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Regioselective Synthesis of Polysubstituted 3,3'-Bi-1H-pyrazole Derivatives *via* 1,3-Dipolar Cycloaddition Reactions

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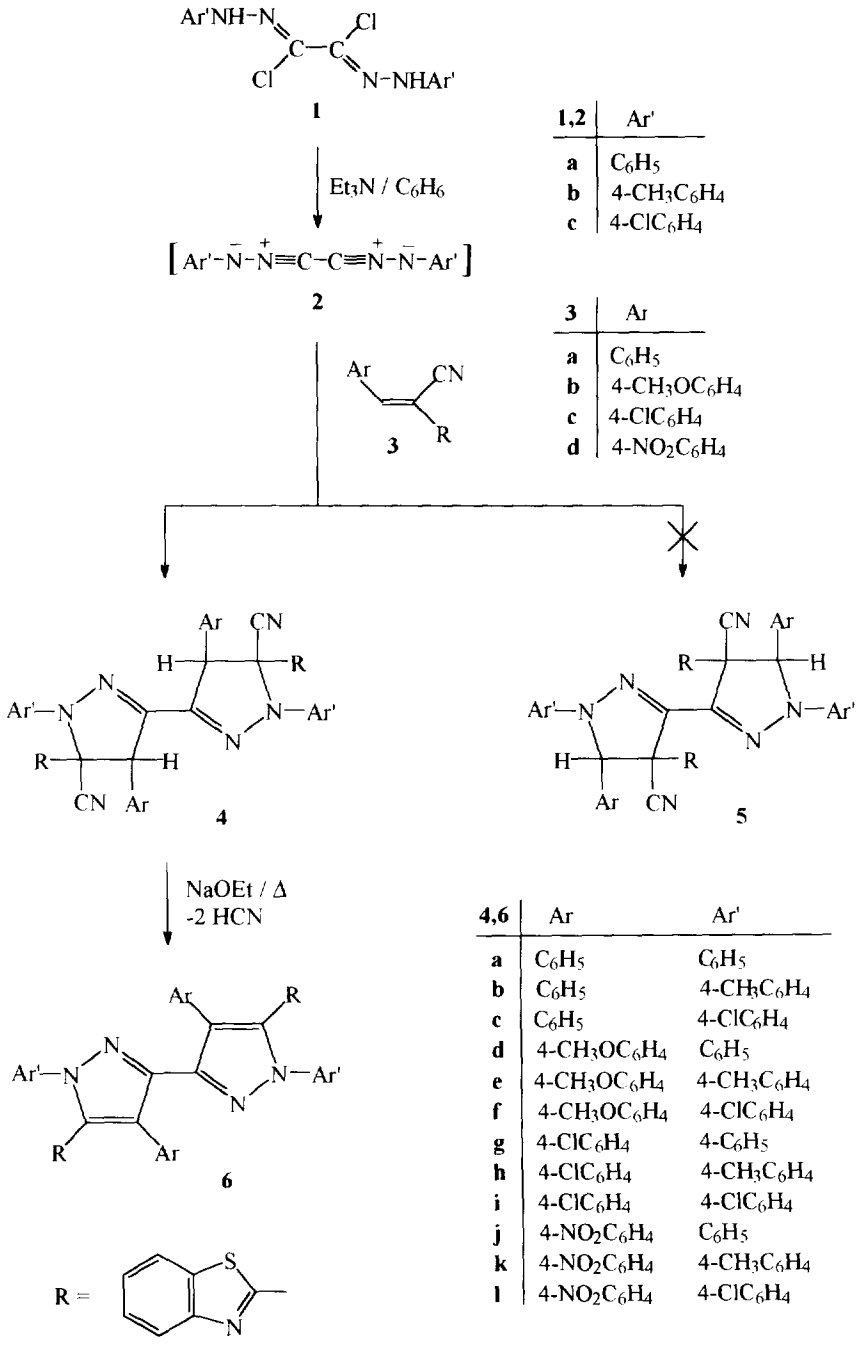
Abstract: N,N'-Diarylbisnitrile imides **2** add regioselectively to α-(benzothiazol-2-yl)cinnamonitriles **3** and α-(1-methylbenzimidazol-2-yl)cinnamonitriles **7** to yield exclusively the cycloadducts 5,5'-dicyano-4,4',5,5'-tetrahydro[3,3'-bi-1H-pyrazoles] **4** and **8**, respectively. Compounds **4** and **8** undergo aromatization *via* thermal elimination of hydrogen cyanide under basic conditions to afford the corresponding 3,3'-bi-1H-pyrazole derivatives **6** and **10**, respectively. The regiochemistry of the cycloadducts is discussed. © 1997 Elsevier Science Ltd.

