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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of oxadiazoline and quinazolinone derivatives and their biological evaluation as nitric oxide synthase inhibitors

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Abstract The synthesis of two new families of compounds with oxadiazoline and quinazolinone structures and their in vitro biological evaluation as inhibitors of both neuronal and inducible nitric oxide synthases (nNOS and iNOS) are described. These derivatives have been obtained from cyclization of substituted benzohydrazides with acid anhydrides followed by reduction, using different synthetic procedures. Their structures were confirmed by high-resolution mass spectroscopy and ^{1}H and ^{13}C nuclear magnetic resonance data. In general, the assayed compounds show better inhibition values of nNOS than of iNOS, being **7d** the most active derivative with a quinazolinone scaffold, and **6t** the best oxadiazoline one and the best nNOS inhibitor of all tested compounds. The structure–activity relationships are discussed in terms of the effects of the substituents on both 2- and 3-positions of the heterocyclic rings.

Keywords Oxadiazolines · Quinazolinones · Inhibition · Neuronal nitric oxide synthase (nNOS) · Inducible nitric oxide synthase (iNOS)

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Introduction

Nitric oxide (NO) is produced by oxidation of L-arginine (Stuehr and Griffith 1992) in a NADPH- and O_2-dependent process catalyzed by nitric oxide synthase (NOS). Three different isoforms of this enzyme have been identified (neuronal or nNOS, endothelial or eNOS, and inducible or iNOS) (Knowles *et al*., 1989; McCall *et al*., 1989). The constitutive endothelial and neuronal isoforms are calcium/calmodulin dependent and are physiologically activated by hormones or neurotransmitters that increase the intracellular calcium concentration. However, the inducible isoform is activated by basal intracellular calcium concentrations, and, once expressed, it remains activated, yielding high NO concentrations. This mechanism is part of the normal immune response against invading pathogens and neoplastic cells (Pozo *et al*., 1998).

Overproduction of NO by nNOS has been associated with several neurodegenerative disorders, such as Parkinson's, Alzheimer's, or Huntington's diseases, as well as migraine (Olesen, 2010; Aquilano *et al*., 2008; Villanueva and Giulivi 2010), while NO overproduction by the inducible isoform has been associated with tissue damage, inflammation, rheumatoid arthritis, and inflammatory bowel disease (Levy and Zochodne 2004; Vallance and Leiper 2002; LaBuda *et al*., 2006; Ijuin *et al*., 2006). Also, inflammatory reaction in Parkinson's disease is associated with iNOS (Dehmer *et al*., 2000). Since nNOS and iNOS represent a therapeutic target, inhibition of these enzymes by means of synthetic derivatives has become an interesting objective in the potential treatment of these diseases (Serafim *et al*., 2012).

Melatonin **1**, the hormone secreted by the pineal gland, is a well-known NOS inhibitor (Bettahi *et al*., 1996; Leon *et al*., 1998). In previous papers, we have described several

compounds with kynurenamine **2** (Entrena *et al*., 2005) and 4,5-dihydro-1*H*-pyrazole **3** structures (Camacho *et al*., 2004), as nNOS inhibitors. The last compounds are rigid analogues of the main brain metabolite of melatonin, the *N*-acetyl-5-methoxykynurenamine (**2**, $R_1 = OCH_3$, $R_2 = CH_3$), which also inhibits the iNOS in sepsis associated with Parkinson's disease (Tapias *et al*., 2009). In addition, we have published compounds with 5-phenyl-1*H*-pyrrole-2-carboxamide structure **4** which show moderate values of nNOS and iNOS inhibition (López-Cara *et al*., 2009). Finally, we have reported a group of 2,3-dihydro-1,3,4-thiadiazoles **5**, which exhibit good iNOS inhibition values (López-Cara *et al*., 2012) (Fig. 1).

In the present work, as an extension of the heterocyclic compounds synthesized as NOS inhibitors, we report a new group of derivatives with an 1,3,4-oxadiazoline scaffold **6**, where the sulfur atom of compounds **5** has been replaced by its isosteric oxygen. In addition, under the last step of the oxadiazolines' synthesis we have found that, when the C-2 of the heterocyclic ring is monosubstituted ($R_1 = H$), the molecules isomerize during the nitro group reduction to yield the quinazolinones **7**. These last derivatives have the NH_2 group forming a pyrimidine ring, and, consequently, their conformational freedom is more restricted. As well as the previously synthesized derivatives **2**–**5** and compounds **6** and **7** have been evaluated as in vitro inhibitors of both neuronal and inducible NOS in order to find new derivatives with interesting pharmacological properties. In this way, oxadiazoles as well as quinazolines are considered to be important chemical synthons with various therapeutic uses (Soares de Oliveira *et al*., 2012; Daidonea *et al*., 1999).

Results and discussion

Chemistry

Scheme 1 represents the general synthetic pathway of the final aminophenyl-oxadiazoline derivatives **6**, as well as the cyclized quinazolinone derivatives **7** described in this paper. The synthesis begins with the transformation of the 2-nitrobenzoic acid **8** into the corresponding ethyl 2-nitrobenzoate, followed by treatment with hydrazine in ethanol to afford the 2-nitrobenzohydrazide **9** (Balo *et al*., 2007). This compound was condensed to reflux with several carbonyl compounds (aldehydes and ketones), to give the benzohydrazides **10**–**15** (Raparti *et al*., 2009; Evans *et al*., 1986), which were cyclized to the 1,3,4-oxadiazole derivatives **16a**–**s** by treatment to reflux with the corresponding acid anhydrides (Chaaban *et al*., 2014; Joshi *et al*., 2008). Finally, reduction of the nitro group belonging to the aromatic ring of the aryloxadiazolines **16** leads different types of compounds depending of the R_1 and R_2 substituents in C-2 of the heterocyclic ring. Thus, when this position is monosubstituted ($R_1 = H$), the reduction of the nitro group belonging to derivatives **16a**–**l**, by refluxing with $Fe/FeSO_4$ in water (Zhu *et al*., 1995), leads to the opening of the oxadiazole ring and to the rearrangement of the final quinazolinones **7a**–**l** (Davidson, 1984). Nevertheless, when C-2 is disubstituted ($R_1 = Me$), the reduction of compounds **16m**–**p** and **16r**–**t** by the same procedure yields the aminophenyl-oxadiazolines **6m**–**p** and **6r**–**t**. Moreover, the reduction of **16p** led not only to compound **6p**, but also to **6q**, due to the presence of a valeric anhydride remainder. Finally, in order to obtain the

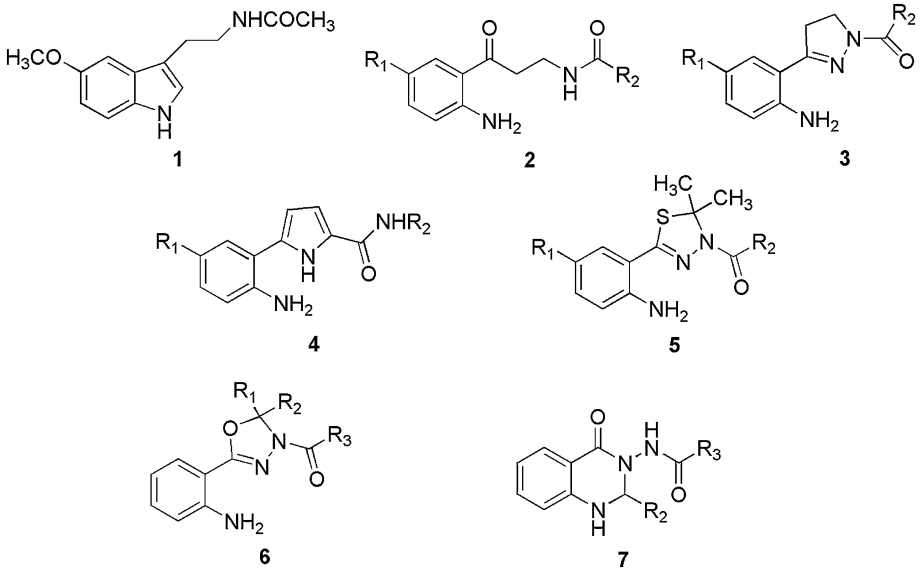
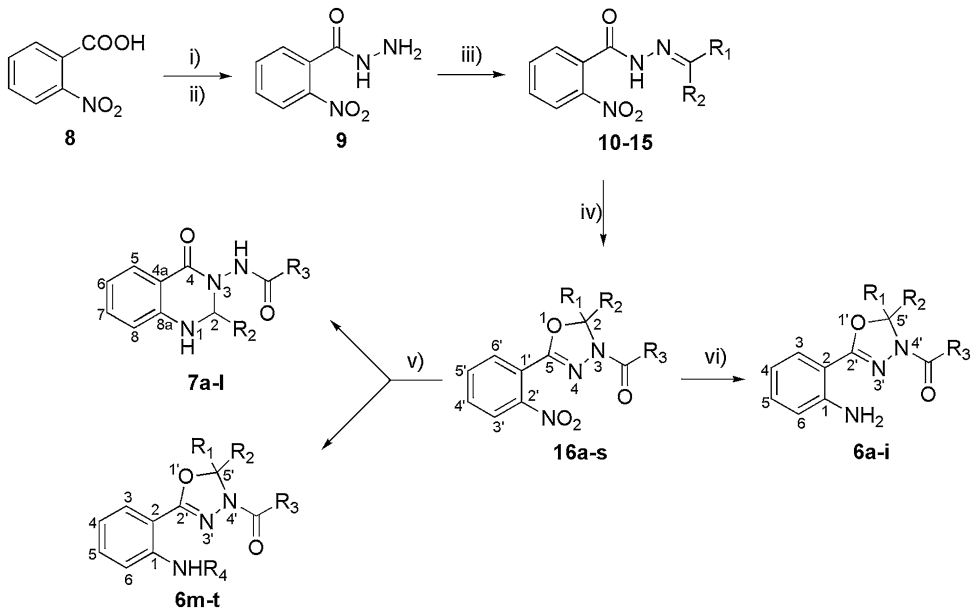


Fig. 1 Melatonin and some NOS inhibitors synthesized by our research group



Scheme 1 General synthetic pathway followed in the preparation of derivatives **6a–i**, **6m–t** and **7a–l**: *i* EtOH/H_2SO_4, reflux, 24 h; *ii* NH_2NH_2, dry EtOH, reflux, 5 h; *iii* R_1COR_2, dry EtOH, reflux, 1.5–24 h; *iv* $(R_3CO)_2O$, reflux, 2 h; *v* Fe/$FeSO_4$, H_2O, reflux, 3 h; *vi* H_2, Pd–C (10 %), MeOH, 1 atm, RT, 3 h

Table 1 Structural data and yields of the intermediate (**10–16**) and final (**6**, **7**) compounds described

