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Some Pyridazinone and Phthalazinone Derivatives and Their Vasodilator Activities

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In this study, 6-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone and 4-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-1(2*H*)-phthalazinone derivatives were synthesized by reacting 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone or 4-(4-aminophenyl)-1(2*H*)-phthalazinone compound with different 4-arylidene-2-phenyl-5(4*H*)-oxazolone derivatives. The vasodilator activities of the compounds were examined both *in vitro* and *in vivo*. Some pyridazinone derivatives showed appreciable activity.

Key words: Pyridazinone, Phthalazinone, Vasodilator activity

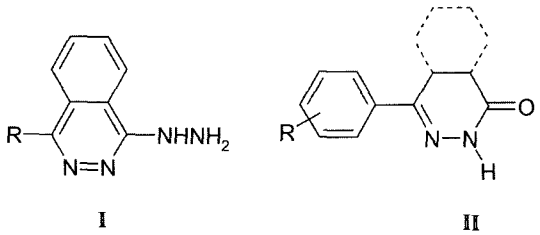
INTRODUCTION

New findings on hydralazine and related drugs **I**, which contain phthalazine, a compound used as a antihypertensive agent, has inspired more detailed studies on pyridazinone and phthalazinone derivatives **II** (Szasz *et al.*, 1991; Foye *et al.*, 1995; Van Zwieten *et al.*, 1997; Wolf *et al.*, 1997). Thus, not only the simpler structures of the analogue series obtained, but also the classical antihypertensive pharmacophoric group hydrazine in hydralazine group drugs were eliminated.

Pyridazinone derivatives are known to have important pharmacological activities (Heinisch *et al.*, 1992): they reduce blood pressure (McEvoy *et al.*, 1974; Curran *et al.*, 1974; Thyes *et al.*, 1983; Cignarella *et al.*, 1989; Seki *et al.*, 1996; Betti *et al.*, 2003), inhibit platelet aggregation (Corsano *et al.*, 1995; Laguna *et al.*, 1997; Montero-Lastres *et al.*, 1999; Sotelo *et al.*, 2002; Sotelo *et al.*, 2002), and exhibit positive inotropic (Sircar *et al.*, 1987; Combs *et al.*, 1990; Van der May *et al.*, 2002) and bronchodilator activity (Yamaguchi *et al.*, 1993) on the cardiovascular system.

Considering that the 6-arylpyridazinone structure is essential for the activity on cardio vascular system, a number of studies on substitution have been performed on both pyridazinone and aryl residues. Reports showed that the *p*-substituted compounds on aryl residue were more active than the *m*-substituted ones. Hence, the compounds were considerably antihypertensive by substituting the amino group (Thyes *et al.*, 1983).

In this paper, we focused on the formation of the imidazolinone ring system using the amino group. For this purpose, the amino compounds were reacted with oxazolinones. Thus, some 6-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone and 4-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-1(2*H*)-phthalazinone derivatives were synthesized by reacting 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone or 4-(4-aminophenyl)-1(2*H*)-phthalazinone with different 4-arylidene-2-phenyl-5(4*H*)-oxazolone derivatives. The antihypertensive activities of the compounds were examined



I II

R : H Hydralazine
R : $NHNH_2$ Dihydralazine

Fig. 1. Structures of hydralazine and dihydralazine

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both *in vitro* and *in vivo*. Some pyridazinone derivatives showed appreciable activity.

MATERIALS AND METHODS

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instruments: FT-IR (Schimadzu 8400S spectrophotometer), ^{1}H-NMR (Bruker DPX 400 NMR spectrometer), MS (VG Zabspec Mass Spectrometer). Analyses for C, H, N were within 0.4 % of the theoretical values.

6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**3**, Thyes *et al.*, 1983), 4-(4-aminophenyl)-1-(2*H*)-phthalazinone (**4**, Haikala *et al.*, 1991), and 4-arylidene-2-phenyl-5(4*H*)-oxazolone derivatives (**5**, Turcki, 1986) required as starting materials, were prepared according to methods in the literature.

General procedure of 6-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-4,5-dihydro-3(2*H*)-pyridazinones (6a-k) and 4-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-1(2*H*)-phthalazinones (7a-f)

A mixture of **3** or **4** (10 mmol) and an appropriate **5** (10 mmol) in acetic acid was refluxed for 6 h. The cooled mixture was poured into ice water and the formed precipitate was filtered and washed with water and cold ethanol. The raw product was crystallized from ethanol. Some characteristics of the compounds are given in Table I.

