Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supplementary Information

An unexpected acid-catalyzed decomposition reaction of cilnidipine and pranidipine to the decarboxylative bridged tricyclic products via cascade rearrangements

Minghua Yang, Shusheng Zhang, Xiang Zhang, Haoyang Wang, Fang Zhang, Yuting Hou, Yue Su and Yin-Long Guo**

1. Analysis of Degradation Products

1.1 LC-MS/MS Conditions

The DAD and MS detectors were both switched on to acquire the data. Chromatographic separations were achieved on an Agilent Poroshell 120EC-C18 column (100mm×2.1mm, 2.7μm (Agilent, USA)). The DAD detector was set at 254nm. A gradient elution was carried out with a mobile phase of acetonitrile and water. The best chromatographic assays were performed at 35°C under the following conditions:

Time (min)	Flow (ml/min)	H_2O (%)	Acetonitrile (%)
0	0.2	70	30
4	0.2	30	70
10	0.2	30	70
10.1	0.2	70	30
20	0.2	70	30

1.2 Preparative HPLC Conditions

The isolation of pranidipine's and cilnidipine's decarboxylation products after acid degradation was achieved using a Kromasil 100-5 C18 column (250mm×50mm, 5μm) (Akzo Nobel, Sweden). The UV detector was set at 254nm. The composition of the mobile phase was 38% acetonitrile. The temperature of the column was set at 20°C.

