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Original article

Molecular modeling study and synthesis of quinazolinone-arylpiperazine derivatives as α_1-adrenoreceptor antagonists

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ABSTRACT

Three series of new 2-[(4-substituted piperazin-1-yl) methyl]quinazolin-4(3*H*)-ones **4a**–**c**, Ethyl 6,7-dimethoxy-4-oxo-3-[2-(4-substituted piperazin-1-yl)acetamido/propanamido]-3,4-dihydroquinazoline-2-carboxylates **9a**–**f** and their 2-methyl analogues **13a**–**l** were designed and synthesized as promising α_1-adrenoceptor antagonists. The final compounds were evaluated for their *in vivo* hypotensive activity in normotensive cats. The most potent hypotensive quinazolinone derivatives **4b**, **9e**, **13i**, **13j** were further tested on isolated thoracic aortic rings of male Wister rats. All the tested compounds displayed α_1-blocking activity with IC_{50} ranging from 0.2 to 0.4 mM less than prazosin. Furthermore, in the present work, molecular modeling study using Accelrys Discovery Studio 2.1 software was performed by mapping the synthesized compounds to the α_1-adrenoceptor antagonist hypothesis in order to predict their mechanism of action. Compound **13j** which has the best-fitting score displayed the highest *in vivo* and *in vitro* activity among the tested compounds.

1. Introduction

Hypertension is one of the most serious health problems in the modern world. It is estimated that there are approximately 1 billion people worldwide that suffer from high blood pressure [1]. Since hypertension is a leading risk factor for cardiovascular disease, such as congestive heart failure, stroke and myocardial infarction, it is major goal in medicinal chemistry to search for new antihypertensive agents.

The α_1-adrenergic receptors (α_1-ARs) – a family of G-protein coupled seven-transmembrane helix receptors – are mainly involved in the cardiovascular and central nervous system [2]. In the last two decades, the search for new selective α_1-ARs antagonists has been intensified, mainly due to their importance in treatment of hypertension, asthma, lower urinary tract symptoms (LUTS) and benign prostatic hypertrophy (BPH) [3–6].

Research efforts in the area of α_1-ARs antagonists have led to the discovery of some clinically useful antihypertensive drugs such as prazosin **I** and related quinazoline derivatives terazosin **II** and doxazosin **III** (Fig. 1) [7,8]. These quinazoline derivatives are considered as the most effective and clinically useful class of selective α_1-ARs antagonists since they have high index of α_1/α_2 adrenoreceptor affinity [6].

In addition, 3-{2-[4-(2-methoxyphenyl)piperazin-l-yl]ethyl}quinazoline-2,4-diones **IV** and **V** were claimed to be potent α_1-antagonists [9,10]. Furthermore, a series of quinazolinedione bioisosteres e.g. thieno[2,3-*d*]pyrimidine-2,4-dione linked to 4-arylpiperazine via alkyl spacer **VI** was reported for their antihypertensive activity [11]. On the other hand, certain anthranilamides linked to 4-arylpiperazine via propionyl spacer **VII** were reported to exhibit α_1-AR antagonist activity [12]. Based on the previous findings, we have recently reported the synthesis of some anthranilates and quinazolinones linked to 4-substituted piperazines via different spacers, which were characterized for their hypotensive activity. Where, compounds **VIII** and **IX** exhibited higher activity than prazosin [13] (Fig. 2).

In the present work, **IV**, **VIII** and **IX** were chosen as lead compounds for further optimization, aiming to enhance their activity. A logical approach was adopted by replacing the ester function in **VIII** with the more enzymatically stable amide function (Fig. 3). But, instead of obtaining the expected amide analogues **3**, the quinazolinone derivatives **4a**–**c** were isolated as result of intramolecular cyclization of the produced anthranilamides (Scheme 1). The unexpected quinazolinone derivatives **4a**–**c** have structural similarities to the lead compound **IX**.

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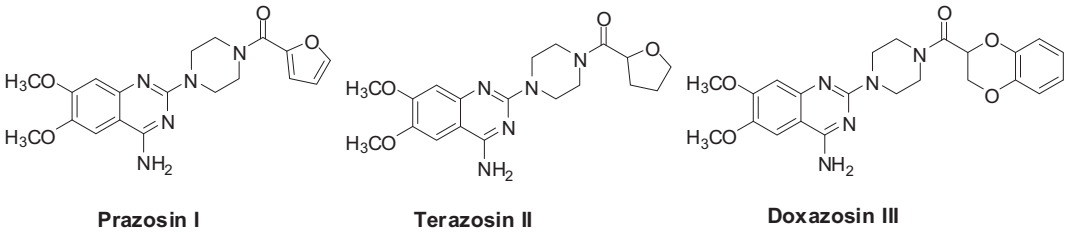


Fig. 1. Structures of clinically useful quinazolines of selective α_1-AR antagonist activity.

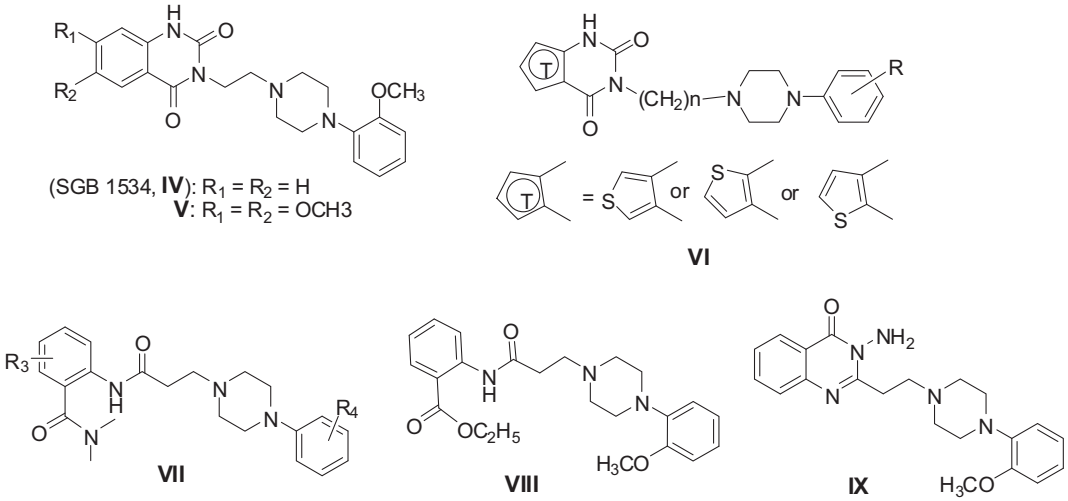


Fig. 2. Structures of some potent selective α_1-AR antagonists and lead compounds.

It has been previously reported that arylpiperazine moiety linked to different heterocyclic systems through polymethylene spacer is a key element for α_1-AR affinity [2]. Moreover, Betti et al. reported [14] the gradual increase in affinity to α_1-AR by increasing the length of the polymethene spacer between the arylpiperazine moiety and the pyridazinone from 2 up to 7 carbons. Therefore, the second approach based on the previous experimental findings was to subject compound **IV** to the following structural modification strategies (Fig. 3):

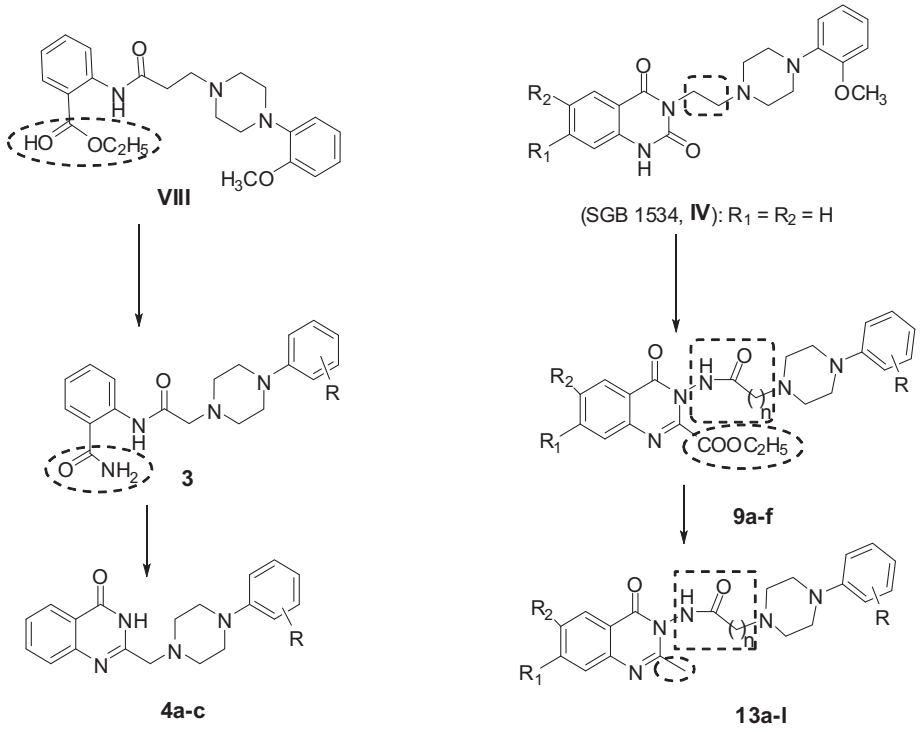
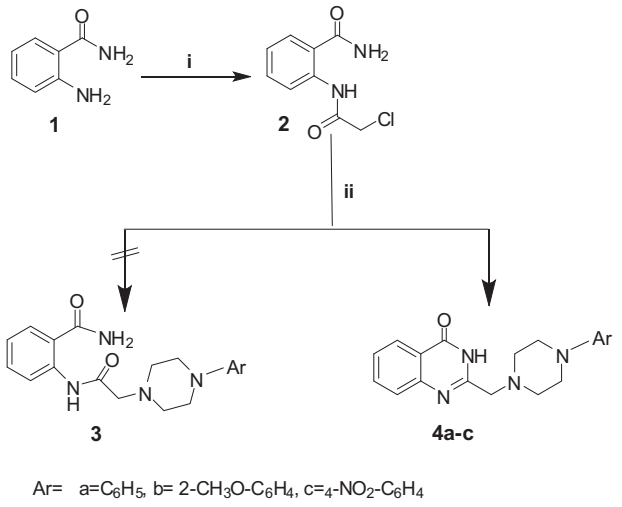


Fig. 3. Strategies for structural modifications of leads **IV** and **VIII**.



Scheme 1. Synthesis of compounds **4a**–**c**. Reagents and condition: (i) CH_3COCl, dry toluene, Et_3N, reflux. (ii) arylpiperazine, K_2CO_3, KI, CH_3CN, reflux.

1. Extension strategy by replacing the ethylene linker with acetamido or propionamido linker.
2. Substituents variation strategy through replacement of oxo group at position 2 on quinazolinedione ring in compound **IV** with an ethyl ester in analogy to **VIII** or methyl group aiming to increase the lipophilicity of the molecule.

Therefore, two different series of quinazolinone derivatives **9a**–**f** and **13a**–**l** were synthesized (Schemes 2 and 3).

Moreover, the relationship between chemical features of the synthesized compounds and their α_1-binding affinity data have been derived on the basis of a previously reported, five features pharmacophore model for α_1-AR antagonists which consist of positive ionizable, three hydrophobic and a hydrogen bond acceptor pharmacophore features [15].

2. Chemistry

2-(2-Chloroacetamido)benzamide **2** was prepared through N-acylation of anthranilamide **1** with chloroacetyl chloride according to the reported methods [16].

The reaction of 2-(2-chloroacetamido)benzamide **2** with various substituted arylpiperazines in acetonitrile in the presence of anhydrous K_2CO_3 and catalytic amount of potassium iodide produced 2-[(4-substituted piperazin-1-yl)methyl]quinazolin-4(3*H*)-ones **4a**–**c** instead of the expected compounds *N*-[(4-substituted piperazin-1-yl)acetyl] anthranilamides **3** (Scheme 1). The NMR spectra of **4a**–**c** showed an exchangeable protons of 3-NH of quinazolinone at 10.10–12.00 ppm. Moreover, the mass spectrum of **4a** showed a molecular ion peak at 320.2 instead of 338.4 for the corresponding anthranilamide derivative **3a**. The Compounds **4a** [17,18] and **4b** [17] were previously reported as phosphodiesterase V (PDE5) inhibitors. These compounds were synthesized adopting another pathway, by the reaction of 2-(chloromethyl)-quinazolin-4(3H)-one with substituted piperazines in DMF in the presence of triethylamine [17].

