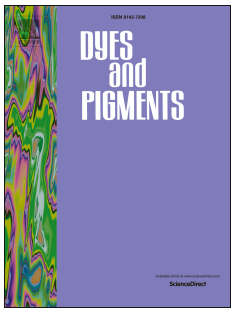
Accepted Manuscript



Synthesis of 4-Amino Substituted 1,8-Naphthalimide Derivatives Using Palladium-mediated Amination

Cassandra L. Fleming , Trent D. Ashton , Frederick M. Pfeffer

PII: S0143-7208(14)00186-7

DOI: 10.1016/j.dyepig.2014.05.006

Reference: DYPI 4378

To appear in: *Dyes and Pigments*

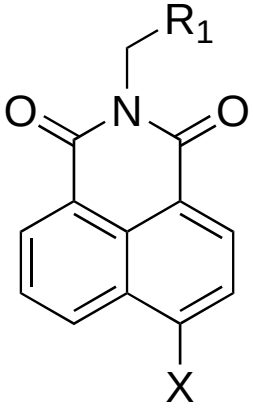
Received Date: 25 February 2014

Revised Date: 4 May 2014

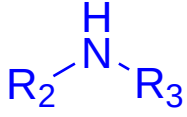
Accepted Date: 6 May 2014

Please cite this article as: Fleming CL, Ashton TD, Pfeffer FM, Synthesis of 4-Amino Substituted 1,8-Naphthalimide Derivatives Using Palladium-mediated Amination, *Dyes and Pigments* (2014), doi: 10.1016/j.dyepig.2014.05.006.

R_1 = 'lengthy/large'



+



Buchwald-Hartwig Amination

This work

X = Br, Pd, 40 °C

Mild reaction conditions

Modest excess of amine (3 equiv)

High yields (70–90%)

S_NAr

X = Br or Cl ≥ 100 °C

Large excess of amine (≥ 10 equiv)

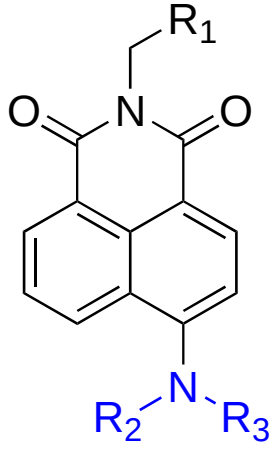
Poor conversion of starting materials

S_NAr

X = NO_2, 21 °C, DMF

Poor mass recovery

Low isolated yields



Synthesis of 4-Amino Substituted 1,8-Naphthalimide Derivatives Using Palladium-mediated Amination

Cassandra L. Fleming, Trent D. Ashton and Frederick M. Pfeffer*

Research Centre for Chemistry and Biotechnology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria, 3216, Australia

*Corresponding author. Tel: +61 3 5227 1439, Email: fred.pfeffer@deakin.edu.au

Graphical Abstract

Abstract

Successful amination of 4-bromo-1,8-naphthalimides with 'lengthy' imide *N*-functionality has been achieved using a general palladium mediated approach (conventional thermal protocols were sub-optimal). Only readily available Pd/ligand combinations were considered and the resulting Buchwald-Hartwig procedure using $Pd_2(dba)_3$, Xantphos and Cs_2CO_3 is high yielding, relatively mild (40–80 °C, 24 h, yields 70–90%), requires only a modest excess of amine (3.0 equiv) and works equally well with other imide *N*-substituents. As such, the protocol complements existing methods but is superior for more complex substrates. Herein we compare this Pd mediated approach to the methods most commonly used and further demonstrate its utility by synthesising a number of new, highly fluorescent, 4-aminonaphthalimides.

Keywords: synthesis, 4-aminonaphthalimides, Buchwald-Hartwig, amination

1. Introduction

Historically, 4-amino-1,8-naphthalimides have been widely employed as components of fluorescent dyes [1]. More recently, these fluorophores have been used in a number of more specialist applications including; cellular imaging [2], DNA intercalation [3] and supramolecular chemistry [4]. With these more sophisticated end uses, higher levels of structural complexity is required. Therefore, more advanced and practical methodology for the synthesis of substituted naphthalimides is necessary. Established methods employed for the synthesis of 4-amino-1,8-naphthalimide derivatives involve nucleophilic aromatic substitution by either (i) heating ($\geq$ 100 °C) 4-halo-naphthalimides with the desired amine [5] or (ii) treating 4-nitro-naphthalimide with the amine in DMF at 21 °C (Figure 1) [6]. While the use of copper catalysts to aid the transformation has been known for some time (Ullmann condensation) [7], it is only recently that a handful of examples of palladium mediated coupling of anilines have also emerged to access highly specific 4-arylamino-1,8-naphthalimide derivatives [8]. Herein, we describe a general, high yielding, Buchwald-Hartwig cross coupling protocol for the synthesis of 4-amino-1,8-naphthalimde derivatives using $Pd_2(dba)_3$ and Xantphos—one of the most readily available (and affordable) Pd source and ligand combinations known.

Figure 1. Comparison of methodology for synthesis of 4-amino-1,8-naphthalimide derivatives. *Top*: existing S_NAr approaches,[9–11] *Bottom*: Buchwald-Hartwig amination.

2. Results and Discussion

Substitution reactions of *N*-ethyl-4-bromo-1,8-naphthalimide (**1**) are usually accomplished using nucleophilic aromatic substitution (S_NAr) [9–11]. For example, nucleophilic substitution of 4-bromonaphthalimide **1** with morpholine (5.0 equiv.) afforded the 4-amino derivative **3** (83%) after heating by microwave irradiation at 100 °C for 4 hours (Scheme 1).

Unfortunately it is our experience that this method gives poor yields with longer/larger *N*-alkyl imide substituents. Indeed, when a solution of *N*-heptyl naphthalimide **2**, morpholine (5.0 equiv) and Et_3N in EtOH was heated by microwave irradiation at 100 °C for 4 hours poor conversion of starting materials was observed and only 40% of the desired 4-amino-1,8-naphthalimide derivative **4** was isolated (Scheme 1). While exceptions exist in the literature [12], protocols for the synthesis of related imides generally require the use of high boiling solvents (eg. 1,4-dioxane or 2-methoxyethanol), high temperatures (≥ 100 °C) [5] and a large excess of amine (≥ 10 equiv) [13]. Such reaction conditions are not always practical.

Scheme 1. Nucleophilic aromatic substitution of 4-bromo naphthalimide derivatives with morpholine highlighting the lower yields obtained when longer N-substituents are present.

When the *N*-imide substituent contained additional functionality such as an ester (for example, imide **7** formed in 92% yield by the condensation of commercially available 1,8-naphthalic anhydride **5** with methyl 6-aminohexanoate hydrochloride), the S_NAr reaction again gave low yields (Scheme 2). Indeed, only 45% of the desired 4-amino-1,8-naphthalimide **9** was isolated after heating 4-bromo naphthalimide **7** with morpholine (5.0 equiv) at 100 °C in EtOH using microwave irradiation. A conventional thermal method was also trialed but again little conversion was noted (< 25% after 24 h). In addition to isolating the desired 4-amino-1,8-naphthalimide derivative **9**, amidation of the methyl ester was also observed (**10**, Scheme 2, X = Br, see Supporting Information Figure S11 and S12).

Scheme 2. Synthesis of 4-amino derivative **9** by nucleophilic aromatic substitution: X = Br, morpholine (5.0 equiv), Et_3N, EtOH, MW 100 °C, 4 h (≤ 45%); X = NO_2, morpholine, DMF, 21 °C, 24 h (≤ 20%).

Moneva *et. al.* described the successful amination of 4-nitro-*N*-phenyl substituted 1,8-naphthalimide derivatives using *N*-allylamines in DMF at 21 °C (Scheme 2, X = NO_2) [6]. Unfortunately, in our hands, the use of the 4-nitro-1,8-naphthalimide derivative **8** also gave poor conversion and low isolated yields (≤ 20%). Only when the temperature was increased to 80 °C were all starting materials consumed. Nevertheless, even with full consumption of starting material, poor mass recovery and low isolated yields (≤ 20%) resulted. In addition, another undesired side reaction occurred, which gave small amounts of the 4-dimethylamino product **11** (Scheme 2, see Supporting Information, Figure S13 and S14) [14].

An alternate methodology involving palladium-catalysed Buchwald-Hartwig cross-coupling was pursued. While a handful of examples exist in which a palladium mediated approach for coupling of specific aromatic amines, anilines and carbazoles with 4-bromo-1,8-naphthalimide derivatives have been reported [8], the reaction conditions vary considerably with each substrate. As such, a more general protocol was sought that would be practical for a range of anilines and amines (both 1° and 2°).

A plethora of possible palladium sources and phosphine ligand combinations are available for Buchwald-Hartwig cross-coupling reactions [15–19] and while many are very high yielding they require either an expensive catalyst/ligand combination or the synthesis of a specialist ligand [20]. As our aim was to develop a protocol that would be more cost effective and user friendly only a selection of common Pd catalysts and readily available ligands were trialled (Table 1). In the initial reaction $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), 4-bromo-1,8-naphthalimide **7**, morpholine and NaO^tBu were heated in toluene for 24 h at 40 °C (Table 1, Entry 1). Whilst the yield for this reaction was poor (5%), formation of the desired compound occurred at low temperature (40 °C) and the previously discussed side products associated with high reaction temperatures were not observed. After screening a small number of palladium and ligand combinations (Entries 1–9), it became clear that (with the

exception of dppf, Entry 7) bulky bidentate bisphosphines, such as (*S*)-BINAP and Xantphos were the ligands of choice (35% and 40% yields, Entries 8 and 9 respectively).

Table 1. Optimisation for the Pd-mediated amination of 4-bromonaphthalimide **7** with morpholine.[α]

Entry	Pd-source	mol%	Ligand	mol%	Base	equiv	Yield (%)
1	$Pd(OAc)_2$	2	PPh_3	4	NaO^tBu	2	5
2	$Pd(OAc)_2$	2	TrixiPhos	4	NaO^tBu	2	N/R
3	$Pd_2(dba)_3 \cdot CHCl_3$	2	RuPhos	4	NaO^tBu	2	16
4	$Pd_2(dba)_3 \cdot CHCl_3$	2	DavePhos	4	NaO^tBu	2	10
5	$Pd_2(dba)_3 \cdot CHCl_3$	2	CyJohnPhos	4	NaO^tBu	2	12
6	$Pd_2(dba)_3 \cdot CHCl_3$	2	JohnPos	4	NaO^tBu	2	6
7	$Pd_2(dba)_3 \cdot CHCl_3$	2	dppf	4	NaO^tBu	2	10
8	$Pd_2(dba)_3 \cdot CHCl_3$	2	Xantphos	4	NaO^tBu	2	35
9	$Pd_2(dba)_3 \cdot CHCl_3$	2	(*S*)-BINAP	4	NaO^tBu	2	40
10	$Pd_2(dba)_3 \cdot CHCl_3$	3	Xantphos	12	NaO^tBu	2	18
11	$Pd_2(dba)_3 \cdot CHCl_3$	3	(*S*)-BINAP	12	NaO^tBu	2	24
12	$Pd_2(dba)_3 \cdot CHCl_3$	4	Xantphos	4	NaO^tBu	2	50
13	$Pd_2(dba)_3 \cdot CHCl_3$	4	(*S*)-BINAP	4	NaO^tBu	2	47
14	$Pd_2(dba)_3 \cdot CHCl_3$	4	Xantphos	4	NaO^tBu	3	10
15	$Pd_2(dba)_3 \cdot CHCl_3$	4	Xantphos	4	Cs_2CO_3	2	24
16	$Pd_2(dba)_3 \cdot CHCl_3$	4	Xantphos	4	Cs_2CO_3	3	90

[α]Reagents and Conditions: 4-Bromo-1,8-naphthalimide (**7**) (0.25 mmol), morpholine (0.74 mmol), Pd, ligand, base (0.49 mmol or 0.74 mmol), PhMe (5 mL), 40 °C, 24 h.

Further investigation into the effect of the palladium/ligand (Pd/L) ratio was conducted using (*S*)-BINAP and Xantphos as the ligands. Lower yields were observed when a Pd/L ratio of 1:2 was used (Table 1, Entries 10 and 11) instead of 1:1 (Entries 8 and 9). However, the 2:1 combination of $Pd_2(dba)_3 \cdot CHCl_3$ (4 mol%) and Xantphos (4 mol%) with NaO^tBu gave the desired adduct in 50% isolated yield (Entry 12). Even though (*S*)-BINAP proved to be as effective as Xantphos (Entry 13), in our hands, Xantphos was removed more easily than (*S*)-BINAP during chromatographic purification and was therefore chosen for further studies.

The use of Cs_2CO_3 is reported to provide a cleaner reaction profile in Buchwald-Hartwig reactions [16] and when Cs_2CO_3 (2 equiv) was used in place of NaO^tBu (2 equiv) in the amination of bromonaphthalimide **7** (Entry 15) the reaction mixture indeed contained fewer by-products according to TLC analysis, however, the isolated yield of product was

significantly lower (24%). Nevertheless, when 3 equivalents of Cs_2CO_3 was used, the reaction proceeded smoothly and the desired 4-morpholino naphthalimide **9** was isolated in 90% (Entry 16), which corresponds to an overall yield of 83% over two steps from naphthalic anhydride **5**. This compares favourably to the 43% overall yield in the previously reported two step synthesis of 4-morpholino naphthalimide **9** using (i) S_NAr reaction of morpholine with the naphthalic anhydride **5**, followed by (ii) nucleophilic acyl substitution to install the imide moiety [21].

To demonstrate the versatility of these reaction conditions, the amination of simple *N*-ethyl, *N*-heptyl, *N*-hydroxyethyl and *N*-benzyl naphthalimides as the aryl bromide partner with morpholine was pursued (Table 2). The palladium-mediated amination performed very well with isolated yields ranging from 60–90%. The reactions were repeated using the conventional S_NAr approach and in most cases the yields obtained using the new Pd-mediated approach were higher than those obtained when nucleophilic substitution methodology was employed (Table 2). As mentioned earlier the most notable differences arose when the imide functionality was lengthy (Table 2, Entries 2-3).

Table 2. Nucleophilic substitution versus Pd-mediated amination of 4-bromonaphthalimide derivatives.[α]

Entry	Product	Yield (%)	
		S_NAr	Pd-Mediated
1	**3**	83	90
2	**4**	40	75
3	**9**	45	90
4	**14**	60	60[β]
5	**15**	54	69

[α]Reagents and Conditions: *S_NAr Method*: 4-Bromo-1,8-naphthalimide derivative, morpholine (5 equiv), Et_3N (4 equiv), EtOH, MW 100 °C, 4 h; *Pd-Mediated Coupling*: 4-Bromo-1,8-naphthalimide derivative, morpholine (3 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (4 mol%), Xantphos (4 mol%), Cs_2CO_3 (4 equiv), PhMe, 40 or 80 °C, 24 h.

[β]Reaction was conducted at 60 °C for 48 h.

In order to further evaluate the scope of the Buchwald-Hartwig cross-coupling reaction, a variety of aryl and alkyl amines (including alkylamines, anilines, benzylamines and heterocyclic arylamine derivatives) were trialled. Using the optimized reaction conditions described above, a family of 4-amino substituted naphthalimides (including 13 previously unreported compounds) were synthesised in good to high yields (Scheme 3).

Scheme 3. Pd-mediated coupling of 4-bromo naphthalimide **7** with various amino substrates.

The coupling reactions of electron deficient anilines and aliphatic amines were the most successful (compounds **16**–**19**, **21**, **25**–**26** and **28**); when sterically hindered aliphatic amines were used (including; *tert*-butylamine and diisopropylamine) the desired products were not formed, possibly due to a slower rate of ligand exchange [22].

As most compounds synthesised herein are new and 4-aminonaphthalimide derivatives are widely used as fluorescent agents a selection were evaluated photophysically (Table 3). High quantum yields (ϕ up to 0.90) and large Stokes shifts (ranging from 67–135 nm) consistent with the 4-aminonaphthalimide class of compounds were recorded [23].

Table 3. Photophysical properties of selected 4-amino naphthalimide derivatives in $CHCl_3$ and DMSO.

Compound	Solvent	λ_{Abs} (nm)[a]	λ_{Em} (nm)[a]	Stokes Shift	ϕ
9	$CHCl_3$	386	502	116	0.55
	DMSO	399	534	135	0.02
17	$CHCl_3$	426	510	84	0.15
	DMSO	442	538	96	<0.01
20	$CHCl_3$	411	478	67	N/A[b]
	DMSO	425	510	85	0.17
21	$CHCl_3$	421	496	75	0.81
	DMSO	439	521	82	0.47
25	$CHCl_3$	427	502	75	0.90
	DMSO	449	528	79	0.60

[a]Wavelengths of maximum absorbance (λ_{Abs}) and emission intensity (λ_{Em}).
[b]A high level of scattering interfered with the emission spectrum.

Consistent with previous reports [7a,8a,24] the maximum wavelength for both absorption and emission was sensitive to the polarity of the solvent used (Table 3) and larger Stokes shifts and a decrease in fluorescence quantum yields were observed in the more polar solvent, DMSO.

3. Conclusion

A convenient, high yielding, Pd-mediated amination methodology to access 4-amino-1,8-naphthalimide derivatives has been developed. The protocol requires only $Pd_2(dba)_3$ and Xantphos (both readily available) and while it complements existing S_NAr methods the new procedure gives high yields when longer/larger *N*-imide substituents are present. These reaction conditions have proven to be applicable to the coupling of a variety of anilines as well as unencumbered primary and secondary amines (13 new compounds have been synthesised) and should find use in situations where the conventional approaches are unsatisfactory.

4. Experimental

4.1. Materials and Instrumentation

All general reagents and solvents were purchased from commercial sources and used as supplied. Column chromatography was performed using 230–400 Mesh silica gel. All NMR spectra (^1H and ^{13}C) were collected on a JEOL Eclipse JNM-Ex 270 MHz, 400 MHz FT-NMR or Bruker Avance 500SB spectrometer as specified. Melting points are uncorrected and were determined using a Bibby Stuart Scientific SMP3 melting point apparatus. High Resolution Mass Spectra (HRMS) analysis were conducted and recorded on an HRMS-ESI-TOF. Those reactions that employed microwave irradiation were conducted using a CEM Discover S-Class Microwave reactor, operating at a frequency of 50/60 Hz and continuous irradiation power from 0 to 200 W. Reaction mixture temperatures were monitored by an

external infrared sensor. All reactions were conducted in either 10 mL or 35 mL microwave vials sealed with a Teflon® crimp cap. UV-visible absorption spectra were collected using a Cary 300 Bio UV-Vis spectrophotometer. Emission spectra were collected with a Cary Eclipse Spectrofluorimeter. All samples were placed in a 1 cm quartz cuvette either for UV or fluorescence measurements. Absolute quantum yields were collected using a 150 mm QuantaPhi integrating sphere and the Symphony II LN_2 cooled CCD detector. Quantum yields were calculated using the supplied Fluorescence (Horiba JY) software and are the average of three replicates.

4.2. Synthesis and characterisation

4.2.1. General Procedure 1: Nucleophilic Aromatic Substitution (S_NAr) Reactions.

In a 10 mL microwave vial, a solution of 4-bromo naphthalimide, morpholine (5 equiv) and Et_3N (4 equiv) in EtOH was heated using microwave irradiation at 100 °C for 4 h. Excess solvent was removed *in vacuo* and the resulting residue was purified by flash column chromatography.

4.2.2. General Procedure 2: Buchwald-Hartwig Amination Reactions.

To a solution of 4-bromo naphthalimide dissolved in toluene (5 mL), $Pd_2(dba)_3 \cdot CHCl_3$ (4 mol%), Xantphos (4 mol%), amine (3 equiv) and Cs_2CO_3 (3 equiv) were added sequentially. The resulting mixture was stirred for 24 h at the temperature stated. After 24 h an appropriate quantity of SiO_2 was added, the solvent was removed *in vacuo* and the resulting residue dry loaded and purified by flash column chromatography.

*4.2.3. 6-Bromo-2-ethylbenzo[de]isoquinoline-1,3-dione (**1**).*

Compound **1** was synthesised according to the method previously described in the literature [10]. Yield 88%, white solid, mp 157–159 °C (lit. 160–162 °C) [10]; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.3 Hz, 3H), 4.25 (q, *J* = 6.9 Hz, 2H), 7.86 (t, *J* = 8.5 Hz, 1H),

8.05 (d, *J* = 7.9 Hz, 1H), 8.43 (d, *J* = 7.9, 1H), 8.58 (d, *J* = 8.5 Hz, 1H), 8.67 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 35.7, 122.4, 123.3, 128.2, 129.1, 130.3, 130.7, 131.2, 131.3, 132.1, 133.3, 163.51, 163.54.

*4.2.4. 6-Bromo-2-heptyl-1H-benzo[de]isoquinoline-1,3(2H)-dione (**2**).*

In a 10 mL microwave vial, a solution of 4-bromo-1,8-naphthalic anhydride **5** (500 mg, 1.80 mmol) and *N*-heptylamine (207 mg, 1.80 mmol) in EtOH (5 mL) was heated using microwave irradiation at 100 °C for 1 h. The solution was then poured into H_2O to precipitate out a solid, which was collected by filtration, washing thoroughly with H_2O and dried to afford the title compound (515 mg, 77%) as a beige solid; mp 69–70 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.32 (m, 8H), 1.70 (m, 2H), 4.15 (t, *J* = 7.9 Hz, 2H), 7.84 (t, *J* = 7.3 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 8.41 (d, *J* = 7.9 Hz, 1H), 8.56 (d, *J* = 8.6 Hz, 1H), 8.65 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.6, 27.1, 28.1, 29.0, 31.8, 40.6, 122.3, 123.2, 128.1, 129.0, 130.2, 130.7, 131.1, 131.2, 132.0, 133.2, 163.62, 163.64; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{19}H_{20}{}^{79}BrNO_2$ 374.0750; Found 374.0765.

*4.2.5. 2-Ethyl-6-morpholino-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3**).*

General Procedure 1: A solution of compound **1** (100 mg, 0.33 mmol), morpholine (143 mg, 1.65 mmol) and Et_3N (133 mg, 1.32 mmol) in EtOH (3 mL) was reacted according to the general procedure. Purification by flash column chromatography (2% MeOH in CH_2Cl_2) afforded the title compound (84 mg, 83%, R_f = 0.22) as a bright yellow solid; *General Procedure 2:* Compound **1** (50 mg, 0.16 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (7 mg, 0.007 mmol), Xantphos (4 mg, 0.007 mmol), morpholine (43 mg, 0.49 mmol) and Cs_2CO_3 (160 mg, 0.49 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (46 mg, 90%, R_f = 0.48) as a bright yellow

solid; mp 191–193 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.29 (t, *J* = 6.9 Hz, 3H), 3.24 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 4.00 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 4.20 (q, *J* = 7.3 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 8.38 (dd, *J* = 7.6, 0.7 Hz, 1H), 8.48 (d, *J* = 7.9 Hz, 1H), 8.54 (dd, *J* = 6.3, 1.0 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 13.5, 35.4, 53.5, 67.0, 115.0, 117.3, 123.4, 125.9, 126.2, 129.9, 130.0, 131.1, 132.4, 155.6, 163.8, 164.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{18}H_{18}N_2O_3$ 311.1390; Found 311.1393.

*4.2.6. 2-Heptyl-6-morpholino-1H-benzo[de]isoquinoline-1,3(2H)-dione (**4**).*

General Procedure 1: A solution of compound **2** (100 mg, 0.27 mmol), morpholine (116 mg, 1.34 mmol) and Et_3N (107 mg, 1.07 mmol) in EtOH (3 mL) was reacted according to the general procedure. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (41 mg, 40%, R_f = 0.53) as a yellow oil that solidified upon standing; *General Procedure 2:* Compound **2** (70 mg, 0.19 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (7 mg, 0.007 mmol), Xantphos (4 mg, 0.007 mmol), morpholine (49 mg, 0.56 mmol) and Cs_2CO_3 (212 mg, 0.56 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (53 mg, 75%, R_f = 0.53) as a yellow oil that solidified upon standing; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.32 (m, 8H), 1.70 (m, 2H), 3.25 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 4.01 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 4.13 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.68 (dd, *J* = 8.4, 7.3 Hz, 1H), 8.39 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.51 (d, *J* = 8.2 Hz, 1H), 8.56 (dd, *J* = 6.3, 1.0 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 14.2, 22.7, 27.2, 28.2, 29.1, 31.9, 40.4, 53.5, 67.1, 115.0, 117.4, 123.5, 125.9, 126.2, 129.9, 130.0, 131.2, 132.5, 155.6, 164.0, 164.4; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{28}N_2O_3$ 381.2173; Found 381.2185.

*4.2.7. Methyl 6-(6-bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**7**).*

In a 35 mL microwave vial, a solution of 4-bromo-1,8-naphthalic anhydride **5** (1.00 g, 3.61 mmol), methyl 6-aminohexanoate hydrochloride [25] (656 mg, 3.61 mmol) and Et_3N (365 mg, 3.61 mmol) in EtOH (5 mL) was heated using microwave irradiation at 100 °C for 45 mins. The resulting mixture was transferred into a separatory funnel and diluted with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 0.1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to afford the title compound (1.34 g, 92%) as a pale yellow oil that solidified upon standing; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.71 (m, 4H), 2.32 (t, *J* = 7.7 Hz, 2H), 3.64 (s, 3H), 4.13 (t, *J* = 7.7 Hz, 2H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 7.6 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.60 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.7, 26.7, 27.8, 34.0, 40.4, 51.6, 122.3, 123.1, 128.1, 129.0, 130.3, 130.7, 131.1, 131.3, 132.1, 133.3, 163.59, 163.61, 174.1; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{19}H_{18}{}^{79}BrNO_4$ 404.0492; Found 404.0493; Characterisation data matched that in the literature [26].

*4.2.8. Methyl 6-(6-nitro-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**8**).*

In a 35 mL microwave vial, a solution of 4-nitro-1,8-naphthalic anhydride **6** (500 mg, 2.06 mmol), methyl 6-aminohexanoate hydrochloride (374 mg, 2.06 mmol) and Et_3N (208 mg, 2.06 mmol) in EtOH (5 mL) was heated using microwave irradiation at 100 °C for 45 mins. The resulting mixture was transferred into a separatory funnel and diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 0.1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to afford the title compound (637 mg, 84%) as a pale yellow oil that solidified upon standing; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.70 (m, 4H), 2.34 (t, *J* = 7.3 Hz, 2H), 3.63 (s, 3H), 4.14 (t, *J* = 7.3 Hz, 2H), 7.95 (t, *J* = 6.9 Hz, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.64 (d, *J* = 7.9 Hz, 1H), 8.68 (d, *J* = 7.2 Hz, 1H), 8.78 (d, *J* =

7.9 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.6, 26.6, 27.7, 33.9, 40.6, 51.6, 123.0, 123.7, 124.0, 127.0, 129.1, 129.4, 129.9, 130.0, 132.5, 149.6, 162.5, 163.3, 174.1; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{19}H_{18}N_2O_6$ 371.1238; Found 371.1235.

*4.2.9. Methyl 6-(6-morpholino-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**9**).*

General Procedure 1: A solution of compound **7** (85 mg, 0.21 mmol), morpholine (91 mg, 1.05 mmol) and Et_3N (85 mg, 0.84 mmol) in EtOH (3 mL) was reacted according to the general procedure. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (38 mg, 45%, R_f = 0.52) as a yellow oil that solidified upon standing; *General Procedure 2:* Compound **7** (200 mg, 0.49 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (21 mg, 0.02 mmol), Xantphos (12 mg, 0.02 mmol), morpholine (129 mg, 1.48 mmol) and Cs_2CO_3 (483 mg, 1.48 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (182 mg, 90%, R_f = 0.52) as a yellow oil that solidified upon standing; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.40 (m, 2H), 1.66 (m, 4H), 2.28 (t, *J* = 7.3 Hz, 2H), 3.21 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 3.61 (s, 3H), 3.97 (app. t, $J_{app.}$ = 4.7 Hz, 4H), 4.10 (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.9 Hz, 1H), 8.36 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.51 (dd, *J* = 6.1, 1.2 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.7, 26.7, 27.8, 34.0, 40.1, 51.5, 53.5, 67.0, 115.0, 117.2, 123.3, 125.9. 126.1, 129.9, 130.1, 131.2, 132.5, 155.6, 163.9, 164.4, 174.1; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{26}N_2O_5$ 411.1915; Found 411.1925; Characterisation data matched that in the literature [21].

