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Synthesis and evaluation of quinazoline derivatives as phosphodiesterase 7 inhibitors

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ABSTRACT

The latest scientific findings concerning PDE7 and PDE4 inhibition suggest that selective small-molecule inhibitors of both enzymes could provide a novel approach to treat a variety of immunological diseases. In this context, we describe a new series of quinazoline derivatives from quinazolin-4-thiones which include a substituted biphenyl fragment. Some of these compounds show inhibitory potencies at submicromolar levels against the catalytic domain of PDE7.

1. Introduction

The social use of phosphodiesterase (PDE) inhibitors such as caffeine has been known for long time, but only by 1957 PDE was identified. The pioneering works of Sutherland et al. recognized the enzyme, 'probably a phosphodiesterase', activated by Mg^{2+} and inhibited by caffeine.[1] The ubiquitous cyclic nucleotide second messengers cAMP (cyclic adenosine 3′,5′-monophosphate) and cGMP (cyclic guanosine 3′,5′-monophosphate) play a central role in a variety of cellular responses. There are two main processes that control the intracellular levels of these nucleotides: The regulation of their synthesis accomplished by the action of adenylate or guanylate cyclase, respectively, and the regulation of their hydrolysis, catalyzed by PDEs.[2] PDEs are isoenzymes organized into 11 subfamilies (PDE1–11) characterized according to their sequence identity, cellular distribution, substrate specificity, and sensitivity to different PDE inhibitors. Since PDEs play crucial role in regulating immune, endocrine and cardiovascular functions, central nervous system, inflammation, oxidative stress, cell proliferation and others, PDE inhibitors may have considerable therapeutic interest as anti-inflammatory agents, antiasthmatics, vasodilators, smooth muscle relaxants, cardiotonic agents, antidepressants, antithrombotics, etc.[3] However, the known PDEs heterogeneity led to the synthesis of highly selective inhibitors, which have demonstrated efficacy in a variety of disorders.[4] Nevertheless, the precise mechanism and the contribution of the various PDEs in modulating tissue-specific intracellular signaling remain to be established. More information is known about PDE4, the major isoenzyme in most T-cell preparations. Its selective inhibitors are able to decrease inflammatory cytokine production and have been widely studied as efficient anti-inflammatory agents for different diseases.[5] However, a major drawback of these compounds is the significant side effects, such as emesis. To overcome these adverse effects, an alternative approach is to target other cAMP specific PDE families that are expressed in pro-inflammatory and immune cells. In this context, PDE7 is also expressed in T-cells and could be a good target for the control of neuroinflammation.[6] There is little information regarding the physiological functions regulated by PDE7. PDE7 is insensitive to rolipram, the specific inhibitor of the PDE4 subfamily, but is sensitive to isobutyl-methylxanthine (IBMX).[7] Few examples of specific inhibitors of PDE7 have been reported. Thus, specific inhibitors such as BRL 50481,[8] IC242,[9] ASB 16165[10] and a thiadiazole[11] family, synthetized by Pfizer, were reported as potential new drugs for the treatment of neurological disorders,[12] chronic skin diseases,[13] immune and inflammatory disorders[14] and others. Regarding the chemical structure, benzothiadiazine and benzothienothiadiazine derivatives constituted the first described heterocyclic family of compounds with PDE7 inhibitory properties.[15] Subsequently, other heterocyclic compounds such as purine and pyrimidine derivatives, spiroquinazolinones,

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sulfonamides and azole derivatives have been described as PDE7 inhibitors.[12b] Recently, a new family of PDE7 inhibitors, with a quinazoline–thione structure has been described with a possible neuroprotective activity.[4]

In the other hand, different pharmacologic studies had also shown that some compounds initially synthesized as angiotensin II antagonists had IC_{50} values in the micromolar range as PDE inhibitors. These compounds include a wide variety of quinazoline rings structurally related to Losartan, the first orally active angiotensin II antagonist.[16]

Our experience in the field of angiotensin II antagonists and the above considerations led us to explore new biphenyl substituted *thio*quinazoline derivatives (quinazolines with a sulfur bridge between the fused heterocycle and the substituted biphenyl moiety) as potential PDE7 inhibitors. Here we describe the synthesis and evaluation of their activity.[17]

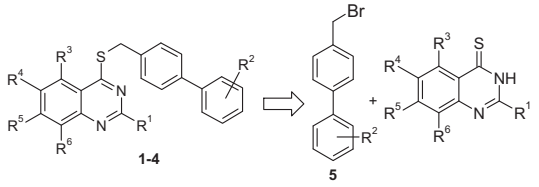
2. Chemistry

The retrosynthetic pathway for the biphenyl substituted thioquinazoline derivatives **1**–**4** is shown in Scheme 1. These derivatives were obtained by the reaction of different biphenyl compounds **5** and the corresponding substituted 3*H*-quinazoline-4-thiones, obtained by conventional chemistry and described methods.

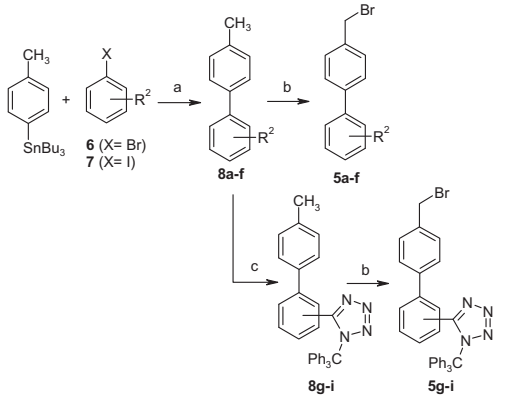
2.1. Biphenyl derivatives synthesis

The biphenyl compounds **5** were obtained following the literature method,[18] from the commercially available tri-*n*-butyl-*p*-tolylstannane and the corresponding substituted bromo (**6**, X = Br) or iodobenzenes (**7**, X = I) (Scheme 2).

