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RESEARCH ARTICLE

Synthesis of a new series of angiotensin II receptor antagonists and antibacterial agents

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Abstract 2-(Arylmethylenehydrazono)-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one **3** underwent regioselective cyclization upon treatment with bromine in acetic acid containing sodium acetate to give the respective 3-substituted-6,6-diphenyl-6,7-dihydro-imidazo[2,1-*c*][1,2,4]triazole-5-one **4** in overall good yields and not the isomeric structure **5**. In addition, compound **4** was synthesized by alternative method via reaction of compound **1** with different acids in acetic acid. The synthesized hydrazone derivatives were screened for their angiotensin II receptor antagonists activity and the results showed promising activity. Also, imidazo[2,1-*c*][1,2,4]triazole-5-ones **4** were screened for the antibacterial activity and the result revealed that two derivatives have excellent activity.

Keywords Hydrazone · Imidazo[2,1-*c*][1,2,4]triazole-5-one · Antibacterial activity · Angiotensin activity

Introduction

Many drugs contain imidazole ring, such as angiotensin II receptor antagonists (Guo et al. 2008; Roumelioti et al. 2002; Shafiee et al. 2000), antimalarial (Pfaller and Krogstad 1983), antibacterial (Khabnadideh et al. 2003), anticancer (Li et al. 2010) and anticytokine agents (Laufer et al. 2002). On the other hand, hydrazones are known as one of the most important classes of organic compounds. They have cathepsin S inhibitors, analgesic, anticancer, antitumor, anti-inflammatory, antibacterial, and antifungal activities (Cywin et al. 2003; El-Gazzar et al. 2008; Ganguly et al. 2001; Kandile et al. 2009, Vicini et al. 2009; Banachiewicz and Kaminska 2001). In addition, substituted imidazo[2,1-*c*] [1,2,4]triazoles derivatives have become of great importance due to their wide range of biological activity (Pavlov et al. 1998; Harb et al. 1990; Sztanke et al. 2004; Singh 1990). Besides, they were used as antioxidant (Sayed et al. 2010) and anti-cancer agents (Sztanke et al. 2008). In view of the above mentioned findings and in continuation of our efforts (Farghaly and Abdalla 2009; Farghaly et al. 2010, 2012; Abdel Hafez et al. 2010; Riyadh et al. 2010) to synthesis a new heterocyclic compounds that may have potent biological activities, we decided in the present work to synthesize new 2-[(substitutedmethylene)hydrazono]-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one used as angiotensin II receptor antagonists and imidazo-[2,1-*c*][1,2,4]triazoles derivatives as antibacterial agents.

Materials and methods

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in a Pye-Unicam SP300 instrument in potassium bromide discs. ^{1}H and ^{13}C NMR spectra were recorded in a Varian Mercury VXR-300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) in DMSO-d_6 and the chemical shifts were related to that of the solvent. Mass spectra were recorded in a GCMS-QP 1000 EX Shimadzu Spectrometer, the ionizing voltage was 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo

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University, Giza, Egypt. Antibacterial activities were carried out at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt.

Preparation of hydrazones **3a–n**

A mixture of hydrazine **1** (2.5 mmol) and the appropriate aldehyde **2** (2.5 mmol) in acetic acid (20 mL) and few drops of conc. hydrochloric acid (≈1 mL) was heated under reflux for 3 h. The reaction mixture was then cooled and diluted with water. The so-formed solid product was then collected by filtration, dried and recrystallized from the proper solvent to afford the corresponding hydrazones **3a–n**.

*4,4-Diphenyl-2-[(phenylmethylene)hydrazono]-1H-imidazol-5(4H)-one (**3a**) (Kottke and Kühmstedt 1978)*

White solid (81 %) mp. 240–242 °C (EtOH) ^{1}H NMR (DMSO-d_6) δ ppm: 3.89 (br s, 1H, NH), 7.29–7.87 (m, 15H, ArH), 8.20 (s, 1H, =CH), 9.33 (s, 1H, NH). IR ν cm^{-1}: 3,341, 3,150 (2NH), 1,735 (CO) cm^{-1}. Ms *m/z* (%) 355 (M$^+$+1, 9), 354 (M$^+$, 34), 249 (24), 248 (100), 182 (25), 165 (28), 106 (53), 104 (71), 90 (37), 77 (78). Anal. Calcd. for $C_{22}H_{18}N_4O$ (354.41) C, 74.56; H, 5.12; N, 15.81. Found: C, 74.29; H, 5.08; N, 15.74 %.

*4,4-Diphenyl-2-[(4-methylphenylmethylene)hydrazono]-1H-imidazol-5(4H)-one (**3b**)*

White solid (85 %) mp. 244–246 °C (EtOH) ^{1}H NMR (DMSO-d_6) δ ppm: 2.33 (s, 3H, CH_3), 3.57 (br s, 1H, NH), 7.22 (d, J = 8 Hz, 2H, Ar–H), 7.31-7.41 (m, 10H, Ar–H), 7.76 (d, J = 8 Hz, 2H, Ar–H), 8.17 (s, 1H, = CH), 9.51 (s, 1H, NH). IR ν cm^{-1}: 3,225, 3,210 (2NH), 1,745 (CO) cm^{-1}. Ms *m/z* (%) 369 (M$^+$+1, 24), 368 (M$^+$, 72), 367 (23), 248 (69), 180 (31), 165 (31), 120 (63), 118 (48), 104 (100), 91 (38), 88 (33), 77 (83). Anal. Calcd. for $C_{23}H_{20}N_4O$ (368.44) C, 74.98; H, 5.47; N, 15.21. Found: C, 74.85; H, 5.38; N, 15.14 %.

*2-[(4-Chlorophenylmethylene)hydrazono]-4,4-diphenyl-1H-imidazol-5(4H)-one (**3c**) (Kottke and Kühmstedt 1978)*

White solid (79 %) mp. 280–282 °C (Dioxane) ^{1}H NMR (DMSO-d_6) δ ppm: 3.80 (br s, 1H, NH), 7.21 (d, J = 8 Hz, 2H, Ar–H), 7.29–7.58 (m, 10H, Ar–H), 7.85 (d, J = 8 Hz, 2H, Ar–H), 8.20 (s, 1H, =CH), 9.61 (s, 1H, NH). IR ν cm^{-1}: 3,250, 3,163 (2NH), 1,747 (CO) cm^{-1}. Ms *m/z* (%) 390 (M$^+$+2, 6), 389 (M$^+$+1, 2), 388 (M$^+$, 17), 387 (32), 248 (100), 247 (57), 207 (28), 182 (42), 180 (51), 165 (49), 139 (47), 138 (26), 111 (32), 90 (21), 77 (64), 76 (89). Anal. Calcd. for $C_{22}H_{17}ClN_4O$ (388.86) C, 67.95; H, 4.41; N, 14.41. Found: C, 67.69; H, 4.26; N, 14.35 %.

