Electronic Supplementary Information

G-quadruplex DNA selective targeting for anticancer therapy. A computational study of a novel Pt^{II} monofunctional complex activated by adaptive binding

Daniele Belletto,[a] Fortuna Ponte,[a] Nico Sanna,[b] Stefano Scoditti,[a]* and Emilia Sicilia[a]

[a] Department of Chemistry and Chemical Technologies, Università della Calabria, Arcavacata di Rende (CS), 87036, Italy;
[b] Department for Innovation in Biology Agro-Food and Forest Systems (DIBAF), University of Tuscia, Largo dell'Università snc, 01100 Viterbo, Italy.

Table of Contents

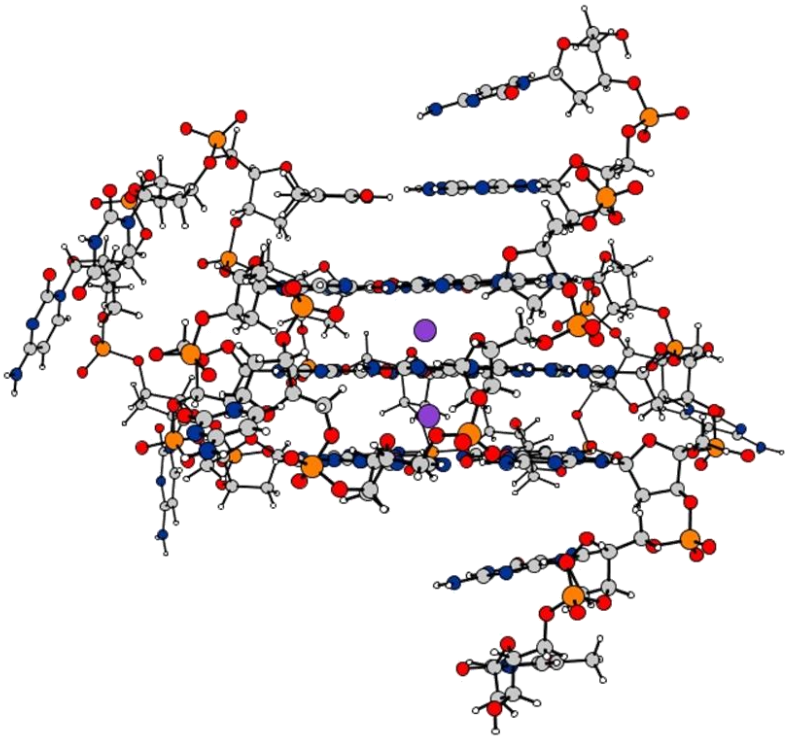
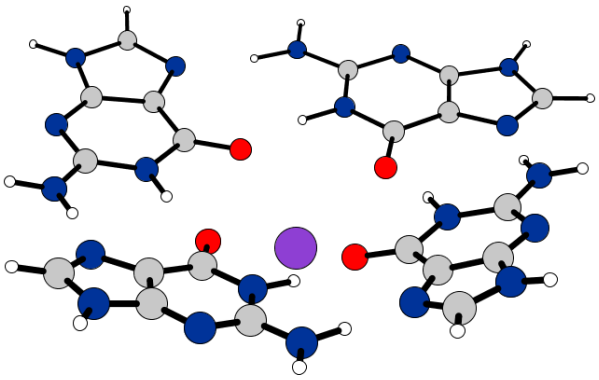
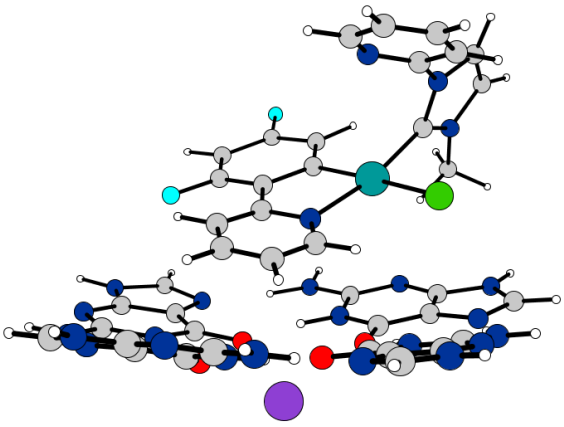


Figure S1



Orientation A



Orientation B

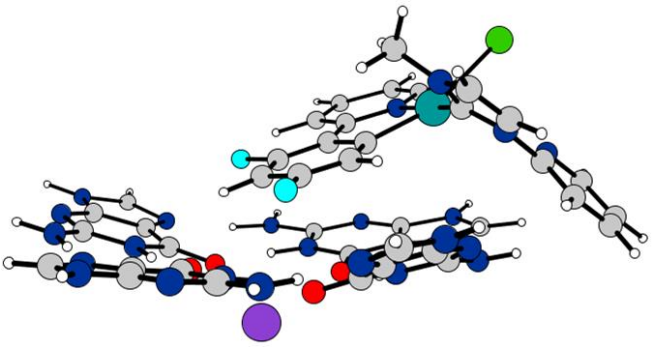


Figure S2.