6a IR (KBr) ν_{max} (cm^{-1}): 3264 (N-H), 1710 (Imidazolinone C=O), 1672 (pyridazinone C=O), 1613-1486 (C=N, C=C), 1374, 1328 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.12 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.07 Hz, pyridazinone C_5-H), 7.31 (1H, s, =CH-), 7.36 (2H, d, J = 8.55 Hz, Ar-H), 7.42-7.60 (8H, m, Ar-H), 7.84 (2H, d, J = 8.53 Hz, Ar-H), 8.38 (2H, d, J = 7.04 Hz, Ar-H), 10.97 (1H, s, N-H).

6b IR (KBr) ν_{max} (cm^{-1}): 3208 (N-H), 1719 (Imidazolinone C=O), 1674 (pyridazinone C=O), 1639-1512 (C=N, C=C), 1374, 1328 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.40 (3H, s, Ar-CH_3), 2.49 (2H, t, J = 8.09 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.02 Hz, pyridazinone C_5-H), 7.28 (1H, s, =CH-), 7.31-7.56 (4H, m, Ar-H), 7.40-7.44 (2H, m, Ar-H), 7.49-7.56 (3H, m, Ar-H), 7.84 (2H,d, J = 8.50 Hz, Ar-H), 8.27 (2H, d, J = 8.20 Hz, Ar-H), 10.97 (1H, s, N-H).

6c IR (KBr) ν_{max} (cm^{-1}): 3163 (N-H), 1710 (Imidazolinone C=O), 1685 (pyridazinone C=O), 1635-1500 (C=N, C=C), 1372, 1330 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 1.26 (6H, d, J = 6.90 Hz, CH_3), 2.49 (2H, t, J = 8.38 Hz, pyridazinone C_4-H), 2.96-3.01 (3H, m, CH and pyridazinone C_5-H), 7.28 (1H, s, =CH-), 7.34 (2H, d, J = 8.64 Hz, Ar-H), 7.39-7.44 (4H, m, Ar-H), 7.49-7.57 (3H, m, Ar-H), 7.84 (2H,d, J = 8.62 Hz, Ar-H), 8.30 (2H, d, J = 7.04 Hz, Ar-H), 10.97 (1H, s, N-H)

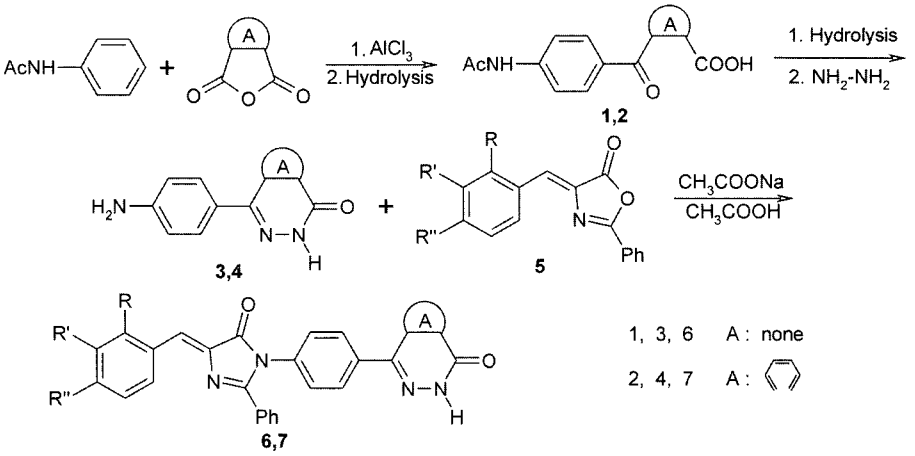
6d IR (KBr) ν_{max} (cm^{-1}): 3196 (N-H), 1710 (Imidazolinone C=O), 1671 (pyridazinone C=O), 1638-1517 (C=N, C=C), 1381, 1348 (pyridazinone), 1284, 1135 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.22 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.11 Hz, pyridazinone C_5-H), 3.87 (3H, s, O-CH_3), 7.13 (1H, d, J = 8.52 Hz, Ar-H), 7.28 (1H, s, =CH-), 7.34 (2H, d, J = 9.0 Hz, Ar-H), 7.41-7.58 (6H, m, Ar-H), 7.84 (2H,d, J = 8.54 Hz, Ar-H), 7.90 (1H, dd, J = 1.45 Hz, J = 1.47 Hz and J = 8.38 Hz, Ar-H), 8.25-8.27 (1H, m, Ar-H), 10.97 (1H, s, N-H). MS (EI) M/z: 450 (M$^+$, %20), 435, 421, 407, 393, 382, 365, 351, 337, 337, 323, 310, 295 (%100), 281,267.

