Synthesis, characterisation and bioactivity of polysubstituted 1-(4-(1H-pyrrol-1-yl)phenyl)-1H-pyrrole derivatives

Abdel-Zaher A. Elassar

Chemistry Department, Faculty of Science, Helwan University, Ain Helwan, Cairo, Egypt

1,4-Phenylenediamine reacted readily with chloroacetone to give 1,4-bis[(2-oxopropyl)amino]benzene which was used to prepare 1-(4-(1H-pyrrol-1-yl)phenyl)-1H-pyrrole derivatives in a one pot reaction with dimethylformamide dimethylacetal or triethyl orthoformate and an active methylene nitrile, an active methylene ketone or an ylidene-malononitrile. Reaction of 1,4-bis[(2-oxopropyl)amino]benzene with arene diazonium salts afforded the hydrazone derivatives which readily cyclised when reacted with malononitrile to give bispyrrole derivatives. The antibacterial activity of some of the products was determined.

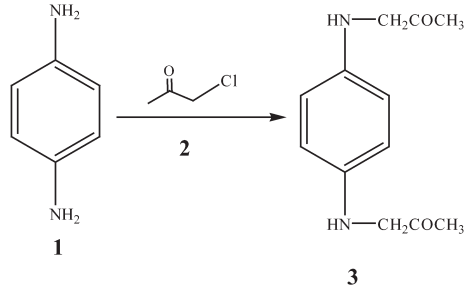
Keywords: bispyrrole, chloroacetone, phenylenediamine, antibacterials

Pyrrole and its fused derivatives have aroused recent attention as potent anticancer agents.[1–4] Several mechanisms are involved in their cytotoxic activities as being dihydrofolate reductase inhibitors,[5] tyrosine kinase inhibitors,[6] cyclin dependant kinase inhibitors[7] or adenosine receptor antagonist.[8] Pyrroles show many types of biological activity, for example, *in vitro* antibacterial activity of novel 3-(1H-pyrrol-1-yl)-2-oxazolidinone analogues of PNU-100480,[9] antiproliferative activity in HL60 cells by tetrasubstituted pyrroles,[10] and cyclase inhibitors.[11] Recently, aryl pyrroles have been reported as potent inhibitors of Ras farnesyltransferase with regression of tumors grown in nude mouse xenograft models.[12]

Many natural products contain a pyrrole subunit 8 as the basic core. Of particular interest is the remarkable diversity of biological activity associated with the 3,4-disubstituted 1*H*-pyrrole scaffold. From a synthetic point of view, pyrroles substituted in position 3 and 4 are difficult to prepare, most of the reactivity being concentrated at the α-position of the pyrrole. We now report the preparation of polysubstituted bispyrroles in one pot reactions upon treating 1,4-bis[(2-oxopropyl)amino]benzene with DMFDMA, and an active methylene nitrile or an active methylene ketone.

Results and discussion

1,4-Phenylenediamine **1** reacted with chloroacetone **2** with molar ratio1:2 in the presence of sodium hydrogen carbonate to give the bis alkylated product **3**[13] (Scheme 1). The structure of Compound **3** was confirmed by elemental analysis and spectral data. The accurate mass showed *m/z* at 220.12, in addition ^{1}H NMR revealed the presence of methylene and methyl protons as singlets at δ 4.16 and 2.50 ppm, respectively. In addition, the aromatic protons appeared at δ 6.92 ppm. ^{13}C NMR showed carbonyl carbon at δ 206.4 and aromatic and sp^3 carbons appeared at δ 148.9, 145.1, 126.4, 125.8, 65.0, 25.3 ppm.