*2-[(2-Chlorophenylmethylene)hydrazono]-4,4-diphenyl-1H-imidazol-5(4H)-one (**3d**)*

White solid (76 %) mp. 204–206 °C (EtOH) ^{1}H NMR (DMSO-d_6) δ ppm: 3.59 (br s, 1H, NH), 7.19–7.78 (m, 14H, ArH), 8.15 (s, 1H, =CH), 9.20 (s, 1H, NH). IR ν cm^{-1}: 3,444, 3,163 (2NH), 1,755 cm^{-1}. Ms *m/z* (%) 390 (M$^+$+2, 10), 389 (M$^+$+1, 11), 388 (M$^+$, 34), 247 (57), 182 (36), 180 (34), 165 (55), 138 (26), 115 (26), 111 (21), 104 (60), 89 (68), 78 (45), 77 (100). Anal. Calcd. for $C_{22}H_{17}ClN_4O$ (388.86) C, 67.95; H, 4.41; N, 14.41. Found: C, 67.69; H, 4.26; N, 14.35 %.

*2-[(4-Bromophenylmethylene)hydrazono]-4,4-diphenyl-1H-imidazol-5(4H)-one (**3e**)*

White solid (83 %) mp. 238–240 °C (EtOH) ^{1}H NMR (DMSO-d_6) δ ppm: 3.81 (br s, 1H, NH), 7.05 (d, J = 8 Hz, 2H, Ar–H), 7.14–7.52 (m, 10H, Ar–H), 8.01 (d, J = 8 Hz, 2H, Ar–H), 8.23 (s, 1H, = CH), 9.781 (s, 1H, NH). IR ν cm^{-1}: 3,405, 3,215 (2NH), 1,742 (CO) cm^{-1}. Ms *m/z* (%) 435 (M$^+$+2, 5), 434 (M$^+$+1, 14), 433 (M$^+$, 10), 432 (15), 248 (100), 182 (18), 165 (25), 104 (45), 77 (38). Anal. Calcd. for $C_{22}H_{17}BrN_4O$ (433.31) C, 60.98; H, 3.95; N, 12.93. Found: C, 60.78; H, 3.86; N, 12.91 %.

*4,4-Diphenyl-2-[(2-hydroxyphenylmethylene)hydrazono]-1H-imidazol-5(4H)-one (**3f**) (Kottke and Kühmstedt 1978)*

White solid (78 %) mp. 216–218 °C (Dioxane) ^{1}H NMR (DMSO-d_6) δ ppm: 3.65 (br s, 1H, NH), 6.99–7.95 (m, 14H, ArH), 8.23 (s, 1H, =CH), 9.39 (s, 1H, NH), 13.50 (s, 1H, OH). IR ν cm^{-1}: br 3,200, 3,166 (2NH and OH), 1,755 (CO) cm^{-1}. Ms *m/z* (%) 371 (M$^+$+1, 47), 370 (M$^+$, 38), 248 (47), 182 (38), 165 (88), 122 (59), 115 (41), 105 (44), 103 (31), 77 (91). Anal. Calcd. for $C_{22}H_{18}N_4O_2$ (370.41) C, 71.34; H, 4.90; N, 15.13. Found: C, 71.25; H, 5.01; N, 15.10 %.

*4,4-Diphenyl-2-[(3-hydroxyphenylmethylene)hydrazono]-1H-imidazol-5(4H)-one (**3g**)*

White solid (74 %) mp. 208–210 °C (EtOH) ^{1}H NMR (DMSO-d_6) δ ppm: 3.78 (br s, 1H, NH), 7.08–7.77 (m, 14H, ArH), 8.05 (s, 1H, =CH), 9.48 (s, 1H, NH), 14.26 (s, 1H, OH). IR ν cm^{-1}: br 3,225, 3,154 (2NH and OH), 1,759 (CO) cm^{-1}. Ms *m/z* (%) 371 (M$^+$+1, 12), 370 (M$^+$, 35), 248 (17), 181 (42), 180 (56), 165 (68), 142 (24), 141 (68), 138 (90), 77 (95). Anal. Calcd. for $C_{22}H_{18}N_4O_2$ (370.41) C,

71.34; H, 4.90; N, 15.13. Found: C, 71.18; H, 5.15; N, 15.32 %.

*2-[(3,4-Dimethoxyphenylmethylene)hydrazono]-4,4-diphenyl-1H-imidazol-5(4H)-one (**3h**)*

White solid (81 %) mp. 260–262 °C (Dioxane) ^{1}H NMR (DMSO-d_6) δ ppm: 3.58, 3.61 (s, 6H, 2OCH_3), 4.05 (br s, 1H, NH), 6.94–7.58 (m, 13H, ArH), 8.12 (s, 1H, =CH), 10.0 (s, 1H, NH). IR ν cm^{-1}: br 3,209 (2NH), 1,759 (CO) cm^{-1}. Ms *m/z* (%) 414 (M^+, 55), 413 (23), 249 (32), 248 (62), 180 (40), 167 (68), 166 (75), 165 (94), 104 (43), 77 (100), 76 (49). Anal. Calcd. for $C_{24}H_{22}N_4O_3$ (414.47) C, 69.55; H, 5.35; N, 13.52. Found: C, 69.34; H, 5.31; N, 13.46 %.

*4,4-Diphenyl-2-[(3,4,5-trimethoxyphenylmethylene) hydrazono]-1H-imidazol-5(4H)-one (**3i**)*

White solid (75 %) mp. 236–238 °C (EtOH) ^{1}H NMR (DMSO-d_6) δ ppm: 3.58, 3.61 (s, 9H, 3OCH_3), 3.95 (br s, 1H, NH), 7.11–7.80 (m, 12H, ArH), 8.11 (s, 1H, =CH), 9.58 (s, 1H, NH). IR ν cm^{-1}: 3,210, 3,170 (2NH), 1,755 (CO) cm^{-1}. Ms *m/z* (%) 445 (M^++1, 26), 444 (M^+, 63), 443 (39), 267 (23), 248 (79), 238 (31), 196 (74), 180 (100), 167 (42), 165 (99), 104 (97), 90 (31), 77 (88), 76 (77). Anal. Calcd. for $C_{25}H_{24}N_4O_4$ (444.48) C, 67.55; H, 5.44; N, 12.60. Found: C, 67.47; H, 5.31; N, 12.50 %.

