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A Cu(I)-promoted one-pot 'S_NAr–click reaction' of fluoronitrobenzenes

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ABSTRACT

A one-pot two-step sequence involving a nucleophilic aromatic substitution (S_NAr) of activated fluorobenzenes with azide nucleophile and in situ Huisgen cycloaddition of the resulting aryl azides with alkynes has been developed for a rapid access to 1,4-substituted triazoles. Control experiments revealed that both the steps are catalyzed by Cu(I) and also the course of reaction as S_NAr followed by [3+2]-cycloaddition.

1. Introduction

The nucleophilic substitution reaction (S_NAr) of activated aryl halides is an important transformation for C–C and C–heteroatom bond formation with aryl rings.[1] These reactions are facilitated by the presence of −M groups like a nitro or a carbonyl *ortho* or *para* to the leaving group in general and with *meta* isomers in some rare cases.[2] Various carbon and heteroatom nucleophiles have been employed in this context.[3] Reports concerning the azide as a nucleophile in S_NAr were mainly limited to the mechanistic investigations.[4–6] In a recent publication,[7] we showed that 1,4-diaryltriazoles can be prepared in one pot from S_NAr of *o*- and *p*-fluoronitrobenzenes with NaN_3 and subsequent Cu-mediated Huisgen [3+2] cycloaddition[8] of intermediate aryl azides[9] with phenyl acetylene and with 2-, 3-, and 4-bromophenyl acetylenes (Fig. 1). Herein we describe a complete compilation of our investigations on a one-pot 'S_NAr–click reaction' and the control experiments establishing the course of the reactions.

2. Results and discussion

Initially, the S_NAr of 2-, 3-, and 4-nitrofluorobenzenes (**1a**–**1c**) with NaN_3 and phenyl acetylene (**2a**) as the dipolarophile was attempted in the absence of any additives. DMSO has been selected as a solvent considering the dependence of rate of S_NAr reactions on the solvent employed.[10] The reactions (Table 1, entries 1–3) were sluggish (heated at 70 °C for 1–3 days) and resulted in products with poor yields. The major product isolated was cycloadduct of phenyl acetylene with sodium azide (4-phenyl-1*H*-1,2,3-triazole, **5a**).[11] In the case of 2-nitrofluorobenzene (**1a**) we could isolate 1,4-diaryltriazole (**3aa**) in only 13% yield.[6] The S_NAr of *m*-isomer **1b** gave exclusively **5a** when the reaction was conducted at 70 °C and when heated at 120 °C, a 1:1 mixture of 1,4- and 1,5-diaryl triazoles **3ba**[12] and **4ba**[13] was isolated in 6% yield.[14] In the case of 4-nitrofluorobenzene (**1c**), after 2 days at 70 °C, a 1:1 mixture of 1,4-disubstituted triazole **3ca**[15] and 1,5-disubstituted triazole **4ca**[16] in 10% yield was obtained.[14]

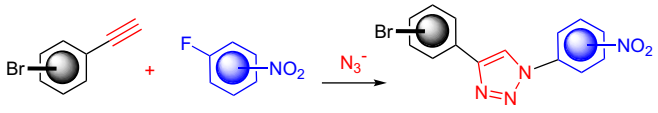

Figure 1. One-pot S_NAr–click reaction for 1,4-diaryltriazoles.

The yields and the regioselectivity dramatically improved when the reactions were carried out under standard 'click reaction' conditions.[9a] The employed conditions involve the heating of a suspension of fluoronitrobenzene (1 equiv), phenyl acetylene (1 equiv) in 9:1 DMSO–H_2O, L-proline (20 mol %), Na_2CO_3 (20 mol %), NaN_3 (1.2 equiv), sodium ascorbate (10 mol %), and $CuSO_4 \cdot 5H_2O$ (5 mol %) until the completion of the reaction. In the case of 1-fluoro-2-nitrobenzene (**1a**) the yield increased from 13% to 79%. The substrate 1-fluoro-3-nitrobenzene (**1b**) was difficult to substitute even under harsh conditions and yielded regioselectively 1-(3-nitrophenyl)-4-phenyl-1*H*-1,2,3-triazole (**3ba**) in 11% yield. The one-pot 'S_NAr–click reaction' of 1-fluoro-4-nitrobenzene (**1c**) was slow and took nearly 2 days for completion and gave exclusively 1,4-isomer **3ca** in 75% yield.

As a control, the S_NAr of fluoronitrobenzenes **1a**–**1c** was carried out with the triazole **5a** (entries 8–10) under similar conditions. The reactions in general were sluggish and resulted in poor yields revealing the activation of S_NAr by Cu(I) catalyst[17] and also that the sequence of reactions as S_NAr followed by cycloaddition. To obtain more information about the role of Cu(I) catalyst on S_NAr, the azide displacement reactions of **1a**–**1c** were carried out under click conditions at room temperatures. The reactions were smooth and took 6 h (**1a**) and 12 h (**1c**) and provided the corresponding azido

