 per group).

of doxorubicin and concanavalin A in some murine models without displaying any effect when tested alone.[9,17]

Conclusion

Our results confirm and extend the preliminary structure −activity data reported for natural flavaglines extracted from plants. The activity of natural flavaglines substituted in position 2 by H, COOMe, $CONMe_2$, CONHMe, and $CONH_2$ had been examined,[1,2] but as far as we know, the systematic comparison of all of these activities in one study has not been reported, nor was the requirement of the 8-methoxy for cytotoxicity or the deleterious effect of amide at C-2 on multidrug resistance. Surprisingly, the configuration of the hydroxyl at C-1 proved not to be crucial, furthermore, this alcohol could even be advantageously replaced by an aminoformyl with the opposite configuration. The results obtained in our allograft model support the continued preclinical development of **18b** in combination with other chemotherapeutic agents. Our findings will facilitate further drug discovery efforts toward the identification of a preclinical candidate to treats cancers.

Experimental Section

General Methods. All reagents and solvents for syntheses were purchased from Sigma-Aldrich, Fluka, or Acros and used without further purification. Intermediates **5b**, **6a**, **6b**, and **12** were prepared according to our previous report.[6] Reagent-grade solvents were purified and dried using standard methods. Reactions were carried out under an argon atmosphere using flame-dried glassware with magnetic stirring and degassed solvents. Column chromatography was carried out on silica gel 60 (Merck, 40−63 mesh). ^1H NMR spectra at 300 MHz and ^{13}C NMR spectra at 75 MHz were recorded with DPX 300 SY Brüker spectrometers, with the deuterated solvent as the lock and residual solvent as the internal reference. Purity of target compounds were over 95% based on reversed-phase HPLC analyses (Hypersil Gold column 30 mm × 1 mm, C18) under the following conditions: flow rate, 0.3 mL/min; buffer A, CH_3CN; buffer B, 0.01% aqueous TFA; gradient, 98−10% buffer B over 8 min (detection: λ = 220/254 nm).

3a-(4-Bromophenyl)-8b-hydroxy-6,8-dimethoxy-3-phenyl-2,-3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-1-one *O*-methyl Oxime (16). Ketone **12**[6] (500 mg, 1 equiv, 1.04 mmol) and *O*-methylhydroxylamine hydrochloride (430 mg, 5.2 mmol) were diluted in absolute ethanol (20 mL) and distilled pyridine (20 mL). The mixture was kept at 70 °C for 4 h before being concentrated in vacuo, extracted with EtOAc (10 mL), washed with HCl (1M, 2 × 10 mL), a saturated solution of Na_2CO_3 (10 mL), and brine (10 mL), and dried over $MgSO_4$. Concentration to dryness quantitatively yielded the desired oxime **16** (530 mg) as a white solid, which was used in the next step without purification. ^1H NMR ($CDCl_3$): 3.07 (2H, m), 3.70 (1H, m), 3.82 (3H, s), 3.84 (3H, s), 4.06 (3H, s), 6.10 (1H, d, J = 2.0 Hz), 6.27 (1H, d, J = 2.0 Hz), 7.00 (4H, m), 7.08 (3H, m), 7.27 (2H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$): 29.9, 49.9, 55.7, 55.9, 62.7, 87.5, 88.8, 93.1, 101.7, 108.2, 121.7, 127.0, 128.0 (2C), 128.1 (2C), 128.7 (2C), 130.9 (2C), 133.8 (2C), 137.5, 158.9, 160.2, 160.4, 164.4.