*4.2.10. 6-Bromo-2-(2-hydroxyethyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**12**).*

In a 10 mL microwave vial, a solution of 4-bromo-1,8-naphthalic anhydride **5** (1 g, 3.16 mmol) and ethanolamine (220 mg, 3.16 mmol) in EtOH (5 mL) was heated using microwave irradiation at 100 °C for 45 min. The solution was then poured into H_2O to precipitate out a

solid, which was collected by filtration, washing thoroughly with H_2O and dried to afford the title compound (1.026 g, 89%) as a beige solid; mp 202–204 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.23 (t, *J* = 5.5 Hz, 1H), 3.99 (q, *J* = 5.5 Hz, 2H), 4.46 (t, *J* = 5.5 Hz, 2H), 7.87 (dd, *J* = 8.6, 8.2 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 8.44 (d, *J* = 7.9 Hz, 1H), 8.61 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.68 (dd, *J* = 6.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.0, 61.6, 122.0, 122.9, 128.2, 129.2, 130.7, 130.8, 131.3, 131.7, 132.5, 133.7, 164.6; HRMS (ESI-TOS) *m*/*z*: $[M+H]^+$ Calcd for $C_{14}H_{10}{}^{79}BrNO_3$ 319.9917; Found 319.9916; Characterisation data matched that in the literature [27].

*4.2.11. 4-Bromo-N-(benzyl)-1,8-naphthalimide (**13**).*

In a 10 mL microwave vial, a solution of 4-bromo-1,8-naphthalic anhydride **5** (150 mg, 0.54 mmol) and benzylamine (58 mg, 0.54 mmol) in EtOH (3 mL) was heated using microwave irradiation at 100 °C for 45 min. The solution was then poured into H_2O to precipitate out a solid, which was collected by filtration, washing thoroughly with H_2O and dried to afford the title compound (160 mg, 81%) as a beige solid; mp 173–174 °C (lit. 174 °C) [26]; ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.36 (s, 2H), 2.27 (m, 3H), 7.53 (d, *J* = 2.2 Hz, 2H), 7.81 (dd, *J* = 8.3, 7.3 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 8.40 (d, *J* = 7.9 Hz, 1H), 8.54 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.64 (dd, *J* = 6.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.8, 122.3, 123.1, 127.7, 128.2, 128.6, 129.1 (2C), 130.5, 130.7, 131.2, 131.5, 132.4, 133.5, 137.1, 163.7; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{19}H_{12}{}^{79}BrNO_2$ 366.0124; Found 366.0112; Characterisation data matched that in the literature [28].

*4.2.12. 2-(2-Hydroxyethyl)-6-morpholino-1H-benzo[de]isoquinoline-1,3(2H)-dione (**14**).*

General Procedure 1: A solution of compound **12** (100 mg, 0.31 mmol), morpholine (135 mg, 1.56 mmol) and Et_3N (125 mg, 1.25 mmol) in EtOH (3 mL) was reacted according to the general procedure. Purification by flash column chromatography (2% MeOH in 1:1

EtOAc/Pet. Spirits) afforded the title compound (59 mg, 60%, R_f = 0.16) as a bright yellow solid; *General Procedure 2:* Compound **12** (100 mg, 0.31 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), morpholine (82 mg, 0.94 mmol) and Cs_2CO_3 (305 mg, 0.94 mmol) were heated at 60 °C for 48 h. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (60 mg, 60%, R_f = 0.16) as a bright yellow solid; mp 166–168 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.18 (br s, 1H), 3.28 (app. t, $J_{app.}$ = 4.3 Hz, 4H), 3.97 (t, J = 5.2 Hz, 2H), 4.03 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 4.46 (t, J = 5.2 Hz, 2H), 7.24 (d, J = 2.9 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 8.44 (d, J = 8.6 Hz, 1H), 8.54 (d, J = 7.9 Hz, 1H), 8.60 (d, J = 7.2 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 42.9, 53.5, 62.2, 67.0, 115.1, 116.9, 123.1, 126.0, 126.2, 130.1, 130.5, 131.6, 133.0, 156.0, 165.0, 165.4; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{18}H_{18}N_2O_4$ 327.1339; Found 327.1354.

*4.2.13. 2-Benzyl-6-morpholino-1H-benzo[de]isoquinoline-1,3(2H)-dione (**15**).*

General Procedure 1: A solution of compound **13** (53 mg, 0.15 mmol), morpholine (63 mg, 0.73 mmol) and Et_3N (58 mg, 0.58 mmol) in EtOH (2 mL) was reacted according to the general procedure. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet. Spirits) afforded the title compound (29 mg, 54%, R_f = 0.44) as a bright yellow solid; *General Procedure 2:* Compound **13** (87 mg, 0.24 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), morpholine (63 mg, 0.71 mmol) and Cs_2CO_3 (233 mg, 0.71 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (60 mg, 69%, R_f = 0.44) as a yellow oil that solidified upon standing; mp 170–172 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.24 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 4.00 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 5.36 (s, 2H), 7.25 (m, 4H), 7.52 (d, J = 6.9 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H), 8.40 (d, J = 7.6 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 8.58 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.5, 53.5, 67.0, 115.1, 117.2,

123.4, 125.9, 126.2, 127.5, 128.5, 129.0, 130.0, 130.3, 131.5, 132.8, 137.6, 155.8, 164.1, 164.5; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{20}N_2O_3$ 373.1547; Found 373.1565.

*4.2.14. Methyl 6-(1,3-dioxo-6-(phenylamino)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**16**).*

Following general procedure 2, compound **7** (200 mg, 0.49 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (21 mg, 0.02 mmol), Xantphos (12 mg, 0.02 mmol), aniline (138 mg, 1.48 mmol) and Cs_2CO_3 (483 mg, 1.48 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (169 mg, 82%, R_f = 0.57) as an orange oil that solidified upon standing; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.45 (m, 2H), 1.70 (m, 4H), 2.32 (t, *J* = 7.6 Hz, 2H), 3.64 (s, 3H), 4.15 (t, *J* = 7.6 Hz, 2H), 6.81 (s, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.29 (m, 3H), 7.43 (t, *J* = 8.2 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.61 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.8, 26.7, 27.9, 34.1, 40.1, 51.5, 109.1, 113.5, 122.0, 122.5, 123.4, 125.0, 125.6, 126.4, 130.0, 131.5, 133.6, 140.0, 146.7, 164.0, 164.6, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{25}H_{24}N_2O_4$ 417.1809; Found 417.1825.

*4.2.15. Methyl 6-(6-((3-fluorophenyl)amino)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**17**).*

Following general procedure 2, compound **7** (200 mg, 0.49 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (21 mg, 0.02 mmol), Xantphos (12 mg, 0.02 mmol), 3-fluoroaniline (165 mg, 1.48 mmol) and Cs_2CO_3 (483 mg, 1.48 mmol) were heated at 80 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (174 mg, 81%, R_f = 0.63) as an orange solid; mp 116–118 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.42 (m, 2H), 1.69 (m, 4H), 2.30 (t, *J* = 7.6 Hz, 2H), 3.63 (s, 3H), 4.13 (t, *J* = 7.6 Hz, 2H), 6.84 (m, 1H), 6.94 (s, 1H), 7.00 (m, 2H), 7.35 (m, 2H), 7.66 (t, *J* = 7.7 Hz, 1H), 8.29 (d, *J* = 7.6 Hz,

1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.56 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 26.6, 27.8, 34.0, 40.0, 51.5, 108.5 (d, *J* = 23.8 Hz), 110.4, 111.0 (d, *J* = 21.3 Hz), 114.4, 117.0 (d, *J* = 2.7 Hz), 122.5, 123.2, 125.8, 126.7, 129.8, 131.0 (d, *J* = 9.6 Hz), 131.5, 133.2, 142.2 (d, *J* = 10.0 Hz), 145.6, 163.4 (d, *J* = 245.2 Hz), 163.8, 164.4, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{25}H_{23}FN_2O_4$ 435.1715; Found 435.1729.

*4.2.16. Methyl 6-(1,3-dioxo-6-((3-(trifluoromethyl)phenyl)amino)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**18**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), 3-(trifluoromethyl)aniline (120 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 80 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (73 mg, 62%, R_f = 0.68) as an orange solid; mp 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.71 (m, 4H), 2.32 (t, *J* = 7.3 Hz, 2H), 3.65 (s, 3H), 4.15 (t, *J* = 7.8 Hz, 2H), 6.92 (s, 1H), 7.39 (t, *J* = 8.3 Hz, 2H), 7.50 (m, 3H), 7.71 (t, *J* = 8.3 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.61 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 26.6, 27.8, 34.0, 40.1, 51.5, 110.5, 114.9, 118.0 (q, *J* = 3.7 Hz), 120.7 (q, *J* = 3.7 Hz), 122.7, 123.4, 123.7 (q, *J* = 270.0 Hz), 124.3, 126.6, 129.8, 130.4, 131.6, 132.0 (q, *J* = 32.4 Hz), 133.1, 141.2, 145.3, 163.7, 164.3, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{26}H_{23}F_3N_2O_4$ 485.1683; Found 485.1685.

*4.2.17. Methyl 6-(6-((3-cyanophenyl)amino)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**19**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), 3-aminobenzonitrile (88 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 80 °C. Purification by flash column

chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the desired compound (80 mg, 74%, R_f = 0.38) as a bright yellow solid; mp 178–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (m, 2H), 1.68 (m, 4H), 2.29 (t, *J* = 7.6 Hz, 2H), 3.63 (s, 3H), 4.11 (t, *J* = 7.3 Hz, 2H), 7.21 (s, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.50 (m, 3H), 7.66 (t, *J* = 9.0 Hz, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.55 (dd, *J* = 6.6, 0.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 26.7, 27.8, 34.0, 40.1, 51.5, 111.5, 113.9, 115.8, 118.3, 123.1, 123.4, 123.5, 124.8, 126.2, 126.6, 127.1, 129.8, 130.8, 131.7, 132.9, 141.9, 144.6, 163.7, 164.2, 174.1; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{26}H_{23}N_3O_4$ 442.1761; Found 442.1765.

*4.2.18. Methyl 6-(1,3-dioxo-6-(pyrazin-2-ylamino)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**20**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), aminopyrazine (71 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (62 mg, 60%, R_f = 0.30) as a yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.45 (m, 2H), 1.70 (m, 4H), 2.33 (t, *J* = 7.6 Hz, 2H), 3.65 (s, 3H), 4.17 (t, *J* = 7.6 Hz, 2H), 7.29 (brs, 1H), 7.78 (t, *J* = 7.9 Hz, 2H), 8.20 (m, 2H), 8.27 (m, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 8.49 (d, *J* = 1.3 Hz, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 8.65 (dd, *J* = 6.3, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 26.6, 27.8, 34.0, 40.1, 51.5, 115.3, 117.3, 123.4, 124.0, 126.5, 126.7, 129.5, 131.5, 132.6, 134.6, 137.3, 141.3, 142.2, 151.2, 163.6, 164.2, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{22}N_4O_4$ 419.1714; Found 419.1732.

*4.2.19. Methyl 6-(6-(benzylamino)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**21**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), benzylamine (79 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 80 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (104 mg, 98%, R_f = 0.47) as a yellow solid; mp 108–110 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.43 (m, 2H), 1.70 (m, 4H), 2.30 (t, *J* = 7.6 Hz, 2H), 3.63 (s, 3H), 4.12 (t, *J* = 7.6 Hz, 2H), 4.59 (d, *J* = 4.9 Hz, 2H), 5.73 (br s, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 7.36 (m, 5H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.54 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 26.8, 27.9, 34.1, 40.0, 48.1, 51.5, 105.1, 111.1, 120.4, 123.3, 125.0, 126.0, 127.8, 128.2, 129.2, 129.8, 131.2, 134.4, 137.1, 149.1, 164.1, 164.7, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{26}H_{26}N_2O_4$ 431.1965; Found 431.1965.

*4.2.20. Methyl 6-(1,3-dioxo-6-((pyridin-3-ylmethyl)amino)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**22**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), 3-picolylamine (81 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 80 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (59 mg, 55%, R_f = 0.34) as a bright yellow solid; mp 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (m, 2H), 1.68 (m, 4H), 2.31 (t, *J* = 7.8 Hz, 2H), 3.64 (s, 3H), 4.14 (t, *J* = 7.3 Hz, 2H), 4.66 (d, *J* = 5.3 Hz, 2H), 5.67 (t, *J* = 4.9 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 7.32 (m, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 8.59 (m, 1H), 8.79 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 26.7, 27.8, 34.0, 40.0, 45.5, 51.5, 105.1, 111.6, 120.4, 123.3, 123.9, 125.2, 125.8, 129.7, 131.3, 132.8, 134.1, 135.3, 148.5, 149.2, 149.6, 164.0, 164.5, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{25}H_{25}N_3O_4$ 432.1918; Found 432.1938.

*4.2.21. Methyl 6-(1,3-dioxo-6-(pyren-1-ylamino)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**23**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), 1-aminopyrene (161 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were reacted according to general procedure 1 at 40 °C. Purification by flash column chromatography (CH_2Cl_2) afforded the title compound (67 mg, 50%, R_f = 0.15) as dark red oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.72 (m, 4H), 2.31 (t, *J* = 7.6 Hz, 2H), 3.64 (s, 3H), 4.15 (t, *J* = 7.6 Hz, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 7.40 (s, 1H). 7.76 (t, *J* = 8.7 Hz, 1H), 8.01 (m, 3H), 8.08 (m, 3H), 8.23 (m, 4H), 8.52 (d, *J* = 7.7 Hz, 1H), 8.65 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.8, 26.7, 27.9, 34.1, 40.1, 51.6, 108.8, 112.8, 121.2, 121.5, 123.4, 123.9, 124.8, 125.6, 125.8, 126.5, 126.6, 127.3, 127.6, 128.5, 130.0, 130.1, 131.1, 131.4, 131.6, 132.7, 133.8, 148.7, 164.0, 164.7, 174.3; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{35}H_{28}N_2O_4$ 541.2122; Found 541.2122.

*4.2.22. Methyl 6-(1,3-dioxo-6-(quinolin-3-ylamino)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**24**).*

Following general procedure 2, compound **7** (100 mg, 0.247 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), 3-aminoquinoline (107 mg, 0.741 mmol) and Cs_2CO_3 (242 mg, 0.741 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 4:3 EtOAc/Pet Spirits) afforded the title compound (57 mg, 50%, R_f = 0.40) as a yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.72 (m, 4H), 2.32 (t, *J* = 7.2 Hz, 2H), 3.64 (s, 3H), 4.16 (t, *J* = 7.6 Hz, 2H), 7.10 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.57 (m, 1H), 7.68 (m, 1H), 7.76 (t, *J* = 7.3 Hz, 1H), 8.00 (d, *J* = 2.3 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 8.40 (d, *J* = 7.6 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 8.64 (dd, *J* = 6.3, 1.0 Hz, 1H), 8.95 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.8, 26.7, 27.9, 34.1, 40.2, 51.6, 110.2, 115.1, 122.7, 123.5, 125.0, 126.2, 126.7, 127.1, 127.9, 128.5, 128.8, 129.2,

130.0, 131.8, 133.2, 134.3, 145.1, 145.6, 146.6, 163.8, 164.4, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{28}H_{25}N_3O_4$ 468.1918; Found 468.1938.

*4.2.23. Methyl 6-(1,3-dioxo-6-(propylamino)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**25**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), *n*-propylamine (44 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (88 mg, 93%, R_f = 0.36) as a yellow solid; mp 134–137 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.10 (t, *J* = 7.2 Hz, 3H), 1.44 (m, 2H), 1.69 (m, 4H), 1.84 (m, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 3.37 (q, *J* = 5.3 Hz, 2H), 3.63 (s, 3H), 4.14 (t, *J* = 7.3 Hz, 2H), 5.26 (brs, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 8.56 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 22.4, 24.8, 26.8, 27.9, 34.1, 40.0, 45.5, 51.5, 104.5, 110.4, 120.2, 123.3, 124.8, 125.8, 129.9, 131.2, 134.6, 149.5, 164.2, 164.8, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{22}H_{26}N_2O_4$ 383.1965; Found 383.1883.

*4.2.24. Methyl 6-(6-(heptylamino)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**26**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), *n*-heptylamine (86 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (101 mg, 93%, R_f = 0.63) as a bright yellow solid; mp 94–96 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.27 (m, 6H), 1.42 (m, 5H), 1.71 (m, 5H), 2.31 (t, *J* = 7.3 Hz, 2H), 3.37 (q, *J* = 7.2 Hz, 2H), 3.63 (s, 3H), 4.13 (t, *J* = 7.2 Hz, 2H), 5.27 (t, *J* = 4.9 Hz, 1H), 6.69 (d, *J*

= 8.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.43 (d, *J* = 8.6 Hz, 1H), 8.54 (d, *J* = 6.6, 0.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.6, 24.7, 26.7, 27.1, 27.8, 29.0, 29.04, 31.7, 34.0, 39.9, 43.7, 51.5, 104.3, 110.2, 120.2, 123.2, 124.6, 125.8, 129.8, 131.1, 134.5, 149.4, 164.1, 164.7, 174.2; HRMS (ESI-TOS) *m*/*z*: $[M+H]^+$ Calcd for $C_{26}H_{34}N_2O_4$ 439.2591; Found 439.2577.

*4.2.25. Methyl 6-(1,3-dioxo-6-(pyrrolidin-1-yl)-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**27**).*

Following general procedure 2, compound **7** (200 mg, 0.49 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (21 mg, 0.02 mmol), Xantphos (12 mg, 0.02 mmol), pyrrolidine (105 mg, 1.48 mmol) and Cs_2CO_3 (483 mg, 1.48 mmol) were heated at 40 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (103 mg, 53%, R_f = 0.50) as an orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.71 (m, 4H), 2.08 (m, 4H), 2.32 (t, *J* = 7.8 Hz, 2H), 3.64 (s, 3H), 3.76 (t, *J* = 6.3 Hz 4H), 4.15 (t, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.54 (t, *J* = 4.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 26.1, 26.7, 27.8, 34.0, 39.9, 51.5, 53.2, 108.5, 110.8, 122.62, 122.64, 123.0, 131.0, 131.2, 131.9, 133.4, 152.7, 164.1, 164.9, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{26}N_2O_4$ 395.1965; Found 395.1970.

*4.2.26. Methyl 6-(6-(benzyl(methyl)amino)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)hexanoate (**28**).*

Following general procedure 2, compound **7** (100 mg, 0.25 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (11 mg, 0.01 mmol), Xantphos (6 mg, 0.01 mmol), *N*-methylbenzylamine (90 mg, 0.74 mmol) and Cs_2CO_3 (242 mg, 0.74 mmol) were heated at 80 °C. Purification by flash column chromatography (2% MeOH in 1:1 EtOAc/Pet Spirits) afforded the title compound (88 mg, 81%, R_f = 0.55) as a yellow solid; mp 105–106 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.46 (m,

2H), 1.69 (m, 4H), 2.32 (t, *J* = 7.9 Hz, 2H), 2.95 (s, 3H), 3.64 (s, 3H), 4.15 (t, *J* = 7.6 Hz, 2H), 4.53 (s, 2H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.36 (m, 5H), 7.61 (t, *J* = 6.4 Hz, 1H), 8.47 (d, *J* = 8.3 Hz, 2H), 8.56 (dd, *J* = 5.9, 1.3 Hz, 1H), 8.56 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 24.8, 26.7, 27.9, 34.1, 40.1, 40.2, 51.6, 61.5, 114.9, 115.7, 123.3, 125.5, 125.8, 127.7, 128.9, 130.2, 130.6, 131.2, 132.6, 137.2, 156.4, 164.1, 164.6, 174.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ Calcd for $C_{27}H_{28}N_2O_4$ 445.2122; Found 445.2139.

Acknowledgements

CLF thanks the Research Centre for Chemistry and Biotechnology for a top up scholarship and Dr Egan Doeven for assistance with photophysical measurements. The authors would like to acknowledge the Australian Research Council for equipment support related to this project (LE120100213).

References

[1] (a) Patrick LGF, Whiting A. Synthesis of some polymerisable fluorescent dyes. Dyes Pigm 2002;55:123–132. (b) Konstantinova TN, Meallier P, Grabchev I. The synthesis of some 1,8-naphthalic anhydride derivatives as dyes for polymeric materials. Dyes Pigm 1993;22:191–8. (c) Peters AT, Bide MJ. Amino derivatives of 1,8-naphthalic anhydride and derived dyes for synthetic-polymer fibres. Dyes Pigm 1985;6:349–375.

[2] (a) Lee MH, Han JH, Kwon PS, Bhuniya S, Kim JY, Sessler JL, Kang C, Kim JS. Hepatocyte-targeting single galactose-appended naphthalimide: A tool for intracellular thiol imaging in vivo. J Am Chem Soc 2012;134:1316–1322. (b) Lee MH, Kin JY, Han JH, Bhuniya S, Sessler JL, Kang C, Kim JS. Direct fluorescence monitoring of the delivery and

cellular uptake of a cancer-targeted RGD peptide-appended naphthalimide theragnostic prodrug. J Am Chem Soc 2012;134:12668–12674. (c) Zhu B, Zhang X, Li Y, Wang P, Zhang H, Zhuang X. A colorimetric and ratiometric fluorescent probe for thiols and its bioimaging applications. Chem Commun 2010;46:5710–2. (d) Parkesh R, Lee TC, Gunnlaugsson T. Fluorescence imaging of bone cracks (microdamage) using visibly emitting 1,8-naphthalimide-based PET sensors. Tetrahedron Lett 2009;50:4114–6.

[3] (a) Banerjee S, Kitchen JA, Bright SA, O'Brien JE, Williams DC, Kelly JM, Gunnlaugsson T. Synthesis, spectroscopic and biological studies of a fluorescent Pt(II) (terpy) based 1,8-naphthalimide conjugate as a DNA targeting agent. Chem Commun 2013;49: 8522–4. (b) Tan S, Yin H, Chen Z, Qian X, Xu Y. Oxo-heterocyclic fused naphthalimides as antitumor agents: Synthesis and biological evaluation. Eur J Med Chem 2013;62:130–8.

[4] (a) Veale EB, Gunnlaugsson T. Bidirectional photoinduced electron-transfer quenching is observed in 4-amino-1,8-naphthalimide-based fluorescent anion sensors. J Org Chem 2008;73:8073–6. (b) Veale EB, Tocci GM, Pfeffer FM, Kruger PE, Gunnlaugsson T. Demonstration of bidirectional photoinduced electron transfer (PET) sensing in 4-amino-1,8-naphthalimide based thiourea anion sensors. Org Biomol Chem 2009;7:3447–3454 (c) Esteban-Gomez D, Fabbrizzi L, Licchelli M. Why, on interaction of urea-based receptors with fluoride, beautiful colors develop. J Org Chem 2005;70:5717–5720.

[5] (a) Gudeika D, Lygaitis R, Mimaite V, Grazulevicius JV, Jankauskas V, Lapkowski M, Data P. Hyrazones containing electron-accepting and electron-donating moieties. Dyes Pigm 2011;91:13–9. (b) Wu A, Xu Y, Qian X, Wang J, Liu J. Novel naphthalimide derivatives as potential apoptosis-inducing agents: Design, synthesis and biological evaluation. Eur J Med Chem 2009;44:4674–4680.

[6] Grabchev I, Moneva I, Bojinov V, Guittonneau S. Synthesis and properties of fluorescent 1,8-naphthalimide dyes for application in liquid crystal displays. J Mater Chem 2000;10:1291–6.

[7] For examples of copper-mediated amination of naphthalimides see: (a) Banerjee S, Kitchen J, Gunnlaugsson T, Kelly JM. The effect of the 4-amino functionality on the photophysical and DNA binding properties of alkyl-pyridinium derived 1,8-naphthalimides. Org Biomol Chem 2013;11:5642–5655. (b) Wang Q, Li C, Zou Y, Wang H, Yi T, Huang C. A highly selective fluorescence sensor for tin (Sn^{4+}) and its application in imaging live cells. Org Biomol Chem 2012;10:6740–6.

[8] For examples of Pd-mediated cross couplings of naphthalimides see: (a) Umeda R, Nishida H, Otono M, Nishiyama Y. Π-Sufficient heteroaromatic compounds fused naphthalimide unit as novel solvatochromic fluorophores. Tetrahedron Lett. 2011;52:5494–6. (b) Jackson RK, Shi Y, Yao X, Burdette SC. FerriNaphth: A fluorescent chemodosimeter for redox active metal ions. Dalton Trans 2010;39:4155–4161. (c) Jiang W, Tang J, Qi Q, Wu W, Sun Y, Fu D. The synthesis, crystal structure and photophysical properties of three novel naphthalimde dyes. Dyes Pigm 2009;80:11–6. (d) Kohl C, Becker S, Müllen K. Bis(rylenedicarboximide)-*a*,*d*-1,5-diaminoanthraquinones as unique infrared absorbing dyes. Chem Commun 2002:2778–9.

[9] Parkesh R, Lee TC, Gunnlaugsson T. Highly selective 4-amino-1,8-naphthalimide based fluorescent photoinduced electron transfer (PET) chemosensors for Zn(II) under physiological pH conditions. Org Biomol Chem 2007;5:310–7.

[10] Gunnlaugsson T, Kruger PE, Jensen P, Tierney J, Ali HDP, Hussey GM. Colorimetric “naked eye” sensing of anions in aqueous solution. J Org Chem 2005;70:10875–8.

[11] Pfeffer FM, Buschgens AM, Barnett NW, Gunnlaugsson T, Kruger PE. 4-Amino-1,8-naphthalimide-based anion receptors: employing the naphthalimide N-H moiety in the cooperative binding of dihydrogenphosphste. Tetrahedron Lett 2005;46:6579–6584.

[12] (a) Berchel M, Haelters JP, Couthon-Gourvès H, Deschamps L, Midoux P, Lehn P, Jaffrès PA. Modular construction of fluorescent lipophosphoramidates by click chemistry. Eur J Org Chem 2011;31:6294–6303. (b) Dobrikov GH, Dobrikov GM, Aleksandrova M. Synthesis and electronic spectra of new low-molecular weight compounds with possible application in electroluminescent layers. Cent Eur J Chem 2011;9:1126–1132. (c) Trupp S, Hoffmann P, Henkel T, Mohr GJ. Novel pH indicator dyes for array preparation *via* NHS ester activation or solid-phase organic synthesis. Org Biomol Chem 2008;6:4319–4322.

[13] (a) Moro AJ, Schmidt J, Doussineau T, Lapresta-Frenandéz A, Wegener J, Mohr GJ. Surface-functionalized fluorescent silica nanoparticles for the detection of ATP. Chem Commun 2011;47:6066–8. (b) Zhou X, Su F, Lu H, Senechal-Willis P, Tian Y, Johnson RH, Meldrum DR. An FRET-based ratiometric chemosensor for *in vitro* cellular fluorescence analyses of pH. Biomaterials 2012;33:171–180.

[14] The formation of side product **11** is consistent with the decomposition of DMF to dimethylamine: Sharma A, Mehta VP, Van der Eycken E. A convenient microwave-assisted desulfitative dimethylamination of the 2(1*H*)-pyrazinone scaffold using *N*,*N*-dimethylformamide. Tetrahedron 2008;64:2605–2610.

[15] Gangjee A, Namjoshi OA, Raghavan S, Queener SF, Kisliuk RL, Cody V. Design, synthesis, and molecular modeling of novel pyrido[2,3-*d*]pyrimidine analogues as antifolates; application of Buchwald–Hartwig aminations of heterocycles. J Med Chem 2013;56:4422–4441.

[16] Surry DS, Buchwald SL. Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide. Chem Sci 2011;2:27–50.

