Synthesis of new multi-functionalised 1,1'-carbonylbispyrazole derivatives

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A new series of multi-functionalised 1,1'-carbonylbispyrazole derivatives were synthesised through cyclisation of pyrazole carbohydrazides with some substituted methylene malononitriles in very good yields. The structures of all synthesised compounds were established on the basis of NMR, IR, MS and elemental analysis.

Keywords: pyrazole carbohydrazide, hetero-cyclisation, substituted methylene malononitrile, secondary amines, Michael addition, multi-functionalised 1,1'-carbonylbispyrazoles

Recent research into the synthesis of bis-heterocyclic compounds, which have various practical applications, have attracted the attention of scientists.[1] Bis-pyrazole derivatives have been used as excellent inhibitors of corrosion for many metals and alloys (**1**, Fig. 1).[2-5] They are also used as efficient ligands in palladium-catalysed C–O and C–N cross-coupling reactions.[6-9] The bispyrazole derivatives have coordination properties to metals and are useful as catalysts,[10] for example, heteroscorpionate [RR'C(pz)$_2$] ligands derived from bis(pyrazol-1-yl)methane (**2**, Fig. 1).[11] The high fluorescence quantum yield of pyrazoline rings add to their wide application in selective recognition of metal ions (**3**, Fig. 1).[12] Bis-pyrazoles have been used in the treatment of Alzheimer's disease, brain ischaemia, heart diseases, gastrointestinal diseases, cancer, ageing and inflammation.[13-16] These compounds are also antibacterial and antifungal agents (**4**, Fig. 1). [17] In addition, palladium and platinum complexes of 5,5'-dimethyl-3,3'-bipyrazole and some poly substituted 1,1'-carbonylbispyrazoles have been reported as potential anti-tumour agents (**5**, Fig. 1).[18,19]

Recently, we have investigated a new versatile route for the synthesis of 1,1'-carbonylbispyrazole derivatives[20]. In an extension of this work, we are undertaking related studies employing bispyrazole derivatives derived from pyrazole carbohydrazides. We now consider the nature of some nucleophiles and the properties of substituted methylene malonitriles which react through Michael addition–cyclisation with the subsequent construction of bis-heterocyclic compounds.

Results and discussion

Ethyl hydrazinecarboxylate **6** reacted with substituted methylene malonitriles **7a–c** in absolute ethanol to give ethyl 5-amino-4-cyano-1*H*-pyrazole-1-carboxylate **8a** and ethyl 5-amino-4-cyano-3-methyl-1*H*-pyrazole-1-carboxylate **8b** which have been reported previously,[20] and ethyl 5-amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carboxylate **8c**. They were prepared in 80–85% yield, respectively (Scheme 1). The formation of compound **8a–c** was confirmed by the presence of the C=O band around 1771 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum of **8c** showed a triplet signal at δ = 1.53 and a quartet signal at δ = 4.53 ppm corresponding to an ethoxy group, a singlet signal at δ = 2.58 corresponding to the thiomethyl group and a broad singlet at δ = 6.18 corresponding to an NH$_2$ group.

Nucleophilic displacement of the ethoxy group with hydrazine hydrate, a bis-nucleophile instead of a simple amine, was carried out using absolute ethanol as the solvent to afford 5-amino-4-cyano-1*H*-pyrazole-1-carbohydrazide (**9a**), 5-amino-4-cyano-3-methyl-1*H*-pyrazole-1-carbohydrazide (**9b**) and 5-amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carbohydrazide (**9c**). The IR spectrum of **9c** showed absorption bands at 3400–3245, 3010, 2770, 2210, 1718 and 1634 cm^{-1} indicating the presence of NH$_2$ and NH, cyano and C=O groups, respectively. The ^{1}H NMR spectrum of **9c** showed a signal at δ = 2.47 ppm corresponding to the thiomethyl group. Moreover, the disappearance of the characteristic pattern of the ethoxy group in addition to the presence of two singlets corresponding to two NH$_2$ and NH protons at δ = 5.90 and δ = 11.85 ppm confirmed the structure of the product. Compounds **7d–f** have been prepared from the substitution of one thiomethyl group of 2-(bis(methylthio) methylene)malononitrile **7c** with secondary amines in absolute ethanol at room temperature. The mass spectrum of 2-((methylthio)(pyrrolidin-1-yl)methylene)malononitrile (**7d**) showed a molecular ion signal at *m/z* 209 [M$^+$] corresponding to the molecular formula $C_9H_{11}N_3OS$. Compound **9a** reacted with **7d** under different reaction conditions. The excellent conversion of this compound (**9a**) into the product **10a** was achieved within 8 h in refluxing pyridine. Under the optimised conditions, the cyclo-condensation of a range of pyrazole carbohydrazides carrying substituents on their aromatic rings, with **7d–f**, proceeded smoothly and gave the corresponding multi-substituted 1,1'-carbonylbispyrazole derivatives (**10a–i**) in very good yields (Scheme 1).

