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ONE-POT SYNTHESIS OF MODEL 1*H*,1'*H*-5,5'-BI(1,2,4-TRIAZOLES)

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Abstract – Direct interaction of diaminomaleonitrile with model *in situ* generated nitrile imine 1,3-dipoles resulted in a direct synthesis of the corresponding 5,5'-bi(1,2,4-triazoles). A plausible mechanism is advanced for this new preparative route.

1,2,4-Triazoles have been reported to possess various biological properties such as antibacterial,[1] antimicrobial,[2] antiasthmatic,[3] antituberculosis,[4] anticancer,[5] anti-inflammatory and analgesic[6] activities. Selected examples of medicinal drugs incorporating 1,2,4-triazole moiety include: ribavirin (antiviral),[7] fluconazole (antifungal),[8] alprazolam (tranquilizer),[9] and trapidil (hypotensive)[10] (Figure 1). Hence, the synthesis and pharmacological activities of 1,2,4-triazoles continue to receive attention, and the subject has been reviewed.[11-13]

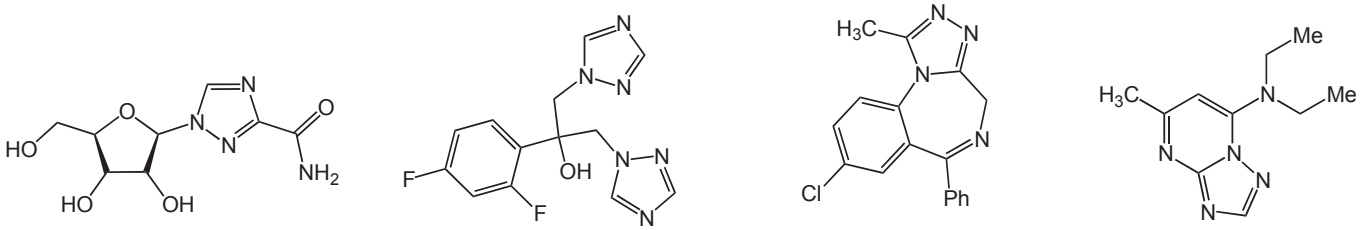


Figure 1. Examples of medicinal drugs containing 1,2,4-triazole fragment

In addition, there has been considerable interest in transition metal complexes of triazole-based ligands as these complexes display important magnetic, photophysical and electrochemical properties.[14] In particular, 3-(pyridin-2-yl)-1,2,4-triazoles have been frequently employed for complexation with metal ions exemplified by Ru(II)[15] and Cu(II)[16] ions. In these complexes, the triazole ring is coordinated to the metal ion *via* the N2' or the N4' atom (Figure 2).

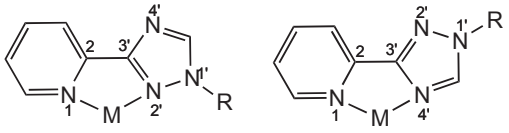
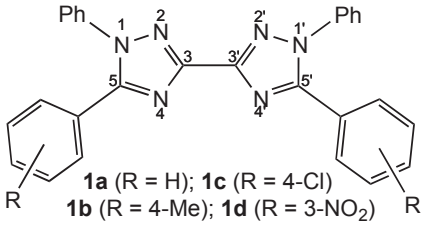


Figure 2. Coordination modes of 3-(pyridin-2-yl)-1,2,4-triazoles

On the other hand, 3,3'-bi-1*H*-1,2,4-triazoles (exemplified by **1a-d** / Figure 3) were prepared in three-step procedures[17] utilizing di-nitrile imine 1,3-dipolar intermediates (accessible from their oxalodihydrazonyl dichloride precursors), and were reported to possess bactericidal, fungicidal and anthelmintic activities.[18]