[17] Maiti D, Fors BP, Henderson JL, Nakamura Y, Buchwald SL. Palladium-catalyzed coupling of functionalized primary and secondary amines with aryl and heteroaryl halides: two ligands suffice in most cases. Chem Sci 2011;2:57–68.

[18] Fors BP, Buchwald SL. A Multiligand Based Pd Catalyst for C−N Cross-Coupling Reactions. J Am Chem Soc 2010;132:15914–7.

[19] Surry DS, Buchwald SL. Biaryl phosphane ligands in palladium-catalyzed mmination. Angew Chem Int Ed 2008;47:6338–6361.

[20] (a) Raders SM, Moore JN, Parks JK, Miller AD, Ließing TM, Kelley SP, Rogers RD, Shaughnessy KH. Trineopentylphosphine: A conformaionally flexible linker for the coupling of sterically demanding substrates in the Buchwald-Hartwig amination and Suzuki-Miyaura reaction. J Org Chem 2013;78:4649–4664. (b) Tardiff BJ, McDonald R, Ferguson MJ, Stradiotto M. Rational and predictable chemoselective synthesis of oligoamines via Buchwald-Hartwig amination of (hetero)aryl chlorides employing Mor-DalPhos. J Org Chem 2012;77:1056–71. (c) Lee DH, Taher A, Hossain S, Jin MJ. An efficient and general method for the Heck and Buchwald-Hartwig coupling reactions of aryl chlorides. Org Lett 2011;13:5540–3.

[21] Wu J, Yi T, Shu T, Yu M, Zhou Z, Xu M, Zhou Y, Zhang H, Han J, Li F, Huang C. Ultrasound switch and thermal self-repair of morphology and surface wettability in a cholesterol-based self-assembly system. Angew Chem Int Ed 2008;47:1063–7.

[22] It is possible that the latter factor may be resolved by the use of an alternate Pd/L combination.

[23] (a) Banerjee S, Veale EB, Phelan CM, Murphy SA, Tocci GM, Gillespie LJ, Frimannsson DO, Kelly JM, Gunnlaugsson T. Recent advances in the development of 1,8-naphthalimide based DNA targeting binders, anticancer and fluorescent cellular imaging agents. Chem Soc Rev 2013;42:1601–1618. (b) Alexiou MS, Tychopoulos V, Ghorbanian S, Tyman JHP, Brown RG, Brittain PI. The UV–visible absorption and fluorescence of some substituted 1,8-naphthalimides and naphthalic anhydrides. J Chem Soc Perkin Trans 2 1990; 837–842.

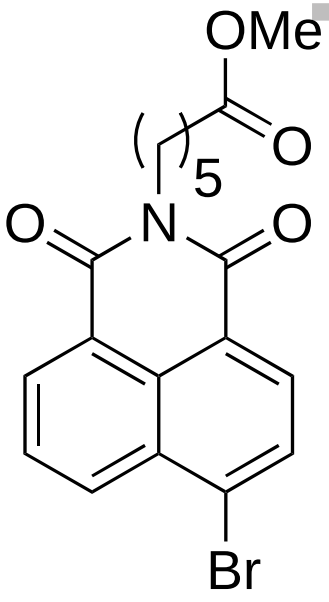
[24] Bardajee GR. Microwave-assisted solvent-free synthesis of fluorescent naphthalimide dyes. Dyes Pigm 2013;99:52–8.

[25] Gigante F, Kaiser M, Brun R, Gilbert IH. SAR studies on azasterols as potential anti-trypanosomal and anti-leishmanial agents. Bioorg Med Chem 2009;17:5950–5961.

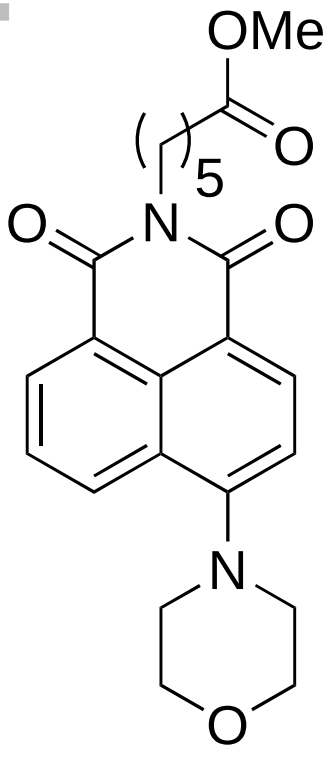
[26] Cao X, Wu Y, Liu K, Yu X, Wu B, Wu H, Gong Z, Yi T. Iridium complex triggered white-light-emitting gel and its response to cysteine. J Mater Chem 2012;22:2650–7.

[27] Zhou J, Liu H, Jin B, Liu X, Fu H, Shangguan D. A guanidine derivative of naphthalimide with excited-state deprotonation coupled intramolecular charge transfer properties and its application. J Mater Chem C 2013;1:4427–4436.

[28] Wang Y, Zhang Y, Yi X, Qin W. Design and synthesis of some 1,8-naphthalimides as fluorescence probes for transition metal ions. Asian J Chem 2012;24:323–6.

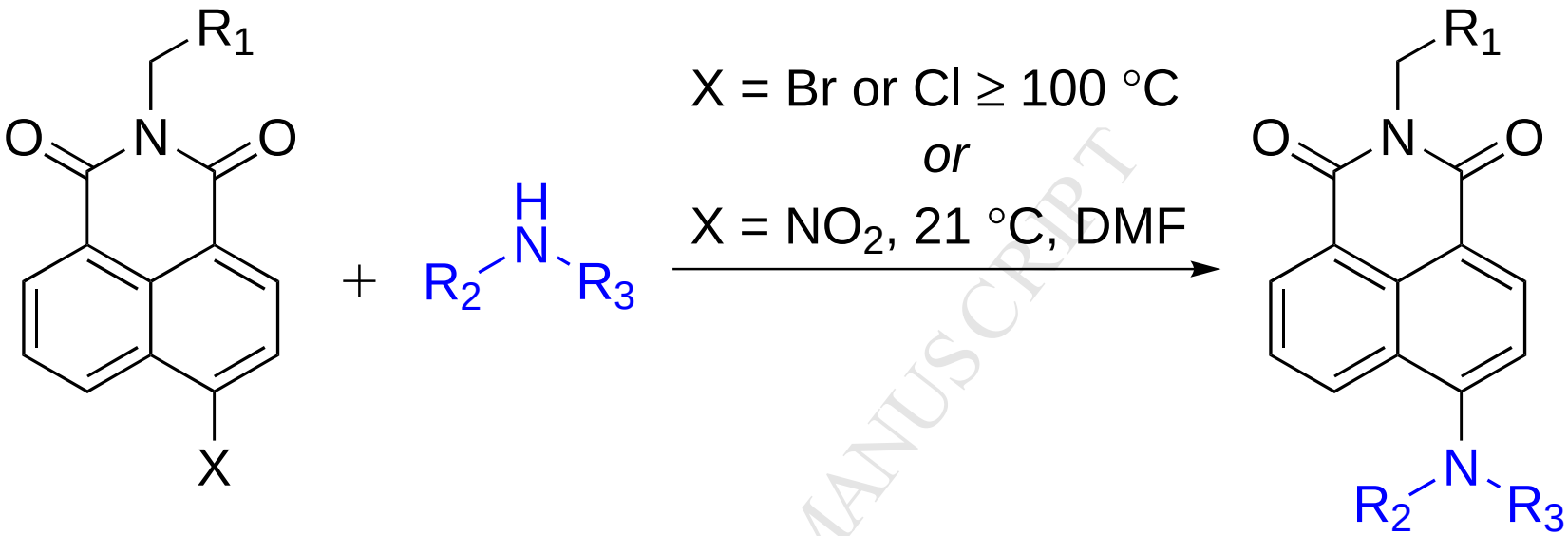


morpholine
Pd, ligand
base, PhMe
40 °C, 24 h

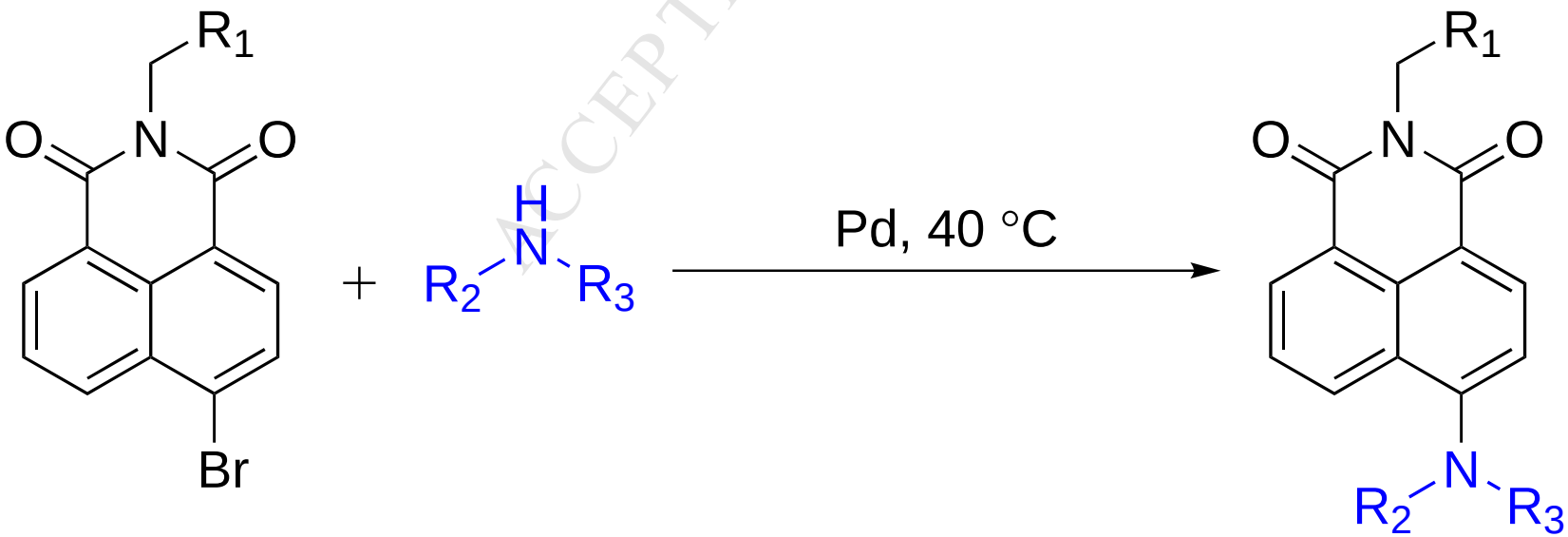


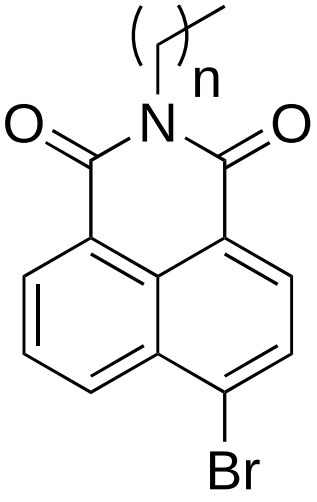
7 **9**

Nucleophilc Aromatic Substitution

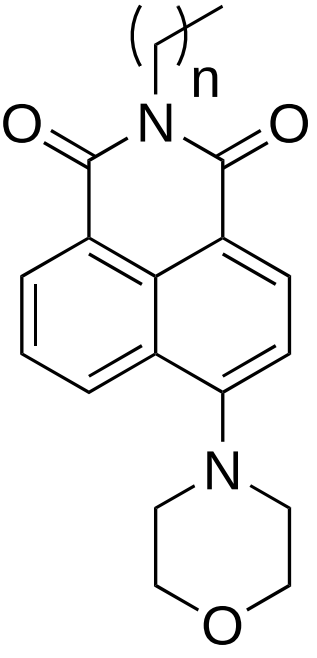


Buchwald-Hartwig Amination (this work)



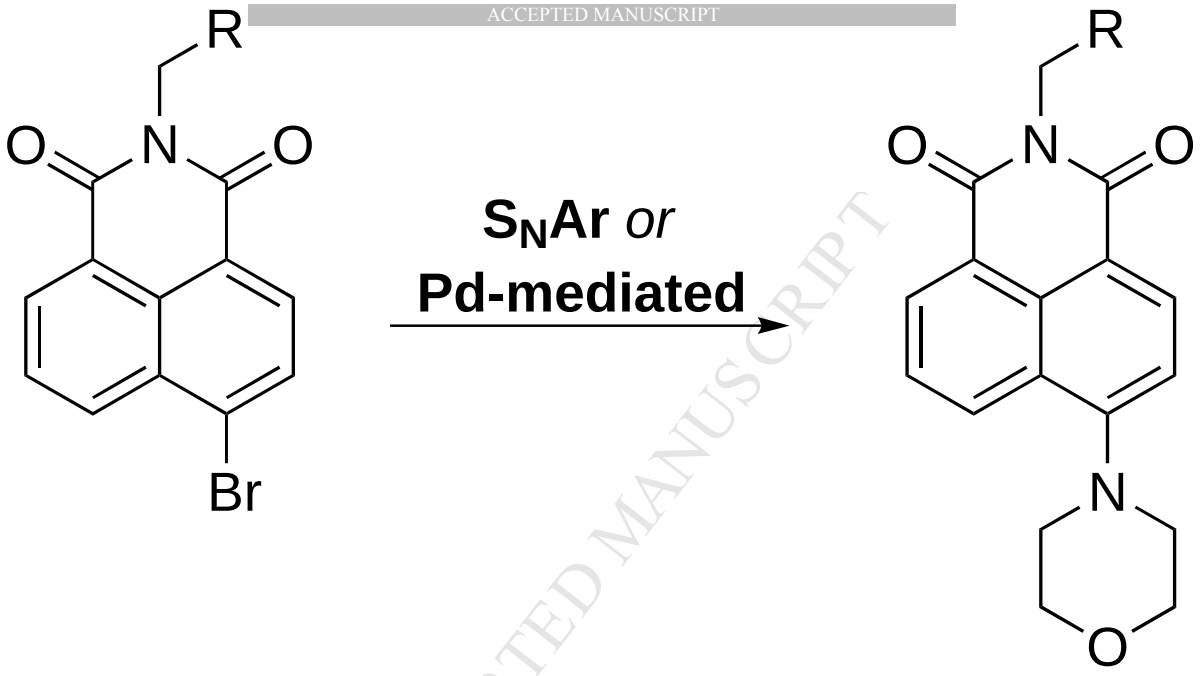


morpholine
Et_3N, EtOH
MW: 100 °C, 4 h



1 n = 1
2 n = 6

3 n = 1 (83%)
4 n = 6 (40%)



1 R = CH_3
2 R = $(CH_2)_5CH_3$
7 R = $(CH_2)_5CO_2CH_3$
12 R = CH_2OH
13 R = Ph

3 R = CH_3
4 R = $(CH_2)_5CH_3$
9 R = $(CH_2)_5CO_2CH_3$
14 R = CH_2OH
15 R = Ph

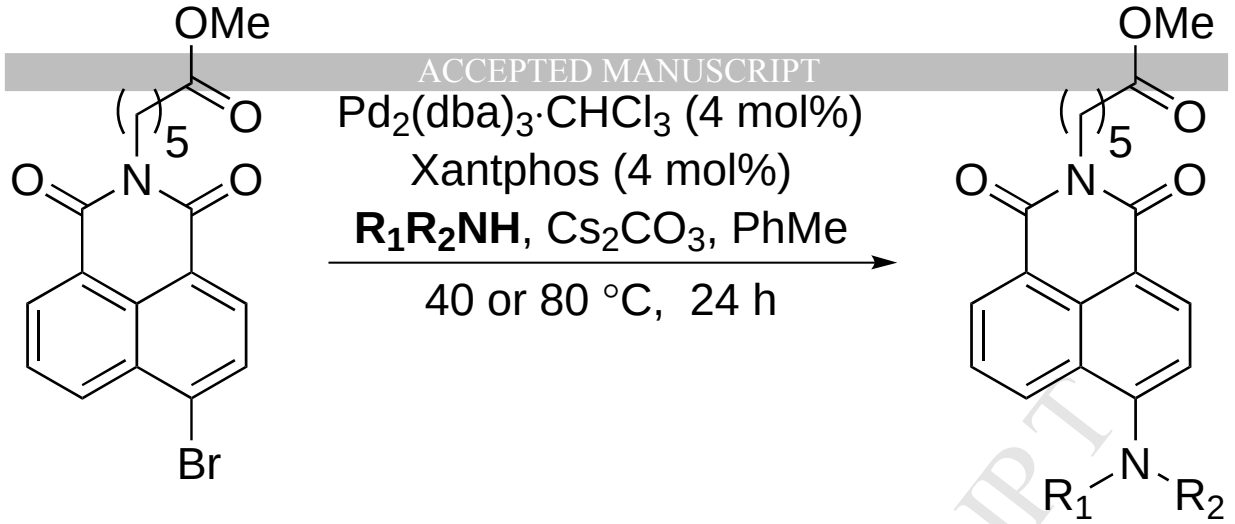
5 X = Br
6 X = NO_2

7 X = Br (92%)
8 X = NO_2 (84%)

9

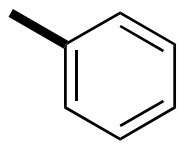
10

11

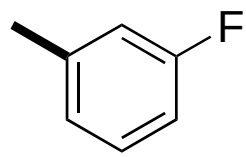


7 **16-28**

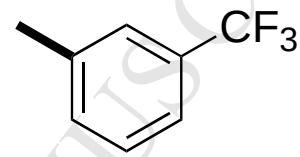
R_1 = H, R_2 =



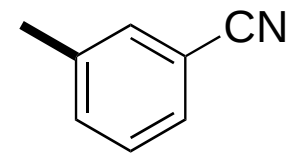
16 (82%)



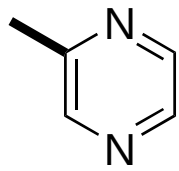
17 (81%)



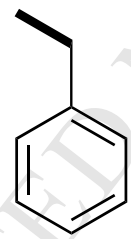
18 (62%)



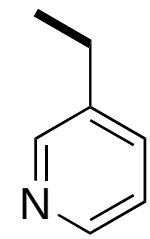
19 (74%)



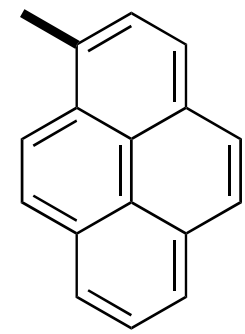
20 (60%)



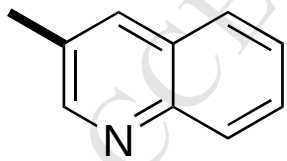
21 (98%)



22 (55%)

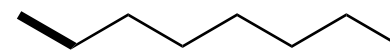


23 (50%)



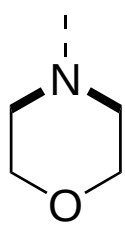
24 (50%)

25 (93%)

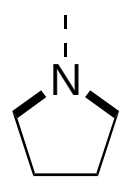


26 (93%)

R_1,R_2 =

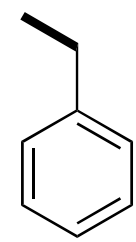


9 (90%)



27 (53%)

R_1 = Me, R_2 =



28 (81%)

Highlights.

- The methodology employs a readily available Pd/ligand combination (as opposed to specialist or custom ligands), relatively mild reaction conditions (40–80 °C) and only a modest excess of amine is needed (3.0 equiv). This compares favourably to the traditionally employed S_NAr protocols, in which high temperatures are required (≥ 100 °C) with a large excess of amine (> 10 equiv).
- The Pd-mediated amination method has proven to be efficient for the coupling of a variety of substituted anilines as well as primary and secondary amines. In doing so, a small library of novel 4-amino-1,8-naphthalimide derivatives has been successfully synthesised and fully characterised including photophysical data.
- This methodology works well with large/bulky naphthalimide N-substituents as opposed to the traditional S_NAr protocols which performed poorly in these instances.

Supporting Information

Synthesis of 4-Amino Substituted 1,8-Naphthalimide Derivatives Using Palladium-mediated Amination.

Cassandra L. Fleming, Trent D. Ashton & Frederick M. Pfeffer*

Research Centre for Chemistry and Biotechnology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria, 3216, Australia

Email: fred.pfeffer@deakin.edu.au

CONTENTS

Figure S1. ^{1}H NMR of compound **2**.

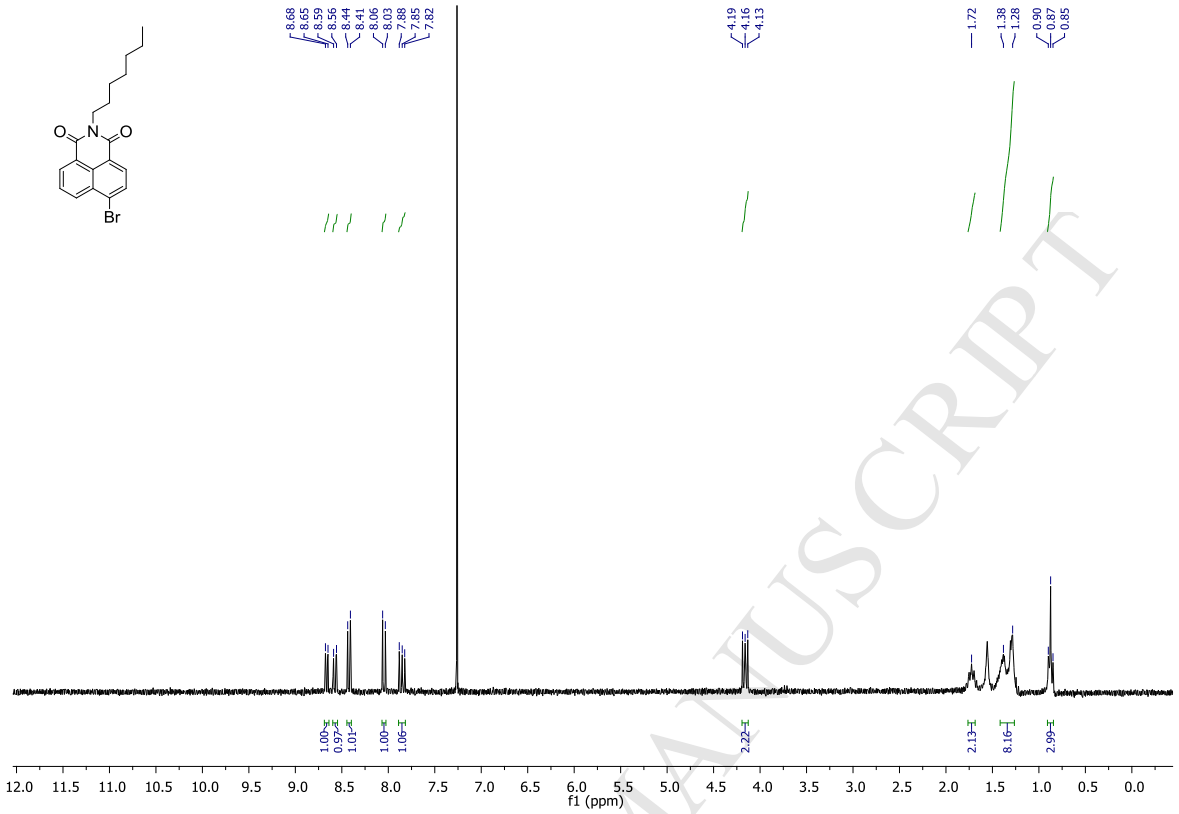


Figure S2. ^{13}C NMR of compound **2**.

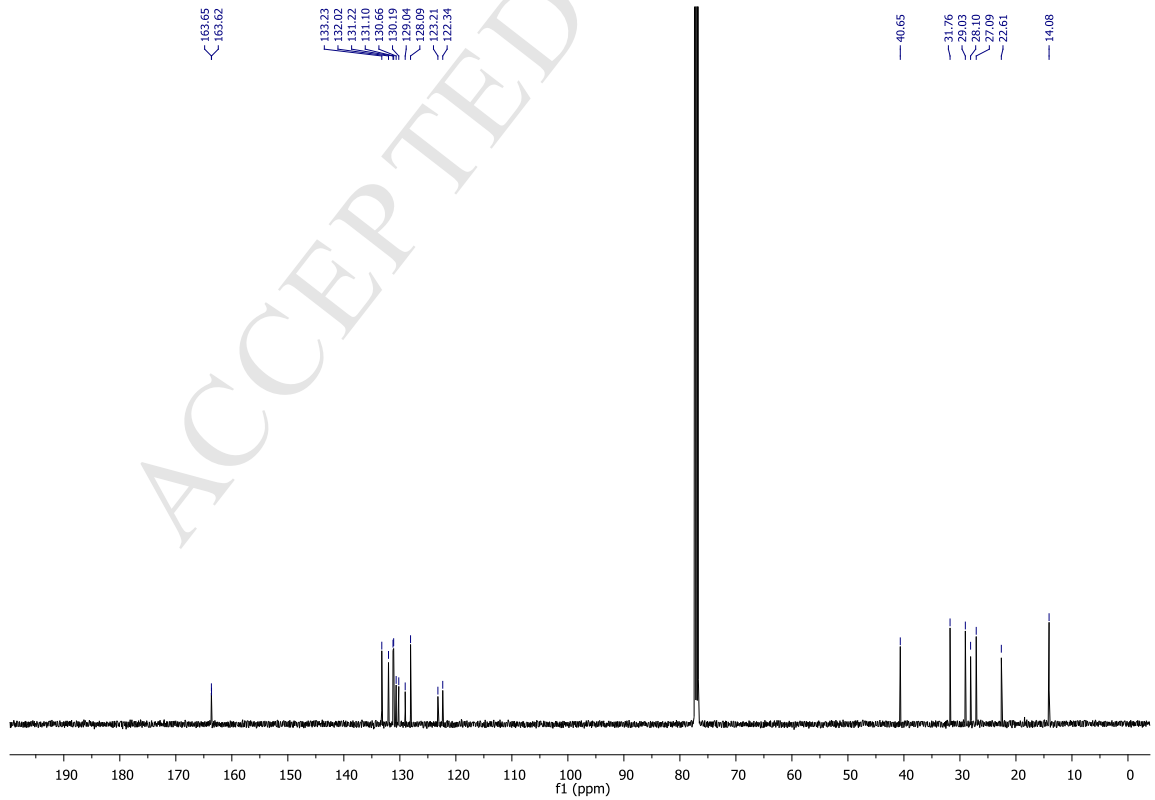


Figure S3. ^{1}H NMR of compound **3**.

