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Original synthesis of 2-substituted-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-naphtho[2,3-*f*]indole-5,10-diones using TDAE and Cu-catalyzed reaction strategy

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Dedicated to the memory of Pr François Tillequin

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ABSTRACT

We report herein an original and rapid synthesis of 2-substituted-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-naphtho[2,3-*f*]indole-5,10-diones by TDAE mediated synthesis of *N*-benzylsulfonamides followed by an intramolecular N-arylation using Cu-catalyzed system.

1. Introduction

Anthracycline derivatives, such as daunomycin and adriamycin possess high antitumor activity due to their capability of intercalating DNA double helix to result dramatic changes in DNA conformation[1] and, furthermore, can also inhibit DNA replication and transcription.[2] Unfortunately, the clinical use is limited by both dose-related cumulative cardiotoxicity and development of drug-resistance.[3] Several synthesis of heterocyclic anthracycline analogs were developed by replacing the cyclohexane ring (A) of anthracycline by a heterocycle.[4] Interesting activity against drug resistant cells has been obtained by modification of the 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione skeleton (Fig. 1).[5] On the other hand, the compounds possessing a furano or pyrano ring fused to polycyclic, aromatic system, such as furanoxanthone,[6] benzopyranoxanthone,[7] and coumarin[8] have exhibited interesting antitumor[9] and anti-inflammatory properties.[10]

Pd-catalyzed and Cu-catalyzed C–N bond forming reactions are extensively used in the medicinal chemistry. Cu-mediated systems have proven their effectiveness under mild conditions in

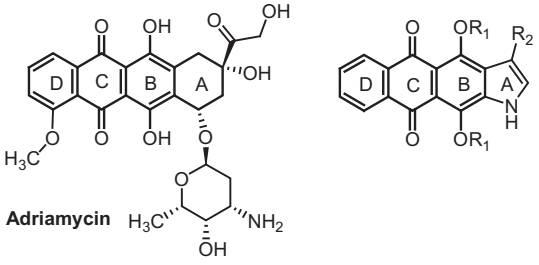

Fig. 1. Adriamycin and heterocyclic anthracycline analogs.

N-arylation of amino derivatives (anilines,[11] amides,[12] hydrazides,[13] alkylamines[14]) and nitrogen heterocycles[15] using various ligands (diamines, diols,…). Among them, Buchwald has developed an extremely efficient and general catalyst system for the amidation of aryl halides and the N-arylation of a wide variety of heterocycles. This catalyst system is based on the use of chelating nitrogen ligands (*N*,*N*′-dimethylated 1,2-diamine ligands) with air stable CuI in the presence of base (K_3PO_4, K_2CO_3, Cs_2CO_3,…).[14]

Tetrakis(dimethyl-amino)ethylene (TDAE) is an organic reducing agent,[16] which reacts with haloalkyl derivatives to generate a carbanion under mild conditions.[17] Since 2003, we have introduced

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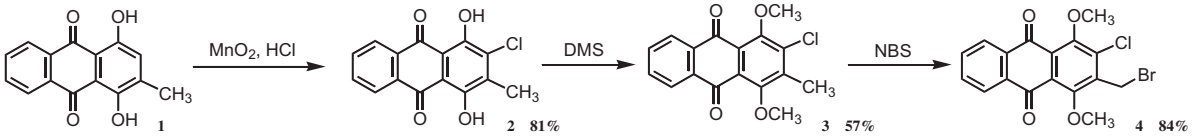
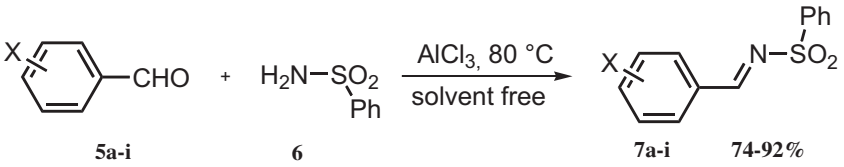
a new program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry.[18] We have shown that from *o*- and *p*-nitrobenzyl chloride, tetrakis(dimethyl-amino)ethylene (TDAE) could generate a nitrobenzyl carbanion, which is able to react with various electrophiles as aromatic aldehydes, α-ketoester, ketomalonate, and α-ketolactam derivatives. We have recently reported the extension of this reactivity in anthraquinone series with aromatic aldehyde and nitro-derivative **2**.[24] After methylation using dimethylsulfate, the obtained 2-chloro-1,4-dimethoxy-3-methylanthracene-9,10-dione (**3**) was brominated using *N*-bromosuccinimide (NBS) giving the bromomethyl derivative **4** (Scheme 1).[24] The substituted *N*-(benzenesulfonyl)benzylimine **7a**–**i** have been prepared by condensation of various benzaldehydes **5a**–**i** and benzenesulfonamide **6** in the presence of $AlCl_3$ in a solvent free procedure as described by Sharghi (Scheme 2) (Table 1).[25]



Scheme 1.



Scheme 2.

anthraquinonic with ketomalonate and α-ketoester derivatives.[19] However, few studies have been reported concerning the nucleophilic additions of carbanion, formed via TDAE strategy, on Carbon–Nitrogen double bond and their synthetic applications.[20]

In order to develop pharmacomodulation studies, our team is interested in the metal-catalyzed reactions, such as Suzuki–Miyaura,[21] Sonogashira, Buchwald and Heck reactions. Recently, we reported the synthesis of new 2-substituted-4,11-dimethoxyanthra[2,3-*b*]furan-5,10-diones by an intramolecular Pd-catalyzed C–O bond forming reaction of halide alcohol derivatives via intramolecular Buchwald reaction.[22] In connection with our program centered on the synthesis of new quinonic compound using the electron transfer methodology and the preparation of new potentially bioactive compounds as anticancer agents,[23] we report herein an original and efficient synthesis of new 2-substituted-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-naphtho[2,3-*f*]indole-5,10-diones (**9a**–**i**) by an intramolecular Cu-catalyzed C–N bond forming reaction of *N*-[1-arylethyl-2-(3-chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)]-benzenesulfonamide derivatives (**8a**–**i**) prepared by the TDAE methodology.

