Supplementary Material

Effect Of Structure Variations On The Quadruplex DNA Binding Ability Of Nickel Schiff Base Complexes

Kimberley J. Davis,[a] Nawal M.O. Assadawi, Son Q.T. Pham,[a] Monica L. Birrento,[a] Christopher Richardson,[a] Jennifer L. Beck,[a] Anthony C. Willis[b] and Stephen F. Ralph[a]*

Table of Contents

X-ray Crystallography

Crystals of (**4**), (**6**), (**10**) and (**12**) suitable for X-ray crystallographic analysis were obtained from MeOH-DMSO solvent mixtures. Table S1 contains a summary of the crystallographic data and structural refinements for all four complexes, while selected bond lengths and bond angles are presented in Table S2. For all four complexes, the coordination geometry around the nickel atom was square planar, with the Ni–N and Ni–O bond distances and bond angles at the metal centre all close to standard values.[1-3]

Description of compounds (4) and (6)

Complexes (**4**) and (**6**) were enantiomers of each other, with the chiral carbons at C8 and C8a assigned as (*R*, *R*) for (**4**) and (*S*, *S*) for (**6**). The description given here for (**4**) also applies to the enantiomorphous structure (**6**), with only small changes in bond lengths and angles. The asymmetric units comprised two half-complexes and two water molecules in the monoclinic space group *C*2. Full complexes are formed by crystallographic two-fold rotation, which ensures the same configurations at the stereogenic carbons of the cyclohexanediamine ring. The so-formed full complexes then exist in a slipped co-facial arrangement. Hydrogen bonds were formed between the hydrogen atoms of the hydroxyl groups in the complexes and the oxygens of the water molecules. For complex (**4**) this resulted in interatomic O–H···O distances of 2.00(3) Å for H1 to O6, and 1.75(3) Å for H2 to O5.

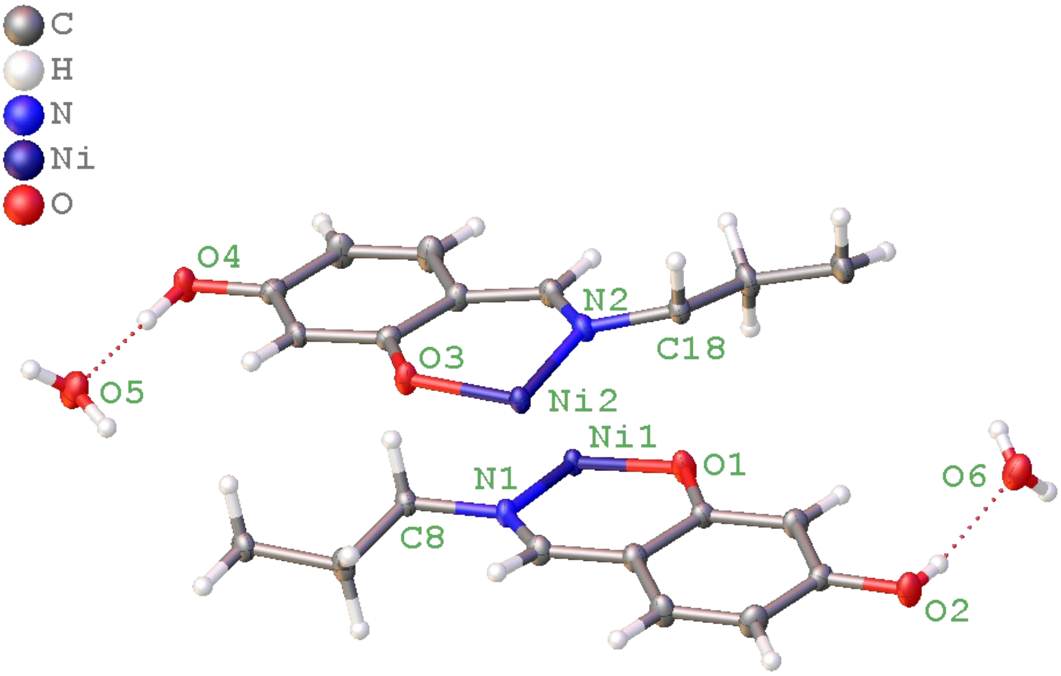


Figure S1 The contents of the asymmetric unit for compound (**4**) with selected atomic labelling.

The average distance between the two complexes is *ca.* 3.9 Å in both cases, however, there are several closer intermolecular contacts arising from H atoms on the cyclohexane ring, which is in a chair conformation. In particular, for (**4**) there is a CH···π close contact between H181 and the C1-C6 centroid plane distance: 2.6133(11) A

There are also contacts between the equivalent H atom (H81) on the other molecule and all six corresponding carbon atoms (C11-C16), giving rise to distances between 2.801 and 2.896 Å.

Description of compound 10

One full metal complex of (**10**) and one molecule of DMSO crystallised as the asymmetric unit in the monoclinic space group $P2_1/n$. The phenolic group of the nickel Schiff base complex is involved in a hydrogen bonding interaction with the oxygen atom of the DMSO molecule (OH···O4 1.79(3) Å). Unlike complex (**9**), and those previously reported,[1] complex (**10**) displays no torsion through the N2-C9-C8-N1 bonds. Also in contrast to most of the other complexes reported here, the nickel molecules are not packed together in a co-facial arrangement. Instead, the molecules assemble with contacts from the phenolic O3 to H221 (attached to C22) of an adjacent complex at 2.61(2) Å and a CH···π interaction between C1-C6 and H211 (attached to C22) at 2.76(2) Å.

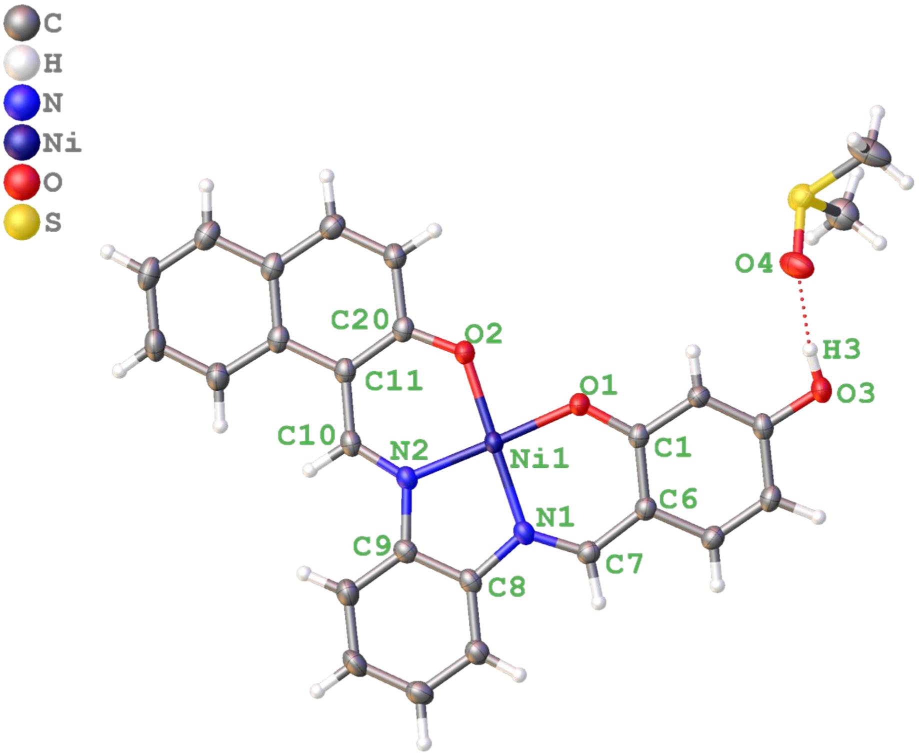


Figure S2 The asymmetric unit of complex (10) with selected atomic labeling.

Description of compound (12)

Compound (**12**) crystallised in the triclinic space group *P*-1 Three molecules of Schiff base complex, here for clarity termed (**12A**), (**12B**) and (**12C**), were present, with the corresponding nickel ions labelled Ni1, Ni2 and Ni3, respectively. One water molecule was also present in the asymmetric unit (O13, H13 and H14).

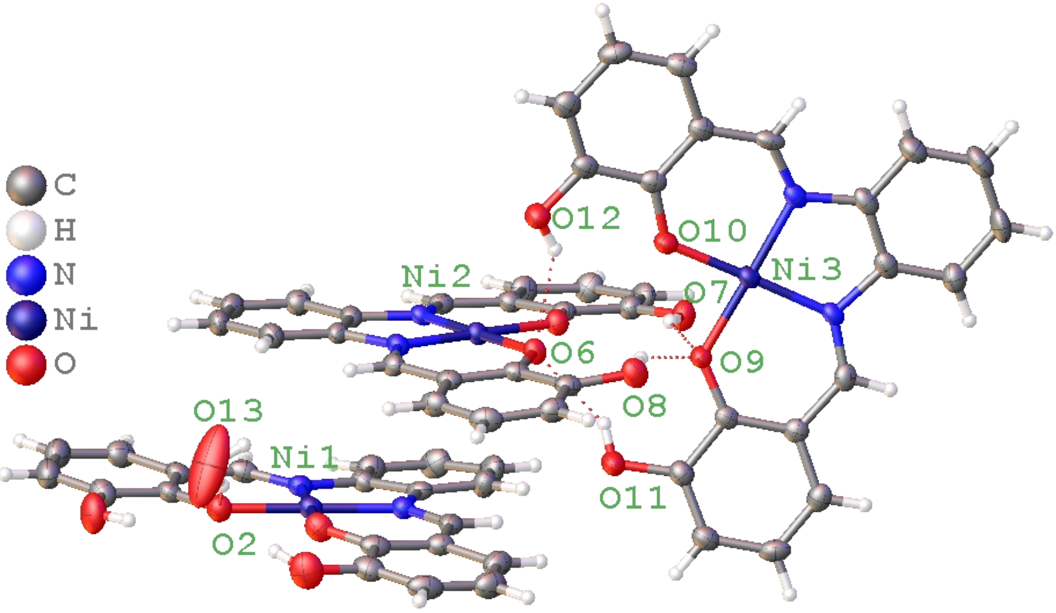


Figure S3 Contents of the asymmetric unit of compound (**12**) with selected atomic labeling.

