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Laboratory note

Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities

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Abstract

In this work, some 2-nonsubstituted/2-methyl-/2-(2-acetyloxyethyl)-6-[4-(substituted pyrrol-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinone, derivatives and 2-nonsubstituted/2-methyl- 4-[4-(substituted pyrrol-1-yl)phenyl]-1(2H)-phthalazinone derivatives were synthesised by reacting hexan-2,5-dion or 1-aryl-3-carbethoxypent-1,4-diones with corresponding 2-substituted/nonsubstituted 6-(4'-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone or 2-substituted/nonsubstituted-4-(4'-aminophenyl)-(2H)-phthalazinone under Paal–Knorr pyrrole synthesis conditions. The antihypertensive activities of the compounds were examined both in vitro and in vivo. Some pyridazinone derivatives showed appreciable activity.

Keywords: Pyridazinone; Phthalazinone; Pyrrole; Antihypertensive activity

1. Introduction

Hypertension is not only the most common cardiovascular disease and the principal cause of stroke but also leads to disease of the coronary arteries with myocardial infarction and sudden cardiac death, and is a major contributor to cardiac failure, renal insufficiency [1]. As a consequence, great efforts have been made on obtaining novel antihypertensive agents acting on different mechanisms [2,3]. Especially the studies on the hydralazine group drugs **I** lead to the synthesis of many pyridazinone and phthalazinone derivatives **II** with a wide activity spectrum on cardiovascular system [4,5]. Beside those reviewed, researches on pyridazinone derivatives and its analogues have still being carried on. During our literature research, we observed that compounds synthesised in the recent studies possessed notable antihypertensive [6–9], platelet aggregation inhibitor [10–17], phosphodiesterase [18–20] and antiasthmatic effects [21–25] on cardiovascular system. Considering the 6-aryl-3(2H)-pyridazinone residue as the pharmacophoric group for the activity [26,27], in this work; we aimed to obtain some new derivatives of this class. Therefore, we focused on the formation of a ring system on the pharmacophoric pyridazinone residue and its benzene condensed analogue phthalazinone with a similar rationale of the cited studies above. For this purpose, pyrrole moiety was selected. Although pyrrole or its reduced form pyrrolidine exists in some antihypertensive compounds such as, angiotensin converting enzyme (ACE) inhibitors like kaptopril, enalapril and fosinopril, some ACE II receptor antagonists [28], and Ca antagonist and vasodilator bepridil, and moreover, pyrrole [29–31] substituted arylpyridazinones were previously reported to possess hopeful activities on cardiovascular system, there is no evidence showing that the pyrrole moiety is directly related with activity. However, it may be concluded that its role as contributor to the pharmacological activity in those compounds is helpful. Using these features and as continuation to our work on 6-aryl-3(2H)-pyridazinones [9], in this study, we synthesised some pyrrole substituted 6-aryl-3(2H)-pyridazinones and

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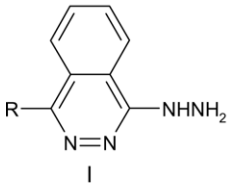
1(2H)-phthalazinones and tested their antihypertensive activities.



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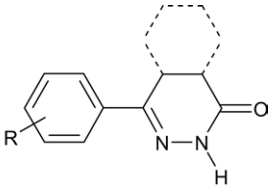

II

R : H Hydralazine
R : $NHNH_2$ Dihydralazine

2. Chemistry

The syntheses of 6-[4-(substituted pyrrol-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinone, **9**, 2-methyl-6-[4-(substituted pyrrol-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinone, **11**, 2-(2-acetyloxyethyl)-6-[4-(substituted pyrrol-1-yl) phenyl]-4,5-dihydro-3(2H)-pyridazinone, **13**, derivatives along with 4-[4-(substituted pyrrol-1-yl)phenyl]-1(2H)-phthalazinone, **10**, and 2-methyl-4-[4-(substituted pyrrol-1-yl)phenyl]-1(2H)-phthalazinone, **12**, derivatives were aimed in this work. 6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone, **3**, 2-methyl-6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone, **5**, 2-(2-hydroxyethyl)-6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone, **7**, 4-(4-aminophenyl)-1-(2H)-phthalazinone, **4**, and 2-methyl-4-(4-aminophenyl)-1-(2H)-phthalazinone, **6**, required as starting material were readily accomplished in high yields by refluxing the requisite γ-keto acid with hydrazine derivatives in ethanol [32–34]. Above-mentioned aminophenyl residue bearing derivatives were reacted with suitable 1,4-dicarbonyl compounds, **8**, in acetic acid under Paal–Knorr pyrrole synthesis conditions to obtain the aimed compounds as depicted in Figs. 1 and 2. In the synthesis of the compounds, **13**, unlike the synthesis of all the other compounds, acetic anhydrite was added to the reaction mixture in order to obtain 2-(2-acetyloxyethyl)-6-[4-(substituted pyrrole-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinones. The structures of the synthesised compounds were elucidated by IR, ^{1}H-NMR, EI-MS spectra and elemental analysis results. In the IR spectra, amide C=O stretching bands of pyridazinone and phthalazinone ring systems, which are characteristic for all compounds, were observed at 1660–1680 cm^{-1} and 1640–1660 cm^{-1} regions, respectively. The stretching bands belonging to pyridazinones' carbonyl group observed in lower frequencies than phthalazinones', this shift might be attributed to the resonance in phthalazinones. The other characteristic groups are the carbonyl group of carbethoxy group on pyrrole ring, i.e. present in most of the compounds, and the carbonyl group of acetyloxy residue of compounds **13**. As expected, they were observed at about 1700–1690 cm^{-1} and 1740 cm^{-1} regions, respectively. In the NMR spectra of pyridazinone residue bearing compounds, pyridazinone C_4 and C_5 protons resonated at 2.7 and 3.2 ppm, respectively. 2-Nonsubstituted pyridazinones' N-H peaks were observed at about 9 ppm. In compounds **13**, methyl and methylene protons of acetyloxy moiety characteristically resonated at 2 ppm for methyl and 4.14 and 4.4 ppm for methylene groups. In phthalazinone residue bearing compounds, characteristic phthalazinone C_5 and C_8 protons resonated as doublets at about 7.8 and 8.5 ppm, respectively. However, phthalazinone $C_{6,7}$ protons resonated

