Preparation of symmetrical and non-symmetrical fluorene sulfonamide scaffolds

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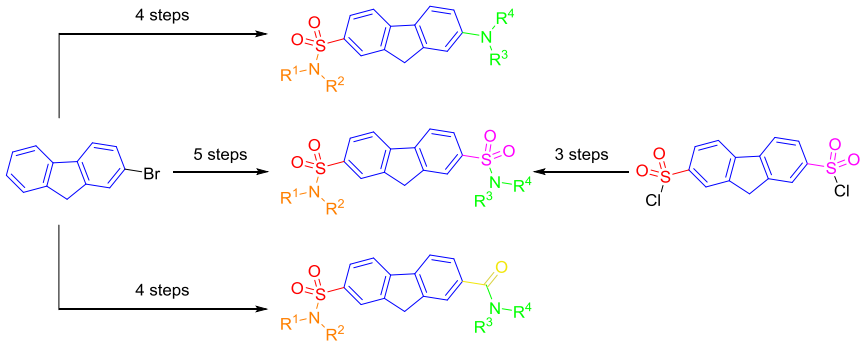


Abstract Methods for the preparation of symmetrical and non-symmetrical 2,7-disubstituted 9H-fluorene derivatives are described.

Key words Fluorene, sulfonamide, microwave assisted synthesis

Fluorene (**1**) represents a privileged structure that has found a wide variety of applications in synthetic, medicinal and materials chemistry. The defined shape and electronics of **1** impart important functional properties on derivatives.[1] For example, C_2 symmetric bis-sulfonamide **2** is an effective ligand in the rhodium catalysed asymmetric transfer hydrogenation of ketones.[2] Bis-sulfonamides are also prevalent in many commercial screening libraries and have been identified as hit compounds on diverse protein targets including alanine racemase,[3] cysteine protease,[4] and 17β-HSD1.[5] In addition, bis-sulfonamide **3** has been used in chemical biology as a novel DNA G quadruplex ligand showing further applications for this class of compound.[6] For each of these examples the rigid scaffold of fluorene provides the requisite geometry for function, holding substituents in a specific position. Along with the structural properties imparted by the framework, the conjugated nature of the two aromatic rings and the acidic methylene protons dictate the properties of derivatives. For example, bis-sulfonylated fluorenes have found use in areas such as self-assembled monolayer arrays for molecular electronic devices,[7] compounds with room temperature phosphorescent emission properties,[8] charge transfer complexes,[9] and merocyanine dyes.[10] Therefore, new methods for the preparation of fluorene derivatives that allow access to alternative and more complex scaffolds will be of interest to the synthetic community.

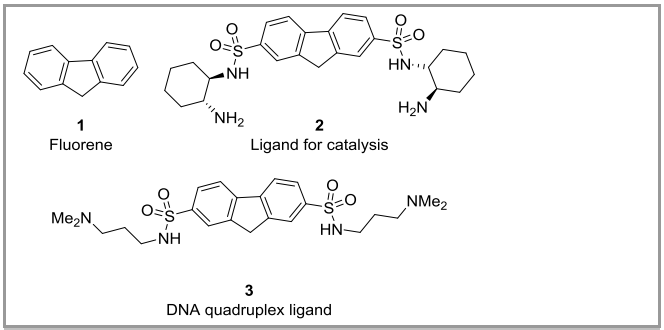
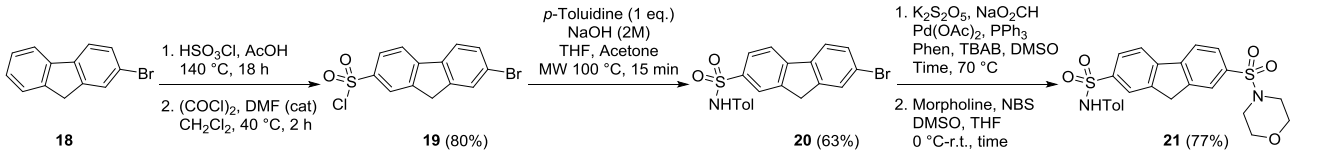


Figure 1 Fluorene **1** and symmetrical bis- sulfonamide derivatives.

