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Catalyst free conjugate addition of indoles and pyrroles to nitro alkenes under solvent free condition (SFC): an effective greener route to access 3-(2-nitro-1-phenylethyl)-1*H*-indole and 2-(2-nitro-1-phenylethyl)-1*H*-pyrrole derivatives

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ABSTRACT

Catalyst free conjugate addition of reactive hetero aromatics (pyrrole and indoles) to nitro alkenes under solvent free condition is described. This method provides several advantages, such as operational simplicity, solvent-free conditions and good yields of products. Also it is environmentally friendly and more cost effective alternative to existing protocols.

1. Introduction

The development of solvent free green processes has gained significant attention in organic synthesis due to increasing global environmental concerns.[1] As a result, many reactions are designed to proceed cleanly and efficiently in the solid state or under solvent free conditions (SFC).[2] The field of solvent free embrace stoichiometric solid-solid reactions,[3a] gas-solid reactions[3b] and supported inorganic reagents,[3c] as well as accelerated through microwave irradiation.[3d] These kinds of reactions promise to be an essential facet of 'Green Chemistry' and are of high interest from both the economical and synthetic point of view over traditional reactions in organic solvents. For example, they not only reduce the burden of organic solvent disposal, but also enhance the rate of many organic reactions.[2] Less chemical pollution, lower cost, easier workup procedure are the main reasons for the increase of popularity of solvent-free reactions recently.

In view of the Principles of Green Chemistry,[4] catalyst-free reactions have been attracting more and more attention from organic chemists.[5] Indeed, great efforts have been implemented in the development of catalyst-free processes to accomplish greener and cleaner syntheses.[6] For the increasing demands of environmental legislation require the minimization or, preferably, the elimination of waste production in chemical syntheses in recent years.[7]

Indole and many of its derivatives are widely distributed in the nature, which possesses biological and pharmacological activity.[8] In particular, the hapalindole alkaloids, which exhibit significant antimycotic, antibacterial activity and several indole alkaloids, such as uleine, aspidospermidine, ibophyllidine alkaloids and numerous tryptamine derivatives are also associated with important biological activity.[9] Likewise, pyrrole and its derivatives are ubiquitous among naturally occurring organic compound[10a] as well as present as an important structural components and can serve as precursors for the synthesis of various biologically active compounds, such as bile pigments, haemin, vitamin B_{12}, chlorophyll, and related natural products.[10b] In addition, several pyrrole derivatives are important intermediates not only for the synthesis of drugs, pigments and pharmaceuticals but also for the development of organic functional groups.[11] Therefore, the development of new strategies to synthesize pyrrole and indole derivatives has been the subject of great interest in the present days.

The Michael addition of nucleophiles to electron deficient alkenes is one of the most important reactions in organic chemistry.[12] Among various nucleophilic additions, Michael addition of indoles and pyrrole to various nucleophiles has been well documented in the literature using either protic or Lewis acids.[13–17] Among them, nitro alkenes are very good Michael acceptors and further the Michael adduct of the nitro alkenes are amenable to transform into a wide range of different functionalized species.[8] Consequently, numerous methods have been reported for the conjugate addition of indole and pyrrole with electron deficient nitroalkene in the presence of acidic catalysts in the literature.[18,19] In addition, recent progress in the stereoselective synthesis of these compounds was reported.[20] Most of the reported procedures suffer from several shortcomings, such as tedious workup procedures, difficulties in product isolation and the use of hazardous catalysts. The most important drawback is the tendency of electron-rich heteroaromatic rings to undergo polymerization under acid catalyzed conditions.[21] Hence, the development of an effective method for the synthesis of 3-substituted indoles and 2-substituted pyrrole has still remained a problem far from resolution.

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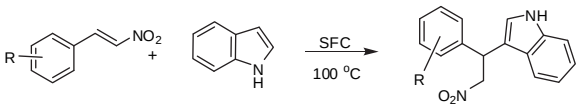
As part of our ongoing program towards the development of new greener synthetic methodologies[22], we report here a convenient route to the synthesis of 3-(2-nitro-1-phenylethyl)-1*H*-indole and pyrrole derivatives from the reaction of β-nitrostyrene on various indole and pyrrole under solvent free (SFC) and catalyst free condition.

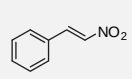
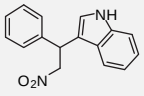
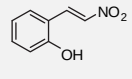
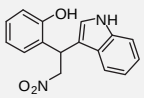
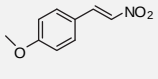
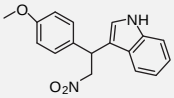
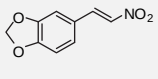
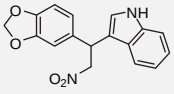
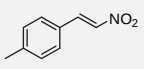
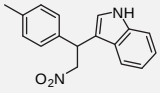
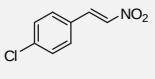
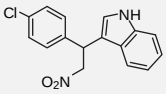
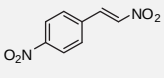
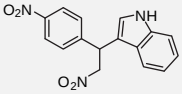
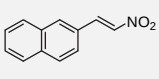
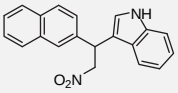
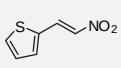
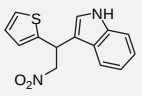
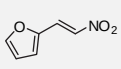
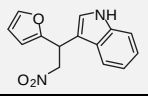
2. Results and discussion