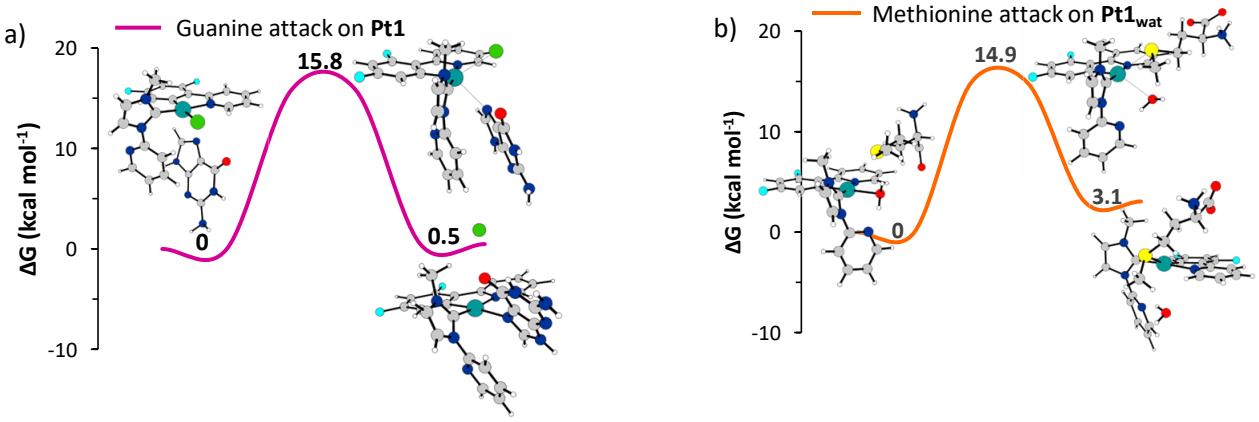
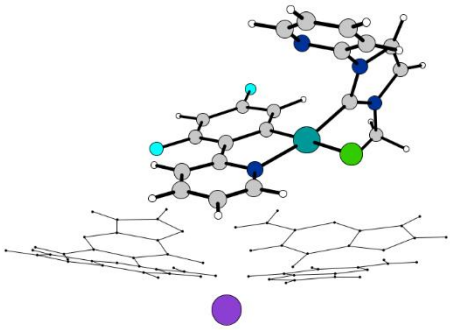

a)
Guanine attack on Pt1
ΔG (kcal mol-1)
20
10
0
-10
15.8
0
0.5
b)
Methionine attack on Pt1wat
ΔG (kcal mol-1)
20
10
0
-10
14.9
0
3.1

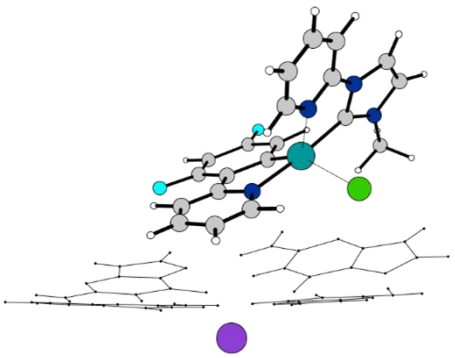
Figure S3

Orientation A

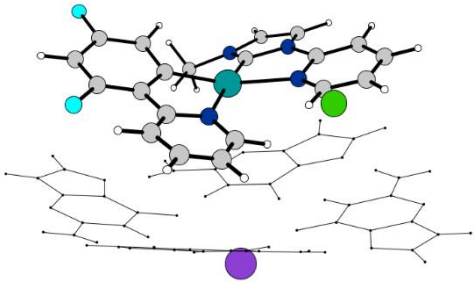
React_G-Q_Pt1(A)



TS_G-Q_Pt1(A)

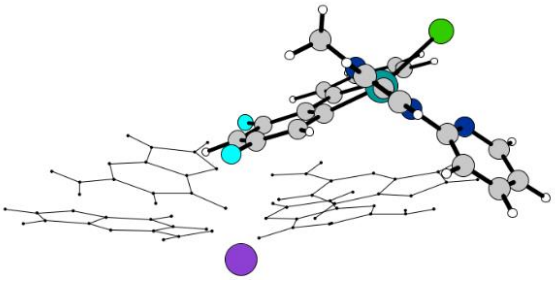


Prod_G-Q_Pt2(A)+Cl^-

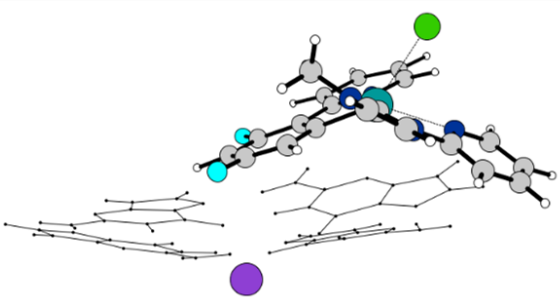


Orientation B

React_G-Q_Pt1(B)



TS_G-Q_Pt1(B)



Prod_G-Q_Pt2(B)+Cl^-

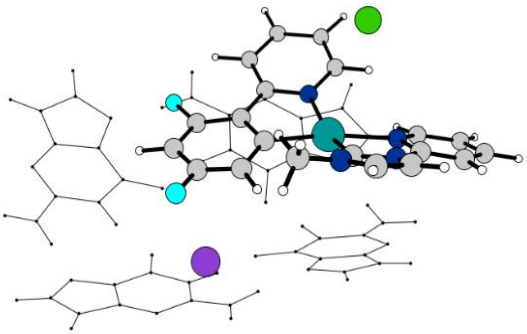
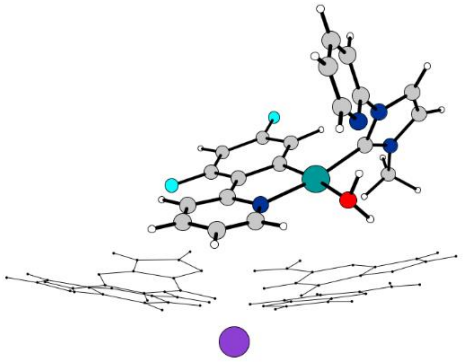