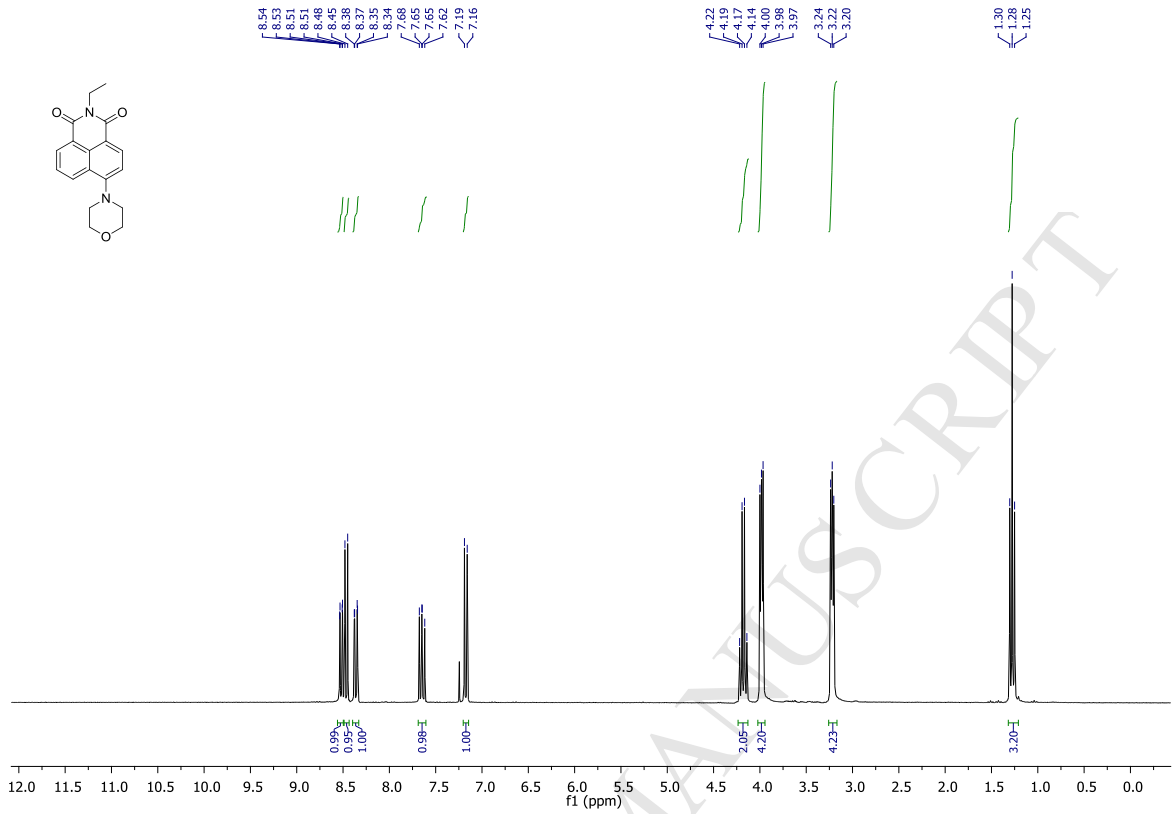


Figure S4. ^{13}C NMR of compound **3**.

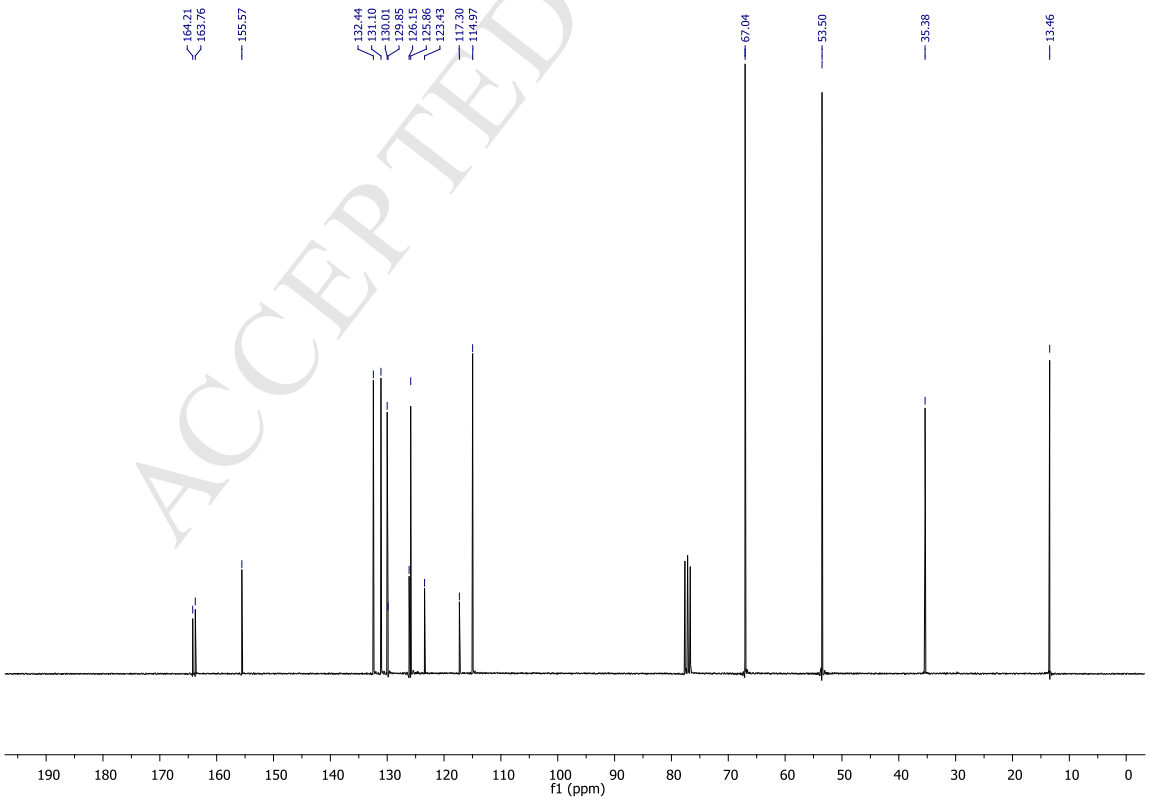


Figure S5. ^{1}H NMR of compound **4**.

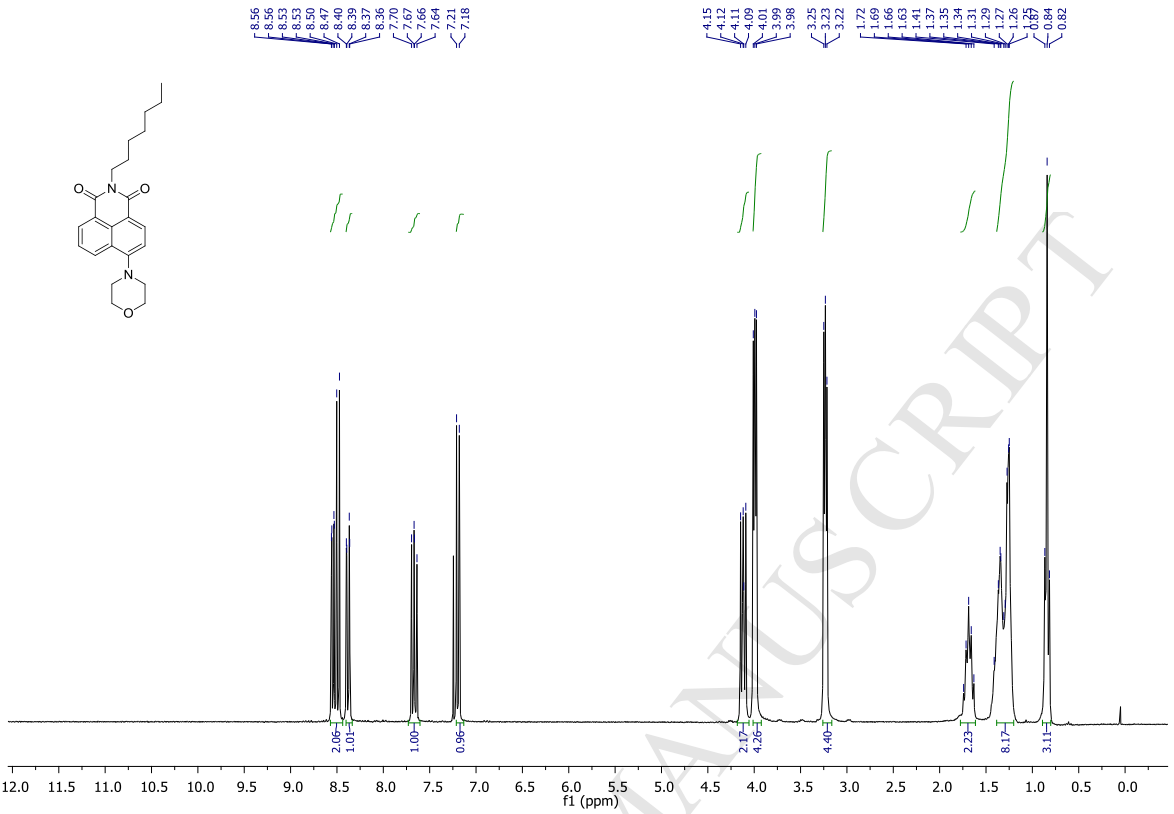


Figure S6. ^{13}C NMR of compound **4**.

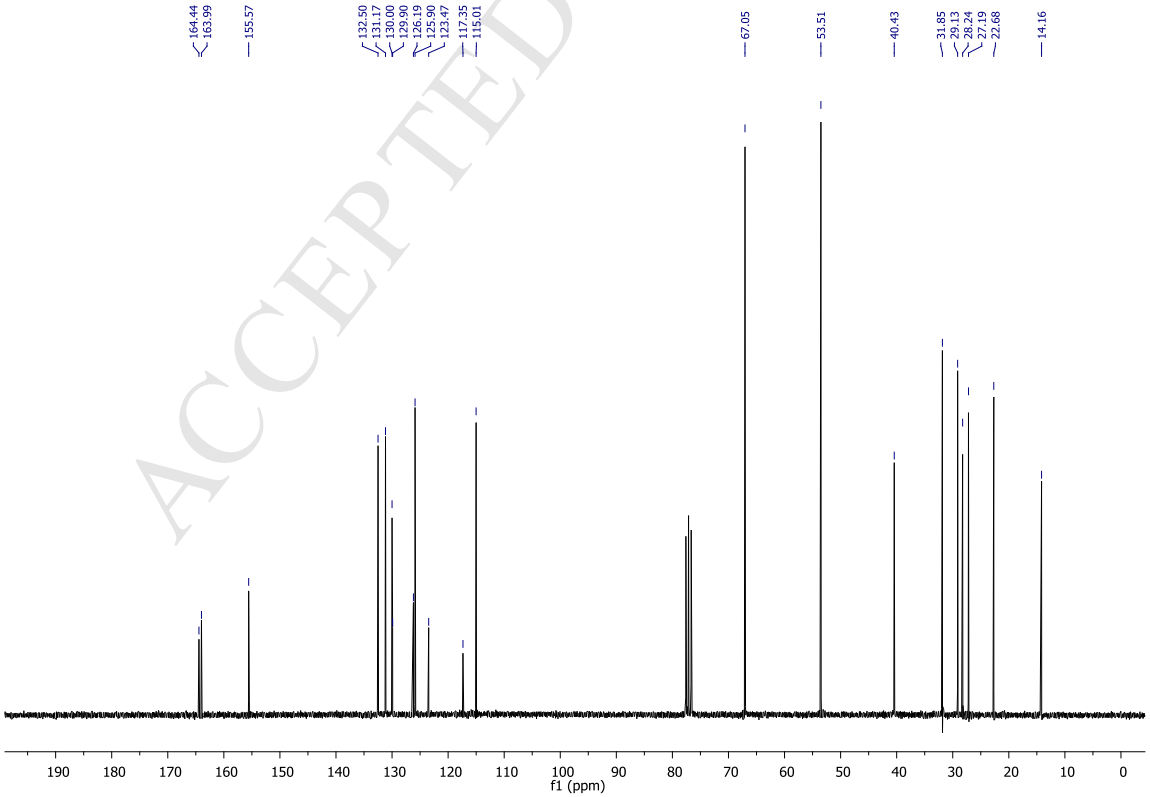


Figure S7. ^{1}H NMR of compound **7**.

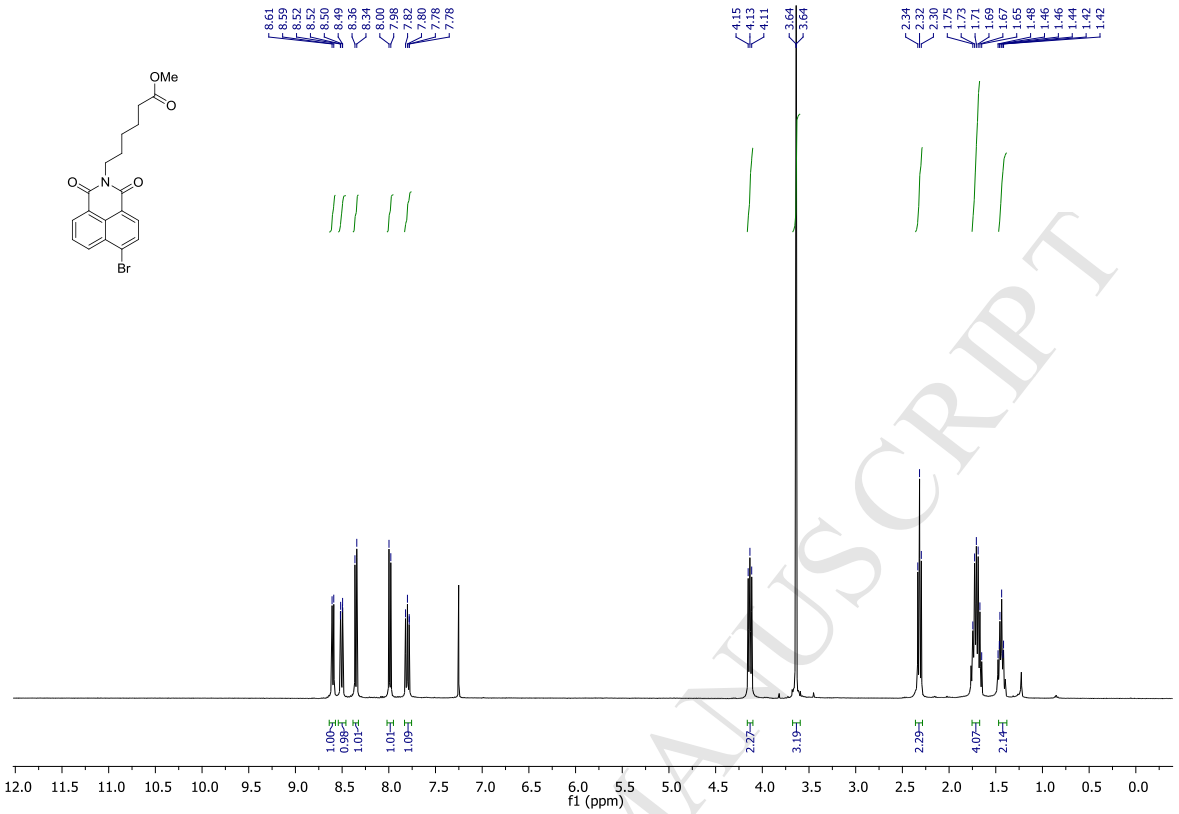


Figure S8. ^{1}H NMR of compound **8**.

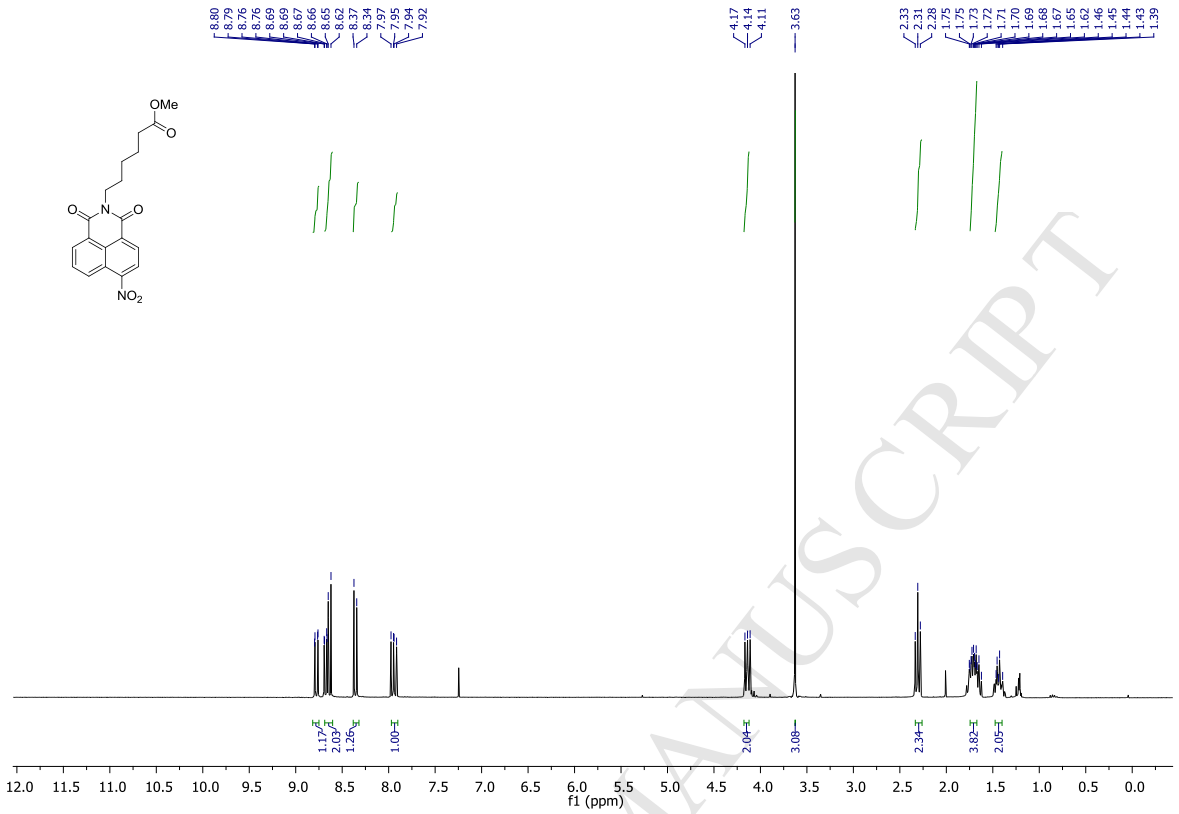


Figure S9. ^{13}C NMR of compound **8**.

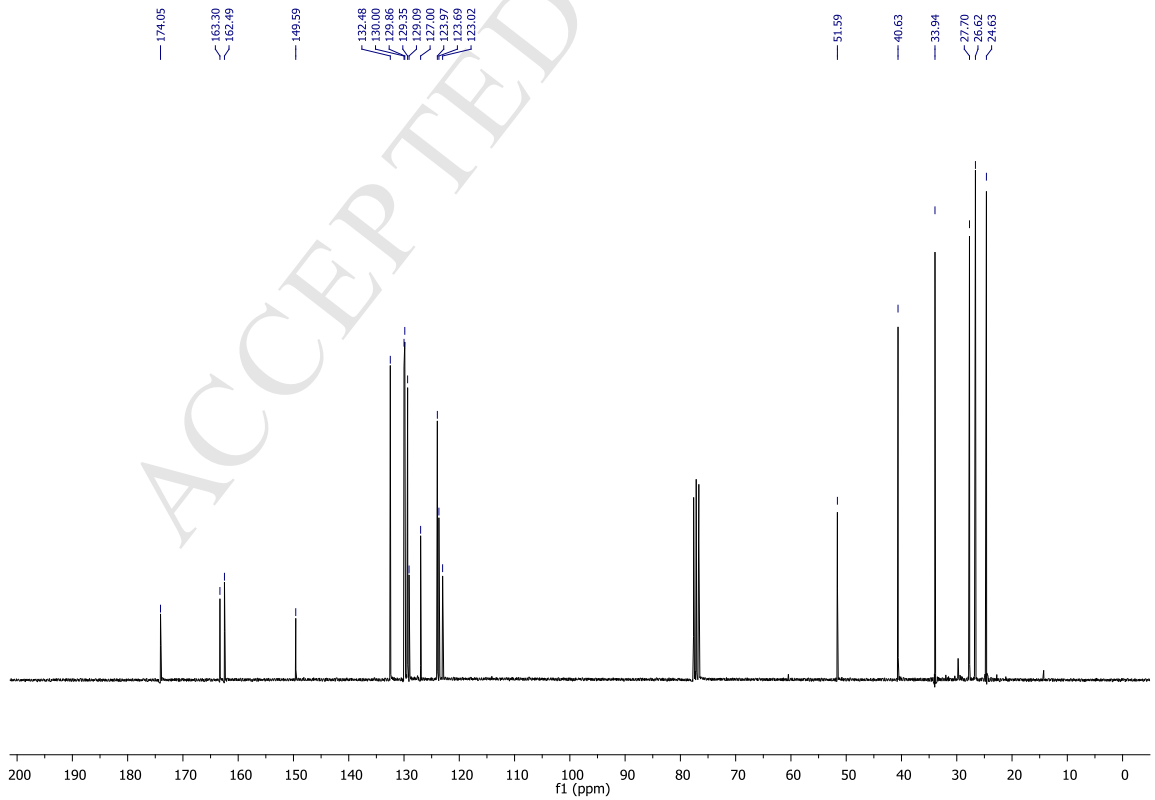
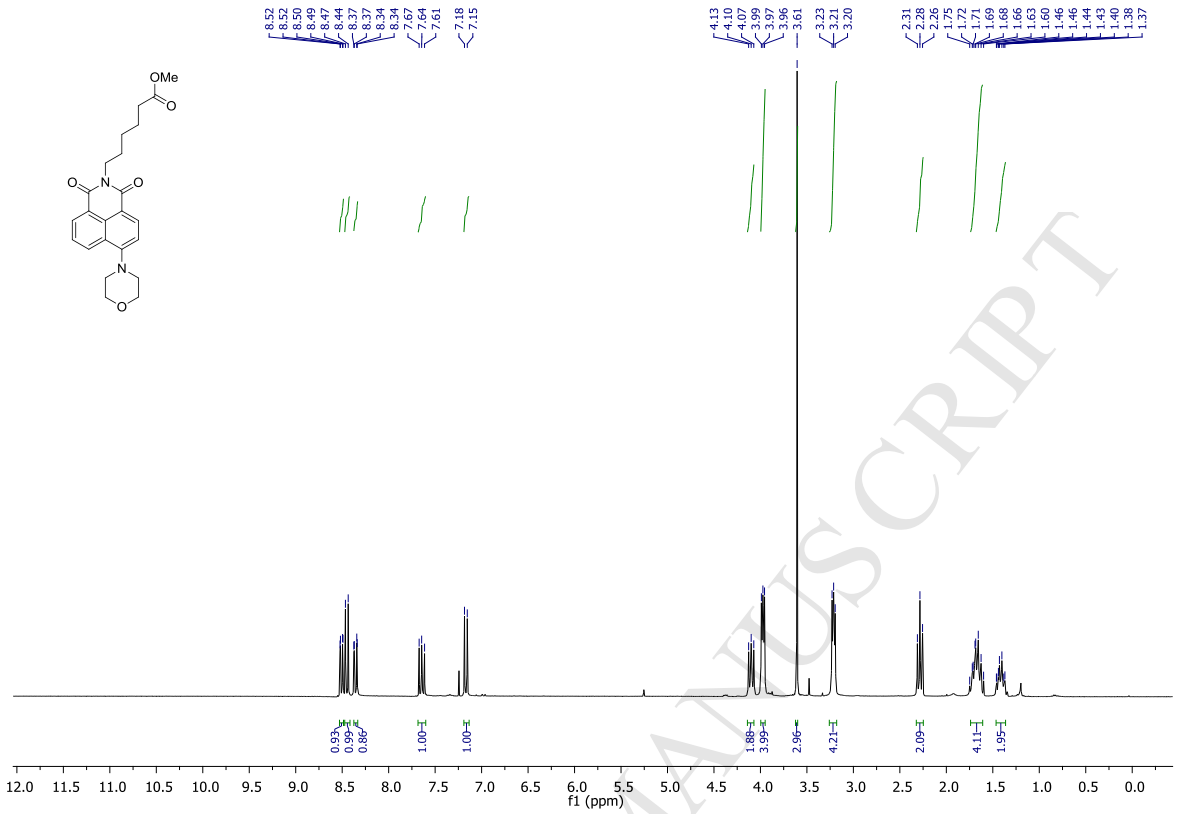


Figure S10. ^{1}H NMR of compound **9**.



Characterisation Data of Side Products:

6-Morpholino-2-(6-morpholino-6-oxohexyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (10). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.48 (m, 2H), 1.73 (m, 4H), 2.33 (t, *J* = 7.9 Hz, 2H), 3.26 (app. t, $J_{app.}$ = 4.3 Hz, 4H), 3.47 (app. t, $J_{app.}$ = 4.3 Hz, 2H), 3.61 (m, 2H), 3.66(m, 4H), 4.02 (app. t, $J_{app.}$ = 4.6 Hz, 4H), 4.16 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.71 (dd, *J* = 8.6, 7.3 Hz, 1H), 8.45 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.52 (d, *J* = 8.2 Hz, 1H), 8.58 (dd, *J* = 6.3, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9, 26.9, 27.8, 32.9, 40.1, 41.9, 46.1, 53.5, 67.0, 115.0, 117.2, 123.3, 125.9, 126.2, 129.9, 130.1, 131.2, 132.5, 155.6, 164.0, 164.4, 171.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{31}N_3O_5$ 466.2336; Found 466.2356.

Methyl 6-(6-(dimethylamino)-1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)hexanoate (11). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.46 (m, 2H), 1.72 (m, 4H), 2.33 (t, *J* = 7.6 Hz, 2H), 3.10 (s, 6H), 3.65 (s, 3H), 4.15 (t, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.65 (dd, *J* = 8.6, 7.6 Hz, 1H), 8.43 (d, *J* = 7.3 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.55 (dd, *J* = 5.9, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 26.7, 27.8, 34.0, 40.0, 44.9, 51.5, 104.0, 113.5, 123.1, 125.0, 125.3, 130.2, 131.1, 132.6, 134.5, 156.6, 164.1, 164.6, 174.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{24}N_2O_4$ 369.1809; Found 369.1818.

Figure S11. ^{1}H NMR of side product **10**.

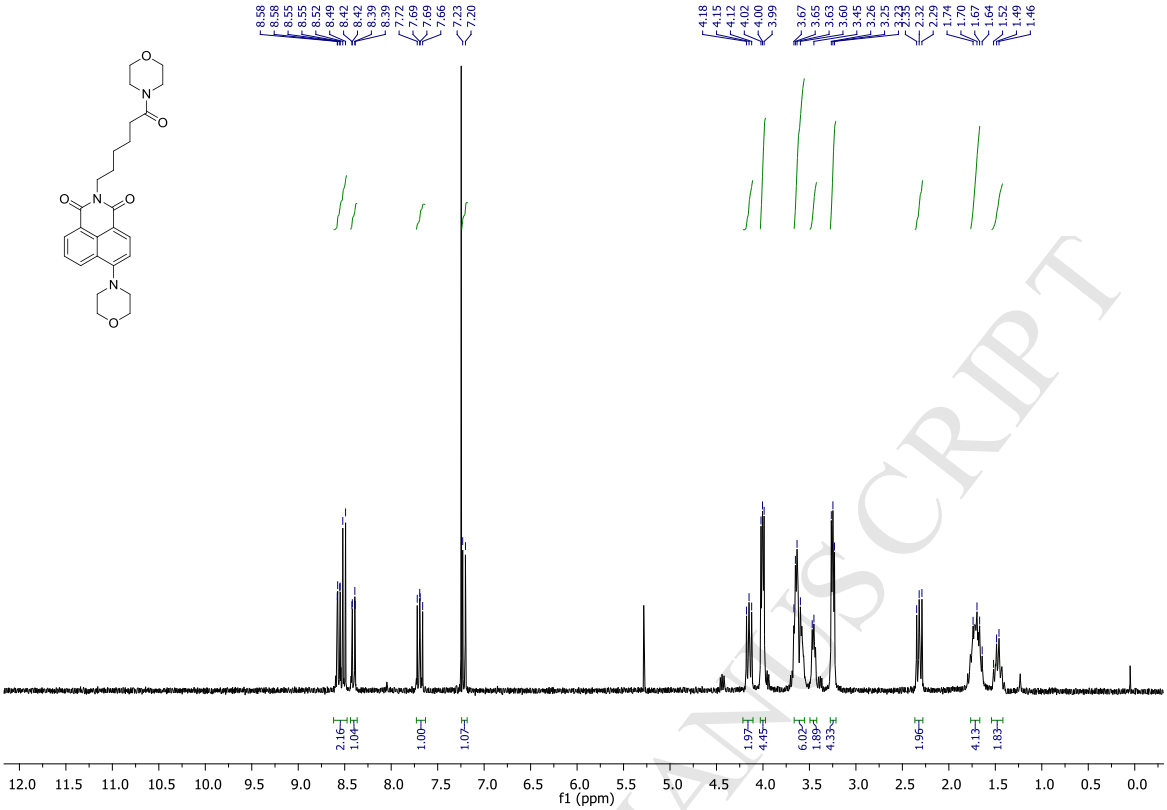


Figure S12. ^{13}C NMR of side product **10**.