When 1.0 mmol of β-nitrostyrene was treated with 1.2 mmol of indole to afford exclusively the corresponding indolyl-nitroalkane in good yield under SFC. To explore the scope and limitations of this methodology further, we tested the alkylation reaction of indole with a wide array of structurally diverse nitro alkenes (Table 1). As could be seen from it, the alkylation of indoles proceeds with various nitroolefine. The variation of results from entry 1–6 may be attributed to electronic and steric factor of the substituents attached to the benzene ring of β-nitrostyrene. The yield decrement from unsubstituted to 2-hydroxy substituted nitrostyrenes (entry 1–2, Table 1) could be attributed to the introduction of an electron donating group as well as steric factor exerted by the 2-substituent. Release of steric hindrance from entry 2 to entry 3 results in higher yield. A highly electron rich benzene ring (entry 4, Table 1) results in only moderate yield of the adduct. The moderate yield in case of 4-nitro substituent is initially appearing to be unexpected (entry 7, Table 1). Naphthalene derivative (Entry 8, Table 1) also formed the adduct smoothly. Acid sensitive heterocyclic substrates, such as 2-thiophene and 2-furan nitroolefine (entries **9** and **10**) also reacted with equal ease to furnish the Michael adduct in good yields.

Substituents on indole ring has also an effect on adduct formation. The reaction of *N*-methyl indole with β-nitrostyrene underwent smoothly to furnish the product (**11a**) in high yield (entry 1, Table 2). The yield decrement in case of 2-methylindole (entry 2, Table 2) is due to steric factor. Keeping consistency with this trend introduction of a 2-phenyl (entry 3, Table 2) substituent result in further reduction of yield. The electron-rich indole, such as 5-methoxyindole alkylated with β-nitrostyrene to obtain the adduct (**14a**) in high yield (entry 4, Table 2). This may be due to the presence of electron-releasing methoxy group, which activates the indole ring towards the nucleophilic attack. However, electron-withdrawing group (Br) bearing indole, such as 5-bromoindole results in lower yield of the corresponding product (**15a**). The results are summarized in Table 2.

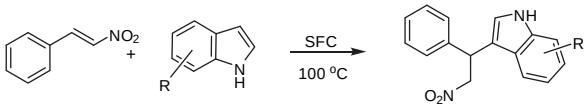
Table 1
Reaction of various β-nitrostyrene with indole under solvent free condition

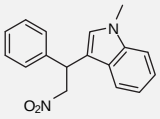
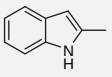
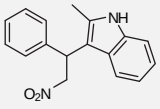
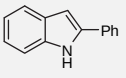
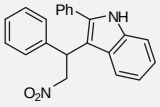
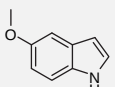
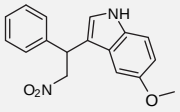
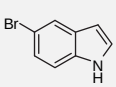
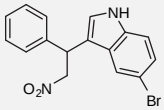


Entry	Substrate[a]	Product		Time (h)	Yield[b,c] %
1			**1a**	4	83
2			**2a**	5	72
3			**3a**	10	76
4			**4a**	9	63
5			**5a**	10	83
6			**6a**	6	79
7			**7a**	10	74
8			**8a**	11	73
9			**9a**	4	72
10			**10a**	11	69

[a] All reactions were performed by using 2 mmol scale and heated at 100 °C in open vessel.
[b] All products were well characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.
[c] Isolated yields.

Table 2
Reaction of β-nitrostyrene with various indoles under solvent free condition



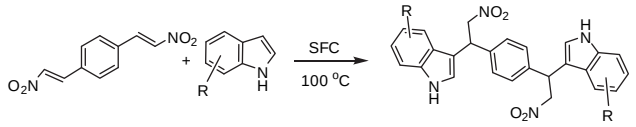
Entry	Substrate[a]	Product		Time (h)	Yield[b,c]
1			**11a**	5	83
2			**12a**	5	78
3			**13a**	6	74
4			**14a**	7	85
5			**15a**	5	71

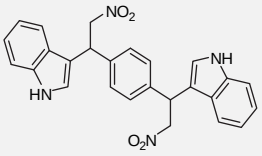
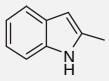
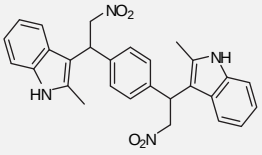
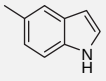
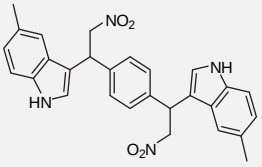
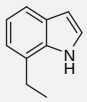
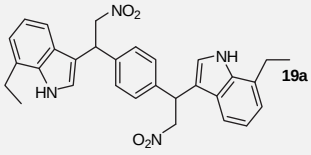
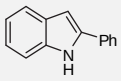
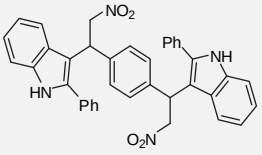
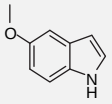
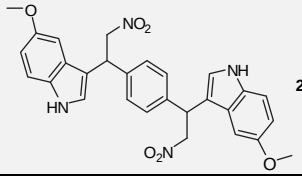
[a] All reactions were performed by using 2 mmol scale and heated at 100 °C in open glass vessel.
[b] All products were well characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.
[c] Isolated yields.

The most important feature of this method is dialkylation of 1,4-bis-(2-nitrovinyl)benzene with indole and substituted indoles. Under the present reaction condition, various indoles reacted with 1,4-bis-(2-nitrovinyl)benzene to give moderate to high yields of the

corresponding bis-indoly adducts, which are shown in Table 3. The 2-substituted indole, such as 2-methylindole and 2-phenyl indole, reacted to 1,4-bis-(2-nitrovinyl)benzene to produce corresponding dialkylated product (**17a**) and (**20a**) in moderate yields. The indole bearing the electron releasing group, such as 5-methylindole, 6-ethylindole and 5-methoxyindole gives corresponding dialkylated adducts (**18a**), (**19a**) and (**21a**) in moderate to good yields.