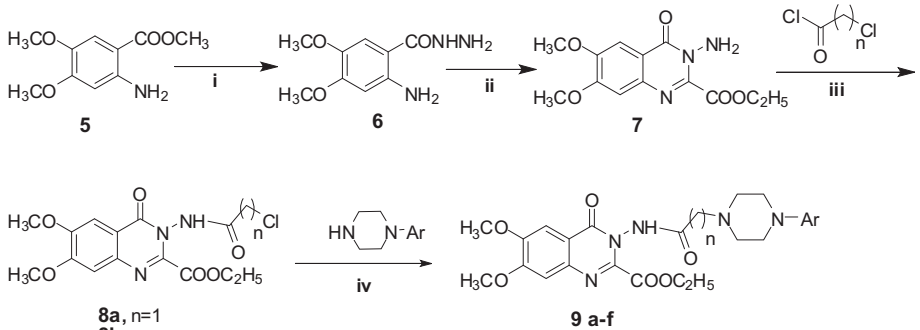
The targeted quinazolinone-2-carboxylates **9a**–**f** were synthesized as shown in Scheme 2. 2-Amino-4,5-dimethoxybenzohydrazide **6** was obtained by the hydrazinolysis of the corresponding methyl anthranilate **5** with hydrazine hydrate [19]. Adopting the method of George et al. [20], the cyclized quinazolinone-2-carboxylate derivative **7** was obtained through heating the hydrazide **6** with excess diethyl oxalate at 180 °C. The N-acylation of **7** with α- or β-chloropropionyl chloride yielded the haloalkanamide quinazolinone derivatives **8a** and **8b**, respectively, which alkylated various arylpiperazines producing the final compounds **9a**–**f**.

Scheme 3 outlines the synthetic pathway for 2-methylquinazolinone analogues **13a**–**l**. Anthranilic acids **10a**,**b** were reacted with acetic anhydride and hydrazine hydrate as reported [21–23]. Acylation of 3-amino group on quinazolinones **11a**,**b** with α- or β-chloropropionyl chloride afforded the corresponding haloalkanamide derivatives **12a**–**d** [22]. Finally, compounds **13a**–**l**. were obtained through the alkylation of certain substituted piperazines with the corresponding haloalkanamide derivatives **12a**–**d**.

3. Results and discussion

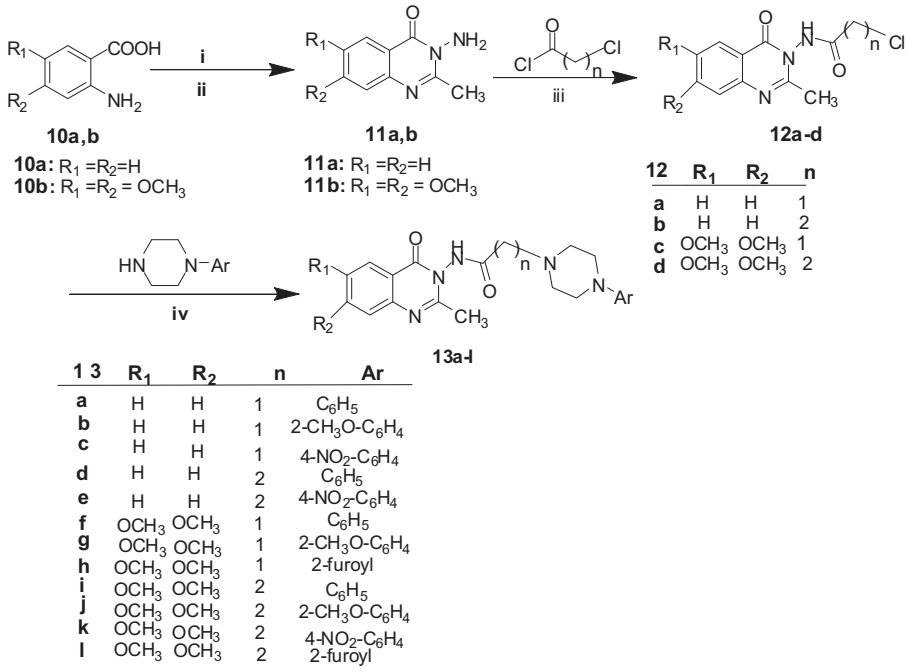
3.1. Molecular modeling

Pharmacophore modeling method has been widely used as a key tool of computer aided drug design in the lead discovery and optimization [24,25]. Pharmacophore can also be used to rationalize the relationship between the structural features and pharmacological activity [2,26]. In this study, the generated α_1-AR antagonist hypothesis was carried out adopting reported method



9	n	Ar
a	1	C_6H_5
b	1	2-CH_3O-C_6H_4
c	1	4-NO_2-C_6H_4
d	2	C_6H_5
e	2	2-CH_3O-C_6H_4
f	2	4-NO_2-C_6H_4

Scheme 2. Synthesis of compounds **9a**–**f**. Reagents and condition: (i) hydrazine hydrate, reflux. (ii) diethyl oxalate, reflux. (iii) dry toluene, Et_3N, reflux. (iv) K_2CO_3, KI, CH_3CN, reflux.



Scheme 3. Synthesis of compounds **13a**–**l**. Reagents and condition: (i) acetic anhydride, (ii) hydrazine hydrate, reflux. (iii) dry toluene, Et_3N, reflux. (iv) K_2CO_3, KI, CH_3CN.

[15] by using Accelrys Discovery Studio 2.1 software and *HipHop* modules. The ideal hypothesis encompassed five features namely; positive ionizable (PI, red sphere), hydrogen bonding acceptor (HBA, green sphere) and three hydrophobic features (HY1, HY2 and HY3, blue sphere). Molecular modeling simulation studies were then conducted by measuring the fit values, separately, between the conformational models of prazosin (reference), **4a**–**c**, **9a**–**f** and **13a**–**l**, and the α_1-AR antagonist hypothesis. The results of the best-fitting value, as well as the relative energy of the best-fitted conformer with this hypothesis are given in Table 1. The fitting values may be a guide for estimating relative affinities of these compounds to their receptor while the relative energy is a guide of stability of the compounds. Also, the mapping of α_1-AR antagonist hypothesis with prazosin **I** and the most active compound **13j** illustrated that all chemical functionalities of the model are all matched by the chemical groups of both (Figs. 4 and 5).

Fig. 5 shows the mapping of compound **13j**, where the arylpiperazinyl moiety mapped the region where a cluster of feature known to be crucial for interaction with the receptor. While the *o*-methoxyphenyl occupied both HY1 and HY2, the piperazinyl N-1 atom was located inside the positive ionizable feature PI. The carbonyl oxygen of quinazolinone system overlapped HBA, while its phenyl ring mapped to YH3.

Evaluation of how well the prepared compounds were able to fit the α_1-AR pharmacophore hypothesis and the correlation of the fitting values with the hypotensive activity highlighted that:

1. Compounds **4b** and **13j** which showed high fit values with low relative energies exhibited the most potent hypotensive activity.
2. The substitution pattern on the arylpiperazinyl moiety is a crucial element that accounts for the relationship between structure properties and α_1-binding affinity. The *o*-methoxy substituent on the phenyl ring of the arylpiperazinyl moiety was highly favorable to α_1-AR affinity, as the *o*-methoxyphenyl perfectly matched the HY1–HY2 system in the model. On the other hand, the unsubstituted phenyl was unable to map one of the HY1–HY2 features with consequent decrease in activity [c.f. **13i** and **13j**]. On the contrary, the nitrogen in *p*-nitrophenyl and the carbonyl of furoyl mapped the HBA. This arrangement derived by reversing the orientation of the ligand might not be favored by ligand–receptor interaction. This accounts for the fact that, derivatives characterized by different substitution on the piperazine ring like **13k** and **13l** were less active than the corresponding *o*-methoxyphenyl analogue **13j**.
3. The length of the amido spacer between the arylpiperazine and the quinazolinone moiety is a key parameter affecting the fitting efficiency of each compound to the pharmacophore. Elongating the alkylamido chain from acetamido to propanamido led to several compounds characterized by higher

Table 1
Fitting and relative energy values of the best-fitted conformers of compounds **4a**–**c**, **9a**–**f** and **13a**–**l**. by mapping onto the pharmacophore model of the α_1-AR antagonist hypothesis.

Compound	Fitting values	Relative energy (kcal mol^{-1})
Prazosin	3.91	4.01
4a	2.93	12.79
4b	3.60	4.57
4c	No mapping	–
9a	3.32	13.54
9b	4.86	16.32
9c	3.28	15.57
9d	3.51	14.37
9e	4.90	4.71
9f	3.36	13.82
13a	3.77	13.95
13b	4.75	14.40
13c	2.63	35.97
13d	3.99	9.78
13e	2.38	31.01
13f	3.56	12.86
13g	4.80	18.69
13h	4.44	17.31
13i	3.99	8.21
13j	4.60	4.48
13k	3.24	13.28
13l	4.80	9.69

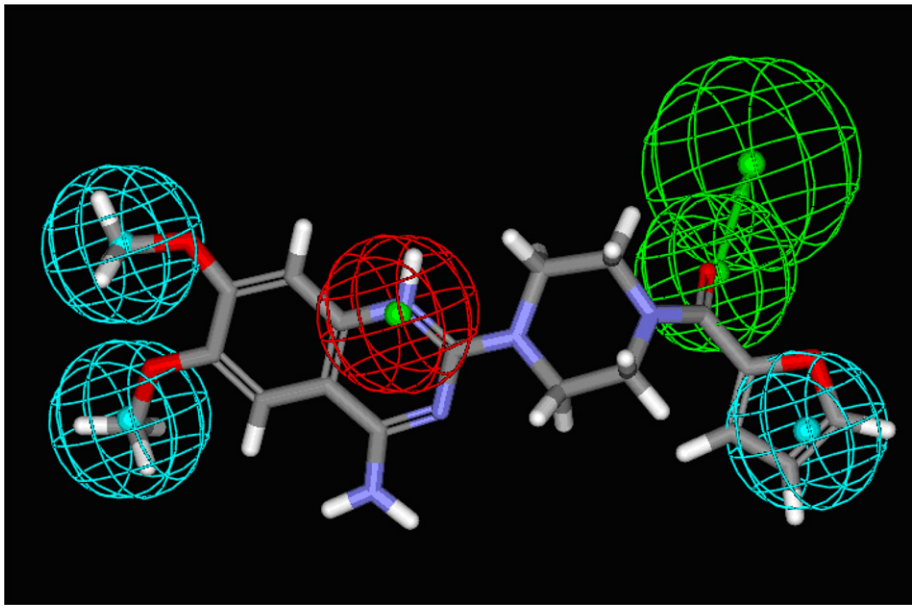


Fig. 4. Mapping of α_1-AR antagonist hypothesis and prazosin. The two o-methoxy groups of quinazoline moiety occupied both HY1 and HY2 (blue sphere) and the quinazoline N-1 atom is located inside the positive ionizable feature PI (red sphere). The oxygen of the carbonyl group attached to piperazine overlapped HBA (green sphere), while the furan ring matched YH3 (blue sphere). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

conformational flexibility, which might be responsible for enhanced fit to the α_1-AR pharmacophore model and consequently more potent hypotensive activity.

4. The presence of the metabolically stable 2-methyl on the 6,7-dimethoxy-quinazolinone greatly improved the pharmacological activity. In fact, while changing the 2-ethyl carboxylate in **9e** with 2-methyl in **13j** had no observable effect on the fitting values to the pharmacophore model; it greatly improved the hypotensive activity, probably due to better pharmacokinetic characters.

3.2. Pharmacology

3.2.1. In vivo hypotensive activity

Nine selected compounds **4b**, **9b**, **9e**, **13b**, **13g**, **13i**, **13j**, **13k** and **13l** were evaluated for their *in vivo* hypotensive activity on blood pressure of normotensive cats at dose of 500 μg/kg [27]. The tested compounds were chosen in a pattern to allow verifying the effect of three structural variations on the hypotensive activity of the designed compounds: (1) the length of the amide spacer, (2) the effect of substitution on the piperazine moiety, (3) the effect of substitution at the 2-position of the quinazolinone ring. Furthermore, the molecular modeling simulation study predicted that, these compounds would have probable affinity for the α_1-AR antagonist hypothesis.

The results of hypotensive evaluation indicated that most of the tested compounds have the ability to reduce the blood pressure with different degrees (Table 2).

Compound **13j** showed 1.5 times more potent hypotensive activity than prazosin, while compound **4b** was comparable to prazosin in hypotensive activity. Moreover, compounds **9e**, **13i** and **13l** elicited moderate activity. Compound **13b** had no hypotensive effect.

