Supporting Information

Aryl Ethynyl Anthraquinones: a Useful Platform for Targeting Telomeric G-quadruplex Structures

Claudia Percivalle,[a] Claudia Sissi,[b] Maria Laura Greco,[b] Caterina Musetti,[b] Angelica Mariani,[a] Anna Artese,[c] Giosuè Costa,[c] Maria Lucia Perrore,[a] Stefano Alcaro,[c] and Mauro Freccero*[a]

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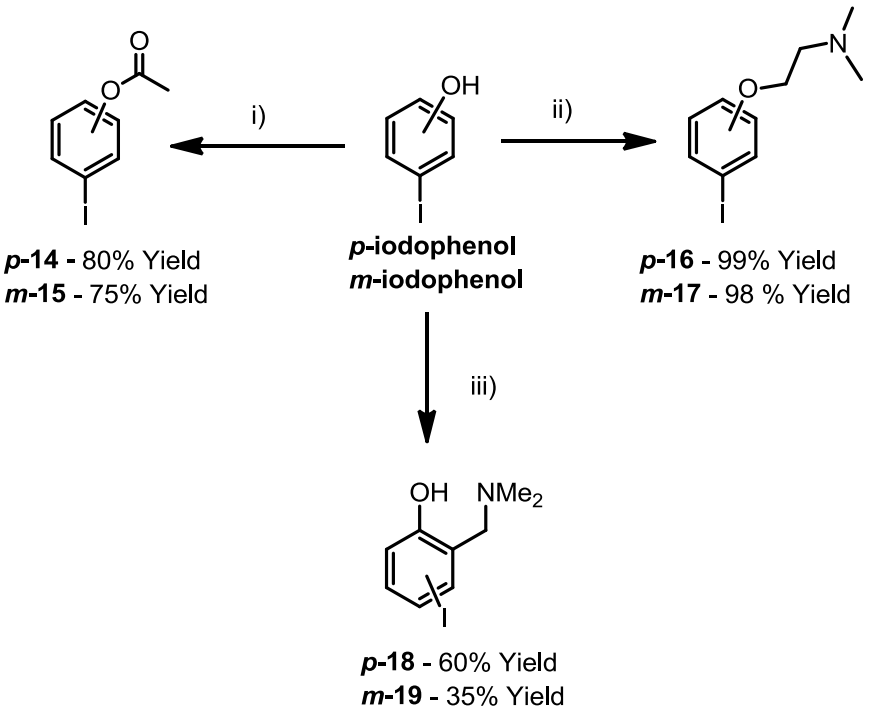
1.0 Experimental details, Procedures and Materials

All the chemicals were purchased from Sigma Aldrich, unless otherwise stated, and used without further purification. ^{1}H, ^{13}C NMR spectra were recorded with a 300 MHz NMR BRUKER AVANCE spectrometer, and the chemical shifts are reported relative to TMS. The structure of new compounds were deduced from the results of ^{1}H, and ^{13}C NMR. Elemental analyses were made on a Carlo Erba CNH analyzer, model 1106. 2-ethanethiol was freshly distilled before use.

Reaction products were purified by column chromatography on Silica gel 60 (79-230 mesh) using, MPLC (Isolera ONE Biotage) or by HPLC (Waters Delta 600, 1489 UV/VIS detector and Fraction Collector III) unless otherwise stated. The analytical HPLC analysis was performed using a X-select CSH Phenyl-Hexyl 3.5 μm (150 x 4.6 mm) (Waters) column; while for the preparative purification of compounds a X-select CSH Prep Phenyl-Hexyl 5 μm (150 x 30 mm) (Waters) column was used. The acetylation of *p*- and *m*-phenol was performed under microwave irradiation, using the following Microwave oven: Discovery System CEM, Model: 908010, S.N.: DU8797.

Synthetic procedures for the synthesis of 14-19



Scheme S1: i) Ac_2O/I_2, μW, closed vessel, 10 min, 300 Watt; ii) 2-chloro-N,N-dimethylethylamine hydrochloride, acetone, K_2CO_3, reflux 8h; vii) EtOH abs, p-CH_2O, $NHMe_2$ in EtOH (33%), reflux, 4h

General procedure for the synthesis of acetyl *p*- and *m*-phenol 14 and 15

The corresponding (para or meta) iodophenol (1.5 g, 6.82 mmol) was put in a microwave vessel and dissolved in 4 ml of Ac_2O. I_2 was added (0.17g, 0.68 mmol) and the mixture was irradiated 10 min at 350 W, T max 130°C in a closed vessel modality.

The reaction was then quenched in ice and Na_2CO_3 was added to neutralize the acidity of AcOH that was formed during the esterification reaction. The aqueous phase was extract with DCM (3x50 ml); the organic layers were recombined and washed with a saturated solution of $NaHCO_3$ (2x50 ml). The dichloromethane solution was then dried over Na_2SO_4 and the solvent removed under reduced pressure to give the crude product.

The acetylphenols were purified by flash chromatography (eluent cyclohexane/ethyl acetate) to afford the correspondent aryl-iodie **14** and **15**.

***p*-acetylphenol. 14**

Yellow oil. Yield 80%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.88 (d, 2H, J = 8.8 Hz), 7.70 (d, 2H, J = 8.8 Hz).

The data are in agreement with those previously reported in literature.[1]

meta-acetylphenol. 15

Yellow oil. Yield 75%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 7.10-7.17 (m, 2H), 7.49 (s, 1H), 7.59-7.57 (m, 1H).

The data are in agreement with those previously reported in literature.[2]

General procedure for the synthesis of 16 and 17

The correspondent (para or meta) iodophenol (1.0 g, 4.6 mmol) was dissolved in acetone 150 ml and 2-chloro-N,N,dimethylethylamine (2.0 g, 13.8 mmol) and K_2CO_3 (3.4 g, 25mmol) were added under stirring.

The mixture was heated to reflux for 8 h. After this period the solution was cooled to room temperature and poured in 100 ml of water. Acetone was removed by evaporation and the aqueous phase was extract with DCM (3x100 ml). The organic phases were collected, dried over Na_2SO_4 and the solvent removed under reduced pressure to give the crude product as colorless oil. The reaction was nearly quantitative and the small traces of reactant were eliminated during the extraction process. For this reason the products did not need any further purification and were used directly for the next synthetic step.

1-(2-(N,N-dimethyl)ethoxy)-4-iodobenzene. 16

Yellow oil. Yield 99 %

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 6H), 2.71 (t, 2H, J =5.7 Hz), 4.03 (t, 2H, J =5.7 Hz), 6.70 (d, 2H, J = 8.9 Hz), 7.41 (d, 2H, J = 8.9 Hz).

The data are in agreement with those previously reported in literature.[3]

1-(2-(N,N-dimethyl)ethoxy)-3-iodobenzene. 17

Yellow oil. Yield 98 %

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 6H), 2.74 (t, 2H, J = 5.7 Hz), 4.04 (t, 2H, J = 5.7 Hz), 6.89 (m, 1H), 7.00 (m, 1H), 7.28 (m, 2H).

The data are in agreement with those previously reported in literature.[4]

Synthesis of 2-((dimethylamino)methyl)-4-iodophenol. 18

p-iodophenol (3g, 13.6 mmol) was dissolved in absolute ethanol (200 ml) and under stirring paraformaldehyde (9g, 0.30 mol) and dimethylamine (33%) in ethanol (17.8 ml, 0.10 mol) were added. The mixture was then heated to reflux under a nitrogen atmosphere for 3-4h.

The solution was cooled to room temperature and the solvent removed by evaporation. The solid residues was dissolved in DCM (150 ml) and this solution was washed with an acidic aqueous solution (HCl 1%, 3x150 ml) to extract selectively the Mannich base product. The aqueous phases were collected and basified with solid $NaHCO_3$ until the solution stop bubbling after the addition of bicarbonate. (final pH of the aqueous solution c.a 7.5-8). The aqueous phase was now extracted with DCM (3x300 ml), the organic layers collected and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford **18** as colorless oil. The product was used without further purification for the next step. Yield: 60%.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 6H), 3.57 (s, 2H), 6.59 (d, 1H, J = 8.5 Hz), 7.23 (d, 1H, J = 2.2 Hz), 7.41 (dd, 1H, J = 2.2, 8.5 Hz), 10.05 (s, 1H).

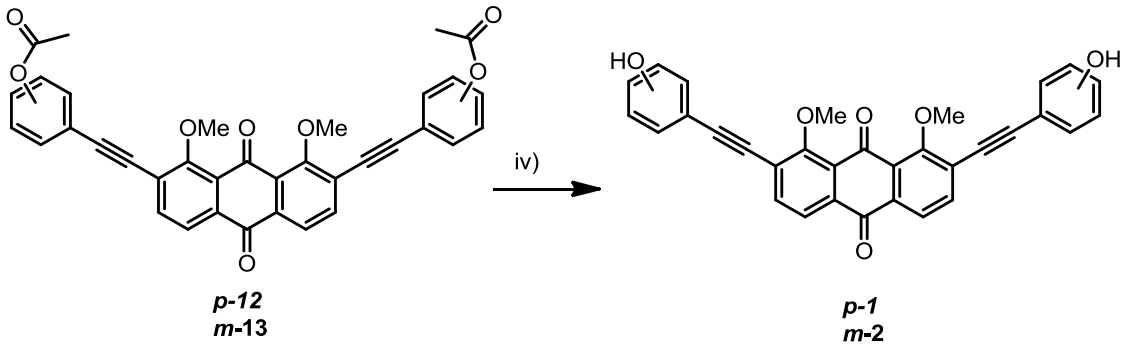
Synthesis of 2-((dimethylamino)methyl)-5-iodophenol. 19

m-iodophenol (3g, 13.6 mmol) was dissolved in absolute ethanol (200 ml) and paraformaldehyde (9g, 0.30 mol) and dimethylamine (33%) in ethanol (17.8 ml, 0.10 mol) were added under stirring. The mixture was heated to reflux under a nitrogen atmosphere for 3-4 h.

The solution was cooled to room temperature and the solvent was removed by evaporation.

The product was purified by flash chromatography (cyclohexane/ethyl acetate both with 3% of TEA) to afford **19** as colorless oil. Yield 35 %.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 6H), 2.82 (s, 2H), 6.67 (d, 1H, J =7.8 Hz), 7.11 (dd, 1H, J=7.8, 1.7 Hz), 7.20 (d, 1H, J = 1.7 Hz).



***p*-12**
***m*-13**

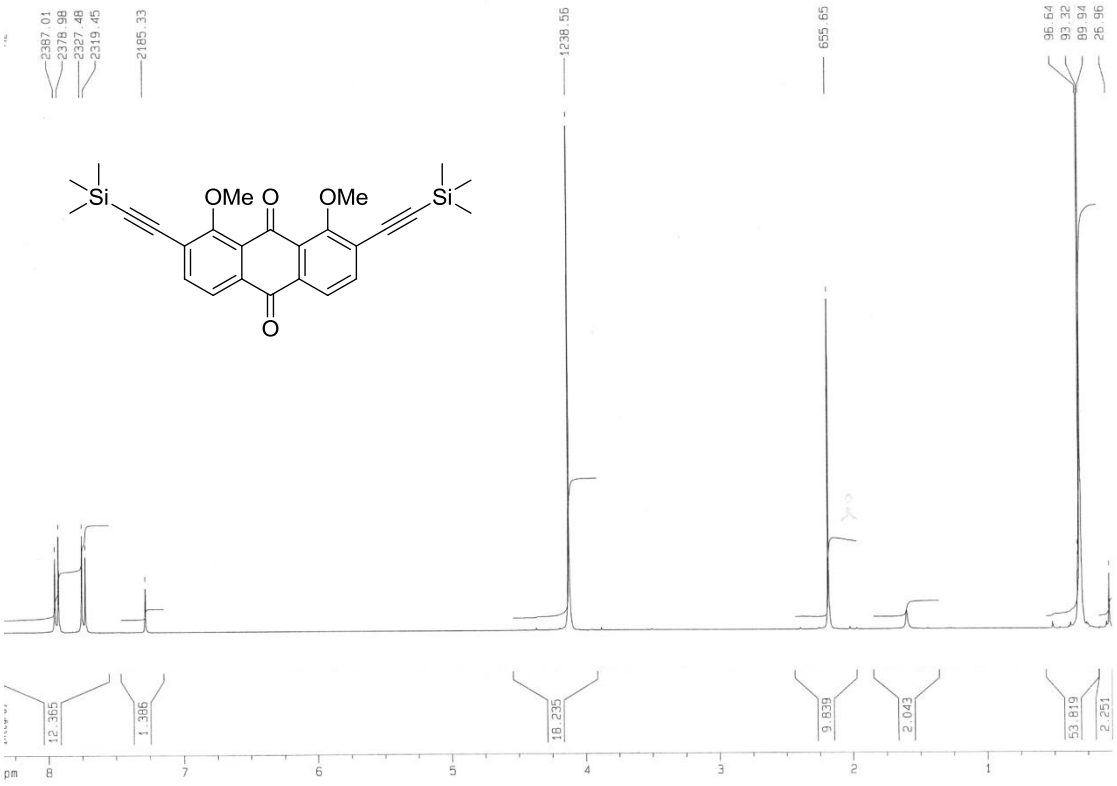
***p*-1**
***m*-2**

Scheme S2: Deprotection of **12** and **13** to afford the final products **1** and **2**. iv) MeOH/H_2O 4:1, K_2CO_3, 5h (**12**), 20h (13), rt, N_2. Yields: 15% (**1**), 10% (**2**).

