Cyclization of 4,5-Diamino Pyrazole Derivatives and Their Antibacterial Activities

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A convenient synthesis of intermediate 4,5-diamino-3-aryl-1-phenylpyrazoles **4a**—**4c** was reported. The different cyclization reactions were carried out with chalcone, 2-mercaptoacetic acid and *p*-anisialdehyde, ethyl chloroformate, glyoxal and thiourea to afford different N and S containing heterocycles. The reaction conditions were compared by conventional heating and microwave irradiation. The structures of the cyclization products were determined by analytical and spectroscopic data. All the synthesized compounds were screened for antibacterial activities *in vitro*.

Keywords 4,5-diaminopyrazole, cyclization, fused heterocyclic ring systems, microwave chemistry, antibacterial activities

Introduction

In the recent years, the chemistry of fused heterocyclic compounds has attracted great attention due to their wide applications for pharmacological screening as drug candidates. The fused heterocyclic compounds containing pyrazole moieties are one of an important classes which display wide range of pharmaceutical and biological activates against depressions, anxiety, and other stress pathologies as well as selective growth associated molecule kinases (GAMK)-receptor modulators,[1a-1e] strong sedative effect and considerable analgesic activity.[2] Various 4,5-diaminopyrazoles have been reported as intermediate in the synthesis of 1,2,4-triazoles,[3] imidazo[4,5-*c*]pyrazoles[4] and benzodiazepines.[5] These fused systems have been evaluated as anti-cancer activity,[6] anti-HIV inhibitors,[7] antiasthmatic and antinflammatory activity.[8] The 4,5-diaminopyrazoles were reported by preparation of different methods.[9-11] In order to find more new N and S containing pyrazole heterocycles with biological activity, here we synthesize a series of new compounds by cyclization of 4,5-diamino pyrazole with different reactions.

Results and discussion

In conjunction to our interest in the synthesis and reactivity of *o*-diaminopyrazoles, we evaluated two routes for synthesis of 1-phenyl-3-aryl-4,5-diaminopyrazoles **4a**—**4c**. Firstly, from 4-nitroso-5-aminopyrazole derivatives **3a**—**3c** by reduction with stannous chloride in aqueous HCl, the yield of the reaction was about 15% —20%. Secondly, from 3-aryl-5-amino-4-arylazopyrazoles derivatives **2a**—**2c** by reduction with sodium dithionite in ethanol, the yield of the reaction was about 61%—75% (Scheme 1). The IR spectra of compounds **2a**—**2c** showed the presence of stretching vibrations for the N=N group at 1600—1650 cm^{-1} and two absorption at 3264—3310 cm^{-1} for amino group. The mass spectra of compounds **2a**—**2c** showed M^+ at 339 (90%), 368 (90%) and 357 (100%) respectively. The IR spectra of compounds **3a**—**3c** showed the presence of stretching vibrations for the NO group at 1600—1640 cm^{-1} and two absorption at 3300—3406 cm^{-1} for amino group. Furthermore, the ^1H NMR spectra of compounds **3a**—**3c** showed the presence of a singlet NH_2 protons at δ 8.2—8.5 which disappeared by mixing with D_2O, and multiplet at 6.7—8.2 for aromatic protons. The mass spectra of compounds **3a**—**3c** showed M^+ at 264 (54%), 278 (90%) and 297 (80%) respectively. The IR spectra of compounds **4a**—**4c** showed the presence of stretching vibrations for the C=N group of pyrazole ring at 1596—1597 cm^{-1} and two absorption at 3182—3300 cm^{-1} for two amino groups. Furthermore, the ^1H NMR spectra of compounds **4a**—**4c** showed a singlet NH_2 protons at position 4 with δ 3.5—4.8, singlet NH_2 protons at position 5 with δ 4.7—5.8 which disappeared by mixing with D_2O, multiplet at 7.1—7.5 for 5 protons of phenyl attached to the nitrogen atom and multiplet at 7.5—8.0 for 4 protons of phenyl attached to the C-3 of the pyrazole nucleus. The mass spectra of compounds **4a**—**4c** showed M^+ at 250 (100%), 264 (100%) and 269 (100%) respectively.

The reaction of 4,5-diamino pyrazoles **4a**—**4c** with one equivalent of 3-(4-methoxyphenyl)-1-*p*-tolylprop-2-ene-1-one (chalcone) in alcohol, in the presence of catalytic amounts of acetic acid gave only one product

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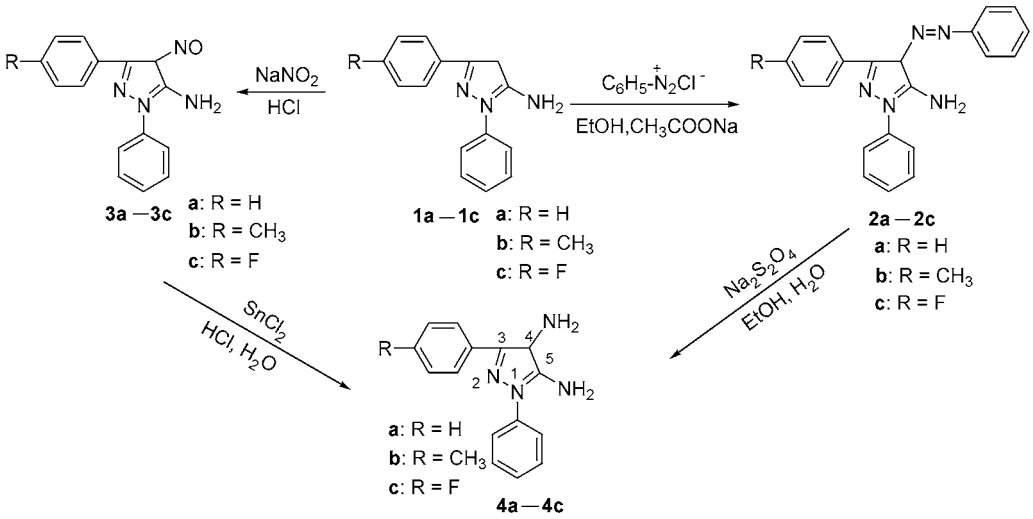
Received August 9, 2010; revised November 12, 2010; accepted March 23, 2011.