Several pyrazole derivatives are important as pharmaceuticals, they have been found to possess analgetic,[1] antipyretic,[1,2] antiinflammatory[1,3] and antimicrobial[1,4] properties. They are also useful as biodegradable agrochemicals[5] and as intermediates in the dye industry.[6] In connection with our previous studies[7,8] and in view of utilizing nitrile imides as highly versatile intermediates for the construction of functionalized pyrazole derivatives of expected potential biological activity, the present study was undertaken to investigate the regioselectivity in 1,3-dipolar cycloaddition reactions of bisnitrile imides **2** to the activated carbon-carbon double bond of cinnamonitrile derivatives substituted in the α-position with benzothiazole or benzimidazole moiety.

Thus, it has been found that α-(benzothiazol-2-yl)cinnamonitriles **3** react with bisnitrile imides **2a-c**, (generated *in situ* from N,N'-diaryloxalodihydrazonoyl dichlorides **1a-c** by the action of triethylamine) in benzene at reflux to afford in each case,only one of the two possible regioisomeric cycloadducts **4** and **5** as deduced from the TLC and ^{1}H NMR analyses of the crude reaction products (Scheme 1).

Structur 5,5'-dicyano-5,5'-di(benzothiazol-2-yl)-4,4',5,5'-tetrahydro-1,1',4,4'-tetrasubstituted[3,3'-bi-1H-pyrazoles] **4a-l** was assigned to the isolated cycloadducts on the basis of their elemental analyses and of their spectroscopic data, mainly ^{1}H and ^{13}C NMR. Number of signals in both type of NMR spectra is reduced to "one-half" in accordance with a symmetry of the molecule. Detailed ^{1}H and ^{13}C NMR analysis of compound **4d** resulted in complete structural assignment of proton (from 1D and 2D-COSY spectra at 500 MHz) as well as carbon atom signals (from 1D proton decoupled and proton coupled spectra, proton-carbon 2D-HMQC and literature NMR data for benzothiazole). Proton and carbon chemical shifts of compound **4d** are summarized in Figure 1A. Coupling constants J(H,C) of the dihydropyrazole proton at δ 5.33 (see Figure 1B) have been determined from the comparison of proton-coupled ^{13}C NMR spectra measured with and without selective irradiation of this proton. The J(H,C) coupling pattern of dihydropyrazole proton is fully consistent with structure **4d** only since in the alternative structure **5d** the additional coupling to the α-carbon of N-phenyl ring (at δ 141.49) should be observed.



1,2	Ar'
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-ClC_6H_4

3	Ar
a	C_6H_5
b	4-$CH_3OC_6H_4$
c	4-ClC_6H_4
d	4-$NO_2C_6H_4$

4,6	Ar	Ar'
a	C_6H_5	C_6H_5
b	C_6H_5	4-$CH_3C_6H_4$
c	C_6H_5	4-ClC_6H_4
d	4-$CH_3OC_6H_4$	C_6H_5
e	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$
f	4-$CH_3OC_6H_4$	4-ClC_6H_4
g	4-ClC_6H_4	4-C_6H_5
h	4-ClC_6H_4	4-$CH_3C_6H_4$
i	4-ClC_6H_4	4-ClC_6H_4
j	4-$NO_2C_6H_4$	C_6H_5
k	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$
l	4-$NO_2C_6H_4$	4-ClC_6H_4

Scheme 1

The IR and ^{1}H NMR spectra of the reaction products **4a-l** are mutually consistent and support the general formula of regioisomer **4**. For example, the IR spectra of the isolated products showed in each case, a weak or no nitrile absorption band. These findings are similar to those reported for aliphatic nitriles activated by an oxygen or a nitrogen atom in the α-position[9-11] such as 5-cyano-4,5-dihydro-1H-pyrazole derivatives. The ^{1}H NMR spectra of **4a-l** revealed in each case, a sharp singlet in the region δ 4.83-6.3 corresponding to the proton at C-4 of the 4,5-dihydropyrazole ring moiety. These chemical shifts are close to those reported[12] for C-4 protons of similar ring systems. However, all attempts to prepare an authentic sample of the regioisomer **5** for comparison were unsuccessful.

