European Journal of Medicinal Chemistry 45 (2010) 5390–5396

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

New octahydroquinazoline derivatives: Synthesis and hypotensive activity

O.I. El-Sabbagh [a,*], Mohamed A. Shabaan [b], Hanan H. Kadry [b], Ehab Saad Al-Din [c]

[a] Department of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt
[b] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Cairo University, Egypt
[c] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt

ARTICLE INFO

Article history:
Received 17 July 2010
Received in revised form
25 August 2010
Accepted 26 August 2010
Available online 20 September 2010

Keywords:
Synthesis
Octahydroquinazoline derivatives
Hypotensive activity

ABSTRACT

Several novel 1-(4-chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-5-oxo-3-(substitutedphenyl) quinazoline derivatives (**2**–**21**) structurally similar to prazosin, were prepared using *Mannich* reaction of 3-(4-chlorophenylamino)-5,5-dimethyl-2-cyclohexenone (**1**) with different aromatic amines in the presence of formaline. The structures of the quinazoline derivatives were established using elemental and spectral analyses. Compounds **18**, **20** and **21** were found to possess a high hypotensive effect through their expected α_1-blocking activity like the clinically used drug prazosin but with advantageous of being did not cause reflex tachycardia and having prolonged duration of action when tested in adrenaline-induced hypertension in anaesthetized rats.

1. Introduction

Among the major risk factors for arterial diseases, hypertension is considered the most important one for the development of stroke, coronary heart disease, and congestive heart failure [1,2] The estimated total number of adults with hypertension in 2000 was 972 million, and this may increase by about 60% to a total of 1.56 billion in 2025 [3].

Quinazoline derived α_1-adrenergic receptor antagonist like prazosin [4,5] terazosin and doxazosin are reputed class of anti-hypertensive agents. Prazosin is considered the prototype of this class which selectively blocks postsynaptic α_1-adrenergic receptors but both doxazosin and terazosin [6,7] were found to possess longer duration and less reflex tachycardia than prazosin [8].

Moreover, it was reported that 4-amino-2-(4-cinnamoylpiperazino)-5,6,7,8-tetrahydroquinazoline [9] showed antihypertensive effect when examined in spontaneously hypertensive rats. In addition, other quinazoline derivatives [10–12] showed promising antihypertensive activity.

In the current study, we aimed to synthesize 1-(4-chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-5-oxo-3-substitutedphenylquinazoline derivatives (**2**–**21**) which are structurally similar to prazosin hoping to act as hypotensive agents with α_1-blocking activity.

2. Results and discussions

2.1. Chemistry

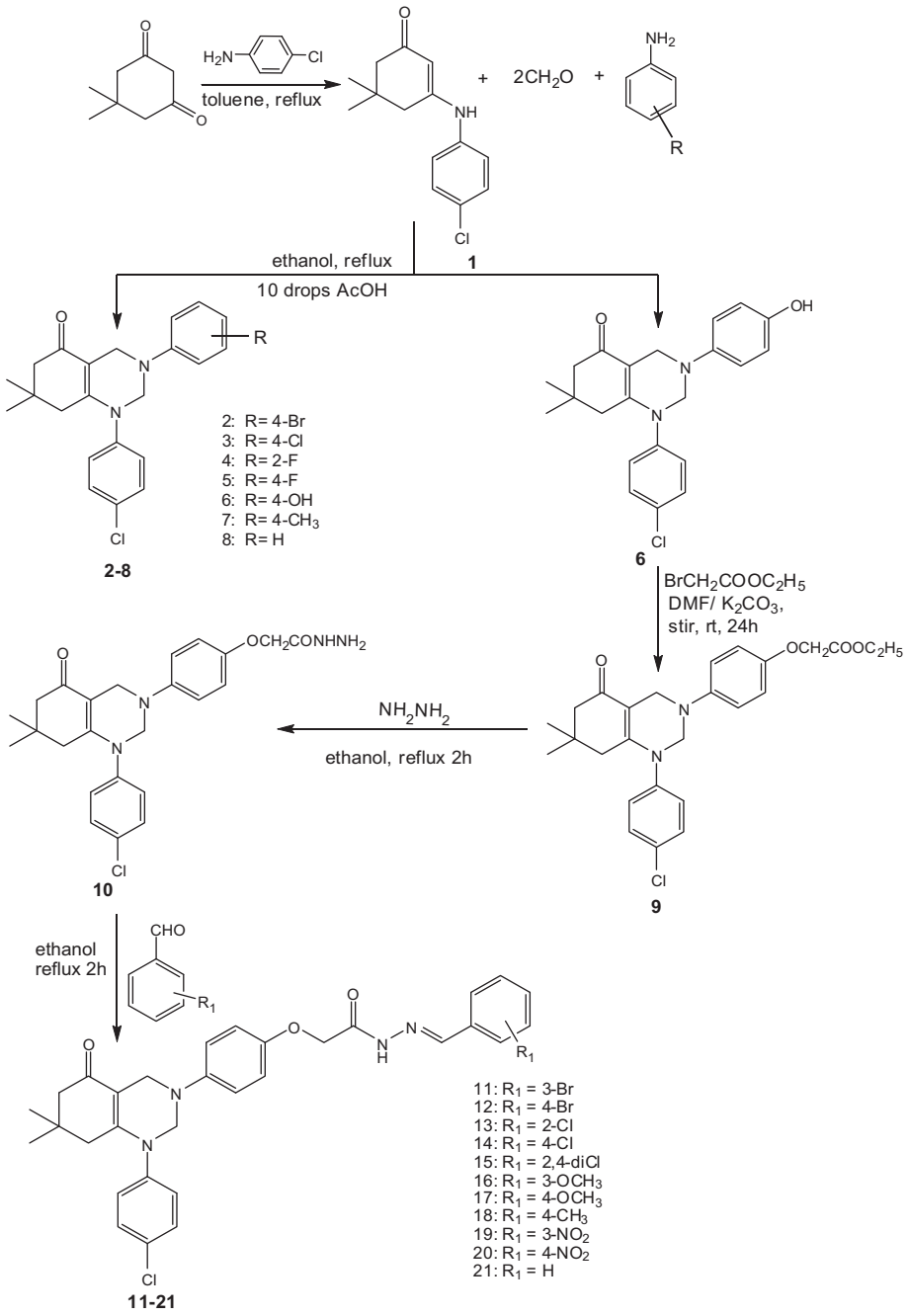
The target 1-(4-chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-5-oxo-3-substitutedphenylquinazoline derivatives (**2**–**21**) were synthesized as shown in Scheme 1.

Condensation of 5,5-dimethyl-1,3-cyclohexanedione with 4-chloroaniline was conducted via heating the reactants at reflux in toluene [13,14] to afford 5,5-dimethyl-3-(4-chlorophenylamino)-2-cyclohexenone (**1**). The novel 5-oxo-octahydroquinazolines (**2**–**8**) were then obtained by heating at reflux equimolar amounts of enaminone (**1**) and the primary aromatic amines with two equivalents of formaline in ethanol containing catalytic amount of glacial acetic acid.

These quinazolines (**2**–**8**) were formed through *Mannich* reaction either at C-2 or arylamino group of the enaminone system. The former would be kinetically favorable being irreversible followed by ring formation using excess formaline (Scheme 1). The structures of 5-oxo-octahydroquinazolines (**2**–**8**) were characterized using elemental and spectral analyses. IR spectral data showed the disappearance of the NH absorption band at 3250 cm^{-1} of the starting enaminone. ^1H NMR proved the disappearance of both singlet at $\delta = 7.85$ ppm due to NH group and also the vinylic proton singlet at $\delta = 5.65$ ppm of the starting enaminone. Moreover, the formation of the 5-oxo-octahydroquinazoline was confirmed through appearance of two characteristic singlets around $\delta = 4.26$ and 4.87 ppm for the two methylene groups at 4- and 2-positions of the quinazoline skeleton.