Thus, the reaction of tri-*n*-butyl-*p*-tolylstannane and the corresponding **6** (**6a**–**c**, X = Br and R^2 = *o*-CN, *m*-CN and *p*-CN, respectively) in the presence of palladium catalysts and LiCl afforded compounds **8a**–**c**, whereas the reaction of tri-*n*-butyl-*p*-tolylstannane with **7d**–**f** (X = I and R^2 = *o*-CO_2Me, *m*-CO_2Me and *p*-CO_2Me, respectively), in the same experimental conditions, supplied compounds **8d**–**f**, in excellent yields. The tetrazole derivatives **8g**–**i** were obtained from the corresponding nitriles **8a**–**c**, in the presence of tri-*n*-butyltin chloride and sodium azide at reflux. Ulterior treatment with sodium hydroxide and triphenylmethyl chloride gave compounds **8g**–**i**. Finally, bromomethyl derivatives **5a**–**i** were obtained by reaction of the corresponding methyl derivative with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide in CCl_4. Table 1 shown results in the preparation of biphenyl compounds **5** and **8**.



Scheme 1. Retrosynthetic analysis for substituted quinazolines **1**–**4**.



Reagents: (a) $Pd(PPh_3)_2Cl_2$, LiCl, DMF; (b) *N*-bromosuccinimide, benzoyl peroxyde, CCl_4; (c) NaN_3, Bu_3SnCl, NaOH, Ph_3CCl, toluene.

Scheme 2. Preparation of biphenyl derivatives **5a**–**i**.

Table 1
Biphenyl derivatives **5** and **8**

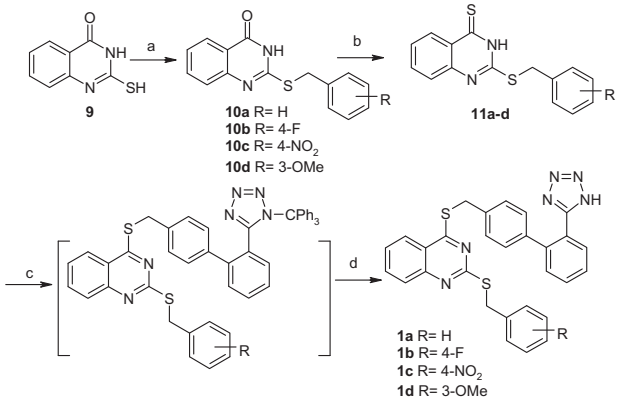
Compound	R^2	Yield (%)
8a	*o*-CN	92
8b	*m*-CN	70
8c	*p*-CN	89
8d	*o*-CO_2Me	86
8e	*m*-CO_2Me	86
8f	*p*-CO_2Me	85
8g	*o*- 	85
8h	*m*- 	82
8i	*p*- 	83
5a	*o*-CN	96
5d	*o*-CO_2Me	82
5e	*m*-CO_2Me	83
5f	*p*-CO_2Me	82
5g	*o*- 	85
5h	*m*- 	84
5i	*p*- 	84

2.2. Quinazoline derivatives synthesis

Quinazoline **1**–**4** series were obtained by conventional chemistry using four different approximations. Thus, thioquinazolines **1** were prepared starting from 2-mercapto-3*H*-quinazolin-4-one **9** by reaction with different benzyl bromides in DMF as solvent and in the presence of potassium carbonate, affording the corresponding benzylsulfanyl derivatives (**10a**–**d**) which were transformed into the quinazolin-3-thiones **11a**–**d** using Lawesson's reagent in anhydrous toluene.[19] Thioquinazolines **1a**–**d** were obtained by reaction of thione derivatives **11a**–**d** with **5g** followed by deprotection of the protected tetrazole ring with HCl (Scheme 3).

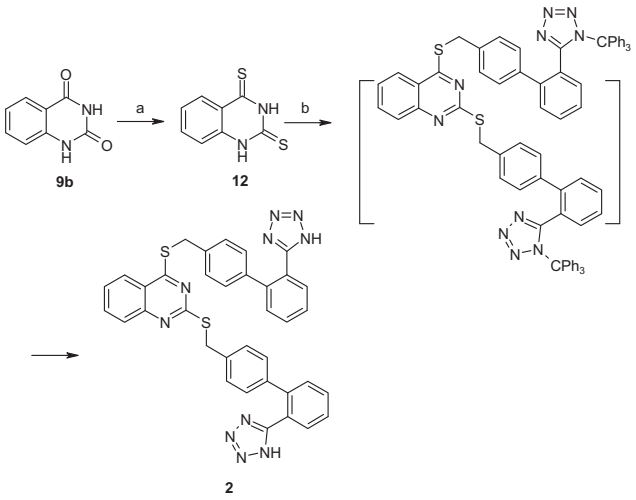
The quinazoline **2** was prepared through quinazolin-2,4-dithione **12**, which was obtained from 1*H*-quinazolin-2,4-dione **9b** and by reaction with the Lawesson's reagent in anhydrous toluene. Subsequent treatment of **12** with potassium carbonate in DMF and in the presence of **5g** yielded derivative **2**, after deprotection of the protected tetrazole rings (Scheme 4).