2. LC-MS/MS Spectra

2.1 LC-MS/MS Spectra of Pranidipine

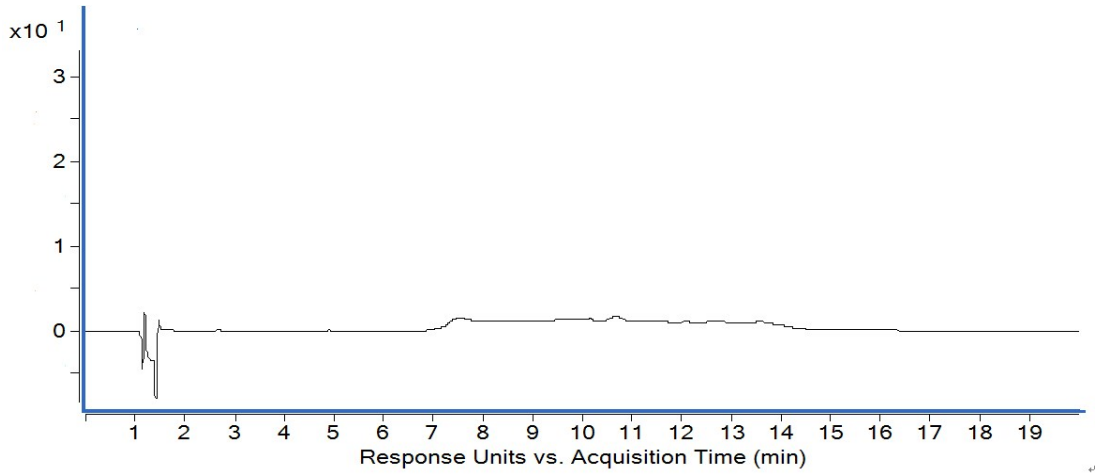


Figure S1: HPLC chromatogram of a blank sample

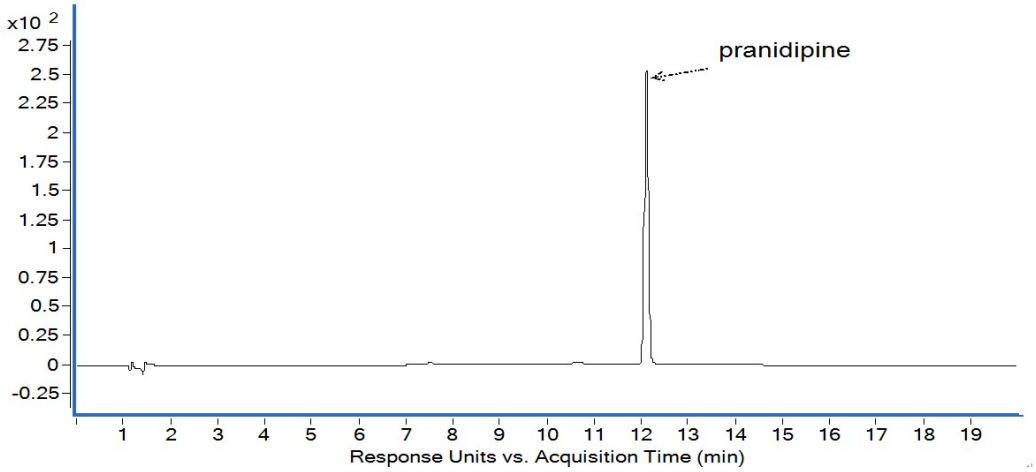


Figure S2: HPLC chromatogram of pranidipine

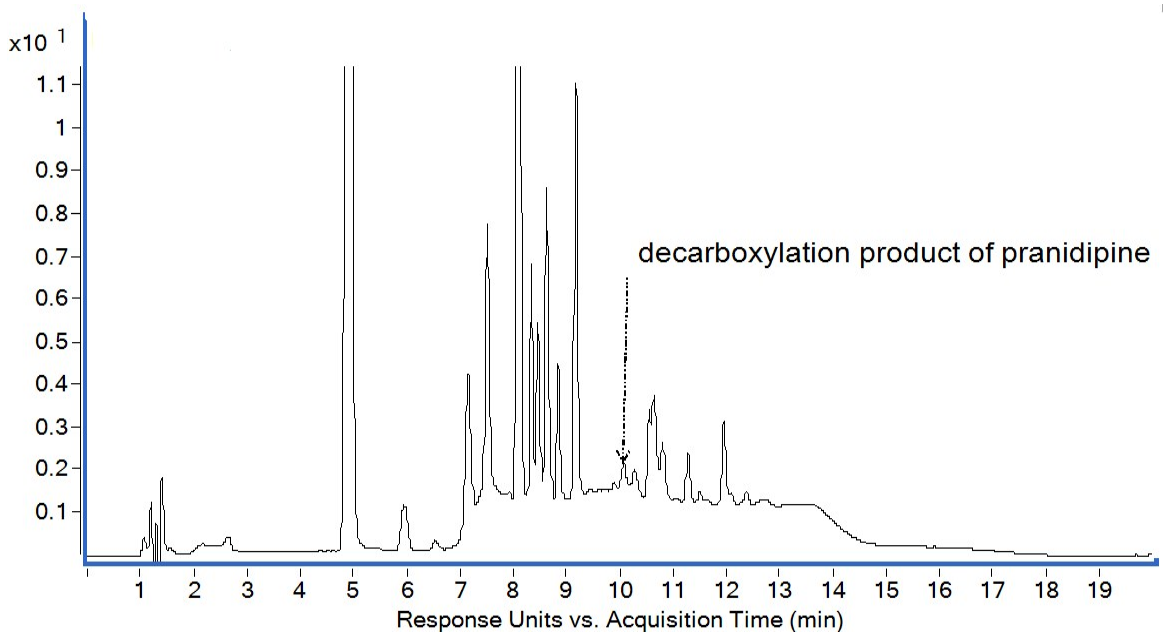


Figure S3: HPLC chromatogram of pranidipine after acid degradation

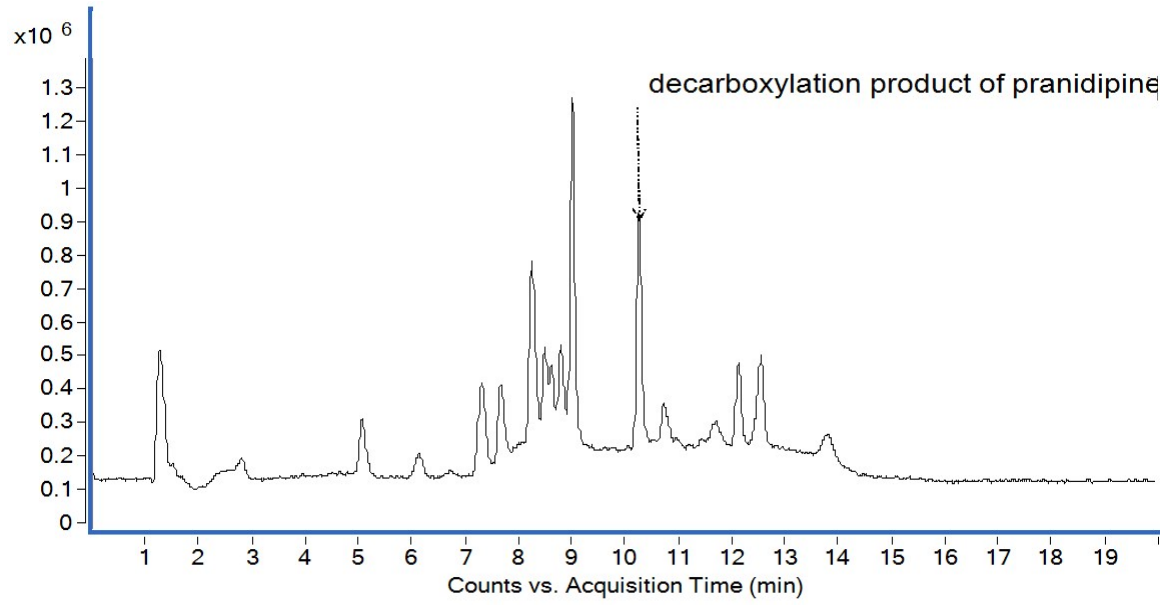


Figure S4: Total ion chromatograph of pranidipine after acid degradation

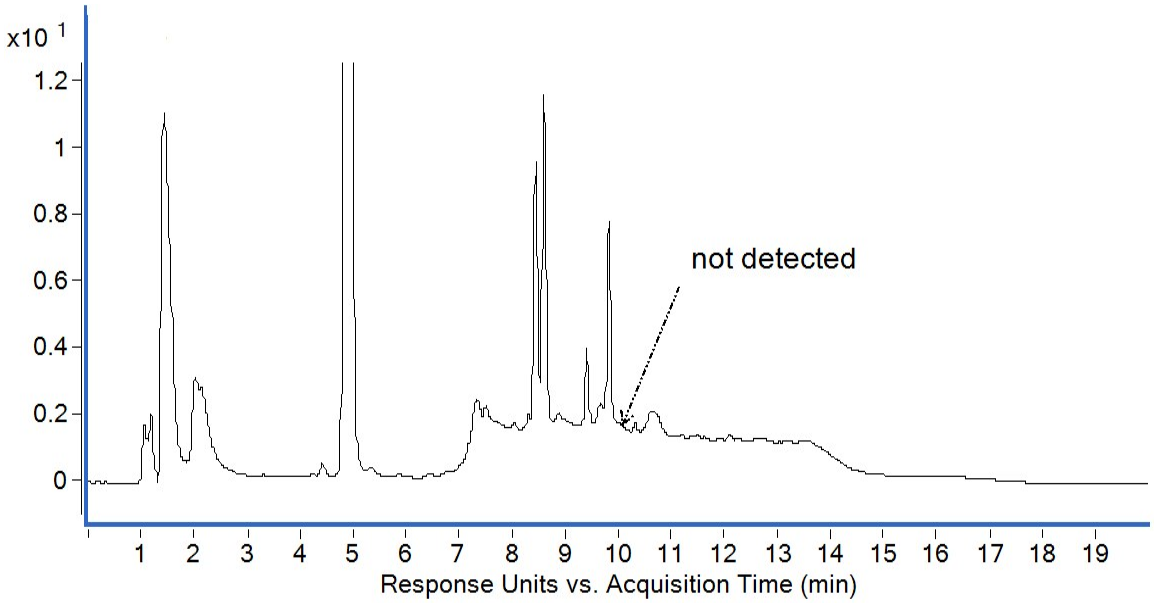


Figure S5: HPLC chromatogram of pranidipine after base degradation

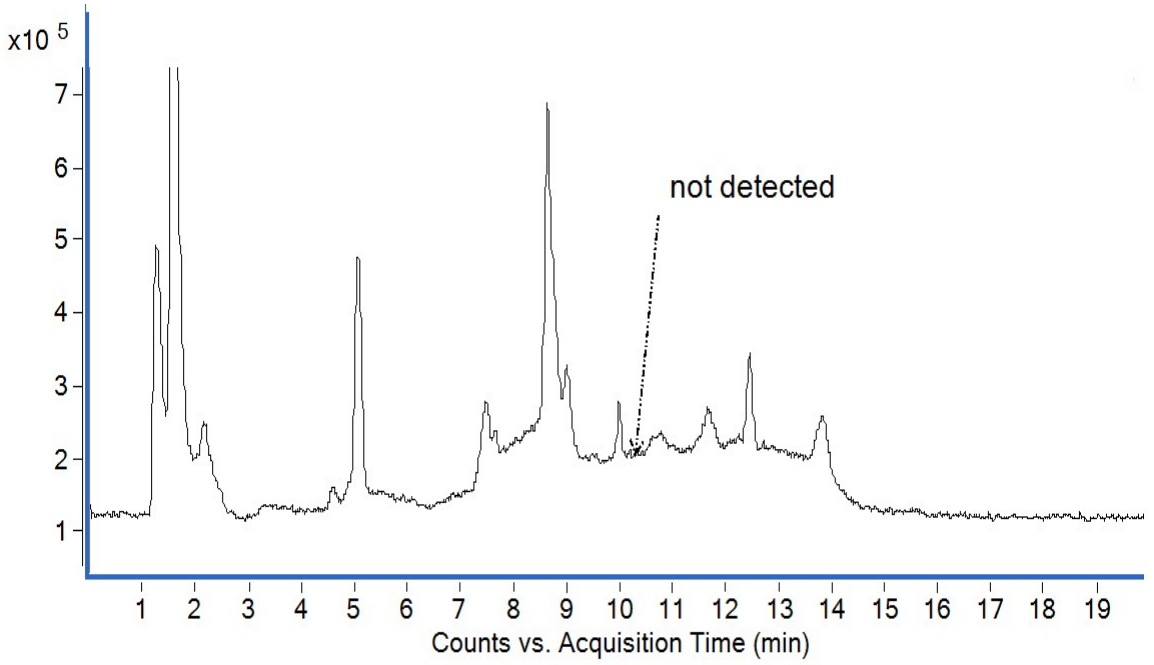


Figure S6: Total ion chromatograph of pranidipine after base degradation

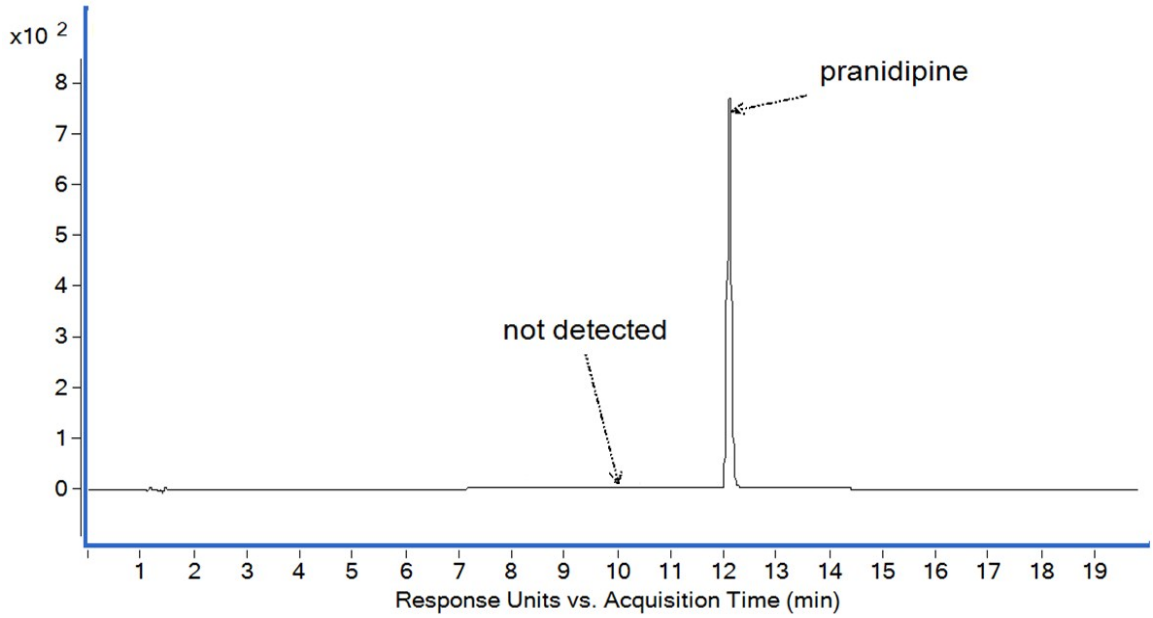


Figure S7: HPLC chromatogram of pranidipine after thermal degradation

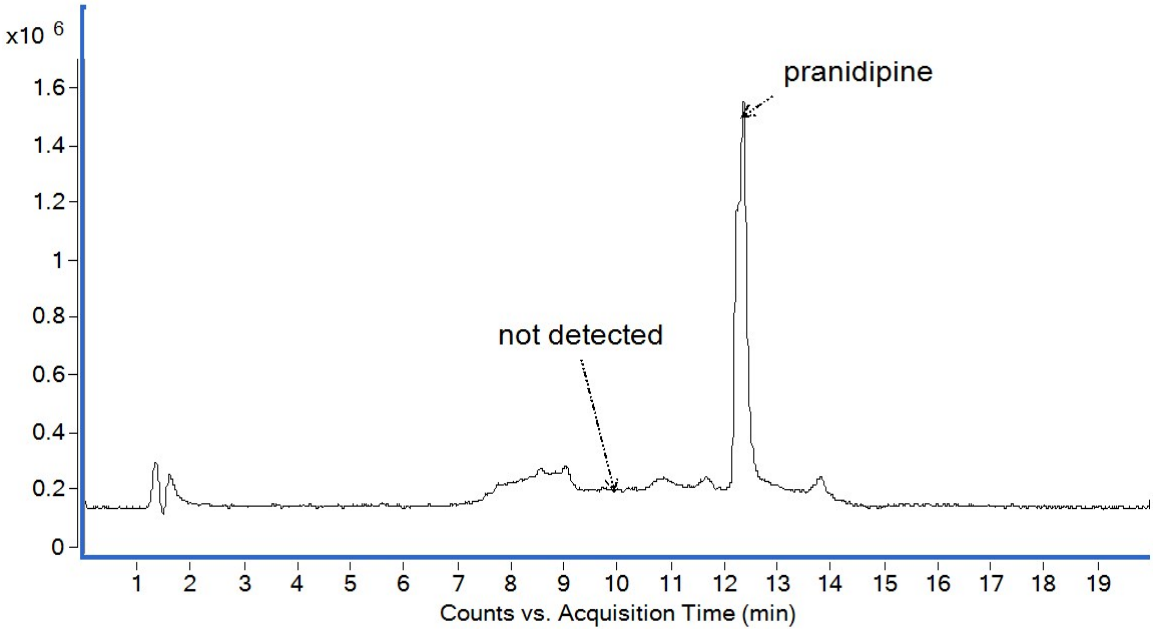


Figure S8: Total ion chromatograph of pranidipine after thermal degradation

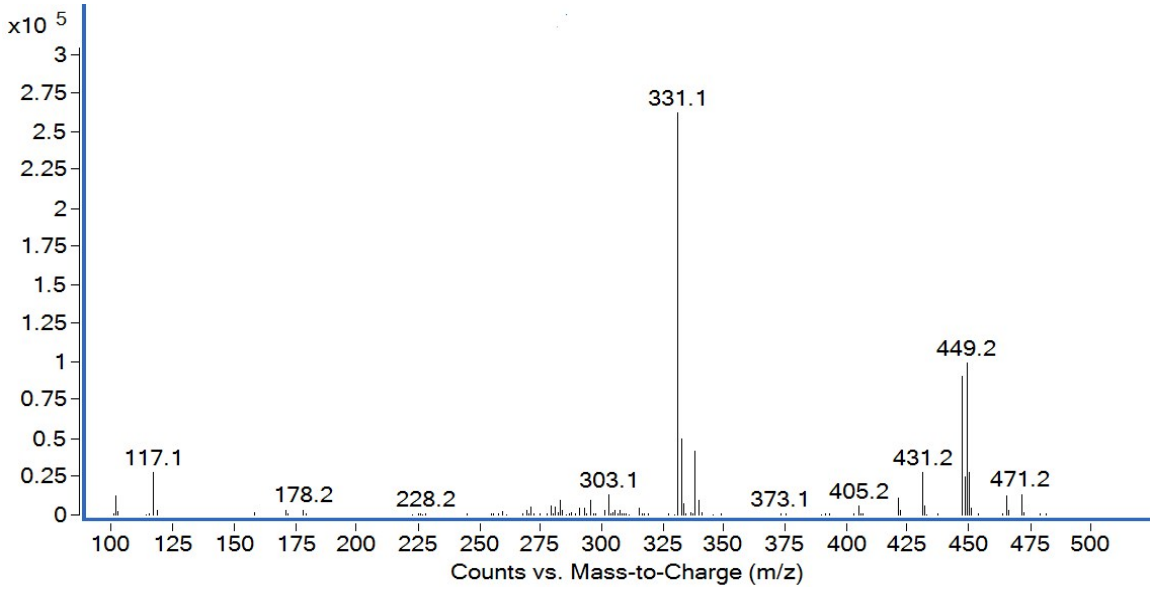


Figure S9: ESI-MS spectrum of pranidipine

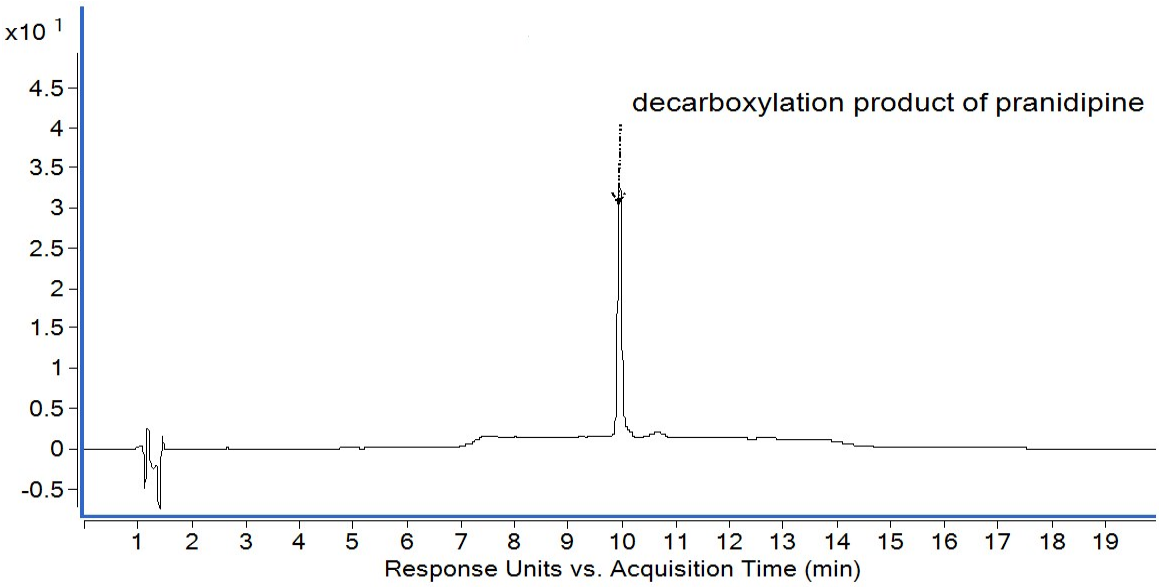


Figure S10: HPLC chromatogram of the isolated pranidipine decarboxylation product (**2d**) after acid degradation

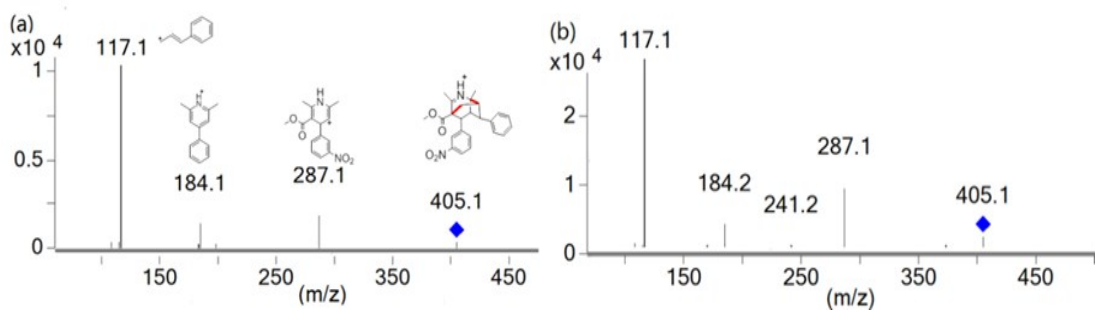


Figure S11. (a) ESI-MS/MS spectrum of the protonated decarboxylation product of pranidipine after acid degradation; (b) MS/MS spectrum of the ion at *m/z* 405 from the in-source decay of protonated pranidipine.