* Corresponding author. Tel.: +20 109610300; fax: +20 552303266.
E-mail addresses: osamaelsabbagh@yahoo.com, elsabbagh_59@zu.edu.eg (O.I. El-Sabbagh).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.08.064



Scheme 1. Synthetic pathways for preparation of the novel compounds **2**–**21**.

The novel ester (**9**) was prepared by stirring equimolar amounts of 3-(4-hydroxyphenyl)-5-oxo-octahydroquinazoline (**6**) and ethyl bromoacetate in dimethylformamide (DMF) containing K_2CO_3 at room temperature for 24 h.

The ester **9** was allowed to condense with hydrazine hydrate through refluxing the reactants in ethanol for 2 h to afford the novel hydrazide **10** in 72% yield. The chemical structures of ester **9** and hydrazide **10** were established using elemental and different spectroscopic methods.

Condensation of the hydrazide key intermediate **10** with aromatic aldehydes in equimolar amounts was conducted through heating the reactants in ethanol containing 10 drops of glacial acetic acid for 2 h to give the novel hydrazone derivatives **11**–**21**.

All the target compounds were controlled using thin-layer chromatography (TLC) and melting point techniques. Both analytical and spectral data of all compounds are in full agreement with the proposed structures.

2.2. Hypotensive activity

All novel 5-oxo-octahydroquinazolines (**2**–**21**) were screened to study their effect on the arterial blood pressure whereas compounds **2**, **4**, **5**, **9**–**17** and **19** which did not produce any effect were excluded. On the other hand, compounds **3**, **6**, **7**, **8**, **18**, **20** and **21** which showed an effect on the arterial blood pressure [15] were subjected to study their α-blocking activity [16] using prazosin as a reference drug.

Results presented in Table 1 showed that intraperitonial (i.p.) injection of prazosin (5 mg/Kg) produced significant ($P < 0.05$) reduction in both systolic and diastolic arterial blood pressure (SABP and DABP) which accompanied with rapidly occurring reflex tachycardia (5 min after injection) declined by time denoting rapid onset and short duration of action (Figs. 1 and 2).

Our results in Table 2 showed that intravenous (i.v.) injection of adrenaline [17] at a dose level of 3 μg/Kg produced significant ($P < 0.05$) increase in both SABP and DABP.

Injection of adrenaline, 30 min after prazosin injection, produced significant ($P < 0.05$) drop in arterial blood pressure due to selective blockade of α_1-receptor by prazosin (adrenaline reversal) [18]. However, injection of adrenaline, 1 h after prazosin injection returned the blood pressure to normal level due to short duration of action of the drug (Figs. 3 and 4).

Compound **3** produced a time-dependent significant ($P < 0.05$) increase in both SABP and DABP without causing tachycardia till 30 min (Table 1). So, this compound may be useful in treating hypotensive cases and subsequently, it was excluded from testing its α-blocking effect. Compound **6** produced non-significant change in both arterial blood pressure and HR (Table 1). It also did not attenuate the pressor effect of adrenaline on the blood pressure and so it has no α-blocking effect as shown in Table 2 and illustrated by Figs. 3 and 4.

Compounds **7** and **8** produced a time-dependent significant ($P < 0.05$) decrease in both SABP and DABP (Table 1) without causing any change in the heart rate. In the same time, Table 2 showed that compounds **7** and **8** reversed the pressor effect of adrenaline after half an hour i.e. they have α-blocking effect but of shorter duration of action like prazosin.

The results presented in Table 1 and illustrated by Figs. 1 and 2 showed that compounds **18**, **20** and **21** produced significant ($P < 0.05$) decrease in both SABP and DABP with rapid onset of action (after 5 min) meanwhile such compounds caused non-significant decrease in the HR. Compounds **18**, **20** and **21** rapidly reversed the vasopressor effect of adrenaline into depressor response after 30 min as shown in Table 2 which were sustained for 1 h (Figs. 3 and 4). Thus, these compounds can be considered as rapidly acting α_1-blockers like prazosin but with advantageous of being did not cause reflex tachycardia and having prolonged duration of action.

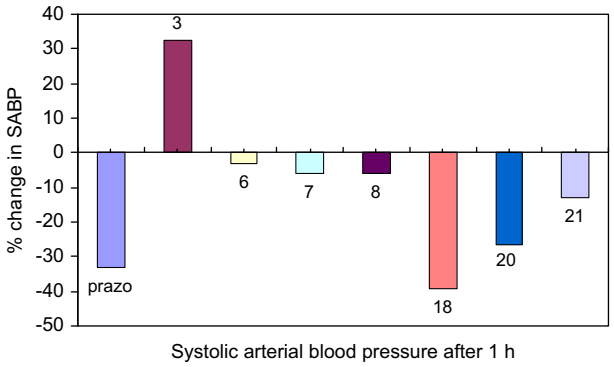


Fig. 1. Effect of i.p. injection of prazosin and compounds **3**, **6**–**8**, **18**, **20**, and **21** at dose of 5 mg/Kg on the systolic blood pressure of male albino rats.

3. Conclusion

The aim of the present study was to generate new effective hypotensive agents with α-blocking activity. Thus, new octahydroquinazoline derivatives (**2**–**21**) were prepared which structurally related to the antihypertensive clinically used α_1-blocker prazosin. The following observations were noticed:

1) Regarding the octahydroquinazolines **3** and **6**–**8**, it was observed that those having electron-withdrawing substituents on phenyl rings at 3-position of the octahydroquinazoline skeleton, such as compound **3** (4-Cl) was devoid of any

Table 1
Effect of prazosin and compounds **3**, **6**–**8**, **18**, **20**, and **21** at dose of 5mg/Kgm on the systolic (SABP), diastolic (DABP) arterial blood pressure and heart rate (HR) of anaesthetized male adult albino rats.

