Synthesis and antihypertensive activity of certain substituted dihydropyridines and pyrimidinones

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Received 17 July 2012
Accepted 10 October 2012

Egyptian Pharmaceutical Journal
2013,12:20–27

Background and objective

Some bulky substituted aromatic aldehydes reacted with urea and ethyl acetoacetate in the presence of acetic acid as a catalyst to yield solely substituted dihydropyridines (Hantzsch-type molecule). In the presence of *p*-toluene sulfonic acid as a catalyst, the products were only dihydropyrimidines (Biginelli compounds). The same aldehydes yielded dihydropyrimidinones on using acetyl acetone instead of ethyl acetoacetate whatever the catalyst used. These two classes of molecules represent a heterocyclic system of a remarkable antihypertensive effect. The aim of this study was to synthesize certain dihydropyridine and pyrimidinone derivatives with aromatic moiety with bulky substituents to be evaluated for their antihypertensive effect.

Methods

The aldehydes 3-(substituted-phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde **3–5,** 4-oxo-4H-chromene-3-carbaldehyde (**6**), and substituted phenylazo-benzaldehyde **7–9** reacted with ethyl acetoacetate and urea in ethanol in the presence of acetic acid to yield dihydropyridines **10–15**. Aldehydes **3–9** reacted with ethyl acetoacetate and urea in the presence of *p*-toluene sulfonic acid to yield dihydropyrimidinones **16–22**. Furthermore, the reaction of the aldehydes **3–9** with ethyl acetoacetate and urea in the presence of either acetic acid or *p*-toluene sulfonic acid yielded the corresponding dihydropyrimidinones **23–29**.

Results and conclusion

The hypotensive activity of compounds **10–14** and **16–20** indicated that the 4-aryl-dihydropyridine derivatives **10–14** showed higher activity than the pyrimidinones **16–20**. The most active compound was 4-(1,3-diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (**10**) at dose levels of 0.6, 1.2, and 2.4 mg/kg. It showed more or less similar hypotensive activity as the reference drug nifedipene at doses of 1.2 and 2.4 mg/kg. Its LD_{50} = 298 mg/kg body weight.

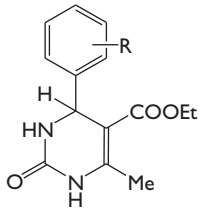
Keywords:
antihypertensive activity, bulky substituted aldehydes, dihydropyridines, dihydropyrimidinones

Egypt Pharm J 12:20–27

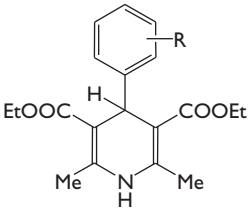
1687-4315

Introduction

The one-pot acid-catalyzed Biginelli [1,2] condensation is the most commonly used reaction to produce dihydropyrimidines (DHPMs, **1**). This very simple reaction involves three component cyclocondensation of urea, an aldehyde and a β-oxoester or 1,3-dicarbonyl compound using ethanol as a solvent and catalytic amounts of HCl, AcOH, or H_2SO_4 among other acids [3–7]. In contrast, in the Hantzsch reaction discussed, more than a century ago [8], the main way to obtain dihydropyridines (DHPs, **2**) and is commonly carried out as a one-pot condensation of a β-dicarbonyl compound with an aldehyde but with ammonia instead of urea using ethanol as a solvent.



1
Biginelli dihydropyrimidines



2
Hantzsch dihydropyridines

These two classes of molecules (**1** and **2**) represent a heterocyclic system with remarkable pharmacological properties that include antiviral [9,10], antitumor [11,12], antibacterial [13,14], and anti-inflammatory [15–18] activities. In addition, a number of these heterocyclic

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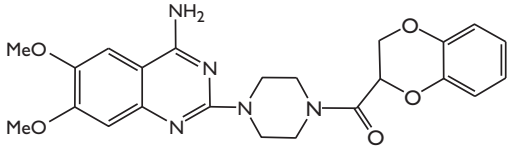
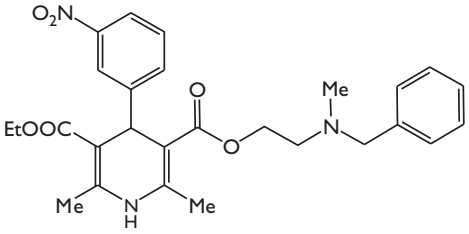
DOI: 10.7123/01.EPJ.0000426587.41764.d4



Doxazosin



Nicardipine

systems have emerged as exerting orally active antihypertensive effects or to act as α-$_{1A}$-adrenoceptor-selective antagonists [19,20], for example nifedipene and amludepine. It is worth mentioning that several examples of highly substituted DHPMs and DHPs are reported to show high antihypertensive activity, for example doxazosin [20] and nicardipine [21,22].