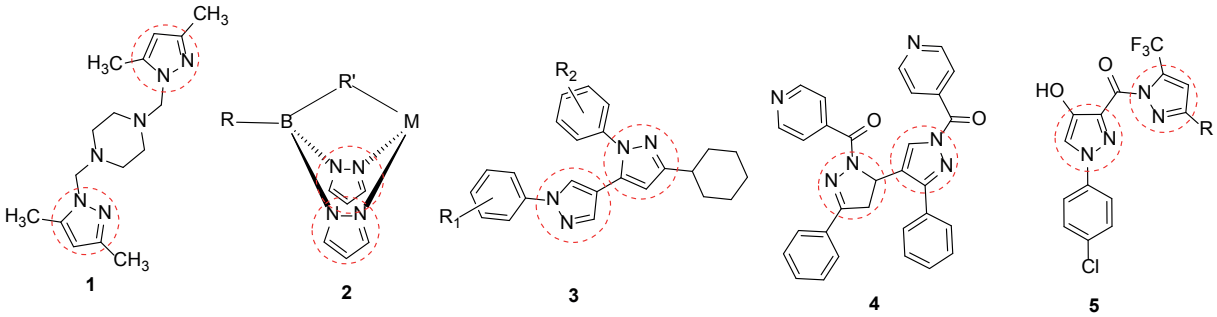

Fig. 1 Scaffold **1–5**.

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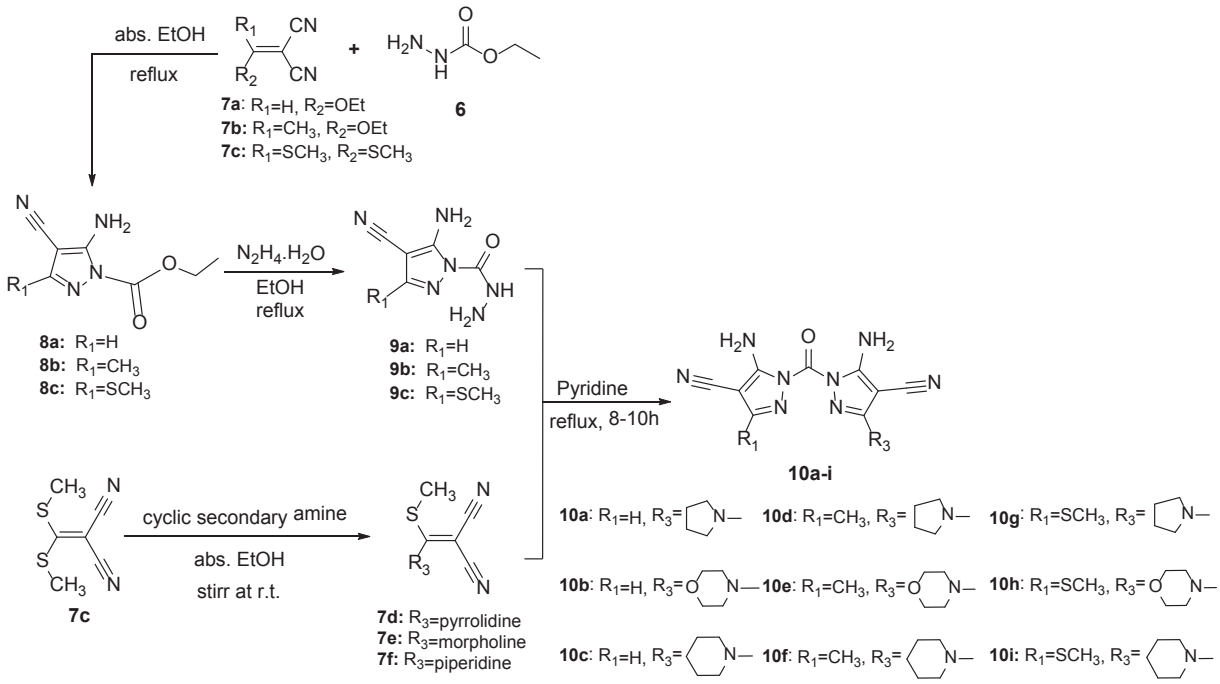