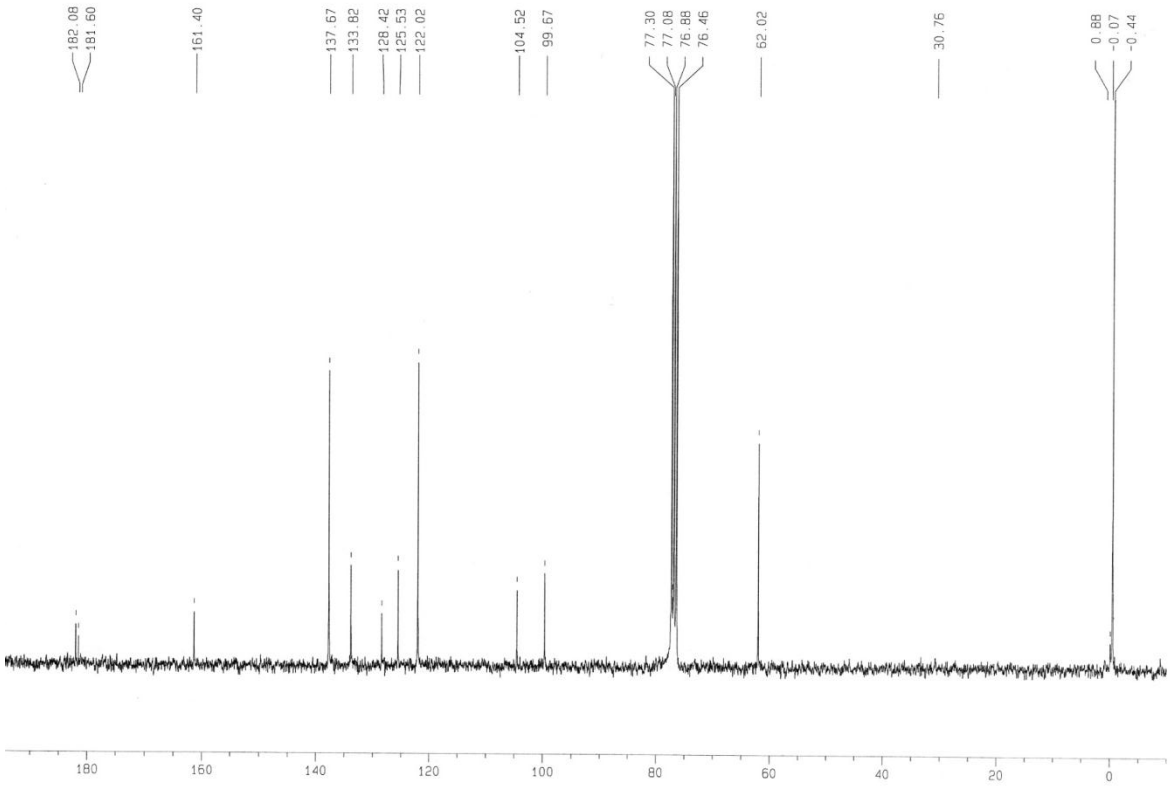
2.0 NMR Spectra

1,8-dimethoxy-2,7-bis((trimethylsilyl)ethynyl)anthracene-9,10-dione. 10

^{1}H-NMR in $CDCl_3$

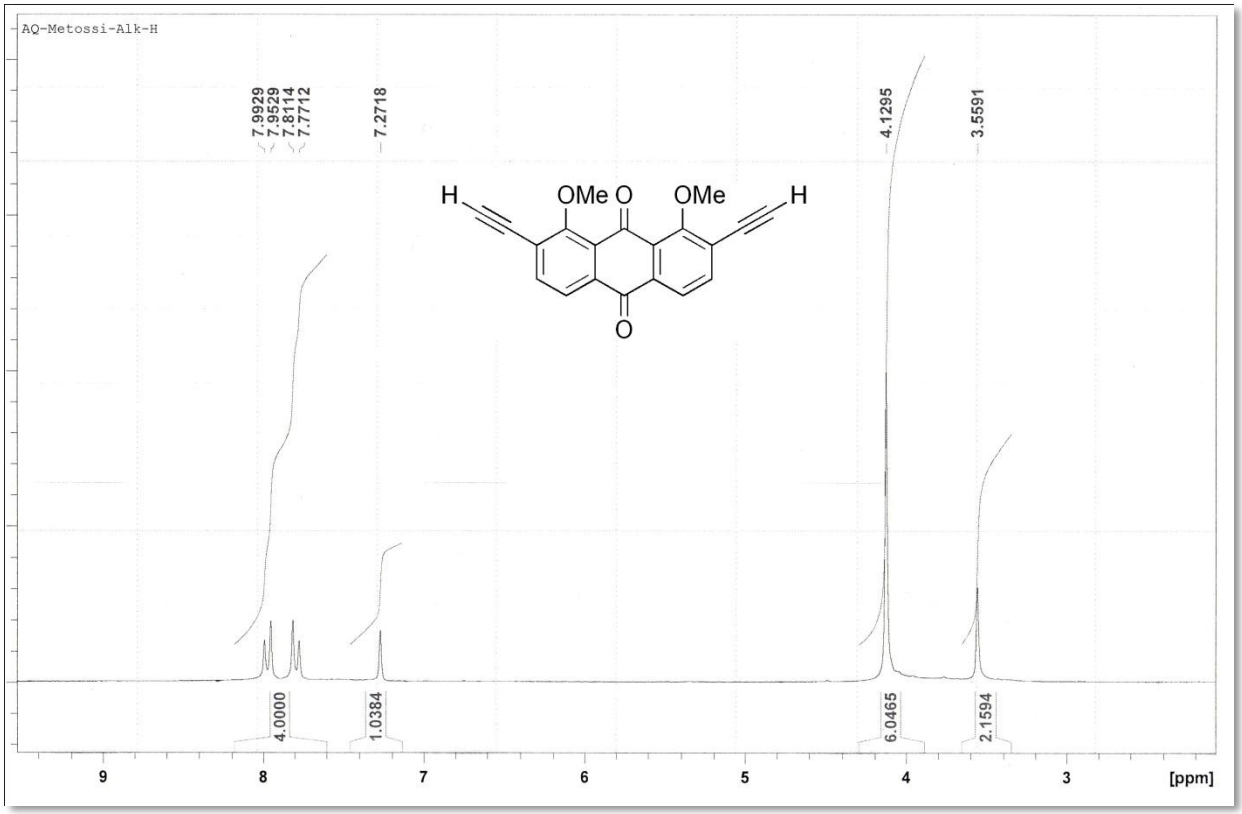


^{13}C-NMR in $CDCl_3$

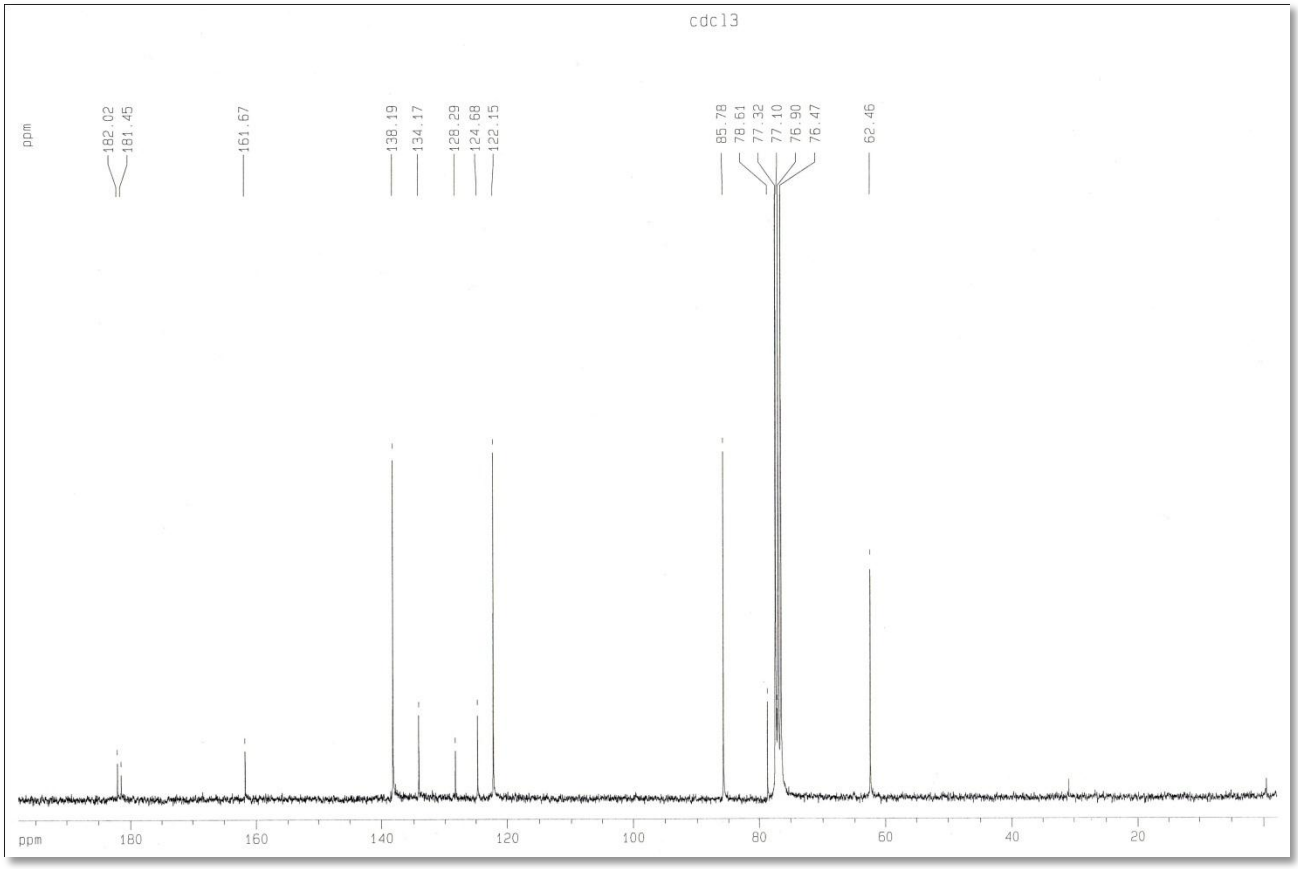


2,7-diethynyl-1,8-dimethoxyanthracene-9,10-dione. 11

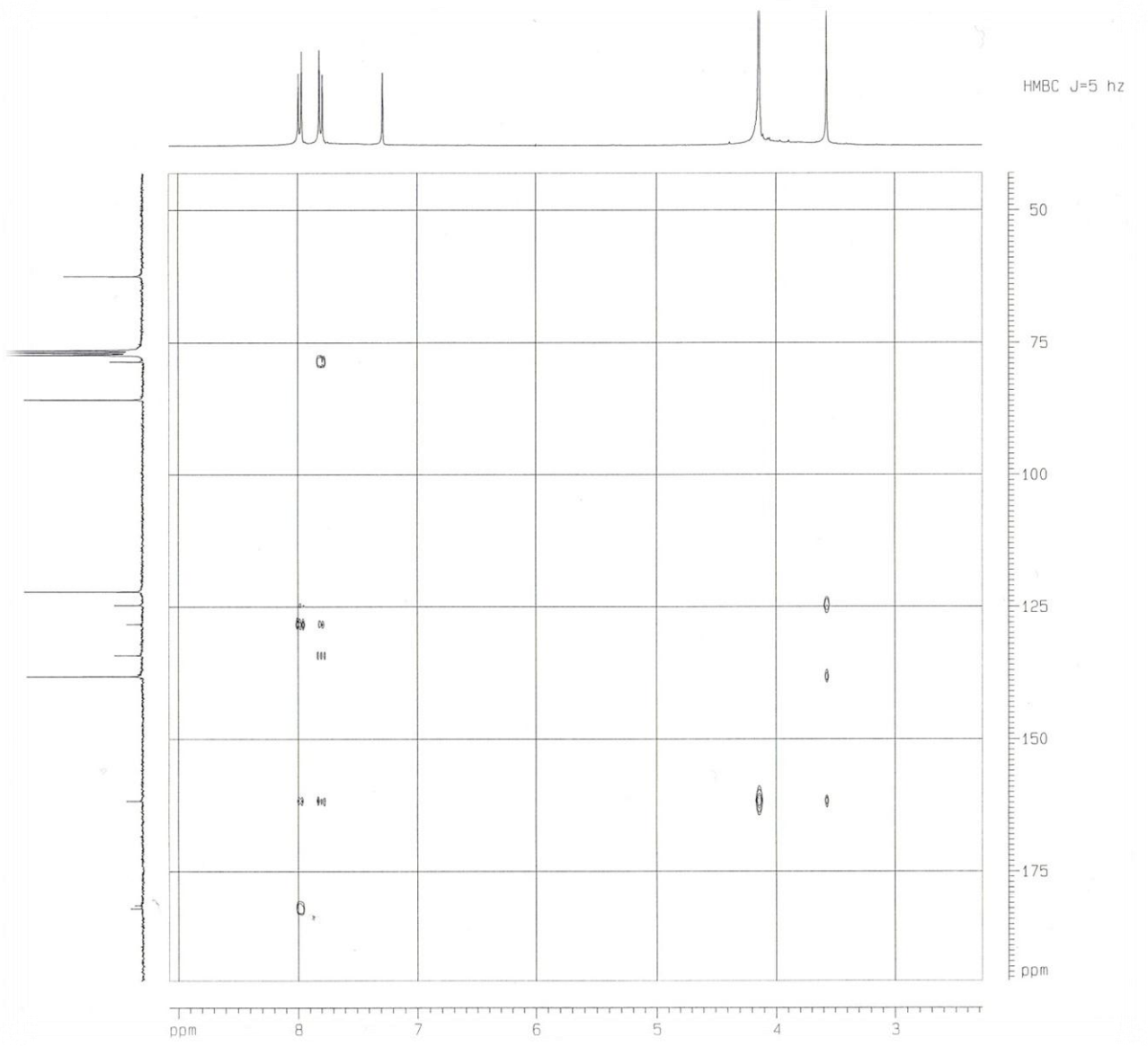
^{1}H-NMR in $CDCl_3$



^{13}C-NMR in $CDCl_3$

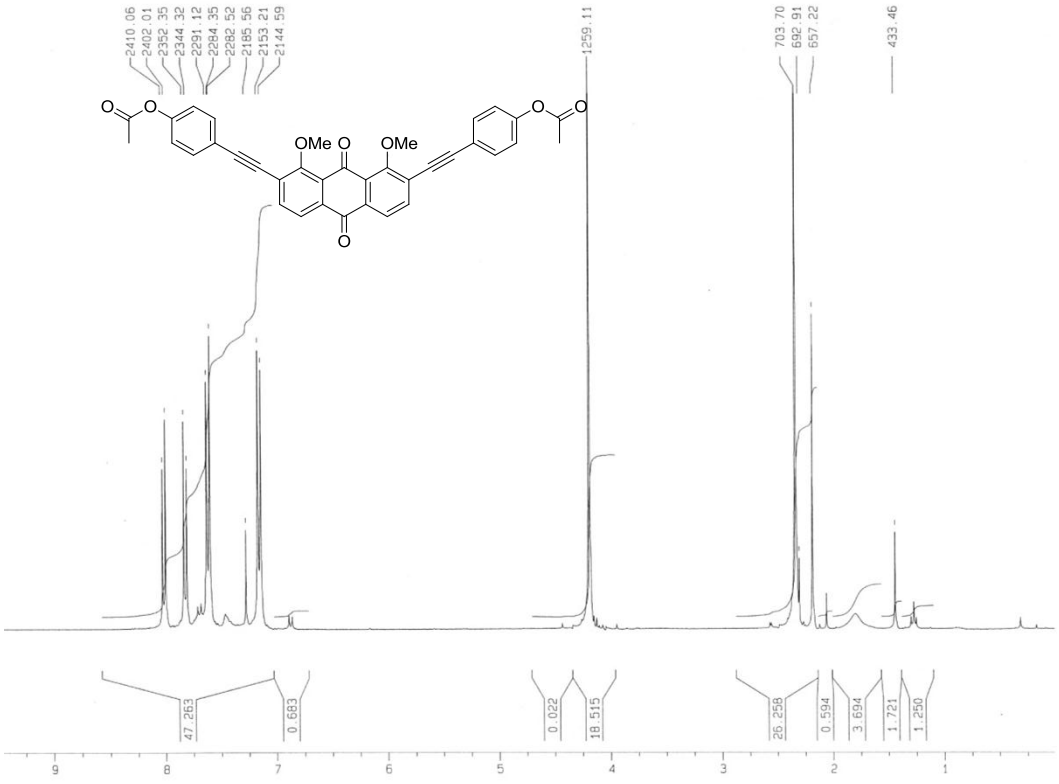


HMBC

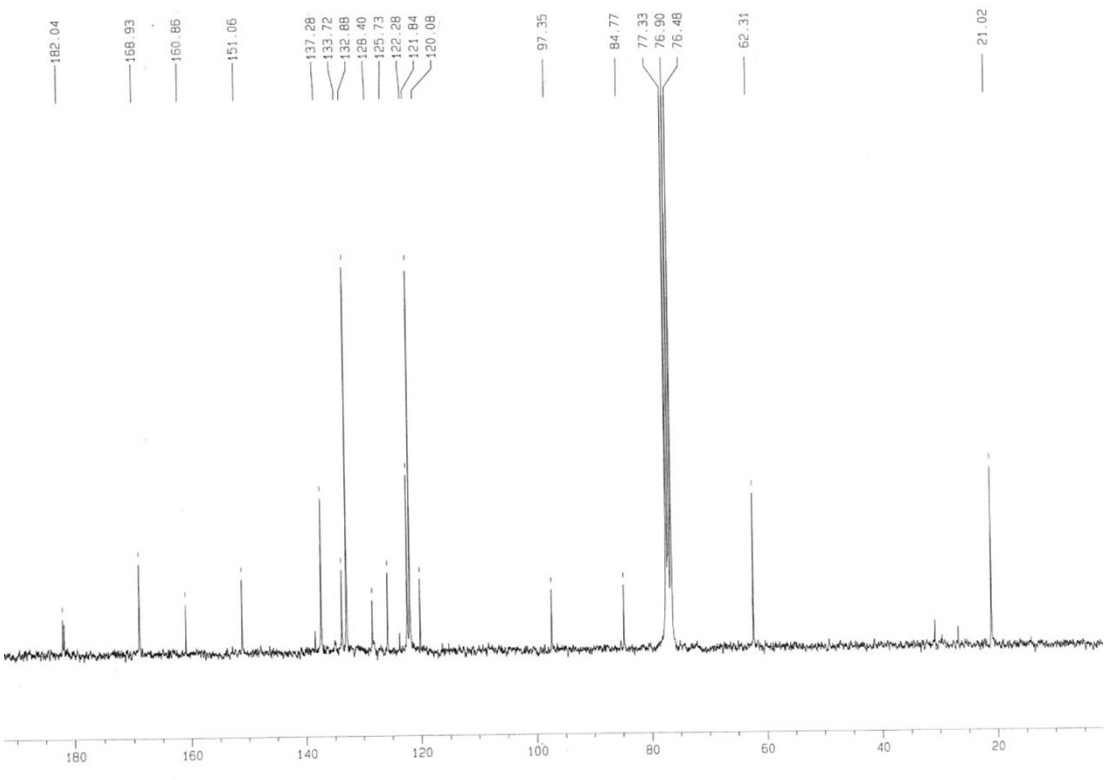


2,7-Bis((p-acetoxylphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione. 12