*4,4-Diphenyl-2-[(3-methoxy-4-hydroxyphenylmethylene) hydrazono]-1H-imidazol-5(4H)-one (**3j**)*

White solid (82 %) mp. 250–252 °C (EtOH/Dioxane) ^{1}H NMR (DMSO-d_6) δ ppm: 1.78 (s, 1H, OH), 3.58 (br s, 1H, NH), 3.83 (s, 3H, OCH_3), 6.80–7.43 (m, 13H, Ar–H), 8.08 (s, 1H, =CH), 9.40 (s, 1H, NH). IR ν cm^{-1}: br 3,250, 3,167 (2NH and OH), 1,747 (CO) cm^{-1}. Ms *m/z* (%) 400 (M^+, 48), 399 (41), 248 (100), 247 (49), 206 (24), 180 (43), 165 (54), 163 (14), 104 (73), 77 (99). Anal. Calcd. for $C_{23}H_{20}N_4O_3$ (400.44) C, 68.99; H, 5.03; N, 13.99. Found: C, 68.78; H, 5.15; N, 13.86 %.

*4,4-Diphenyl-2-[styrylmethylenehydrazono]-1H-imidazol-5(4H)-one (**3k**)*

White solid (74 %) mp. 284–286 °C (EtOH) ^{1}H NMR (DMSO-d_6) δ ppm: 3.61 (br s, 1H, NH), 5.62 (d, J = 12 Hz, 1H, = CH), 6.98–7.33 (m, 15H, Ar–H), 7.50 (d, J = 12 Hz, 1H, =CH), 8.27 (s, 1H, =CH), 9.87 (s, 1H, NH). IR ν cm^{-1}: 3,440, 3,067 (2NH), 1,755 (CO) cm^{-1}. Ms *m/z* (%) 381 (M^++1, 21), 380 (M^+, 16), 268 (42), 248 (81), 207 (49), 196 (51), 179 (51), 164 (56), 132 (56), 119 (51), 104 (88), 103 (49), 89 (23), 77 (86). Anal. Calcd. for $C_{24}H_{20}N_4O$ (380.44) C, 75.77; H, 5.30; N, 14.73. Found: C, 75.54; H, 5.20; N, 14.89 %.

*4,4-Diphenyl-2-[methylenehydrazono]-1H-imidazol-5(4H)-one (**3l**)*

White solid (80 %) mp. 168–170 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ ppm: 3.34 (br s, 1H, NH), 7.15–7.58 (m, 12H, Ar-H and =CH_2), 9.32 (s, 1H, NH). IR ν cm^{-1}: 3,231, 3,187 (2NH), 1,728 (CO) cm^{-1}. Ms *m/z* (%) 278 (M^+, 23), 252 (29), 180 (100), 165 (47), 77 (78). Anal. Calcd. for $C_{16}H_{14}N_4O$ (278.31) C, 69.05; H, 5.07; N, 20.13. Found: C, 69.18; H, 5.0; N, 20.01 %.

*2-[Ethylenehydrazono]-4,4-diphenyl-1H-imidazol-5(4H)-one (**3m**)*

White solid (80 %) mp. 112–114 °C (EtOH/Dioxane) ^{1}H NMR (DMSO-d_6) δ ppm: 1.87 (d, 3H, CH_3), 3.38 (br s, 1H, NH), 7.11–7.50 (m, 11H, Ar–H and =CH), 9.20 (s, 1H, NH). IR ν cm^{-1}: 3,225, 3,160 (2NH), 1,725 (CO) cm^{-1}. Ms *m/z* (%) 292 (M^+, 10), 248 (37), 223 (20), 180 (80), 179 (51), 165 (41), 104 (100), 77 (92). Anal. Calcd. for $C_{17}H_{16}N_4O$ (292.31) C, 69.85; H, 5.52; N, 19.17. Found: C, 69.74; H, 5.32; N, 19.09 %.

*4,4-Diphenyl-2-[(2-thionylmethylene)hydrazono]-1H-imidazol-5(4H)-one (**3n**)*

White solid (83 %) mp. 240–242 °C (EtOH/Dioxane) ^{1}H NMR (DMSO-d_6) δ ppm: 3.33 (br s, 1H, NH), 7.12–7.44 (m, 13H, Ar–H), 8.39 (s, 1H, =CH), 9.30 (s, 1H, NH). IR ν cm^{-1}: 3,429, 3,228 (2NH), 1,700 (CO) cm^{-1}. Ms *m/z* (%) 361 (M^++1, 15), 360 (M^+, 39), 248 (100), 180 (26), 165 (49), 112 (49), 111 (43), 104 (75), 96 (78), 77 (64). Anal. Calcd. for $C_{20}H_{16}N_4OS$ (360.43) C, 66.65; H, 4.47; N, 15.54. Found: C, 66.42; H, 4.20; N, 15.22 %.

Synthesis of 3-substituted-6,6-diphenyl-6,7-dihydro-pyrazolo[2,1-c][1,2,4]triazole-5-one (**4b**, **c**, **f**, **h–j**, **l**, **m**)

Method A Bromine (0.052 g, 1 mmol) in acetic acid (5 mL) was added dropwise to a stirred solution of the appropriate hydrazone **3a–m** (1 mmol of each) in acetic acid (10 mL) and sodium acetate (0.5 g). The reaction mixture was then poured onto ice cold water, and the solid that precipitated was filtered off, washed with sodium bicarbonate solution and then with water, dried and crystallized from EtOH\DMF to give the respective compounds **4b**, **c**, **f**, **h–j**, **l**, **m** but the other derivatives **4a**, **d**, **e**, **g**, **k** can't cyclized.

Method B General procedure: A mixture of compound **1** (0.266 g, 10 mmol) and the appropriate acid (10 mmol of

each) in glacial acetic acid (20 mL) was refluxed for 6 h. After cooling, the precipitate was collected by filtration and crystallized from EtOH\DMF to afford products which were found to be identical in all respects (mp. mixed mp. and IR) with products **4**.

*6,6-Diphenyl-6,7-dihydro-3-(4-methylphenyl)-pyrazolo[2,1-c][1,2,4]triazole-5-one (**4b**)*

Yellow solid (60 %) mp. 214 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 2.49 (s, 3H, CH_3), 7.31–8.05 (m, 14H, Ar–H), 9.18 (s, 1H, NH). IR ν cm^{-1}: 3,166 (NH), 1,751 (CO) cm^{-1}. Ms *m/z* (%) 367 (M^++1, 21), 366 (M^+, 100), 104 (70), 92 (70), 77 (38). Anal. Calcd. for $C_{23}H_{18}N_4O$ (366.43) C, 75.39; H, 4.95; N, 15.29. Found: C, 75.12; H, 4.70; N, 15.05 %.