The aim of this work was to synthesize some DHPs and pyrimidinones with the aromatic moiety bearing bulky substituents to be evaluated for their antihypertensive activity.

Experimental

Chemistry

All melting points were determined in open capillary tubes using silicon oil on a Gallen Kamp Apparatus (Finsbury, London, England) and were uncorrected. ^{1}H-NMR spectra were determined using a JEOL EX-270 NMR spectrometer (Musashino 3-chome, Akishima, Tokyo, Japan) with tetramethylsilane as an internal standard. Mass spectra were performed using a GC-MS-QP 1000EX Schimadzu Gas Chromatography MS Spectrometer (Columbia, Maryland, USA). The infrared spectra were recorded on an FT/IR330E infrared spectrophotometer using KBr discs. Elemental analyses were carried out at the Micro analytical Laboratory of the National Research Center, Dokki, Cairo, Egypt. The reactions were followed up by thin layer chromatography (TLC) using chloroform/methanol (9 : 1) as an eluent and detected using a UV lamp.

General procedure for the preparation of substituted dihydropyridine compounds (10–15)

A mixture of the appropriate aldehydes **3–9** (6 mmol), urea (0.9 g, 15 mmol), ethyl acetoacetate (1.17 ml, 9 mmol), and glacial acetic acid (2 ml) in absolute ethanol (50 ml) was heated under reflux for several hours (12–18 h) (monitored by TLC). After the completion of the reaction, the solvent was removed under vacuum and the precipitated product was treated with water, filtered off, washed with water, dried, and crystallized from methanol.

4-(1,3-Diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (10)

Yield 72%, m.p. 154–156°C, IR (KBr, cm^{-1}): 3343 (NH), 1682 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 0.91 (t, 6H, $2CH_3$), 2.22 (s, 6H, $2CH_3$), 3.84 (q, 4H, $2CH_2$), 5.16 (s, 1H, C_4-H), 7.26–7.88 (m, 10H, Ar-Hs), 8.00 (s, 1H, pyrazole), 8.78 (s, 1H, NH, D_2O exchangeable); Ms: *m/z* (%): 469 [(M^+-2, (62)], 441 (100%), 397 (83), 326 (71), 251 (93), 220 (90), 206 (22), 179 (32), 77 (99). Analysis: for $C_{28}H_{29}N_3O_4$ (471.55), calcd: C, 71.32; H, 6.20; N, 8.91%. Found: C, 71.45; H, 6.30; N, 8.71%.

2,6-Dimethyl-4-[3-(4-nitrophenyl)-1-phenyl-1-H-pyrazole-4-yl]-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (11)

Yield 75%, m.p. 110–113°C, IR (KBr, cm^{-1}): 3369 (NH), 1683 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm) 0.87 (t, 6H, $2CH_3$), 2.24 (s, 6H, $2CH_3$), 3.87 (q, 4H, $2CH_2$), 5.18 (s, 1H, C4-H), 7.31–8.36 (m, 10H, 9Ar-Hs and 1H pyrazole), 8.81 (s, 1H, NH); Ms: *m/z* (%): 514 [(M^+-2, (22)], 486 (70), 442 (100), 251 (52). Analysis: for $C_{28}H_{28}N_4O_6$ (516.55), calcd: C, 65.11; H, 5.46; N, 10.85%. Found: C, 65.33; H: 5.19; N, 10.67%.

4-[3-(2-Hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (12)

Yield 68%, m.p. 98–100°C, IR (KBr, cm^{-1}): 3357 (OH), 3249 (NH) and 1693 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm), 0.98 (t, 6H, $2CH_3$), 2.13 (s, 6H, $2CH_3$), 3.87 (q, 4H, $2CH_2$), 5.10 (s, 1H, C4-H), 6.91–7.77 (m, 9H, Ar-Hs), 8.12 (s, 1H, pyrazole-H), 8.54 (s, 1H, NH) and 9.59 (s, 1H, OH); Ms: *m/z* (%): 485 [(M^+-2, (94%)], 457 (24), 438 (100), 413 (43), 394 (20), 252 (16), 236 (27). Analysis: for $C_{28}H_{29}N_3O_5$ (487.55), calcd: C, 68.98; H, 6.00; N, 8.62%. Found: C, 68.86; H, 5.79; N, 8.52%.