R_1	R_2	R_3	R_4	Comp.	Comp.	mg obtained (%Rto.)	Comp.	mg obtained (%Rto.)	Comp.	mg obtained (%Rto.)
H	Me	Me	H		**16a**	177 (71)	**6a**	85 (94)	**7a**	72 (63)
H	Me	Et	H	**10**	**16b**	183 (70)	**6b**	87 (90)	**7b**	82 (67)
H	Me	Pr	H		**16c**	186 (67)	**6c**	92 (90)	**7c**	85 (66)
H	Me	Bu	H		**16d**	213 (73)	**6d**	102 (94)	**7d**	90 (66)
H	Et	Me	H		**16e**	189 (72)	**6e**	89 (92)	**7e**	89 (73)
H	Et	Et	H	**11**	**16f**	222(80)	**6f**	97 (95)	**7f**	83 (64)
H	Et	Pr	H		**16g**	198 (68)	**6g**	99 (92)	**7g**	93 (68)
H	Et	Bu	H		**16h**	232 (76)	**6h**	103 (90)	**7h**	71 (49)
H	Ph	Me	H		**16i**	196 (63)	**6i**	107 (92)	**7i**	80 (54)
H	Ph	Et	H	**12**	**16j**	234 (72)			**7j**	73 (47)
H	Ph	Pr	H		**16k**	200 (59)			**7k**	65 (40)
H	Ph	Bu	H		**16l**	227 (63)			**7l**	127 (75)
Me	Me	Me	H		**16m**	168 (64)	**6m**	62 (51)		
Me	Me	Et	H		**16n**	233 (84)	**6n**	79 (61)		
Me	Me	Pr	H	**13**	**16o**	236 (81)	**6o**	111 (81)		
Me	Me	Bu	H		**16p**	238 (78)	**6p**	82 (57)		
Me	Me	Bu	COBu				**6q**	37 (27)		
Me	Et	Me	H	**14**	**16r**	208 (75)	**6r**	107 (83)		
Me	Et	Et	H		**16s**	230 (79)	**6s**	107 (78)		
Me	Ph	Me	H	**15**	**16t**	267 (82)	**6t**	124 (80)		

aminophenyl-1,3,4-oxadiazoline derivatives **6a–i** with $R_1 = H$, we carried out the reduction of compounds **16a–i** by catalytic hydrogenation (Pd–C), with the purpose of avoiding the formation of quinazoline derivatives. Table 1 shows the structural data of all the intermediate and final compounds synthesized.

nNOS and iNOS inhibition

The biological activities of final compounds **6** and **7** as inhibitors of both nNOS and iNOS have been evaluated by means of in vitro assays using recombinant isoenzymes (Bredt and Snyder 1990). In order to identify the most

potent compounds, a first assay using 1 mM concentration of each compound was performed. Figure 2 shows the percentages of residual activity of both isoforms in the presence of each compound in relation to the control (**c**), and Table 2 illustrates the inhibition percentages versus iNOS and nNOS. The thiadiazolines **5a–e** (**5a**: $R_1 = H$, $R_2 = Me$; **5b**: $R_1 = H$, $R_2 = Et$; **5c**: $R_1 = H$, $R_2 = Pr$; **5d**: $R_1 = H$, $R_2 = Bu$; **5e**: $R_1 = H$, $R_2 = c\text{-}C_3H_5$) (Fig. 1) previously described by our research group (López-Cara *et al*., 2012) and the well-known NOS inhibitor L-NAME (Kilbourn and Griffith 1992) have been introduced as controls to compare them with the new oxadiazolines and quinazolinones.

In general, regarding the iNOS inhibition values, oxadiazolines **6** are better inhibitors than quinazolinones **7**. In derivatives with structure type **6**, there are six compounds which show more than 40 % of inhibition. Nevertheless, some conclusions can be inferred from the experimental data. From a qualitative point of view, the influence of R_1 and R_2 over the iNOS activity is variable. When $R_1 = H$ (**6a–i**), compounds with $R_2 = Et$ (**6e–h**) have better values of inhibitory activity than molecules with $R_2 = Me$ (**6a–d**) or Ph (**6i**), being **6f**, **6g,** and **6h** the best inhibitors of this group with 43.5, 41.0, and 41.8 % of inhibition, respectively. Furthermore, when $R_1 = Me$ (**6m–t**), derivatives with $R_2 = Et$ or Ph show the best inhibition values, being **6s** ($R_2 = R_3 = Et$, 52.9 %) and **6t** ($R_2 = Ph$, $R_3 = Me$, 52.1 %) the most potent compounds of this group and the best iNOS inhibitors of all the oxadiazoline derivatives tested. On the other hand, improved inhibitory activity is observed when the volume in R_3 increases (from Me to Bu), maintaining the same R_1 and R_2 substituents on the heterocyclic ring, with the exception of **6f** ($R_3 = Et$), which is more potent than **6g** and **6h**, with less volume in R_3. Among the quinazolinones **7**, there are not compounds that exhibit a significant value of inhibition of this isoform.

Table 2 also shows the nNOS inhibition values observed in the presence of 1 mM concentration of final compounds **6** and **7**. In this case, oxadiazolines have also better values of inhibition than quinazolinones, since four compounds display more than 40 % of inhibition versus only two quinazolinones. Regarding oxadiazolines with the same substituents $R_1 = R_2 = Me$ (**6m–q**), the most potent compounds have a methyl group (**6m**, 41.1 %) or a butyl one (**6p**, 55.1 % and **6q**, 48.8 %) in R_3. In addition, **6t** ($R_1 = R_3 = Me$, $R_2 = Ph$) is the most potent compound of this group (74.0 % of inhibition) and the best nNOS inhibitor of all the tested compounds. In quinazolinones, compounds with $R_2 = Me$ (**7a–d**) show better inhibition values than derivatives with Et (**7e–h**) or Ph (**7i–l**), being the most active compounds **7a** ($R_3 = Me$, 43.1 %) and **7d** ($R_3 = Bu$, 65.3 %), which is the most potent inhibitor of this family.

Furthermore, Table 2 includes the inhibition values for both isoenzymes of several thiadiazolines **5** previously published (López-Cara *et al*., 2012). Although some of these compounds have demonstrated to be selective iNOS/nNOS inhibitors, the comparison of compounds **5a–d** and **6m–p** wearing the same substituents in both the heterocyclic ring and the acyl group indicates that oxadiazolines have slightly higher values of inhibition than their isosteres with a sulfur atom. In general, oxadiazolines have higher potency versus nNOS than thiadiazolines, proving that the

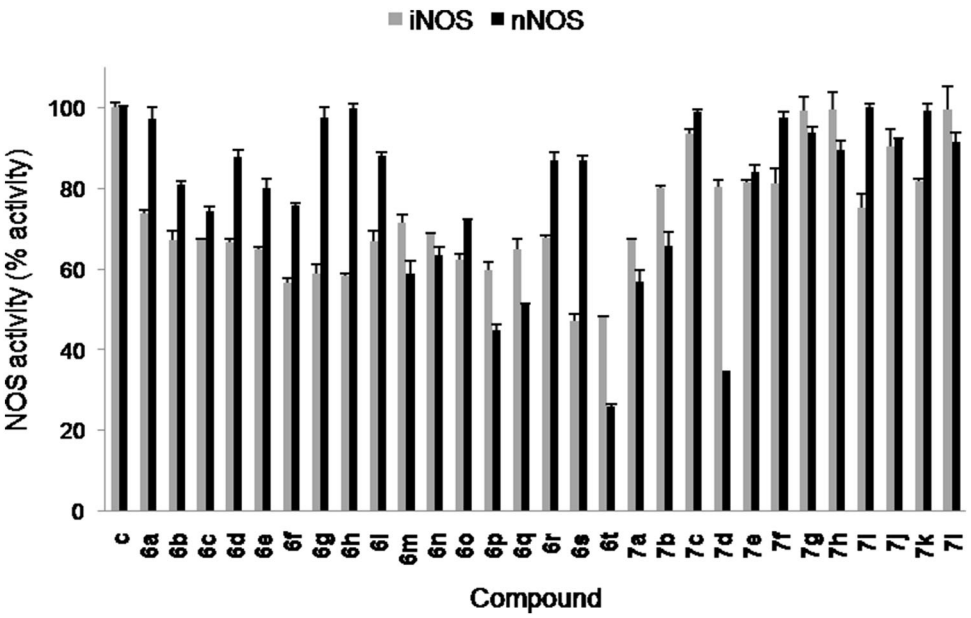


Fig. 2 Percentage of iNOS and nNOS residual activities in the presence of 1 mM of the oxadiazolines (compounds **6a–t**) and the quinazolinones (compounds **7a–l**) assayed as compared to those of untreated samples (**c**). Each value is the mean of three experiments performed in triplicate using recombinant iNOS or nNOS enzymes

Table 2 In vitro nNOS and iNOS inhibition (%) observed in the presence of 1 mM concentration of final compounds **6a–t** and **7a–l**. Thiadiazolines **5a–e** and **L-NAME** are included as controls

Comp.	% iNOS inhibition[a]	% nNOS inhibition[a]	iNOS/nNOS selectivity	Comp.	% iNOS inhibition[a]	% nNOS inhibition[a]	iNOS/nNOS selectivity
6a	26.15 ± 0.70	20.56 ± 2.82	1.27	**7a**	32.81 ± 0.37	43.08 ± 2.87	0.76
6b	32.78 ± 2.36	18.98 ± 0.87	2.73	**7b**	19.81 ± 0.43	34.18 ± 3.26	0.58
6c	32.96 ± 0.53	25.59 ± 1.21	1.29	**7c**	6.40 ± 1.03	0.97 ± 0.45	6.60
6d	33.51 ± 0.86	12.24 ± 1.85	2.74	**7d**	19.61 ± 1.73	65.32 ± 0.23	0.30
6e	35.23 ± 0.59	19.93 ± 2.21	1.77	**7e**	18.46 ± 0.48	15.89 ± 1.58	1.17
6f	43.55 ± 1.40	24.03 ± 0.71	1.81	**7f**	18.93 ± 3.87	2.47 ± 1.33	7.66
6g	41.04 ± 2.11	2.36 ± 2.51	17.39	**7g**	0.68 ± 3.29	6.26 ± 1.38	0.11
6h	41.76 ± 0.76	0.09 ± 1.20	464.0	**7h**	0.50 ± 4.23	10.46 ± 2.38	0.05
6i	33.13 ± 2.66	11.85 ± 0.67	2.80	**7i**	24.91 ± 3.57	0.02 ± 0.97	1245.5
6m	28.41 ± 1.76	41.08 ± 3.12	0.69	**7j**	9.51 ± 4.06	7.78 ± 0.11	1.22
6n	31.38 ± 0.23	36.50 ± 2.04	0.86	**7k**	18.26 ± 0.59	0.81 ± 1.87	22.54
6o	37.63 ± 1.33	28.01 ± 0.32	1.34	**7l**	0.39 ± 5.74	8.34 ± 2.22	0.05
6p	40.28 ± 1.89	55.11 ± 1.25	0.73	**5a**[b]	22.85 ± 1.21	13.27 ± 2.12	1.72
6q	34.98 ± 2.32	48.78 ± 0.21	0.72	**5b**[b]	19.24 ± 1.75	24.21 ± 1.23	0.79
6r	32.20 ± 0.45	13,11 ± 2.03	2.46	**5c**[b]	35.18 ± 2.01	17.46 ± 1.94	2.01
6s	52.85 ± 1.58	13.32 ± 1.23	3.97	**5d**[b]	39.05 ± 1.32	38.05 ± 0.73	1.03
6t	52.10 ± 0.46	73.95 ± 0.49	0.71	**5e**[b]	92.96 ± 0.68	7.32 ± 3.65	12.69
				L-NAME[c]	77.01 ± 0.96	100.0 ± 1.03	0.77

[a] Data represent the mean ± SEM of the percentage of iNOS and nNOS inhibition produced by 1 mM concentration of each compound. Each value is the mean of three experiments performed by triplicate using recombinant iNOS and nNOS enzymes

[b] See Ref. López-Cara *et al*. (2012)

[c] See Ref. Kilbourn and Griffith (1992)

Table 3 IC_{50} values (mM) for the iNOS and nNOS inhibition by the derivatives **6p**, **6s**, **6t**, and **7d**

Compound	IC_{50} iNOS[a]	IC_{50} nNOS[a]
6p	b	0.928
6s	0.968	b
6t	0.981	0.468
7d	b	0.879

[a] Data were obtained by measuring percentage of inhibition with at least five concentrations of inhibitor

[b] Not tested

presence of an oxygen atom in the heterocyclic ring improves the nNOS inhibition.

