Synthesis of spiro(cyclohexa-diene-pyrazolo[1,5-*a*]pyrimidine-4-ylidene)-malononitrile derivatives

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The reaction of 4-substituted aryldiazenyl-1*H*-pyrazole-3,5-diamines with 7,7',8,8'-tetra-cyanoquinodimethane gave 2-(2',7'-diamino-6'-cyano-3'-(aryldiazenyl)-4'*H*-spiro(cyclohexa[2,5]-diene-1,5'-pyrazolo[1,5-*a*]pyrimidine-4-ylidene) malononitriles in 63–79% yield, while, by reaction of 2-aminobenzimidazole with 7,7',8,8'-tetracyanoquinodimethane, 2-(3'-amino-4'-cyano-6'*H*-spiro-(cyclohexa[2',5']diene-1,5'-benzo(*d*)-imidazo[1,2-*a*]pyrimidine)-4-ylidene)malononitrile was formed in 71% yield. Rationales for these transformations are presented.

Keywords: aminopyrazole, tetracyanoquinodimethane, spiropyrazolo[1,5-*a*]pyrimidines

In recent years, attention has been increasing regarding the synthesis of spiroheterocyclic compounds which exhibit various biological activities,[1-6] pharmaceutical[7] and antitumor properties.[8] Pyrazolopyrimidines and related fused heterocycles have been identified as bioactive molecules.[1-6] They are known to function as CNS (Central Nervous System) depressants[9] and can be tuberculostatic.[10]

The biological and medicinal activities of condensed pyrazoles initiated considerable interest in the development of the synthesis of these molecules.[11-13] The synthesis and chemistry of pyrazolo[1,5-*a*]pyrimidines has recently been revived as revealed by the vast number of papers and patents which report routes for the synthesis of different biologically active pyrazolo[1,5-*a*]pyrimidine derivatives.[14-16]

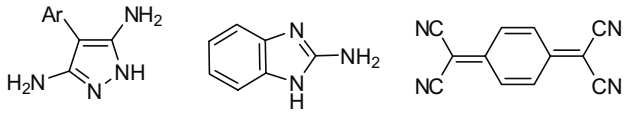
Robins and co-workers reported that certain 3-substituted pyrazolo[1,5-*a*]pyrimidines inhibit the metabolism of snails of Schistosomiasis.[17,18] Since, schistosomiasis is a health problem in Egypt, it has been reported that 2-aminopyrazolo[1,5-*a*]-pyrimidines showed strong antischistosomiasal activity.[19,20]

The reaction of 4-substituted aryldiazenyl-1*H*-pyrazole-3,5-diamines **1a–d** with ethenetetracarbonitrile[21,22] and (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile[23-25] afforded pyrazolo[1,5-*a*]pyrimidine derivatives.

Tetracyanoquinodimethane (**3**, TCNQ) has been widely used as an acceptor molecule to form highly conducting charge-transfer complexes.[26] It has been reported that the addition of **3** to acylthiosemicarbazides,[27] 2,5-dithiobiureas,[28] as well as aldehydic 4-phenylthiosemicarbazones gave different spiroheterocyclic compounds.[29]

We report an extension to our strategy based upon synthesis of heterocycles which have prospective biological and pharmaceutical activities,[30,31] In this publication we investigate the reaction of 4-substituted aryldiazenyl-1*H*-pyrazole-3,5-diamine **1a–d** and 2-aminobenzimidazole (**2**) with tetracyano-quinodimethane (**3**, **TCNQ**) as a π-electron deficient acceptor aiming to obtain spiropyrazolopyrimidines which might have prospective biological activities towards Schistosomiasal. Compounds **1a–d** (Fig. 1) have two exocyclic nitrogen and one endocyclic nitrogen that do enjoy nucleophilic sites.