1 **2** **3**

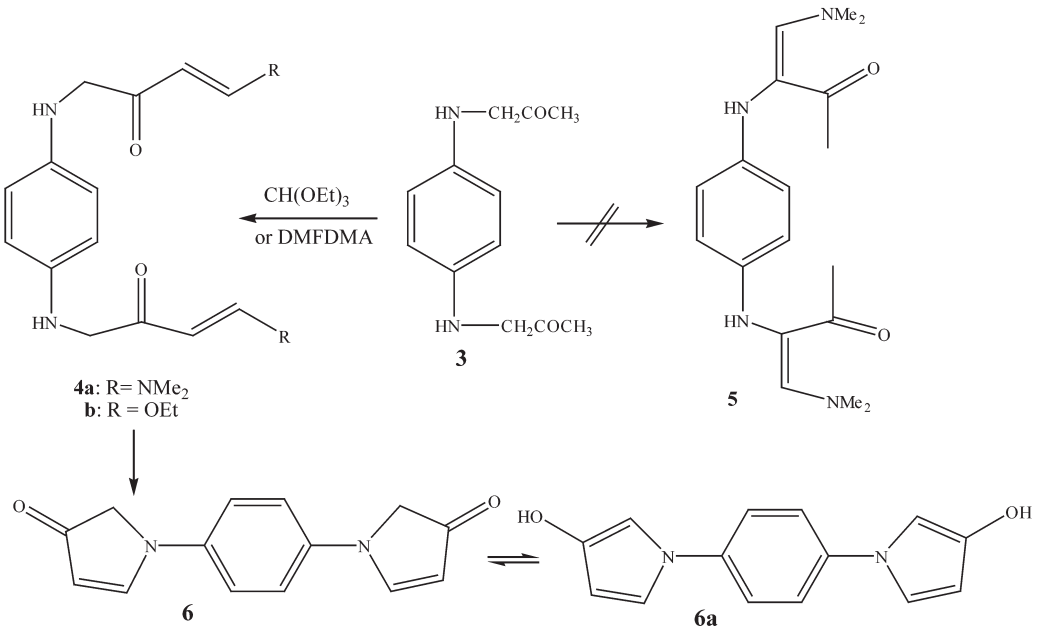
Scheme 1

Compound **3** reacted with dimethylformamide dimethyl acetal (DMFDMA) to give α,β-unsaturated ketone **4a** or **5**. The latter Compound **5** was ruled out based on the ^{1}H NMR, which confirmed Compound **4a** as the *E*-structure, the ethylenic protons appearing at δ 5.12 and 7.63 ppm with J = 13 Hz as required for such E-coupled protons.[14] Compound **4a** cyclised under basic conditions to give via loss of two molecules dimethylamine, **6**, which tautomerised to 1-(4-(3-hydroxy-1H-pyrrol-1-yl)phenyl)-1H-pyrrol-3-ol, **6a**. The same reaction product **6a** was obtained from reaction of Compound **3** and triethyl orthoformate in a one-pot reaction. This product was believed to proceed through formation of the non isolated intermediate **4b** followed by loss of two ethanol molecules to give the final isolated product **6a**. The IR (KBr disc) revealed the presence of a hydroxyl group at 3419 cm^{-1} which means Compound **6** must predominate as **6a** in the solid state. MS showed accurate mass at *m/z* 240.09 which agreed with the molecular formula $C_{14}H_{12}N_2O_2$. ^{1}H NMR showed a singlet aromatic proton at δ 6.91 ppm which reflects the symmetry of the 1,4-substitutent. Pyrrole protons appeared as two compiled doublets at δ 6.85 and 6.53 ppm (J = 8.4 Hz) and a singlet at δ 6.35 ppm. The hydroxyl proton appeared at δ 5.03 ppm.

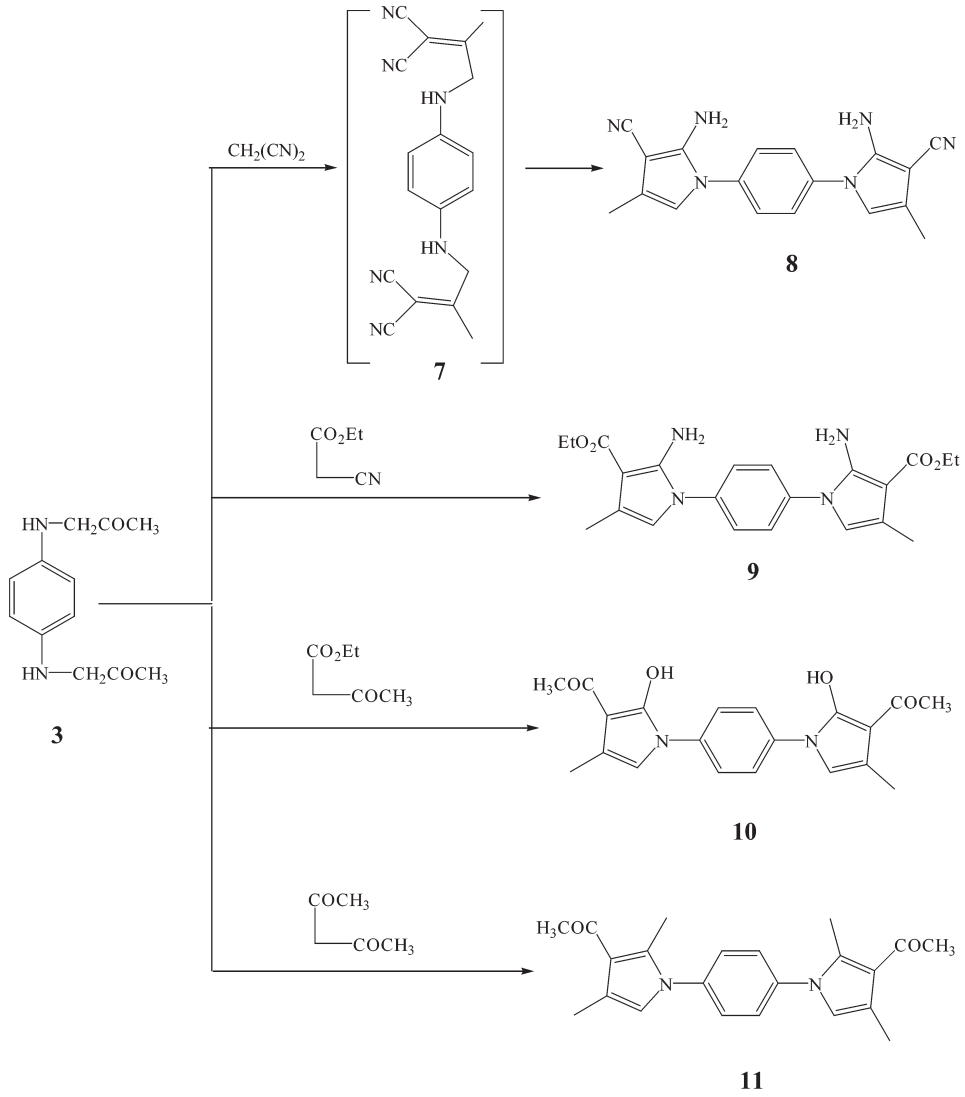
Bispyrroles could also be obtained upon treating Compound **3** with an active methylene nitrile or an active methylene ketone. For example, Compound **3** reacted with malononitrile to give 2-amino-4-methyl-1-(4-(2-amin-3-cyano-4-methyl-1*H*-pyrrol-1-yl)phenyl)-1*H*-pyrrol-3-carbonitrile **8**. The reaction product is assumed to form via addition of the methylene group of malononitrile to the electrophilic carbonyl carbon followed by loss of a water molecule to give the non isolated condensation intermediate **7**. The intermediate **7** cyclised under the reaction conditions via addition of NH to the cyano group to give the final isolated product **8**. Compound **8** showed accurate mass 316.14, in addition IR revealed the presence of an amino and a cyano group at 3358, 3226 and 2187 cm^{-1}, respectively. Similarly, Compound **3** reacted with ethyl cyanoacetate, ethyl acetoacetate and acetyl acetone to give bispyrrole derivatives **9**, **10** and **11**, respectively. The reaction products were formed via condensation followed by cyclisation and tautomerisation. Structure elucidation was confirmed by elemental analysis and spectral data (see Experimental).