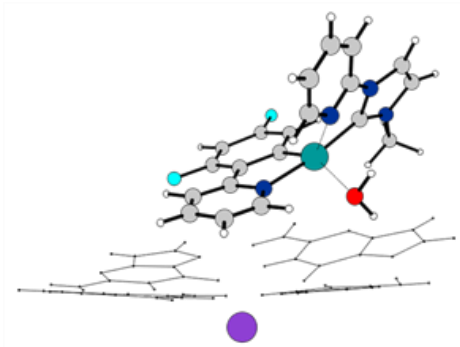
Figure S4

Orientation A

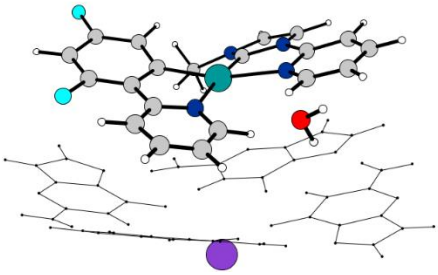
React_G-Q_Pt1$_{wat}$(A)



TS_G-Q_Pt1$_{wat}$(A)

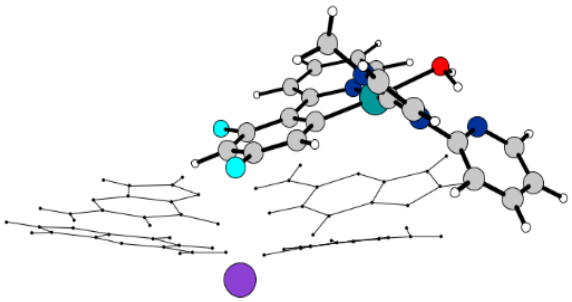


Prod_G-Q_Pt2(A)+H_2O

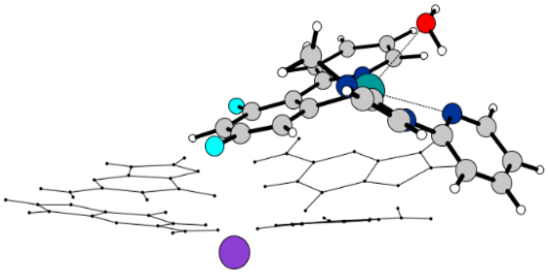


Orientation B

React_G-Q_Pt1$_{wat}$(B)



TS_G-Q_Pt1$_{wat}$(B)



Prod_G-Q_Pt2(B)+H_2O

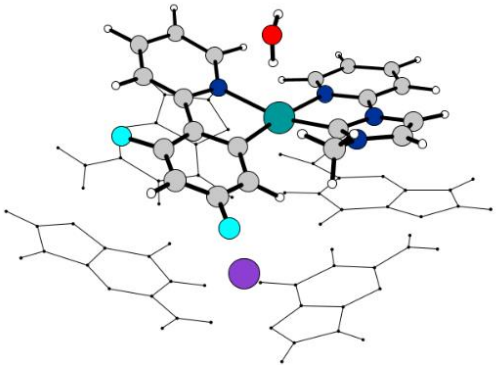


Figure S5

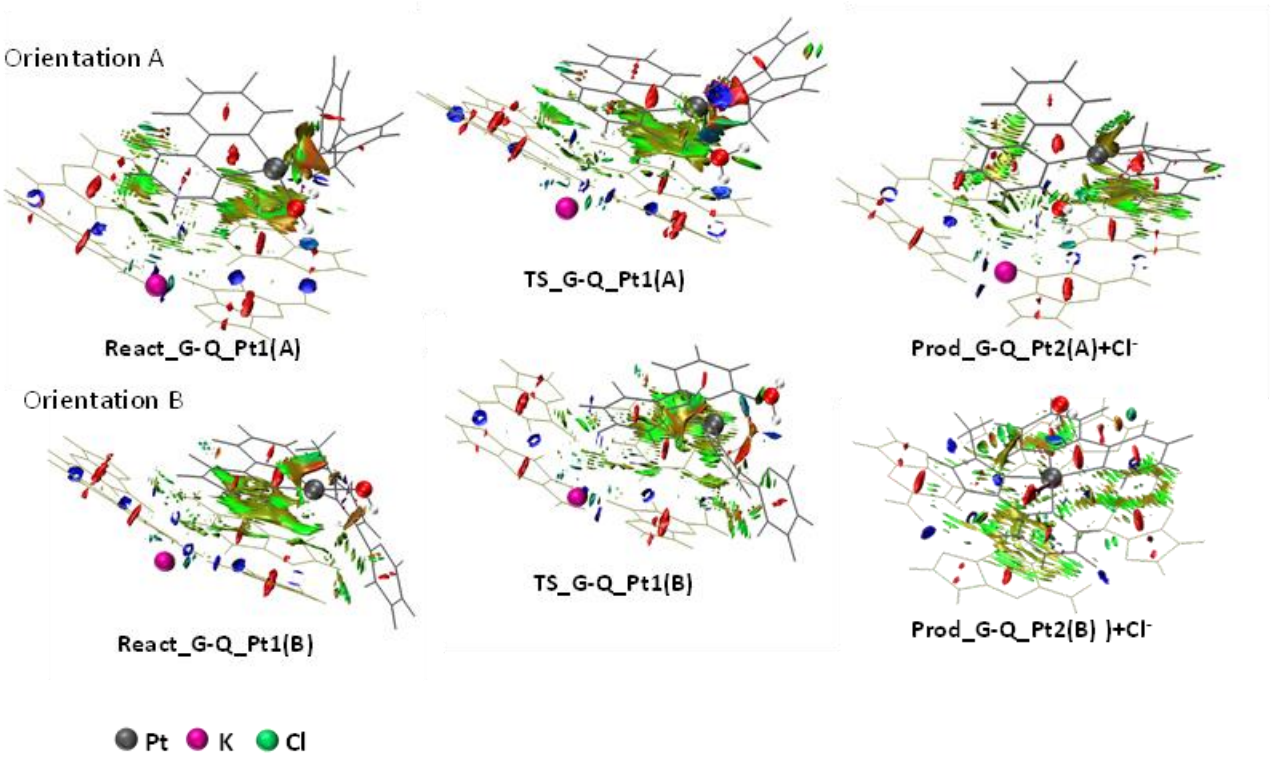
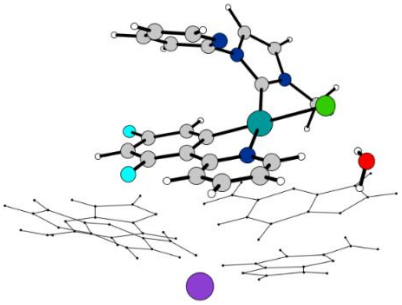