To introduce some diversity on the heterocyclic ring of the quinazoline nucleus, other quinazolin-4-ones, as the commercially available 3*H*-quinazoline-4-one **9c**, 2-methyl-3*H*-quinazoline-4-



Reagents: (a) $ArCH_2Br$, K_2CO_3, DMF; (b) Lawesson´s reagent, toluene anh.; (c) **5g**, K_2CO_3, DMF; (d) HCl 10%

Scheme 3. Preparation of quinazolines **1a**–**d**.



Reagents: (a) Lawesson´s reagent, toluene anh.; (b) **5g**, K_2CO_3, DMF; (c) HCl 10%.

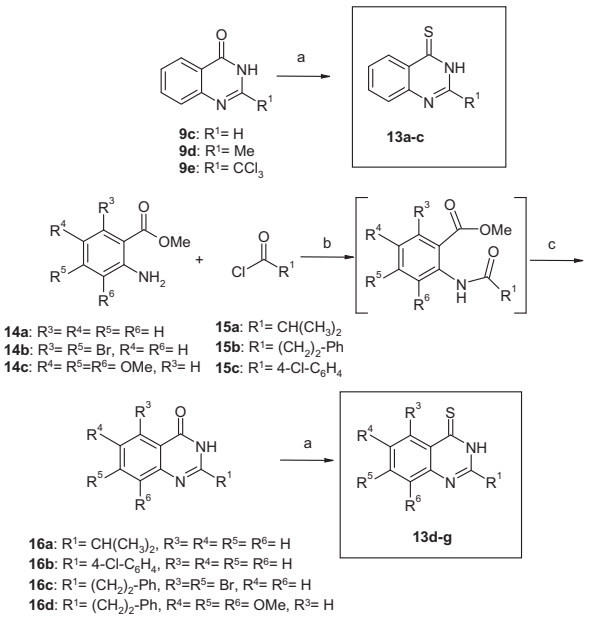
Scheme 4. Preparation of quinazoline **2**.

one **9d** and 2-trichloromethyl-3*H*-quinazoline-4-one **9e** were also treated with Lawesson's reagent to obtain the corresponding quinazolin-4-thiones **13a**–**c** in high yields (Scheme 5). In addition, and to introduce diversity on carbocyclic and/or heterocyclic rings of the quinazoline nucleus, substituted *o*-amino methyl benzoates **14** were reacted with different acyl chlorides **15** in the presence of a base, yielding intermediate amides, which with NH_4OH, in a pressure reactor, yielded quinazoline-4-ones **16a**–**d** in moderate yields.[20]

Treatment of **16a**–**d** with Laweson's reagent produced the quinazolin-4-thiones **13d**–**g** in good yield (Scheme 5). Finally, the reaction of quinazolin-4-thiones **13a**–**g** with biphenyl bromides **5g**–**i** in the presence of potassium carbonate and DMF, followed by deprotection of the tetrazole group afforded **3a**–**k** (Scheme 6). Quinazolines **3** obtained and their yields are shown in Table 2.

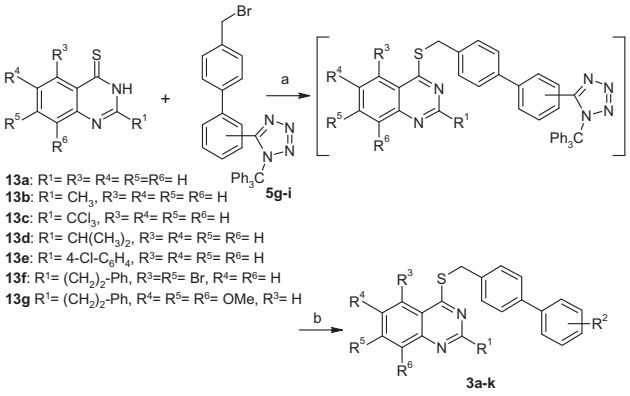
A new quinazoline series was obtained from the reaction of biphenylderivative **5a**, containing an *o*-cyano group, with quinazolin-4-thiones **11a**–**c** and **13a**–**d** (Scheme 7).

To complete the SAR study, biphenyl compounds bearing a methoxycarbonyl substituent in different positions (**5d**–**f**) were also employed. All of them were reacted with **13d** to give the corresponding quinazoline derivatives **4h**–**j**, which, upon treatment with a solution of lithium hydroxide afforded the carboxylic acids **4k**–**m** (Scheme 7, Table 3).



Reagents: (a) Lawesson´s reagent, toluene anh. r.t.; (b) Py/$CHCl_3$ r.t.12 h.; (c) NH_4OH 30% 12 h.

Scheme 5. Preparation of starting material **13a**–**g**.



Reagents: (a) K_2CO_3, DMf, r.t.; (d) HCl 10%

Scheme 6. Preparation of quinazolines **3a**–**k**.

3. Biological results and discussion

3.1. PDE7 assay procedure and SAR studies

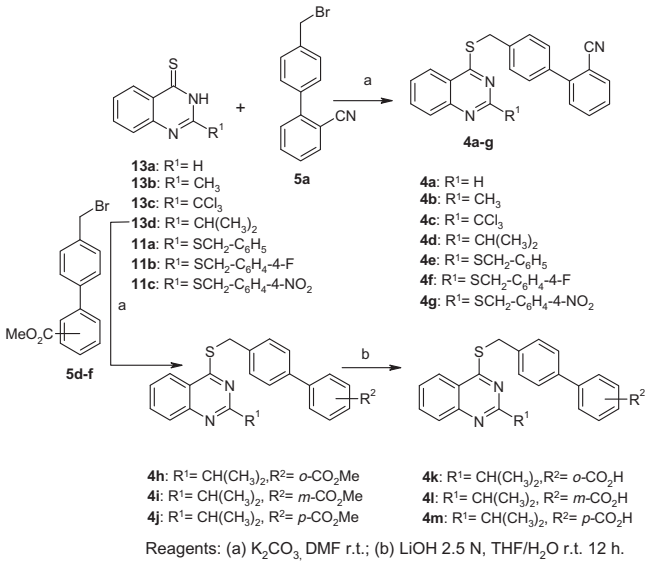
The results of in vitro evaluation of PDE7 inhibition of the new synthesized compounds are indicated in Table 4.