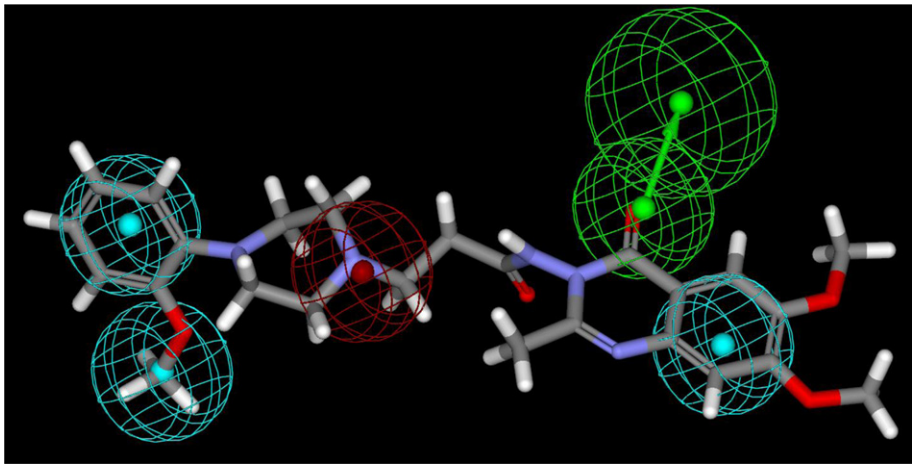


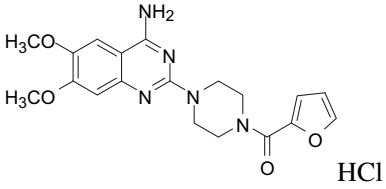
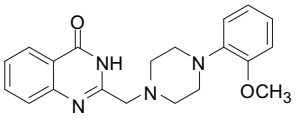
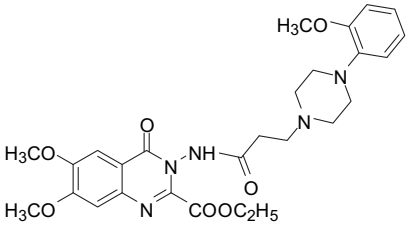
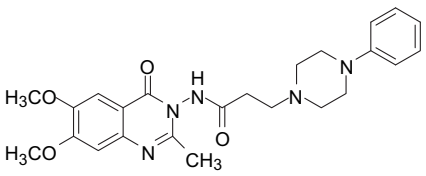
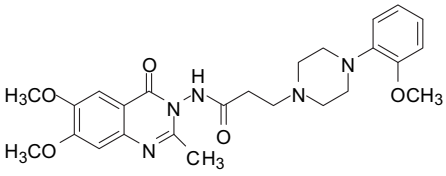
Fig. 5. Mapping of α_1-AR antagonist hypothesis and the most active compound **13j**. *o*-Methoxyphenyl attached to piperazine moiety occupied both HY1 and HY2 (blue sphere) and the piperazinyl N-1 atom is located inside the positive ionizable feature PI (red sphere). The carbonyl oxygen of quinazolinone system overlapped HBA (green sphere), while its phenyl ring matched YH3 (blue sphere). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 2
Effects of test compounds **4b**, **9b**,**e**, **13b**, **g**, **i**–**l** on systolic (SBP) and diastolic blood pressure (DBP) of anaesthetized normotensive cats at dose 500 μg/kg.

Compound	SBP (mmHg) mean ± SD	Mean change %	DBP (mmHg) mean ± SD	Mean change %
Control	120.00 ± 2.45	_	110.00 ± 2.37	_
Prazosin	82.20 ± 1.72[a]	29.00	78.10 ± 2.58[a]	29.00
4b	91.58 ± 1.50[a]	23.68	86.17 ± 1.72[a]	21.66
9b	117.33 ± 2.73	2.22	105.58 ± 2.25[a]	4.02
9e	105.17 ± 3.55[a]	12.36	94.75 ± 2.23[a]	13.86
13b	120.00 ± 2.83	0.00	110.00 ± 4.86	0.00
13g	116.25 ± 3.68	3.13	107.00 ± 3.79	2.78
13i	101.33 ± 1.37[a]	15.56	94.67 ± 2.07[a]	13.94
13j	69.33 ± 1.97[a]	42.22	66.00 ± 1.41[a]	40.00
13k	114.00 ± 2.10[a]	5.00	102.50 ± 3.21[a]	6.82
13l	108.75 ± 1.54[a]	9.38	97.78 ± 2.45[a]	11.11

[a] Significant different from control using one way analysis of variance (ANOVA) at $P < 0.05$.

Table 3
Concentration of compounds **4b**, **9e**, **13i**, **13j** necessary to reduce the maximal norepinephrine hydrochloride induced contracture by 50% (IC_{50}) in thoracic rat aortic rings.

Compound	Structure	Potency (IC_{50}), mM
Prazosin HCl		0.487
4b		0.303
9e		0.400
13i		0.303
13j		0.201

3.2.2. Structure activity relationship SAR

The data in Table 2 indicates that compound **9b** produced low hypotensive effect compared to prazosin. Replacement of the acetamido spacer in **9b** by propanamido linker in **9e**, led to 3 and 6 folds increase in the potency of reducing diastolic and systolic blood pressure. Changing the 2-ethyl carboxylate on quinazolinone ring in **9e** with the more metabolically stable 2-methyl in **13j** produced the most potent hypotensive analogue. As expected, replacing the propanamido in **13j** by acetamido in **13g** resulted in sever drop in potency. Replacing the propanamido in **13j** with acetamido function in addition to removal 6,7-dimethoxy groups of the quinazolinone ring **13b** abolished the activity.

With respect to substitution on the piperazine moiety, substituting *o*-methoxyphenyl in **13j** with phenyl **13i**, *p*-nitrophenyl **13k** or furoyl moiety **13l** decreased the activity.

3.2.3. In vitro vasodilatation activity (functional bioassay)

Based on the hypotensive activity, the most potent compounds **4b**, **9e**, **13i** and **13j** were subjected to functional bioassay to evaluate their α_1-adrenoreceptors antagonistic activity, according the standard procedure [28,29]. The antagonistic activity was assessed by inhibition of (±) norepinephrine-induced contraction on isolated rat aorta tissues which predominantly express the α_{1D}-AR subtype [6,30]. Stimulation of α_{1D}-AR subtype is known to cause blood vessels contraction and control blood pressure. From the observed data (Table 3, Fig. 6) it can has been noticed that all the tested compounds had lower IC_{50} and higher potency relative to prazosin. Furthermore, the results of the antagonistic potency were in agreement with the *in vivo* hypotensive activity, where the most potent hypotensive agent **13j** revealed the lowest IC_{50} (0.201 mM). On the other hand, the less active quinazolinone-2-carboxylate analogue **9e** showed the highest IC_{50} (0.400 mM). In summary, the consistency between the *in vivo* hypotensive results and the functional bioassay data proved that the obtained hypotensive effect is mediated through the blockage of α_1-adrenoreceptors.

4. Conclusion

Some compounds belonging to a class of arylpiperazine-quinazolinone-2-carboxylate and their 2-methyl analogues have been prepared through the variation of alkylamido linker between quinazolinone and the arylpiperazine in addition to modification of the substitution on the phenylpiperazine moiety. Fitting of the proposed compounds to previously built pharmacophore model [15] was done to prioritize the synthesized compounds and to correlate the chemical structure of the studied compounds to their pharmacological data. Compounds **4b**, **9b**, **9e**, **13b**, **13g**, **13i**, **13j**, **13k** and **13l** were evaluated for their *in vivo* hypotensive activity on blood pressure of normotensive cats. Moreover, the most potent hypotensive compounds **4b**, **9e**, **13i** and **13j** were tested for their α_1-adrenoceptors antagonistic activity on isolated thoracic rat aorta. The four compounds revealed superior activity to prazosin as reference standard.

Some structural features have been demonstrated to markedly affect the affinity of α_1-AR antagonists and hypotensive activity. In particular, the addition of *o*-methoxyphenyl on piperazine ring, propanamido spacer and methyl at 2-position of quinazolinone led to the best α_1-affinity profile (high fitting value = 4.60) and the highest hypotensive activity (40.00 and 42.22% reduction of diastolic and systolic blood pressure) as shown by compound **13j**. In addition, the results of the functional bioassay demonstrated that **13j** was the most active α_1-adrenoceptors antagonist among the tested arylpiperazine-quinazolinone derivatives ($IC_{50} = 0.201$ mM).

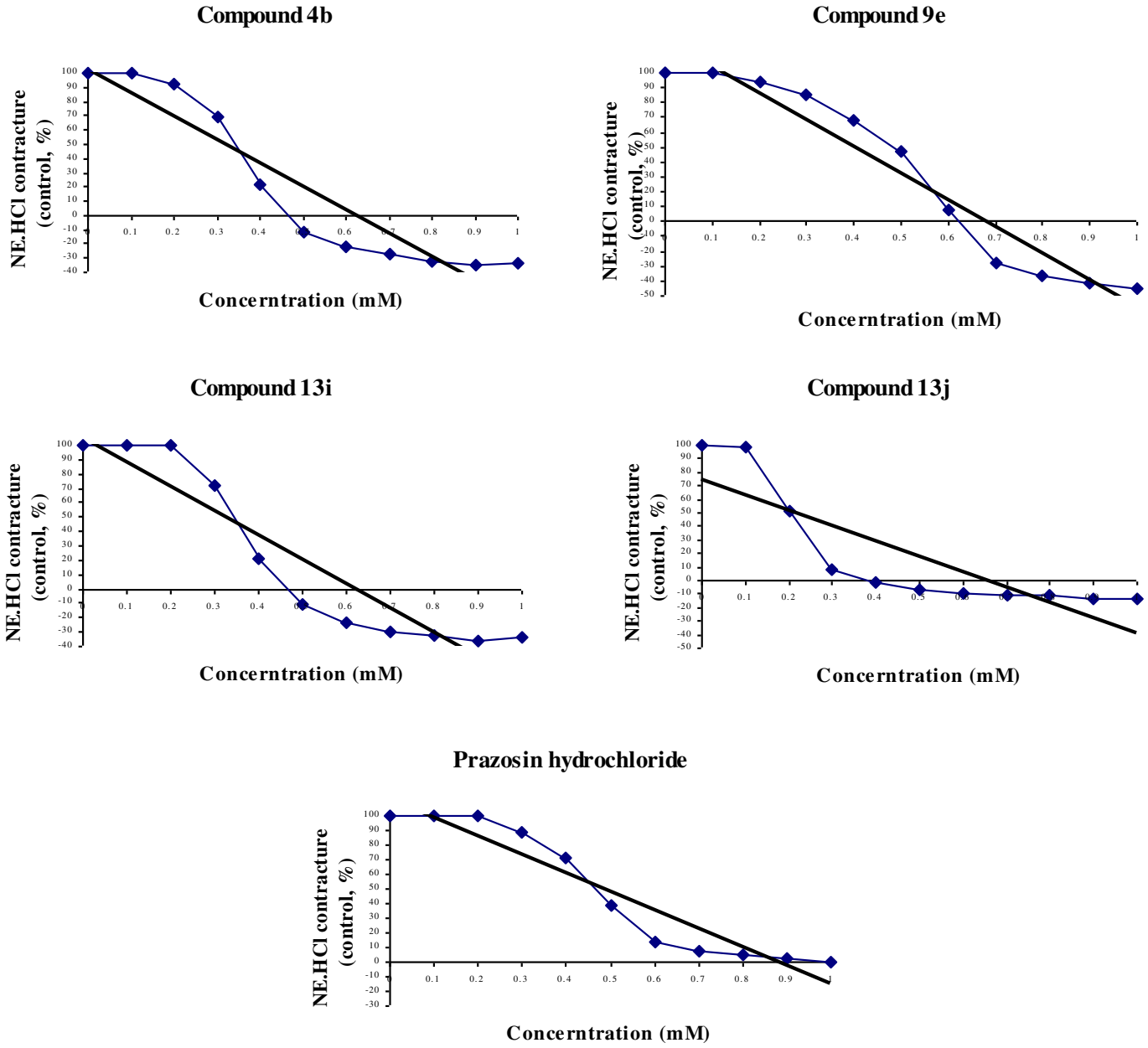


Fig. 6. Effect of the tested compounds on contracture induced by norepinepherine hydrochloride (NE·HCl) on thoracic rat aortic rings.