2.2 LC-MS/MS Spectra of Cilnidipine

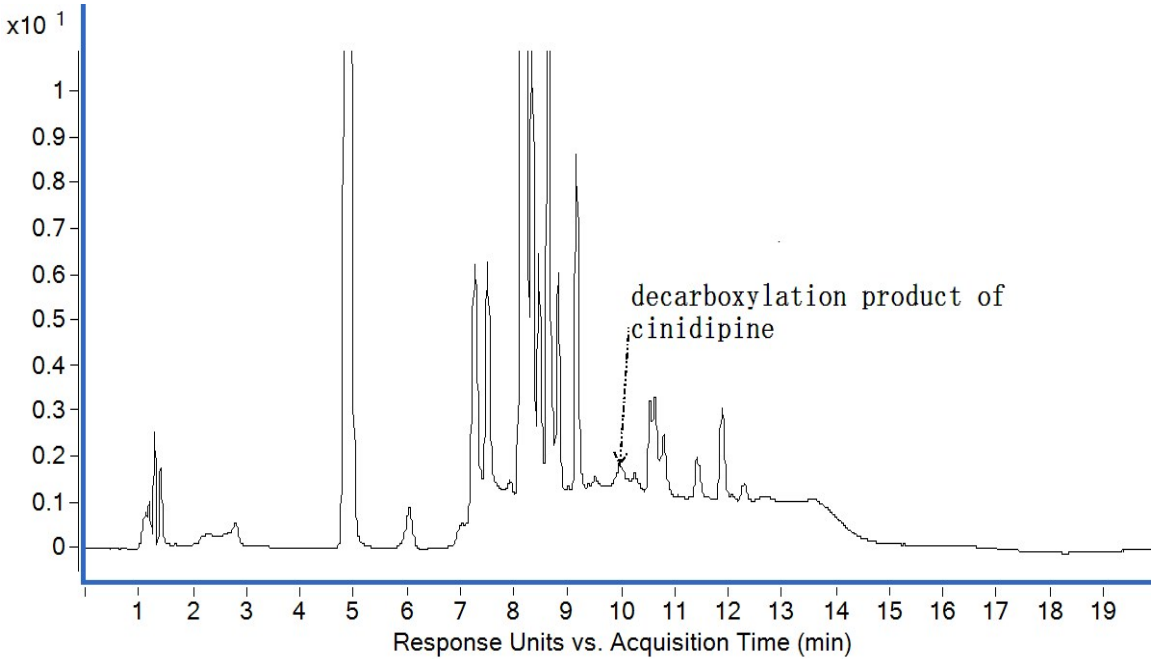


Figure S12: HPLC chromatogram of cilnidipine after acid degradation

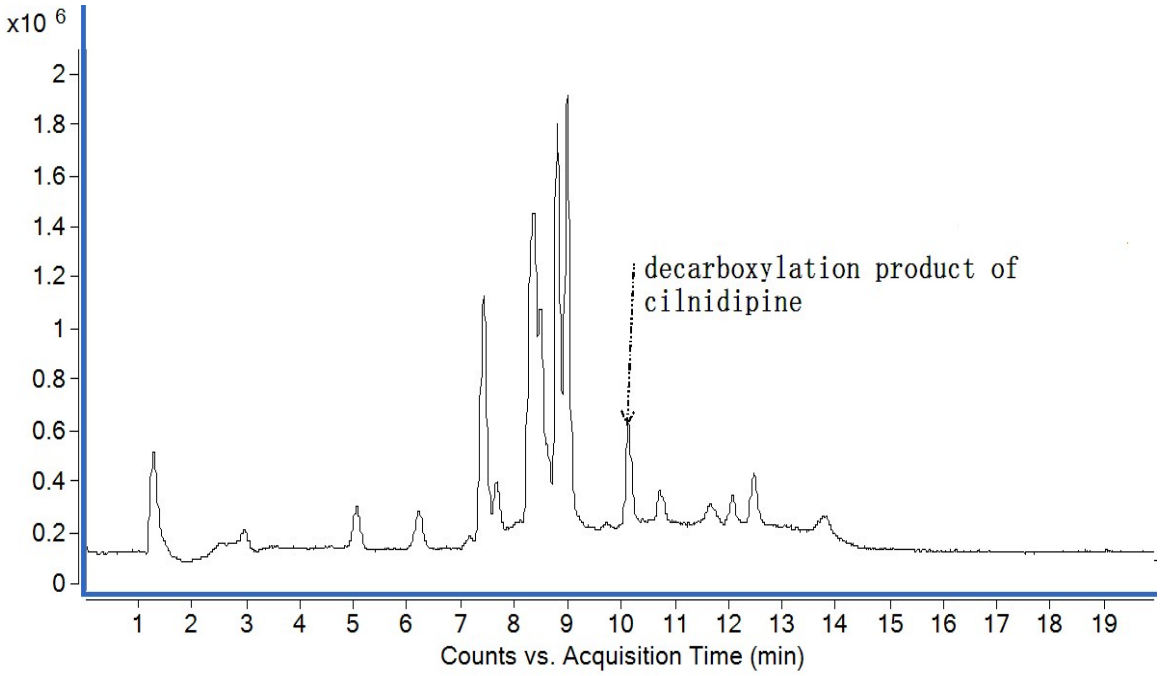


Figure S13: Total ion chromatograph of cilnidipine after acid degradation

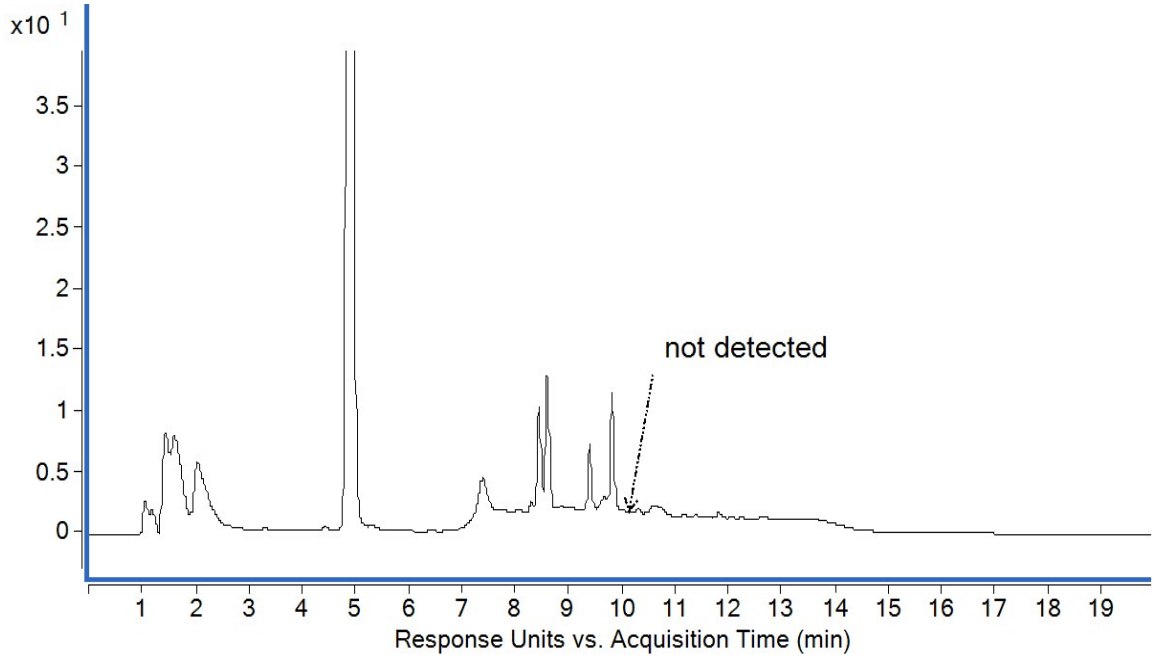


Figure S14: HPLC chromatogram of cilnidipine after base degradation

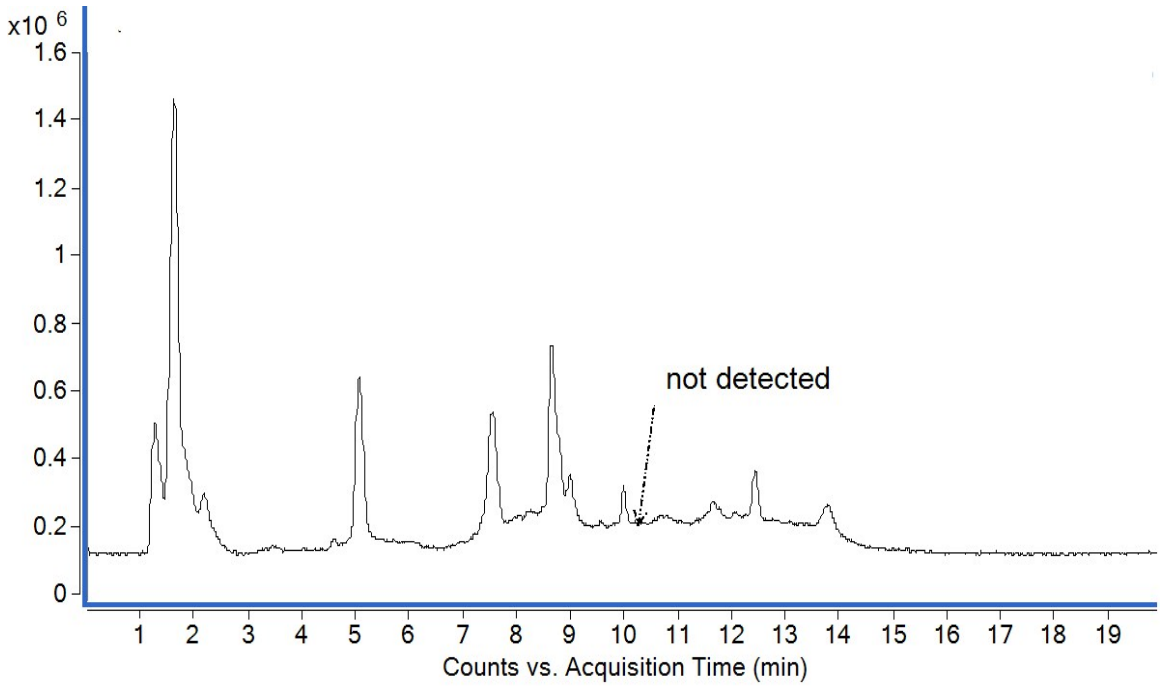


Figure S15: Total ion chromatograph of cilnidipine after base degradation

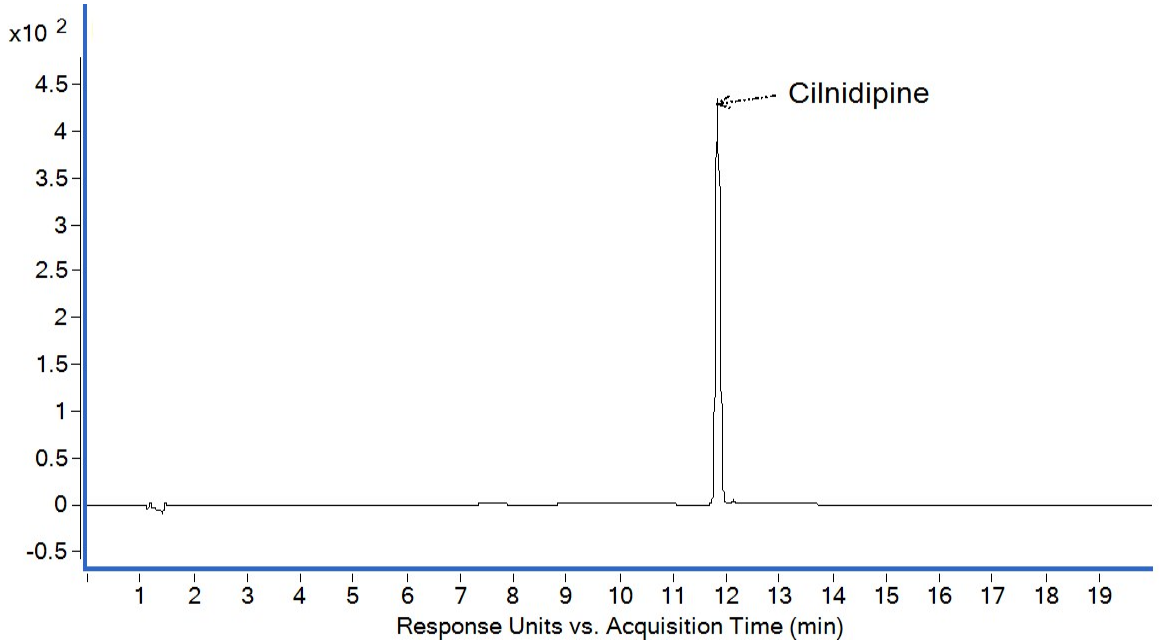


Figure S16: HPLC chromatogram of cilnidipine after thermal degradation

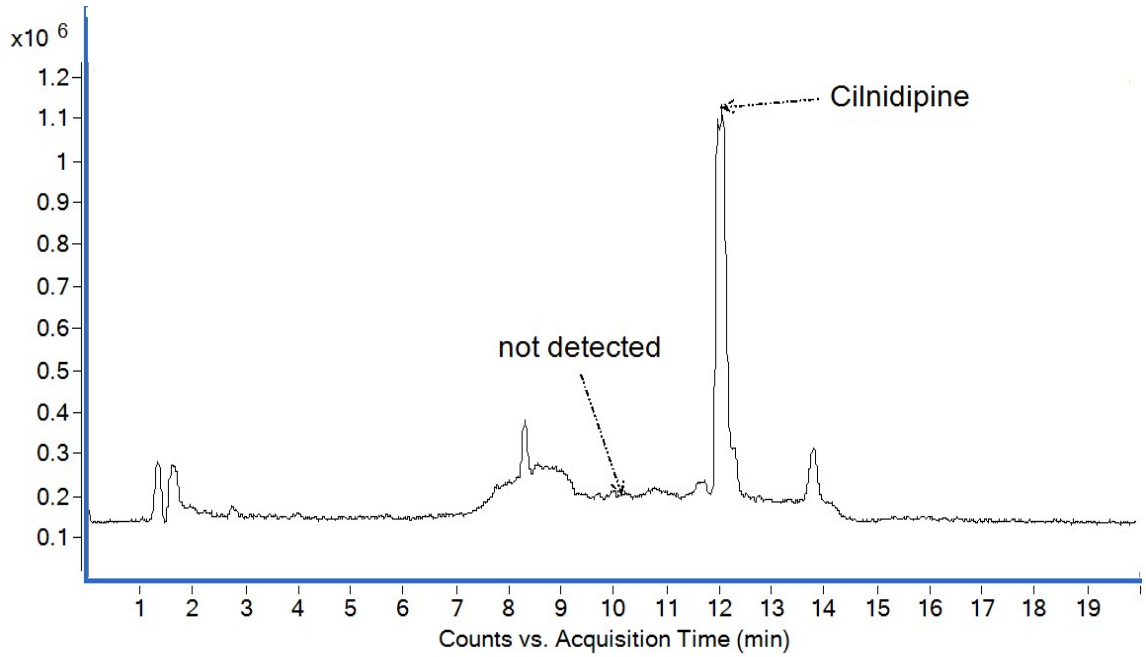


Figure S17: Total ion chromatograph of cilnidipine after thermal degradation

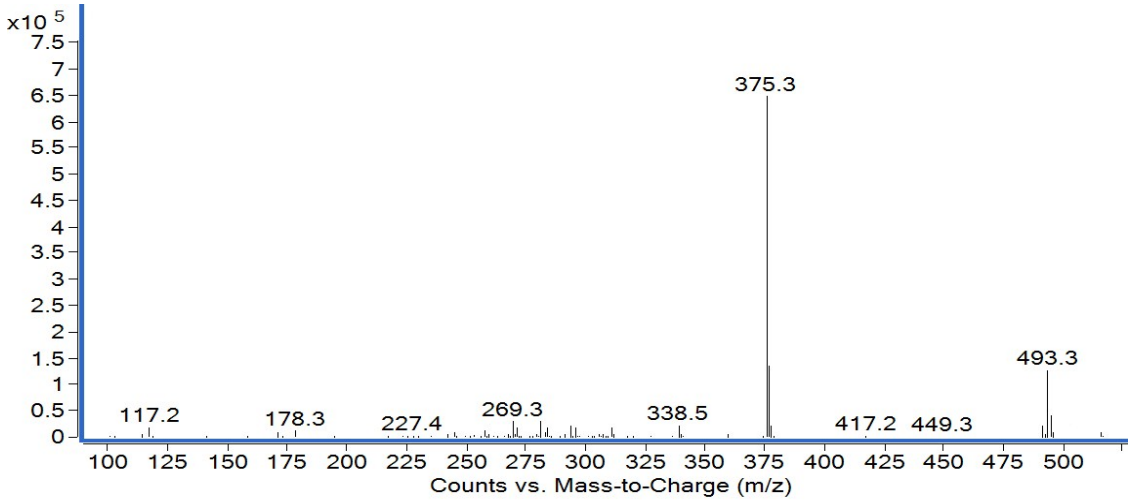


Figure S18: ESI-MS spectrum of cilnidipine

2.3 HRMS Results

Table S1. Molecular formulae of pranidipine fragmentation peaks and their measured masses from ESI-TOFMS