2. Results and discussion

2.1. Preparation of starting materials

The required starting material for TDAE-initiated reaction in anthraquinonic series, 2-chloro-3-bromomethyl-1,4-dimethoxyanthracene-9,10-dione (**4**), was synthesized in three steps from 1,4-dihydroxy-2-methylanthracene-9,10-dione **1** as previously described.[19a] The chloration via oxidation of **1** furnished the chloro

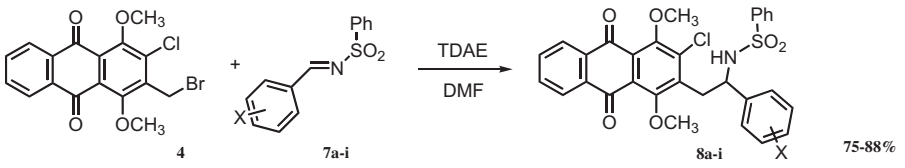
Table 1
Synthesis of the substituted *N*-(benzenesulfonyl)benzylimines **7a**–**i**

X	Aldehyde	*N*-(Benzenesulfonyl)benzylimine	Yield %[a]
H	**5a**	**7a**	84
4-CH_3	**5b**	**7b**	92
2,5-$(CH_3)_2$	**5c**	**7c**	75
4-OCH_3	**5d**	**7d**	74
4-CF_3	**5e**	**7e**	75
4-F	**5f**	**7f**	75
3-F	**5g**	**7g**	88
2-F	**5h**	**7h**	83
2-Cl	**5i**	**7i**	90

[a] All yields refer to chromatographically isolated pure products and are relative to aldehyde **5a**–**i**.

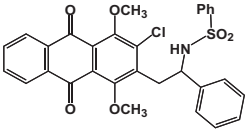
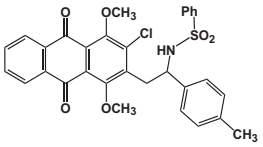
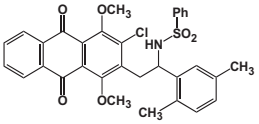
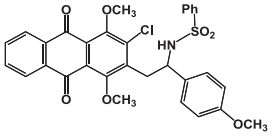
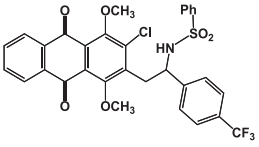
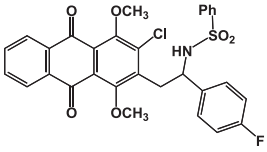
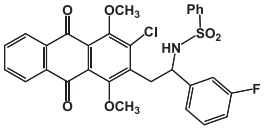
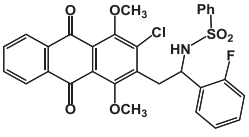
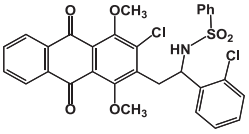
2.2. TDAE reactivity

Among the Carbon–Nitrogen double bonds, we have chosen the sulfonylaldimines, which are able to react with TDAE in fluorine chemistry as described by Dolbier[20] and Medebielle.[20] To extend the reactivity of the sulfonylaldimines with non-fluorine compounds, we have considered our TDAE conditions described in anthraquinonic series. The reaction of 2-chloro-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione (**4**) with the substituted *N*-(benzenesulfonyl)benzylimines **7a**–**i** in the presence of TDAE at −20 °C for 1 h, followed by 2 h at rt led to the corresponding *N*-substituted benzenesulfonamides **8a**–**i** in good yields (75–88%) as shown in Scheme 3 and Table 2. These several compounds **8a**–**i** were synthesized for the investigation of the intramolecular Cu-catalyzed substitution of an aryl chloride with an arylsulfonamide.



Scheme 3.

Table 2
Reaction of 2-chloro-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione **4** with substituted *N*-(benzenesulfonyl)benzylimines **7a**–**i** using TDAE strategy[a]

Entry	X	*N*-Substituted benzenesulfonamide		Yield (%)[b]
1	H	**8a**		78
2	4-CH_3	**8b**		76
3	2,5-$(CH_3)_2$	**8c**		76
4	4-OCH_3	**8d**		75
5	4-CF_3	**8e**		81
6	4-F	**8f**		84
7	3-F	**8g**		88
8	2-F	**8h**		85
9	2-Cl	**8i**		80

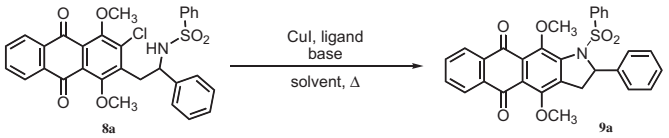
[a] All the reactions are performed using 3 equiv of substituted *N*-(benzenesulfonyl) benzylimines **7a**–**i**, 1 equiv of bromide **4** and 1 equiv of TDAE in anhydrous DMF stirred at −20 °C for 1 h and then warmed up to rt for 2 h.

[b] All yields refer to chromatographically isolated pure products and are relative to bromide **4**.

2.3. Intramolecular Buchwald reaction

As observed in compounds **8a**–**i**, an intramolecular C–N bond forming reaction corresponds to a reaction between an *ortho* substituted aryl chloride and an arylsulfonamide, which are limited in Pd-catalyzed chemistry.[15a] So, we directed our investigations to the efficient and general catalyst system developed by Buchwald for amidation of aryl halide. We studied the intramolecular reactivity of compounds **8a** using Cu-diamine catalyst system. Moreover, we envisaged the use of microwave irradiation for heating to decrease reaction time.