^{1}H-NMR in $CDCl_3$

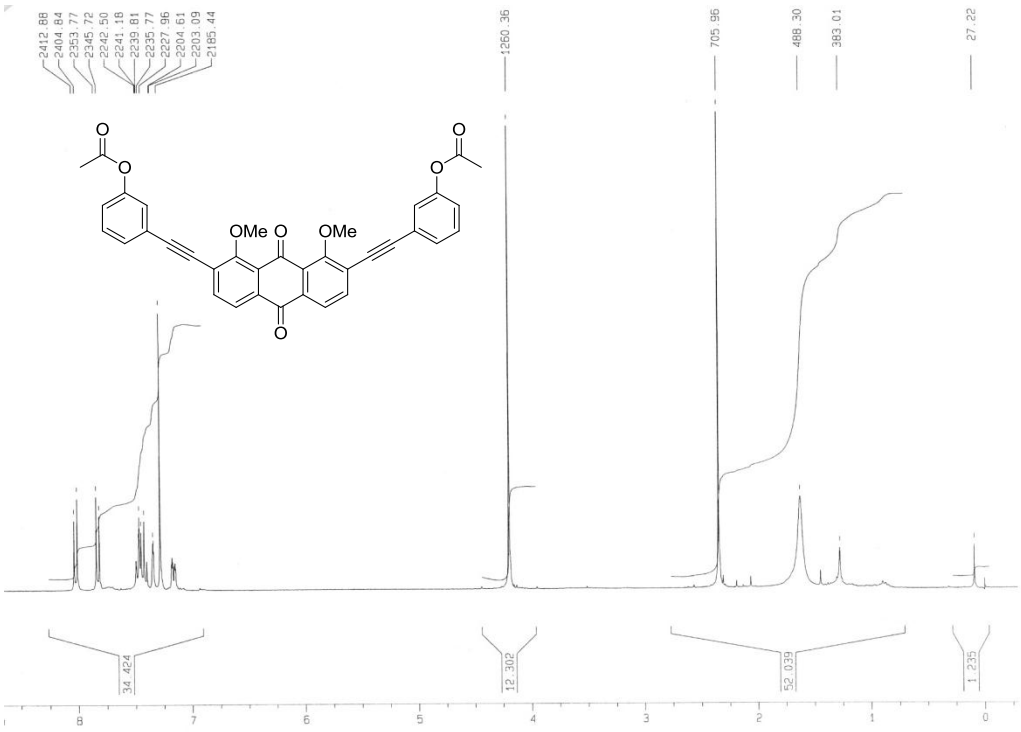


^{13}C-NMR in $CDCl_3$

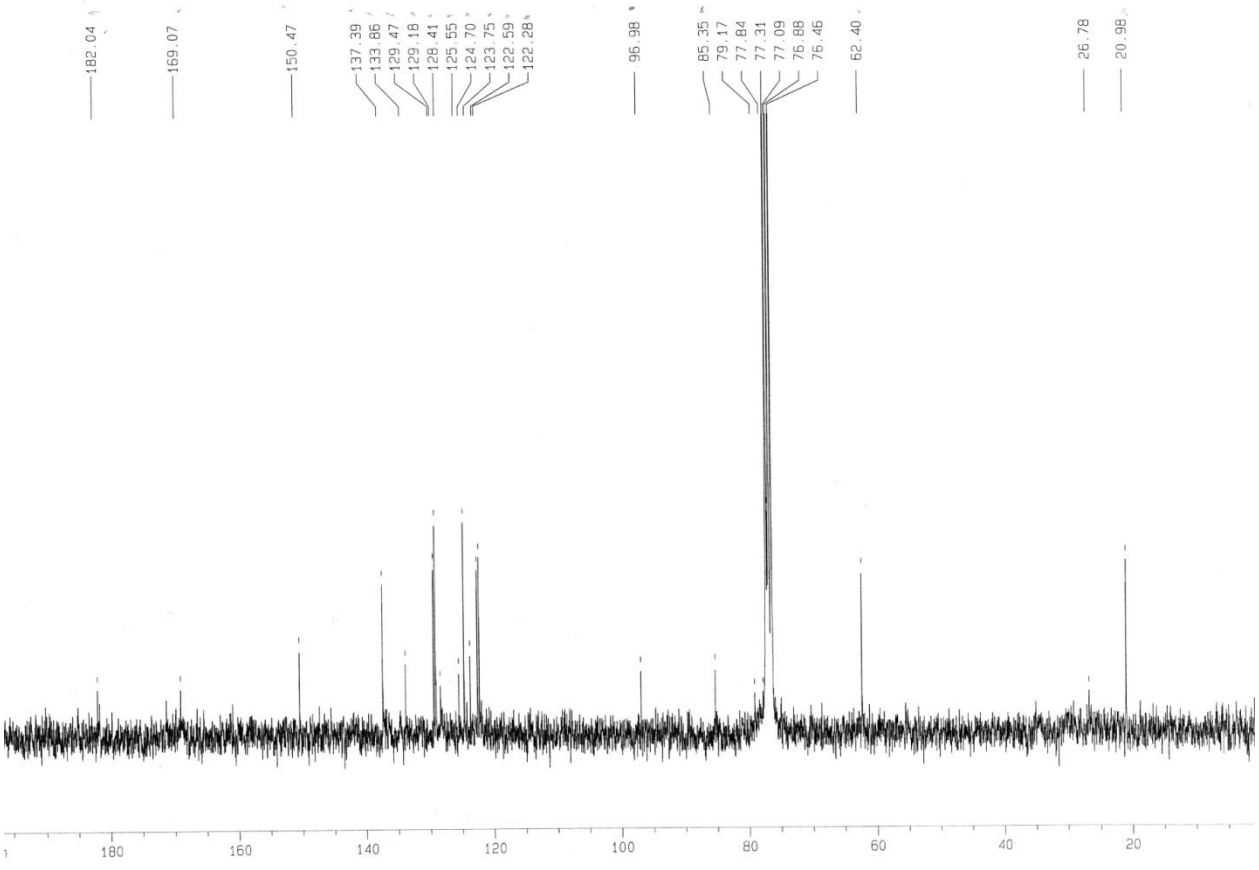


2,7-Bis((m-acetoxyphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione. 13