Compound **3** also reacted with a series of ylidenemalononitriles **12a–d** to give 5-acetyl-2-amino-4-aryl-1-(4-(5-acetyl-2-amino-3-cyano-4-aryl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitriles, **14a–d** or **15**.Compound **15** was ruled out based on IR which revealed the presence of a carbonyl group at 1684 to 1704 cm^{-1} as expected for **14a–d**. The isolated product **14a–d** were believed to be formed via Michael addition of the active methylene group in Compound **3** to the ylidene double bond to give intermediate **13**. This intermediate cyclised under the reactions condition to give the final isolated products **14a–d**.

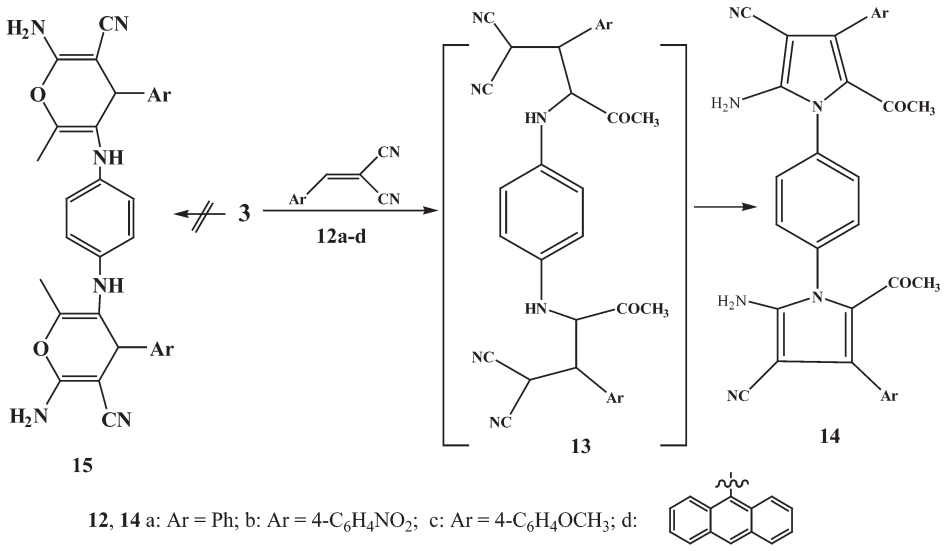
* Correspondent. E-mail: aelassar@yahoo.com



Scheme 2



Scheme 3



12, **14** a: Ar = Ph; b: Ar = 4-$C_6H_4NO_2$; c: Ar = 4-$C_6H_4OCH_3$; d:

Scheme 4

The nitrogen electrophile of arene diazonium salts **16a–c** coupled with compound **3** to form hydrazone derivatives **17a–c** (Scheme 5). The MS of products **17a–c** showed *m/z* at 428.5, 518.5 and 497.0, respectively. IR, showed a carbonyl group at 1689 cm^{-1} for each of **17a–c**; this is may be due to hydrogen bonding with the NH group. All other data *e.g.* ^1H NMR, ^{13}C NMR and elemental analysis confirmed the formation of the reaction products **17a–c** (see experimental). Heating of compound **17** with malononitrile in the presence of ammonium acetate at 160 °C gave the bispyrrole derivatives **18a–c**. The latter could also be obtained via coupling of compound **8** with an arene diazonium salt **16a–c**.

Bioactivity of synthesised compounds: The diverse biological activities of pyrroles[3,9–11,15–20] prompted us to test and study the biological activities of some of the newly synthesised products. Table 1 shows that most of the tested compounds had high activity. Indeed, compounds **18c** with *E. Coli*; **6**, **9**, **10** with *S. Aureus*; **9** with *B. Subtilis* and **8** with *P. Aeruginosa* showed high 8 effects. While Compounds **6**, **8**, **11**, **18b** with *E. coli*; **18a** with *S. aureus*; **3**, **6**, **10**, **18b** with *B. subtilis* and **10**, **11** with *P. Aeruginosa* showed high effects. Other Compounds showed with different microorganisms a moderate to weak effect (see Table 1).

Conclusions

In summary, using *N*-alkylated *p*-phenylenediamine provided an efficient synthesis of substituted bisazoles.