We started this study by an adaptation of the conditions defined by Buchwald[12] for amidation of aryl chloride with CuI (10 mol %), *N*,*N*′-dimethylcyclohexyl-1,2-diamine (15 mol %) as ligand and K_2CO_3 (2 equiv) as base at 110 °C in toluene for 1.5 h under microwave irradiation. The reaction of compound **8a** under these conditions furnished the awaited 2-phenyl-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-naphtho[2,3-*f*]indole-5,10-dione **9a** (Scheme 4, Table 3, entry 1) in 81% yield. We have used the air stable CuI with the three more efficient diamine ligands (*N*,*N*′-dimethylethane-1,2-diamine, *N*,*N*′-dimethylcyclohexyl-1,2-diamine, cyclohexyl-1,2-diamine), in the presence of base (K_3PO_4, K_2CO_3, Cs_2CO_3), in various solvent (toluene, DMF, 1,4-dioxane). The main results of this optimization are reported in Table 3.



Scheme 4.

The best yield of compound **9a** (84%) was observed in entry 3 (Table 3) using 10 mol % of CuI, 15 mol % of *N*,*N*′-dimethylethane-1,2-diamine as ligand, 2 equiv of K_2CO_3 as base in toluene at 110 °C for 1.5 h under microwave irradiation. The same reaction conducted under classical heating furnished the compound **9a** in 73% yield after 5 h.

These encouraging results led us to generalize this Cu-catalyzed C–N bond forming reaction with the other *N*-substituted benzenesulfonamides **8a**–**i** to prepare a new series of 2-substituted-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-naphtho[2,3-*f*]indole-5,10-dione **9a**–**i** in good yields (80–89%) as reported in Scheme 5 and Table 4. From the general protocol, an adaptation of the reaction time has been realized especially with derivatives **8g**–**i**, which require 3 h of reaction.

3. Conclusion

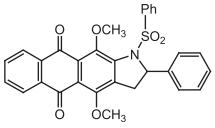
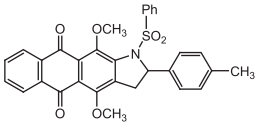
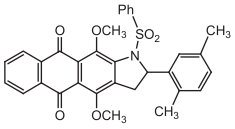
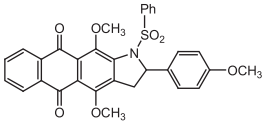
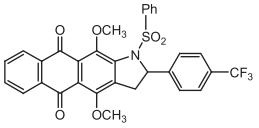
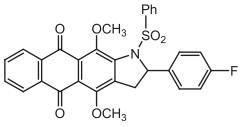
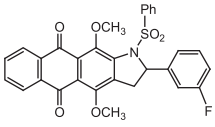
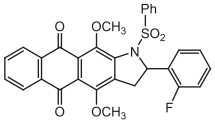
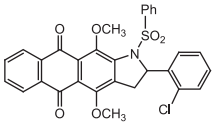
In conclusion, we expand the TDAE methodology to the reaction of 2-chloro-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione (**4**) with various *N*-(benzenesulfonyl)benzylimines, leading to the corresponding *N*-substituted benzenesulfonamides **8a**–**i** in good yields (75–88%). This reaction is the first example of nucleophilic addition of a carbanion, generated by TDAE methodology, on a Carbon–Nitrogen double bond as electrophile in non-fluorine series. The obtained products were good candidates for intramolecular Cu-catalyzed C–N bond forming reaction to synthesize 2-substituted-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-naphtho[2,3-*f*]indole-5,10-dione compounds **9a**–**i** in good yields (80–89%). These results constitute the first example of intramolecular Cu-catalyzed C–N bond forming reaction in

Table 3
Optimization study of Cu-catalyzed C–N bond forming reaction[a]

Entry	Heating conditions	Base	Ligand	Solvent	Yield % (**9a**)[b]
1	MW, 110 °C, 1.5 h	K_2CO_3	*trans*-*N*,*N*′-Dimethylcyclohexyl-1,2-diamine	Toluene	81
2	MW, 110 °C, 1.5 h	K_2CO_3	Cyclohexyl-1,2-diamine	Toluene	79
3	MW, 110 °C, 1.5 h	K_2CO_3	*N*,*N*′-Dimethylethane-1,2-diamine	Toluene	84
4	MW, 101 °C, 1.5 h	K_2CO_3	*N*,*N*′-Dimethylethane-1,2-diamine	1,4-Dioxane	63
5	MW, 120 °C, 1.5 h	K_2CO_3	*N*,*N*′-Dimethylethane-1,2-diamine	DMF	0
6	MW, 110 °C, 1.5 h	K_3PO_4	*N*,*N*′-Dimethylethane-1,2-diamine	Toluene	62
7	MW, 110 °C, 1.5 h	Cs_2CO_3	*N*,*N*′-Dimethylethane-1,2-diamine	Toluene	67
8	Classical, 110 °C, 5 h	K_2CO_3	*N*,*N*′-Dimethylethane-1,2-diamine	Toluene	73

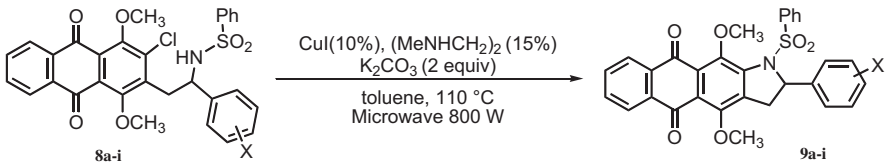
[a] All the reactions are performed using 10 mol % CuI, 15 mol % ligand, 2 equiv of base.
[b] All yields refer to chromatographically isolated pure products and are relative to substrate **8a**.