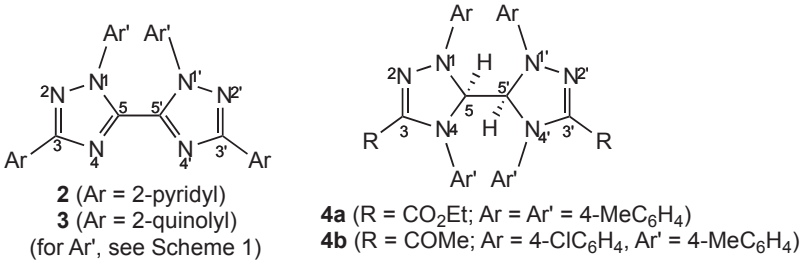
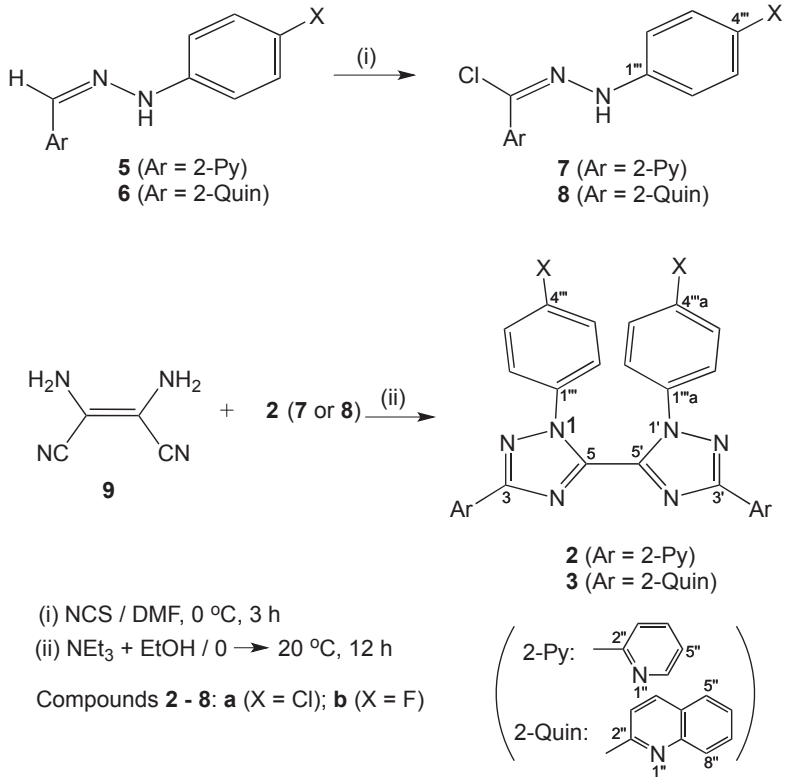


Figure 3. Structures of the bi-1,2,4-triazoles (1-4)

We envisaged it is worthwhile to tackle a new synthetic approach to the isomeric 5,5'-bi(1,2,4-triazoles) **2** and **3** (Figure 3) for comparative study. The latter bi-heteroring system is hitherto undescribed, whilst the synthesis of its 4,4',5,5'-tetrahydro form **4** (Figure 3) has been reported[19] utilizing 1,4-diaryl-1,4-diaza-1,3-butadiene and hydrazonyl chlorides (precursors of nitrile imine 1,3-dipolar species). In the present work, we wish to bridge this gap and attain a successful one-pot synthesis of a selected set of 5,5'-bi(1,2,4-triazoles) **2a**,**b** and **3a**,**b** utilizing diaminomaleonitrile (**9**) and approporiate hydrazonyl chlorides **7, 8** as outlined in Scheme 1. Noteworthy is that diaminomaleonitrile (**9**) has been utilized in the synthesis of various aza-heteroaromatics such as imidazoles, pyrazines, pyrimidines and purines, and the subject has been reviewed.[20]

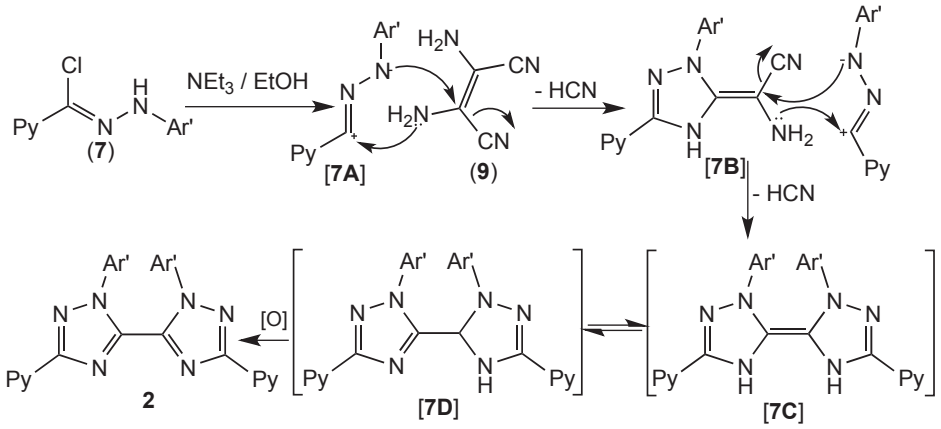
In the present study, a new route towards synthesis of model 5,5'-bi(1,2,4-triazoles) **2a**,**b** and **3a**,**b** is outlined in Scheme 1. Thus, direct interaction between diaminomaleonitrile (**9**) and the appropriate nitrile imine (1,3-dipolar species generated *in situ* from the respective hydazonoyl chloride precursors **7**, **8** by the action of triethyamine) afforded the corresponding targeted products **2**, **3**. The latter new compounds were