Table 3 shows the IC_{50} values measured for the nNOS and iNOS inhibition of the most interesting compounds observed in the initial in vitro assay. The oxadiazoline **6t** and the quinazolinone **7d** show the best results versus nNOS, with IC_{50} values between 0.47 and 0.88 mM, respectively, confirming that **6t** is the most potent inhibitor of all synthesized compounds versus nNOS. Respect to iNOS, IC_{50} values are around 0.97 mM.

Conclusions

In summary, in this paper we report the synthesis of 17 novel oxadiazole derivatives **6** structurally related to the above-described thiadiazolines **5**, as well as 12 new quinazolinones **7**. In this second family, the NH_2 group of the benzene ring, present in the previous inhibitors, is now included in a pyrimidine ring, giving more conformationally restricted molecules. In addition, we evaluate the nNOS and iNOS activities of these new structures. Although they mostly reveal moderate activity, several compounds show promising values. In general, the tested derivatives have better nNOS inhibition values than those of iNOS, and the oxadiazolines are more potent than the less flexible quinazolinones, showing that the inclusion of the free amine group in a new ring is detrimental for the inhibitory activity. Moreover, we have demonstrated that the presence of an oxygen atom in the heterocyclic ring of derivatives **6** leads to better inhibitory activity against nNOS, in contrast to the higher potency of the isosteric thiadiazolines **5** versus iNOS. Compound **7d** is the most potent nNOS inhibitor with a quinazolinone skeleton, and **6t** is the best one with an oxadiazoline heterocycle, being also the best nNOS inhibitor of all the tested compounds.

Thus, **6t** should be an interesting starting point in the development of therapeutic agents for the treatment of NO-related diseases, where both isoforms are implied, such as Parkinson's.

Experimental

Instruments and reagent

Melting points were determined using an Electrothermal-1A-6301 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer operating at 300.160 for ^{1}H and 75.479 MHz for ^{13}C, and on a Bruker ARX 400 spectrometer operating at 400.132 MHz for ^{1}H and 100.623 MHz for ^{13}C, in $CDCl_3$, $(CD_3)_2CO$, and $(CD_3)_2SO$ at room temperature (rt). The peaks are reported in ppm (δ) and are referenced to the residual solvent peak. High-resolution nano-assisted laser desorption/ionization or electrospray ionization mass spectra were carried out on a Bruker Autoflex or a Waters LCT Premier mass spectrometer, respectively. Analytical thin layer chromatography was performed using Merck Kieselgel 60 F254 aluminum sheets, the spots being developed with UV light ($\lambda = 254$ nm). Flash chromatography was carried out using silica gel 60, 230–240 mesh (Merck), and the solvent mixture reported within parentheses was used as eluent.

General synthetic procedure

*General procedure for the preparation of compounds **16a–p** and **16r–t***

A mixture of the appropriate benzohydrazides **10–15** (1.0 mmol) and the corresponding acid anhydride (53.0 mmol) was heated under reflux for 2 h. The reaction mixture was then concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and filtered. Evaporation of the solvent rendered a residue that was purified by flash chromatography (ethyl acetate/hexane 1:1), to give **16**.

*3-Acetyl-2-methyl-5-(2-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (**16a**)* Yield 71 % (0.171 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.88$ (2H, m, H-3′, H-6′), 7.70 (2H, m, H-4′, H-5′), 6.39 (1H, q, $J = 5.4$ Hz, H-2), 2.30 (3H, s, $COCH_3$), 1.71 (3H, d, $J = 5.0$ Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 168.04$ (C, C=O), 152.92 (C, C-5), 146.22 (C, C-2′), 132.65 (CH, C-4′), 132.34 (CH, C-5′), 130.88 (CH, C-6′), 124.46 (CH, C-3′), 119.32 (C, C-1′), 91.32 (CH, C-2), 21.61 (CH_3, $COCH_3$), 20.13 (CH_3, CH_3).

*2-Methyl-5-(2-nitrophenyl)-3-propionyl-2,3-dihydro-1,3,4-oxadiazole (**16b**)* Yield 70 % (0.183 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.83$ (2H, m, H-3′, H-6′), 7.64 (2H, m, H-4′, H-5′), 6.34 (1H, q, $J = 4.0$ Hz, H-2), 2.60 (2H, q, $J = 6.0$ Hz, $COCH_2CH_3$), 1.66 (3H, d, $J = 4.0$ Hz, CH_3), 1.16 (3H, t, $J = 6.0$ Hz, $COCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 171.62$ (C, C=O), 152.71 (C, C-5), 149.17 (C, C-2′), 132.57 (CH, C-4′), 132.28 (CH, C-5′), 130.81 (CH, C-6′), 124.39 (CH, C-3′), 119.30 (C, C-1′), 91.32 (CH, C-2), 27.37 (CH_2, $COCH_2CH_3$), 20.16 (CH_3, CH_3), 8.82 (CH_3, $COCH_2CH_3$).

*3-Butyryl-2-methyl-5-(2-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (**16c**)* Yield 67 % (0.186 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.86$ (2H, m, H-3′, H-6′), 7.64 (2H, m, H-4′, H-5′), 6.37 (1H, q, $J = 6.0$ Hz, H-2), 2.60 (2H, m, $COCH_2CH_2CH_3$), 1.70 (5H, m, $COCH_2CH_2CH_3$, CH_3), 1.01 (3H, t, $J = 9.0$ Hz, $COCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 170.82$ (C, C=O), 152.70 (C, C-5), 150.85 (C, C-2′), 132.57 (CH, C-4′), 132.27 (CH, C-5′), 130.84 (CH, C-6′), 124.41 (CH, C-3′), 119.36 (C, C-1′), 91.31 (CH, C-2), 35.91 (CH_2, $COCH_2CH_2CH_3$), 20.15 (CH_3, CH_3), 18.33 (CH_2, $COCH_2CH_2CH_3$), 14.06 (CH_3, $COCH_2CH_2CH_3$).

*2-Methyl-5-(2-nitrophenyl)-3-pentanoyl-2,3-dihydro-1,3,4-oxadiazole (**16d**)* Yield 73 % (0.213 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.86$ (2H, m, H-3′, H-6′), 7.68 (2H, m, H-4′, H-5′), 6.36 (1H, q, $J = 6.0$ Hz, H-2), 2.61 (2H, m, $COCH_2CH_2CH_2CH_3$), 1.68 (5H, m, $COCH_2CH_2CH_2CH_3$, CH_3), 1.41 (2H, m, $COCH_2CH_2CH_2CH_3$), 0.95 (3H, t, $J = 9.0$ Hz, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 170.99$ (C, C=O), 152.69 (C, C-5), 149.17 (C, C-2′), 132.58 (CH, C-4′), 132.27 (CH, C-5′), 130.83 (CH, C-6′), 124.39 (CH, C-3′), 119.33 (C, C-1′), 91.29 (CH, C-2), 33.74 (CH_2, $COCH_2CH_2CH_2CH_3$), 26.94 (CH_2, $COCH_2CH_2CH_2CH_3$), 22.64 (CH_2, $COCH_2CH_2CH_2CH_3$), 20.12 (CH_3, CH_3), 14.06 (CH_3, $COCH_2CH_2CH_2CH_3$).

*3-Acetyl-2-ethyl-5-(2-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (**16e**)* Yield 72 % (0.189 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.87$ (2H, m, H-3′, H-6′), 7.69 (2H, m, H-4′, H-5′), 6.28 (1H, q, $J = 3.0$ Hz, H-2), 2.31 (3H, s, $COCH_3$), 2.07 (2H, m, CH_2CH_3), 1.02 (3H, t, $J = 6.0$ Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 168.32$ (C, C=O), 153.13 (C, C-5), 147.84 (C, C-2′), 132.50 (CH, C-4′), 132.30 (CH, C-5′), 130.75 (CH, C-6′), 124.36 (CH, C-3′), 119.16 (C, C-1′), 95.10 (CH, C-2), 26.68 (CH_2, CH_2CH_3), 21.64 (CH_3, CH_3), 7.12 (CH_3, $COCH_3$).

*2-Ethyl-5-(2-nitrophenyl)-3-propionyl-2,3-dihydro-1,3,4-oxadiazole (**16f**)* Yield 80 % (0.222 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.75$ (2H, m, H-3′, H-6′), 7.

58 (2H, m, H-4′, H-5′), 6.16 (1H, q, $J = 3.0$ Hz, H-2), 2.55 (2H, m, $COCH_2CH_3$), 1.96 (2H, m, CH_2CH_3), 1.10 (3H, t, $J = 9.0$ Hz, $COCH_2CH_3$), 0.90 (3H, t, $J = 9.0$ H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.88$ (C, C=O), 152.86 (C, C-5), 146.43 (C, C-2′), 132.41 (CH, C-4′), 132.21 (CH, C-5′), 130.65 (CH, C-6′), 124.28 (CH, C-3′), 119.16 (C, C-1′), 95.07 (CH, C-2), 27.44 (CH_2, $COCH_2CH_3$), 26.69 (CH_2, CH_2CH_3), 8.88 (CH_3, $COCH_2CH_3$), 7.12 (CH_3, CH_2CH_3).

*3-Butyryl-2-ethyl-5-(2-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (**16g**)* Yield 68 % (0.198 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.86$ (2H, m, H-3′, H-6′), 7.68 (2H, m, H-4′, H-5′), 6.27 (1H, q, $J = 3.0$ Hz, H-2), 2.60 (2H, m, $COCH_2CH_2CH_3$), 1.72 (4H, m, CH_2CH_3, $COCH_2CH_2CH_3$), 1.00 (6H, m, CH_2CH_3, $COCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.15$ (C, C=O), 152.98 (C, C-5), 146.43 (C, C-2′), 132.45 (CH, C-4′), 132.26 (CH, C-5′), 130.71 (CH, C-6′), 124.31 (CH, C-3′), 119.16 (C, C-1′), 95.05 (CH, C-2), 35.97 (CH_2, $COCH_2CH_2CH_3$), 26.63 (CH_2, CH_2CH_3), 18.41 (CH_2, $COCH_2CH_2CH_3$), 14.06 (CH_3, $COCH_2CH_2CH_3$), 7.03 (CH_3, CH_2CH_3).