Compounds **4** undergo aromatization *via* thermal elimination of hydrogen cyanide under basic conditions to afford the corresponding pyrazole derivatives **6**. Thus, when compound **4c**, taken as a typical example of the series prepared, was heated in ethanolic sodium ethoxide solution, it afforded the corresponding 5,5'-di(benzothiazol-2-yl)-1,1'-di(4-chlorophenyl)-4,4'-diphenyl[3,3'-bi-1H-pyrazole] **(6c)** in high yield (Scheme 1). The structure of the latter product was supported by its ^{1}H NMR spectrum which revealed the disappearance of the characteristic signal of the proton at C-4 in the 4,5-dihydropyrazole ring moiety.

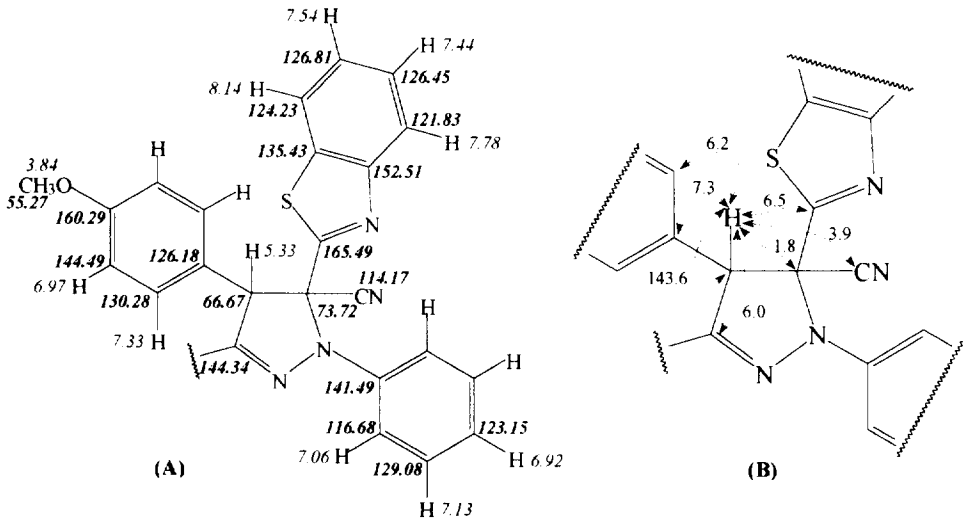
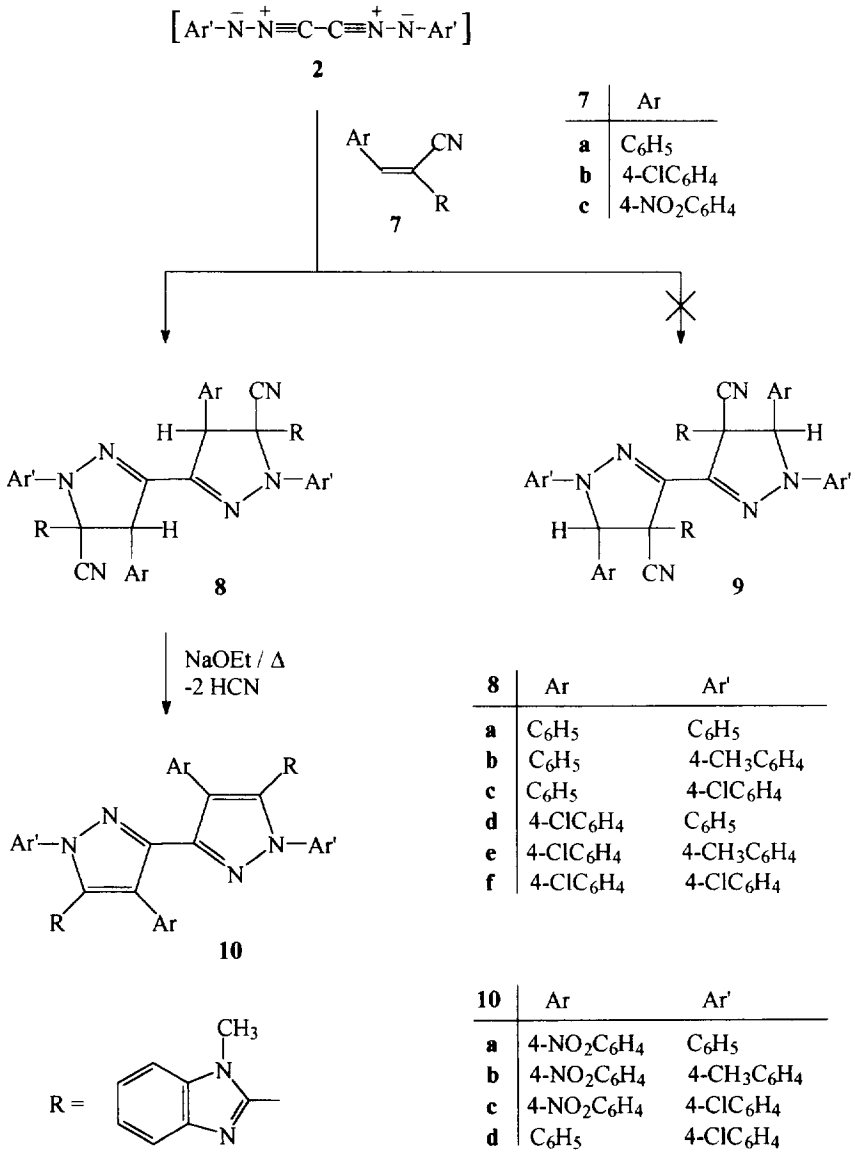