characterized by, IR, MS and NMR spectral data. These data, detailed in the experimental section, are consistent with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high-resolution mass spectral (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H and ^{13}C signal assignments to the different carbons and their attached and/or neighboring hydrogens.



Scheme 1

A plausible mechanism to account for the formation of bi-1,2,4-triazoles **2** (and by inference **3**) is postulated in Scheme 2. The initial step in constructing the first triazole ring probably involves nucleophilic addition of the amino group in **9** onto the carbon-positive pole of the nitrile imine 1,3-dipole **7A**; this is accompanied by concurrent intramolecular conjugate addition of the nitrogen-negative pole of **7A** across the sp^2-carbon with consequent displacement of the cyano group and formation of **7B** (an allowed *5-Exo-Trig* process[21]). The second dihydrotriazole ring is constructed by similar consecutive reaction steps between intermediate **7B** and another 1,3-dipole, furnishing **7C** ⟸ **7D**. Aromatization of the latter, *via* air-oxidation, gave the respective 5,5'-bi(1,2,4-triazoles) **2**. However, simultaneous construction of both triazole rings in **2** and **3** might not be excluded.



Scheme 2

By analogy to the coordination modes of 3-(pyridin-2-yl)-1,2,4-triazoles (*vide supra*, Figure 2), the closely related 5,5'-bi(1,2,4-triazoles) **2** and **3** are expected to serve as bidentate (2N) or tetradentate (4N) ligands. Currently, their complexation with transition metal ions is under investigation.

EXPERIMENTAL

Diaminomaleonitrile, 2-pyridinecarboxaldehyde, 2-quinolinecarboxaldehyde, 4-chlorophenylhydrazine hydrochloride, 4-fluorophenylhydrazine hydrochloride and *N*-chlorosuccinimide (NCS) were purchased from Acros and used as received. Melting points (uncorrected) were determined on a Stuart scientific melting temperature apparatus in open capillary tubes. IR spectra were measured with a Thermo Nicolet Nexus 670 FT-IR instrument. ^{1}H-, ^{13}C-, and 2D NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III) with TMS as internal standard. Chemical shifts are expressed in δ units; J values for ^{1}H-^{1}H, ^{1}H-F and ^{13}C-F coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were measured (in positive ion mode) using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-IV (7 Tesla) instrument.

The following *N*-(4-halophenyl)hydrazones employed in this study: **5a**,[22] **5b**,[24] **6a**[25] and **6b**[26] have been previously prepared *via* direct condensation of the appropriate hetaryl aldehyde with the respective *N*-(4-halophenyl)hydrazines.

Preparation of hydrazonoyl chlorides 7 and 8. *N*-(4-Chlorophenyl)-2-pyridinecarbohydrazonoyl chloride (**7a**) has recently been prepared and characterized.[22] The rest compounds **7b**, **8a**, **8b** are prepared herein by the following procedure which is essentially similar to that reported for **7a**,[22] and analogous systems[23]: A solution of the appropriate *N*-(4-halophenyl)hydrazone (10 mmol) in DMF (50 mL) was cooled to 0 ºC. To this stirred solution, NCS (12 mmol) was added in small portions and the reaction

mixture was further stirred for 3 h. Thereafter H_2O (150 mL) was added, the resulting precipitate was filtered under suction, washed with *n*-hexane and air-dried.