Compd No.	Parameter	Control	Changes by time after i.p. injection							
			5 min	% change	15 min	% change	30 min	% change	60 min	% change
Prazosin	SABP	$120^{a} \pm 6$	$95^{b} \pm 3.2$	−20.8	$85^{c} \pm 4$	−29.2	$80^{c} \pm 3$	−33.3	$80^{c} \pm 2.5$	−33.3
	DABP	$90^{a} \pm 2.1$	$70^{b} \pm 1.9$	−22.22	$70^{b} \pm 3$	−22.22	$65^{c} \pm 2.4$	−27.7	$55^{d} \pm 1.9$	−38.8
	HR	$295^{c} \pm 20$	$420^{a} \pm 12$	+30	$400^{a} \pm 18$	+26	$350^{b} \pm 15$	+16	$280^{c} \pm 13$	−5.1
3	SABP	$115^{d} \pm 3.8$	$140^{c} \pm 4$	+17.8	$150^{b} \pm 4.8$	+23	$170^{a} \pm 2.6$	+32.4	$170^{a} \pm 3.1$	+32.4
	DABP	$90^{c} \pm 2.1$	$110^{b} \pm 3$	+18.2	$120^{a} \pm 4$	+25	$125^{a} \pm 2.2$	+28	$125^{a} \pm 3$	+28
	HR	$240^{a} \pm 15$	$240^{a} \pm 12$	0	$240^{a} \pm 14$	0	$255^{a} \pm 15$	+6	$255^{a} \pm 11$	+6
6	SABP	$160^{a} \pm 4.8$	$160^{a} \pm 5.1$	0	$160^{a} \pm 7$	0	$155^{a} \pm 3.4$	−3	$155^{a} \pm 2.1$	−3
	DABP	$100^{a} \pm 2.3$	$100^{a} \pm 5$	0	$100^{a} \pm 4.6$	0	$100^{a} \pm 3.5$	0	$95^{a} \pm 1.9$	−5
	HR	$375^{a} \pm 14$	$375^{a} \pm 12$	0	$375^{a} \pm 13$	0	$375^{a} \pm 16$	0	$370^{a} \pm 12$	–
7	SABP	$180^{a} \pm 5.3$	$180^{a} \pm 3.6$	0	$180^{a} \pm 3.9$	0	$170^{b} \pm 3.2$	−6	$170^{b} \pm 2.7$	−6
	DABP	$160^{a} \pm 3.2$	$160^{a} \pm 4$	0	$160^{a} \pm 5$	0	$150^{b} \pm 4$	−6.25	$130^{c} \pm 6$	−18.7
	HR	$290^{a} \pm 18$	$290^{a} \pm 13$	0	$290^{a} \pm 15$	0	$290^{a} \pm 11$	0	$290^{a} \pm 12$	0
8	SABP	$160^{a} \pm 3.9$	$160^{a} \pm 5.1$	0	$160^{a} \pm 4.2$	0	$160^{a} \pm 5$	0	$150^{b} \pm 5$	−6
	DABP	$130^{a} \pm 4.5$	$130^{a} \pm 2.8$	0	$130^{a} \pm 3.3$	0	$120^{b} \pm 3.4$	−7.7	$120^{b} \pm 2.1$	−7.7
	HR	$240^{b} \pm 18$	$240^{b} \pm 13$	0	$240^{b} \pm 15$	0	$255^{ab} \pm 11$	+6.25	$270^{a} \pm 12$	+12
18	SABP	$140^{a} \pm 3.2$	$115^{b} \pm 4$	−17.8	$110^{b} \pm 2.1$	−21.4	$90^{c} \pm 3$	−35.8	$85^{c} \pm 3$	−39.3
	DABP	$120^{a} \pm 4$	$90^{b} \pm 4.1$	−25	$90^{b} \pm 2.5$	−25	$85^{b} \pm 3$	−29.16	$75^{c} \pm 3$	−37.5
	HR	$320^{a} \pm 19$	$315^{a} \pm 19$	−2	$305^{a} \pm 19$	−5	$300^{a} \pm 13$	−6.3	$300^{a} \pm 10$	−6.3
20	SABP	$150^{a} \pm 4.5$	$130^{b} \pm 2.7$	−13	$125^{b} \pm 2.2$	−17	$110^{c} \pm 3.1$	−26.5	$110^{c} \pm 1.8$	−26.5
	DABP	$80^{a} \pm 4$	$70^{b} \pm 3$	−12.5	$60^{c} \pm 3$	−25	$55^{c} \pm 3$	−31.25	$55^{c} \pm 3$	−31.25
	HR	$240^{a} \pm 20$	$240^{a} \pm 32$	0	$235^{a} \pm 18$	−2.1	$235^{a} \pm 15$	−2.1	$225^{a} \pm 15$	−6.2
21	SABP	$160^{a} \pm 5.3$	$130^{c} \pm 3.2$	−19	$140^{b} \pm 2.1$	−13	$145^{b} \pm 4$	−10	$140^{b} \pm 3$	−13
	DABP	$100^{a} \pm 2.9$	$90^{b} \pm 3$	−10	$90^{b} \pm 3.1$	−10	$85^{bc} \pm 3$	−15	$80^{c} \pm 3$	−20
	HR	$345^{a} \pm 15$	$345^{a} \pm 13$	0	$330^{a} \pm 18$	−4	$345^{a} \pm 15$	0	$345^{a} \pm 12$	0

Values were expressed as mean ± S.D.; Number of experiments = 6 in each parameter; Values with different superscript letters are significantly different at $P < 0.05$ (within the same horizontal line).

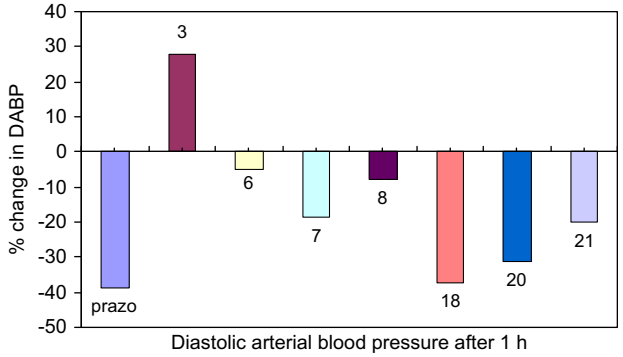


Fig. 2. Effect of i.p. injection of prazosin and compounds **3**, **6**–**8**, **18**, **20**, and **21** at dose of 5 mg/Kg on the diastolic blood pressure of male albino rats.

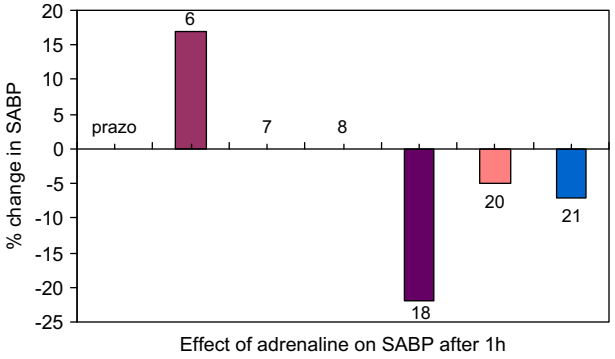


Fig. 3. Effect of i.v. injection of adrenaline (3 μg/Kg) 1 h after prazosin and compounds **6**–**8**, **18**, **20**, and **21** at dose of 5 mg/Kg on systolic blood pressure of anaesthetized male albino rats.

hypotensive activity. It was noted also through analysis of Tables 1 and 2 that the quinazolines **7** and **8** showed α-adrenoceptor blocking activity in adrenaline-induced hypertension in anaesthetized rats but of shorter duration of action as prazosin.

2) Compound **6** showed lower hypotensive effect with no α- blocking activity (Table 2) but its modification using the drug extension tactic led to more active compounds **18**, **20** and **21** which may be attributable to the extra binding interactions. These compounds were found to have α_1-blocking activity (Table 2) like prazosin with advantageous of less reflex tachycardia and prolonged duration of action.

4. Experimental protocols

4.1. Chemistry

Melting points were determined with a Gallenkamp (London, U.K.) melting point apparatus and are uncorrected. IR spectra (KBr, cm^{-1}) were recorded on Bruker Vector, 22FT-IR (Fourier Transform Infrared (FTIR)) (Germany) spectrometer. ^1H NMR spectra were recorded on a Varian Gemini-200 (200-MHz, Foster City, Calif., USA), MacNMR5.3-AC250(250 MHz) and Varian Mercury-300 (300-MHz, City: Palo Alto, State: Calif., USA) spectrometers using dimethylsulphoxide (DMSO)-d_6 or $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard (Chemical shift in δ, ppm). ^{13}C NMR spectra were recorded on a MacNMR5.3-AC250 using $CDCl_3$ as a solvent. Mass spectra were determined using Mass spectrometer GC/MS Shimadzu QP 1000 EX (Shimadzu Corporation, Tokyo, Japan) with ionization energy 70 eV. Elemental analyses were determined using Manual Elemental Analyzer Heraeus (Germany) and Automatic Elemental Analyzer CHN Model 2400 Perkin Elmer (USA) at Microanalytical Center, Faculty of Science, Cairo University, Egypt. All the results of elemental analyses corresponded to the calculated values within experimental error. Progress of the reaction was monitored by thin-layer chromatography (TLC) using precoated TLC sheets with ultraviolet (UV) fluorescent silica gel (Merck 60F254) and spots were visualized by iodine vapors or irradiation with UV light (254 nm). All the chemicals were purchased from Sigma–Aldrich.