*2-Ethyl-5-(2-nitrophenyl)-3-pentanoyl-2,3-dihydro-1,3,4-oxadiazole (**16h**)* Yield 76 % (0.232 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.82$ (2H, m, H-3′, H-6′), 7.64 (2H, m, H-4′, H-5′), 6.24 (1H, q, $J = 3.0$ Hz, H-2), 2.62 (2H, m, $COCH_2CH_2CH_2CH_3$), 1.63 (2H, m, $COCH_2CH_2CH_2CH_3$), 1.37 (4H, m, CH_2CH_3, $COCH_2CH_2CH_2CH_3$), 0.91 (6H, m, CH_2CH_3, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 169.87$ (C, C=O), 153.14 (C, C-5), 146.53 (C, C-2′), 132.43 (CH, C-4′), 132.24 (CH, C-5′), 130.70 (CH, C-6′), 124.31 (CH, C-3′), 119.17 (C, C-1′), 95.06 (CH, C-2), 35.24 (CH_2, $COCH_2CH_2CH_2CH_3$), 33.92 (CH_2, $COCH_2CH_2CH_2CH_3$), 27.00 (CH_2, CH_2CH_3), 22.52 (CH_2, $COCH_2CH_2CH_2CH_3$), 14.06 (CH_3, $COCH_2CH_2CH_2CH_3$), 7.04 (CH_3, CH_2CH_3).

*3-Acetyl-5-(2-nitrophenyl)-2-phenyl-2,3-dihydro-1,3,4-oxadiazole (**16i**)* Yield 63 % (0.196 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.31$–7.80 (9H, m, H-3′–H-6′, H-2″–H-6″), 6.99 (1H, d, 1H, $J = 3.0$ Hz, H-2), 1.90 (3H, s, $COCH_3$). ^{13}C NMR (75 MHz. $CDCl_3$) $\delta = 168.49$ (C, C=O), 157.93 (C, C-5), 149.12 (C, C-2′), 135.96 (C, C-1″), 132.59 (CH, C-4′), 132.46 (CH, C-5′), 130.79 (CH, C-6′), 129.17 (2CH, C-3″, C-5″), 127.01 (2CH, C-2″, C-6″), 126.63 (CH, C-4″), 124.41 (CH, C-3′), 118.84 (C, C-1′), 93.77 (CH, C-2), 21.71 (CH_3, $COCH_3$).

*5-(2-Nitrophenyl)-2-phenyl-3-propionyl-2,3-dihydro-1,3,4-oxadiazole (**16j**)* Yield 72 % (0.234 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11–7.31 (9H, m, H-3′–H-6′, H-2″–H-6″), 6.99 (1H, d, $J = 6.0$ Hz, H-2), 2.57 (2H, q, $J = 6.0$ Hz, $COCH_2CH_3$), 1.08 (3H, t, $J = 6.0$ Hz, $COCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.06 (C, C=O), 165.22 (C, C-5), 152.40 (C, C-2′), 136.10 (C, C-1″), 132.51 (CH, C-4′), 132.38 (CH, C-5′), 130.73 (CH, C-6′), 129.07 (2CH, C-3″, C-5″), 127.39 (CH, C-4″), 127.01 (2CH, C-2″, C-6″), 124.36 (CH, C-3′), 118.85 (C, C-1′), 93.81 (CH, C-2), 27.50 (CH_2, $COCH_2CH_3$), 8.70 (CH_3, $COCH_2CH_3$).

*3-Butyryl-5-(2-nitrophenyl)-2-phenyl-2,3-dihydro-1,3,4-oxadiazole (**16k**)* Yield 59 % (0.200 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.19$–7.40 (9H, m, H-3′–H-6′, H-2″–H-6″), 7.12 (1H, d, $J = 3.0$ Hz, H-2), 2.30 (2H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_3$), 1.66 (2H, m, $COCH_2CH_2CH_3$), 0.95 (3H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 173.49$ (C, C=O), 163.97 (C, C-5), 156.97 (C, C-2′), 136.13 (C, C-1″), 132.50 (CH, C-4′), 132.35 (CH, C-5′), 130.68 (CH, C-6′), 129.77 (2CH, C-3″, C-5″), 127.40 (CH, C-4″), 126.99 (2CH, C-2″, C-6″), 124.37 (CH, C-3′), 118.12 (C, C-1′), 93.80 (CH, C-2), 27.63 (CH_2, $COCH_2CH_2CH_3$), 19.21 (CH_2, $COCH_2CH_2CH_3$), 13.65 (CH_3, $COCH_2CH_2CH_3$).

*5-(2-Nitrophenyl)-3-pentanoyl-2-phenyl-2,3-dihydro-1,3,4-oxadiazole (**16l**)* Yield 63 % (0.227 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.19$ (1H, d, $J = 3$ Hz, H-6′), 7.85 (2H, m, H-3′, H-4′), 7.65 (3H, m, H-5′, H-2″, H-6″), 7.25 (3H, m, $J = 3.1$ Hz, H-3″–H-5″), 7.05 (1H, d, $J = 3.0$ Hz, H-2), 2.29 (2H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_2CH_3$), 1.61 (2H, m, $COCH_2CH_2CH_2CH_3$), 1.51 (2H, m, $COCH_2CH_2CH_2CH_3$), 0.90 (3H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta =$ 173.62 (C, C=O), 163.79 (C, C-5), 153.92 (C, C-2′), 135.16 (C, C-1″), 133.52 (CH, C-4′), 132.85 (CH, C-5′), 131.76 (CH, C-6′), 128.99 (2CH, C-3″, C-5″), 127.32 (CH, C-4″), 126.91 (2CH, C-2″, C-6″), 125.21 (CH, C-3′), 118.27 (C, C-1′), 95.81 (CH, C-2), 40.17 (CH_2, $COCH_2CH_2CH_2CH_3$), 26.63 (CH_2, $COCH_2CH_2CH_2CH_3$), 25.65 (CH_2, $COCH_2CH_2CH_2CH_3$), 13.51 (CH_3, $COCH_2CH_2CH_2CH_3$).

*3-Acetyl-2,2-dimethyl-5-(2-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (**16m**)* Yield 64 % (0.168 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.86$ (2H, m, H-3′, H-6′), 7.68 (2H, m, H-4′, H-5′), 2.28 (3H, s, $COCH_3$), 1.85 (6H, s, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 167.53$ (C, C=O), 151.16 (C, C-5), 149.13 (C, C-2′), 132.57 (CH, C-4′), 132.13 (CH, C-5′), 130.83 (CH, C-6′), 124.38 (CH, C-3′), 119.62 (C, C-1′), 102.11 (C, C-2), 24.78 ($2CH_3$, $2CH_3$), 22.55 (CH_3, $COCH_3$).

*2,2-Dimethyl-5-(2-nitrophenyl)-3-propionyl-2,3-dihydro-1,3,4-oxadiazole (**16n**)* Yield 84 % (0.233 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.86$ (2H, m, H-3′, H-6′), 7.75 (2H, m, H-4′, H-5′), 2.62 (2H, q, $J = 8.0$ Hz, $COCH_2CH_3$), 1.87 (6H, s, $2CH_3$), 1.16 (3H, t, $J = 8.0$ Hz, $COCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.20$ (C, C=O), 151.08 (C, C-5), 148.98 (C, C-2′), 132.48 (CH, C-4′), 132.07 (CH, C-5′), 130.75 (CH, C-6′), 124.33 (CH, C-3′), 119.62 (C, C-1′), 102.09 (C, C-2), 28.02 (CH_2, $COCH_2CH_3$), 24.78 ($2CH_3$, $2CH_3$), 9.05 (CH_3, $COCH_2CH_3$).

*3-Butyryl-2,2-dimethyl-5-(2-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (**16o**)* Yield 81 % (0.236 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.82$ (2H, m, H-3′, H-6′), 7.65 (2H, m, H-4′, H-5′), 2.24 (2H, t, $J = 6.0$ Hz, $COC\underline{H}_2CH_2CH_3$), 1.85 (6H, s, $2CH_3$), 1.69 (2H, m, $COCH_2C\underline{H}_2CH_3$), 0.97 (3H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.26$ (C, C=O), 150.93 (C, C-5), 149.12 (C, C-2′), 132.51 (CH, C-4′), 132.07 (CH, C-5′), 130.76 (CH, C-6′), 124.32 (CH, C-3′), 119.62 (C, C-1′), 102.04 (C, C-2), 36.54 (CH_2, $CO\underline{C}H_2CH_2CH_3$), 24.79 ($2CH_3$, $2CH_3$), 18.36 (CH_2, $COCH_2\underline{C}H_2CH_3$), 13.98 ($CH_3$, $COCH_2CH_2CH_3$).

*2,2-Dimethyl-5-(2-nitrophenyl)-3-pentanoyl-2,3-dihydro-1,3,4-oxadiazole (**16p**)* Yield 78 % (0.238 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.98$ (1H, dd, $J = 2.0$, 7.2, H-6′), 7.75 (2H, m, H-3′, H-4′), 7.62 (1H, m, H-5′), 2.27 (2H, t, $J = 7.5$ Hz, $COC\underline{H}_2CH_2CH_2CH_3$), 1.67 (2H, m, $COCH_2C\underline{H}_2CH_2CH_3$), 1.63 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.53 (2H, m, $COCH_2CH_2C\underline{H}_2CH_3$), 0.93 (3H, t, $J = 7.5$ Hz, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 172.16$ (C, C=O), 155.13 (C, C-5), 148.02 (C, C-2′), 131.91 (CH, C-4′), 130.03 (CH, C-5′), 127.83 (CH, C-6′), 116.82 (CH, C-3′), 101.62 (C, C-2), 40.53 (CH_2, $CO\underline{C}H_2CH_2CH_2CH_3$), 26.56 ($CH_2$, $COCH_2\underline{C}H_2CH_2CH_3$), 23.49 ($2CH_3$, $2CH_3$), 21.67 (CH_2, $COCH_2CH_2\underline{C}H_2CH_3$), 13.48 ($CH_3$, $COCH_2CH_2CH_2CH_3$).

*3-Acetyl-2-ethyl-2-methyl-5-(2-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (**16r**)* Yield 75 % (0.208 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.02$ (1H, m, H-6′), 7.83 (2H, m, H-3′, H-4′), 7.72 (1H, m, H-5′), 2.17 (3H, s, $COCH_3$), 1. 94 (2H, m, CH_2CH_3), 1.65 (3H, s, CH_3), 0.87 (3H, t, $J = 7.5$ Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 167.56$ (C, C=O), 163.28 (C, C-5), 147.05 (C, C-2′), 131.93 (CH, C-4′), 126.23 (CH, C-5′), 125.53 (CH, C-6′), 123.62 (CH, C-3′), 114.12 (C, C-1′), 101.83 (C, C-2), 26.13 (CH_2, CH_2CH_3), 23.56 (CH_3, $COCH_3$), 19.17 (CH_3, CH_3,), 9.45 (CH_3, CH_2CH_3).

*2-Ethyl-2-methyl-5-(2-nitrophenyl)-3-propionyl-2,3-dihydro-1,3,4-oxadiazole (**16s**)* Yield 79 % (0.230 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.98$ (1H, dd, $J = 1.9$, 7.1 Hz, H-6′), 7.86 (2H, m, H-3′, H-4′), 7.63 (1H, m, H-5′), 2.47 (2H, q, $J = 8.0$ Hz, $COCH_2CH_3$), 1.77 (2H, m, CH_2CH_3), 1.63 (3H, s, CH_3), 0.97 (3H, t, $J = 7.6$ Hz, $COCH_2CH_3$), 0.79 (3H, t, $J = 7.8$, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 170.88$ (C, C=O), 163.32 (C, C-5), 147.23 (C, C-2′), 131.95 (CH, C-4′), 126.13 (CH, C-5′), 125.64 (CH, C-6′), 123.60 (CH, C-3′), 116.67 (C, C-1′), 103.25 (C, C-2), 29.81 (CH_2, $COCH_2CH_3$), 26.33 (CH_2, CH_2CH_3), 20.76 (CH_3, CH_3), 9.57 (CH_3, CH_2CH_3), 8.75 (CH_3, $COCH_2CH_3$).