Table 4
Cu-catalyzed C–N bond forming reaction of compounds **8a**–**i** [a]

Entry	Substrate	2-Substituted-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1*H*-naphtho[2,3-*f*]indole-5,10-dione		Yield (%)[b]
1	**8a**	**9a**		83
2	**8b**	**9b**		80
3	**8c**	**9c**		82
4	**8d**	**9d**		80
5	**8e**	**9e**		80
6	**8f**	**9f**		89
7	**8g**	**9g**		86[c]
8	**8h**	**9h**		80[c]
9	**8i**	**9i**		85[c]

[a] All the reactions are performed using 10 mol % CuI, 15 mol % *N*,*N*′-dimethylethane-1,2-diamine, 2 equiv of K_2CO_3 in toluene at 110 °C for 1.5 h.
[b] All yields refer to chromatographically isolated pure products and are relative to substrate **8a**–**i**.
[c] Reaction time: 3 h.

anthraquinone series under microwave irradiation. The pharmacological evaluation of these compounds is under active investigation.



Scheme 5.

4. Experimental section

4.1. General

Melting points were determined on a Büchi melting point B-540 apparatus and are uncorrected. Element analyses were performed on a Thermo Finnigan EA1112 at the spectropole of the University of Aix-Marseille III. Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 200 spectrometer. The ^{1}H the ^{13}C chemical shifts are reported from $CDCl_3$ peaks: ^{1}H (7.26 ppm) and ^{13}C (76.9 ppm). Multiplicities are represented by the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets. The following adsorbents were used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm×10 cm aluminum plates coated with silica gel 60 F_{254} (Merck) in an appropriate solvent.

4.2. Preparation of substituted *N*-(benzenesulfonyl) benzylimines

The substituted *N*-(benzenesulfonyl)benzylimine **7a**–**i** have been prepared as previously described by Sharghi.[25] New products:

*4.2.1. (E)-N-(4-Fluorobenzylidene)benzenesulfonamide (**7f**).* White solid; mp 108 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.18 (t, J=5.0 Hz, 2H, Ar), 7.51–7.61 (m, 3H, Ar), 7.92–8.02 (m, 4H, Ar), 9.03 (s, 1H, –CH=N–). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 116.7 (d, J=22.3 Hz), 128.0, 129.2, 133.6, 133.8, 134.0, 138.1, 166.1 (d, J=258.0 Hz), 169.0. Anal. Calcd for $C_{13}H_{10}FNO_2S$ C, 59.30; H, 3.83; N, 5.32. Found: C, 58.90; H, 3.90; N, 5.43.

*4.2.2. (E)-N-(3-Fluorobenzylidene)benzenesulfonamide (**7g**).* White solid; mp 94 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.47–7.70 (m, 7H, Ar), 8.00–8.03 (m, 2H, Ar), 9.03 (s, 1H, –CH=N–). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 116.6, (d, J=22.3 Hz), 122.1 (d, J=21.6 Hz), 126.4, 128.1, 129.2, 130.8 (d, J=7.7 Hz), 134.4 (d, J=7.7 Hz), 137.8, 162.3 (d, J=249.2 Hz), 169.2. Anal. Calcd for $C_{13}H_{10}FNO_2S$ C, 59.30; H, 3.83; N, 5.32. Found: C, 59.01; H, 3.86; N, 5.38.

*4.2.3. (E)-N-(2-Fluorobenzylidene)benzenesulfonamide (**7h**).* White solid; mp 130 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.13–7.24 (m, 2H, Ar), 7.53–7.65 (m, 5H, Ar), 8.00–8.04 (m, 2H, Ar), 9.39 (s, 1H, –CH=N–). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 116.4 (d, J=20.5 Hz), 120.4 (d, J=8.8 Hz), 124.8 (d, J=3.6 Hz), 126.4, 128.1, 129.2, 133.7, 137.1 (d, J=9.1 Hz), 137.8, 164.1 (d, J=6.2 Hz), 164.3. Anal. Calcd for $C_{13}H_{10}FNO_2S$ C, 59.30; H, 3.83; N, 5.32. Found: C, 59.11; H, 3.88; N, 5.32.

4.3. General procedure for TDAE reaction

Into a two-necked flask equipped with a drying tube (silica gel) and a nitrogen inlet was added 10 mL of anhydrous DMF solution of 2-chloro-3-bromomethyl-1,4-dimethoxy-anthracene-9,10-dione (**4**) (0.4 g, 1.01 mmol) and corresponding *N*-(benzenesulfonyl) benzylimines **7a**–**i** (3 equiv). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.15 g, 0.75 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20 °C for 1 h and then warmed up to rt for 8 h. After this time, TLC analysis (CH_2Cl_2) clearly showed that compound (**4**) was totally consumed. The solution was filtered (to remove the octamethyl-oxamidinium dibromide) and hydrolyzed with 70 mL of H_2O. The aqueous solution was extracted with chloroform (3×40 mL), the combined organic layers washed with H_2O (2×40 mL) and dried over $MgSO_4$. Evaporation of the solvent furnished an orange viscous liquid as crude product. Purification by silica gel chromatography (CH_2Cl_2) and recrystallization from isopropanol gave corresponding *N*-substituted benzenesulfonamide derivatives (**8a**–**i**).