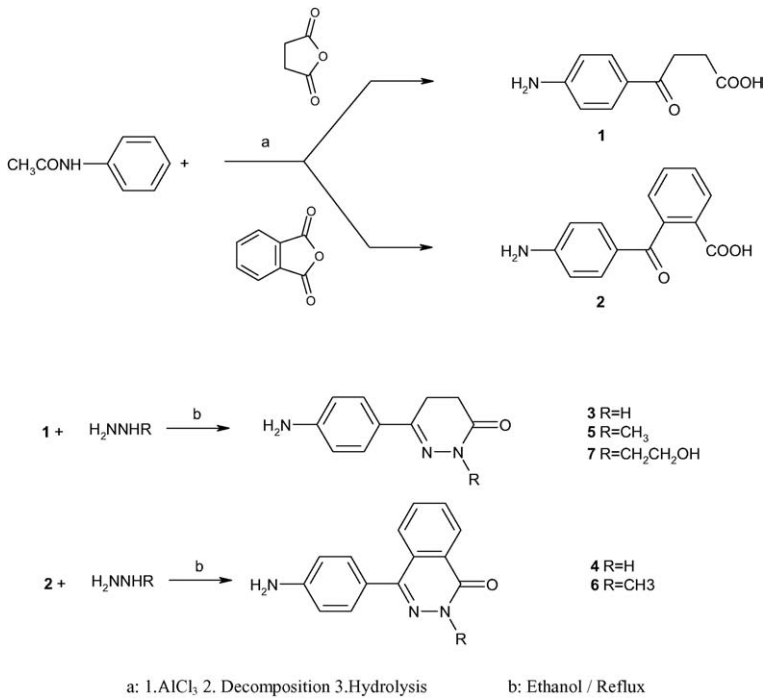

Fig. 1. Syntheses of the starting compounds.

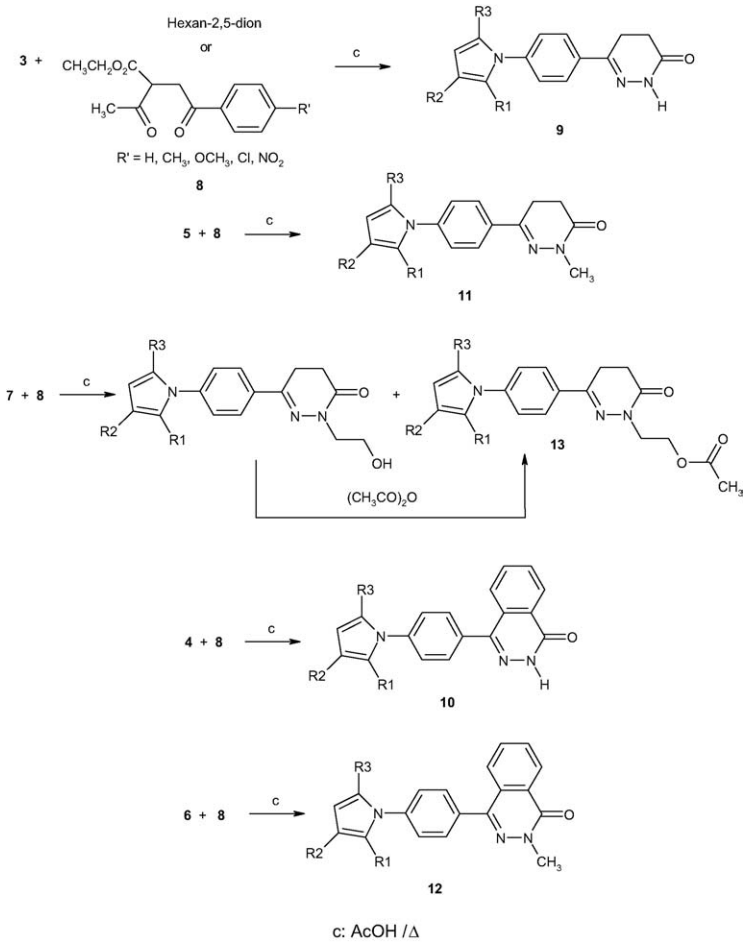

Fig. 2. Syntheses of the compounds.