*3-(4-Chlorophenyl)-6,6-diphenyl-6,7-dihydro-pyrazolo[2,1-c][1,2,4]triazole-5-one (**4c**)*

White solid (63 %) mp. 260 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 7.21–7.58 (m, 14H, Ar–H), 9.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ ppm: 81.02, 122.32, 126.12, 129.01, 130.04, 135.24, 136.11, 142.05, 149.36, 150.24, 157.19, 170.02. IR ν cm^{-1}: 3,409 (NH), 1,700 (CO) cm^{-1}. Ms *m/z* (%) 389 (M^++2, 13), 388 (M^++1, 24), 387 (M^+, 25), 248 (100), 180 (27), 165 (58), 111 (9), 104 (74), 89 (70), 77 (42). Anal. Calcd. for $C_{22}H_{15}ClN_4O$ (386.84) C, 68.31; H, 3.91; N, 14.48. Found: C, 68.10; H, 4.05; N, 14.34 %.

*6,6-Diphenyl-6,7-dihydro-3-(2-hydroxyphenyl)-pyrazolo[2,1-c][1,2,4]triazole-5-one (**4f**)*

Yellow solid (66 %) mp. 170–172 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 6.94–7.87 (m, 14H, Ar–H), 9.20 (s, 1H, NH), 13.42 (s, 1H, OH). IR ν cm^{-1}: br 3,220, 3,160 (NH and OH), 1,720 (CO) cm^{-1}. Ms *m/z* (%) 368 (M^+, 28), 248 (58), 180 (27), 165 (69), 104 (100), 77 (85). Anal. Calcd. for $C_{22}H_{16}N_4O_2$ (368.39) C, 71.73; H, 4.38; N, 15.21. Found: C, 71.56; H, 4.15; N, 15.08 %.

*6,6-Diphenyl-6,7-dihydro-3-(3,4-dimethoxyphenyl)-pyrazolo[2,1-c][1,2,4]triazole-5-one (**4h**)*

White solid (69 %) mp. 240 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 3.50, 3.58 (s, 6H, $2OCH_3$), 6.98–7.78 (m, 13H, ArH), 9.54 (s, 1H, NH). IR ν cm^{-1}: 3,421 (NH), 1,728 (CO) cm^{-1}. Ms *m/z* (%) 412 (M^+, 47), 248 (30), 180 (22), 179 (100), 165 (73), 149 (32), 104 (58), 77 (78). Anal. Calcd. for $C_{24}H_{20}N_4O_3$ (412.44) C, 69.89; H, 4.89; N, 13.58. Found: C, 69.77; H, 4.71; N, 13.30 %.

*6,6-Diphenyl-6,7-dihydro-3-(3,4,5-trimethoxyphenyl)-pyrazolo[2,1-c][1,2,4]triazole-5-one (**4i**)*

White solid (67 %) mp. 266 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 3.78, 3.86, 3.92 (3 s, 9H, $3OCH_3$), 7.17 (s, 1H, Ar–H), 7.24 (s, 1H, Ar–H), 7.28–7.73 (m, 10H, Ar–H), 9.28 (s, 1H, NH). IR ν cm^{-1}: 3,406 (NH), 1,710 (CO) cm^{-1}. Ms *m/z* (%) 443 (M^++1, 100), 442 (M^+, 37), 250 (26), 230 (33), 181 (41), 165 (78), 104 (78), 77 (52). Anal. Calcd. for $C_{25}H_{22}N_4O_4$ (442.48) C, 67.86; H, 5.01; N, 12.66. Found: C, 67.68; H, 4.95; N, 12.42 %.

*6,6-Diphenyl-6,7-dihydro-3-(3-methoxy-4-hydroxyphenyl)-pyrazolo[2,1-c][1,2,4] triazole-5-one (**4j**)*

White solid (65 %) mp. 270–272 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 1.73(s, 1H, OH), 3.87 (s, 3H, OCH_3), 7.20–7.62 (m, 13H, Ar–H), 9.34 (s, 1H, NH). IR ν cm^{-1}: 3,282–3,154 (NH andOH), 1,720 (CO) cm^{-1}. Ms *m/z* (%) 398 (M^+, 16), 397 (29), 290 (18), 91 (41), 90 (100), 77 (77). Anal. Calcd. for $C_{23}H_{18}N_4O_3$ (398.41) C, 69.34; H, 4.55; N, 14.06. Found: C, 69.20; H, 4.35; N, 14.28 %.

*6,6-Diphenyl-6,7-dihydro-pyrazolo[2,1-c][1,2,4] triazole-5-one (**4l**)*

Yellow solid (61 %) mp. 262–264 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 7.13–7.43 (m, 10H, Ar–H), 8.68 (s, 1H, triazole-CH) 9.52 (s, 1H, NH). IR ν cm^{-1} 3,265 (NH), 1,714 (CO) cm^{-1}. Ms *m/z* (%) 276 (M^+, 7), 252 (32), 223 (40), 180 (100), 165 (34), 104 (88), 77 (99). Anal. Calcd. for $C_{16}H_{12}N_4O$ (276.30) C, 69.55; H, 4.38; N, 20.28. Found: C, 69.43; H, 4.18; N, 20.07 %.

*6,6-Diphenyl-6,7-dihydro-3-methyl-pyrazolo[2,1-c][1,2,4] triazole-5-one (**4m**)*

Yellow solid (68 %) mp. 290–292 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H, CH_3), 7.27–7.62 (m, 10H, Ar–H), 8.27 (s, 1H, NH). IR ν cm^{-1}: 3,231 (NH), 1,718 (CO) cm^{-1}. Ms *m/z* (%) 290 (M^+, 48), 287 (27), 286 (41), 180 (59), 165 (41), 142 (72), 103 (100), 89 (46), 77 (64). Anal. Calcd. for $C_{17}H_{14}N_4O$ (290.33) C, 70.33; H, 4.86; N, 19.30. Found: C, 70.19; H, 4.72; N, 19.18 %.

Determination of the angiotensin II receptor antagonists in vivo

Male Sprague-Dawley rats are anesthetized with 100 mg/kg i.p. Inactin® and placed on servo-controlled heating pads to maintain body temperature between 37 and 38 °C. PE50 catheters are implanted in the femoral artery and vein to measure arterial blood pressure and administer

compounds, respectively. A catheter is placed in the trachea to ensure airway patency.