***N*'-(4-Fluorophenyl)pyridine-2-carbohydrazonoyl chloride (7b):** Yield: 1.9 g (76%), mp 106-108 ºC. IR (ν_{max}): 3302, 3192, 2985, 1609, 1507, 1465, 1425, 1293, 1201, 1153, 1090, 992, 954, 833 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.05 (pseudo t, 2H, H-2''' / H-6'''), 7.18 (dd, J_{H-H} = 8.6 Hz, J_{H-F} = 13.2 Hz, 2H, H-3''' / H-5'''), 7.29 (pseudo t, 1H, H-5''), 7.75 (pseudo t, 1H, H-4''), 8.06 (d, J = 8.1 Hz, 1H, H-3''), 8.25 (s, 1H, N-H, exchangeable with D_2O), 8.68 (d, J = 4.4 Hz, 1H, H-6''). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 114.7 (d, J_{C-F} = 7.7 Hz, C-2''' / C-6'''), 116.0 (d, J_{C-F} = 22.9 Hz, C-3''' / C-5'''), 121.1 (C-3''), 123.5 (C-5''), 125.3 (C-1'''), 136.3 (C-4''), 139.2 (Cl-*C*=N), 149.1 (C-6''), 151.3 (C-2''), 158.2 (d, J_{C-F} = 239.9 Hz, C-4'''). HRMS ((+)-ESI): *m/z* = 250.05415 (calcd. 250.05418 for $C_{12}H_{10}{}^{35}Cl\,FN_3$, $[M + H]^+$); *m/z* = 252.05122 (cacld. 252.05123 for $C_{12}H_{10}{}^{37}ClFN_3$, $[M + 2 + H]^+$).

***N*'-(4-Chlorophenyl)quinoline-2-carbohydrazonoyl chloride (8a):** Yield: 2.8 g (89%), mp 158-160 ºC. IR (ν_{max}): 3308, 3058, 1593, 1567, 1494, 1421, 1400, 1303, 1232, 1149, 1112, 1087, 987, 952, 927, 871, 811 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 8.1 Hz, 2H, H-2''' / H-6'''), 7.33 (d, J = 8.1 Hz, 2H, H-3''' / H-5'''), 7.58 (pseudo t, 1H, H-6''), 7.76 (pseudo t, 1H, H-7''), 7.83 (d, J = 8.0 Hz, 1H, H-5''), 8.15 (d, J = 8.5 Hz, 1H, H-4''), 8.16 (d, J = 8.5 Hz, 1H, H-3''), 8.21 (d, J = 7.9 Hz, 1H, H-8''), 8.41 (s, 1H, N-H, exchangeable with D_2O). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 114.9 (C-2''' / C-6'''), 118.7 (C-3''), 126.7 (C-4''a), 127.0 (C-4'''), 127.2 (C-6''), 127.5 (C-5''), 127.9 (Cl-*C*=N), 129.4 (C-3''' / C-5'''), 129.8 (C-8''), 129.9 (C-7''), 136.0 (C-4''), 141.4 (C-1'''), 147.6 (C-8''a), 150.8 (C-2''). HRMS ((+)-ESI): *m/z* = 316.04067 (calcd. 316.04028 for $C_{16}H_{12}{}^{35}Cl_2N_3$, $[M + H]^+$); *m/z* = 318.03778 (cacld. 318.03733 for $C_{16}H_{12}{}^{35}Cl^{37}ClN_3$, $[M + 2 + H]^+$); *m/z* = 320.03483 (cacld. 320.03438 for $C_{16}H_{12}{}^{37}Cl_2N_3$, $[M + 4 + H]^+$).

***N*'-(4-Fluorophenyl)quinoline-2-carbohydrazonoyl chloride (8b):** Yield: 2.1 g (69%), mp 146-148 ºC. IR (ν_{max}): 3339, 3048, 1604, 1505, 1417, 1304, 1252, 1199, 1163, 1112, 1091, 986, 929, 820 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.09 (pseudo t, 2H, H-2''' / H-6'''), 7.24 (dd, J_{H-H} = 9.0 Hz, J_{H-F} = 13.5 Hz, 2H, H-3''' / H-5'''), 7.59 (pseudo t, 1H, H-6''), 7.76 (pseudo t, 1H, H-7''), 7.85 (d, J = 7.9 Hz, 1H, H-5''), 8.17 (d, J = 8.8 Hz, 1H, H-4''), 8.20 (d, J = 8.8 Hz, 1H, H-3''), 8.22 (d, J = 7.9 Hz, 1H, H-8''), 8.39 (s, 1H, N-H, exchangeable with D_2O). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 114.9 (d, J_{C-F} = 7.7 Hz, C-2''' / C-6'''), 116.1 (d, J_{C-F} = 22.8 Hz, C-3''' / C-5'''), 118.7 (C-3''), 126.3 (C-4''a), 127.1 (C-6''), 127.5 (C-5''), 127.9 (Cl-*C*=N), 129.8 (C-8''), 129.9 (C-7''), 136.1 (C-4''), 139.1 (C-1'''), 147.6 (C-8''a), 150.8 (C-2''), 158.3 (d, J_{C-F} = 241.5 Hz, C-4'''). HRMS ((+)-ESI): *m/z* = 300.06817 (calcd. 300.06983 for $C_{16}H_{12}{}^{35}Cl\,FN_3$, $[M + H]^+$); *m/z* = 302.06511 (cacld. 302.06688 for $C_{16}H_{12}{}^{37}ClFN_3$, $[M + 2 + H]^+$).