Ion	Measured mass/Da	Calculated mass/Da	Diff/ppm	Elemental composition
[M+H]	449.1687	449.1707	4.49	$C_{25}H_{25}N_2O_6$
	431.1598	431.1601	0.81	$C_{25}H_{23}N_2O_5$
	405.1801	405.1809	1.94	$C_{24}H_{25}N_2O_4$
	331.0915	331.0925	2.92	$C_{16}H_{15}N_2O_6$
	117.0697	117.0699	1.52	C_9H_9

Table S2. Molecular formulae of cilnidipine fragmentation peaks and their measured masses from ESI-TOFMS

Ion	Measured mass/Da	Calculated mass/Da	Diff/ppm	Elemental composition
[M+H]	493.1952	493.1969	3.5	$C_{27}H_{29}N_2O_7$
	475.1866	475.1864	-0.5	$C_{27}H_{27}N_2O_6$
	449.2057	449.2071	3.11	$C_{26}H_{29}N_2O_5$
	375.1170	375.1187	4.47	$C_{18}H_{19}N_2O_7$
	117.0695	117.0699	3.32	C_9H_9

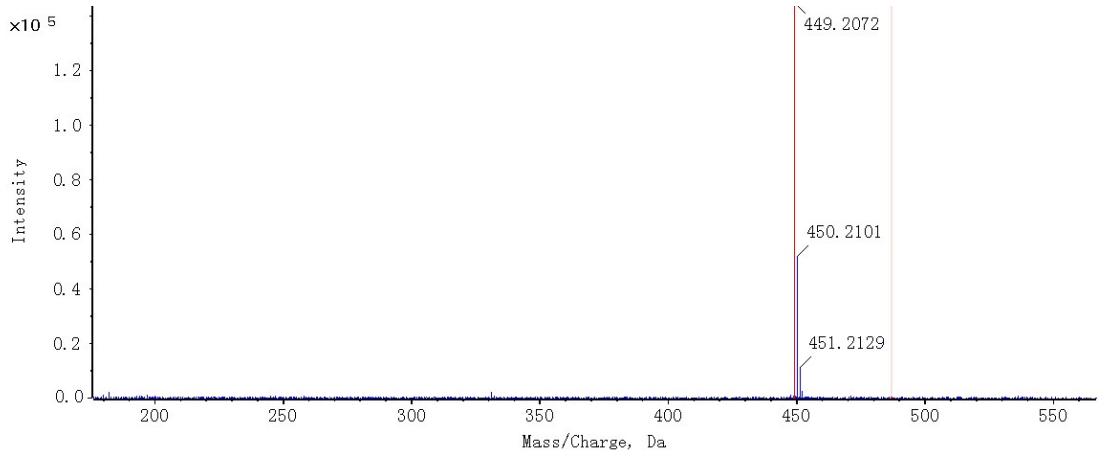


Fig. S19 Q-TOF spectrum of degradation product of cilnidipine (**1d**) (its calculated mass is 449.2071Da, the measured mass is 449.2072Da, the difference is -0.22ppm)

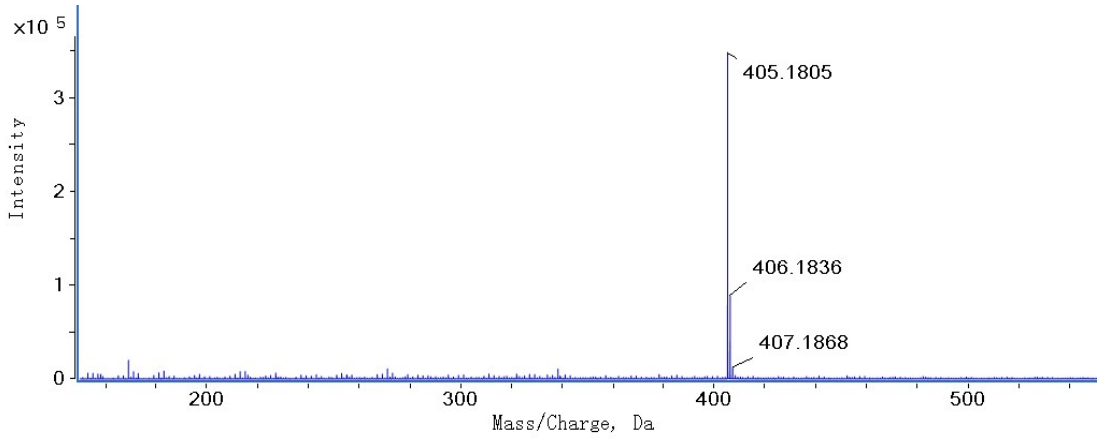
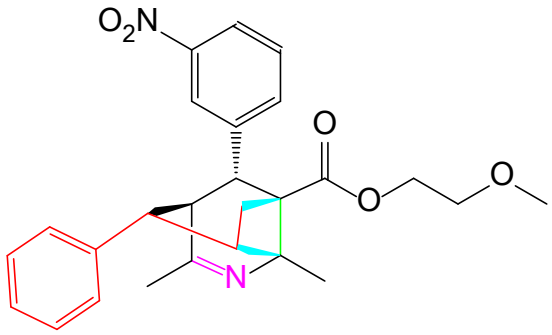


Fig. S20 Q-TOF spectrum of degradation product of pranidipine (**2d**) (its calculated mass is 405.1809Da, the measured mass is 405.1805Da, the difference is 0.99ppm)

3. NMR Spectral Data

3.1 Degradation Product of Cilnidipine (1d)



^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06-8.02 (m, 2H), 7.36-7.34 (m, 2H), 7.26-7.22 (m, 2H), 7.18-7.15 (m, 1H), 6.93-6.91 (m, 2H), 4.00-3.94 (m, 1H), 3.82-3.76 (m, 1H), 3.74 (d, 1H), 3.43 (d, 1H), 3.28-3.23 (m, 2H), 3.15 (s, 3H), 3.12-3.07 (m, 1H), 2.76 (dd, 1H), 2.29 (d, 1H), 2.10 (s, 3H), 1.67 (d, 1H), 1.24 (s, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 177.00, 171.33, 147.86, 141.68, 141.41, 134.77, 128.92, 128.31, 127.59, 126.59, 124.19, 121.93, 70.04, 62.95, 60.59, 58.64, 54.75, 53.87, 52.78, 48.35, 41.79, 39.05, 27.57, 22.83.