2,6-Dimethyl-4-(4-oxo-4H-chromen-3-yl)-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (13)

Yield 65%, m.p. 213–215°C; ^{1}H-NMR (d_6-DMSO, δ, ppm) 1.10 (t, 6H, $2CH_3$), 1.12 (t, 6H, $2CH_3$), 2.22 (s, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 3.96 (q, 4H, $2CH_2$), 4.02 (q, 4H, $2CH_2$), 4.82 (s, 1H, C4-H), 5.24 (s, 1H, C4-H), 7.43 (t, 1H, H-6), 7.50 (t, 1H, H-6), 7.55 (d, 1H, H-8), 7.57 (d, 1H, H-8), 7.64 (t, 1H, H-7), 7.73 (t, 1H, H-7), 7.93 (s, 1H, H-2), 8.14 (s, 1H, H-2), 8.00 (d, 1H, H-5), 8.02 (d, 1H, H-5), 8.82 (s, 1H, NH), 9.18 (s, 1H, NH); Ms *m/z* (%) 397 (M^+, 12%), 352 (7), 324 (100), 294 (10), 252 (32), 223 (17). Analysis: for $C_{22}H_{23}NO_6$ (397.42), calcd: C, 66.49; H, 5.83; N, 3.52%. Found: C, 66.80; H, 5.70; N, 3.41%.

2,6-Dimethyl-4-(2-hydroxy-3-methoxy-5-phenylazo-phenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (14)

Yield 75%, m.p. 124–126°C; IR (KBr, cm^{-1}): 3448 (OH), 3344 (NH), 1693 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 1.10 (t, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.00 (q, 2H, CH_2), 5.17 (s, 1H, C4-H), 7.03 (s, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 7.56 (t, 3H, Ar-Hs), 7.80 (s, 1H, N^3H, D_2O exchangeable), 7.98 (d, 2H, Ar-Hs), 9.26 (s, 1H, N^1H, D_2O exchangeable), 10.99 (s, 1H, OH); Ms: *m/z* (%): 477 [M^+-2, (34)], 431 (12), 372 (38), 354 (32), 252 (81), 238 (41), 105 (55), 93 (86) and 77 (100). Analysis: for $C_{26}H_{29}N_3O_6$ (479.52), calcd: C, 65.12; H, 6.10; N, 8.76%. Found: C, 65.29; H, 6.12; N, 8.95%.

2,4-Dimethyl-5-oxo-9-phenylazo-5H-chromeno[3,4-c]pyridine-1-carboxylic acid ethyl ester (15)

Yield 66%, m.p. 203–206°C; IR (KBr, cm^{-1}): 1730 (CO), 1684 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 1.33 (t, 3H, CH_3), 2.69 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 4.58 (q, 2H, CH_2), 7.61 (t, 3H, Ar-Hs), 7.64 (d, 1H, Ar-H), 7.88 (d, 1H, Ar-H), 8.22 (d, 2H, Ar-Hs), 8.31 (s, 1H, Ar-H); Ms: *m/z* (%), 400 [M^+-1, (27)], 356 (10), 329 (17), 268 (37), 250 (60), 224 (24), 169 (91), 105 (55), 77 (100). Analysis: for $C_{23}H_{19}N_3O_4$ (401.41), calcd: C, 68.82; H, 4.78; N, 10.47%. Found: C, 68.63; H, 4.91; N, 10.60%.

4-(Aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylicacid ethyl ester (16–22)

General procedure

A mixture of the appropriate aldehydes **3–9** (10 mmol), urea (1.5 g, 25 mmol), ethyl acetoacetate (1.95 ml, 15 mmol), and *p*-toluene sulfonic acid (1.72 g, 10 mmol) in absolute ethanol (35 ml) was heated under reflux for 6–8 h (monitored by TLC). After completion of the reaction, the solvent was removed under vacuum and the precipitated product was treated with water, filtered, washed with water, and dried. Crystallization from the appropriate solvent yielded the desired compounds **16–22**.

4-[1,3-Diphenyl-1H-pyrazole-4-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (16)

Yield 74%, m.p. 178–180°C (methanol); IR (KBr, cm^{-1}): 3349 (NH), 3222 (NH), 1693 (CO), 1642 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 0.82 (t, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.80 (q, 2H, CH_2), 5.38 (s, 1H, C4-H), 7.27–7.90 (m, 11H, 10Ar-Hs and 1H pyrazole), 8.35 (s, 1H, N^3H) and 9.16 (s, 1H, N^1H). Analysis: for $C_{23}H_{22}N_4O_3$ (402.45), calcd: C, 68.64; H, 5.51; N, 13.92%. Found: C, 68.80; H, 5.34; N, 13.71%.

6-Methyl-4-[3-(4-nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (17)

Yield 83%, m.p. 190–193°C; IR (KBr, cm^{-1}): 3439 (OH), 3210 (NH), 3122 (NH), 1713 (CO), 1657 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 0.87 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.82 (q, 2H, CH_2), 5.44 (s, 1H, C4-H), 6.87–7.89 (m, 10H, 9Ar-Hs and 1H pyrazole), 8.34 (s, 1H, N^3H), 9.20 (s, 1H, N^1H). Analysis: for $C_{23}H_{21}N_5O_5$ (447.44), calcd: C, 61.74; H, 4.73; N, 15.65%. Found: C, 61.96; H, 4.53; N, 15.85%.