Arterial pressure is measured continuously by connecting the arterial catheter to transducer coupled to a Gould pressure transducer. The output is recorded on a polygraph. Mean arterial pressure is derived electronically.

After a 30–45 min stabilization period, autonomic transmission is blocked by treatment with mecamylamine (3 mg/kg i.v.) and atropine (0.4 mg/kg i.v.). After arterial pressure has stabilized, angiotensin is infused i.v.in isotonic saline with a syringe pump. When the pressure response to angiotensin has stabilized, angiotensin II receptor antagonists are given in increasing doses. The doses are given intravenously in a cumulative fashion, i.e., the next highest dose is given at the time of maximum response to the prior dose.

Data are presented as percent inhibition of the angiotensin pressor response to each dose of the antagonists and plotted against the log of the cumulative doses of antagonist. Linear regression is used to calculate the dose at which the response to angiotensin is inhibited 50 % (ID_{50}) for each rat. Mean ± SEM are calculated.

Antibacterial activity

Agar diffusion well method to determine the antibacterial activity

The microorganism inoculums were uniformly spread using sterile cotton swab on a sterile Petri dish containing nutrient agar (for bacteria). Each sample (100 µL) was added to each well (6 mm diameter holes cut in the agar gel, 20 mm apart from one another). The systems were incubated for 24–48 h at 37 °C for bacteria. After incubation, microorganism growth was observed. Inhibition of the bacterial growth were measured in mm. Tests were performed in triplicate (Smania et al. 1999).

Results and discussion

2-Hydrazinyl-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one (**1**) was prepared as previously reported (Gomha and Hassaneen 2011). Condensation of 2-hydrazinyl-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one (**1**) with different aldehydes **2a**–**n** in acetic acid containing few drops of conc. hydrochloric acid gave the corresponding hydrazone derivatives **3a**–**n** (Scheme 1). The mass spectra of the isolated products **3a–n** showed the molecular ion peaks at the expected *m*/*z* values. Their IR spectra showed the disappearance of the NH_2 group, and revealed in each case a carbonyl band in the region 1,759–1,700 cm^{-1} and two bands at 3,444–3,200 and 3,170–3,067 cm^{-1} assignable for 2NH groups. Also, ^1H NMR spectra showed, in each case, the presence of the azomethine and 2NH protons at δ = 8.39–8.08, 9.61–9.20 and 3.89–3.38 ppm, respectively.

Oxidative cyclization of the hydrazone derivatives **3a**–**n** with bromine in acetic acid in the presence of sodium acetate at room temperature yields in each case one isolable product **4** (Scheme 1), while the other isomeric structure **5** was discarded on the basis of ^{13}C NMR spectra of the isolated products. The ^{13}C NMR of compound **4c**, taken as a model example of the series prepared, revealed the signal for the carbonyl carbon resonance at δ = 170.02 ppm. This chemical shift value suggested that N(4) near C=O is sp^3 hybridized nitrogen atom and differ from the sp^2 hybridized nitrogen which appear at 184–189 ppm (Chande et al. 2007; SaÇmaci et al. 2005; Abbiati et al. 2001; Allouche et al. 2004). Based on the above finding we conclude that the isolated product has structure **4** and not the isomeric structure **5**. In addition, compound **4** was synthesized by alternative method via reaction of compound **1** with different acids in acetic acid.

Due to many drugs for angiotensin II receptor antagonists have imidazole moiety, such as Eprosartan, Losartan, Canesartan and Irbesartan (Chart 1), we screened some representative examples of the imidazole derivatives **3** for this property.

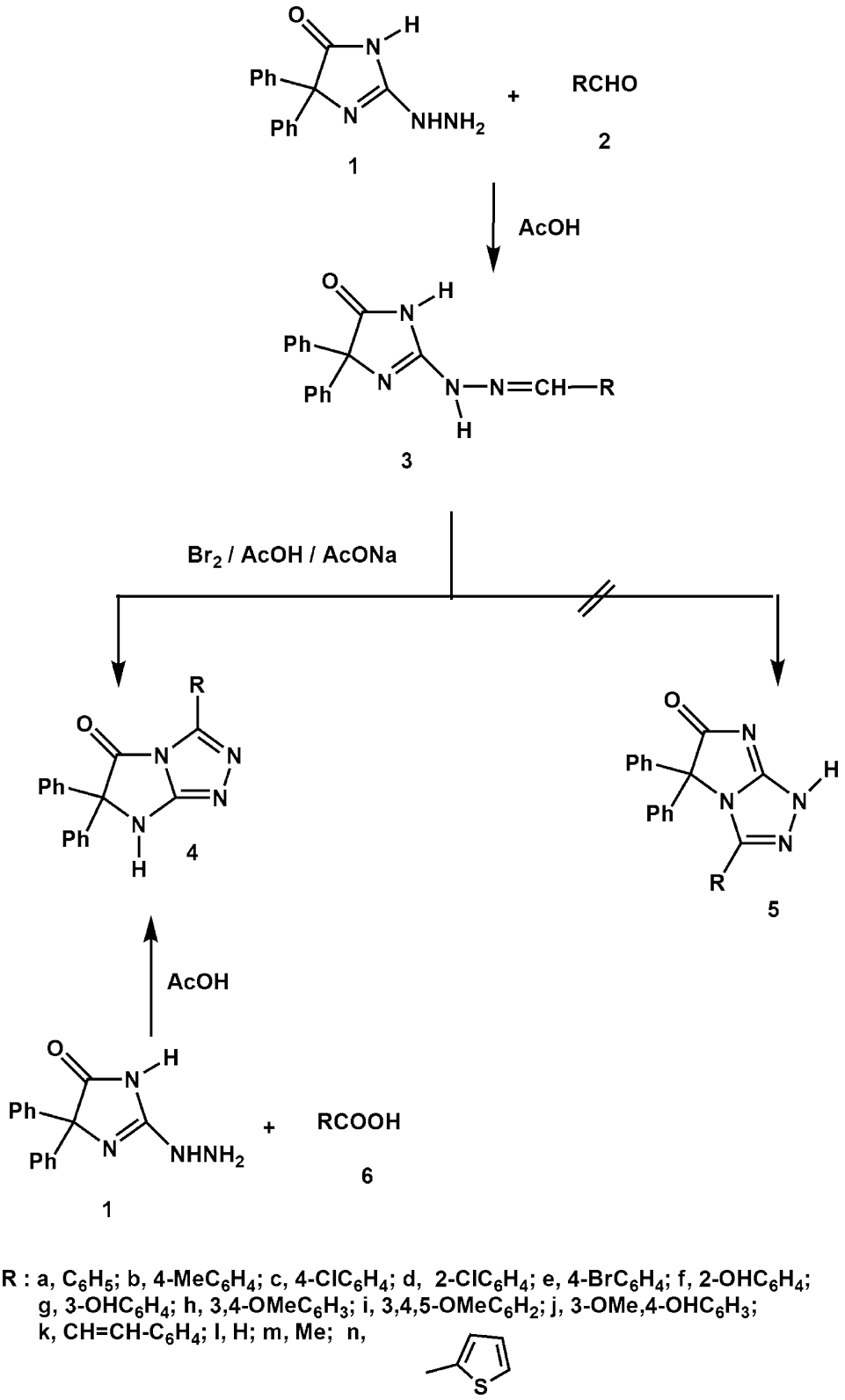
Evaluation of the angiotensin II receptor antagonists activities in vivo

