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Cytotoxic effects and reversal of multidrug resistance by ibogan and related indole alkaloids

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Abstract—A series of indole alkaloids of the ibogan-type was assessed for their cytotoxic effects as well as their potential in reversing MDR in vincristine-resistant KB cells. Of a total of 25 compounds tested, 3(*S*)-cyanocoronaridine, 3(*S*)-cyanoisovoacangine, 3(*S*)-cyanovoacangine, and 10,11-demethoxychippiine were found to show appreciable cytotoxicity toward KB cells, while coronaridine, heyneanine, 19-*epi*-heyneanine, dippinine B, and dippinine C, were found to reverse MDR in vincristine-resistant KB cells.

The phenomenon of multidrug resistance (MDR) constitutes a major obstacle associated with cancer chemotherapy.[1–3] As such the search for effective modulators for circumvention of MDR represents an active area of research. Among potential candidates, which are being screened for their ability to reverse MDR are plant natural products, including indole alkaloids.[2–7] We have previously reported the results of our screening of a series of aspidofractinine-type indole alkaloids (e.g., kopsiflorine **1**),[5,7] as well as vobasinyl-iboga bisindoles (e.g., conodiparine A **2**),[6,8] with respect to their action in reversing MDR in vincristine-resistant KB cells. In the case of the aspidofractinine compound, kopsiflorine **1**, we have also reported the results of more detailed studies, which indicated that **1** inhibits efflux of antitumor agents by its direct interaction with P-glycoprotein.[7] In continuation of our ongoing screening of alkaloidal compounds for their potential in reversing MDR, we would like to report the results for the iboga group of compounds.[8–11]

The results are presented in Table 1. The IC_{50} values of vincristine against sensitive (KB/S) and resistant (KB/VJ300) strains are 0.014 and 1.05 μg/mL, respectively, in the present experiments (75-fold resistance shown by the resistant strain).[12] Examination of Table 1 showed that the 3-cyanosubstituted ibogan derivatives (**11**, **12**, **13**) as well as the unsubstituted chippiine compound (**10**) showed appreciable cytotoxicity toward sensitive (KB/S) as well as vincristine-resistant (KB/VJ300) cells. The remaining compounds showed only weak or moderate cytotoxicity toward the sensitive as well as resistant KB cells, but compounds **3**–**7** significantly inhibited cell growth of the resistant strain (KB/VJ300) in a dose-dependent manner, when applied in the presence of vincristine (0.1 or 0.25 μg/mL).

The results also revealed some clear structure–activity correlations for these ibogan compounds. The ibogan alkaloids **3**–**7** showed appreciable activity in reversing MDR while the remaining compounds **14**–**27** are practically inactive. It appears that the presence of a basic ibogan skeleton with an intact C(16)-methyl ester function, as exemplified by coronaridine is necessary; absence of the C(16)-ester group results in substantial loss of activity (cf. coronaridine **3** vs ibogamine **14**). The presence of a hydroxyl substituent on the C(19) ethyl side chain does not produce an undesired effect as seen in the case of 19-*epi*-heyneanine **5** and heyneanine **4** compared to coronaridine **3**, although it would appear that a 19*S* configuration is preferred (cf. **5** vs **4**). An unsubstituted aromatic ring appears to be desirable, while the presence

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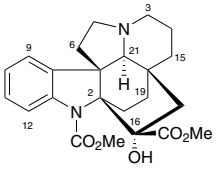
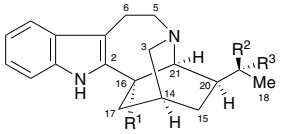
of an aromatic methoxy substituent appear to adversely affect the activity (cf. **3** vs **15**, **16**; **5** vs **18**; **4** vs **17**). Functionalization of position 3 of the ibogan carbon skeleton produces an undesirable effect as seen in the case of 3-oxo-coronaridine **21** and 3-oxo-19-*epi*-heyneanine **22**, and the 3-ethoxy derivatives of coronaridine, heyneanine, and 19-*epi*-heyneanine (**23**, **24**, **25**, respectively).

Disruption of the aromatic indole chromophore results in loss of activity (cf. **26** vs **3**), as does scission of the *N*(4)–C(3) bond, as seen in the *seco*-ibogan derivative **27**. The ibogan-derived dippinine compounds,[10] dippinines B **6** and C **7**, although possessing a rearranged carbon skeleton, were also found to be effective. Comparison of the dippinine compounds showed that formation of an additional tetrahydro-1,3-oxazine ring as in **7** does not affect the biological activity, but the presence of an aromatic methoxy substituent was undesirable (cf. **6** vs **8**; **7** vs **9**).

The above results indicate that the basic ibogan structure with an intact 16-methyl ester function, as exemplified by coronaridine and 19-*epi*-heyneanine, is essential for manifestation of reversal of MDR, whereas aromatic substitution, or a drastic departure from the basic ibogan skeleton results in loss of activity (with the exception of the dippinine compounds). The undesirable effect of aromatic substitution has been previously



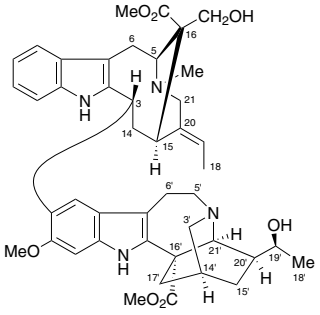
1



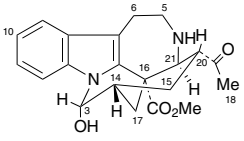
3 $R^1 = CO_2Me$, R^2, R^3 = H (Coronaridine)