Solutions of **1a–d** in dry pyridine were added dropwise to a solution of **3** (**TCNQ**) in the same solvent. The mixture were gently warmed to 50–60 °C and kept at this temperature for 3 h with stirring and finally warmed to 80 °C for 5 min. The residue obtained from concentration at 50 °C consisted of complex mixture containing a deep blue main component and numerous coloured byproducts each in small quantities. From their gross composition and spectroscopic evidence, the main products from **6a–d** were found to be formed from one molecule of **1** and one molecule of **3**. The visible absorptions in acetonitrile solution are around 650 nm. The IR spectra are



a, Ar = NNC_6H_5
b, Ar = NNC_6H_4-*p*-CH_3
c, Ar = NNC_6H_4-*p*-OCH_3
d, Ar = NNC_6H_4-*p*-Cl

Fig. 1

characterised by strong cyano-absorptions (2210–2220 cm^{-1}), NH_2 (3440–3446, 3387–3395 cm^{-1}), NH (3170–3186 cm^{-1}) and aryl C=C at 1590–1600 cm^{-1} as expected. The ^1H NMR spectrum of **6b**, for example clearly shows three broad signals with the ratio of 1 : 2 : 2 centred at δ_H = 9.88, 8.68 and 7.20 ppm. due to pyrimidine-NH, NH_2 attached to pyrimindine ring and NH_2 attached to pyrazole ring, respectively. The expected signals for CH_3 (δ_H = 2.23 ppm), hexadiene-CH (δ_H = 6.24, 6.52 ppm) and phenyl protons are observed. The salient features of ^{13}C NMR spectra (including ^{13}C DEPT spectra) of **6b** are the signals at δ_c = 18.62 (CH_3), 47.13 (q-C-1,5'), 73.18 [$C(CN)_2$], 78.92 (C-3'), 118.02, 118.56, 118.63 (CN), 152.42 (C-2) and 160.66 ppm (C-4).[32,33] Further peaks for C-6' and C-7' resonated at δ_c = 66.98 and 155.69 ppm., respectively, are in accordance with the observed trends in the δ values for C-atoms in push-pull alkenes.[34,35]

The EI mass spectra of **6a–d** are characterised by molecular ions of low intensity. The following common fragmentation patterns lend support to the assigned structures: Loss of CH_3 giving intense [M^+-15] ions and loss of ArN_2 giving rise to the ion *m/z* = 301 common in the spectra of all four compounds.

Compounds **1a–d** reacted with **3** to yield pyrazolo[1,5-*a*]pyrimidines that may be formulated as **6a–d** or isomeric **7a–d**. Thus if the initial addition involves ring nitrogen atom N-2, as has been assumed earlier,[21-25] Michael adduct **5** would be formed. This then cyclises to yield **7**. On the other hand, if the exocyclic amino function reacts with the acceptor **3**, compound **4** would be formed. Its cyclisation would then afford **6** (Scheme 1).

The *a priori* possible isomeric structures **7** were ruled out on the bases of ^{13}C NMR of compounds **6a–d**, the pyrimidine C-7' is regularly upfield shifted; **6a** (C-7' = 155.81 ppm); **6b** (C-7' = 155.69); **6c** (C-7' = 155.44); **6d** (C-7' = 155.31) compared to pyrimidine-C-5' in compound **7** which resonates downfield in 3-aminopyridazine derivatives at 166.59 ppm[36] and in 2-aminopyrrole derivatives at 166.25 ppm,[36] due to the presence of NH_2 and NH attached to pyrimidine-C-5'.

Attempts to react the product of **1a** and **3** with another molecule of **3** by heating them in pyridine failed and the reaction does not take place to form compound **8**.