4-[3-(2-Hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (18)

Yield 79%, m.p. 201–204°C; IR (KBr, cm^{-1}): 3223 (NH), 3109 (NH), 1698 (CO), 1649 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 0.83 (t, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.82 (q, 2H, CH_2), 5.44 (s, 1H, C4-H), 7.13–8.50 (m, 10H, 9Ar-Hs and 1H pyrazole), 7.85 (s, 1H, N^3H, D_2O exchangeable), 9.23 (s, 1H, N^1H, D_2O exchangeable). Analysis: for $C_{23}H_{22}N_4O_4$ (418.45), calcd: C, 66.02; H, 5.30; N, 13.39%. Found: C, 66.37; H, 5.49; N, 13.21%.

6-Methyl-2-oxo-4-(4-oxo-4H-chromen-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (19)

Yield 78%, m.p. 287–290°C, IR (KBr, cm^{-1}): 3386 (NH), 3281 (NH), 1710 (CO), 1669 (CO), 1638 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 1.00 (t, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.98 (q, 2H, CH_2), 5.23 (s, 1H, C4-H), 7.24 (s, 1H, H-2), 7.45 (t, 1H, H-6), 7.63 (d, 1H, H-8), 7.78 (t, 1H, H-7), 8.12 (d, 1H, H-5), 8.23 (s, 1H, N^3H), 9.31 (s, 1H, N^1H); Ms: *m/z* (%): 328 (M^+, 12), 269 (17%), 255 (100%), 169 (18%); Analysis: for $C_{17}H_{16}N_2O_5$ (328.32), calcd: C, 62.19; H, 4.91; N, 8.53%. Found: C, 62.37; H, 4.79; N, 8.37%.

4-(2-Hydroxy-3-methoxy-5-phenylazo-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (20)

Yield 74%, m.p. 210–212°C, IR (KBr, cm^{-1}): 3357 (OH), 3214 (NH), 3198 (NH), 1689 (CO), 1640 (CO); ^{1}H-NMR (d_6-DMSO δ, ppm): 1.10 (t, 3H, CH_3,), 2.28 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.00 (q, 2H, CH_2), 5.17 (s, 1H, C4-H), 7.03 (s, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 7.56 (t, 3H, Ar-Hs), 7.80 (s, 1H, N^3H, D_2O exchangeable), 7.98 (d, 2H, Ar-Hs), 9.26 (s, 1H, N^1H, D_2O exchangeable), 10.99 (s, 1H, OH, D_2O exchangeable); Ms: *m/z* (%), 410 [M^+ (12)], 302 (44), 210 (32), 105 (42), 93 (52), 77 (100). Analysis: for $C_{21}H_{22}N_4O_5$ (410.43), calcd: C, 61.46; H, 5.40; N, 13.65%. Found: C, 61.35; H, 5.35; N, 13.68%.

4-(2-Hydroxy-5-phenylazo-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (21)

m.p. 167–170°C, IR (KBr, cm^{-1}): 3455 (OH), 3220 (NH), 3210 (NH), 1690 (CO), 1662 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm) 1.05 (t, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.98 (q, 2H, CH_2), 5.52 (s, 1H, C4-H), 6.93 (d, 1H, Ar-H), 7.37 (s, 1H, N^3H, D_2O exchangeable), 7.51 (t, 3H, Ar-Hs), 7.63 (s, 1H, Ar-H), 7.75 (d, 1H, Ar-H), 7.84 (d, 2H, Ar-Hs), 9.23 (s, 1H, N^1H, D_2O exchangeable), 10.61 (s, 1H, OH, D_2O exchangeable); Ms: *m/z* (%), 380 (M^+, 20), 183 (22), 105 (21), 93 (28), 77 (100). Analysis: for $C_{20}H_{20}N_4O_4$ (380.40), calcd: C, 63.15; H, 5.30; N, 14.73%. Found: C, 63.38; H, 5.40; N, 14.87%.

4-[2-Hydroxy-5-(4-nitrophenylazo)phenyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (22)

Yield 74%, m.p. 158–161°C, IR (KBr, cm^{-1}): 3356 (OH), 3234 (NH), 3114 (NH), 1687 (CO), 1651 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 1.07 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.97 (q, 2H, CH_2), 5.50 (s, 1H,C4-H), 7.00 (d, 1H, Ar-H), 7.38 (s, 1H, N^3H), 7.69 (s, 1H, Ar-H), 7.72–8.07 (m, 5H, Ar-Hs), 9.21 (s, 1H, N^1H), 10.90 (s, 1H, OH). Analysis: for $C_{20}H_{19}N_5O_6$ (425.39), calcd: C, 56.47; H, 4.50; N, 16.46%. Found: C, 56.66; H, 4.23; N, 16.64%.