The effect of angiotensin II receptor antagonists on blood pressure has been measured in anesthetized normotensive and hypertensive rats. From Table 1 we found that, all the tested compounds showed potent angiotensin II receptor antagonists activities in vivo and the ascending order of activities was **3n**, **3d**, **3m**, **3b**, **3g**, **3e**, **3f**, **3c**, **3l**, **3h**, **3j**, **3i**, and **3a**. From the results in Table 1, it was found that the best results were obtained by compounds bearing unsubstituted phenyl group (**3a**) and substituted phenyl group with electron donating groups such as trimethoxy (**3i**), methoxy, hydroxyl group (**3j**) dimethoxy (**3h**). On the other hand, derivatives **3n** which contain thiophene ring showed poor activity.

Antibacterial activity

In *vitro* antimicrobial screening of compounds **4b**, **c**, **h**, **i**, **j**, **l**, **m** prepared in this study was carried out using cultures of eight bacteria species, namely, Gram positive Bacteria, *Staphylococcus aureus* (RCMB 000106) (*S. aureus*), *Bacillus subtilis* (RCMB 000108) (*B. subtilis*), *Enterococcus faecalis* (RCMB010068) (*E. faecalis*), *Staphylococcus pyogenes* (RCMB 010015) (*S. pyogenes*) and Gram negative Bacteria, *Pseudomonas aeruginosa* (RCMB

Scheme 1 Synthesis of compounds **3** and **4**



010043) (*P. aeruginosa*), *Escherichia coli* (*E. coli*) (RCMB 010052), *Salmonella typhimurium* (RCMB 010072) (*S. typhimurim*) *and Klebsiella pneumoniae* (RCMB 0010093) (*K. pneumonia*). *Ampicillin* as an antibacterial agent for gram (+) bacteria and *Gentamicin* as an antibacterial agent for gram (−) bacteria were used as references to evaluate

Chart 1 Drugs for angiotensin II receptor antagonists have imidazole moiety

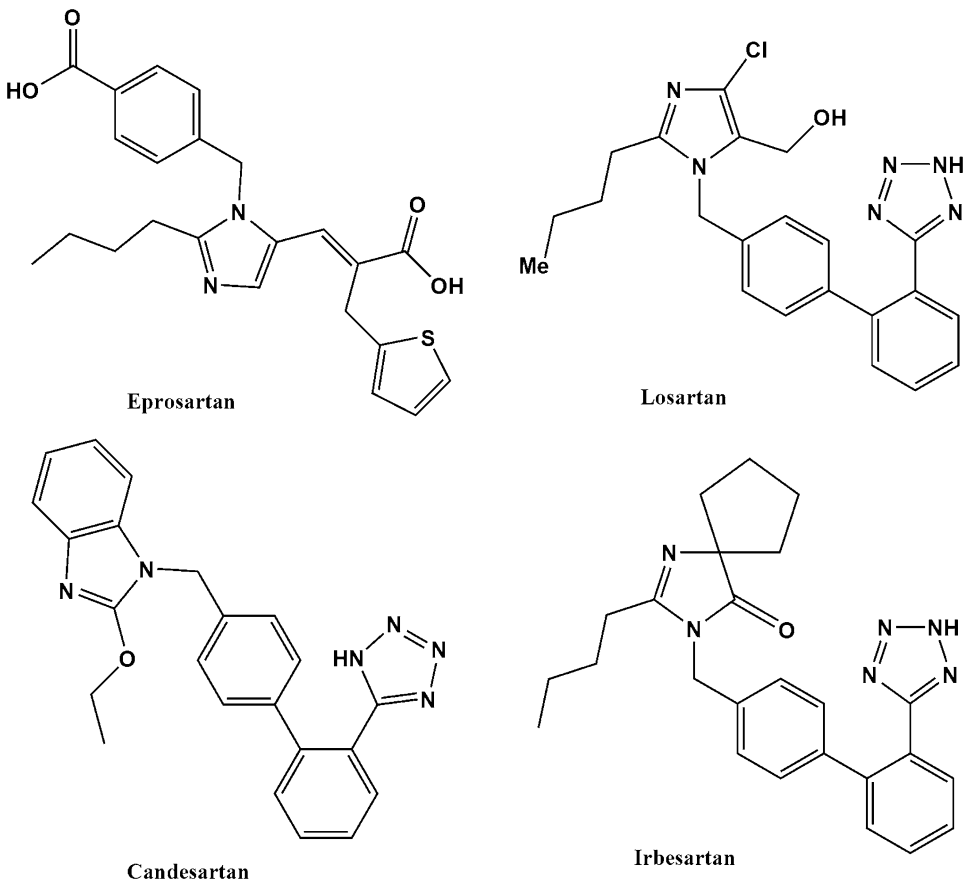


Table 1 Evaluation of ID_{50} and LD_{50} of angiotensin II receptor antagonists activities of compounds 3

