# Structures and Cytotoxic Properties of Sponge-Derived Bisannulated Acridines

Zia Thale,[a] Tyler Johnson,[a] Karen Tenney,[a] Philip J. Wenzel,[a] Emil Lobkovsky,[b] Jon Clardy,[b] Joe Media,[c] Halina Pietraszkewicz,[c] Frederick A. Valeriote,[c] and Phillip Crews*[,a]

[a]Department of Chemistry and Biochemistry and Institute for Marine Sciences, University of California, Santa Cruz, California 95064.
[b]*Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 41853-1301.*
[c]*Josephine Ford Cancer Center, Henry Ford Health Systems, Detroit, Michigan 48202*
*file name: SI_joc0264590_r2*

## Supporting Information

**Table S1.** Cytotoxicity in zone units from the disk diffusion soft agar colony formation assay.[a]

| | | Murine | | | Human | | | |
|---|---|---|---|---|---|---|---|---|
| | Extracts | L1210 | C38 | CFU-GM | H116 | H125 | CEM | CFU-GM |
| *X. cf. exigua* | | | | | | | | |
| (91608) | FD | 550 | 700 | 300 | 550 | 600 | 300 | 300 |
| | FM | 350 | 400 | 250 | 600 | 700 | 500 | |
| | WB | 300 | 550 | 300 | 250 | 350 | 300 | |
| | DMM | 300 | 650 | 200 | 400 | 500 | 300 | |
| **X. cf. cabonaria** | | | | | | | | |
| (94634) | FD | 350 | 500 | 350 | 400 | 650 | 250 | 600 |
| | FM | 100 | 150 | 0 | 150 | 300 | 700 | |
| | WB | 150 | 200 | 50 | 150 | 400 | 200 | |
| | DMM | 550 | 650 | 350 | 650 | 750 | 350 | 500 |
| | DMM HP1 | 0 | 100 | | 0 | 0 | ND* | |
| | DMM HP2 | 400 | 650 | 100 | 300 | 600 | 0 | |
| | DMM HP3 | 700 | 1050 | 500 | 600 | 800 | 299 | |
| | DMM HP4 | 300 | 700 | 250 | 300 | 550 | 0 | |
| Amphimedine (**1**) | | 50 | 350 | 0 | 150 | 200 | ND* | |
| Neoamphimedine (**2**) | | 350 | 350 | 100 | 350 | 450 | 100 | 100 |
| 5-methoxy-neoamphimedine (**4**) | | 550 | >1000 | 400 | 660 | 800 | -- | |
| Alpkinidine (**7**) | | 100 | 400 | 100 | 100 | 150 | ND* | |

[a]dose: extracts = 50 µg/disk, pure compounds = 5 µg/disk; 200 zone units = 6mm. Murine cell lines: L1210 (lymphocytic leukemia), C38 (colon adenocarcinoma), CFU-GM (colony-forming unit granulocyte macrophage; normal hematopoietic); Human cell lines: H116 (colon), H125 (lung), CEM (leukemia), CFU-GM (colony-forming unit-granulocyte macrophage; normal hematopoietic).

*Not determined: zone units for H116 or H123 <250 at 50 µg/disk.

**Table S2.** Summary of sponge-derived bisannulated acridines.

| Ring System | Name | Taxonomic ID | Collection site | Ref (s) |
|---|---|---|---|---|
| I-A | Amphimedine (**1**) | *Amphimedon* sp. | Guam Island | a, b, c |
| | | *Xestospongia* cf. *carbonaria* | Indonesia | |
| | | | Philippines | |
| | Neoamphimedine (**3**) | *Xestospongia* cf. *carbonaria* | Palau | b, c |
| | | | Philippines | |
| | Deoxyamphimedine | *Xestospongia* cf. *carbonaria* | Philippines | b, c |
| | Petrosamine | *Petrosia* sp. | Belize | d |
| I-B | Meridine* | *Corticum* sp. | Bahamas | e, f, g |
| I-C | 11-Hydroxyascididemin* (=cystodamine) | *Biemna* sp. | Japan | g, h, i |
| | 8,9-dihydro-11-hydroxyascididemin | | Japan | i |
| | | *Biemna* sp. | | |
| I-D | Kuanoniamines C* | | Bahamas, Micronesia | j, k, l, m |
| | (=dercitamide) | *Stelletta* sp. | Palau | |
| | | *Oceanapia* sp. | | |
| | | *Oceanapia sagittaria* | | |
| | Kuanoniamines D* | | Micronesia | j, l |
| | | *Oceanapia* sp. | | |
| | N-Deacteylkuanoniamine C | | Micronesia | l |
| | | *Oceanapia* sp. | | |
| | Nordercitin | *Stelleta* sp. | Bahamas | n |
| | Dercitamine | *Dercitus* sp. | Bahamas | n, k |
| | | *Stelleta* sp. | | |
| | Dercitin | *Dercitus* sp. | Bahamas | o |
| | Sagitol | | Palau | m |
| | | *Oceanapia* sp. | | |
| II-E | Plakinidine A (**2**)# | | Vanuatu | p |
| | | | Fiji | |
| | | *Plakortis* sp. | | |
| | Plakinidine B | | Vanuatu | q |
| | | | Fiji | |
| | | *Plakortis* sp. | | |
| | Plakinidine C | | Fiji | r |
| | | *Plakotis* sp. | | |

*The compound has also been isolated from a tunicate.

#Other members of the series have been reported from a tunicate.

a) Schmitz, F.J.; Agarwal, S.K.; Gunasekera, S.P.; Schmidt, P.G.; Shoolery, J.N. *J. Am. Chem. Soc.* **1983**, *105*, 4835-4836.; b) De Guzman,F.S.; Carte, B.; Troupe, N.; Faulkner, D.J.; Harper, M.K.; Concepción, G.P.; Mangalindan, G.C.; Matsumoto, S.S.; Barrows, L.R.; Ireland, C. M. *J. Org. Chem.* **1999**, *64*, 1400-1402.; c) Tasdemir,D.; Marshall, K.M.;Mangalindan, G.C.; Concepción, G.P.; Barrows, L.R.; Harper, M.K.; Ireland, C.M. *J. Org. Chem.* **2001**, *66*, 3246-3248; d) Molinski, T.F.; Fahy, E.; Faulkner, D.J.; Van Duyne, G.D.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 1340-1341; e) McCarthy, P.J.; Pitts. T.P.; Gunawardana, G.P.; Kelly-Borges, M.; Pomponi, S.A. *J. Nat. Prod.* **1992,** *5*, 1664-1668; f) Schmitz, F.J.; De Guzman, F.S.; Choi, Y.-H.; Hossain, M.B.; Rizvi, S.K.; Van der Helm, D. *Pure Appl.Chem.* **1990**, *62*, 1393-1396; g) Schmitz, F.J.; De Guzman, F.S.; Hossain, M.B.; Van der Helm, D. *J. Org. Chem.* **1991**, 5*6*, 804-808; h) Bontemps, N.; Bonnard, I.; Banaigs, B.; Combaut, G.; Francisco, C. *Tetradedron Lett.* **1994**, *35*, 7023-7026; i) Zeng, C.M.; Ishibashi, M; Matsumoto, K.; Nakaike, S.; Kobayashi, J. *Tetrahedron* **1993**, *49*, 8337-8342; j) Carroll, A.R.; Scheuer, P.J. *J. Org. Chem.* **1990**, *55*, 4426-4431; k) Gunawardana, G.P.; Koehn, F.E.; Lee, A.Y.; Clardy, J.; He, H.-Y.; Faulkner, D.J. *J. Org. Chem.* **1992**, *57*, 1523-1526; l) Eder, C.; Schupp, P.; Proksch, P.; Wray, V.; Steube, K.; Miller, C.E.; Frobenius, W.; Herderich, M.; van Soest, R.W.M. *J. Nat. Prod.* **1998**, *61*, 301-305; m) Salomon, C.E.; Faulkner, D.J. *Tetrahedron Lett.* **1996**, *37*, 9147-9148; n) Gunawardana, G.P.; Kohmoto, S.; Burres, N.S.; *Tetradedron Lett.* **1989**, *30*, 4359-4362; o) Gunawardana, G.P.; Kohmotoa, S.; Gunasekera, S.P.; McConnell, O.J.; Koehn, F.E. *J. Am. Chem. Soc.* **1988**, *110*, 4856-4858; p) Inman, W.D.; O'Neill-Johnson, M.; Crews, P. *J. Am. Chem. Soc.* **1990**, *112*, 1-4; q) West, R.R.; Maybe, C.L.; Ireland, C.M.; Brinen, L.S.; Clardy, J. *Tetrahedron Lett.* **1990**, *31*, 3271-3274; r) Ford, P.W.; Davidson, B.S. *J. Nat. Prod.* **1997**, *60*, 1051-1053.

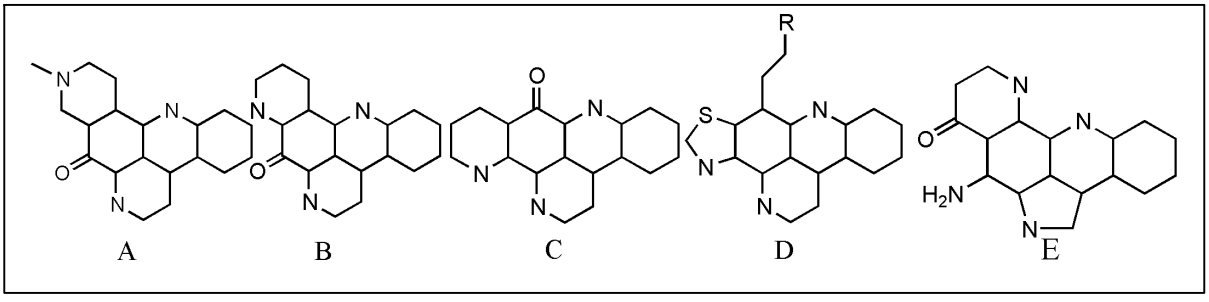


Table S3. Crystal data and structure refinement for aplkinidine (**7**).

| | | |
|---|---|---|
| Identification code | PC#700 | |
| Empirical formula | C19 H13 N3 O3 | |
| Formula weight | 331.32 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 7.4529(6) Å | α= 90°. |
| | b = 8.8995(7) Å | β= 91.739(2)°. |
| | c = 21.6764(18) Å | γ = 90°. |
| Volume | 1437.1(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.531 $Mg/m^3$ | |
| Absorption coefficient | 0.107 $mm^{-1}$ | |
| F(000) | 688 | |
| Crystal size | 0.80 x 0.10 x 0.05 $mm^3$ | |
| Theta range for data collection | 2.47 to 24.71°. | |
| Index ranges | -8<=h<=8, -10<=k<=10, -25<=l<=24 | |
| Reflections collected | 10377 | |
| Independent reflections | 2454 [R(int) = 0.0644] | |
| Completeness to theta = 24.71° | 99.9 % | |
| Absorption correction | SADABS | |
| Max. and min. transmission | 0.9947 and 0.554724 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2454 / 0 / 278 | |
| Goodness-of-fit on $F^2$ | 0.930 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0491, wR2 = 0.1215 | |
| R indices (all data) | R1 = 0.0710, wR2 = 0.1356 | |
| Largest diff. peak and hole | 0.233 and -0.332 $e.Å^{-3}$ | |