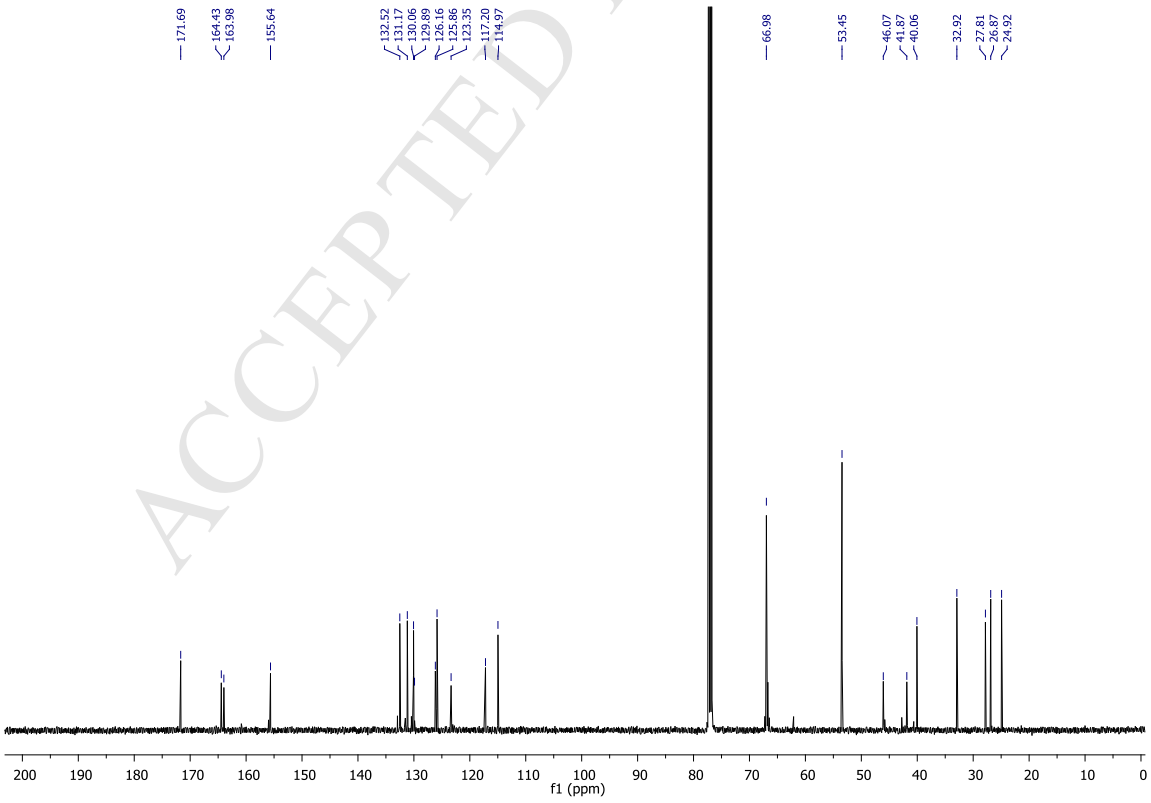


Figure S13. ^{1}H NMR of side product **11**.

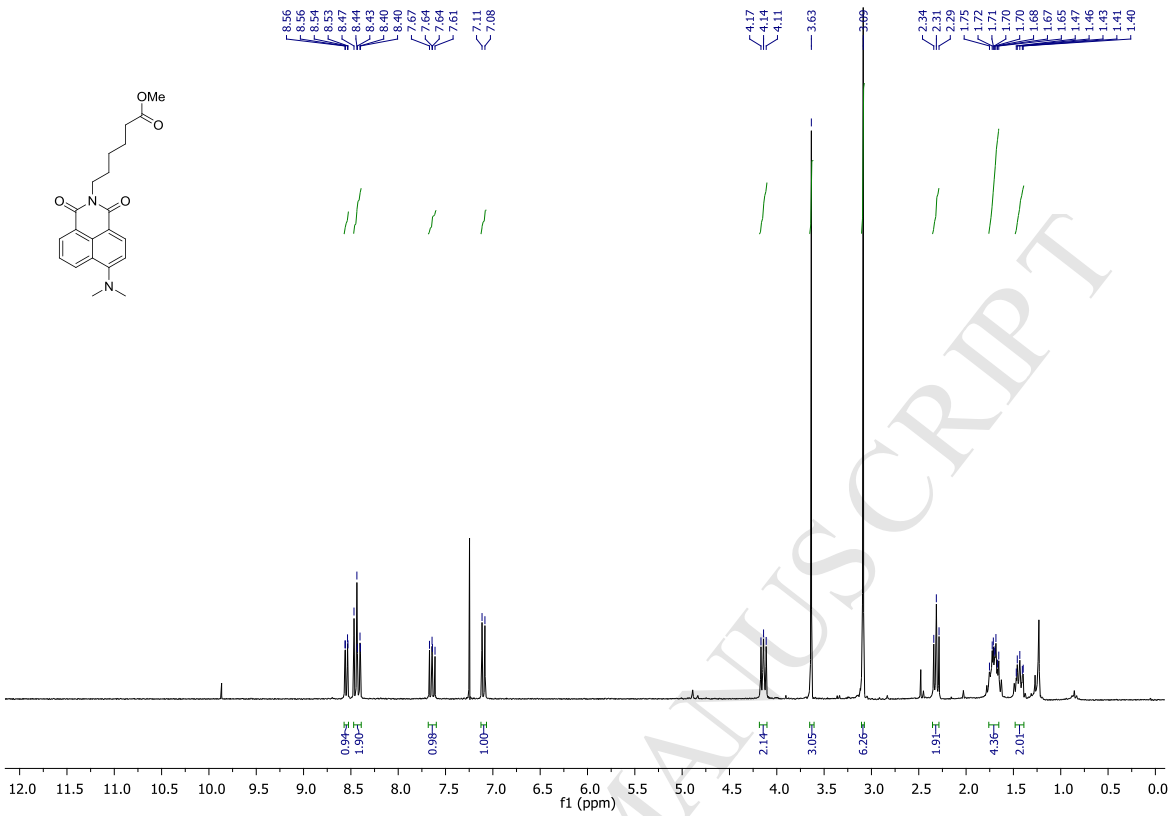


Figure S14. ^{13}C NMR of side product **11**.

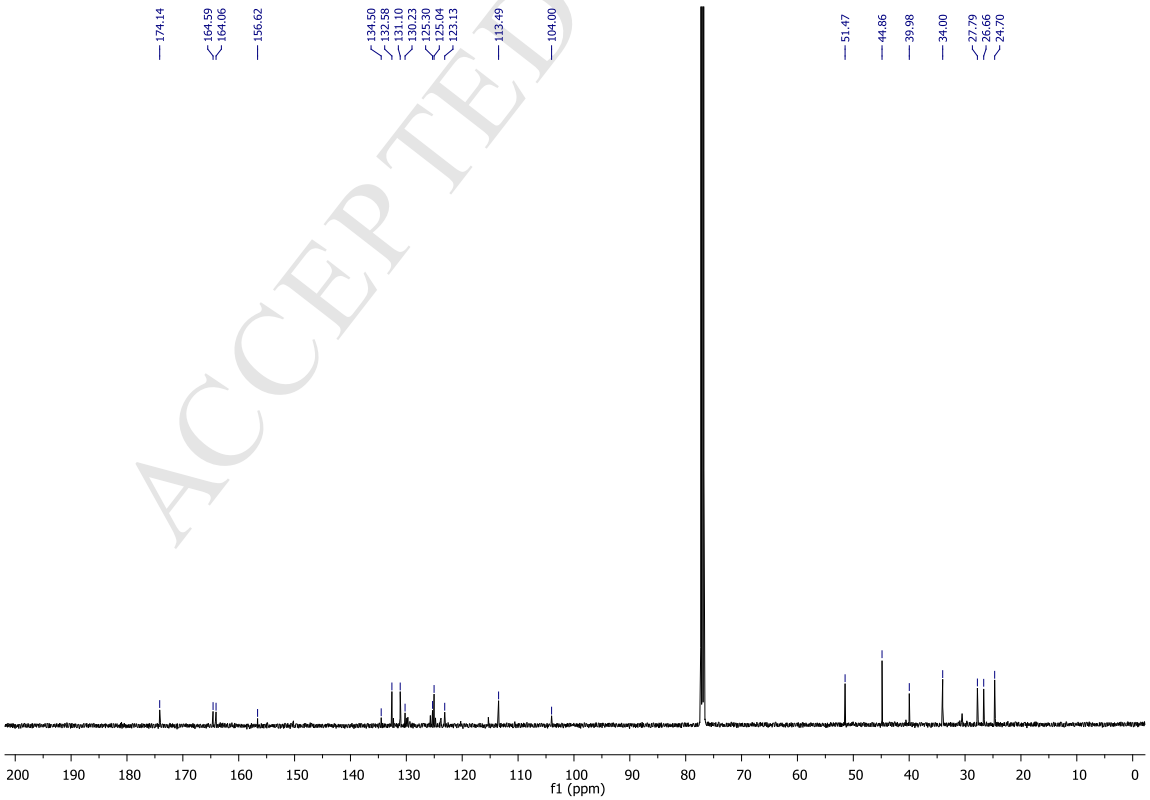


Figure S15. ^{1}H NMR of compound **12**.

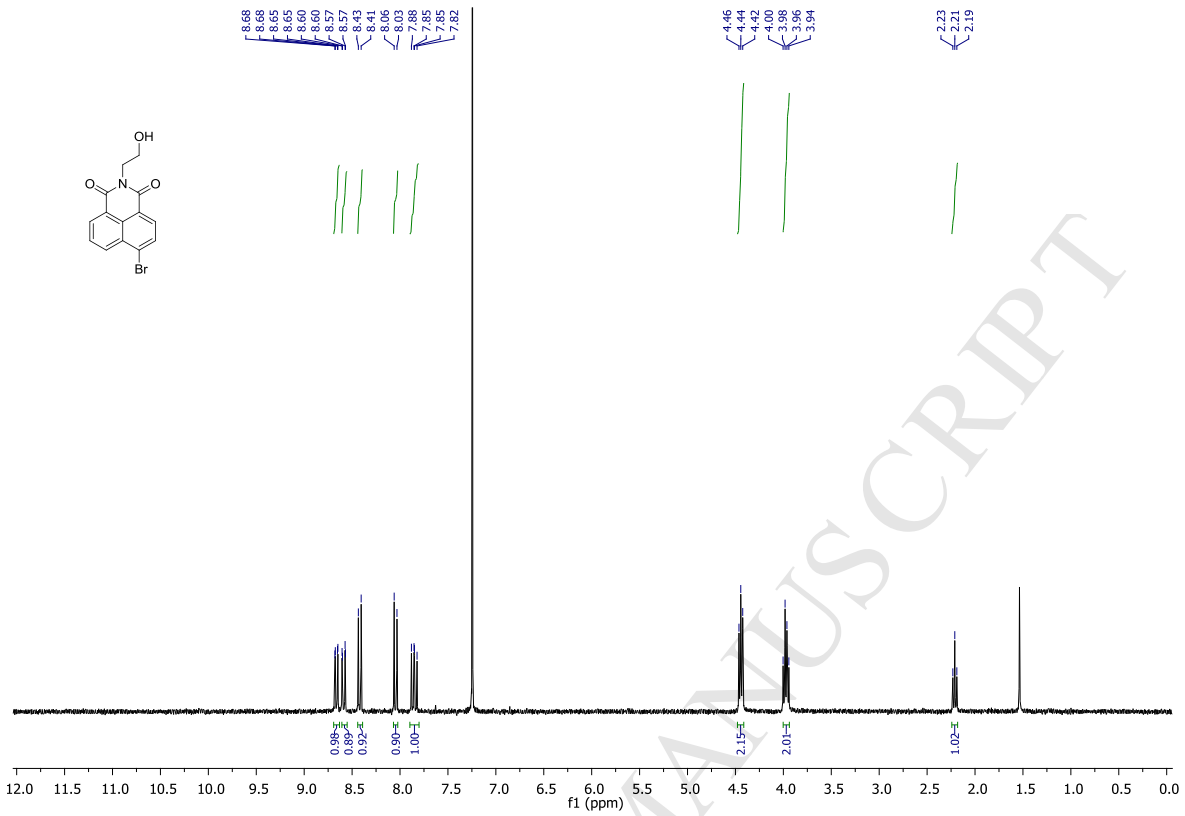


Figure S16. ^{1}H NMR of compound **13**.

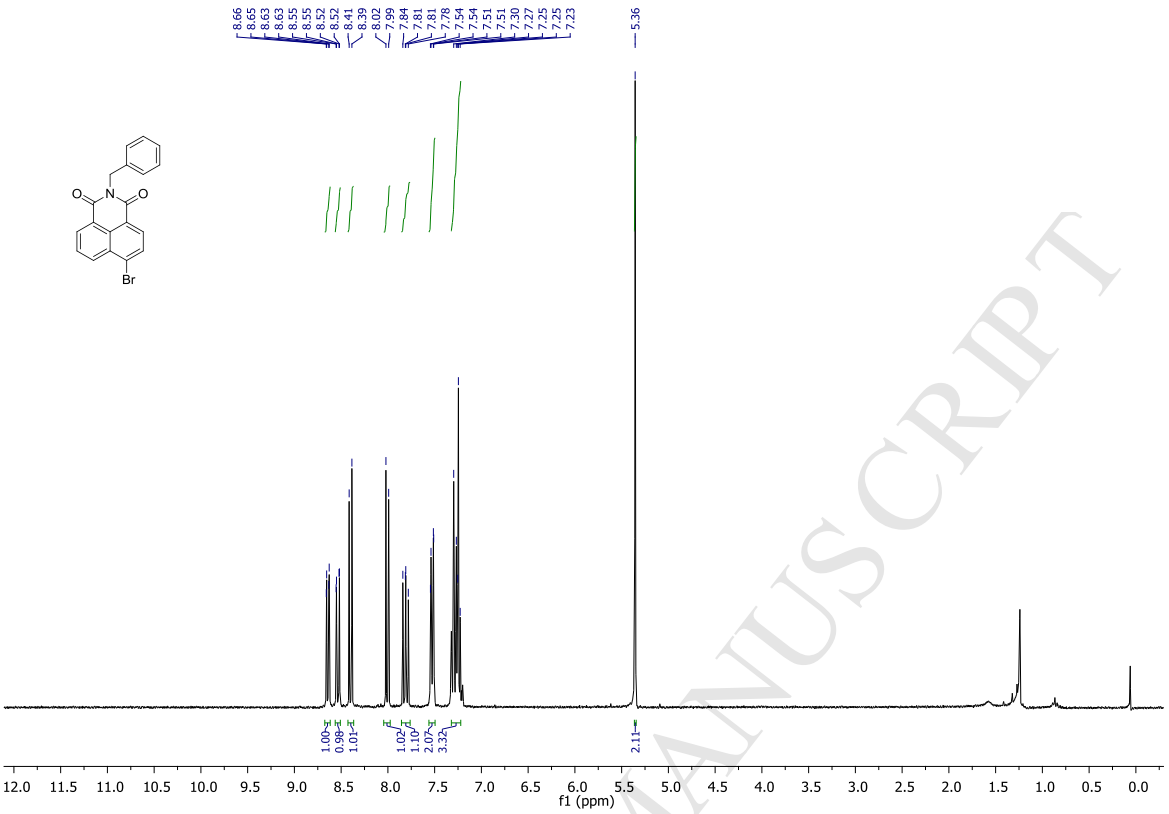


Figure S17. ^{1}H NMR of compound **14**.

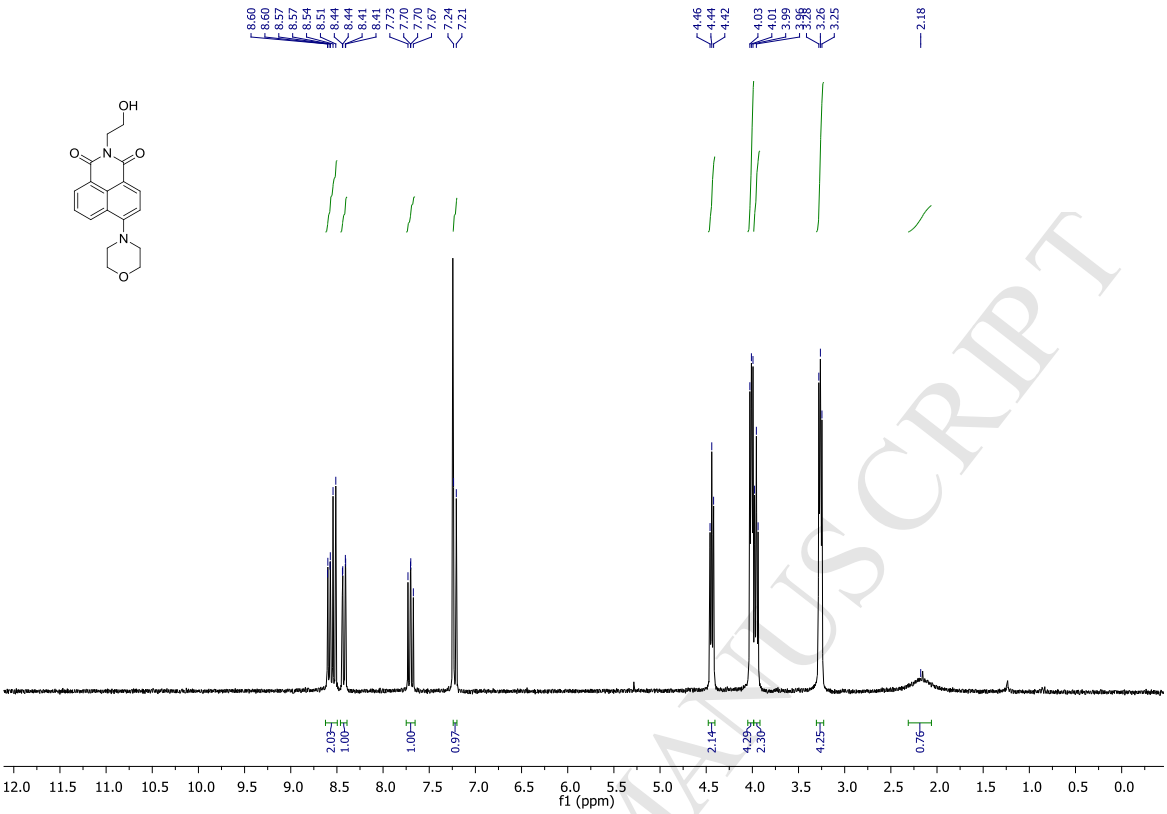


Figure S18. ^{13}C NMR of compound **14**.

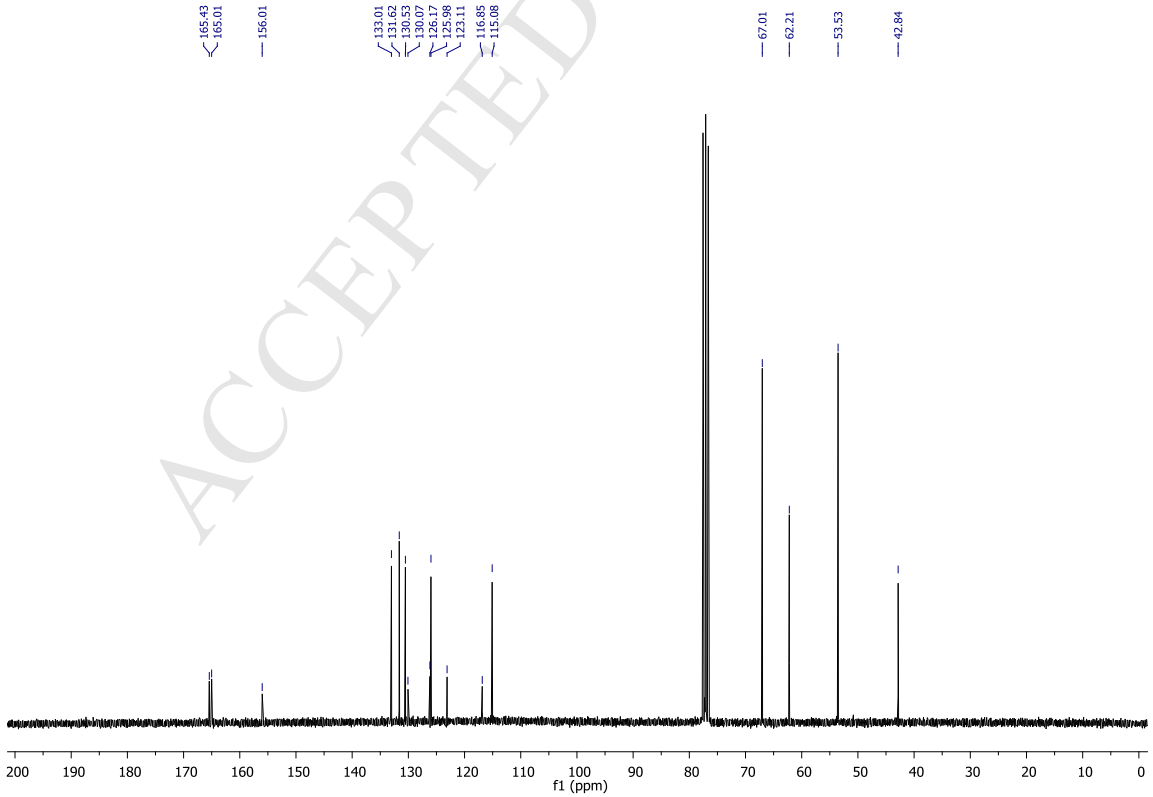


Figure S19. ^{1}H NMR of compound **15**.

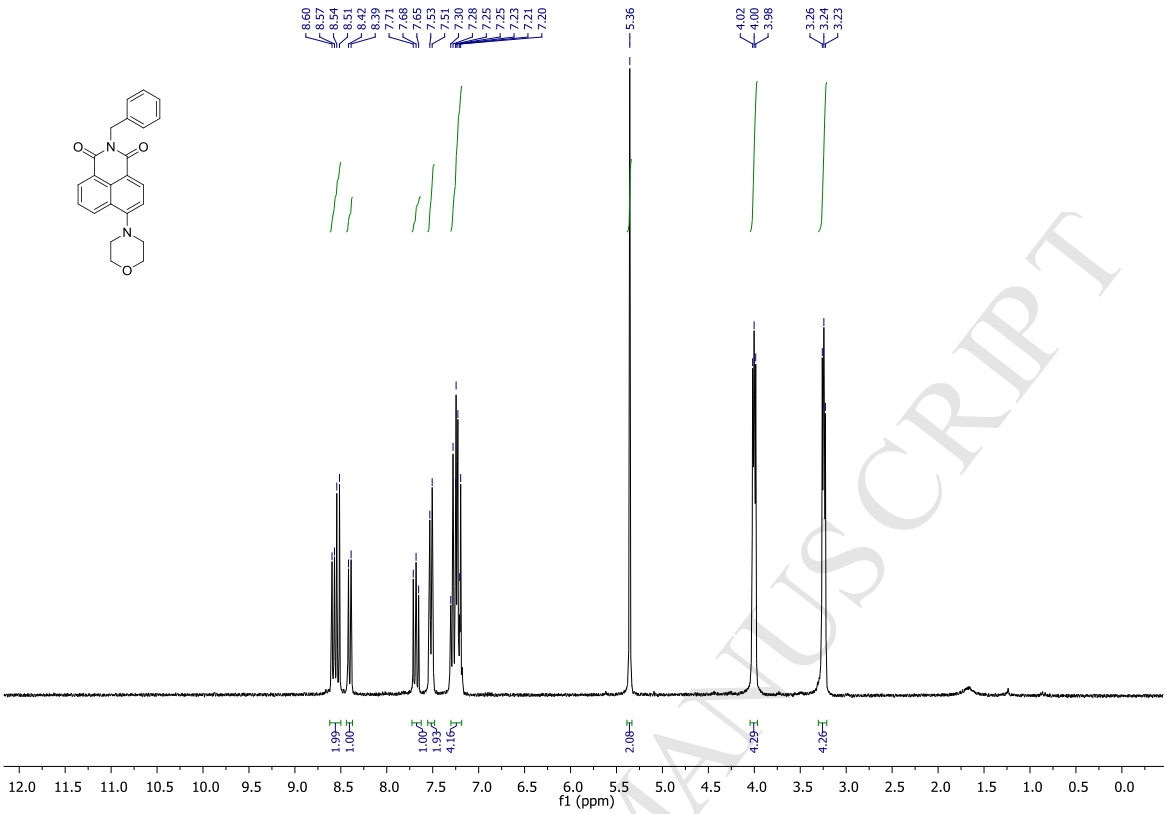


Figure S20. ^{13}C NMR of compound **15**.

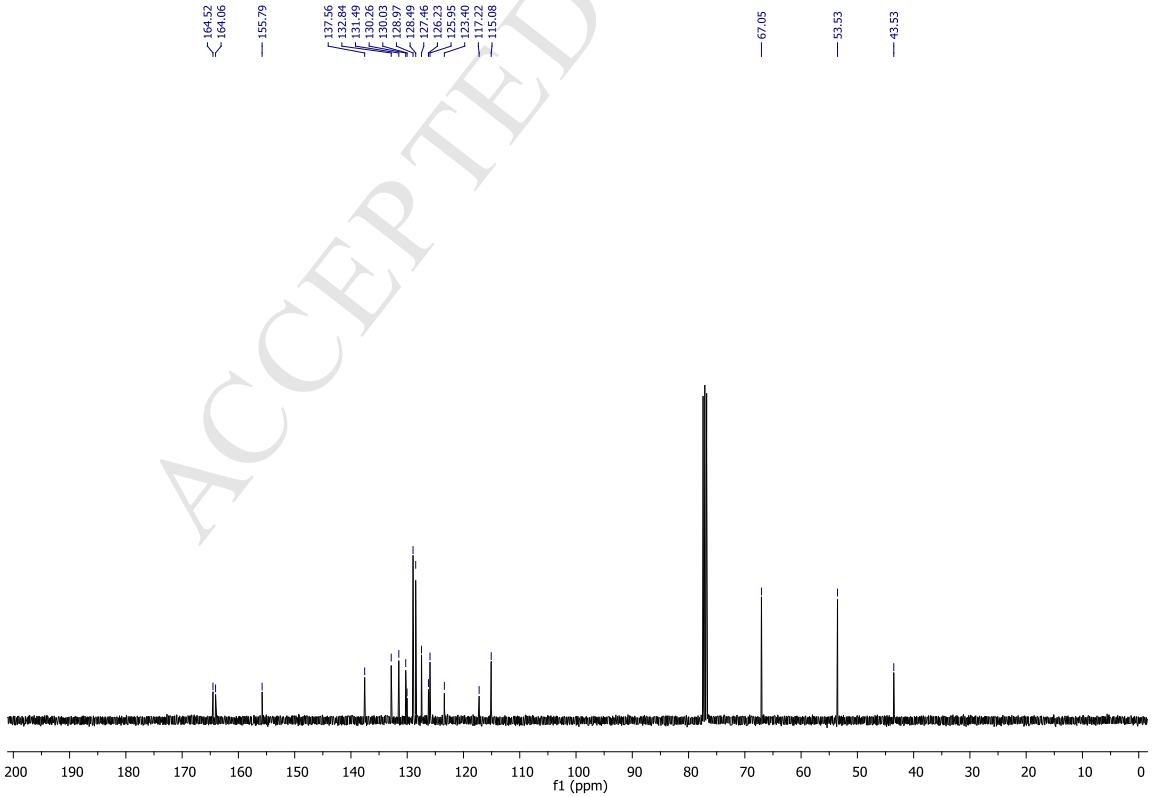


Figure S21. ^{1}H NMR of compound **16**.