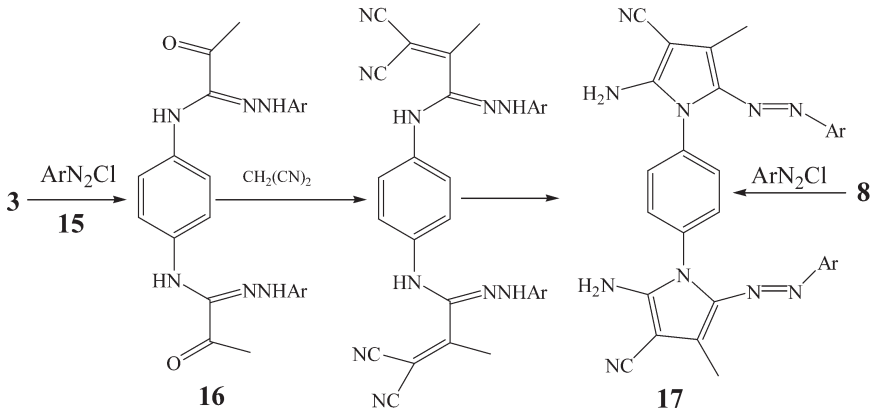
Experimental

All melting points are uncorrected. IR spectra were recorded in KBr with an IR spectrophotometer Shimadzu 408. ^1H NMR and ^{13}C NMR spectra were recorded on Varian EM-390 MHz spectrometer using TMS as internal standard reference and chemical shifts are expressed as δ ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt.

Synthesis of 1,4-bis[(2-oxopropyl)amino]benzene (**3**):[13] To a solution of *p*-phenylenediamine (0.01 mol) in acetone (30 mL) containing sodium hydrogen carbonate (0.01 mol), 1-chloropropanone (0.01 mol) was added drop wise over a period of 1h. The reaction mixture was left overnight at room temperature and then the solid product formed collected by filtration, washed thoroughly with water and then dried over anhydrous sodium sulfate and recrystallised.

Pale brown crystals (80%) from DMSO/EtOH, m.p. > 250 °C; IR: 3327 (NH), 1704 cm^{-1} (CO); ^1H NMR: δ 8.03 (br, 2H, 2NH, D_2O-exchange), 6.92 (s, 4H, aromatic-H), 4.16 ppm (s, 4H, $2CH_2$), 2.50 (s, 6H, 2Me); ^{13}C NMR: δ 206.4 (CO), 148.9, 145.1, 126.4, 125.8, 65.0, 25.3 (aromatic, carbons methylene and methyl carbons); Accurate mass: *m/z* 220.12; Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.33; H, 6.96; N, 12.64%.

(E)-4-(dimethylamino)-1-(phenylamino)but-3-en-2-one (**4a**): To a solution of **3** (0.01 mol) in DMF (30 mL), dimethyl formamide dimethyl acetal (0.01 mol) was added. The reaction mixture was warmed and left overnight. The solid product formed was collected by filtration, washed thoroughly with water and then recrystallised. Brown crystals (70%) from DMF/EtOH, m.p. 140 °C; IR: 3327 (NH),



15, 16, 17 a: Ar = Ph; **b**: Ar = C_6H_4-p-NO_2 ; **c**: Ar = C_6H_4-4-Cl

Scheme 5

Table 1 Biological activity of the prepared compounds

Cpd	*E. Coli*	*S. Aureus*	*B. Subtilis*	*P. Aeruginosa*
3	++	+++	+++	++
6	+++	++++	+++	++
8	+++	++	++	++++
9	+	++++	++++	+
10	++	++++	+++	+++
11	+++	++	++	+++
17a	++	+++	++	++
17b	+++	++	+++	++
17c	++++	++	++	+

++++ Severe effect (>30 mm), +++ high effect (25–29 mm), ++ moderate effect (20–24 mm), + weak effect (< 20 mm)

1704 cm^{-1} (CO); ^{1}H NMR: δ 8.03 (br, 2H, 2NH, D_2O-exchange), 6.78 (s, 4H, aromatic-H), 5.12 and 7.63 (d, 4H, 4CH=, *J* = 13 Hz), 4.32 ppm (s, 4H, $2CH_2$), 2.96 (s, 12H, $2NMe_2$); ^{13}C NMR: δ 196.4 (CO), 152.2, 140.9, 136.1, 101.1 (aromatic and ethylenic carbons), 62.2 (CH_2), 43.3 (NMe_2); Accurate mass: *m/z* 330.21; Anal. Calcd for $C_{18}H_{26}N_4O_2$ (330.42): C, 65.43; H, 7.93; N, 16.96. Found: C, 65.49; H, 7.69; N, 16.76%.

Synthesis of 1-(4-(3-hydroxy-1H-pyrrol-1-yl)phenyl)-1H-pyrrol-3-ol (**6a**)

Method A: To a solution of **4a** (0.01 mol) in DMF (30 mL), triethylamine (10 drops) was added. The reaction mixture was heated under reflux for 3h. The solid product formed was collected by filtration, washed thoroughly with water and then recrystallised.

Method B: To a solution of **3** (0.01 mol) in DMF (30 mL) and triethylamine (10 drops), triethyl orthoformate or dimethyl formamide dimethyl acetal (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon addition of water was collected by filtration, washed thoroughly with water and then dried over anhydrous sodium sulfate and recrystallised.