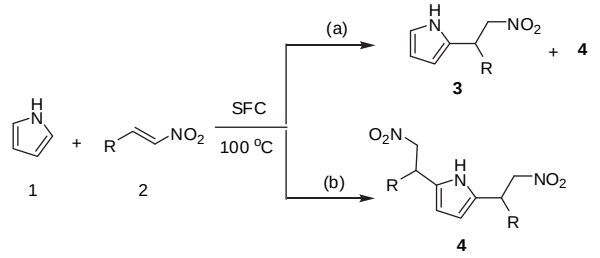
Table 3
Reaction of 1, 4-bis-(2-nitrovinyl) benzene with various indoles



Entry	Substrate[a]	Product	Time (h)	Yield[b,c]
1		 **16a**	8	73
2		 **17a**	13	63
3		 **18a**	12	68
4		 **19a**	8	71
5		 **20a**	11	67
6		 **21a**	13	74

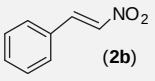
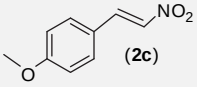
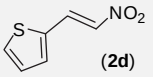
[a] All reactions were performed by using 2 mmol scale and heated at 100 °C in open glass vessel.
[b] All products were well characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.
[c] Isolated yields.

Further, we have extended this protocol to 1*H*-pyrrole, which reacted with electron deficient β-nitroalkene under the present reaction conditions to afforded 2-mono and 2,5-dialkylated products in moderate to good yields (Scheme 1, Table 4). When the β-nitrostyrene **2** (1.0 mmol.) treated with the 1*H*-pyrrole (**1**) (1.2 mmol.) to obtain the 2-monoalkylated product (**3**) along with substantial amounts of 2,5-dialkylated product (**4**) (Table 4). Regardless of the substitution at the phenyl ring the yields are appearing to be comparable. While p-methoxy derivative (entry 3, Table 4) showed better selectivity towards mono adduct may be due to the alkene moiety is more electron rich than the unsubstituted counterpart (entry 1, Table 4). Thiophene derivatives also underwent smooth reaction to form the adduct in high yield. However, increasing the amount of the nitrostyrene to 2.5 equiv gave 2,5-dialkylated product (**4**) as a sole product in case of entries **2**, **4** and **6** (Table 4).



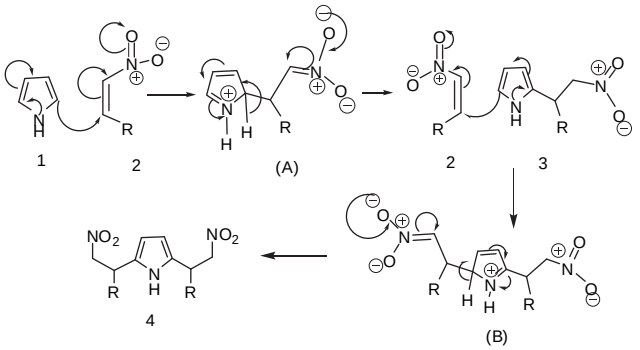
Scheme 1. Reaction of pyrrole with various β-nitrostyrenes: (a) 1 mmol of β-nitrostyrene (2) was used, at 100 °C. (b) 2.4 mmol of β-nitrostyrene (2) was used, at 100 °C.

Table 4
Reaction of pyrrole with various β-nitrostyrenes

Entry[a]	Substrate (2)[b]	Time (h)	2-Alkyl pyrrole (**3**) Yield[c] (%)	2,5-Dialkyl pyrrole (**4**) Yield[c] (%)
1	 (**2b**)	3	34 (**3b**)	48 (**4b**)
2	(**2b**)	5	—	75 (**4b**)
3	 (**2c**)	5	47 (**3c**)	18 (**4c**)
4	(**2c**)	8	—	73 (**4c**)
5	 (**2d**)	4	58 (**3d**)	24 (**4d**)
6	(**2d**)	5	—	82 (**4d**)

[a] In entries 1, 3 and 5, in which 1.0 mmol of electron deficient olefins are used and for the entries 2, 4 and 6 in which 2.4 mmol electron deficient olefin are used.
[b] All reactions were performed by using 2.0 mmol scale and heated at 100 °C in open vessel.
[c] Isolated yields and all products were well characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

All the reactions proceeded smoothly at elevated temperature and this method does not require any acidic promoters or activators or anhydrous conditions. The reactions are clean and the products are obtained in good yields without the formation of any side products, such as dimers or trimers that are normally observed under the influence of strong acids.[21] Indeed, the reaction conditions are very mild so that no side products or decomposition of the products are observed. The plausible mechanism for the C-alkylation of 1*H*-pyrrole with electron deficient olefins are as shown Scheme 2, in which the formation of the monoalkylated (**3**) and 2,5-dialkylated pyrrol (**4**) products are dipicted.



Scheme 2. Plausible mechanism for the C-alkylation of 1*H*-pyrrol with electron deficient nitroolefins.

We speculate, 1*H*-pyrrole (**1**), attack on electron deficient nitroalkene (**2**) to form the intermediate (A), which was readily converted to the monoalkylated 1*H*-pyrrol (**3**). Then the monoalkylated 1*H*-pyrrole (**3a**) reacted with excess of the nitrolefine (**2**), which is present in a reaction mixture to form the dialkylated product of 1*H*-pyrrole (**4**), through the intermediate (**B**). This reaction probably proceeds through an intermediate σ-complex **A** and **B** as shown Scheme 2.[23]

3. Conclusion

In conclusion, we have achieved a novel un-catalyzed organic-solvent free Fredel-Craft alkylation of indole and 1*H*-pyrrole with β-nitrostyrenes. The procedure is entirely green and applied for structurally diverse indoles and 1*H*-pyrrole as well as nitro alkenes to obtained good yield. Simple reaction conditions, easy isolation, avoid the use of toxic and expensive reagents and low costs make this method useful and attractive method over the existing reports.

