

Supporting Information

Cationic Corrole Derivatives : A New Family of G-quadruplex Inducing and Stabilising Ligands

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Synthesis of corrole 3 and 5.

Synthesis of compound 1 (5, 10, 15-tris[4-pyridyl]-corrole): pyrrole (4.2 mL, 40.5 mmol) and aldehyde (2.21 g, 20.2 mmol) were dissolved in 200 mL of acetic acid. The solution was heated and stirred under 110 °C. The reaction course was monitored by UV/Vis spectroscopy. After 4 h, the reaction mixture was cooled down and the solvent with excess pyrrole were evaporated under reduced pressure. The crude product was crushed down and further isolated by the chromatography on neutral alumina (200-300 mesh). After elution with ethyl acetate/CH₃OH = 10/ 1) collected desired compound, isolated compound **1** was obtained after evaporation of solvents. Further purification was finished by crystallization from CH₂Cl₂/Hexane and obtained pure solid compound **1** (94 mg, yield, 2.6%). UV/vis(CH₂Cl₂): $\lambda_{\max}$ [nm](log ϵ) = 417 (4.55), 576 (3.81), 616 (3.59), 651 (3.43); ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.10 (d, 2 H, J = 4.5 Hz, 2 H), 8.26 (d, J = 4.5 Hz, 4 H), 8.60 (d, J = 3.6 Hz, 2 H), 8.64 (d, J = 3.6 Hz, 2 H), 8.93 (m, 4 H), 8.99 (s, 4 H), 9.04 (s, 2 H); ¹³C NMR (CDCl₃) δ (ppm) 98.5, 108.8, 113.2, 117.3, 117.3, 122.9, 126.5, 127.2, 130.0, 131.8, 135.0, 140.0, 140.5, 147.2, 148.8, 149.4, 150.1; MS FAB (positive) m/z : calculated for: C₃₄H₂₃N₈⁺, 530; found: 530.

Synthesis of compound 3 (5, 10, 15-tris[*N*-methyl-4-pyridium]-corrole): compound **1** (30 mg, 0.057 mmol) was dissolved in 25 mL of DMF. CH₃I (5 mL) was added into the solution and the reaction mixture was stirred at room temperature in dark for a whole night. The solvent and excess CH₃I were evaporated under reduced pressure. The crude product was further crystallized by Et₂O/DMF and purified compound **2** was obtained (45 mg, yield: 87%). UV/vis(CH₃OH): $\lambda_{\max}$ [nm] (log ϵ) = 527 (8.06), 702 (7.72) ¹H NMR (300MHz, [D₆]DMSO): δ (ppm) 8.67 (d, 2 H, J = 4.2 Hz), 8.78 (s, 4 H), 8.91 (d, 4 H, J = 5.7 Hz), 8.97 (d, 2 H, J = 4.2 Hz), 9.25 (d, 6 H, J = 4.5 Hz), 9.30 (d, 2H, J = 6.6 Hz); ¹³C NMR ([D₆]DMSO): δ (ppm) 108.1, 109.5, 119.8, 124.2, 126.1, 126.8, 132.6, 133.1, 134.7, 136.1, 139.3, 140.7, 144.2, 144.6, 155.9, 159.5; HRMS(ESI), m/z : calculated for: (M³⁺-3I)/3 = 191.4239; (M²⁺-3I-H)/2 = 286.6315; found: 191.4234 (M³⁺-3I)/3, 286.6317 (M²⁺-3I-H)/2; elemental analysis calcd (%) for C₃₇H₃₂N₇I₃; C 46.51, H 3.38, N 10.26; found: C 46.19, H 2.92, N 10.09; **melting point: >300°C; green solid.**