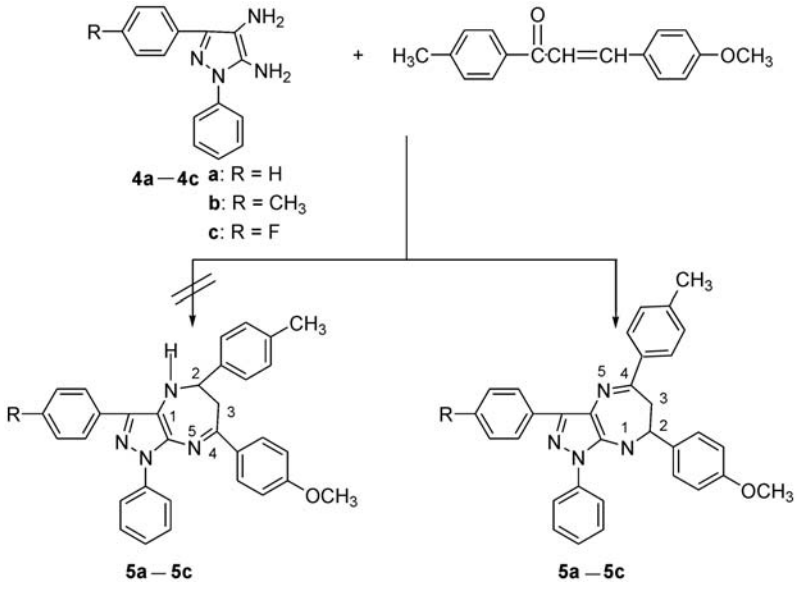
Scheme 1



5a—**5c** as seen clearly from TLC and ^{1}H NMR spectra. This result can be attributed to the non equivalence of the two amino groups in pyrazole nucleus. We assume that, the initial step, is the condensation reaction between the carbonyl group of chalcone and the amino group in position 4 of **4a**—**4c** (with higher nucleophile activity), followed by Michael addition of the less nucleophilic amino group at position 5 to the C=C bond[12a-12d] (Scheme 2). The IR spectra of **5a**—**5c** showed typical absorption bands for NH between 3301 and 3361 cm^{-1} and 1597—1604 cm^{-1} for the C=N group of pyrazole ring. The ^{1}H NMR spectra showed the proton on N-1 as doublet at δ 5.3—5.9 indicating the coupling of the vicinal proton on C-2, the protons on C-2 are triplet at δ 4.6—5.4. The geminal protons on C-3 are at δ 2.7—2.9, 3.3—3.8 (two doublet of doublet), and the aromatic protons appeared as unresolved multiplet at δ 6.7—8.5, the mass spectra of compounds **5a**—**5c** showed M^+ at 484 (50%)**,** 498 (30%) and 502 (100%) respectively.

The reaction of 4,5-diaminopyrazole derivatives **4a**—**4c** in three components system with 2-mercaptoacetic acid and *p*-anisaldehyde gave 4-(4-methoxyphenyl)-1-phenyl-3-substituted-4*H*,6*H*-thiazolo[3,4-*a*]pyrazoloimidazole **6a**—**6c** (Scheme 3), these results were in accordance to the previously reported.[13] The structure of compounds **6a**—**6c** was confirmed by ^{1}H NMR spectra which showed a singlet at δ 3.6 for OCH_3 group, δ 5.2—5.3, 5.5—5.7 (two doublet of doublet) for CH_2, singlet at δ 6.2—6.4 for CH of thiazole moiety and multiplet at δ 6.4—7.7 of the aromatic moieties, the mass spectra of compounds **6a**—**6c** showed M^++2 at 426 (50%)**,** 453 (70%) and 443 (80%) respectively.

Scheme 2



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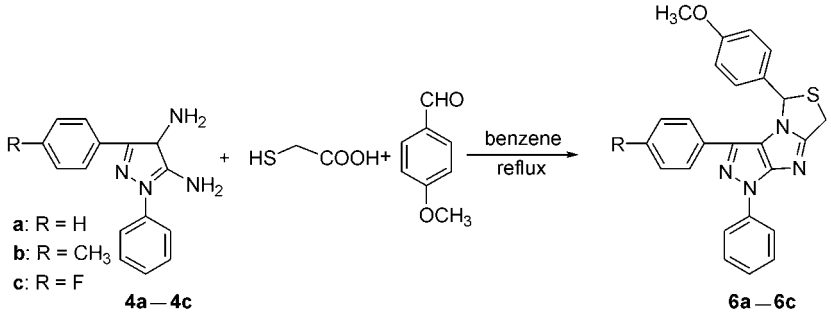
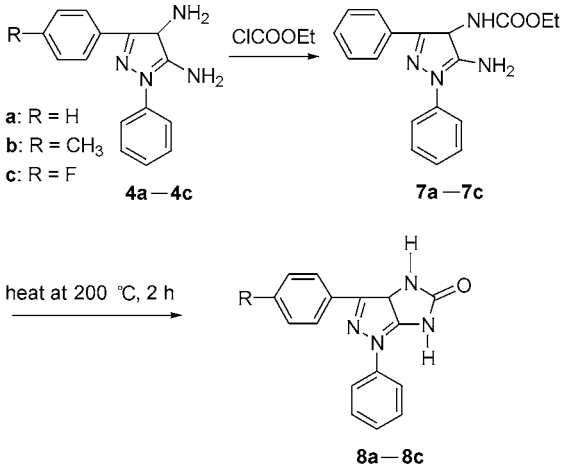
Scheme 3



The reaction of 4,5-diaminopyrazole derivatives **4a**—**4c** with ethyl chloroformate gave 5-amino-4-ethoxycarbonylamino pyrazoles **7a**—**7c**. Their structures were confirmed by IR spectra which showed absorption bands at 1730—1750 cm^{-1} assigned to C=O group, two absorptions at 3310—3350 cm^{-1} attributed to amino group. The ^1H NMR spectra showed a triplet at δ 1.3—1.5 for CH_2 group, quartet at δ 4.4—4.5 for CH_3 of ethoxy group, and singlet at 5.6—5.7 assigned to amino group. Heating **7a**—**7c** for 2 h at 200 ℃ afforded imidazo[4,5-*c*]pyrazol-5-one **8a**—**8c** (Scheme 4). The structure of compounds **7a**—**7c** was confirmed by IR spectra which showed absorption bands at 1677—1684 cm^{-1} for C=O group and the absent absorption of NH_2 group. ^1H NMR spectra showed a broad signal for 2NH groups at δ 8.3—8.7 which disappeared by mixing of D_2O and a multiplet at δ 6.4—7.7 for aromatic protons. The mass spectra of compounds **8a**—**8c** showed M^+ at 276 (64%), 290 (100%) and 294 (30%) respectively.

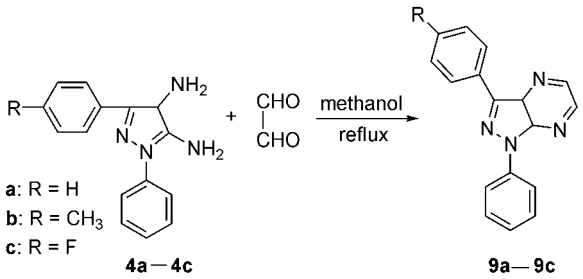
Scheme 4



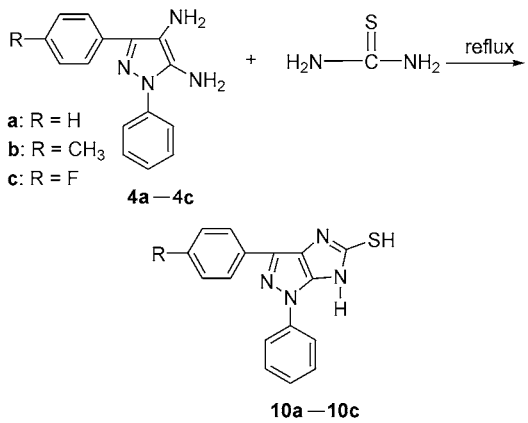
Refluxing of 4,5-diamino pyrazole derivatives **4a**—**4c** with glyoxal in methanol gave pyrazolo[2,3-*d*]-pyrazine **9a**—**9c** (Scheme 5). The mass spectra of compounds **9a**—**9c** showed M^+ at 274 (80%), 286 (100%) and 290 (25%) respectively.

Refluxing of diamino compounds **4a**—**4c** with thiourea in diphenyl ether afforded directly the desired compounds 1-phenyl-3-substituted-1,6-dihydroimidazo-[4,5-*c*]pyrazole-5-thiol **10a**—**10c** (Scheme 6). It is worthy to note that Hofmann[14] reported that, the preparation of the similar products could be conducted by the reaction of *o*-phenylenediamine with urea followed by thiation with phosphorus pentasulfide in pyridine. The IR spectra of such compounds showed absorption bands for the SH group at 2317—2363 cm^{-1}. The mass spectra of compounds **10a—10c** showed M^+ at 292 (90%), 306 (30%) and 310 (27%) respectively.