as multiplets at about 8 ppm. 2-Nonsubstituted phthalazinones' N-H peaks were shifted and observed at about 13 ppm. As denoted, pyridazinones' N-H peaks were observed at about 9 ppm, this situation may be attributable to the increased acidity of the mentioned protons' by comparison of the more aromatic character bearing phthalazinone residue with pyridazinone residue. All the other aromatic and aliphatic protons resonated as expected. In the EI-MS spectra, molecular ion peaks were not obtained for compounds **10d** and **10e**, for the other compounds the molecular peaks were obtained, but molecular peak intensities were quite lower for ester residue carrying compounds (almost lower than 5% for all the compounds). This is an expected situation for ester residue carrying compounds [35]. It is noteworthy that, in these compounds, the peaks of the proposed fragments formed with cleavage of the ester residue formed notable peaks; even in compounds **10d**, **10e** and **12b** M-46 fragment formed the base peak.

3. Results and discussion

The compounds were investigated for vasorelaxant effects on isolated rat aorta. The results were shown in Table 1. Since the endothelium layer was removed in our experiments, the effects of compounds were endothelium independent in nature. It was found **9c** and **9d** were highest effective compounds in this group. The following effective compounds are **9a**, **9b** and **9f**. In consideration of the inhibition values obtained, it is seen that the pyridazinone derivatives, **9**, are

Table 1
Inhibitory effects of the compounds on isolated rat aorta

Compound (10^{-4} M)	% Inhibition of Phe contractions (±SEM)
9a	38 ± 4.2
9b	29 ± 6.8 *
9c	48.8 ± 7.9 *
9d	44.2 ± 4.5 *
9e	25.2 ± 6.5 *
9f	36 ± 3.9 *
10a	27 ± 5.6
10b	24.6 ± 7.7 *
10d	17.45 ± 3.6
10e	24.8 ± 5.9
11a	29 ± 6.1
11b	28.8 ± 6.7 *
11c	16.5 ± 5.3
12b	27.6 ± 6.5
13b	33.9 ± 8.3
13c	24.1 ± 4.7
13d	28.9 ± 4.5

(* $P < 0.05$).

Table 2
Systolic blood pressures (mmHg)

Compound (20 mg/kg)	The mean of systolic blood pressure
Control	107.29 ± 6.94
DMSO	105.2 ± 3.66
Hydralazine [a]	83.59 ± 6.39
9a	80.05 ± 4.25
9b	83.07 ± 3.15*
9c	82.77 ± 4.46
9d	83.89 ± 9.87
9e	89.8 ± 12.3
9f	70.30 ± 6.34*
10a	93.07 ± 3.55
10b	100.72 ± 3.70
10d	82.34 ± 1.82*
10e	91.25 ± 3.02
11a	90.5 ± 5.03
11b	101.4 ± 3.25
11c	110.40 ± 3.53
12b	109.80 ± 1.93
13b	86.8 ± 2.48*
13c	97.96 ± 4.96
13d	89.80 ± 1.83

All the values were expressed as mean ± SEM (*$P \leq 0.05$).
[a] Dose of hydralazine was taken as 2.6 mg/kg [43].

more active, i.e. not only the smallest of the synthesised compounds in volume but also N-nonsubstituted pyridazinone derivatives. When reports in the literature on N-nonsubstituted pyridazinone derivatives possessing higher vasodilator activity were taken into account, we may conclude that a parallel result was obtained in our study.

Antihypertensive activities of the compounds were tested by using Tail–Cuff method. The results were shown in Table 2. In the antihypertensive activity tests, when the blood pressure values of the control group and DMSO, i.e. used for solving the compounds, were compared, we may say that the effect of this solvent on blood pressure is in a negligible amount. In these test, hydralazine, which has a similar chemical structure with our compounds, was used as control antihypertensive. Although there is difference between the dose of hydralazine and our compounds tested, when the systolic blood pressure values obtained was compared, it is seen that the most significant activity was observed for compound **9f**. Also, in these tests we may conclude that, in analogy with the vasorelaxant activity tests, the most active compound group seems to be the first members of the synthesised series, i.e. N-nonsubstituted pyridazinones, **9**. Besides, it is seen that also the compounds **10d** and **13b** showed significant activity.

