TITLE

The Iboga Enigma: The Chemistry and Neuropharmacology of Iboga Alkaloids and Related Analogs

AUTHOR INFORMATION

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SUPPLEMENTARY INFORMATION

Table S1:

Compound	Plant Source	Plant Tissue	Region	Characterization Data
9	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, NOESY, HMBC, MS, X-ray, ECD, OR, UV, IR
10	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, NOESY, HMBC, MS, X-ray, ECD, OR, UV, IR
11	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, NOESY, HMBC, MS, X-ray, ECD, OR, UV, IR
12	*Ervatamia hainanensis*	Aerial Parts	China	^{1}H, ^{13}C, COSY, DEPT, HSQC, HMBC, OR, IR, UV, X-ray
13	*Tabernaemontana divaricata*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, HMBC, ROESY, MS, X-Ray, UV, OR
14	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, NOESY, HMBC, MS, X-ray, ECD, OR, UV, IR
15	*Tabernaemontana hystrix*	Root Bark	Brazil	^{1}H, ^{13}C, COSY, HMBC, HMQC, MS, OR, IR
16	*Tabernaemontana inconspicua*	Stems	Cameroon	^{1}H, ^{13}C, COSY, HMBC, MS

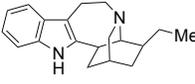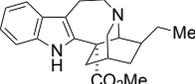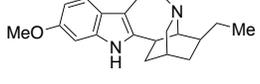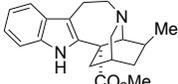|				
17	*Tabernaemontana contorta Stapf*	Fruits	Cameroon	^{1}H, ^{13}C, COSY, HMBC, NOESY, MS, OR
18	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, NOESY, HMBC, MS, X-ray, ECD, OR, UV, IR
19	*Ervatamia hainanensis*	Twigs and Leaves	China	^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, X-Ray, MS, IR, OR, ECD
20	*Ervatamia hainanensis*	Twigs and Leaves	China	^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, X-Ray, MS, IR, OR, ECD
21	*Tabernaemontana corymbosa*	Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMQC, HMBC, MS, OR, UV, IR, X-Ray
22	*Ervatamia hainanensis*	Aerial Parts	China	^{1}H, ^{13}C, COSY, DEPT, HSQC, HMBC, OR, IR, UV, X-ray
23	*Ervatamia hainanensis*	Aerial Parts	China	^{1}H, ^{13}C, COSY, DEPT, HSQC, HMBC, OR, IR, UV, X-ray
24	*Ervatamia pandacaqui*	Twigs and Leaves	China	[1]H, ^{13}C, NOESY, MS, OR, UV
25	*Tabernaemontana corymbosa*	Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, HRMS, OR, X-ray
26	*Tabernaemontana corymbosa*	Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, MS, OR, X-ray
27	*Tabernaemontana corymbosa*	Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, HSQC, NOE, MS, X-Ray, OR, UV, IR, ECD
28	*Tabernaemontana corymbosa*	Ground Leaf and Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, NOE, MS, X-Ray, OR, UV, IR
29	*Tabernaemontana corymbosa*	Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, HSQC, NOE, MS, X-Ray, OR, UV, IR
30	*Tabernaemontana corymbosa*	Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, HSQC, NOE, MS, OR, UV

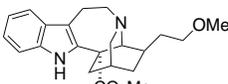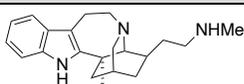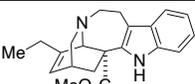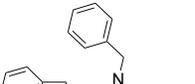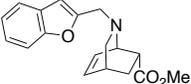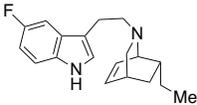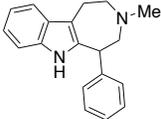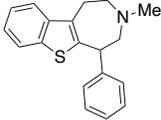|				
31	*Tabernaemontana corymbosa*	Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, HSQC, NOE, MS, X-Ray, OR, UV, IR, ECD
32	*Tabernaemontana corymbosa*	Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMBC, HSQC, NOE, MS, OR, UV, IR, ECD
33	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, HMBC, NOE, MS, ECD, IR, UV, OR
34	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, HMBC, NOE, MS, ECD, IR, UV, OR
35	*Tabernaemontana corymbosa*	Stem Bark	Malaysia	^{1}H, ^{13}C, COSY, HMQC, HMBC, MS, OR, UV, IR, X-Ray
36	*Tabernaemontana divaricata*	Branches and Leaves	China	^{1}H, ^{13}C, HMBC, ROESY, MS, OR, UV
37	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, NOESY, HMBC, MS, X-ray, ECD, OR, UV, IR
38	*Ervatamia hainanensis*	Twigs and Leaves	China	^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, X-Ray, MS, IR, OR, ECD
39	*Ervatamia hainanensis*	Twigs and Leaves	China	^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, X-Ray, MS, IR, OR, ECD
40	*Ervatamia hainanensis*	Twigs and Leaves	China	^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, X-Ray, MS, IR, OR, ECD
41	*Ervatamia pandacaqui*	Twigs and Leaves	China	^{1}H, ^{13}C, NOESY, MS, OR, UV
42	*Tabernaemontana divaricata*	Branches and Leaves	China	^{1}H, ^{13}C, HMBC, ROESY, MS, OR, UV
43	*Ervatamia hainanensis*	Aerial Parts	China	^{1}H, ^{13}C, COSY, DEPT, HSQC, HMBC, OR, IR, UV, X-ray
44	*Tabernaemontana divaricata*	Branches and Leaves	China	^{1}H, ^{13}C, HMBC, ROESY, MS, OR, UV