4. Experimental

4.1. General

All reactions were performed at 100 °C. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by use of E. Merck silica gel 60 (230–400 mesh). MS or HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Aavance EX 400.

4.2. Material

β-Nitrostyrenes were prepared according to the literature procedures and spectral data were consistent with the literature report.[24] Indole and pyrrole were purchased from Aldrich Chemical Co.

4.3. Typical experimental procedure for the synthesis of adducts (1a–15a)

A mixture of indole (1.2 mmol) and β-nitrostyrene (1.0 mmol) was suspended in open glass vessel and heated the reaction at 100 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture directly gives crude product. Further purification was achieved by column chromatography using EA/Hexane as eluent.

4.4. Typical experimental procedure for the synthesis of adducts (16a–21a)

Indole (2.4 mmol) was added to a 1,4-bis-(2-nitrovinyl) benzene (1.0 mmol) in open glass vessel and heated the reaction mixture to the 100 °C for several minutes to hours. After completion the reaction (monitored by TLC), it directly afforded the crude products, which was purified by column chromatography.

4.5. Typical experimental procedure for the synthesis of adducts (3b, 3c, 3d and 4b, 4c, 4d)

Pyrrole 1 (1.2 mmol) was added to a β-nitrostyrene 2 (1.0 mmol) in round bottle and heated the reaction mixture to the 100 °C with open vessel for several minutes to hours. After completion the reaction (monitored by TLC), it directly afforded the crude products of 2-monoalkylated and 2,5-dialkylated pyrrole, which was purified by column chromatography.

4.6. Typical experimental procedure for the synthesis of adducts (4b, 4c and 4d)

Pyrrole 1 (1.0 mmol) was added to a β-nitrostyrene 2 (2.4 mmol) in open vessel and heated the reaction mixture to the 100 °C for several minutes to hours. After completion the reaction (monitored by TLC), it directly afforded the crude 2,5-dialkylated products, which was future purified by column chromatography.

4.7. Spectral data

*4.7.1. 3-(2-Nitro-1-phenylethyl)-1H-indole (**1a**).* Solid, mp 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93 (s, 1H), 7.40 (d, *J*=8.0 Hz, 1H), 7.27–7.10 (m, 8H), 6.82 (d, *J*=2.4 Hz, 1H), 5.12 (dd, *J*=8.4, 7.7 Hz, 1H), 4.95 (dd, *J*=12.5, 7.7 Hz, 1H), 4.84 (dd, *J*=12.5, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.1, 136.3, 128.7, 127.5, 127.3, 125.8, 122.3, 121.5, 119.6, 118.6, 113.8, 111.3, 79.3, 41.3. MS *m*/*z* (relative intensity) 266 (M^+, 8), 219 (100), 204 (44), 178 (19), 115 (11), 108 (17). HRMS calcd for $C_{16}H_{14}N_2O_2$ (M^+) 266.1055; found: 266.1051.

*4.7.2. 2-(1-(1H-Indol-3-yl)- 2-nitroethyl) phenol (**2a**).* Solid, mp 72–74 °C. ^{1}H NMR (CDCl3, 400 MHz): δ=8.10 (br s, 1H), 7.48 (d, *J*=7.8 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.18–7.06 (m, 5H), 6.84 (t, *J*=8.0 Hz, 1H), 6.76 (d, *J*=8.0 Hz, 1H), 5.48 (t, *J*=7.8 Hz, 1H), 5.34 (br s, 1H), 5.12–5.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=154.3, 136.6, 129.3, 128.7, 126.6, 125.7, 122.6, 122.3, 120.6, 119.8, 119.2, 116.2, 113.8, 111.5, 78.2, 36.3. Ms (*m*/*z*) (relative intensity) 282 (M^+, 30), 235 (12), 234 (18), 220 (100), 204 (12), 165 (12), 143 (12), 130 (12), 117 (24), 91 (12), 77.1 (10). HRMS calcd for $C_{16}H_{14}N_2O_3$ (M^+) 282.0999; found 282.1000.

*4.7.3. 3-(1-(4-Methoxyphenyl)-2-nitroethyl)-1H-indole (**3a**).* Solid, mp 151–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.06 (s, 1H), 7.43 (d, *J*=7.9 Hz, 1H), 7.36 (d, *J*=8.1 Hz, 1H), 7.25–7.17 (m, 3H), 7.07 (t, *J*=7.5 Hz, 1H), 7.02 (d, *J*=2.0 Hz, 1H), 6.85 (d, *J*=8.6 Hz, 2H), 5.13 (dd, *J*=8.4, 7.5 Hz, 1H), 5.04 (dd, *J*=12.2, 7.5 Hz, 1H), 4.89 (dd, *J*=12.2, 8.4 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.9, 136.5, 131.2, 128.8, 126.1, 122.7, 121.4, 119.9, 119.0, 114.8, 114.3, 111.3, 79.7, 55.2, 41.1. MS *m*/*z* (relative intensity) 296 (M^+, 38), 250 (32), 249 (88), 236 (100), 218 (20), 115 (12). HRMS calcd for $C_{17}H_{16}O_3N_2$ (M^+) 296.1161; found: 296.1155.