A key feature of fluorene chemistry that directs many of the applications of this framework is the regiospecific electrophilic aromatic sulfonylation,[7a] nitration[11] and halogenation,[12] which leads to 2,7-disubstituted systems for further elaboration. Surprisingly, the majority of fluorene derivatives reported to have function within the literature are symmetrical derivatives, presumably due to their ease of synthesis, and we were unable to identify effective methods to prepare non-symmetrical compounds despite the potential applications of these products. Within this paper we describe simple and effective methods for the preparation of mono-sulfonamides together with symmetrical and non-symmetrical bis-sulfonamides from commercial fluorene building blocks and also provide preliminary data to show a method for the preparation of aniline and amide substituted fluorene mono-sulfonamides.

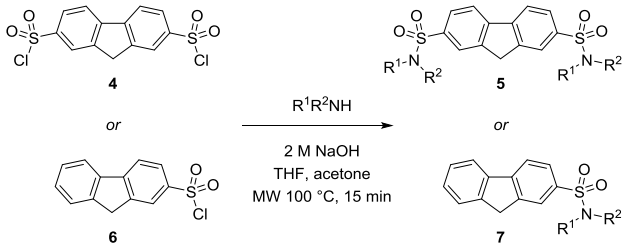
As part of our ongoing investigations in nuclear receptor chemistry,[13] virtual screening identified the symmetrical bis-sulfonamide **9** as a potential hit compound which was therefore physically required for biological evaluation. Bis-sulfonyl chloride **4** was prepared by a modified literature procedure[7a] and isolated without the need for purification by chromatography (see the Supporting Information for full



Scheme 1 Preparation of non-symmetrical fluorene derived bis-sulfonamides.

details). To our surprise, an experimental procedure for the mono- sulfonylation of fluorene has not been detailed in the literature.[14] Application of standard reaction conditions with careful control of stoichiometry led to the selective sulfonylation of fluorene, and subsequent chlorination gave mono-sulfonyl chloride **6** in 75% yield over two steps.

Thermal methods have been described for the preparation of sulfonamides from the corresponding sulfonyl chloride. Whilst these methods proved effective, an alternative microwave procedure was established which proved more convenient due to the short reaction times involved (typically <15 minutes). (Table 1).



Entry	Reactant	R^1	R^2	Product	Yield[a]
1	**4**	H	Ph	**8**	93
2	**4**	H	4-MeC_6H_4	**9**	54
3[b]	**4**	H	4-HOC_6H_4	**10**	34
4	**4**	Me	4-MeC_6H_4	**11**	85
5	**4**	H	Cy	**12**	60
6	**4**	H	^{i}Pr	**13**	71
7	**4**	H	4-THP	**14**	55
8	**6**	H	^{i}Pr	**15**	77
9	**6**	H	4-MeC_6H_4	**16**	62
10	**6**	$-CH_2(CH_2)_2CH_2-$		**17**	83

[a]Isolated yield after purification by column chromatography.
[b]Reaction heated for 1 h.

Table 1 Preparation of fluorene derived sulfonamides.

Heating bis-sulfonyl chloride **4** in the presence of 2 equivalents of aniline in a mixture of THF, NaOH (2 M) and acetone at 100 °C for 15 minutes provided the bis-sulfonamide **8** (Entry 1, 93%) after purification by column chromatography. This method proved effective for both primary (Entries 1–3) and secondary (Entry 4) anilines. Aliphatic amines were also shown to be efficient substrates for the transformation (Entries 5–7) and suggest this should be an effective and general method for the preparation of this class of compound. Reaction of mono-sulfonyl chloride **6** with 1 equivalent of amine gave the corresponding mono-sulfonamides in good yields. The reaction was found to be tolerant of primary and secondary amines along with aniline substrates (Entries 8–10).

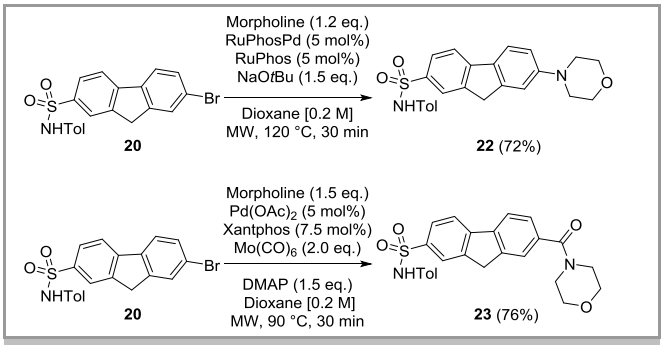
Having prepared a series of symmetrical bis- and mono-sulfonamides we were eager to discover if we could also access non-symmetrical derivatives. Attempts were made to use mono-sulfonamides **7** as precursors to non-symmetrical bis-sulfonamides, however, standard sulfonylation conditions (HSO_3Cl, AcOH, 140 °C) proved incompatible with the existing sulfonamide functionality, leading to intractable mixtures of products.