Scheme 1

The structure assignment of compounds **10a–i** was based on spectroscopic and microanalytical data. For example, the IR spectrum of **10f** revealed the presence of an additional cyano band at 2220 cm^{-1}. The ^1H NMR spectrum of **10f** showed the presence of a singlet signal at δ = 2.45 ppm corresponding to a methyl group, the multiplet signals in the range of δ = 1.79–1.89 ppm and a triplet signal at 3.89 ppm correspond to the piperidinyl protons. Whereas ^1H NMR spectrum of **9b** in $CDCl_3$ showed the signals corresponding to NH_2 and NH at δ = 6.82 and δ =12.09 ppm, respectively, which disappeared on addition of D_2O, the ^1H NMR spectrum of the cyclised product 10f did not show these resonances. Instead, an exchangeable broad singlet at δ = 5.99 ppm in $CDCl_3$ confirmed that heterocyclisation had occurred. The ^{13}C NMR spectrum of 10f revealed the appearance of two signals at δ = 113.9 and δ = 115.9 ppm, attributed to the two cyano groups confirming that heterocyclisation with 2-[(methylthio)(piperidin-1-yl) methylene]malononitrile (**7f**) had occurred. The carbonyl carbon interfacing the two pyrazole rings of **10f** appeared as a resonance at δ = 156.33 ppm. Moreover, the chemical shift of the methyl group and the piperidinyl carbons in **10f** were reported at δ 13.7 ppm and δ 23.7, 26.2 and 52.5 ppm respectively. The mass spectrum of **10f** showed a molecular ion signal at *m/z* 339 [M^+] corresponding to the molecular formula $C_{15}H_{17}N_9O$. Moreover, this compound gave satisfactory elemental analysis.

Conclusion

In summary, a new series of multi-functionalised 1,1'-carbonylbispyrazole derivatives (**10a–i**) has been successfully synthesised in good yields through cyclisation of pyrazole carbohydrazides (**9a–c**) with different methylene malonitriles (**7d–f**), through a related procedure which has been reported.[20] Moreover, the presence of functionalities such as NH_2, CH_3, SCH_3, CN and cyclic amines like pyrrolidinyl, morpholinyl and piperidinyl on the pyrazole rings are expected to be of interest because of their potential relevance to biological activity and drug research.

Experimental

All reagents were purchased from Merck Company and used without further purification. The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on an Avatar 370 FT-IR Thermo Nicolet and only noteworthy absorptions are listed. The ^1H NMR (400 MHz) and the ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance, using DMSO-d_6 or $CDCl_3$ as solvents. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyser.