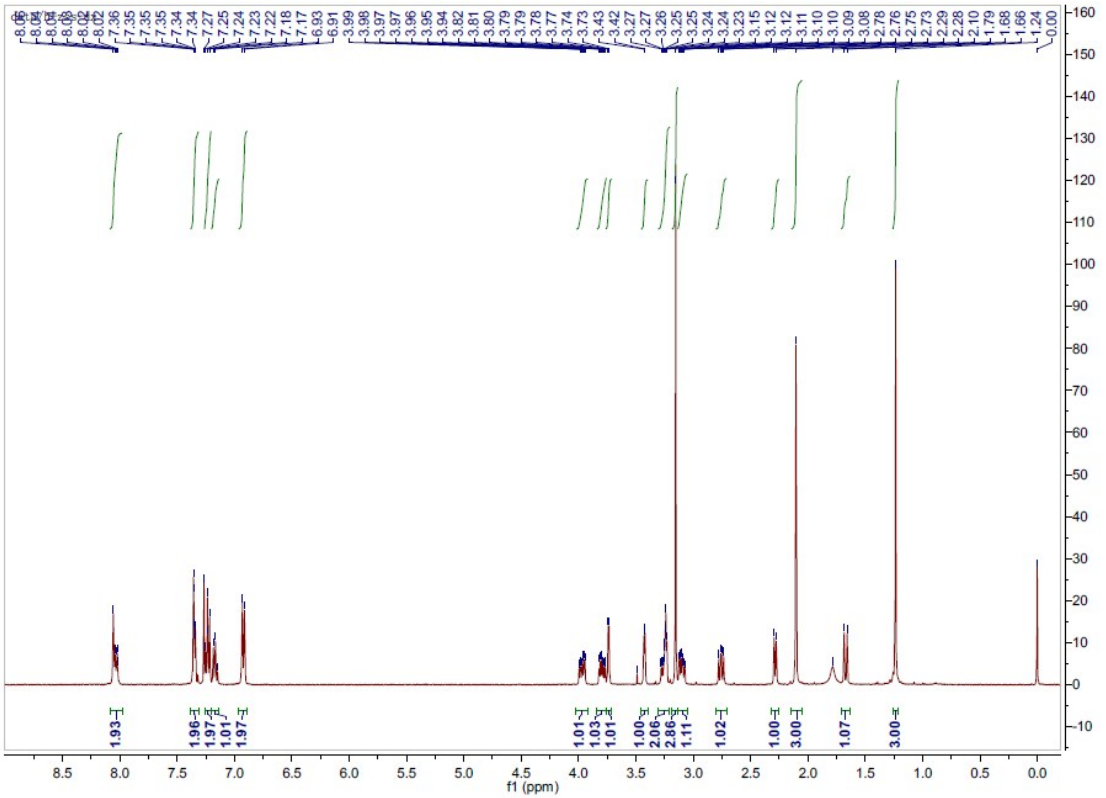


Figure S21: ^{1}H NMR (CDCl3, 400 MHz) of **1d**

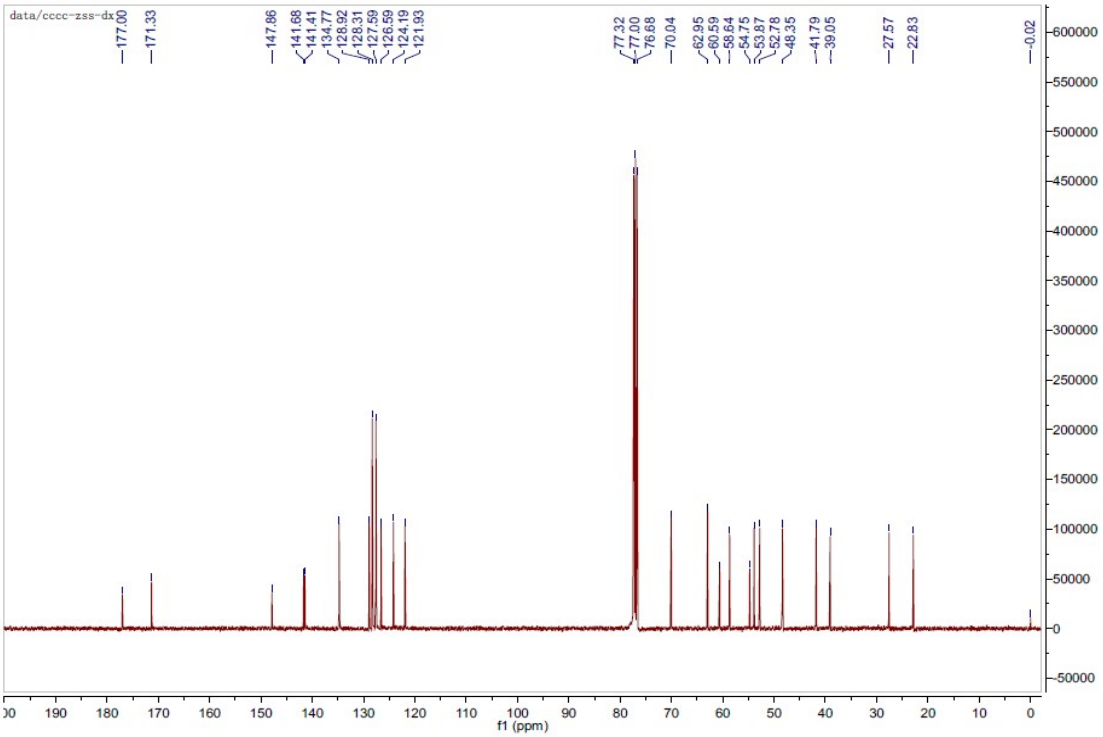


Figure S22: ^{13}C NMR ($CDCl_3$, 100.50 MHz) of **1d**

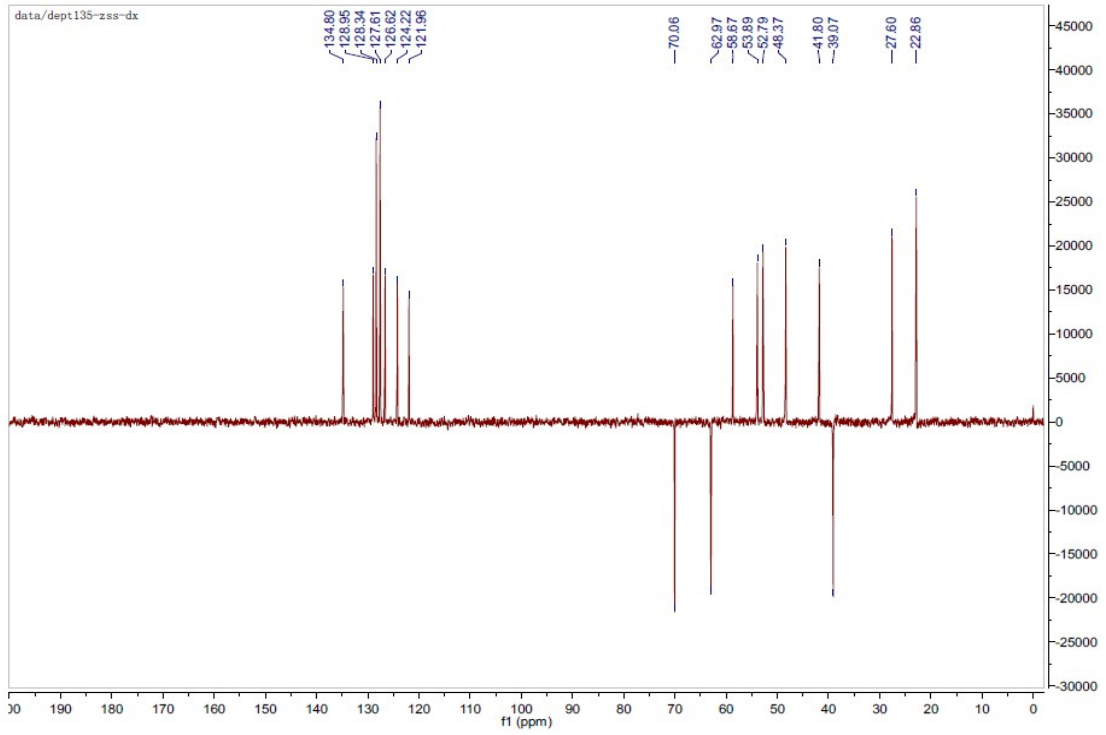


Figure S23: Dept-135 of **1d**

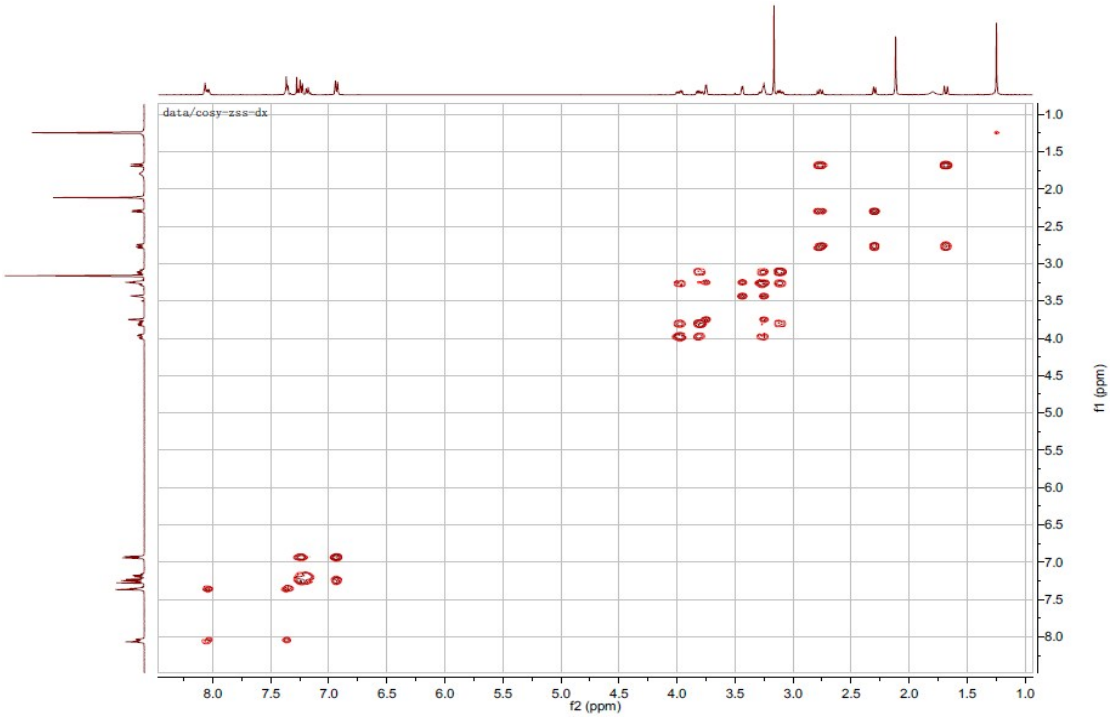


Figure S24: H-H COSY of **1d**

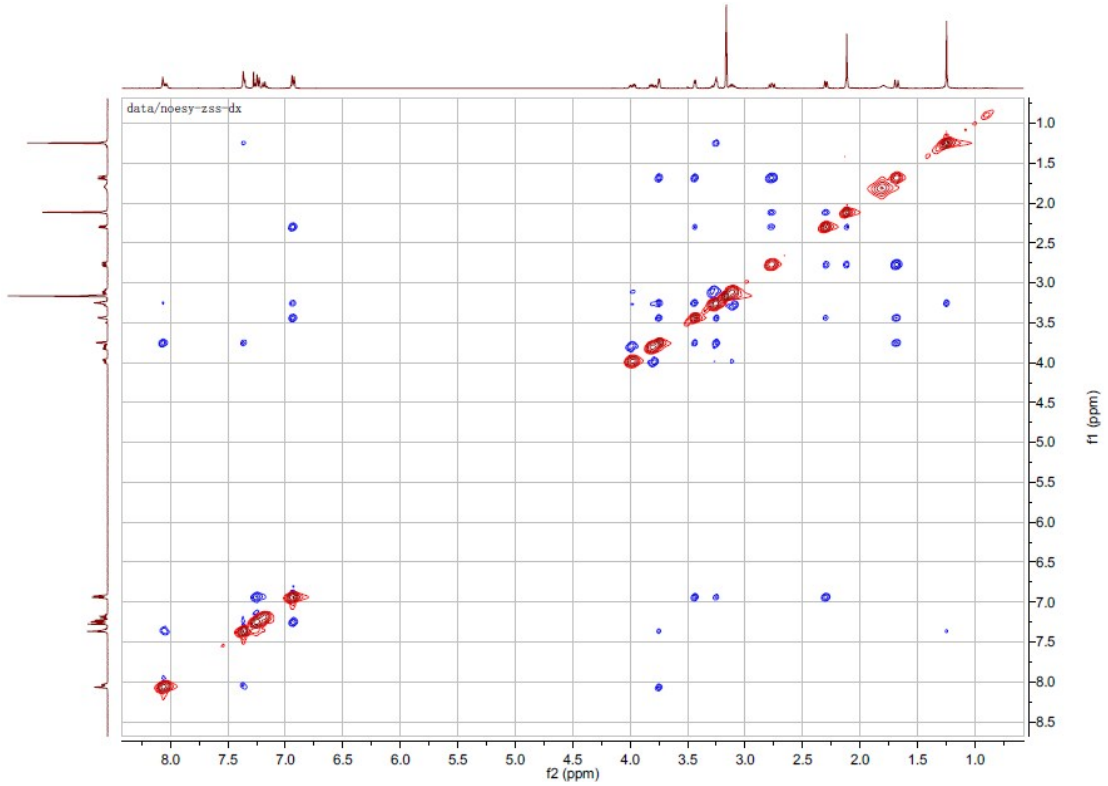


Figure S25: NOESY of **1d**

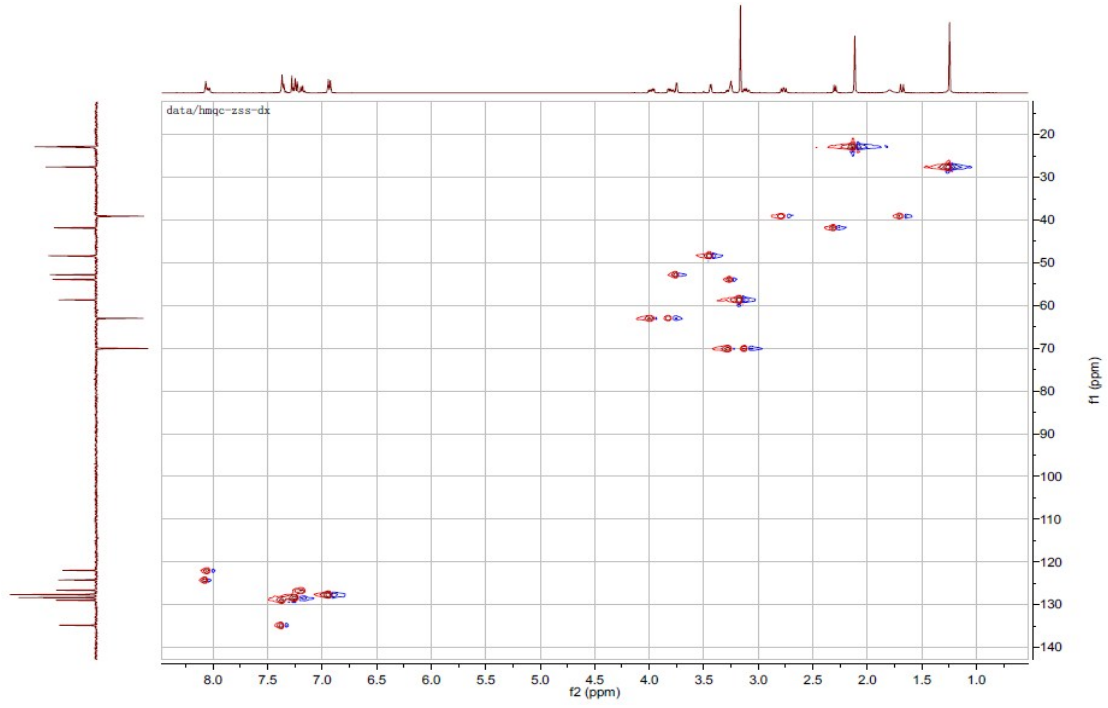
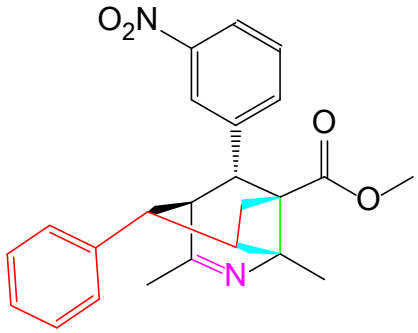


Figure S26: HMQC of **1d**

3.2 Degradation Product of Pranidipine (2d)



^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 7.97 (m, 2H), 7.35 – 7.29 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.16 (d, *J* = 6.9 Hz, 1H), 6.94 – 6.86 (m, 2H), 3.68 (d, *J* = 3.0 Hz, 1H), 3.40 (d, *J* = 3.5 Hz, 1H), 3.30 (s, 3H), 3.22 (t, *J* = 3.3 Hz, 1H), 2.72 (dd, *J* = 10.4, 7.1 Hz, 1H), 2.26 (d, *J* = 7.1 Hz, 1H), 2.07 (s, 3H), 1.62 (d, *J* = 10.4 Hz, 1H), 1.21 (s, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 176.97, 171.90, 147.81, 141.64, 141.37, 134.62, 128.91, 128.30, 127.56, 126.58, 124.03, 122.00, 77.30, 76.98, 76.66, 60.50, 54.83, 53.81, 52.93, 51.11, 48.30, 41.73, 39.02, 27.58, 22.87.

