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Reaction of Some Substituted (Un)Substituted Isatins with 1,ω-Alkanes and Their Products with Sodium Azide †

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Abstract: Azide derivatives of isatins were the needed initial materials for click chemistry in order to form 1,2,3-triazoles in order to synthesize the hybrid compounds of 1,2,3-triazole–isatin having monosaccharide moieties. Required substituted isatin were prepared according to Sandmeyer method from corresponding subsituted anilines. N-(ω-Bromoalkyl)isatins were prepared by nucleophilic reaction S_N2 of (un)substituted isatins with appropriate dibromoalkanes. Some ω-azidoalkylisatins were synthesized by reaction of corresponding ω-bromoalkylisatins with sodium azide. The reactions were performed in dry DMF as solvent in the presence of K_2CO_3 as base and KI as promotive agent. Product yields achived 30–85%.

Keywords: azide; alkylation; azidation dibromoalkanes; isatins

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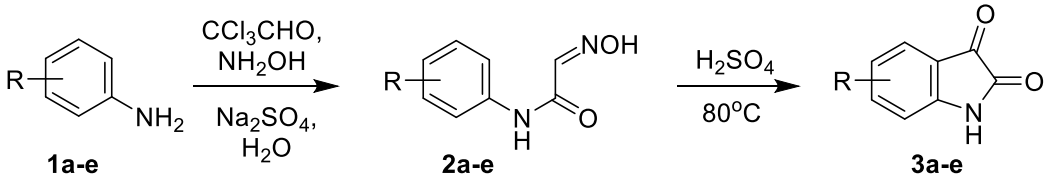
1. Introduction

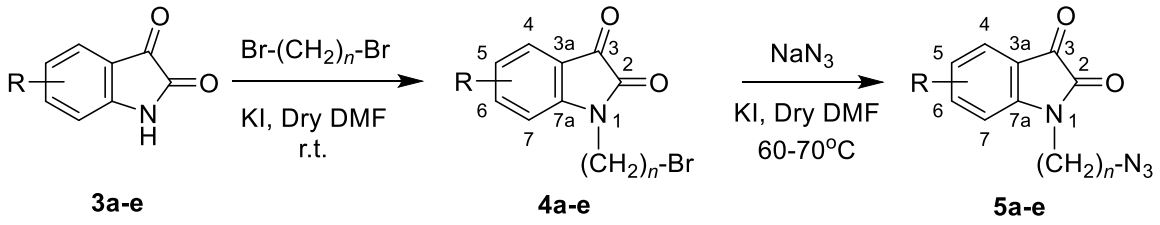
Recently, the chemistry of isatin is still of interest to scientists [1] because derivatives of isatin, such as hydrazones [2] and thiosemicarbazones [3], and hybrid compounds containing simultaneous isatin ring and other heterocycles have diverse biological activity [4-6], including antiviral, antibacterial, anticancer, anticonvulsant and antidepressant activity [7-9]. Isatin and its derivatives had specific reactivity towards electrophiles [6,10], including alkyl halides (*N*-alkylation), formaldehyde and amines (Mannich reaction), halogens (halogenation on the aromatic nucleus), acyl chlorides or anhydrides (*N*-acylation), sulfonyl chlorides (*N*-sulfonylation). Among the reactions of isatin to different agents, the substitution reactions of hydrogen atom of N−H link on position N-1 by different alkylation agents were particularly important [6,10]. The alkylation reaction was used in order to functionalize isatin and its derivatives and was carried out by reaction to alkyl halide in the presence of bases (such as sodium or calcium hydrides, potassium or caesium carbonates) [11]. A variety of methods have been developed for the *N*-alkylation of isatins to the target products with high yields, such as iodin and *tert*-butyl hydroperoxide in DMSO as solvent (to give isatin *N*-methyl and *N*-benzyl isatins) [12], 2-iodoxybenzoic acid-SO_3K