6e IR (KBr) ν_{max} (cm^{-1}): 3193 (N-H), 1715 (Imidazolinone C=O), 1669 (pyridazinone C=O), 1640-1509 (C=N, C=C), 1377, 1349 (pyridazinone), 1255, 1161 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, pyridazinone C_4-H), 2.99 (2H, t, pyridazinone C_5-H), 3.87 (3H, s, O-CH_3), 7.11 (2H, d, J = 8.96 Hz, Ar-H), 7.28 (1H, s, =CH-), 7.34 (2H, d, J = 8.64 Hz, aryl residue of 6-arylpyridazinone $C_{3,5}$-H), 7.41-7.57 (5H, m, Ar-H), 7.84 (2H, d, J = 8.63 Hz, Ar-H), 8.37 (2H, d, J = 8.93 Hz, Ar-H), 10.97 (1H, s, N-H).

6f IR (KBr) ν_{max} (cm^{-1}): 3192 (N-H), 1715 (Imidazolinone C=O), 1670 (pyridazinone C=O), 1639-1512 (C=N, C=C), 1376, 1349 (pyridazinone), 1259, 1131 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.09 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.01 Hz, pyridazinone C_5-H), 6.16 (2H, s, O-CH_2-O), 7.09 (1H, d, J = 8.14 Hz, Ar-H), 7.26 (1H, s, =CH-), 7.34 (2H, d, J = 8.65 Hz, Ar-H),

Table I. Some characteristics of the compounds

Comp.	M.p. (°C)	Yield (%)	Molecular formula
6a	283-184	72	$C_{26}H_{20}N_4O_2$
6b	291-292	68	$C_{27}H_{22}N_4O_2$
6c	306-308	62	$C_{29}H_{27}N_4O_2$
6d	330-331	70	$C_{27}H_{22}N_4O_3$
6e	277-278	70	$C_{27}H_{22}N_4O_3$
6f	313-314	75	$C_{27}H_{20}N_4O_4$
6g	310-311	78	$C_{26}H_{19}ClN_4O_2$
6h	269-271	76	$C_{26}H_{19}ClN_4O_2$
6i	310-312	75	$C_{26}H_{19}ClN_4O_2$
6j	247-248	85	$C_{26}H_{18}Cl_2N_4O_2$
6k	325-326	76	$C_{26}H_{18}Cl_2N_4O_2$
7a	306-307	68	$C_{30}H_{15}N_4O_2$
7b	325-326	71	$C_{31}H_{22}N_4O_2$
7e	294-296	65	$C_{31}H_{22}N_4O_3$
7f	326-328	65	$C_{31}H_{20}N_4O_4$
7i	329-330	78	$C_{30}H_{19}ClN_4O_2$
7k	300-301	72	$C_{30}H_{18}Cl_2N_4O_2$



Comp. **5, 6, 7**	**R**	R'	R"
a	H	H	H
b	H	H	CH_3
c	H	H	$CH(CH_3)_2$
d	OCH_3	H	H
e	H	H	OCH_3
f	H	-O-CH_2-O-	
g	Cl	H	H
h	H	Cl	H
i	H	H	Cl
j	Cl	H	Cl
k	H	Cl	Cl

Scheme 1. Synthesis of the compounds.

7.41-7.57 (5H, m, Ar-H), 7.78 and 7.81 (1H, dd, J = 1.69 Hz, J = 1.49 Hz and J = 8.39 Hz, Ar-H), 7.84 (2H, d, J = 8.83 Hz, Ar-H), 8.29 (1H, d, J = 1.48 Hz, Ar-H), 10.97 (1H, s, N-H).

6g IR (KBr) ν_{max} (cm^{-1}): 3199 (N-H), 1721 (Imidazolinone C=O), 1666 (pyridazinone C=O), 1641-1515 (C=N, C=C), 1379, 1350 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.05 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.04 Hz, pyridazinone C_5-H), 7.32 (1H, s, =CH-), 7.36 (2H, d, J = 8.58 Hz, Ar-H), 7.44-7.59 (5H, m, Ar-H), 7.81 (2H, d, J = 8.45 Hz, Ar-H), 7.85 (2H, d, J = 8.59 Hz, Ar-H) 8.40 and 8.41 (1H, dd, J = 1.84 Hz, J = 1.83 Hz and J = 8.01 Hz, Ar-H), 8.64-8.65 (1H, m, Ar-H), 10.97 (1H, s, N-H).