4.1.1. General procedure for preparation of compounds *2*–*8*

To a solution of enaminone **1** (1.70 mmol) in ethanol (30 ml), the appropriate aromatic amines (1.70 mmol), 40% formalin (3.40 mmol) and 10 drops of glacial acetic acid were added. The reaction mixture was heated under reflux for 3 h and then left to stand overnight at room temperature. The reaction mixture was diluted with water, basified with NH_4OH to pH 8 and then left in refrigerator for 3 h. The separated product was filtered, washed with water (20 ml) and crystallized from suitable solvent.

Table 2
Effect of adrenaline alone and after injection of compounds **6**, **7**, **8**, **18**, **20**, **21** on systolic (SABP) and diastolic (DABP) arterial blood pressure in male adult albino rats.

Compd No.	Parameter	Effect of adrenaline alone			Effect of adrenaline after 1/2h. from inj. test comp.			Effect of adrenaline after 1h. from inj. test comp.		
		Control	effect	% change	30 min	effect	% change	60 min	effect	% change
Prazosin	SABP	130 ± 5	150 ± 2.5*	+15	90 ± 3	80 ± 1.8*	−11	90 ± 2.5	90 ± 3$^{n.s}$	0
	DABP	100 ± 2.2	120 ± 2.8*	+20	60 ± 1.1	55 ± 2.1*	−8	55 ± 2.0	55 ± 1.7$^{n.s}$	0
6	SABP	150 ± 5.0	190 ± 6.1*	+27	145 ± 3.2	170 ± 4.6*	+17	145 ± 2.1	170 ± 3.7*	+17
	DABP	100 ± 2.6	120 ± 4.2*	+20	100 ± 3.1	110 ± 4.8*	+10	95 ± 1.6	110 ± 3.1*	+16
7	SABP	150 ± 5.3	190 ± 5.1*	+27	140 ± 3.4	125 ± 2.9*	−11	140 ± 2.5	140 ± 2.9^{ns}	0
	DABP	130 ± 3.3	160 ± 3.4*	+23	120 ± 4.2	110 ± 3.6*	−8	100 ± 4.5	100 ± 1.4^{ns}	0
8	SABP	160 ± 2.9	200 ± 6.1*	+25	150 ± 5	140 ± 3.1*	−7	140 ± 3.3	140 ± 3.5^{ns}	0
	DABP	120 ± 4.1	150 ± 3.2*	+25	110 ± 3.6	100 ± 2.8*	−9	110 ± 2.3	110 ± 2.8^{ns}	0
18	SABP	150 ± 2.2	190 ± 3.4*	+27	95 ± 2.8	85 ± 1.5*	−11	90 ± 2.3	70 ± 2.1*	−22
	DABP	120 ± 3.5	150 ± 3.7*	+25	80 ± 2.4	65 ± 2.2*	−19	70 ± 2.1	50 ± 1.3*	−28.5
20	SABP	130 ± 4.1	180 ± 4.2*	+38	100 ± 3.1	90 ± 2.5*	−10	100 ± 1.7	95 ± 1.6*	−5
	DABP	110 ± 2.5	130 ± 3.7*	+18	55 ± 3.4	50 ± 2.9$^{n.s}$	−9	55 ± 3.2	50 ± 2.9$^{n.s}$	−9
21	SABP	140 ± 3.0	190 ± 5.9*	+36	145 ± 3.5	135 ± 3.1*	−7	140 ± 3.1	130 ± 2.7*	−7
	DABP	105 ± 2.9	130 ± 5.9*	+24	80 ± 1.9	75 ± 2.1$^{n.s}$	−6	75 ± 2.5	70 ± 2.8^{ns}	−7

Values were expressed as mean ± S.D. Number of experiments = 6 in each parameters.
*Significantly different from respective control value at $P < 0.05$.
n.s. = non-significantly different from respective control value at $P < 0.05$.

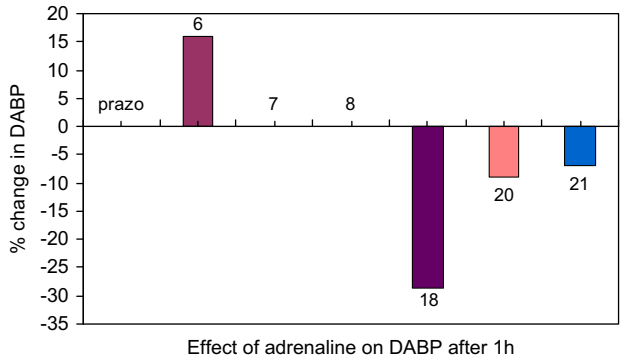


Fig. 4. Effect of i.v. injection of adrenaline (3 μg/Kg) 1h after prazosin and compounds **6**–**8**, **18**, **20**, and **21** at dose of 5 mg/kg on diastolic blood pressure of anaesthetized male albino rats.

*4.1.1.1. 3-(4-Bromophenyl)-1-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**2**).* Yield: 65%; mp.: 99–100 °C; crystallized from petroleum ether(60/80); IR: υ = 3050 (CH, aromatic), 2950 (CH, aliphatic), 1608 (CO), 1567 (C=C) cm^{-1}; ^1H NMR (250 MHz): δ = 0.936 (s,6H, $2CH_3$),1.980 (s, 2H, CH_2), 2.223 (s, 2H, CH_2) 4.260 (s, 2H, CH_2), 4.874 (s, 2H, CH_2), 6.776–6.920 (2d, 4H, ArH), 7.254–7.364 (2d, 4H, ArH) ppm. ^{13}C NMR: δ = 28.35($2CH_3$), 32.79 (C$(CH_3)_2$), 41.08 (CH_2), 45.46(CH_2), 50.06(CH_2),69.98(CH_2),105.36(C^{sp2}), 113.20–156.76 (C^{sp2} + phenyl-C), 194.38 (C=O) ppm. MS: *m/z* (rel. int.) = 445 (M^+, 31), 444 (20.70), 260 (37.90), 226 (55.20), 182 (65.50), 137 (86.20), 83 (100.00). Anal. calcd for $C_{22}H_{22}BrClN_2O$: C, 59.27; H, 4.97; N, 6.28.Found: C, 59.27; H, 4.92; N, 5.95%.

*4.1.1.2. 1-(4-Chlorophenyl)-3-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**3**).* Yield: 70%; mp.: 109–111 °C; crystallized from petroleum ether (60/80); IR: υ = 3050 (CH, aromatic), 2951 (CH, aliphatic), 1608 (CO), 1568 (C=C) cm^{-1}; ^1H NMR (250 MHz): δ = 0.936 (s, 6H, $2CH_3$),1.979 (s, 2H, CH_2), 2.223 (s, 2H, CH_2) 4.262 (s, 2H, CH_2),4.875 (s, 2H, CH_2),6.831–6.865(m,4H, ArH),7.163–7.330(2d,4H, ArH) ppm; ^{13}C NMR : δ = 28.35 ($2CH_3$), 32.79 (C $(CH_3)_2$), 41.08 (CH_2),45.54 (CH_2), 50.06(CH_2), 70.18 (CH_2), 105.35(C^{sp2}), 118.95–156.79 (C^{sp2} + phenyl-C), 194.38 (C=O) ppm. MS: *m/z* (rel. int.) = 403 (M + 2, 11.00), 402 (M + 1, 18.50), 401 (M^+, 13.70), 274(77.00), 226(100.0), 177(15.80), 138(41.60), 83(64.20). Anal. calcd for $C_{22}H_{22}Cl_2N_2O$: C, 65.84; H,5.53; N, 6.98. Found: C, 65.61; H, 5.84; N, 6.94%.