Preparation of 5-acetyl-4-(3-aryl-1-phenyl-1H-pyrazole-4-yl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (23–29)

General procedure

A mixture of the selected aldehyde, **3–9** (10 mmol), urea (1.5 g, 25 mmol) and acetylacetone (1.5 ml, 15 mmol) in ethanol (50 ml) acidified with glacial acetic acid (2 ml) or *p*-toluene sulfonic acid (1.72 g, 10 mmol) was heated under reflux for 5–6 h. The solvent was then evaporated under reduced pressure and the residue formed was treated with water, filtered off, washed with water, dried, and crystallized from methanol.

5-Acetyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (23)

Yield 70%, m.p. 218–220°C, IR (KBr, cm^{-1}): 3327 (NH), 3222 (NH), 1696 (CO), 1671 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 2.16 (s, 3H, CH_3), 2.25 (s, 3H, $COCH_3$), 5.43 (s, 1H, C4-H), 7.30–7.87 (m, 11H, 10Ar-Hs and 1H pyrazole), 8.28 (s, 1H, N^3H), 9.12 (s, 1H, N^1H); MS: *m/z* (%): 372 (M^+, 93), 357 (38), 329 (36), 254 (8), 221 (100), and 153 (43). Analysis: for $C_{22}H_{20}N_4O_2$ (372.42), calcd: C, 70.95; H, 5.41; N, 15.04%. Found: C, 70.79; H, 5.51; N, 15.19%.

5-Acetyl-6-methyl-4-[3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl]-3,4-dihydro-1H-pyrimidin-2-one (24)

Yield 67%, m.p. 178–180°C, IR (KBr, cm^{-1}): 3402 (OH), 3235 (NH), 3165 (NH), 1655 (CO), 1620 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm); MS: *m/z* (%): 386 (M^+-2, 10), 345 (8), 235 (11), 221 (21), 154 (17) and 66 (100). Analysis: for $C_{22}H_{19}N_5O_4$ (417.42), calcd: C, 63.30; H, 4.59; N, 16.78%. Found: C, 63.47; H, 4.68; N, 16.92%.

5-Acetyl-4-[3-(2-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (25)

Yield 82%, m.p. 193–196°C, IR (KBr, cm^{-1}): 3227 (NH), 3114 (NH), 1656 (CO), 1619 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 2.07 (s, 3H, CH_3), 2.33 (s, 3H, $COCH_3$), 5.50 (s, 1H, C4-H), 7.12–8.36 (m, 10H, 9Ar-Hs and 1H pyrazole), 7.83 (s, 1H, N^3H, D_2O exchangeable), 9.20 (s, 1H, N^1H, D_2O exchangeable); MS, *m/z* (%): 416 (M^+-1, 41), 373 (40), 326 (17), 266 (72), 235 (15), 153 (100) and 124 (50). Analysis: for $C_{22}H_{19}N_5O_4$ (417.42), calcd: C, 68.03; H, 5.19; N, 14.42%. Found: C, 68.23; H, 5.32; N, 14.61%.

5-Acetyl-6-methyl-4-(4-oxo-4H-chromen-3-yl)-3,4-dihydro-1H-pyrimidin-2-one (26)

Yield 75%, m.p. 218–220°C; IR (KBr, cm^{-1}): 3340 (NH), 3273 (NH), 1703 (CO), 1671 (CO), 1645 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 2.15 (s, 3H, CH_3), 2.31 (s, 3H, $COCH_3$), 5.34 (s, 1H, C4-H), 7.25 (s, 1H, H-2), 7.45 (t, 1H, H-6), 7.63 (d, 1H, H-8), 7.78 (t, 1H, H-7), 8.12 (d, 1H, H-5), 8.25 (s, 1H, N^3H), 9.32 (s, 1H, N^1H); Ms: *m/z* (%), 255 (100), 239 (8), 153 (18), 146 (26), 121 (31), 105 (35). Analysis: for $C_{16}H_{14}N_2O_4$ (298.29), calcd: C, 64.42; H, 4.73; N, 9.39%. Found: C, 64.56; H, 4.42; N, 9.61%.

5-Acetyl-4-(2-hydroxy-3-methoxy-5-phenylazo-phenyl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (27)

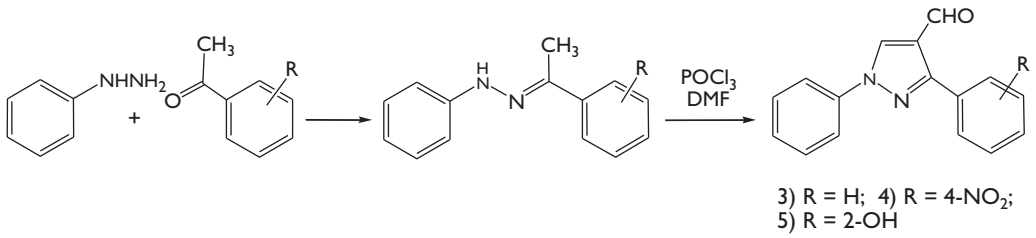
Yield 74%, m.p. 228–230°C, IR (KBr, cm^{-1}): 3383 (OH), 3255 (NH), 3112 (NH), 1707 (CO), 1663 (CO). ^{1}H-NMR (d_6-DMSO, δ, ppm); MS, *m/z* (%): 379 (M^+-1, 7), 350 (52), 335 (21), 322 (27), 258 (39), 244 (9), 153 (17), 93 (100), 124 (43). Analysis: for $C_{20}H_{20}N_4O_4$ (380.40), calcd: C, 63.15; H, 5.30; N, 14.73%. Found: C, 63.40; H, 5.31; N, 14.55%.