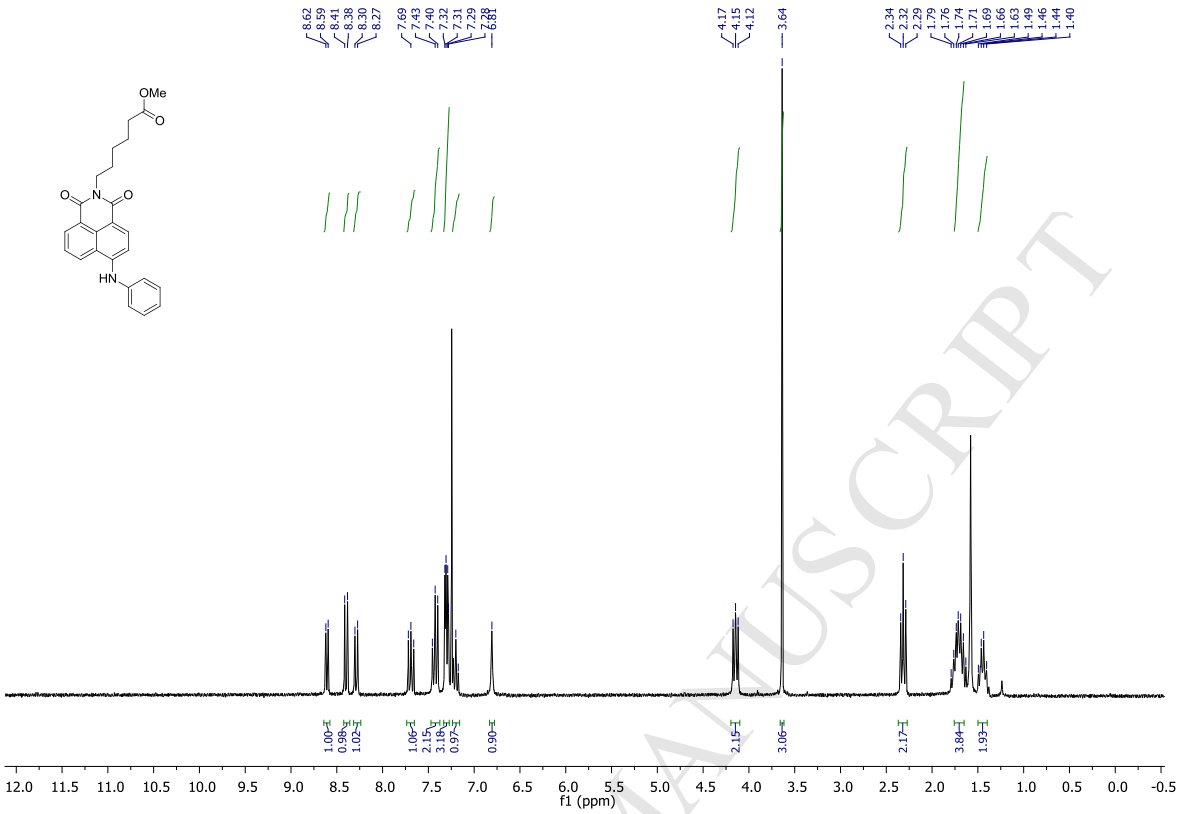


Figure S22. ^{13}C NMR of compound **16**.

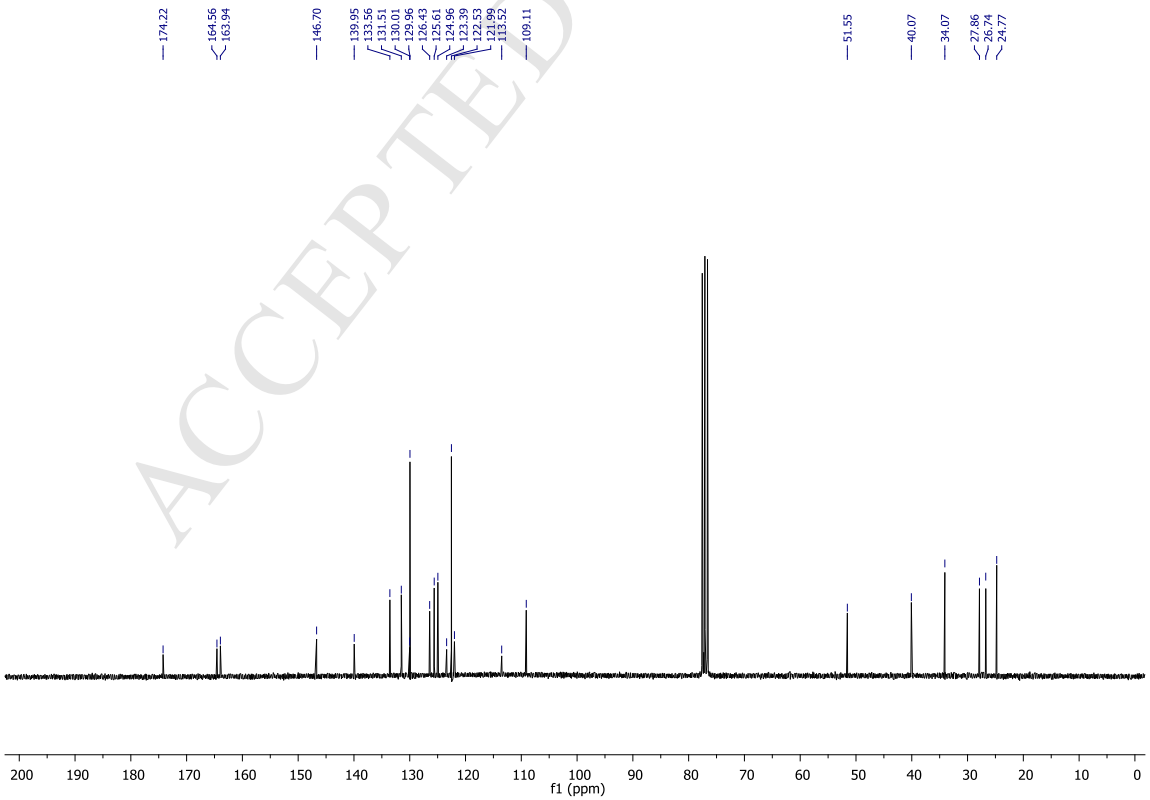


Figure S23. ^{1}H NMR of compound **17**.

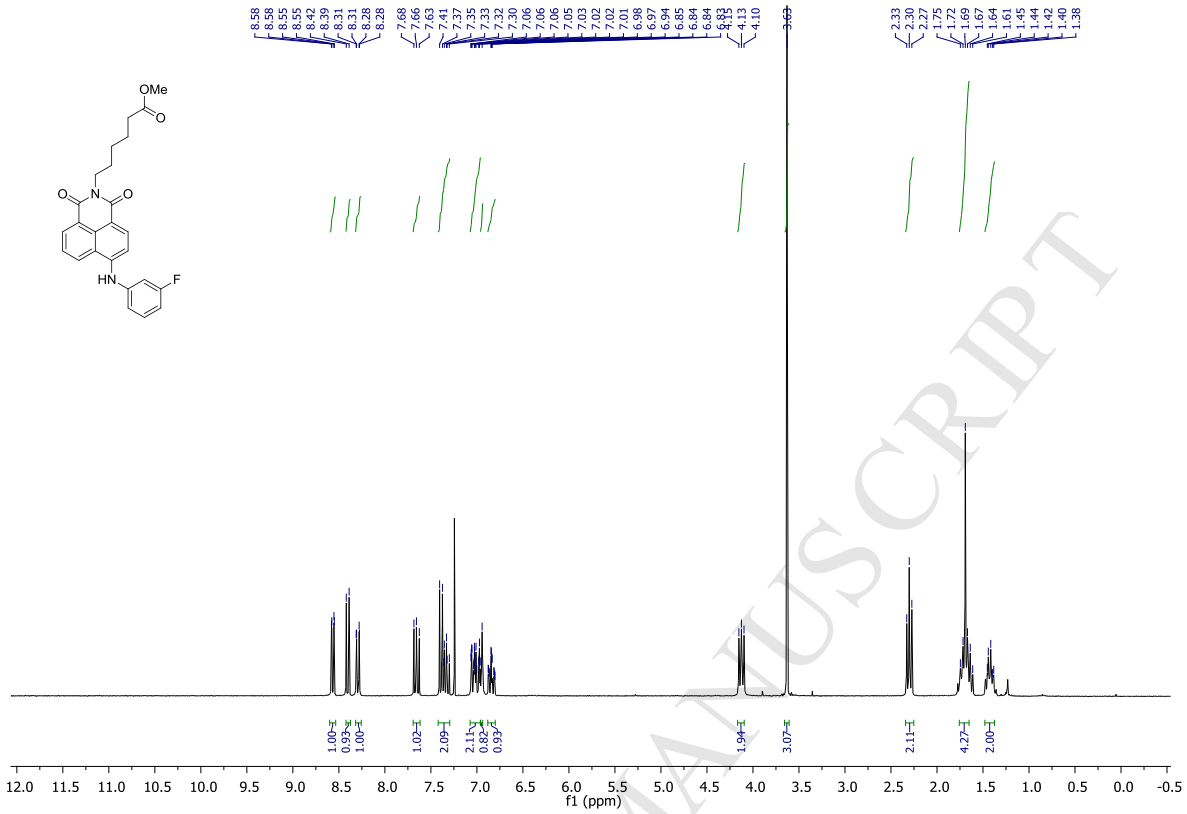


Figure S24. ^{13}C NMR of compound **17**.

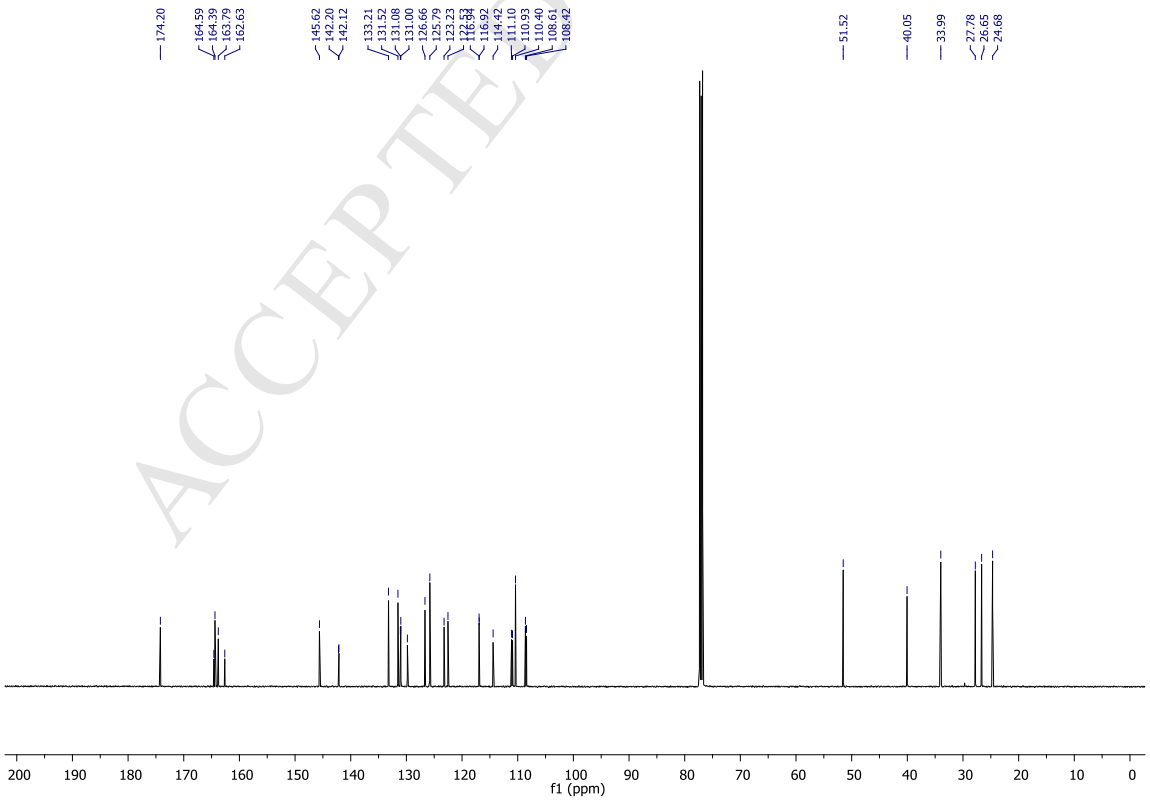


Figure S25. ^{1}H NMR of compound **18**.

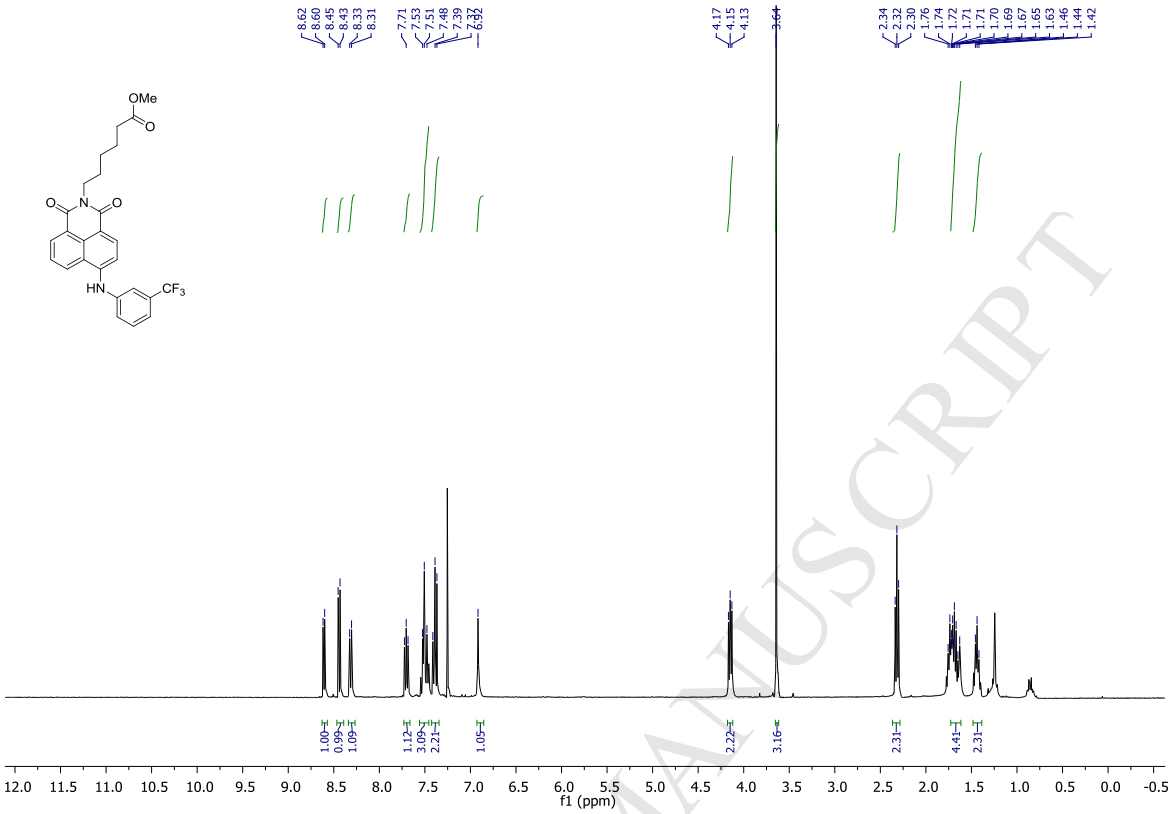


Figure S26. ^{13}C NMR of compound **18**.

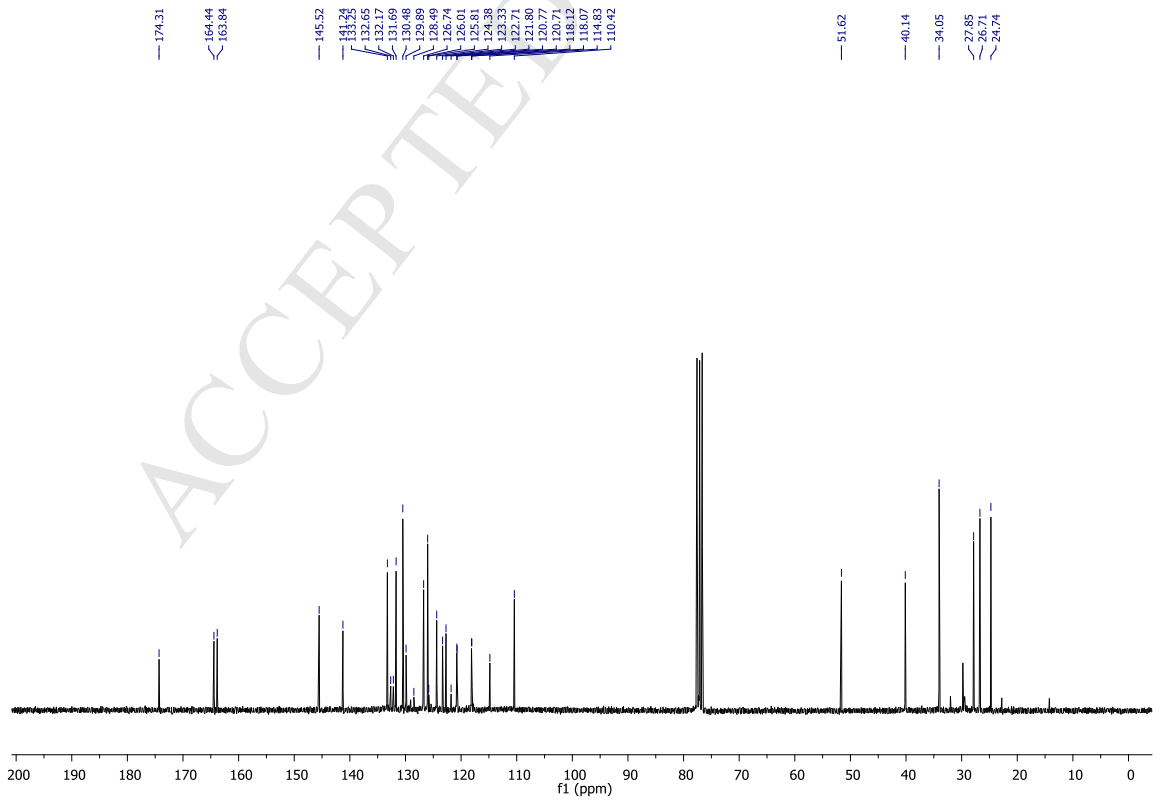


Figure S27. ^{1}H NMR of compound **19**.

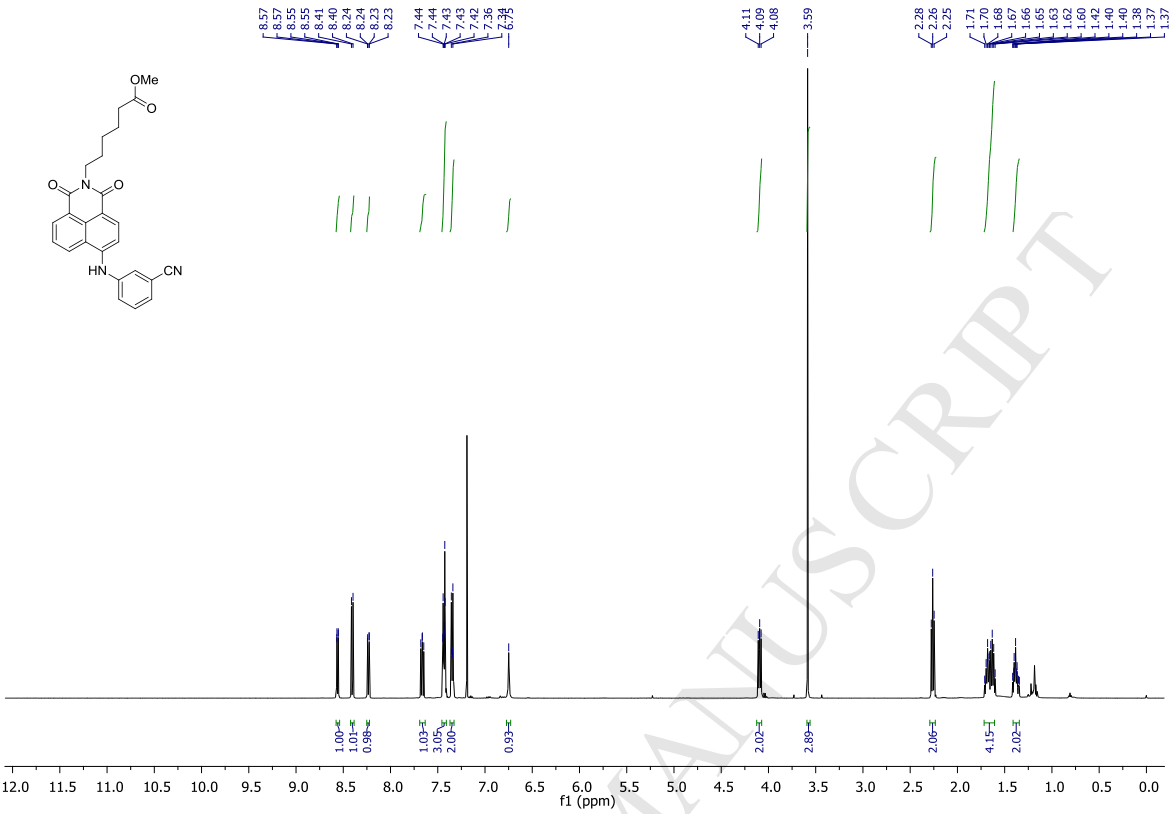


Figure S28. ^{13}C NMR of compound **19**.

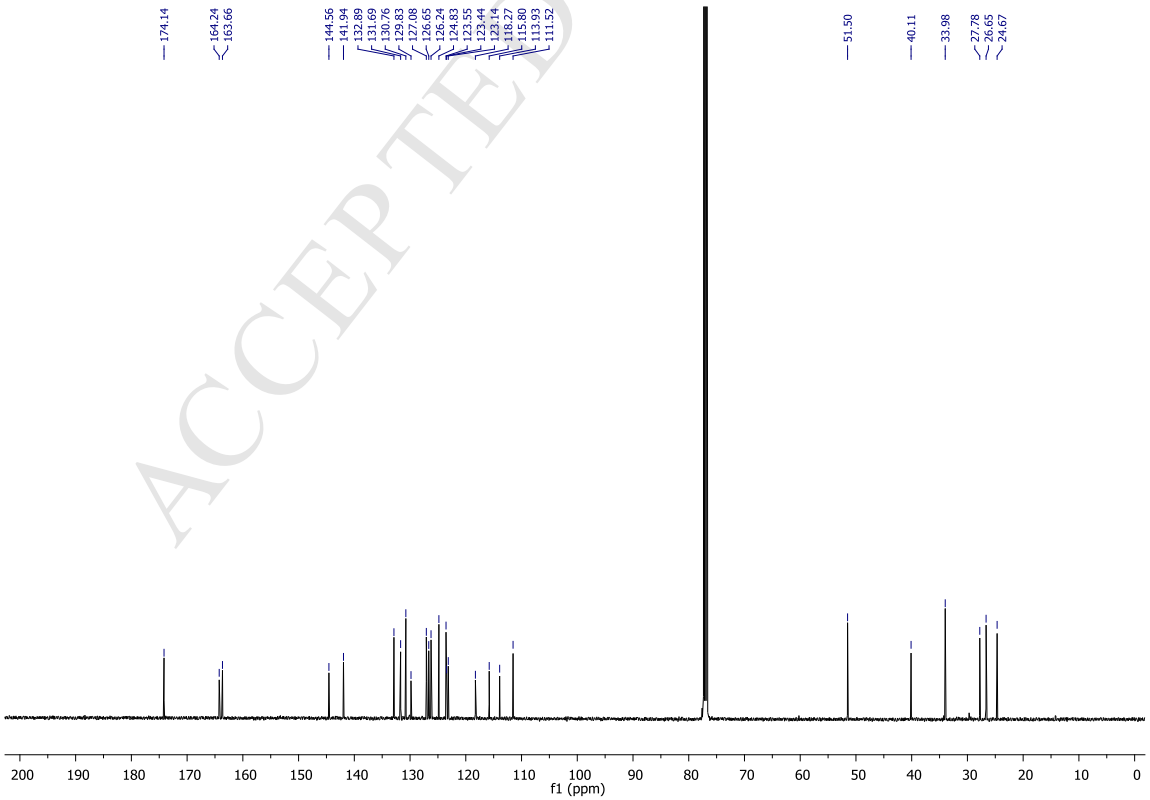


Figure S29. ^{1}H NMR of compound **20**.

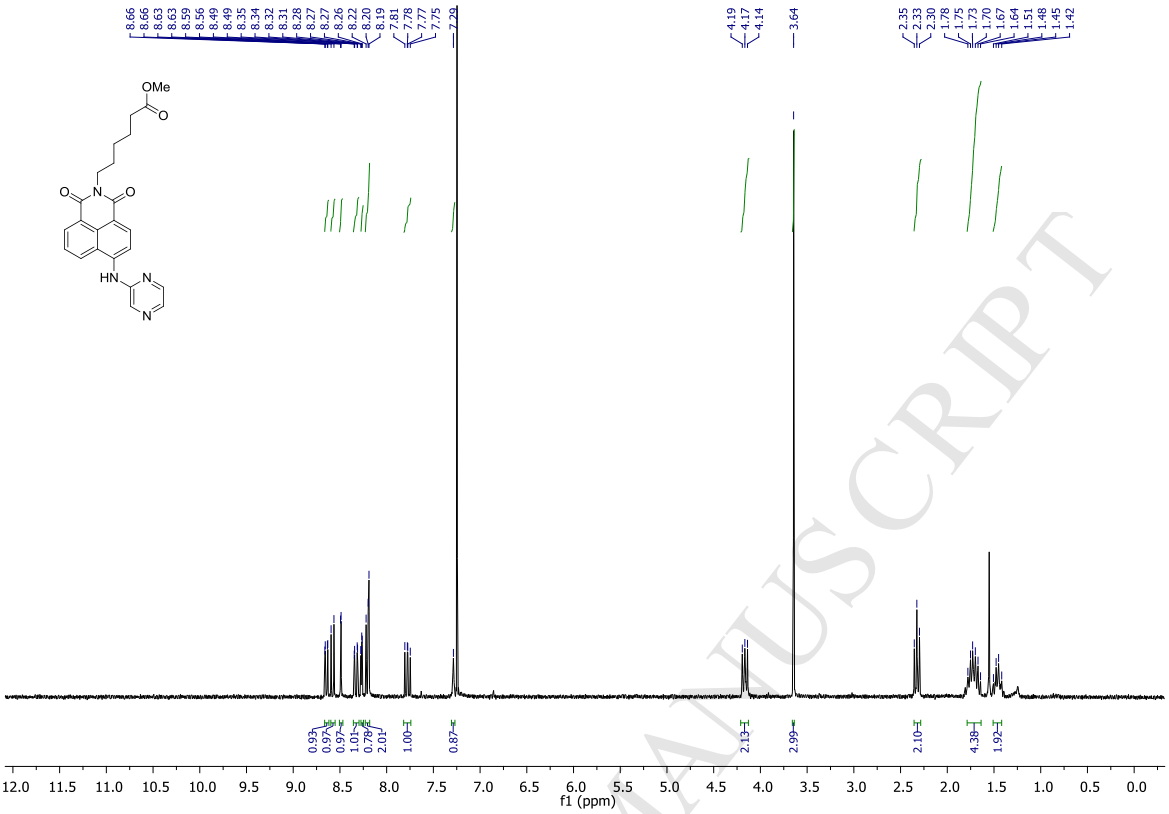


Figure S30. ^{13}C NMR of compound **20**.