*4.1.1.3. 1-(4-Chlorophenyl)-7,7-dimethyl-3-(2-fluorophenyl)-5-oxo-1,2,3, 4,5,6,7,8-octahydroquinazoline (**4**).* Yield: 78%; mp.: 116–117 °C; crystallized from petroleum ether(60/80); IR: υ = 3046 (CH, aromatic), 2923 (CH, aliphatic), 1613(CO), 1561 (C=C) cm^{-1}; ^1H NMR (250 MHz): δ = 0.961 (s, 6H, $2CH_3$), 1.998(s, 2H, CH_2), 2.250 (s, 2H, CH_2) 4.229 (s, 2H, CH_2) 4.829 (s, 2H, CH_2), 6.736–7.279 (m, 8H, ArH) ppm. ^{13}C NMR: δ = 28.40($2CH_3$), 32.79 (C$(CH_3)_2$), 41.13 (CH_2),46.19 (CH_2),50.13 (CH_2),70.52(CH_2), 105.44(C^{sp2}), 116.15–157.38 (C^{sp2} + phenyl-C), 194.31 (C=O)ppm. MS: *m/z* (rel. int.) = 385 (M + 1, 12.90), 384 (M^+, 25.80), 366 (45.20), 261 (64.50), 226 (100.00), 208 (29.00), 177 (19.40), 151 (64.50), 123 (77.40), 69 (71.00). Anal. calcd for $C_{22}H_{22}ClFN_2O$: C, 68.66; H, 5.76; N, 7.28.Found: C, 68.94; H, 5.68; N, 7.38%.

*4.1.1.4. 1-(4-Chlorophenyl)-7,7-dimethyl-3-(4-fluorophenyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**5**).* Yield: 80%; mp.: 94–95 °C; crystallized from petroleum ether(60/80); IR: υ = 3050 (CH, aromatic), 2950 (CH, aliphatic), 1610 (CO),1568 (C=C)cm^{-1}; ^1H NMR (250 MHz):δ = 0.932 (s, 6H, $2CH_3$), 1.976 (s, 2H, CH_2), 2.219 (s, 2H, CH_2) 4.234 (s, 2H, CH_2) 4.840 (s, 2H, CH_2), 6.838–7.333 (m, 8H, ArH) ppm. ^{13}C NMR: δ = 28.35($2CH_3$), 32.78 (C$(CH_3)_2$), 41.10 (CH_2), 45.90 (CH_2), 50.09(CH_2),71.13 (CH_2), 105.30(C^{sp2}), 115.63–159.58 (C^{sp2} + phenyl-C), 194.35 (C=O)ppm. Anal. calcd for $C_{22}H_{22}ClFN_2O$: C, 68.66; H, 5.76; N, 7.28.Found: C, 68.80; H, 5.50; N, 7.13%.

*4.1.1.5. 1-(4-Chlorophenyl)-7,7-dimethyl-3-(4-hydroxyphenyl)-5-oxo-1,2, 3,4,5,6,7,8-octahydroquinazoline (**6**).* Yield: 85%; mp.: 195–96 °C; crystallized from ethanol; IR: υ = 3259(OH), 3060 (CH, aromatic), 2924 (CH, aliphatic), 1605 (CO), 1556(C=C) cm^{-1}. ^1H NMR (250 MHz): δ = 0.878 (s, 6H, $2CH_3$), 1. 947 (s, 2H, CH_2), 2.264 (s, 2H, CH_2) 4.297 (s, 2H, CH_2) 4.888 (s, 2H, CH_2), 6.754–6.876 (m, 4H, ArH) 7.254–7.337 (m,4H, ArH),8.20 (br s, 1H, OH) ppm. ^{13}C NMR: δ = 28.33 ($2CH_3$), 32.87 (C$(CH_3)_2$), 41.14 (CH_2),45.34(CH_2), 49.58 (CH_2),72.34 (CH_2),104.14(C^{sp2}), 116.14–158.87 (C^{sp2}+phenyl-C),195.08 (C=O) ppm. MS: *m/z* (rel. int.) = 384 (M + 2, 7.4), 383 (M + 1, 8.9), 382 (M^+, 19.40), 260 (54.30), 226 (100.00).Anal. calcd for $C_{22}H_{23}ClN_2O_2$: C, 69.01; H, 6.05; N, 7.32.Found: C, 68.71; H, 5.83; N, 7.80%.

*4.1.1.6. 1-(4-Chlorophenyl)-7,7-dimethyl-3-(4-methylphenyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**7**).* Yield: 75%; mp.: 112 °C; crystallized from petroleum ether(60/80); IR: υ = 3027 (CH, aromatic), 2926 (CH, aliphatic), 1613(CO), 1514(C=C) cm^{-1}; ^1H NMR (250 MHz): δ = 0.943(s, 6H, $2CH_3$), 1.980 (s, 2H, CH_2), 2.225 (s, 2H, CH_2) 2.260 (s, 3H, CH_3) 4.264 (s, 2H, CH_2) 4.872 (s, 2H, CH_2), 6.821–6.903 (m, 4H, ArH) 7.020–7.340 (2d, 4H, ArH) ppm. ^{13}C NMR: δ = 20.56(CH_3), 28.38($2CH_3$), 32.76 (C$(CH_3)_2$), 41.13 (CH_2),45.62 (CH_2), 50.09 (CH_2),70.68 (CH_2),105.61(C^{sp2}), 117.88–156.77 (C^{sp2} + phenyl-C), 194.35 (C=O)ppm. MS : *m/z* (rel. int.) = 384 (M +2, 7.4), 383(M + 1, 8.9), 382 (M^+,19.40), 260(54.30), 226 (100.00). Anal. calcd for $C_{23}H_{25}$ ClN_2O: C, 72.52; H, 6.05; N, 7.32.Found: C, 72.31; H, 6.22; N, 7.74%.

*4.1.1.7. 1-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-3-phenyl-1,2,3,4,5,6,7, 8-octahydroquinazoline (**8**).* Yield: 73%; mp.: 105–106 °C; crystallized from petrolium ether(60/80); IR: υ = 3055 (CH, aromatic), 2931 (CH, aliphatic), 1609(CO) cm^{-1}. ^1H NMR (300 MHz): δ = 0.967 (s, 6H, $2CH_3$), 2.009 (s, 2H, CH_2), 2.249 (s, 2H, CH_2) 4.307 (s, 2H, CH_2) 4.911 (s, 2H, CH_2), 6.902–7.358 (m, 9H, ArH) ppm. MS: *m/z* (rel. int.) = 368 (M + 2, 19.60), 366 (M^+, 43.50), 260 (34.80), 226 (60.90), 163 (15.20), 104 (100.00). Anal. calcd for $C_{22}H_{23}$ ClN_2O: C, 72.02; H, 6.32; N, 7.64.Found: C, 71.99; H, 6.09; N, 7.33%.

*4.1.2. 1-(4-Chlorophenyl)-7,7-dimethyl-3-[4-(ethyoxycarbonyl-methoxy) phenyl]-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**9**)*

A mixture of compound **6** (5.24 mmol), ethyl bromoacetate (6.28 mmol) and K_2CO_3 (10.48 mmol) was stirred in DMF (10 ml) at room temperature for 24 h. The reaction mixture was filtered, poured on ice water (20 ml) and left on the refrigerator overnight. The formed product was filtered and crystallized from ethanol.