Synthesis of compound 4 (5, 10, 15-tris[4-aminophenyl]-corrole):²

Compound **2**¹ (420 mg, 0.635 mmol) and SnCl₂·2H₂O (1.29 g, 5.72 mmol) were mixed to form a homogeneous powder and this mixture was dissolved in 37% aq. HCl (50 mL). The reaction was protected by the N₂ without light. After the mixture was stirred for 2 h at 75°C, the solution was cooled by adding ice. The crude product was neutralized to pH = 7 by NH₃·H₂O. The reaction mixture was diluted with a very large excess of water (400 mL) and extracted with ethyl acetate (3 × 300 mL). The organic layers were combined and the solvents were removed under the reduced pressure. The crude product was purified by chromatography over silica gel (eluent: CH₂Cl₂/ethyl acetate = 1: 1 vol) and purified compound was obtained in 140 mg after crystallization from acetone/petroleum ether. The yield was 38%. UV/vis (acetone): λ_{max}[nm] (logε) = 429 (5.60), 526 (4.80), 565 (4.83), 637 (4.80), 661 (4.82); ¹H NMR (300 MHz, [d₆]-acetone) δ (ppm) -2.59 (s, 3 H), 5.13 (s, 4 H), 5.24 (s, 2 H), 6.55-6.74 (m, 6 H), 7.12 (d, 4 H, *J* = 8.4 Hz), 7.34 (m, 2 H), 7.93 (d, *J* = 8.1 Hz, 4 H), 8.95 (s, 4 H); ¹³C NMR ([d₆]-acetone) δ (ppm) 113.05, 113.71, 114.39, 114.66, 117.28, 118.21, 119.53, 120.89, 124.94, 127.38, 128.27, 130.58, 131.29, 133.06, 135.23, 135.76, 148.57, 150.93; HRMS(MALDI-TOF), *m/z*: calculated for C₃₇H₂₉N₇, 571.2484; found: 571.2479.

Synthesis of 5 (5, 10, 15-tris[*N*-trimethyl-4-aminiumphenyl]-corrole):

Compound **4** (43 mg, 0.075 mmol) was dissolved in 40 mL of acetone and 10 mL of CH₃I was added to the solution. The mixture was stirring under 40°C oil bath for seven days. The course of the reaction was monitored by ESI-MS. The rest of CH₃I and solvent was removed under reduced pressure. The desired product was crystallized with Et₂O/acetone in 53 mg (yield 65%). Uv/vis:(acetone) (logε) = 416 nm (4.88), 579 (4.09), 617 (3.98); ¹H NMR (300 MHz, d₆-acetone) δ (ppm) 4.24 (s, 27 H), 8.56-8.61 (brs, 14 H), 8.97 (s, 4 H), 9.22 (s, 2 H); ¹³C NMR([d₆]-acetone) δ (ppm) 58.39, 119.30, 120.19, 121.37, 136.68, 137.12, 144.71, 147.56, 148.16; HRMS(ESI), *m/z*: calculated for: (M³⁺-3I)/3 = 233.4703; found: 233.4693; elemental analysis calcd (%) for C₄₆H₅₀N₇I₃: C 51.08, H 4.66, N 9.06; found: C 50.79, H 4.50, N 8.87; melting point: >300°C; black-green solid.

Reference:

1. R. Paolesse, S. Nardis, F. Sagone, R. G. Khoury, *J. Org. Chem.* 2001, **66**, 550.
2. J. P. Collman, Decreau, R. A. *Org Lett.* 2005, **6**, 975.

General material

Four 5'-biotin-labeled oligomers were used in surface plasmon resonance studies: [G4]: 5'-biotin-AG₃(TTAG₃)₃-3'; [AT]: 5'-biotin-CGAATTCGTCTCCGAATTCG-3'; [GC]: 5'-biotin-CGCGCGC GT TTTTCGCGCGC-3'; DNA duplex: 5' biotin- TTTCT GCGGC CGATT GTGAA CA-3' Its complementary strand: (5'-TGTTT ACAAT CGGCC GCAG-3'). The template

sequence HT4 (5'-TCCAA CTATG TATAC TTAGGG TTAGGG TTAGGG TTAGGG ACATA TCGAT GAAAT TGCTA TAGTG AGTCG TATTA-3') and 5'Tamra labeled P18 (5'-TAATA CGACT CACTATAG-3') were used for DNA polymerase stop assay. The products in DNA polymerase stop assay were separated on a 20% denaturing polyacrylamide gel for electrophoresis, and the gel was autoradiographed on a Typhoon Phosphor Imager (Amersham Biosciences, AB, Uppsala, Sweden).

CD melting curves were measured by monitoring the absorbance at 295 nm on a Jasco-810 spectropolarimeter (Jasco, Easton, MD) using a quartz cell of 1-mm optical path length with a digital circulating water bath, while the temperature was ramped from 25 to 90°C at about 1.5°C/min.