*3-Acetyl-2-methyl-5-(2-nitrophenyl)-2-phenyl-2,3-dihydro-1,3,4-oxadiazole (**16t**)* Yield 82 % (0.267 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.99$ (1H, dd, $J = 2.0$, 7.3 Hz, H-6′), 7.87 (2H, m, H-3′, H-4′), 7.78 (2H, m, H-2″, H-6″), 7.64 (1H, m, H-5′), 7.22 (3H, m, H-3″–H-5″), 2.18 (3H, s, $COCH_3$), 2.09 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 167.48$ (C, C=O), 162.26 (C, C-5), 156.08 (C, C-2′), 134.57 (C, C-1″), 134.22 (CH, C-5′), 130.32 (CH, C-4′), 129.51 (CH, C-6′), 128.82 (2CH, C-3″, C-5″), 127.42 (CH, C-4″), 125.97 (2CH, C-2″, C-6″), 124.39 (CH, C-3′), 119.23 (C, C-1′), 100.97 (C, C-2), 22.89 (CH_3, $COCH_3$), 22.35 (CH_3, CH_3,).

*General procedure for the preparation of compounds **6a–i***

A mixture of nitroarene **16a–i** (0.414 mmol), palladium/carbon (10 %, 10 mg), and methanol (20 mL) was stirred at room temperature under a hydrogen atmosphere (1 atm). After 3 h, the suspension was filtered through Celite and evaporated. The residue was dissolved in CH_2Cl_2, and this solution was washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane 1:1), to afford the corresponding aromatic amines **6a–i**.

*[2-(4-Acetyl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6a**)* Mp: 130–132 °C. Yield 94 % (0.085 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.62$ (1H, dd, $J = 1.6$, 8.0 Hz, H-3), 7.25 (1H, t, $J = 8.0$ Hz, H-5), 6.73 (2H, m, H-4, H-6), 6.25 (1H, q, $J = 5.4$ Hz, H-5′), 5.50 (2H, bs, NH_2), 2.30 (3H, s, $COCH_3$), 1.65 (3H, d, $J = 4.0$ Hz, CH_3). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 167.19$ (C, C=O), 156.23 (C, C-2′), 147.02 (C, C-1), 132.62 (CH, C-5), 128.68 (CH, C-3), 117.14 (CH, C-4), 116.06 (CH, C-6), 106.62 (C, C-2), 88.20 (CH, C-5′), 21.78 (CH_3, $COCH_3$), 20.31 (CH_3, CH_3). HRESIMS m/z (pos): 242.0903 $C_{11}H_{13}N_3O_2Na$ (calcd. 242.0905).

*[2-(5-Methyl-4-propionyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6b**)* Mp 124–127 °C. Yield 90 % (0.087 g) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.61$ (1H, dd, $J = 1.5$, 8.0 Hz, H-3), 7.23 (1H, t, $J = 8.0$ Hz, H-5), 6.74 (2H, m, H-4, H-6), 6.25 (1H, q, $J = 5.3$ Hz, H-5′), 2.63 (2H, q, $J = 7.6$ Hz, $COC\underline{H}_2CH_3$), 1.64 (3H, d, $J = 5.3$ Hz, CH_3), 1.19 (3H, t, $J = 7.6$ Hz, $COCH_2CH_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 170.45$ (C, C=O), 155.76 (C, C-2′), 146.25 (C, C-1), 132.31 (CH, C-5), 128.42 (CH, C-3), 117.20 (CH, C-4), 116.02 (CH, C-6), 106.84 (C, C-2), 88.15 (CH, C-5′), 27.18 (CH_2, $COCH_2CH_3$), 19.34 (CH_3, CH_3), 8.52 (CH_3, $COCH_2CH_3$). HRESIMS m/z (pos): 234.1234 $C_{12}H_{16}N_3O_2$ (calcd. 234.1243).

*[2-(4-Butyryl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6c**)* Mp 132–135 °C. Yield 90 % (0.092 g) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.60$ (1H, dd, $J = 1.5$, 8.0 Hz, H-3), 7.24 (1H, m, H-5), 7.15 (1H, m, H-4), 6.73 (1H, m, H-6), 6.26 (1H, q, $J = 5.9$ Hz, H-5′), 5.26 (2H, bs, NH_2), 2.59 (2H, m, $COC\underline{H}_2CH_2CH_3$), 1.73 (2H, m, $COCH_2C\underline{H}_2CH_3$), 1.63 (3H, d, $J = 4.0$ Hz, CH_3), 0.99 (3H, t, $J = 8.0$ Hz, $COCH_2CH_2CH_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 169.64$ (C, C=O), 155.78 (C, C-2′), 146.53 (C, C-1), 132.30 (CH, C-5), 128.41 (CH, C-3), 117.00 (CH, C-4), 115.87 (CH, C-6), 106.59 (C, C-2), 88.08 (CH, C-5′), 35.81 (CH_2, $CO\underline{C}H_2CH_2CH_3$, 20.09 ($CH_3$, CH_3), 17.97 (CH_2,$COCH_2\underline{C}H_2CH_3$, 13.92 ($CH_3$, $COCH_2CH_2CH_3$). HRESIMS m/z (pos): 248.1395 $C_{13}H_{18}N_3O_2$ (calcd. 248.1399).

*[2-(5-Methyl-4-pentanoyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6d**)* Mp 103–105 °C. Yield 94 % (0.102 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.63$ (1H, dd, $J = 1.1$, 8.6 Hz, H-3), 7.28 (1H, dd, $J = 1.6$, 8.0 Hz, H-5), 7.16 (1H, m, H-4); 6.78 (1H, m, H-6), 6.33 (1H, q, $J = 5.3$ Hz, H-5′), 2.57 (2H, m, $COC\underline{H}_2CH_2CH_2CH_3$), 1.73 (2H, m, $COCH_2C\underline{H}_2CH_2CH_3$), 1.70 (3H, d, $J = 5.3$ Hz, CH_3), 1.44 (2H, m, $COCH_2CH_2C\underline{H}_2CH_3$), 0.98 (3H, t, $J = 7.3$ Hz, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 169.61$ (C, C=O), 155.19 (C, C-2′), 138.27 (C, C-1), 132.81 (CH, C-5), 128.17 (CH, C-3), 122.79 (CH, C-4), 120.03 (CH, C-6), 110.65 (C, C-2), 88.83 (CH, C-5′), 38.53 (CH_2, $CO\underline{C}H_2CH_2CH_2CH_3$), 27.72 ($CH_2$, $COCH_2\underline{C}H_2CH_2CH_3$), 22.52 ($CH_2$, $COCH_2CH_2\underline{C}H_2CH_3$), 20.14 ($CH_3$, CH_3), 13.85 (CH_3, $COCH_2CH_2CH_2\underline{C}H_3$). HRESIMS m/z (pos): 262.1548 $C_{14}H_{20}N_3O_2$ (calcd. 262.1556).

*[2-(4-Acetyl-5-ethyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6e**)* Mp 96–97 °C. Yield 92 % (0.089 g) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.66$ (1H, dd, $J = 1.6$, 8.0 Hz, H-3), 7.27 (1H, m, H-5), 6.80 (2H, m, H-4, H-6), 6.21 (1H, q, $J = 2.8$ Hz, H-5′), 5.17 (2H, bs, NH_2), 2.33 (3H, s, $COCH_3$), 2.03 (2H, m, CH_2CH_3), 0.99 (3H, t, $J = 7.5$, CH_2CH_3). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 167.24$ (C, C=O), 156.25 (C, C-2′), 146.62 (C, C-1), 132.37 (CH, C-5), 128.44 (CH, C-3), 117.39 (CH, C-4), 116.18 (CH, C-6), 107.51 (C, C-2), 91.74 (CH, C-5′), 26.43 (CH_2, CH_2CH_3), 21.56 (CH_3, $COCH_3$), 6.70 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 234.1242 $C_{12}H_{16}N_3O_2$ (calcd. 234.1243).

*[2-(5-Ethyl-4-propionyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6f**)* Mp 122–125 °C. Yield 95 % (0.097 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.65$ (1H, dd, $J = 1.6$, 8.0 Hz, H-3), 7.27 (1H, m, H-5), 6.77 (2H, m, H-4, H-6), 6.20 (1H, q, $J = 2.8$ Hz, H-5′), 5.15 (2H, bs, NH_2), 2.67 (2H, m, $COCH_2CH_3$), 2.02 (2H, m, CH_2CH_3), 1.22 (3H, t, $J = 7.6$, $COCH_2CH_3$), 0.99 (3H, t, $J = 7.5$, CH_2CH_3). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 170.73$ (C, C=O), 156.17 (C, C-2′), 146.34 (C, C-1), 132.28 (CH, C-5), 128.40 (CH, C-3), 117.15 (CH, C-4), 115.98 (CH, C-6), 106.60 (C, C-2), 91.72 (CH, C-5′), 27.24 (CH_2, $COCH_2CH_3$), 26.44 (CH_2, CH_2CH_3), 8.59 (CH_3, $COCH_2CH_3$), 6.65 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 248.1392 $C_{13}H_{18}N_3O_2$ (calcd. 248.1399).

*[2-(4-Butyryl-5-ethyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6g**)* Mp 129–131 °C. Yield 92 % (0.099 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.81$ (1H, dd, $J = 1.0$, 6.5 Hz, H-3), 7.67 (1H, m, H-5), 7.29 (1H, m, H-4), 6.80 (1H, m, H-6), 6.26 (1H, q, $J = 2.8$ Hz, H-5′), 2.66 (2H, m, $COC\underline{H}_2CH_2CH_3$), 2.06 (2H, m, CH_2CH_3), 1.82 (2H, m, $COCH_2C\underline{H}_2CH_3$); 1.06 (3H, t, $J = 7.4$ Hz, $COCH_2CH_2CH_3$), 1.02 (3H, t, $J = 7.5$, $CH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 169.73$ (C, C=O), 155.61 (C, C-2′), 138.27 (C, C-1), 132.82 (CH, C-5), 128.14 (CH, C-3), 122.83 (CH, C-4), 120.06 (CH, C-6), 110.58 (C, C-2), 92.39 (CH, C-5′), 36.13 (CH_2, $CO\underline{C}H_2CH_2CH_3$), 19.18 ($CH_2$, $COCH_2\underline{C}H_2CH_3$), 18.08 ($CH_2$, CH_2CH_3), 13.82 (CH_3, $COCH_2CH_2\underline{C}H_3$), 6.58 ($CH_3$, CH_2CH_3). HRESIMS m/z (pos): 262.1548 $C_{14}H_{20}N_3O_2$ (calcd. 262.1556).