6h IR (KBr) ν_{max} (cm^{-1}): 3206 (N-H), 1722 (Imidazolinone C=O), 1672 (pyridazinone C=O), 1643-1514 (C=N, C=C), 1380, 1348 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.10 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.03 Hz, pyridazinone C_5-H), 7.31 (1H, s, =CH-), 7.36 (2H, d, J = 8.60 Hz, Ar-H), 7.43-7.59 (7H, m, Ar-H), 7.84 (2H, d, J = 8.53 Hz, Ar-H), 8.33-8.34 (1H, m, Ar-H), 8.48-8.49 (1H, m, Ar-H), 10.97 (1H, s, N-H).

6i IR (KBr) ν_{max} (cm^{-1}): 3193 (N-H), 1716 (Imidazolinone C=O), 1667 (pyridazinone C=O), 1638-1486 (C=N, C=C), 1375, 1347 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.10 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.02 Hz, pyridazinone C_5-H), 7.32 (1H, s, =CH-), 7.36 (2H, d, J = 8.64 Hz, Ar-H), 7.40-7.44 (2H, m, Ar-H), 7.50-7.60 (5H, m, Ar-H) 7.83 (2H, d, J = 8.63 Hz, Ar-H), 8.40 (2H, d, J = 8.65 Hz, Ar-H), 10.97 (1H, s, N-H).

6j IR (KBr) ν_{max} (cm^{-1}): 3210 (N-H), 1721 (Imidazolinone C=O), 1667 (pyridazinone C=O), 1667-1514 (C=N, C=C), 1379, 1349 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.12 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.05 Hz, pyridazinone C_5-H), 7.36 (2H, d, J = 8.57 Hz, Ar-H), 7.40-7.44 (3H, m, Ar-H and =CH-), 7.51-7.58 (3H, m, Ar-H), 7.65 and 7.67 (H, dd, J = 1.99 Hz, J = 1.97 Hz and J = 8.64 Hz, Ar-H), 7.81 (1H, d, J = 2.09 Hz, Ar-H), 7.85 (2H, d, J = 8.57 Hz, Ar-H), 9.04 (1H, d, J = 8.66 Hz, Ar-H), 10.97 (1H, s, N-H).

6k IR (KBr) ν_{max} (cm^{-1}): 3182 (N-H), 1715 (Imidazolinone C=O), 1691 (pyridazinone C=O), 1666-1513 (C=N, C=C), 1375, 1350 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (2H, t, J = 8.12 Hz, pyridazinone C_4-H), 2.99 (2H, t, J = 8.05 Hz, pyridazinone C_5-H), 7.32 (1H, s, =CH-), 7.36 (2H, d, J = 8.57 Hz, Ar-H), 7.42-7.45 (2H, m, Ar-H), 7.52-7.59 (3H, m, Ar-H), 7.81 (1H, d, J = 8.46 Hz, Ar-H), 7.85 (2H, d, J = 8.53 Hz, Ar-H), 8.39 and 8.41 (1H, dd, J = 1.78 Hz, J = 1.81 Hz and J = 8.54 Hz, Ar-H), 8.64 (1H, d,

J = 1.74 Hz, Ar-H), 10.97 (1H, s, N-H).

7a IR (KBr) ν_{max} (cm^{-1}): 3195, 3165 (N-H), 1740 (Imidazolinone C=O), 1655 (pyridazinone C=O), 1623-1520 (C=N, C=C), 1374, 1325 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.34 (1H, s, =CH-), 7.45-7.56 (7H, m, Ar-H), 7.62 (2H, d, J = 7.33 Hz, Ar-H), 7.68-7.72 (3H, m, Ar-H), 7.90-7.97 (2H, m, Ar-H), 8.04-8.36 (1H, m, Ar-H), 8.40 (2H, d, J = 7.19 Hz, Ar-H), 12.93 (1H, s, N-H).

