Synthesis and biological activity of some new pyrazole derivatives

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1-Substituted-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazoles were prepared via condensation of 3,4,5-(trimethoxy)benzal-2,4-(dimethoxy)acetophenone with hydrazine derivatives in ethanol and/or condensation with hydrazine hydrate in acidic medium. The product with ethyl iodide, phenyl isothiocyanate, benzoyl chloride and nitrous acid yielded the corresponding 1-substituted-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazoles respectively. The antimicrobial activity of some new compounds has been screened.

In the course of recent investigations^{1,2} involving 2,4-dimethoxyacetophenone and 3,4,5-trimethoxybenzaldehyde, it was found that 3,4,5-trimethoxybenzal-2,4-(dimethoxy)acetophenone (**1**) is converted into 1,3,5-trisubstituted pyrazoles (**2** and **3**) by the action of hydrazine derivatives^{3,4} in ethanol or hydrazine hydrate in different acids under reflux. It has been reported that pyrazoles have antimicrobial activities and recently they have respiratory and cardiovascular activities^{5,6}.

The aim of this work is to synthesis of some new pyrazoles which might have biological activities⁷.

Results and discussion

3,4,5-(Trimethoxy)benzal-2,4-(dimethoxy)acetophenone (**1**) was prepared via condensation of 2,4-dimethoxyacetophenone with 3,4,5-trimethoxybenzaldehyde in the presence of base. The ethanolic solution^{8,9} of **1** reacts with hydrazines, namely hydrazine hydrate, phenylhydrazine and/or *p*-tolylsulfonyl hydrazine to afford the corresponding 1,3,5-trisubstituted-4,5-dihydropyrazoles (**2a-c**).

Treatment of acidic solution of **1** (formic acid, acetic acid and propionic acid) with hydrazine hydrate under reflux gave the corresponding 1,3,5-trisubstituted-4,5-dihydropyrazoles (**3a-c**, Scheme 1).

Alkylation of 1*H*-3,5-disubstituted-4,5-dihydropyrazole (**2a**) with ethyl iodide in presence of anhydrous potassium carbonate in dry acetone, gave the corresponding 1-ethyl-3,5-disubstituted-4,5-dihydropyrazole (**4**). The structure of **4** was also established via reduction¹⁰ of 1-acetyl-3,5-disubstituted-4,5-dihydropyrazole (**3b**) with lithium aluminum hydride in ether. Treatment of **2a** with phenyl

isothiocyanate in ether produced 1-(phenylamino)-thiocarbonyl-4,5-disubstituted-3,5-dihydropyrazole (**5**, Scheme 1).

Compound **2a** was allowed to react with benzoyl chloride and *p*-toluene-sulphonyl chloride in pyridine to give the corresponding 1-benzoyl-3,5-disubstituted-4,5-dihydropyrazole (**6**) and 1-*p*-tolylsulphonyl-3,5-disubstituted-4,5-dihydropyrazole (**2c**), respectively.

Bromination of 1*H*-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (**2a**) by bromine in chloroform gave the corresponding 1*H*-4-bromo-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl) pyrazole (**6**, Scheme 1).

Treatment of 1*H*-3,5-disubstituted-4,5-dihydropyrazole (**2a**) with nitrous acid afforded the corresponding 1-nitroso-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (**8**, Scheme 1).

Biological activity :

Using the agar plate diffusion technique¹¹ with concentrations of 75, 125, 175 and 250 ppm, all the newly synthesized compounds were tested for antimicrobial effect against *Staphylococcus aureus*, *Bacillus cereus*, *Serratia marcescens*, *Proteus merabitis* and *Aspergillus fumigatus*. After 24 h the growth in the broth was evaluated visually according to its zone of inhibition. The screening results (given in Table 1) indicated that the compounds **2c** and **7** exhibited marked activity against different types of bacteria, while the compounds **2a** and **3b** exhibited moderate activity against different types of bacteria. The results indicated that all newly synthesized compounds **2a**, **2c**, **3b** and **7** exhibited moderate activity against *Aspergillus fumigatus* with concentration 250 ppm.

Scheme 1

Experimental

IR spectra were recorded as KBr pellet on a Pye Unicam SP 2000 spectrophotometer and PMR spectra on a Varian EM-360-60 MHz NMR spectrometer using TMS internal standard. Mass spectra were obtained on a GCMS-QP 100 Ex mass spectrometer. Microanalysis were conducted using an elemental analyzer 1106, in Faculty of

Science, Cairo University. Melting points were determined on a Richter Hot stage and uncorrected.