Compounds included in series **1**, having different benzylsulfanyl groups in R^1 position of the quinazoline ring and a tetrazole ring on 2′-position of the biphenyl moiety, show moderate activity, with very similar IC_{50} values (entries 1–4). Substitution on benzene ring of the benzylsulfanyl fragment seems to have little effect on the activity (entries 2–4) when compared with unsubstituted derivative (entry 1), electrowithdrawing substituents, however, such as 4-F, 4-NO_2 and 3-OMe (the last one with only –I effect operative) showed a slight increase of PDE7 inhibition (entries 2–4).

Series **3a**–**k** having H, alkyl, 4-chlorophenyl or phenethyl groups in the quinazoline R^1 position, as well as in some cases, different substituents on the carbocyclic ring of the quinazoline system (R^3–R^6), as well as a tetrazole ring on 2′-, 3′-, or 4′-position

Table 2
Quinazolines **3a**–**k**

3	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)
3a	H	*m*-	H	H	H	H	25
3b	H	*p*-	H	H	H	H	16
3c	CH_3	*o*-	H	H	H	H	78
3d	CH_3	*m*-	H	H	H	H	48
3e	CH_3	*p*-	H	H	H	H	61
3f	CCl_3	*o*-	H	H	H	H	59
3g	$CH(CH_3)_2$	*o*-	H	H	H	H	72
3h	$CH(CH_3)_2$	*m*-	H	H	H	H	57
3i	4-Cl-C_6H_4	*o*-	H	H	H	H	69
3j	$(CH_2)_2$-Ph	*m*-	Br	H	Br	H	68
3k	$(CH_2)_2$-Ph	*o*-	H	OMe	OMe	OMe	68



Scheme 7. Preparation of quinazolines **4a**–**m**.

of the biphenyl moiety, show a wide range of PDE7 inhibition activity (0.77–>100 μM, entries 6–16). From the few examples substituted in the positions R^3–R^6 of the quinazoline ring, only **3k**, the example bearing alkoxy substituents (R^4–R^6 = OMe) and a tetrazole ring on 2′-position of the biphenyl fragment, showed some activity (entry 16) and should be explored in future projects.

Table 3
Quinazolines **4a**–**m**

Compound	R^1	R^2	Yield (%)
4a	H		91
4b	CH_3		75
4c	CCl_3		65
4d	$CH(CH_3)_2$		77
4e	SCH_2Ph		69
4f	$SCH_2C_6H_4$-4-F		94
4g	$SCH_2C_6H_4$-4-NO_2		60
4h	$CH(CH_3)_2$	*o*-CO_2Me	67
4i	$CH(CH_3)_2$	*m*-CO_2Me	58
4j	$CH(CH_3)_2$	*p*-CO_2Me	80
4k	$CH(CH_3)_2$	*o*-CO_2H	72
4l	$CH(CH_3)_2$	*m*-CO_2H	69
4m	$CH(CH_3)_2$	*p*-CO_2H	89

Table 4
PDE7 inhibition of the new synthesized compounds

Entry	Compound	PDE7IC_{50}[a] (μM)
1	**1a**	7.1
2	**1b**	6.8
3	**1c**	4.9
4	**1d**	3.3
5	**2**	—[b]
6	**3a**	8.2
7	**3b**	7.2
8	**3c**	11
9	**3d**	2.5
10	**3e**	8
11	**3f**	2.6
12	**3g**	0.77
13	**3h**	0.89
14	**3i**	12
15	**3j**	>100
16	**3k**	3.6
17	**4a**	>100
18	**4b**	>100
19	**4c**	>100
20	**4d**	>100
21	**4e**	—[b]
22	**4f**	>100
23	**4g**	>100
24	**4h**	>100
25	**4i**	>100
26	**4j**	33
27	**4k**	44
28	**4l**	0.85
29	**4m**	0.93

[a] IC_{50}: 50% inhibitory concentration of PDE7. Assays were performed in triplicate.
[b] Not tested by solubility problems.

The more active compounds of the series are **3g** and **3h** (entries 12 and 13) having an isopropyl substituent at R^1 position. In general, the position of the tetrazole ring in the biaryl moiety has little effect on the activity of the products, whereas more important differences appear depending of R^1 substitution. Thus, comparing compounds **3a** and **3b** (entries 6 and 7), **3c**–**e** (entries 8–10) or **3g** and **3h** (entries 12 and 13), a different position of tetrazole ring on biaryl moiety, produces small differences in activity, being the optimal position variable in every set. A more significant difference in activity was found for derivatives **3a**, **3d** and **3e** (entries 6, 9 and 10), where activities increase for R^1: H <Me <*i*Pro, (presumable with the change in size and lipophilicity of the substituent in R^1) being **3d** (entry 9) the comparative optimum, while 4-Cl-phenyl in R^1 (**3i**, entry 14) showed again a reduced activity. The compound **3c**, (entry 8), previously reported as PDE4 inhibitor, and according with published results[16] only shown a weak activity as PDE7 inhibitor.