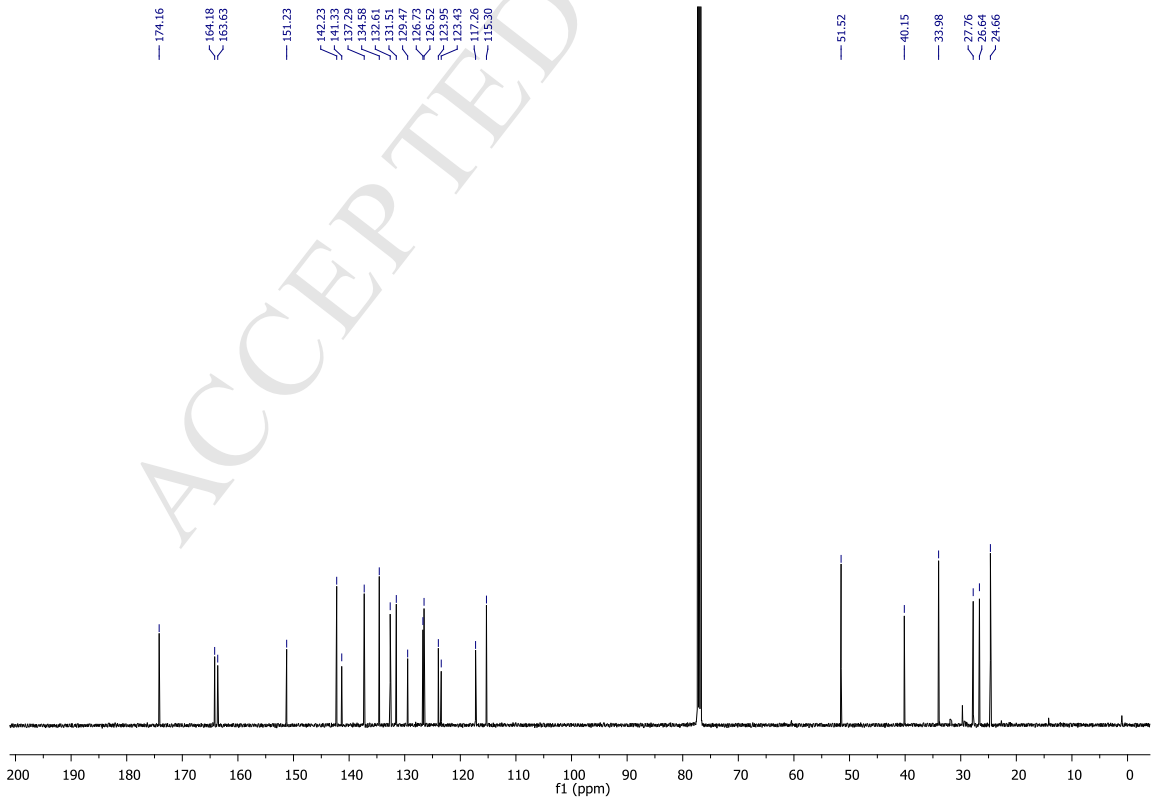


Figure S31. ^{1}H NMR of compound **21**.

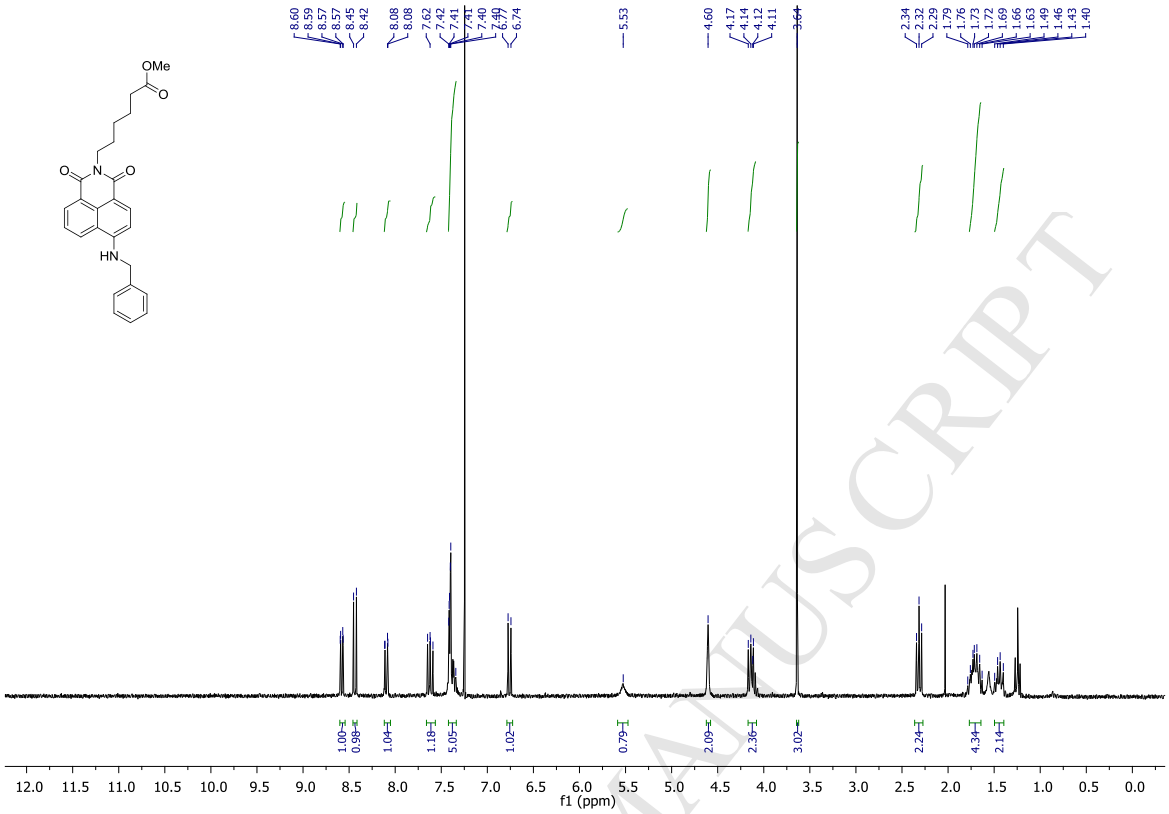


Figure S32. ^{13}C NMR of compound **21**.

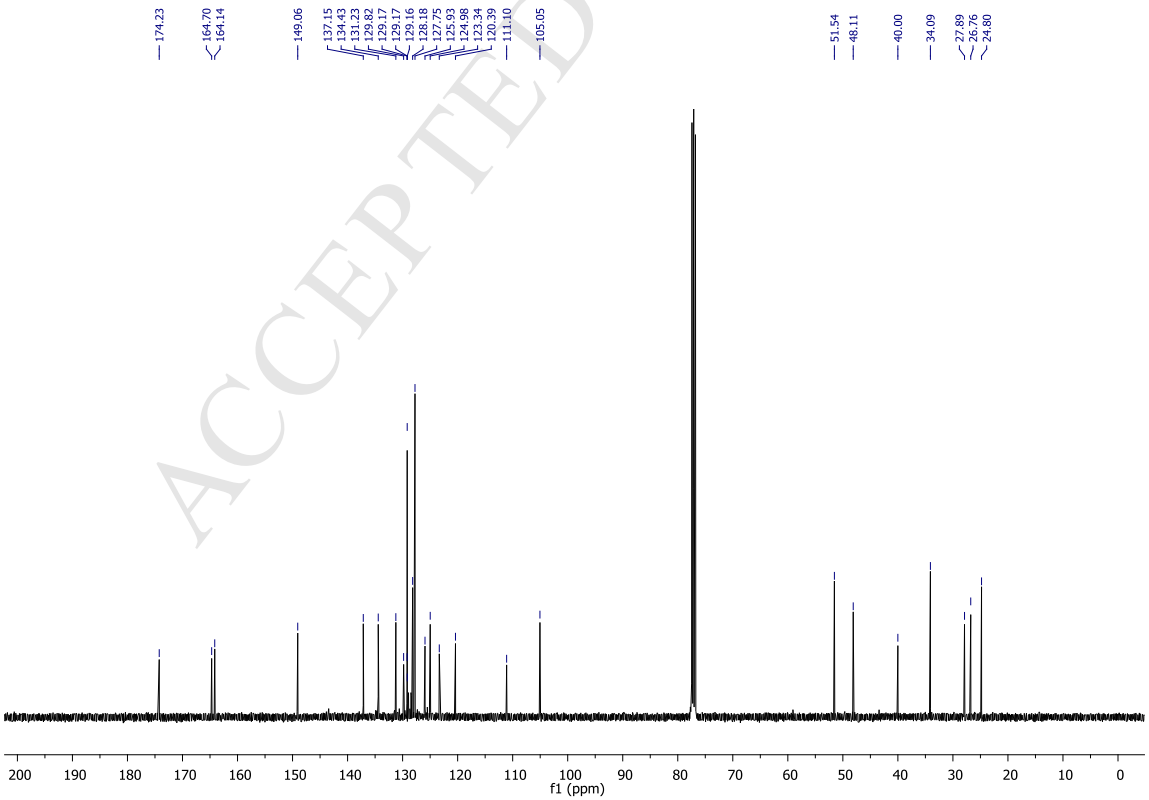


Figure S33. ^{1}H NMR of compound **22**.

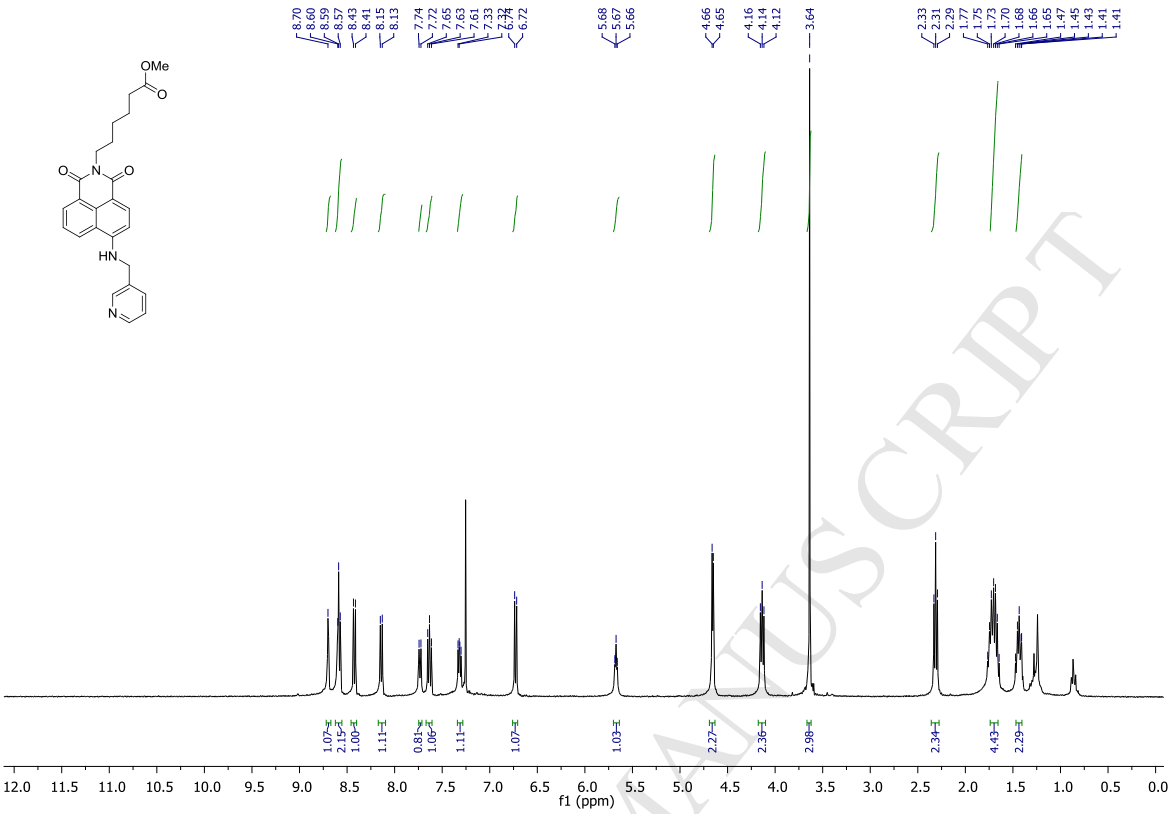


Figure S34. ^{13}C NMR of compound **22**.

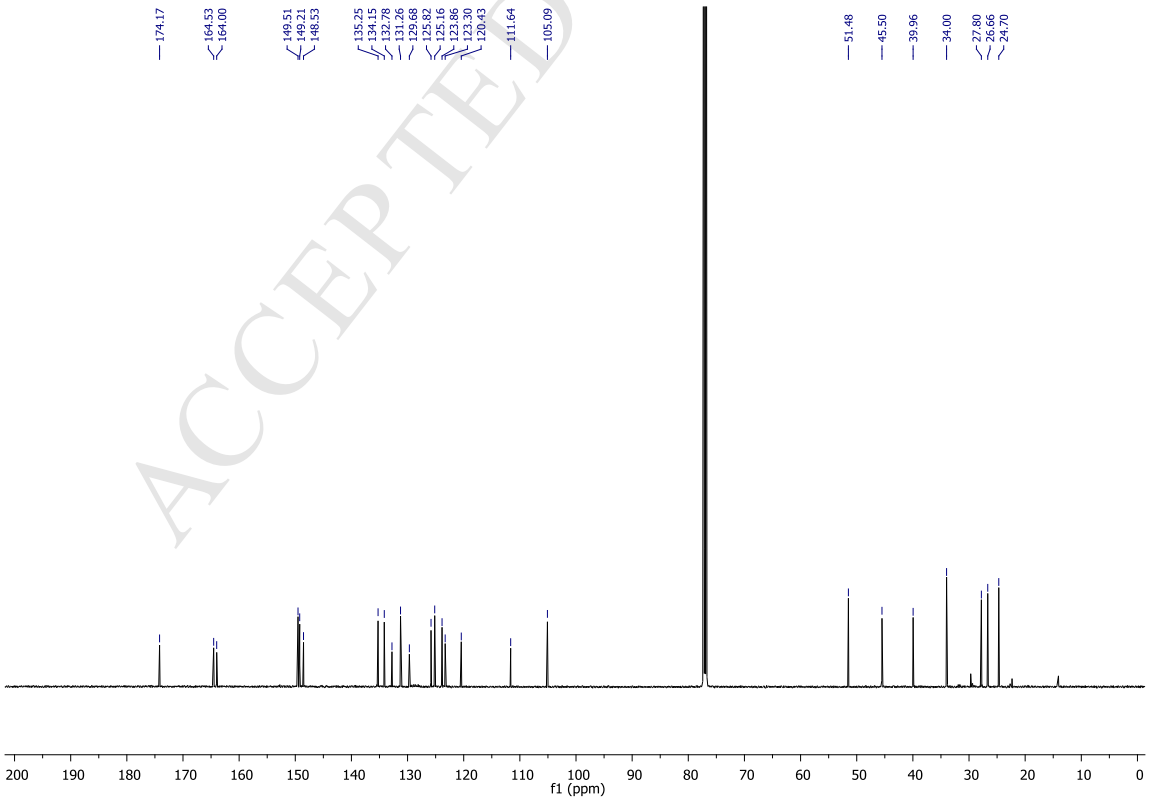


Figure S35. ^{1}H NMR of compound **23**.

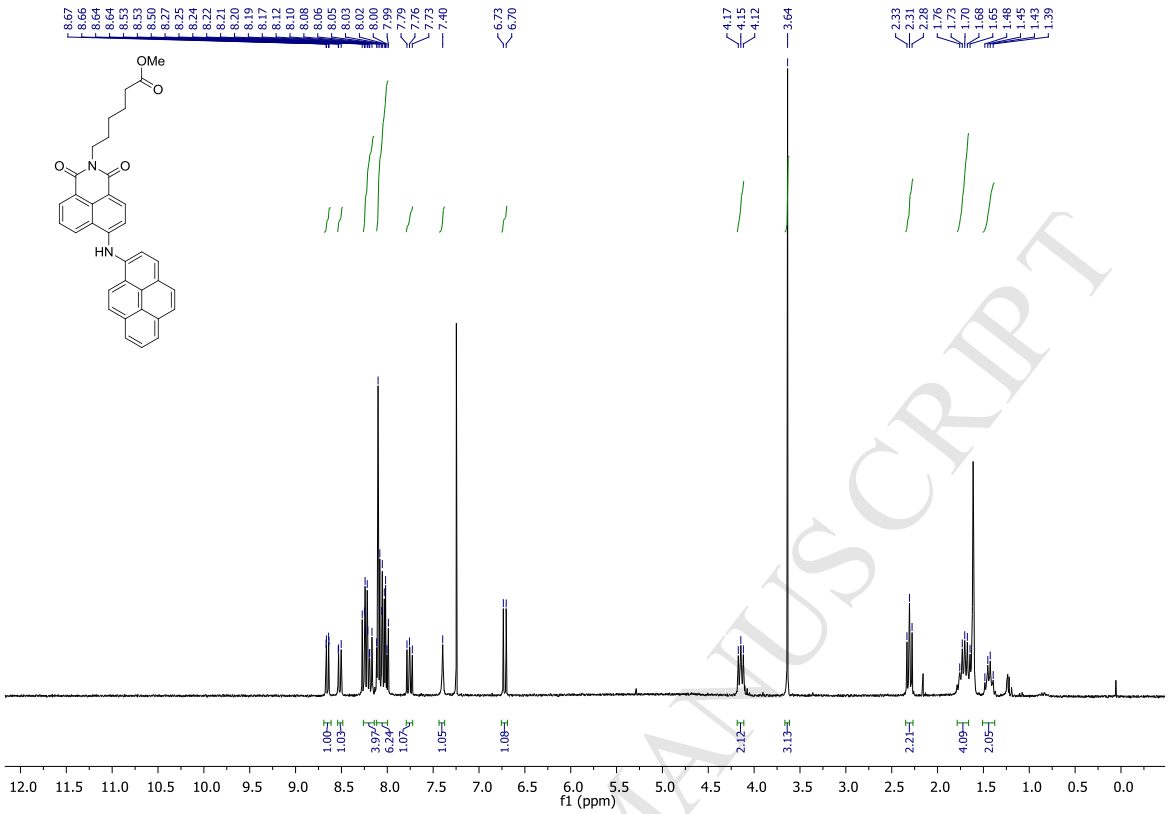


Figure S36. ^{13}C NMR of compound **23**.

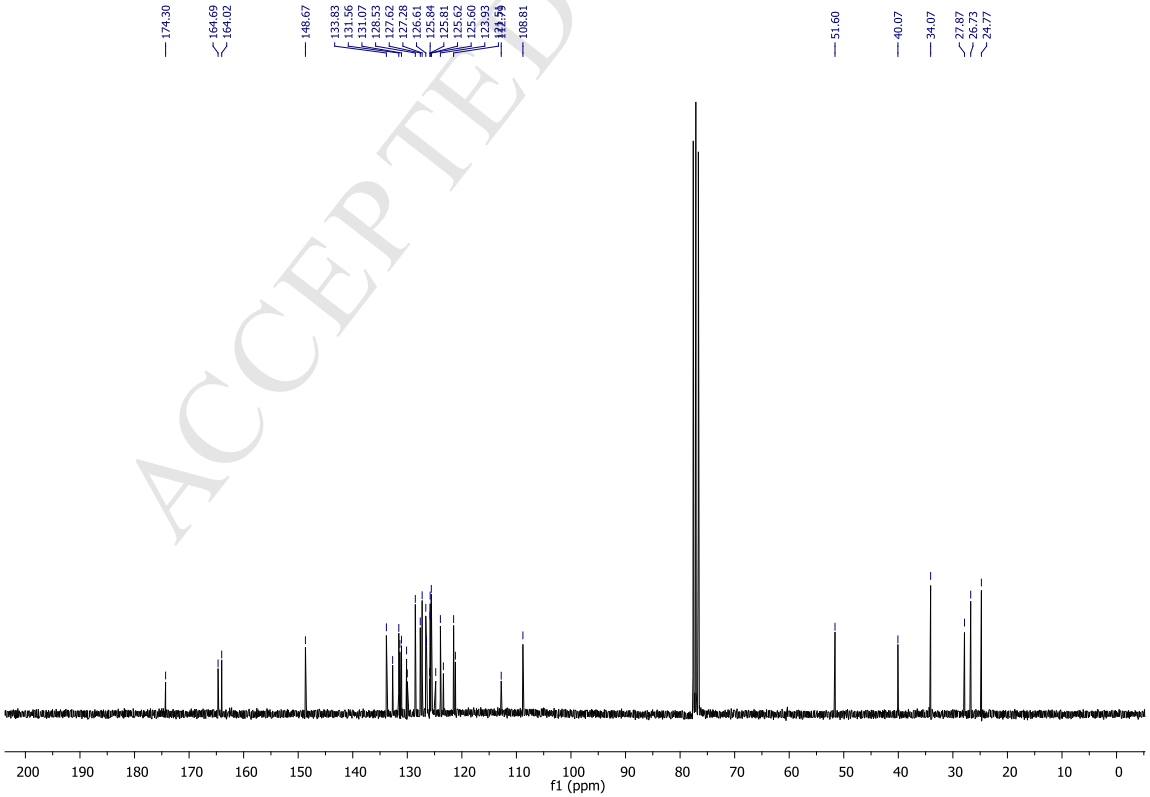


Figure S37. ^{1}H NMR of compound **24**.

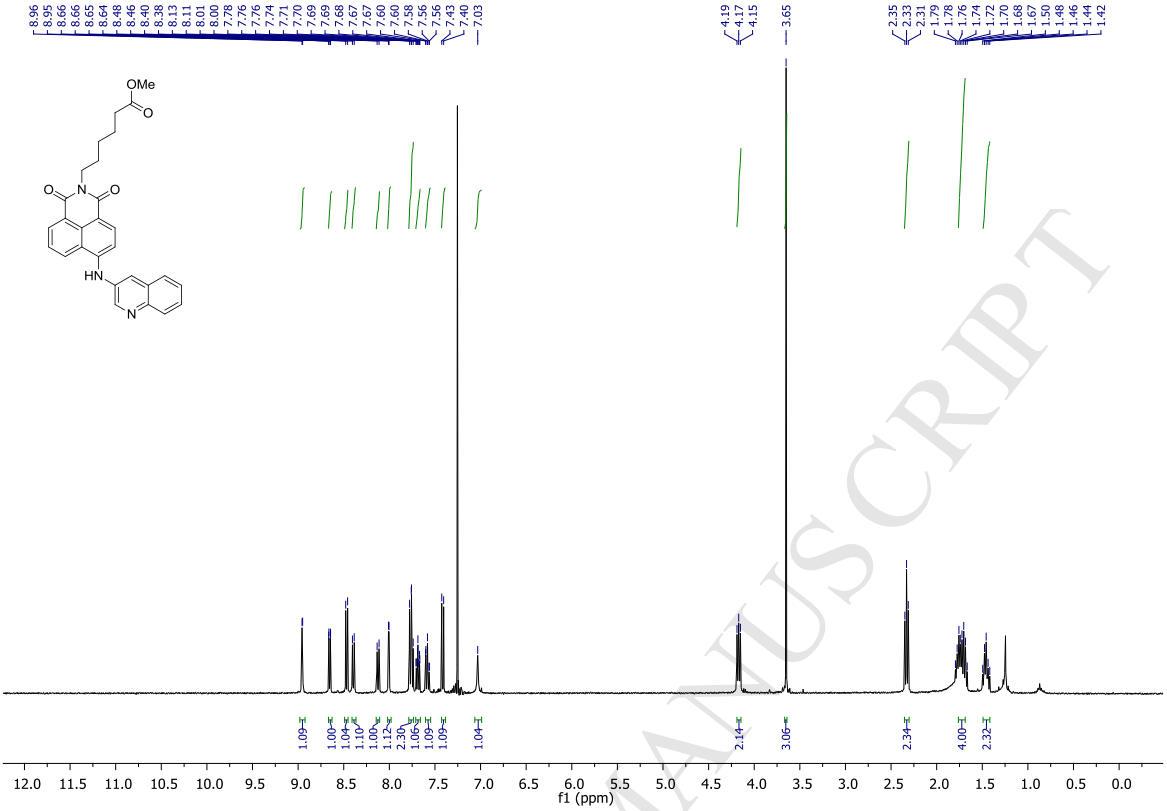


Figure S38. ^{13}C NMR of compound **24**.

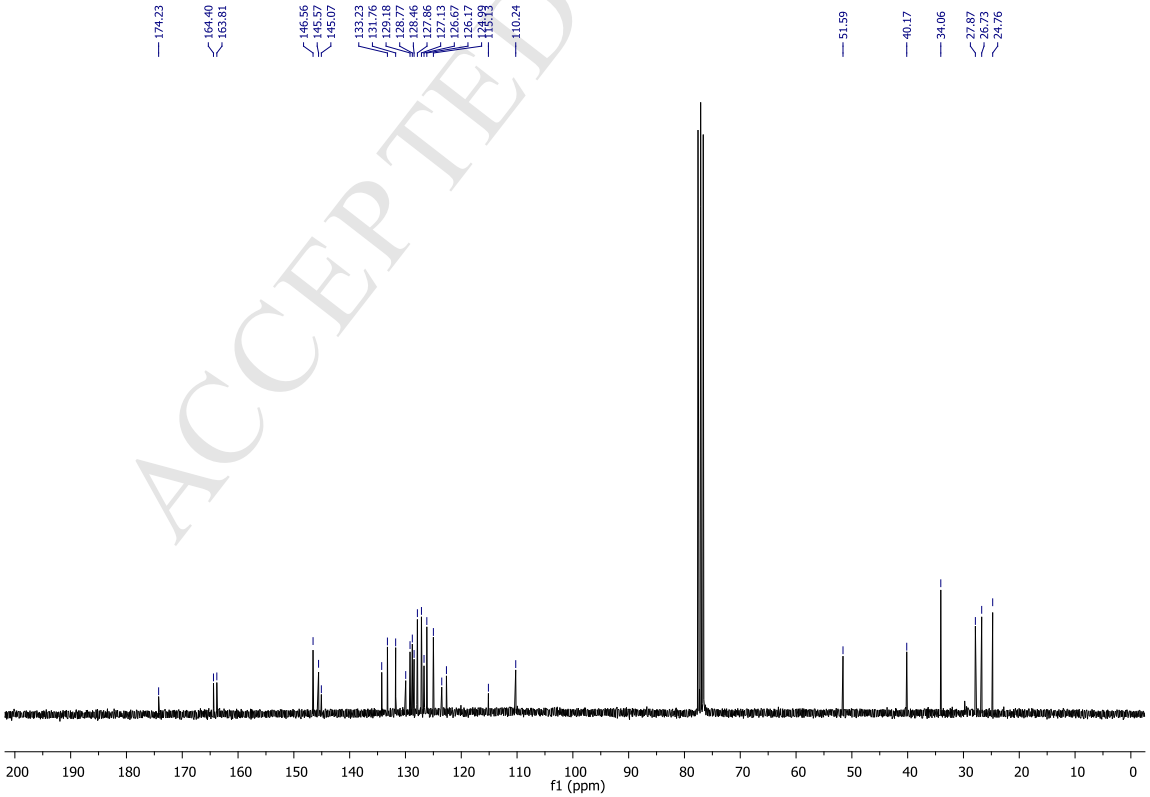


Figure S39. ^{1}H NMR of compound **25**.