1-Amino-3a-(4-bromophenyl)-6,8-dimethoxy-3-phenyl-2,3,3a,-8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-8b-ol (17a and 17b). Borane−tetrahydrofuran complex (20 mL, 20 mmol, 1M) was added dropwise to a solution of oxime **16** (538 mg, 1 equiv, 1.04 mmol) in THF (5 mL) at 0 °C. The mixture was heated under reflux for 12 h and cooled in an ice/water bath. A solution of NaOH (30 mL, 3 N) was carefully added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over

$MgSO_4$, and concentrated to dryness. Purification by flash chromatography (Et_2O/MeOH: 70/30) provided 221 mg (44%) of the desired amines **17a** and **17b** as an inseparable mixture in a 30:70 ratio. ^{1}H NMR ($CDCl_3$): 2.02−2.12 (1H, m), 2.43−2.49 (1H, m), 3.57 (1H, dd, J = 5.9, 14.4 Hz), 3.79 (6H, s), 3.82 (1H, m), 6.06 (1H, d, J = 2 Hz), 6.21 (1H, d, J = 2.0 Hz), 7.02 (2H, d, J = 8.7 Hz), 6.99−7.11 (5H, m), 7.19 (2H, d, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$): 36.9, 52.0, 55.7, 55.8, 57.0, 86.4, 88.9, 92.5, 101.9, 112.1, 121.0, 126.6, 128.0, 128.1, 129.5, 130.2, 135.9, 138.3, 157.6, 159.7, 163.4.

***N*-(3a-(4-Bromophenyl)-8b-hydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-1-yl)formamide (18a and 18b).** A 3:7 mixture of amines **17a** and **17b** (130 mg, 0.27 mmol) was heated under reflux for 12 h in THF (2 mL), ethyl formate (0.35 mL, 4.31 mmol), and a drop of acetic acid. Concentration and purification by flash chromatography (Et_2O/AcOEt: 6/4) afforded formamides **18a** (11 mg, 8%) and **18b** (60 mg, 44%) as white solids.

18a. ^{1}H NMR ($CDCl_3$): 2.09 (1H, m), 2.82 (1H, m), 3.84 (7H, m), 4.98 (1H, m), 6.08 (1H, d, J = 2.0 Hz), 6.21 (1H, d, J = 2.0 Hz), 6.90−7.10 (7H, m), 7.15 (2H, d, J = 8.7 Hz), 8.07 (1H, s). ^{13}C NMR ($CDCl_3$): 34.1, 53.7, 55.4, 55.5, 58.3, 88.9, 92.4, 92.6, 102.4, 106.4, 121.1, 126.4, 127.9 (2C), 128.3 (2C), 129.4 (2C), 129.8 (2C), 135.0, 138.6, 157.6, 161.0, 161.9, 163.9. IR (thin film): 3338, 2928, 1673, 1596, 700 cm^{-1}. LC-MS: calculated, 509.1; found, 492.0 $(M + H - H_2O)^+$.

18b. ^{1}H NMR ($CDCl_3$): 2.25 (1H, m), 2.70 (1H, m), 3.56 (1H, m), 3.76 (3H, s), 3.80 (3H, s), 4.69 (1H, m), 6.06 (1H, d, J = 2.0 Hz), 6.21 (1H, d, J = 2.0 Hz), 6.96 (2H, m), 7.02−7.08 (5H, m), 7.19 (2H, d, J = 8.8 Hz), 8.24 (1H, s). ^{13}C NMR ($CDCl_3$): 35.4, 53.7, 53.9, 55.1, 55.3, 86.2, 88.6, 92.0, 101.7, 110.6, 120.7, 126.3, 127.5 (2C), 127.7 (2C), 129.3 (2C), 129.7 (2C), 135.1, 137.5, 157.6, 159.2, 161.6, 163.5. IR (thin film): 3585, 3386, 2944, 2839, 1666, 1694, 698 cm^{-1}. LC-MS: calculated, 509.1; found, 492.0 $(M + H - H_2O)^+$.

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Supporting Information Available: Supplementary biological data, in vitro neuronal toxicity, cytotoxicity on 3LL cells, and acute toxicity of **18b**, cytotoxicity against cancer cell lines (IC_{50} with standard deviations), synthesis of compounds **1b**, **6c**, **7a**, **8a**, **9a**, **9b**, and **7b**, and supplementary biological assay methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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