*Synthesis of pyrazoles (**8a–c**); general procedure*

A 50 mL round-bottomed flask was charged with a mixture of hydrazinecarboxylic acid ethyl ester (6, 2.13 g, 20.5 mmol) and **7a–c** (20 mmol) in absolute EtOH (30 mL) and the reaction mixture was refluxed for 4 h. After this time, the mixture was cooled to room temperature and stayed in the refrigerator overnight; the precipitate was filtered and washed with cold Et_2O to afford **8** as colourless needles. Ethyl 5-amino-4-cyano-1*H*-pyrazole-1-carboxylate (**8a**) and ethyl 5-amino-4-cyano-3-methyl-1*H*-pyrazole-1-carboxylate (**8b**) are well known.[20]

*Ethyl 5-amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carboxylate* (**8c**): Yield 85%; m.p. 194°C; IR (KBr, υ_{max}/cm^{-1}): 3481, 3275, 3210, 3110, 2207, 1772, 1634. ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (t, *J*=7.6 Hz, 3H, $CH_2\underline{CH_3}$), 2.58 (s, 3H, SCH_3), 4.53 (q, *J*=7.6 Hz, 2H, $\underline{CH_2}CH_3$), 6.48 (br.s, 2H, NH_2). Anal calcd for $C_8H_{10}N_4O_2S$: C, 42.47, H, 4.46, N, 24.76, S, 14.17; found: C, 42.27, H, 4.13, N, 24.12, S, 14.61%.

*Synthesis of 1*H*-pyrazole-1-carbohydrazides (**9a–c**); general procedure*

A mixture of **8a–c** (15 mmol) and hydrazine monohydrate (3 mL, 62 mmol) in absolute ethanol (10 mL) was refluxed for 3 h. After completion of the reaction (TLC), the excess of solvent was distilled off, and the crude product obtained was poured into ice water, then the products were removed from water. The product obtained is sufficiently pure for further reaction. 5-Amino-4-cyano-1*H*-pyrazole-1-carbohydrazide (**9a**) and 5-amino-4-cyano-3-methyl-1*H*-pyrazole-

1-carbohydrazide (**9b**) are well known.[20] Compound **9c** is a known compound[21] but we have synthesised it in a new pathway.

*5-Amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carbohydrazide* (**9c**): Yield 87%; m.p. 230 °C (lit.[21] not reported) IR (KBr, υ_{max}/cm^{-1}): 3429, 3403, 3344, 3245, 3010, 2770, 2210, 1718, 1634; ^{1}H NMR (100 MHz, CD_3COCD_3): 2.47 (s, 3H, SCH_3), 5.90 (br. s, 4H, $2NH_2$), 11.85 (br. s, 1H, NH). Anal calcd for $C_6H_8N_6OS$: C, 33.96, H, 3.80, N, 39.60; found: C, 33.58, H, 4.03, N, 39.78%.

*Synthesis of 1,1'-carbonyl-bispyrazole derivatives (***10a–i***); general procedure*

A mixture of compound **9** (5 mmol) and compound **7d–f** (5 mmol) was stirred under reflux in dry pyridine (25 mL) for 8–10 h. The mixture was cooled to room temperature, then H_2O (5mL) was added, and the mixture was neutralised by HCl. The collected solid was purified by preparative TLC (1:15 MeOH:$CHCl_3$). The crude product was rinsed in MeOH and the organic layer phase was filtered and evaporated under reduced pressure to give the pure product.

*5-Amino-1-(5-amino-4-cyano-1*H*-pyrazole-1-carbonyl)-3-(pyrrolidin-1-yl)-1*H*-pyrazole-4-carbonitrile* (**10a**): Yield 75%; white solid; m.p. >300°C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94 (t, *J*=6.4 Hz, 4H, $2CH_2$), 4.15 (t, *J*=6 Hz, 4H, $2CH_2$), 7.35 (br.s, 4H, NH_2, D_2O exchangeable), 8.23 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.8, 22.8, 54.6, 54.6, 65.2, 76.1, 114.9, 117.7, 145.9, 149.7, 154.5, 160.9, 162.9. *m/z* calcd for $C_{13}H_{13}N_9O$ [M]$^+$: 311.12, found: 311.0. Anal. calcd for $C_{13}H_{13}N_9O$: C, 50.16; H, 4.21; N, 40.49; found: C, 50.66; H, 4.40; N, 40.61%.