*4.7.4. 3-(1-(Benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-1H-indole (**4a**).* Solid, mp 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.28 (s, 1H), 7.44 (d, *J*=7.9 Hz, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.21 (t, *J*=7.2 Hz, 1H), 7.15 (t, *J*=7.3 Hz, 1H), 7.07 (s, 1H), 6.95–6.67 (m, 3H), 5.91 (d, *J*=6.4 Hz, 2H), 5.11 (t, *J*=7.8 Hz, 1H), 5.07–4.98 (m, 1H), 4.88–4.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.1, 136.5, 133.1, 126.1, 122.7, 121.3, 121.1, 119.9, 118.9, 145.5, 111.4, 108.5, 108.1, 101.1, 79.7,

41.3. MS *m*/*z* (relative intensity) 310 (M^+, 20), 225 (50), 220 (30), 212 (40). HRMS calcd for $C_{17}H_{14}N_2O_4$ (M^+) 310.0954; found: 310.0938.

*4.7.5. 3-(1-(4-Methylphenyl)-2-nitroethyl)-1H-indole (**5a**).* Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (s, 1H), 7.40 (d, *J*=7.8 Hz, 1H), 7.23–7.01 (m, 7H), 6.84 (s, 1H), 5.09 (dd, *J*=8.6, 7.7 Hz, 1H), 4.95 (dd, *J*=12.3, 7.7 Hz, 1H), 4.83 (dd, *J*=12.3, 8.6 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.3, 136.6, 136.3, 129.7, 127.7, 126.2, 122.7, 121.7, 119.9, 119.0, 114.5, 111.6, 79.8, 41.3, 21.2. MS *m*/*z* (relative intensity) 280 (M^+, 26), 272 (29), 233 (86), 225 (100), 220 (72), 212 (70). HRMS calcd for $C_{17}H_{16}N_2O_2$ (M^+) 280.1212; found: 280.1208.

*4.7.6. 3-(1-(4-Chlorophenyl)-2-nitroethyl)-1H-indole (**6a**).* Solid, mp 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (s, 1H), 7.38 (d, *J*=7.9 Hz, 1H), 7.33 (d, *J*=8.2 Hz, 1H), 7.28–7.17 (m, 5H), 7.07 (t, *J*=7.5 Hz, 1H), 6.96 (d, *J*=1.7 Hz, 1H), 5.14 (dd, *J*=8.6, 7.4 Hz, 1H), 5.02 (dd, *J*=12.5, 7.4 Hz, 1H), 4.88 (dd, *J*=12.5, 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.6, 136.2, 133.0, 128.9, 128.8, 125.6, 122.5, 121.4, 119.8, 118.5, 113.3, 111.4, 79.0, 41.0. MS *m*/*z* (relative intensity) 302 (M^{+2}, 2), 300 (M^+, 33), 254 (41), 253 (100), 240 (64), 218 (37), 115 (14), 108 (25). HRMS calcd for $C_{16}H_{13}ClN_2O_2$ (M^+), 300.0666; found: 300.0671.

*4.7.7. 3-(1-(4-Nitrophenyl)-2-nitroethyl)-1H-indole (**7a**).* Solid, mp 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.20 (s, 1H), 8.16 (d, *J*=8.7 Hz, 2H), 7.51 (d, *J*=8.6 Hz, 2H), 7.37 (t, *J*=7.3 Hz, 2H), 7.25–7.20 (m, 1H), 7.09 (t, *J*=7.7 Hz, 1H), 7.04 (d, *J*=2.2 Hz, 1H), 5.29 (dd, *J*=8.9, 7.0 Hz, 1H), 5.10 (dd, *J*=12.8, 7.0 Hz, 1H), 4.98 (dd, *J*=12.8, 8.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.5, 146.9, 136.7, 129.0, 125.8, 124.4, 123.3, 121.8, 120.5, 118.7, 113.1, 111.9, 78.9, 41.4. MS *m*/*z* (relative intensity) 311 (M^+, 7), 264 (21), 185 (24), 110 (47), 97 (43), 71 (71), 57 (100). HRMS calcd for $C_{16}H_{13}N_3O_4$ (M^+), 311.0906; found: 311.0901.

*4.7.8. 3-(1-Naphthalen-2-yl)-2-nitroethyl-1H-indole (**8a**).* Solid, mp 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (s, 1H), 7.76 (m, 4H), 7.45 (d, *J*=7.1 Hz, 3H), 7.39 (d, *J*=8.5 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 7.17 (t, *J*=7.5 Hz, 1H), 7.05–6.99 (m, 2H), 5.33 (t, *J*=7.8 Hz, 1H), 5.11 (m, 1H), 5.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.6, 136.5, 133.4, 132.7, 128.8, 127.9, 127.6, 126.4, 126.3, 126.1, 126.0, 125.8, 122.7, 121.7, 120.0, 118.9, 114.3, 111.4, 79.4, 41.6. MS *m*/*z* (relative intensity) 316 (M^+, 31), 270 (29), 269 (100), 268 (30), 256 (65), 254 (49), 149 (21), 127 (20), 57 (33). HRMS calcd for $C_{20}H_{16}O_2N_2$ (M^+), 316.1212; found: 316.1.

*4.7.9. 3-(2-Nitro-1-(thiophen-2-yl)ethyl)-1H-indole (**9a**).* Solid, mp 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (s, 1H), 7.52 (d, *J*=8.0 Hz, 1H), 7.37 (d, *J*=8.1 Hz, 1H), 7.25–7.19 (m, 2H), 7.11 (t, *J*=7.4 Hz, 2H), 6.99–6.93 (m, 2H), 5.45 (t, *J*=7.9 Hz, 1H), 5.06–4.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=143.1, 136.6, 127.1, 125.9, 125.4, 125.1, 122.9, 122.2, 120.2, 119.0, 114.1, 111.7, 80.2, 37.1. MS *m*/*z* (relative intensity) 274 (M^{+2}, 3), 272 (M^+, 42), 225 (100), 212 (72). HRMS calcd for $C_{14}H_{12}N_2O_2S$ (M^+), 272.0619; found: 272.0614.