Recent work has shown that aryl sulfonamides can be accessed in a two-step one-pot procedure through a palladium catalysed sulfination followed by reaction of the aryl sulfinate intermediate with an amine in the presence of *N*-bromosuccinimide (NBS).[15] With this in mind, we envisaged non-symmetrical bis-sulfonamides could be accessed by the route outlined in Scheme 1.

Conversion of 2-bromofluorene **18** to the sulfonyl chloride **19** proceeded smoothly under standard reaction conditions (80%, two steps), which was treated with *p*-toluidine (1 eq.) to give the corresponding sulfonamide **20** (63%). Reaction of this substrate with morpholine under the conditions described by Shavnya *et al*.[15] gave the corresponding sulfonamide **21** in 77% yield. Unfortunately, complex mixtures of products were observed when performing this protocol using aniline or primary amine starting materials. The fluorene scaffold can readily undergo both oxidation and deprotonation which we believe to be the origin of the multiple products observed when using alternative amines within this protocol.

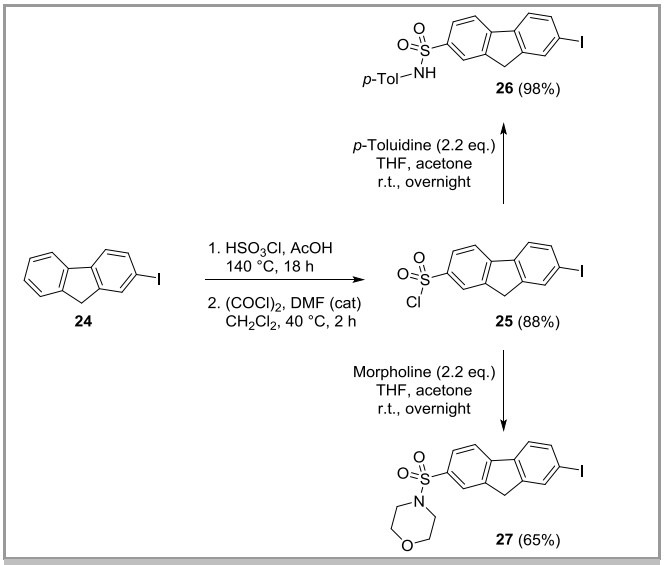
We also examined alternative palladium catalysed coupling processes for the introduction of additional functional groups of relevance to catalysis, medicinal chemistry and materials chemistry (Scheme 2). Treatment of bromo sulfonamide **20** with morpholine in the presence of RuPhosPd under microwave irradiation at 120 °C for 30 minutes provided the Buchwald-Hartwig coupling product **22** in 72% isolated yield after purification by column chromatography.[16] We were also able to directly access amide derivatives of **20** by microwave irradiation at 90 °C for 30 minutes in the presence of morpholine, $Pd(OAc)_2$, xantphos as a supporting ligand, $Mo(CO)_6$

and DMAP, providing **23** in 76% isolated yield.[17] These initial examples suggest that **20** should be an effective substrate for a variety of palladium catalysed coupling procedures, further adding to the potential diversity and subsequent application of the products.



Scheme 2 Palladium catalysed synthesis of non-symmetrical fluorene derivatives.