45	*Tabernaemontana divaricata*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, HMBC, DEPT, MS, ECD, OR, UV, IR
46	*Tabernaemontana divaricata*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, HMBC, DEPT, MS, ECD, OR, UV, IR
47	*Ervatamia hainanensis*	Twigs and Leaves	China	^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, X-Ray, MS, IR, OR, ECD
48	*Tabernaemontana divaricata*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, HMBC, ROESY, MS, X-Ray, UV, OR
49	*Ervatamia officinalis*	Twigs and Leaves	China	^{1}H, ^{13}C, COSY, NOESY, HMBC, MS, X-ray, ECD, OR, UV, IR

Table S1. Sources and characterization data available for newly isolated iboga alkaloids. The available NMR data is listed. OR = optical rotation, ECD = electronic circular dichroism, MS = mass spectrometry, UV = UV/Vis spectroscopy, IR = infrared spectroscopy, X-Ray = X-ray crystallography.

Table S2:

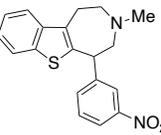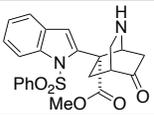| Compound	Structure	Efficacy Data	Safety Data
(-)-Ibogaine (**1**)		NMDA IC_{50} = 1.11 μM[1] Muscle AChR IC_{50} = 17 μM[2] Human $\alpha 3\beta 4$ AChR IC_{50} = 0.95 μM[3] MOR IC_{50} = 3.76 μM[4] KOR IC_{50} = 29.8 μM[1] MOR K_i = 3.76 μM[5] KOR K_i = 3.77 μM[6] DAT IC_{50} = 4.11 μM[4] SERT IC_{50} = 0.59 μM[4] DAT K_i = 1.98 μM[7] SERT K_i = 0.5487 μM M[7] D1 IC_{50} = >10 μM[4] D2 IC_{50} = >10 μM[4] D3 IC_{50} = >10 μM[4] σ_1 K_i = 8.554 μM[8] σ_2 K_i = 0.201 μM[8] Reduces opioid self-administration[9] Reduces cocaine self-administration[9] Reduces alcohol consumption[10] Reduces nicotine preference[11]	Tremorigenic[12] Cerebellar toxicity[13] hERG IC_{50} = 3.53 μM[14]
(-)-Noribogaine (**2**)		NMDA IC_{50} = 5.48 μM[1] KOR IC_{50} = 0.28 μM[1] Human $\alpha 3\beta 4$ AChR IC_{50} = 6.82 μM[3] NMDA IC_{50} = 31.41 μM[15] DAT K_i = 2.05 μM[7] SERT K_i = 0.0407 μM[7] σ_1 K_i = 15.006 μM[8] σ_2 K_i = 5.226 μM[8] MOR K_i = 0.16 μM[5] KOR K_i = 0.96 μM[6] Reduces opioid self-administration[16] Reduces cocaine self-administration[16] Reduces alcohol consumption[17]	Not tremorigenic[12] hERG IC_{50} = 2.86 μM[14]
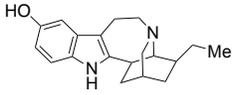
		Reduces nicotine self-administration[18]	
(±)-Ibogamine (**81**)		NMDA IC_{50} = 5.52 μM[1] σ_1 K_i = 1.835 μM[8] σ_2 K_i = 0.137 μM[8] Reduces opioid self-administration[9] Reduces cocaine self-administration[9]	Not tremorigenic[9]
(±)-Coronaridine (**4**)		NMDA IC_{50} = 6.24 μM[1] σ_1 K_i = 35.688 μM[8] σ_2 K_i = >26 μM[8] Reduces opioid self-administration[9] Reduces cocaine self-administration[9]	Not tremorigenic[9]
(-)-Tabernanthine (**5**)		NMDA IC_{50} = 10.5 μM[1] σ_1 K_i = 2.872 μM[8] σ_2 K_i = 0.194 μM[8] Reduces opioid self-administration[9] Reduces cocaine self-administration[9]	Tremorigenic[19]
(±)-**190**		NMDA IC_{50} = 67.9 μM[1]	Unknown
(±)-**191**		NMDA IC_{50} = 252 μM[1] Reduces opioid self-administration[9] Reduces cocaine self-administration[9]	Tremorigenic[9]
(-)-**192**		NMDA IC_{50} = 179 μM[1] KOR IC_{50} = 16.7 μM[1]	Unknown