5. Experimental

5.1. Chemistry

Melting points were determined with a Kofler apparatus and are uncorrected. FT-IR spectra were recorded on a Perkin–Elmer spectrophotometer and measured by υ' cm^{-1} scale using KBr cell. ^1H NMR spectra were measured in δ scale on Brucker 200, 300 and 500 MHz spectrometers and Jeol As 500 MHz spectrometer. ^{13}C NMR spectra were measured in δ scale on Brucker 200 and 500 MHz spectrometers Jeol As 500 MHz spectrometer. The electron impact (EI) mass spectra were recorded on Finnigan Mat SSQ 7000 (70 ev) mass spectrometer. Analytical thin layer chromatography (TLC) on silica gel plates containing UV indicator was employed routinely to follow the course of reactions and to check the purity of products. All reagents and solvents were purified and dried by standard techniques. Elemental microanalysis was performed at Microanalytical Center, Vienna and Cairo Universities. 2-Amino-4,5-dimethoxybenzohydrazide **6** was prepared by modification of the reported procedure [18]. The preparation compounds **2** [16], **11a**,**b** [21–23] and **12a**,**b** [22] was performed according to reported procedures.

5.1.1. 2-[(4-Substituted piperazin-1-yl) methyl]quinazolin-4(3H)-ones (**4a**–**c**)

General procedure: A mixture of **2** (4.0 mmol), the appropriate arylpiperazine (4.0 mmol), anhydrous potassium carbonate (6.0 mmol), and potassium iodide (0.2 mmol) in dry acetonitrile (10 mL) was refluxed for 6 h. The solvent was evaporated and the residue was triturated with water. The obtained solid product **4a**–**c** was filtered, washed with ether and recrystallized from the appropriate solvent.

*5.1.1.1. 2-[(4-Phenylpiperazin-1-yl)methyl]quinazolin-4(3H)-one (**4a**).* Recrystallization from methanol (yield 84%), m.p. 147–149 °C. IR (KBr, cm^{-1}): 3111 (NH), 2930, 2884 and 2837 (CH_2), 1692 (C=O), 1616 (C=C). ^1H NMR, 300 MHz ($CDCl_3$): δ 2.85 (t, 4H, J = 4.80 Hz, $2CH_2$ of piperazine), 3.28 (s, 2H, CH_2), 3.38 (t, 4H, J = 4.80 Hz, $2CH_2$ of piperazine), 6.89 (t, 1H, J = 7.20 Hz, H-4′ of C_6H_5), 6.96 (m, 2H, H-2′ and H-6′ of C_6H_5), 7.15 (t, 2H, J = 7.30 Hz, H-3′ and H-5′ of C_6H_5), 7.20 (t, 1H, J = 8.10 Hz, H-7), 7.63 (m, 2H, H-6 and H-8), 8.54 (d, 1H, J = 8.40 Hz. H-5), 10.17 (s, br, 1H, NH, D_2O exchangeable). MS (m/z, %): 320.2 (M^+, 34.17), 175.2 (100.0).

*5.1.1.2. 2-{[4-(2-Methoxyphenyl)piperazin-1-yl]methyl}quinazolin-4(3H)-one (**4b**).* Recrystallization from acetone (yield 84%), m.p. 203–205 °C. IR (KBr, cm^{-1}): 3163 (NH), 2936, 2881 and 2825 (CH_2), 1666 (C=O), 1607 (C=C). ^1H NMR, 300 MHz ($CDCl_3$): δ 2.81 (t, 4H, J = 4.80 Hz, $2CH_2$ of piperazine), 3.17 (br, 4H, $2CH_2$ of piperazine), 3.67 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 6.88–7.04 (m, 4H, H3′-6′ of C_6H_4), 7.48 (t, 1H, J = 7.80 Hz, H-6), 7.69 (d, 1H, J = 7.80 Hz, H-8), 7.74 (t, 1H, J = 7.80 Hz, H-7), 8.29 (d, 1H, J = 7.80 Hz, H-5), 10.10 (s, br, 1H, NH, D_2O exchangeable).

*5.1.1.3. 2-{[4-(4-Nitrophenyl)piperazin-1-yl]methyl}quinazolin-4(3H)-one (**4c**).* Recrystallization from DMF (yield 92%), m.p. 251–253 °C. IR (KBr, cm^{-1}): 3174 (NH), 2939 and 2854 (CH_2), 1658 (C=O), 1612 (C=C). ^1H NMR, 300 MHz (DMSO-d_6): δ 2.64 (t, 4H, J = 4.6 Hz, $2CH_2$ of piperazine), 3.45–3.52 (m, 6H, $2CH_2$ of piperazine and CH_2), 6.70 (d, 2H, J = 9.60 Hz, H-2′ and H-6′ of 4′-NO_2–C_6H_5), 7.48 (t, 1H, J = 8.40 Hz, H-7), 7.63 (d, 1H, J = 8.40 Hz, H-8), 7.77 (t, 1H, J = 8.40 Hz, H-6), 8.03 (d, 2H, J = 9.60 Hz, H-3′ and H-5′ of 4′-NO_2–C_6H_5), 8.10 (d, 1H, J = 8.40 Hz, H-5), 12.00 (s, br, 1H, NH, D_2O exchangeable). ^{13}C NMR, 500 MHz (DMSO-d_6): δ 46.48 ($2CH_2$ of piperazine), 54.05 ($2CH_2$ of piperazine), 60.84 (CH_2), 113.17 (C-2′ and C-6′), 121.91 (C-4a), 122.94 (C-3′ and C-5′), 126.23, 127.01 and 129.05 (C-5, C-6 and C-8), 134.87 (C-7), 137.45 (C-4′), 154.48 and 155.21 (C-8a and C-1′), 162.13 (C-4), 169.5 (C-2), Anal. Calc. for $C_{19}H_{19}N_5O$: C, 62.46; H, 5.24; N, 19.17. Found: C, 62.00; H, 5.34; N, 19.34.

*5.1.2. 2-Amino-4,5-dimethoxybenzohydrazide (**6**)*

A mixture of **5** (2.5 mmol) and hydrazine hydrate (10 mL) was heated under reflux for 6 h, and then concentrated under reduced pressure. After cooling the separated solid was filtered, washed with water and dried; yield (68%). The product was recrystallized from methanol (yield 68%), m.p. 182–184 °C (reported 178–179 °C) [19]. IR (KBr, cm^{-1}): 3412, 3303 and 3256 (NH and NH–NH_2), 3014 (CH aromatic), 2948 and 2840 (CH_2)s, 1630 (C=O), 1592 (C=C).

*5.1.3. Ethyl 3-amino-6,7-dimethoxy-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**7**)*

A mixture of the 2-amino-4,5-dimethoxybenzohydrazide **6** (2.5 mmol) in diethyl oxalate (8 ml) was stirred at 180 °C in an oil bath for 6 h. The excess diethyl oxalate was removed under vacuum. The resulting semi solidified mass was treated with ethanol to afford a white precipitate. The precipitate was filtered, washed with aqueous ethanol and dried; yield (40%), then recrystallized from acetone, m.p. 191–193 °C. IR (KBr, cm^{-1}): 3325 and 3248 (NH_2), 2977 and 2941 (CH, CH_3), 1750 (C=O ester), 1667 (C=O). ^1H NMR, 500 MHz ($CDCl_3$): δ 1.42 (t, 3H, J = 5.35 Hz, $COOCH_2\underline{CH_3}$), 3.94 and 3.97 (s,s, 2× 3H, $2OCH_3$), 4.48 (q, 2H, J = 5.35 Hz, $COO\underline{CH_2}CH_3$), 5.22 (s, br, 1H, NH_2, D_2O exchangeable), 7.09 (s, 1H, H-8), 7.48 (s, 1H, H-5). ^{13}C NMR, 500 MHz ($CDCl_3$): 14.07 ($COOCH_2\underline{CH_3}$), 56.38 (OCH_3), 56.42 (OCH_3), 63.05 ($COO\underline{CH_2}CH_3$), 105.39 (C-5), 108.47 (C-8), 114.98 (C-4a), 142.49 (C-8a), 145.66 (C-6), 150.19 (C-7), 155.17 (C-2), 159.70 ($\underline{CO}OCH_2CH_3$), 161.14 (C-4). Anal. Calc. for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.16; N, 14.33, Found: C, 52.81; H, 4.87; N, 14.43.

*5.1.4. Ethyl 3-(2-chloroacetamido/3-chloropropanamido)-6,7-dimethoxy-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**8a**, **8b**)*

General procedure: Chloroacetyl chloride or chlorpropionyl chloride (36 mmol) was added gradually to a stirred solution of **7** (30 mmol) in dry toluene (20 mL). The reaction mixture was allowed to reflux for 2 h. The solvent was evaporated and the residue was triturated with petroleum ether. The obtained solid product was filtered, washed with petroleum ether and recrystallized from suitable solvent.

*5.1.4.1. Ethyl 3-(2-chloroacetamido)-6,7-dimethoxy-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**8a**).* Recrystallized from methanol (yield 86%); m.p. 222–224 °C. IR (KBr, cm^{-1}): 3514 (NH), 2974 and 2939 (CH_2, CH_3), 1747 (C=O ester),1678 (C=O), 1607 (C=C). ^1H NMR, 500 MHz (DMSO-d_6): δ 1.27 (t, 3H, J = 6.90 Hz, $COOCH_2\underline{CH_3}$), 3.89 and 3.91 (s,s, 2× 3H, $2CH_3O$), 4.32–4.35 (m, 4H, $COO\underline{CH_2}CH_3$ and $CO\underline{CH_2}Cl$), 7.27 (s, 1H, H-8), 7.47 (s, 1H, H-5), 11.66 (s, 1H, CONH, D_2O exchangeable). ^{13}C NMR, 500 MHz (DMSO-d_6): 14.29 ($COOCH_2\underline{CH_3}$), 40.22 ($CO\underline{CH_2}Cl$), 56.52 (OCH_3), 56.83 (OCH_3), 63.28 ($COO\underline{CH_2}CH_3$), 106.24 (C-5), 109.44 (C-8), 115.49 (C-4a), 142.09 (C-8a), 146.63 (C-6), 150.51 (C-7), 155.84 (C-2), 157.61 ($\underline{CO}OCH_2CH_3$), 160.15 (C-4), 166.76 (CONH). MS (m/z, %): 369.2 (M^+, 75.0) (M + 2, 25.26), 296.1 (100.0). Anal. Calc. for $C_{15}H_{16}ClN_3O_6 \cdot 0.5H_2O$: C, 47.65; H, 4.49; N, 11.10, Found: C, 47.52; H, 4.69; N, 10.86.

*5.1.4.2. Ethyl 3-(3-chloropropanamido)-6,7-dimethoxy-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**8b**).* Recrystallized from acetone (yield 92%); m.p. 216–8 °C. IR (KBr, cm^{-1}): 3297 (NH), 3001 and 2944 (CH_2, CH_3), 1735 (C=O ester), 1697 (C=O), 1607 (C=C). ^1H NMR, 500 MHz ($CDCl_3$): δ 1.39 (t, 3H, J = 6.90 Hz, $COOCH_2\underline{CH_3}$), 2.92 (t, 2H, J = 6.10 Hz, $CO\underline{CH_2}CH_2Cl$), 3.85 (t, 2H, J = 6.10 Hz, $COCH_2\underline{CH_2}Cl$), 3.99 (s, 6H, $2CH_3O$), 4.44 (q, 2H, J = 6.90 Hz, $COO\underline{CH_2}CH_3$), 7.15 (s, 1H, H-8), 7.52 (s, 1H, H-5), 8.82 (s, br, 1H, CONH, D_2O exchangeable). ^{13}C NMR, 500 MHz ($CDCl_3$): 14.03 ($COOCH_2\underline{CH_3}$), 37.36 ($CO\underline{CH_2}CH_2Cl$), 38.89 ($COCH_2\underline{CH_2}Cl$), 56.47 (OCH_3), 63.46 ($COO\underline{CH_2}CH_3$), 106.13 (C-5), 109.04 (C-8), 115.65 (C-4a), 142.05 (C-8a), 145.56 (C-6), 150.51 (C-7), 155.64 (C-2), 158.50 ($\underline{CO}OCH_2CH_3$), 160.02(C-4), 169.25 (CONH). Anal. Calc. for $C_{16}H_{18}ClN_3O_6$: C, 50.07; H, 4.73; N, 10.95, Found: C, 50.12; H, 4.52; N, 10.93.