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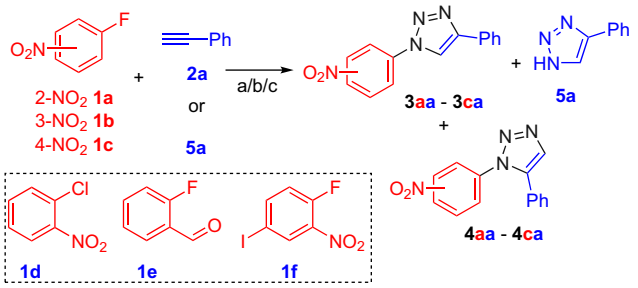
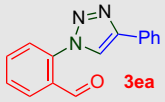
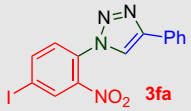
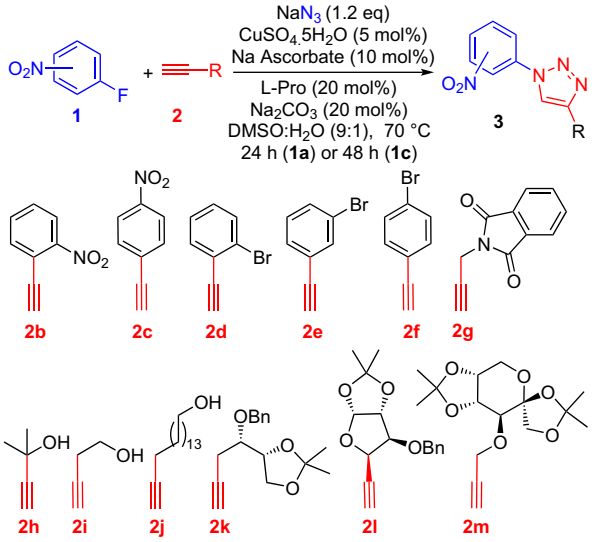
Table 1
Optimization of one-pot S_NAR with azide and azide–alkyne cycloaddition



Entry	Reactants		Conditions (time/temp)	Products/yield		
				3	4	5
1	**1a**	**2a**	a (24 h/70 °C)	13%	—	67%
2	**1b**	**2a**	a (72 h/70 °C)	—	—	71%
3	**1b**	**2a**	a (72 h/120 °C)	3%	3%	89%[a]
4	**1c**	**2a**	a (48 h/70 °C)	5%	5%	87%[a]
5	**1a**	**2a**	b (24 h/70 °C)	79%	—	—
6	**1b**	**2a**	b (72 h/120 °C)	11%	—	67%
7	**1c**	**2a**	b (48 h/70 °C)	75%	—	—
8	**1a**	**5a**	c (48 h/70 °C)	9%	—	—
9	**1b**	**5a**	c (72 h/120 °C)	—	—	—
10	**1c**	**5a**	c (48 h/70 °C)	4%	—	—
11	**1d**	**2a**	b (24 h/70 °C)	71%	—	—
12	**1e**	**2a**	b (24 h/70 °C)	15%	 **3ea** 15%	
13	**1f**	**2a**	b (24 h/70 °C)	61%	 **3fa** 61%	

Reagents and Conditions: a) NaN_3, DMSO-H_2O; b) NaN_3, DMSO-H_2O, $CuSO_4.5H_2O$, Na ascorbate, L-Proline, Na_2CO_3; c) **5a**, under conditions b.
[a] Yields base on HPLC.

Table 2
The one-pot 'S_NAr–click reaction' employing functionalized alkynes **2b**–**2m**



Entry	Reactants		Product	Yield
1	**1a**	**2b**	**3ab**	61%
2	**1a**	**2c**	**3ac**	64%
3	**1a**	**2d**	**3ad**	65%
4	**1a**	**2e**	**3ae**	71%
5	**1a**	**2f**	**3af**	57%
6	**1a**	**2g**	**3ag**	68%
7	**1a**	**2h**	**3ah**	73%
8	**1a**	**2i**	**3ai**	71%
9	**1a**	**2j**[22]	**3aj**	79%
10	**1a**	**2k**[23]	**3ak**	65%
11	**1a**	**2l**[24]	**3al**	71%
12	**1a**	**2m**[25]	**3am**	78%
13	**1c**	**2d**	**3cd**	83%
14	**1c**	**2e**	**3ce**	81%
15	**1c**	**2f**	**3cf**	81%
16	**1c**	**2g**	**3cg**	61%
17	**1c**	**2h**	**3ch**	63%
18	**1c**	**2i**	**3ci**[26]	61%
19	**1c**	**2m**	**3cm**	71%

benzenes in 79% and 91%, respectively. With **1b**, starting compound remained unchanged even at 60 °C. As expected, the azide displacement reactions of **1a** and **1c** without any additives were not facile and starting compounds remain unchanged even after prolonged heating. Thus, the room temperature azido displacement with **1a** and **1c** under click reaction conditions revealed a significant role of Cu(I) catalyst over the S_NAR reactions.

The reaction is even applicable for chloro displacement, as in the case of 1-chloro-2-nitrobenzene (**1d**, entry 11). With the less activated 2-fluorobenzaldehyde (**1e**, entry 12), the S_NAr reaction was sluggish and the corresponding 1,4-diaryltriazole **3ea** was obtained in poor yield. The 1-fluoro-4-iodo-2-nitrobenzene (**1f**, entry 13) has been employed as a substrate to find out the compatibility of other leaving groups and found that fluorine was displaced selectively leaving the iodo group intact. The structural characterization of all the compounds was carried out with the help of spectral and analytical data and the structures of **4ba**, **3fa**, and **3ch** (Table 2, entry 17) were further confirmed by single crystal X-ray structural analyses (Fig. 2a and b).[18–20]

When we are at an advanced stage, the S_NAr of *o*-fluoronitrobenzene employing Cu(I) generated in situ by redox process was reported.[6] It has been indicated that when Cu(I) catalyst (in ^tBuOH solvent) was employed directly, the reactions resulted in poor yields. This is anticipated by considering the dramatic influence of solvents on the rate of aromatic nucleophilic substitution reactions of azide ion, which indeed has been verified theoretically.[21]

The one-pot 'S_NAr–click reactions' of **1a** and **1c** have been generalized by employing various functionalized terminal alkynes, which include the nitroaryl alkynes, long chain aliphatic alkynes, and various sugar derived alkynes. The reactions are smooth and resulted exclusively with 1,4-disubstituted-1,2,3-triazoles (Table 2).