*[2-(5-Ethyl-4-pentanoyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6h**)* Mp 126–129 °C. Yield 90 % (0.103 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.74$ (1H, dd, $J = 1.1$, 8.5 Hz, H-3), 7.60 (1H, dd, $J = 1.6$, 7.0 Hz, H-5), 7.51 (1H, m, H-4), 7.14 (1H, m, H-6), 6.25 (1H, q, $J = 2.8$ Hz, H-5′), 2.68 (2H, m, $COC\underline{H}_2CH_2CH_2CH_3$), 2.06 (2H, m, CH_2CH_3), 1.76 (2H, m, $COCH_2C\underline{H}_2CH_2CH_3$), 1.44 (2H, m, $COCH_2CH_2C\underline{H}_2CH_3$), 0.98 (6H, m, $COCH_2CH_2CH_2C\underline{H}_3$, $CH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 169.86$ (C, C=O), 155.60 (C, C-2′), 138.28 (C, C-1), 132.82 (CH, C-5), 128.14 (CH, C-3), 122.81 (CH, C-4), 120.05 (CH, C-6), 110.58 (C, C-2), 92.39 (CH, C-5′),

38.53 (CH_2, $CO\underline{C}H_2CH_2CH_2CH_3$), 33.84 ($CH_2$, $COCH_2\underline{C}H_2CH_2CH_3$), 26.61 ($CH_2$, $COCH_2CH_2\underline{C}H_2CH_3$), 22.54 ($CH_2$, CH_2CH_3), 13.85 (CH_3, $COCH_2CH_2CH_2CH_3$), 6.59 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 276.1673 $C_{15}H_{22}N_3O_2$ (calcd. 276.1679).

*[2-(5-Phenyl-4-acetyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6i**)* Mp 117–120 °C. Yield 92 % (0.107 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.42$–7.27 (7H, m, H-3, H-5, H-2″–H-6″), 6.69 (1H, d, $J = 8.3$ Hz, H-4), 6.62 (1H, m, H-6), 6.00 (1H, s, H-5′), 2.36 (3H, s, $COCH_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 168.74$ (C, C=O), 148.68 (C, C-2′), 145.52 (C, C-1), 137.58 (C, C-1″), 132.73 (CH, C-5), 129.07 (2CH, C-3″, C-5″), 128.57 (2CH, C-2″, C-6″), 127.64 (CH, C-4″), 126.89 (CH, C-3), 117.24 (CH, C-4), 116.74 (CH, C-6), 114.98 (C, C-2), 93.20 (CH, C-5′), 21.36 (CH_3, $COCH_3$). HRESIMS m/z (pos): 282.1236 $C_{16}H_{16}N_3O_2$ (calcd. 282.1243).

*General procedure for the preparation of compounds **6m–t***

Fe (5.24 mmol) and $FeSO_4$ (0.524 mmol) were suspended in water (11.0 mL), and the corresponding nitroarene **16m–p** and **16r–t** (0.524 mmol) was added over the reaction mixture and refluxed for 3 h. After cooling, the reaction mixture was filtered through Celite and washed thoroughly with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to yield a residue that was purified by flash chromatography (ethyl acetate/hexane 1:1), to give the corresponding aromatic amines **6m–p** and **16r–t**. Compound **6q** was obtained along with **6p**, when **16p** was treated with Fe/$FeSO_4$, due to the presence of a valeric anhydride remainder.

*[2-(4-Acetyl-5,5-dimethyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6m**)* Mp 126–128 °C. Yield 51 % (0.062 g) as a yellow solid. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) $\delta = 7.76$ (1H, d, $J = 7.7$ Hz, H-3); 7.31 (1H, m, H-5), 6.76 (2H, m, H-4, H-6), 6.11 (2H, bs, NH_2), 2.37 (3H, s, $COCH_3$), 1.60 (3H, s, CH_3), 1.57 (3H, s, CH_3). ^{13}C NMR 75 MHz, $(CD_3)_2CO$) $\delta = 168.53$ (C, C=O), 161.55 (C, C-2′), 157.55 (C, C-1), 133.71 (CH, C-5), 128.27 (CH, C-3), 117.70 (CH, C-4), 114.83 (CH, C-6), 111.88 (C, C-2), 98.85 (C, C-5′), 23.48 (CH_3, CH_3), 22.53 (CH_3, CH_3), 20.15 (CH_3, $COCH_3$). HRESIMS m/z (pos): 256.1057 $C_{12}H_{15}N_3O_2Na$ (calcd. 256.1062).

*[2-(5,5-Dimethyl-4-propionyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6n**)* Mp 133–134 °C. Yield 61 % (0.079 g) as a yellow solid. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) $\delta = 7.73$ (1H, d, $J = 6.0$ Hz, H-3); 7.33 (1H, m, H-5), 6.76 (2H, m, H-4, H-6), 2.41 (2H, q, $J = 6.0$ Hz, $COCH_2$-CH_3), 1.55 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.24 (t, 3H, $J = 6.0$ Hz, $COCH_2CH_3$). ^{13}C NMR (75 MHz, CD_3CO) $\delta = 170.05$ (C, C=O), 154.29 (C, C-2′), 146.66 (C, C-1), 132.35 (CH, C-5), 128.59 (CH, C-3), 117.24 (CH, C-4), 116.14 (CH, C-6), 107.19 (C, C-2), 98.70 (C, C-5′), 28.14 (CH_2, $COCH_2CH_3$), 24.90 (CH_3, CH_3), 23.48 (CH_3, CH_3), 8.78 (CH_3, $COCH_2CH_3$). HRESIMS m/z (pos): 248.1395 $C_{13}H_{18}N_3O_2$ (calcd. 248.1399).

*[2-(4-Butyryl-5,5-dimethyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6o**)* Mp 95–96 °C. Yield 81 % (0.111 g) as a yellow solid. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) $\delta = 7.55$ (1H, d, $J = 9.0$ Hz, H-3), 7.24 (1H, m, H-5), 6.83 (1H, m, H-6), 6.67 (1H, m, H-4), 2.64 (2H, t, $J = 6.0$ Hz, $COC\underline{H}_2CH_2CH_3$), 1.87 (3H, s, CH_3), 1.84 (3H, s, CH_3), 1.74 (2H, m, $COCH_2C\underline{H}_2CH_3$), 1.03 (3H, t, $J = 9.0$ Hz, $COCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, CD_3CD) $\delta = 169.89$ (C, C=O), 155.00 (C, C-2′), 148.07 (C, C-1), 132.24 (CH, C-5), 127.95 (CH, C-3), 115.90 (CH, C-4), 115.54 (CH, C-6), 105.69 (C, C-2), 98.34 (C, C-5′), 36.31 (CH_2, $CO\underline{C}H_2CH_2CH_3$), 23.58 ($CH_3$, CH_3), 21.87 (CH_3, CH_3), 18.11 (CH_2, $COCH_2\underline{C}H_2CH_3$), 12.97 ($CH_3$, $COCH_2CH_2CH_3$). HRESIMS m/z (pos): 284.13735 $C_{14}H_{19}N_3O_2Na$ (calcd. 284.1375).

*[2-(5,5-Dimethyl-4-pentanoyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6p**)* Mp 132–135 °C. Yield 57 % (0.082 g) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.58$ (1H, dd, $J = 1.5$, 7.8 Hz, H-3), 7.23 (1H, m, H-5), 6.72 (2H, m, H-4, H-6), 2.59 (2H, t, $J = 7.5$ Hz, $COC\underline{H}_2CH_2CH_2CH_3$), 1.83 (6H, s, $2CH_3$), 1.66 (2H, m, $COCH_2C\underline{H}_2CH_2CH_3$), 1.39 (2H, m, $COCH_2CH_2C\underline{H}_2CH_3$), 0.93 (3H, t, $J = 7.4$ Hz, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 169.23$ (C, C=O), 154.00 (C, C-2′), 146.55 (C, C-1), 132.08 (CH, C-5), 128.32 (CH, C-3), 116.86 (CH, C-4), 115.77 (CH, C-6), 106.83 (C, C-2), 98.44 (C, C-5′), 34.35 (CH_2, $CO\underline{C}H_2CH_2CH_2CH_3$), 26.69 ($CH_2$, $COCH_2\underline{C}H_2CH_2CH_3$), 24.67 ($CH_3$, CH_3), 24.65 (CH_3, CH_3), 22.49 (CH_2, $COCH_2CH_2\underline{C}H_2CH_3$), 13.91 ($CH_3$, $COCH_2CH_2CH_2CH_3$). HRESIMS m/z (pos): 276.1711 $C_{15}H_{21}N_3O_2$ (calcd. 276.1712).

*N-[2-(5,5-Dimethyl-4-pentanoyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]pentanamide (**6q**)* Mp 96–98 °C. Yield 27 % (0.037 g) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 10.27$ (1H, s, NH), 8.71 (1H, dd, $J = 1.1$, 8.6 Hz, H-3), 7.73 (1H, dd, $J = 1.6$, 7.9 Hz, H-6), 7.46 (1H, m, H-5), 7.10 (1H, m, H-4), 2.63 (2H, t, $J = 7.5$ Hz, $NHCOC\underline{H}_2CH_2CH_2CH_3$), 2.42 (2H, t, $J = 7.5$ Hz, $COC\underline{H}_2CH_2CH_2CH_3$), 1.86 (6H, s, $2CH_3$), 1.72 (4H, m, $NHCOCH_2C\underline{H}_2CH_2CH_3$, $COCH_2C\underline{H}_2CH_2CH_3$), 1.39 (4H, m, $NHCOCH_2CH_2C\underline{H}_2CH_3$, $COCH_2CH_2C\underline{H}_2CH_3$), 0.95

(3H, t, $J = 7.6$ Hz, $NHCOCH_2CH_2CH_2CH_3$), 0.93 (3H, t, $J = 7.3$ Hz, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 171.78$ (C, NHC=O), 168.87 (C, C=O), 153.41 (C, C-2′), 138.19 (C, C-1), 132.58 (CH, C-5), 128.05 (CH, C-3), 122.68 (CH, C-6), 119.93 (CH, C-4), 110.86 (C, C-2), 99.39 (C, C-5′), 38.49 (CH_2, $CO\underline{C}H_2CH_2CH_2CH_3$), 34.42 ($CH_2$, $NHCO\underline{C}H_2CH_2CH_2CH_3$), 27.70 ($CH_2$, $COCH_2\underline{C}H_2CH_2CH_3$), 26.51 ($CH_2$, $NHCOCH_2\underline{C}H_2CH_2CH_3$), 24.26 ($CH_3$, CH_3), 24.62 (CH_3, CH_3), 22.46 (CH_2, $COCH_2CH_2\underline{C}H_2CH_3$), 22.41 ($CH_2$, $NHCOCH_2CH_2\underline{C}H_2CH_3$), 13.88 ($CH_3$, $COCH_2CH_2CH_2CH_3$), 13.77 (CH_3, $NHCOCH_2CH_2CH_2CH_3$). HRESIMS m/z (pos): 360.2292 $C_{20}H_{30}N_3O_3$ (calcd. 360.2287).

*[2-(4-Acetyl-5-ethyl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6r**)* Mp 132–135 °C. Yield 83 % (0.107 g) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) $\delta =$ 7.65 (1H, dd, $J = 1.5$, 7.8 Hz, H-3), 7.26 (1H, m, H-5), 6.80 (2H, m, H-4, H-6), 2.51 (3H, s, $COCH_3$), 2.07 (2H, m, CH_2CH_3), 2.06 (3H, s, CH_3), 0.86 (3H, t, $J = 7.4$ Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 170.58$ (C, C=O), 155.72 (C, C-2′), 148.66 (C, C-1), 133.37 (CH, C-5), 128.70 (CH, C-3), 120.56 (CH, C-4), 117.48 (CH, C-6), 114.95 (C, C-2), 109.94 (C, C-5′), 23.60 (CH_2, CH_2CH_3), 21.27 (CH_3, $COCH_3$), 20.98 (CH_3, CH_3), 8.29 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 248.1395 $C_{13}H_{18}N_3O_2$ (calcd. 248.1399).