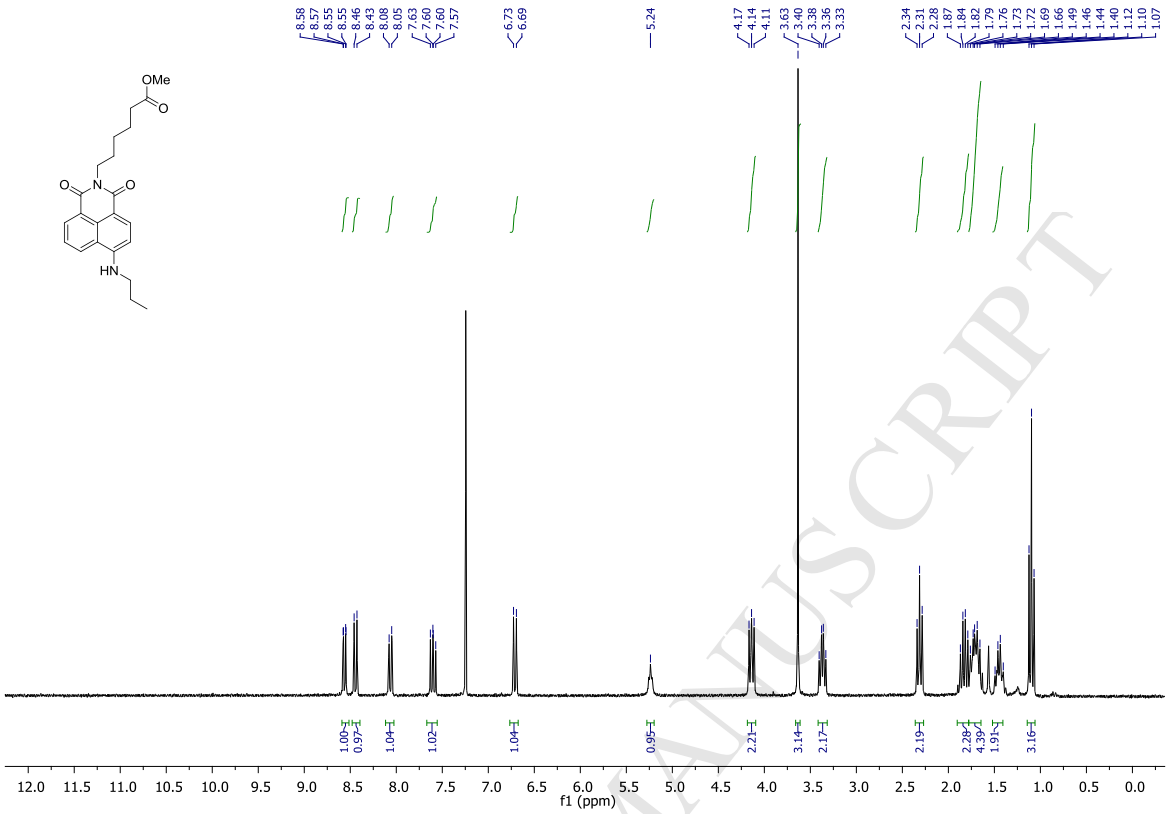


Figure S40. ^{13}C NMR of compound **25**.

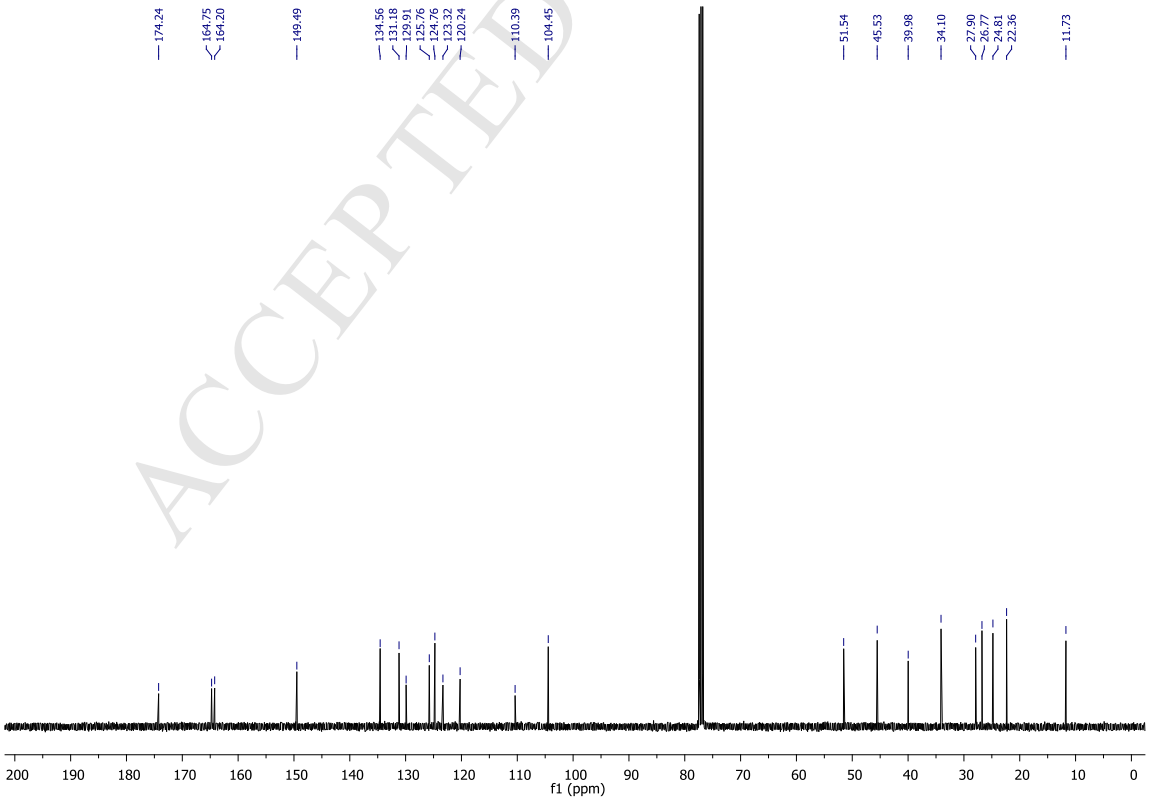


Figure S41. ^{1}H NMR of compound **26**.

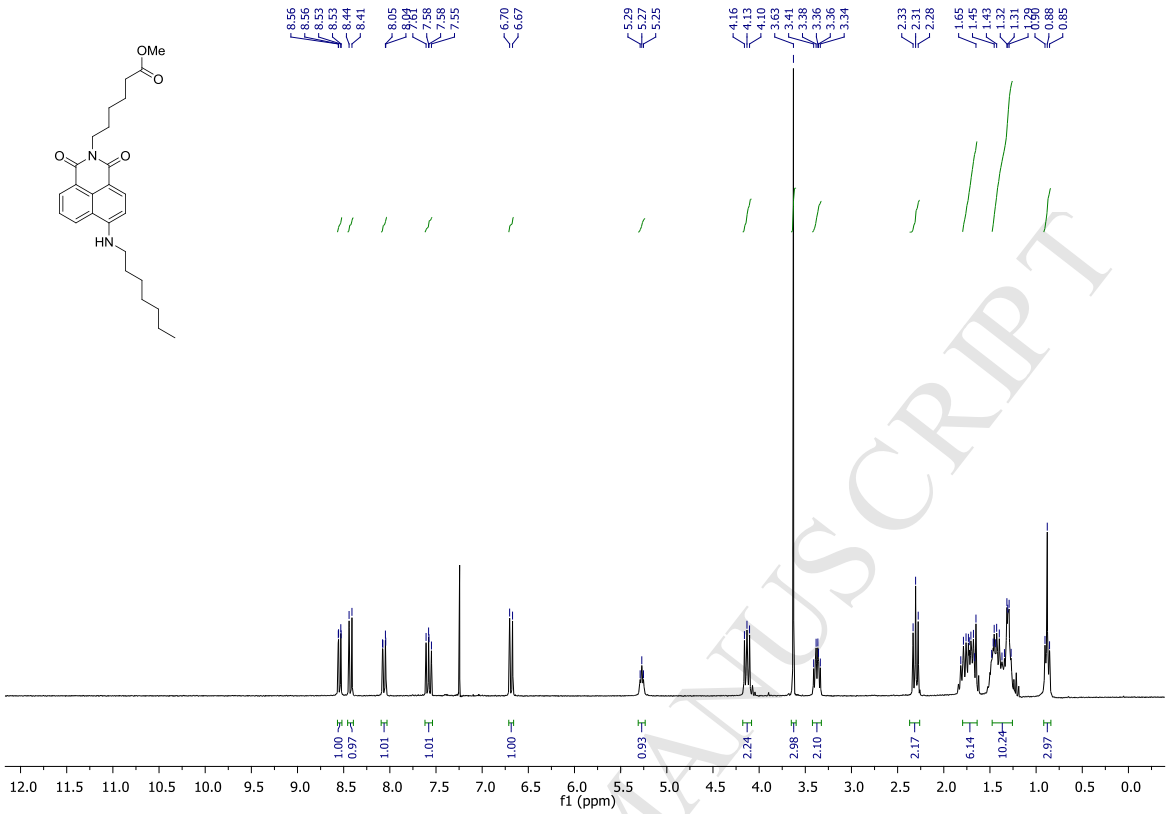


Figure S42. ^{13}C NMR of compound **26**.

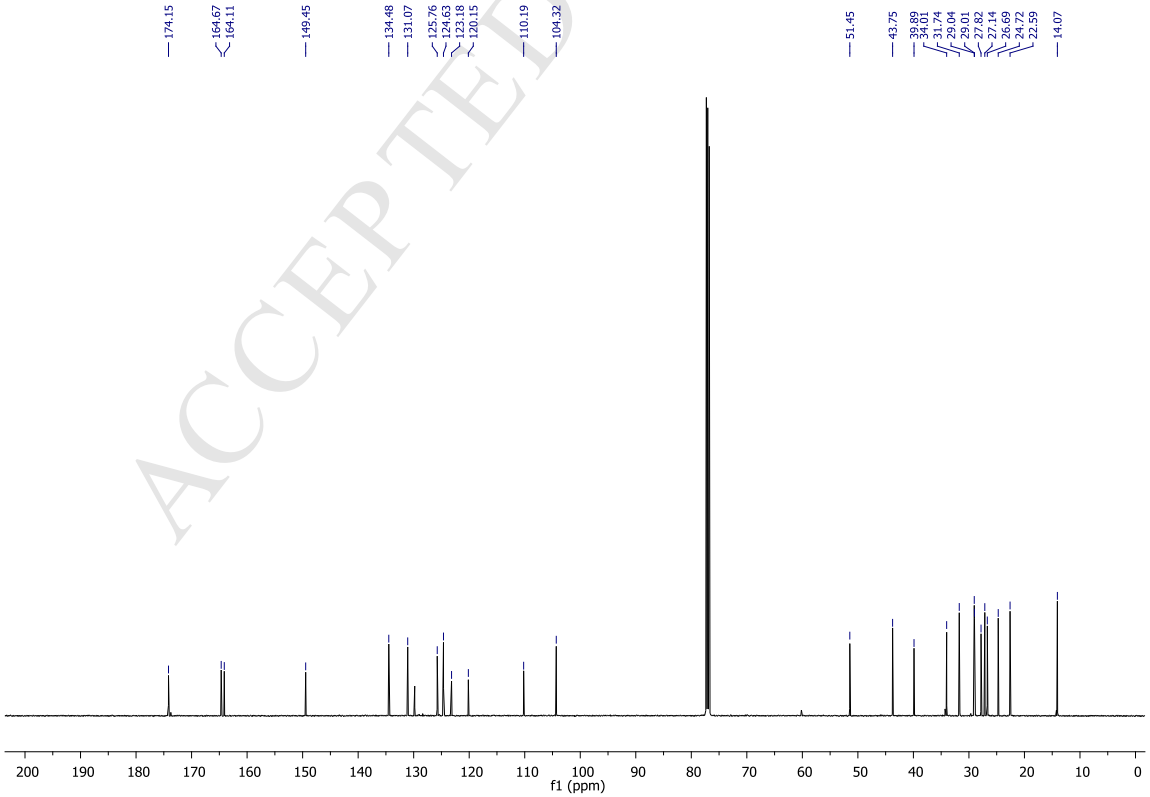


Figure S43. ^{1}H NMR of compound **27**.

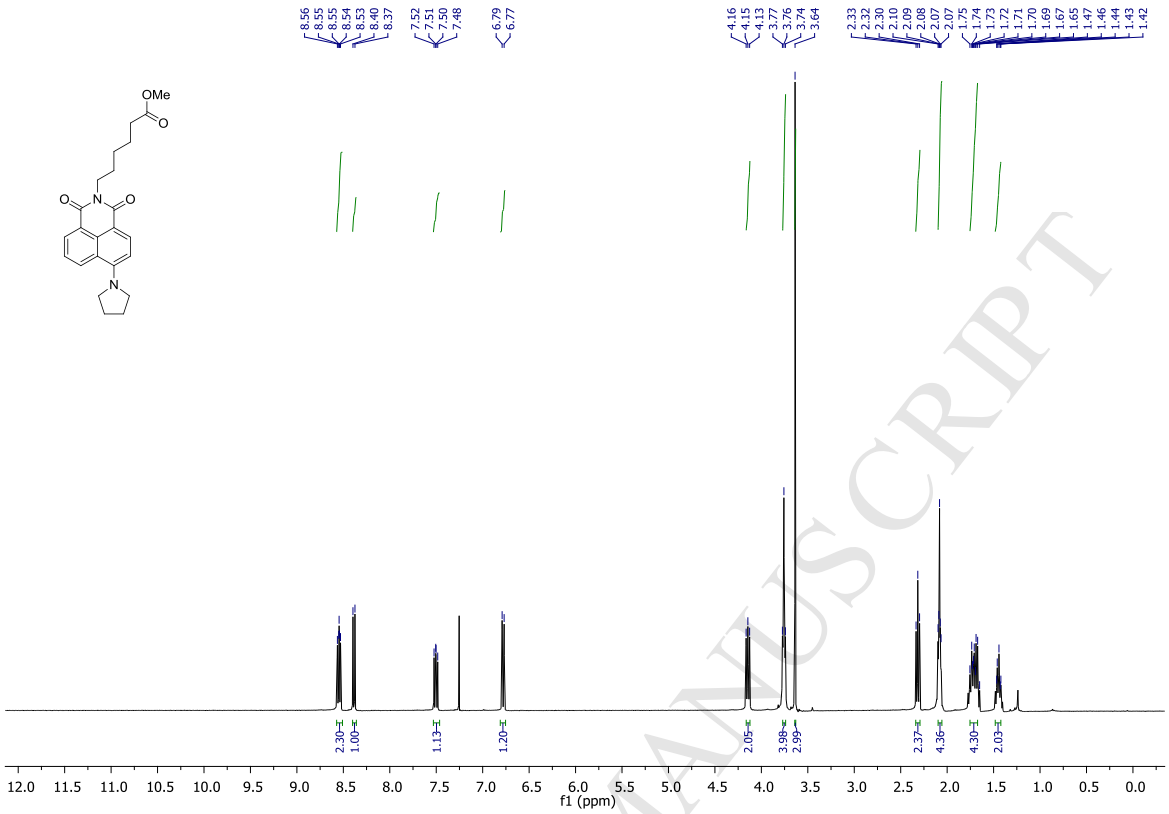


Figure S44. ^{13}C NMR of compound **27**.

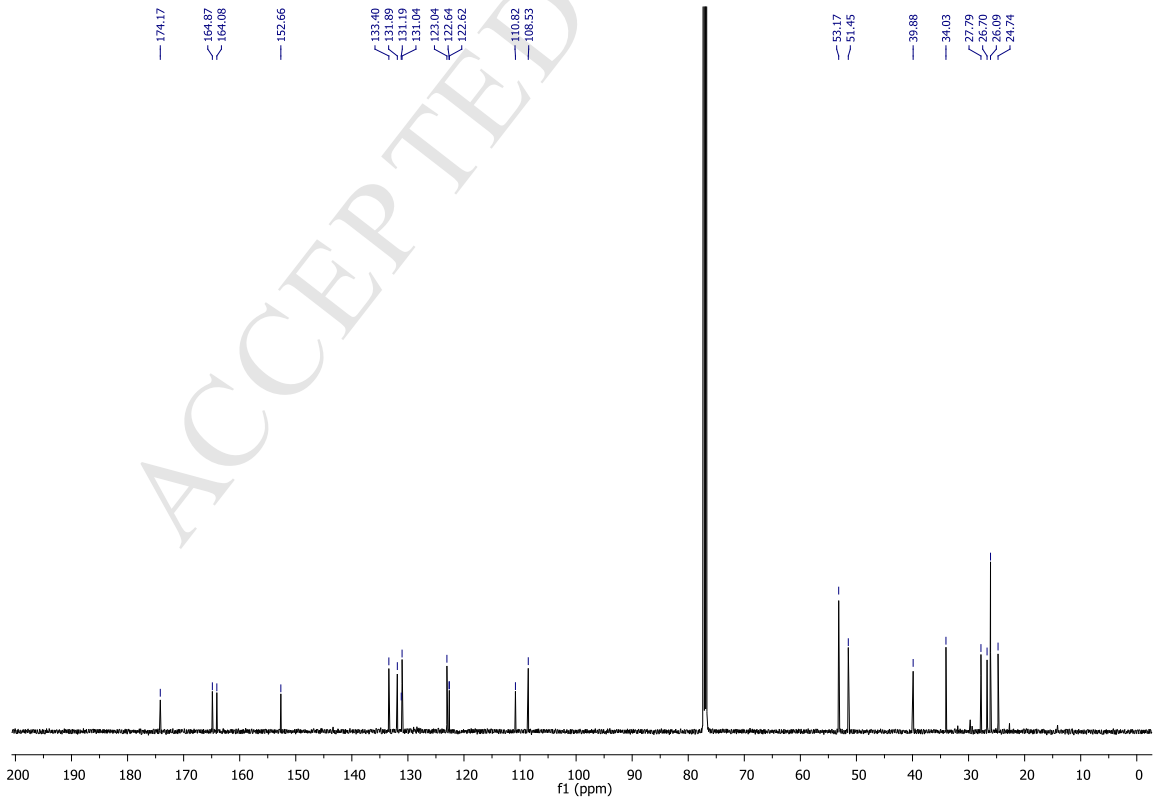


Figure S45. ^{1}H NMR of compound **28**.

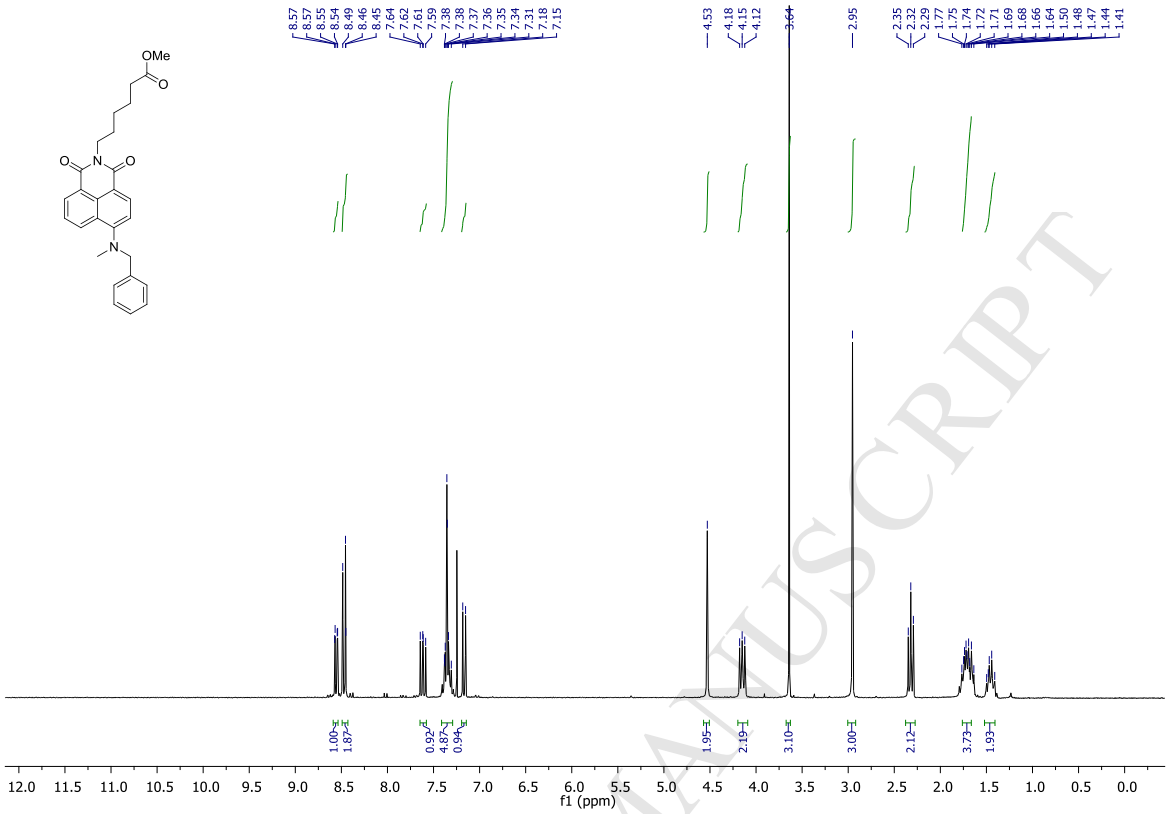


Figure S46. ^{13}C NMR of compound **28**.

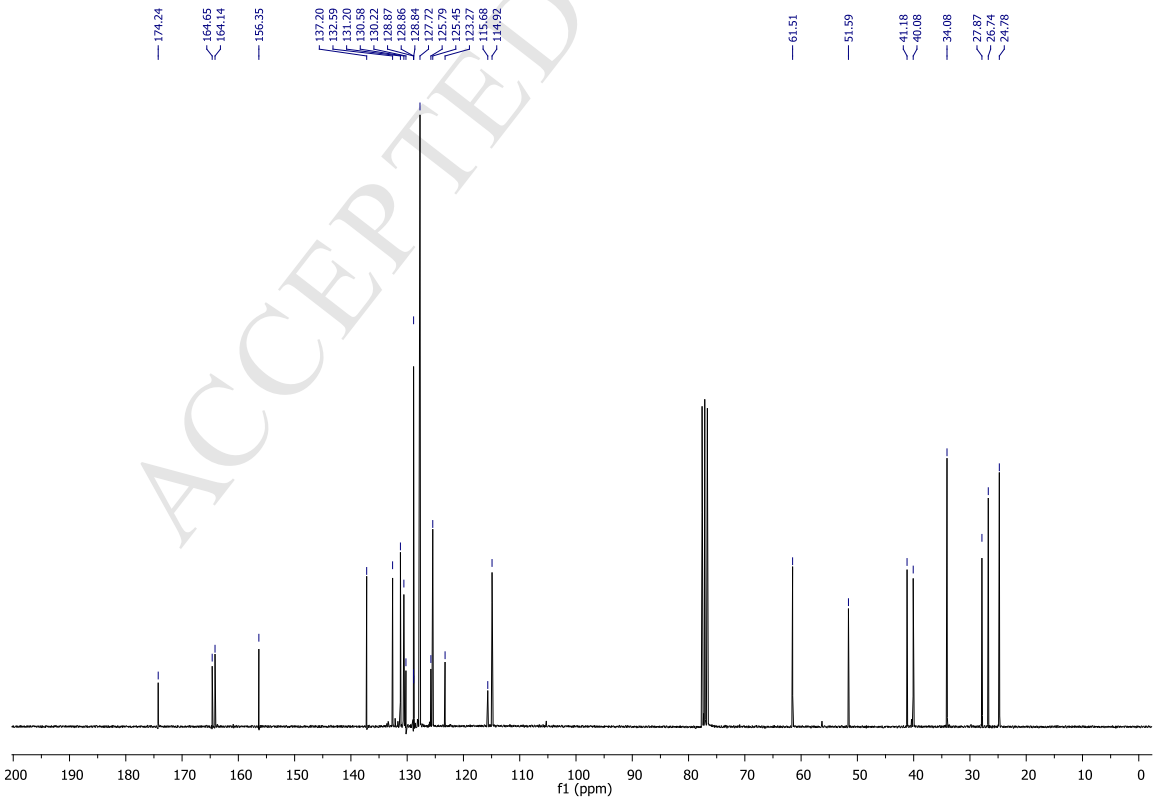


Figure S47. Normalised absorption and emission spectra of compound **9** in $CHCl_3$ and DMSO.

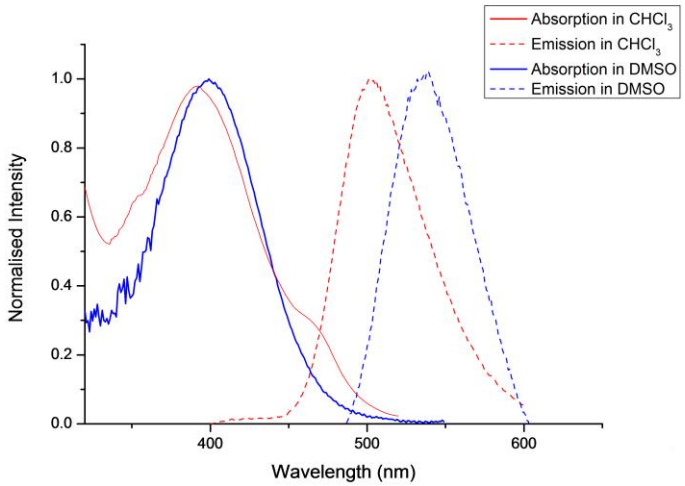


Figure S48. Normalised absorption and emission spectra of compound **17** in $CHCl_3$ and DMSO.

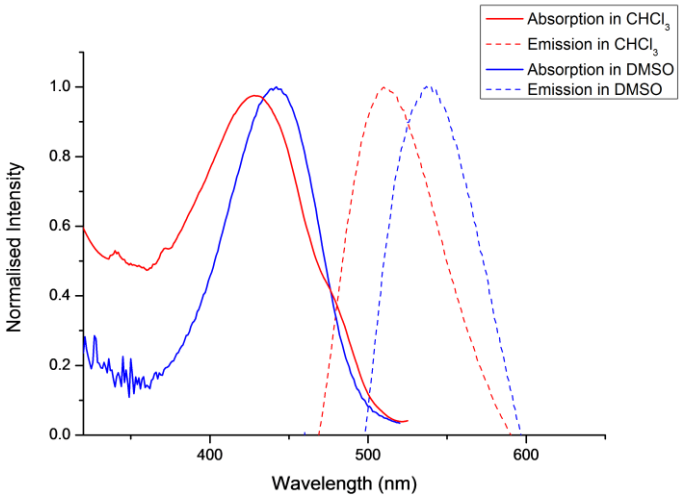


Figure S49. Normalised absorption and emission spectra of compound **20** in $CHCl_3$ and DMSO.

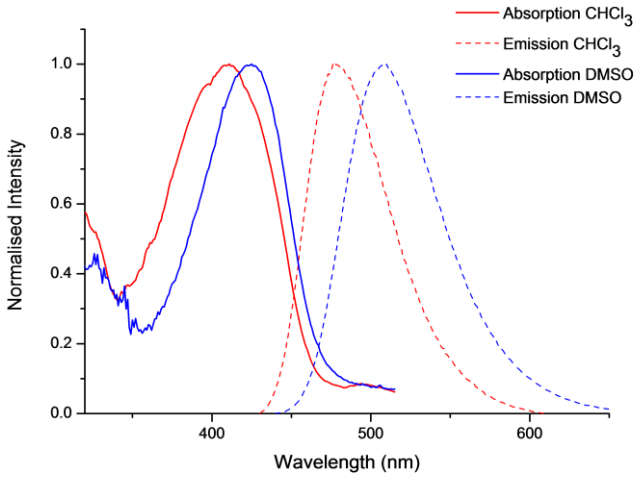


Figure S50. Normalised absorption and emission spectra of compound **21** in $CHCl_3$ and DMSO.

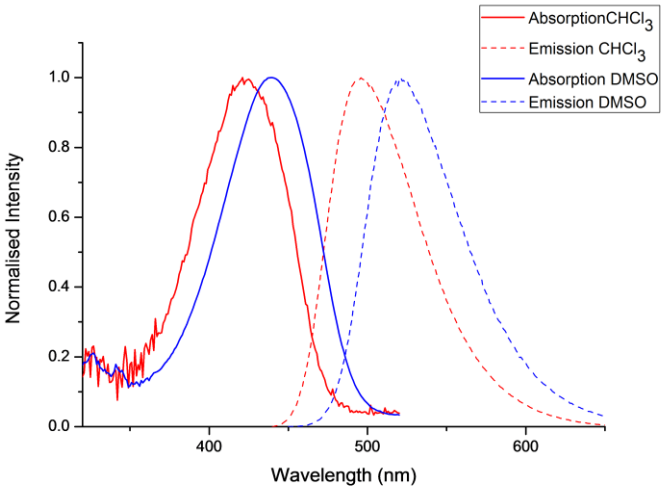


Figure S51. Normalised absorption and emission spectra of compound **25** in $CHCl_3$ and DMSO.