^{1}H-NMR in $CDCl_3$

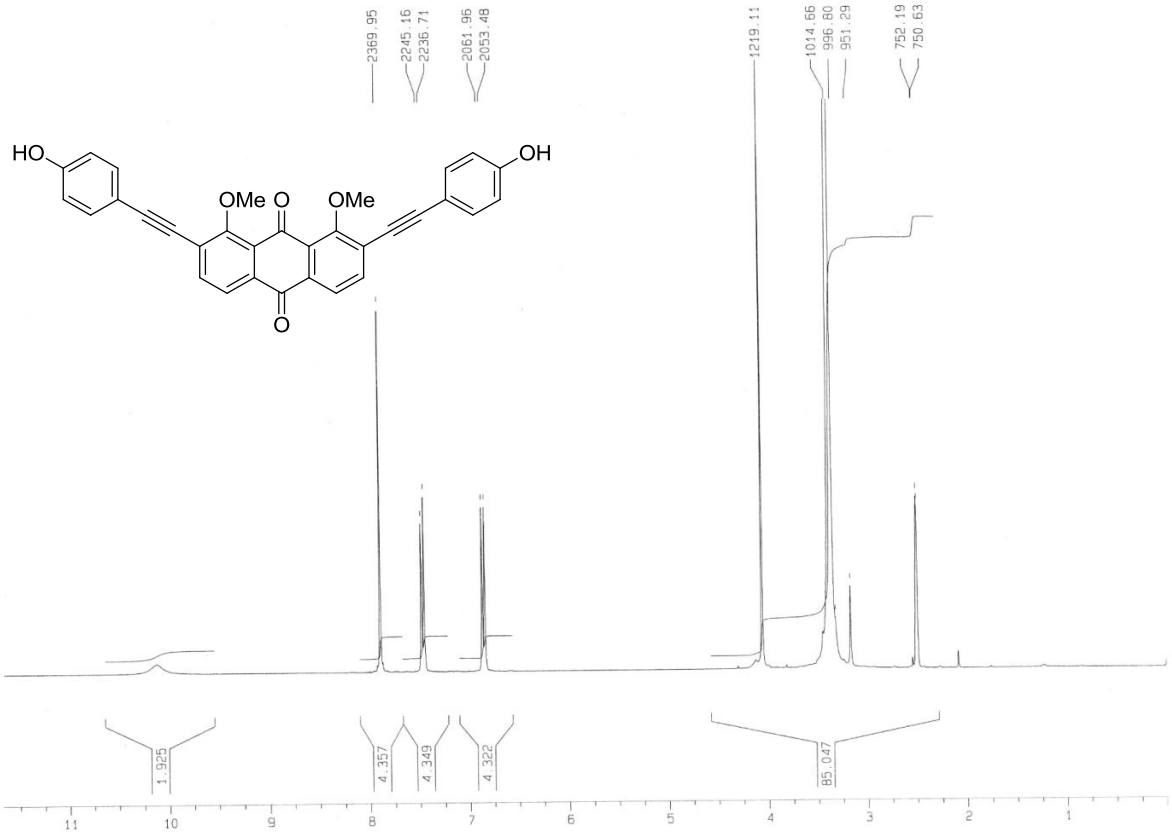


^{13}C-NMR in $CDCl_3$

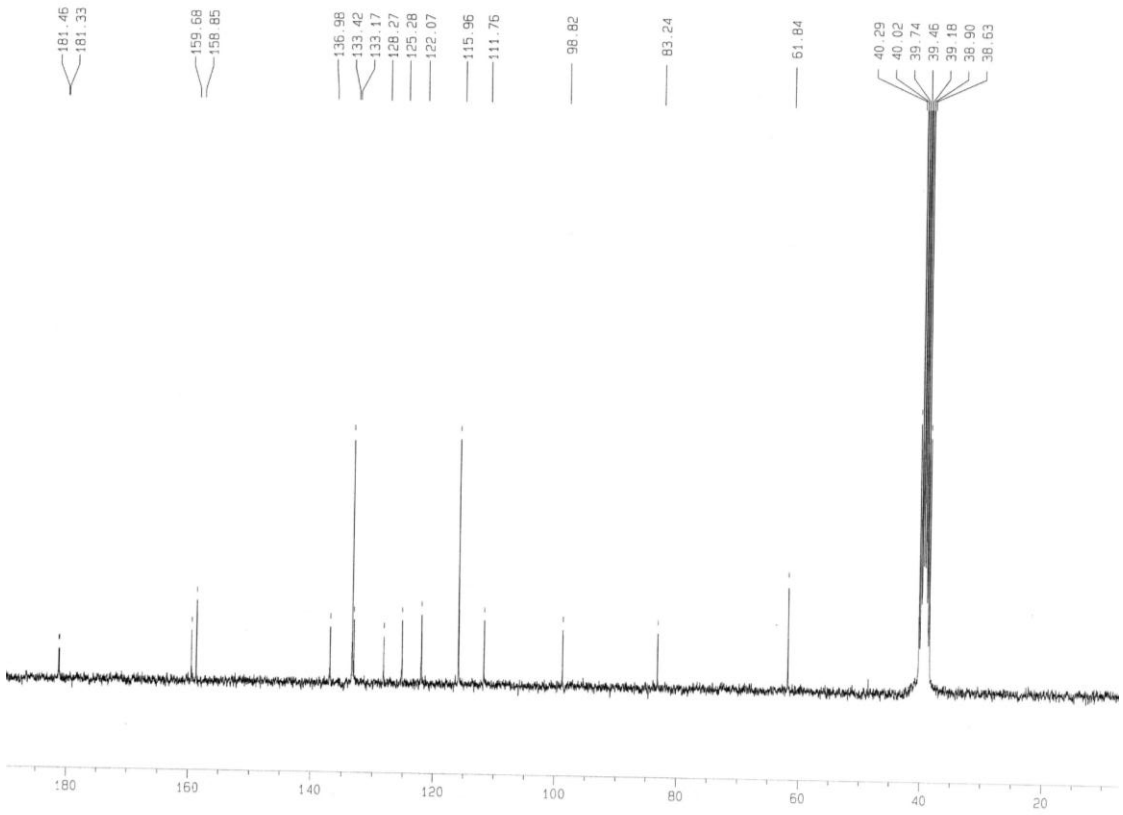


2,7-Bis((p-idroxyphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione. 1

^{1}H-NMR in DMSO-d^{6}

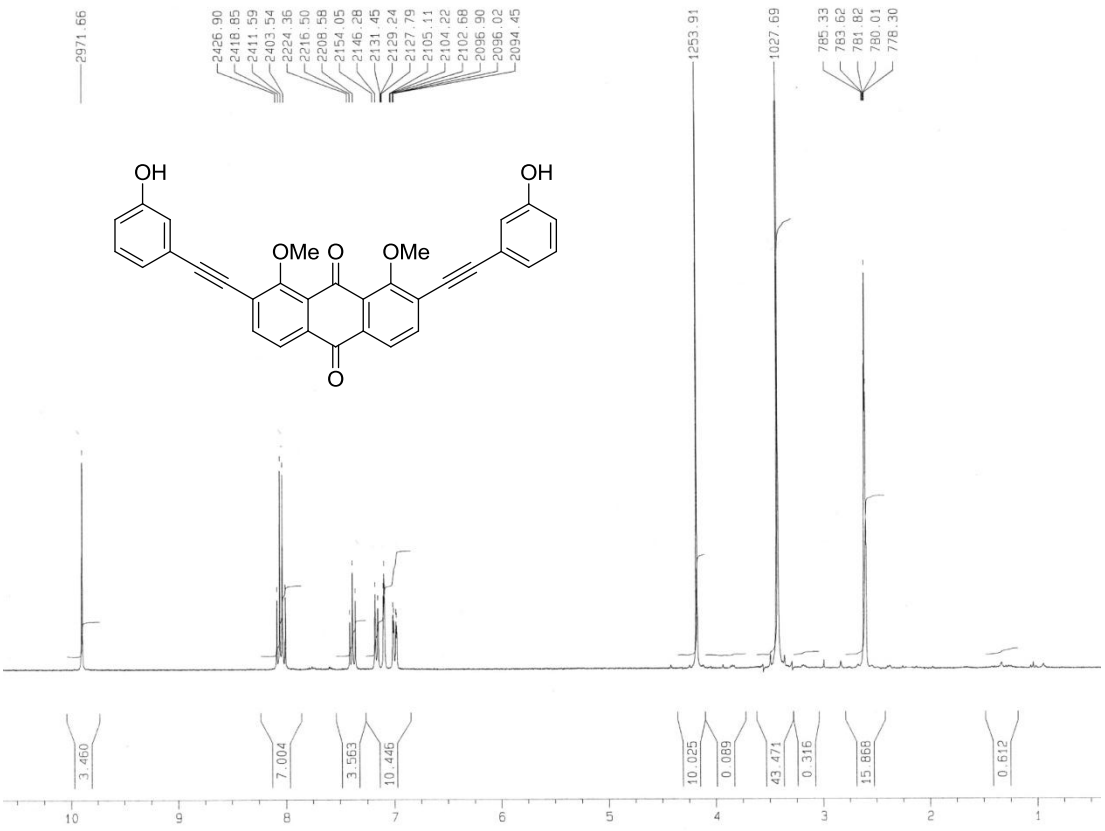


^{13}C-NMR in DMSO-d^{6}

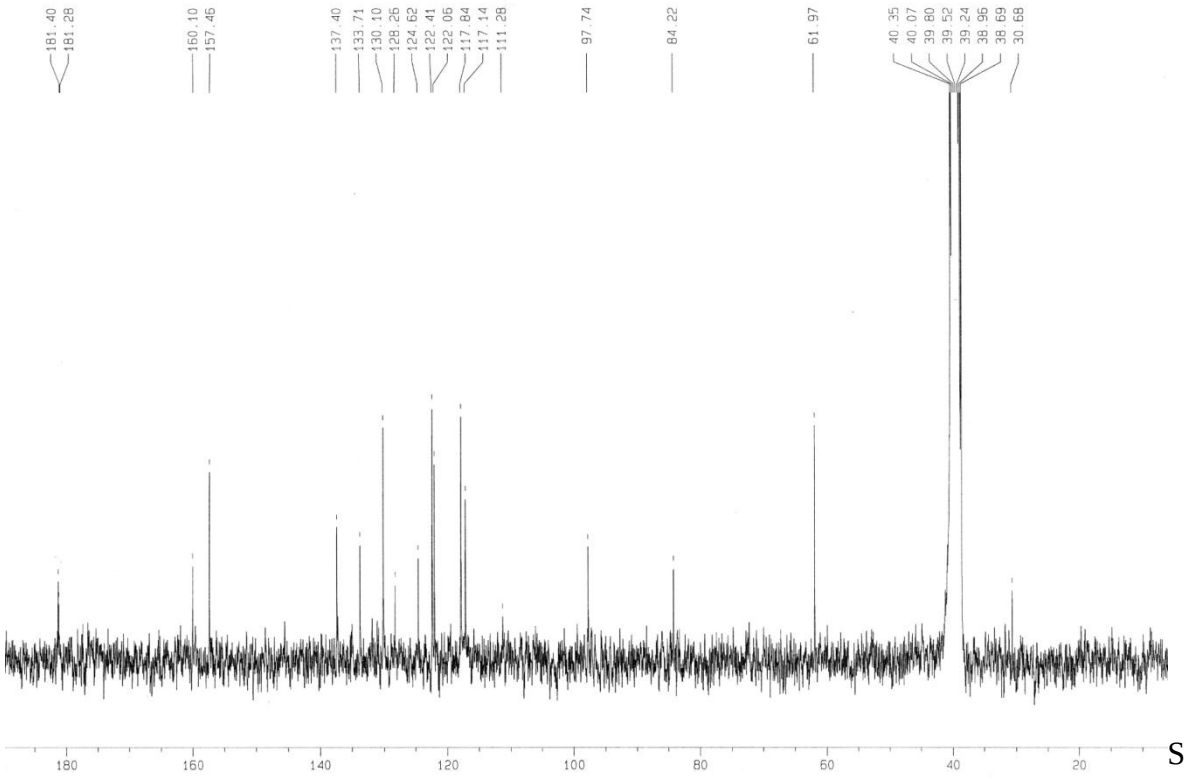


2,7-Bis((m-idroxyphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione. 2

^{1}H-NMR in DMSO-d^{6}

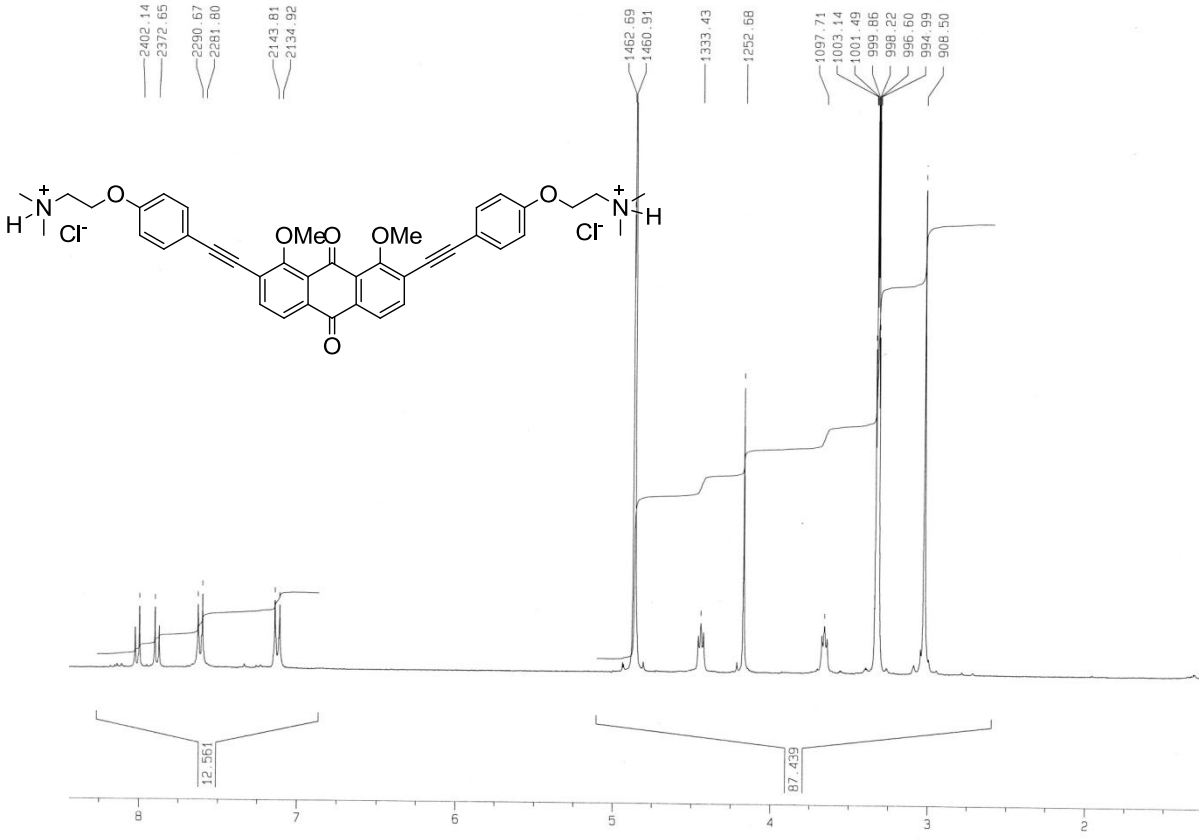


^{13}C-NMR in DMSO-d^{6}

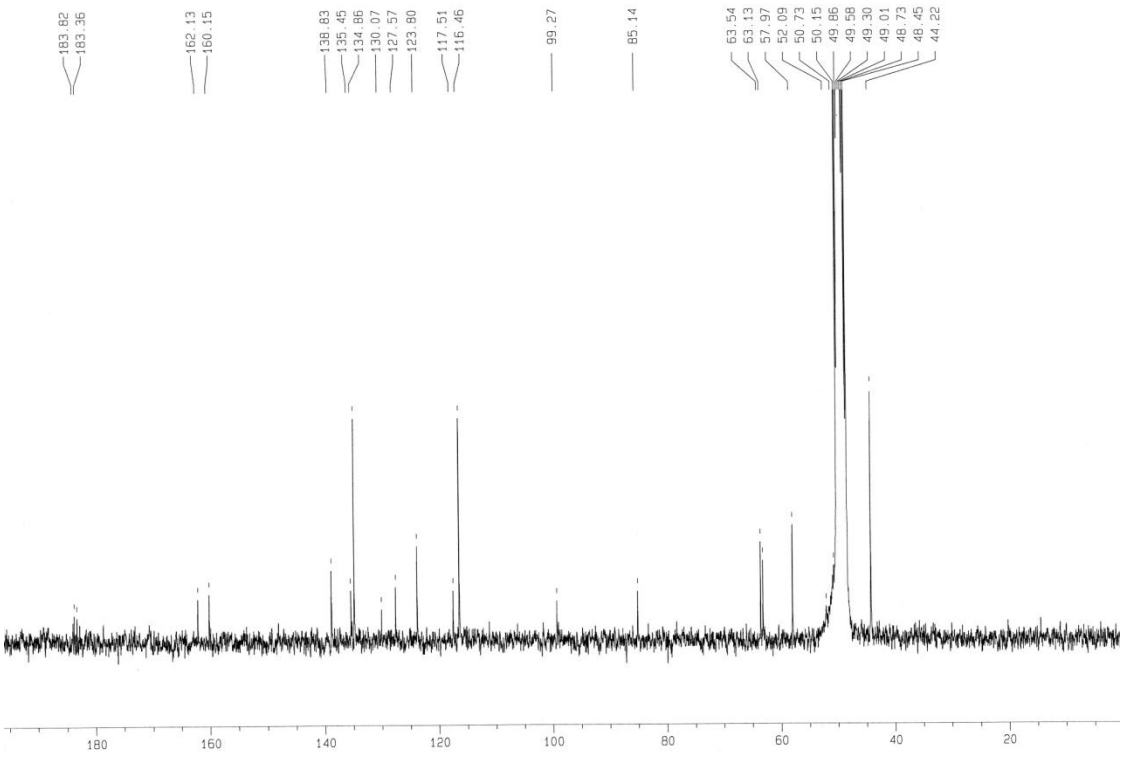


2,7-Bis(4-(2-(dimethylamino)ethoxyphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione· 2HCl . 3

^{1}H-NMR in CD_3OD

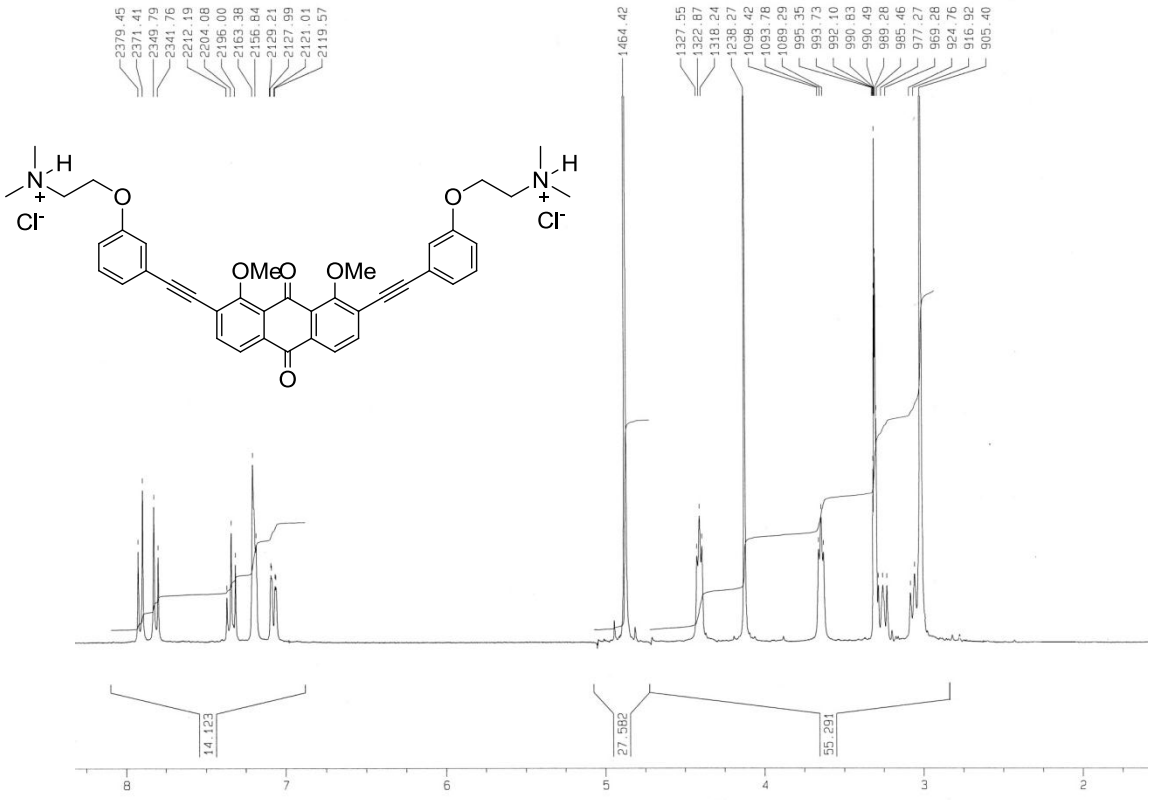


^{13}C-NMR in CD_3OD

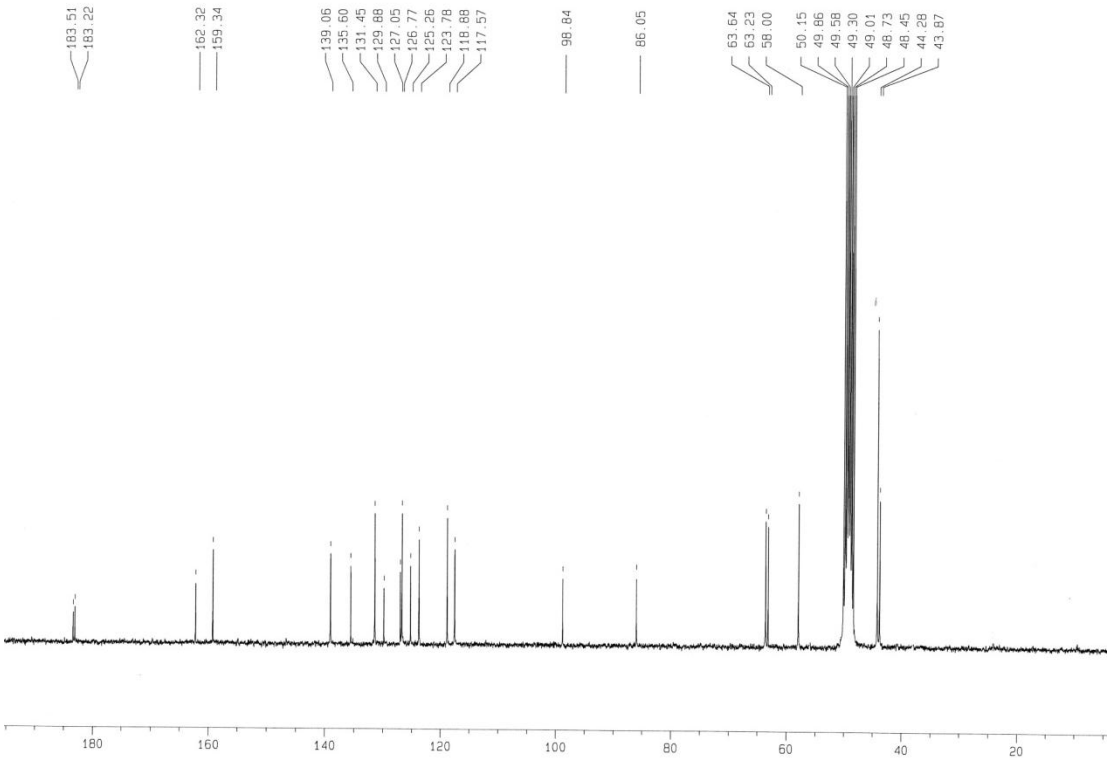


2,7-Bis(3-(2-(dimethylamino)ethoxyphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione· 2HCl . 4