When vasorelaxant activity was taken into consideration, most active compounds are bearing methyl and methoxy substitutions, while this substitution is the nitro group for antihypertensive activity. Therefore, it is seen that there is no meaningful difference between different substituent groups and activity.

4. Experimental protocols

4.1. Chemistry

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, Leco CHNS Analyser.

6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone, (M.p.: 236–7 °C. Lit. [27] M.p: 237–8 °C), 2-methyl-6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone (M.p.: 216–7 °C, Lit. [36] M.p.: 216–8 °C), 2-(2-hydroxyethyl)-6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone (M.p.: 147–9 °C), 4-(4-aminophenyl)-1-(2H)-phthalazinone, (M.p.: 245–7 °C, Lit. [37] M.p.: 246–8 °C) 2-methyl-4-(4-aminophenyl)-1-(2H)-phthalazinone (M.p.: 219–20 °C, Lit. [38] M.p.: 220 °C) and 1-aryl-3-carbethoxy-1,4-pentadiones [39] required as starting materials were prepared according to the literature methods.

Some characteristics of the compounds are shown in Table 3.

2-Nonsubstituted/2-methyl 6-(4'-substituted pyrrol-1-yl)phenyl-4,5-dihydro-3(2H)-pyridazinone and 2-nonsubstituted/2-methyl 4-(4'-substituted pyrrol-1-yl)phenyl-1(2H)-phthalazinone derivatives **9**,**10**,**11**,**12**.

A mixture of **3** or **(4** or **5** or **6)** (10 mmol) and an appropriate **8** (10 mmol) was refluxed in acetic acid for 1 h. The reaction mixture was poured into ice water. The precipitate formed was filtered and crystallised from ethanol-DMF mixture.

9a IR(KBr)ν_{max}(cm^{-1}) : 3274(N-H), 1681(C=O), 1614-1540(C=N, C=C). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 2.18 (s, 6H), 2.82 (t, 2H, J = 8.12 Hz), 3.16 (t, 2H, J = 8.18 Hz), 6.16 (s, 2H), 7.26 (d, 2H, J = 8.32 Hz), 7.92 (d, 2H, J = 8.37 Hz), 9.01 (bs, 1H).

9b IR(KBr)ν_{max}(cm^{-1}) : 3217(N-H), 1703(Ester C=O), 1681(C=O), 1618-1558(C=N, C=C). ^{1}H-NMR(400 MHz) ($CDCl_3$) δ (ppm) : 1.54 (t, 3H, J = 7.12 Hz), 2.58 (s, 3H), 2.80 (t, 2H, J = 8.23 Hz), 3.16 (t, 2H, J = 8.23 Hz), 4.49 (q, 2H, J = 7.12 Hz), 6.97 (s, 1H), 7.22 (d, 2H, J = 7.92 Hz), 7.30-7.36 (m, 5H), 7.92 (d, 2H, J = 8.57 Hz), 9.03 (s, 1H). EI-MS: *m/z*: 401.80 M$^+$, 401.16, 371.50, 115.09, 43.38 (%100).

9c IR(KBr)ν_{max}(cm^{-1}) : 3222(N-H), 1703(Ester C=O), 1681(C=O), 1612-1558(C=N, C=C). ^{1}H-NMR(400 MHz) ($CDCl_3$) δ (ppm) : 1.54 (t, 3H, J = 7.11 Hz), 2.42 (s, 3H), 2.58 (s, 3H), 2.81 (t, 2H, J = 8.21 Hz), 3.17 (t, 2H, J = 8.23 Hz), 4.49 (q, 2H, J = 7.12 Hz), 6.93 (s, 1H), 7.11 (d, 2H, J = 8.64 Hz), 7.13 (d, 2H, J = 8.57 Hz), 7.35 (d, 2H, J = 8.52 Hz), 7.92 (d, 2H, J = 8.53 Hz), 8.93 (bs, 1H).

9d IR(KBr)ν_{max}(cm^{-1}) : 3211(N-H), 1693(Ester C=O), 1670(C=O), 1614-1533(C=N, C=C). ^{1}H-NMR(400 MHz) ($CDCl_3$) δ (ppm) : 1.54 (t, 3H, J = 7.23 Hz), 2.57 (s, 3H), 2.49 (s, 3H), 2.81 (t, 2H, J = 8.22 Hz), 3.17 (t, 2H, J = 8.25 Hz),