in DMSO-water at 60 °C (to give isatin *N*-methyl and *N*-benzyl isatins) [13], oxygen and *tert*-butyl nitrite in THF (to give isatin, *N*-methyl, *N*-phenyl, *N*-benzyl, and *N*-Boc isatins) [14]. But these methods could not use for synthesis of isatins with *N*-propargyl group because 1-alkyne could be changed under these reaction conditions. By using this method, the direct *N*-alkylation method were performed easily and gave high yields of *N*-alkyl isatins [11,15,16]. Some of the more general methods include the use of sodium hydride for substrate activation in nucleophilic substitution reactions in DMF at 25–80 °C [17] as well as of calcium hydride in DMF at 40–60 °C for 2–4 h with yields of 21–96% [18,19] or at 100 °C for 4 h with yield of 89% [20], anhydrous K_2CO_3 or Cs_2CO_3 in DMF (r.t. to 80 °C for 5–24 h in the presence of KI with yields of 25–93% [21], K_2CO_3/DMF (with yields of 76–94%) or NaOEt/EtOH (with yields of 24–81%) in a domestic microwave oven [15], K_2CO_3 or Cs_2CO_3 and DMF or *N*-methyl-2-pyrrolidinone (NMP) [11], K_2CO_3/KI in acetonitrile under microwave conditions (160 °C, 10 min) [22], and in DMF at 150 °C for 5–15 min under microwave irradiation with product's yields of 53–96% [23].

Among *N*-alkyl isatins, *N*-(ω-azidoalkyl) isatins played an important role in the conversion of isatin rings into hybrid compounds, isatin/1,2,3-triazole hybrid compounds [24-27]. Isatin derivatives having azido group or 1-alkyne components (*N*-propargylated isatins) were one of two reagents necessary for click chemistry [28-31]. The synthesis of *N*-functionalized isatins with ω-azidoalkyl group made these derivatives to become the azido component in click chemistry. Therefore, in this article, we report on the synthesis of some (un)substituted 2-amino-7-hydroxy-4H-chromene-3- carbonitriles via a one-pot three-component reaction in aqueous media (Schemes 1 and 2).



Scheme 1. Synthetic rout for subsituted isatins from corresponding anilines, where, **1a-e**,**2a-e**,**3a-e:** R = 5-Me, *n* = 4 (**a**); 7-Me, *n* = 4 (**b**); 5-Et, *n* = 4 (**c**); 5-*i*Pr, *n* = 4 (**d**); 5-F, *n* = 3 (**e**).



Scheme 2. Synthetic rout for subsituted *N*-(ω-azidoalkyl)isatins from corresponding isatins, where, **3a-e**,**4a-e**,**5a-e:** R = 5-Me, *n* = 4 (**a**); 7-Me, *n* = 4 (**b**); 5-Et, *n* = 4 (**c**); 5-*i*Pr, *n* = 4 (**d**); 5-F, *n* = 3 (**e**); H, *n* = 3 (**f**); H, *n* = 4 (**g**).

2. Results and Discussion

With the exception of isatin that cannot be available for use (for the preparation of ω-bromoalkyl compounds **4f-g** and ω-azidoalkyl compounds **5f-g**, respectively), other remaining isatins (**3a-g**) are synthesized from anilines corresponding **1a-g** containing appropriate substituents by the Sandmeyer reaction of *N*-isonitrosoacetanilide derivatives **2a-g** (Scheme 1). 2a-e compounds are easily obtained by reacting with the reaction of such anilines to chloral hydrate and hydroxylamine in a solution of saturated sodium sulfate [32,33]. *N*-(ω-Bromoalkyl)isatin derivatives are synthesized by the nucleophile reaction of corresponding 1,ω-dibromoalkane derivatives to appropriate isatins (Scheme 2). This alkylization reaction is carried out in the solvent dry DMF in the presence of anhydrous

potassium carbonate as a base. Potassium iodide is added in order to promote this nucleophilic substituted reaction. The reaction is carried out by stirring the reaction mixture at temperatures of 25–27 °C.

Next, ω-bromoalkylisatins **3a-g** are converted into ω-azidoalkyl derivatives by reaction to sodium azide. Potassium iodide is also used as a promoter for this reaction. The reaction is carried out by heating on water-bath at 70°C. The reaction times are 1.5–3 h. The end of the reaction is determined by TLC with the solvent system of *n*-hexane/ethyl acetate with ratio of 7:3 (in volume). The results are represented in Table 1.