Scheme 5



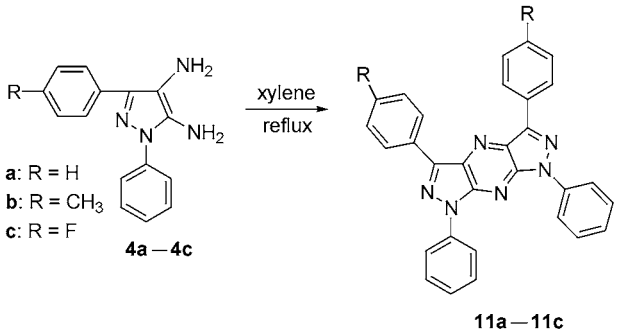
Scheme 6



Refluxing of diamino compounds **4a**—**4c** in xylene for 2 h led to formation of bispyrazolopyrazine compounds **11a**—**11c** by the dimerization and loss of two molecules of ammonia and one molecule of hydrogen (Scheme 7). The mass spectra of compounds **11a**—**11c**

showed M^+ at 464 (90%), 492 (100%) and 500 (60%) respectively.

Scheme 7



All the above mentioned reactions were compared by single step process involving the microwave irradiation of an equimolar mixture of starting materials and reagents in a suitable solvent. The results are grouped in Table 1.

Table1 Experimental conditions for microwave irradiation[a]

Product	Temperature/℃	Time/min	Yield/%	Solvent
5a—**5c**	160	15	92, 98, 94	Ethanol
6a—**6c**	160	20	91, 92, 95	Benzene
8a—**8c**[a]	160	20	95, 90, 97	Ethyl acetate
9a—**9c**	140	20	98, 90, 92	Methanol
10a—**10c**	160	20	91, 91, 93	Diphenyl ether
11a—**11c**	140	15	90, 93, 96	Xylene

[a] The obtained product was the cyclized form directly from the reaction medium.

The following observations were concluded: (a) The different reactions were carried out at 140—160 ℃. (b) The reactions were done in a few minutes (15—20 min). (c) The yield of the most reactions was over 90%. (d) Most of the products were obtained in pure form.

Experimental

All melting points were uncorrected. IR spectra were recorded on a Perkin-Elmer1430 spectrophotometer using KBr disk technique. ^{1}H NMR spectra were measured on a Bruker AC spectrometer (300 MHz for ^{1}H) in deuterated dimethylsulphoxide (DMSO-d_6) using tetramethylsilane (TMS) as the internal reference. Electron impact mass spectra (EI) were obtained using a Finnigan MAT 8222 spectrometer at 70 eV. Microanalyses for C, H and N were performed on a Perkin-Elmer 240 elemental analyzer. Reactions under microwave irradiation were preformed using Synthos 3000 dual magnetrons system in closed vessels under magnetic stirring and with maximum power of 400 W. Progress of reactions was monitored by the thin-layer chromatography (TLC) using benzene/ethyl acetate (9∶1, *V*/*V*) as eluent. Compounds **1a**—**1c** were previously reported,[15a-15f] **2a**,[16] **3a**, **3b**,[17,15c] **4a**,[18] **7a** & **8a**,[19] **9a**[20], **10a**[17] and **11a**.[21] It was worthy to note that compounds **8a**, **9a**, **10a** and **11a** were prepared by other routes and also by microwave irradiation. All the experimental and spectroscopic data were mentioned for the synthesized compounds.

General procedures for the synthesis of 1-phenyl-3-substituted-4-(phenyldiazenyl)-1*H*-pyrazol-5-amine (2a—2c)

A solution of sodium nitrite (0.9 g, 12.7 mmol) in water (10 mL) was added drop wise to a cold solution of aniline (1.27 mL, 13.7 mmol) in concentated HCl (4 mL). The diazonium salt obtained was added with continuous stirring to a cold solution of 5-aminopyrazoles **1a**—**1c** (8.5 mmol) in ethanol (42 mL) containing sodium acetate (3.4 g) at pH＝6. The reaction mixture was stirred at 0 ℃ for 2 h and the colored solid formed was filtered, washed with water, dried and crystallized from ethanol.

1,3-Diphenyl-4-(phenyldiazenyl)-1*H*-pyrazol-5-amine (2a) Product in 80% yield, as yellow crystals, m.p. 180—182 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.1—7.8 (m, 15H, Ar-H), 8.2 (s, exch., 2H, NH_2); IR (KBr) *v*: 3264 (NH_2), 1600 (N＝N) cm^{-1}; MS *m/z* (%): 339.2 (M^+, 90), 245 (47), 235 (52), 77 (60), 51 (37). Anal. calcd for $C_{21}H_{17}N_5$ (339.39): C 74.32, H 5.05, N 20.63; found C 74.45, H 5.10, N 20.63.

1-Phenyl-4-(phenyldiazenyl)-3-*p*-tolyl-1*H*-pyrazol-5-amine (2b) Product in 80% yield, as yellow crystals, m.p. 160—162 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.3—7.8 (m, 14H, Ar-H), 8.2 (s, exch., 2H, NH_2); IR (KBr) *v*: 3294 (NH_2), 1630 (N＝N), 2.3 (s, 3H, CH_3) cm^{-1}; MS *m/z* (%): 368.2 (M^+, 90), 242 (20), 191 (80), 169 (70), 139 (75), 107 (30), 77 (70), 51 (57). Anal. calcd for $C_{23}H_{22}N_5$ (368.45): C 74.97, H 6.02, N 19.01; found C 74.75, H 6.10, N 19.23.

3-(4-Fluorophenyl)-1-phenyl-4-(phenyldiazenyl)-1*H*-pyrazol-5-amine (2c) Product in 80% yield, as yellow crystals, m.p. 190—192 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.3—8.0 (m, 14H, Ar-H), 8.4 (s, exch., 2H, NH_2); IR (KBr) *v*: 3310 (NH_2), 1650 (N＝N) cm^{-1}; MS *m/z* (%): 357.2 (M^+, 100), 245 (67), 235 (58), 77 (76), 51 (47). Anal. calcd for $C_{21}H_{16}FN_5$ (357.38): C 70.58, H 4.51, N 19.60, F 5.32; found C 70.75, H 4.43, N 19.60, F 5.32.

General procedures for the synthesis of 4-nitroso-1-phenyl-3-substituted-1*H*-pyrazol-5-amine (3a—3c)

A solution of $NaNO_2$ (0.260 g, 3.77 mmol) in water (2.5 mL) was added drop wise to a solution of 5-aminopyrazoles **1a**—**1c** (3.77 mmol) in aqueous 4.5 mol/L HCl (50 mL) at 0 ℃. The solution was stirred at 0 ℃ for 10 min and then the resultant reaction was allowed to warm slowly to room temperature and stirred for 15 min and the colored solid formed was filtered, washed with water, dried and crystallized from ethanol.