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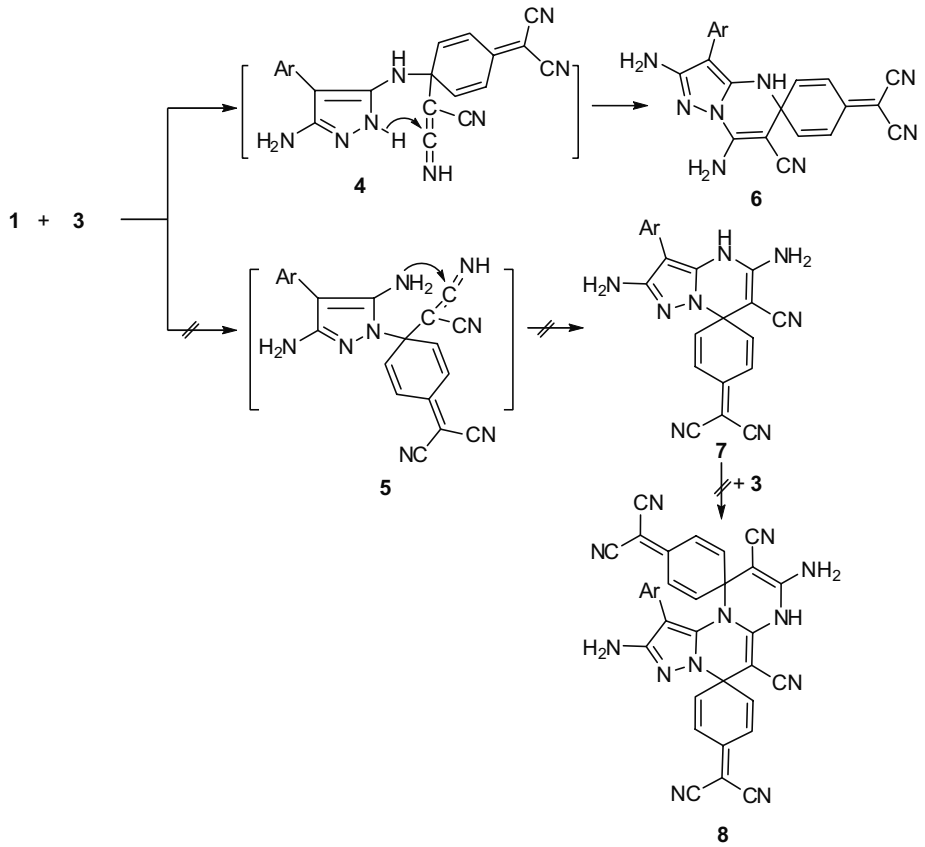


Scheme 1

Interestingly, the molecular modelling (MM2)[37] of **6a** as an example suggested structural feature of **6a** as indicated in Scheme 1. Since, the steric energy value of compound **6a** is found to be ΔE = 672.038 kcal mol^{-1} based on the aforementioned semi-empirical calculations using the MM2 level of theory,[37] whereas this value is increased in the case of **7** by 13 kcal mol^{-1}. The stability of compound **6** in this form supports the exclusion of any other expected isomeric forms.

Furthermore, Elnagdi *et al.*[38] reported recently, the reaction of 4-(arylazo)-5-ethyl-1*H*-pyrazol-3-ylamine with benzylidenemalononitrile in pyridine to afford pyrazolo[1,5-*a*]-pyrimidines *via* the reaction of exocyclic amino function followed by cyclisation. The regioorientation of the reagents has been determined by ^{15}N, ^{1}H/HMBC measurements as well as an X-ray crystal structure.

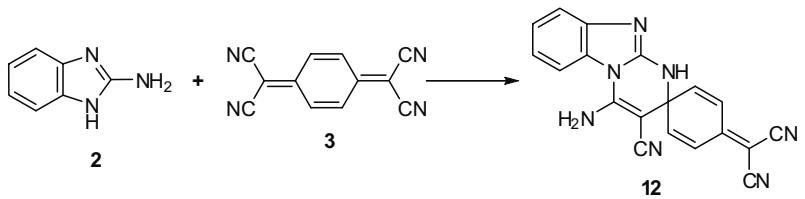
The analytical data of compound **6b** could also match for other isomers of products **9–11** (Fig. 2). The alternative structures **10** and **11** could be ruled out on the bases of ^{1}H NMR, due to the presence of one group NH_2 and three or four NH, whereas our spectral data of **6a–d** showed two groups of NH_2 and one NH. On the other hand, the alternative structure **9** could be ruled out also due to the presence of only one C=N group in ^{13}C NMR spectrum of **6a–d**.