General procedure for the synthesis of the targeted bi(1,2,4-triazoles) 2 and 3. To a stirred and cooled (-5 – 0 ºC) solution of the appropriate hydrazonoyl chloride **7 / 8** (1.8 mmol) and NEt_3 (0.5 mL) in EtOH (20 mL) was added diaminomaleonitrile (0.9 mmol). The reaction mixture was further stirred at 0 – 3 ºC for 20

– 30 min, and then at rt overnight. Thereafter, the resulting mixture was cooled at -4 to -10 ºC for 4 h, and the resulting greenish solid product was filtered, washed with hexane (3×50 mL) and dried.

1,1'-Bis(4-chlorophenyl)-3,3'-di(pyridin-2-yl)-1*H*,1'*H*-5,5'-bi(1,2,4-triazole) (2a): Yield: 0.17 g (36%), mp 308-310 ºC. IR (ν_{max}): 3064, 1618, 1588, 1513, 1489, 1445, 1416, 1335, 1248, 1161, 1086, 973, 828 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.10 (d, J = 8.2 Hz, 2H, H-2''' / H-6'''), 7.22 (d, J = 8.2 Hz, 2H, H-3''' / H-5'''), 7.37 (pseudo t, 1H, H-5''), 7.83 (pseudo t, 1H, H-4''), 8.21 (d, J = 7.7 Hz, 1H, H-3''), 8.75 (d, J = 3.4 Hz, 1H, H-6''). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 122.4 (C-3''), 124.8 (C-5''), 125.1 (C-2''' / C-6'''), 129.4 (C-3''' / C-5'''), 134.8 (C-1'''), 135.4 (C-4'''), 137.4 (C-4''), 143.9 (C-5), 148.3 (C-2''), 150.0 (C-6''), 162.5 (C-3). HRMS ((+)-ESI): *m/z* = 533.07556 (calcd. 533.07672 for $C_{26}H_{16}{}^{35}Cl_2N_8Na$, $[M + Na]^+$); *m/z* = 535.07325 (calcd. 535.07378 for $C_{26}H_{16}{}^{35}Cl^{37}ClN_8Na$, $[M + 2 + Na]^+$); *m/z* = 537.06985 (calcd. 537.07083 for $C_{26}H_{16}{}^{37}Cl_2N_8Na$, $[M + 4 + Na]^+$).

1,1'-Bis(4-fluorophenyl)-3,3'-di(pyridin-2-yl)-1*H*,1'*H*-5,5'-bi(1,2,4-triazole) (2b): Yield: 0.20 g (45%), mp 278-280 ºC. IR (ν_{max}): 3082, 1647, 1594, 1506, 1468, 1415, 1336, 1224, 1159, 1089, 976, 832 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.99 (pseudo t, 2H, H-3''' / H-5'''), 7.18 (dd, $J_{H\text{-}H}$ = 8.4 Hz, $J_{H\text{-}F}$ = 4.4 Hz, 2H, H-2''' / H-6'''), 7.41 (pseudo t, 1H, H-5''), 7.87 (pseudo t, 1H, H-4''), 8.25 (d, J = 7.8 Hz, 1H, H-3''), 8.79 (d, J = 4.0 Hz, 1H, H-6''). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 116.3 (d, $J_{C\text{-}F}$ = 23.3 Hz, C-3''' / C-5'''), 122.3 (C-3''), 124.7 (C-5''), 125.9 (d, $J_{C\text{-}F}$ = 8.7 Hz, C-2''' / C-6'''), 132.6 (C-1'''), 137.0 (C-4''), 144.0 (C-5), 148.6 (C-2''), 150.2 (C-6''), 162.6 (d, J = 250.9 Hz, C-4'''), 162.7 (C-3). HRMS ((+)-ESI): *m/z* = 501.13432 (calcd. 501.13582 for $C_{26}H_{16}F_2N_8Na$, $[M + Na]^+$).