Table 3
Some characteristics of the compounds

Comp.	R_1	R_2	R_3	M.p. (C)	Yield (%)	Mol. Formula (Anal. C,H,N)
9a	CH_3	H	CH_3	290 Dec.	22	$C_{16}H_{17}N_3O$
9b	CH_3	$COOCH_2CH_3$	$-C_6H_5$	169–70	66	$C_{24}H_{23}N_3O_3$
9c	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-CH_3	233–234	59	$C_{25}H_{25}N_3O_3$
9d	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-OCH_3	210–212	83	$C_{25}H_{25}N_3O_4$
9e	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-Cl	261–263	95	$C_{24}H_{22}ClN_3O_3$
9f	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-NO_2	303–305	55	$C_{24}H_{22}N_4O_5$
10a	CH_3	H	CH_3	310 Dec.	15	$C_{20}H_{17}N_3O$
10b	CH_3	$COOCH_2CH_3$	$-C_6H_5$	242–245	38	$C_{28}H_{23}N_3O_3$
10c	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-CH_3	247–248	18	$C_{29}H_{25}N_3O_3$
10d	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-OCH_3	249–250	95	$C_{29}H_{25}N_3O_4$
10e	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-Cl	272–274	90	$C_{28}H_{22}ClN_3O_3$
10f	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-NO_2	288–290	42	$C_{28}H_{22}N_4O_5$
11a	CH_3	H	CH_3	110–111	25	$C_{17}H_{19}N_3O$
11b	CH_3	$COOCH_2CH_3$	$-C_6H_5$	146–147	45	$C_{25}H_{25}N_3O_3$
11c	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-Cl	201–203	45	$C_{25}H_{24}ClN_3O_3$
12a	CH_3	H	CH_3	240–243	32	$C_{21}H_{19}N_3O$
12b	CH_3	$COOCH_2CH_3$	$-C_6H_5$	219–220	31	$C_{29}H_{25}N_3O_3$
12c	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-Cl	198–199	48	$C_{29}H_{24}ClN_3O_3$
13a	CH_3	H	CH_3	78–80	21	$C_{20}H_{23}N_3O_3$
13b	CH_3	$COOCH_2CH_3$	$-C_6H_5$	92–94	37	$C_{28}H_{29}N_3O_5$
13c	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-CH_3	103–105	41	$C_{29}H_{31}N_3O_5$
13d	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-Cl	157–158	57	$C_{28}H_{28}ClN_3O_5$
13e	CH_3	$COOCH_2CH_3$	$-C_6H_4$-p-NO_2	139–140	43	$C_{28}H_{28}N_4O_7$

4.49 (q, 2H, *J* = 7.10 Hz), 6.96-6.98 (m, 3H), 7.21 (d, 2H, *J* = 8.55 Hz), 7.32 (d, 2H, *J* = 8.52 Hz), 7.92 (d, 2H, *J* = 8.53 Hz), 8.97 (bs, 1H).

9e IR(KBr)ν_{max}(cm^{-1}) : 3205(N-H), 1693(Ester C=O), 1670(C=O), 1622-1556(C=N, C=C). ^{1}H-NMR(400 MHz) ($CDCl_3$) δ (ppm) : 1.54 (t, 3H, *J* = 7.11 Hz), 2.58 (s, 3H), 2.82 (t, 2H, *J* = 8.21 Hz), 3.18 (t, 2H, *J* = 8.23 Hz), 4.49 (q, 2H, *J* = 7.12 Hz), 6.96 (s, 1H), 7.14 (d, 2H, *J* = 8.59 Hz), 7.29 (d, 2H, *J* = 8.59 Hz), 7.34 (d, 2H, *J* = 8.57 Hz), 7.94 (d, 2H, *J* = 8.56 Hz), 8.80 (s, 1H). EI-MS: *m/z*: 435.59 M^+, 408.70, 409.89, 408.70, 406.06 (%100), 364.23, 115.34.

9f IR(KBr)ν_{max}(cm^{-1}) : 3199(N-H), 1697(Ester C=O), 1672(C=O), 1595-1558(C=N, C=C), 1515, 1342(N=O). ^{1}H-NMR(400 MHz)(DMSO-d_6) δ (ppm) : 1.53 (t, 3H, *J* = 7.08 Hz), 2.58 (s, 3H), 2.69 (t, 2H, *J* = 8.14 Hz), 3.21 (t, 2H, *J* = 8.25 Hz), 4.49 (q, 2H, *J* = 7.08 Hz), 6.96 (s, 1H), 7.27 (d, 2H, *J* = 8.84 Hz), 7.33 (d, 2H, *J* = 8.50 Hz), 7.83 (d, 2H, *J* = 8.50 Hz), 7.99 (d, 2H, *J* = 8.84 Hz), 10.96 (s, 1H).

10a IR(KBr)ν_{max}(cm^{-1}): 3295(N-H), 1664(C=O), 1606-1519(C=N, C=C). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 2.26 (s, 6H), 6.18 (s, 2H), 7.61 (d, 2H, *J* = 8.30 Hz), 7.94 (d, 2H, *J* = 8.29 Hz), 8.09-8.06 (m, 3H), 8.78 (m, 1H), 11.26 (s, 1H). EI-MS: *m/z*: 315.65 M^+, 314.75 M-1, 189.54, 162.85, 43.41, 41.42 (%100).