Compound No.	ID_{50} μg/kg (mean ± SEM)	LD_{50} μg/kg
3a	$0.11 \pm 0.0011 \times 10^{-7}$	234.56 ± 2.33
3i	$0.19 \pm 0.0012 \times 10^{-7}$	456.44 ± 4.56
3j	$0.22 \pm 0.0014 \times 10^{-7}$	576.32 ± 6.43
3h	$0.23 \pm 0.0017 \times 10^{-7}$	385.87 ± 6.77
3l	$0.29 \pm 0.0019 \times 10^{-7}$	453.56 ± 4.55
3c	$0.32 \pm 0.0013 \times 10^{-7}$	387.56 ± 3.66
3f	$0.34 \pm 0.0022 \times 10^{-7}$	458.54 ± 5.66
3g	$0.49 \pm 0.0032 \times 10^{-7}$	875.48 ± 4.76
3e	$0.44 \pm 0.0024 \times 10^{-7}$	573.58 ± 3.46
3b	$0.56 \pm 0.0044 \times 10^{-7}$	485.67 ± 5.46
3m	$0.66 \pm 0.0045 \times 10^{-7}$	573.56 ± 4.32
3d	$0.77 \pm 0.0067 \times 10^{-7}$	485.67 ± 6.44
3n	$0.89 \pm 0.007 \times 10^{-7}$	489.57 ± 3.44

the potency of the tested compounds under the same conditions. The results of antibacterial activities for some of the newly synthesized compounds showed promising effect with respect to control drugs (see Table 2). Compounds **4b** and **4i** have high potency as antibacterial reagent except for *S. pyogenes* and *P. aeruginosa*. This result indicated that the presence of electron donating groups such as methyl or trimethoxy groups at position 3 in imidazotriazole system increase the activity. In contrast to the above result, compounds **4h** and **4j** (have an electron donating groups dimethoxy, methoxy and hydroxyl groups) decrease the activity. Also, the presence of hydrogen and methyl moieties decreases the reactivity as in compound **4l** and **4m**, respectively (Table 2). All biological activities done are preliminary tests and will be completed in due course.

Conclusions

Two series of 2-(arylmethylenehydrazono)-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one and 3-substituted-6,6-diphenyl-6,7-dihydro-imidazo[2,1-*c*][1,2,4]triazole-5-one were synthesized. The hydrazone derivatives were screened for their angiotensin II receptor antagonists activity and the results showed promising activity. Also, it was found that the best results were obtained by compounds bearing unsubstituted phenyl group and substituted phenyl group with electron donating groups such as trimethoxy, methoxy, hydroxyl and dimethoxy. Imidazo[2,1-*c*][1,2,4]triazole-5-ones were screened for the antibacterial activity and the result revealed that two derivatives with electron donating groups

Table 2 Antimicrobial activity expressed as inhibition diameter zones in millimeter (mm) of compounds against the pathological strains based on well diffusion as assay

Comp. No.	Gram positive bacteria				Gram negative bacteria			
	S. aureus	*B. subtilis*	*E. faecalis*	*S. pyogenes*	*P. aeruginosa*	*E. coli*	*S. typhimurim*	*K. pneumonia*
4b	22.8 (±0.28)	26.3 (±0.58)	18.4 (0.44)	NA	NA	19.8 (±0.28)	20.1 (±0.37)	22.6 (±0.58)
4c	16.9 (±0.28)	18.2 (±0.19)	15.1 (±0.19)	NA	NA	16.1 (±0.28)	16.8 (±0.58)	18.1 (±0.28)
4h	17.4 (±0.44)	19.6 (±0.58)	16.2 (±0.37)	NA	NA	18.2 (±0.58)	19.3 (±0.44)	18.9 (±0.44)
4i	21.6 (±0.28)	23.7 (±0.44)	17.2 (±0.44)	NA	NA	18.4 (±0.19)	18.9 (±0.58)	20.8 (±0.19)
4j	12.9 (±0.28)	14.6 (±0.44)	12.1 (±0.44)	NA	NA	14.3 (±0.28)	15.3 (±0.19)	15.9 (±0.37)
4l	12.6 (±1.58)	15.8 (±0.28)	13.4 (0.37)	NA	NA	13.5 (±0.28)	15.2 (±0.58)	16.3 (±0.44)
4m	13.7 (±0.58)	15.4 (±0.44)	14.7 (±0.19)	NA	NA	15.2 (±0.44)	16.1 (±0.28)	16.9 (±0.58)
Ampicillin	27.4 (±0.18)	33.1 (±0.3)	20.4 (±0.11)	26.4 (±0.34)	NA	NA	NA	NA
Gentamicin	NA	NA	NA	NA	17.3 (±0.15)	28.8 (±0.24)	22.3 (±0.18)	26.3 (±0.15)

The experiment was carried out in triplicate and average zone of inhibition was calculated;(100 μL was tested) (NA = no activity), data are expressed in the form of mean ± SD

such as methyl or trimethoxy groups at position 3 have excellent activity.

References

Abbiati, G., A. Arcadi, O.A. Attanasi, L. De Crescentinic, and E. Rossia. 2001. Synthesis of functionalised pyrazolones and imidazolines/imidazoles through divergent cyclisation reactions. *Tetrahedron* 57: 2031–2038.

Abdel Hafez, N.A., T.A. Farghaly, M.A. Al-Omar, and M.M. Abdalla. 2010. Synthesis of bioactive polyheterocyclic ring systems as 5α-reductase inhibitors. *European Journal of Medicinal Chemistry* 45: 4838–4844.

Allouche, F., F. Chabchoub, B.B. Hassine, and M. Salem. 2004. Synthesis of new N1 tosyl-1, 2, 4-triazoles from condensation of aldehydes with N1tosylamidrazones. *Heterocyclic Communications* 10(1): 63–66.

Banachiewicz, B.M., and T. Kaminska. 2001. Antiviral activity of the products of cyclization of dimethyl 2-[(1-arylamino-1-aryl methylidene)hydrazono]-succinate. *European Journal of Medicinal Chemistry* 36(1): 93–99.

Chande, M.S., P.A. Barve, and V. Suryanarayan. 2007. Synthesis and antimicrobial activity of novel spirocompounds with pyrazolone and pyrazolthione moiety. *Journal of Heterocyclic Chemistry* 44: 49–53.

Cywin, C.L., R.A. Firestone, D.W. McNeil, C.A. Grygon, K.M. Crane, D.M. White, P.R. Kinkade, J.L. Hopkins, W. Davidson, M.E. Labadia, J. Wildeson, M.M. Morelock, J.D. Peterson, E.L. Raymond, M.L. Brown, and D.M. Spero. 2003. The design of potent hydrazones and disulfides as cathepsin S inhibitors. *Bioorganic & Medicinal Chemistry* 11: 733–740.

El-Gazzar, A.B.A., M.M. El-Enany, and M.N. Mahmoud. 2008. Synthesis, analgesic, anti-inflammatory, and antimicrobial activity of some novel pyrimido[4,5-*b*]quinolin-4-ones. *Bioorganic & Medicinal Chemistry* 16: 3261–3273.

Farghaly, T.A., and M.M. Abdalla. 2009. Synthesis, tautomerism, antimicrobial, anti-HCV, anti-SSPE, antioxidant and antitumor activities of arylazobenzosuberones. *Bioorganic & Medicinal Chemistry* 17: 8012–8019.