Figure 1 Carbon-13 and proton NMR chemical shifts **(A)** and proton-carbon coupling constants of the dihidropyrazole proton **(B)** observed in compound **4d**

In analogous manner, the bisnitrile imides **2a-c** add regioselectively to the carbon-carbon double bond of α-(1-methylbenzimidazol-2-yl)cinnamonitriles **7a,b** in benzene at reflux to afford the corresponding 1 : 2 cycloadducts which were identified as 5,5'-dicyano-4,4',5,5'-tetrahydro-5,5'-di(1-methyl-1H-benzimidazol-2-yl)-1,1',4,4'-tetrasubstituted[3,3'-bi-1H-pyrazoles] **8a-f** (Scheme 2). The structures of the latter products were assigned on the basis of their elemental analyses and spectral data in a similar way as in the case of

compounds **4a-l**. For example, the IR spectra of the isolated cycloadducts revealed in each case, a weak or no nitrile absorption band as it is the case for 5-cyano-4,5-dihydropyrazoles. Structure **8** was further supported by the ^{1}H NMR spectra of the isolated cycloadducts. For example, the ^{1}H NMR spectra of the latter products showed in each case, a sharp signal in the region δ 5-6.1 of the proton at C-4 of the 4,5-dihydropyrazole ring moiety.



7	Ar
a	C_6H_5
b	4-ClC_6H_4
c	4-$NO_2C_6H_4$

8	Ar	Ar'
a	C_6H_5	C_6H_5
b	C_6H_5	4-$CH_3C_6H_4$
c	C_6H_5	4-ClC_6H_4
d	4-ClC_6H_4	C_6H_5
e	4-ClC_6H_4	4-$CH_3C_6H_4$
f	4-ClC_6H_4	4-ClC_6H_4

10	Ar	Ar'
a	4-$NO_2C_6H_4$	C_6H_5
b	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$
c	4-$NO_2C_6H_4$	4-ClC_6H_4
d	C_6H_5	4-ClC_6H_4

Scheme 2

It should be noticed that, in the case of the reaction of bisnitrile imides **2a-c** with α-(1-methylbenzimidazol-2-yl)-4-nitrocinnamonitrile (**7c**), the 5,5'-di(1-methyl-1H-benzimidazol-2-yl)-4,4'-di(4-nitrophenyl)-1,1'-disubstituted[3,3'-bi-1H-pyrazoles] **10a-c** were obtained directly *via* elimination of hydrogen cyanide from the corresponding non-isolable intermediate cycloadducts 4,5-dihydropyrazoles **8** under the reaction conditions. This finding was supported by the elemental analyses and spectral data of the isolated products. In the ^{1}H NMR spectrum of **10b** for example, the signal corresponding to the proton at C-4 of the pyrazoline moiety was absent. On the other hand, the dihydropyrazole cycloadducts **8** underwent aromatization *via* loss of hydrogen cyanide when heated under strong basic conditions. For example, when **8c** was heated in ethanolic sodium ethoxide solution, it afforded the corresponding 1,1'-di(4-chlorophenyl)-5,5'-di(1-methyl-1H-benzimidazol-2-yl)-4,4'-diphenyl[3,3'-bi-1H-pyrazole] (**10d**) (Scheme 2). The structure of the latter product was confirmed by its ^{1}H NMR spectrum, which revealed the disappearance of the proton signal at C-4.