*4.7.10. 3-(1-(Furan-2-yl)-2-nitroethyl)-1H-indole (**10a**).* Solid, mp 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (s, 1H), 7.53 (d, *J*=7.9 Hz, 1H), 7.35 (d, *J*=1 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 1H), 7.21–7.17 (m, 1H), 7.11 (t, *J*=7.4 Hz, 1H), 7.02 (d, *J*=2.4 Hz, 1H), 6.28–6.27 (m, 1H), 6.13 (d, *J*=3.2 Hz, 1H), 5.22 (dd, *J*=8.1, 7.4 Hz, 1H), 5.02 (dd, *J*=12.5, 8.1 Hz, 1H), 4.87 (dd, *J*=12.5, 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.0, 142.2, 136.3, 125.3, 122.6, 120.1, 118.7, 111.7, 111.5, 110.2, 107.4, 77.5, 35.7. MS *m*/*z* (relative intensity) 256 (M^+, 32), 210 (22), 209 (100), 196 (84), 167 (23), 117 (16), 115 (12). HRMS calcd for $C_{14}H_{12}O_3N_2$ (M^+) 256.0848; found: 256.0846.

*4.7.11. 2-(N-Methylindol-3-yl)-2-phenyl-1-nitroethane (**11a**).* Solid, mp 94–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45 (d, *J*=8.0 Hz, 1H), 7.35–7.32 (m, 4H), 7.28–7.20 (m, 3H), 7.09–7.05 (m, 1H), 6.86 (s, 1H), 5.18 (dd, *J*=8.5, 7.5 Hz, 1H), 5.05 (dd, *J*=12.5, 7.5 Hz, 1H), 4.93 (dd, *J*=12.5, 8.5 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.3, 137.5, 129.1, 127.4, 127.1, 126.3, 126.0, 121.8, 119.1, 118.7, 112.4, 109.3, 79.1, 41.2, 32.2. MS *m*/*z* (relative intensity) 280 (M^+, 44), 234 (50), 233 (74), 220 (100), 217 (17), 146 (17), 115 (13). HRMS calcd for $C_{17}H_{16}O_2N_2$ (M^+) 280.1212; found: 280.1213.

*4.7.12. 2-(2-Methylindol-3-yl)-2-phenyl-1-nitroethane (**12a**).* Solid, mp 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.76 (s, 1H), 7.34 (d, *J*=7.8 Hz, 1H), 7.28–7.23 (m, 4H), 7.20–7.16 (m, 2H), 7.07 (t, *J*=7.7 Hz, 1H), 7.00 (m, 1H), 5.20–5.13 (m, 2H), 5.10–5.02 (m, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.3, 135.1, 132.8, 128.4, 127.0, 126.7, 126.5, 120.8, 119.3, 118.2, 110.6, 108.2, 78.2, 40.2, 11.2. MS *m*/*z* (relative intensity) 280 (M^+, 62), 234 (49), 220 (100), 146 (49), 115 (8), 77 (8). HRMS calcd for $C_{17}H_{16}O_2N_2$ (M^+) 280.1212; found: 280.1218.

*4.7.13. 3-(2-Nitro-1-phenylethyl)-2-phenyl-1H-indole (**13a**).* Solid, mp 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.14 (s, 1H), 7.52 (d, *J*=8.0 Hz, 1H), 7.44–7.19 (m, 12H), 7.11 (t, *J*=7.5 Hz, 1H), 5.32 (t, *J*=8.0 Hz, 1H), 5.20–5.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.1, 137.2, 136.3, 132.4, 129.2, 129.1, 129.0, 128.8, 127.7, 127.4, 127.2, 122.7, 120.5, 120.2, 111.6, 109.8, 79.3, 41.0. MS *m*/*z* (relative intensity) 342 (M^+, 65), 294 (70), 282 (81), 208 (100), 204 (53). HRMS calcd for $C_{22}H_{18}N_2O_2$ (M^+) 342.1368; found: 342.1363.

*4.7.14. 5-Methoxy-3-(2-nitro-1-phenylethyl)-1H-indole (**14a**).* Solid, mp 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.99 (s, 1H), 7.30–7.16 (m, 6H), 6.92 (d, *J*=2.2 Hz, 1H), 6.84 (d, *J*=2.2 Hz, 1H), 6.82 (s, 1H), 5.11 (dd, *J*=8.4, 7.6 Hz, 1H), 5.00 (dd, *J*=12.4, 7.6 Hz, 1H), 4.89 (dd, *J*=12.4, 8.4 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.1, 139.1, 131.5, 128.8, 127.7, 127.5, 126.5, 122.2, 113.9, 112.6, 112.1, 100.8, 79.4, 55.8, 41.4. MS *m*/*z* (relative intensity) 296 (M^+, 86), 250 (75), 249 (100), 236 (98). HRMS calcd for $C_{17}H_{16}N_2O_3$ 296.1161; found: 296.1163.

*4.7.15. 5-Bromo-3-(2-nitro-1-phenylethyl)-1H-indole (**15a**).* Solid, mp 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.16 (s, 1H), 7.53 (s, 1H), 7.33–7.24 (m, 6H), 7.17 (d, *J*=8.6 Hz, 1H), 7.02 (d, *J*=1.9 Hz, 1H), 5.10 (t, *J*=8.0 Hz, 1H), 4.99 (dd, *J*=12.5, 8.0 Hz, 1H), 4.90 (dd, *J*=12.5, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.9, 135.3, 129.2, 128.1, 128.0, 127.8, 125.8, 123.0, 121.6, 114.2, 113.4, 113.1, 79.6, 41.5. MS *m*/*z* (relative intensity) 346 (M^{+2}, 26), 344 (M^+, 27), 297 (100), 284 (54), 218 (88), 204 (27). HRMS calcd for $C_{16}H_{13}BrN_2O_2$ 344.0160; found: 344.0155.