7b IR (KBr) ν_{max} (cm^{-1}): 3212 (N-H), 1735 (Imidazolinone C=O), 1658 (pyridazinone C=O), 1645-1520 (C=N, C=C), 1370, 1315 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.39 (3H, s), 7.33 (1H, s, =CH-), 7.45-7.50 (4H, m, Ar-H), 7.51-7.53 (1H, m, Ar-H), 7.58-7.72 (5H, m, Ar-H), 7.91-7.95 (4H, m, Ar-H), 8.32-8.41 (3H, m, Ar-H), 12.90 (1H, s, N-H).

7e IR (KBr) ν_{max} (cm^{-1}): 3209, 3160 (N-H), 1732 (Imidazolinone C=O), 1658 (pyridazinone C=O), 1643-1517 (C=N, C=C), 1375, 1325 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.86 (3H, s, OCH_3), 7.11 (2H, d, J = 8.8 Hz, Ar-H), 7.31 (1H, s, =CH-), 7.44-7.54 (5H, m, Ar-H), 7.59 (2H, d, J = 8.5 Hz, Ar-H), 7.69-7.71 (3H, m, Ar-H), 7.90-7.96 (2H, m, Ar-H), 8.35-8.40 (3H, m, Ar-H), 12.92 (1H, s, N-H).

7f IR (KBr) ν_{max} (cm^{-1}): 3208 (N-H), 1738 (Imidazolinone C=O), 1654 (pyridazinone C=O), 1622-1500 (C=N, C=C), 1376, 1330 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 6.26 (2H, s), 7.11 (1H, d, J = 8.14 Hz), 7.32 (1H, s, =CH-) 7.43-7.47 (4H, m, Ar-H), 7.51-7.54 (1H, m, Ar-H), 7.58 (2H, d, J = 8.45 Hz, Ar-H), 7.68-7.72 (3H, m, Ar-H), 7.90-7.96 (2H, m, Ar-H), 8.34-8.40 (3H, m, Ar-H), 8.15 (1H, d, J = 1.48 Hz, Ar-H), 12.90 (1H, s, N-H).

7i IR (KBr) ν_{max} (cm^{-1}): 3215 (N-H), 1738 (Imidazolinone C=O), 1662 (pyridazinone C=O), 1630-1520 (C=N, C=C), 1375, 1325 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33 (1H, s, =CH-), 7.35 (2H, d, J = 8.08 Hz, Ar-H), 7.42-7.44 (3H, m, Ar-H), 7.50-7.60 (6H, m, Ar-H), 7.83 (2H, d, J = 8.12 Hz, Ar-H), 7.89-7.94 (2H, m, Ar-H), 8.39-8.42 (2H, m, Ar-H), 12.91 (1H, s, N-H).

7k IR (KBr) ν_{max} (cm^{-1}): 3210, 3174 (N-H), 1742 (Imidazolinone C=O), 1660 (pyridazinone C=O), 1630-1515 (C=N, C=C), 1377, 1325 (pyridazinone). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.36 (1H, s, =CH-), 7.46-7.50 (4H, m, Ar-H), 7.54-7.56 (1H, m, Ar-H), 7.60-7.62 (2H, m, Ar-H), 7.68-7.72 (3H, m, Ar-H), 7.82 (1H, d, J = 8.44 Hz, Ar-H), 7.90-7.96 (2H, m, Ar-H), 8.36, 8.42 (2H, dd, J = 1.3 Hz, J = 1.54 Hz, J = 8.40 Hz, Ar-H), 8.66-6.67 (1H, s, Ar-H), 12.93 (1H, s, N-H).

Vasodilator activity

In vitro

Sheep carotid artery taken from a slaughterhouse were cut into 0.3 mm rings and put in an organ bath of 10 mL capacity containing Tyrod solution in a gas of 95% O_2 and 5% CO_2. Two g of tensionwas applied. The preparation was allowed to equilibrate for 60 min with regular washes every 15 min. In order to check the vasodilator activity, 8 mM potassium chloride was included in the concentrations. After thorough washing, this process was repeated until the amplitude of the concentrations became constant. The substances were investigated using the single dose technique. Between administrations of the individual substances, the preparations were washed until the initial situation was reestablished and the potassium chloride concentrations were induced. The concentrations were recorded with a 96 Transducer Data Acquisition System (Ankara, Turkey).