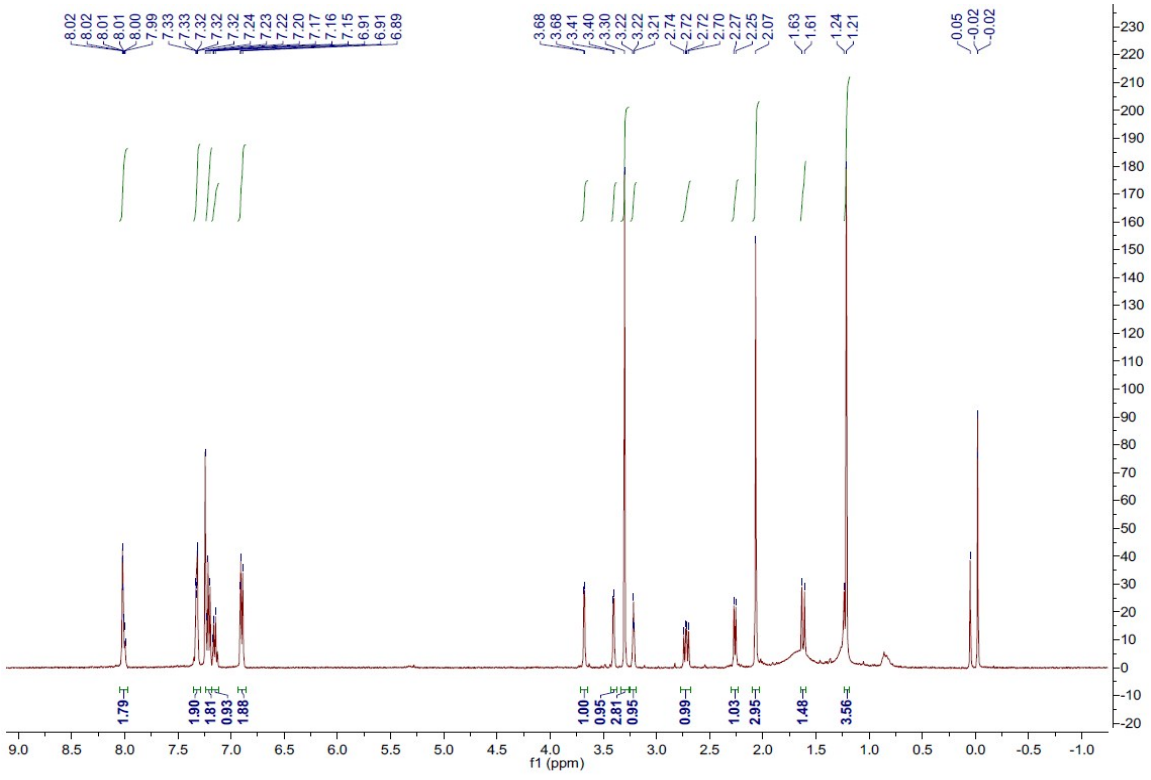


Figure S27: ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **2d**

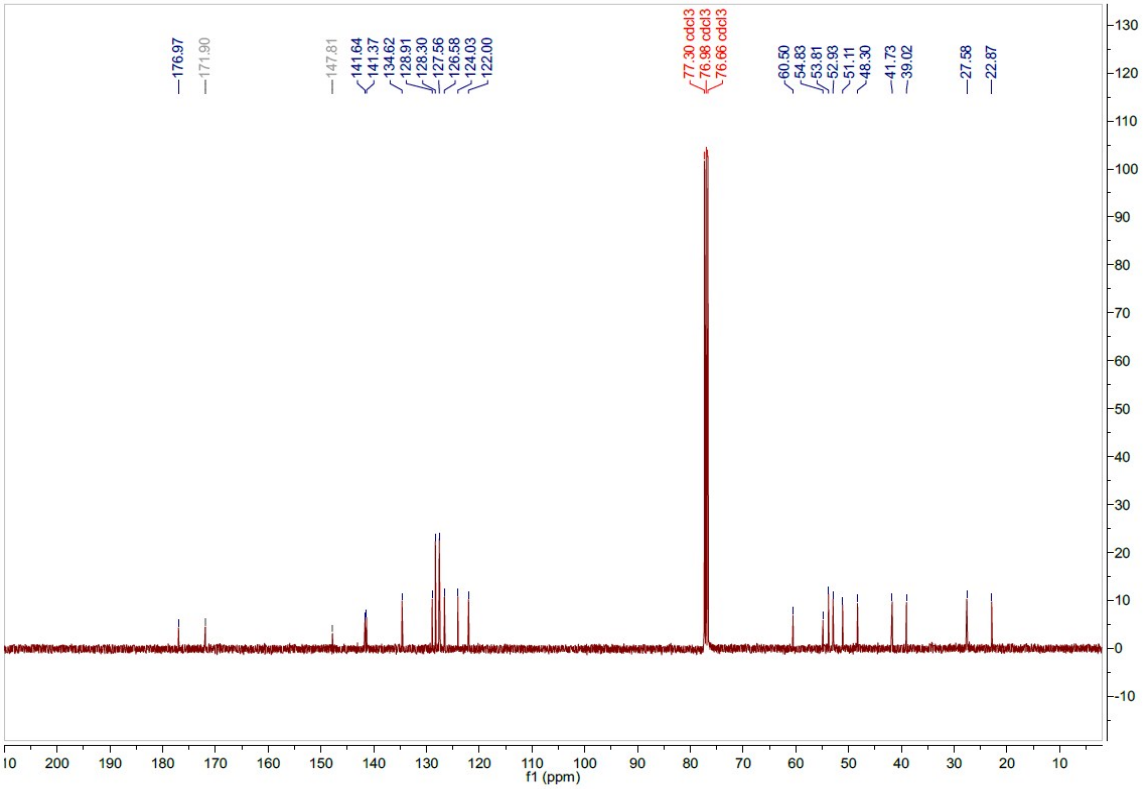


Figure S28: ^{13}C NMR ($CDCl_3$, 100.50 MHz) of compound **2d**

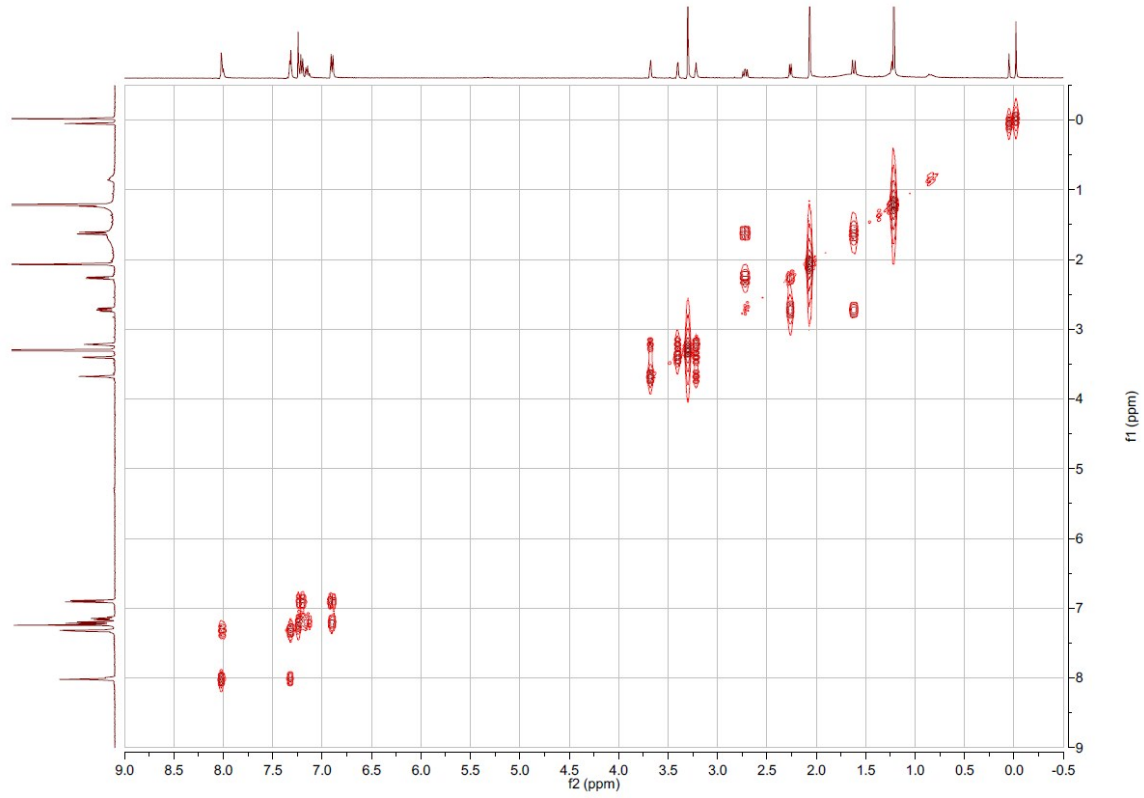


Figure S29: H-H COSY of compound **2d**

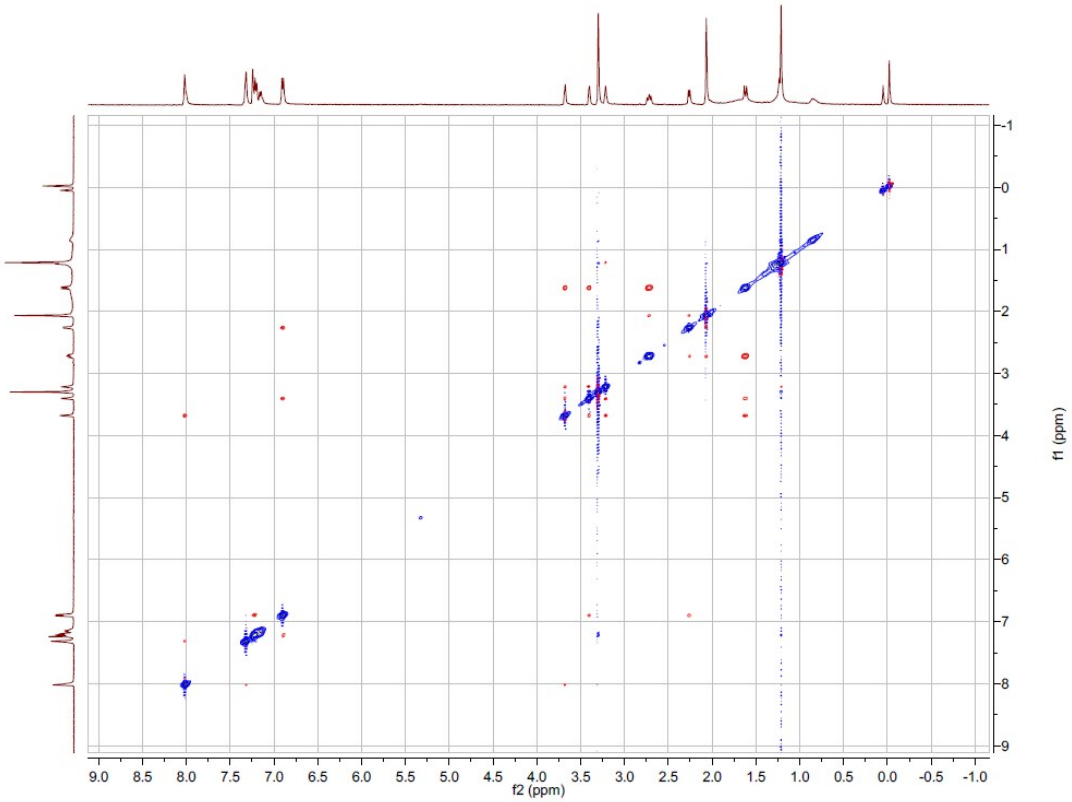


Figure S30: NOESY of compound **2d**

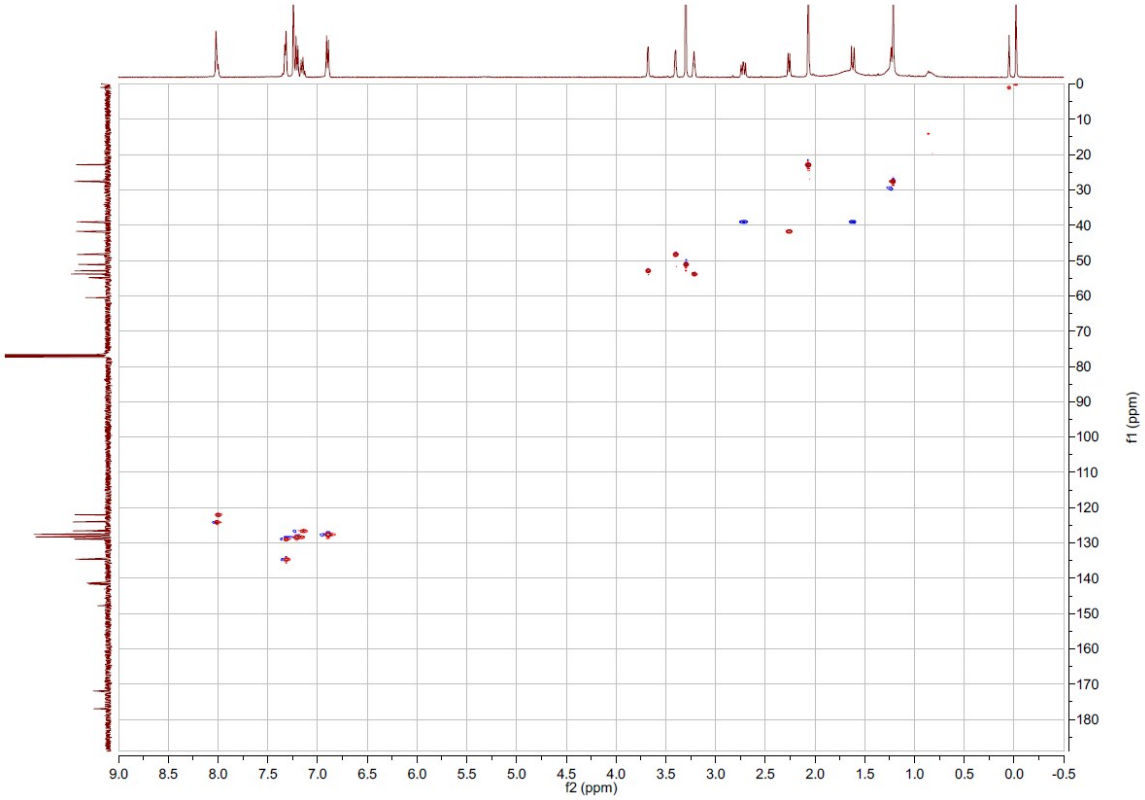


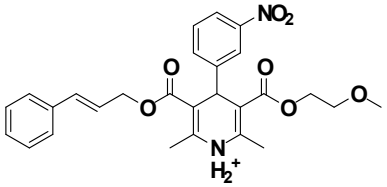
Figure S31: HSQC of compound **2d**

4. Theoretical Computational Methods Details

All structures were computed on the basis of the hybrid density functional theory (RB3LYP)[1] and the 6-31G(d) basis set, which were implemented in the Gaussian 09 program package.[2] All the gas-phase minima and transition structures (herein also referred to as transition states) were characterized by frequency analysis. Frequency calculations identified the minimum structures with all real frequencies and the transition states with only one imaginary frequency. Zero-point energy (ZPE) corrections were applied at the same level of theory.[3] To obtain more reliable energetic data, higher-level single-point energy calculations were performed at the RB3LYP/6-311+G(d, p) level by using the RB3LYP/6-31G(d) optimized geometries. The solvent effect was also taken into account. The solvation free energies were calculated using the SMD solvation model.[4] The Gibbs free energies presented in this article are the B3LYP electronic energies modified with ZPE, thermal, and entropy corrections and solvation-energy corrections.