1-Substituted-3-(2,3-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazoles (2a-c) :

A mixture of 1 (0.01 mol), hydrazine hydrate, phenylhydrazine and/or *p*-toluenesulphonyl hydrazine (0.01 mol) in ethanol (30 ml) was heated for 5 h. After

Table 1. Antimicrobial activity of some synthesized compounds at different concentrations (ppm)

Compd./ Concn.	<i>S. aureus</i> (ATCC-6538-P)				<i>B. cereus</i> (NRRL-B-569)				<i>S. marcescens</i> (IMRV-70)				<i>P. merabititis</i> (NTC-289)				<i>A. fumigatus</i> (PP-29)			
	75	125	175	250	75	125	175	250	75	125	175	250	75	125	175	250	75	125	175	250
2a	+	+	++	+++	+	+	++	++	+	++	++	+++	+	++	++	++	-	-	++	++
2c	+	++	+++	+++	+	+	+++	+++	+	++	++	+++	+	+	++	+++	-	-	+	++
3b	+	+	+	++	+	+	++	++	+	+	++	++	+	+	++	++	-	+	+	++
7	+	++	+++	+++	+	++	+++	+++	+	++	++	+++	+	+	++	+++	-	-	+	++

- No antimicrobial activity, + mild activity, ++ moderate activity, +++ marked activity.

- Compound 2a gave us markdy antimicrobial activity with *Staphylococcus aureus* and *Ser. Mar* at MI (250).

cooling, the product was filtered off, dried and purified by recrystallization with ethanol to give **2**.

1H-3-(2,4-Dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (2a) was obtained as colourless crystals, m.p. 95°C, yield 62%. $\nu_{\max}$ (KBr) 3221 (NH), 1620 (C=N), 1035 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 3.70–3.72 (2H, d, CH_2CH), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.48 (1H, t, CHCH_2), 6.91–7.63 (5H, m, Ar-H), 10.31 (1H, s, NH) ppm. m/z (%) 372 (M^+ , 46.30), 371 ($\text{M}^+ - 1$, 76.35), 194 (38.30) (Found : C, 64.63; H, 6.39; N, 7.60. $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_5$ Calcd. : C, 64.51; H, 6.45; N, 7.53%).

1-Phenyl-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxy)-4,5-dihydropyrazole (2b) was obtained as pale yellow crystals, yield 81%, m.p. 71°C. $\nu_{\max}$ (KBr) 1615 (C=N), 1605, 1585 (C=C), 1037, 1012 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 3.71–3.73 (2H, dd, CH_2CH), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.48 (1H, t, CHCH_2), 6.91–7.81 (9H, m, Ar-H) ppm. m/z (%) 449 ($\text{M}^+ + 1$, 1.35), 448 (M^+ , 23.20), 371 (53.03), 194 (21.21), 193 (17.81), 77 (25.30) (Found : C, 69.80; H, 6.30; N, 6.40. $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_5$ Calcd. : C, 69.64; H, 6.25; N, 6.25%).

1-p-Tolylsulphonyl-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (2c) was obtained as pale yellow crystals, yield 68%, m.p. 180°C. $\nu_{\max}$ (KBr) 1617 (C=N), 1603, 1590 (C=C), 1120, 1033, 1010 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 2.30 (3H, s, CH_3), 3.70–3.72 (2H, dd, CH_2CH), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.49 (1H, t, CHCH_2), 6.91–7.80 (8H, m, Ar-H) ppm. m/z (%) 527 (M^+ , 11.31), 526 ($\text{M}^+ - 1$, 23.51), 372 (23.51), 371 (100), 205 (46.33), 163 (17.31), 156 (23.05), 91 (21.32) (Found : C, 61.63; H, 5.63; N, 5.50; S, 5.89. $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_7\text{S}$ Calcd. : C, 61.60; H, 5.70; N, 5.32; S, 6.08%).

1-Substituted-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (3a-c) :

A mixture of **1** (0.01 mol) and hydrazine hydrate (0.01 mol) in acid (such as formic acid, acetic acid and propionic acid) (30 ml) was heated for 5 h after cooling, the formed solid was filtered off, dried and purified by recrystallization from ethanol to give **3**.

1-Formyl-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (3a) was obtained as

pale yellow crystals, yield 81%, m.p. 140°C. $\nu_{\max}$ (KBr) 1640 (C=O), 1613 (C=N), 1604, 1591 (C=C), 1210, 1030, 1015 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 3.71–3.73 (2H, dd, CH_2CH), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.49 (1H, t, CHCH_2), 6.90–7.65 (5H, m, Ar-H), 9.42 (1H, s, CHO) ppm. m/z (%) 401 ($\text{M}^+ + 1$, 1.30), 400 (M^+ , 21.56), 399 ($\text{M}^+ - 1$, 33.61), 372 (63.52), 194 (38.91), 193 (22.05), 163 (19.23) (Found : C, 62.89; H, 6.10; N, 6.83. $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$ Calcd. : C, 63.00; H, 6.00; N, 7.00%).