10b IR(KBr)ν_{max}(cm^{-1}): 3294(N-H), 1693(Ester C=O), 1654(C=O), 1600-1556(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm) : 1.46 (t, 3H, *J* = 7.09 Hz), 2.57 (s, 3H), 4.40 (q, 2H, *J* = 7.10 Hz), 6.89 (s, 1H), 7.27-7.41 (m, 5H), 7.59 (d, 2H, *J* = 8.39 Hz), 7.78 (d, 1H, *J* = 7.65 Hz), 7.83 (d, 2H, *J* = 8.38 Hz), 8.08 (m, 2H), 8.50 (d, 1H, *J* = 7.67 Hz), 13.07 (s, 1H).

10c IR(KBr)ν_{max}(cm^{-1}): 3248(N-H), 1680-1660(Ester C=O, C=O), 1602-1556(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm) : 1.48 (t, 3H, *J* = 7.11 Hz), 2.42 (s, 3H), 2.58 (s, 3H), 4.48 (q, 2H, *J* = 7.09 Hz), 6.88 (s, 1H), 7.12 (d, 2H, *J* = 8.75 Hz), 7.17 (d, 2H, *J* = 8.68 Hz), 7.60 (d, 2H, *J* = 8.52 Hz), 7.78 (d, 1H, *J* = 8.03 Hz), 7.83 (d, 2H, *J* = 8.51 Hz), 8.08 (m, 2H), 8.50 (d, 1H, *J* = 8.25 Hz), 13.00 (s, 1H).

10d IR(KBr)ν_{max}(cm^{-1}) : 3202(N-H), 1687(Ester C=O), 1658(C=O), 1606-1558(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm) : 1.45 (t, 3H, *J* = 7.09 Hz), 2.55 (s, 3H), 3.85 (s, 3H), 4.40 (q, 2H, *J* = 7.09 Hz), 6.77 (s, 1H), 6.96 (d, 2H, *J* = 8.79 Hz), 7.20 (d, 2H, *J* = 8.67 Hz), 7.57 (d, 2H, *J* = 8.32 Hz), 7.78 (d, 1H, *J* = 8.01 Hz), 7.83 (d, 2H, *J* = 8.31 Hz), 8.08 (m, 2H), 8.51 (d, 1H, *J* = 8.27 Hz), 13.07 (s, 1H). EI-MS: *m/z*: 456.91, 455.85, 454.60, 451.86, 449.29 (%100), 190.09.

10e IR(KBr)ν_{max}(cm^{-1}) : 3249(N-H), 1672(Ester C=O), 1654(C=O), 1606-1556(C=N, C=C). ^{1}H-NMR(400 MHz) (DMSO-d_6) δ (ppm) : 1.46 (t, 3H, *J* = 7.08 Hz), 2.57 (s, 3H), 4.40 (q, 2H, *J* = 7.04 Hz), 6.93 (s, 1H), 7.28 (d, 2H, *J* = 8.53 Hz), 7.46 (d, 2H, *J* = 8.50 Hz), 7.60 (d, 2H, *J* = 8.23 Hz), 7.80 (d, 1H, *J* = 7.70 Hz), 7.85 (d, 2H, *J* = 8.22 Hz), 8.08 (m, 2H), 8.51 (d, 1H, *J* = 8.18 Hz), 13.08 (s, 1H). EI-MS: *m/z*: 458.65, 457.02, 455.04, 453.13 (%100), 189.28.

10f IR(KBr)ν_{max}(cm^{-1}) : 3205(N-H), 1693(Ester C=O), 1650(C=O), 1606-1556(C=N, C=C), 1508, 1338(N=O). ^{1}H-NMR(400 MHz)(DMSO-d_6) δ (ppm) : 1.53 (t, 3H, *J* = 7.10 Hz), 2.58 (s, 3H), 3.85 (s, 3H), 4.50 (q, 2H, *J* = 7.10 Hz), 6.97 (s, 1H), 7.23 (d, 2H, *J* = 8.69 Hz), 7.60 (d,

2H, *J* = 8.32 Hz), 7.83 (d, 1H, *J* = 8.01 Hz), 7.78 (d, 2H, *J* = 8.31 Hz), 7.85 (d, 2H, *J* = 8.70 Hz), 8.10 (m, 2H), 8.49 (d, 1H, *J* = 8.27 Hz), 13.05 (s, 1H).

11a IR(KBr)ν_{max}(cm^{-1}) : 1662(C=O), 1614-1515(C=N, C=C). ^{1}H-NMR(400 MHz)(DMSO-d_6) δ (ppm) : 2.14 (s, 6H), 2.69 (t, 2H, *J* = 8.22 Hz), 3.19 (t, 2H, *J* = 8.22 Hz), 3.49 (s, 3H), 5.97 (s, 2H), 7.48 (d, 2H, *J* = 8.54 Hz), 8.05 (d, 2H, *J* = 8.54 Hz).