4-Nitroso-1,3-diphenyl-1*H*-pyrazol-5-amine (3a)

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Product in 87% yield, as orange crystals, m.p. 180—182 ℃; ^{1}H NMR (DMSO-d_6) δ: 8.2 (s, 2H, NH_2), 6.7—8.1 (m, 10H, Ar-H); IR (KBr) v: 3402 (NH_2), 1600 (N=O) cm^{-1}; MS *m/z* (%): 264.1 (M^+, 54), 143 (66.6), 130 (22.3), 103 (17.3) 77 (100), 51 (66.9). Anal. calcd for $C_{15}H_{12}N_4O$ (264.282): C 68.17, H 4.58, N 21.20; found C 68.27, H 4.66, N 21.42.

4-Nitroso-1-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-amine (3b) Product in 79% yield, as reddish crystals, m.p. 195—197 ℃; ^{1}H NMR (DMSO-d_6) δ: 8.5 (s, 2H, NH_2) 2.3 (s, 3H, CH_3), 6.7—8.2 (m, 9H, Ar-H); IR (KBr) v: 3332 (NH_2), 1640 (N=O) cm^{-1}; MS *m/z* (%): 278.1 (M^+, 90), 235 (60), 191 (25), 103 (17), 77 (100), 51 (90). Anal. calcd for $C_{16}H_{14}N_4O$ (278.1): C 69.05, H 5.07, N 20.13; found C 69.11, H 5.07, N 20.33.

3-(4-Fluorophenyl)-4-nitroso-1-phenyl-1*H*-pyrazol-5-amine (3c) Product in 83% yield, as brown crystals, m.p. 183—185 ℃; ^{1}H NMR (DMSO-d_6) δ: 8.4 (s, 2H, NH_2), 6.7—8.3 (m, 9H, Ar-H); IR (KBr) v: 3355 (NH_2), 1630 (N=O) cm^{-1}; MS *m/z* (%): 282.27 (M^+, 80), 64 (80), 235 (60), 130 (35), 103 (30), 77 (100), 51 (70). Anal. calcd for $C_{15}H_{11}FN_4O$ (282.27): C 63.83, H 3.93, N 19.85, F 6.73; found C 63.55, H 3.77, N 19.93, F 6.62.

General procedures for the synthesis of 1-phenyl-3-substituted-4,5-diaminopyrazole (4a—4c)

Method A A solution of $NaNO_2$ (0.26 g, 3.77 mmol) in water (2.5 mL) was added dropwise to a solution of 5-aminopyrazoles **1a**—**1c** (3.77 mmol) in aqueous 4.5 mol/L HCl (50 mL) at 0 ℃. The solution was stirred at 0 ℃ for 10 min and then a solution of stannous chloride dehydrate (3.4 g, 15.1 mmol) in concentrated HCl (20 mL) was added slowly. The resultant reaction mixture was allowed to warm slowly to room temperature and stirred for 15 min. The solution was then basified with NaOH and extracted with ethyl acetate, the combined extracts were dried over anhydrous magnesium sulphate. Removal of the solvent at reduced pressure gave the desired products **4a**—**4c** in yields of 15%, 17% and 20%, respectively.

Method B 3-Aryl-4-azo pyrazoles (**2a**—**2c**) (0.05 mmol) was stirred in boiling aqueous (80%, 25 mL) ethanol and small portions of powdered sodium dithionite were added until the dye had dissolved and a faint yellow solution resulted. The solution was then diluted to 200 mL with hot water; the reaction mixture was distilled at reduced pressure, the solid obtained was filtered to give the desired *o*-diamino compounds **4a**—**4c**.

1,3-Diphenyl-1*H*-pyrazole-4,5-diamine (4a) Product in 61% yield, as buff crystals, m.p. 138—140 ℃; ^{1}H NMR (DMSO-d_6) δ: 3.5 (s, 2H, NH_2), 4.8 (s, 2H, NH_2), 7.2—7.9 (m, 9H, Ar-H); IR (KBr) v: 3364 (NH_2), 1596 (N=N) cm^{-1}; MS *m/z* (%): 250.1 (M^+, 100), 146 (37), 104 (52), 77 (60), 51 (37). Anal. calcd for $C_{15}H_{14}N_4$ (250.29): C 72.70, H 5.64, N 22.38; found C 72.65, H 5.60, N 22.28.

1-Phenyl-3-*p*-tolyl-1*H*-pyrazole-4,5-diamine (4b) Product in 67% yield, as buff crystals, m.p. 148—150 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.3 (s, 3H, CH_3), 4.7 (s, 2H, NH_2), 5.2 (s, 2H, NH_2), 7.1—7.7 (m, 9H, Ar-H); IR (KBr) v: 33402 (NH_2), 1597 (N=N) cm^{-1}; MS *m/z* (%): 264.1 (M^+, 100), 191 (50), 165 (40), 77 (50), 51 (60). Anal. calcd for $C_{16}H_{16}N_4$ (264.32): C 72.70, H 6.10, N 21.20; found C 72.55, H 5.98, N 21.20.

3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazole-4,5-diamine (4c) Product in 75% yield, as buff crystals, m.p. 122—124 ℃; ^{1}H NMR (DMSO-d_6) δ: 4.8 (s, 2H, NH_2), 5.6 (s, 2H, NH_2), 7.1—8.3 (m, 9H, Ar-H); IR (KBr) v: 3370 (NH_2), 1597 (N=N) cm^{-1}; MS *m/z* (%): 268.1 (M^+, 100), 242 (10), 191 (20), 165 (20), 74 (50). Anal. calcd for $C_{15}H_{13}N_4F$ (268.28): C 67.15, H 4.88, N 20.88; found C 67.05, H 4.79, N 20.96.

General procedures for the synthesis of 7-(4-methoxyphenyl)-1-phenyl-3-substituted-5-*p*-tolyl-1,6,7,8-tetrahydropyrazolo[4,3-*b*][1,4]diazepine (5a—5c)

A mixture of **4a**—**4c** (3.2 mmol) and of 3-(4-methoxyphenyl)-1-*p*-tolylprop-2-en-1-one (0.8 g, 3.2 mmol) was refluxed in absolute ethanol (10 mL) and acetic acid (0.4 mL) for 8 h. The reaction mixture was cooled to 0 ℃ and the precipitates were collected by filtration. The solid obtained was crystallized from ethanol.

1,3-Diphenyl-7-(4-methoxyphenyl)-5-*p*-tolyl-1,6,7,8-tetrahydropyrazolo[4,3-*b*][1,4]diazepine (5a) Product in 81% yield, as yellow crystals, m.p. 270—272 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.3 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 2.7 (d, J_{trans}=6.2 Hz, 1H, CH_2 at C-3), 3.3 (d, J_{cis}=1.4 Hz, 1H, CH_2 at C-3), 4.1 (t, J=−14.9 Hz, 1H, CH at C-2), 5.3 (d, J=4.9 Hz, 1H, NH), 7.1—7.8 (m, 24H, Ar-H); IR (KBr) v: 3361 (NH), 1597 (C=N) cm^{-1}; MS *m/z* (%): 484.3 (M^+, 50), 337 (57), 267 (23), 235 (87), 160 (46), 121 (45), 77 (100), 51 (22). Anal. calcd for $C_{32}H_{28}N_4O$ (484.5): C 79.31, H 5.82, N 11.56; found C 79.11, H 5.89, N 11.76.