Series **4a**–**m**, having H, alkyl, or substituted benzylsulfanyl groups in R^1 position of the quinazoline and a CN on 2′-position of the biphenyl, a CO_2Me or a CO_2H on the 2′-, 3′- and 4′-positions of the biphenyl moiety, show a very distinct behavior as PDE7 inhibitors (entries 17–29, Table 4), mostly showing activity only associated to the presence of a carboxylic group. Thus, only compound **4j**, bearing methoxycarbonyl group in 4′-position of the biphenyl fragment showed some activity (entry 26). However, derivatives with carboxylic acid **4k**–**m** show better activities, specially compounds **4l** and **4m**, bearing the carboxylic substituent in *meta*- or *para*-positions, respectively, on the biaryl moiety (entries 28 and 29) display a IC_{50} significantly improved, while the carboxy group in *ortho*-position showed a low activity (**4k**, entry 27). In fact, compounds **4l** and **4m** can be considered two of the most active synthesized compounds.

In conclusion, new series of biphenyl-4-methylsulfanyl quinazoline derivatives have been synthesized and tested as PDE7 inhibitors. Results showed interesting PDE7 inhibitory activity for some of these quinazoline, with compounds **3g 3h**, **4l**, and **4m** in the range 0.7–0.9 μM. These compounds would be studied in further in vivo developments.

4. Experimental

4.1. Chemical procedures

4.1.1. Instrumentation and general materials

All experiments were carried out under a dry argon atmosphere, with solvents freshly distilled under anhydrous conditions, unless stated otherwise. All chemicals were used without further purification. ^{1}H NMR was recorded on at 200 and 300 spectrometer in Varian Unity. Chemical shifts are reported in ppm relative to trimethylchlorosilane. Column chromatography was performed using silica gel (60 F254, 70–200 mm) as the stationary phase. All melting points are uncorrected in Electrothermal LA6304. IR: IR for liquids were run as film between NaCl crystals and solids as KBr pellets in FT-IR spectrometer Perkin–Elmer 883. MS was recorded on Hewllett–Packard 5988A and HPLC/MS in Agilent Hewlett–Packard 110 electrospray, with column Luna C18 (150 × 4.6 mm) 5 μm Phenomenex. Elemental analyses were carried out in a Heraeus CHN Rapid.

The following compounds have been previously described: **3a**,[16] **5a**,[21] **5d**,[18] **5e**,[22] **5f**,[23] **5g**,[22] **5h**,[24] **5i**,[25] **8a**,[18] **8b**,[21] **8c**,[26] **8d**,[18] **8e**,[22] **8f**,[23] **8g**,[18] **10a**,[27] **11a**,[28] **12**,[29] **13a**,[30] **13b**,[31] **13d**,[32] **13e**,[33] **16a**,[34] **16b**[35] and **16d**.[36]

4.1.2. Syntheses of biphenyl derivatives (8h and 8i).

A stirred solution of corresponding 4-methyl-biphenyl-carbonitrile **8b** or **8c** (4.5 g, 23.5 mmol), sodium azide (1.5 g, 23.5 mmol), tri-*n*-butyltin chloride (8.4 g, 25 mmol) and toluene (30 mL) was heated at 115 °C for 70 h. The mixture was diluted with toluene (35 mL) and cooled to room temperature. NaOH 10 N (2.7 mL, 27 mmol)) and triphenylmethyl chloride (6.7 g, 24 mmol) were added and the resulting mixture stirred for 3 h at room temperature. Toluene was removed in vacuo, the residue triturated with hexane and the solid filtered. Recrystallization from dichloromethane–ethyl acetate yielded pure compound.

4.1.2.1. 5-(4′-Methyl-biphenyl-3-yl)-1-trityl-1*H*-tetrazole (8h). White solid. Yield: 82%. Mp 165–166 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ: 2.28 (3H, s), 7.12–7.20 (6H, m), 7.22–7.38 (11H, m), 7.46–7.56 (3H, m), 7.63 (1H, d, J = 8.0 Hz), 8.07 (1H, d, J = 7.9 Hz), 8.34 (s, 1H). MS (CI) m/z 479.0 ([M+H],$^+$ 100). Anal. Calcd for $C_{33}H_{26}N_4$: C, 82.82; H, 5.48; N, 11.71. Found: C, 83.01; H, 5.78; N, 11.65.

4.1.2.2. 5-(4′-Methyl-biphenyl-4-yl)-1-trityl-1*H*-tetrazole (8i). White solid. Yield: 83%. Mp 168–169 °C. ^{1}H NMR (300 MHz $CDCl_3$) δ: 2.38 (3H, s), 7.12–7.20 (6H, m), 7.22–7.40 (11H, m), 7.51 (2H, d, J = 7.9 Hz), 7.64 (2H, d, J = 8.4 Hz), 8.18 (2H, d, J = 8.4 Hz). MS (CI) m/z 479.0 ([M+H],$^+$ 100). Anal. Calcd for $C_{33}H_{26}N_4$: C, 82.82; H, 5.48; N, 11.71. Found: C, 82.67; H, 5.63; N, 12.05.

4.1.3. Synthesis of 2-benzylsulfanyl-3*H*-quinazolin-4-ones (10a–d).

To a solution of the 2-mercapto-3*H*-quinazolin-4-one (**9a**) (2.01 g, 11.3 mmol) in 20 mL of anhydrous DMF, K_2CO_3 (3.09 g, 22.4 mmol) and the corresponding benzyl bromide (11.3 mmol) were added. The solution was stirred at room temperature for 12 h and then it was poured in a mixture water/ice (25 mL) and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The products were used in the next step without further purification.

4.1.3.1. 2-Benzylsulfanyl-3*H*-quinazolin-4-one (10a). White solid. Yield: 64%. Mp 214–216 °C. [lit.[27] 212–213 °C].