*4.7.16. 1,4-Bis(1-(1H-indol-3-yl)-2-nitroethyl)benzene (**16a**).* Solid, mp 191–193 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ=11.00 (br s, 2H), 7.46 (dd, *J*=7.6, 5.6 Hz, 2H), 7.36–7.35 (m, 6H), 7.31 (d, *J*=8.1 Hz, 2H), 7.05–7.02 (m, 2H), 6.93–6.88 (m, 2H) 5.32–5.20 (m, 4H), 4.99–4.90 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=139.2, 136.1, 127.9, 126.0, 122.3, 121.3, 118.6, 118.3, 113.3, 111.5, 79.0, 40.2. MS *m*/*z* (relative intensity) 454 (M^+, 25), 374 (40), 216 (10), 187 (10), 143 (100), 131 (30). HRMS calcd for $C_{26}H_{22}N_4O_4$ (M^+) 454.1641; found 454.1632.

*4.7.17. 1,4-Bis(1-(2-methyl-1H-indol-3-yl)-2-nitroethyl) benzene (**17a**).* Solid, mp 238–240 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ=10.9 (br s, 2H), 7.44 (d, *J*=8.0 Hz, 2H), 7.30 (s, 4H), 7.22 (d, *J*=8.0 Hz, 2H), 6.95 (t, *J*=7.6 Hz, 2H), 6.84 (t, *J*=7.6 Hz, 2H) 5.47–5.42 (m, 2H) 5.25–5.31 (m, 2H), 4.97–5.10 (m, 2H), 2.39 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=138.9, 135.5, 133.2, 127.6, 126.5, 120.3, 118.7, 118.5, 110.9, 108.2, 78.2, 40.2, 11.7. MS *m*/*z* (relative intensity) 482 (M^+, 12), 422 (9), 374 (16), 216 (6), 187 (6), 143 (100), 129 (30). HRMS calcd for $C_{28}H_{26}N_4O_4$ (M^+) 482.1954; found 482.1949.

*4.7.18. 1,4-Bis(1-(5-methyl-1H-indol-3-yl)-2-nitroethyl) benzene (**18a**).* Solid, mp 272–274 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.87 (s, 2H), 7.77 (S, 4H), 7.59 (d, *J*=8 Hz, 2H), 7.35–7.24 (m, 2H), 7.20

(d, J=8.2 Hz, 2H), 6.87 (d, J=8.2 Hz, 2H), 5.28–5.17 (m, 4H), 4.98 (t, J=8.2 Hz, 2H), 2.25 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=139.8, 135.0, 128.4, 127.6, 126.7, 123.4, 122.9, 118.3, 113.2, 111.7, 79.6, 40.7, 21.7. MS m/z (relative intensity) 482 (M^+, 100), 435 (50), 388 (25), 375 (10), 146 (10), 131 (10). HRMS calcd for $C_{28}H_{26}N_4O_4$ (M^+) 482.1949; found 482.1971.

*4.7.19. 1,4-Bis(1-(7-ethyl-1H-indol-3-yl)-2-nitroethyl)benzene (**19a**).* Solid, mp 207–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93 (d, J=12 Hz, 2H), 7.27–7.22 (m, 6H), 7.02–7.01 (m, 4H), 6.83 (dd, J=16, J=2.0 Hz, 2H), 5.13 (t, J=8.0 Hz, 2H), 5.00–4.94 (m, 2H), 4.85–4.80 (m, 2H), 2.79–2.74 (m, 4H), 1.30–1.26 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=138.7, 135.5, 128.3, 127.3, 125.9, 121.8, 120.8, 119.9, 116.4, 114.0, 79.5, 41.3, 23.9, 13.9. MS m/z (relative intensity) 510 (M^+, 100), 463 (30), 416 (20), 216 (6), 160 (15). HRMS calcd for $C_{30}H_{30}N_4O_4$ (M^+) 510.2262; found 510.2281.

*4.7.20. 1,4-Bis(2-nitro-1-(2-phenyl-1H-indol-3-yl)ethyl) benzene (**20a**).* Solid, mp 265–267 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ=11.39 (s, 2H), 7.62 (t, J=9.0 Hz, 2H), 7.50–7.43 (m, 10H), 7.36–7.33 (m, 2H), 7.23 (s, 4H), 7.09 (m, 2H), 6.94 (m, 2H), 5.49 (m, 2H), 5.41 (m, 2H), 5.15 (t, J=8.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=139.2, 136.9, 136.6, 132.8, 129.2, 129.1, 128.6, 128.0, 127.9, 126.6, 121.9, 120.2, 119.7, 112.1, 109.0, 78.4, 40.3. MS m/z (relative intensity) 606 (M^+, 100), 413 (70), 364 (25), 208 (85), 193 (100). HRMS calcd for $C_{38}H_{30}N_4O_4$ (M^+) 606.2262; found 606.2273.