^{1}H-NMR in CD_3OD

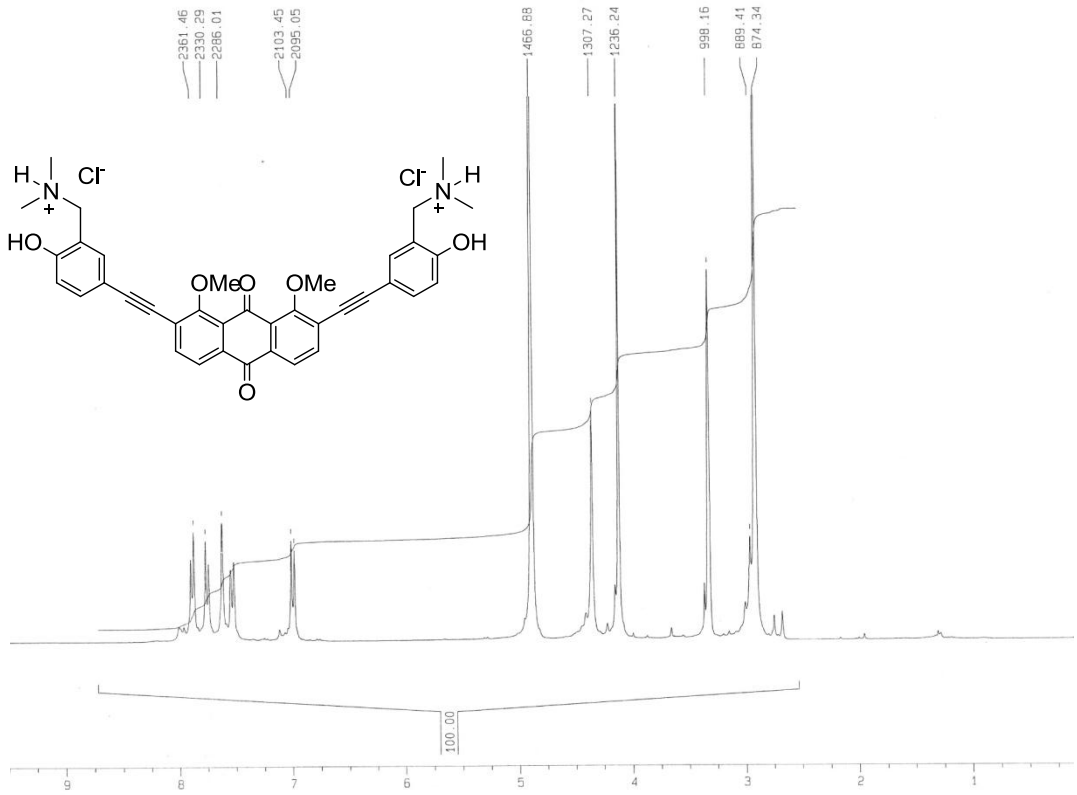


^{13}C-NMR in CD_3OD

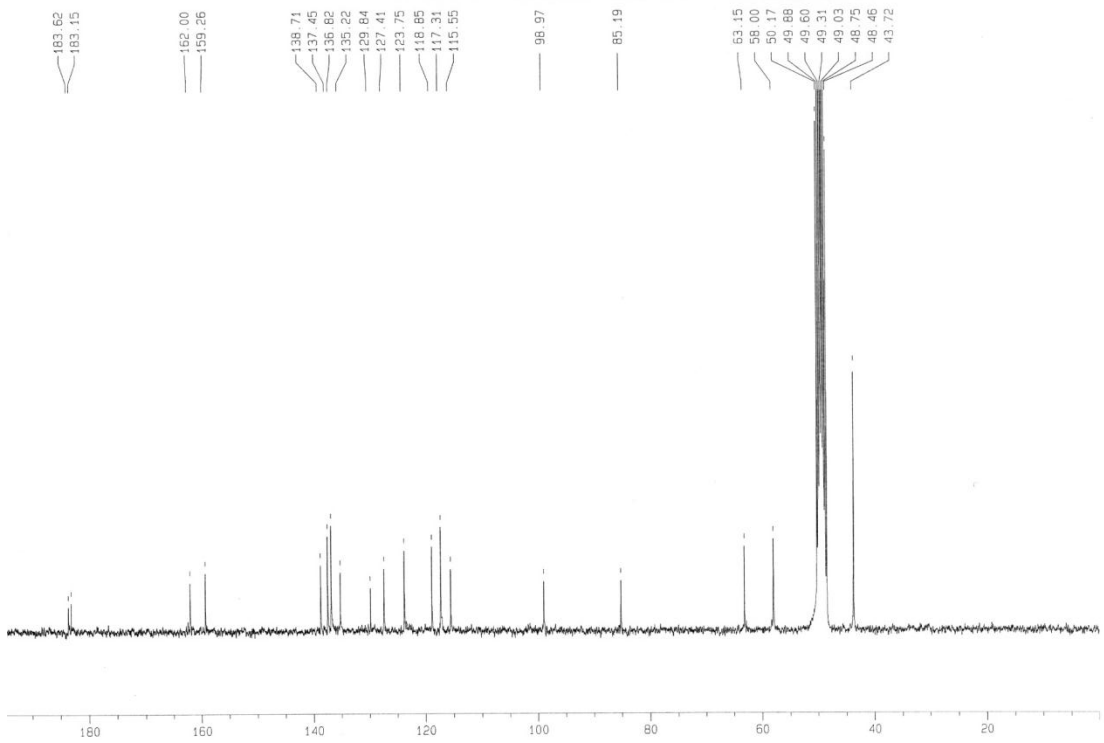


2,7-Bis((3-((dimethylamino)methyl)-4-idroxyphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione· 2HCl . 5

^{1}H-NMR in CD_3OD

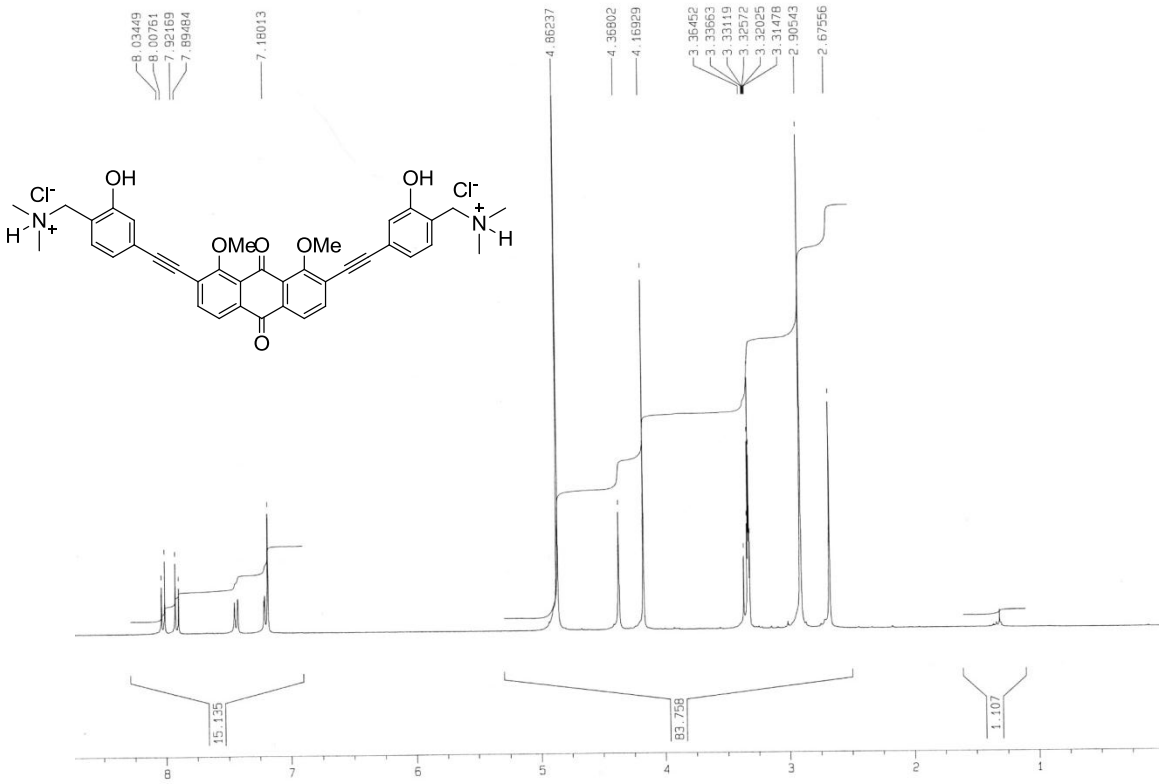


^{13}C-NMR in CD_3OD



2,7-Bis((4-((dimethylamino)methyl)-3-idroxyphenyl)ethynyl)-1,8-dimethoxyanthracene-9,10-dione· 2HCl . 6

^{1}H-NMR in CD_3OD



^{13}C-NMR in CD_3OD

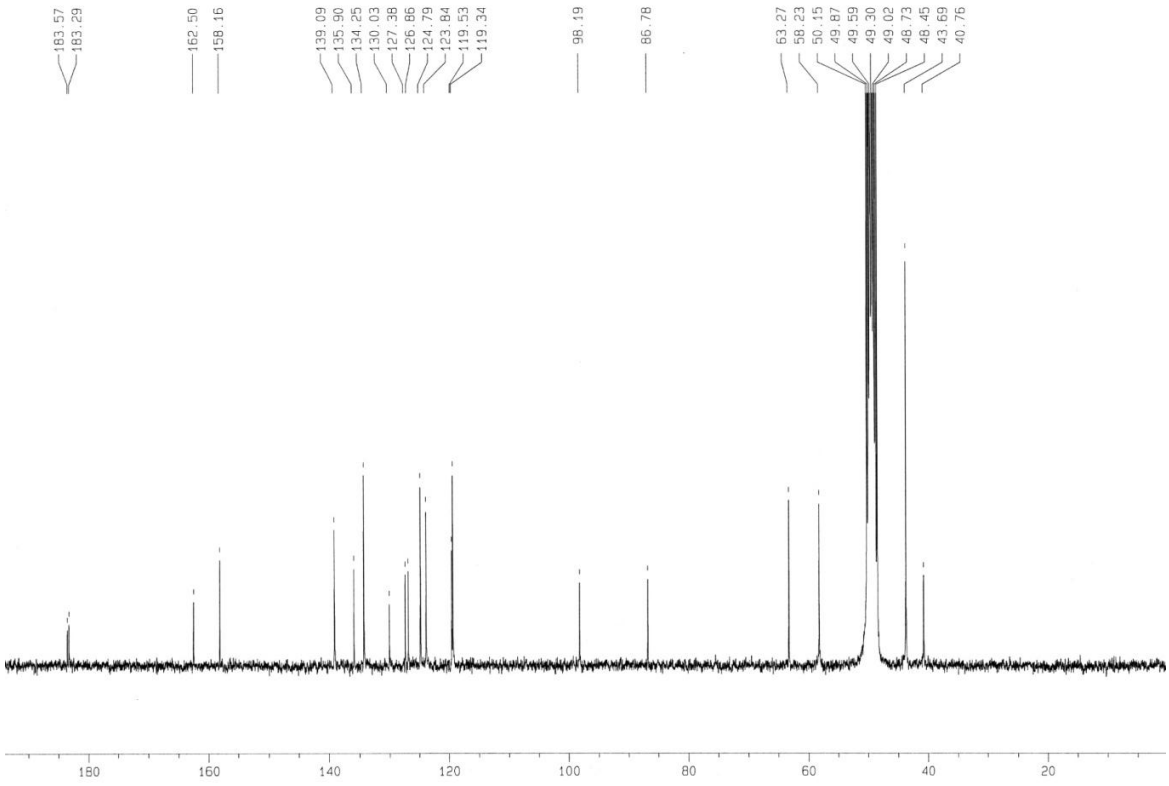


Table S1. IFD scores, expressed in kcal mol^{-1}, of ligands **1-6** against the PDB human telomeric sequence *d*[$AG_3(T_2AG_3)_3$] folds. Consensus score indicates the average IFD score obtained considering all the G-quadruplex folds.

Ligand	**1KF1**	**143D**	**2JPZ**	**2HY9**	**2JSL**	**2JSM**	***Consensus score***
1	-7.44	-5.75	-6.91	-5.30	-7.08	-6.05	-6.42
2	-6.87	-5.06	-6.21	-6.92	-7.20	-8.48	-6.79
3	-8.58	-8.61	-7.82	-8.07	-10.39	-9.59	-8.84
4	-9.25	-6.84	-7.58	-8.37	-12.09	-9.90	-9.01
5	-9.47	-7.80	-8.30	-8.49	-10.32	-11.38	-9.29
6	-9.22	-8.25	-8.15	-8.28	-10.24	-9.85	-9.00

Figure S1. 1 best pose against 1KF1 PDB model obtained by IFD method. **1** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

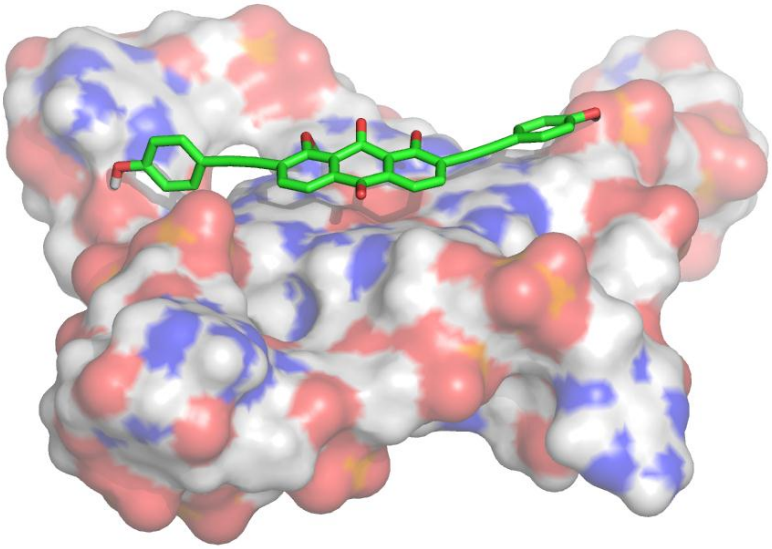


Figure S2. 2 best pose against 1KF1 PDB model obtained by IFD method. **2** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

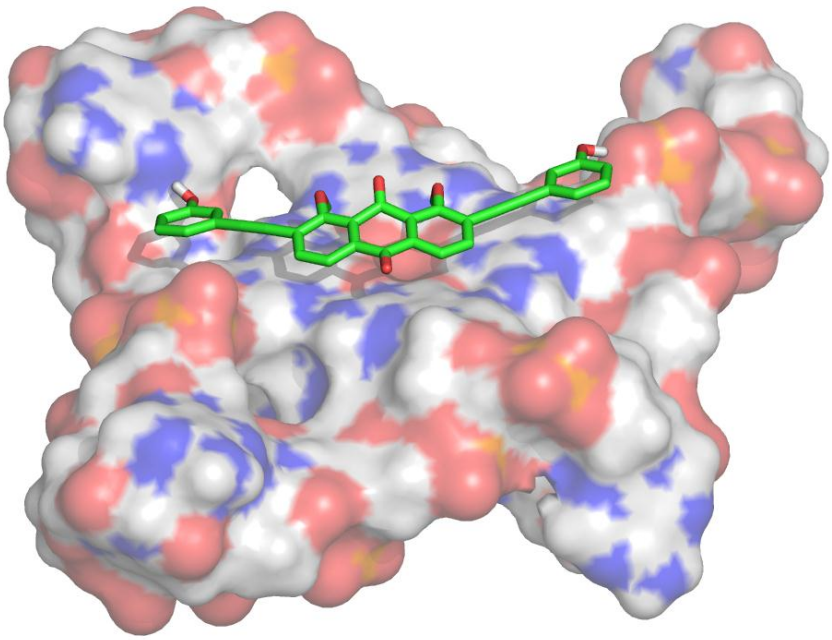


Figure S3. 3 best pose against 1KF1 PDB model obtained by IFD method. **3** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