5-Acetyl-4-(2-hydroxy-5-phenylazo-phenyl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (28)

Yield 78%, m.p. 202–205°C, IR (KBr, cm^{-1}): 3400 (OH), 3235 (NH), 3150 (NH), 1681 (CO), 1621 (CO); ^{1}H-NMR (d_6-DMSO, δ, ppm): 2.11 (s, 3H, CH_3), 2.33 (s, 3H, $COCH_3$), 5.63 (s, 1H, C4-H), 7.00 (d, 1H, Ar-H), 7.04 (s, 1H, N^3H, D_2O exchangeable), 7.53 (t, 3H, Ar-Hs), 7.62 (s, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.82 (d, 2H, Ar-Hs), 9.27 (s, 1H, N^1H, D_2O exchangeable), 10.59 (s, 1H, OH, D_2O exchangeable); MS *m/z* (%): 350 (M^+, 13), 307 (10), 198 (23), 153 (16), 93 (100). Analysis: for $C_{19}H_{18}N_4O_3$ (350.37), calcd: C, 65.13; H, 5.18; N, 15.99%. Found: C, 65.33; H, 5.28; N, 16.25%.

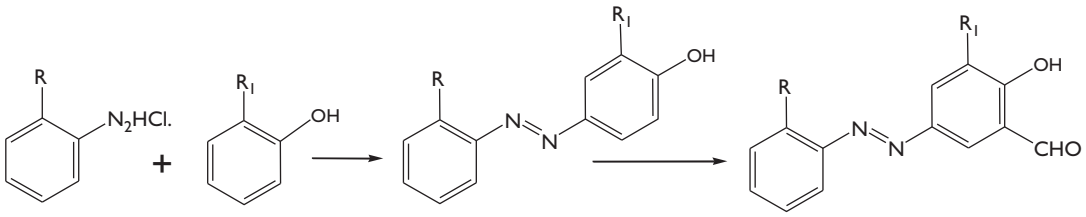
5-Acetyl-4-[2-hydroxy-5-(2-nitro-phenylazo)-phenyl]-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (29)

Yield 70%, m.p. 213–216°C, IR (KBr, cm^{-1}): 3364 (OH), 3281 (NH), 3230 (NH), 1697 (CO), 1650 (CO); MS *m/z* (%): 396 (M^+ + 1, 10), 350 (12), 337 (17), 257 (30), 243 (13), 337 (17), 257 (30), 243 (13), 226 (15), 153 (20%), 93 (100). Analysis: for $C_{19}H_{17}N_5O_5$ (395.37), calcd: C:

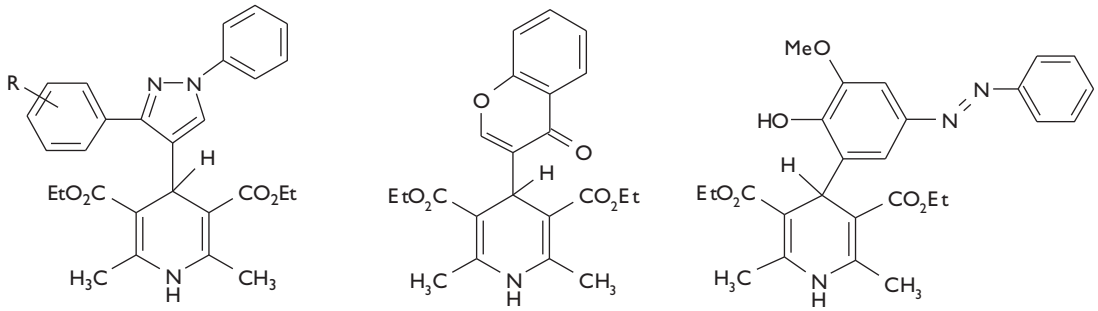


3) R = H; 4) R = 4-NO_2;
5) R = 2-OH

6



7, R = H, R_1 = OMe
8, R = R_1 = H,
9, R = NO_2 R_1 = H



10) R = H
11) R = 4 -NO_2
12) R = 2-OH

13

14

57.72; H, 4.33; N, 17.71%. Found: C, 57.58; H, 4.41; N, 17.63%.