4.1.3.2. 2-(4-Fluoro-benzylsulfanyl)-3*H*-quinazolin-4-one (10b). Yellow solid. Yield: 65%. Mp 217–219 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.51 (2H, s), 6.95–6.99 (2H, m), 7.36–7.46 (3H, m), 7.63 (1H, d, J = 8.0 Hz), 7.72 (1H, dt, J = 8.6 and 1.4 Hz), 8.01 (1H, br s, OH for enolic form), 8.22 (1H, dd, J = 8.0 and 1.4 Hz), 11.38 (s, 1H, NH for cetonic form). MS (CI) m/z 287.0 ([M+H]$^+$, 100).

4.1.3.3. 2-(4-Nitro-benzylsulfanyl)-3*H*-quinazolin-4-one (10c). Yellow solid. Yield: 72%. Mp 235–237 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.58 (2H, s), 7.40 (1H, dt, J = 8.3 and 1.2 Hz), 7.58 (1H, d, J = 8.0 Hz), 7.73–7.78 (3H, m), 7.72 (1H, dt, J = 8.6 and 1.4 Hz), 7.93 (1H, br s, OH for enolic form), 8.22 (1H, dd, J = 8.0 and 1.2 Hz), 8.15 (2H, d, J = 8.0 Hz), 11.50 (br s, 1H, NH for cetonic form). MS (CI) m/z 314.0 ([M+H]$^+$, 100).

4.1.3.4. 2-(3-Methoxy-benzylsulfanyl)-3*H*-quinazolin-4-one (10d). Yellow solid. Yield: 95%. Mp 235–237 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) ^{1}H NMR (300 MHz, DMSO-d_6) : 3.70 (3H, s), 4.44 (2H, s), 6.78 (1H, ddd, J = 8.4, 2.8 and 1.2 Hz), 7.02 (1H, d, J = 7.4 Hz), 7.04–7.08 (1H, m), 7.21 (1H, t, J = 7.9 Hz), 7.41 (1H, dt, J = 7.4 and 1.2 Hz), 7.57 (1H, d, J = 7.6 Hz), 7.76 (1H, dt, J = 8.4 and 1.6 Hz), 7.93 (1H, br s, OH for enolic form). 8.00 (1H, dd, J = 8.1 and 1.6 Hz), 12.20 (br s, 1H, NH for cetonic form). MS (CI) m/z 299.0 ([M+H]$^+$, 100).

4.1.4. Synthesis of 2-benzylsulfanyl-3*H*-quinazolin-4-thiones (11a–d).

To a solution of the corresponding benzylsulfanyl)-3*H*-quinazolin-4-one (**10a**–**d**) (6.2 mmol) in anhydrous toluene (100 mL), under an atmosphere of dry argon, the Lawesson's reagent was added (5.00 g, 12.40 mmol), and the reaction was heated under reflux until no starting material was detected by TLC (2–10 h). Then, a solution of 3 N NaOH (40 mL) was added and the aqueous layer was neutralized with HCl 1 N. The solid thus obtained was filtered and dried under vacuum. This product was used in the next step without further purification.

4.1.4.1. 2-Benzylsulfanyl-3*H*-quinazolin-4-thione (11a). Yellow solid. Yield: 90%. Mp 198–200 °C [lit.[28] 200–202 °C].

4.1.4.2. 2-(4-Fluoro-benzylsulfanyl)-3*H*-quinazolin-4-thione (11b). Yellow solid. Yield: 99 %. Mp >250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) : 4.47 (2H, s), 7.10–7.15 (2H, m), 7.44–7.55 (3H, m), 7.63 (1H, d, J = 8.4 Hz), 7.83 (1H, dt, J = 8.4 and 1.7 Hz),

8.43 (1H, dd, J = 8.3 and 1.7 Hz), 14.09 (br s, 1H). MS (CI) m/z 303.0 ([M+H]$^+$, 100). Anal. Calcd for $C_{15}H_{11}FN_2S_2$: C, 59.58; H, 3.67; N, 9.26. Found: C, 59.51; H, 3.79; N, 9.53.

4.1.4.3. 2-(4-Nitro-benzylsulfanyl)-3*H*-quinazolin-4-thione (11c). Yellow solid. Yield: 85 %. Mp >250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) : 4.59 (2H, s), 7.31 (1H, t, J = 8.2 Hz), 7.47 (1H, t, J = 7.7 Hz), 7.63 (1H, d, J = 8.2 Hz), 7.76 (2H, d, J = 8.7 Hz), 8.15 (2H, d, J = 8.7 Hz), 8.43 (1H, d, J = 7.7 Hz) 14.09 (br s, 1H). MS (CI) m/z 330.0 ([M+H]$^+$, 100). Anal. Calcd for $C_{15}H_{11}N_3O_2S_2$: C, 54.70; H, 3.37; N, 12.76. Found: C, 54.52; H, 3.67; N, 12.52.

4.1.4.4. 2-(3-Methoxy-benzylsulfanyl)-3*H*-quinazolin-4-thione (11d). Yellow solid. Yield: 83%. Mp 247–248 °C. ^{1}H NMR (300 MHz, DMSO-d_6) : 3.79 (3H, s), 4.45 (2H, s), 6.74–6.83 (2H, m), 7.08–7.12 (2H, m), 7.21–7.31 (2H, m), 7.767–.82 (1H, m), 8.45 (1H, d, J = 7.9 Hz), 14.09 (br s, 1H). MS (CI) m/z 315.0 ([M+H]$^+$, 100). Anal. Calcd for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91. Found: C, 61.44; H, 4.67; N, 8.65.