As shown in Fig. 2, structure **6b** fits best to all the spectroscopic data (see experimental).

2-Aminobenzimidazole (**2**) was reacted similarly to **3** (TCNQ) with **1a–d** in pyridine with the formation of 2-(3'-amino-4'-cyano-6'*H*-spiro(cyclohexa[2',5']diene-1,5'-benzo(*d*)-imidazo[1,2-*a*]pyrimidine)-4-ylidene)malononitrile **12** (Scheme 2).

The structure assignment of **12** was supported by the following spectral data. In its ^{13}C NMR spectrum, the characteristic resonance signals of [C(CN)$_2$] and (C-4) appeared at δ_C = 72.94 and 160.08 ppm, respectively. Also, ^{13}C NMR spectrum shows signals at δ_C = 57.29 (q-C-1,5'), 66.85 (C-4'), 152.11 (C-1') and 155.37 (C-3'). The low-field pyrimidine-NH is presented at δ_H = 9.86 ppm, whereas another broad signals centred at 8.67 due to exocyclic pyrimidine-NH_2. The AA'BB' system of (3-H and 6-H) and (4-H and 5-H) appear as base line separated, AA' and BB' parts instead of narrow multiplets at 7.38 and 7.29 ppm, respectively.

From the elemental analysis and mass spectrometry, a net release of H_2N-C=C-CN (M wt, 66) had occurred. The mass spectrum showed also the following fragments 337 [M$^+$-66], *m/z* 90 (C_6H_4N), as well as dicyanomethylenehexadienyl fragment at *m/z* 141. The spectroscopic data found for the reaction product between **2** and **3** fit best for structure **12** which is perfectly analogous to structure **6**.