3. Conclusions

To conclude, a three-component one-pot 'S_NAr–click reaction' has been explored by employing *o*- and *p*-nitrofluorobenzenes and a diverse set of alkynes. Control experiments reveal the course of the reaction as S_NAr with azide nucleophile followed by the cycloaddition of the resulting nitroazidobenzene intermediate and both the reactions being catalyzed by Cu(I). The reactions are generally regioselective and various commonly employed protecting groups are found to be compatible with the conditions employed.

4. Experimental

4.1. General methods

All experiments involving the heating of NaN_3 solutions were performed in a well-ventilated fume hood and behind a blast shield.

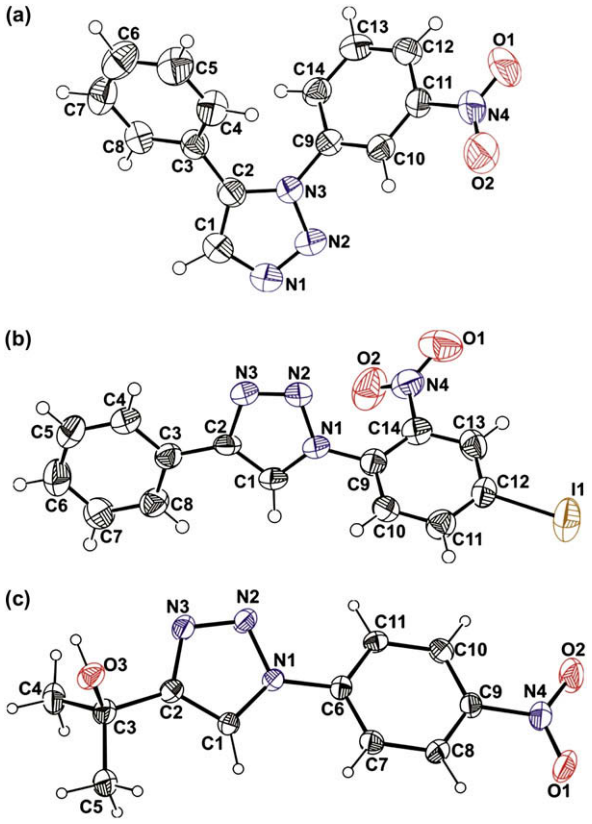


Figure 2. The molecular structures of compounds (a) **4ba**, (b) **3fa**, and (c) **3ch**.

During the work up, use of strong acids and also dichloromethane is avoided. The reactions were carried out in DMSO (distilled from CaH_2 prior to use) under argon atmosphere. Column chromatography was carried out by using Spectrochem silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are measured at 25 °C and given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$ or Nujol and reported in wave number (cm^{-1}). ^{1}H and ^{13}C NMR chemical shifts are reported in $CDCl_3$ or DMSO-d_6 with $CHCl_3$ (7.27 ppm for ^{1}H, 77 ppm for ^{13}C) and DMSO (2.50 ppm for ^{1}H, 39.5 ppm for ^{13}C) as standards and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

4.2. General procedure A (products precipitate from the reaction mixture)

Fluoronitrobenzene (100 mg, 0.71 mmol) was mixed with phenyl acetylene (72 mg, 0.71 mmol) in 9:1 DMSO–H_2O (10 mL). To the mixture were added L-proline (16 mg, 0.142 mmol), Na_2CO_3 (15 mg, 0.142 mmol), NaN_3 (55 mg, 0.852 mmol), sodium ascorbate (14 mg, 0.071 mmol), and $CuSO_4 \cdot 5H_2O$ (9 mg, 0.036 mmol). The mixture was stirred for 24–48 h at 70 °C (bath temperature) and then the mixture was poured into 30 mL of ice-cold water. The solid residue was filtered and crystallized from appropriate solvent systems to procure white to yellow crystalline solids in 57–83% yield.

4.3. General procedure B (3aa, 4ba, 4ca, 3ad, 3ai, 3ak, 3al, 3am, 3cd, 3cm: products purified by column chromatography)

The reactions were carried out as described above and after completion, the contents were poured into 30 mL of water and combined water layer was thoroughly extracted with ethyl acetate (3×25 mL). Organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude solid was purified by column chromatography over 60–120 silica gel using ethyl acetate–light petroleum (1:4) to obtain white to yellow solids (65–77%).

4.3.1. 1-(2-Nitrophenyl)-4-phenyl-1H-1,2,3-triazole[6] (**3aa**)

Mp: 140–141 °C (lit. 144–145 °C). IR (Nujol): ν 3143, 2725, 1641, 1605, 1526, 1507, 1462, 1376, 1356, 1227 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 (tt, J=1.2, 7.3 Hz, 1H), 7.49–7.53 (m, 2H), 7.87 (ddd, J=2.2, 7.1, 9.1 Hz, 1H), 7.94–7.97 (m, 2H), 7.98–8.02 (m, 2H), 7.87 (dd, J=1.0, 8.1 Hz, 1H), 9.20 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 120.7 (d), 125.4 (d, 2C), 125.6 (d), 127.4 (d), 128.5 (d), 129.1 (d, 3C), 129.8 (s), 131.3 (s), 134.5 (d), 144.0 (s), 147.1 (s). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.99; H, 3.67; N, 21.19.