Orientation A
React_G-Q_Pt1(A)
TS_G-Q_Pt1(A)
Prod_G-Q_Pt2(A)+Cl-
Orientation B
React_G-Q_Pt1(B)
TS_G-Q_Pt1(B)
Prod_G-Q_Pt2(B))+Cl-
Pt
K
Cl

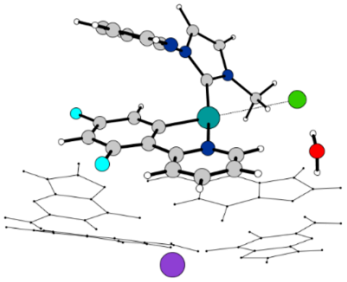
Figure S6

Orientation C

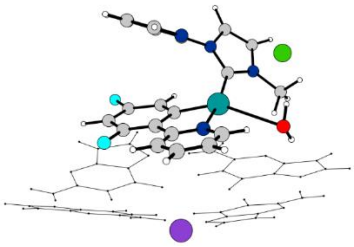
React_G-Q_Pt1(C)



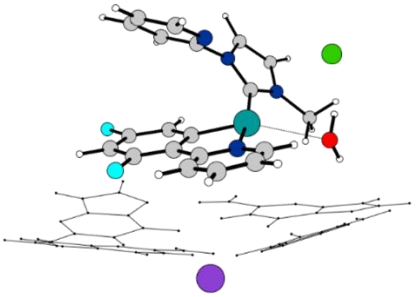
TS1_G-Q_Pt1(C)



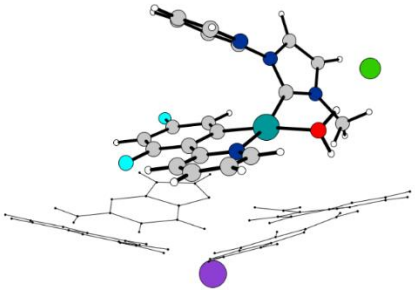
Int_G-Q_Pt1(C)



TS2_G-Q_Pt1(C)

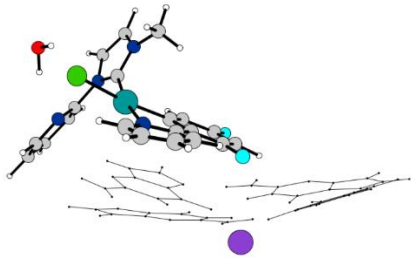


Prod_G-Q_Pt1(C)

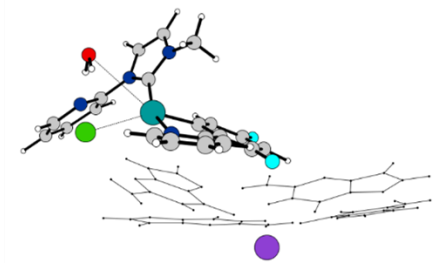


Orientation D

React_G-Q_Pt1(D)



TS_G-Q_Pt1(D)



Prod_G-Q_Pt1(C)