*[2-(5-Ethyl-5-methyl-4-propionyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6s**)* Mp 125–129 °C. Yield 78 % (0.107 g) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.59$ (1H, d, $J = 8.0$ Hz, H-3), 7.22 (1H, m, H-5), 6.71 (2H, m, H-4, H-6), 2.64 (2H, q, $J = 7.5$ Hz, $COCH_2CH_3$), 2.24 (2H, m, CH_2CH_3), 1.80 (3H, s, CH_3), 1.18 (3H, t, $J =$ 7.5 Hz, $COCH_2CH_3$), 0.87 (3H, t, $J = 7.5$ Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 169.78$ (C, C=O), 154.52 (C, C-2′), 146.61 (C, C-1), 132.06 (CH, C-5), 128.28 (CH, C-3), 116.82 (CH, C-4), 115.76 (CH, C-6), 106.67 (C, C-2), 100.96 (C, C-5′), 29.89 (CH_2, $COCH_2CH_3$), 27.89 (CH_2, CH_2CH_3), 23.64 (CH_3, CH_3), 8.68 (CH_3, $COCH_2CH_3$), 7.16 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 262.1557 $C_{14}H_{20}N_3O_2$ (calcd. 262.1556).

*[2-(4-Acetyl-5-methyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]amine (**6t**)* Mp 137–139 °C. Yield 80 % (0.124 g) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.65$–7.24 (7H, H-3, H-5, H-2″–H-6″), 6.74 (2H, m, H-4, H-6), 2.30 (3H, s, $COCH_3$), 2.27 (3H, s, CH_3). ^{13}C NMR (100 MHz, CD_3Cl) $\delta = 166.35$ (C, C=O), 154.22 (C, C-2′), 146.72 (C, C-1), 139.32 (C, C-1″), 132.30 (CH, C-5), 129.09 (CH, C-4″), 128.56 (2CH, C-3″, C-5″), 128.39 (CH, C-3), 125.78 (2CH, C-2″, C-6″), 116.94 (CH, C-4), 115.80 (CH, C-6), 106.42 (C, C-2), 98.75 (C, C-5′), 23.13 (CH_3, CH_3), 22.74 (CH_3, $COCH_3$). HRESIMS m/z (pos): 296.1394 $C_{17}H_{18}N_3O_2$ (calcd. 296.1399).

*General procedure for the preparation of compounds **7a–l***

From the synthetic intermediates **16a–l**, and following the same procedure as for the preparation of compounds **6m–t**, the derivatives **7a–l** were obtained. The final compounds were purified by flash chromatography (ethyl acetate/hexane 1:1).

*N-(2-methyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)acetamide (**7a**)* Mp 130–132 °C. Yield 63 % (0.072 g) as a white solid. ^1H NMR (300 MHz, $(CD_3)_2CO$) $\delta = 9.10$ (1H, bs, NHCO), 7.79 (1H, d, $J = 7.0$ Hz, H-5), 7.33 (1H, m, H-7), 6.80 (2H, m, H-6, H-8), 6.13 (1H, bs, H-1), 5.30 (1H, q, $J = 6.0$ Hz, H-2), 2.03 (3H, s, $COCH_3$), 1.48 (3H, d, $J = 6.0$ Hz, CH_3). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) $\delta =$ 169.06 (C, NHC=O), 163.08 (C, C-4), 148.15 (C, C-8a), 133.71 (CH, C-7), 128.55 (CH, C-5), 118.21 (CH, C-6), 115.16 (C, C-4a), 114.85 (CH, C-8), 68.34 (CH, C-2), 20.00 (CH_3, $COCH_3$), 19.20 (CH_3, CH_3). HRESIMS m/z (pos): 242.0911 $C_{11}H_{13}N_3O_2Na$ (calcd. 242.0905).

*N-(2-methyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)propanamide (**7b**)* Mp 148–150 °C. Yield 67 % (0.082 g) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.33$ (1H, bs, NHCO), 7.88 (1H, d, $J = 9.0$ Hz, H-5), 7.29 (1H, m, H-7), 6.88 (1H, m, H-6), 6.72 (1H, d, $J = 6.0$ Hz, H-8), 5.31 (1H, q, $J = 6.0$ Hz, H-2), 3.48 (1H, bs, H-1), 2.39 (2H, q, $J = 6.0$ Hz, $COCH_2CH_3$), 1.49 (3H, d, $J = 6.0$ Hz, CH_3), 1.23 (3H, t, $J = 6.0$ Hz, $COCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 174.43$ (C, NHC=O), 164.09 (C, C-4), 146.52 (C, C-8a), 134.43 (CH, C-7), 129.18 (CH, C-5), 119.89 (CH, C-6), 115.57 (CH, C-8), 115.43 (C, C-4a), 68.43 (CH, C-2), 27.52 (CH_2, $COCH_2CH_3$), 19.55 (CH_3, CH_3), 9.64 (CH_3, $COCH_2CH_3$). HRESIMS m/z (pos): 256.1051 $C_{12}H_{15}N_3O_2Na$ (calcd. 256.1062).

*N-(2-methyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)butanamide (**7c**)* Mp 153–155 °C. Yield 66 % (0.085 g) as a white solid. ^1H NMR (300 MHz, $(CD_3)_2CO$) $\delta = 9.07$ (1H, bs, NHCO); 7.78 (1H, d, $J = 9.0$ Hz, H-5), 7.32 (1H, m, H-7), 6.80 (2H, m, H-6, H-8), 6.14 (1H, bs, H-1), 5.30 (1H, q, $J = 6.0$ Hz, H-2), 2.30 (2H, t, $J = 6.0$ Hz, $COC\underline{H}_2CH_2CH_3$), 1.71 (2H, m, $COCH_2C\underline{H}_2CH_3$), 1.49 (3H, d, $J = 6.0$ Hz, CH_3), 1.01 (3H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) $\delta =$ 172.10 (C, NHC=O), 163.13 (C, C-4), 148.18 (C, C-8a), 133.68 (CH, C-7), 128.57 (CH, C-5), 118.22 (CH, C-6), 115.26 (C, C-4a), 114.84 (CH, C-8), 68.35 (CH, C-2), 35.

58 (CH_2, $CO\underline{C}H_2CH_2CH_3$), 19.23 ($CH_3$, CH_3), 18.87 (CH_2, $COCH_2\underline{C}H_2CH_3$), 13.38 ($CH_3$, $COCH_2CH_2CH_3$). HRESIMS m/z (pos): 270.1214 $C_{13}H_{17}N_3O_2Na$ (calcd. 270.1218).

*N-(2-methyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)pentanamide (**7d**)* Mp 154–156 °C. Yield 66 % (0.090 g) as a light yellow solid. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) $\delta = 9.08$ (1H, bs, NHCO), 7.78 (1H, d, $J = 9.0$ Hz, H-5), 7.32 (1H, m, H-7), 6.80 (2H, m, H-6, H-8), 6.14 (1H, bs, H-1), 5.30 (1H, q, $J = 6.0$ Hz, H-2), 2.33 (2H, t, $J = 6.0$ Hz, $CO\underline{CH_2}CH_2CH_2CH_3$), 1.68 (2H, m, $COCH_2\underline{CH_2}CH_2CH_3$), 1.45 (5H, m, CH_3, $COCH_2CH_2\underline{CH_2}CH_3$), 0.95 (3H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_2CH_3$), ^{13}C NMR (75 MHz, $(CD_3)_2CO$) $\delta = 172.25$ (C, NHC=O), 163.15 (C, C-4), 148.19 (C, C-8a), 133.69 (CH, C-7), 128.57 (CH, C-5), 118.22 (CH, C-6), 115.24 (C, C-4a), 114.85 (CH, C-8), 68.35 (CH, C-2), 33.41 (CH_2, $CO\underline{C}H_2CH_2CH_2CH_3$), 27.62 ($CH_2$, $COCH_2\underline{C}H_2CH_2CH_3$), 22.30 ($CH_2$, $COCH_2CH_2\underline{C}H_2CH_3$), 19.23 ($CH_3$, CH_3), 13.48 (CH_3, $COCH_2CH_2\underline{C}H_2CH_3$). HRESIMS m/z (pos): 284.1381 $C_{14}H_{19}N_3O_2Na$ (calcd. 284.1375).

*N-(2-ethyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)acetamide (**7e**)* Mp 186–188 °C. Yield 73 % (0.089 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 10.08$ (1H, bs, NHCO), 7.60 (1H, d, $J = 9.0$ Hz, H-5), 7.29 (1H, t, $J = 9.0$ Hz, H-7), 6.93 (1H, bs, H-1), 6.72 (2H, m, H-6, H-8), 4.88 (1H, t, $J = 6.0$ Hz, H-2), 1.92 (3H, s, $COCH_3$), 1.70 (2H, m, CH_2CH_3), 0.92 (3H, t, $J = 6.0$ Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) $\delta = 169.23$ (C, NHCO), 161.92 (C, C-4), 148.25 (C, C-8a), 134.39 (CH, C-7), 128.49 (CH, C-5), 117.53 (CH, C-6), 115.08 (CH, C-8), 114.27 (C, C-4a), 72.59 (CH, C-2), 26.20 (CH_2, CH_2CH_3), 15.65 (CH_3, $COCH_3$), 8.67 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 256.1067 $C_{12}H_{15}N_3O_2Na$ (calcd. 256.1062).

*N-(2-ethyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)propanamide (**7f**)* Mp 154–156 °C. Yield 64 % (0.083 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 10.00$ (1H, bs, NHCO), 7.60 (1H, d, $J = 9.0$ Hz, H-5), 7.29 (m, 1H, $J = 9.0$ Hz, H-7), 6.90 (1H, bs, H-1), 6.75 (2H, m, H-6, H-8), 4.90 (1H, t, $J = 6.0$ Hz, H-2), 2.19 (2H, q, $J = 9.0$ Hz, $COCH_2CH_3$), 1.70 (2H, m, CH_2CH_3), 1.07 (3H, t, $J = 9.0$ Hz, $COCH_2CH_3$), 0.93 (3H, t, $J = 9.0$ Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) $\delta = 173.05$ (C, NHCO), 163.02 (C, C-4), 148.32 (C, C-8a), 134.36 (CH, C-7), 128.49 (CH, C-5), 117.72 (CH, C-6), 115.08 (CH, C-8), 114.19 (C, C-4a), 72.57 (CH, C-2), 27.09 (CH_2, $COCH_2CH_3$), 26.18 (CH_2, CH_2CH_3), 10.24 (CH_3, $COCH_2CH_3$), 8.64 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 270.1217 $C_{13}H_{17}N_3O_2Na$ (calcd. 270.1218).