*5.1.5. Ethyl 6,7-dimethoxy-4-oxo-3-[2-(4-subistituted piperazin-1-yl)acetamido]-3,4-dihydroquinazoline-2-carboxylates (**9a**–**c**)*

General procedure: A mixture **8a** (4.0 mmol), the appropriate arylpiperazine (4.0 mmol), anhydrous potassium carbonate (6.0 mmol), and potassium iodide (0.2 mmol) in dry acetonitrile (10 mL) was refluxed for 4 h. The solvent was evaporated under vacuum. The residue was dissolved in water and neutralized with acetic acid. The solution was extracted with chloroform. The chloroformic layer was dried over anhydrous sodium sulfate, and then evaporated to dryness. The obtained solid product was recrystallized from the appropriate solvent.

*5.1.5.1. Ethyl 6,7-dimethoxy-4-oxo-3-[2-(4-phenylpiperazin-1-yl)acetamido]-3,4-dihydroquinazoline-2-carboxylate (**9a**).* Recrystallized from acetone (yield 80%); m.p. 253–255 °C. IR (KBr, cm^{-1}): 3387 (NH), 2830 (CH_2, CH_3), 1658, 1650 and 1641 (3C=O), 1598(C=C). ^1H NMR, 500 MHz (DMSO-d_6): δ 1.24 (t, 3H, J = 6.10 Hz, $COOCH_2\underline{CH_3}$), 2.56 (br, 4H, $2CH_2$ of piperazine), 2.83 (s, 2H, $COCH_2$), 3.11 (br, 4H, $2CH_2$ of piperazine), 3.85 (s, 6H, $2CH_3O$), 4.23 (q, 4H, J = 6.10 Hz, $COO\underline{CH_2}CH_3$), 6.75 (t, 1H, J = 6.85, H-4′ of C_6H_5), 6.92 (t, 2H, J = 6.85, H-2′ and H-6′ of C_6H_5), 7.07 (s, 1H, H-8), 7.18 (t, 2H, J = 6.85, H-3′ and H-5′ of C_6H_5), 7.39 (s, 1H, H-5). ^{13}C NMR, 500 MHz (DMSO-d_6): 14.45 ($COOCH_2\underline{CH_3}$), 48.59 ($2CH_2$ of piperazine), 53.36 ($2CH_2$ of piperazine), 56.18 (OCH_3), 56.37 (OCH_3), 61.50 ($COCH_2N$), 63.12 ($COO\underline{CH_2}CH_3$), 105.54 (C-5), 107.96 (C-8), 109.50 (C-4a), 115.71 (C-2′ and C-6′), 118.99 (C-4′), 129.39 (C-3′ and C-5′), 143.07 (C-8a), 148.01

(C-6), 149.29 (C-1′), 153.00 (C-7), 156.5 (C-2), 158.50 ($\underline{CO}OCH_2CH_3$), 166.50 (C-4), 171.45 (CONH). MS (*m*/*z*, %): 495.4 (M^+, 7.75), 175.2 (100.0). Anal. Calc. for $C_{25}H_{29}N_5O_6\cdot 2H_2O$: C, 56.49; H, 6.26; N, 13.18, Found: C, 56.79; H, 5.67; N, 13.37.

*5.1.5.2. Ethyl 6,7-dimethoxy-3-{2-[4-(2-methoxyphenyl)piperazin-1-yl]-acetamido}-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**9b**).* Recrystallized from acetone/ethyl acetate (yield 65%); m.p. 180–182 °C. IR (KBr, cm^{-1}): 3517 (NH), 2936 and 2823 (CH_2, CH_3), 1731 (C=O ester), 1664 (2C=O), 1611 (C=C). ^{1}H NMR, 300 MHz (DMSO-d_6): δ 1.14 (br, 3H, $COOCH_2\underline{CH_3}$), 2.49 (br, 4H, $2CH_2$ of piperazine), 3.54 (overlapped, $2CH_2$ of piperazine), 3.79 (s, 3H, CH_3O of C_6H_4), 3.82 and 3.92 (s,s, 2× 3H, $2CH_3O$ of quinazoline), 4.21 (br, 2H, $COCH_2$), 4.69 (br, 2H, $COO\underline{CH_2}CH_3$), 6.89–7.07 (m, 4H, H3′-6′ of C_6H_4), 7.26 (s, 1H, H-8), 7.52 (s, 1H, H-5). Anal. Calc. for $C_{26}H_{31}N_5O_7$: C, 59.42; H, 5.95; N, 13.18, Found: C, 59.60; H, 5.63; N, 13.28.

*5.1.5.3. Ethyl 6,7-dimethoxy-3-{2-[4-(4-nitrophenyl)piperazin-1-yl] acetamido}-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**9c**).* Recry stallized from benzene (yield 56%); m.p. 168–170 °C. IR (KBr, cm^{-1}): 3535 (NH), 2925 and 2832 (CH_2, CH_3), 1738 (C=O ester), 1690 and 1679 (2C=O), 1594 (C=C). ^{1}H NMR, 500 MHz ($CDCl_3$): δ 1.39 (t, 3H, J = 6.90 Hz, $COOCH_2\underline{CH_3}$), 2.86 (br, 4H, $2CH_2$ of piperazine), 3.31 (s, 2H, $COCH_2$), 3.46 (br, 4H, $2CH_2$ of piperazine), 3.94 and 3.69 (s,s, 2× 3H, $2CH_3O$), 4.42 (q, 2H, J = 6.90 Hz, $COO\underline{CH_2}CH_3$), 6.79 (d, 2H, J = 9.20 Hz, H-2′ and H-6′ of 4-NO_2–C_6H_5), 7.20 (s, 1H, H-8), 7.54 (s, 1H, H-5), 8.08 (d, 2H, J = 9.20 Hz, H-3′ and H-5′ of 4-NO_2–C_6H_5), 9.55 (s, 1H, NHCO). ^{13}C NMR, 500 MHz ($CDCl_3$): δ 14.09 ($COOCH_2\underline{CH_3}$), 47.24 ($2CH_2$ of piperazine), 53.10 ($2CH_2$ of piperazine), 56.49 (OCH_3), 56.54 (OCH_3), 60.77 ($COCH_2N$), 63.26 ($COO\underline{CH_2}CH_3$), 106.08 (C-5), 109.21 (C-8), 113.04 (C-2′ and C-6′), 116.00 (C-4a), 125.94 (C-3′ and C-5′), 138.95 (C-4′), 141.18 (C-8a), 145.50 (C-6), 150.67 (C-7), 154.75 (C-1′), 155.69 (C-2), 158.50 ($\underline{CO}OCH_2CH_3$), 160.05 (C-4), 169.36 (CONH). Anal. Calc. for $C_{25}H_{28}N_6O_8\cdot 1.5H_2O$: C, 52.91; H, 5.51; N, 14.81, Found: C, 53.12; H, 5.36; N, 15.16.

*5.1.6. Ethyl 6,7-dimethoxy-4-oxo-3-[3-(4-substituted piperazin-1-yl) propanamido]-3,4-dihydroquinazoline-2-carboxylate (**9d**–**f**)*

General procedure: A mixture of **8b** (4.0 mmol), the appropriate arylpiperazine (4.0 mmol), anhydrous potassium carbonate (6.0 mmol), and potassium iodide (0.2 mmol) in dry acetonitrile (10 mL) was refluxed for 6 h. The solvent was evaporated and the residue was triturated with water. The obtained solid product was filtered, washed with ether and recrystallized from the appropriate solvent.

*5.1.6.1. Ethyl 6,7-dimethoxy-4-oxo-3-[3-(4-phenylpiperazin-1-yl)propanamido]-3,4-dihydroquinazoline-2-carboxylate (**9d**).* Recrystallized from acetone (yield 76%); m.p. 175–177 °C. IR (KBr, cm^{-1}): 3442 (NH), 2946 and 2831 (CH_2, CH_3), 1645 and 1616 broad (3C=O), 1616 (C=C). ^{1}H NMR, 500 MHz (DMSO-d_6): δ 1.03 (t, 3H, J = 7.65 Hz, $COOCH_2\underline{CH_3}$), 2.57 (br, 2H, $CO\underline{CH_2}CH_2N$), 2.72 (t, 4H, $2CH_2$, J = 4.80 of piperazine), 3.13 (br, 2H, $CO\underline{CH_2}\underline{CH_2}N$), 3.34 (overlapped, $2CH_2$ of piperazine), 3.85 and 3.89 (s,s, 2× 3H, $2CH_3O$), 4.33 (br, 2H, $COO\underline{CH_2}CH_3$), 6.74 (t, 1H, J = 7.65 Hz, H-4′ of C_6H_5), 6.91 (d, 2H, J = 6.90 Hz, H-2′ and H-6′ of C_6H_5), 7.18 (t, 2H, J = 7.65, H-3′ and H-5′ of C_6H_5), 7.45 (s, 1H, H-8), 8.06 (s, 1H, H-5), 11.25 (s, br, 1H, NHCO, D_2O exchangeable). ^{13}C NMR, 500 MHz (DMSO-d_6): δ 14.09 ($COOCH_2\underline{CH_3}$), 32.50 ($CO\underline{CH_2}CH_2N$), 48.67 ($2CH_2$ of piperazine), 52.88 ($2CH_2$ of piperazine), 53.74 ($COCH_2\underline{CH_2}N$), 56.39 (OCH_3), 56.62 (OCH_3), 63.26 ($COO\underline{CH_2}CH_3$), 105.98 (C-5), 108.90 (C-8), 115.58 (C-4a), 115.90 (C-2′ and C-6′), 119.33 (C-4′), 129.43 (C-3′ and C-5′), 144.00 (C-8a), 147.84 (C-6), 149.52 (C-1′), 151.53 (C-7), 155.37, 158.35 (C-2, C-4 and $\underline{CO}OCH_2CH_3$), 172.10 (CONH). Anal. Calc. for $C_{26}H_{31}N_5O_6\cdot 1.5H_2O$: C, 58.20; H, 6.39; N, 13.05, Found: C, 57.79; H, 5.69; N, 13.05.

*5.1.6.2. Ethyl 6,7-dimethoxy-3-{3-[4-(2-methoxyphenyl)piperazin-1-yl]-propanamido}-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**9e**).* Recrystallized from methanol/ethyl acetate (yield 64%); m.p. 212–214 °C. IR (KBr, cm^{-1}): 3424 (NH), 2944 and 2833 (CH_2, CH_3), 1620 broad (3C=O). ^{1}H NMR, 500 MHz (DMSO-d_6): δ 1.54 (t, 3H, J = 6.90 Hz, $COOCH_2\underline{CH_3}$), 2.32 (m, 2H, $CO\underline{CH_2}CH_2N$), 2.51–2.58 (m, 6H, $2CH_2$ of piperazine and $COCH_2\underline{CH_2}N$), 2.92 (br, 4H, $2CH_2$ of piperazine), 3.74 (s, 3H, CH_3O of C_6H_4), 3.83 and 3.87 (s,s, 2× 3H, $2CH_3O$ of quinazoline), 3.90 (overlapped, 2H, $COO\underline{CH_2}CH_3$), 6.83–6.89 (m, 4H, H3′-6′ of C_6H_4), 6.96 (s, 1H, H-8), 7.32 (s, 1H, H-5). ^{13}C NMR, 500 MHz (DMSO-d_6): δ 13.00 ($COOCH_2\underline{CH_3}$), 32.13 ($CO\underline{CH_2}CH_2N$), 50.55 ($2CH_2$ of piperazine), 53.22 ($2CH_2$ of piperazine), 54.26 ($COCH_2\underline{CH_2}N$), 55.88 (OCH_3), 56.14 (OCH_3), 56.41 (OCH_3), 67.35 ($COO\underline{CH_2}CH_3$), 105.86 (C-5), 108.32 (C-8), 112.53 (C-3′), 114.58 (C-4a), 118.45 (C-5′), 121.39 (C-4′), 122.83 (C-6′), 141.86 (C-8a), 144.29 (C-2′), 148.30 (C-6), 152.53 (C-7), 154.87 (C-2), 156.50 ($\underline{CO}OCH_2CH_3$), 158.73 (C-4), 164.00 (C-1′), 171.63 (CONH). Anal. Calc. for $C_{27}H_{33}N_5O_7$: C, 60.10; H, 6.16; N, 12.98, Found: C, 59.93; H, 6.20; N, 12.78.