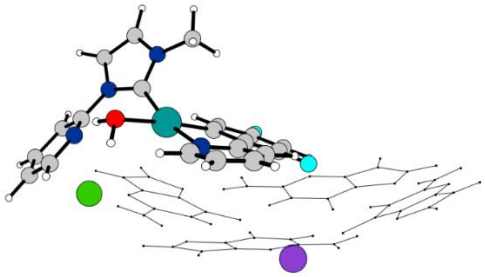


Figure S7

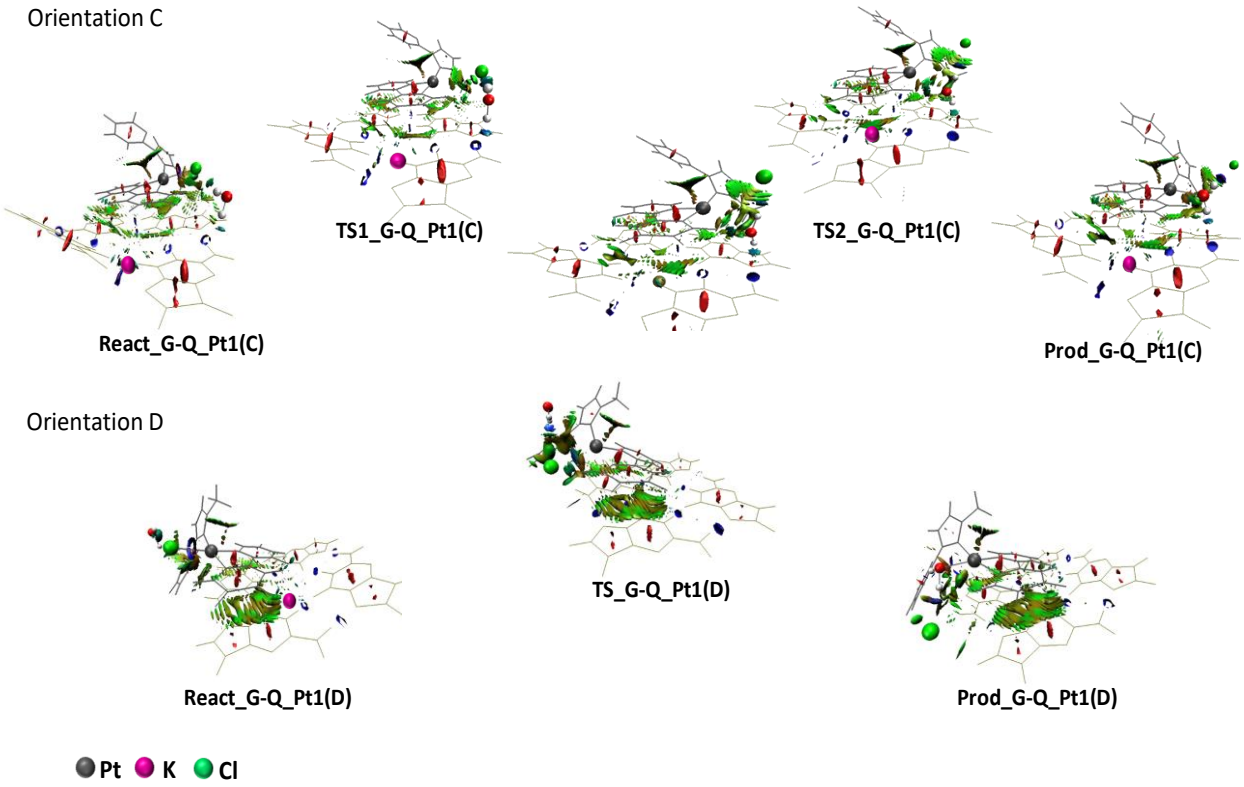

Orientation C
TS1_G-Q_Pt1(C)
TS2_G-Q_Pt1(C)
React_G-Q_Pt1(C)
Prod_G-Q_Pt1(C)
Orientation D
TS_G-Q_Pt1(D)
React_G-Q_Pt1(D)
Prod_G-Q_Pt1(D)
Pt
K
Cl