*4.7.21. 1,4-Bis(1-(5-methoxy-1H-indol-3-yl)-2-nitroethyl) benzene (**21a**).* Solid mp 218–220 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.83 (s, 2H), 7.38 (d, J=4 Hz, 4H), 7.30 (s, 2H), 7.20 (d, J=8.8 Hz, 2H), 6.89 (s, 2H), 6.69–6.66 (m, 2H), 5.27–5.22 (m, 4H), 4.94 (t, J=8.0 Hz, 2H), 3.63 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=153.6, 139.7, 131.8, 128.4, 126.8, 123.4, 113.6, 112.7, 111.9, 100.8, 79.6, 55.8, 40.7. MS m/z (relative intensity) 514 (M^+, 100), 467 (30), 422 (10), 367 (10), 320 (10), 277 (10), 160 (40), 147 (90), 132 (30). HRMS calcd for $C_{28}H_{26}N_4O_6$ (M^+) 514.1847; found: 514.1885.

*4.7.22. 2-(2-Nitro-1-phenylethyl)-1H-pyrrole (**3b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.83 (s, 1H), 7.35–7.19 (m, 5H), 6.40 (dd, J=4.04, 2.60 Hz, 1H), 6.14 (dd, J=6.0, 2.8 Hz, 1H), 6.05–6.07 (m, 1H), 4.94 (dd, J=11.8, 7.2 Hz, 1H), 4.86 (dd, J=7.5, 7.2 Hz, 1H), 4.76 (dd, J=11.8, 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=137.9, 129.1, 128.8, 128.0, 127.8, 118.1, 108.5, 105.7, 79.12, 42.8. MS m/z (relative intensity) 216 (M^+, 10), 170 (22), 169 (100), 156 (40), 154 (39), 77 (12). HRMS calcd for $C_{12}H_{12}N_2O_2$ (M^+) 216.0899; found 216.0900.

*4.7.23. 2,5-Bis(2-nitro-1-phenylethyl)-1H-pyrrole (**4b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.58 (s, 1H), 7.32–7.25 (m, 6H), 7.15 (t, J=5.7 Hz, 4H), 6.00 (dd, J=7.5, 2.7 Hz, 2H), 4.90–4.86 (m, 2H), 4.78–4.10 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=138.2, 129.7, 129.2, 128.1, 127.9, 106.5, 106.2, 79.5, 42.9. MS m/z (relative intensity) 365 (M^+, 10), 340 (22), 169 (50), 156 (20), 154 (50), 77 (5). HRMS calcd for $C_{20}H_{19}N_3O_4$ (M^+) 365.1376; found 365.1368.

*4.7.24. 2-(1-(4-Methoxyphenyl)-2-nitroethyl)-1H-pyrrole (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.85 (s, 1H), 7.14–7.11 (m, 2H), 6.88–6.84 (m, 2H), 6.67–6.65 (dd, J=5.9, 2.7 Hz, 1H), 6.16–6.14 (m, 1H), 6.06–6.04 (m, 1H), 4.94 (dd, J=11.9, 6.9 Hz, 1H), 4.82 (dd, J=8.0, 6.96 Hz, 1H), 4.74 (dd, J=11.9, 8.0 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=159.30, 129.84, 129.24, 128.98, 118.03, 114.53, 108.58, 105.54, 79.37, 55.26, 42.18. MS m/z (relative intensity) 246 (M^+, 13), 199 (100), 186 (66), 171 (14), 168 (20), 77 (9). HRMS calcd for $C_{13}H_{14}N_2O_3$ (M^+) 246.1004; found 246.1006.

*4.7.25. 2,5-Bis(1-(4-methoxyphenyl)-2-nitroethyl)-1H-pyrrole (**4c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.50 (d, J=15 Hz, 1H), 7.07 (d, J=7.0 Hz, 4H), 6.85–6.81 (m, 4H), 5.98 (dd, J=2.5, 7.2 Hz, 2H), 4.91–4.84 (m, 2H), 4.74–4.66 (m, 4H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=129.9, 129.8, 129.7, 129.0, 128.9, 114.6, 114.5, 106.2, 105.9, 79.4, 79.3, 55.3, 42.1. MS m/z (relative intensity) 425 (M^+, 30), 340 (20), 169 (100), 156 (5), 154 (20), 77 (5). HRMS calcd for $C_{22}H_{23}N_3O_6$ (M^+) 425.1587; found 425.1580.

*4.7.26. 2-(2-Nitro-1-(thiophen-2-yl)ethyl)-1H-pyrrole (**3d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.03 (s, 1H), 7.25–7.23 (m, 1H), 6.93–6.92 (m, 2H), 6.68–6.70 (m, 1H), 6.18–6.15 (m, 1H), 6.11–6.09 (m, 1H), 5.19 (dd, J=7.9, 7.5 Hz, 1H), 4.92 (dd, J=12.8, 7.52 Hz, 1H), 4.82 (dd, J=12.8, 7.96 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=140.9, 128.2, 127.1, 125.8, 125.5, 118.2, 108.8, 105.9, 79.6, 38.1. MS m/z (relative intensity) 222 (M^+, 1), 206 (2), 168 (11), 88 (37), 73 (40), 79 (78), 61 (100). HRMS calcd for $C_{10}H_{10}N_2O_2S$ (M^+) 222.0463; found 222.0540.

*4.7.27. 2,5-Bis (2-nitro-1-(thiophen-2-yl) ethyl)-1H-pyrrole (**4d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.00 (s, 1H), 7.21 (d, J=5.0 Hz, 2H), 6.96–6.93 (m, 2H), 6.83 (d, J=3.2 Hz, 2H), 6.04 (d, J=2.4 Hz, 2H), 5.07–5.03 (m, 2H), 4.84–4.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=141.0, 140.9, 129.2, 129.1, 127.3, 126.0, 125.9 125.7, 125.6, 106.7, 106.6, 79.6, 38.8. MS m/z (relative intensity) 377 (M^+, 12), 340 (20), 169 (100), 156 (40), 154 (39), 77 (12). HRMS calcd for $C_{16}H_{15}N_3O_4S_2$ (M^+) 377.0504; found 377.0496.

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