Table S4. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for alpkinidine (**7**). U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 4663(2) | 7107(2) | 696(1) | 29(1) |
| O(2) | 4935(2) | 8218(2) | 1766(1) | 31(1) |
| O(3) | 2299(2) | 7963(2) | -1646(1) | 34(1) |
| C(1) | 3806(3) | 8368(2) | 509(1) | 22(1) |
| C(2) | 3495(3) | 9591(2) | 947(1) | 22(1) |
| C(3) | 4087(3) | 9357(2) | 1579(1) | 24(1) |
| N(4) | 3683(2) | 10451(2) | 2000(1) | 26(1) |
| C(5) | 2840(3) | 11763(2) | 1831(1) | 28(1) |
| C(6) | 2327(3) | 12034(2) | 1240(1) | 26(1) |
| C(7) | 2637(3) | 10939(2) | 781(1) | 22(1) |
| C(8) | 2053(3) | 11155(2) | 141(1) | 22(1) |
| N(9) | 1252(2) | 12397(2) | -73(1) | 24(1) |
| C(10) | 753(3) | 12433(2) | -686(1) | 24(1) |
| C(11) | -125(3) | 13748(3) | -911(1) | 31(1) |
| C(12) | -673(3) | 13856(3) | -1513(1) | 35(1) |
| C(13) | -403(3) | 12666(3) | -1935(1) | 33(1) |
| C(14) | 444(3) | 11391(3) | -1741(1) | 28(1) |
| C(15) | 1043(3) | 11222(2) | -1116(1) | 24(1) |
| C(16) | 1893(3) | 9939(2) | -869(1) | 23(1) |
| C(17) | 2442(3) | 8455(2) | -1119(1) | 24(1) |
| N(18) | 3195(2) | 7681(2) | -617(1) | 24(1) |
| C(19) | 3184(3) | 8570(2) | -82(1) | 22(1) |
| C(20) | 2363(3) | 9932(2) | -252(1) | 21(1) |
| C(21) | 4173(4) | 10162(3) | 2650(1) | 38(1) |
| C(22) | 3858(4) | 6146(2) | -655(1) | 32(1) |

Table S5. Bond lengths [Å] and angles [°] for alpkinidine (**7**).

| | |
|---|---|
| O(1)-C(1) | 1.347(2) |
| O(2)-C(3) | 1.255(3) |
| O(3)-C(17) | 1.226(3) |
| C(1)-C(19) | 1.362(3) |
| C(1)-C(2) | 1.466(3) |
| C(2)-C(7) | 1.401(3) |
| C(2)-C(3) | 1.441(3) |
| C(3)-N(4) | 1.375(3) |
| N(4)-C(5) | 1.370(3) |
| N(4)-C(21) | 1.467(3) |
| C(5)-C(6) | 1.347(3) |
| C(6)-C(7) | 1.416(3) |
| C(7)-C(8) | 1.456(3) |
| C(8)-N(9) | 1.333(3) |
| C(8)-C(20) | 1.405(3) |
| N(9)-C(10) | 1.368(3) |
| C(10)-C(11) | 1.420(3) |
| C(10)-C(15) | 1.446(3) |
| C(11)-C(12) | 1.358(3) |
| C(12)-C(13) | 1.418(4) |
| C(13)-C(14) | 1.359(3) |
| C(14)-C(15) | 1.421(3) |
| C(15)-C(16) | 1.404(3) |
| C(16)-C(20) | 1.373(3) |
| C(16)-C(17) | 1.489(3) |
| C(17)-N(18) | 1.390(3) |
| N(18)-C(19) | 1.404(3) |
| N(18)-C(22) | 1.456(3) |
| C(19)-C(20) | 1.402(3) |
| | |
| O(1)-C(1)-C(19) | 122.53(19) |
| O(1)-C(1)-C(2) | 120.4(2) |
| C(19)-C(1)-C(2) | 117.05(18) |
| C(7)-C(2)-C(3) | 119.38(19) |

| | |
|---|---|
| C(7)-C(2)-C(1) | 123.4(2) |
| C(3)-C(2)-C(1) | 117.26(18) |
| O(2)-C(3)-N(4) | 118.4(2) |
| O(2)-C(3)-C(2) | 124.06(19) |
| N(4)-C(3)-C(2) | 117.56(18) |
| C(5)-N(4)-C(3) | 122.22(19) |
| C(5)-N(4)-C(21) | 120.35(19) |
| C(3)-N(4)-C(21) | 117.43(19) |
| C(6)-C(5)-N(4) | 121.4(2) |
| C(5)-C(6)-C(7) | 119.8(2) |
| C(2)-C(7)-C(6) | 119.5(2) |
| C(2)-C(7)-C(8) | 118.57(19) |
| C(6)-C(7)-C(8) | 121.92(19) |
| N(9)-C(8)-C(20) | 120.8(2) |
| N(9)-C(8)-C(7) | 124.01(19) |
| C(20)-C(8)-C(7) | 115.21(18) |
| C(8)-N(9)-C(10) | 117.55(18) |
| N(9)-C(10)-C(11) | 117.5(2) |
| N(9)-C(10)-C(15) | 124.56(19) |
| C(11)-C(10)-C(15) | 117.9(2) |
| C(12)-C(11)-C(10) | 120.7(2) |
| C(11)-C(12)-C(13) | 121.5(2) |
| C(14)-C(13)-C(12) | 119.8(3) |
| C(13)-C(14)-C(15) | 120.9(2) |
| C(16)-C(15)-C(14) | 125.1(2) |
| C(16)-C(15)-C(10) | 115.8(2) |
| C(14)-C(15)-C(10) | 119.2(2) |
| C(20)-C(16)-C(15) | 118.30(19) |
| C(20)-C(16)-C(17) | 106.57(18) |
| C(15)-C(16)-C(17) | 135.1(2) |
| O(3)-C(17)-N(18) | 125.00(19) |
| O(3)-C(17)-C(16) | 129.7(2) |
| N(18)-C(17)-C(16) | 105.31(18) |
| C(17)-N(18)-C(19) | 110.75(17) |
| C(17)-N(18)-C(22) | 123.43(19) |
| C(19)-N(18)-C(22) | 125.8(2) |

| | |
|---|---|
| C(1)-C(19)-N(18) | 133.84(19) |
| C(1)-C(19)-C(20) | 119.65(18) |
| N(18)-C(19)-C(20) | 106.49(19) |
| C(16)-C(20)-C(19) | 110.87(18) |
| C(16)-C(20)-C(8) | 123.05(19) |
| C(19)-C(20)-C(8) | 126.1(2) |

Symmetry transformations used to generate equivalent atoms

Table S6. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for alpkinidine (**7**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 36(1) | 24(1) | 27(1) | 2(1) | 1(1) | 6(1) |
| O(2) | 37(1) | 29(1) | 27(1) | 3(1) | 1(1) | 4(1) |
| O(3) | 41(1) | 36(1) | 26(1) | -8(1) | -2(1) | 3(1) |
| C(1) | 20(1) | 21(1) | 25(1) | 2(1) | 4(1) | 0(1) |
| C(2) | 19(1) | 23(1) | 24(1) | 2(1) | 6(1) | -5(1) |
| C(3) | 23(1) | 24(1) | 24(1) | 4(1) | 5(1) | -4(1) |
| N(4) | 33(1) | 25(1) | 20(1) | 0(1) | 3(1) | -4(1) |
| C(5) | 35(1) | 25(1) | 26(1) | -2(1) | 6(1) | -2(1) |
| C(6) | 28(1) | 24(1) | 26(1) | 1(1) | 6(1) | 2(1) |
| C(7) | 18(1) | 23(1) | 26(1) | 0(1) | 6(1) | -2(1) |
| C(8) | 17(1) | 23(1) | 26(1) | 2(1) | 6(1) | -1(1) |
| N(9) | 20(1) | 24(1) | 27(1) | 1(1) | 4(1) | -1(1) |
| C(10) | 20(1) | 27(1) | 24(1) | 2(1) | 3(1) | -3(1) |
| C(11) | 30(1) | 29(1) | 32(2) | -1(1) | 0(1) | 2(1) |
| C(12) | 37(1) | 33(1) | 34(2) | 7(1) | -2(1) | 7(1) |
| C(13) | 30(1) | 42(1) | 27(2) | 6(1) | -2(1) | -1(1) |
| C(14) | 26(1) | 31(1) | 25(1) | 1(1) | -1(1) | -3(1) |
| C(15) | 19(1) | 28(1) | 25(1) | 2(1) | 5(1) | -4(1) |
| C(16) | 19(1) | 26(1) | 24(1) | -1(1) | 4(1) | -5(1) |
| C(17) | 22(1) | 27(1) | 23(1) | -3(1) | 2(1) | -2(1) |
| N(18) | 27(1) | 20(1) | 24(1) | -3(1) | 4(1) | 1(1) |
| C(19) | 20(1) | 21(1) | 25(1) | -4(1) | 5(1) | -2(1) |
| C(20) | 17(1) | 23(1) | 24(1) | -1(1) | 4(1) | -4(1) |
| C(21) | 61(2) | 29(1) | 25(2) | -1(1) | -3(1) | -2(1) |
| C(22) | 42(2) | 22(1) | 31(2) | -4(1) | 4(1) | 4(1) |

Table S7. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for alpkinidine (**7**).

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1O) | 4970(40) | 7300(40) | 1113(17) | 73(11) |
| H(5) | 2650(30) | 12490(30) | 2179(12) | 37(7) |
| H(6) | 1710(30) | 12910(30) | 1123(11) | 30(6) |
| H(11) | -330(30) | 14550(30) | -620(10) | 27(6) |
| H(12) | -1260(30) | 14750(30) | -1665(12) | 41(7) |
| H(13) | -850(30) | 12770(30) | -2365(13) | 35(7) |
| H(14) | 670(30) | 10560(20) | -2034(11) | 28(6) |
| H(21C) | 3770(30) | 9200(30) | 2743(12) | 49(8) |
| H(21B) | 3570(40) | 10950(30) | 2901(13) | 54(8) |
| H(21A) | 5490(50) | 10220(30) | 2713(14) | 66(9) |
| H(22C) | 5150(40) | 6070(30) | -515(13) | 57(8) |
| H(22B) | 3210(40) | 5510(30) | -368(13) | 54(8) |
| H(22A) | 3670(40) | 5820(30) | -1097(16) | 67(9) |

Figure S1. $^{1}$H NMR Spectrum of 5-methoxy neoamphimidine (**4**), DMSO, 500 MHz.