Scheme 2

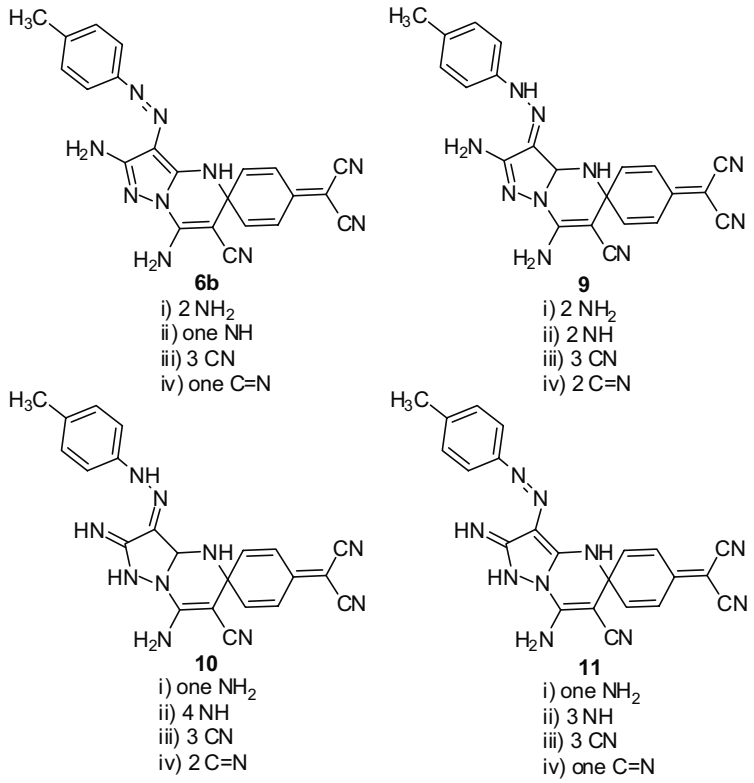


Fig. 2

Experimental

Melting points have been determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were determined by the Microanalytical Centre, Cairo University, Egypt. The IR spectra were recorded on Perkin-Elmer 397 and Shimadzu 480 spectrometers using potassium bromide pellets. The UV-vis spectra were recorded on Perkin-Elmer Lambda-2 spectrophotometer, stoppered 1.0 cm silica cell. ^{1}H NMR 300 MHz and ^{13}C NMR 75 MHz spectra were recorded on Bruker WM300 instrument and Bruker AM 400 (400.134 MHz and 100.60 MHz). The chemical shifts are expressed as δ [ppm] with reference tetramethylsilane as internal standard, s = singlet, d = doublet, dd = doublet of doublet and b = broad. ^{13}C assignments (qC = sp^2 quaternary carbon atoms) were made with the aid of DEPT 135/90 spectra. For EI (70 eV) mass spectra Varian MAT CH-7 was used. For preparation layer chromatography (plc) 1.0 mm thick air-dried layers of slurry applied silica gel Merck Pf_{254} on 48 cm wide and 20 cm high glass plates were used. Zones were detected by their colour and indicator fluorescence quenching upon 254 nm light and extracted with acetone.

Starting materials: 4-Aryldiazenyl-1H-pyrazole-3,5-diamines **1a–d**, were prepared utilising the procedure originally reported by Elnagdi et al.[39,40] 2-Aminobenzimidazole (2) and 7,7',8,8'-tetracyanoquinodimethane (3, TCNQ) were purchased from Aldrich and used as purchased.

Reaction of 7,7',8,8'-tetracyanoquinodimethane **(3,** *TCNQ) with 4-aryldiazenyl-1H-pyrazol-3,5-diamines* **1a–d** *or 2-aminobenzimidazole* **(2):** To a solution of **3** (TCNQ) (416 mg, 2.0 mmol) in dry pyridine (15 mL) a solution of **1a–d** or **2** (1.0 mmol each) in (5 mL) of dry pyridine was add dropwise over 5 minutes at room temperature with stirring. The mixture was warmed gently to 50–60 °C and kept at this temperature with stirring and admission of air for 3 h., then warmed to maximum 80 °C for 5 minutes and concentrated to dryness 50 °C. The residue was taken up several times with cold ethanol (15 mL) and the slurry was concentrated again to remove any residual pyridine. This operation was repeated four times. The residue was dissolved in (5 mL) acetone, this solution in each case was applied to five (PLC) plates and developed with toluene/ethyl acetate (2:1) for the run with **1a,d**, toluene/ethyl acetate (3:1) for the run with **1b,c** and **2**. Intense blue main zones from **1a–d** and from **2** were extracted. Crystallisation from acetonitrile afforded pure samples of **6a–d** and **12**, all appearing black (but tinted to some extent) with a metallic shine in incident light, but giving blue solutions in acetone or methanol. Numerous other mostly coloured zones were observed but it always contained too little materials to allow for isolation of significant amounts and had to be discarded as well as the tarry materials remaining at the start line.

2-(2',7'-Diamino-6'-cyano-3'-(phenyldiazenyl)-4'H-spiro(cyclohexa-[2,5]diene-1,5'-pyrazolo[1,5-a]pyrimidine)-4-ylidene)malononitrile **(6a):** Blue crystals (0.304 g, 75%), m.p. 284–286 °C (acetonitrile). IR (KBr): 3445, 3390 (NH_2), 3170 (NH), 2220, 2215 (CN), 1600 (ArC=C). UV-vis (acetonitrile) λ_{max} (log ε) = 653 (3.84). ^{1}H NMR (DMSO-d_6): δ = 6.26, 6.55 (dd, 4H, cyclohexadiene-H), 7.22 (br, 2H, NH_2 attached to pyrazole ring), 7.37–7.52 (m, 5H, ArH), 8.64 (br, 2H, NH_2 attached to pyrimidine ring), 9.91 (br, 1H, pyrimidine-NH). ^{13}C NMR (DMSO-d_6): δ = 56.93 (q-C-5'), 67.14 (C-6'), 73.26 ($C(CN)_2$), 79.12 (C-3'), 117.87, 118.41, 118.67 (CN), 124.14, 125.73 (cyclohexadiene-CH), 127.98, 128.41, 128.45 (ArCH), 131.23 (ArC), 151.74 (C-3'a), 152.36 (C-2'), 155.81 (C-7'), 161.12 (C-4). MS (*m/z*, %): 406 (M^+, 29), 301 (44), 235 (22), 179 (14), 105 (100), 77 (86), 66 (51). $C_{21}H_{14}N_{10}$ (406.40): Calcd C, 62.06; H, 3.47; N, 34.47. Found: C, 61.89; H, 3.61; N, 34.29%.