*4.3.1. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-phenylethyl]-benzenesulfonamide (**8a**).* Yellow solid; mp 200 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.15 (1H, dd, J=13.5, 4.5 Hz, CH_2), 3.26 (1H, dd, J=13.5, 10.7 Hz, CH_2), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.67–4.78 (1H, m, CH), 5.66 (1H, d, J=6.7 Hz, NH), 6.91–6.96 (3H, m, Ar), 7.28–7.48 (7H, m, Ar), 7.81–7.87 (2H, m, Ar), 8.20–8.26 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.4, 57.6, 61.8, 62.8, 125.0, 125.9, 126.1, 126.6, 126.7, 127.7, 127.8, 128.5, 128.7, 131.7, 133.6, 133.8, 134.0, 134.1, 137.8, 138.8, 140.2, 142.0, 152.9, 154.9, 181.5, 181.8. Anal. Calcd for $C_{30}H_{24}ClNO_6S$: C, 64.11; H, 4.30; N, 2.49. Found: C, 64.03; H, 4.46; N, 2.46.

*4.3.2. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-p-tolylethyl]-benzenesulfonamide (**8b**).* Yellow solid; mp 215 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.35 (3H, s, CH_3), 3.14 (1H, dd, J=13.5, 9.0 Hz, CH_2), 3.28 (1H, dd, J=13.5, 4.7 Hz, CH_2), 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.63–4.74 (1H, m, CH), 5.58 (1H, d, J=6.7 Hz, NH), 6.90–6.96 (3H, m, Ar), 7.18 (2H, d, J=7.9 Hz, Ar), 7.36 (2H, d, J=7.9 Hz, Ar), 7.43–7.48 (2H, m, Ar), 7.81–7.86 (2H, m, Ar), 8.20–8.26 (2H, m, Ar).^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 36.4, 57.4, 61.8, 62.8, 125.0, 125.8, 126.2, 126.6, 126.7, 127.4, 128.4, 129.4, 131.7, 133.6, 133.8, 134.0, 134.1, 137.5, 137.8, 138.9, 139.1, 140.2, 152.9, 154.9, 181.6, 181.8. Anal. Calcd for $C_{31}H_{26}ClNO_6S$: C, 64.63; H, 4.55; N, 2.43. Found: C, 64.40; H, 4.59; N, 2.36.

*4.3.3. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-(2,5-dimethyl-phenyl)ethyl]benzenesulfonamide (**8c**).* Yellow solid; mp 139 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.28 (3H, s, CH_3), 2.42 (3H, s, CH_3), 3.05 (1H, dd, J=13.6, 4.3 Hz, CH_2), 3.27 (1H, dd, J=13.6, 11.2 Hz, CH_2), 3.93 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.89–5.00 (1H, m, CH), 4.75 (1H, d, J=7.3 Hz, NH), 6.92–7.02 (5H, m, Ar), 7.2 (1H, s, Ar), 7.41–7.45 (2H, m, Ar), 7.77–7.86 (2H, m, Ar), 8.19–8.26 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.7, 21.0, 35.4, 53.9, 61.7, 62.8, 124.9, 126.1, 126.5, 126.6, 126.7, 127.3, 128.3, 128.4, 130.5, 131.2, 131.6, 133.6, 133.8, 134.0, 134.1, 136.0, 137.8, 138.8, 139.8,

140.3, 152.8, 155.2, 181.6, 181.8. Anal. Calcd for $C_{32}H_{28}ClNO_6S$: C, 65.13; H, 4.78; N, 2.37. Found: C, 65.63; H, 4.31; N, 3.02.

*4.3.4. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-(4-methoxy-phenyl)ethyl]benzenesulfonamide (**8d**).* Yellow solid; mp 208 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.13 (1H, dd, J=13.6, 4.4 Hz, CH_2), 3.25 (1H, dd, J=13.6, 10.8 Hz, CH_2), 3.81 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.63–4.74 (1H, m, CH), 5.58 (1H, d, J=6.6 Hz, NH), 6.89 (2H, d, J=8.7 Hz, Ar), 6.95 (2H, dd, J=5.4, 1.9 Hz, Ar), 7.38 (2H, d, J=8.7 Hz, Ar), 7.43–7.48 (2H, m, Ar), 7.52–7.60 (1H, m, Ar), 7.81–7.85 (2H, m, Ar), 8.20–8.26 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.4, 55.3, 57.2, 61.8, 62.8, 114.1, 126.2, 126.4, 126.6, 126.7, 127.1, 128.5, 129.1, 131.7, 133.6, 133.8, 134.0, 134.1, 134.2, 137.8, 138.9, 140.2, 152.8, 154.9, 159.1, 181.6, 181.8. Anal. Calcd for $C_{31}H_{26}ClNO_7S$: C, 62.89; H, 4.43; N, 2.37. Found: C, 62.60; H, 4.47; N, 2.34.

*4.3.5. N-{2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-[4-(trifluoro-methyl)phenyl]ethyl}benzenesulfonamide (**8e**).* Yellow solid; mp 198 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.13 (1H, dd, J=13.6, 4.4 Hz, CH_2), 3.23 (1H, dd, J=13.6, 10.7 Hz, CH_2), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.68–4.79 (1H, m, CH), 5.78 (1H, d, J=6.2 Hz, NH), 6.93–6.98 (3H, m, Ar), 7.42–7.47 (2H, m, Ar), 7.63 (4H, s, Ar), 7.82–7.86 (2H, m, Ar), 8.21–8.27 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.0, 57.4, 61.9, 62.9, 124.0 (q, J=271.1 Hz), 125.1, 125.7 (q, J=4.0 Hz), 126.1, 126.5, 126.7, 126.8, 127.7, 128.6, 130.0 (q, J=32.6 Hz), 131.9, 133.6, 133.7, 134.1, 134.2, 137.7, 138.1, 139.8, 146.0, 146.1, 152.9, 154.6, 181.4, 181.7. Anal. Calcd for $C_{31}H_{23}ClF_3NO_6S$: C, 59.10; H, 3.68; N, 2.22. Found: C, 58.55; H, 3.84; N, 2.21.