4.3.2. 1-(3-Nitrophenyl)-4-phenyl-1H-1,2,3-triazole[12] (**3ba**)

Mp: 204–205 °C (lit. 198–200 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.54 (m, 3H), 7.78 (t, J=8.21 Hz, 1H), 7.91–7.96 (m, 2H), 8.25–8.36 (m, 2H), 8.32 (s, 1H), 8.66 (t, J=2.15 Hz, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 115.0 (d), 120.4 (d), 123.5 (d), 125.8 (d, 2C), 126.3 (d), 128.9 (d), 129.5 (d, 2C), 130.2 (s), 132.0 (d), 137.5 (s), 148.1 (s), 148.9 (s). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.06; H, 3.88; N, 20.89.

4.3.3. 1-(3-Nitrophenyl)-5-phenyl-1H-1,2,3-triazole[13] (**4ba**)

Mp: 133–134 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21–7.26 (m, 2H), 7.37–7.43 (m, 3H), 7.58–7.66 (m, 1H), 7.71 (td, J=1.8, 8.2 Hz, 1H), 7.87 (s, 1H), 8.28–8.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.1 (d), 123.7 (d), 126.1 (d), 128.8 (d, 2C), 129.3 (d, 2C), 130.0 (d), 130.3 (d), 130.4 (d), 133.9 (s), 137.6 (s), 137.9 (s), 148.7 (s). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.21; H, 3.75; N, 20.97.

Crystal data for **4ba** ($C_{14}H_{10}N_4O_2$): M=266.26, crystal dimensions 0.62×0.23×0.01 mm^3, monoclinic, space group $P2_1/n$, a=7.533(11), b=18.94(3), c=9.546(14) Å, β=98.37(3)°, V=1347(3) Å^3, Z=4; ρ_{calcd}=1.313 g cm^{-3}, μ(Mo Kα)=0.092 mm^{-1}, F(000)=552, T=297(2) K, $2\theta_{max}$=50.00°, 6348 reflections collected, 2346 unique, 1322 observed ($I>2\sigma(I)$) reflections, 221 refined parameters, R value 0.0542, $wR2$=0.1111 (all data R=0.1090, $wR2$=0.1366), S=1.002, minimum and maximum transmission 0.9450 and 0.9991, respectively, maximum and minimum residual electron densities +0.216and −0.169 e Å^{-3}.

4.3.4. 1-(4-Nitrophenyl)-4-phenyl-1H-1,2,3-triazole[15] (**3ca**)

Mp: 236–238 °C. IR ($CHCl_3$): ν 3018, 2925, 2855, 1598, 1521, 1348, 1215, 855, 759 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.41–7.56 (m, 3H), 7.93–7.98 (m, 2H), 8.23–8.28 (m, 2H), 8.47–8.51 (m, 2H), 9.48 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 120.1 (d), 120.6 (d, 2C), 125.5 (d, 2C), 125.7 (d, 2C), 128.7 (d), 129.2 (d, 2C), 129.8 (s), 140.9 (s), 146.8 (s), 148.0 (s). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04; Found: C, 63.31; H, 3.53; N, 20.91.

4.3.5. 1-(4-Nitrophenyl)-5-phenyl-1H-1,2,3-triazole[16] (**4ca**)

Mp: 165–166 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21–7.26 (m, 2H), 7.36–7.46 (m, 3H), 7.54–7.61 (m, 2H), 7.86 (s, 1H), 8.26–8.34 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 126.0 (d), 126.1 (d), 127.5 (d, 2C), 127.8 (d, 2C), 128.3 (d, 2C), 130.1 (d, 2C), 130.1 (s), 140.9 (s), 144.7 (s), 146.2 (s). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.11; H, 3.73; N, 20.97.

4.3.6. 2-(4-Phenyl-1H-1,2,3-triazol-1-yl)benzaldehyde (**3ea**)

IR (Nujol): ν 3017, 1696, 1601, 1456, 1216, 1024, 694, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.49 (m, 3H), 7.58 (dd, J=1.4, 7.8 Hz, 1H), 7.66–7.70 (m, 1H), 7.75–7.82 (m, 2H), 7.92–7.94 (m, 1H), 8.13 (dd, J=1.6, 7.7 Hz, 1H), 8.19 (s, 1H), 9.99 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.5 (d), 125.3 (d), 125.9 (d, 2C), 128.7 (d), 129.0 (d, 2C),

129.5 (s), 129.6 (d), 130.1 (d), 130.4 (s), 134.7 (d), 138.3 (s), 148.5 (s), 188.5 (d). Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.31; H, 4.49; N, 16.80.

*4.3.7. 1-(4-Iodo-2-nitrophenyl)-4-phenyl-1H-1,2,3-triazole (**3fa**)*

Mp: 199–201 °C. IR (Nujol): ν 2926, 2854, 146, 1377, 1215, 764, 669 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.23–7.40 (m, 3H), 7.57 (d, J=8.1 Hz, 1H), 7.81–7.91 (m, 2H), 8.16 (d, J=7.3 Hz, 1H), 8.33 (s, 1H), 8.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 93.6 (s), 120.3 (d), 124.0 (d, 2C), 126.7 (d), 126.9 (d), 127.2 (d, 2C), 127.4 (s), 128.2 (s), 132.0 (d), 141.2 (d), 142.5 (s), 146.0 (s). Anal. Calcd for $C_{14}H_9IN_4O_2$: C, 42.88; H, 2.31; N, 14.29. Found: C, 42.93; H, 2.27; N, 14.24.