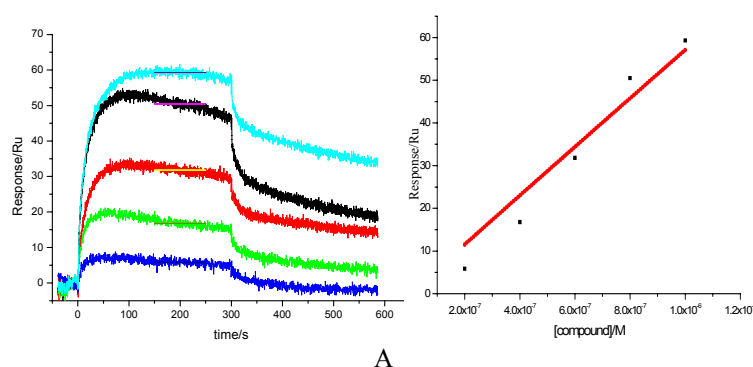
CD spectra were recorded on a Jasco-810 spectropolarimeter (Jasco, Easton, MD) using a quartz cell of 1-mm optical path length and an instrument scanning speed of 100 nm/min with a response time of 1 s, and over a wavelength range of 220-350 nm. All CD spectra were baseline-corrected for signal contributions due to the buffer.

Table S1. Equilibrium Binding constants determined by SPR using general fit and the kinetic constants determined from BIAcore analysis of 1:1 Langmuir global fitting

	DNA	$K_A(1/M)^{[a]}$	$k_a(1/MS)^{[b]}$	$k_d(1/S)^{[b]}$	$K_A(1/M)^{[c]}$
Corrole 2	[G4]	2.19×10^6	6.02×10^3	3.08×10^{-4}	1.95×10^7
	[GC]	5.0×10^5	2.25×10^3	2.03×10^{-3}	1.11×10^6
	[AT]	1.16×10^4	66.7	5.18×10^{-5}	1.29×10^6
	dsDNA	2.25×10^5	302	1.57×10^{-3}	1.93×10^5
Corrole 5	[G4]	2.36×10^6	0.41×10^3	3.86×10^{-5}	1.07×10^7
	[GC]	2.12×10^4	2.15×10^3	4.61×10^{-3}	4.66×10^5
	[AT]	1.48×10^4	26.8	5.07×10^{-5}	5.3×10^5
	dsDNA	5.21×10^4	563	3.08×10^{-3}	1.83×10^5

[a] Equilibrium Binding constants determined by SPR using general fit of 300s association in 100s steady-state region.

[b] Kinetic constants determined from BIAcore analysis of 1: 1 Langmuir global fitting of 40s association and 40s disassociation. [c] Determined by k_a/k_d .