*4.3.6. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-(4-fluorophenyl)-ethyl]benzenesulfonamide (**8f**).* Yellow solid; mp 201 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.11 (1H, dd, J=13.6, 4.3 Hz, CH_2), 3.22 (1H, dd, J=13.6, 10.7 Hz, CH_2), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.63–4.74 (1H, m, CH), 667 (1H, d, J=7.6 Hz, NH), 6.91–7.10 (5H, m, Ar), 7.42–7.49 (4H, m, Ar), 7.82–7.86 (2H, m, Ar), 8.20–8.26 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.4, 57.1, 61.8, 62.9, 115.6 (d, J=21.6 Hz), 125.1, 1261, 126.6, 126.8, 127.6 (d, J=8.0 Hz), 128.5, 131.8, 133.6, 133.7, 134.1, 134.2, 137.7 (d, J=5.8 Hz), 137.9, 138.5, 140.0, 152.9, 154.7 (2C), 162.2 (d, J=245.9 Hz), 181.5, 181.8. Anal. Calcd for $C_{30}H_{23}ClFNO_6S$: C, 62.12; H, 4.00; N, 2.41. Found: C, 62.29; H, 4.11; N, 2.34.

*4.3.7. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-(3-fluorophenyl)-ethyl]benzenesulfonamide (**8g**).* Yellow solid; mp 193 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.13 (1H, dd, J=13.8, 4.9 Hz, CH_2), 3.27 (1H, dd, J=13.8, 10.0 Hz, CH_2), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.64–4.75 (1H, m, CH), 5.68 (1H, d, J=6.5 Hz, NH), 6.89–7.03 (5H, m, Ar), 7.17–7.36 (2H, m, Ar), 7.43–7.45 (2H, m, Ar), 7.81–7.86 (2H, m, Ar), 8.20–8.26 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.1, 57.2, 57.3, 62.9, 113.1 (d, J=22.3 Hz), 114.7 (d, J=21.2 Hz), 121.6 (d, J=2.54 Hz), 125.1, 126.1, 126.6, 126.8, 127.6, 128.5, 130.4 (d, J=8.4 Hz), 131.8, 133.7 (d, J=8.4 Hz), 134.1, 134.2, 137.7, 138.3, 140.0, 144.6, 144.7, 152.9, 154.7, 163.0 (d, J=240.0 Hz), 181.5, 181.8. Anal. Calcd for $C_{30}H_{23}ClFNO_6S$: C, 62.12; H, 4.00; N, 2.41. Found: C, 62.03; H, 4.04; N, 2.42.

*4.3.8. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-(2-fluorophenyl)-ethyl]benzenesulfonamide (**8h**).* Yellow solid; mp 209 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.22 (1H, dd, J=13.5, 4.6 Hz, CH_2), 3.37 (1H, dd, J=13.5, 11.1 Hz, CH_2), 3.92 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.86–4.98 (1H, m, CH), 5.72 (1H, d, J=7.7 Hz, NH), 6.93–7.03 (4H, m, Ar), 7.08–7.16 (2H, m, Ar), 7.44–7.49 (3H, m, Ar), 7.80–7.85 (2H, m, Ar), 8.20–8.26 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) 34.3, 53.6, 61.8, 62.7, 115.8 (d, J=21.6 Hz), 124.5 (d, J=3.3 Hz), 124.9, 126.2, 126.6 (2C), 126.7, 127.5, 128.4 (d, J=4.4 Hz), 128.5, 128.7 (d, J=12.8 Hz), 129.6, (d, J=8.4 Hz), 131.8, 133.7, (d, J=8.4 Hz), 134.0, 134.1, 138.1, 138.5, 140.1, 152.8, 155.2, 160.2 (d, J=246.2 Hz), 181.6, 181.9. Anal. Calcd for $C_{30}H_{23}ClFNO_6S$: C, 62.12; H, 4.00; N, 2.41. Found: C, 62.12; H, 3.95; N, 2.40.

*4.3.9. N-[2-(3-Chloro-1,4-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-1-(2-chlorophenyl)-ethyl]benzenesulfonamide (**8i**).* Yellow solid; mp 203 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.20 (1H, dd, J=13.5, 4.8 Hz, CH_2), 3.36 (1H, dd, J=13.5, 10.8 Hz, CH_2), 3.92 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.05–5.16 (1H, m, CH), 5.99 (1H, d, J=7.5 Hz, NH), 6.93–7.04 (3H, m, Ar), 7.16–7.34 (3H, m, Ar), 7.47–7.48 (3H, m, Ar), 7.79–7.84 (2H, m, Ar), 8.19–8.24 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.1, 55.2, 61.7, 62.8, 124.9, 126.2, 126.6, 126.7, 127.4, 127.5, 128.5, 128.6, 129.0, 130.0, 131.8, 132.0, 133.6, 133.8, 134.0, 134.1, 138.2, 138.3, 139.0, 139.9, 152.8, 155.2, 181.6, 181.8. Anal. Calcd for $C_{30}H_{23}C_{l2}NO_6S$: C, 60.41; H, 3.89; N, 2.35. Found: C, 60.00; H, 3.98; N, 2.29.

4.4. General procedure for intramolecular Buchwald reaction

Into a two-necked flask equipped with an argon inlet, CuI (10 mol %), *N,N′*-dimethylethane-1,2-diamine (15 mol %) and K_2CO_3 (2 equiv) were added. Then the halogenated amine (**8a**–**i**) (0.20 g, 1 equiv) dissolved in toluene (10 mL) was added to the flask. The resulting mixture was heated at 110 °C in microwave (800 W) until the disappearance of the starting material as monitored by TLC. The reaction mixture was filtered through Celite. The filtrate was concentrated in vacuo, diluted with chloroform, washed with H_2O (3×40 mL) and dried over $MgSO_4$. After evaporation, the crude product was purified by silica gel chromatography (CH_2Cl_2) and recrystallized from isopropanol.