(±)-18-MC (**193**)		Muscle AChR IC_{50} = 6.8 μM[2] Human $\alpha3\beta4$ AChR IC_{50} = 1.47 μM[3] Human $\alpha4\beta2$ AChR IC_{50} = 6.3 μM[20] Human $\alpha7$ AChR IC_{50} = 0.95 μM[20] Reduces opioid self-administration[21] Reduces cocaine self-administration[21] Reduces alcohol consumption[22] Reduces nicotine self-administration[23] Reduces nicotine preference[11]	Not tremorigenic[21] No cerebellar toxicity[21] hERG IC_{50} > 50 μM[14]
(±)-18-MAC (**194**)		Muscle AChR IC_{50} = 5.9 μM[2] Human $\alpha3\beta4$ AChR IC_{50} = 2.62 μM[3] Human $\alpha4\beta2$ AChR IC_{50} = 20.7 μM[20] Human $\alpha7$ AChR IC_{50} = Inactive[20]	Unknown
(+)-Catharanthine (**7**)		Muscle AChR IC_{50} = 20 μM[2] Human $\alpha3\beta4$ AChR IC_{50} = 0.68 μM[3] Human $\alpha4\beta2$ AChR IC_{50} = 12.6 μM[20] Human $\alpha7$ AChR IC_{50} = 21.8 μM[20]	Unknown
(±)-**195**		NMDA IC_{50} = 31.5 μM[24] KOR IC_{50} = 19.5 μM[24] DAT IC_{50} = 4.4 μM[24] SERT IC_{50} = 0.5 μM[24]	Unknown
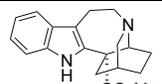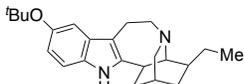
(±)-**196**		KOR IC_{50} = 29.8 μM[25] Analgesic[25]	Not tremorigenic[25]
(±)-XL-008 (**197**)		Induces GDNF release[26]	Unknown
(±)-**198**		KOR IC_{50} = 21.2 μM[4] MOR IC_{50} = 3.1 μM[4] DAT IC_{50} = 0.18 μM[4] SERT IC_{50} = 0.19 μM[4] D1 IC_{50} = 20 μM[4] D2 IC_{50} = 27.2 μM[4] D3 IC_{50} = 4.2 μM[4]	Unknown
(±)-**199**		NMDA IC_{50} = 42 μM[4] KOR IC_{50} = 1.3 μM[4] MOR IC_{50} = 2.2 μM[4] DAT IC_{50} = 0.14 μM[4] SERT IC_{50} = 0.30 μM[4] D1 IC_{50} = 3 μM[4] D2 IC_{50} = 5.0 μM[4] D3 IC_{50} = 0.6 μM[4]	Unknown
(±)-**200**		NMDA IC_{50} = 46.6 μM[4] KOR IC_{50} = 12.5 μM[4] MOR IC_{50} = 5.0 μM[4] DAT IC_{50} = 0.21 μM[4] SERT IC_{50} = 4.30 μM[4] D1 IC_{50} = 5 μM[4] D2 IC_{50} = 3.5 μM[4] D3 IC_{50} = 2.0 μM[4]	Unknown
(±)-**201**		NMDA IC_{50} = 32 μM[4] KOR IC_{50} = 16.2 μM[4] MOR IC_{50} = 3.1 μM[4] DAT IC_{50} = 0.25 μM[4] SERT IC_{50} = 1.10 μM[4] D1 IC_{50} = 5 μM[4] D2 IC_{50} = 3.1 μM[4] D3 IC_{50} = 0.6 μM[4]	Unknown
(±)-**202**		NMDA IC_{50} = 81 μM[4] KOR IC_{50} = 15.9 μM[4] MOR IC_{50} = 54.5 μM[4] DAT IC_{50} = 0.25 μM[4] SERT IC_{50} = 1.20 μM[4] D1 IC_{50} = 70 μM[4] D2 IC_{50} = 5.0 μM[4] D3 IC_{50} = 2.0 μM[4]	Unknown
(±)-**203**[27]		Unknown	Unknown
(±)-**204**[28]		Unknown	Unknown
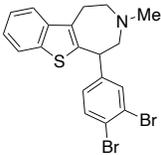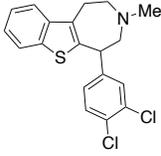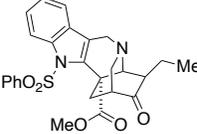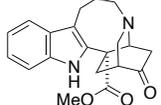
(±)-**205**[27]		Unknown	Unknown
(±)-**206**[29]		Unknown	Unknown
(±)-**207**[29]		Unknown	Unknown
(±)-**208**[30]		Unknown	Unknown
(±)-**209**[31]		Unknown	Unknown
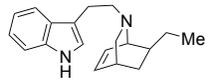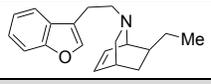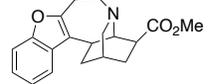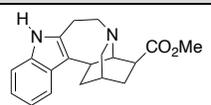
Table 4. Structures of ibogalogs. References disclosing efficacy or safety data are indicated. For compounds lacking biological data, a reference for the synthesis of compound is shown next to the compound number.

Supplementary References

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