*5.1.6.3. Ethyl 6,7-dimethoxy-3-{3-[4-(4-nitrophenyl)piperazin-1-yl]-propanamido}-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**9f**).* Recrystallized from acetone/ethyl acetate (yield 69%); m.p. 230–232 °C. IR (KBr, cm^{-1}): 3446 (NH), 2937 and 2834 (CH_2, CH_3), 1688 broad (3C=O), 1598 (C=C). ^{1}H NMR, 500 MHz (DMSO-d_6): δ 1.19 (t, 3H, J = 7.20 Hz, $COOCH_2\underline{CH_3}$), 2.62–2.79 (m, 6H, $2CH_2$ of piperazine and $CO\underline{CH_2}CH_2N$), 3.64 (br, 6H, $2CH_2$ of piperazine and $COCH_2\underline{CH_2}N$), 3.87 and 3.9 (s,s, 2× 3H, $2CH_3O$), 4.32 (m, 2H, $COO\underline{CH_2}CH_3$), 6.94 (d, 2H, J = 8.40 Hz, H-2′ and H-6′ of 4-NO_2–C_6H_5), 7.01 (s, 1H, H-8), 7.44 (s, 1H, H-5), 8.02 (d, 2H, J = 8.40 Hz, H-3′ and H-5′ of 4-NO_2–C_6H_5), 11.38 (s, 1H, NHCO). ^{13}C NMR, 500 MHz (DMSO-d_6): δ 14.38 ($COOCH_2\underline{CH_3}$), 31.11 ($CO\underline{CH_2}CH_2N$), 46.28 ($2CH_2$ of piperazine), 52.16 ($2CH_2$ of piperazine), 53.50 ($COCH_2\underline{CH_2}N$), 56.50 (OCH_3), 56.80 (OCH_3), 63.13 ($COO\underline{CH_2}CH_3$), 106.19 (C-5), 109.33 (C-8), 113.34 (C-2′ and C-6′), 115.56 (C-4a), 126.17 (C-3′ and C-5′), 137.72 (C-4′), 142.20 (C-8a), 150.39 (C-6), 154.61, 155.05 and 155.74 (C-7, C-1′ and C-2), 157.87 ($\underline{CO}OCH_2CH_3$), 160.38 (C-4), 171.45 (CONH). Anal. Calc. for $C_{26}H_{30}N_6O_8$: C, 56.31; H, 5.45; N, 15.15, Found: C, 56.23; H, 5.46; N, 15.40.

*5.1.7. 2-Chloro-N-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3 (4H)-yl)acetamide (**12c**) and 3-chloro-N-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-propanamide (**12d**)*

General procedure: Chloroacetyl chloride or chloropropionyl chloride (36 mmol) was added gradually to a stirred solution of 3-amino-6,7-dimethoxy-2-methylquinazolin-4(3H)-one **11b** (30 mmol) in dry toluene (20 mL). The reaction mixture was allowed to reflux for 4 h. After cooling, the formed precipitate was filtered to produce **12c** and **12d**.

*5.1.7.1. Compound **12c**.* Yield = 96%; m.p. = 122–125 °C. IR (KBr, cm^{-1}): 3251 (NH), 2951 and 2889 (CH_2), 1696 and 1669 (2C=O). ^{1}H NMR, 200 MHz ($CDCl_3$): δ 2.52 (s, 3H, CH_3), 3.97 and 3.99 (s,s, 2× 3H, $2CH_3O$), 3.31 (d, 2H, J = 3.2 Hz, $COCH_2Cl$), 7.06 (s, 1H, H-8), 7.47 (s, 1H, H-5), 9.17 (s, 1H, NHCO). ^{13}C NMR, 200 MHz ($CDCl_3$): δ 21.43 (CH_3), 41.52 ($COCH_2N$), 56.65 (OCH_3), 56.73 (OCH_3), 106.08, 108.06, 143.63, 149.39, 153.85, 155.94, 159.45, 166.89.

*5.1.7.2. Compound **12d**.* Yield = 96%; m.p. = 133–135 °C. IR (KBr, cm^{-1}): 3251 (NH), 2951 and 2889 (CH_2), 1696 and 1669 (2C=O). ^{1}H NMR, 200 MHz (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 2.92 (t, 2H, J = 6.8 Hz, $CO\underline{CH_2}CH_2Cl$), 3.87 and 3.91 (s,s, 2× 3H, $2CH_3O$), 4.65 (br, 2H, $COCH_2\underline{CH_2}Cl$), 7.18 (s, 1H, H-8), 7.40 (s, 1H, H-5), 11.46 (s, 1H, NHCO). ^{13}C NMR, 200 MHz (DMSO-d_6): δ 20.76 (CH_3), 36.75 ($CO\underline{CH_2}CH_2Cl$), 41.09 ($COCH_2\underline{CH_2}Cl$), 56.22 (OCH_3), 56.49 (OCH_3), 105.95, 107.01, 141.74, 149.05, 155.43, 155.78, 158.99, 169.48

*5.1.8. N-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-substituted piperazin-1-yl) acetamide (**13a**–**c**), N-(2-methyl-4-oxoquinazolin-3 (4H)-yl)-3-(4-substituted piperazin-1-yl)propanamide (**13d**,**e**), N-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-substituted piperazin-1-yl)acetamide (**13f**–**h**) and N-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(4-substituted piperazin-1-yl)propanamide (**13i**–**l**)*

General procedure: A mixture of **12a**/**b**/**c**/**d** (4.0 mmol), the appropriate arylpiperazine (4.0 mmol), anhydrous potassium carbonate (6.0 mmol), and potassium iodide (0.2 mmol) in dry acetonitrile (10 mL) was refluxed for 6 h. The solvent was evaporated and the residue was triturated with water. The obtained solid product **13a**–**l** was filtered, washed with ether and recrystallized from the appropriate solvent.

*5.1.8.1. N-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-phenylpiperazin-1-yl)-acetamide (**13a**).* Recrystallized from ethanol (yield 38%); m.p. 89–91 °C. IR (KBr, cm^{-1}): 3541 (NH), 2933 and 2819 (CH_2), 1700 and 1669 (2C=O), 1603 (C=C). ^1H NMR, 200 MHz ($CDCl_3$): δ 2.56 (s, 3H, CH_3), 2.81 (br, 2H, CH_2 of piperazine), 3.11 (t, 2H, CH_2 of piperazine), 3.32 (t, 4H, CH_2 of piperazine, J = 5.3 Hz, 2), 3.38 (s, 2H, $COCH_2$), 6.86–6.98 (m, 3H, H-2′, H-4′ and H-6′ of C_6H_5), 7.29 (m, 2H, H-3′ and H-5′ of C_6H_5), 7.47 (t, 1H, J = 7.60 Hz, H-6), 7.69 (d, 1H, J = 7.60 Hz, H-8), 7.78 (t, 1H, J = 7.60 Hz, H-7), 8.22 (d, 1H, J = 7.60 Hz, H-5). ^{13}C NMR, 200 MHz ($CDCl_3$): δ 21.43 (CH_3), 49.28 (2CH_2 of piperazine), 53.74 (2CH_2 of piperazine), 60.94 ($COCH_2N$), 116.19, 120.06, 126.73, 126.83, 127.18, 129.51, 134.92, 140.80, 146.94, 150.91, 158.70, 170.94. Anal. Calc. for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55, Found: C, 66.64; H, 6.07; N, 18.30.

*5.1.8.2. N-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-(2-methoxyphenyl)-piperazin-1-yl)-acetamide (**13b**).* Recrystallized from ethanol (yield 53%); m.p. 183–185 °C. IR (KBr, cm^{-1}): 3145 (NH), 2951 and 2828 (CH_2), 1713 and 1696 (2C=O), 1603 (C=C). ^1H NMR, 500 MHz ($CDCl_3$): δ 2.54 (s, 3H, CH_3), 2.82 (br, 2H, CH_2 of piperazine), 3.18 (br, 6H, 3CH_2 of piperazine), 3.34 and 3.45 (d,d, 2H, J = 13.39 Hz, $COCH_2$), 3.87 (s, 3H, CH_3O), 6.86 (d, 1H, J = 8.19 Hz, H-3′ of C_6H_4), 6.92 (t, 1H, $J_{5',6'}$ = 8.19 Hz, H-5′ of C_6H_4), 6.98 (dd, 1H, $J_{6',5'}$ = 8.19 Hz, $J_{6',4'}$ = 1.5 Hz, H-6′ of C_6H_4), 6.98 (td, 1H, $J_{4',5'} = J_{4',3'}$ = 8.19 Hz, $J_{4',6'}$ = 1.5 Hz, H-4′ of C_6H_4), 7.45 (t, 1H, $J_{6,5} = J_{6,7}$ = 8.69 Hz, H-6), 7.65 (d, 1H, $J_{8,7}$ = 8.69 Hz, H-8), 7.78 (td, 1H, $J_{7,6} = J_{7,8}$ = 8.69 Hz, $J_{7,5}$ = 1.5 Hz, H-7), 8.20 (dd, 1H, $J_{5,6}$ = 8.69 Hz, $J_{5,7}$ = 1.50 Hz, H-5). ^{13}C NMR, 500 MHz ($CDCl_3$): δ 21.46 (CH_3), 50.64 (2CH_2 of piperazine), 54.00 (2CH_2 of piperazine), 55.34 (OCH_3), 60.99 ($COCH_2N$), 111.19 (C-3′), 118.18 (C-6′), 120.69 (C-4a), 120.94 (C-5′), 123.15 (C-4′), 126.67, 126.82 and 127.16 (C-5, C-6, C-8), 134.55 (C-7), 140.80 (C-1′), 146.95 (C-8a), 152.19 (C-2′), 155.27 (C-2), 159.86 (C-4), 171.08 (CONH). MS (m/z, %): 335.15 (M^+, 4.9), 145.0 (100.0). Anal. Calc. for $C_{22}H_{25}N_5O_3$: C, 64.85; H, 6.18; N, 17.19, Found: C, 64.76; H, 6.14; N, 16.97.

*5.1.8.3. N-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-2-[4-(4-nitrophenyl) piperazin-1-yl]acetamide (**13c**).* Recrystallized from methanol (yield 85%); m.p. 208–211 °C. IR (KBr, cm^{-1}): 3295 (NH), 2950 and 2828 (CH_2), 1710 and 1687 (2C=O), 1599 (C=C). ^1H NMR, 200 MHz (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 2.81 (br, 4H, 2CH_2 of piperazine), 327 (br, 4H, 2CH_2 of piperazine), 3.45 (s, 2H, $COCH_2$), 7.07 (d, 2H, J = 8.6 Hz, H-2′ and H-6′ of 4′-NO_2–C_6H_5), 7.55 (t, 1H, J = 7.51 Hz, H-7), 7.66 (d, 1H, J = 7.51 Hz, H-8), 7.86 (t, 1H, J = 7.51 Hz, H-6), 8.06 (m, 3H, H-5, H-3′ and H-5′). ^{13}C NMR, 200 MHz (DMSO-d_6): δ 22.24 (CH_3), 47.31 (2CH_2 of piperazine), 53.39 (2CH_2 of piperazine), 60.79 ($COCH_2N$), 113.42, 113.77, 121.66, 127.49, 127.90, 128.00, 136.13, 137.97, 147.67, 155.80, 157.30, 159.95, 170.32. Anal. Calc. for $C_{21}H_{22}N_6O_4$: C, 59.71; H, 5.25; N, 19.89, Found: C, 59.33; H, 5.21; N, 19.73.

*5.1.8.4. N-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-3-(4-phenylpiperazin-1-yl)-propanamide (**13d**).* Recrystallized from ethanol/water (yield 73%); m.p. 79–81 °C. IR (KBr, cm^{-1}): 3480 (NH), 2933 and 2829 (CH_2), 1705 and 1674 (2C=O), 1603 (C=C). ^1H NMR, 500 MHz ($CDCl_3$): δ 2.53 (s, 3H, CH_3), 2.68 (m, 2H, $COCH_2CH_2N$), 2.94 (m, 4H, 2CH_2 of piperazine), 3.02 (m, 2H, $COCH_2CH_2N$), 3.25 (br, 4H, 2CH_2 of piperazine), 6.85 (t, 1H, J = 7.50, H-4′ of C_6H_5), 6.91 (d, 2H, J = 7.50, H-2′ and H-6′ of C_6H_5), 7.24 (t, 2H, J = 7.50, H-3′ and H-5′ of C_6H_5), 7.42 (t, 1H, J = 8.5 Hz, H-6), 7.64 (d, 1H, J = 8.5 Hz, H-8), 7.72 (t, 1H, J = 8.5 Hz, H-7), 8.18 (d, 1H, J = 8.5 Hz, H-5), 9.98 (s, 1H, NH). ^{13}C NMR, 500 MHz ($CDCl_3$): δ 21.41 (CH_3), 31.20 ($COCH_2CH_2N$), 49.18 (2CH_2 of piperazine), 52.19 (2CH_2 of piperazine), 52.76 ($COCH_2CH_2N$), 116.12 (C-2′ and C-6′), 120.03 (C-4′), 120.72 (C-4a), 126.39 (C-5), 126.71 (C-6), 126.96 (C-8), 129.02 (C-3′ and C-5′), 134.59 (C-7), 146.94 (C-8a), 150.77 (C-1′), 155.42 (C-2), 159.62 (C-4), 173.21 (CONH). MS (m/z, %): 391.4 (M^+, 7.16), 54.95 (100.0). Anal. Calc. for $C_{22}H_{25}N_5O_2 \cdot 0.25H_2O$: C, 66.73; H, 6.49; N, 17.69, Found: C, 66.55; H, 6.51; N, 17.55.