5. Cartesian Coordinates of All Species

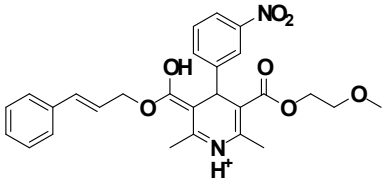
The Cartesian coordinates of all species structures at the (R)B3LYP/6-31G(d) level are listed as follows:



N	0.900588000	-3.318944000	1.161153000
C	2.527398000	-1.595337000	0.615640000
C	0.129082000	-1.471620000	-0.210531000
C	1.434676000	-0.738532000	0.017712000
C	-0.152626000	-2.670980000	0.304089000
C	2.311888000	-2.799721000	1.157131000
H	1.773614000	-0.411937000	-0.968917000
C	3.238176000	-3.788039000	1.794549000
H	2.947827000	-3.987119000	2.835714000
H	4.253459000	-3.396825000	1.802396000
H	3.224716000	-4.746222000	1.255697000
C	-1.354858000	-3.556729000	0.190592000
H	-1.787522000	-3.767483000	1.178528000
H	-1.096606000	-4.519244000	-0.273354000
H	-2.124014000	-3.075210000	-0.408650000
C	3.933906000	-1.024812000	0.592533000
O	4.029733000	-0.078490000	-0.345261000
C	5.306407000	0.613350000	-0.477415000

H	5.778153000	0.691770000	0.502655000
H	5.049092000	1.603687000	-0.853801000
O	4.831239000	-1.378913000	1.326430000
C	1.200306000	0.536125000	0.848141000
C	0.740188000	2.875610000	2.347046000
C	0.955864000	0.470872000	2.226521000
C	1.212315000	1.782086000	0.216523000
C	0.982221000	2.924146000	0.977311000
C	0.729630000	1.629240000	2.971004000
H	0.951925000	-0.490338000	2.735272000
H	1.387172000	1.877755000	-0.848042000
H	0.547999000	1.562189000	4.038952000
H	0.569816000	3.794179000	2.895042000
N	0.999112000	4.238632000	0.299144000
O	0.759641000	5.228043000	0.984822000
O	1.250898000	4.248672000	-0.903312000
H	0.943545000	-4.313591000	0.894885000
C	-0.788669000	-0.736507000	-1.169491000
O	-2.083809000	-0.907606000	-0.922314000
O	-0.321214000	-0.045288000	-2.050205000
C	-3.015170000	-0.179064000	-1.827084000
H	-2.758807000	-0.484123000	-2.845920000
H	-2.802172000	0.887052000	-1.719928000
C	-4.407914000	-0.526433000	-1.441491000
H	-4.722974000	-1.550346000	-1.632596000
C	-5.256842000	0.377876000	-0.923628000
H	-4.877196000	1.387280000	-0.758076000
C	-6.661747000	0.187317000	-0.548572000
C	-9.356009000	-0.068914000	0.225677000
C	-7.361552000	-1.014865000	-0.765337000
C	-7.345225000	1.256395000	0.057178000
C	-8.678407000	1.131072000	0.442947000
C	-8.692290000	-1.140341000	-0.381252000
H	-6.867052000	-1.853609000	-1.246993000
H	-6.821613000	2.194616000	0.225583000
H	-9.187542000	1.969858000	0.908722000
H	-9.218682000	-2.073723000	-0.559986000
H	-10.396392000	-0.169968000	0.520949000
H	0.564424000	-3.337933000	2.136555000
C	6.210864000	-0.118877000	-1.463007000
H	6.466409000	-1.118387000	-1.073804000
H	5.688015000	-0.252062000	-2.425244000
O	7.352141000	0.689296000	-1.599666000
C	8.314440000	0.151492000	-2.491769000

H	9.148626000	0.855279000	-2.517799000
H	8.678674000	-0.828139000	-2.147284000
H	7.903869000	0.040221000	-3.506686000



N	0.133110000	-2.471047000	1.901034000
C	2.079796000	-1.527532000	0.915965000
C	-0.271374000	-0.730233000	0.369558000
C	1.232496000	-0.433613000	0.265654000
C	-0.757167000	-1.719484000	1.223354000
C	1.533396000	-2.463733000	1.723626000
H	1.504051000	-0.415257000	-0.796159000
C	2.210316000	-3.570653000	2.480327000
H	2.114541000	-3.397422000	3.560683000
H	3.269081000	-3.620289000	2.242105000
H	1.733895000	-4.532695000	2.252343000
C	-2.201357000	-2.052178000	1.483305000
H	-2.294607000	-2.708681000	2.353278000
H	-2.639052000	-2.559681000	0.617738000
H	-2.797431000	-1.154351000	1.655481000
C	3.546865000	-1.524258000	0.621097000
O	3.808113000	-0.780058000	-0.475315000
C	5.200781000	-0.646654000	-0.867708000
H	5.828261000	-0.610253000	0.023765000
H	5.254992000	0.302621000	-1.403062000
O	4.401871000	-2.103307000	1.259922000
C	1.591001000	0.953090000	0.831332000
C	2.260130000	3.497190000	1.857288000
C	1.257458000	1.311592000	2.148935000
C	2.265886000	1.881566000	0.030517000
C	2.583197000	3.134254000	0.556108000
C	1.591436000	2.565839000	2.656059000
H	0.740105000	0.599164000	2.785814000
H	2.583137000	1.639740000	-0.978003000
H	1.333436000	2.824125000	3.678316000
H	2.531431000	4.479330000	2.225132000
N	3.299571000	4.097817000	-0.307430000
O	3.559239000	5.196880000	0.169975000
O	3.580960000	3.728008000	-1.445926000
C	-1.140156000	0.049020000	-0.432075000

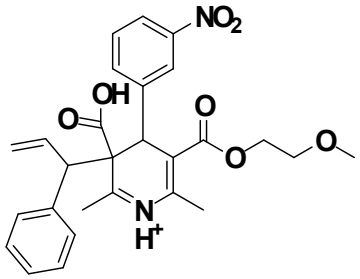
O	-2.390645000	-0.258475000	-0.596223000
O	-0.726346000	1.115986000	-1.090230000
C	-3.303414000	0.644292000	-1.400326000
H	-2.859462000	0.687743000	-2.397361000
H	-3.260243000	1.630754000	-0.935019000
C	-4.658212000	0.047847000	-1.377014000
H	-4.794117000	-0.868174000	-1.946279000
C	-5.681213000	0.629555000	-0.722800000
H	-5.470695000	1.550924000	-0.177057000
C	-7.075473000	0.189253000	-0.652858000
C	-9.774948000	-0.568933000	-0.434917000
C	-7.561369000	-0.941983000	-1.336807000
C	-7.972967000	0.931662000	0.135758000
C	-9.310146000	0.556644000	0.246134000
C	-8.895991000	-1.315622000	-1.227200000
H	-6.896684000	-1.528112000	-1.964823000
H	-7.614665000	1.811582000	0.665109000
H	-9.987806000	1.143270000	0.859315000
H	-9.256820000	-2.188404000	-1.763638000
H	-10.817372000	-0.863018000	-0.354595000
H	-0.232885000	-3.180720000	2.523862000
C	5.620781000	-1.795792000	-1.777909000
H	5.593668000	-2.747248000	-1.223206000
H	4.921365000	-1.877115000	-2.627826000
O	6.923577000	-1.486967000	-2.209194000
C	7.486085000	-2.484912000	-3.042901000
H	8.489260000	-2.146252000	-3.309930000
H	7.558139000	-3.451637000	-2.521798000
H	6.895699000	-2.622572000	-3.961876000
H	0.152833000	1.421371000	-0.776629000

TS1

N	1.485305000	-1.089534000	2.093655000
C	-0.221969000	-0.608556000	0.525240000
C	2.095315000	0.494202000	0.426800000
C	0.612854000	0.554762000	0.000992000
C	2.384599000	-0.216873000	1.642464000
C	0.203237000	-1.375709000	1.544445000
H	0.560057000	0.478784000	-1.090764000
C	-0.445773000	-2.553516000	2.210082000
H	-1.394280000	-2.798554000	1.741636000
H	0.215824000	-3.427002000	2.155824000
H	-0.636822000	-2.337973000	3.269917000
C	3.651097000	-0.120122000	2.431771000

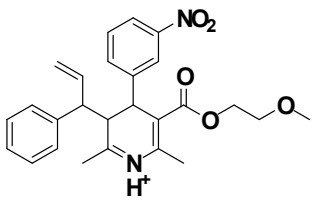
H	3.658499000	-0.840817000	3.255643000
H	4.522018000	-0.280207000	1.790731000
H	3.774305000	0.893625000	2.823667000
C	-1.476482000	-0.825866000	-0.264400000
O	-2.475911000	-1.405956000	0.409910000
C	-3.706249000	-1.620165000	-0.338922000
H	-4.042124000	-0.669067000	-0.757314000
H	-3.512773000	-2.312883000	-1.161651000
O	-1.554847000	-0.470900000	-1.425807000
C	-0.081150000	1.876173000	0.382392000
C	-1.402888000	4.276770000	1.055657000
C	0.004556000	2.408931000	1.679268000
C	-0.845880000	2.551257000	-0.576284000
C	-1.486943000	3.736425000	-0.222019000
C	-0.646655000	3.596194000	2.010997000
H	0.586278000	1.898146000	2.442003000
H	-0.976298000	2.162089000	-1.580121000
H	-0.564346000	3.996858000	3.016335000
H	-1.917752000	5.202232000	1.282991000
N	-2.287045000	4.439016000	-1.249461000
O	-2.873540000	5.459317000	-0.903671000
O	-2.306101000	3.950433000	-2.376677000
C	2.925608000	1.730467000	0.159871000
O	3.958822000	1.980655000	0.736269000
O	2.549243000	2.504123000	-0.883514000
C	5.295328000	0.232019000	-1.270362000
H	4.929979000	1.098096000	-1.815119000
H	6.370492000	0.161206000	-1.137203000
C	4.470862000	-0.720861000	-0.799094000
H	4.895122000	-1.580430000	-0.286791000
C	3.027075000	-0.706087000	-1.022701000
H	2.714555000	0.019063000	-1.772893000
C	2.314729000	-1.992910000	-1.121364000
C	1.009457000	-4.457485000	-1.472960000
C	2.645305000	-3.102985000	-0.316204000
C	1.319662000	-2.147046000	-2.107030000
C	0.675995000	-3.368904000	-2.282591000
C	1.995868000	-4.321599000	-0.490137000
H	3.420195000	-3.020291000	0.440615000
H	1.062432000	-1.311199000	-2.750965000
H	-0.077589000	-3.472865000	-3.057012000
H	2.269720000	-5.172722000	0.126600000
H	0.513829000	-5.413279000	-1.615157000
H	1.738475000	-1.627948000	2.915867000

C	-4.727641000	-2.188934000	0.633915000
H	-4.899568000	-1.479825000	1.460955000
H	-4.353975000	-3.129443000	1.075282000
O	-5.893975000	-2.401447000	-0.119930000
C	-6.971028000	-2.911624000	0.648417000
H	-7.815122000	-3.033865000	-0.033023000
H	-7.254535000	-2.217759000	1.454029000
H	-6.721480000	-3.886999000	1.093140000
H	1.604204000	2.419116000	-1.098686000



N	0.702382000	-1.546848000	2.089709000
C	-0.601461000	-0.484835000	0.422997000
C	1.979145000	-0.548941000	0.313937000
C	0.654052000	0.222391000	-0.054833000
C	1.888042000	-1.189389000	1.665662000
C	-0.573806000	-1.330998000	1.466409000
C	-1.655943000	-2.149927000	2.104389000
H	-1.409058000	-3.216445000	2.034552000
H	-2.610944000	-1.977593000	1.616231000
H	-1.767565000	-1.891695000	3.166256000
C	3.056135000	-1.503213000	2.535411000
H	2.801280000	-2.229957000	3.312886000
H	3.408996000	-0.572774000	2.994757000
H	3.896843000	-1.869089000	1.940789000
C	-1.810248000	-0.163037000	-0.412482000
O	-2.976129000	-0.272104000	0.233339000
C	-4.164634000	0.040243000	-0.549638000
H	-4.252680000	-0.675352000	-1.370712000
H	-4.063095000	1.042763000	-0.970470000
O	-1.693657000	0.186198000	-1.569067000
C	3.143763000	0.461520000	0.251273000
O	3.804170000	0.840955000	1.188598000
C	4.721256000	-1.998702000	-1.396102000
H	5.672824000	-2.509782000	-1.283086000
H	4.673292000	-1.219647000	-2.152399000
C	3.664019000	-2.331956000	-0.651928000
C	2.291669000	-1.713936000	-0.804397000

C	1.205173000	-2.770307000	-0.954163000
C	-0.787640000	-4.724406000	-1.340731000
C	1.120697000	-3.888917000	-0.108897000
C	0.284940000	-2.661361000	-2.007551000
C	-0.705443000	-3.625442000	-2.197136000
C	0.132316000	-4.856255000	-0.298467000
H	1.841792000	-4.033015000	0.692176000
H	0.342103000	-1.817683000	-2.689983000
H	-1.402396000	-3.522334000	-3.023543000
H	0.095101000	-5.723689000	0.354849000
H	-1.549645000	-5.482662000	-1.494930000
O	3.302351000	0.916497000	-1.003408000
H	4.009598000	1.591227000	-0.983068000
H	2.298981000	-1.110723000	-1.716277000
H	3.765718000	-3.147306000	0.061291000
H	0.664114000	-2.060613000	2.968134000
C	-5.355370000	-0.048400000	0.392219000
H	-5.240537000	0.673513000	1.218172000
H	-5.416145000	-1.056580000	0.838138000
O	-6.484127000	0.236209000	-0.393991000
C	-7.696429000	0.221158000	0.341498000
H	-7.690527000	0.976206000	1.141954000
H	-8.496649000	0.452831000	-0.364009000
H	-7.883640000	-0.767048000	0.788359000
C	0.611589000	1.689289000	0.393482000
C	0.456653000	2.055804000	1.739624000
C	0.705533000	2.697355000	-0.571057000
C	0.410787000	3.397157000	2.120156000
H	0.359144000	1.292060000	2.506421000
C	0.655805000	4.028981000	-0.171354000
H	0.813342000	2.467028000	-1.623968000
C	0.509570000	4.403658000	1.160551000
H	0.293985000	3.660532000	3.166562000
H	0.473842000	5.454008000	1.422700000
N	0.767603000	5.080530000	-1.204872000
O	0.959605000	4.713867000	-2.362253000
O	0.667536000	6.246150000	-0.834933000
H	0.603021000	0.230667000	-1.145179000