The phenylenediamine moieties in (**12**) have small N-C-C-N torsion angles of 4.2(5)°, 0.1(6)° and -0.4(4)° for (**12A**), (**12B**) and (**12C**), respectively.

Oxygen atoms O1 and O2 coordinated to the nickel atom of (**12A**) participated in hydrogen bonding with H14 of the lattice water molecule (H14⋯O1 2.192(2) Å and H14⋯O2 2.160(3) Å) The hydrogens of the phenolic groups (H3 and H4) make longer contacts with O13 of the lattice water molecule (H3⋯O13 2.290(4) Å and O13⋯H4 2.345(6) Å).

Complexes (**12A**) and (**12B**) are essentially coplanar with a fold angle of only 2.092(16)° between their all-atom meanplanes and have a meanplane-to-meanplane separation of 3.35 Å. This pair of complexes are co-facial and offset from one another and differ in their orientation by an approximate one-third rotation (Figure S4) and not by crystallographic inversion, as for many of the other complexes reported here.

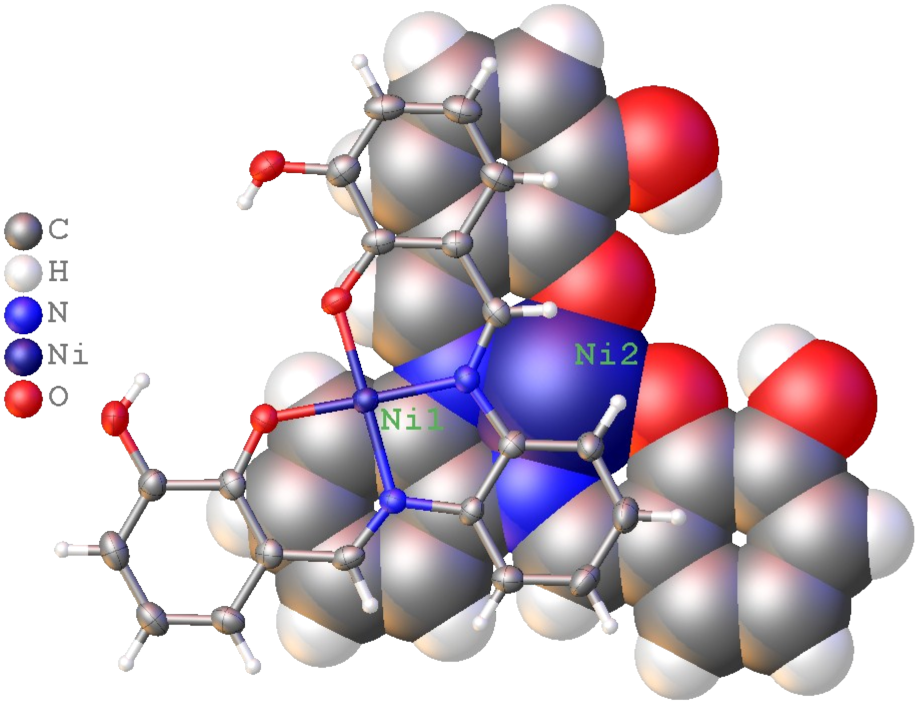


Figure S4 A view of (**12A**) and (**12B**) perpendicular to their meanplanes.

Molecules (**12B**) and (**12C**) assemble together around a set of intermolecular O–H···O hydrogen bonds (Figure S5). Complex (**12B**) makes contacts from donors H7 and H8 to acceptor O9 on complex (**12C**) (H7···O9 2.113(2) Å and H8···O9 2.099(2) Å) with complex (**12C**) participating in a similar set of contacts from donors H11 and H12 to acceptor O6 on complex (**12B**) (H11···O6 2.137(2) Å and H12···O6 2.092(3) Å). This arrangement results in the complexes being almost orthogonally orientated, with an angle of 94.100(13) between their all-atom meanplanes.

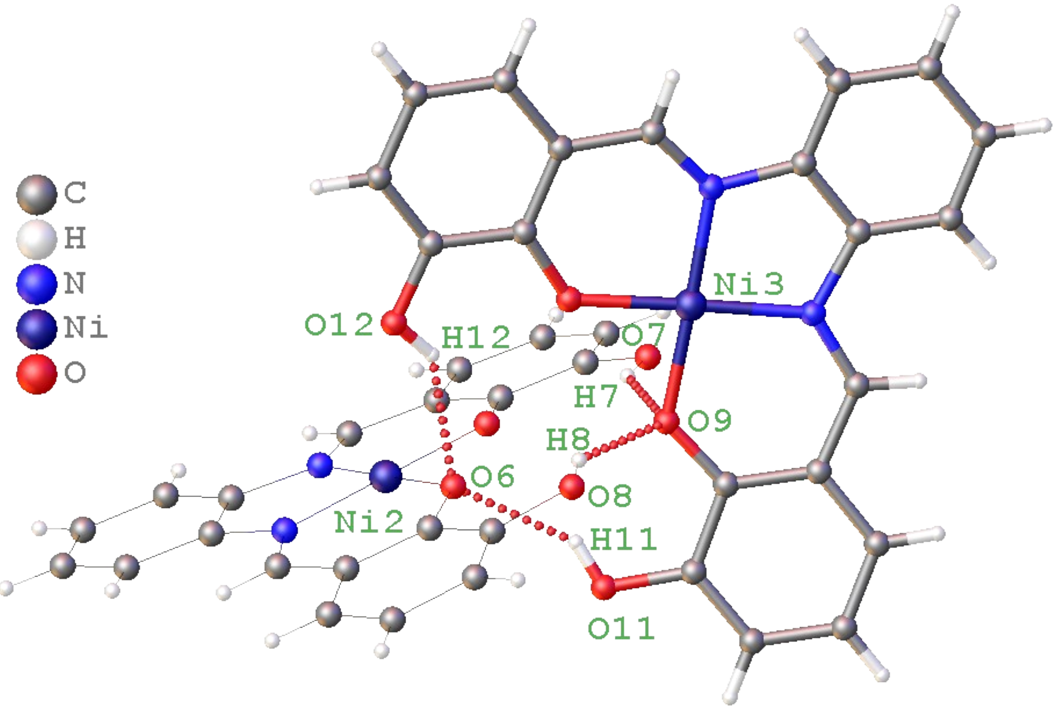


Figure S5 A view of the hydrogen bonding contacts between molecules (**12B**) and (**12C**).

The only contact observed between complexes (**12A**) and (**12C**) was between the phenolic oxygen atom O11 on complex (**12A**) and the hydrogen atom H71, which is bonded to C7 on complex (**12C**), at a distance of 2.59 Å.

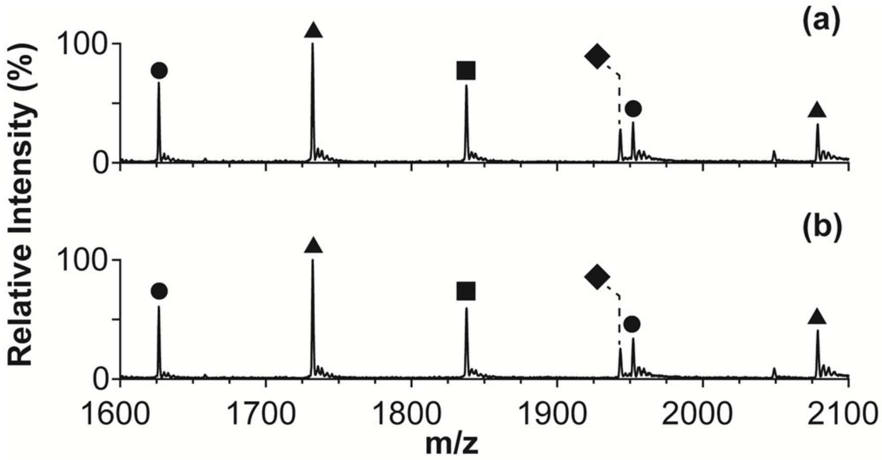


Figure S6 Negative ion ESI mass spectra of solutions containing a 6:1 ratio of different nickel complexes and D2: (a) (5) and (b) (7).

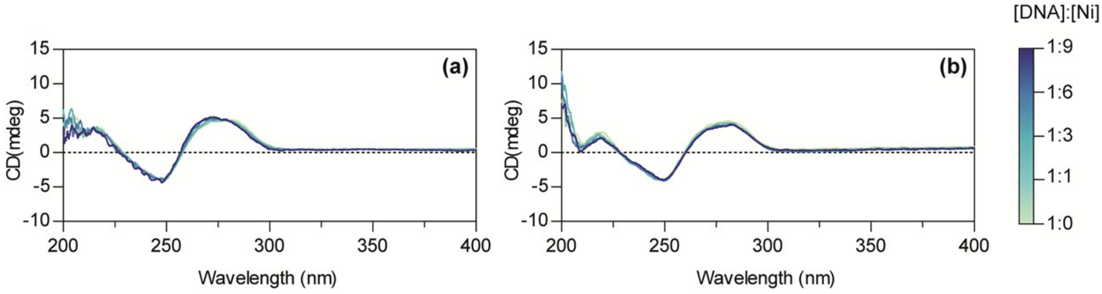


Figure S7 Circular dichroism spectra of solutions containing different ratios of nickel complexes and D2: (a) D2 + (2) and (b) D2 + (11).