Figure S8

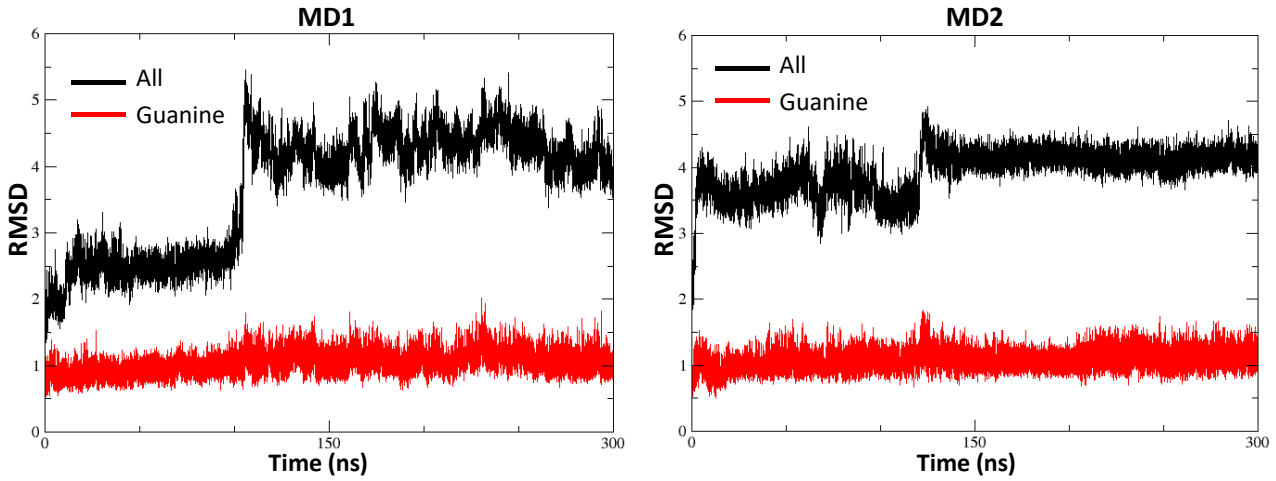


Figure S9

Side View **Top View** **Top wiew Pt2**

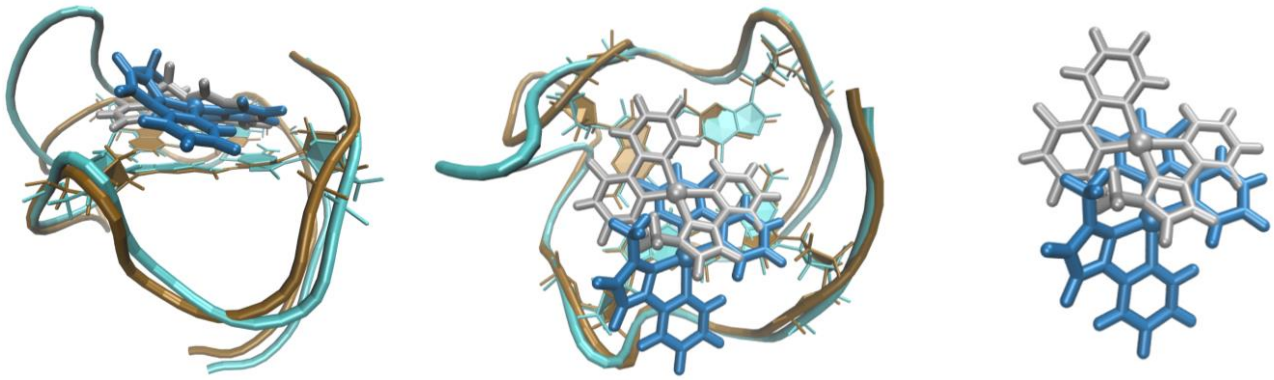


Figure S10

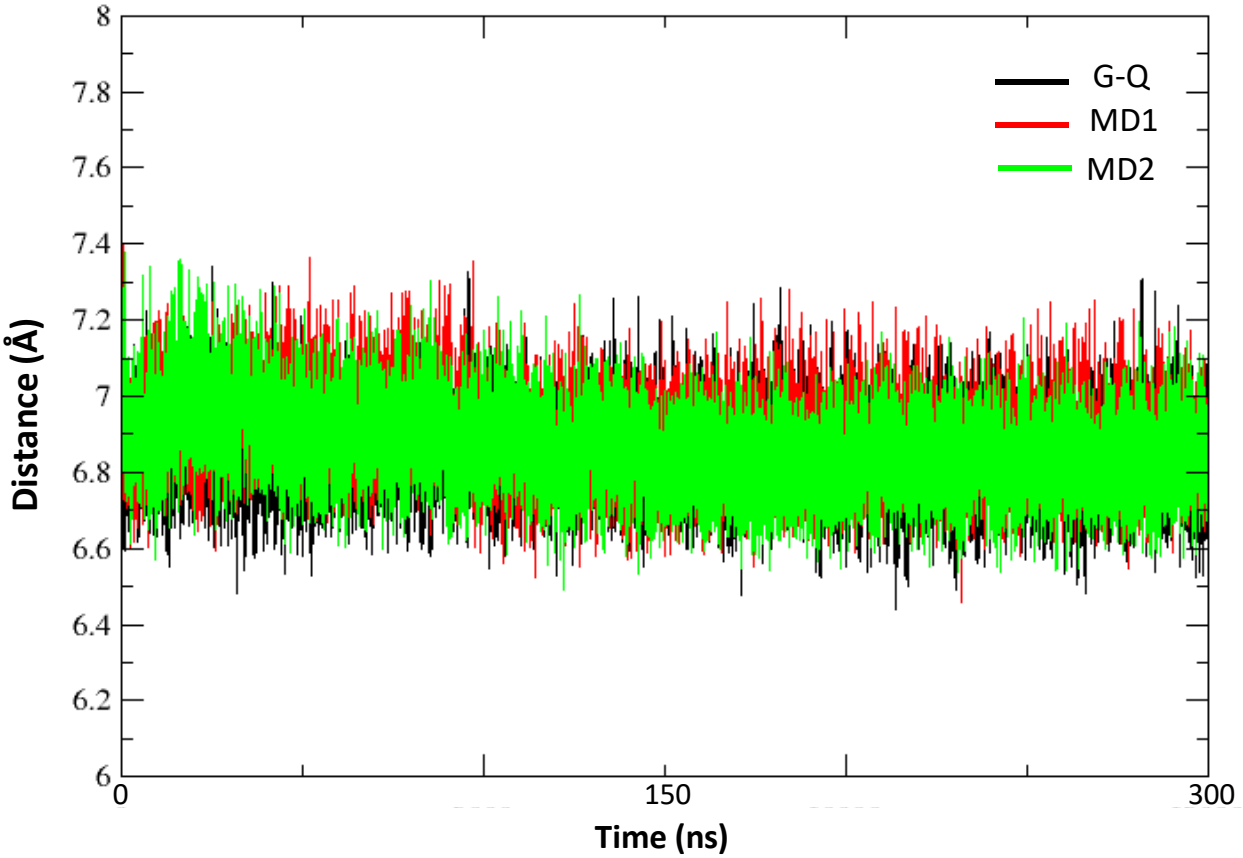


Figure S11

Table S2. Contributions to the MM-GBSA binding free energy for the G-quadruplex complex adducts. Van der Waals (VDWAALS), electrostatic (EEL), polar (EGB) and non-polar (ESURF) contributions to the solvation free energy, total gas phase (ΔG gas) and solvation (ΔG solv) binding energy, resulting MM-GBSA binding energy (ΔG TOTAL) and the estimation of the entropy term by quasi-harmonic analysis are reported. All the values are in kcal mol^{-1}.

	MD1	MD2
Energy component		
VDWAALS	-43.9	-48.6
EEL	-529.5	-553.6
EGB	542.4	568.4
ESURF	-3.2	-3.9
ΔG gas	-573.4	-602.1
ΔG solv	539.2	564.4
ΔG TOTAL	-34.2	-37.7
Quasi-harmonic entropy approximation	-9.4	-13.1
ΔG binding	**-24.8**	**-24.6**

Developed parameters for Pt2

The phenylpyridine ligand bound to the platinum centers is named as AMN. Platinum center is named as PT. The carbene-pyridine ligand to platinum is named as AMQ.

a) PT

```
  0   0   2

This is a remark line
molecule.res
PT    INT  0
CORRECT     OMIT DU   BEG
 0.0000
  1  DUMM  DU    M    0  -1  -2     0.000     .0       .0     .00000
  2  DUMM  DU    M    1   0  -1     1.449     .0       .0     .00000
  3  DUMM  DU    M    2   1   0     1.523   111.21      .0     .00000
  4  PT    M1    M    3   2   1     1.540   111.208  -180.000 -0.059578


LOOP

IMPROPER

DONE
STOP
```