1,1'-Bis(4-chlorophenyl)-3,3'-di(quinolin-2-yl)-1*H*,1'*H*-5,5'-bi(1,2,4-triazole) (3a): Yield: 0.18 g (33%), mp > 360 ºC. IR (ν_{max}): 3058, 1695, 1620, 1594, 1561, 1489, 1418, 1342, 1311, 1248, 1211, 1138, 1086, 1007, 975, 942, 829 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.1 Hz, 2H, H-2''' / H-6'''), 7.32 (d, J = 8.1 Hz, 2H, H-3''' / H-5'''), 7.64 (pseudo t, 1H, H-6''), 7.80 (pseudo t, 1H, H-7''), 7.91 (d, J = 7.9 Hz, 1H, H-5''), 8.35 (d, J = 8.4 Hz, 1H, H-4''), 8.36 (d, J = 8.7 Hz, 1H, H-8''), 8.41 (d, J = 8.4 Hz, 1H, H-3''). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 119.8 (C-3''), 125.3 (C-2''' / C-6'''), 127.5 (C-6''), 127.6 (C-5''), 128.5 (C-4''a), 129.5 (C-3''' / C-5'''), 130.1 (C-7''), 130.3 (C-8''), 134.9 (C-1'''), 135.5 (C-4'''), 137.3 (C-4''), 144.2 (C-5), 148.2 (C-8''a), 148.5 (C-2''), 163.0 (C-3). HRMS ((+)-ESI): *m/z* = 611.12673 (calcd. 611.12607 for $C_{34}H_{21}{}^{35}Cl_2N_8$, $[M + H]^+$); *m/z* = 613.12364 (cacld. 613.12314 for $C_{34}H_{21}{}^{35}Cl^{37}ClN_8$, $[M + 2 + H]^+$); *m/z* = 615.11993 (cacld. 615.12018 for $C_{34}H_{21}{}^{37}Cl_2N_8$, $[M + 4 + H]^+$).

1,1'-Bis(4-fluorophenyl)-3,3'-di(quinolin-2-yl)-1*H*,1'*H*-5,5'-bi(1,2,4-triazole) (3b): Yield: 0.22 g (43%), mp 355-357 ºC. IR (ν_{max}): 3056, 1692, 1597, 1502, 1436, 1374, 1294, 1219, 1151, 1081, 1007, 975, 939, 824 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.04 (pseudo t, 2H, H-2''' / H-6'''), 7.27 (dd, $J_{H\text{-}H}$ = 8.8 Hz, $J_{H\text{-}F}$ = 11.4 Hz, 2H, H-3''' / H-5'''), 7.64 (pseudo t, 1H, H-6''), 7.80 (pseudo t, 1H, H-7''), 7.92 (d, J = 7.9 Hz, 1H, H-5''), 8.36 (d, J = 8.5 Hz, 1H, H-4''), 8.37 (d, J = 8.6 Hz, 1H, H-8''), 8.42 (d, J = 8.5 Hz, 1H, H-3'').

^{13}C-NMR (125 MHz, $CDCl_3$) : δ 116.4 (d, $J_{C\text{-}F}$ = 23.3 Hz, C-3''' / C-5'''), 119.8 (C-3''), 126.2 (d, $J_{C\text{-}F}$ = 8.7 Hz, C-2''' / C-6'''), 127.4 (C-6''), 127.6 (C-5''), 128.5 (C-4''a), 130.1 (C-7''), 130.3 (C-8''), 132.3 (C-1'''), 137.3 (C-4''), 144.3 (C-5), 148.2 (C-8''a), 148.6 (C-2''), 162.7 (d, d, $J_{C\text{-}F}$ = 252.9 Hz, C-4'''), 162.9 (C-3). HRMS ((+)-ESI): *m/z* = 601.16876 (calcd. 601.16712 for $C_{34}H_{20}F_2N_8Na$, $[M + Na]^+$).

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