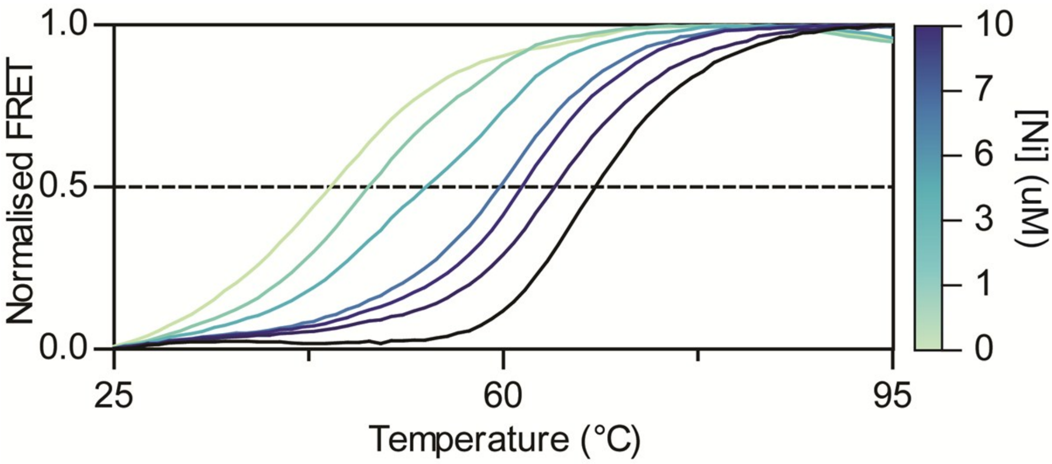


Figure S8 Typical raw FRET melting curves obtained using solutions containing different concentrations of **(7)** and the antiparallel, unimolecular qDNA F21T.

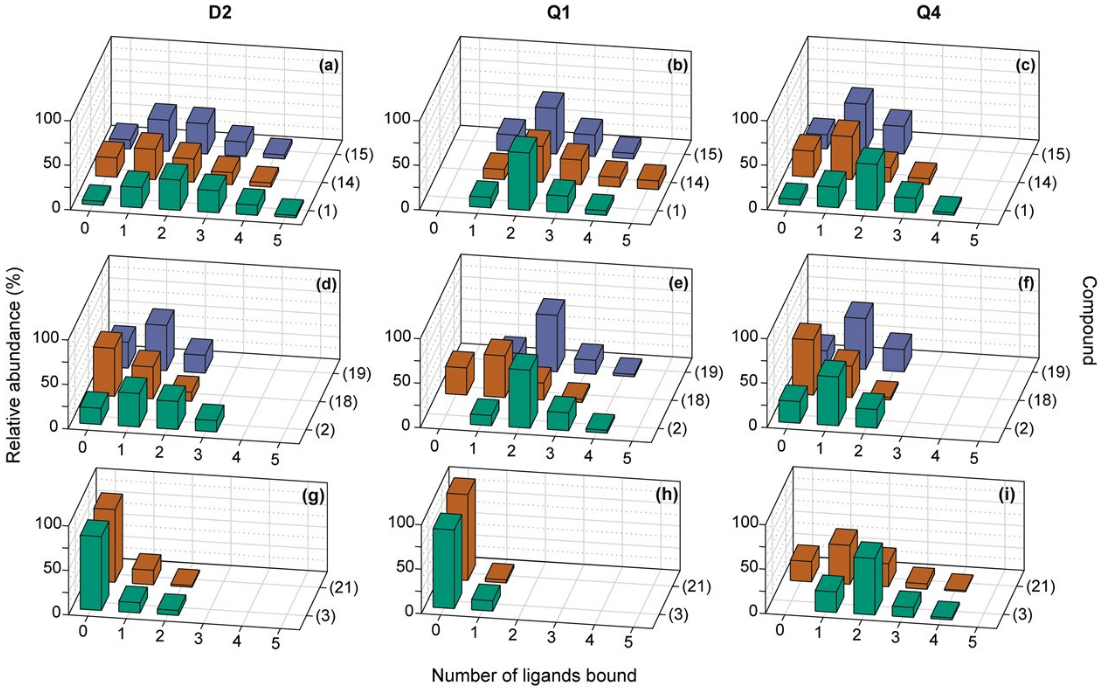


Figure S9 Relative abundances of ions corresponding to free DNA and non-covalent complexes containing different numbers of nickel molecules bound to DNA, found in ESI mass spectra of solutions containing a 6:1 ratio of nickel Schiff base complexes and dsDNA (D2), unimolecular G4-DNA (Q1) or tetramolecular G4-DNA (Q4): (a), (d) and (g) show results obtained from solutions containing D2; (b), (e) and (h) show results obtained from solutions containing Q1; and (c), (f) and (i) show results obtained from solutions containing Q4.

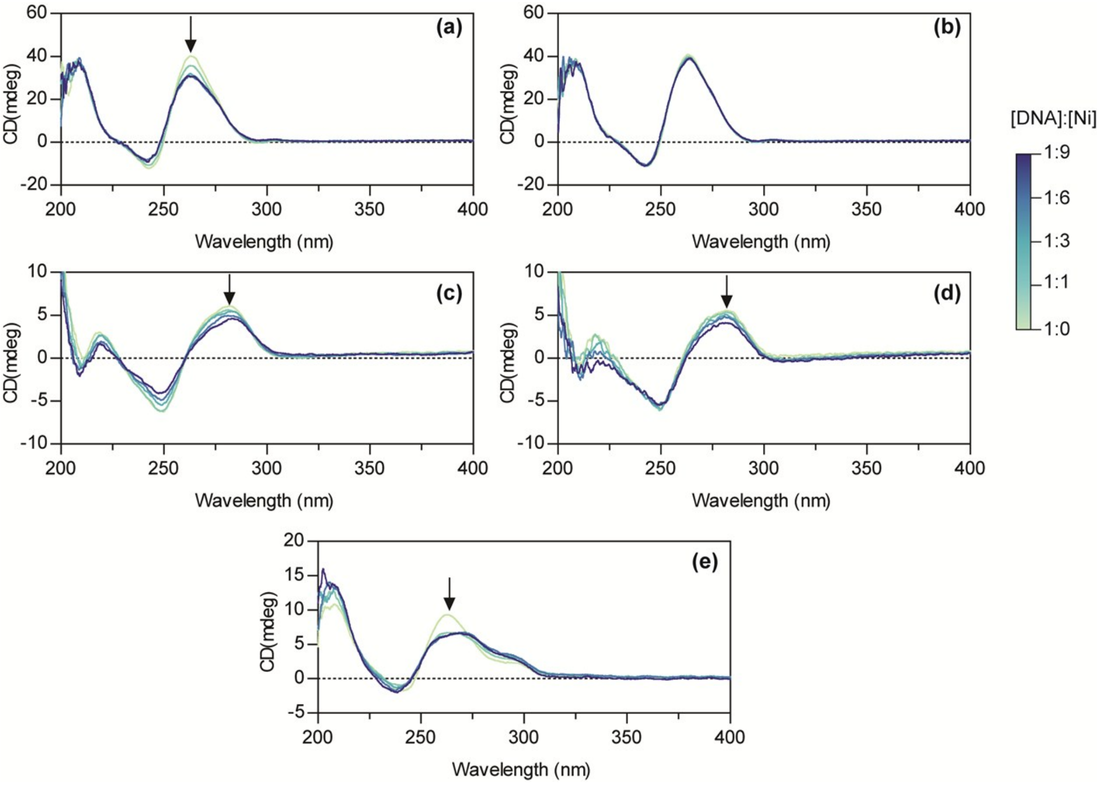


Figure S10 Circular dichroism spectra of solutions containing different ratios (1:0 to 1:9) of D2 and nickel Schiff base complexes. (a) Q4 + (**19**); (b) Q4 + (**18**); (c) D2 + (**15**); (d) D2 + (**14**); (e) Q1 + **(19)**.