Yield: 81.3%; mp.: 80 °C; IR: υ = 3061 (CH, aromatic), 2941 (CH, aliphatic),1751, 1605(CO), 1513(C=C) cm^{-1}; ^1H NMR (200 MHz): δ = 0.911 (s, 6H, $2CH_3$), 1.213–1.285 (t, 3H, *J* = 7 Hz,CH_3 of ester), 1.946 (s, 2H, CH_2), 2.196 (s, 2H, CH_2) 4.191–4.273 (m, 4H, *J* = 7 Hz, OCH_2 +CH_2 of ester) 4.521 (s, 2H, CH_2) 4.788 (s, 2H, CH_2) 6.746–7.30 3(m, 8H, ArH) ppm. MS: *m/z* (rel. int.) = 470.84 (M + 2, 3.70) 469.85 (M + 1, 10.50) 468.81 (M^+, 10.20), 394.86 (2.70), 317.70 (1.50), 273.89 (19.10), 225.96 (36.50), 206.95 (100.00). Anal. calcd for $C_{26}H_{29}ClN_2O_4$: C, 66.59; H, 6.23; N, 5.97.Found: C, 66.26; H, 6.01; N, 5.90%.

*4.1.3. 1-(4-Chlorophenyl)-7,7-dimethyl-3-[4-(hydrazinocarbonylm-ethoxy) phenyl]-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**10**)*

A mixture of ester **9** (2.14 mmol), and hydrazine hydrate (6.42 mmol) in ethanol (10 ml) was refluxed for 2 h. The reaction

mixture was evaporated under reduced pressure and then poured on crushed-ice. The separated product was filtered and crystallized from ethanol.

Yield: 72%; mp.: 90 °C; IR: $\upsilon = 3420, 3340, 3240$(NH, NH_2), 3020 (CH, aromatic), 2930 (CH, aliphatic), 1667,1601 (CO), 1563 (C=C) cm^{-1}; ^1H NMR (200 MHz):$\delta = 0.899$(s, 6H, $2CH_3$), 1.943(s, 2H, CH_2), 2.181 (s, 2H, CH_2),3.095(br s, 2H, NH_2, exch.),4.176 (s, 2H, OCH_2), 4.461 (s, 2H, CH_2) 4.778 (s, 2H, CH_2) 6.717–7.30 4(m,8H, ArH) 7.730 (s, 1H, NH, exch.) ppm. MS: *m/z* (rel. int.) = 456 (M + 2, 4.50) 455 (M + 1, 9.50) 454 (M^+, 12.20), 383(11.3), 317 (20.7), 262 (83.0), 225 (79.5), 107 (100.00). Anal. calcd for $C_{24}H_{27}ClN_4O_3$:C, 63.36; H, 5.98; N, 12.31. Found: C, 63.60; H, 5.98; N, 12.62%.

*4.1.4. General procedure for preparation of compounds **11–21***

A mixture of the hydrazide **10** (1.1 mmol), and aromatic aldehyde (1.1 mmol) was refluxed in ethanol (10 ml) containing 10 drops of glacial acetic acid for 2 h. The reaction mixture was concentrated under reduced pressure and then poured onto ice. The formed precipitate was filtered and crystallized from aqueous ethanol.

*4.1.4.1. 3-[4-(N_2-Bromophenylhydrazino carbonylmethoxy)phenyl]-1-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**11**).* Yield: 65%; mp.: 130 °C; IR: $\upsilon = 3421$(tautomeric OH), 3211(NH),3056 (CH, aromatic), 2954 (CH, aliphatic), 1697 (CO),1560 (C=C) cm^{-1}. ^1H NMR (200 MHz) $\delta = 0.698$ (s, 6H, $2CH_3$), 1.746 (s, 2H, CH_2), 1.985 (s, 2H, CH_2), 3.990 (s, 2H, CH_2) 4.369(s, 1H, CH_2CO), 4.593 (s, 2H, CH_2), 4.852, 9.709 (2 s, 1H, CH_2CO + tautomeric OH, exch.), 6.593–7.687 (m, 12H, ArH), 7.971(s, 1H, CH=N), 9.448 (s, 1H, NH, exch.) ppm. MS: *m/z* (rel. int.) = 622 (M + 1, 4.50), 621 (M^+, 13.70), 512 (7.80), 359 (25.50), 300 (19.60), 262 (25.50), 226 (39.20), 178 (39.20), 120 (60.80), 77(100.00). Anal. calcd for $C_{31}H_{30}BrClN_4O_3$: C, 59.87; H, 4.86; N, 9.01. Found: C, 60.09; H, 4.78; N, 8.99%.

*4.1.4.2. 3-[4-(N_2-4-Bromophenyl-hydrazinocarbonylmethoxy)phenyl]-1-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**12**).* Yield: 70%; mp.: 140–141 °C; ^1H NMR (250 MHz) $\delta = 0.917$ (s, 6H, $2CH_3$), 1.964 (s, 2H, CH_2), 2.210 (s, 2H, CH_2), 4.208 (s, 2H, CH_2), 4.585(s, 1H, CH_2CO), 4.801 (s, 2H, CH_2), 5.067, 10.43(2 s, 1H, CH_2CO + tautomeric OH),6.819–7.818 (m, 12H, ArH), 8.178 (s, 1H, CH=N), 9.790 (s, 1H, NH), ppm. Anal. calcd for $C_{31}H_{30}BrClN_4O_3$: C, 59.87; H, 4.86; N, 9.01. Found: C, 60.09; H, 4.78; N, 8.99%.

*4.1.4.3. 3-[4-(N_2-2-Chlorophenyl-hydrazinocarbonylmethoxy)phenyl]-1-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**13**).* Yield: 58%; mp.: 125 °C; IR: $\upsilon = 3425$ (tautomeric OH), 3210(NH),3057 (CH, aromatic), 2954 (CH, aliphatic), 1699 (CO),1560 (C=C) cm^{-1}; ^1H NMR (250 MHz) $\delta = 0.924$ (s, 6H, $2CH_3$), 1.969 (s, 2H, CH_2), 2.218 (s, 2H, CH_2), 4.226 (s, 2H, CH_2) 4.615(s, 1H, CH_2CO), 4.830 (s, 2H, CH_2), 5.077, 9.74(2 s, 1H, CH_2CO + tautomeric OH), 6.818–8.241 (m, 12H, ArH), 8.590 (s, 1H, CH=N), 9.879 (s, 1H, NH) ppm. MS: *m/z* (rel. int.) = 579 (M +2, 7.5), 578 (M + 1, 9.20), 577 (M^+, 14.70), 515 (15.80), 315 (23.80), 281(26.30), 226 (39.50), 166 (34.20), 121 (86.80), 83 (100.00). Anal. calcd for $C_{31}H_{30}Cl_2N_4O_3$:C, 64.47; H, 5.24; N, 9.70. Found: C, 64.30; H, 5.22; N, 9.56%.

*4.1.4.4. 3-[4-(N_2-4-Chlorophenyl-hydrazinocarbonylmethoxy)phenyl]-1-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**14**).* Yield: 72%; mp.: 161 °C; ^1H NMR (200 MHz) $\delta = 0.862$ (s, 6H, $2CH_3$), 1.907(s, 2H, CH_2), 2.151 (s, 2H, CH_2), 4.149 (s, 2H, CH_2) 4.530 (s, 1H, CH_2CO),4.757(s, 2H, CH_2), 5.088, 10.05 (2 s, 1H, CH_2CO + tautomeric OH exch.), 6.794–7.621 (m, 12H, ArH), 8.151 (s, 1H, CH=N), 9.614 (s, 1H, NH exch.) ppm. Anal. calcd for $C_{31}H_3$ °$Cl_2N_4O_3$: C, 64.47; H, 5.24; N, 9.70. Found: C, 64.30; H, 5.22; N, 9.56%.