Crystal data for **3fa** ($C_{14}H_9IN_4O_2$): M=392.15, crystal dimensions 0.68×0.15×0.05 mm^3, monoclinic, space group $P2_1/c$, a=5.5301(12), b=17.085(4), c=15.094(3) Å, β=93.124(4)°, V=1424.0(5) $Å^3$, Z=4; ρ_{calcd}=1.829 g cm^{-3}, μ(Mo Kα)=2.258 mm^{-1}, F(000)=760, T=297(2) K, $2\theta_{max}$=50.00°, 7072 reflections collected, 2501 unique, 1831 observed ($I>2\sigma(I)$) reflections, 190 refined parameters, R value 0.0548, $wR2$=0.1245 (all data R=0.0762, $wR2$=0.1362), S=1.094, minimum and maximum transmission 0.3089 and 0.8955, respectively, maximum and minimum residual electron densities +1.454 and −0.679 e $Å^{-3}$.

*4.3.8. 1,4-Bis(2-nitrophenyl)-1H-1,2,3-triazole (**3ab**)*

Mp: 215–216 °C. IR ($CHCl_3$): ν 2924, 2854, 1377, 761 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.69 (t, J=7.3 Hz, 1H), δ 7.83 (t, J=7.5 Hz, 1H), 7.87–7.91 (m, 2H), 7.96–8.02 (m, 3H), 8.27 (d, J=7.8 Hz, 1H), 9.15 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 122.7 (s), 124.3 (d), 125.0 (d), 125.7 (d), 127.7 (d), 128.8 (s), 130.0 (d), 130.6 (d), 131.6 (d), 132.8 (d), 134.6 (d), 142.6 (s), 144.0 (s), 148.2 (s). Anal. Calcd for $C_{14}H_9N_5O_4$: C, 54.02; H, 2.91; N, 22.50. Found: C, 53.98; H, 2.88; N, 22.46.

*4.3.9. 1-(2-Nitrophenyl)-4-(4-nitrophenyl)-1H-1,2,3-triazole (**3ac**)*

Mp: 290–292 °C. IR (Nujol): ν 3147, 1604, 1534, 1511, 1459, 1339, 1108, 1024, 854, 756 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.88–7.92 (m, 1H), 7.99–8.05 (m, 2H), 7.21 (d, J=8.5 Hz, 2H), 8.28 (d, J=8.0 Hz, 1H), 8.39 (d, J=8.8 Hz, 2H), 9.45 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.6 (d, 2C), 124.9 (d), 125.8 (d), 126.3 (d, 2C), 127.6 (d), 128.9 (s), 131.6 (d), 134.7 (d), 136.2 (s), 144.0 (s), 145.2 (s), 147.0 (s). Anal. Calcd for $C_{14}H_9N_5O_4$: C, 54.02; H, 2.91; N, 22.50. Found: C, 54.10; H, 2.87; N, 22.44.

*4.3.10. 4-(2-Bromophenyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole (**3ad**)*

Mp: 125 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (dt, J=1.7, 7.8 Hz, 1H), 7.46 (dt, J=1.2, 7.8 Hz, 1H), 7.68 (dd, J=1.0, 8.1 Hz, 1H), 7.73 (br s, 1H), 7.75 (br s, 1H), 7.83 (dt, J=1.6, 8.1 Hz, 1H), 8.12 (dd, J=1.5, 8.2 Hz, 1H), 8.24 (dd, J=1.8, 7.8 Hz, 1H), 8.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.3 (s), 124.3 (d), 125.7 (d, 2C), 127.4 (s), 127.8 (d), 128.1 (s), 129.7 (d), 130.7 (d), 130.9 (d), 133.7 (d, 2C), 142.0 (s), 145.9 (s). Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23. Found: C, 48.98; H, 2.39; Br, 23.19; N, 16.51.

*4.3.11. 4-(3-Bromophenyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole (**3ae**)*

Mp: 101 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.02–7.44 (m, 3H), 7.58–7.82 (m, 4H), 7.94–8.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.4 (d), 123.1 (s), 124.5 (d), 125.7 (d), 126.9 (d), 127.90 (d), 129.0 (d), 130.5 (d), 130.8 (d), 131.5 (d), 131.8 (s), 133.8 (s), 144.4 (s), 146.9 (s). Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23. Found: C, 48.76; H, 2.52; Br, 23.42; N, 16.11.

*4.3.12. 4-(4-Bromophenyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole (**3af**)*

Mp: 136–137 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.50 (m, 1H), 7.57 (dt, J=2.2, 8.7 Hz, 1H), 7.65–7.88 (m, 5H), 8.06 (s, 1H), 8.06–8.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.0 (d), 122.7 (s), 125.6 (d), 127.5 (d, 2C), 127.9 (d), 129.8 (s), 130.8 (d), 132.2 (d, 2C), 132.4 (s), 133.8 (d), 144.4 (s), 147.4 (s). Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23. Found: C, 48.44; H, 2.40; Br, 23.11; N, 16.41.