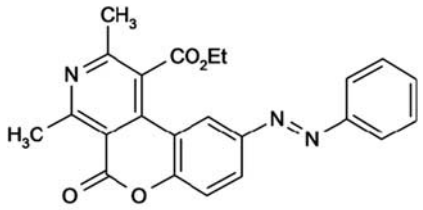
Chemistry

The aldehydes 3-(substituted-phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde **3–5** [23] 4-oxo-4H-chromene-3-carbaldehyde (**6**) [24] and substituted phenylazo-benzaldehyde **7–9** [25] reacted with ethyl acetaoaetate and urea in ethanol in the presence of acetic acid to yield DHPs **10–15**.

Compound **8** reacted similarly but underwent intramolecular condensation and aromatization to yield 2,4-dimethyl-5-oxo-9-phenylazo-5H-chromeno[3,4–c]pyridine-1-carboxylic acid ethyl ester (**15**). Similar behavior has been reported previously [26].

Also, compound **9** yielded a mixture of products that were hardly separable; perhaps, decomposition occurred because of the long reaction time.

Moreover, aldehydes **3–9** reacted with urea and ethyl acetoacetate in the presence of *p*-toluene sulfonic acid to yield dihydropyrimidinones **16–22**.



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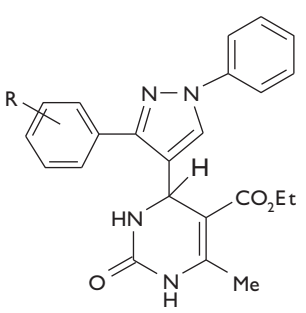
Furthermore, reaction of the aldehydes **3–9** with urea and acetyl acetone in alcohol as a solvent in the presence of either acetic acid or *p*-toluene sulfonic acid yielded the corresponding dihydropyrimidinones **23–29**.

Antihypertensive activity

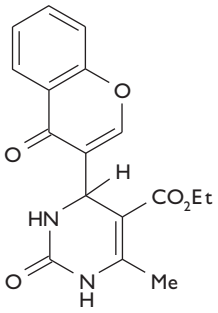
Ten of the newly synthesized substituted DHPs **10–14** and tetrahydropyrimidines **16–20** were screened for their hypotensive activity using normotensive cat models [27].

Materials and methods

Male cats of local strains weighing from 2.5 to 4.0 kg were housed (one per cage) in the animal facility (Faculty of



16, R = H,
17, R = 4- NO_2
18, R = 2-OH



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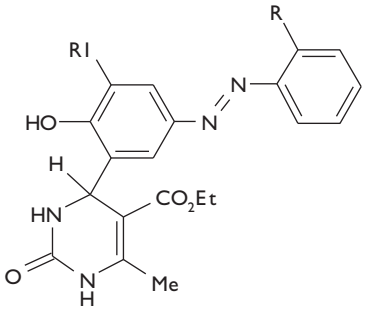
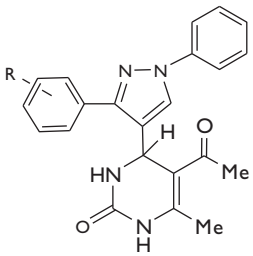
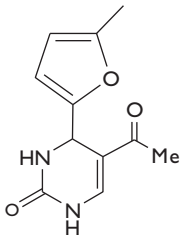


20, R = H, R_1 = OMe
21, R = R1 = H
22, R = NO_2, R1 = H



23, R = H,
24, R = 4-NO_2
25, R = 2-OH



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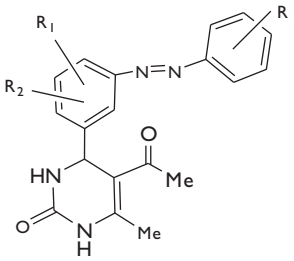

27, R = NO_2, R_1 = 2-OH, R_2 = H
28, R = H, R_1 = 2-OH, R_2 = H
29, R = H, R_1 = 4-OH, R_2 =3-OCH_3

Medicine, El-Azhar University) for 7 days before the experiment. Animals were always kept at 22 ± 2 h and a 12 h light/12 h dark cycle. Stressful conditions or manipulation were avoided. Cats were divided into groups; each group included four cats and one group was used as a control. All cats were anesthetized with phenobarbital sodium (35 mg/kg, intraperitoneally) and their blood pressures (BP) were recorded from the carotid artery. BP of each cat was measured before and 30 min after the intravenous injection of the tested compounds. The tested compounds were dissolved in DMSO and administered at different doses (0.6, 1.2, 2.4 mg/kg) in 0.5 ml volume in the same way as the reference drug nifedipine. The same volume of DMSO was administered to animals in the control group. The reduction of BP between two measurements was recorded as mmHg. These results were expressed as mean ± SEM; analysis variance (two-way) was used for statistical analysis. LD_{50} was preformed according to the procedure described in the study conducted by Kerber [28].