7-(4-Methoxyphenyl)-1-phenyl-3,5-di-*p*-tolyl-1,6,7,8-tetrahydropyrazolo[4,3-*b*][1,4]diazepine (5b) Product in 79% yield, as yellow crystals, m.p. 300—302 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.1 (s, 3H, CH_3), 3.6 (s, 3H, OCH_3), 2.7 (d, J_{trans}=6.0 Hz, 1H, CH_2 at C-3), 3.6 (d, J_{cis}=1.6 Hz, 1H, CH_2 at C-3), 4.9 (t, J=−14.8 Hz, 1H, CH at C-2), 6.7 (d, J=4.8 Hz, 1H, NH), 6.8—8.5 (m, 23H, Ar-H); IR (KBr) v: 3361 (NH), 1597 (C=N) cm^{-1}; MS *m/z* (%): 498.3 (M^+, 25), 445 (10), 242 (20), 191 (80), 169 (70), 139(75), 107 (30). Anal. calcd for $C_{33}H_{30}N_4O$ (498.6): C 79.49, H 6.06, N 11.24; found C 79.49, H 6.98, N 11.22.

3-(4-Fluorophenyl)-7-(4-methoxyphenyl)-1-phenyl-5-*p*-tolyl-1,6,7,8-tetrahydropyrazolo[4,3-*b*][1,4]diazepine (5c) Product in 80% yield, as yellow crystals, m.p. 274—276 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.2 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 2.9 (d, J_{trans}=6.1 Hz, 1H, CH_2 at C-3), 3.9 (d, J_{cis}=1.5 Hz, 1H, CH_2 at C-3), 5.4 (t, J=−14.9 Hz, 1H, CH at C-2), 5.8 (d, J=4.7 Hz, 1H, NH), 6.7—8.2 (m, 23H, Ar-H); IR (KBr) v: 3301 (NH), 1604 (C=N) cm^{-1}; MS *m/z* (%): 503.3 (M^++1, 75), 461

(25), 369 (31), 337 (27), 262 (27), 232 (27), 160 (36), 121 (45), 77 (22), 51 (22). Anal. calcd for $C_{32}H_{27}N_4F$ (502.2): C 76.47, H 5.41, N 11.15, F 3.78; found C 76.67, H 5.32, N 11.09, F 3.78.

General procedure for the synthesis of 4-(4-methoxyphenyl)-1-phenyl-3-substituted-4*H*,6*H*-thiazolo[3,4-*a*]pyrazoloimidazole (6a—6c)

To a stirred solution of 1-phenyl-3-aryl-4,5-diaminopyrazoles **4a**—**4c** (0.01 mmol) in dry benzene (7 mL), 2-mercaptoacetic acid (1.82 g, 0.02 mmol) and the *p*-ansialdehyde (0.14 g, 1 mmol) were added. The reaction mixture was refluxed for 48 h and then neutralized by a solution of sodium hydrogen carbonate. After removal of the solvent under reduced pressure, the precipitates formed were filtered, washed with water, dried and crystallized from benzene to give compounds **6a**—**6c**.

1,3-Diphenyl-4-(4-methoxyphenyl)-4*H*,6*H*-thiazolo-[3,4-*a*]pyrazoloimidazole (6a) Product in 62.5% yield, as brown crystals, m.p. 124—126 ℃; ^{1}H NMR (DMSO-d_6) δ: 3.7 (s, 3H, OCH_3), 5.2 (d, J=1.9 Hz, 1H, CH_2), 5.5 (d, J=−15 Hz, 1H, CH_2), 6.4 (s, 1H, CH), 6.7—7.7 (m, 13H, Ar-H); IR (KBr) ν: 2989 (Aliph-H), 3158 (Arom-H) cm^{-1}; MS *m/z* (%): 425.2 (M^++1, 50), 413 (10), 191 (30), 117 (20), 74 (100). Anal. calcd for $C_{25}H_{20}N_4OS$ (424.5): C 70.73, H 4.75, N 13.20, S 7.55; found C 70.83, H 4.91, N 13.18, S 7.45.

4-(4-Methoxyphenyl)-1-phenyl-3-*p*-tolyl-4*H*,6*H*-thiazolo[3,4-*a*]pyrazoloimidazole (6b) Product in 82% yield, as brown crystals, m.p. 128—130 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.3 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 5.3 (d, J=2.1 Hz, 1H, CH_2), 5.6 (d, J=−14.8 Hz, 1H, CH_2), 6.2 (s, 1H, CH), 7.0—7.3 (m, 12H, Ar-H); IR (KBr) ν: 2923 (Aliph-H), 3056 (Arom-H) cm^{-1}; MS *m/z* (%): 453.3 (M^+, 70), 400 (34), 195 (10), 191 (30), 117 (20), 77 (100), 51 (80). Anal. calcd for $C_{25}H_{20}N_4OS$ (438.5): C 71.21, H 5.06, N 12.78, S 7.31; found C 70.83, H 5.11, N 12.78, S 7.45.

3-(4-Fluorophenyl)-4-(4-methoxyphenyl)-1-phenyl-4*H*,6*H*-thiazolo[3,4-*a*]pyrazoloimidazole (6c) Product in 85% yield, as brown crystals, m.p. 111—113 ℃; ^{1}H NMR (DMSO-d_6) δ: 3.6 (s, 3H, OCH_3), 5.2 (d, J=1.7 Hz, 1H, CH_2), 5.7 (d, J=−14.8 Hz, 1H, CH_2), 6.4 (s, 1H, CH), 6.7—7.6 (m, 12H, Ar-H); IR (KBr) ν: 2989 (Aliph-H), 3158 (Arom-H) cm^{-1}; MS *m/z* (%): 443.2 (M^++1, 70), 415 (10), 353 (10), 242 (20), 242 (20), 191 (100), 107 (10). Anal. calcd for $C_{25}H_{19}N_4OSF$ (442.5): C 67.86, H 4.33, N 12.66, S 7.2, F 4.29; found C 67.86, H 4.21, N 12.59, S 6.99, F 4.39.

General procedure for the synthesis of 5-amino-4-ethoxycarbonylaminopyrazole (7a—7c)

A solution of ethyl chloroformate (0.95 mL, 10 mmol) in ethyl acetate (10 mL) and sodium hydrogen carbonate (0.84 g, 10 mmol) in water (20 mL) were simultaneously added to a vigorously stirred solution of the appropriate 4,5-diaminopyrazoles (**4a**—**4c**) (10 mmol) in ethyl acetate (80 mL). After 2 h the organic layer was washed with water, dried over anhydrous magnesium sulfate, evaporated to dryness, separated and purified.

Ethyl-5-amino-1,3-diphenyl-1*H*-pyrazol-4-ylcarbamate (7a) This compound was obtained as crystal product in 80% yield, m.p. 120—122 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.25 (t, J=7.0 Hz, 3H, CH_3), 4.3 (q, J=7.1 Hz, 2H, CH_2), 5.5 (s, 2H, NH_2), 7.4—8.2 (m, 9H, Ar-H), 8.3 (s, 1H, NH); IR (KBr) ν: 3335 (NH), 1722 (C=O), 1650 (C=N) cm^{-1}. Anal. calcd for $C_{18}H_{18}N_4O_2$ (322.36): C 67.07, H 5.63, N 17.38; found C 67.1, H 5.64, N 17.35.

Ethyl-5-amino-1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-ylcarbamate (7b) This compound was obtained as liquid product in 78.2% yield; ^{1}H NMR (DMSO-d_6) δ: 1.3 (t, J=7.0 Hz, 3H, CH_3), 4.4 (q, J=7.0 Hz, 2H, CH_2), 5.6 (s, 2H, NH_2), 7.4—8.0 (m, 9H, Ar-H), 8.2 (s, 1H, NH); IR (KBr) ν: 3310 (NH), 1730 (C=O), 1620 (C=N) cm^{-1}. Anal. calcd for $C_{18}H_{18}N_4O_2$ (306.36): C 70.57, H 5.92, N 18.29; found C 70.67, H 5.84, N 18.35.