*4.3.13. 2-((1-(2-Nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-isoindoline-1,3-dione (**3ag**)*

Mp: 213–214 °C. IR (Nujol): ν 2921, 2724, 1765, 1717, 1586, 1604, 1528, 1463, 1376, 1312, 1041, 934, 714 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 4.95 (s, 2H), 7.77–7.96 (m, 7H), 8.16–8.21 (m, 1H), 8.68 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 32.9 (t), 123.4 (d, 2C), 124.7 (d), 125.6 (d), 127.6 (d), 129.1 (s), 131.3 (d), 131.7 (s), 134.5 (d), 134.8 (d, 2C), 143.4 (s, 2C), 144.1 (s), 167.5 (s, 2C). Anal. Calcd for $C_{17}H_{11}N_5O_4$: C, 58.45; H, 3.17; N, 20.05; Found: C, 58.50; H, 3.20; N, 20.10.

*4.3.14. 2-(1-(2-Nitrophenyl)-1H-1,2,3-triazol-4-yl)propan-2-ol (**3ah**)*

Mp: 111–113 °C. IR (Nujol): ν 3349, 3149, 2924, 1607, 1538, 1506, 1462, 1376, 1362, 1234 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 1.53 (s, 6H), 5.34 (s, 1H), 7.76–7.82 (m, 1H), 7.84–7.85 (m, 1H), 7.89–7.98 (m, 1H), 8.18 (dd, J=1.4, 8.1 Hz, 1H), 8.45 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 30.7 (q, 2C), 67.2 (s), 121.9 (d), 125.5 (d), 127.2 (d), 129.4 (s), 130.8 (d), 134.3 (d), 144.2 (s), 156.8 (s). Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.18; H, 4.82; N, 22.52.

*4.3.15. 2-(1-(2-Nitrophenyl)-1H-1,2,3-triazol-4-yl)ethanol (**3ai**)*

Mp: 92–93 °C. IR (Nujol): ν 3326, 3137, 2724, 1605, 1536, 1503, 1460, 1376, 1365, 1241 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 2.88 (t, J=6.9 Hz, 2H), 3.67–3.75 (m, 2H), 4.83 (t, J=5.1 Hz, 1H) 7.76–7.81 (m, 1H), 7.84 (d, J=0.8 Hz, 1H), 7.89–7.98 (m, 1H), 8.15–8.20 (m, 1H), 8.43 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 29.1 (t), 60.3 (t), 123.8 (d), 125.5 (d), 127.2 (d), 129.4 (s), 130.9 (d), 134.3 (d), 144.2 (s), 145.7 (s). Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.34; H, 4.35; N, 23.84.

*4.3.16. 15-(1-(2-Nitrophenyl)-1H-1,2,3-triazol-4-yl)pentadecan-1-ol (**3aj**)*

Mp: 95–96 °C. IR ($CHCl_3$): ν 3420, 3019, 2928, 2855, 2400, 1610, 1538, 1505, 1466, 1354, 1215, 1042, 7557, 668 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.22 (s, 18H), 1.31–1.34 (m, 4H), 1.38 (q, J=6.6 Hz, 2H), 1.65 (q, J=7.3 Hz, 2H), 2.70 (t, J=7.4 Hz, 2H), 3.35 (dd, J=6.2, 11.8 Hz, 2H), 4.35 (t, J=4.9 Hz, 1H), 7.79–7.84 (m, 2H), 7.93 (t, J=7.7 Hz, 1H), 8.17 (d, J=7.8 Hz, 1H), 8.42 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.8 (t), 25.5 (t), 28.5 (t), 28.7 (t), 28.8 (t), 29.0 (t, 2C), 29.1 (t, 4C), 29.1 (t, 2C), 32.6 (t), 60.8 (t), 123.1 (d), 125.4 (d), 127.1 (d), 129.3 (s), 130.8 (d), 134.2 (d), 144.1 (s), 147.9 (s). Anal. Calcd for $C_{23}H_{36}N_4O_3$: C, 66.32; H, 8.71; N, 13.45. Found: C, 66.26; H, 8.77; N, 13.49.

*4.3.17. 4,5-O-Isopropylidene-3-O-benzyl-1-deoxy-1-C-[(1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)]-D-erythritol (**3ak**)*

Pale yellow oil. $[\alpha]_D^{25}$ +7.0 (c 3.5, $CHCl_3$). IR ($CHCl_3$): ν 3144, 2987, 2885, 1720, 1609, 1588, 1537, 1506, 1454, 1355, 1214, 1071, 852, 748, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.45 (s, 3H), 3.06 (dd, J=6.7, 15.2 Hz, 1H), 3.26 (dd, J=4.1, 15.2 Hz, 1H), 3.86–3.94 (m, 2H), 4.02–4.17 (m, 2H), 4.61 (s, 2H), 7.24–7.31 (m, 5H), 7.54 (dd, J=1.6, 7.6 Hz, 1H), 7.65 (s, 1H), 7.67 (dt, J=1.7, 7.7 Hz, 1H), 7.77 (dt, J=1.8, 7.7 Hz, 1H), 8.06 (dd, J=1.7, 7.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.8 (q), 26.2 (q), 27.0 (t), 65.9 (t), 72.2 (t), 76.5 (d), 78.2 (d), 108.8 (s), 123.5 (d), 125.0 (d), 127.0 (d), 127.2 (d), 127.4 (d, 2C), 127.9 (d, 2C), 129.6 (s), 130.2 (d), 133.4 (d), 137.7 (s), 143.9 (s), 144.2 (s). Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.19; H, 5.67; N, 13.18.