*5-Amino-1-(5-amino-4-cyano-1*H*-pyrazole-1-carbonyl)-3-morpholino-1*H*-pyrazole-4-carbonitrile* (**10b**): Yield 70%; white solid; m.p. 260–261°C (dec.); IR (KBr, υ_{max}/cm^{-1}): 3455, 3318, 3100, 2970, 2859, 2214, 1659, 1608. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78–3.84 (m, 8H, morpholine), 7.65 (br.s, 4H, NH_2, D_2O exchangeable), 8.39 (s, 1H, aromatic); ^{13}C NMR (100 MHz, DMSO-d_6): 51.4, 51.4, 66.3, 66.3, 70.9, 76.8, 114.7, 116.1, 147, 153.4, 154.1, 160.3. *m/z* calcd for $C_{13}H_{13}N_9O_2$ [M]$^+$: 327.12, found: 327.0. Anal. calcd for $C_{13}H_{13}N_9O_2$: C, 47.71; H, 4.00; N, 38.52; found: C, 47.24; H, 4.08; N, 39.08%.

*5-Amino-1-(5-amino-4-cyano-1*H*-pyrazole-1-carbonyl)-3-(piperidin-1-yl)-1*H*-pyrazole-4-carbonitrile* (**10c**): Yield 73%; pale yellow solid; m.p. 234 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.7 (br. s, 6H, $3CH_2$), 3.77 (br. s, 4H, $2CH_2$), 7.58–7.74 (br.s, 4H, $2NH_2$, D_2O exchangeable), 8.40 (s, 1H, aromatic); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.5, 26.3, 26.3, 52.3, 52.3, 70.4, 76.7, 114.8, 116.2, 146.8, 146.8, 153.7, 154.2, 160.3. *m/z* calcd for $C_{14}H_{15}N_9O$ [M]$^+$: 325.14, found: 325.0. Anal. calcd for $C_{14}H_{15}N_9O$: C, 51.69; H, 4.65; N, 38.75; found: C, 51.36; H, 4.51; N, 38.98%.

*5-Amino-1-(5-amino-4-cyano-3-(pyrrolidin-1-yl)-1*H*-pyrazole-1-carbonyl)-3-methyl-1*H*-pyrazole-4-carbonitrile* (**10d**): Yield 60%; white solid; m.p. 286-287 °C (dec.); IR (KBr, υ_{max}/cm^{-1}): 3462, 3303, 3248, 3164, 2987, 2217, 2196, 1641, 1603; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92 (t, *J*=6.5 Hz, 4H, $2CH_2$), 2.43 (s, 3H, CH_3), 3.85 (t, *J*=6.5 Hz, 4H, $2CH_2$), 6.95 (b, 4H, NH_2, D_2O exchangeable), 8.23 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.7, 23.6, 23.6, 53.8, 53.8, 62.9, 75.4, 113.9, 116.6, 145.7, 150.6, 153.7, 161.2, 162.7. *m/z* calcd for $C_{14}H_{15}N_9O$ [M]$^+$: 325.14, found: 324.0. Anal. calcd for $C_{14}H_{15}N_9O$: C, 51.69; H, 4.65; N, 38.75; found: C, 51.91; H, 4.29; N, 39.09%.

*5-Amino-1-(5-amino-4-cyano-3-methyl-1*H*-pyrazole-1-carbonyl)-3-morpholino-1*H*-pyrazole-4-carbonitrile* (**10e**): Yield 65%; white solid; m.p. 268 °C (dec.); white solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 3.77–3.82 (m, $4CH_2$, 8H, morpholine), 7.52 (br.s, 4H, NH_2, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.8, 46.9, 51.3, 51.3, 66.7, 66.7, 70.3, 77, 114.8, 116.3, 152.8, 154.5, 156.2, 160.2. *m/z* calcd for $C_{14}H_{15}N_9O_2$ [M]$^+$: 341.13, found: 341.0. Anal. calcd for $C_{14}H_{15}N_9O_2$: C, 49.26; H, 4.43; N, 36.93; found: C, 49.49; H, 4.56; N, 37.37%.