6a: Brown crystals (80%) from DMSO/EtOH, m.p.>250 °C; IR: 3419 cm^{-1} (OH); ^{1}H NMR: δ 5.03 (br, 2H, 2OH, D_2O-exchange), 6.91 (s, 4H, aromatic-H), 6.85, 6.53 (dd, 4H, 2pyrrole-H, *J* = 8.4 Hz), 6.35 (s, 2H, 2pyrrole-H); ^{13}C NMR: δ 145.1, 137.3, 129.6, 120.8, 117.0, 114.2, 115.1 (aromatic and pyrrole carbons). Accurate mass: *m/z* 240.09; Anal. Calcd for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66. Found: C, 70.10; H, 4.96; N, 11.64%.

Synthesis of 2-amino-1-(4-(2-amino-3-cyano-4-methyl-1H-pyrrol-1-yl)phenyl)-4-methyl-1H-pyrrole-3-carbonitrile (**8**); *ethyl 2-amino-1-(4-(2-amino-3-ethylcarboxylate-4-methyl-1H-pyrrol-1-yl)phenyl)-4-methyl-1H-pyrrole-3-carboxylate* (**9**); *3-acetyl-2-hydroxy-1-(4-(3-acetyl-2-hydroxy-4-methyl-1H-pyrrol-1-yl)phenyl)-4-methyl-1H-pyrrole* (**10**); *3-acetyl-1-(4-(3-acetyl-2,4-dimethyl-1H-pyrrol-1-yl)-phenyl)-2,4-dimethyl-1H-pyrrole* (**11**).

To a solution of **3** (0.01 mol) in DMF (30 mL), triethylamine (0.01mole), malononitrile or ethyl cyanoacetate, ethyl acetoacetate or acetyl acetone (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon addition of water was collected by filtration, washed thoroughly with water and then dried over anhydrous sodium sulfate and recrystallised.

8: Brown crystals (60%) from acetone, m.p. > 250 °C; IR: 3358, 3226 (NH_2), 2187 cm^{-1} (CN); ^{1}H NMR: δ 6.93 (s, 4H, C_6H_4), 7.24 (br, 4H, $2NH_2$, D_2O-exchange), 6.64 (s, 2H, pyrrole-H), 2.08 (s,6H, 2Me); ^{13}C NMR: δ 137.6, 121.0 (C_6H_4 carbons). 120.8, 120.7, 120.6, 114.3 (pyrrole carbons), 117.9 (CN), 24.0 (Me); Accurate mass: *m/z* 316.14; Anal. Calcd for $C_{18}H_{16}N_6$ (316.36): C, 68.34; H, 5.10; N, 26.56. Found: C, 68.33; H, 4.98; N, 26.64%.

9: Pale brown crystals (70%) from acetone, m.p.> 250 °C; IR: 3358, 3226 (NH_2), 1736 cm^{-1} (CO); ^{1}H NMR: δ 6.91 (s, 4H, C_6H_4), 7.25 (br, 4H, $2NH_2$, D_2O-exchange), 6.70 (s, 2H, pyrrole-H), 4.20 (q, 4H, $2CH_2$), 2.23 (s, 6 H, 2Me), 1.31 (t, 6H, 2Me); ^{13}C NMR: δ 165.5 (CO), 137.6, 121.1 (C_6H_4 carbons). 121.0, 120.6, 120.6, 114.3 (pyrrole carbons), 60.6 (CH_2), 14.5 (Me); Accurate mass: *m/z* 410.20; Anal. Calcd for $C_{22}H_{26}N_4O_4$ (410.47): C, 64.37; H, 6.38; N, 13.65. Found: C, 64.33; H, 6.38; N, 13.64%.

10: Pale brown crystals (74%) from acetone, m.p. > 250 °C; IR: 3443 (OH), 1711 cm^{-1} (CO); ^{1}H NMR: δ 6.90 (s, 4H, C_6H_4), 6.23 (br, 2H, 2OH, D_2O-exchange), 6.78 (s, 2H, pyrrole-H), 2.53 (s, 6H, 2Me), 2.08 (s, 6H, 2Me); ^{13}C NMR: δ 201.0 (CO), 137.9, 122.1 (C_6H_4 carbons). 121.0, 120.8, 120.6, 114.3 (pyrrole carbons), 28.6, 14.7 (2Me); Accurate mass: *m/z* 352.14; Anal. Calcd for $C_{20}H_{20}N_2O_4$ (352.38): C, 68.17; H, 5.72; N, 7.95. Found: C, 68.33; H, 5.98; N, 7.64%.

11: Pale brown crystals (70%) from acetone, m.p. > 250 °C; IR: 1711 cm^{-1} (CO); ^{1}H NMR: δ 6.92 (s, 4H, C_6H_4), 6.78 (s, 2H, pyrrole-H), 2.55 (s, 6H, 2Me), 2.23 (s, 6H, 2Me), 2.08 (s, 6H, 2Me); ^{13}C NMR: δ 200.9 (CO), 137.9, 122.1 (C_6H_4 carbons), 136.4 122.0, 120.8, 120.6 (pyrrole carbons), 29.0, 14.7, 12.8 (3Me); Accurate mass: *m/z* 348.18; Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.44): C, 75.83; H, 6.94; N, 8.04. Found: C, 75.76; H, 6.98; N, 7.98%.

Synthesis of 2-(anthracen-9-ylmethylene)malononitrile (**12d**)

To a solution of anthracene-9-carbaldehyde (0.01 mol) and malononitrile (0.01 mol) in ethanol (20 mL), triethylamine (five drops) was added. The reaction mixture was warmed and then left at room temperature for 2 h. The solid product was collected by filtration and recrystallised.