11b IR(KBr)ν_{max}(cm^{-1}) : 1693(Ester C=O), 1658(C=O), 1606-1558(C=N, C=C). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 1.54 (t, 3H, *J* = 7.11 Hz), 2.58 (s, 3H), 2.80 (t, 2H, *J* = 8.20 Hz), 3.14 (t, 2H, *J* = 8.17 Hz), 3.60 (s, 3H), 4.49 (q, 2H, *J* = 7.11 Hz), 6.98 (s, 1H), 7.20 (d, 2H, *J* = 8.45 Hz), 7.30-7.37 (m, 5H,), 7.92 (d, 2H, *J* = 8.50 Hz).

11c IR(KBr)ν_{max}(cm^{-1}) : 1697(Ester C=O), 1672(C=O), 1606-1552(C=N, C=C). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 1.54 (t, 3H, *J* = 7.11 Hz), 2.58 (s, 3H), 2.79 (t, 2H, *J* = 8.23 Hz), 3.14 (t, 2H, *J* = 8.17 Hz), 3.64 (s, 3H), 4.49 (q, 2H, *J* = 7.11 Hz), 6.96 (s, 1H), 7.15 (d, 2H, *J* = 8.53 Hz), 7.30 (d, 2H, *J* = 8.45 Hz), 7.34 (d, 2H, *J* = 8.47 Hz), 7.96 (d, 2H, *J* = 8.50 Hz). EI-MS: *m/z*: 449.86 M+1, 448.95 M^+, 420.46, 101.21, 41.91 (%100).

12a IR(KBr)ν_{max}(cm^{-1}) : 1643(C=O), 1581-1577(C=N, C=C). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 2.30 (s, 6H), 4.11 (s, 3H), 6.12 (s, 2H), 7.56 (d, 2H, *J* = 8.44 Hz), 7.88 (d, 2H, *J* = 8.45 Hz), 7.94-8.00 (m, 3H), 8.72-8.75 (m, 1H).

12b IR(KBr)ν_{max}(cm^{-1}) : 1699(Ester C=O), 1645(C=O), 1585-1519(C=N, C=C). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 1.59 (t, 3H, *J* = 7.12 Hz), 2.70 (s, 3H), 4.14 (s, 3H), 4.55 (q, 2H, *J* = 7.12 Hz), 7.04 (s, 1H), 7.32-7.41 (m, 5H), 7.52 (d, 2H, *J* = 8.37 Hz), 7.84 (m, 3H), 8.00 (m, 2H), 8.75 (d, 1H, *J* = 7.72 Hz). EI-MS: *m/z*: 463.32 M^+, 434.11 (%100), 233.17, 189.80, 42.88.

12c IR(KBr)ν_{max}(cm^{-1}): 1697(Ester C=O), 1641(C=O), 1583-1556(C=N, C=C). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 1.46 (t, 3H, *J* = 7.10 Hz), 2.58 (s, 3H), 4.10 (s, 3H), 4.42 (q, 2H, *J* = 7.11 Hz), 6.96 (s, 1H), 7.28 (d, 2H, *J* = 8.37 Hz), 7.46 (d, 2H, *J* = 7.72 Hz), 7.60 (d, 2H, *J* = 7.75 Hz), 7.86-8.00 (m, 5H), 8.72-8.75 (m,1H).

*5.1. 2-(2-Acetyloxyethyl)-6-(4'-substituted pyrrol-1-yl) phenyl-4,5-dihydro-3(2H)-pyridazinones **13***

A mixture of **7** (10 mmol) and an appropriate **8** (10 mmol) was refluxed in acetic acid for 45 min then excess acetic anhydrite was added and heated for 15 min. The reaction mixture was poured into ice water. The precipitate formed was filtered and crystallised from diethyl ether–ethanol mixture.

13a IR(KBr)ν_{max}(cm^{-1}) : 1739(Acetyl C=O), 1670(C=O), 1541-1516(C=N, C=C). ^{1}H-NMR(400 MHz) ($CDCl_3$) δ (ppm) : 2.10 (s, 3H), 2.20 (s, 6H), 2.70 (t, 2H, *J* = 8.12 Hz), 3.15 (t, 2H, *J* = 8.16 Hz), 4.14 (t, 2H, *J* = 5.65 Hz). 4.42 (t, 2H, *J* = 5.69 Hz), 6.16 (s, 2H), 7.47 (d, 2H, *J* = 8.32 Hz), 8.05 (d, 2H, *J* = 8.37 Hz).

13b IR(KBr)ν_{max}(cm^{-1}) : 1741(Acetyl C=O), 1695(Ester C=O), 1672(C=O), 1604-1558(C=N, C=C). ^{1}H-NMR (400 MHz)(DMSO-d_6) δ (ppm) : 1.44 (t, 3H, *J* = 7.08 Hz), 2.08 (s, 3H), 2.49 (s, 3H), 2.70 (t, 2H, *J* = 8.15 Hz), 3.15 (t, 2H, *J* = 8.11 Hz), 4.15 (t, 2H, *J* = 5.45 Hz), 4.37 (q, 2H, *J* = 7.10 Hz), 4.46 (t, 2H, *J* = 5.47 Hz), 6.89 (s, 1H), 7.21-7.46 (m, 5H), 7.49 (d, 2H, *J* = 8.25 Hz), 8.03 (d, 2H, *J* = 8.25 Hz).