1-Acetyl-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (3b) was obtained as pale yellow crystals, yield 62%; m.p. 130°C. $\nu_{\max}$ (KBr) 1698 (C=O), 1613 (C=N), 1604, 1595 (C=C), 1210, 1038, 1015 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 2.41 (3H, s, COCH_3), 3.70–3.72 (2H, dd, CH_2CH), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.49 (1H, t, CHCH_2), 6.90–7.80 (5H, m, Ar-H) ppm. m/z (%) 415 ($\text{M}^+ + 1$, 9.31), 414 (M^+ , 13.56), 372 (53.62), 371 (43.61), 163 (18.25) (Found : C, 63.50; H, 6.41; N, 6.70. $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_6$ Calcd. : C, 63.77; H, 6.28; N, 6.76%).

1-Propionyl-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (3c) as pale yellow crystals, yield 70%, m.p. 65°C. $\nu_{\max}$ (KBr) 1695 (C=O), 1614 (C=N), 1603, 1559 (C=C), 1230, 1039, 1012 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 1.2 (3H, t, CH_3), 2.53 (2H, q, COCH_2), 3.71–3.73 (2H, dd, CH_2CH), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.46 (1H, t, CHCH_2), 6.93–7.76 (5H, m, Ar-H) ppm. m/z (%) 429 ($\text{M}^+ + 1$, 3.61), 428 (M^+ , 16.35), 372 (51.31), 371 (63.25), 164 (20.31), 163 (17.20) (Found : C, 64.31; H, 6.40; N, 6.60. $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_6$ Calcd. : C, 64.49; H, 6.54; N, 6.54%).

1-Ethyl-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (4) :

A mixture of **3b** (0.01 mol) and lithium aluminum hydride (0.01 mol) in dry ether (30 ml) was heated on water bath for 5 h. While hot, the reaction mixture was filtered and excess of solvent was removed by evaporation. The solid obtained was purified by recrystallization from methanol to give **4** as pale yellow crystals, yield 45%, m.p. 300°C. $\nu_{\max}$ (KBr) 1615 (C=N), 1605, 1598 (C=C), 1210, 1031, 1012 (C-O) cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$) 1.21 (3H, t, CH_3), 3.01 (2H, q, CH_2), 3.70–3.72 (2H,

dd, CH_2CH), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.93–7.70 (5H, m, Ar-H) ppm. m/z (%) 401 ($\text{M}^+ + 1$, 9.61), 400 (M^+ , 18.32), 372 (52.56), 371 (63.62), 194 (19.63), 163 (17.68) (Found : C, 65.81; H, 6.90; N, 7.10. $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5$ Calcd. : C, 66.00; H, 7.00; N, 7.00%).

Alkylation of 2a with ethyl iodide, Formation of 4 :

A mixture of 2a (0.01 mol), ethyl iodide (0.01 mol) and anhydrous potassium carbonate (0.03 mol) in dry acetone (30 ml) heated for 15 h. The reaction mixture was cooled and poured into water. The obtained solid was filtered off, washed with water, dried and purified by recrystallization with methanol to give 4.

1-(Phenylamino)thiocarbonyl-3-(2,3-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (5) :

A mixture of 2a (0.01 mol) and phenyl isothiocyanate (0.01 mol) in ether (30 ml) was heated on water bath for 5 h. After evaporation of the solvent the obtained product was purified by recrystallization from ethanol to give 5 as yellow crystals, yield 45%, m.p. 115°C . ν_{max} (KBr) 3225 (NH), 1620 (C=N), 1605, 1591 (C=C), 1318 (C=S), 1121, 1035, 1013 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 3.71–3.72 (2H, dd, CH_2CH), 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.40 (3H, s, OCH_2), 3.95 (3H, s, OCH_3), 5.48 (1H, t, CHCH_2), 6.91–7.73 (10H, m, Ar-H), 10.32 (1H, s, NH) ppm. m/z (%) 508 ($\text{M}^+ + 1$, 8.03), 507 (M^+ , 19.35), 372 (100), 371 (52.11), 205 (33.90), 163 (32.21), 135 (19.25) (Found : C, 63.80; H, 5.70; N, 8.32; S, 6.09. $\text{C}_{27}\text{H}_{29}\text{N}_3\text{O}_5\text{S}$ Calcd. : C, 63.91; H, 5.72; N, 8.28; S, 6.31%).