*5-Amino-1-(5-amino-4-cyano-3-(piperidin-1-yl)-1*H*-pyrazole-1-carbonyl)-3-methyl-1*H*-pyrazole-4-carbonitrile* (**10f**): Yield 65%; white solid; m.p. 230–231°C, IR (KBr, υ_{max}/cm^{-1}): 3463, 3309, 3163, 3115, 2986, 2884, 2218, 2220, 1640, 1603, 1561; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79–1.81 (m, 2H, CH_2), 1.83–1.89 (m, 4H, $2CH_2$), 2.45(s, 3H, CH_3), 3.89 (t, *J*=5.6 Hz, 4H, $2CH_2$), 5.99 (br.s, 4H, NH_2, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.7, 23.7, 26.2, 26.2, 52.5, 52.5, 69.6, 79, 102, 113.95, 115.9, 152.5, 154.1, 156.8, 159.3. *m/z* calcd for $C_{15}H_{17}N_9O$ [M]$^+$: 339.16, found: 337.0. Anal. calcd for $C_{15}H_{17}N_9O$: C, 53.09; H, 5.05; N, 37.15; found: C, 53.49; H, 5.20; N, 37.40%.

*5-Amino-1-(5-amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carbonyl)-3-(pyrrolidin-1-yl)-1*H*-pyrazole-4-carbonitrile* (**10g**): Yield 63%; white solid; m.p. 270 °C (dec.), ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94 (t, *J*=6.4 Hz, 4H, $2CH_2$), 2.56 (s, 3H, SCH_3), 4.15 (t, *J*=6.4 Hz, 4H, $2CH_2$), 7.35 (br.s, 4H, $2NH_2$, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.3, 25.8, 25.8, 54.4, 54.4, 64.7, 75.1, 114.1, 117.7, 124.5, 148.7, 155.1, 155.4, 161.1. *m/z* calcd for $C_{14}H_{15}N_9OS$ [M]$^+$: 357.11, found: 357.0. Anal. calcd for $C_{14}H_{15}N_9OS$: C, 47.05; H, 4.23; N, 35.27; found: C, 47.35; H, 4.35; N, 35.48%.

*5-Amino-1-(5-amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carbonyl)-3-morpholino-1*H*-pyrazole-4-carbonitrile* (**10h**): Yield 60%, pale yellow solid; m.p. 243 °C; IR (KBr, υ_{max}/cm^{-1}): 3477, 3452, 3315, 3204, 2974, 2929, 2872, 2212, 1646, 1614, 1552; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.59 (s, 3H, SCH_3), 3.82–3.83 (m, 8H, $4CH_2$ morpholine), 7.65 (br.s, 4H, $2NH_2$, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.1, 51.3, 51.3, 66.7, 66.7, 69.8, 75.6, 113.9, 116.1, 124.5, 152.2, 155.1, 156.6, 160.4. *m/z* calcd for $C_{14}H_{15}N_9O_2S$ [M]$^+$: 373.11, found: 372.0. Anal. calcd for $C_{14}H_{15}N_9O_2S$: C, 45.03; H, 4.05; N, 33.76; found: C, 45.28; H, 4.14; N, 34.07%.

*5-Amino-1-(5-amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carbonyl)-3-(piperidin-1-yl)-1*H*-pyrazole-4-carbonitrile* (**10i**): Yield 55%; white solid; m.p. >300 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72 (m, 6H, $3CH_2$ piperidine), 2.61 (s, 3H, SCH_3), 3.74 (m, 4H, $2CH_2$ piperidine), 7.60 (br.s, 4H, $2NH_2$, D_2O exchangeable); ^{13}C NMR(100 MHz, DMSO-d_6): δ 13.1, 23.5, 26.2, 26.2, 52.2, 52.22, 69.4, 75.5, 114.1, 116.3, 152.4, 155.2, 156.4, 160.5. *m/z* calcd for $C_{15}H_{17}N_9OS$ [M]$^+$: 371.11, found: 371.0. Anal. calcd for $C_{15}H_{17}N_9OS$: C, 48.51; H, 4.61; N, 33.94; found: C, 48.72; H, 4.47; N, 33.76%.

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