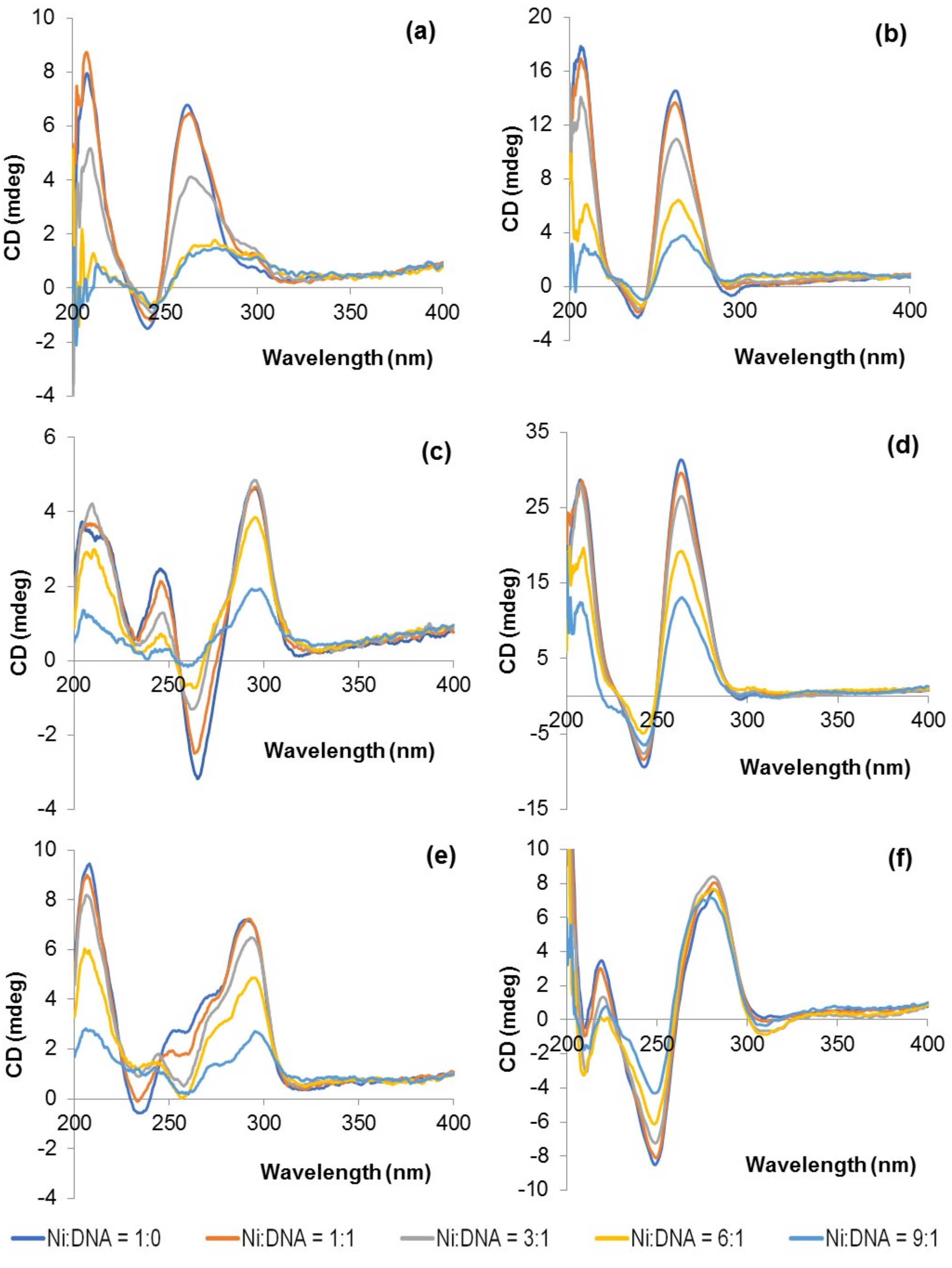


Figure S11. Circular dichroism spectra of solutions containing different ratios of **(1)** and various DNA: (a) Parallel Q1 + **(1)**; (b) Parallel c-kit1 + **(1)**; (c) Anti-parallel Q1 + **(1)**; (d) Parallel Q4 + **(1)**; (e) Hybrid-type 1 Q1 + **(1)**; (f) D2 + **(1).**

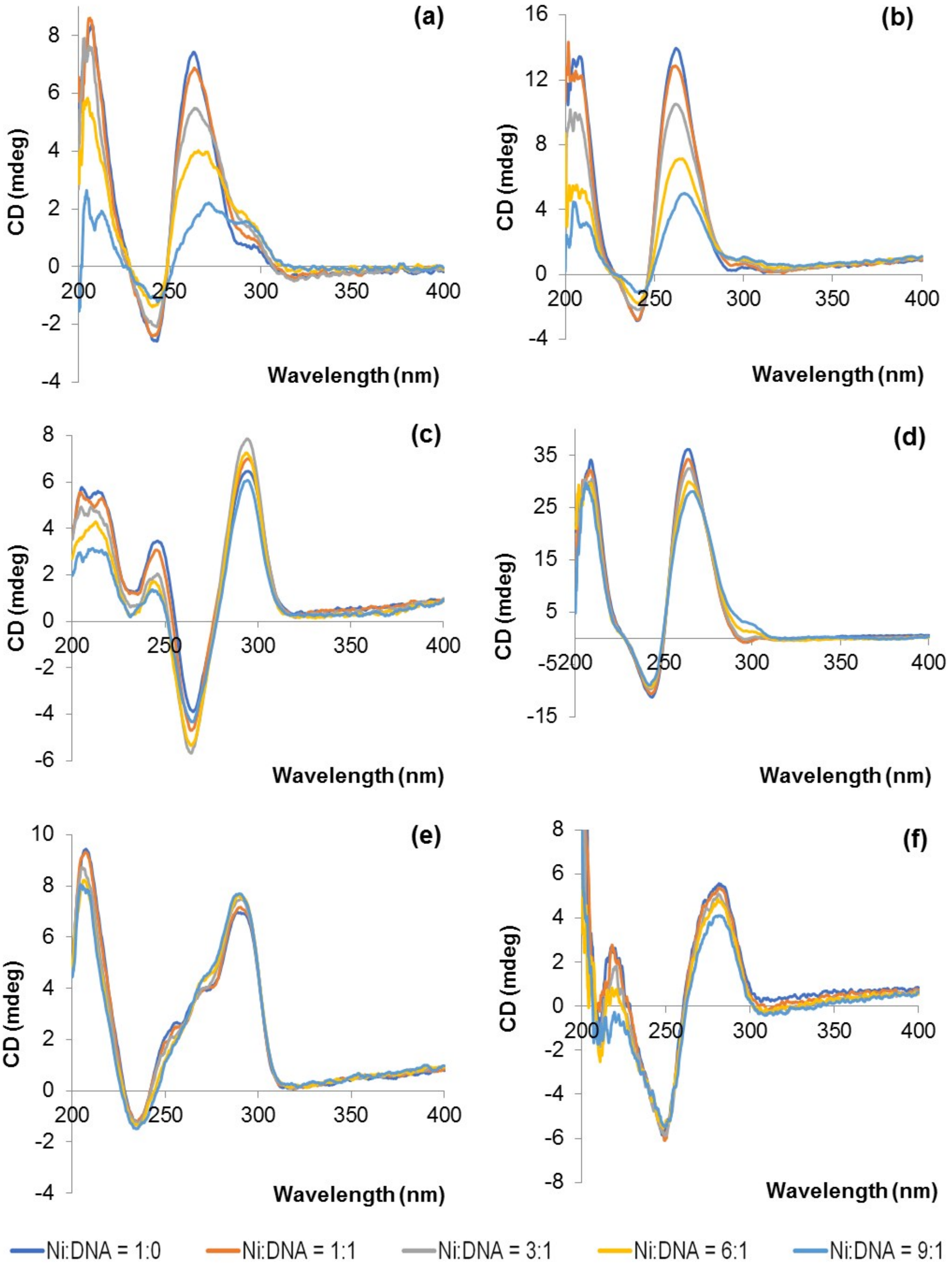


Figure S12. Circular dichroism spectra of solutions containing different ratios of **(14)** and various DNA: (a) Parallel Q1 + **(14)**; (b) Parallel c-kit1 + **(14)**; (c) Anti-parallel Q1 + **(14)**; (d) Parallel Q4 + **(14)**; (e) Hybrid-type 1 Q1 + **(14)**; (f) D2 + **(14)**.

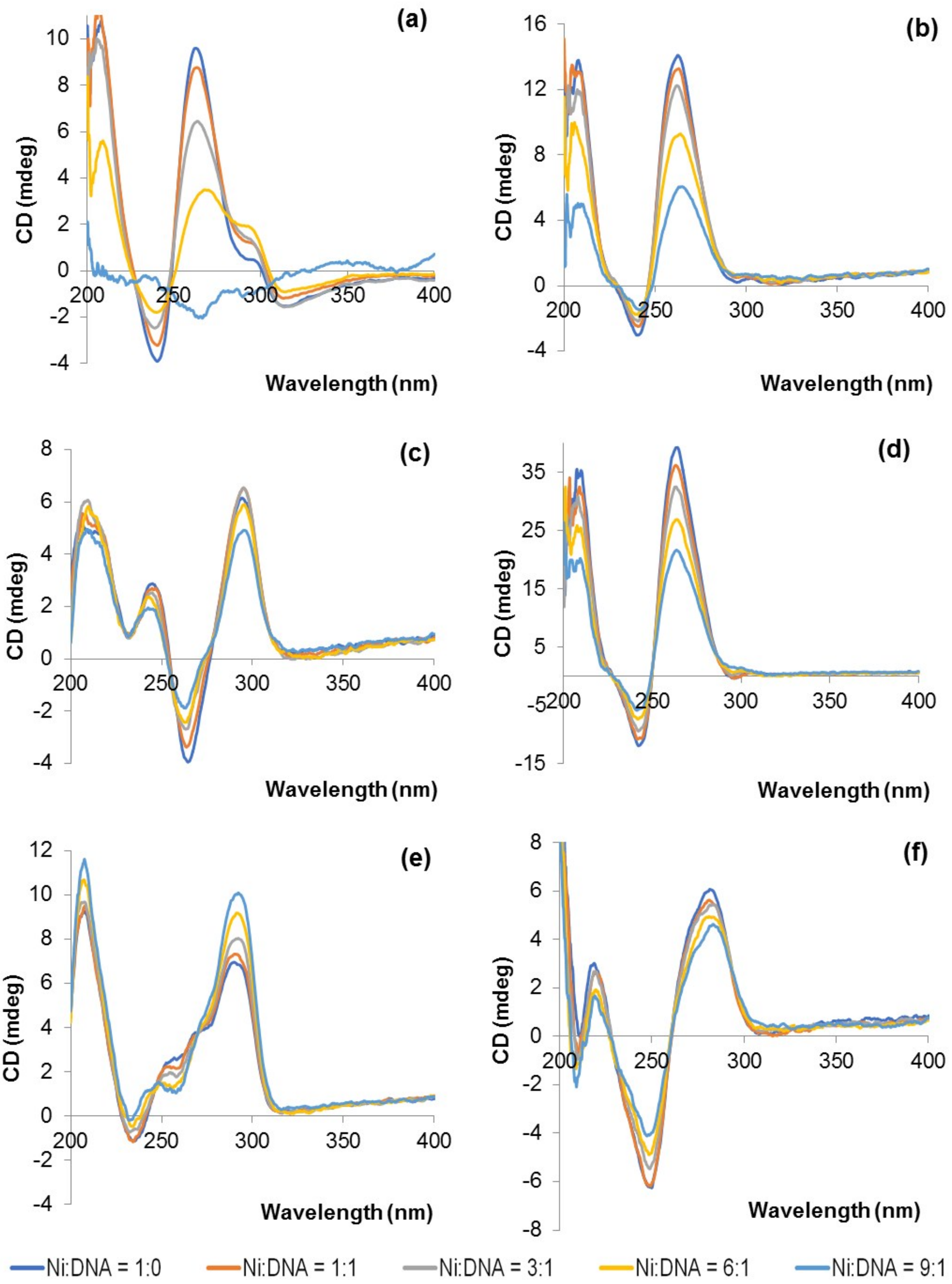


Figure S13. Circular dichroism spectra of solutions containing different ratios of **(15)** and various DNA: (a) Parallel Q1 + **(15)**; (b) Parallel c-kit1 + **(15)**; (c) Anti-parallel Q1 + **(15)**; (d) Parallel Q4 + **(15)**; (e) Hybrid-type 1 Q1 + **(15)**; (f) D2 + **(15)**.