*4.3.18. (4R)-1,2-O-Isopropylidene-3-O-benzyl-4-C-[(1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)]-L-threofuranose (**3al**)*

Pale yellow oil. $[\alpha]_D^{25}$ +5.6 (*c* 1.2, $CHCl_3$). IR ($CHCl_3$): ν 3018, 2923, 1725, 1609, 1539, 1508, 1454, 1355, 1076, 1026, 753, 666 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.58 (s, 3H), 4.23 (d, *J*=3.0 Hz, 1H), 4.46 (dd, *J*=12.0, 19.2 Hz, 2H), 4.75 (d, *J*=3.7 Hz, 1H), 5.64 (d, *J*=3.0 Hz, 1H), 6.06 (d, *J*=3.7 Hz, 1H), 7.14–7.19 (m, 2H), 7.24–7.30 (m, 3H), 7.46–7.51 (m, 1H), 7.65–7.81 (m, 2H), 7.96 (d, *J*=0.6 Hz, 1H), 8.07–8.11 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.2 (q), 26.7 (q), 72.5 (t), 76.1 (d), 82.4 (d), 83.0 (d), 104.6 (d), 112.1 (s), 125.3 (d), 125.5 (d), 127.5 (d, 2C), 127.8 (d), 128.4 (d, 2C), 129.6 (d), 130.1 (s), 130.7 (d), 133.7 (d), 137.1 (s), 144.2 (s), 144.4 (s). Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.31; H, 5.12; N, 12.74.

*4.3.19. 1,2:4,5-Di-O-isopropylidene-3-O-[(1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl]-D-fructopyranose (**3am**)*

Pale yellow oil. $[\alpha]_D^{25}$ −62.23 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): ν 3018, 2935, 2400, 1734, 1609, 1541, 1508, 1457, 1382, 1218, 1117, 1082, 1017, 882, 768, 668 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.49 (s, 3H), 1.59 (s, 3H), 3.62 (d, *J*=7.3 Hz, 1H), 3.92 (d, *J*=8.59 Hz, 1H), 4.05–4.14 (m, 3H), 4.23 (dd, *J*=1.9, 5.6 Hz, 1H), 4.39 (dd, *J*=5.9, 7.2 Hz, 1H), 4.94 (d, *J*=12.7 Hz, 1H), 5.17 (d, *J*=12.7 Hz, 1H), 7.62 (dd, *J*=1.4, 7.6 Hz, 1H), 7.72 (dd, *J*=1.6, 7.8 Hz, 1H), 7.78 (dd, *J*=1.7, 7.5 Hz, 1H), 7.86 (s, 1H), 8.08 (dd, *J*=1.6, 7.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5 (q), 25.8 (q), 26.4 (q), 27.8 (q), 59.7 (t), 64.2 (t), 71.3 (t), 73.4 (d), 76.2 (d), 77.0 (d), 103.8 (s), 108.7 (s), 111.6 (s), 123.8 (d), 125.1 (d), 127.2 (d), 129.5 (s), 130.5 (d), 133.6 (d), 144.0 (s), 145.4 (s). Anal. Calcd for $C_{21}H_{26}N_4O_8$: C, 60.39; H, 7.43. Found: C, 60.44; H, 7.39.

*4.3.20. 4-(2-Bromophenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (**3cd**)*

Mp: 170–171 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (ddd, *J*=1.8, 7.4, 9.2 Hz, 1H), 7.47 (dt, *J*=1.2, 7.8 Hz, 1H), 7.69 (dd, *J*=1.2, 7.9 Hz, 1H), 8.04 (t, *J*=2.6 Hz, 1H), 8.09 (t, *J*=2.6 Hz, 1H), 8.2 (dd, *J*=1.6, 7.8 Hz, 1H), 8.42 (t, *J*=2.6 Hz, 1H), 8.47 (t, *J*=2.6 Hz, 1H), 8.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.5 (d), 121.3 (s), 124.1 (d), 124.9 (d), 125.6 (d), 127.9 (d), 130.0 (d), 130.2 (d), 130.8 (d), 131.9 (s), 133.8 (d), 141.1 (s), 146.7 (s), 147.3 (s). Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23. Found: C, 48.57; H, 2.90; Br, 22.89; N, 16.12.

*4.3.21. 4-(3-Bromophenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (**3ce**)*

Mp: 217–218 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.36–7.54 (m, 2H), 7.96 (dt, *J*=1.8, 7.6 Hz, 1H), 8.14 (t, *J*=1.6 Hz, 1H), 8.26, 8.31, 8.45, 8.51 (4br m, 4H), 9.47 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.6 (d, 2C), 120.8 (d), 122.6 (s), 123.8 (d), 124.1 (d), 126.5 (d), 127.4 (d), 129.1 (d), 129.4 (d), 130.5 (s), 139.3 (s), 145.0 (s), 145.1 (s). Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23. Found: C, 48.63; H, 2.88; Br, 23.29; N, 16.48.

*4.3.22. 4-(4-Bromophenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (**3cf**)*

Mp: 149–150 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 (t, *J*=2.2 Hz, 1H), 7.64 (t, *J*=2.2 Hz, 1H), 7.77 (t, *J*=2.2 Hz, 1H), 7.82 (t, *J*=2.2 Hz, 1H), 8.01 (t, *J*=2.2 Hz, 1H), 8.06 (t, *J*=2.2 Hz, 1H), 8.28 (t, *J*=2.2 Hz, 1H), 8.44 (t, *J*=2.2 Hz, 1H), 8.48 (t, *J*=2.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.2 (d), 118.5 (d, 2C), 119.9 (s), 123.7 (d, 2C), 125.5 (d, 2C), 127.3 (s), 130.1 (d, 2C), 139.1 (s), 144.9 (s), 145.2 (s). Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23. Found: C, 48.70; H, 2.40; Br, 23.43; N, 16.01.