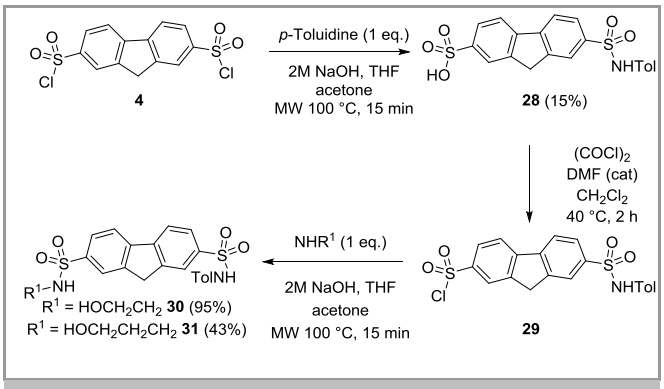
It is established that aryl iodides can be beneficial in palladium catalysed transformations due to an increased rate of oxidative addition. We envisaged that the scope of the sulfonamide forming reaction could be improved through the use of aryl iodide substrate **24** (Scheme 3). Sulfonyl chloride **25** was prepared using standard conditions in an excellent yield over two steps (88%), without the need for chromatographic purification. The intermediate sulfonyl chloride **25** was sensitive to heating in the presence of a base, but a modified procedure employing 2 equivalents of amine and stirring at room temperature overnight overcame this problem, giving sulfonamides **26** and **27** in good yields (See Supporting Information for full details).



Scheme 3 Preparation of iodo sulfonamides.

Sulfonamide **26** was reacted with morpholine under the conditions described by Shavnya *et al.*,[15] however, a complex mixture of products was observed by LCMS. A modest yield (48%) of **21** was achieved by using 5 equivalents of $K_2S_2O_5$, however, despite extensive exploration of reaction conditions, a number of unidentified products predominated when using primary amines or anilines in this reaction. Alternative reported methods for the preparation of aryl sulfonamides from aryl halides were applied to sulfonamides **26** and **27**, however, in each case multiple products were observed.[18]

A non-elegant, transition-metal free solution to the preparation of non-symmetrical bis-sulfonamides was found by treating bis-sulfonyl chloride **4** with one equivalent of *p*-toluidine under basic reaction conditions, giving sulfonamide **28** in 15% yield after purification by column chromatography (Scheme 4). Subsequent reaction with oxalyl chloride gave sulfonyl chloride **29** which was then reacted with ethanolamine or 3-hydroxypropylamine to give the non-symmetrical bis-sulfonamides **30** (95%) and **31** (43%) respectively. Of the methods examined this provided the most convenient process to access arrays of non-symmetrical bis-sulfonamide targets in a reliable, time efficient and cost effective manner.



Scheme 4 Preparation of non-symmetrical fluorene derived bis-sulfonamides.

In summary, we have described methods for the preparation of symmetrical and non-symmetrical fluorene sulfonamide derivatives. Mono- and symmetrical bis-sulfonamides can be readily accessed through the microwave irradiation of the corresponding sulfonyl chloride in the presence of an amine, allowing access to the products in short reaction times. Non-symmetrical bis-sulfonamides can be prepared in lower yields through the mono-functionalisation of bis-sulfonyl chloride **4**, followed by purification, reaction with oxalyl chloride and then treatment with a second amine. Application of a palladium catalysed sulfonylation process also provides access to selected non-symmetrical bis-sulfonamides but this transformation proved dependent on the structure of the amine nucleophile. Aniline and amide derivatives of the fluorene scaffold can also be prepared using transition-metal catalysed coupling processes, adding to the structural diversity accessible through this methodology. Given the significant number of applications known for symmetrical fluorene derivatives in diverse areas including asymmetric catalysis, medicinal chemistry and materials science it is expected that this work will provide the impetus for further discovery in the application of the fluorene skeleton.

Acknowledgment

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References and Notes

General procedure for the microwave assisted formation of sulfonamides:

9H-Fluorene-2,7-disulfonyl dichloride **4** (100 mg, 0.28 mmol), acetone (1.52 mL), THF (0.28 mL), amine (0.56 mmol) and 2M NaOH (aq) (0.32 mL) were added to a 5 mL microwave vial equipped with a magnetic stirrer bar. The mixture was heated in a Biotage Initiator at 100 °C for 15 min, and allowed to cool to room temperature. Dichloromethane (10 mL) was added, and the mixture washed with water (10 mL), saturated sodium carbonate solution (10 mL), 2M HCl (aq) solution (10 mL) and brine (10 mL). The organic extract was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the crude product.