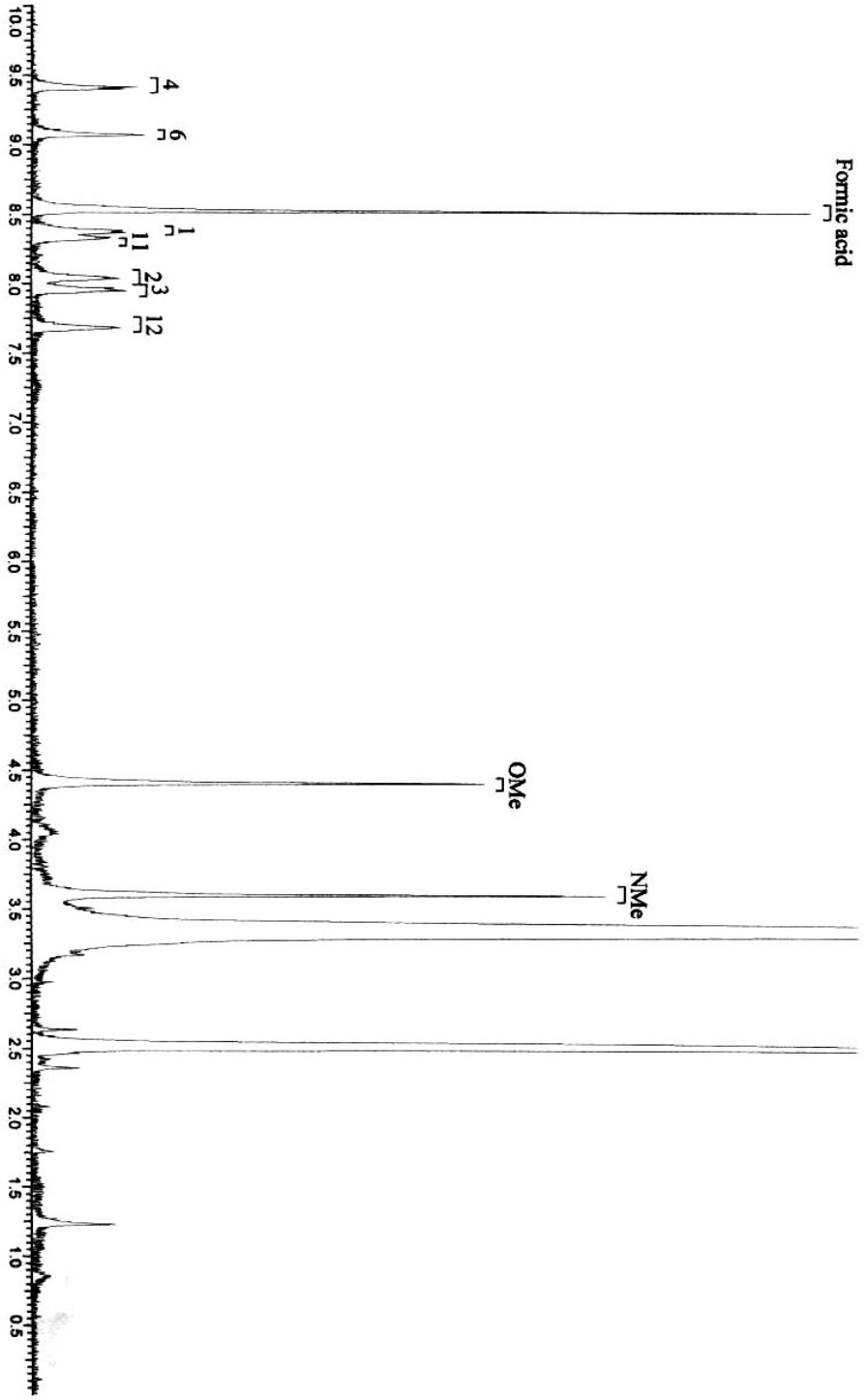


Figure S2. $^{13}C$ NMR spectrum of 5-methoxy neoamphimidine (**4**), DMSO, 125 MHz.

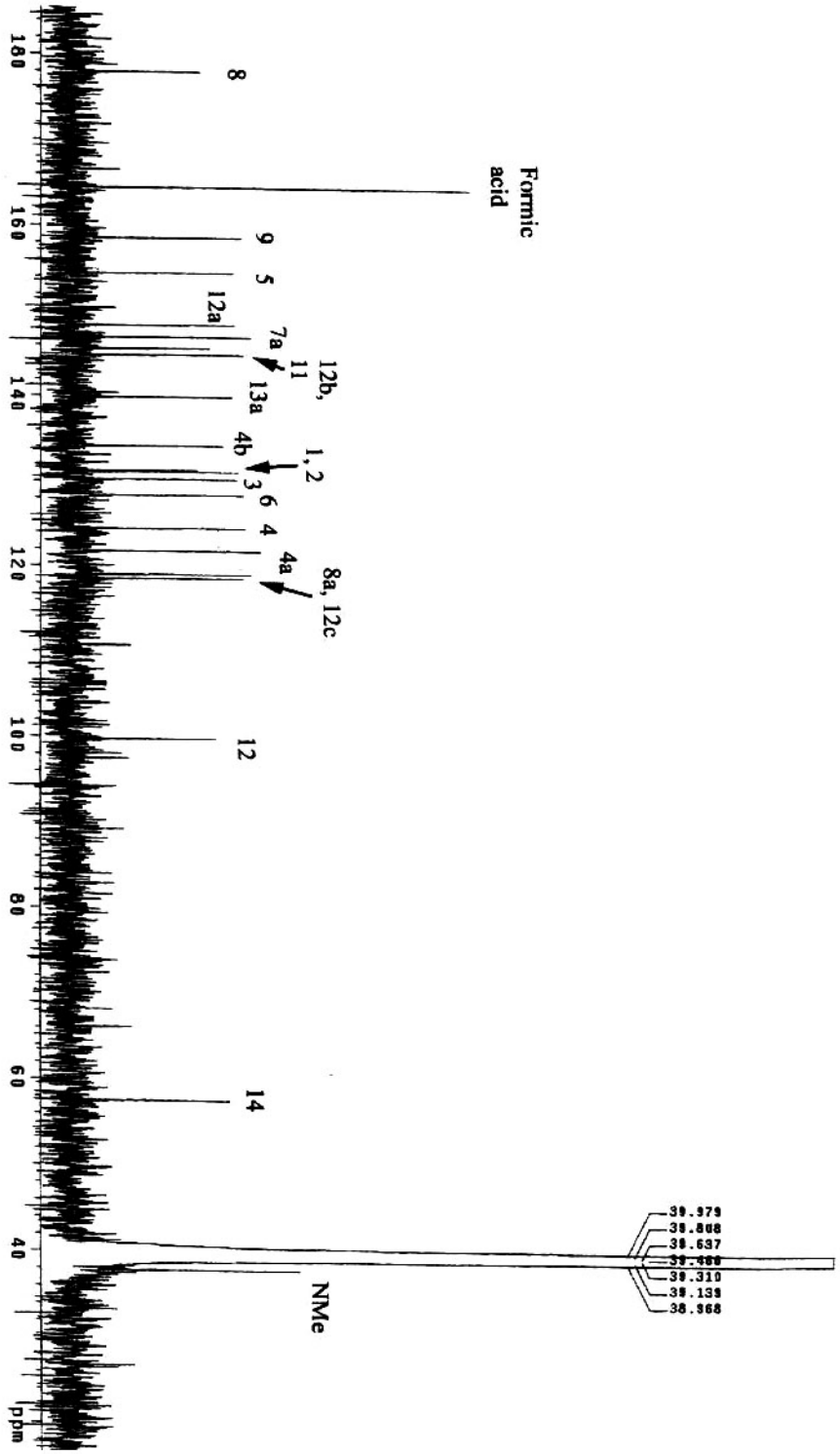


Figure S3. $^{1}$H NMR Spectrum of neoamphimidine Y (**5**), $CDCl_3$:MeOH-$d_4$ 2:1, 500 MHz.