12d: Orange crystals (90%) from ethanol, m.p. 202–204 °C; IR: 2229 cm^{-1} (CN); ^{1}H NMR: δ 8.86 (s, 1H, ethylenic-H)), 9.66 (s, 1H, anthracene-H_8), 8.22–8.17 (t, 4H, anthracene-H), 7.71–7.64 (m, 4H, anthracene-H); ^{13}C NMR: δ 162.5 (CH=), 135.2, 131.4, 130.6, 129.3, 128.4, 125.8, 125.1 (anthracene carbons), 113.4, 112.2 (2CN), 92.0 (C=); accurate mass: *m/z* 254.08; Anal. Calcd for $C_{18}H_{10}N_2$ (254.29): C, 85.02; H, 3.96; N, 11.02. Found: C, 85.12; H, 3.98; N, 10.99%.

Synthesis of 5-acetyl-2-amino-4-phenyl-1-(4-(5-acetyl-2-amino-3-cyano-4-phenyl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile (**14a**); *5-acetyl-2-amino-4-*p*-nitrophenyl-1-(4-(5-acetyl-2-amino-3-cyano-4-*p*-nitrophenyl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile* (**14b**); *5-acetyl-2-amino-4-*p*-methoxyphenyl-1-(4-(5-acetyl-2-amino-3-cyano-4-*p*-methoxy phenyl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile* (**14c**); *5-acetyl-2-amino-4-anthracen-10-yl-1-(4-(5-acetyl-2-amino-3-cyano-4-anthracen-9-yl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile* (**14d**)

To a solution of **3** (0.01 mol) in DMF (30 mL), benzylidenemalononitrile or *p*-nitrobenzylidene-malononitrile or *p*-methoxybenzylidenemalononitrile or 2-(anthracen-10-ylmethylene)malon-onitrile (0.01 mol) and 10 drops triethylamine were added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon addition of water was collected by filtration, washed thoroughly with water then dried over anhydrous sodium sulfate and recrystallised.

5-Acetyl-2-amino-4-phenyl-1-(4-(5-acetyl-2-amino-3-cyano-4-phenyl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile (**14a**): Brown crystals (56%) from acetone, m.p. 186–188 °C; IR: 3374, 3236 (NH_2), 2188 (CN), 1688 cm^{-1} (CO); ^{1}H NMR: δ 7.59–7.02 (m, 10H, $2C_6H_5$), 6.93 (m, 4H, C_6H_4), 7.32 (br, 4H, $2NH_2$), 2.50 (s, 6H, 2Me); ^{13}C NMR: δ 201.0 (CO), 136.9, 121.6 (C_6H_4 carbons), 136.3, 129.3, 128.8, 127.5, 126.8 (phenyl carbons), 136.8,129.0, 127.9, 108.1 (pyrrole carbons), 20.9, 20.1 (2Me); MS: *m/z* 524.5; Anal. Calcd for $C_{32}H_{24}N_6O_2$ (524.57): C, 73.27; H, 4.61; N, 16.02. Found: C, 73.32; H, 4.78; N, 16.42%.

*5-Acetyl-2-amino-4-*p*-nitrophenyl-1-(4-(5-acetyl-2-amino-3-cyano-4-*p*-nitrophenyl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile* (**14b**): Brown crystals (56%) from acetone, m.p. 117–119 °C; IR: 3359, 3256 (NH_2), 2188 (CN), 1704 cm^{-1} (CO), ^{1}H NMR: δ 8.37–7.78 (m, 8H, $2C_6H_4$), 6.94 (m, 4H, $2C_6H_4$), 7.64 (br, 4H, $2NH_2$), 2.50 (s, 6H, 2Me); ^{13}C NMR: δ 153.4 (CO), 131.0, 123.4 (C_6H_4 carbons), 148.6, 143.9, 128.9, 120.6 (*p*-nitrophenyl carbons), 136.8,129.4, 127.4, 112.7 (pyrrole carbons), 20.9, 18.5 (2Me); MS: *m/z* 614.5; Anal. Calcd for $C_{32}H_{22}N_8O_6$ (614.57): C, 62.54; H, 3.61; N, 18.23. Found: C, 62.45; H, 3.77; N, 18.20%.

*5-Acetyl-2-amino-4-*p*-methoxyphenyl-1-(4-(5-acetyl-2-amino-3-cyano-4-*p*-methoxyphenyl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile* (**14c**): Brown crystals (73%) from acetone, m.p. > 250 °C; IR: 3417, 3386 (NH_2), 2183 (CN), 1684 cm^{-1} (CO); ^{1}H NMR: δ 7.87–7.42 (m, 8H, $2C_6H_4$), 6.96 (m, 4H, C_6H_4), 7.30 (br, 4H, $2NH_2$), 3.01 (s, 6H, 2OMe), 2.50 (s, 6H, 2Me); ^{13}C NMR: δ 201.0 (CO), 137.9, 122.6 (C_6H_4 carbons), 155.4, 129.3, 128.8, 127.5, 126.8 (*p*-methoxyphenyl carbons), 136.8,129.0, 127.9, 108.1 (pyrrole carbons), 49.5, 50.1 (2OMe), 20.9, 20.1 (2Me); MS: *m/z* 584.5; Anal. Calcd for $C_{34}H_{28}N_6O_4$ (584.62): C, 69.85; H, 4.83; N, 14.38. Found: C, 70.01; H, 4.77; N, 14.34%.