b) AMN

```
  0   0   2

This is a remark line
molecule.res
AMN   INT  0
CORRECT     OMIT DU   BEG
 0.0000
  1  DUMM  DU    M    0  -1  -2     0.000     .0       .0     .00000
  2  DUMM  DU    M    1   0  -1     1.449     .0       .0     .00000
  3  DUMM  DU    M    2   1   0     1.523   111.21      .0     .00000
  4  F61   f     M    3   2   1     1.540   111.208  -180.000 -0.132729
  5  C64   ca    M    4   3   2     1.350    35.574   178.322  0.155668
  6  C63   ca    M    5   4   3     1.384   116.794  -163.040 -0.184660
  7  H61   ha    E    6   5   4     1.081   120.993    -0.830  0.177256
  8  C62   ca    M    6   5   4     1.384   117.077   177.886  0.208039
  9  F62   f     E    8   6   5     1.342   118.844  -178.668 -0.147670
 10  C61   ca    M    8   6   5     1.390   122.565     1.331 -0.149811
 11  H60   ha    E   10   8   6     1.079   117.928  -177.675  0.140883
 12  C66   Y3    M   10   8   6     1.393   119.843     0.614 -0.158412
 13  C65   ca    M   12  10   8     1.422   119.144    -2.772  0.010746
 14  C67   ca    M   13  12  10     1.462   116.446  -173.578  0.112614
 15  C68   ca    M   14  13  12     1.400   126.816  -172.071 -0.063229
 16  H62   ha    E   15  14  13     1.077   119.576    -1.346  0.131453
 17  C69   ca    M   15  14  13     1.387   119.894   177.778 -0.119015
 18  H63   ha    E   17  15  14     1.084   119.863  -179.848  0.166841
 19  C70   ca    M   17  15  14     1.392   119.642    -0.921 -0.106136
 20  H64   ha    E   19  17  15     1.081   121.928  -178.526  0.149840
 21  C71   ca    M   19  17  15     1.384   118.055     1.036 -0.052221
 22  H65   h4    E   21  19  17     1.081   120.887  -177.792  0.116524
 23  N61   Y1    M   21  19  17     1.343   122.839     0.734  0.002217


LOOP
 C65  C64
 N61  C67
```

```
IMPROPER
 C65  C63  C64  F61
 C64  C62  C63  H61
 C63  C61  C62  F62
 C66  C62  C61  H60
 C66  C67  C65  C64
 C65  C68  C67  N61
 C67  C69  C68  H62
 C68  C70  C69  H63
 C69  C71  C70  H64
 C70  H65  C71  N61

DONE
STOP
```

c) AMQ

```
  0   0   2

This is a remark line
molecule.res
AMQ   INT  0
CORRECT     OMIT DU   BEG
  0.0000
   1  DUMM  DU    M    0  -1  -2     0.000      .0       .0      .00000
   2  DUMM  DU    M    1   0  -1     1.449      .0       .0      .00000
   3  DUMM  DU    M    2   1   0     1.523   111.21      .0      .00000
   4  N62   Y2    M    3   2   1     1.540   111.208  -180.000 -0.044813
   5  C73   ca    M    4   3   2     1.344    77.936    20.806 -0.027419
   6  H71   h4    E    5   4   3     1.080   116.142  -163.377  0.147205
   7  C74   ca    M    5   4   3     1.386   122.789    17.246 -0.113392
   8  H72   ha    E    7   5   4     1.082   119.878  -179.269  0.153929
   9  C75   ca    M    7   5   4     1.392   118.684     1.211 -0.065698
  10  H73   ha    E    9   7   5     1.083   120.745   179.539  0.165506
  11  C76   ca    M    9   7   5     1.390   119.303     0.616 -0.144187
  12  H74   ha    E   11   9   7     1.081   121.114   177.557  0.150468
  13  C77   ca    M   11   9   7     1.389   118.100    -1.070  0.182166
  14  N64   nh    M   13  11   9     1.405   123.221   178.976  0.106369
  15  C72   Y4    M   14  13  11     1.378   119.416  -170.049 -0.078770
  16  N63   nh    M   15  14  13     1.349   104.643  -170.879  0.107616
  17  C78   c3    3   16  15  14     1.466   126.591   170.879 -0.096800
  18  H66   h1    E   17  16  15     1.085   108.877    -8.238  0.093458
  19  H67   h1    E   17  16  15     1.090   108.468  -127.321  0.093458
  20  H68   h1    E   17  16  15     1.090   110.531   112.526  0.093458
  21  C79   c2    M   16  15  14     1.395   110.598    -1.605 -0.128416
  22  H69   h4    E   21  16  15     1.076   121.758  -179.577  0.195685
  23  C80   c2    M   21  16  15     1.349   107.803     1.247 -0.201846
  24  H70   h4    E   23  21  16     1.075   130.578   178.525  0.213404


LOOP
 C77  N62
 C80  N64

IMPROPER
 C74  H71  C73  N62
 C73  C75  C74  H72
 C76  C74  C75  H73
 C77  C75  C76  H74
 C76  N62  C77  N64
 C72  C80  N64  C77
 C80  H69  C79  N63
 C79  H70  C80  N64
```