*4.4.1. 4,11-Dimethoxy-2-phenyl-1-(phenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-f]indole-5,10-dione (**9a**).* Yellow solid; mp 182 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.21 (1H, dd, J=17.2, 2.3 Hz, CH_2), 3.29 (3H, s, OCH_3), 3.80 (1H, dd, J=17.2, 9.8 Hz, CH_2), 3.89 (3H, s, OCH_3), 6.20 (1H, dd, J=9.8, 2.3 Hz, CH), 7.30–7.43 (7H, m, Ar), 7.49–7.56 (1H, m, Ar), 7.62–7.66 (2H, m, Ar), 7.70–7.75 (2H, m, Ar), 8.12–8.18 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.6, 61.1, 61.2, 66.0, 124.9, 125.9, 126.5, 126.6, 127.2, 128.0, 128.4, 128.6, 129.1, 132.6, 133.5, 133.6, 133.8, 134.0, 135.6, 140.5, 141.8, 143.2, 147.3, 153.6, 182.3, 182.7. Anal. Calcd for $C_{30}H_{23}NO_6S$: C, 68.56; H, 4.41; N, 2.67. Found: C, 68.23; H, 4.56; N, 2.61.

*4.4.2. 4,11-Dimethoxy-1-(phenylsulfonyl)-2-p-tolyl-2,3-dihydro-1H-naphtho[2,3-f]indole-5,10-dione (**9b**).* Yellow solid; mp 143 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.35 (3H, s, CH_3), 3.23 (3H, s, OCH_3), 3.24 (1H, dd, J=17.4, 2.1 Hz, CH_2), 3.23 (3H, s, OCH_3), 3.76 (1H, dd, J=17.4, 9.7 Hz, CH_2), 3.88 (3H, s, OCH_3), 6.15 (1H, dd, J=9.7, 2.1 Hz, CH), 7.12–7.21 (4H, m, Ar), 7.36–7.52 (3H, m, Ar), 7.63–7.74 (4H, m, Ar), 8.11–8.17 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 35.6, 61.1, 61.2, 65.9, 124.9, 125.8, 126.4, 126.5, 127.2, 128.0, 128.6, 129.7, 132.6, 133.5, 133.6, 133.8, 134.0, 135.8, 138.2, 138.8, 140.5, 143.1, 147.4, 153.6, 182.2, 182.7. Anal. Calcd for $C_{31}H_{25}NO_6S$: C, 69.00; H, 4.67; N, 2.60. Found: C, 68.45; H, 4.53; N, 2.74.

*4.4.3. 2-(2,5-Dimethylphenyl)-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-f]indole-5,10-dione (**9c**).* Yellow solid; mp 109 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.99 (1H, dd, J=17.2, 2.9 Hz, CH_2), 3.26 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.88 (1H, dd, J=17.2, 10.0 Hz, CH_2), 6.43 (1H, dd, J=10.0, 2.9 Hz, CH), 6.89 (1H, s, Ar), 6.96–7.17 (3H, m, Ar), 7.38–7.58 (3H, m, Ar), 7.69–7.74 (3H, m, Ar), 8.11–8.18 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.0, 21.1, 35.7, 61.1, 61.2, 63.2, 124.8, 125.6, 126.4, 126.6, 127.53, 127.9, 128.4, 128.6, 131.1, 131.3, 132.6, 133.5, 133.6, 133.8,

134.0, 135.1, 135.7, 139.9, 140.6, 143.9, 147.0, 153.9, 182.3, 182.7. Anal. Calcd for $C_{32}H_{27}NO_6S$: C, 69.42; H, 4.92; N, 2.53. Found: C, 68.99; H, 5.05; N, 2.62.

*4.4.4. 4,11-Dimethoxy-2-(4-methoxyphenyl)-1-(phenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-f]indole-5,10-dione (**9d**).* Yellow solid; mp 100 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.18 (1H, dd, J=17.2, 2.2 Hz, CH_2), 3.20 (3H, s, OCH_3), 3.75 (1H, dd, J=17.2, 9.7 Hz, CH_2), 3.80 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.13 (1H, dd, J=9.7, 2.2 Hz, CH), 6.87 (2H, d, J=8.6 Hz, Ar), 7.22 (2H, d, J=8.6 Hz, Ar), 7.36–7.52 (3H, m, Ar), 7.61–7.65 (2H, m, Ar), 7.69–7.76 (2H, m, Ar), 8.11–8.17 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.5, 55.3, 61.1, 61.2, 65.7, 114.3, 124.8, 126.3, 126.4, 126.6, 127.1, 127.3, 128.0, 128.6, 129.0, 132.6, 133.5, 133.6, 133.8, 134.0, 135.8, 140.6, 143.0, 147.3, 153.6, 159.6, 182.2, 182.7. Anal. Calcd for $C_{31}H_{25}NO_7S$: C, 67.01; H, 4.54; N, 2.52. Found: C, 66.30; H, 4.61; N, 2.48.

*4.4.5. 4,11-Dimethoxy-1-(phenylsulfonyl)-2-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1H-naphtho-[2,3-f]indole-5,10-dione (**9e**).* Yellow solid; mp 207 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.16 (1H, dd, J=17.4, 2.3 Hz, CH_2), 3.34 (3H, s, OCH_3), 3.81 (1H, dd, J=17.4, 9.8 Hz, CH_2), 3.88 (3H, s, OCH_3), 6.24 (1H, dd, J=9.8, 2.3 Hz, CH), 7.40–7.47 (4H, m, Ar), 7.53–7.78 (7H, m, Ar), 8.13–8.18 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.6, 61.2, 61.3, 65.4, 123.8 (q, J=272.2 Hz), 125.2, 126.1 (q, J=3.7 Hz), 126.3, 126.5, 126.6, 127.3, 128.2, 128.8, 129.0, 130.1 (q, J=32.6 Hz), 133.0, 133.6, 133.7, 133.9, 135.0, 140.1, 142.8, 145.6, 147.5, 153.6, 182.2, 182.6. Anal. Calcd for $C_{31}H_{22}F_3NO_6S$: C, 62.73; H, 3.74; N, 2.36. Found: C, 62.78; H, 3.97; N, 2.34.