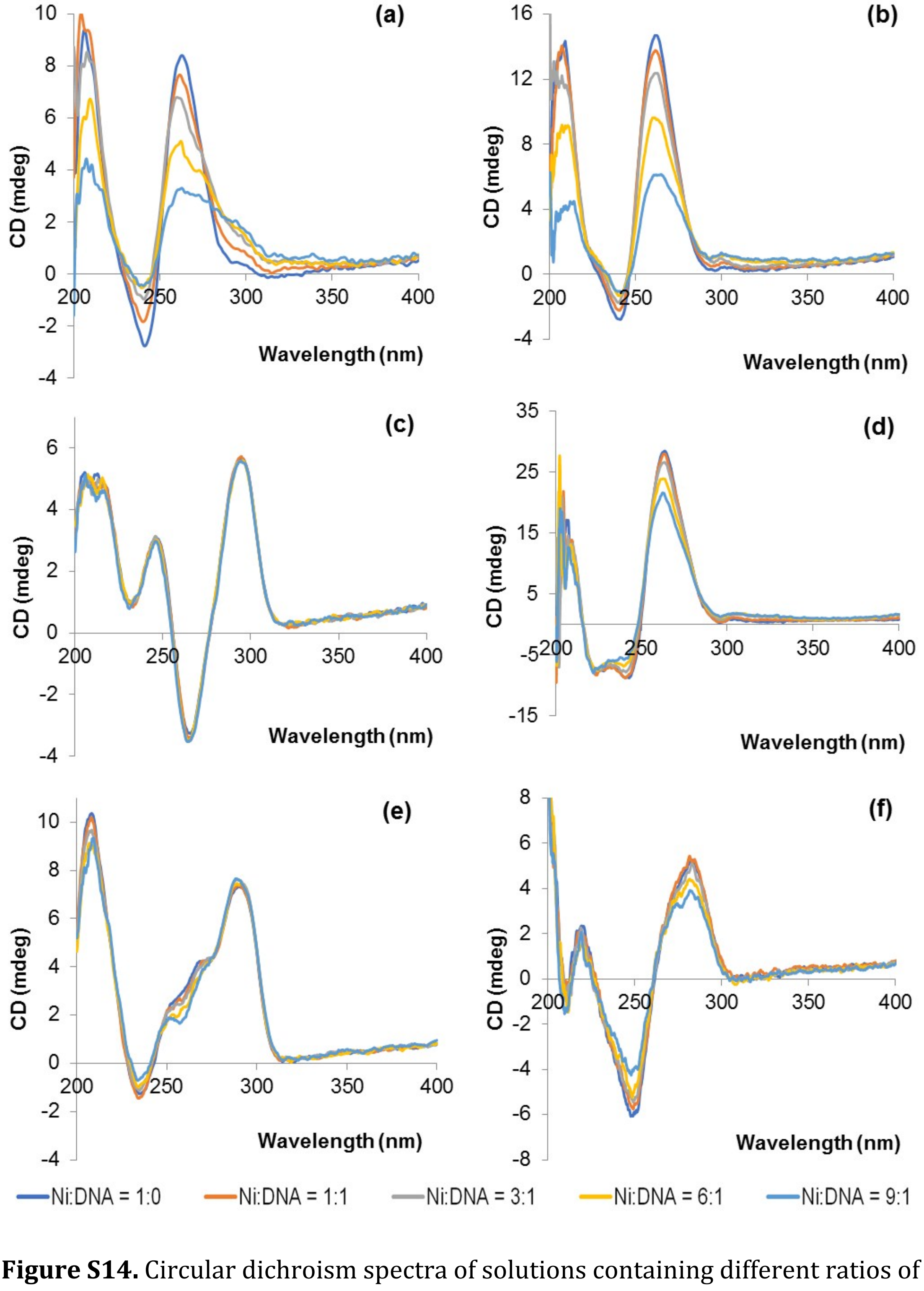


Figure S14. Circular dichroism spectra of solutions containing different ratios of **(3)** and various DNA: (a) Parallel Q1 + **(3)**; (b) Parallel c-kit1 + **(3)**; (c) Anti-parallel Q1 + **(3)**; (d) Parallel Q4 + **(3)**; (e) Hybrid-type 1 Q1 + **(3)**; (f) D2 + **(3).**

Table S1 Summary of crystallographic data for complexes (**4**), (**6**), (**10**) and (**12**).

	(4)	*(6)*	*(10)*	*(12)*
Formula	$C_{20}H_{20}N_2NiO_4 \cdot 2H_2O$	$C_{20}H_{20}N_2NiO_4 \cdot 2H_2O$	$C_{24}H_{16}N_2NiO_3 \cdot C_2H_6OS$	$(C_{20}H_{14}N_2NiO_4)_3 \cdot H_2O$
M_r	447.13	447.13	517.25	1233.18
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$C2$	$C2$	$P2_1/n$	*P-1*
a (Å)	11.1634(2)	11.1734(2)	15.2582(2)	12.2000(4)
b (Å)	20.7999(3)	20.8139(3)	5.6873(1)	15.0224(5)
c (Å)	8.9866(1)	8.9919(2)	26.0174(3)	15.4129(6)
α (°)	90	90	90	74.102(3)
β (°)	112.1248(18)	112.121(2)	102.6233(12)	71.068(3)
γ (°)	90	90	90	69.971(3)
V (Å^3)	1933.02(6)	1937.24(7)	2203.16(6)	2467.88(16)
D_x (Mg m^{-3})	1.536	1.533	1.559	1.659
Z	4	4	4	2
Number of unique reflections	4958	4879	4294	12283
R_{int}	0.020	0.024	0.033	0.066
$R[F^2 > 2\sigma(F^2)]$	0.022	0.024	0.033	0.058
$wR(F^2)$	0.056	0.057	0.089	0.106
Flack parameter	0.004(12)	-0.006(13)	-----	-----
CCDC number	1838238	1838239	1838240	1838241

Table S2 Selected bond lengths (Å) and angles (°) for complexes (**4**), (**6**), (**10**) and (**12**).

	(4)	***(6)***	***(10)***	***(12)***
Ni-O1	1.837(2)	1.839(2)	1.8460(12)	1.847(2)
Ni-O2	1.837(2)	1.839(2)	1.8430(12)	1.843(3)
Ni-N1	1.850(2)	1.850(3)	1.8563(15)	1.855(3)
Ni-N2	1.850(2)	1.850(3)	1.8508(14)	1.862(3)
O1-Ni-O2	82.42(13)	82.65(15)	84.38(5)	83.82(11)
O2-Ni-N2	95.38(8)	95.36(9)	95.20(6)	95.12(12)
O1-Ni-N2	177.19(11)	177.30(12)	178.73(6)	178.25(12)
O2-Ni-N1	177.19(11)	177.30(12)	178.45(6)	178.58(12)
O1-Ni-N1	95.38(8)	95.36(9)	84.07(6)	94.76(12)
N1-Ni-N2	86.87(15)	86.70(17)	86.35(6)	86.29(13)

Table S3 Effect on the CD spectrum of D2 of addition of nickel Schiff base complexes.[a]

	Positive CD band at 279 nm		*Negative CD band at 247 nm*	
Nickel Complex	*Δλ (nm)*	*Δε (mdeg)*	*Δλ (nm)*	*Δε (mdeg)*
(**1**)	-1.9	0.4	-0.1	2.5
(**2**)	-5.8	0.3	0.4	0.3
(**3**)	0.8	1.6	-0.7	2.0
(**5**)	-7.9	1.8	-1.3	0.1
(**7**)	-7.1	0.8	2.9	0.3
(**9**)	-7.5	4.5	1.0	0.3
(**11**)	1.0	-0.5	-1.0	0.1

[a] All Δλ and Δε values are the difference between the values for free DNA and those for a solution containing a DNA:metal complex ratio of 1:9. Negative Δλ values indicate a blue shift; positive values indicate a red shift. Δε values are the difference between ε at this wavelength for the solution containing no metal complex, and ε at the wavelength of maximum ellipticity for the solution with the highest DNA:metal complex ratio.

Table S4 Effect on the CD spectrum of Q4 of addition of nickel Schiff base complexes.[a]

	Positive CD band at 260 nm		*Negative CD band at 240 nm*	
Nickel Complex	*Δλ (nm)*	*Δε (mdeg)*	*Δλ (nm)*	*Δε (mdeg)*
(**1**)	0.7	11.6	0.6	0.4
(**2**)	-1.3	2.0	-0.9	1.7
(**3**)	-1.4	6.5	-1.5	3.1
(**5**)	-1.3	5.2	0.2	1.8
(**7**)	-0.6	6.7	-0.2	3.4
(**9**)	0	0.8	-0.9	0.6
(**11**)	-0.6	1.1	-0.4	0.4

[a] All Δλ and Δε values are the difference between the values for free DNA and those for a solution containing a DNA:metal complex ratio of 1:7. Negative Δλ values indicate a blue shift; positive values indicate a red shift. Δε values are the difference between ε at this wavelength for the solution containing no metal complex, and ε at the wavelength of maximum ellipticity for the solution with the highest DNA:metal complex ratio.