DONE
STOP

d) frcmod file for Pt2

```
REMARK GOES HERE, THIS FILE IS GENERATED BY MCPB.PY
MASS
M1 195.08                  Pt ion
Y3 12.01       0.360       Sp2 C in pure aromatic systems
Y1 14.01       0.530       Sp2 N in pure aromatic systems
Y2 14.01       0.530       Sp2 N in pure aromatic systems
Y4 12.01       0.360       Sp2 carbons in non-pure aromatic systems

BOND
M1-Y1  104.9    2.1188     Created by Seminario method using MCPB.py
M1-Y2   32.6    2.2399     Created by Seminario method using MCPB.py
M1-Y3  147.3    2.0099     Created by Seminario method using MCPB.py
M1-Y4  132.3    1.9946     Created by Seminario method using MCPB.py
Y2-ca  488.0    1.3390       SOURCE3_SOURCE5    6806                  0.0055
Y4-nh  435.2    1.3735       SOURCE3_SOURCE5     976                  0.0106
ca-Y1  488.0    1.3390       SOURCE3_SOURCE5    6806                  0.0055
ca-Y3  461.1    1.3984       SOURCE1_SOURCE5  121206                  0.0061

ANGL
M1-Y1-ca   140.24    119.70    Created by Seminario method using MCPB.py
M1-Y2-ca   144.15    120.06    Created by Seminario method using MCPB.py
M1-Y3-ca   193.78    120.02    Created by Seminario method using MCPB.py
M1-Y4-nh   200.53    127.25    Created by Seminario method using MCPB.py
Y1-M1-Y3   206.93     79.61    Created by Seminario method using MCPB.py
Y2-M1-Y1   154.47    104.81    Created by Seminario method using MCPB.py
Y2-M1-Y3    86.22    161.14    Created by Seminario method using MCPB.py
Y4-M1-Y1   115.58    167.30    Created by Seminario method using MCPB.py
Y4-M1-Y2   134.85     76.73    Created by Seminario method using MCPB.py
Y4-M1-Y3   168.63    103.08    Created by Seminario method using MCPB.py
Y2-ca-ca   68.83     122.94       SOURCE3_SOURCE5     5507    1.1495
Y2-ca-h4   51.88     116.03       SOURCE3_SOURCE5     2217    0.2861
Y2-ca-nh   72.66     116.94       SOURCE4_SOURCE5     2042    0.7868
Y3-ca-ca   66.62     120.02       SOURCE3_SOURCE5   108055    0.7701
Y4-nh-c2   63.86     126.35          CORR_SOURCE5       14    0.8394
Y4-nh-c3   63.70     119.72          CORR_SOURCE5      638    2.4802
Y4-nh-ca   63.03     129.80          CORR_SOURCE5       49    1.2126
ca-Y1-ca   68.35     117.22       SOURCE3_SOURCE5     3343    1.0306
ca-Y2-ca   68.35     117.22       SOURCE3_SOURCE5     3343    1.0306
ca-Y3-ca   66.62     120.02       SOURCE3_SOURCE5   108055    0.7701
ca-ca-Y1   68.83     122.94       SOURCE3_SOURCE5     5507    1.1495
h4-ca-Y1   51.88     116.03       SOURCE3_SOURCE5     2217    0.2861
ha-ca-Y3   48.18     119.88       SOURCE3_SOURCE5   126779    0.4424
nh-Y4-nh   72.43     115.96             SOURCE3        1

DIHE
X -Y2-ca-X    2      9.6     180.0   2.0     same as X-CA-NC-X
X -Y3-ca-X    4     14.5     180.0   2.0     intrpol.bsd.on C6H6
X -Y4-nh-X    4      4.2     180.0   2.0     same as X-ca-nh-X
X -ca-Y1-X    2      9.6     180.0   2.0     same as X-CA-NC-X
M1-Y1-ca-ca   3      0.00      0.00  3.0    Treat as zero by MCPB.py
M1-Y1-ca-h4   3      0.00      0.00  3.0    Treat as zero by MCPB.py
M1-Y2-ca-ca   3      0.00      0.00  3.0    Treat as zero by MCPB.py
M1-Y2-ca-h4   3      0.00      0.00  3.0    Treat as zero by MCPB.py
M1-Y2-ca-nh   3      0.00      0.00  3.0    Treat as zero by MCPB.py
M1-Y3-ca-ca   3      0.00      0.00  3.0    Treat as zero by MCPB.py
M1-Y3-ca-ha   3      0.00      0.00  3.0    Treat as zero by MCPB.py
```

M1-Y4-nh-c2 3 0.00 0.00 3.0 Treat as zero by MCPB.py
M1-Y4-nh-c3 3 0.00 0.00 3.0 Treat as zero by MCPB.py
M1-Y4-nh-ca 3 0.00 0.00 3.0 Treat as zero by MCPB.py
Y1-M1-Y3-ca 3 0.00 0.00 3.0 Treat as zero by MCPB.py
Y2-M1-Y1-ca 3 0.00 0.00 3.0 Treat as zero by MCPB.py
Y2-M1-Y3-ca 3 0.00 0.00 3.0 Treat as zero by MCPB.py
Y4-M1-Y1-ca 3 0.00 0.00 3.0 Treat as zero by MCPB.py
Y4-M1-Y2-ca 3 0.00 0.00 3.0 Treat as zero by MCPB.py
Y4-M1-Y3-ca 3 0.00 0.00 3.0 Treat as zero by MCPB.py
ca-Y1-M1-Y3 3 0.00 0.00 3.0 Treat as zero by MCPB.py
ca-Y2-M1-Y1 3 0.00 0.00 3.0 Treat as zero by MCPB.py
ca-Y2-M1-Y3 3 0.00 0.00 3.0 Treat as zero by MCPB.py
nh-Y4-M1-Y1 3 0.00 0.00 3.0 Treat as zero by MCPB.py
nh-Y4-M1-Y2 3 0.00 0.00 3.0 Treat as zero by MCPB.py
nh-Y4-M1-Y3 3 0.00 0.00 3.0 Treat as zero by MCPB.py

IMPR
Y1-ca-ca-ca 1.1 180.0 2.0 Using the default value
Y4-c2-nh-c3 1.1 180.0 2.0 Using the default value
Y4-c2-nh-ca 1.1 180.0 2.0 Using the default value
Y2-ca-ca-nh 1.1 180.0 2.0 Using the default value
Y3-ca-ca-ca 1.1 180.0 2.0 Using the default value
Y2-ca-ca-h4 1.1 180.0 2.0 Same as X -X -ca-ha, penalty score= 44.3 (use general term))
Y1-ca-ca-h4 1.1 180.0 2.0 Same as X -X -ca-ha, penalty score= 44.3 (use general term))
Y3-ca-ca-ha 1.1 180.0 2.0 Using general improper torsional angle X- X-ca-ha, penalty score= 6.0)

NONB
M1 1.2660 0.0030764200 CM set for Pt2+ ion in TIP3P water from Li et al. JCTC, 2013, 9, 2733
Y3 1.9080 0.0860 OPLS
Y1 1.8240 0.1700 OPLS
Y2 1.8240 0.1700 OPLS
Y4 1.9080 0.0860 OPLS