2-(2',7'-Diamino-6'-cyano-3'-(4-methylphenyldiazenyl)-4'H-spiro(cyclohexa[2,5]diene-1,5'-pyrazolo[1,5-a]pyrimidine)-4-ylidene)malononitrile **(6b)**: Blue crystals (0.332 g, 79%), m.p. 311–313 °C (acetonitrile). IR (KBr): 3440, 3395 (NH_2), 3180 (NH), 2220, 2215 (CN), 1595 (ArC=C). UV-vis (acetonitrile) λ_{max} (log ε) = 660 (3.96). ^{1}H NMR (DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 6.52, 6.28 (dd, 4H, cyclohexadiene-H, J = 8.41 Hz), 7.20 (br, 2H, NH_2 attached to pyrazole ring), 7.31 (d, 2H, 3',5'-ArH, J = 8.0 Hz), 7.49 (d, 2H, 2',6'-ArH, J = 8.0 Hz), 8.68 (br, 2H, NH_2 attached to pyrimidine ring), 9.88 (br, 1H, pyrimidine-NH). ^{13}C NMR (DMSO-d_6): δ = 18.02 (CH_3), 57.13 (q-C-5'), 66.98 (C-6'), 73.18 ($C(CN)_2$), 78.92 (C-3'), 118.02, 118.56, 118.63 (CN), 124.19, 125.69 (cyclohexadiene-CH), 127.81, 128.39 (ArCH), 132.16, 139.22 (ArC), 152.14 (C-3'a), 152.42 (C-2'), 155.69 (C-7'), 160.66 (C-4). MS (*m/z*,%): 420 (M^+, 41), 405 (22), 301 (35), 235 (18), 179 (11), 119 (93), 91 (100), 77 (56), 66 (63). $C_{22}H_{16}N_{10}$ (420.43): Calcd C, 62.85; H, 3.84; N, 33.32. Found: C, 63.04; H, 3.95; N, 33.19%.

2-(2',7'-Diamino-6'-cyano-3'-(4-methoxyphenyldiazenyl)-4'H-spiro(cyclohexa[2,5]diene-1,5'-pyrazolo[1,5-a]pyrimidine)-4-ylidene)malononitrile **(6c)**: Blue crystals (0.314 g, 72%), m.p. 332–334 °C (acetonitrile). IR (KBr): 3445, 3390 (NH_2), 3186 (NH), 2218, 2210 (CN), 1600 (ArC=C). UV-vis (acetonitrile) λ_{max} (log ε) = 664 (4.02). ^{1}H NMR (DMSO-d_6): δ = 3.87 (s, 3H, OCH_3), 6.25, 6.54 (dd, 4H, cyclohexadiene-H, J = 8.03 Hz), 7.18 (br, 2H, NH_2 attached to

pyrazole ring), 7.27 (d, 2H, 3',5'-ArH, J = 8.27 Hz), 7.47 (d, 2H, 2',6'-ArH, J = 8.27 Hz), 8.65 (br, 2H, NH_2 attached to pyrimidine ring), 9.90 (br, 1H, pyrimidine-NH). ^{13}C NMR (DMSO-d_6): δ = 56.97 (q-C-5'), 59.27 (OCH_3), 67.08 (C-6'), 73.22 ($C(CN)_2$), 79.06 (C-3'), 117.92, 118.49, 118.58 (CN), 124.22, 125.62 (cyclohexadiene-CH), 127.85, 128.41 (ArCH), 139.65 (ArC), 151.94 (C-3'a), 152.51 (C-2'), 154.16 (ArC-O), 155.44 (C-7'), 159.96 (C-4). MS (*m/z*,%): 436 (M^+, 37), 421 (278), 301 (19), 235 (26), 179 (18), 135 (69), 107 (81), 92 (100), 77 (93), 66 (57). $C_{22}H_{16}N_{10}O$ (436.43): Calcd C, 60.54; H, 3.70; N, 32.09. Found: C, 60.71; H, 3.58; N, 31.88%.