Table 1. Synthesis of ω-azidoalkyl derivatives **5a-g.**

Compound	R	*n*	Reaction Time (h)	Yield (%)
5a	5-Me	4	1.5	79
5b	7-Me	4	1.5	46
5c	5-Et	4	2	70
5d	5-iPr	4	2	85
5e	5-F	3	1.5	62
5f	H	3	1,5	35
5g	H	4	3	76

The formation of azide derivatives from the corresponding bromo derivatives of aboved-mentioned isatins can be identified by the IR spectra. Figure 1 displays the IR spectra comparison of representative compounds, including *N*-(4-bromoprop)isatin and corresponding azide derivative, *N*-(4-azidopropyl)isatin. This showed that the stretching vibrations of the two functional groups, C=O of lactam and C=O ketone, are virtually unchanged, whereas a strong absorption band appears at $\nu = 2092$ cm^{-1} in the IR spectrum of azide derivative. This confirms that the conversion of bromide derivatives into azide derivatives has been successful. The ketone carbonyl group of **5a-g** compounds is characteristically absorbed in the region at $\nu = 1738–1726$ cm^{-1}. The characteristic band of >C=O lactam group is located in $\nu = 1622–1620$ cm^{-1} region, in some cases, this absorption band is superimposed by the stronger absorption band of ketone carbonyl group.

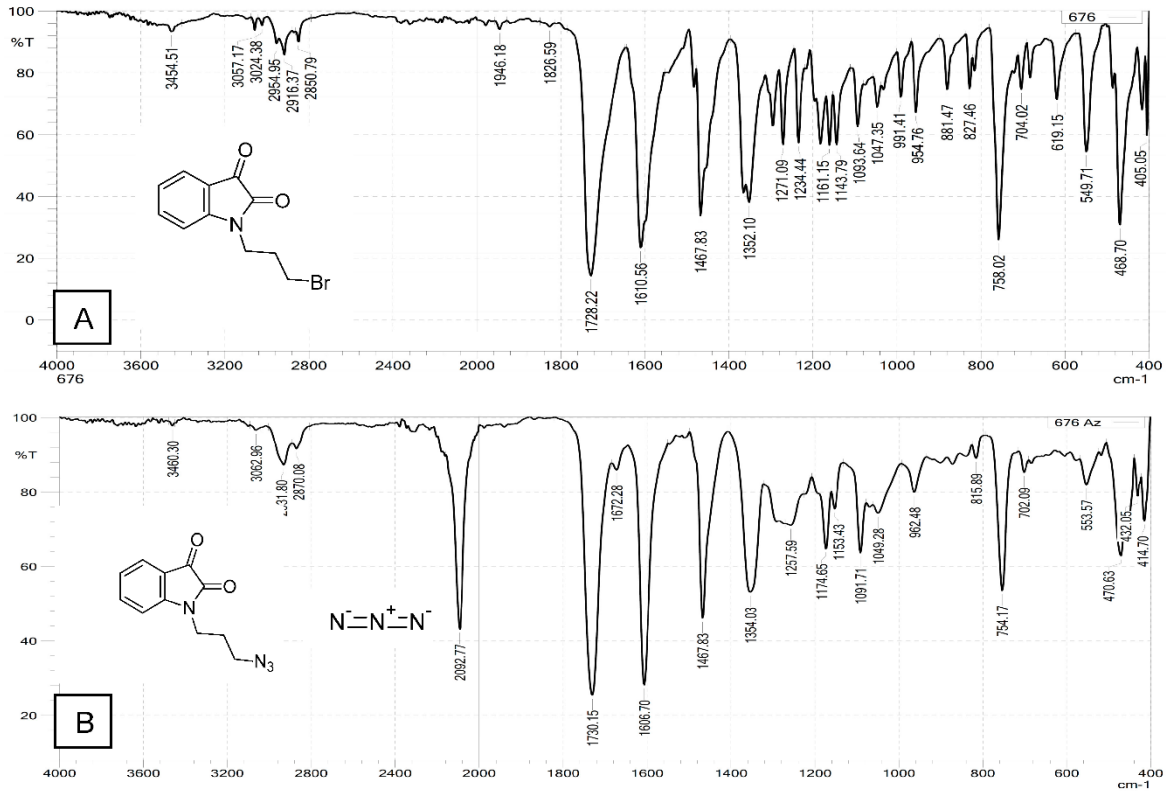


Figure 1. Comparisons of IR spectra of *N*-(3-bromopropyl)isatin **4g** (**A**) and *N*-(3-azidopropyl)isatin **5g** (**B**).