Farghaly, T.A., N.A. Abdel Hafez, E.A. Ragab, H.M. Awad, and M.M. Abdalla. 2010. Synthesis, anti-HCV, antioxidant, and peroxynitrite inhibitory activity of fused benzosuberone derivatives. *European Journal of Medicinal Chemistry* 45: 492–500.

Farghaly, T.A., S.M. Gomha, E.M. Abbas, and M.M. Abdalla. 2012. Hydrazonoyl halides as precursors for new fused heterocycles of 5a-reductase inhibitors. *Archiv der Pharmazie* 345: 117–122.

Ganguly, A.K., A.K. Doll, and V.M. Girijavallabhan. 2001. Farnesyl protein transferase inhibition: a novel approach to anti-tumor therapy. The discovery and development of SCH 66336. *Current Medicinal Chemistry* 8: 1419–1436.

Gomha, S.M., and H.M.E. Hassaneen. 2011. Synthesis and antimicrobial activity of some new pyrazoles, fused pyrazolo[3,4-*d*]-pyrimidine and 1,2-dihydroimidazo-[2,1-*c*][1,2,4]triazin-6-one derivatives. *Molecules* 16: 6549–6560.

Guo, X., L. Shi, R. Wang, X. Liu, B. Li, and X. Lu. 2008. Synthesis and biological activities of novel nonpeptide angiotensin II receptor antagonists based on benzimidazole derivatives bearing a heterocyclic ring. *Bioorganic & Medicinal Chemistry* 16: 10301–10310.

Harb, A.A., F.H. Mostafa, and S.A. Metwally. 1990. Synthesis of some heterocycles of potential biological activity. *Archives of Pharmacal Research* 13(2): 187–191.

Kandile, N.G., M.I. Mohamed, H. Zaky, and H.M. Mohamed. 2009. Novel pyridazine derivatives: Synthesis and antimicrobial activity evaluation. *European Journal of Medicinal Chemistry* 44(5): 1989–1996.

Khabnadideh, S., Z. Rezaei, A. Khalafi-Nezhad, R. Bahrinajafi, R. Mohamadi, and A.A. Farrokhroz. 2003. Synthesis of *N*-alkylated derivatives of imidazole as antibacterial agents. *Bioorganic & Medicinal Chemistry Letters* 13: 2863–2865.

Kottke, K., and H. Kühmstedt. 1978. The preparation of 2-hydrazino-3-arylquinzolones-(4)-synthesis of compounds with an amino-guanidine structure. *Pharmazie* 33: 19–23.

Laufer, S.A., H.A. Striegel, and K.W. Gerd. 2002. Imidazole inhibitors of cytokine release: probing substituents in the 2 position. *Journal of Medicinal Chemistry* 45: 2695–2705.

Li, W.T., D.R. Hwang, J.S. Song, C.P. Chen, J.J. Chuu, C.B. Hu, et al. 2010. Synthesis and biological activities of 2-amino-1-arylidenamino imidazoles as orally active anticancer agents. *Journal of Medicinal Chemistry* 53: 2409–2417.

Pavlov, P.A., NYu. Bosova, and P.P. Pavlov. 1998. Synthesis and antimicrobial activity of some nitrofuran-containing imidazotriazoles. *Pharmaceutical Chemistry Journal* 32(7): 376–377.

Pfaller, M.A., and D.J. Krogstad. 1983. Oxygen enhances the antimalarial activity of the imidazoles. *American Journal of Tropical Medicine and Hygiene* 32: 660–665.

Riyadh, S.M., T.A. Farghaly, and S.M. Gomha. 2010. Novel polyaza-heterocyclic systems: synthesis, antitumor, and antimicrobial Activities. *Archives of Pharmacal Research* 33: 1721–1728.

Roumelioti, P., L. Polevaya, P. Zoumpoulakis, N. Giatas, I. Mutule, T. Keivish, A. Zoga, D. Vlahakos, E. Iliodromitis, D. Kremastinos, S.G. Grdadolnik, T. Mavromoustakos, and J. Matsoukas. 2002. Design, synthesis and biological evaluation of cyclic angiotensin II analogues with 3,5 side-chain bridges: role of C-terminal aromatic residue and ring cluster for activity and implications in the drug design of AT1 non-peptide antagonists. *Bioorganic & Medicinal Chemistry Letters* 12: 2627–2633.

SaÇmaci, M., E. Saripinar, and Y. AkÇamur. 2005. Synthesis of novel proponohydrazides and their hydrolysis reactions. *Turkish Journal of Chemistry* 29: 401–407.

Sayed, H., E. Morsy, and E. Flefel. 2010. Synthesis and reactions of some novel nicotinonitrile, thiazolotriazole, and imidazolotriazole derivatives for antioxidant evaluation. *Synthetic Communications* 40(9): 1360–1370.

Shafiee, A., F. Hadizadeh, and S.B. Noori. 2000. Syntheses of 2-alkylthio-1-[4-(*N*-α-ethoxycarbonylbenzyl)aminobenzyl]-5-hydroxymethylimidazoles. *Journal of Heterocyclic Chemistry* 37: 1015–1018.

Singh, H., K.N. Shukla, and L.D.S. Yadav. 1990. Synthesis of some new heterocyclic compounds containing bridgehead nitrogen atom as antifungal drugs. *Indian Journal of Pharmaceutical Sciences* 52(1): 9–12.

Smania, J.A., F.D. Monache, E.F.A. Smania, and R.S. Cuneo. 1999. Antibacterial activity of steroidal compounds isolated from *Ganoderma applanatum* (Pers.) Pat. (Aphyllophoromycetideae) fruit body. *International Journal of Medicinal Mushrooms* 1: 325–330.

Sztanke, K., A. Sidor-Wójtowicz, J. Truchlińska, K. Pasternak, and M. Sztanke. 2004. The susceptibility of certain microbial strains to fused 1,2,4-triazole derivatives. *Annales Universitatis Mariae Curie-Sklodowska* 59(2): 100–103.

Sztanke, K., T. Tuzimski, J. Rzymowska, K. Pasternak, and M.K. Szerszen. 2008. Synthesis, determination of the lipophilicity, anticancer and antimicrobial properties of some fused 1,2,4-triazole derivatives. *European Journal of Medicinal Chemistry* 43: 404–419.

Vicini, P., M. Incerti, P.L. Colla, and R. Loddo. 2009. Anti-HIV evaluation of benzo[*d*]isothiazole hydrazones. *European Journal of Medicinal Chemistry* 44(4): 1801–1807.