4 $R^1 = CO_2Me$, R^2 = OH, R^3 = H

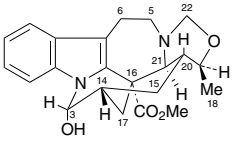
5 $R^1 = CO_2Me$, R^2 = H, R^3 = OH



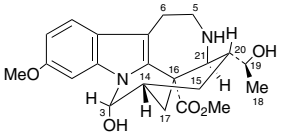
2



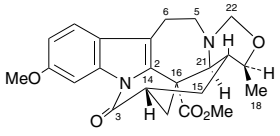
6 Dippinine B



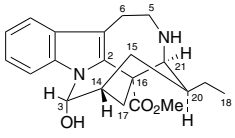
7 Dippinine C



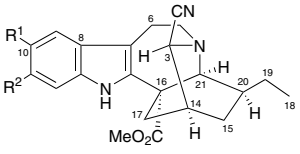
8 Dippinine A



9 Dippinine D



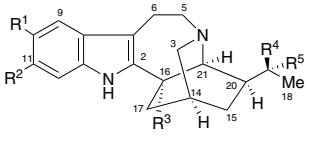
10 10,11-Demethoxychippiine



11 R^1, R^2 = H

12 R^1 = H, R^2 = OMe

13 R^1 = OMe, R^2 = H



14 R^1, R^2, R^3, R^4, R^5 = H

15 R^1 = OMe, $R^3 = CO_2Me$, R^2, R^4, R^5 = H

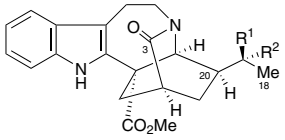
16 R^1, R^4, R^5 = H, R^2 = OMe, $R^3 = CO_2Me$

17 R^1, R^5 = H, R^2 = OMe, $R^3 = CO_2Me$, R^4 = OH

18 R^1, R^4 = H, R^2 = OMe, $R^3 = CO_2Me$, R^5 = OH

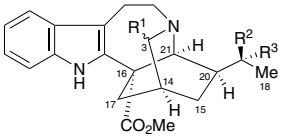
19 R^1 = H, R^2 = OMe, $R^3 = CO_2Me$, R^4, R^5 = O

20 R^1, R^2 , R^3, R^5 = H, R^4 = OH



21 R^1, R^2 = H

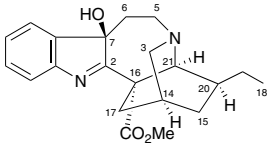
22 R^1 = H, R^2 = OH



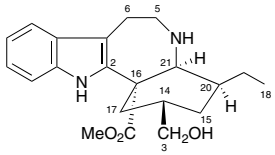
23 R^1 = OEt, R^2, R^3 = H

24 R^1 = OEt, R^2 = OH, R^3 = H

25 R^1 = OEt, R^2 = H, R^3 = OH



26 Coronaridine-7-hydroxyindolenine



27 3-Hydroxy-3,4-*seco*-coronaridine

Table 1. Cytotoxic activity of compounds **3**–**27**[a]

Compound	IC_{50} (μg/mL)	
	(KB/S)	(KB/VJ300)[b]
1 Kopsiflorine[5,7]	>25	0.64[c]
3 Coronaridine[9]	11.5	2.6
4 Heyneanine[9]	>25	8.5
5 19-*epi*-Heyneanine[9]	25	3.5
6 Dippinine B[10]	25	2
7 Dippinine C[10]	25	4
8 Dippinine A[10]	>25	>25
9 Dippinine D[10]	>25	>25
10 10,11-Demethoxychippiine[11,13]	3.5	2.5
11 3(*S*)-Cyanocoronaridine[11]	2.2	1.4
12 3(*S*)-Cyanoisovoacangine[11]	1.9	1.1
13 3(*S*)-Cyanovoacangine[11]	9.4	7.0
14 Ibogamine[9]	>25	>25
15 Voacangine[9]	>25	>25
16 Isovoacangine[9]	>25	>25
17 Isovoacristine[9]	>25	18.8[c]
18 19-*epi*-Isovoacristine[9]	>25	>25
19 Isovoacryptine[9]	>25	14.5[c]
20 19-(*S*)-Hydroxyibogamine[9]	16.1	7.8
21 3-Oxo-coronaridine[9]	>25	>25
22 3-Oxo-19-*epi*-heyneanine[9]	>25	>25
23 3-(*R*/*S*)-Ethoxycoronaridine[9]	>25	13
24 3-(*R*/*S*)-Ethoxyheyneanine[9]	>25	>25
25 3-(*R*/*S*)-Ethoxy19-*epi*-heyneanine[9]	>25	>25
26 Coronaridine-7-hydroxyindolenine[9]	>25	>25
27 3-Hydroxy-3,4-*seco*-coronaridine[9]	>25	>25

[a] KB/S and KB/VJ300 are vincristine-sensitive and -resistant human oral epidermoid carcinoma cell line, respectively.[12]

[b] With added vincristine 0.1 μg/mL, which did not affect the growth of the KB/VJ300 cells.

[c] With added vincristine 0.25 μg/mL, which did not affect the growth of the KB/VJ300 cells.

observed in the aspidofractinine series.[5] However in contrast to the results for the aspidofractinine compounds, the presence of an indolic *N*H in the iboga series does not appear to have an unfavorable effect on the activity.

Acknowledgements

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