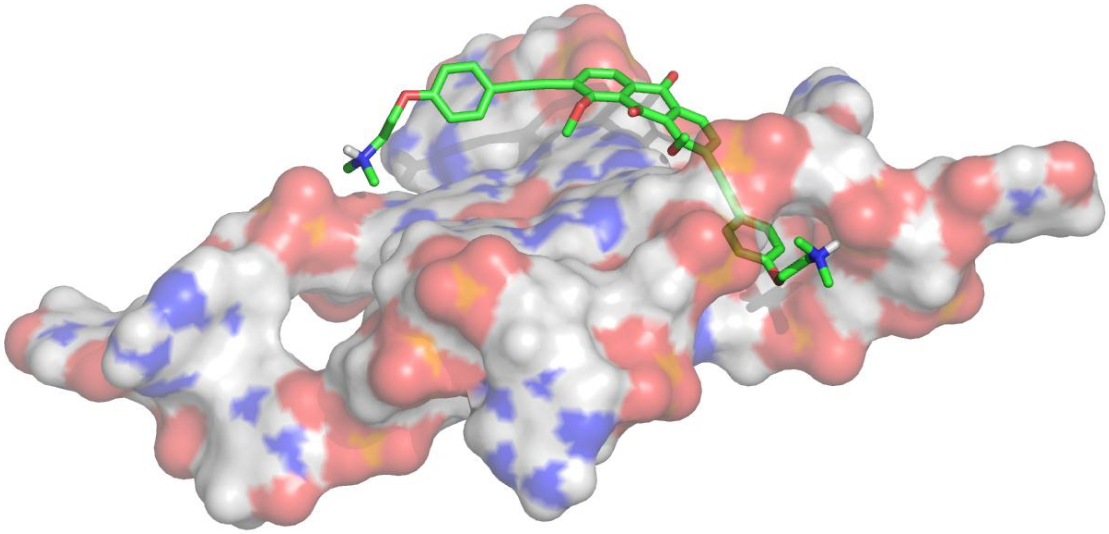


Figure S4. 4 best pose against 1KF1 PDB model obtained by IFD method. **4** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

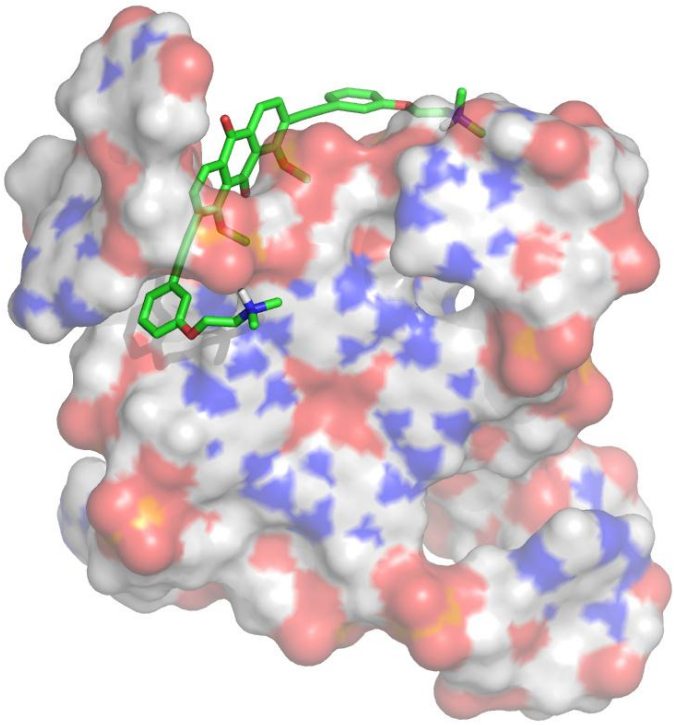


Figure S5. 5 best pose against 1KF1 PDB model obtained by IFD method. **5** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

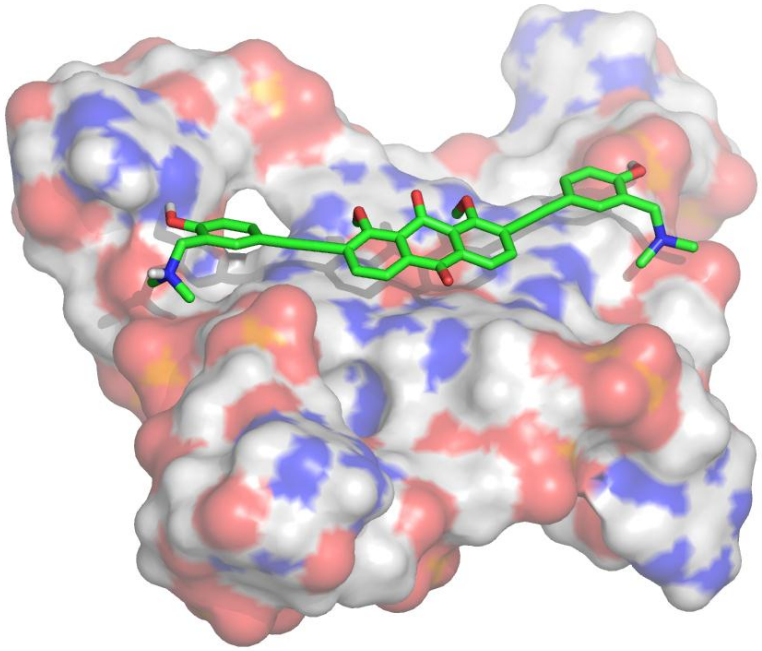


Figure S6. 6 best pose against 1KF1 PDB model obtained by IFD method. **6** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

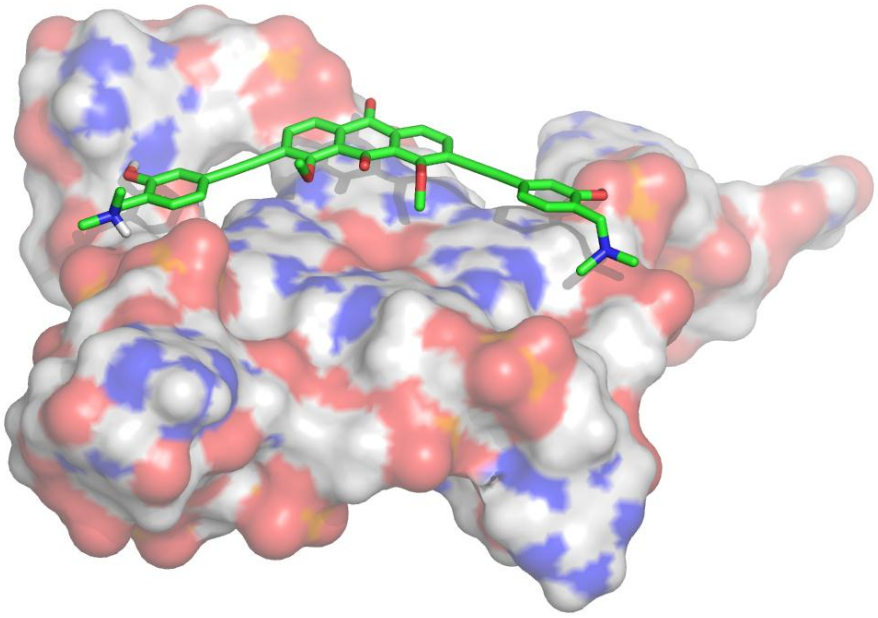


Figure S7. 1 best pose against 143D PDB model obtained by IFD method. **1** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

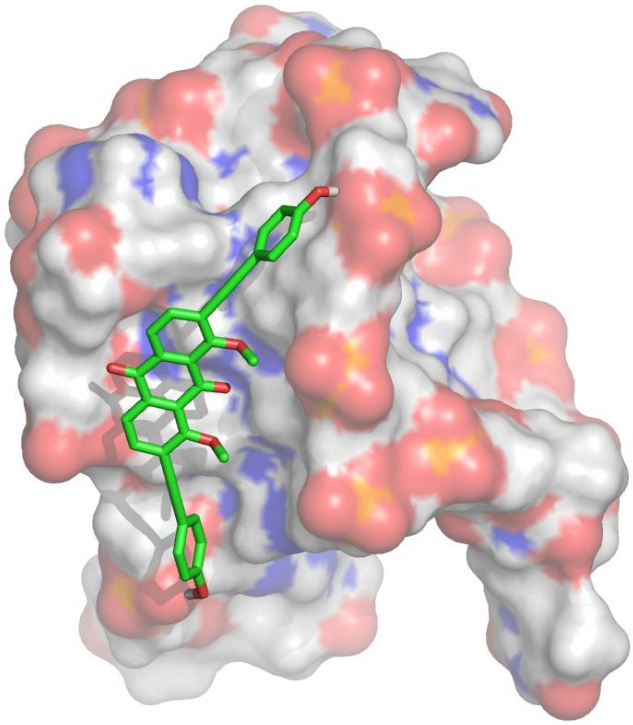


Figure S8. 2 best pose against 143D PDB model obtained by IFD method. **2** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

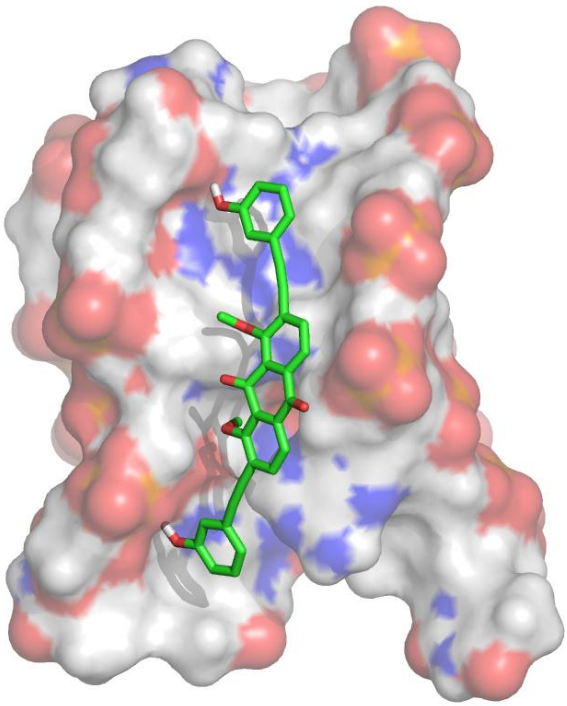


Figure S19. 3 best pose against 143D PDB model obtained by IFD method. **3** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

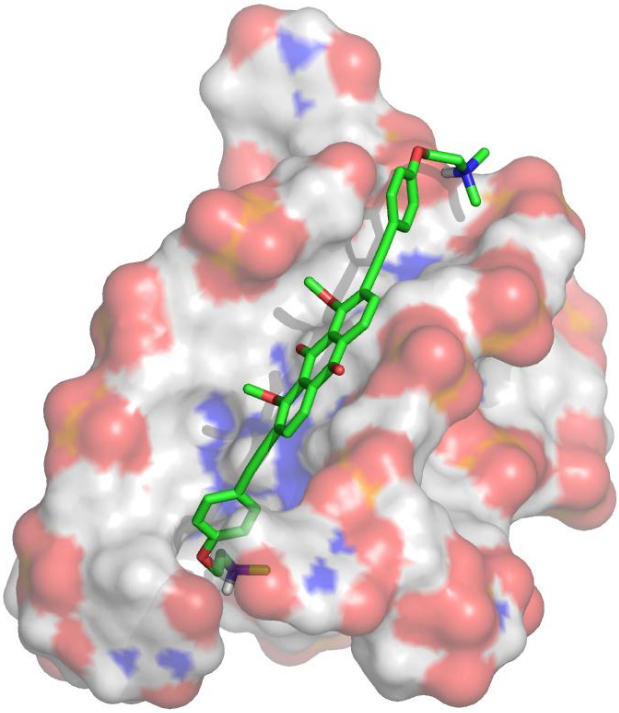


Figure S10. 4 best pose against 143D PDB model obtained by IFD method. **4** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

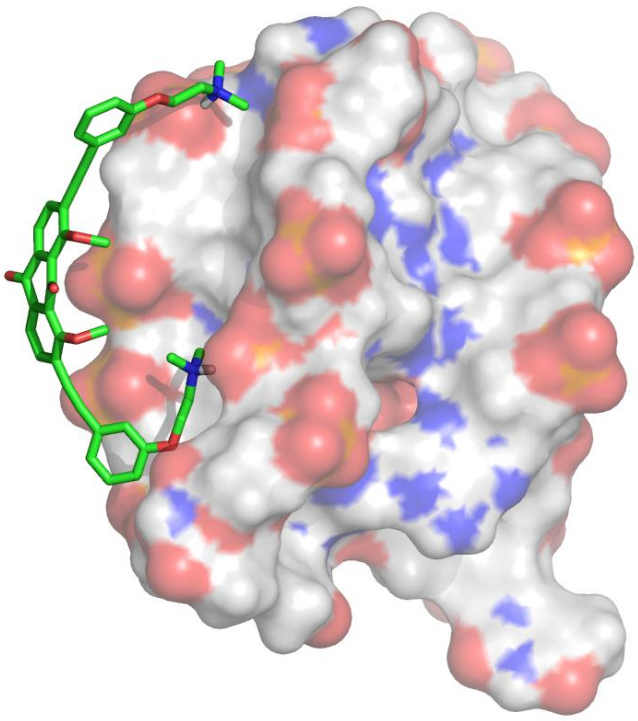


Figure S11. 5 best pose against 143D PDB model obtained by IFD method. **5** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

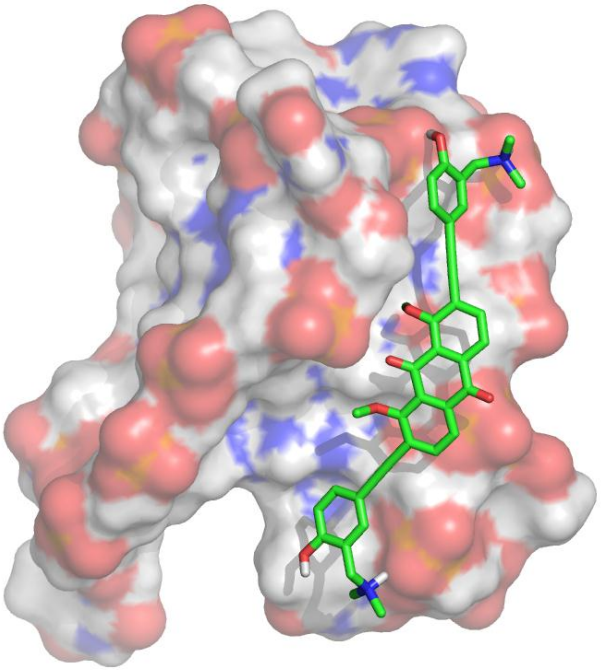


Figure S12. 6 best pose against 143D PDB model obtained by IFD method. **6** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

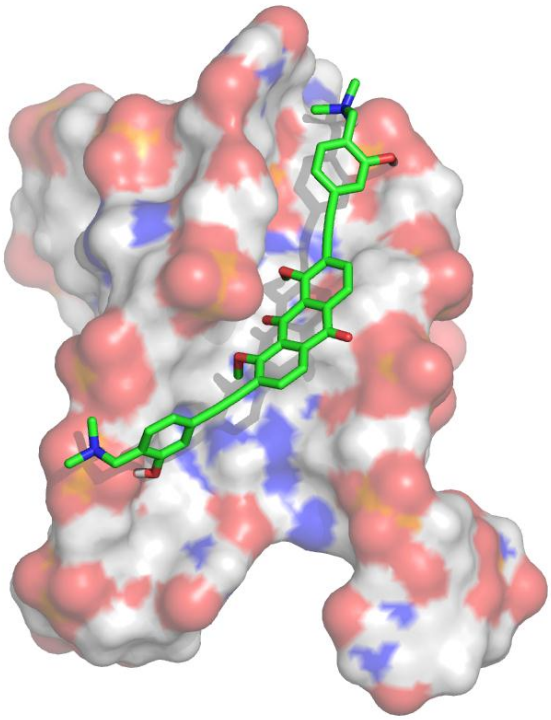


Figure S13. 1 best pose against 2JPZ PDB model obtained by IFD method. **1** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