5-Acetyl-2-amino-4-anthracen-10-yl-1-(4-(5-acetyl-2-amino-3-cyano-4-anthracen-9-yl-1H-pyrrol-2-yl)phenyl)-1H-pyrrole-3-carbonitrile (**14d**): Brown crystals (56%) from acetone, m.p. 186–188 °C; IR: 3374, 3226 (NH_2), 2191 (CN), 1684 cm^{-1} (CO); ^{1}H NMR: δ 8.86–7.51 (m, 18H, 2 anthracene), 6.74 (m, 4H, $2C_6H_4$), 7.39 (br, 4H,

$2NH_2$), 2.53 (s, 6H, 2Me); ^{13}C NMR: δ 162.7 (CO), 131.3, 121.9 (C_6H_4 carbons), 131.1, 131.0, 129.7, 128.9, 128.6, 127.4, 126.5 (anthracene carbons), 136.8,129.0, 127.4, 114.8 (pyrrole carbons), 116.8, 116.1 (2CN), 36.2, 31.2 (2Me); MS: *m/z* 724.8; Anal. Calcd for $C_{48}H_{32}N_6O_2$ (724.81): C, 79.54; H, 4.45; N, 11.59. Found: C, 79.33; H, 4.62; N, 11.54%.

Synthesis of 1,4-bis[(2-oxopropyl-3-phenylhydrazo)amino]benzene (**17a**); *1,4-bis[(2-oxopropyl-3-(*p-*nitrophenylhydrazo))amino]benzene* (**17b**); *1,4-bis[(2-oxopropyl-3-(*p-*chlorophenylhydr azo))amino] benzene* (**17c**).

A mixture of **3** (0.01 mol) in DMF (30 mL), sodium hydroxide (1.0 g), the appropriate arene diazonium chloride (0.01 mol) [prepared by adding sodium nitrite (0.02 mol) to the appropriate primary aromatic amine (0.01 mol) in concentrated HCl (2 mL) at 0–5 °C while stirring] was added dropwise while cooling at 0–5 °C and stirring. The reaction mixture was left at 5 °C for 3 h. The solid product that formed was filtered off and washed many times with water and then recrystallised.

1,4-Bis[(2-oxopropyl-3-phenylhydrazo)amino]benzene (**17a**): Brown crystals (51%) from acetone, m.p. > 250 °C; IR: 3334, 3223 (2NH), 1689 cm^{-1} (CO); ^{1}H NMR: δ 7.01–6.76 (m, 10H, 2 phenyl), 6.74 (m, 4H, $2C_6H_4$),10.23, 7.39 (br, 4H, 4NH), 2.23 (s, 6H, 2Me); ^{13}C NMR: δ 176.7 (CO), 156.2 (C=N), 135.3, 121.7 (C_6H_4 carbons), 143.2, 131.2, 122.2, 121.3 (phenyl carbons), 28.2, 28.4 (2Me); MS: *m/z* 428.5; Anal. Calcd for $C_{24}H_{24}N_6O_2$ (428.49): C, 67.27; H, 5.65; N, 19.61. Found: C, 67.43; H, 5.56; N, 19.70%.

*1,4-Bis[(2-oxopropyl-3-(*p-*nitrophenylhydrazo))amino]benzene* (**17b**): Brown crystals (51%) from acetone, m.p. > 250 °C; IR: 3334, 3223 (2NH), 1689 cm^{-1} (CO); ^{1}H NMR: δ 8.01–7.76 (m, 8H, 2 *p*-nitrophenyl), 6.76 (m, 4H, C_6H_4),10.33, 7.39 (br, 4H, 4NH), 2.33 (s, 6H, 2Me); ^{13}C NMR: δ 193.0 (CO), 156.2 (C=N), 135.3, 121.7 (C_6H_4 carbons), 152.0, 143.2, 123.2, 122.0 (*p*-nitrophenyl carbons), 29.3, 29.4 (2Me); MS: *m/z* 518.5; Anal. Calcd for $C_{24}H_{22}N_8O_6$ (518.48): C, 55.60; H, 4.28; N, 21.61. Found: C, 55.55; H, 4.43; N, 21.71%.

*1,4-Bis[(2-oxopropyl-3-(*p-*chlorophenylhydrazo))amino]benzene* (**17c**): Brown crystals (56%) from acetone, m.p. > 250 °C; IR: 3334, 3223 (2NH), 1689 cm^{-1} (CO); ^{1}H NMR: δ 7.81–6.56 (m, 8H, 2 *p*-chlorophenyl), 6.95 (m, 4H, C_6H_4),10.33, 7.39 (br, 4H, 4NH), 2.23 (s, 6H, 2Me); ^{13}C NMR: δ 176.7 (CO), 156.3 (C=N), 135.4, 121.6 (C_6H_4 carbons), 143.8, 131.6, 122.3, 121.3 (p-chlorophenyl carbons), 28.4, 28.5 (2Me); MS: *m/z* 497.0; Anal. Calcd for $C_{24}H_{22}Cl_2N_6O_2$ (497.38): C, 57.96; H, 4.46; N, 16.90. Found: C, 58.01; H, 4.56; N, 16.71%.