*5.1.8.5. N-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-3-[4-(4-nitrophenyl) piperazin-1-yl]propanamide (**13e**).* Recrystallized from methanol (yield 30%); m.p. 183–186 °C. IR (KBr, cm^{-1}): 3277 (NH), 2925 and 2828 (CH_2), 1697 and 1661 (2C=O), 1594 (C=C). ^1H NMR, 200 MHz ($CDCl_3$): δ 2.53 (s, 3H, CH_3), 2.70 (m, 2H, $COCH_2CH_2N$), 2.86 (m, 4H, 2CH_2 of piperazine), 2.91 (m, 2H, $COCH_2CH_2N$), 3.48 (br, 4H, 2CH_2 of piperazine), 6.81 (d, 2H, J = 9.45 Hz, H-2′ and H-6′ of 4′-NO_2–C_6H_5), 7.43 (t, 1H, J = 7.62 Hz, H-7), 7.61 (d, 1H, J = 7.62 Hz, H-8), 7.73 (t, 1H, J = 7.62 Hz, H-6), 8.08 (d, 2H, J = 9.45 Hz, H-3′ and H-5′ of 4′-NO_2–C_6H_5), 8.17 (d, 1H, J = 7.62 Hz, H-5). ^{13}C NMR, 200 MHz ($CDCl_3$): δ 21.79 (CH_3), 31.66 ($COCH_2CH_2N$), 47.36 (2CH_2 of piperazine), 52.15 (2CH_2 of piperazine), 53.12 ($COCH_2CH_2N$), 113.82, 121.04, 126.16, 126.86, 127.06, 127.48, 135.08, 139.13, 147.39, 154.94, 155.65, 160.13, 173.51. Anal. Calc. for $C_{22}H_{24}N_6O_4$: C, 60.54; H, 5.54; N, 19.25, Found: C, 60.09; H, 5.48; N, 19.00.

*5.1.8.6. N-(6,7-Dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-phenylpiperazin-1-yl)acetamide (**13f**).* Recrystallized from ethanol/water (yield 29%); m.p. 90–92 °C. IR (KBr, cm^{-1}): 3506 (NH), 2916 and 2819 (CH_2), 1705 and 1678 (2C=O), 1599 (C=C). ^1H NMR, 500 MHz (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.73 (m, 2H, CH_2 of piperazine moiety), 2.89 (m, 2H, CH_2 of piperazine), 3.15 (d, 1H, J = 15.95 Hz, $COCH_2$), 3.23 (br, 4H, 2CH_2 of piperazine), 3.45 (d, 1H, J = 15.95 Hz, $COCH_2$), 3.86 and 3.90 (s,s, 2× 3H, 2OCH_3), 6.77 (t, 1H, J = 7.41 Hz, H-4′ of C_6H_5), 6.96 (d, 2H, J = 7.41 Hz, H-2′ and H-6′ of C_6H_5), 7.12 (s, 1H, H-8), 7.22 (t, 2H, J = 7.41 Hz, H-3′ and H-5′ of C_6H_5), 7.41 (s, 1H, H-5), 10.73 (br, 1H, NHCO). ^{13}C NMR, 500 MHz (DMSO-d_6): δ 20.98 (CH_3), 47.97 (2CH_2 of piperazine), 52.79 (2CH_2 of piperazine), 55.75 and 56.03 (2OCH_3), 60.07 ($COCH_2N$), 105 (C-5), 107.78 (C-8), 113.49 (C-4a), 115.35 (C-2′ and C-6′), 118.79 (C-4′), 128.95 (C-3′ and C-5′), 142.82 (C-8a), 148.40 (C-6), 150.97 (C-1′), 154.47 (C-2), 154.87 (C-7), 158.24 (C-4), 169.22 ($NHCOCH_2$). MS (m/z, %): 437.5 (M^+, 20.29), 42.05 (100.0). Anal. Calc. for $C_{23}H_{27}N_5O_4 \cdot 0.5H_2O$: C, 61.87; H, 6.30; N, 15.69, Found: C, 61.97; H, 6.69; N, 15.77.

*5.1.8.7. N-(6,7-Dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]acetamide (**13g**).* Recrystallized from methanol/water (yield 67%); m.p. 104–106 °C. IR (KBr, cm^{-1}): 3506 (NH), 2933 and 2819 (CH_2), 1705 and 1678 (2C=O), 1608 (C=C). ^1H NMR, 200 MHz (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.71 (br, 2H, CH_2 of piperazine), 2.83 (br, 2H, CH_2 of piperazine), 3.21(m, 4H, 2CH_2 of piperazine), 3.44 (s, 2H, $COCH_2$), 3.78 (s, 3H, 2′-CH_3O of C_6H_4), 3.86 and 3.90 (s,s, 2× 3H, 2CH_3O of quinazoline), 6.90–6.93 (m, 4H, H-3′-6′ of C_6H_4), 7.13 (s, 1H, H-8), 7.41 (s, 1H, H-5). ^{13}C NMR, 200 MHz (DMSO-d_6): δ 22.22 (CH_3), 51.07 (2CH_2 of piperazine), 54.38 (2CH_2 of piperazine), 56.55, 57.00 and 57.27 (3OCH_3), 61.42

(COCH$_2$N), 106.99, 109.03, 113.16, 114.76, 119.12, 122.10, 123.63, 142.43, 144.07, 149.64, 153.22, 155.75, 156.11, 159.48, 170.54. Anal. Calc. for $C_{24}H_{29}N_5O_5 \cdot H_2O$: C, 59.37; H, 6.44; N, 14.42, Found: C, 58.89; H, 6.34; N, 13.97.

*5.1.8.8. N-(6,7-Dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-[4-(furan-2-carbonyl)piperazin-1-yl]acetamide (**13h**).* Recrystallized from ethanol (yield 33%); m.p. 120–122 °C. IR (KBr, cm^{-1}): 3506 (NH), 2925 and 2845 (CH$_2$), 1705 and 1683 (2C=O), 1612 (C=C). ^{1}H NMR, 200 MHz (CDCl$_3$): δ 2.71 (s, 3H, CH$_3$), 2.73 (br, 4H, CH$_2$ of piperazine), 3.13 (m, 4H, 2CH$_2$ of piperazine), 3.48 and 3.61 (br, 2× 1H, COCH$_2$), 4.15 and 4.18 (s,s, 2× 3H, 2OCH$_3$), 6.67 (m, 1H, H-4′ of furoyl), 7.23 (m, 2H, H-3′ and H-5′ of furoyl), 7.44 (s, 1H, H-8), 8.67 (s, 1H, H-5). ^{13}C NMR, 200 MHz (CDCl$_3$): δ 21.46 (CH$_3$), 53.88 (4CH$_2$ of piperazine), 56.45 and 56.49 (2OCH$_3$), 61.06 (COCH$_2$N), 102.17, 105.75, 107.90, 111.54, 113.86, 116.99, 143.58, 143.95, 147.86, 149.11, 154.00, 155.59, 159.24, 170.89. Anal. Calc. for $C_{22}H_{25}N_5O_6$: C, 58.01; H, 5.53; N, 15.38, Found: C, 58.04; H, 5.55; N, 15.59.

*5.1.8.9. N-(6,7-Dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(4-phenylpiperazin-1-yl)propanamide (**13i**).* Recrystallized from ethanol (yield 63%); m.p. 143–145 °C. IR (KBr, cm^{-1}): 3506 (NH), 2916 and 2819 (CH$_2$), 1705 and 1678 (2C=O), 1599 (C=C). ^{1}H NMR, 200 MHz (DMSO-d_6): δ 2.37 (s, 3H, CH$_3$), 2.50–288 (m, 8H, COCH$_2$CH$_2$N and 2CH$_2$ of piperazine), 3.12 (br, 4H, 2CH$_2$ of piperazine), 3.86 and 3.90 (s,s, 2× 3H, 2OCH$_3$), 6.76 (t, 1H, J = 7.41 Hz, H-4′ of C$_6$H$_5$), 6.93 (d, 2H, J = 7.41 Hz, H-2′ and H-6′ of C$_6$H$_5$), 7.12 (s, 1H, H-8), 7.20 (t, 2H, J = 7.41 Hz, H-3′ and H-5′ of C$_6$H$_5$), 7.39 (s, 1H, H-5), 11.01 (br, 1H, NHCO). ^{13}C NMR, 200 MHz (DMSO-d_6): δ 22.33 (CH$_3$), 32.66 (COCH$_2$CH$_2$N), 49.40 (2CH$_2$ of piperazine), 53.69 (2CH$_2$ of piperazine), 54.84 (COCH$_2$CH$_2$N), 57.01 and 57.27 (2OCH$_3$), 106.63, 109.05, 114.76, 116.57, 120.03, 130.16, 144.11, 149.61, 152.23, 155.81, 156.10, 159.61, 172.30. MS (m/z, %): 451.1 (M$^+$, 0.60), 55.00 (100.0). Anal. Calc. for $C_{24}H_{29}N_5O_4 \cdot H_2O$: C, 61.39; H, 6.65; N, 14.92, Found: C, 61.81; H, 6.58; N, 14.93.

*5.1.8.10. N-(6,7-Dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]propanamide (**13j**).* Recrystallized from ethanol/water (yield 45%); m.p. 83–85 °C. IR (KBr, cm^{-1}): 3463 (NH), 2933 and 2819 (CH$_2$), 1678 (br, 2C=O), 1608 (C=C). ^{1}H NMR, 200 MHz (DMSO-d_6): δ 2.39 (s, 3H, CH$_3$), 2.64 (m, 2H, COCH$_2$CH$_2$N), 2.85–2.99 (m, 6H, 2CH$_2$ of piperazine and COCH$_2$CH$_2$N), 3.13 (br, 4H, 2CH$_2$ of piperazine), 3.85 (s, 3H, 2′-CH$_3$O of C$_6$H$_4$), 3.94 and 3.96 (s,s, 2× 3H, 2CH$_3$O of quinazoline), 6.82–6.95 (m, 4H, H-3′-6′ of C$_6$H$_4$), 7.12 (s, 1H, H-8), 7.49 (s, 1H, H-5). ^{13}C NMR, 200 MHz (DMSO-d_6): δ 21.65 (CH$_3$), 31.47 (COCH$_2$CH$_2$N), 50.92, (2CH$_2$ of piperazine), 52.70 (2CH$_2$ of piperazine), 53.14 (COCH$_2$CH$_2$N), 55.61, 56.52 and 56.89 (3 OCH$_3$), 105.97, 107.82, 111.42, 114.25, 118.45, 121.16, 123.47, 140.94, 143.70, 148.93, 152.38, 154.49, 155.36, 159.34, 173.67. Anal. Calc. for $C_{24}H_{31}N_5O_5 \cdot H_2O$: C, 60.11; H, 6.66; N, 14.02, Found: C, 60.38; H, 6.60; N, 13.91.

*5.1.8.11. N-(6,7-Dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-[4-(4-nitrophenyl)piperazin-1-yl]propanamide (**13k**).* Recrystallized from methanol/acetone (yield 58%); m.p. 147–149 °C. IR (KBr, cm^{-1}): 3480 (NH), 2949 and 2828 (CH$_2$), 1674 (br, 2C=O), 1599 (C=C). ^{1}H NMR, 200 MHz (CDCl$_3$): δ 1.97 (s, 3H, CH$_3$), 2.10–2.35 (m, 6H, COCH$_2$CH$_2$N and 2CH$_2$ of piperazine), 3.01 (br, 2H, COCH$_2$CH$_2$N), 3.13 (br, 4H, 2CH$_2$ of piperazine), 3.46 and 3.48 (s,s, 2× 3H, 2CH$_3$O of quinazoline), 6.83 (d, 2H, J = 7.40 Hz, H-2′ and H-6′ of 4′-NO$_2$–C$_6$H$_5$), 6.93 (s, 1H, H-8), 7.32 (s, 1H, H-5), 7.95 (d, 2H, J = 7.40 Hz, H-3′ and H-5′). ^{13}C NMR, 200 MHz (CDCl$_3$): δ 20.27 (CH$_3$), 30.88 (COCH$_2$CH$_2$N), 45.47, (2CH$_2$ of piperazine), 51.04 (2CH$_2$ of piperazine), 52.79 (COCH$_2$CH$_2$N), 54.75 and 54.86 (2OCH$_3$), 104.40, 106.35, 111.42, 112.91, 124.55, 127.26, 142.03, 147.10, 153.51, 153.64, 153.73, 157.62, 170.64. Anal. Calc. for $C_{24}H_{29}N_5O_5 \cdot 1.5H_2O$: C, 55.06; H, 5.97; N, 16.05, Found: C, 55.10; H, 5.84; N, 15.93.