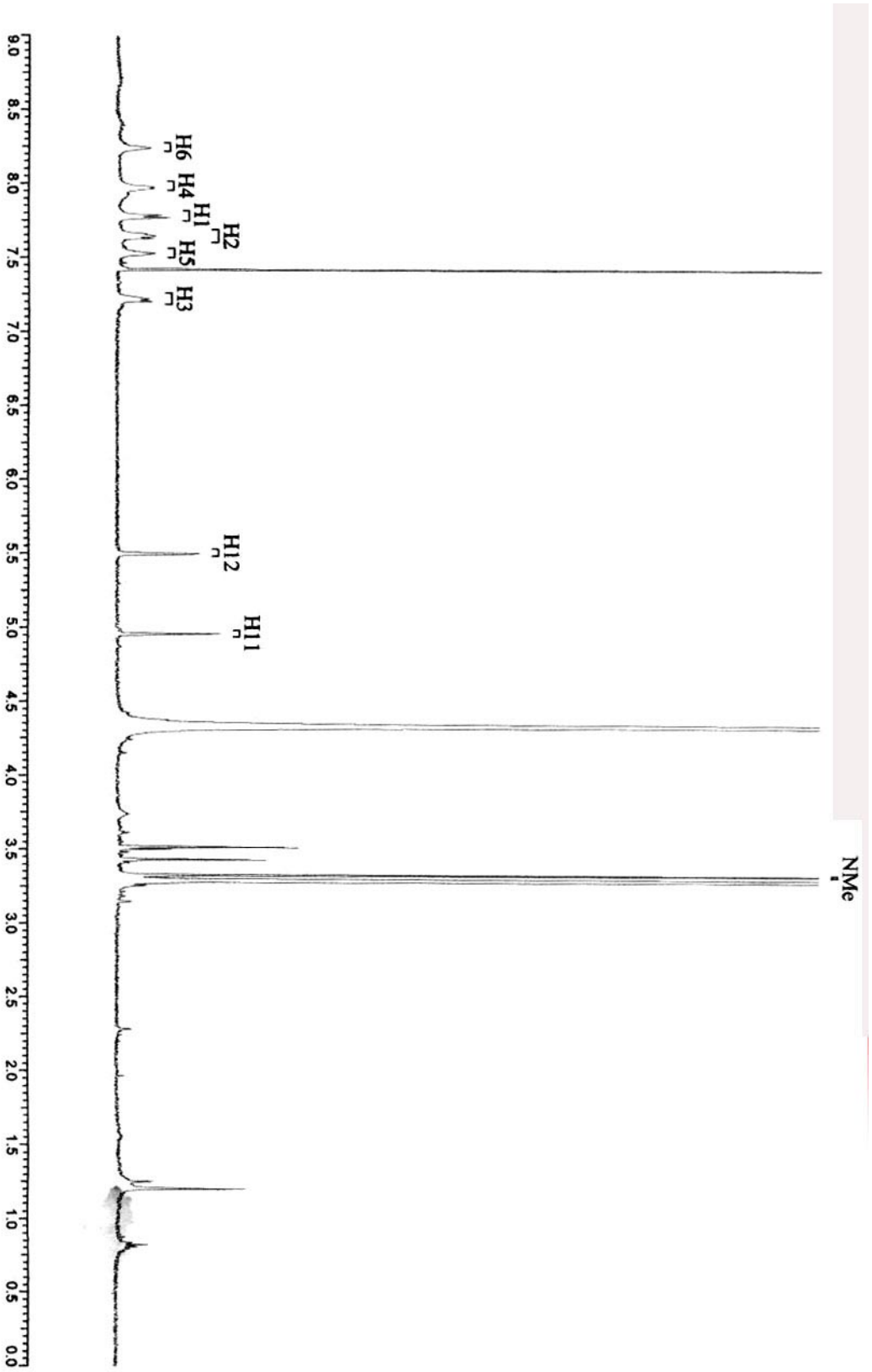


Figure S4. $^{13}C$ NMR spectrum of neoamphimidine Y (**5**), $CDCl_3$:MeOH-$d_4$ 2:1, 125 MHz.

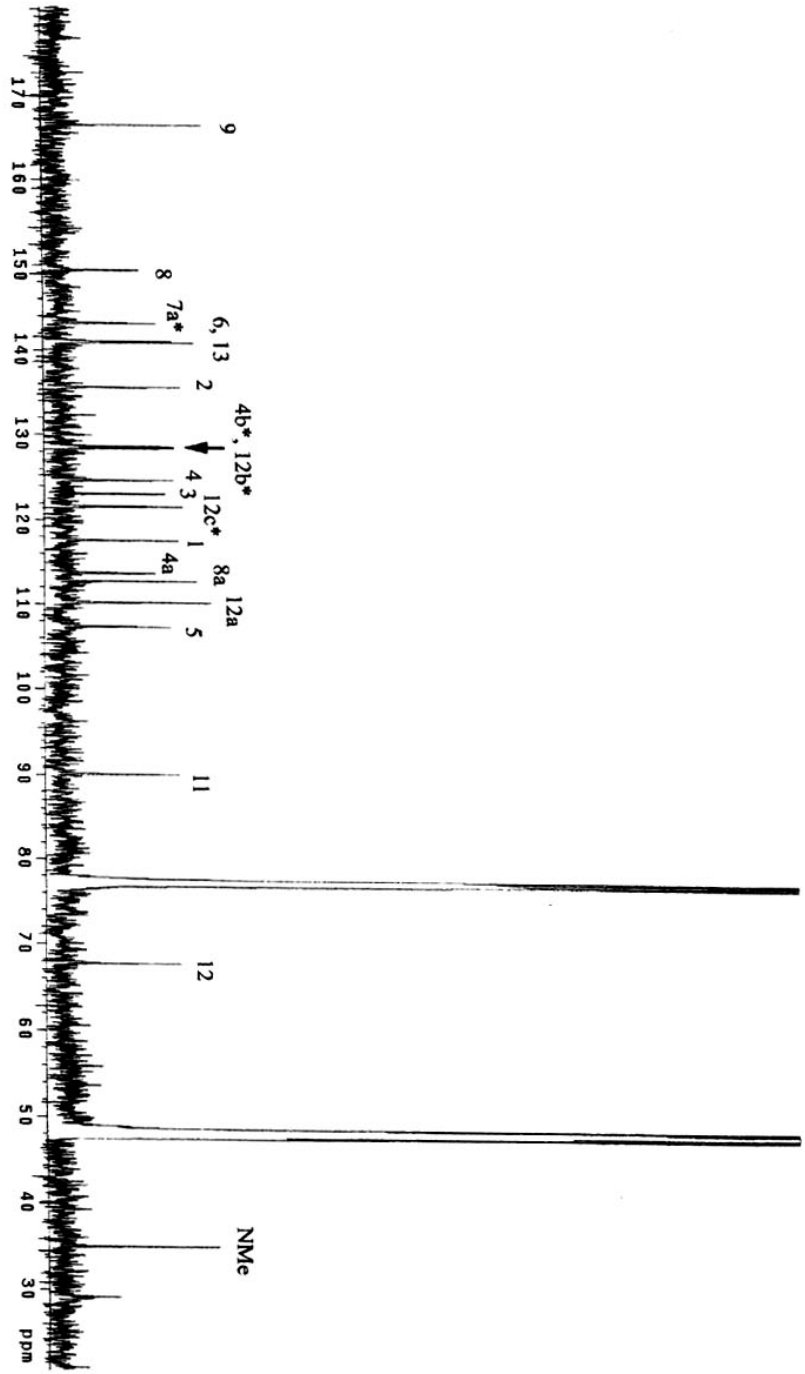


Figure S5. $^{1}$H NMR Spectrum of neoamphimidine Z (**6**), DMSO, 500 MHz.

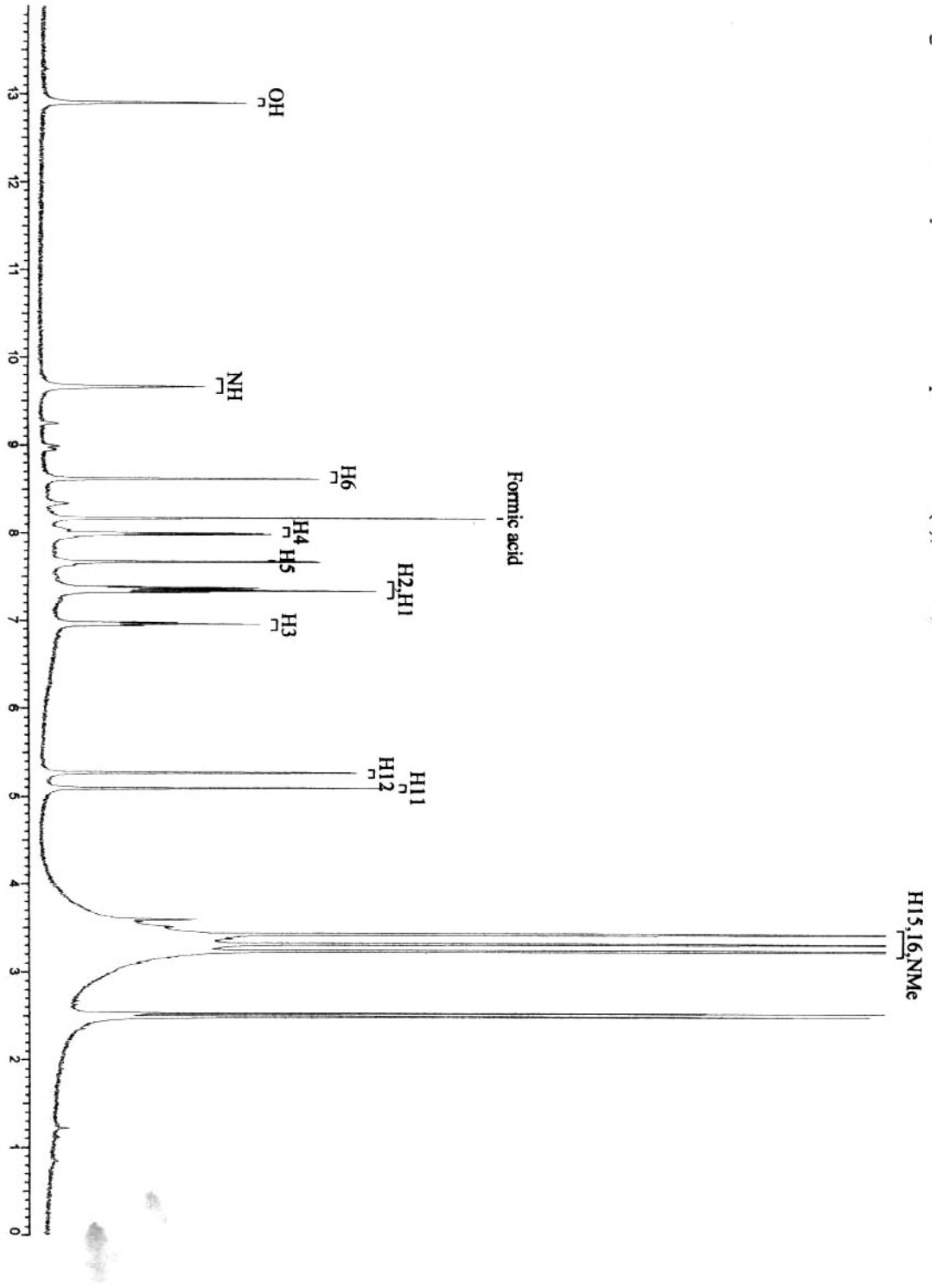


Figure S6. $^{13}C$ NMR Spectrum of neoamphimidine Z (**6**), DMSO, 125 MHz.