*4.1.4.5. 1-(4-Chlorophenyl)-3-[4-(N_2-2,4-dichlorophenyl-hydrazinocarbonylmethoxy)phenyl]-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**15**).* Yield: 70%; mp.: 135 °C; IR: $\upsilon = 3425$ (tautomeric OH), 3210(NH),2950 (CH, aliphatic), 1697 (CO),1557 (C=C) cm^{-1}. ^1H NMR (200 MHz) $\delta = 0.906$ (s, 6H, $2CH_3$), 1.946(s, 2H, CH_2), 2.198 (s, 2H, CH_2), 4.193(s, 2H, CH_2), 4.591(s, 1H, CH_2CO), 4.796 (s, 2H, CH_2), 5.035, 9.807(2 s, 1H, CH_2CO + tautomeric OH, exch.),6.850–8.107(m, 12H, ArH), 8.525 (s, 1H, CH=N),9.499(s,1H, NH, exch.) ppm. Anal. calcd for $C_{31}H_{29}Cl_3N_4O_3$: C, 60.84; H, 4.78; N, 9.16.Found: C, 60.80; H, 4.91; N, 9.36%.

*4.1.4.6. 1-(4-Chlorophenyl)-7,7-dimethyl-3-[4-(N_2-3-methoxyphenylhydrazinocarbonylmethoxy)phenyl]-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**16**).* Yield: 60%; mp.: 95 °C; IR: $\upsilon = 3430$ (tautomeric OH),3200(NH),3020 (CH, aromatic), 2955 (CH, aliphatic), 1692 (CO),1564 (C=C) cm^{-1}; ^1H NMR (250 MHz) $\delta = 0.921$ (s, 6H, $2CH_3$), 1.966(s, 2H, CH_2), 2.213 (s, 2H, CH_2), 3.808(s, 3H, OCH_3), 4.217 (s, 2H, CH_2), 4.594(s, 1H, CH_2CO), 4.822 (s,2H, CH_2), 5.088, 9.941(2 s, 1H, CH_2CO + tautomeric OH), 6.816–7.821 (m, 12H, ArH), 8.173 (s, 1H, CH=N), 9.590 (s, 1H, NH)ppm. Anal. calcd for $C_{32}H_{33}ClN_4O_4$: C, 67.07; H, 5.80; N, 9.78.Found: C, 66.87; H, 5.79; N, 10.01%.

*4.1.4.7. 1-(4-Chlorophenyl)-7,7-dimethyl-3-[4-(N_2-4-methoxyphenylhydrazinocarbonylmethoxy)phenyl]-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**17**).* Yield: 65%; mp.: 110 °C; IR: $\upsilon = 3431$ (tautomeric OH), 3210(NH),3049 (CH, aromatic), 2954 (CH, aliphatic), 1693,1605 (CO),1562(C=C) cm^{-1}; ^1H NMR (250 MHz)$\delta = 0.919$ (s, 6H, $2CH_3$), 1.964 (s, 2H, CH_2), 2.142(s, 2H, CH_2), 3.810 (s, 3H, OCH_3), 4.214 (s,2H, CH_2), 4.580(s, 1H, CH_2CO), 4.819 (s,2H, CH_2),5.072, 9.989 (2 s, 1H, CH_2CO + tautomeric OH), 6.814–7.788 (m, 12H, ArH), 8.113 (s, 1H, CH=N), 9.569 (s, 1H, NH) ppm. MS: *m/z* (rel. int.) = 575 (M +2, 6.70), 574 (M + 1, 11.50), 573 (M^+, 15.00), 421 (77.00), 366 (10.30), 311 (24.10), 261 (22.40), 226 (50.00), 191(34.50), 139 (36.40), 121 (77.60), 77(100.00). Anal. calcd for $C_{32}H_{33}ClN_4O_4$: C, 67.07; H, 5.80; N, 9.78.Found: C, 66.87; H, 5.79; N, 10.00%.

*4.1.4.8. 1-(4-Chlorophenyl)-7,7-dimethyl-3-[4-(N_2-4-methylphenylhydrazinocarbonylmethoxy)phenyl]-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**18**).* Yield: 72%; mp.: 106 °C; IR: $\upsilon = 3431$ (tautomeric OH), 3216(NH),3048 (CH, aromatic), 2954 (CH, aliphatic), 1695 (CO),1562(C=C) cm^{-1} ;^1H NMR (250 MHz) $\delta = 0.932$ (s, 6H, $2CH_3$), 1.978 (s, 2H, CH_2), 2.223 (s, 2H, CH_2), 2.357(s, 3H, CH_3), 4.229 (s, 2H, CH_2) 4.597(s, 1H, CH_2CO), 4.831(s,2H, CH_2),5.093,9.915(2 s, 1H, CH_2CO + tautomeric OH),6.823–7.807 (m, 12H, ArH), 8.152 (s, 1H, CH=N), 9.569 (s, 1H, NH) ppm. Anal. calcd for $C_{32}H_{33}ClN_4O_3$: C, 68.99; H, 5.97; N, 10.06.Found: C, 68.89; H, 6.24; N, 9.77%.

*4.1.4.9. 1-(4-chlorophenyl)-7,7-dimethyl-3-[4-(N_2-3-nitrophenylhydrazinocarbonylmethoxy)phenyl]-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**19**).* Yield: 65%; mp.: 117 °C; IR: $\upsilon = 3220$(NH),3050 (CH, aromatic), 2955 (CH, aliphatic), 1696 (CO), 1560 (C=C),1532, 1351 (NO_2) cm^{-1}. ^1H NMR (200 MHz) $\delta = 0.847$ (s, 6H, $2CH_3$), 1.897(s, 2H, CH_2), 2.137 (s, 2H, CH_2), 4.142 (s, 2H, CH_2), 4.535(s, 1H, CH_2CO), 4.747 (s, 2H, CH_2), 5.030, 9.966 (2 s, 1H, CH_2CO + tautomeric OH, exch.), 6.794–8.405 (m, 13H, ArH + CH=N), 9.770(s, 1H, NH, exch.) ppm. Anal. calcd for $C_{31}H_{30}ClN_5O_5$: C, 63.32; H, 5.14; N, 11.91.Found: C, 63.41; H, 5.29; N, 12.11%.

*4.1.4.10. 1-(4-Chlorophenyl)-7,7-dimethyl-3-[4-(N_2-4-nitrophenylhydrazinocarbonylmethoxy)phenyl]-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**20**).* Yield: 75%; mp.: 194–195 °C; IR: $\upsilon = 3238$ (NH),3080 (CH, aromatic), 2953 (CH, aliphatic), 1709 (CO), 1605 (C=N) 1580 (C=C) and 1511, 1342 (NO_2) cm^{-1}. ^1H NMR (200 MHz) $\delta = 0.955$ (s, 6H, $2CH_3$), 2.002 (s, 2H, CH_2), 2.244 (s, 2H, CH_2), 4.247 (s, 2H, CH_2), 4.642, 5.123(2 s, 2H, CH_2CO), 4.850 (s, 2H, CH_2),

6.916–8.359 (m, 12H, ArH), 8.449 (s, 1H, CH=N), 9.78 (s, 1H, NH, exch.) ppm. Anal. calcd for $C_{31}H_{30}ClN_5O_5$: C, 63.32; H, 5.14; N, 11.91.Found: C, 63.41; H, 5.29; N, 12.11%.