EXPERIMENTAL

All melting points were measured on a Gallenkamp electrothermal melting point apparatus. The infrared spectra were taken for potassium bromide discs on a Pye-Unicam SP 3-300 spectrophotometer. The ^{1}H NMR spectra were recorded in deuterated dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. The 1D and 2D proton and carbon-13 NMR spectra of compound **4d** were measured on a Varian UNITY-500 spectrometer (^{1}H at 500 MHz and ^{13}C at 125.7 MHz, resp.). Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo University. N,N'-Diaryloxalodihydrazonoyl dichlorides **1**,[13] α-(benzothiazol-2-yl)cinnamonitriles **3**[14] and α-(1-methylbenzimidazol-2-yl)cinnamonitriles **7**[15] were prepared according to literature procedures.

5,5'-Dicyano-5,5'-di(benzothiazol-2-yl)-4,4',5,5'-tetrahydro-1,1',4,4'-tetra-substituted [3,3'-bi-1H-pyrazoles] 4a-l, 5,5'-dicyano-5,5'-di(1-methyl-1H-benzimidazol-2-yl)-4,4', 5,5'-tetrahydro-1,1',4,4'-tetra-subsituted[3,3'-bi-1H-pyrazoles] 8a-f and 5,5'-di(1-methyl-1H-benzimidazol-2-yl)-4,4'-di(4-nitrophenyl)-1,1'-disubstituted[3,3'-bi-1H-pyrazoles] 10a-c. General procedure.

To a solution of the appropriate α-(substituted)cinnamonitriles **3a-d** or **7a-c** (20 mmol) and the corresponding N,N'-diaryloxalodihydrazonoyl dichlorides **1a-c** (10 mmol) in dry benzene (15 ml), was added triethylamine (0.2 ml, 20 mmol) and the reaction mixture was refluxed for 4h, then left to cool. The reaction mixture was filtered off to remove the precipitated triethylamine hydrochloride and the solvent was evaporated under reduced pressure. The solid residue was triturated with methanol and collected by filtration. The crude product was crystallized from dimethylformamide/ water to afford **4a-l** and **8a-f**, respectively. Reaction of **7c** with **1a-c** when carried out under the same experimental conditions, afforded **10a-c**.

4a: Yield (60%), m.p. 295-6°C; IR (KBr) ν 1600 (C=N) cm^{-1}; ^{1}H NMR (DMSO) δ 7.12-8.56 (m, 28H), 5.81 (s, 2H); MS, m/e (%) 704 (M^+-2 HCN, 76.6), 352 (56.5); (Calcd. for $C_{46}H_{30}N_8S_2$: C, 72.79; H, 3.98; N, 14.77; S, 8.45. Found: C, 73.00; H, 4.10; N, 14.80; S, 8.22).

4b: Yield (62%), m.p. > 300°C; IR (KBr) ν 1610 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.0-8.18 (m, 26H), 6.12 (s, 2H), 2.24 (s, 6H); MS, m/e (%) 786 (M^+, 7.12), 7.32 (83.8), 366 (89.2); (Calcd. for $C_{48}H_{34}N_8S_2$: C, 73.26; H, 4.36; N, 14.24; S, 8.15. Found: C, 73.39; H, 4.48; N, 14.31; S, 7.98).

4c: Yield (53%), m.p. > 300°C; IR (KBr) ν 1673 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 6.88-8.2 (m, 26H), 5.97 (s, 2H); MS, m/e (%) 827 (M^+, 1.8), 773 (55.7), 386 (93.0); (Calcd. for $C_{46}H_{28}N_8S_2Cl_2$: C, 66.74; H, 3.41; N, 13.54; Cl, 8.57; S, 7.75. Found: C, 66.88; H, 3.50; N, 13.32; Cl, 8.42; S, 7.80).