*5.1.8.12. N-(6,7-Dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-[4-(furan-2-carbonyl)piperazin-1-yl]propanamide (**13l**).* Recrystallized from ethanol/acetonitrile (yield 62%); m.p. 94–96 °C. IR (KBr, cm^{-1}): 3462 (NH), 2933 and 2819 (CH$_2$), 1678 (br, 2C=O), 1608 (C=C). ^{1}H NMR, 200 MHz (CDCl$_3$): δ 2.51 (s, 3H, CH$_3$), 2.65–2.94 (m, 10H, COCH$_2$CH$_2$N and 4H, 2CH$_2$ of piperazine), 3.75 (t,br, 2H, COCH$_2$CH$_2$N), 3.95 and 3.97 (s,s, 2× 3H, 2OCH$_3$), 6.47 (m, 1H, H-4′ of furoyl), 7.00 (d, 1H, J = 3.28 Hz, H-5′ of furoyl), 7.05 (s, 1H, H-8), 7.46 (m, 1H, H-3′ of furoyl), 7.48 (s, 1H, H-5). ^{13}C NMR, 200 MHz (CDCl$_3$): δ 21.89 (CH$_3$), 31.81 (COCH$_2$CH$_2$N), 52.97 (4CH$_2$ of piperazine), 53.36 (COCH$_2$CH$_2$N), 56.75 and 56.86 (2OCH$_3$), 106.15, 108.18, 109.65, 111.90, 114.39, 117.29, 144.03, 144.33, 148.20, 149.32, 154.58, 155.78, 159.57, 173.77. Anal. Calc. for $C_{23}H_{27}N_5O_6$: C, 58.84; H, 5.80; N, 14.92, Found: C, 58.43; H, 6.20; N, 14.74.

5.2. Computational study

In this work, we utilized pharmacophore model for a set of potent α_1-AR antagonists developed in a previous publication to prioritize the designed compounds by mapping them to the generated pharmacophore model [15].

The pharmacophore hypothesis was produced using Accelrys Discovery Studio 2.1 (Accelrys Inc., San Diego, CA, USA). HipHop algorithm, which identifies common chemical features from a set of ligands without the use of affinity data, was used to develop the pharmacophore model. The set of conformational models of each structure of the lead compounds was performed and was used to generate the common feature hypotheses. The ideal hypothesis encompassed five features; positive ionizable nitrogen, three hydrophobic pockets and a hydrogen bond acceptor group.

The calculation of fitting and relative energy values of the best-fitted conformers of the target compounds preceded as follows:

1. The structures of the test set of the target quinazolinones were built using the Discovery studio software.
2. Their conformational models were generated in the energy range of 20 kcal/mol above the estimated global energy minimum to ensure conformational diversity.
3. The fitting of the tested compounds was performed using ligand pharmacophore mapping protocol. The best fit option has been selected which manipulate conformers of each compound to find, when possible, different mapping modes of the ligand within the model. Different mappings for all the conformers of each compound of the test set to the hypothesis were visualized and the fit values of the best-fitting conformers were found and are listed in Table 1.

5.3. Pharmacology

5.3.1. In vivo biological evaluation

In vivo biological evaluation of the hypotensive effect of the tested compounds on the arterial blood pressure of normotensive adult cats was conducted adopting the reported method [27].

Male cats weighing 2–3 kg were housed in the animal facility for 7 days prior to the experiment. Animals were kept at 22 ± 2 °C and 12 h light/12 h dark cycle. Stressful condition or manipulation was avoided. Experiments were performed between 8 and 10 a.m.

Cats were divided into groups, each of six animals. Cats were anaesthetized with phenobarbitone sodium (30 mg/kg ip). The right femoral artery of the leg was exposed, cleared from connective tissue for a distance of about 2 cm and was used for blood

pressure determination. The left femoral vein was exposed and then connected to saline infusion through a cannula. Tested drugs were all dissolved in 1 mL DMSO and then diluted with water to the final volume. Tested compounds were injected in 500 μg/kg dose through the femoral vein and washed with 1 mL saline. Blood pressure was recorded using Washington 400 MD2C mercury manometers on smoked kymograph. The effects of prazosin (reference drug) and saline/DMSO (control) were compared to those of the tested compounds. The results are given in Table 2.

5.3.2. In vitro vasodilatation activity (functional bioassay)

The vasodilatation activity screening procedures were carried out according to the standard reported techniques [28,29] by testing the effects of the most potent hypotensive quinazolinone derivatives **4b**, **9e**, **13i**, **13j** on isolated thoracic aortic rings of male Wister rats (250–350 g). After light ether anesthesia, the rats were sacrificed by cervical dislocation and bleeding. The aorta was immediately excised, freed of extraneous tissues and prepared for isometric tension recording. Aorta was cut in 3–5 mm long rings and placed in a vertical chamber "10 mL jacketed automatic multi-chamber organ bath system (model no. ML870B6/C, Panlab, Spain)" filled with modified Krebse Henseleit solution composed of (in mM): NaCl, 118.0; KCl, 4.7; $NaHCO_3$, 25.0; $CaCl_2$, 1.8; NaH_2PO_4, 1.2; $MgSO_4$, 1.2; glucose, 11.0 and oxygenated with carbogen gas (95% O_2/5% CO_2) at 37 ± 0.5 °C. Each aorta ring was mounted between two stainless steel hooks passed through its lumen. The lower hook was fixed between two plates, while the upper one was attached to a force displacement transducer (Model no. MLT0201/Panlab, Spain) connected to an amplifier (powerLab, AD Instruments Pty. Ltd) which is connected to a computer. The Chart for windows (v 3.4) software was used to record and elaborate data.

Preparations were stabilized under 2 g resting tension during 2 h. The lack of endothelium was confirmed by the absence of acetylcholine (1 μM) vasorelaxent action in aortic rings precotracted by noradrenaline (0.1 μM). The contractile response to norepinephrine hydrochloride (10^{-6} M) was measured before and after exposure to increasing concentrations of the tested compounds. The compounds **4b**, **9e**, **13i**, **13j** as well as prazosin hydrochloride (as reference standard) were dissolved in dimethylsulfoxide (DMSO) as stock solution (10 mL of 0.01 M). Control experiments were performed in the presence of DMSO alone, at the same concentrations as those used with the derivatives tested, which demonstrated that the solvent did not affect the contractile response of isolated aorta. The observed vasodilatation activity data are reported (Table 3, Fig. 6) and the potency (IC_{50}, concentration necessary for 50% reduction of maximal norepinephrine hydrochloride induced contracture) was determined by the best fit line technique.

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References

[1] A. Ferro, R. Gilbert, H. Krum, Int. J. Clin. Pract. 60 (2006) 577–581 American Heart Association, Statistics: (2007).
[2] R. Barbaro, L. Betti, M. Botta, F. Corelli, G. Giannaccini, L. Maccari, F. Manetti, G. Strappaghetti, F. Corsano, J. Med. Chem. 44 (2001) 2118–2132.
[3] D. Bylund, D. Eikenberg, J. Heieble, S. Langer, R. Lefkowiskitz, K. Minneman, P. Molinoff, R. Rufolo, U. Trendelenburg, Pharmacol. Rev. 46 (1994) 121–136.
[4] C. Forray, J. Wetzel, T. Brancheck, J. Bard, G. Chin, E. Shapiro, R. Tang, H. Lepor, P. Hartig, R. Weinshbank, C. Gluchowski, Mol. Pharmacol. 45 (1994) 703–708.
[5] A. Michael, L. Ann, P. Theodore, S. Raymond, W. Richard, D. Jerry, F. Carlos, J. Med. Chem. 41 (1998) 1206–1210.
[6] J. Handzlik, D. Maciag, M. Kubacka, S. Mogliski, B. Filipek, K. Stadnicka, K. Kiec-Kononowicz, Bioorg. Med. Chem. 16 (2008) 5982–5998.
[7] V. Alabaster, S. Campbell, J. Danilewicz, C. Greengrass, R.M. Plews, J. Med. Chem. 30 (1987) 999–1003.
[8] H. Lepor, Prostate Suppl. 3 (1990) 75–84.
[9] H. Nagano, M. Takagi, N. Kubodera, I. Matsunaga, H. Nabata, Y. Ohba, K. Sakai, S. Hata, Y. Uchida, Eur. Pat. 89065, 1983, Chugai Pharmaceutical Co., Ltd., Japan; Chem. Abstr. 100 (1983) 6547p.
[10] V. Bandurco, C. Schwender, R. Falotico, A. Tobia, J. Eur. Patent 0 219 259, 1987, Ortho Pharmaceutical Corp., U.S. Route 202 P.O. Box 300, Raritan New Jersey 08869–0602(US).
[11] R. Russell, J. Press, R. Rampulla, J. McNally, R. Falotico, J. Keiser, D. Bright, A. Tobia, J. Med. Chem. 31 (1988) 1786–1793.
[12] T. Elworthy, A. Ford, G. Bantle, D. Morgans, J. Med. Chem. 40 (1997) 2674–2687.
[13] D.A. Abou El Ella, R.A. Taha, Bull. Fac. Pharm. Cairo Univ. 45 (2007) 267–281.
[14] L. Betti, M. Botto, F. Corelli, M. Floridi, P. Fossa, G. Giannaccini, F. Manetti, G. Strappaghetti, S. Corasno, Bioorg. Med. Chem. Lett. 12 (2002) 437–440.
[15] M.A.H. Ismail, M.N.Y. Aboul-Enein, K.A.M. Abouzid, R.A.T. Serya, Bioorg. Med. Chem. 14 (2006) 898–910.
[16] K.I. Ozaki, Y. Yamada, T. Oine, Chem. Pharm. Bull. 31 (1983) 2234–2243.
[17] D. Tworowski, R. Matsievitch, PCT Int. Appl. 2007, 108pp. CODEN: PIXXD2 WO 2007110868 A2 20071004.
[18] C.M. Gupta, A.P. Bhaduri, N.M. Khanna, J. Med. Chem. 11 (1968) 392–395.
[19] E. Schuler, N. Juanico, J. Teixido, E.L. Michelotti, J.I. Borrell, Heterocycles 67 (2006) 161–173.
[20] T. George, D.V. Mehta, R. Tahilramani, Indian J. Chem. 9 (1971) 755–758.
[21] L.A. Errede, J. Org. Chem. 41 (1976) 1763–1767.
[22] S. Bueyuektimkin, Pharmazie 40 (1985) 393–395.
[23] V. Alagarsamy, Pharmazie 59 (2004) 753–755.
[24] J. Zou, H.Z. Xie, S.Y. Yang, J.J. Chen, J.X. Ren, Y.Q. Wei, J. Mol. Graph. Model. 27 (2008) 430–438.
[25] S. Ekins, J. Mestres, B. Testa, Br. J. Pharmacol. 152 (2007) 21–37.
[26] R. Barbaro, L. Betti, M. Botta, F. Corelli, G. Giannaccini, L. Maccari, F. Manetti, G. Strappaghetti, F. Corsano, Bioorg. Med. Chem. 10 (2002) 361–369.
[27] T. Litchfield, A. Wilcoxon, J. Pharmacol. Exp. Ther. 96 (1949) 99–113.
[28] A.S. Girgis, N. Mishriky, A.M. Forag, W.I. El-Eraky, H. Farag, Eur. J. Med. Chem. 43 (2008) 1818–1827.
[29] A.S. Girgis, A. Kalmouch, M. Ellithey, Bioorg. Med. Chem. 14 (2006) 8488–8494.
[30] G.H. Kuo, C. Prouty, W.V. Murray, V. Pulito, L. Jolliffe, P. Cheung, S. Varga, M. Evangelisto, C. Shaw, Bioorg. Med. Chem. 8 (2000) 2263–2275.