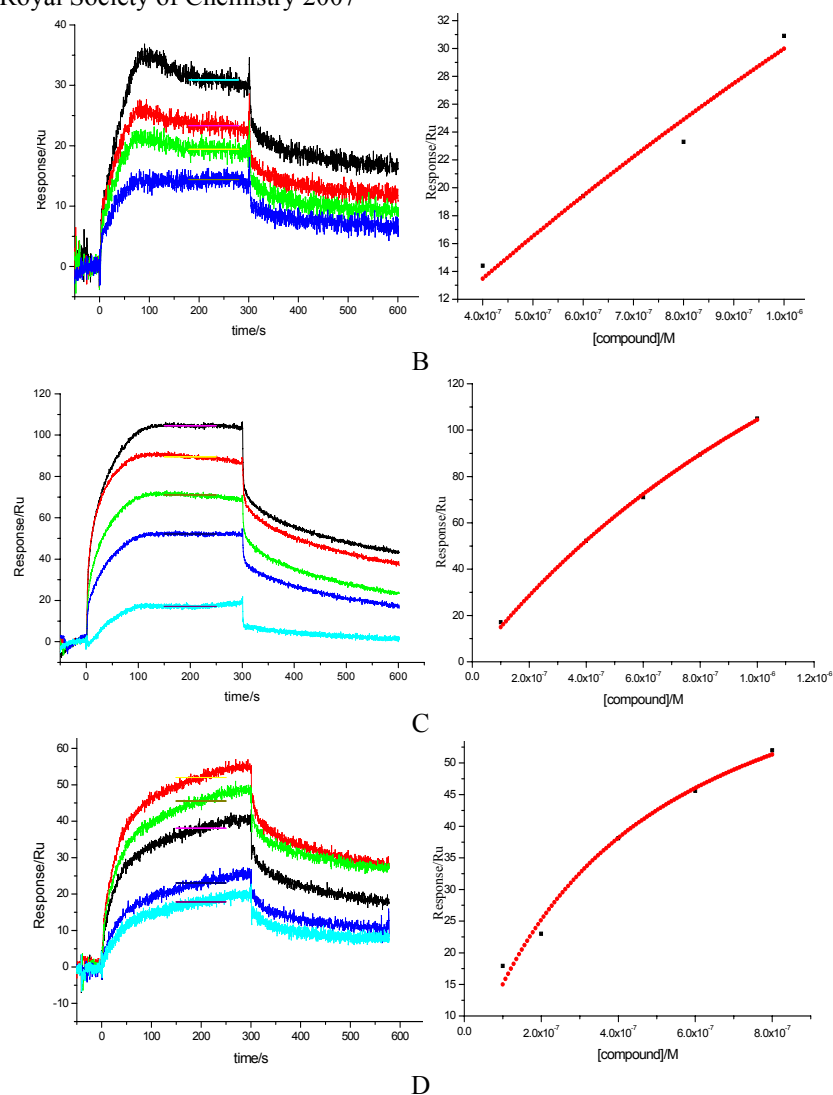


Figure S1. SPR sensorgram overlay for binding of ligands to different sequences DNA at 25°C used for general fit of 100s steady-state region and the corresponding fitting curves.

(A) [AT] sequence. The unbound corrole 3 concentrations in the flow solution were 200, 400, 600, 800, 1000 nM from the lowest curve to the top curve.

(B) DNA duplex sequence. The unbound corrole 3 concentrations in the flow solution were 400, 600, 800, 1000 nM from the lowest curve to the top curve.

(C) [GC] sequence. The unbound corrole 3 concentrations in the flow solution were 200, 400, 600, 800, 1000 nM from the lowest curve to the top curve.

(D) [G4] sequence. The unbound corrole 5 concentrations in the flow solution were 100, 200, 400, 600, 800 nM from the lowest curve to the top curve.

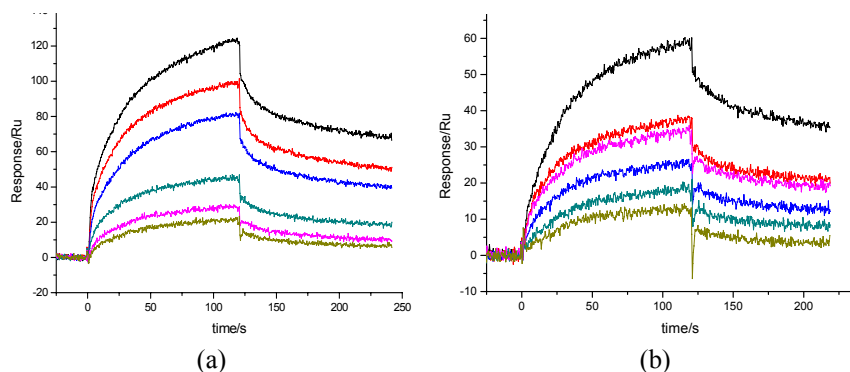


Figure S2. SPR sensorgram overlay for binding of ligands to [G4] sequence DNA at 25°C used for 1:1 Langmuir global fitting.

(a) [G4] sequence. The unbound corrole **3** concentrations in the flow solution were 50, 100, 200, 400, 600, 800 nM from the lowest curve to the top curve

(b) [G4] sequence. The unbound corrole **5** concentrations in the flow solution were 100, 200, 400, 600, 800 1000 nM from the lowest curve to the top curve

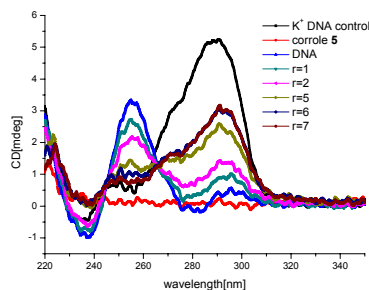


Figure S3. CD titration of d[T₂AG₃]₄ in 10mM Tris-HCl buffer at pH 7.4 for corrole **5**.