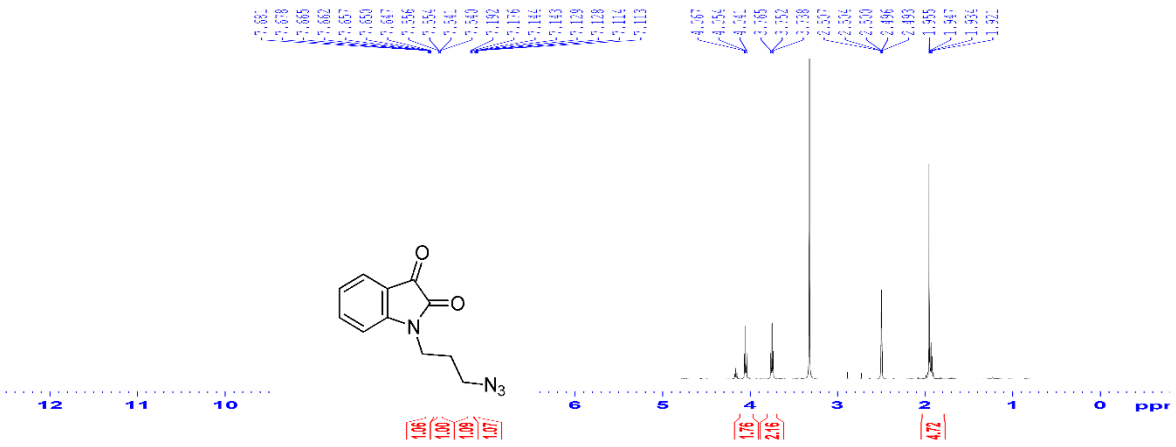


Figure 2. ^{1}H NMR spectra of *N*-(3-azidopropyl)isatin **5g**.

The ^{1}H NMR spectra of **5a-g** compounds show resonance signals of all protons in the molecule, including signals in region at δ = 7.66–7.04 ppm of aromatic protons. The methylene protons in alkane chains attached to nitrogen atom of isatin appear in the region at δ= with δ = 4.05–3.67 ppm for methylene groups associated with nitrogen-isatin. Whereas, methylene group associated with azido group have signals located at low field with δ = 3.39–3.36 ppm. The methylene groups in the middle of the alkane chains have chemical shifts in higher fields (δ = 1.69–1.18 ppm). Alkyl groups attached to benzene aromatic rings have distinct resonance signals, for example, 5-methyl group has δ = 2.27 ppm; 7-methyl, δ = 2.48 ppm.

3. Conclusions

N-(ω-Bromoalkyl)isatins have been synthesized from appropriate insatins and converted into corresponding *N*-(ω-azidoalkyl)isatin derivatives with yields of 35−85%. The structure of azide derivatives is confirmed by ir spectrum and 1H NMR.

4. Experimental

Melting points were determined by open capillary method on STUART SMP3 (BIBBY STERILIN, UK). The IR spectra were recorded on FT-IR Affinity-1S Spectrometer (Shimadzu, Japan) in KBr pellet. The ^{1}H NMR spectra were recorded at 500 MHz (on Avance AV500 Spectrometer, Bruker, Germany) and at 600 MHz (on AvanceNEO Spectrometer, Bruker, Germany), and ^{13}C NMR spectra at 125 and 160 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal standard. ESI-mass spectra were recorded on LC-MS LTQ Orbitrap XL (Thermo Fisher Scientific Inc., USA) in methanol/dichloromethane or methanol using ESI method. The analytical thin-layer chromatography (TLC) was performed on silica gel 60WF_{254} No. 5715 aluminium sheets (Merck, Germany) with toluene:ethyl acetate (1:1 by volume) as solvent system, and spots were visualized directly due to own colour of corresponding isatins. All chemical reagents in high purity (reagent grade for organic synthesis) were purchased from the Merck Chemical Company.