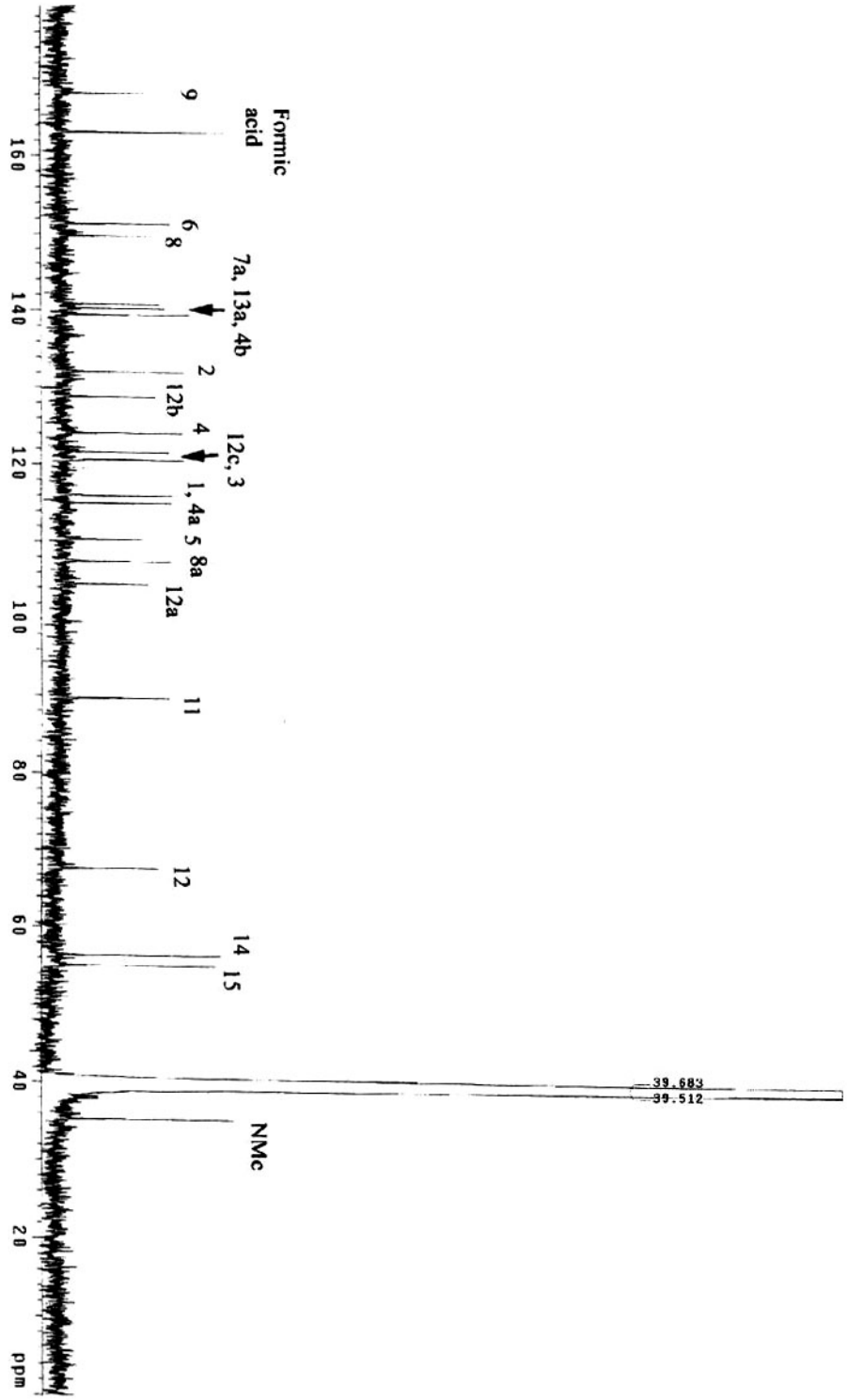


Figure S7. $^{1}$H-$^{1}$H gCOSY NMR spectrum of neoamphimidine Z (**6**), DMSO, 500 MHz.

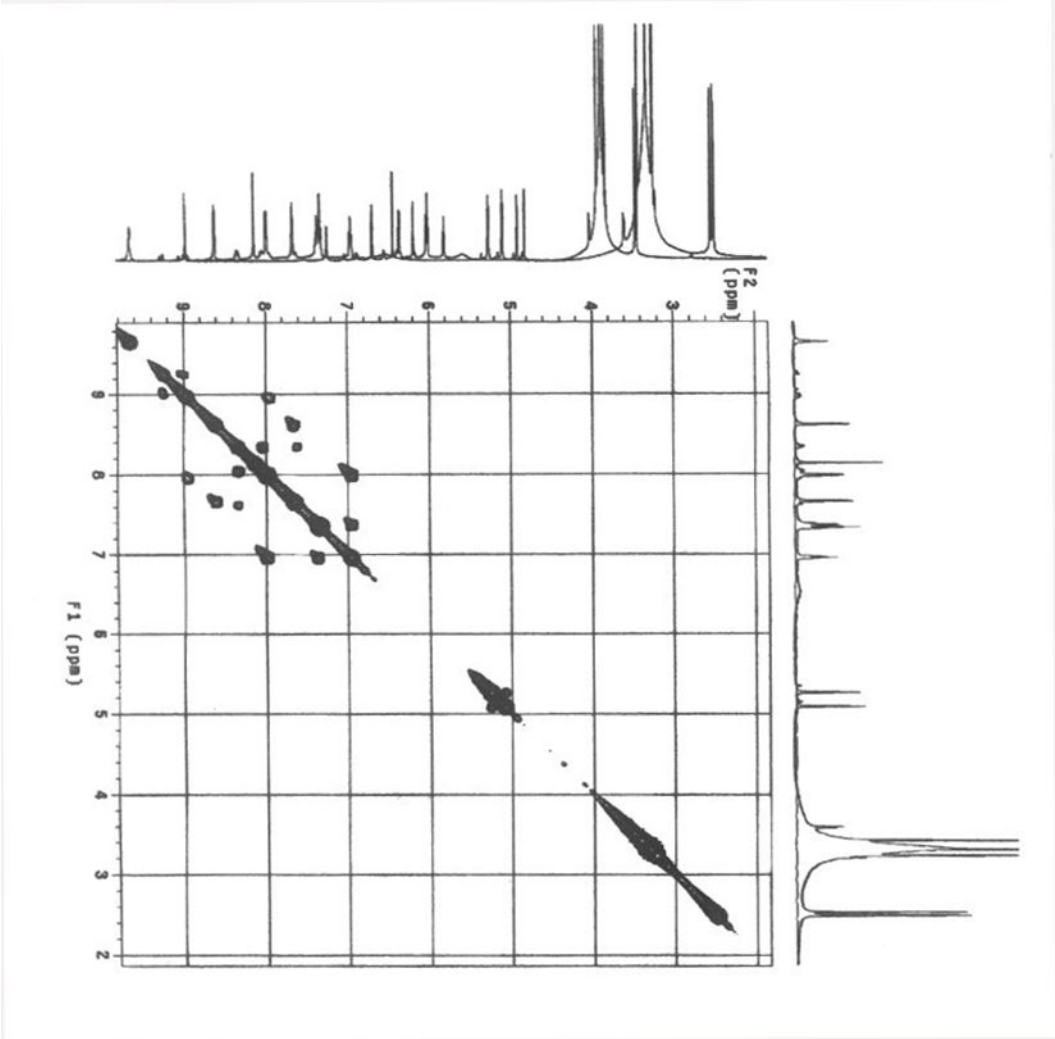


Figure S8. gHMQC NMR spectrum of neoamphimidine Z (**6**), DMSO, 500 MHz.

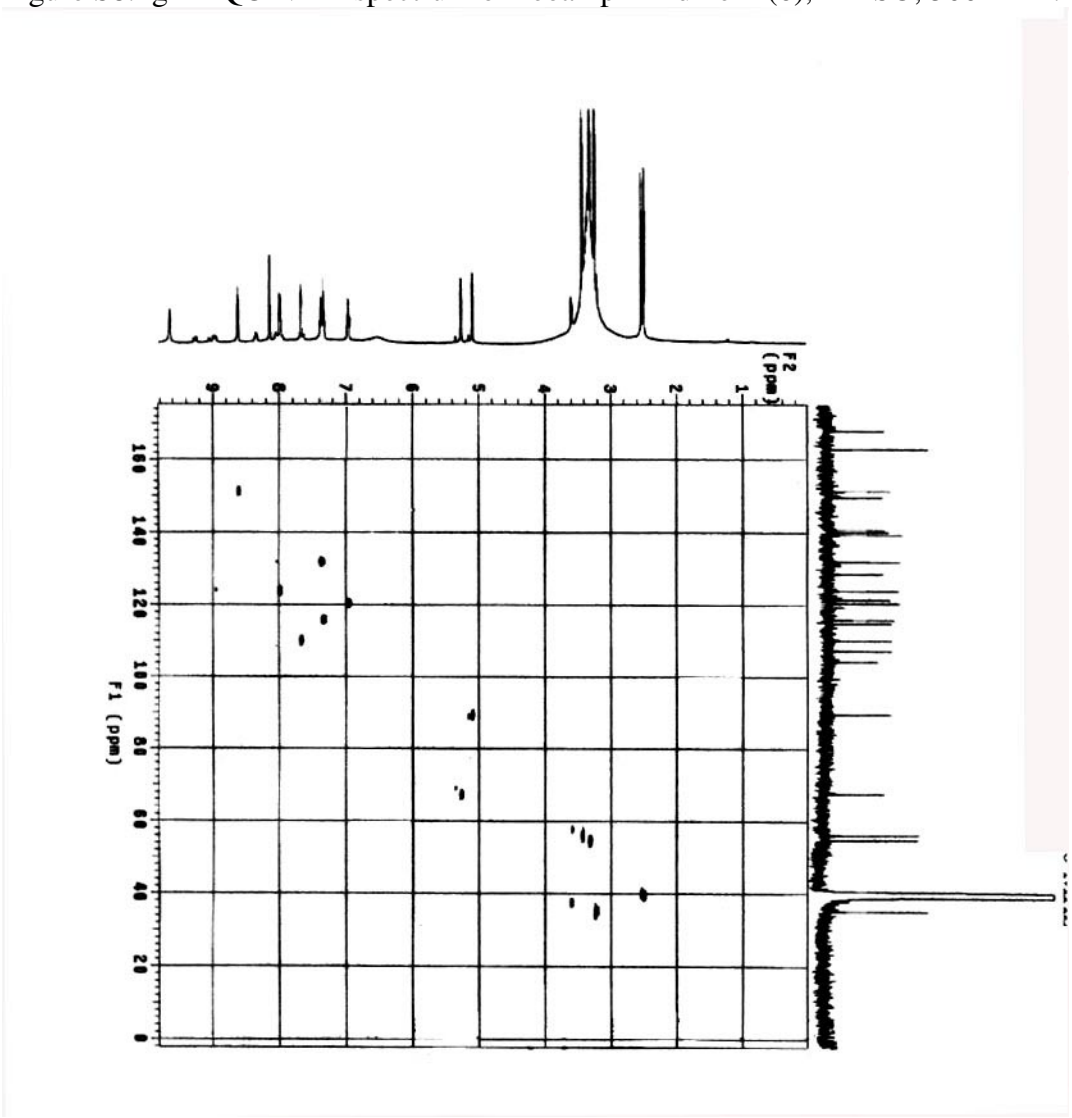


Figure S9. gHMBC NMR Spectrum of neoamphimidine Z (**6**), DMSO, 500 MHz.