*4.3.23. 2-((1-(4-Nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-isoindoline-1,3-dione (**3cg**)*

Mp: 266–268 °C. IR ($CHCl_3$): ν 3129, 2725, 1764, 1717, 1594, 1520, 1503, 1455, 1338, 1246, 1043, 935, 857, 773, 718 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 4.95 (s, 2H), 7.86–7.93 (m, 4H), 8.18 (d, *J*=9.1 Hz, 2H), 8.42 (d, *J*=9.1 Hz, 2H), 9.00 (s, 1H). ^{13}C (125 MHz, DMSO-d_6) δ 32.9 (t), 120.6 (d, 2C), 121.8 (d), 123.3 (d, 2C), 125.6 (d, 2C), 131.7 (s, 2C), 134.6 (d, 2C), 140.8 (s), 144.4 (s), 146.7 (s), 167.4 (s, 2C). Anal. Calcd for $C_{17}H_{11}N_5O_4$: C, 58.45; H, 3.17; N, 20.05; Found: C, 58.51; H, 3.21; N, 19.99.

*4.3.24. 2-(1-(4-Nitrophenyl)-1H-1,2,3-triazol-4-yl)propan-2-ol (**3ch**)*

Mp: 121–122 °C. IR (Nujol): ν 3401, 3019, 2982, 1599, 1530, 1507, 1344, 1235, 1215, 1036, 855, 757, 668 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.54 (s, 6H), 5.34 (s, 1H), 8.23 (dd, *J*=2.2, 7.1 Hz, 2H), 8.41 (dd, *J*=2.2, 7.1 Hz, 2H), 8.81 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.5 (q, 2C), 67.0 (s), 119.3 (d), 120.3 (d, 2C), 125.5 (d, 2C), 141.1 (s), 146.5 (s), 157.6 (s). Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.29; H, 4.93; N, 22.61.

Crystal data for **3ch** ($C_{11}H_{12}N_4O_3$): *M*=248.25, crystal dimensions 0.30×0.12×0.06 mm^3, monoclinic, space group $P2_1/c$, *a*=13.948(4), *b*=12.875(4), *c*=6.5711(18) Å, β=93.463(5)°, *V*=1177.9(6) $Å^3$, *Z*=4; ρ_{calcd}=1.400 g cm^{-3}, μ(Mo Kα)=0.105 mm^{-1}, *F*(000)=520, *T*=133(2) K, $2\theta_{max}$=51.00°, 8641 reflections collected, 2183 unique, 1969 observed ($I>2\sigma(I)$) reflections, 211 refined parameters, *R* value 0.0599, *wR2*=0.1505 (all data *R*=0.0651, *wR2*=0.1526), *S*=1.155, minimum and maximum transmission 0.9691 and 0.9937, respectively, maximum and minimum residual electron densities +0.353 and −0.224 e $Å^{-3}$.

*4.3.25. 2-(1-(4-Nitrophenyl)-1H-1,2,3-triazol-4-yl)ethanol[23] (**3ci**)*

Mp: 148–150 °C. IR ($CHCl_3$): ν 3311, 1596, 1528, 1502, 1462, 1376, 1340, 1242, 1045, 853 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 2.87 (t, *J*=6.8 Hz, 2H), 3.70–3.74 (m, 2H), 4.81 (t, *J*=5.4 Hz, 1H), 7.14–7.18 (m, 2H), 8.38–8.41 (m, 2H), 8.75 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 29.1 (t), 60.1 (t), 120.2 (d, 2C), 121.2 (d), 125.6 (d, 2C), 141.0 (s), 146.4 (s), 146.5 (s). Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.34; H, 4.26; N, 23.87.

*4.3.26. 1,2:4,5-Di-O-isopropylidene-3-O-[(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl]-D-fructopyranose (**3cm**)*

Mp: 135–137 °C. IR ($CHCl_3$): ν 3400, 2990, 2935, 1599, 1528, 1508, 1382, 1342, 1218, 1118, 1082, 854, 751 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.41 (s, 3H), 1.50 (s, 3H), 1.57 (s, 3H), 3.63 (d, *J*=7.6 Hz, 1H), 3.96 (d, *J*=8.6 Hz, 1H), 4.04 (d, *J*=13.4 Hz, 1H), 4.12–4.17 (m, 2H), 4.25 (dd, *J*=2.2, 5.6 Hz, 1H), 4.39 (dd, *J*=5.6, 7.1 Hz, 1H), 4.92 (d, *J*=12.5 Hz, 1H), 5.17 (d, *J*=12.7 Hz, 1H), 7.98 (dd, *J*=2.0, 7.1 Hz, 2H), 8.14 (s, 1H), 8.42–8.45 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1 (q), 26.2 (q), 26.6 (q), 28.2 (q), 60.2 (t), 65.1 (t), 71.9 (t), 73.8 (d), 77.3 (d), 77.4 (d), 104.2 (s), 109.2 (s), 112.1 (s), 120.3 (d, 2C), 120.4 (d), 125.5 (d, 2C), 141.1 (s), 147.1 (s), 147.2 (s). Anal. Calcd for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67; N, 12.12. Found: C, 54.60; H, 5.71; N, 12.18.

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