1-Benzoyl-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (6) :

A mixture of 2a (0.01 mol) and benzoyl chloride (0.01 mol) in pyridine (15 ml) was heated on water bath for 2 h. The reaction mixture was cooled and acidified with 4 N hydrochloric acid. The obtained solid was filtered off, washed with water, dried, and purified by recrystallization from ethanol to give 6 as pale yellow crystals, yield 63%, m.p. 100°C . ν_{max} (KBr) 1695 (C=O), 1619 (C=N), 1604, 1593 (C=C), 1120, 1030, 1015 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 3.70–3.72 (2H, dd, CH_2CH), 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.49 (1H, t, CHCH_2), 6.93–7.78 (10H, m, Ar-H) ppm. m/z (%) 477 ($\text{M}^+ + 1$, 5.21), 476 (M^+ , 52.50), 372 (12.90), 371 (62.50), 312 (25.40), 194 (16.60), 105 (100), 77 (39.90)

(Found : C, 68.20; H, 5.68; N, 5.80. $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_6$ Calcd. : C, 68.07; H, 5.88; N, 5.88%).

1H-3-(2,4-Dimethoxyphenyl)-4-bromo-5-(3,4,5-trimethoxyphenyl)pyrazole (7) :

A solution of 2a (0.01 mol) in chloroform (20 ml) was added dropwise to a solution of bromine (0.03 mol) in chloroform (20 ml) with stirring for 15 min. After addition the mixture was stirred for further 30 min. The formed solid was collected, washed with water, dried and purified by recrystallization from acetone to give 7 as yellow crystals, yield 83%, m.p. 182°C . ν_{max} (KBr) 3225 (NH), 1625 (C=N), 1605, 1585 (C=C), 1250, 1038, 1012 (C-O) cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$) 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.95–7.60 (5H, m, Ar-H), 10.63 (1H, s, NH) ppm (Found : C, 53.30; H, 4.56; N, 6.10. $\text{C}_{20}\text{H}_{23}\text{BrN}_2\text{O}_5$ Calcd. : C, 53.22; H, 5.10; N, 6.21%).

1-Nitroso-3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazole (8) :

A solution of 2a (0.01 mol) in concentrated hydrochloric acid (10 ml) was chilled in ice to -5°C . A cold solution of the sodium nitrite (0.02 mol) in water (10 mL) was added dropwise with stirring for 30 min. The precipitate was collected, washed with water, dried and purified by recrystallization from acetone to give 8 as yellow crystals, yield 35%, m.p. 125°C . ν_{max} (KBr) 1616 (C=N), 1605, 1595 (C=C), 1490 (N=O), 1210, 1035, 1015 (C-O) cm^{-1} ; δ_{H} (CDCl_3) 3.71–3.73 (2H, d, CH_2CH), 3.73 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.49 (1H, t, CHCH_2), 6.91–7.70 (5H, m, Ar-H) ppm. m/z (%) 402 ($\text{M}^+ + 1$, 13.50), 401 (M^+ , 27.10), 371 (56.35), 205 (17.50), 163 (29.10) (Found : C, 59.67; H, 5.74; N, 10.50. $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_6$ Calcd. : C, 59.85; H, 5.74; N, 10.47%).

References

1. ZJ-Jia, Y. Wu, W. Huang, P. Zhang, L. A. Clizbe, E. A. Goldman, U. Sinha, A. Clizbe, E. A. Goldman, U. Sinha, A. E. Arfsten, S. T. Edwards, M. Alphonso, A. Hutchaleelaha, R. M. Scarborough and B. Yzhu, *Bioorg. & Medicinal Chem. Lett.*, 2004, 14, 1221.
2. L. Deluca, G. Giacomelli, A. Porcheddu, M. Salaris, M. Salaris and M. Taddei, *C. R. Chimie*, 2003, 6, 607.
3. M. A. Saleh, M. F. Abdel-Megeed, M. A. Abdo and M. S. Abdel-Basset, *Molecules*, 2003, 8, 363.

4. L. Commeiras, S. C. Woodcock, J. E. Baldwin, R. M. Adlington, A. R. Cowlex and P. D. Wilkinson, *Tetrahedron*, 2004, **60**, 933.
5. A. H. El-Masry, H. H. Fahmy and S. H. A. Abdelwahed, *Molecules*, 2000, **5**, 1429.
6. R. Anikwue, J. W. Huffman *et al.*, *J. Pharmacol. Exp. Ther.*, 2002, **303**, 340.
7. M. A. Berghot and E. B. Moawad, *European J. Pharm. Sci.*, 2003, **20**, 173.
8. Algaforova and Mileklina, *Doke Akad Nauk*, 1966, **171**, 125.
9. Grandberg, *Kost Zhur Ibshechi*, 1960, **30**, 1373 (*Chem. Abst.*, 1961, **55**, 518).
10. G. H. Sayed and H. Kjsen, *J. Prak. Chemie*, 1980, **322**, 716.
11. J. C. Gould and J. M. Boure, *Med. J. Chem.*, 1952, **178**, 59.