Ethyl-5-amino-3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-ylcarbamate (7c) This compound was obtained as liquid product in 69.5% yield; ^{1}H NMR (DMSO-d_6) δ: 1.54 (t, J=7.1 Hz, 3H, CH_3), 4.2 (q, J=7.0 Hz, 2H, CH_2), 5.7 (s, 2H, NH_2), 7.1—8.07 (m, 9H, Ar-H), 8.09 (s, 1H, NH); IR (KBr) ν: 3350 (NH), 1750 (C=O), 1640 (C=N) cm^{-1}. Anal. calcd for $C_{17}H_{15}N_4O_2F$ (310.3): C 65.8, H 4.87, N 18.05, F 6.12; found C 65.77, H 4.87, N 17.98, F 5.99.

General procedure for the synthesis of imidazo[4,5-*c*]pyrazol-5-ones (8a—8c)

The appropriate 5-amino-4-ethoxycarbonylpyrazoles (**7a**—**7c**) (10 mmol) were heated at 200 ℃ for 2 h. The solid was collected, washed with ethyl ether, dried and crystallized from DMF.

1,3-Diphenylimidazo[4,5-*c*]pyrazol-5(1*H*,4*H*,6*H*)-one (8a) Product in 66% yield, as orange crystals, m.p. >360 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.2—7.7 (m, 9H, Ar-H), 8.3—8.5 (br, 2H, 2NH); IR (KBr) ν: 3264—3275 (NH), 1690 (C=O), 1605 (C=N) cm^{-1}; MS *m/z* (%): 276.1 (M^+, 64), 198 (30), 171 (45), 140 (20), 77 (100), 51 (50). Anal. calcd for $C_{16}H_{12}N_4O$ (276.101): C 69.55, H 4.38, N 20.28; found C 69.45, H 4.38, N 20.11.

1-Phenyl-3-*p*-tolylimidazo[4,5-*c*]pyrazol-5(1*H*,4*H*,6*H*)-one (8b) Product in 53% yield, as orange crystals, m.p. >360 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.3 (s, 3H, CH_3), 7.2—8.0 (m, 9H, Ar-H), 8.3—8.6 (br, 2H, 2NH); IR (KBr) ν: 3258 (NH), 1684 (C=O), 1604 (C=N) cm^{-1}; MS *m/z* (%): 290.1 (M^+, 50), 196 (20), 140 (76), 77 (100), 51 (89). Anal. calcd for $C_{17}H_{14}N_4O$ (290.31): C 70.33, H 4.86, N 19.30; found C 70.33, H 4.99, N 19.28.

3-(4-Fluorophenyl)-1-phenylimidazo[4,5-*c*]pyrazol-5(1*H*,4*H*,6*H*)-one (8c) Product in 78% yield, as orange crystals, m.p. >360 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.2—8.3 (m, 9H, Ar-H), 8.4—8.7 (br, 2H, 2NH); IR

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(KBr) *v*: 3417 (NH), 1677 (C=O), 1599 (C=N) cm^{-1}; MS *m/z* (%): 294.1 (M^+, 29), 198 (14), 120 (30), 77 (100), 51 (74). Anal. calcd for $C_{16}H_{11}N_4OF$ (294.28): C 65.30, H 3.77, N 19.04, F 6.46; found C 65.30, H 3.89, N 19.19, F 6.56.

General procedure for the synthesis of 1-phenyl-3-substituted-1*H*-pyrazolo[3,4-*b*]pyrazine (9a—9c)

1-Phenyl-3-aryl-4,5-diaminopyrazoles **4a** — **4c** (0.019 mmol) were dissolved in 15 mL of methanol, 40% aqueous solution of glyoxal (1.07 mL, 0.019 mmol) was added, the mixture refluxed for 7 h. The reaction mixture was cooled; the formed precipitate was filtered and crystallized from ethyl acetate to give compounds **9a—9c.**

1,3-Diphenyl-3,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyrazine (9a) Product in 63% yield, as yellow crystals, m.p. 147—149 ℃; ^{1}H NMR (DMSO-d_6) δ: 7—8.4 (m, 11H, Ar-H); IR (KBr) *v*: 3050 (Arom-H) cm^{-1}; MS *m/z* (%): 272.1 (M^+, 90), 235 (87), 191 (82), 125 (54), 77 (100), 51 (52). Anal. calcd for $C_{17}H_{12}N_4$ (272.3): C 74.98, H 4.44, N 20.58; found C 74.98, H 4.49, N 20.46.

1-Phenyl-3-*p*-tolyl-3,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyrazine (9b) Product in 65% yield, as yellow crystals, m.p. 113—115 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.2 (s, 3H, CH_3), 7.1—8.8 (m, 11H, Ar-H); IR (KBr) *v*: 3050 (Arom-H) cm^{-1}; MS *m/z* (%): 286.1 (M^+, 100), 271 (10), 209 (20), 195 (30), 77 (55), 51 (40). Anal. calcd for $C_{18}H_{14}N_4$ (286.3): C 75.50, H 4.93, N 19.57; found C 75.43, H 4.89, N 19.86.

3-(4-Fluorophenyl)-1-phenyl-3,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyrazine (9c) Product in 75% yield, as yellow crystals, m.p. 160 — 162 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.1—8.0 (m, 11H, Ar-H); IR (KBr) *v*: 3050 (Arom-H) cm^{-1}; MS *m/z* (%): 290.1 (M^+, 44.4), 236 (41), 168 (82), 125 (41), 77 (100), 51 (52). Anal. calcd for $C_{17}H_{11}N_4F$ (290.2): C 70.34, H 3.82, F 6.54, N 19.30; found C 70.59, H 3.79, F 6.56, N 19.16.

General procedure for the synthesis of 1-phenyl-3-substituted-1,6-dihydro-imidazo[4,5-*c*]pyrazole-5-thiol (10a—10c)

A mixture of *o*-diamino compounds **4a—4c** (3.73 mmol) and thiourea (0.38 g, 5 mmol) in 15 mL of diphenyl ether, was heated at 240 ℃ for 5 h. After cooling the reaction mixture was poured into 40 mL hexane, stirred well and filtered, the precipitate was collected and crystallized from benzene to give compounds **10a—10c**.

1,3-Diphenyl-1,6-dihydroimidazo[4,5-*c*]pyrazole-5-thiol (10a) Product in 70 % yield, as reddish brown crystals, m.p. 261—263 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.3 (s, 3H, CH_3), 7.0—7.5 (m, 9H, Ar-H), 12.5 (s, 1H, NH); IR (KBr) *v*: 2317 (SH) cm^{-1}; MS *m/z* (%): 292.1 (M^+, 50), 231 (30), 206 (20), 172 (10), 156 (34), 77 (100), 51 (65). Anal. calcd for $C_{16}H_{12}N_4S$ (292.3): C 65.73, H 4.14, N 19.16, S 10.97; found C 65.78, H 4.39, N 19.26, S 10.69.