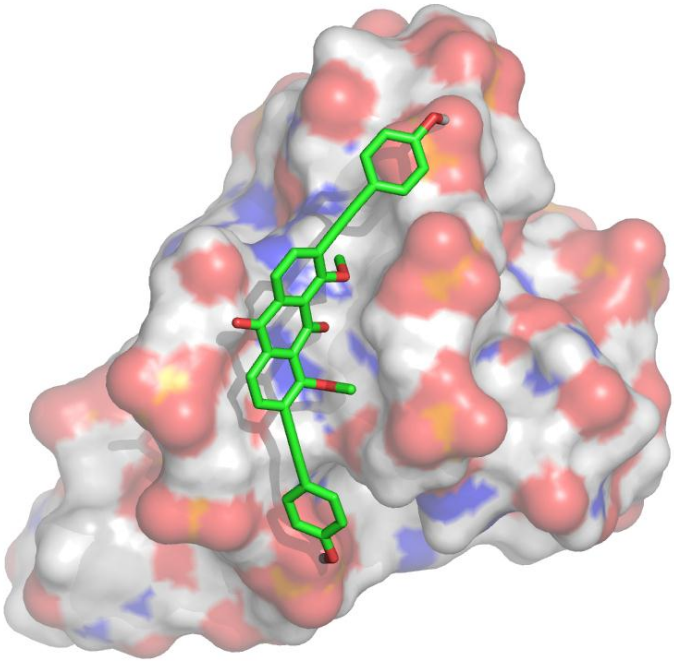


Figure S14. 2 best pose against 2JPZ PDB model obtained by IFD method. **2** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

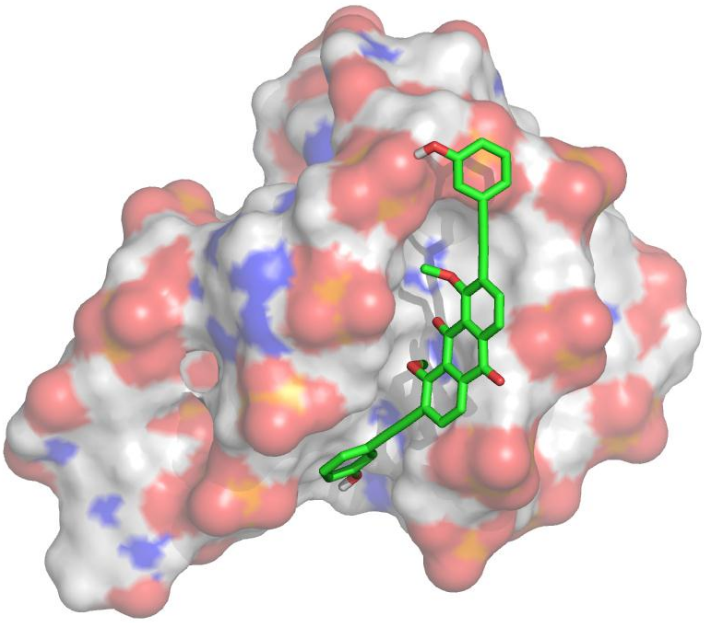


Figure S15. 3 best pose against 2JPZ PDB model obtained by IFD method. **3** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

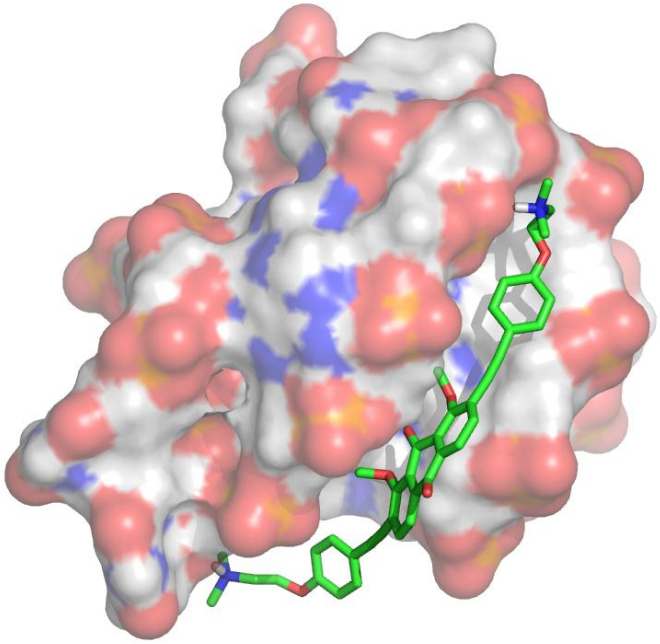


Figure S16. 4 best pose against 2JPZ PDB model obtained by IFD method. **4** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

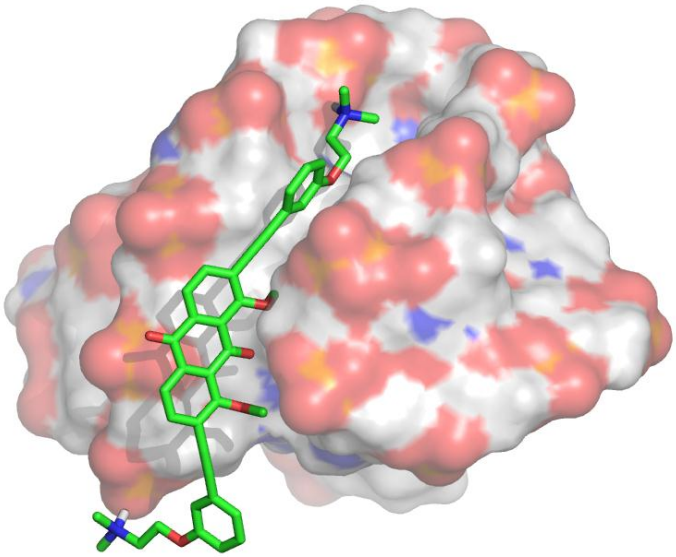


Figure S17. 5 best pose against 2JPZ PDB model obtained by IFD method. **5** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

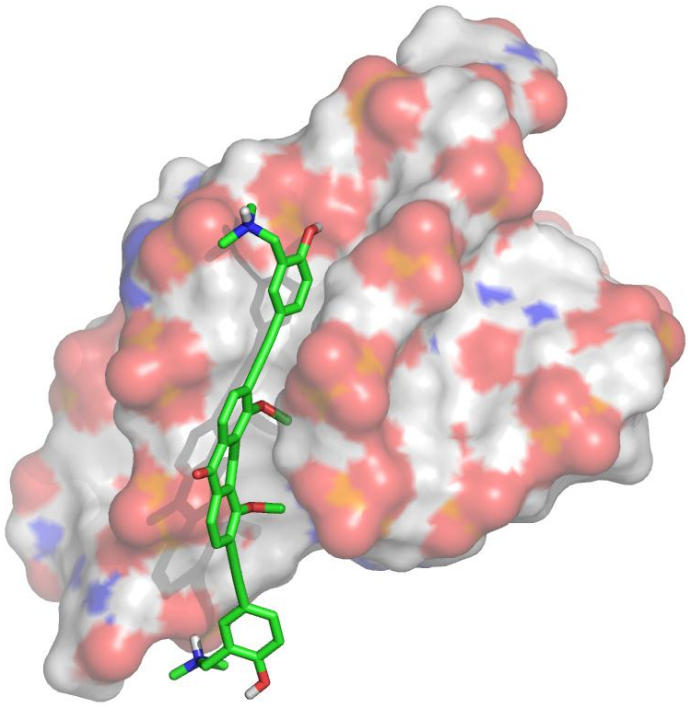


Figure S18. 6 best pose against 2JPZ PDB model obtained by IFD method. **6** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

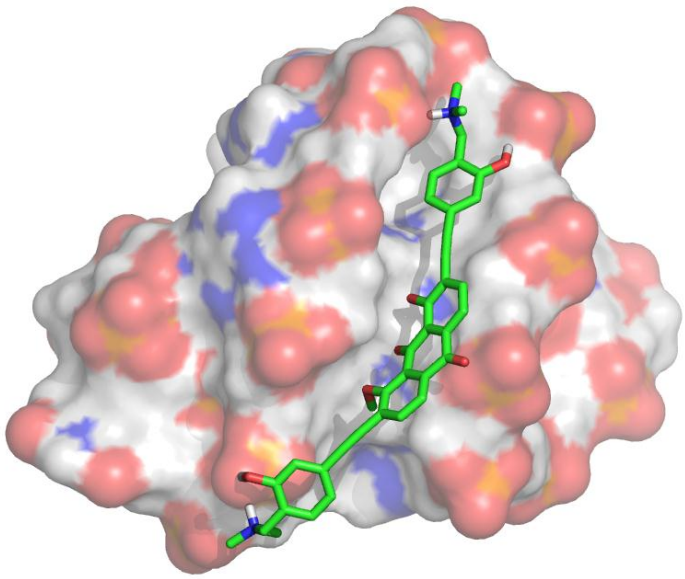


Figure S19. 1 best pose against 2HY9 PDB model obtained by IFD method. **1** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

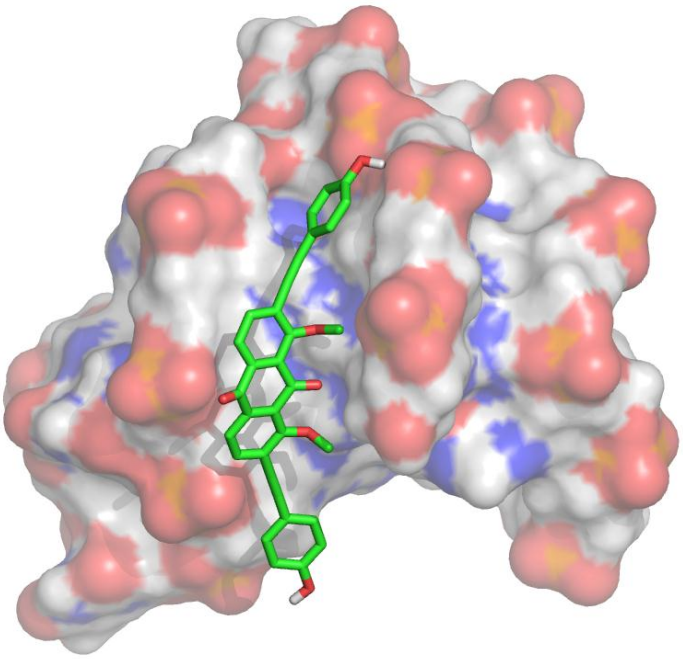


Figure S20. 2 best pose against 2HY9 PDB model obtained by IFD method. **2** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

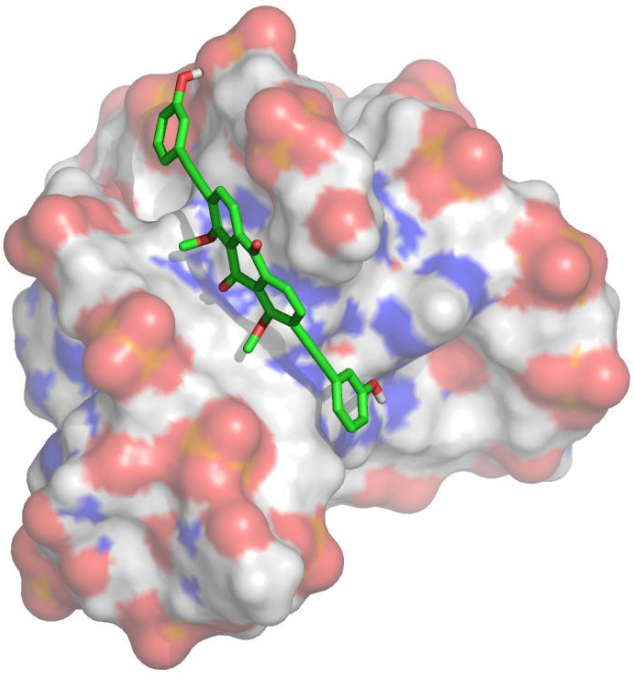


Figure S21. 3 best pose against 2HY9 PDB model obtained by IFD method. **3** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

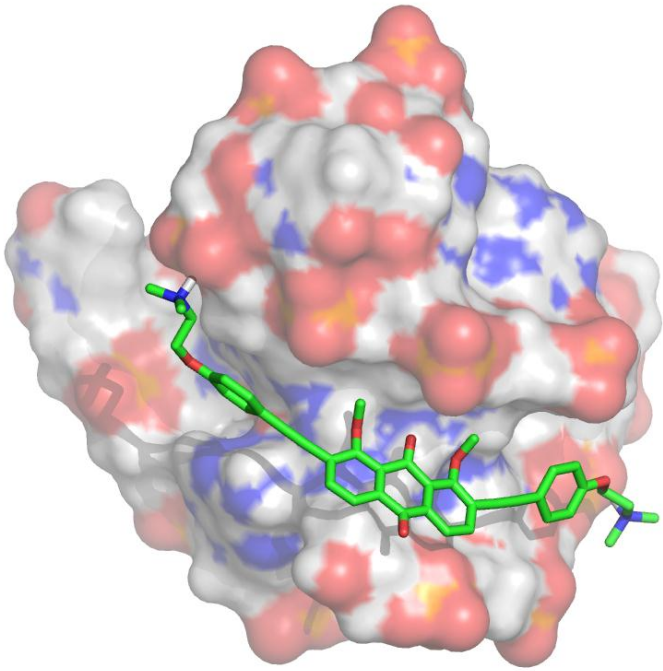


Figure S22. 4 best pose against 2HY9 PDB model obtained by IFD method. **4** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

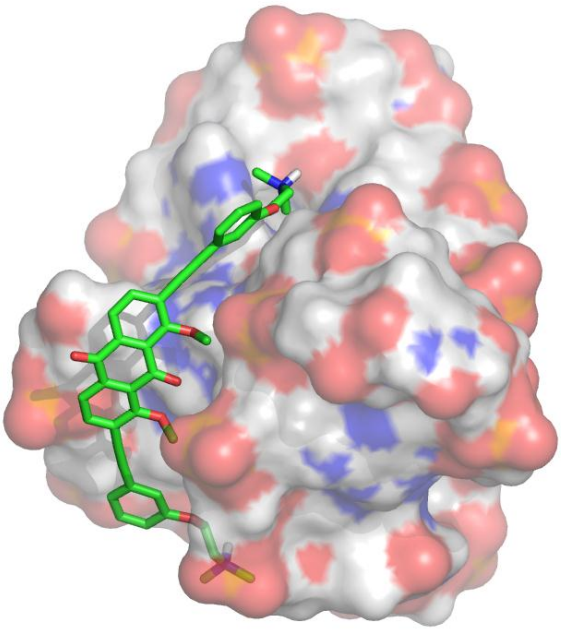


Figure S23. 5 best pose against 2HY9 PDB model obtained by IFD method. **5** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

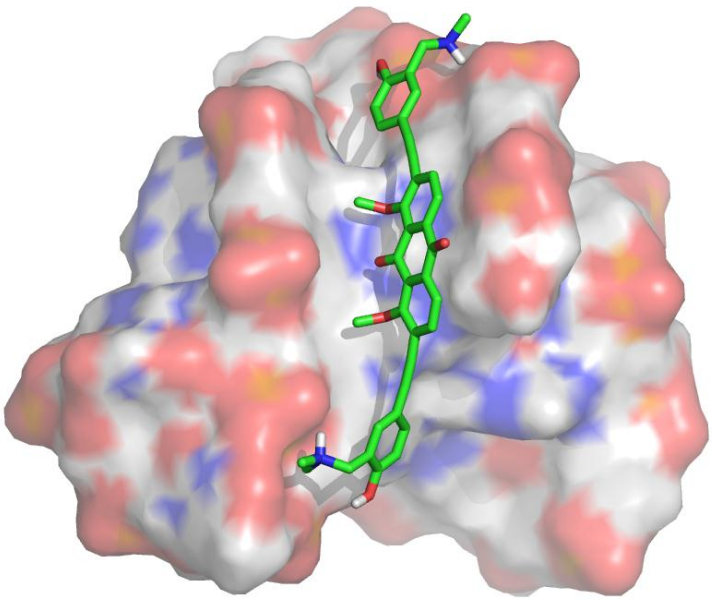


Figure S24. 6 best pose against 2HY9 PDB model obtained by IFD method. **6** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