*General Procedure for Synthesis of N-(ω-azidoalkyl)isatins (**5a-g**)*

A reaction mixture consists of *N*-(ω-bromoalkyl)isatins (**4a-g**, 1 mmol), sodium azide (1.5 mmol, 945 mg) and some KI crystals in anhydrous DMF (5 mL) is stirred on a water-bath at temperature of 70−75°C for 1.5−3 h. The reaction is monitored by thin-layer chromatography. After the reaction is over, water (10 ml) is added to the mixture to quench the reaction and to dissolve the inorganic salts. The mixture is extracted with ethyl acetate (3×5 mL). The combined extract is dried with anhydrous sodium sulfate. Filter out the drying agent. After distilling the solvent, the product is isolated from the residue by column chromatography on silica gel with the appropriate solvent system.

***N*-(4-Azidobutyl)-5-methylisatin** (**5a**): From **4a** (1 mmol, 296 mg). Yield: 204 mg. M.p. 48−50 °C. IR (KBr), ν (cm^{-1}): 2928, 2867, 2098, 1737, 1622, 1599, 1491, 1346, 822; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.45 (d, *J* = 2.0, 8.0 Hz, 1H, H-6), 7.34 (d, *J* = 2.0 Hz, 1H, H-4), 7.08 (d, *J* = 8.0 Hz, 1H, H-7), 3.66 (t, *J* = 6.75 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$CH$_2$N$_3$), 3.36 (t, *J* = 6.5 Hz, 2H, >NCH$_2$CH$_2$CH$_2$**CH$_2$**N$_3$), 2.27 (s, 3H, 5-**CH$_3$**), 1.68−1.63 (m, 2H, >NCH$_2$**CH$_2$**CH$_2$CH$_2$N$_3$), 1.61−1.56 (m, 2H, >NCH$_2$CH$_2$**CH$_2$**CH$_2$N$_3$).

***N*-(4-Azidobutyl)-7-methylisatin** (**5b**): From **4b** (1 mmol, 296 mg). Yield: 119 mg. IR (KBr), ν (cm^{-1}): 3024, 2939, 2870, 2092, 1726, 1597, 1485, 1346, 1305, 781; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.46 (d, *J* = 7.0 Hz, 1H, H-4), 7.40 (dd, *J* = 1.5, 7.0 Hz, 1H, H-6), 7.04 (t, *J* = 7.0 Hz, 1H, H-5), 3.85 (t, *J* = 7.0 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$CH$_2$N$_3$), 3.39 (t, *J* = 7.75 Hz, 2H, >NCH$_2$CH$_2$CH$_2$**CH$_2$**N$_3$), 2.48 (s, 3H, 7-**CH$_3$**), 1.69−1.66 (m, 2H, >NCH$_2$**CH$_2$**CH$_2$CH$_2$N$_3$), 1.65−1.59 (m, 2H, >NCH$_2$CH$_2$ **CH$_2$**CH$_2$N$_3$).

***N*-(4-Azidobutyl)-5-ethylisatin** (**5c**): From **4c** (1 mmol, 310 mg). Yield: 190 mg. IR (KBr), ν (cm^{-1}): 2964, 2931, 2870, 2090, 1728, 1618, 1487, 1346, 1168, 827; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.51 (dd, *J* = 1.5, 8.0 Hz, 1H, H-6), 7.38 (d, *J* = 1.5 Hz, 1H, H-4), 7.11 (d, *J* = 8.0 Hz, 1H, H-7), 3.67 (t, *J* = 7.5 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$CH$_2$N$_3$), 3.36 (t, *J* = 6.75 Hz, 2H, >NCH$_2$CH$_2$CH$_2$C**H$_2$**N$_3$), 2.58 (q, *J* = 7.5 Hz, 2H, 5-**CH$_2$**CH$_3$), 1.69−1.63 (m, 2H, >NCH$_2$**CH$_2$**CH$_2$CH$_2$N$_3$), 1.62−1.56 (m, 2H, >NCH$_2$CH$_2$**CH$_2$**CH$_2$N$_3$), 1.16 (t, *J* = 7.5 Hz, 3H, 5-CH$_2$**CH$_3$**).