Table S5 Effect on the CD spectrum of Q1 of addition of nickel Schiff base complexes.[a]

	Positive CD band at 260 nm		*Negative CD band at 240 nm*	
Nickel Complex	*Δλ (nm)*	*Δε (mdeg)*	*Δλ (nm)*	*Δε (mdeg)*
(**1**)	2.8	7.0	0.9	1.9
(**2**)	-4.3	1.9	-0.7	1.0
(**3**)	-1.6	5.5	-4.3	3.3
(**5**)	-5.0	0.3	0.6	0
(**7**)	1.9	3.3	-0.1	2.3
(**9**)	0.9	0.1	-1.5	0.5
(**11**)	1.4	1.8	-1.4	0.6

[a] All Δλ and Δε values are the difference between the values for free DNA and those for a solution containing a DNA:metal complex ratio of 1:7. Negative Δλ values indicate a blue shift; positive values indicate a red shift. Δε values are the difference between ε at this wavelength for the solution containing no metal complex, and ε at the wavelength of maximum ellipticity for the solution with the highest DNA:metal complex ratio.

Table S6 Values of ΔT_m derived from FRET melting experiments performed using solutions containing different concentrations of nickel complexes and F21T. The concentration of F21T in all experiments was 0.2 mM. Tm for F21T alone was 43.63 ± 0.26 °C [a]

	ΔT_m (°C)					
	1 μM	*2 μM*	*4 μM*	*5 μM*	*7 μM*	*10 μM*
(**1**)	21.74 ± 0.31	33.86 ± 0.27	41.75 ± 0.14	43.61 ± 0.25	46.21 ± 0.45	45.22 ± 0.41
(**5**)	3.47 ± 0.26	8.62 ± 0.19	16.31 ± 0.57	16.5 ± 0.32	20.12 ± 0.13	24.93 ± 0.14
(**7**)	4.16 ± 0.30	9.31 ± 0.16	16.13 ± 0.09	18.29 ± 0.10	21.35 ± 0.14	24.96 ±0.17
(**9**)	1.15 ± 0.24	2.84 ± 0.19	9.24 ± 0.23	10.42 ± 0.31	13.92 ± 0.23	20.51 ± 0.43
(**11**)	1.26 ± 0.22	2.90 ± 0.28	12.05 ± 0.41	10.33 ± 0.31	18.94 ± 0.33	31.89 ± 0.31

[a] All error values are standard errors.

Table S7 Effect on the CD spectrum of D2 of addition of nickel Schiff base complexes featuring pendant groups in different positions.[a]

	Positive CD band at 279 nm		*Negative CD band at 247 nm*	
Nickel Complex	*Δλ (nm)*	*Δε (mdeg)*	*Δλ (nm)*	*Δε (mdeg)*
(**1**)	-1.9	0.4	-0.1	2.5
(**14**)	0.7	1.5	1.5	0.4
(**15**)	1.9	1.5	-2.6	2.2
(**2**)	-5.8	0.3	0.4	0.3
(**18**)	1.1	0.8	2.2	1.2
(1**9**)	-2.8	1.4	-2.6	3.3
(**3**)	0.8	1.6	-0.7	2.0
(21)	0.7	1.2	0.6	0.9

[a] All Δλ and Δε values are the difference between the values for free DNA and those for a solution containing a DNA:metal complex ratio of 1:9. Negative Δλ values indicate a blue shift; positive values indicate a red shift. Δε values are the difference between ε at this wavelength for the solution containing no metal complex, and ε at the wavelength of maximum ellipticity for the solution with the highest DNA:metal complex ratio.

Table S8 Effect on the CD spectrum of Q4 of addition of nickel Schiff base complexes featuring pendant groups in different positions.[a]

	Positive CD band at 260 nm		*Negative CD band at 240 nm*	
Nickel Complex	*Δλ (nm)*	*Δε (mdeg)*	*Δλ (nm)*	*Δε (mdeg)*
(**1**)	0.7	11.6	0.6	0.4
(**14**)	2.9	8.1	-1.7	2.3
(**15**)	-0.5	17.6	-0.9	6.1
(**2**)	-1.3	2.0	-0.9	1.7
(**18**)	0.9	1.7	-0.8	0.0
(**19**)	-1.2	9.2	-0.4	3.0
(**3**)	-1.4	6.5	-1.5	3.1
(21)	1.5	11.8	-1.2	5.1

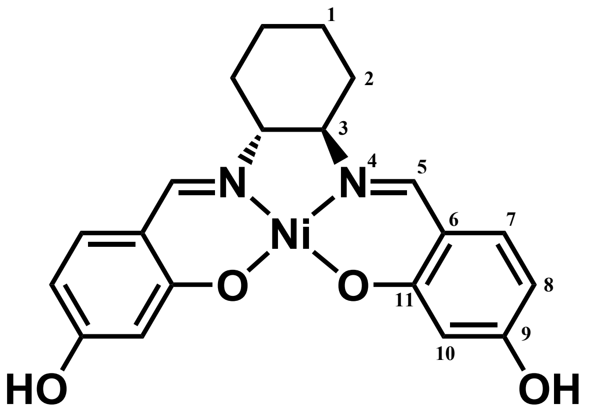
[a] All Δλ and Δε values are the difference between the values for free DNA and those for a solution containing a DNA:metal complex ratio of 1:9. Negative Δλ values indicate a blue shift; positive values indicate a red shift. Δε values are the difference between ε at this wavelength for the solution containing no metal complex, and ε at the wavelength of maximum ellipticity for the solution with the highest DNA:metal complex ratio.

Table S9 Effect on the CD spectrum of Q1 of addition of nickel Schiff base complexes featuring pendant groups in different positions.[a]

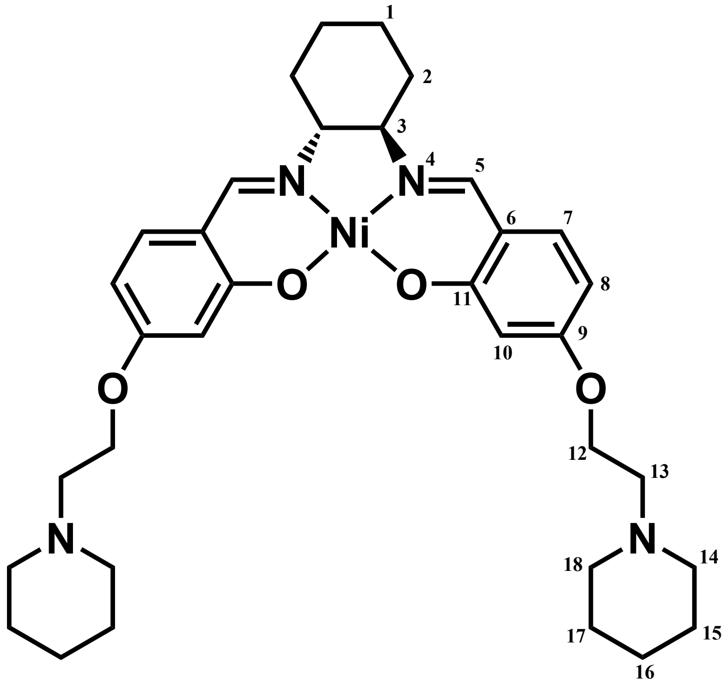
	Positive CD band at 260 nm		*Negative CD band at 240 nm*	
Nickel Complex	*Δλ (nm)*	*Δε (mdeg)*	*Δλ (nm)*	*Δε (mdeg)*
(**1**)	2.8	7.0	0.9	1.9
(**14**)	2.7	3.4	-2.4	1.2
(**15**)	5.3	6.1	0.1	2.1
(**2**)	-4.3	1.9	-0.7	1.0
(**18**)	0.2	1.4	0.4	0.3
(**19**)	6.6	2.6	-2.9	0.0
(**3**)	-1.6	5.5	-4.3	3.3
(21)	-0.2	3.1	2.3	0.7

[a] All Δλ and Δε values are the difference between the values for free DNA and those for a solution containing a DNA:metal complex ratio of 1:9. Negative Δλ values indicate a blue shift; positive values indicate a red shift. Δε values are the difference between ε at this wavelength for the solution containing no metal complex, and ε at the wavelength of maximum ellipticity for the solution with the highest DNA:metal complex ratio.

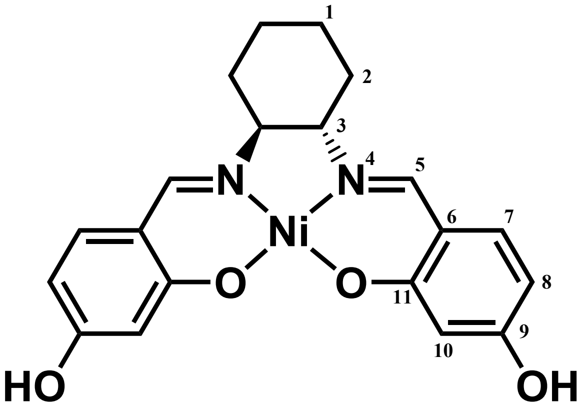
Chemical structures of (4)–(21) featuring the numbering scheme of carbon (and hydrogen) atoms used for assigning NMR signals.