13c IR(KBr)ν_{max}(cm^{-1}) : 1735(Acetyl C=O), 1699(Ester C=O), 1672(C=O), 1575-1533(C=N, C=C). ^{1}H-NMR (400 MHz)(DMSO-d_6) δ (ppm) : 1.48 (t, 3H, *J* = 7.10 Hz), 2.10 (s, 3H), 2.49 (s, 3H), 2.78 (t, 2H, *J* = 8.20 Hz), 3.16 (t, 2H, *J* = 8.22 Hz), 4.15 (t, 2H, *J* = 5.45 Hz), 4.36 (q, 2H, *J* = 7.12 Hz), 4.42 (t, 2H, *J* = 5.10 Hz), 6.90 (s, 1H), 7.15 (d, 2H, *J* = 8.50 Hz), 7.30 (d, 2H, *J* = 8.50 Hz), 7.49 (d, 2H, *J* = 8.25 Hz), 8.02 (d, 2H, *J* = 8.27 Hz).

13d IR(KBr)ν_{max}(cm^{-1}) : 1739(Acetyl C=O), 1690-1677(Ester C=O, C=O), 1602-1558(C=N, C=C). ^{1}H-NMR(400 MHz)(DMSO-d_6) δ (ppm) : 1.44 (t, 3H, *J* = 7.08 Hz), 2.08 (s, 3H), 2.48 (s, 3H), 2.69 (t, 2H, *J* = 8.23 Hz), 3.15 (t, 2H, *J* = 8.21 Hz), 4.14 (t, 2H, *J* = 5.45 Hz), 4.38 (q, 2H, *J* = 7.09 Hz), 4.42 (t, 2H, *J* = 5.49 Hz), 6.89 (s, 1H), 7.23 (d, 2H, *J* = 8.55 Hz), 7.42 (d, 2H, *J* = 8.55 Hz), 7.49 (d, 2H, *J* = 8.55 Hz), 8.03 (d, 2H, *J* = 8.53 Hz). EI-MS: *m/z*: 521.83 M+1, 521.07M^+, 432.68, 431.54, 334.76, 73.28, 55.38, 43.38 (%100).

13e IR(KBr)ν_{max}(cm^{-1}) : 1735(Acetyl C=O), 1690-1680(Ester C=O, C=O), 1595-1560(C=N, C=C), 1514, 1342(N=O). ^{1}H-NMR(400 MHz)(DMSO-d_6) δ (ppm) : 1.45 (t, 3H, *J* = 7.08 Hz), 2.08 (s, 3H), 2.51 (s, 3H), 2.70 (t, 2H, *J* = 8.23 Hz), 3.15 (t, 2H, *J* = 8.50 Hz), 4.14 (t, 2H, *J* = 5.45 Hz), 4.40 (q, 2H, *J* = 7.15 Hz), 4.42 (t, 2H, *J* = 5.42 Hz), 7.17 (s, 1H), 7.47 (d, 2H, *J* = 8.91 Hz), 7.56 (d, 2H, *J* = 8.55 Hz) , 8.06 (d, 2H, *J* = 8.54 Hz), 8.19 (d, 2H, *J* = 8.92 Hz).

4.2. Pharmacology

Male wistar rats between 200 and 300 g were killed by cervical dislocation. For the endothelium-denuded rings, segments of thoracic aorta (3–5 mm) were gently rubbed to remove the endothelium. Using a resting tension of 1 g, tissues were set up in 10-ml organ baths containing Krebs–Henseleit solution at 37 °C and bubbled with 95% O_2–5% CO_2. To assess phenylephrine (10^{-6} M) (Sigma, St. Louis, MO) induced contractions, isometric transducers and Gemini recorders (Ugo Basile, Varese, Italy) were used for recording organ responses [40]. Rings of aorta were precontracted with phenylephrine (Phe) (10^{-6} M) and exposed to acetylcholine (ACh) (10^{-6} M) to test endothelium-dependent relaxations (EDR) [41]. Test material was dissolved in DMSO. Compounds were applied to the organ bath at a concentration of 10^{-4} M.

Systolic blood pressure was measured in conscious rats using Tail–Cuff method [42]. Wistar rats (body weight 200–250 g) were used in the present study. Rats were assigned to groups of five animals each. The compounds were dissolved in DMSO. The compounds at the dose level of 20 mg/kg body weight were injected intraperitoneally. The Tail–Cuff

and piezoelectric pulse sensor were placed at the base of the tail and were connected to blood pressure analyser (May 9610, Ankara, Turkey). The blood pressures of each rat were measured before and 30 min after drug administration, the reduction of blood pressure was recorded as mmHg.

All the values were expressed as mean ± SEM. ($n = 5$) and Student's *t*-test was used to assess statistical significance.

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