Synthesis of 2-amino-1-(4-(2-amino-3-cyano-4-methyl-5-phenyldiazenyl-1H-pyrrol-1-yl)phenyl)-4-methyl-5-phenyldiazenyl-1H-pyrrole-3-carbonitrile (**18a**); *2-amino-1-(4-(2-amino-3-cyano-4-methyl-5-*p-*nitrophenyldiazenyl-1H-pyrrol-1-yl)phenyl)-4-methyl-5-*p-*nitrophenyldiazenyl-1H-pyrro-le-3-carbonitrile* (**18b**); *2-amino-1-(4-(2-amino-3-cyano-4-methyl-5-*p-*chlorophenyldiaz-enyl-1H-pyrrol-1-yl) phenyl)-4-methyl-5-*p-*chlorophenyldi-azenyl-1H-pyrrole-3-carbonitrile* (**18c**)

A mixture of **17** (0.01 mol), ammonium acetate (5–7g) and malononitrile (0.01 mol) was heated at 160 °C for 2h. The solid product so formed was collected by filtration, washed thoroughly with water and then dried over sodium sulfate anhydrous and recrystallised from proper solvent.

2-Amino-1-(4-(2-amino-3-cyano-4-methyl-5-phenyldiazenyl-1H-pyrrol-1-yl)phenyl)-4-methyl-5-phenyldiazenyl-1H-pyrrole-3-carbonitrile (**18a**): Brown crystals (56%) from acetone, m.p. > 250 °C; IR: 3342, 3348 ($2NH_2$), 2210, 2212 cm^{-1} (CN); ^{1}H NMR: δ 10.43 (br, 4H, $2NH_2$), 7.61–7.32 (m, 10H, phenyl), 6.94 (m, 4H, C_6H_4), 2.11 (s, 6H, 2Me); δ ^{13}C NMR: δ 128.4, 126.3, 124.7, 124.2 (pyrrole carbons), 137.4, 121.6 (C_6H_4 carbons), 133.6, 131.6, 122. 1, 121.5 (phenyl carbons), 21.9, 21.7 (2Me); MS: *m/z* 524.5; Anal. Calcd for $C_{30}H_{24}N_{10}$ (524.58): C, 68.69; H, 4.61; N, 26.70. Found: C, 68.63; H,4.51; N, 26.81%.

*2-Amino-1-(4-(2-amino-3-cyano-4-methyl-5-*p-*nitrophenyldiazenyl-1H-pyrrol-1-yl)phenyl)-4-methyl-5-*p-*nitrophenyldiazenyl-1H-pyrrole-3-carbonitrile* (**18b**): Brown crystals (56%) from acetone, m.p. > 250 °C; IR: 3340, 3342 ($2NH_2$), 2210, 2212 cm^{-1} (CN); ^{1}H NMR: δ 10.48 (br, 4H, $2NH_2$), 8.51–7.32 (m, 8H, p-nitrophenyl), 6.93 (m, 4H, C_6H_4), 2.14 (s, 6H, 2Me); δ ^{13}C NMR: δ 128.6, 126.2, 124.5, 124.1 (pyrrole carbons), 137.4, 121.7 (C_6H_4 carbons), 138.6, 137.6, 122.1, 121.5 (p-nitrophenyl carbons), 22.9, 22.8 (2Me); MS: *m/z* 614.5; Anal. Calcd for $C_{30}H_{22}N_{12}O_4$ (614.57): C, 58.63; H, 3.61; N, 27.35. Found: C, 58.50; H, 3.44; N, 27.55%.

*2-amino-1-(4-(2-amino-3-cyano-4-methyl-5-*p-*chlorophenyldiazenyl-1H-pyrrol-1-yl)phenyl)-4-methyl-5-*p-*chlorophenyldiazenyl-1H-pyrrole-3-carbonitrile* (**18c**): Brown crystals (56%) from acetone, m.p. > 250 °C; IR: 3340, 3342 ($2NH_2$), 2210, 2213 cm^{-1} (CN); ^{1}H NMR: δ 10.23 (br, 4H, $2NH_2$), 7.60–7.33 (m, 8H, p-chlorophenyl), 6.91 (m, 4H, C_6H_4), 2.23 (s, 6H, 2Me); δ ^{13}C NMR: δ 128.4, 126.5, 124.6, 124.2 (pyrrole carbons), 137.4, 121.6 (C_6H_4 carbons), 133.5, 131.2, 122.2, 121.5 (phenyl carbons), 21.9, 21.8 (2Me); MS: *m/z* 593.50; Anal. Calcd for $C_{30}H_{20}Cl_2N_{10}$ (593.47): C, 60.71; H, 3.74; N, 23.60. Found: C, 60.62; H, 3.51; N, 23.74%.

Bioactivity: minimum inhibitory concentration (MIC)

The selected compounds were screened for their antibacterial activity against *E. coli*, *P. aeruginosa*, *B. subtlitis* and *S. aureus*. MIC was evaluated by the turbidity method. A loopful of bacteria was inoculated in 100 mL of nutrient broth at 37 °C for 20 h in a test-tube shaker at 150 rev min^{-1}. The test Compounds were prepared by dissolving in a minimal volume of DMSO and were serially diluted in Mueller-Hinton broth at concentrations in the range of 1–100 mg mL^{-1}. The 24-h bacterial cultures were then transferred into 10 mL of Muller-Hinton broth (control and test Compounds) and incubated at 37 °C for 24h. The growth of the bacteria was determined by measuring the turbidity after 24h. Thus, the MIC was generally read as the smallest concentration of drug in the series that prevents the development of visible growth of test organism. All the experiments were done in triplicate.

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