4.1.5. Synthesis of 4-(2′-(1*H*-tetrazol-5-yl)biphenyl quinazolines (1a–d).

Corresponding 2-benzylsulfanyl-3*H*-quinazolin-4-thione (**11**) (0.5 mmol) was dissolved in anhydrous DMF (5 mL) and K_2CO_3 (0.14 g, 1.0 mmol) and 5-(4′-bromomethyl-biphenyl-2-yl)-1-trimethylphenyl-1*H*-tetrazole (**5g**) (0.56 g, 1.0 mmol) were added. The reaction mixture was stirred at room temperature for 12 h. Afterwards the crude reaction was poured into distilled water (10 mL), and extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$, saturated solution of NaCl, dried (Na_2SO_4), and concentrated under vacuum. The residue thus obtained was dissolved in anhydrous THF (10 mL) and HCl 10% (6 mL) was added. The reaction mixture was stirred at room temperature for 18 h and then, NaOH (10%) was added until pH 10. The solution was washed with diethyl ether and the aqueous layer acidified with HCl 10% until pH 3. The yellow solid obtained was filtrated and dried under vacuum and recrystallised from methanol.

4.1.5.1. 2-Benzylsulfanyl-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl]quinazoline (1a). Yellow solid. Yield: 32%. Mp >250 °C. IR (KBr): 3412, 2973, 1611, 1559, 1443, 1336, 1279, 1172, 992, 759 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.50 (2H, s), 4.56 (2H, s), 7.02 (2H, d, J = 7.7 Hz), 7.18–7.26 (1H, m), 7.30 (2H, t, J = 7.3 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.44–7.70 (7H, m), 7.81 (1H, d, J = 8.4 Hz), 7.91 (1H, t, J = 7.3 Hz), 7.99 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{22}N_6S_2$: C, 67.16; H, 4.28; N, 16.20. Found: C, 66.84; H, 4.65; N, 15.82.

4.1.5.2. 2-(4-Fluoro-benzylsulfanyl)-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl]-quinazoline (1b). Yellow solid. Yield: 19%. Mp >250 °C. IR (KBr): 3414, 2992, 1617, 1560, 1443, 1280, 1173, 1064, 993, 759 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.49 (2H, s), 4.56 (2H, s), 7.00–7.20 (4H, m), 7.38 (2H, d, J = 8.2 Hz), 7.50–7.65 (7H, m), 7.81 (1H, d, J = 8.2 Hz), 7.92 (1H, t, J = 7.2 Hz), 7.99 (1H, d, J = 7.2 Hz). Anal. Calcd for $C_{29}H_{21}FN_6S_2$: C, 64.91; H, 3.94; N, 15.66. Found: C, 64.84; H, 3.65; N, 15.82.

4.1.5.3. 2-(4-Nitro-benzylsulfanyl)-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl]-quinazoline (1c). Yellow solid. Yield: 61%. Mp >250 °C. IR (KBr): 3414, 2904, 1637, 1519, 1444, 1342, 1173, 994, 760 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.54 (2H, s), 4.61 (2H, s), 7.02 (2H, d, J = 8.4 Hz), 7.33–737 (3H, m), 7.49–7.63 (4H, m), 7.75–7.83 (3H, m), 7.90 (1H, t, J = 8.4 Hz), 7.97 (1H, d, J = 8.2 Hz), 8.14 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{29}H_{21}N_7O_2S_2$: C, 61.80; H, 3.76; N, 17.39. Found: C, 61.84; H, 3.66; N, 17.62.

4.1.5.4. 2-(3-Methoxy-benzylsulfanyl)-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl]-quinazoline (1d). Yellow solid. Yield: 50%. Mp >250 °C. IR (KBr): 3415, 2904, 1613, 1479, 1336, 1132, 876, 713 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.69 (3H, s), 4.47 (2H, s), 4.56 (2H, s), 6.79 (1H, dd, J = 8.2 and 2.6 Hz), 7.01–7.05 (4H, m), 7.20 (1H, t, J = 8.0 Hz), 7.30–7.40 (3H, m), 7.48–7.60 (2H, m), 7.63 (2H, d, J = 7.7 Hz), 7.81 (1H, d, J = 8.4 Hz), 7.91 (1H, t, J = 7.7 Hz), 7.98 (1H, d, J = 8.7 Hz). Anal. Calcd for $C_{30}H_{24}N_6OS_2$: C, 65.67; H, 4.41; N, 15.32. Found: C, 65.85; H, 4.23; N, 15.66.

4.1.6. Synthesis of 1*H*-quinazoline-2,4-dithione (12).

Starting from 1*H*-quinazoline-2,4-dione **9b** (1.00 g, 6.2 mmol) in the presence the Lawesson's reagent (5.00 g, 12.40 mmol), the reaction was carried out as described in the preparation of compounds **11a–d**. The product was used in the next step without further purification. Yellow solid. Yield: 92%. Mp >250 °C [lit.[29] 334–337 °C].

4.1.7. Synthesis of 4-[2′-(1*H*-tetrazole-5-yl)-biphenyl-4-ylmethylsulfanyl]-2-[3′-(1*H*-tetrazole-5-yl)-biphenyl-4-ylmethylsulfanyl]-quinazoline (2).