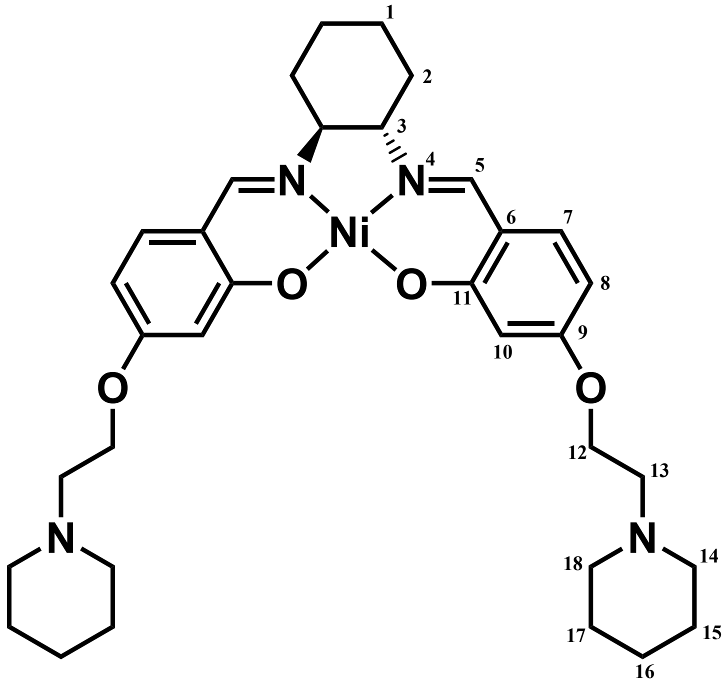
N,N′-Bis-(4-hydroxysalicylidine)-(*1R,2R*)-diaminocyclohexanenickel(II) **(4)**



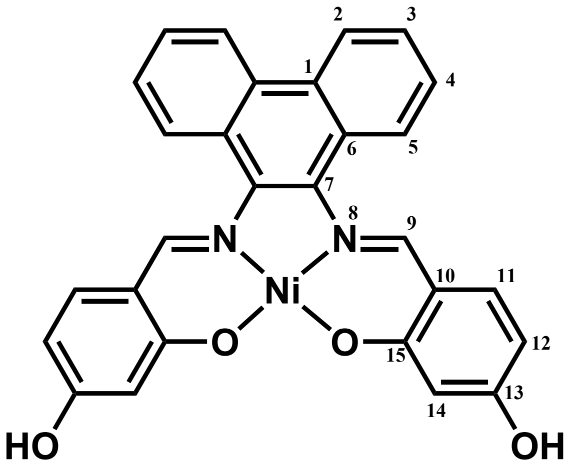
N,N′-Bis-[(4-(piperidin-1-yl)ethoxy)salicylidine]-(*1R,2R*)-diaminocyclohexanenickel(II) **(5)**



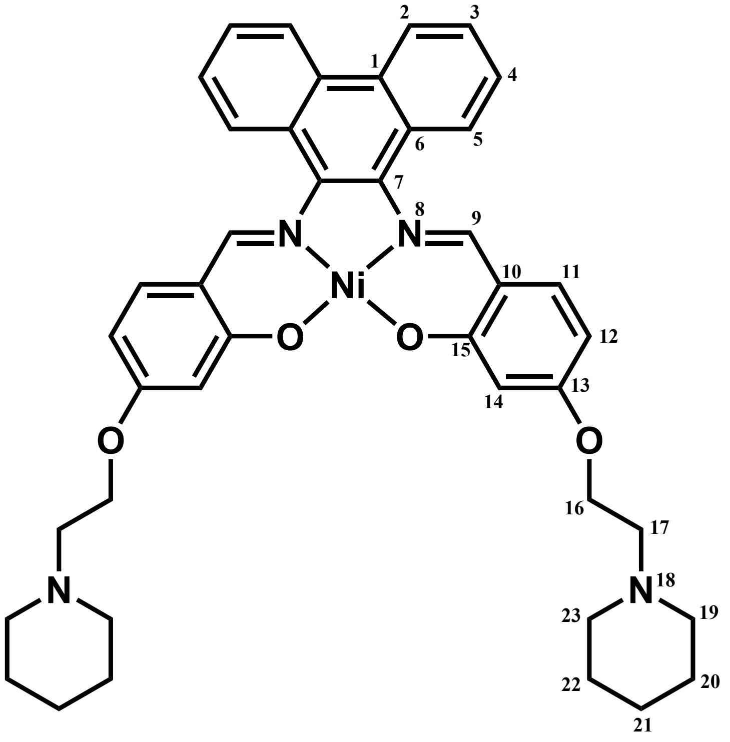
N,N′-Bis-(4-hydroxysalicylidine)-(*1S,2S*)-diaminocyclohexanenickel(II) **(6)**



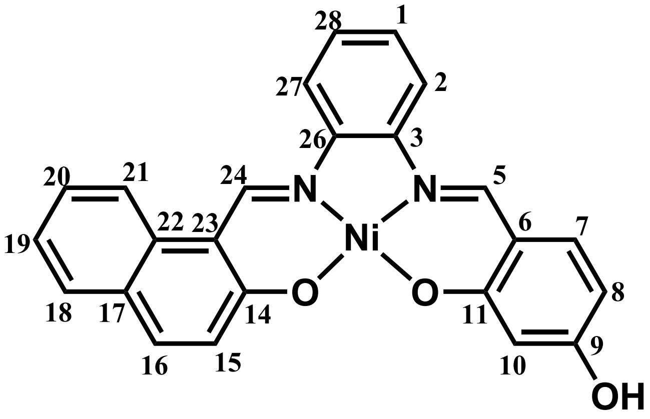
N,N′-Bis-[(4-(piperidin-1-yl)ethoxy)salicylidine]-(*1S,2S*)-diaminocyclohexanenickel(II) **(7)**



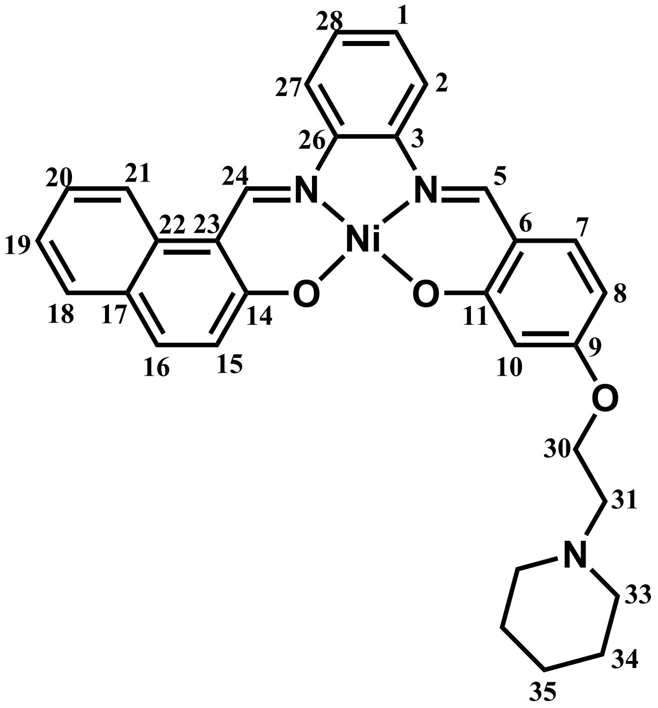
N,N′-Bis-(4-hydroxysalicylidine)diaminophenanthrenenickel(II) **(8)**



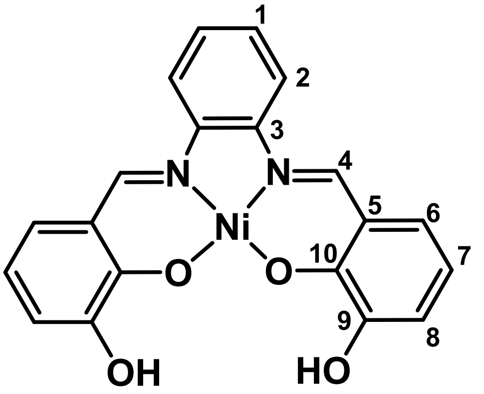
N,N′-Bis-[4-((piperidin-1-yl)ethoxy)salicylidine]diaminophenanthrene nickel(II) **(9)**



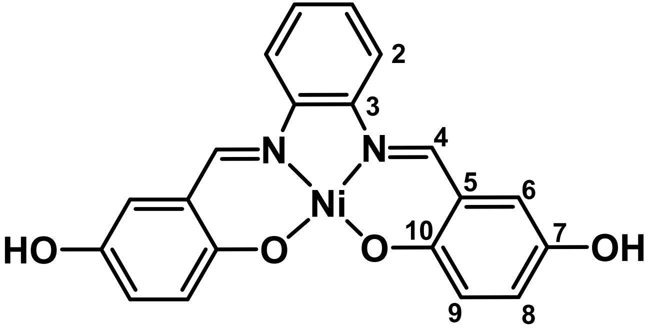
(4-Hydroxysalicylidine)(naphthalen-2-oxy)phenylenediaminenickel(II) **(10)**



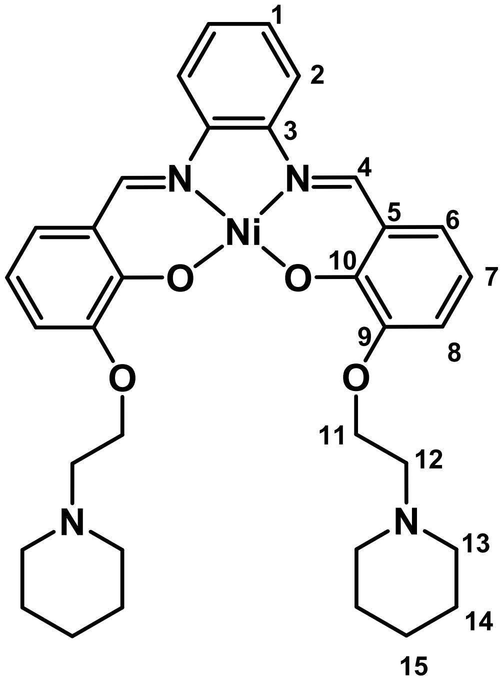
((Piperidin-1-yl)ethoxy)salicylidine-2-(naphthyloxy)-phenylenediaminenickel(II) **(11)**