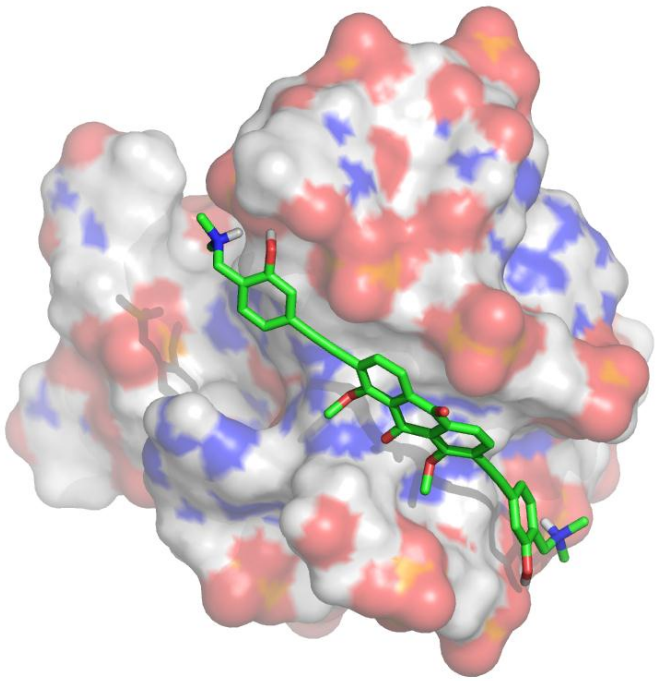


Figure S25. 1 best pose against 2JSL PDB model obtained by IFD method. **1** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

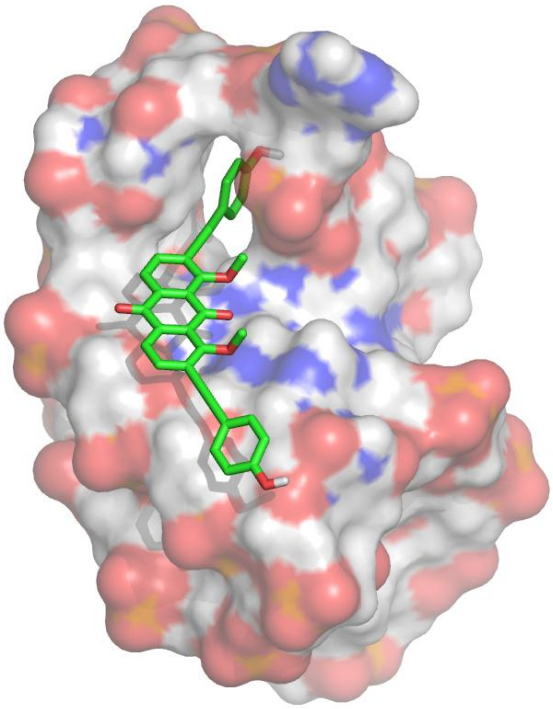


Figure S26. 2 best pose against 2JSL PDB model obtained by IFD method. **2** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

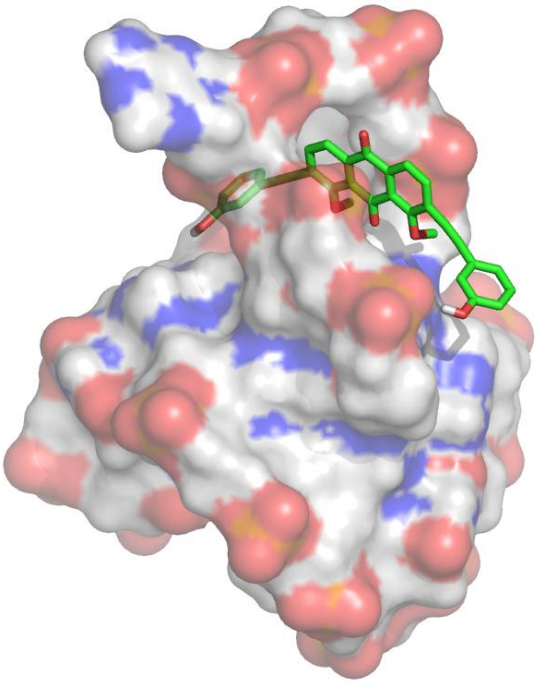


Figure S27. 3 best pose against 2JSL PDB model obtained by IFD method. **3** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

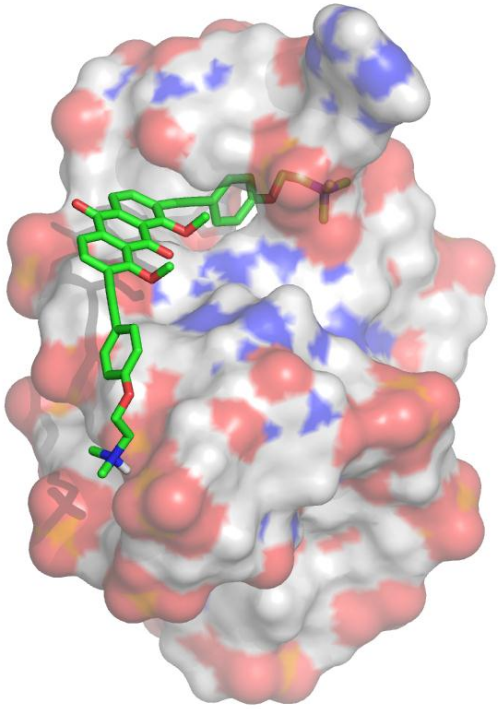


Figure S28. 4 best pose against 2JSL PDB model obtained by IFD method. **4** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

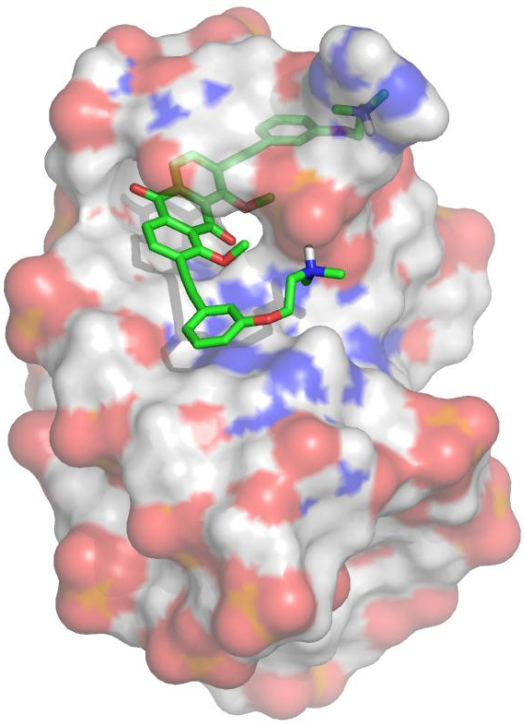


Figure S29. 5 best pose against 2JSL PDB model obtained by IFD method. **5** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

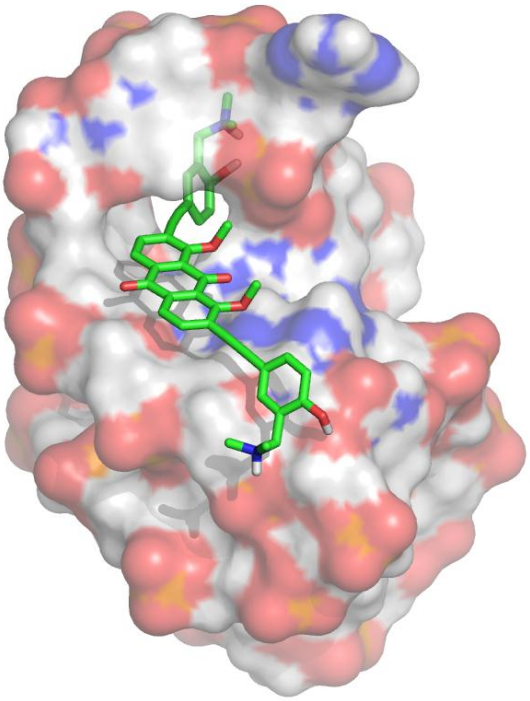


Figure S30. 6 best pose against 2JSL PDB model obtained by IFD method. **6** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

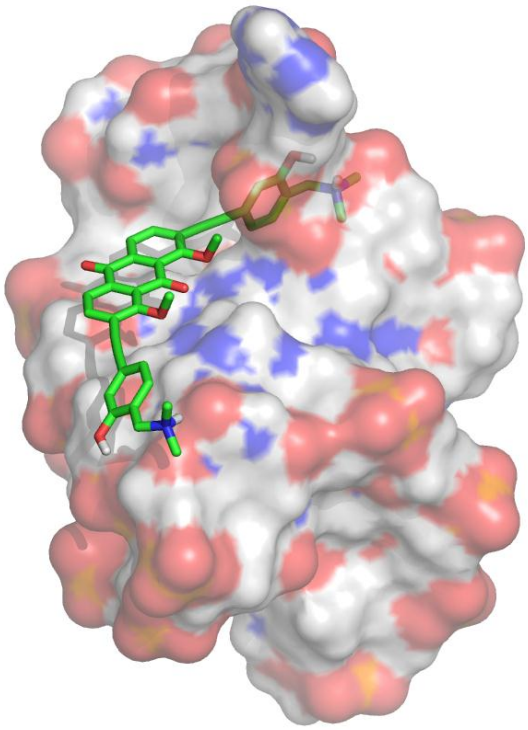


Figure S31. 1 best pose against 2JSM PDB model obtained by IFD method. **1** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

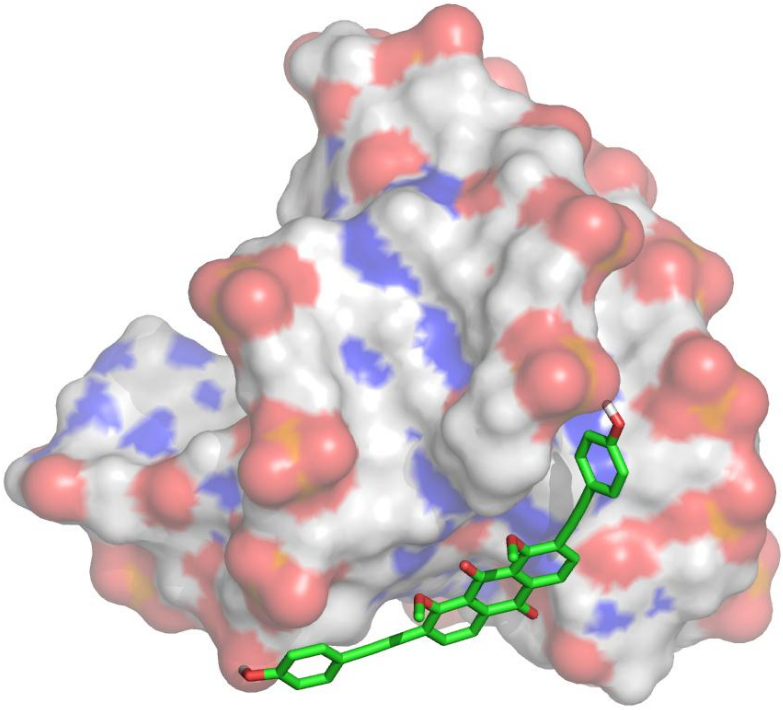


Figure S32. 2 best pose against 2JSM PDB model obtained by IFD method. **2** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

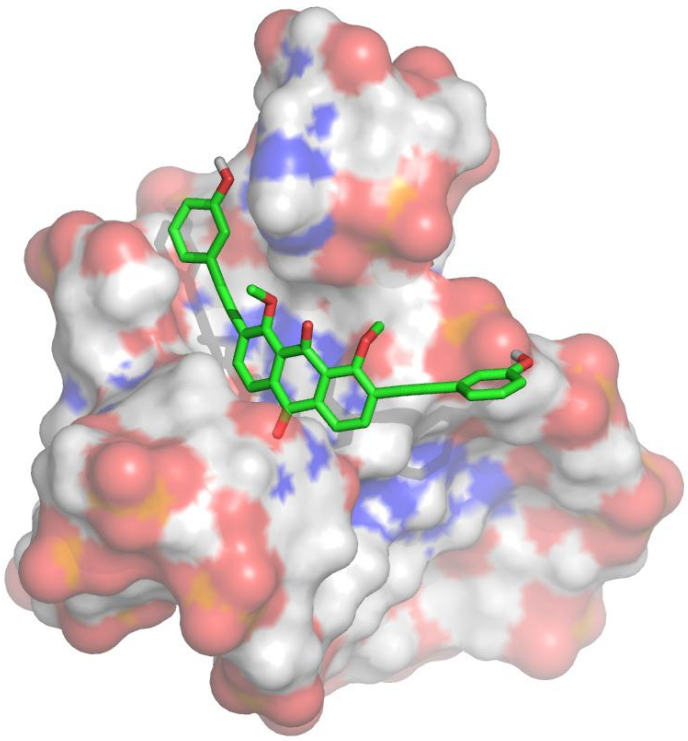


Figure S33. 3 best pose against 2JSM PDB model obtained by IFD method. **3** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.

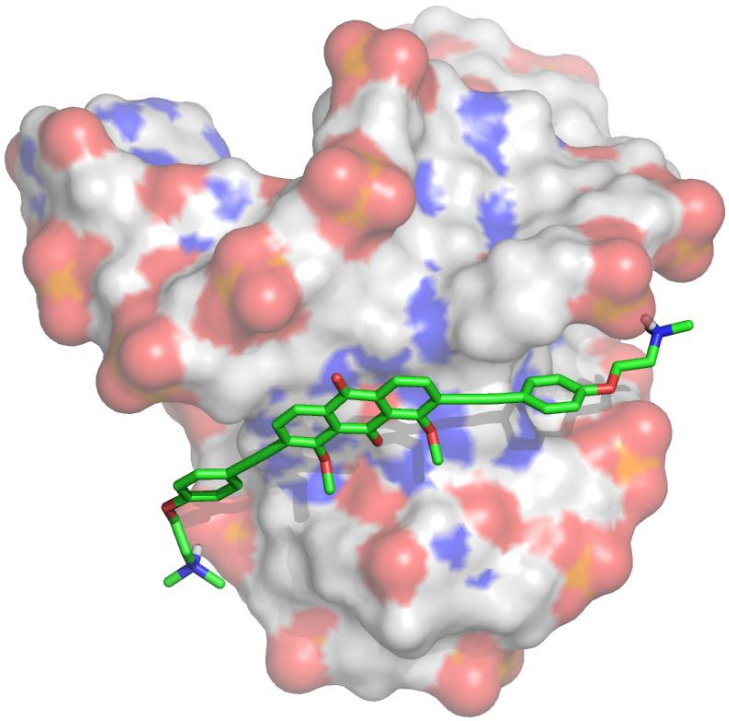
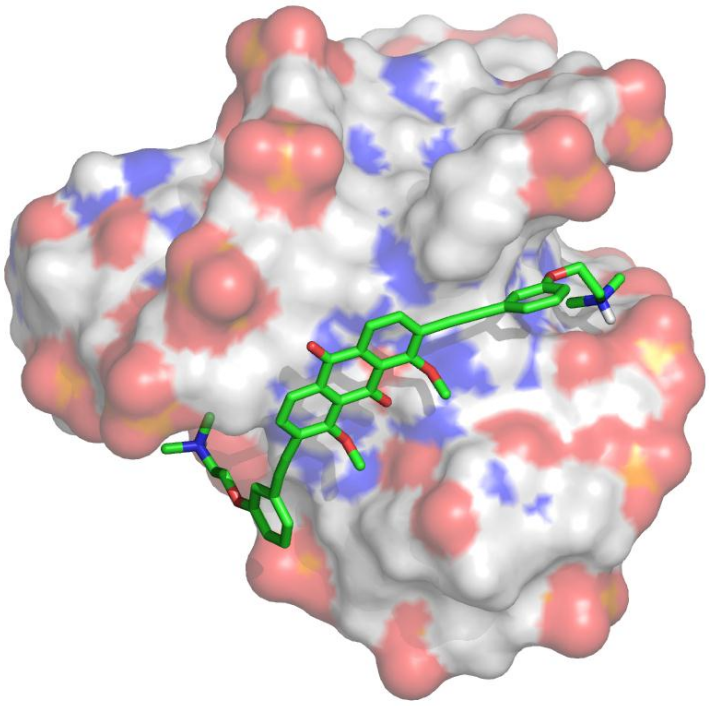


Figure S34. 4 best pose against 2JSM PDB model obtained by IFD method. **4** is indicated as green carbon stick representation, while the DNA is shown as transparent surface. Nonpolar hydrogen atoms are omitted for sake of clarity.



6.0 References.

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