Results and discussion

The hypotensive effect of the tested DHP derivatives **10–14** and DHPMs **16–20** is shown in Table 1 in comparison with nifedipine as a reference drug. In the DHP series, the test compounds showed significant hypotensive activity at all dose levels (0.6, 1.2, and 2.4 mg/kg). The 4-(1,3-diphenyl-1H-pyrazolyl) derivative **10** was the most active at all dose levels. Also, it had more

Table 1 Effect of tested compounds (10–14 and 16–20) on the mean blood pressure of anesthetized normotensive cats compared with the reference drug nifedipine

Dose (mg/kg)	Compounds	Mean reduction in BP
0.6 mg/kg	Control (DMSO)	100.17 ± 1.82
	Nifedipine	44.17 ± 1.45
	10	55.40 ± 1.40
	11	79.00 ± 1.24
	12	61.67 ± 2.23
	13	65.00 ± 1.71
	14	75.00 ± 1.59
	16	76.23 ± 2.60
	17	74.17 ± 1.60
	18	76.50 ± 1.24
	19	61.00 ± 1.10
	20	89.50 ± 1.28
1.2 mg/kg	Nifedipine	22.17 ± 1.42
	10	27.17 ± 1.91
	11	77.83 ± 0.87
	12	51.50 ± 1.61
	13	64.33 ± 1.71
	14	67.00 ± 0.45
	16	68.33 ± 1.89
	17	70.00 ± 1.19
	18	62.33 ± 0.87
	19	58.00 ± 1.46
	20	88.83 ± 1.71
2.4 mg/kg	Nifedipine	15.17 ± 1.01
	10	13.00 ± 0.82
	11	62.00 ± 1.53
	12	15.50 ± 0.92
	13	60.33 ± 0.88
	14	60.50 ± 1.18
	16	64.50 ± 1.34
	17	68.00 ± 1.39
	18	57.00 ± 1.51
	19	47.67 ± 1.09
	20	85.67 ± 0.92

BP, blood pressure; DMSO, dimethyl sulfoxide.

Table 2 LD_{50} in male mice after an intraperitoneal administration of compound 10

Group number	Oral doses (mg/kg body weight)	Number of dead animals	Dose difference	Mean[a]	Product[b]
1	240	–	–	–	–
2	260	1	20	0.5	10
3	280	3	20	2	40
5	300	5	20	4	80
6	320	7	20	6	120
7	340	10	20	8.5	170
Total					420

Number of animals/group = 10 mice.
LD_{50}: 340 – (420/10) = 298 mg/kg body weight.
LD_{50}, lethal dose, 50%.
[a]Interval mean of the number of dead animals (mice).
[b]Product of the interval mean and the dose difference.

or less similar potency as nifidipine (refrerence standerd) at doses of 1.2 and 2.4 mg/kg. The other tested DHPs **11** and **12** bearing 3-aryl-1-phenyl-1H-pyrazolyl as well as the chromonyl derivative **13** and 4-hydroxy-3-methoxy-5-(phenylazo)-phenyl substituent at the 4-position **14** showed weak activities compared with the reference drug. For tetrahydropyrimidine series **16–20**, the evaluated data showed that the 4-chromonyl derivative **19** had significant hypertensive activity (61.00 ± 1.10), which was higher than the 4-pyrazolyl analogous **16–18** at a dose of 0.6 mg/kg. A nonsignificant change was observed in the presence of 4-[4-hydroxy-3-methoxy-5-(phenylazo)-phenyl] derivative **20** when administered at the same dose level. The hypotensive values of this series were negligible compared with those of nifedipine at doses of 0.6, 1.2, and 2.4 mg/kg.

Moreover, Table 2 shows that LD_{50} of the most active compound **10** was equal to 298 mg/kg body weight.

Conclusively, the 4-aryl-DHP derivatives **10–14** showed higher hypotensive activity than the tetrahydropyrimidines **16–20** carrying the same aryl substituents at the same position. The most active compound was 4-(1,3-diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester **10** at dose levels of 0.6, 1.2, and 2.4 mg/kg. It showed more or less similar hypotensive activity as the reference drug nifedipine at doses of 1.2 and 2.4 mg/kg.

Conclusion

The synthesis of substituted DHPs **10–15** and pyrimidinones **16–29** was achieved. The comparison of the tested compounds **10–14** and **16–20** for their hypotensive activity using the nonselective cat models led to the conclusion that the 4-aryl-DHP derivatives **10–14** showed higher hypotensive activity than the pyrimidinones derivatives carrying the same aryl substituent at the same position. The most active compound was 4-(1, 3-diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester **10** at dose levels of 0.6, 1.2, and 2.4 mg/kg. It showed more or less similar hypotensive activity as the reference drug nifedipine at doses of 1.2 and 2.4 mg/kg. Its LD_{50} is 298 mg/kg body weight, which would present a fruitful matrix for the development of a potent antihypertensive agent.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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