4d: Yield (40%), m.p. 284-5°C; IR (KBr) ν 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$ - see Figure 1); MS, m/e (%) 764 (M+ -2 HCN, 20.7), 383 (43.1), 382 (4.0); (Calcd. for $C_{48}H_{34}N_8S_2O_2$: C, 70.39; H, 4.18; N, 13.68; S, 7.83. Found: C, 70.50; H, 4.27; N, 13.55; S, 7.63).

4e: Yield (70%), m.p. > 300°C; IR (KBr) ν 1610 (C=N) cm^{-1}; (Calcd. for $C_{50}H_{38}N_8S_2O_2$: C, 70.90; H, 4.52; N, 13.23; S, 7.57. Found: C, 70.73; H, 4.43; N, 12.98; S, 7.43).

4f: Yield (70%), m.p. > 300°C; IR (KBr) ν 1675 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 6.9-8.2 (m, 24H), 5.87 (s, 2H), 3.8 (s, 6H); (Calcd. for $C_{48}H_{32}N_8S_2Cl_2O_2$: C, 64.93; H, 3.63; N, 12.62; Cl, 7.99; S, 7.22. Found: C, 64.80; H, 3.70; N, 12.53; Cl, 7.83; S, 7.12).

4g: Yield (75%), m.p. > 300°C; IR (KBr) ν 1600 (C=N) cm^{-1}; (Calcd. for $C_{46}H_{28}N_8S_2Cl_2$: C, 66.74; H, 3.41; N, 13.54; Cl, 8.57; S, 7.75. Found: C, 66.66; H, 3.20; N, 13.30 Cl, 8.40; S, 7.83).

4h: Yield (65%), m.p. > 300°C; IR (KBr) ν 1600 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.1-8.2 (m, 25H), 5.82 (s, 2H), 2.3 (s, 6H); MS, m/e (%) 801 (M^+-2HCN, 21.8), 400 (93.4). (Calcd. for $C_{48}H_{32}N_8S_2Cl_2$: C, 67.36; H, 3.77; N, 13.09; Cl, 8.29; S, 7.49. Found: C, 67.42; H, 3.68; N, 12.90; Cl, 8.31; S, 7.37).

4i: Yield (62%), m.p. > 300°C; IR (KBr) ν 1664 (C=N) cm^{-1}; (Calcd. for $C_{46}H_{26}N_8S_2Cl_4$: C, 61.61; H, 2.92; N, 12.50; Cl, 15.82; S, 7.15. Found: C, 61.78; H, 2.86; N, 12.49; Cl, 15.78; S, 6.96).

4j: Yield (45%), m.p. > 300°C; IR (KBr) ν 1600 (C=N), 1500 (NO_2) cm^{-1}; (Calcd. for $C_{46}H_{28}N_{10}S_2O_4$: C, 65.08; H, 3.32; N, 16.50; S, 7.55. Found: C, 64.90; H, 3.22; N, 16.45; S, 7.48).

4k: Yield (60%), m.p. > 300°C; IR (KBr) ν 1604 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.2-8.2 (m, 24H), 6.3 (s, 2H), 2.3 (s, 6H); (Calcd. for $C_{48}H_{32}N_{10}S_2O_2$: C, 65.74; H, 3.68; N, 15.97; S, 7.31. Found: C, 65.86; H, 3.58; N, 15.86; S, 7.29).

4l: Yield (68%), m.p. > 300°C; IR (KBr) ν 1617 (C=N), 1523 (NO_2) cm^{-1}; ^1H NMR spectrum was not recorded because of insufficient solubility in the common NMR solvents; (Calcd. for $C_{46}H_{26}N_{10}S_2O_4Cl_2$: C, 60.19; H, 2.86; N, 15.26; Cl, 7.73; S, 6.99. Found: C, 60.20; H, 2.80; N, 15.03; Cl, 7.62; S, 7.12).

8a: Yield (70%), m.p. 300°C; IR (KBr) ν 2208 (C≡N), 1670 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 6.6-7.8 (m, 28H), 6.1 (s, 2H), 4.4 (s, 6H); (Calcd. for $C_{48}H_{36}N_{10}$: C, 76.57; H, 4.82; N, 18.61. Found: C, 76.43; H, 4.80; N, 18.42).

8b: Yield (66%), m.p. 290-1°C; IR (KBr) ν 1613 (C=N) cm^{-1}; MS, m/e (%) 726 (M^+-2HCN, 68.4), 390 (8.9), 363 (90.3); (Calcd. for $C_{50}H_{40}N_{10}$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.63; H, 4.93; N, 17.68).