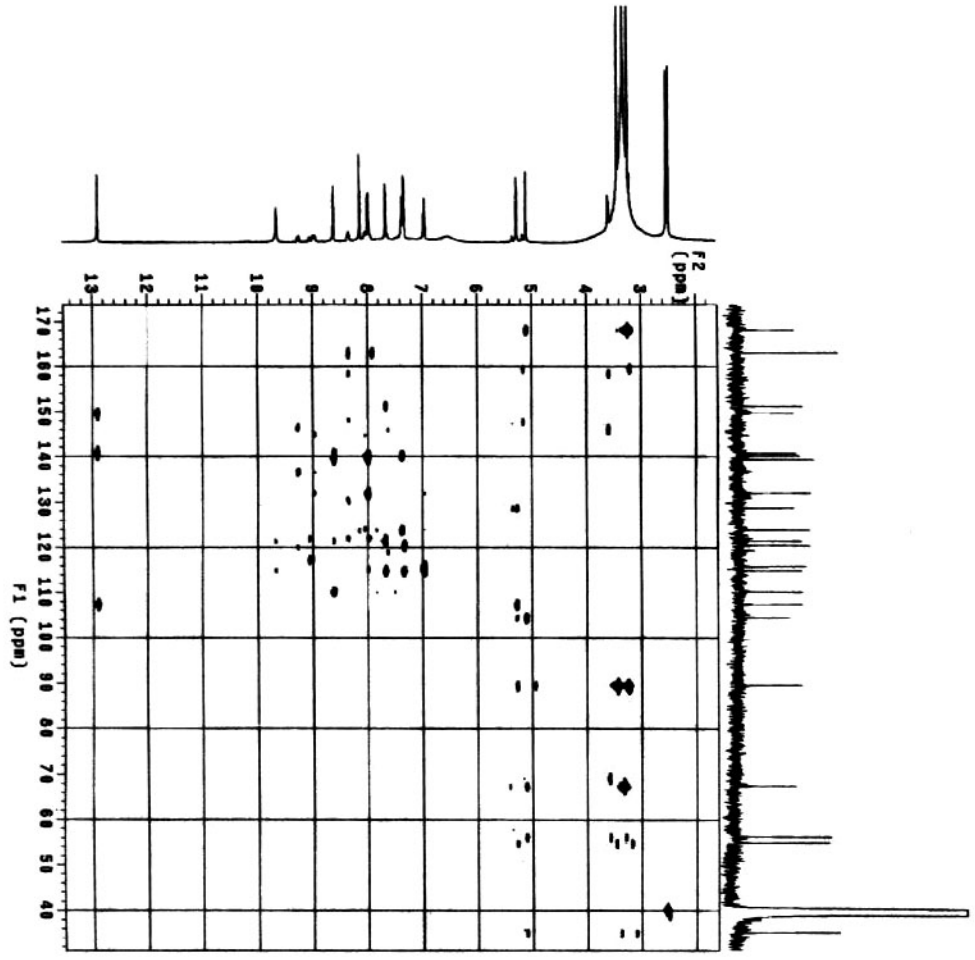


Figure S10. Long range gHMBC NMR Spectrum of neoamphimidine Z (**6**), DMSO, 500 MHz.

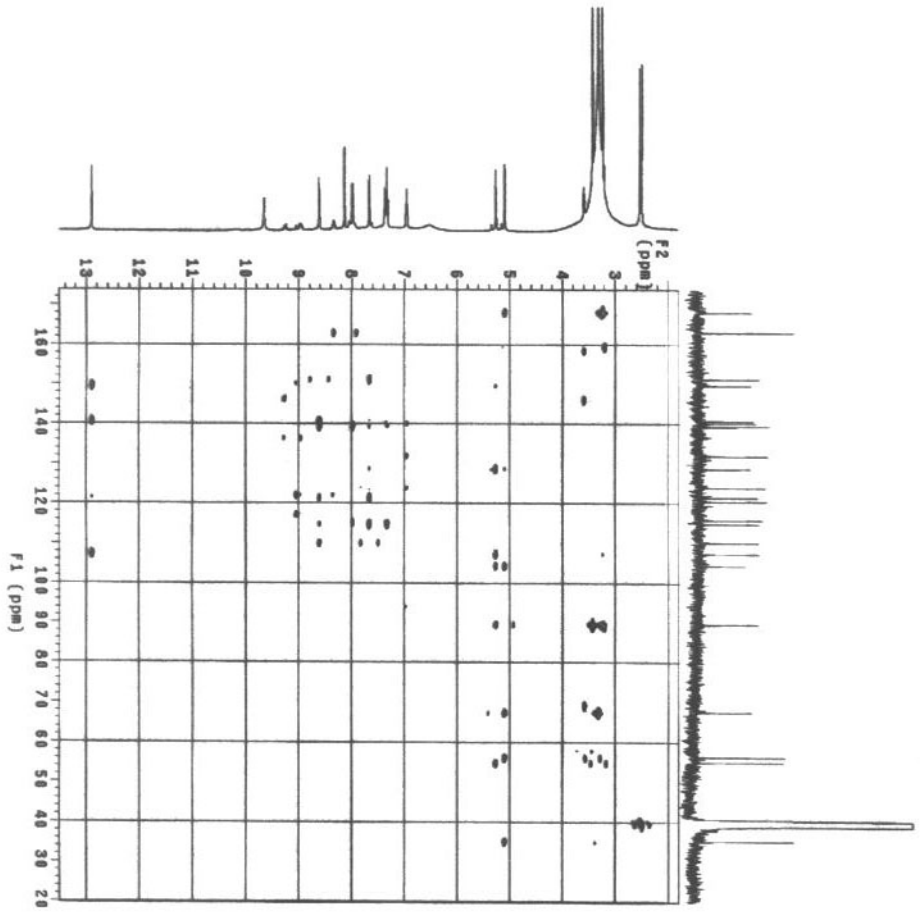


Figure S11. $^{1}$H NMR Spectrum of alpkinidine (**7**), $CDCl_3$, 500 MHz.

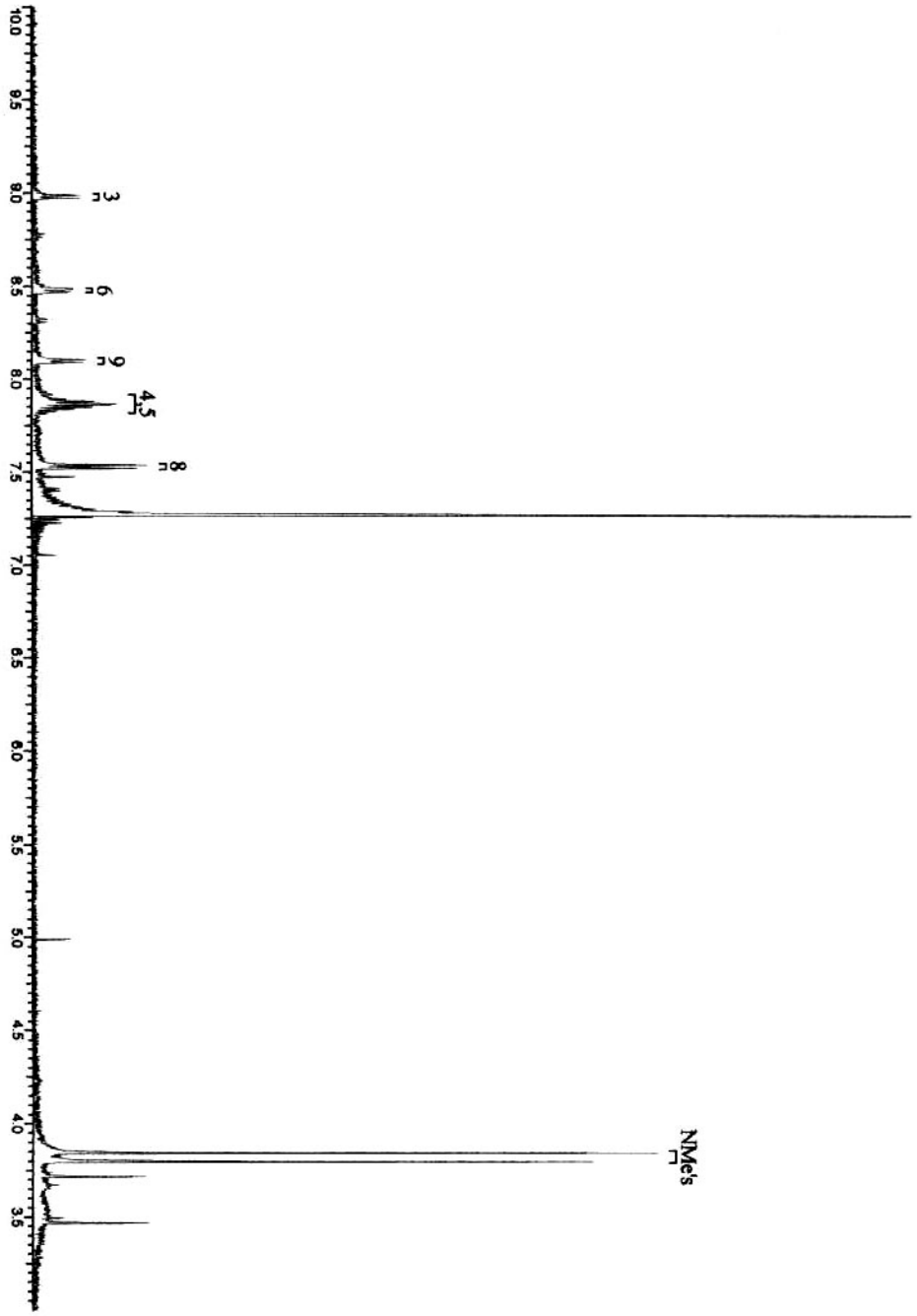


Figure S12. $^{1}H$-$^{1}H$ COSY NMR spectrum of alpkinidine (**7**), $CDCl_3$, 500 MHz.