*4.1.4.11. 1-(4-Chloropheyl)-7,7-dimethyl-5-oxo-3-[4-(N_2-phenylhydrazinocarbonylmethoxy)phenyl]-1,2,3,4,5,6,7,8-octahydroquinazoline (**21**).* Yield: 60%; mp.: 100 °C; ^{1}H NMR (200 MHz) $\delta = 0.796$ (s, 6H, $2CH_3$), 1.841 (s, 2H, CH_2), 2.093 (s, 2H, CH_2), 4.088 (s, 2H, CH_2) 4.469 (s, 1H, CH_2CO), 4.691 (s, 2H, CH_2), 4.965, 9.736 (2 s, 1H, CH_2CO + tautomeric OH, exch.), 6.755–8.085 (m, 13H, ArH), 8.210 (s, 1H, CH=N), 9.416 (s, 1H, NH, exch.) ppm. MS: *m/z* (rel. int.) = 545 (M + 2, 7.20), 544 (M + 1, 15.60), 543 (M^+, 12.70), 281 (17.30), 196 (16.40), 161 (24.50), 120 (40.90), 65 (100.00). Anal. calcd for $C_{31}H_{31}ClN_4O_3$: C, 68.56; H, 5.75; N, 10.32.Found: C, 68.36; H, 5.81; N, 10.00%.

4.2. Hypotensive activity

Rats were maintained on a 12 h-light/dark cycle under regulated temperature (25 ± 2 °C) and humidity (50 ± 10%) as well as fed with standard diet and water *ad libitum*. They were allowed to acclimate seven days before use. This protocol was approved by the Animal Care and Use Committee of the Pharmacology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

4.2.1. Determination of arterial blood pressure and heart rate

Fifty four male rats weighing (180–220 g) were classified into 9 groups; each of 6 rats. All the test compounds were dissolved in tween 80 and diluted with distilled water to the final volume (1:3). Tween 80 was used as a solvent for the test compounds because it did not show any effect on the activity (solvent-treated group). These groups were used to study the effect of solvent, prazosin (Sigma Chemicals Co. USA), and the test compounds on the arterial blood pressure and heart rate, which were recorded 5, 15, 30 and 60 min after i.p. injection of 5 mg/Kg of each compounds (Table 1).

4.2.2. Determination of α-blocking activity

Another forty eight rats were classified into 8 groups to investigate the blocking effect of the aforementioned compounds. In each experiment, the effect of adrenaline (epinephrine, BDH Chemicals Ltd, Poole, England), at a dose of 3 μg/Kg intravenously [17], on the arterial blood pressure was recorded alone 30 min before i.p. injection of the test compound and then its effect was determined again after 30 min as well as after 1h from injection of the test compound. Compounds with the α-blocking activity will convert the pressor effect of adrenaline to a depressor response "epinephrine reversal" [18].

4.2.3. Method of recording the arterial blood pressure and ECG

Animals were anaesthetized with ethyl carbamate (urethane) at a dose of 1.75–2.0 g/Kg i.p. as freshly prepared aqueous solution [17]. The blood pressure was determined employing the method of Burden et al. [15] through introduction of polyethylene arterial cannula with 3-way valve (filled with heparinized saline solution 16 I.U./ml to inhibit blood clotting) [16] in the common carotid artery. The cannula was connected to PT 400 blood pressure transducer, which was connected to FC137 strain gauge coupler which was fixed to one of the 4-channel oscillograph MD_4 (Bioscience, U.K.). The blood pressure was recorded on chart paper. ECG was recorded according the method of Burden et al. [15]. The ECG limb cable was connected to FC123 coupler which switched on lead II and connected to another channel of the 4-channel oscillograph MD_4.

4.2.4. Statistical analysis

The values of the systolic and diastolic arterial blood pressure as well as the heart rate were presented as mean ± S.E. and subjected to either one-way ANOVA test or unpaired "t" test for statistical analysis [19].

Acknowledgements

The authors would like to express their thanks to Dr. Rasha Husseiny Mohamed in the Central Biochemistry Laboratory at Faculty of Medicine, Zagazig University and Dr. Gamal A. El-Sherbiny in the Pharmacology and Toxicology Department, Faculty of Pharmacy, Beni Suief University, Egypt for their efforts in performing hypotensive activity and statistical analysis.

References

[1] J.M. Geleijnse, Vasc. Health Risk Manage. 4 (5) (2008) 963–970.
[2] S. MacMahon, R. Petro, J. Cutler, R. Collins, P. Sorlie, J. Neaton, R. Abbort, J. Godwin, A. Dyer, J. Stamler, Lancet 335 (1990) 765–774.
[3] P.M. Kearney, M. Whelton, K. Reynolds, P. Muntner, P.K. Whelton, J. He, Lancet 365 (2005) 217–223.
[4] A. Leonardi, G. Motta, C. Boi, R. Testa, E. Poggesi, P.G. De Benedetti, M.C. Menziani, J. Med. Chem. 42 (1999) 427–437.
[5] P. Karczewski, H. Haase, P. Hempel, M. Bimmler, Mol. Cell. Biochem. 333 (2010) 233–242.
[6] N.A. Colabufo, V. Pagliarulo, F. Berardi, M. Contino, R. Perrone, M. Niso, G. Albo, G. de Rienzo, A. Pagliarulo, Eur. J. Pharmacol. 577 (2007) 150–155.
[7] K.S. Jain, J.B. Bariwal, M.K. Kathiravan, M.S. Phoujdar, R.S. Sahne, B.S. Chauhan, A.K. Shah, M.R. Yadav, Bioorg. Med. Chem. 16 (2008) 4759–4800.
[8] M.L. Bolognesi, G. Marucci, P. Angeli, M. Buccioni, A. Minarini, M. Rosini, V. Tumiatti, C. Melchiorre, J. Med. Chem. 44 (2001) 362–371.
[9] T. Sekiya, H. Hiranuma, S. Hata, S. Mizogami, M. Hanazuka, S. Yamada, J. Med. Chem. 26 (1983) 411–416.
[10] V. Alagarsamy, U.S. Pathak, Bioorg. Med. Chem. 15 (2007) 3457–3462.
[11] G.P. McCafferty, D.P. Naselsky, J.P. Hieble, Gen. Pharmacol. 33 (1999) 99–105.
[12] Z. Chen, G. Hu, D. Li, J. Chen, Y. Li, H. Zhou, Y. Xie, Bioorg. Med. Chem. 17 (2009) 2351–2359.
[13] I.O. Edafiogho, C.N. Hinko, H. Chang, J.A. Moore, D. Mulzac, J.M. Nicholson, K.R. Scott, J. Med. Chem. 35 (1992) 2798–2805.
[14] M.E. El-Sadek, M. Aboukull, O.I. El-Sabbagh, H.M. Shallal, Monatsh. Chem. 138 (2007) 219–225.
[15] D.T. Burden, L.C. Blaber, I.L. Natoff, Pharmacol. Ther. 5 (1979) 99–102.
[16] R.R. Tuttle, J. Mills, Circ. Res. 36 (1975) 185–196.
[17] M.N. Ghosh, Fundamentals of Experimental Pharmacology, first ed. Scientific Book Agency, Calcutta, India, 1971, p. 116.
[18] B.B. Hoffman, B.G. Katzung, seventh ed. Appleton and Lange, Connecticut., 1998 p. 136.
[19] P. Armitage, Blackwell Scientific Publication, London, U.K., 1974 pp. 116–120 and 269–284.