8c: Yield (40%), m.p. 275°C; IR (KBr) ν 1627 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 6.4-7.8 (m, 26H), 5.0 (s, 2H), 3.95 (s, 6H); (Calcd. for $C_{48}H_{34}N_{10}Cl_2$: C, 70.15; H, 4.17; N, 17.05; Cl, 8.63;. Found: C, 69.85; H, 3.98; N, 17.10; Cl, 8.50).

8d: Yield (55%), m.p. 274-5°C; IR (KBr) ν 1600 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 6.7-8.0 (m, 26H), 6.2 (s, 2H), 3.6 (s, 6H); (Calcd. for $C_{48}H_{34}N_{10}Cl_2$: C, 70.15; H, 4.17; N, 17.05; Cl, 8.63. Found: C, 69.88; H, 4.20; N, 17.19; Cl, 8.43).

8e: Yield (45%), m.p. 276-8°C; IR (KBr) ν 1609 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 6.5-7.9 (m, 24H), 6.12 (s, 2H), 3.6 (s, 6H), 2.15 (s, 6H); MS m/e (%) 795 (M^+- 2HCN, 14.5), 397 (44.3); (Calcd. for $C_{50}H_{38}N_{10}Cl_2$: C, 70.67; H, 4.51; N, 16.48; Cl, 8.34. Found: C, 70.52; H, 4.60; N, 16.38; Cl, 8.22).

8f: Yield (66%), m.p. > 300°C; IR (KBr) ν 1655 (C=N) cm^{-1}; (Calcd. for $C_{48}H_{32}N_{10}Cl_4$: C, 64.73; H, 3.62; N, 15.73; Cl, 15.92. Found: C, 64.51; H, 3.65; N, 15.76; Cl, 15.80).

10a: Yield (70%), m.p. > 300°C; IR (KBr) ν 1660 (C=N), 1500 (NO_2) cm^{-1}; MS m/e (%) 788 (M^+, 60.7), 394 (45.2); (Calcd. for $C_{46}H_{32}N_{10}O_4$: C, 68.40; H, 4.07; N, 19.94. Found: C, 68.33; H, 4.05; N, 19.85).

10b: Yield (68%), m.p. > 300 °C; IR (KBr) ν 1600 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.5-8.3 (m, 24H), 3.6 (s, 6H), 2.36 (s, 6H); (Calcd. for $C_{48}H_{36}N_{10}O_4$: C, 70.57; H, 4.44; N, 17.15. Found: C, 70.48; H, 4.38; N, 17.22).

10c: Yield (69%), m.p. > 300°C; IR (KBr) ν 1602 (C=N) cm^{-1}; MS m/e (%) 859 (M^+ + 2, 31.6), 858 (M^+ + 1, 57.0), 857 (M^+ , 50.6), 429 (100) 428 (53.2); (Calcd. for $C_{46}H_{30}N_{10}O_4Cl_2$: C, 64.41; H, 3.53; N, 16.33; Cl, 8.27. Found: C, 64.35; H, 3.36; N, 16.28; Cl, 8.38).

3,3'-Bipyrazole derivatives 6c and 10d. General procedure.

A mixture of **4c** or **8c** (4 mmol) and sodium ethoxide [prepared from sodium metal (0.14 g, 6 mmol) in ethanol (25 ml)] was heated under reflux for 1h, then left to cool. The precipitated solid was collected by filtration, washed with water and crystallized from dimethylformamide / water to afford **6c** and **10d**, respectively.

6c: Yield (70%), m.p. > 300 °C; IR (KBr) ν 1600 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.14-8.11 (m, ArH); (Calcd. for $C_{44}H_{26}N_6S_2Cl_2$: C, 68.30; H, 3.39; N, 10.86; Cl, 9.16; S, 8.28. Found: C, 68.10; H, 3.28; N, 10.68; Cl, 9.05; S, 8.01).

10d: Yield (75%), m.p. > 300 °C; IR (KBr) ν 1600 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 6.65-7.70 (m, 26H), 3.95 (s, 6H); (Calcd. for $C_{46}H_{32}N_8Cl_2$: C, 71.97; H, 4.20; N, 14.60; Cl, 9.24. Found: C, 71.81; H, 4.10; N, 14.43; Cl, 9.32).

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