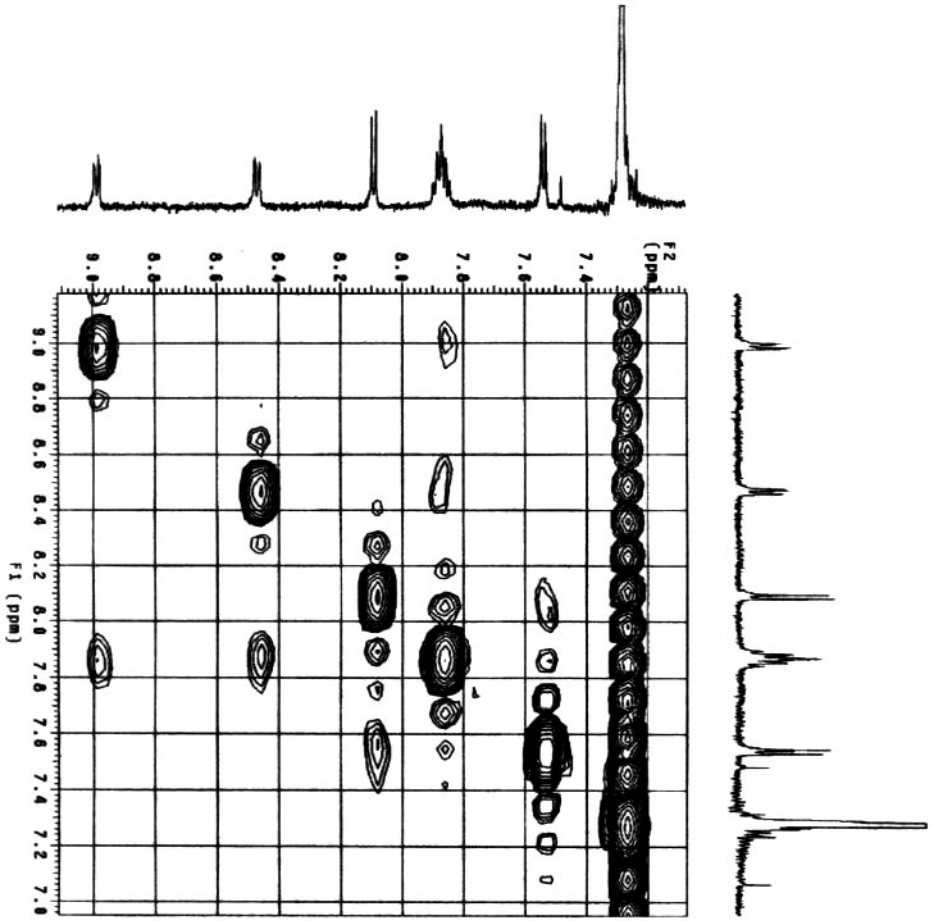
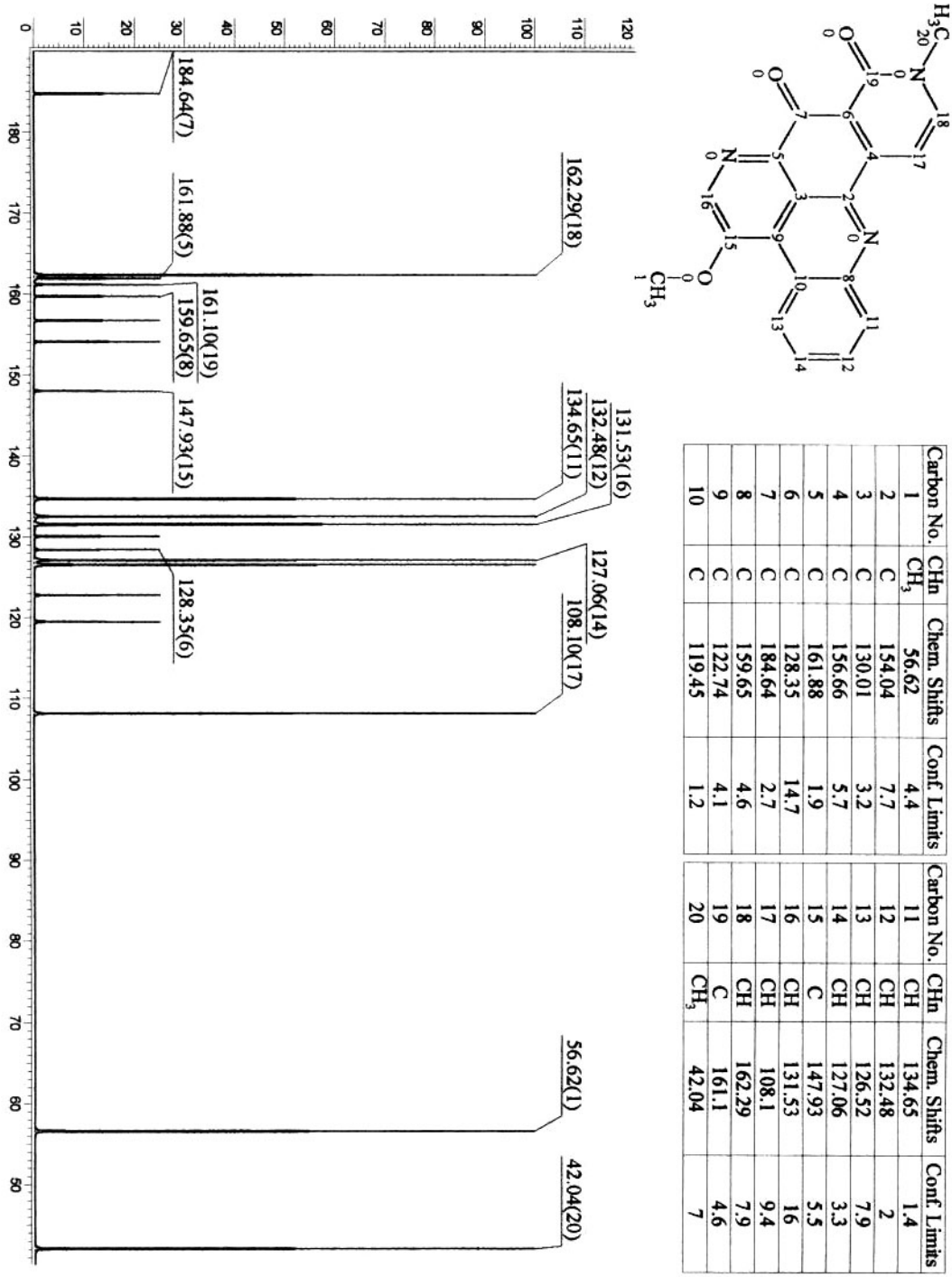


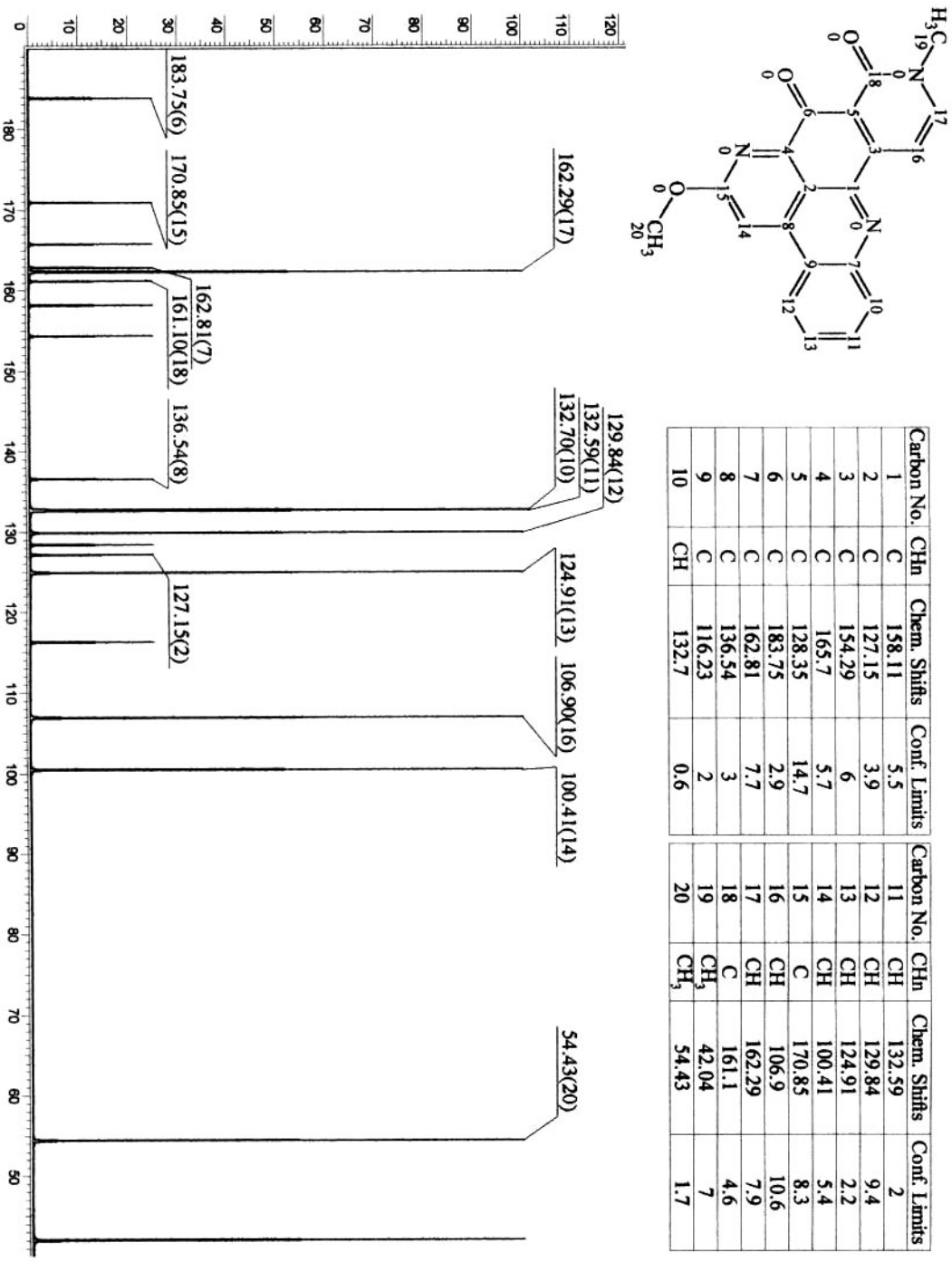
Figure S13. ACD calculated spectrum of 5-methoxy neoamphimedine.




| Carbon No. | CHn | Chem. Shifts | Conf. Limits |
|---|---|---|---|
| 1 | $CH_3$ | 56.62 | 4.4 |
| 2 | C | 154.04 | 7.7 |
| 3 | C | 130.01 | 3.2 |
| 4 | C | 156.66 | 5.7 |
| 5 | C | 161.88 | 1.9 |
| 6 | C | 128.35 | 14.7 |
| 7 | C | 184.64 | 2.7 |
| 8 | C | 159.65 | 4.6 |
| 9 | C | 122.74 | 4.1 |
| 10 | C | 119.45 | 1.2 |

| Carbon No. | CHn | Chem. Shifts | Conf. Limits |
|---|---|---|---|
| 11 | CH | 134.65 | 1.4 |
| 12 | CH | 132.48 | 2 |
| 13 | CH | 126.52 | 7.9 |
| 14 | CH | 127.06 | 3.3 |
| 15 | C | 147.93 | 5.5 |
| 16 | CH | 131.53 | 16 |
| 17 | CH | 108.1 | 9.4 |
| 18 | CH | 162.29 | 7.9 |
| 19 | C | 161.1 | 4.6 |
| 20 | $CH_3$ | 42.04 | 7 |

Figure S14. ACD calculated spectrum of 6-methoxy neoamphimedine.




| Carbon No. | CHn | Chem. Shifts | Conf. Limits |
|---|---|---|---|
| 1 | C | 158.11 | 5.5 |
| 2 | C | 127.15 | 3.9 |
| 3 | C | 154.29 | 6 |
| 4 | C | 165.7 | 5.7 |
| 5 | C | 128.35 | 14.7 |
| 6 | C | 183.75 | 2.9 |
| 7 | C | 162.81 | 7.7 |
| 8 | C | 136.54 | 3 |
| 9 | C | 116.23 | 2 |
| 10 | CH | 132.7 | 0.6 |

| Carbon No. | CHn | Chem. Shifts | Conf. Limits |
|---|---|---|---|
| 11 | CH | 132.59 | 2 |
| 12 | CH | 129.84 | 9.4 |
| 13 | CH | 124.91 | 2.2 |
| 14 | CH | 100.41 | 5.4 |
| 15 | C | 170.85 | 8.3 |
| 16 | CH | 106.9 | 10.6 |
| 17 | CH | 162.29 | 7.9 |
| 18 | C | 161.1 | 4.6 |
| 19 | $CH_3$ | 42.04 | 7 |
| 20 | $CH_3$ | 54.43 | 1.7 |

**Chart S1.** Soft agar disk diffusion assay guided isolation of pyridoacridines from the sponge *Xestospongia* cf. *exigua* (91608). Zone unit differentials to assess murine tumor selectivity as shown in Table 1.