***N,N*-Diisopropyl-9*H*-fluorene-2,7-disulfonamide 13.** Prepared by the General Procedure, using isopropylamine (0.05 mL, 0.58 mmol). Purified by column chromatography on silica (2:1 petroleum ether: ethyl acetate, followed by 1:1) to give **13** as a yellow-orange solid (80 mg, 71%); m.p. 194–195 °C; IR (ATR/cm^{-1}): 3054, 2990, 1456, 1403, 1304, 1235, 1181, 1103; ^{1}H (400 MHz, DMSO d_6) δ 8.21 (2H, d, *J* = 8.1 Hz), 8.06 (2H, d, *J* = 0.8 Hz), 7.89 (2H, dd, *J* = 8.1, 1.5 Hz), 7.61 (2H, d, *J* = 7.2 Hz), 4.18 (2H, s), 3.22–3.35 (2H, m), 0.96 (12H, d, *J* = 6.5 Hz); ^{13}C (101 MHz, DMSO d_6) δ 144.7 (quat C), 143.0 (quat C), 141.1 (quat C), 125.5 (CH), 123.4 (CH), 121.5 (CH), 45.2 (CH), 36.7 (CH_2), 23.2 (CH_3); LCMS *m/z* = 407.1 $(M-1)^+$; HRMS calc. for $C_{19}H_{23}O_4N_2S_2$ 407.1105, found 407.1107.

Palladium catalysed procedures:

7-(Morpholinosulfonyl)-*N*-(*p*-tolyl)-9*H*-fluorene-2-sulfonamide 21. A microwave vial was charged with **20** (30.0 mg, 0.062 mmol), potassium metabisulfite (33.0 mg, 0.148 mmol), tetra-*n*-butylammonium bromide (26.3 mg, 0.082 mmol), sodium formate (12.0 mg, 0.176 mmol), palladium acetate (1.0 mg, 5 mol %), triphenylphosphine (3.0 mg, 0.013 mmol), 1,10-phenanthroline (2.0 mg, 0.011 mmol) and DMSO (0.2 mL). The mixture was degassed by bubbling nitrogen through the solvent for 10 minutes, and then heated under argon at 70 °C for 3 hours. Following cooling to room temperature, a solution of morpholine (12.6 mg, 0.145 mmol) in anhydrous THF (1.0 mL) was added and the mixture cooled to 0 °C. A solution of *N*-bromosuccinimide (25.8 mg, 0.145 mmol) in THF (1.0 mL) was added drop-wise and the mixture left to warm to room temperature over one hour. Water (10 mL) was added, and the mixture extracted with ethyl acetate (3 × 10 mL). The organics were combined and washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (1:1 petroleum ether: ethyl acetate) to give **21** as a yellow solid (27 mg, 77%); ^{1}H NMR (400 MHz, Acetone d_6) δ 8.87 (1H, s), 8.19 (1H, d, *J* = 8.0 Hz), 8.11 (1H, d, *J* = 8.4 Hz), 8.01–8.06 (2H, m), 7.81–7.88 (2H, m), 7.11 (2H, d, *J* = 8.4 Hz), 7.04 (2H, d, *J* = 8.4 Hz), 4.14 (2H, s), 3.62–3.72 (4H, m), 2.93–3.03 (4H, m), 2.21 (3H, s); ^{13}C NMR (101 MHz, Acetone d_6) δ 146.2 (quat C), 145.9 (quat C), 145.2 (quat C), 144.8 (quat C), 140.5 (quat C), 136.1 (quat C), 135.7 (quat C), 135.3 (quat C), 130.5 (CH), 128.0 (CH), 127.3 (CH), 125.8 (CH), 125.1 (CH), 122.5 (CH), 122.3 (CH), 122.2 (CH), 66.7 (CH_2), 47.1 (CH_2), 37.7 (CH_2), 20.7 (CH_3); LCMS *m/z* = 483.2 $(M-1)^+$; HRMS *m/z*: calcd. for $C_{25}H_{25}N_2O_5S_2$ 485.1199, found 485.1189.