*4.4.6. 2-(4-Fluorophenyl)-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-f] indole-5,10-dione (**9f**).* Yellow solid; mp 185 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.17 (1H, dd, J=17.4, 2.4 Hz, CH_2), 3.25 (3H, s, OCH_3), 3.78 (1H, dd, J=17.4, 9.7 Hz, CH_2), 3.89 (3H, s, OCH_3), 6.17 (1H, dd, J=9.7, 2.4 Hz, CH), 7.00–7.09 (2H, m, Ar), 7.26–7.32 (2H, m, Ar), 7.38–7.46 (2H, m, Ar), 7.51–7.58 (1H, m, Ar), 7.62–7.66 (2H, m, Ar), 7.71–7.75 (2H, m, Ar), 8.12–8.19 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.6, 61.1, 61.2, 65.3, 116.0 (d, J=21.6 Hz), 125.0, 126.5 (d, J=6.6 Hz), 127.2, 127.7, 127.8, 128.1, 128.7, 132.8, 133.5, 133.6, 133.7, 133.9, 135.3, 137.7 (d, J=3.3 Hz) 140.4, 142.9, 147.4, 153.6, 162.5 (d, J=247.4 Hz), 182.2, 182.6. Anal. Calcd for $C_{30}H_{22}FNO_6S$: C, 66.29; H, 4.08; N, 2.58. Found: C, 66.19; H, 4.22; N, 2.53.

*4.4.7. 2-(3-Fluorophenyl)-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-f] indole-5,10-dione (**9g**).* Yellow solid; mp 195 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.15 (1H, dd, J=17.3, 2.2 Hz, CH_2), 3.30 (3H, s, OCH_3), 3.79 (1H, dd, J=17.3, 9.7 Hz, CH_2), 3.89 (3H, s, OCH_3), 6.19 (1H, dd, J=9.7, 2.3 Hz, CH), 6.95–7.22 (3H, m, Ar), 7.29–7.60 (4H, m, Ar), 7.67–7.75 (4H, m, Ar), 8.13–8.18 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.6, 61.1, 61.2, 65.4 (d, J=1.5 Hz), 112.9 (d, J=22.3 Hz), 115.4 (d, J=21.2 Hz), 121.6 (d, J=2.9 Hz), 125.1, 125.3, 126.4, 126.6, 127.3, 128.7, 130.8 (d, J=8.0 Hz), 132.9, 133.6, 133.7, 133.8 (d, J=10.2 Hz), 135.2, 140.2, 142.9, 144.2, 144.3, 147.4, 153.6, 163.0 (d, J=247.7 Hz), 181.2, 181.6. Anal. Calcd for $C_{30}H_{22}FNO_6S$: C, 66.29; H, 4.08; N, 2.58. Found: C, 65.90; H, 4.18; N, 2.54.

*4.4.8. 2-(2-Fluorophenyl)-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-f] indole-5,10-dione (**9h**).* Yellow solid; mp 193 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.15 (1H, dd, J=17.4, 2.0 Hz, CH_2), 3.28 (3H, s, OCH_3), 3.84 (1H, dd, J=17.4, 10.1 Hz, CH_2), 3.88 (3H, s, OCH_3), 6.41 (1H, dd, J=10.1, 2.0 Hz, CH), 7.06–7.17 (2H, m, Ar), 7.24–7.58 (5H, m, Ar), 7.66–7.74 (4H, m, Ar), 8.10–8.19 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.3, 61.1, 61.2, 61.5 (d, J=2.2 Hz), 116.2 (d, J=20.8 Hz), 124.4 (d, J=5.8 Hz), 124.9, 126.4, 126.6, 127.3, 127.9 (d, J=4.0 Hz), 128.0, 128.6, 129.0, 130.1 (d, J=8.0 Hz), 132.8, 133.5, 133.7, 133.8, 134.0, 135.4, 140.3, 143.2, 147.3, 153.6, 159.8 (d, J=248.1 Hz), 182.3, 182.7. Anal. Calcd for $C_{30}H_{22}FNO_6S$: C, 66.29; H, 4.08; N, 2.58. Found: C, 66.21; H, 4.12; N, 2.55.

*4.4.9. 2-(2-Chlorophenyl)-4,11-dimethoxy-1-(phenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-f] indole-5,10-dione (**9i**).* Yellow solid; mp 114 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.06 (1H, dd, J=17.4, 2.6 Hz, CH_2), 3.41 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.88 (1H, dd, J=17.4, 9.9 Hz, CH_2), 6.53 (1H, dd, J=9.9, 2.6 Hz, CH), 7.13–7.32 (3H, m, Ar), 7.41–7.60 (4H, m, Ar), 7.68–7.79 (4H, m, Ar), 8.12–8.18 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.7, 61.2, 61.3, 63.9, 125.1, 126.4, 126.6, 126.9, 127.0, 127.5, 128.0, 128.6, 129.4, 130.4, 132.0, 132.9, 133.5, 133.6, 133.7, 133.9, 135.2, 138.9, 140.1, 143.6, 147.3, 153.8, 182.2, 182.7. Anal. Calcd for $C_{30}H_{22}ClNO_6S$: C, 64.34; H, 3.96; N, 2.50. Found: C, 63.51; H, 3.95; N, 2.46.

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