1-Phenyl-3-*p*-tolyl-1,6-dihydroimidazo[4,5-*c*]pyrazole-5-thiol (10b) Product in 65% yield, as reddish brown crystals, m.p. 200—202 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.34 (s, 3H, CH_3), 3 (s, 1H, SH), 7.12—7.6 (m, 9H, Ar-H), 13.0 (s, 1H, NH); IR (KBr) *v*: 2363 (SH) cm^{-1}; MS *m/z* (%): 306.2 (M^+, 20), 285 (20), 259 (10), 249 (90), 219 (40), 192 (10), 91 (60), 77 (100), 51 (30). Anal. calcd for $C_{17}H_{14}N_4S$ (306.3): C 66.64, H 4.61, N 18.29, S 10.47; found C 66.46, H 4.59, N 18.46, S 10.47.

3-(4-Fluorophenyl)-1-phenyl-1,6-dihydroimidazo-[4,5-*c*]pyrazole-5-thiol (10c) Product in 75% yield, as reddish brown crystals, m.p. 180—182 ℃; ^{1}H NMR (DMSO-d_6) δ: 3.1 (s, 1H, SH), 7.3—7.9 (m, 9H, Ar-H), 13.4 (s, 1H, NH); IR (KBr) *v*: 2357 (SH) cm^{-1}; MS *m/z* (%): 310.2 (M^+, 30.3), 253 (27), 121 (100), 93 (78), 77 (90), 51 (21). Anal. calcd for $C_{16}H_{11}N_4FS$ (310.3): C 61.92, H 3.57, N 18.05, S 10.33, F 6.12; found C 61.92, H 3.69, N 18.26, S 10.23, F 6.26.

General procedure for the synthesis of 3,5-disustituted-1,7-diphenylbispyrazolo[3,4-*b*;4',3'-*e*]pyrazine (11a—11c)

A solution of o-diamino compounds **4a—4c** (10 mmol) in xylene (30 mL) was refluxed for 2 h. After cooling the precipitate was filtered off and crystallized from ethanol to give compounds **11a—11c**.

3,5-Diphenyl-1,7-diphenylbispyrazolo[3,4-*b*;4',3'-*e*]-pyrazine (11a) Product in 70% yield, as orange crystals, m.p. >360 ℃; ^{1}H NMR (DMSO-d_6) δ: 7—8.2 (m, 20H, Ar-H); IR (KBr) *v*: 2926 (Aliph-H), 3059 (Arom-H) cm^{-1}; MS *m/z* (%): 334.2 (M^+, 23.8), 290 (70), 235 (20), 191 (72), 91 (43), 77 (50), 51 (100). Anal. calcd for $C_{30}H_{20}N_6$ (464.5): C 77.57, H 4.34, N 18.09; found C 77.60, H 4.49, N 18.26.

3,5-*p*-Tolyl-1,7-diphenylbispyrazolo[3,4-*b*;4',3'-*e*]-pyrazine (11b) Product in 83% yield, as orange crystals, m.p. 279—281 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.3 (s, 3H, CH_3), 7.1—8.7 (m, 18H, Ar-H); IR (KBr) *v*: 2923 (Aliph-H), 3057 (Arom-H) cm^{-1}; MS *m/z* (%): 492.3 (M^+, 95), 401 (90), 374 (20), 284 (30), 219 (10), 155 (32), 91 (43), 77 (50), 51 (80). Anal. calcd for $C_{32}H_{24}N_6$ (492.5): C 78.03, H 4.91, N 17.06; found C 68.10, H 4.89, N 16.96.

3,5-(4-Fluorophenyl)-1,7-diphenylbispyrazolo[3,4-*b*;4',3'-*e*]pyrazine (11c) Product in 85% yield, as orange crystals, m.p. >360 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.3—8.8 (m, 20H, Ar-H); IR (KBr) *v*: 2925 (Aliph-H), 3061 (Arom-H) cm^{-1}; MS *m/z* (%): 500.3 (M^+, 59.9), 378 (10), 141 (10), 77 (100), 51 (41). Anal. calcd for $C_{30}H_{18}F_2N_6$ (500.15): C 71.99, H 3.62, N 16.79, F 7.59; found C 71.89, H 3.59, N 16.76, F 7.56.

General procedure for microwave irradiation

Equimolecular quantities of the starting compounds **4a—4c** and the suitable reagent were mixed in the mentioned solvent, and subjected to microwave irradiation in closed vessel under magnetic stirring for the mentioned time and temperature with maximum power of

400 W. The resulting reaction mixture was cooled and evaporated, affording a precipitate which was collected by filtration, washed with dry ether to give compounds **5a—5c**, **6a—6c**, **8a—c**, **9a—9c**, **10a—10c** and **11a—11c**.

Tested organisms

The microorganisms used in this study included Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia sp. and Aeromonas hydrophila*), Gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*). The strains under studies were obtained from the culture collection of Bacteriology Laboratory (Microbiology Unit, Faculty of Science, Tanta University, Tanta, Egypt). Bacteria were maintained on nutrient agar.

Antibacterial screening and activities

Antibacterial activities of the synthesized compounds were tested *in vitro* against six different types of bacteria by the cut plug method according to Pridham *et al*.[22] The assay plates were inoculated with the test bacteria by addition of 1 mL containing the diluted inoculums (10^7 CFU/mL) of each tested organism and spreaded on the corresponding media after solidification. It must be noted that, preliminary investigation had indicated that 10 mg/mL of the different compounds were the minimums inhibitory concentration (MIC) for the most tested bacteria. The wells were made, then one mg of the synthesized compounds was dissolved in 100 mL DMSO and poured in the wells. The plates were incubated at 30 ℃ for 24 h, thereafter the diameters of inhibition zones were evaluated. Chloroamphinicol and Streptomycin were used as positive control. The results of the antibacterial activities are summarized in Table 2. It is clear that the intermediates **4a—4c** and the presence of thiozole or imidazole or pyrazine moieties fused with **4a—4c** exhibited antibacterial activity of higher order represented by compounds **4a—4c**, **6a**, **6b**, **8b**, **11b** and **11c** against the tested bacterial strains. The rest of the compounds **5a—5c**, **6c**, **8c**, **9a—9c**, **10a—10c**, and **11a**, exhibited nill to moderate activity against all strain of tested organisms.

Table 2 Diameters of inhibition zones (mm) of newly synthesized compounds against different test bacteria on nutrient agar at 30 ℃ after 24 h by the cut-plug method [a]

Gram positive bacteria		Gram negative bacteria				Compound
Pseudomonas aeroginosa	*Staphylococcus aures*	*Aeromonas hydrophila*	*Serratia*	*Bacillus cereus*	*Escherichia coli*	
22.6	28	23.3	24.3	17	24.6	**4a**
24.3	34	28	22	28.3	30	**4b**
13.6	11	-ve	14.3	28.6	14.6	**4c**
-ve	-ve	-ve	-ve	-ve	-ve	**5a**
-ve	14.6	-ve	-ve	23.6	-ve	**5b**
-ve	7.6	-ve	ve-	-ve	-ve	**5c**
13.3	11.6	-ve	11.6	16	24.6	**6a**
23.6	22.6	25	24.3	25	22	**6b**
6.6	22.3	-ve	-ve	-ve	25.6	**6c**
-ve	32	-ve	25.3	11.3	14.3	**8b**
-ve	11.6	-ve	-ve	-ve	-ve	**8c**
-ve	24	11	13	-ve	-ve	**9a**
5.6	13.6	13	16	13.3	10.3	**9b**
-ve	9	13	9	8.6	5.3	**9c**
-ve	-ve	-ve	8	21.6	-ve	**10a**
-ve	-ve	5	13	12.3	5.6	**10b**
-ve	20.3	-ve	12	-ve	9.6	**10c**
-ve	21.3	-ve	-ve	13.5	-ve	**11a**
-ve	24	21	13	-ve	12.3	**11b**
12.3	10.6	15	-ve	12.3	20.3	**11c**
21.3	37	20	22	19.6	29.6	Chloroamphinicol
13	11.6	11	12	22.6	-ve	Streptomycin

[a] The concentration used is 10 mg/mL. Control discs were performed in DMSO (dimethylsulphoxide) and no zones of inhibitions were observed. -ve＝resistant.