By tail cuff method (*in vivo*)

Albino rats of both sexes weighing 200±10 g were used in this study. There were seven animals in each group. The compounds were dissolved in DMSO. The arterial blood pressures of the conscious rats were measured by the tail-cuff method using an indirect blood pressure recorder system MAY 9610 (Turkey). The blood pressure of each rat was measured before and 30 min. after the intraperitoneal injection of the compounds. Each compound was given 20 mg/kg dose in 0.1 mL volume. 0.1 mL DMSO was administered to the animals in the control group. The reduction of blood pressure between two measurements was recorded as mmHg. The results were expressed as mean±S.E.M. Student's test was used for statistical analyses.

RESULTS AND DISCUSSION

Chemistry

6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**3**), and 4-(4-aminophenyl)-1-(2*H*)-phthalazinone (**4**), required as starting material, were readily accomplished in high yields by refluxing the requisite γ-keto acid with hydrazine hydrate in ethanol (Tishler, *et al.*, 1968, 1979, 1990). The other starting materials, 4-arylidene-2-phenyl-5(4*H*)-oxazolones (**5**), were prepared by heating hippuric acid with an appropriate aromatic aldehyde in the presence of anhydrous sodium acetate in acetic anhydride in the conditions of the Erlenmeyer Reaction (Turcki, 1986).

The resulting compounds, 6-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-4,5-dihydro-3(2*H*)-pyridazinones and 4-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-1(2*H*)-phthalazinones were synthesized by reacting **3** or **4** and an appropriate **5** in acetic acid.

Vasodilator activity

Vasodilator activity was assayed *in vitro* using sheep carotid arteries (Table II) and *in vivo* using the tail-cuff

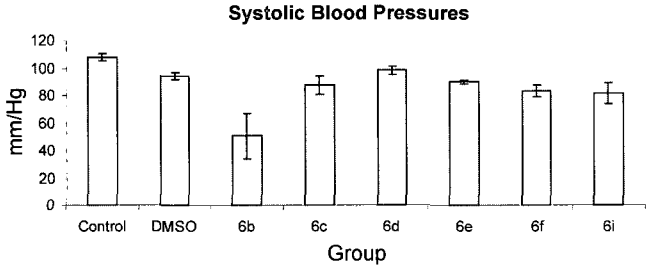
Table II. Vasodilator activity of the compounds

Comp. (10^{-4} M)	% Inh. of KCl Contractions (8 mM)
6a	7.30±11.62
6b	17.95±15.25
6c	33.04±3.87
6d	8.67±7.03
6e	18.27±16.02
6f	26.49±22.59
6g	5.78±13.04
6h	7.36±8.87
6i	13.56±11.46
6j	17.86±19.57
6k	2.00±33.13
Clonidine	78.5±13.6

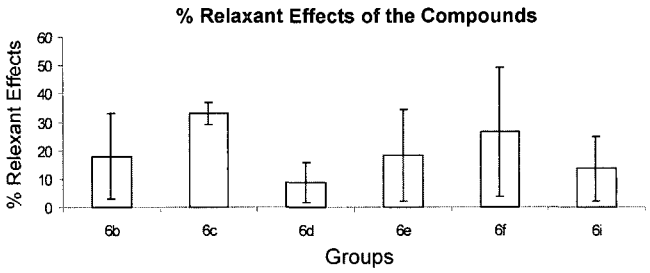
Table III. Systolic blood pressures (mmHg)

Groups	Mean Values
Control	108.19±2.27
DMSO	94.28±2.34
6b	50.66±16.52
6c	87.76±6.55
6d	98.61±3.02
6e	89.85±1.43
6f	83.42±4.44
6i	81.90±7.73

method (Table III and Graph 1 and 2) (Demirayak *et al.*, 1997). In accordance with the *in vitro* test results and considering the effect of clonidine, which was used as a control vasodilator agent, some pyridazinones were found to show appreciable vasodilator activity. However, phthalazinone derivatives did not show any vasodilator activity. This inactiveness was probably due to the solubility problems of these compounds. The most active compound was **6c**, which inhibited the contraction obtained with 8 mM KCl. Another noticeable compound was **6f**, with 26.49 percent inhibition value. Unfortunately, no correlation between the substituents and biological activities of the compounds was noticeable.



Graph 1. Systolic blood pressures of the compounds



Graph 2. % Relaxant effects of the compounds

The most significant decrease in blood pressure *in vivo* occurred in compound **6b**, with a ratio of 50 percent. As seen in the graph of percent relaxant effect, **6c** and **6f** had remarkable activity. Thus, the relaxant effects of **6c** and **6f** are in accordance with the *in vitro* test results as mentioned above.

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