*N-(2-ethyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)butanamide (**7g**)* Mp 175–178 °C. Yield 68 % (0.093 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 9.95$ (1H, bs, NHCO), 7.52 (1H, d, $J = 6.0$ Hz, H-5), 7.20 (1H, t, $J = 9.0$ Hz, H-7), 6.83 (1H, bs, H-1), 6.63 (2H, m, H-6, H-8), 4.81 (1H, t, $J = 6.0$ Hz, H-2), 2.07 (2H, t, $J = 6.0$ Hz, $COC\underline{H_2}CH_2CH_3$), 1.43–1.61 (4H, 2 m, $COCH_2C\underline{H_2}CH_3$, $C\underline{H_2}CH_3$), 0.84 (6H, m, $CH_2C\underline{H_3}$, $COCH_2CH_2C\underline{H_3}$). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) $\delta = 172.15$ (C, NHCO), 163.00 (C, C-4), 148.32 (C, C-8a), 134.36 (CH, C-7), 128.51 (CH, C-5), 117.72 (CH, C-6), 115.08 (CH, C-8), 114.18 (C, C-4a), 72.58 (CH, C-2), 35.76 (CH_2, $CO\underline{C}H_2CH_2CH_3$), 26.18 ($CH_2$, CH_2CH_3), 19.17 (CH_2, $COCH_2\underline{C}H_2CH_3$), 14.24 ($CH_3$, $COCH_2CH_2CH_3$), 8.62 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 284.1374 $C_{14}H_{19}N_3O_2Na$ (calcd. 284.1375).

*N-(2-ethyl-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)pentanamide (**7h**)* Mp 194–196 °C. Yield 49 % (0.071 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 10.04$ (1H, bs, NHCO), 7.61 (1H, d, $J = 6.0$ Hz, H-5), 7.29 (1H, t, $J = 6.0$ Hz, H-7), 6.91 (1H, bs, H-1), 6.72 (2H, m, H-6, H-8), 4.90 (1H, t, $J = 6.0$ Hz, H-2), 2.19 (2H, t, $J = 9.0$ Hz, $COC\underline{H_2}CH_2CH_2CH_3$), 1.18–1.75 (6H, 3 m, $COCH_2C\underline{H_2}CH_2CH_3$, $COCH_2CH_2C\underline{H_2}CH_3$, $C\underline{H_2}CH_3$), 0.90 (6H, m, $CH_2C\underline{H_3}$, $COCH_2CH_2CH_2C\underline{H_3}$). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) $\delta = 172.27$ (C, NHCO), 163.01 (C, C-4), 148.32 (C, C-8a), 134.36 (CH, C-7), 128.51 (CH, C-5), 117.72 (CH, C-6), 115.08 (CH, C-8), 114.18 (C, C-4a), 72.56 (CH, C-2), 33.54 (CH_2, $CO\underline{C}H_2CH_2CH_2CH_3$), 27.83 ($CH_2$, $COCH_2\underline{C}H_2CH_2CH_3$), 26.18 ($CH_2$, CH_2CH_3), 22.39 (CH_2, $COCH_2CH_2\underline{C}H_2CH_3$), 14.42 ($CH_3$, $COCH_2CH_2CH_2CH_3$), 8.62 (CH_3, CH_2CH_3). HRESIMS m/z (pos): 298.1536 $C_{15}H_{21}N_3O_2Na$ (calcd. 298.1531).

*N-(4-oxo-2-phenyl-1,4-dihydroquinazolin-3(2H)-yl)acetamide (**7i**)* Mp 146–148 °C. Yield 54 % (0.080 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 9.86$ (1H, bs, NHCO), 7.70 (1H, d, $J = 9.0$ Hz, H-5), 7.40 (6H, m, H-7, H-2′–H-6′), 6.76 (2H, m, H-6, H-8), 6.00 (1H, s, H-2), 1.73 (3H, s, $COCH_3$). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) $\delta =$ 168.96 (C, NHCO), 163.27 (C, C-4), 148.24 (C, C-8a), 139.48 (C, C-1′), 134.62 (CH, C-7) 129.78 (CH, C-5), 129.08 (2CH, C-3′, C-5′), 128.63 (CH, C-4′), 128.26 (2CH, C-2′, C-6′), 118.29 (CH, C-6), 115.18 (CH, C-8), 114.23 (C, C-4a), 74.77 (CH, C-2), 20.96 (CH_3, $COCH_3$). HRESIMS m/z (pos): 304.1061 $C_{16}H_{15}N_3O_2Na$ (calcd. 304.1062).

*N-(4-oxo-2-phenyl-1,4-dihydroquinazolin-3(2H)-yl)propanamide (**7j**)* Mp 153–157 °C. Yield 47 % (0.075 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 9.78$ (1H,

bs, NHCO), 7.70 (1H, d, $J = 9.0$ Hz, H-5), 7.40 (6H, m, H-7, H-2′–H-6′), 6.77 (2H, m, H-6, H-8), 6.02 (1H, s, H-2), 1.96 (2H, m, $COCH_2CH_3$), 0.87 (3H, t, $J = 6.0$ Hz, $COCH_2CH_3$). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) $\delta = 172.68$ (C, NHCO), 163.44 (C, C-4), 148.41 (C, C-8a), 139.15 (C, C-1′), 134.57 (CH, C-7), 129.83 (CH, C-5), 129.99 (2CH, C-3′, C-5′), 128.65 (CH, C-4′), 128.51 (2CH, C-2′, C-6′), 118.35 (CH, C-6), 115.22 (CH, C-8), 114.34 (C, C-4a), 74.87 (CH, C-2), 20.93 (CH_2, $COCH_2CH_3$), 10.26 (CH_3, $COCH_2CH_3$). HRESIMS m/z (pos): 318.1222 $C_{17}H_{17}N_3O_2Na$ (calcd. 318.1218).

*N-(4-oxo-2-phenyl-1,4-dihydroquinazolin-3(2H)-yl)butanamide (**7k**)* Mp 166–168 °C. Yield 40 % (0.065 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 9.79$ (1H, bs, NHCO) 7.69 (1H, d, $J = 9.0$ Hz, H-5); 7.40 (6H, m, H-7, H-2′–H-6′), 6.77 (2H, m, H-6, H-8), 6.02 (1H, s, H-2), 1.93 (2H, m, $COCH_2CH_2CH_3$), 1.38 (2H, m, $COCH_2CH_2CH_3$), 0.74 (3H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) $\delta = 171.80$ (C, NHCO), 163.48 (C, C-4), 148.42 (C, C-8a), 139.12 (C, C-1′), 134.57 (CH, C-7), 129.83 (CH, C-5), 128.98 (2CH, C-3′, C-5′), 128.67 (CH, C-4′), 128.56 (2CH, C-2′, C-6′), 118.35 (CH, C-6), 115.21 (CH, C-8), 114.35 (C, C-4a), 74.99 (CH, C-2), 35.55 (CH_2, $COCH_2CH_2CH_3$), 19.07 (CH_2, $COCH_2CH_2CH_3$), 14.05 (CH_3, $COCH_2CH_2CH_3$). HRESIMS m/z (pos): 332.1380 $C_{18}H_{19}N_3O_2Na$ (calcd. 332.1375).

*N-(4-oxo-2-phenyl-1,4-dihydroquinazolin-3(2H)-yl)pentanamide (**7l**)* Mp 178–180 °C. Yield 75 % (0.127 g) as a white solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) $\delta = 9.78$ (1H, bs, NHCO), 7.69 (1H, d, $J = 9.0$ Hz, H-5), 7.40 (6H, m, H-7, H-2′–H-6′), 6.77 (2H, m, H-6, H-8), 6.02 (1H, s, H-2), 1.95 (2H, m, $COCH_2CH_2CH_2CH_3$), 1.33 (2H, m, $COCH_2CH_2CH_2CH_3$), 1.11 (2H, m, $COCH_2CH_2CH_2CH_3$), 0.77 (3H, t, $J = 6.0$ Hz, $COCH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MH, $(CD_3)_2SO$) $\delta = 171.89$ (C, NHCO), 163.51 (C, C-4), 148.44 (C, C-8a), 139.05 (C, C-1′), 134.57 (CH, C-7), 129.81 (CH, C-5), 128.96 (2CH, C-3′, C-5′), 128.59 (3CH, C-2′, C-4′, C-6′), 118.36 (CH, C-6), 115.21 (CH, C-8), 114.37 (C, C-4a), 74.99 (CH, C-2), 33.32 (CH_2, $COCH_2CH_2CH_2CH_3$), 27.75 (CH_2, $COCH_2CH_2CH_2CH_3$), 22.11 (CH_2, $COCH_2CH_2CH_2CH_3$), 14.34 (CH_3, $COCH_2CH_2CH_2CH_3$). HRESIMS m/z (pos): 346.1485 $C_{19}H_{21}N_3O_2Na$ (calcd. 346.1489).

In vitro nNOS and iNOS activities determination

L-Arginine, *L*-citrulline, *N*-(2-hydroxymethyl)piperazine-*N*′-(2-ethanesulfonic acid) (HEPES), DL-dithiothreitol (DTT), hypoxanthine-9-β-D-ribofuranoside (inosine), ethylene glycol-bis-(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA), bovine serum albumin (BSA), Dowex-50 W (50 × 8–200), FAD, NADPH and 5,6,7,8-tetrahydro-L-biopterin dihydrocloride (H_4-biopterin), tris-(hydroxymethyl)-aminomethane (Tris–HCl), and calcium chloride were obtained from Sigma-Aldrich Química (Spain). L-[^{3}H]-arginine (54 Ci mmol^{-1}) was obtained from Amersham (Amersham Biosciences, Spain).

Tris-(hydroxymethyl)-aminomethane (Tris–HCl) and calcium chloride were obtained from Merck (Spain). Calmodulin from bovine brain, and recombinant iNOS and nNOS enzymes, were obtained from Alexis Biochemicals (Enzo Life Sciences, Grupo Taper, Seville, Spain).

The nNOS activity was measured by the Bredt and Snyder method (Bredt and Snyder 1990), monitoring the conversion of L-[^{3}H]-arginine to L-[^{3}H]-citrulline. The final incubation volume was 100 μL and consisted of 10 μL of an aliquot of recombinant i/nNOS added to a buffer with a final concentration of 25 mM Tris–HCl, 1 mM DTT, 4 μM H_4-biopterin, 10 μM FAD, 0.5 mM inosine, 0.5 mg/mL BSA, 0.1 mM $CaCl_2$, 10 μM L-arginine, 10 μg/mL calmodulin (only for nNOS) and 50 nM *L*-[^{3}H]-arginine, at pH 7.6 and 7.0 for iNOS and nNOS, respectively. The reaction was started by the addition of 10 μL of 0.75 mM NADPH and 10 μL of each 2,3-dihydro-1,3,4-oxadiazole or 2,3-dihydroquinazolin-4(1*H*)-one derivative in ethanol (20 %) to give a final concentration of 1 mM. The tubes were vortex and incubated at 37 °C for 30 min. Control incubations were performed by the omission of NADPH. The reaction was halted by the addition of 400 μL of cold 0.1 M HEPES, 10 mM EGTA, and 0.175 mg/mL L-citrulline, pH 5.5. The reaction mixture was decanted into a 2-mL column packet with Dowex-50 W ion-exchange resin (Na^+ form) and eluted with 1.2 mL of water. L-[^{3}H]-citrulline was quantified by liquid scintillation spectroscopy. The retention of L-[^{3}H]-arginine in this process was greater than 98 %. Specific enzyme activity was determined by subtracting the control value, which usually amounted less than 1 % of the radioactivity added. The nNOS activity was expressed as picomoles of L-[^{3}H]-citrulline produced (/mg of protein/min).

Statistical analysis

Data are expressed as the mean ± SEM. Statistically significant differences between groups were calculated by Student's t test for unpaired observations or for multiple comparisons. An ANOVA followed by the Newmane-Keuls multiple range test was used. A $p < 0.05$ was considered statistically significant.

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