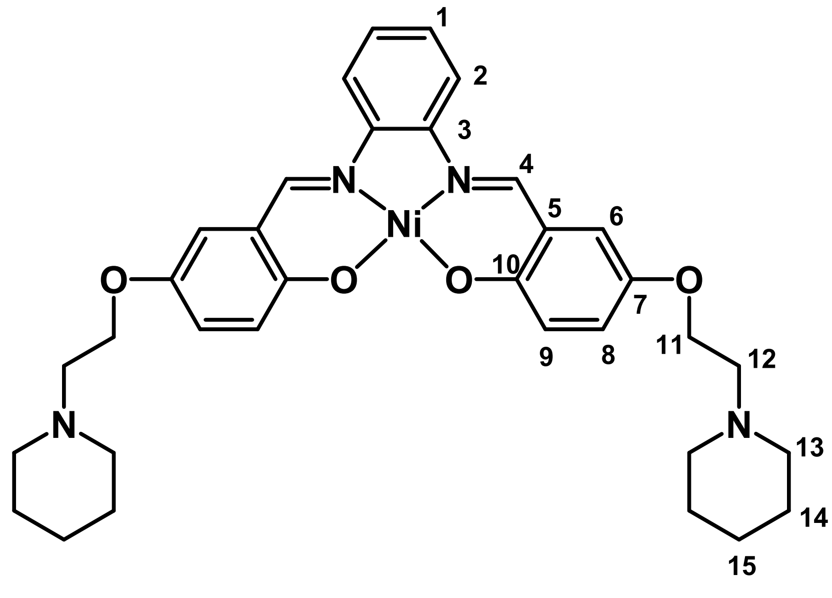
N,N′-Bis-(3-hydroxysalicylidine)phenylenediaminenickel(II) **(12)**



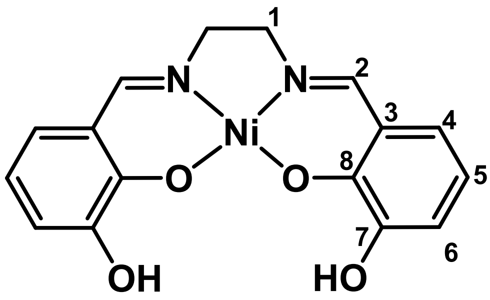
N,N′-Bis-(5-hydroxysalicylidine)phenylenediaminenickel(II) **(13)**



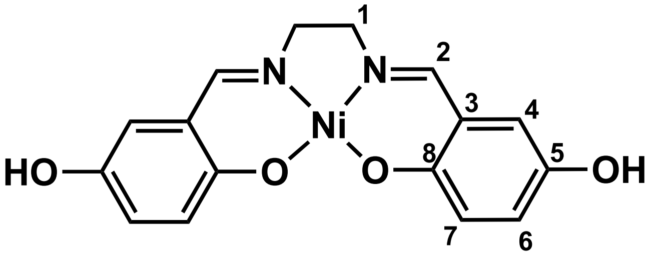
N,N′-Bis[3-((piperidin-1-yl)ethoxy)salicylidine]phenylenediaminenickel(II) **(14)**



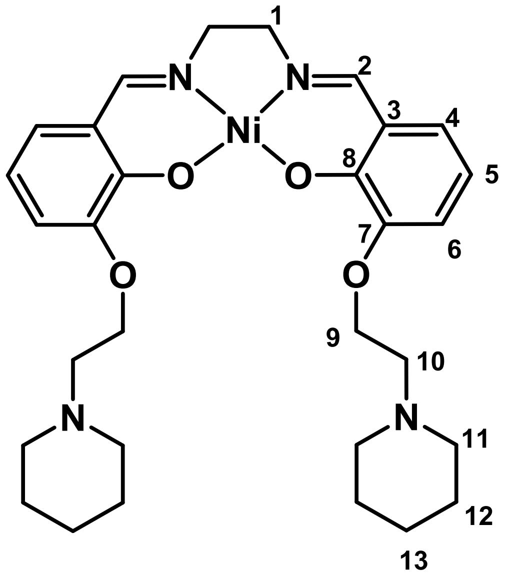
N,N′-Bis[5-((piperidin-1-yl)ethoxy)salicylidine]phenylendiaminenickel(II) **(15)**



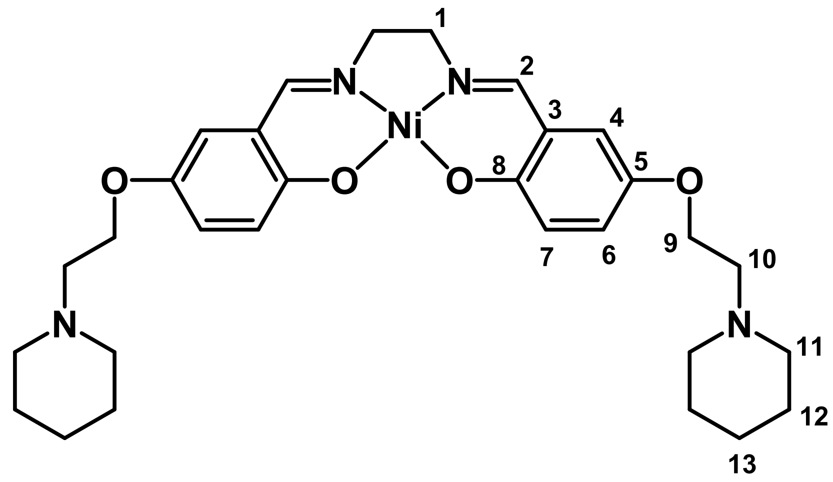
N,N′-Bis-(3-hydroxysalicylidine)ethylenediaminenickel(II) **(16)**



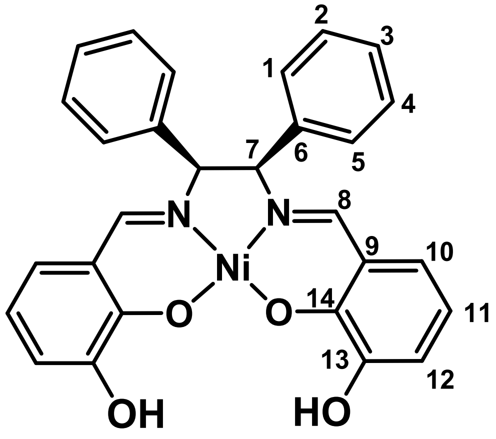
N,N′-Bis-(5-hydroxysalicylidine)ethylenediaminenickel(II) **(17)**



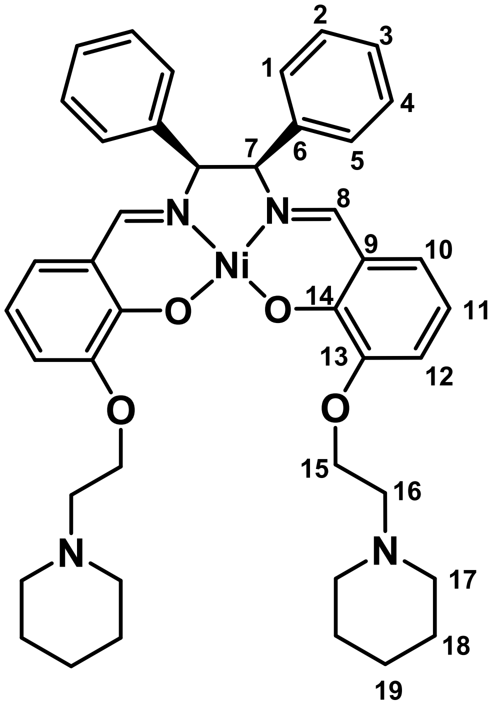
N,N′-Bis[3-((piperidin-1-yl)ethoxy)salicylidine]ethylenediaminenickel(II) **(18)**



N,N′-Bis[5-((piperidin-1-yl)ethoxy)salicylidine]ethylenediaminenickel(II) **(19)**



N,N′-Bis-(3-hydroxysalicylidine)-*meso*-diphenylethylenediaminenickel(II) **(20)**



N,N′-Bis[3-((piperidin-1-yl)ethoxy)salicylidine]-*meso*-diphenyl-ethylenediaminenickel(II) **(21)**

References:

1. Davis, K. J.; Richardson, C.; Beck, J. L.; Knowles, B. M.; Guedin, A.; Mergny, J.-L.; Willis, A. C.; Ralph, S. F., Synthesis and characterisation of nickel Schiff base complexes containing the meso-1,2-diphenylethylenediamine moiety: selective interactions with a tetramolecular DNA quadruplex. *Dalton transactions (Cambridge, England : 2003)* **2015,** *44*, 3136-3150.
2. Arola-Arnal, A.; Benet-Buchholz, J.; Neidle, S.; Vilar, R., Effects of metal coordination geometry on stabilization of human telomeric quadruplex DNA by square-planar and square-pyramidal metal complexes. *Inorganic Chemistry* **2008,** *47* (24), 11910-11919.
3. Carbonaro, L.; Isola, M.; La Pegna, P.; Senatore, L.; Marchetti, F., Spectrophotometric study of the equilibria between nickel(II) Schiff base complexes and alkaline earth or nickel(II) cations in acetonitrile solution. *Inorganic Chemistry* **1999,** *38* (24), 5519-5525.