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Acknowledgement

The authors express their deep thanks to Dr. Abd-Raheem R. El-shanshoury, Professor of Microbiology, Botany Department, Faculty of Science, Tanta University, Tanta, for carrying out the biological activities at his research laboratory.

References

1 (a) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Jung, D. K.; Sexton, C. J.; Boud, F. L.; Peel, M. R. *Tetrahedron* **2003**, *59*, 9001.
(b) Gudmundsson, K. S.; Johns, B. A.; Wang, Z.; Turner, E. M.; Allen, S. H.; Freeman, G. A.; Lesleboyd, F.; Sexton, C. D.; Sellseth, D. W.; Moniri, K. R.; Greeh, K. L. *Bioorg*. *Med*. *Chem*. **2005**, *13*, 5346.
(c) Wilcoxen, R.; Huang, C. Q.; McCarthy, J. R.; Grigoriadis, D. G.; Chen, C. *Bioorg*. *Med*. *Chem*. *Lett*. **2003**, *13*, 1183.
(d) Chimichi, S.; Boccalini, M.; Hassan, M. M. M.; Viola, G.; DallÁcqua, F.; Curini, M. *Tetrahedron* **2006**, *62*, 90.
(e) Gross, R. S.; Guo, Z.; Dyck, B.; Coon, T.; Huang, C. Q.; Lowe, R.; Marinkowic, W. D.; Moorjani, M.; Nelson, J.; Zamani, K. S. D.; Grigoriadis, E.; Hoare, E. R. J.; Crowe, P. D.; Bu, J. H.; Haddach, M.; Mc Carthy, J.; Saunders, J.; Sullivan, R.; Kung, C. T.; Williams, J. P. *J*. *Med*. *Chem*. **2005**, *48*, 5780.
2 Menegatti, R.; Silva, G. M. S.; Zapata, G.; Sudo, J. M.; Raimundo, R. T.; Sudo, E. J.; Barreiro, C. A. M. F. *Bioorg*. *Med*. *Chem*. **2006**, *14*, 677.
3 Moderhack, D. *Liebigs Ann*. **1996**, 777.
4 Veronese, C. B. A. C.; Giori, M. G. *Tetrahedron Lett*. **1998**, *29*, 6171.
5 Braulio, I. O.; Henry, I. I Q.; Jairo, P. *J*. *Heterocycl*. *Chem*. **1999**, *36*, 635.
6 Bouabdallah, I.; M'barek, I. A.; Zyad, A.; Ramadane, A.; Zidane, I.; Melhaout, A. *Nat*. *Prod*. *Res*. **2006**, *20*, 1024.
7 Larsen, J. S.; Zahran, M. A.; Pedersen, E. B.; Nielsen, C. *Monatsh*. *Chem*. **1999**, *130*, 1167
8 Fray, M. J.; Bull, D. J.; Cooper, K.; Parry, M. J.; Stefaniak, M. H. *J*. *Med*. *Chem*. **1995**, *38*, 3524.
9 Eid, E. E.; Bonner, T. G.; Lewis, D. *J*. *Heterocycl*. *Chem*. **1983**, *20*, 1501.
10 Benjamin, E. B.; Srivastava, K. R.; Anil, A. L.; Coburn, L.; William, S. *Tetrahedron Lett*. **2003**, *44*, 3009.
11 Vicentini, C. B.; Ferretti, V.; Veronese, A. C.; Guarneri, M. M.; Manfrini, G. P. *Heterocycles* **1995**, *41*, 497.
12 (a) Insuasty, B. O.; Insuasty, H. I.; Quiroga, J. P. *J*. *Heterocycl*. *Chem*. **1999**, *36*, 635.
(b) Insuasty, B. O.; Rodriguez, R.; Quiroga, J. P. *J*. *Heterocycl*. *Chem*. **1997**, *34*, 1131.
(c) Insuasty, B. O.; Perez, A.; Valencia, J.; Quiroga, J. P. *J*. *Heterocycl*. *Chem*. **1997**, *34*, 1555.
(d) Insuasty, B. O.; Ramos, M. *J*. *Heterocycl*. *Chem*. **1994**, *31*, 61.
13 Cgimirri, A.; Monforte, P.; Musumeci, L.; Rao, A.; Zappala, M.; Manforte, A. M. *Arch*. *Pharm*. *Med*. *Chem*. **2001**, *334*, 203.
14 Weissberger, A. In *Imidazle and Its Derivatives*, Part I, Ed.: Hoffmann, K., Wiley Interscience, New York, **1953**, p. 247.
15 (a) Mark, C. B.; Terence, D.; Matthew, C. D.; Caroline, S.; Widdowson, D. K. *Org*. *Biomol*. *Chem*. **2006**, *4*, 4158.
(b) Duncan, L. B.; John, B. T.; Andrew, P.; Joseph, P. A. H. *J*. *Org*. *Chem*. **2010**, *75*, 984.
(c) Benson, D. A.; Karsch-Mizrachi, I.; Lipman, D. J.; Ostel, l. J.; Rapp, B. A.; Wheeler, D. L. *Nucl*. *Acids Res*. **2000**, *28*, 15.
(d) Reddy, G. J.; Latha, D.; Rao, K.; Srinivasa, R, D. *Org*. *Prep*. *Proced*. *Int*. **2004**, *36*, 494.
(e) Joshi, K. C.; Dubey, K.; Dandia, A. *Heterocycyles* **1981**, *16*, 71.
(f) Joshi, K. C.; Pathak, V. N.; Garg, U. *J*. *Heterocycl*. *Chem*. **1979**, *16*, 1141.
16 Fahmy, H. M.; Elnagdi, M. H.; Mahgoup, A. E.; Kasem, A. *J*. *Chin*. *Chem*. *Soc*. **1985**, *32*, 99.
17 Chiiara, B. V.; Maurizio, M.; Manuela, M.; Angelo, S.; Carlo, R.; Donatella, M. *Arch*. *Pharm*. *Pharm*. *Med*. *Chem*. **1999**, *332*, 337.
18 Benjamin, E. B.; Anil, S.; Keith, R. C.; Amy, l. F.; William, L. S. *Tetrahedron Lett*. **2003**, *44*, 3009.
19 Vicentini, C. B.; Veronese, A. C.; Manfrini, M. *J*. *Heterocycl*. *Chem*. **1997**, *34*, 629.
20 GalalEldin, H. E.; Hassan, A. E.; Said, A. S. G.; Mohamed, H. E. *Bull*. *Chem*. *Soc*. *Jpn*. **1984**, *57*, 1650.
21 Orlov, V. D.; Quiroga, J.; Kolos, N. N. *Khim. Geterotsikl*. *Soedin* **1988**, *9*, 1222.
22 Pridham, T. G.; Lindenfelser, L. A.; Shotwell, O. L.; Stodola, F.; Benedict, R. G.; Foley, C.; Jacks, P. W.; Zaumeyer, W. J.; Perston, W. H.; Mitchell, J. W. *Phytopathology* **1956**, *46*, 568.

(E1008095 Zhao, X.)