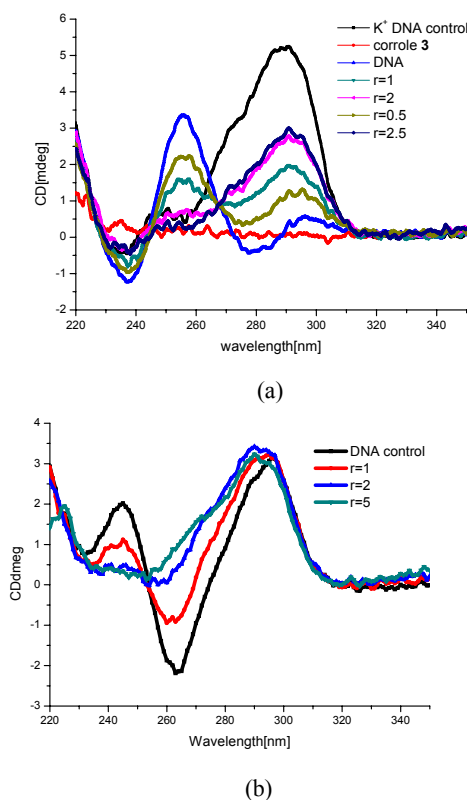


Fig. S4. (a) CD titration of d[T₂AG₃]₄ (12.5 μM) in 10mM Tris-HCl buffer at pH 7.4. (b) CD titration of d[T₂AG₃]₄ in 10 mM Tris-HCl at pH 7.4, 100 mM NaCl, 1mM EDTA buffer. (r = corrole **3**/DNA strand concentration) CD spectra were recorded on a Jasco-810 spectropolarimeter (Jasco, Easton, MD), scanning speed of 100 nm/min with a response time of 1 s, and over a wavelength range of 220-350 nm at room temperature.

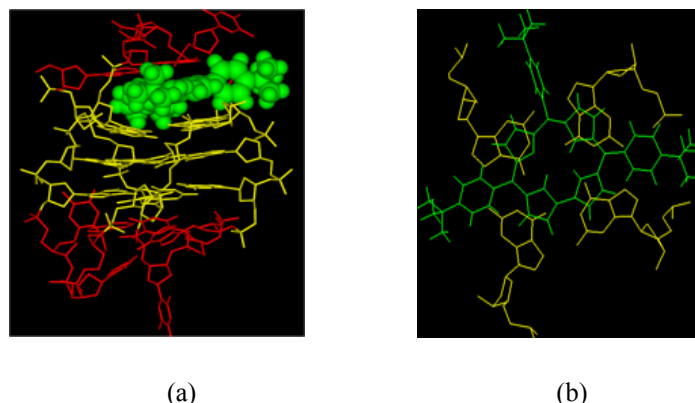


Fig. S5. (a) Minimized model of a complex between corrole **5** and the human d(AG₃[T₂AG₃]₃) quadruplex. The G is colored in yellow, the lateral loop and diagonal loop are in red, and the ligand in green. The hydrogens of G-quadruplex are omitted for clarity. (b) The top view of complex a. Only the terminal G-quartet is shown

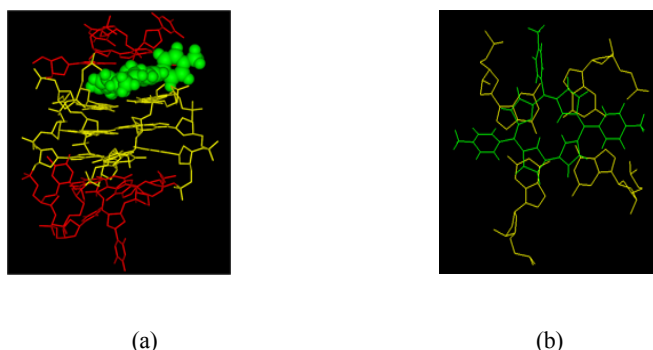
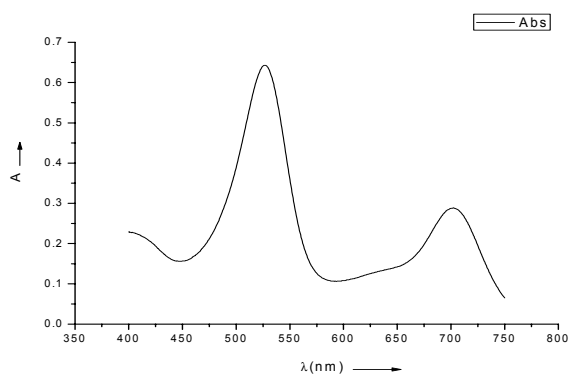