7-Morpholino-*N*-(*p*-tolyl)-9*H*-fluorene-2-sulfonamide 22. A mixture of RuPhos Palladacycle (7 mg, 0.05 equiv.), RuPhos (5 mg, 0.05 equiv.), sodium *tert*-butoxide (29 mg, 0.30 mmol), 7-bromo-*N*-(*p*-tolyl)-9*H*-fluorene-2-sulfonamide (83 mg, 0.20 mmol) and morpholine (0.021 mL, 0.24 mmol) in 1,4-dioxane (0.50 mL) was sealed and heated in a Biotage Initiator at 120 °C for 30 min. After cooling, the sample was passed through a plug of celite using MeOH (10.0 mL), then concentrated under reduced pressure to give the crude product, which was purified by column chromatography (1:1 petroleum ether: ethyl acetate) to give **21** (59 mg, 72%) as a yellow solid; m.p. 170 °C (decomp.); IR (ATR/cm^{-1}): 2922, 1612, 1512, 1451, 1419, 1243, 1189, 1111; ^{1}H (400 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 1.2 Hz), 7.70 (1H, dd, *J* = 8.0, 0.8 Hz), 7.67 (1H, d, *J* = 8.8 Hz), 7.64 (1H, d, *J* = 8.4 Hz), 7.10 (1H, d, *J* = 2.0 Hz), 6.99–7.04 (2H, m), 6.92–6.98 (3H, m), 6.41 (1H, s), 3.86–3.92 (4H, m), 3.83 (2H, s), 3.20–3.28 (4H, m), 2.26 (3H, s); ^{13}C (101 MHz, $CDCl_3$) δ 152.1 (quat C), 146.8 (quat C), 146.2 (quat C), 143.1 (quat C), 135.6 (quat C), 135.4 (quat C), 134.0 (quat C), 133.3 (quat C), 130.0 (CH), 126.7 (CH), 123.8 (CH), 122.7 (CH), 121.8 (CH), 118.9 (CH), 115.2 (CH), 112.1 (CH), 67.0 (CH_2), 49.5 (CH_2), 37.1 (CH_2), 21.0 (CH_3); LCMS *m/z* = 421.1 $(M+1)^+$; HRMS *m/z*: calcd. for $C_{24}H_{25}N_2O_3S$ 422.1580, found 422.1577.

7-(Morpholine-4-carbonyl)-*N*-(*p*-tolyl)-9*H*-fluorene-2-sulfonamide 23. A mixture of palladium acetate (2.0 mg, 0.05 eq.), Xantphos (6.0 mg, 0.05 eq.), Molybdenum hexacarbonyl (53.0 mg, 0.05 equiv.), DMAP (37.0 mg, 0.30 mmol), 7-bromo-*N*-(*p*-tolyl)-9*H*-fluorene-2-sulfonamide (83.0 mg, 0.20 mmol) and morpholine (0.034 mL, 0.39 mmol) in 1,4-dioxane (0.50 ml) was sealed and heated in a Biotage Initiator at 90 °C for 30 min. After cooling, the reaction mixture was passed through celite using MeOH (10.0 mL), then concentrated under reduced pressure to give the crude product, which was purified by column chromatography (4:1 petroleum ether: ethyl acetate) to give **22** as a yellow solid (0.068 g, 76%); m.p. 210 °C (decomp.); IR (ATR/cm^{-1}): 2925, 2853, 1619, 1605, 1445, 1332, 1243, 1191, 1148, 1111, 1049; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 0.7 Hz), 7.82 (1H, d, *J* = 8.0 Hz), 7.75–7.80 (2H, m), 7.62 (1H, d, *J* = 0.8 Hz), 7.45 (1H, dd, *J* = 8.0, 1.2 Hz, 1H), 7.02 (2H, d, *J* = 8.0 Hz), 6.96 (2H, d, *J* = 8.0 Hz), 6.77 (1H, br s), 3.91 (2H, s), 3.50 – 3.87 (8H, m), 2.25 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (quat C), 145.3 (quat C), 144.6 (quat C), 144.1 (quat C), 141.6 (quat C), 137.9 (quat C), 135.7 (quat C), 135.2 (quat C), 133.8 (quat C), 130.0 (CH), 126.7 (CH), 126.4 (CH), 124.4 (CH), 124.2 (CH), 122.7 (CH), 121.0 (CH), 120.6 (CH), 67.0 (CH_2), 37.1 (CH_2), 21.0 (CH_3), *1 carbon missing*; LCMS *m/z* = 449.1 $(M+1)^+$; HRMS *m/z*: calcd. for $C_{25}H_{25}N_2O_4S$ 449.1530, found 449.1530.

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