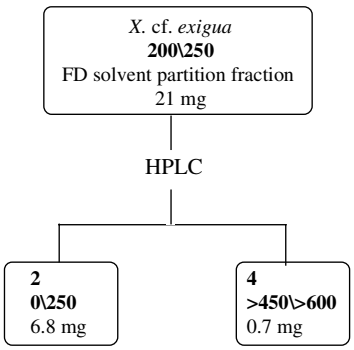


**Chart S2.** Soft agar disk diffusion assay guided isolation of pyrido- and pyrroloacridines from the sponge *Xestospongia* cf. *carbonaria* (94634). Zone unit differentials to assess murine tumor selectivity as shown in Table 1 and Table S1.

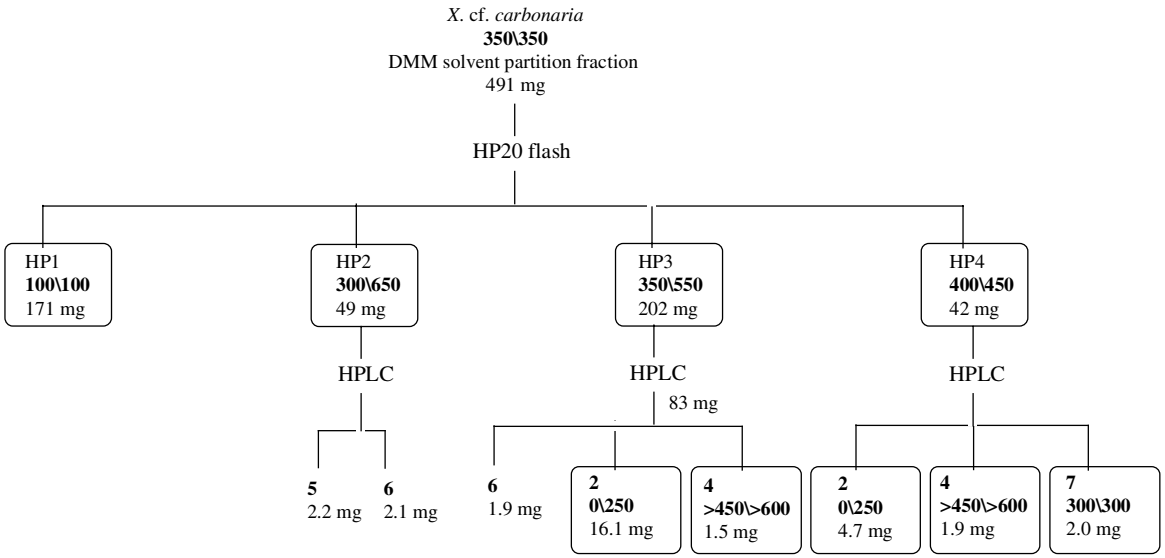
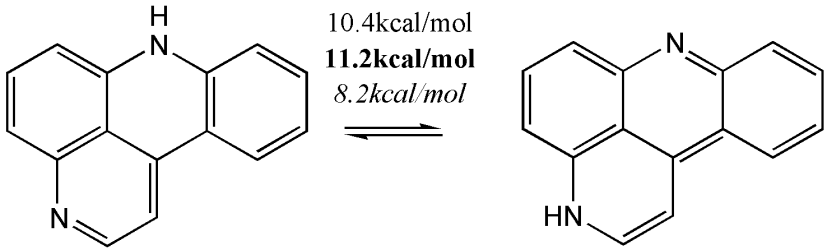
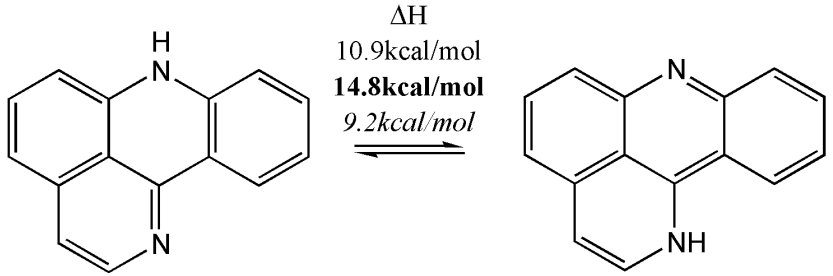


Chart S3. Comparison between the tautomeric equilibria of pyrido[2,3,4-kl]acridine and pyrido[4,3,2-kl]acridine.



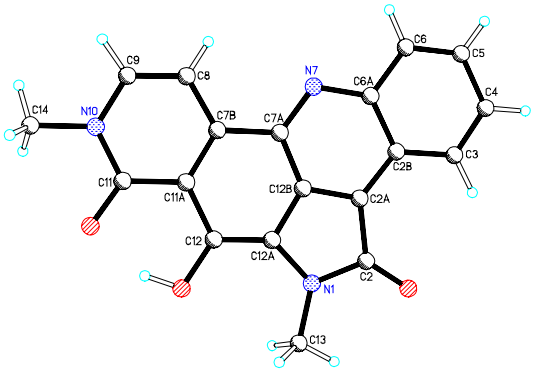

| | | |
|---|---|---|
| AM-1 | 0.1343008 | 0.1509876 |
| zpe | 137.98 | 137.95 |
| **3-21G*** | **-678.9664957** | **-678. 9484201** |
| **zpe** | **145.05** | **144.87** |
| *B3LYP/6-31+G(d)/3-21G** | *-687.174531117* | *-687.161427014* |



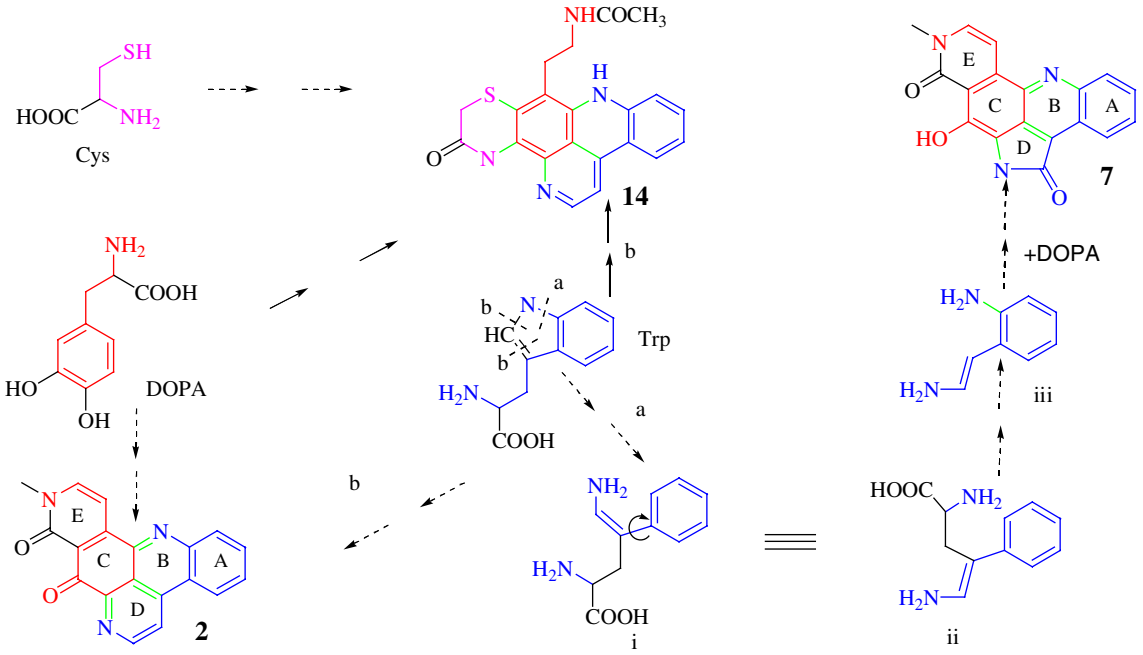

| | | |
|---|---|---|
| AM-1 | 0.1327138 | 0.150018 |
| zpe | 137.95 | 137.95 |
| **3-21G*** | **-678.9745997** | **-678.9505068** |
| **zpe** | **145.13** | **144.83** |
| *B3LYP/6-31+G(d)/3-21G** | *-687.1775689* | *-687.1628868* |

In each case the more stable tautomer demonstrates a more converged geometry, the bond lengths vary more greatly in the less stable tautomer. The symmetry about the A, B, and C rings of the 8H tautomers conveys the stabilization of the NH group to the π-system.

**Scheme S1.** Computer-generated perspective drawing (all hydrogens shown) of alpkinidine (**7**) based on the X-ray results.



**Scheme S2.** Extending the original biosynthetic pathway, proposed by Steffan, for shermilamine B (**14**)[25] to rationalize the formation of neoamphimedine (**2**), and alpkinidine (**7**). There are common starter units: Trp (blue), DOPA (red), or Cys (purple); new bonds in green; and atoms lost or acquired in black.




An *o*-quinone of dopamine is also putatively formed prior to condensation and finally incorporation of cysteine leads to the thiazinone ring. Building on these ideas we propose neoamphimedine (**2**) may be formed by a process wherein its A, B, D rings arise from tryptophan (cleavage points "b") while the C and E rings may be shaped from the ring and side chain of dopamine *o*-quinone. Although, the creation of a pyrrolo-ring in alpkinidine (**7**) seems less straightforward it could be rationalized as arising by a different cleavage of the tryptophan ring (break point "a") leading to structure **i**. Rotation of the side chain could line up the precursor (see structure **ii**) to generate the aromatic amine **iii** which could allow closure to generate the A, B, D rings. Analogous to the steps proposed above, a dopamine *o*-quinone could supply the structural elements to form the C and E rings.