Fig. S6. (a) Minimized model of a complex between corrole **3** and the human d(AG₃[T₂AG₃]₃) quadruplex. The G is colored in yellow, the lateral loop and diagonal loop are in red, and the ligand in green. The hydrogens of G-quadruplex are omitted for clarity. (b) The top view of complex. Only the terminal G-quartet is shown.

Molecular Modeling: Models were built by the SYBYL¹ package. The coordinates of the folded intramolecular G-quadruplex human telomeric repeat d(AG₃[T₂AG₃]₃) were obtained from the Brookhaven Protein Data Bank (PDB entry: 143D). The models of ligands were built manually and optimized by Gaussian03² using DFT method at 6-31G level. Hydrogen-bonding constraints were added to the G-tetrads. Ligand was inserted above the G-tetrad, and the complex was allowed to minimize using Gasteiger-Hückel charges, the Tripos force field (First 1000 steps steepest descent then 1000 steps conjugate gradient to a terminal gradient of 0.05 kcal/mol).

Reference:

1. Sybyl, version 7.0; Tripos Inc.: St. Louis, MO
2. Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, Jr., T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K. G.; Voth, A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.;



UV of 5, 10, 15-tri(*N*-methyl-4pyridyl)-corrole **3** (CH₃OH)

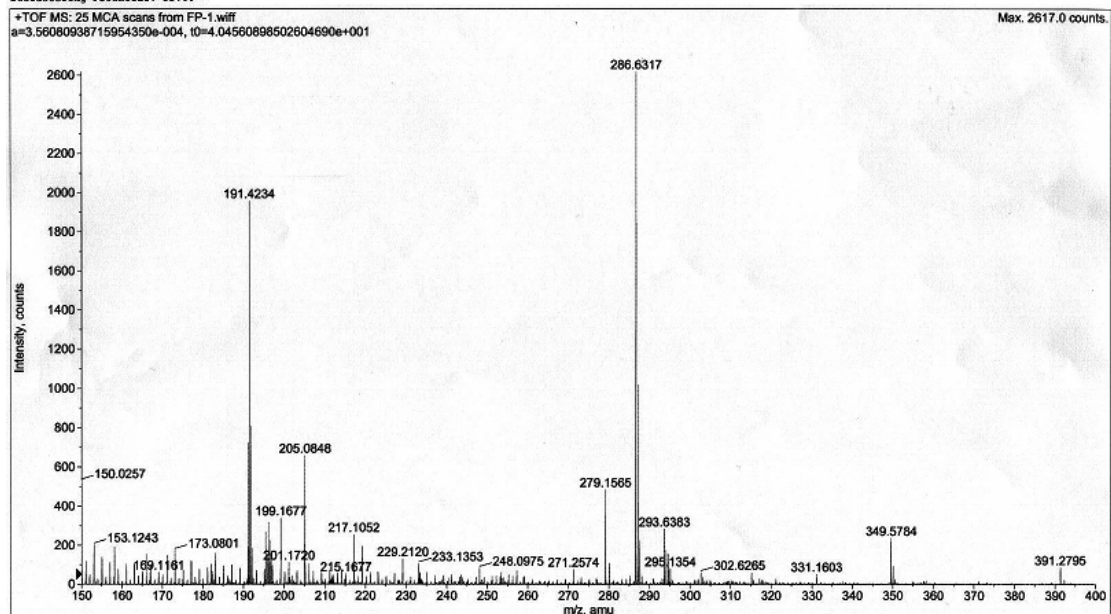
HRMS (ESI) of corrole **3**

Supplementary Material (ESI) for Chemical Communications
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Printing Date: Monday, October 03, 2005
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^1H NMR of corrole 2

File: 11-17-2