2-(2',7'-Diamino-6'-cyano-3'-(4-chlorophenyldiazenyl)-4'H-spiro(cyclohexa[2,5]diene-1,5'-pyrazolo[1,5-a]pyrimidine)-4-ylidene)malononitrile **(6d)**: Blue crystals (0.277 g, 63%), m.p. 347–349 °C (acetonitrile). IR (KBr): 3440, 3387 (NH_2), 3175 (NH), 2215, 2210 (CN), 1590 (ArC=C). UV-vis (acetonitrile) λ_{max} (log ε) = 649 (3.90). ^{1}H NMR (DMSO-d_6): δ = 6.22, 6.52 (dd, 4H, cyclohexadiene-H, J = 7.96 Hz), 7.22 (br, 2H, NH_2 attached to pyrazole ring), 7.30 (d, 2H, 3',5'-ArH, J = 8.14 Hz), 7.55 (d, 2H, 2',6'-ArH, J = 8.14 Hz), 8.61 (br, 2H, NH_2 attached to pyrimidine ring), 9.87 (br, 1H, pyrimidine-NH). ^{13}C NMR (DMSO-d_6): δ = 56.92 (q-C-5'), 66.90 (C-6'), 73.19 ($C(CN)_2$), 78.94 (C-3'), 117.91, 118.42, 118.55 (CN), 124.44, 125.28 (cyclohexadiene-CH), 127.35, 128.51 (ArCH), 130.26, 138.26 (ArC), 152.08 (C-3'a), 152.46 (C-2'), 155.31 (C-7'), 159.93 (C-4). MS (*m/z*, %): 442/440 (M^+, 29), 405 (55), 301 (38), 235 (22), 179 (17), 140 (55), 112 (36), 77 (100), 66 (84). $C_{21}H_{13}ClN_{10}$ (440.85): Calcd C, 57.21; H, 2.97; Cl, 8.04; N, 31.77. Found: C, 56.98; H, 3.09; Cl, 7.87; N, 31.92%.

2-(3-Amino-4-cyano-6'H-spiro(cyclohexa[2',5']diene-1,5-benzo-[d]imidazo[1,2-a]-pyrimidine)-4-ylidene)malononitrile **(12)**: Blue crystals (0.239 g, 71%), m.p. 243–245 °C (acetonitrile). IR (KBr): 3420 (NH_2), 3190 (NH), 2220, 2215 (CN), 1630 (C=N), 1590 (ArC=C). UV-vis (acetonitrile) λ_{max} (log ε) = 610 (3.76). ^{1}H NMR (DMSO-d_6): δ = 6.27, 6.58 (dd, 4H, cyclohexadiene-H, *J* = 8.11 Hz), 7.29 (m, BB', 2H, 4,5-ArH), 7.38 (m, 2H, AA', 3,6-A.r-H), 8.67 (br, 2H, NH_2 attached to pyrimidine ring), 9.86 (br, 1H, pyrimidine-NH). ^{13}C NMR (DMSO-d_6): δ = 57.29 (q-*C*-1,5), 67.05 (*C*-4), 72.96 (*C*$(CN)_2$), 124.27, 125.43 (cyclohexadiene-*C*H), 126.87, 127.32 (ArCH), 139.66 (Ar*C*), 152.11 (*C*-1), 155.23 (*C*-3), 160.08 (*C*-4). MS (*m/z*,%): 337 (M^+, 29), 271 (37), 181 (21), 141 (47), 90 (100), 77 (82), 66 (55). $C_{19}H_{11}N_7$ (337.34): Calcd C, 67.65; H, 3.29; N, 29.06. Found: C, 67.81; H, 3.40; N, 28.87%.

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