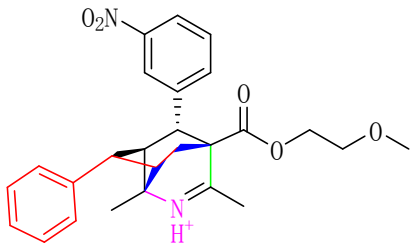
N	2.575857000	2.184773000	-1.449435000
C	0.275637000	1.869899000	-0.917862000
C	1.964706000	-0.109149000	-0.990987000
C	0.530728000	0.399593000	-0.615014000
C	2.982717000	0.962473000	-1.237509000
C	1.242247000	2.706220000	-1.337964000
C	1.174043000	4.166662000	-1.677379000
H	1.873202000	4.744056000	-1.058073000
H	0.166293000	4.548768000	-1.533144000
H	1.442710000	4.327230000	-2.729882000
C	4.438623000	0.675067000	-1.386618000
H	4.845326000	0.359806000	-0.418882000
H	4.997665000	1.547777000	-1.736573000
H	4.589736000	-0.155346000	-2.083396000
C	-1.113288000	2.400991000	-0.662638000
O	-1.677678000	1.751006000	0.361601000
C	-3.035632000	2.145930000	0.708993000
H	-3.671816000	2.057304000	-0.174545000
H	-3.032679000	3.189445000	1.033093000
O	-1.636336000	3.296740000	-1.289635000
C	3.128323000	-3.267639000	-1.432698000
H	3.899798000	-3.907266000	-1.851154000
H	2.098933000	-3.542105000	-1.656148000
C	3.432561000	-2.212743000	-0.674439000
C	2.394397000	-1.289294000	-0.049374000
C	2.780808000	-0.886092000	1.376615000
C	3.517008000	-0.306395000	4.038349000
C	2.806312000	0.433016000	1.847405000
C	3.122997000	-1.913117000	2.272470000
C	3.486855000	-1.628281000	3.586350000
C	3.173741000	0.722999000	3.165537000
H	2.515890000	1.263008000	1.207837000
H	3.106477000	-2.945149000	1.932474000
H	3.747350000	-2.440338000	4.258782000
H	3.183394000	1.754547000	3.505761000
H	3.800605000	-0.083764000	5.062498000
H	1.472269000	-1.882194000	0.016051000
H	4.475963000	-2.005763000	-0.444625000
H	1.898331000	-0.574576000	-1.990175000
H	3.281167000	2.876073000	-1.699061000
C	-3.498420000	1.221389000	1.825162000
H	-2.816942000	1.299931000	2.689543000
H	-3.485608000	0.171941000	1.486394000
O	-4.799310000	1.642098000	2.151190000

C	-5.400507000	0.851984000	3.164588000
H	-4.828462000	0.900139000	4.103529000
H	-6.399251000	1.260009000	3.331985000
H	-5.485211000	-0.200542000	2.855908000
C	-0.521048000	-0.486622000	-1.290129000
C	-0.670157000	-0.504419000	-2.685608000
C	-1.361911000	-1.284012000	-0.511584000
C	-1.628841000	-1.316491000	-3.294780000
H	-0.044806000	0.130915000	-3.308799000
C	-2.317580000	-2.078822000	-1.137354000
H	-1.300771000	-1.286055000	0.570045000
C	-2.464889000	-2.120256000	-2.520550000
H	-1.732596000	-1.315210000	-4.375140000
H	-3.221656000	-2.756667000	-2.962870000
N	-3.218371000	-2.889230000	-0.292346000
O	-3.159291000	-2.712287000	0.924868000
O	-3.967041000	-3.677962000	-0.858399000
H	0.402970000	0.281114000	0.466137000

TS2

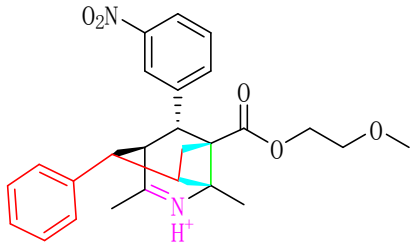
N	-1.742078000	-0.695622000	2.579533000
C	0.073059000	-1.198340000	1.210972000
C	-1.748064000	0.371220000	0.310978000
C	-0.230409000	0.039469000	0.344760000
C	-2.473711000	-0.228283000	1.525823000
C	-0.527261000	-1.309552000	2.459625000
H	0.071478000	-0.203006000	-0.675162000
C	-0.061610000	-2.097457000	3.651600000
H	-0.701201000	-1.895333000	4.517761000
H	0.971718000	-1.853295000	3.904601000
H	-0.077726000	-3.171655000	3.444766000
C	-3.837026000	0.296413000	1.895107000
H	-4.484459000	0.366953000	1.020445000
H	-3.736972000	1.310151000	2.306568000
H	-4.327512000	-0.334144000	2.644877000
C	1.334432000	-1.975289000	0.949910000
O	1.846039000	-1.695216000	-0.257195000
C	3.080297000	-2.387902000	-0.608720000
H	2.856800000	-3.444031000	-0.780326000
H	3.783067000	-2.310770000	0.222876000
O	1.802538000	-2.785052000	1.723260000
C	0.656049000	1.209773000	0.781624000
C	2.354418000	3.350874000	1.505949000
C	0.414793000	1.965819000	1.940339000

C	1.758906000	1.538578000	-0.011287000
C	2.586706000	2.591317000	0.364101000
C	1.251465000	3.025619000	2.294767000
H	-0.433881000	1.738066000	2.579064000
H	1.986831000	0.987605000	-0.914483000
H	1.044074000	3.601681000	3.191098000
H	3.022247000	4.165661000	1.757603000
N	3.754711000	2.903324000	-0.485320000
O	4.438501000	3.871350000	-0.171875000
O	3.964905000	2.167999000	-1.450485000
C	-1.573774000	-2.563443000	0.218801000
H	-1.616812000	-3.429693000	0.873503000
H	-0.816456000	-2.600605000	-0.558417000
C	-2.649160000	-1.684827000	0.112325000
C	-2.480144000	-0.453670000	-0.788961000
C	-3.746185000	0.130807000	-1.394015000
C	-6.033920000	1.181085000	-2.653067000
C	-3.820610000	1.491876000	-1.725370000
C	-4.829289000	-0.698038000	-1.720817000
C	-5.965509000	-0.177107000	-2.342729000
C	-4.955316000	2.013116000	-2.347107000
H	-2.985710000	2.154993000	-1.513048000
H	-4.785930000	-1.763579000	-1.509977000
H	-6.793047000	-0.836156000	-2.588428000
H	-4.994019000	3.069678000	-2.595598000
H	-6.917228000	1.587486000	-3.136368000
H	-1.784926000	-0.678138000	-1.609458000
H	-3.633504000	-2.023115000	0.429255000
H	-1.884968000	1.456575000	0.257912000
H	-2.241352000	-0.848012000	3.452420000
C	3.628461000	-1.728744000	-1.865642000
H	2.875977000	-1.760498000	-2.672819000
H	3.865694000	-0.669942000	-1.670568000
O	4.778799000	-2.462720000	-2.201613000
C	5.465726000	-1.937750000	-3.327214000
H	5.794412000	-0.903266000	-3.149965000
H	6.339980000	-2.571993000	-3.486226000
H	4.834789000	-1.959802000	-4.228645000



N	-1.041073000	0.994999000	2.140591000
C	0.646392000	-0.345172000	1.272624000
C	-1.420410000	-0.040227000	-0.156005000
C	0.121560000	0.022860000	-0.193825000
C	-1.933922000	0.162927000	1.321012000
C	0.246864000	0.804322000	2.154817000
H	0.482170000	-0.785876000	-0.834311000
C	1.117227000	1.685336000	2.978404000
H	1.638400000	1.095558000	3.738261000
H	0.536217000	2.482605000	3.451094000
H	1.905091000	2.118522000	2.354840000
C	-3.363378000	0.651526000	1.498047000
H	-4.049518000	0.055281000	0.896486000
H	-3.462690000	1.696913000	1.181342000
H	-3.676842000	0.568001000	2.545492000
C	2.140566000	-0.686999000	1.320599000
O	2.452803000	-1.562271000	0.358011000
C	3.828121000	-2.048171000	0.351704000
H	4.051808000	-2.501766000	1.319684000
H	4.504870000	-1.204780000	0.196762000
O	2.917378000	-0.271368000	2.150672000
C	0.708201000	1.329489000	-0.716451000
C	1.853464000	3.726136000	-1.699728000
C	1.929707000	1.321983000	-1.411812000
C	0.061948000	2.555070000	-0.530307000
C	0.643956000	3.723447000	-1.013816000
C	2.493923000	2.502787000	-1.896963000
H	2.437542000	0.377877000	-1.587014000
H	-0.896049000	2.637998000	-0.034077000
H	3.434318000	2.469631000	-2.437873000
H	2.265677000	4.658392000	-2.066210000
N	-0.060432000	5.000196000	-0.777572000
O	0.422616000	6.013104000	-1.269152000
O	-1.083663000	4.960084000	-0.091848000
C	-0.182992000	-1.579795000	1.815922000
C	-1.667266000	-1.377109000	1.489426000
C	-1.877487000	-1.530718000	-0.048867000
C	-3.265405000	-1.888110000	-0.551474000

C	-5.772247000	-2.667902000	-1.566664000
C	-4.046467000	-2.839253000	0.120287000
C	-3.754302000	-1.345761000	-1.748628000
C	-4.998167000	-1.729983000	-2.251227000
C	-5.290586000	-3.224583000	-0.381125000
H	-3.683270000	-3.296475000	1.037169000
H	-3.160796000	-0.624483000	-2.304824000
H	-5.359866000	-1.296762000	-3.179269000
H	-5.881137000	-3.961924000	0.154916000
H	-6.741006000	-2.965825000	-1.956391000
H	-1.156744000	-2.224609000	-0.502085000
H	-1.878040000	0.595007000	-0.917009000
H	-0.007056000	-1.674606000	2.893018000
H	0.195360000	-2.488966000	1.340833000
H	-2.323753000	-1.914252000	2.177923000
H	-1.444208000	1.754297000	2.687836000
C	3.937992000	-3.061951000	-0.776863000
H	3.240445000	-3.899277000	-0.605440000
H	3.662833000	-2.594357000	-1.738392000
O	5.275203000	-3.489237000	-0.772224000
C	5.554808000	-4.466102000	-1.762879000
H	6.611795000	-4.720377000	-1.665056000
H	4.949182000	-5.372604000	-1.614914000
H	5.368519000	-4.076258000	-2.774854000



N	-1.484204000	-0.908243000	1.603023000
C	0.334727000	-1.180266000	-0.172157000
C	-1.647193000	0.374017000	-0.328243000
C	-0.083371000	0.288882000	-0.516611000
C	-1.936523000	0.211594000	1.122917000
C	-0.794888000	-1.855221000	0.714826000
H	0.096509000	0.422326000	-1.587891000
C	-0.441440000	-3.113703000	1.494663000
H	-1.353254000	-3.586862000	1.878165000
H	0.238916000	-2.892347000	2.320357000
H	0.055816000	-3.841845000	0.850408000
C	-2.676091000	1.197216000	1.947557000
H	-2.151934000	2.160047000	1.916314000

H	-2.791915000	0.880499000	2.987673000
H	-3.666627000	1.355001000	1.502749000
C	1.777745000	-1.316368000	0.281248000
O	2.599432000	-1.162175000	-0.762014000
C	4.032926000	-1.206251000	-0.507513000
H	4.238375000	-0.807338000	0.486573000
H	4.475160000	-0.563815000	-1.269609000
O	2.117178000	-1.527873000	1.427764000
C	0.622479000	1.444730000	0.187885000
C	1.817734000	3.715027000	1.383485000
C	1.021136000	1.429285000	1.535724000
C	0.833955000	2.612870000	-0.554461000
C	1.418381000	3.719738000	0.050672000
C	1.614743000	2.550973000	2.121547000
H	0.914729000	0.529128000	2.130681000
H	0.557723000	2.680019000	-1.601149000
H	1.930073000	2.510669000	3.159491000
H	2.278086000	4.597030000	1.811679000
N	1.622220000	4.940424000	-0.759181000
O	2.153437000	5.898717000	-0.207808000
O	1.240193000	4.911142000	-1.927301000
C	-2.341282000	-0.842583000	-1.061089000
C	-3.843671000	-0.866293000	-0.807810000
C	-6.624704000	-0.781927000	-0.375239000
C	-4.655717000	0.031631000	-1.518683000
C	-4.450515000	-1.724456000	0.119535000
C	-5.831122000	-1.683880000	0.332709000
C	-6.032579000	0.076372000	-1.304910000
H	-4.208168000	0.691403000	-2.259477000
H	-3.857970000	-2.449217000	0.671557000
H	-6.284711000	-2.365464000	1.046538000
H	-6.643753000	0.771736000	-1.872677000
H	-7.698016000	-0.754890000	-0.213276000
H	-2.184818000	-0.669344000	-2.132610000
H	-2.029548000	1.328226000	-0.694631000
C	4.555456000	-2.632341000	-0.638918000
H	4.280815000	-3.044160000	-1.624889000
H	4.102647000	-3.274292000	0.135156000
O	5.949585000	-2.543305000	-0.484028000
C	6.604278000	-3.797576000	-0.575090000
H	6.258276000	-4.489741000	0.207476000
H	7.670894000	-3.607959000	-0.439487000
H	6.442996000	-4.265479000	-1.558057000
C	-1.548163000	-2.098845000	-0.655348000

H	-2.140987000	-3.013769000	-0.716719000
C	-0.157215000	-2.091621000	-1.332354000
H	-0.091155000	-1.679584000	-2.342347000
H	0.322195000	-3.072952000	-1.321071000
H	-1.619581000	-1.150352000	2.583215000

6. References

[1] D. Becke. *J. Chem. Phys.* **1993**, *98*, 5648.

[2] M.J.Frisch, et al., Gaussian 09, Revision A.1, Gaussian, Inc., Wallingford CT, **2009.**

[3] A. P. Scott, L. Radom. *J. Phys. Chem.* **1996**,*100*, 16502.

[4] A. V. Marenich, C. J. Cramer, D. G. Truhlar. *J. Phys. Chem. B.* **2009**, *113*, 6378.