***N*-(4-Azidobutyl)-5-isopropylisatin** (**5d**): From **5d** (1 mmol, 324 mg). Yield: 243 mg. IR (KBr), ν (cm^{-1}): 2958, 2868, 2092, 1732, 1620, 1597, 1487, 1352, 1174; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.55 (dd, *J* = 2.0, 8.0 Hz, 1H, H-6), 7.42 (d, *J* = 2.0 Hz, 1H, H-4), 7.12 (d, *J* = 8.0 Hz, 1H, H-7), 3.67 (t, *J* = 6.75 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$CH$_2$N$_3$), 3.36 (t, *J* = 6.75 Hz, 2H, >NCH$_2$CH$_2$CH$_2$**CH$_2$**N$_3$), 2.90 [quintet, *J* = 7.0 Hz, 1H, 5-**CH(**CH$_3$)$_2$], 1.69−1.63 (m, 2H,

>NCH$_2$**CH$_2$**CH$_2$CH$_2$N$_3$), 1.61−1.56 (m, 2H, >NCH$_2$CH$_2$**CH$_2$**CH$_2$N$_3$), 1.19 [d, *J* = 7.0 Hz, 6H, 5-CH**CH$_3$)$_2$**].

***N*-(3-Azidopropyl)-5-fluoroisatin** (**5e**): From **5e** (1 mmol, 286 mg). Yield: 154 mg. IR (KBr), ν (cm^{-1}): 3069, 2933, 2873, 2094, 1730, 1620, 1608, 1481, 1261, 1168, 823; ^{1}H NMR (DMSO-*d*$_6$), δ (ppm): 7.5 (td, J_{FH} = 2.75 Hz, J_{HH} = 9.0 Hz, 1H, H-6), 7.45 (dd, J_{HH} = 2.5 Hz, J_{FH} = 7.0 Hz, 1H, H-4), 7.22 (dd, J_{FH} = 3.75 Hz, J_{HH} = 9.0 Hz, 1H, H-7), 3.73 (t, *J* = 6.75 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$N$_3$), 3.44 (t, *J* = 6.75 Hz, 2H, >NCH$_2$CH$_2$**CH$_2$**N$_3$), 1.84 (quintet, *J* = 6.75 Hz, 2H, >NCH$_2$**CH$_2$**CH$_2$N$_3$).

***N*-(3-Azidopropyl)isatin** (**5f**): From **5f** (1 mmol, 268 mg). Yield: 81 mg (35%). IR (KBr), ν (cm^{-1}): 3062, 2931, 2870, 2092, 1730, 1606, 1467, 1354, 1091, 754; ^{1}H NMR (DMSO-*d*$_6$), δ (ppm): 7.66 (td, *J* = 1.5, 8.0 Hz, 1H, H-6), 7.55 (dd, *J* = 0.5, 7.5 Hz, 1H, H-4), 7.18 (d, *J* = 8.0 Hz, 1H, H-7), 7.13 (td, *J* = 0.5, 7.5 Hz, 1H, H-5), 4.05 (t, *J* = 6.25 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$N$_3$), 3.75 (t, *J* = 6.25 Hz, 2H, >NCH$_2$CH$_2$**CH$_2$**N$_3$), 1.93 (quintet, *J* = 6.25 Hz, 2H, >NCH$_2$**CH$_2$**CH$_2$N$_3$).

***N*-(4-Azidobutyl)isatin** (**5g**): From **5g** (1 mmol, 282 mg). Yield: 185 mg. IR (KBr), ν (cm^{-1}): 3062, 2935, 2874, 2069, 1738, 1611, 1468, 1360, 1092, 753; ^{1}H NMR (DMSO-*d*$_6$), δ (ppm): 7.65 (td, *J* = 1.0, 8.0 Hz, 1H, H-6), 7.53 (d, *J* = 7.5 Hz, 1H, H-4), 7.19 (d, *J* = 8.0 Hz, 1H, H-7), 7.12 (t, *J* = 7.5 Hz, 1H, H-5), 3.69 (t, *J* = 7.0 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$CH$_2$N$_3$), 3.56 (t, *J* = 6.75 Hz, 2H, >NCH$_2$CH$_2$CH$_2$**CH$_2$**N$_3$), 1.88 (quintet, *J* = 7.0 Hz, 2H, >NCH$_2$**CH$_2$**CH$_2$CH$_2$N$_3$), 1.74 (sextet, *J* = 7.0 Hz, 2H, >NCH$_2$CH$_2$**CH$_2$**CH$_2$N$_3$).

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

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