Starting from 1*H*-quinazoline-2,4-dithione **12** (97 mg, 0.5 mmol), in the presence of 5-(4′-bromomethyl-biphenyl-2-yl)-1-trimethylphenyl-1*H*-tetrazole (**5g**) (0.56 g, 1.0 mmol), the reaction was carried out as described in the preparation of compounds **1a–d**. Yellow solid. Yield: 75%. Mp >250 °C. IR (KBr): 3413, 2974, 1612, 1550, 1463, 1336, 1173, 993, 760 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.57 (2H, s), 4.51 (2H, s), 7.03 (4H, dd, J = 8.5 and 1.6 Hz), 7.40 (4H, t, J = 8.8 Hz), 7.50–7.58 (5H, m), 7.62–7.67 (4H, m), 7.48–7.60 (2H, m), 7.63 (2H, d, J = 7.7 Hz), 7.81 (1H, d, J = 8.4 Hz), 7.83 (1H, d, J = 8.4 Hz), 7.91 (1H, t, J = 7.4 Hz), 7.99 (1H, d, J = 8.5 Hz). Anal. Calcd for $C_{36}H_{26}N_{10}S_2$: C, 65.24; H, 3.95; N, 21.13. Found: C, 65.25; H, 4.23; N, 20.96.

4.1.8. Synthesis of substituted 3*H*-quinazolin-4-ones (16).

Corresponding 2-amino methyl benzoate **14** (2.9 mmol) was dissolved in $CHCl_3$ (50 mL) and pyridine (30 mL). The mixture was cooled to 0 °C and the corresponding acyl chloride **15** was added (4.3 mmol). The reaction was stirred for 12 h at room temperature. After this time the mixture was washed with HCl 2 N and saturated solution of NaCl. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Then, the solid obtained was placed in a pressure reactor, NH_4OH 30% (40 mL) was added, and the reactor heated at 120 °C for 12 h. The solution was neutralized with aqueous diluted HCl and the resulting solid filtered, washed with distilled water (50 mL), and dried under vacuum. The solid obtained was used in the next step without further purification.

4.1.8.1. 2-Isopropyl-3*H*-quinazolin-4-one (16a). Brown solid. Yield: 73 %. Mp 212–214 °C [lit.[34] 212–214 °C].

4.1.8.2. 2-(4-Chloro-phenyl)-3*H*-quinazolin-4-one (16b). White solid. Yield: 64%. Mp >250 °C. [lit.[35] 299–300 °C].

4.1.8.3. 5,7-Dibromo-2-phenethyl-3*H*-quinazolin-4-one (16c). Yellow solid. Yield: 77 %. Mp 231–234 °C. ^{1}H NMR (300 MHz, DMSO-d_6) : 2.49–2.58 (2H, m), 2.85–3.26 (2H, m), 7.20–7.25 (5H, m), 7.83 (1H, s), 8.10 (1H, s), 9.94 (3H, s). MS (CI) m/z 409.0 ([M+H],$^+$ 100). Anal. Calcd for $C_{16}H_{12}Br_2N_2O$: C, 47.09; H, 2.96; N, 6.86. Found: C, 47.25; H, 3.22; N, 6.96.

4.1.8.4. 6,7,8-Trimethoxy-2-phenethyl-3*H*-quinazolin-4-one (16d). Brown solid. Yield: 64%. Mp.: 215–216 °C. ^{1}H NMR (200 MHz, DMSO-d_6) : 2.87 (2H, t, J = 8.0 Hz), 3.04 (2H, t, J = 8.0 Hz), 3.83 (3H, s), 3.85 (3H, s), 3.90 (3H, s), 7.15–7.27 (6H, m), 10.29 (1H, br s). MS (CI) m/z 341.0 ([M+H],$^+$ 100). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.97; H, 6.00; N, 8.56.

4.1.9. Synthesis of substituted 3*H*-quinazoline-4-thiones (13).

Starting from corresponding substituted 3*H*-quinazolin-4-one **9c–e** or **16a–d** (6.2 mmol) in the presence the Lawesson's reagent (5.00 g, 12.40 mmol), the reaction was carried out as described in the preparation of compounds **11a–d**.

4.1.9.0.1. 3*H*-Quinazoline-4-thione (13a). Yellow solid. Yield: 95%. Mp >300 °C [lit.[30] 324–325 °C].

4.1.9.1. 2-Methyl-3*H*-quinazoline-4-thione (13b). Yellow solid. Yield: 89%. Mp. 216–217 °C [lit.[31] 217–219 °C].

4.1.9.2. 2-Trichloromethyl-3*H*-quinazoline-4-thione (13c). Yellow solid. Yield: 80%. Mp >250 °C. ^{1}H NMR (200 MHz, DMSO-d_6) : 7.63–7.70 (1H, m), 7.77 (1H, t, J = 8.0 Hz), 7.85–7.90 (1H, m), 8.57 (1H, t, J = 8.8 Hz), 14.34 (1H, br s). MS (CI) m/z 280.0 ([M+H],$^+$ 100). Anal. Calcd for $C_9H_5Cl_3N_2S$: C, 38.67; H, 1.80; N, 10.02. Found: C, 38.95; H, 2.00; N, 10.16.

4.1.9.3. 2-Isopropyl-3*H*-quinazolin-4-thione (13d). Brown solid. Yield: 80%. Mp 199–200 °C [lit.[32] 201 °C].

4.1.9.4. 2-(4-Chloro-phenyl)-3*H*-quinazolin-4-thione (13e). Brown solid. Yield: 87%. Mp >250 °C [lit.[33] 285 °C].

4.1.9.5. 5,7-Dibromo-2-phenethyl-3*H*-quinazolin-4-thione (13f). Brown solid. Yield: 92%. Mp 238–240 °C. ^{1}H NMR (300 MHz, DMSO-d_6) : 2.40–2.53 (2H, m), 2.86–3.23 (2H, m), 7.18–7.20 (5H, m), 7.79 (1H, s), 8.11 (1H, s), 9.92 (1H, br s). MS (CI) m/z 424.8 ([M+H],$^+$ 100). Anal. Calcd for $C_{16}H_{12}Br_2N_2S$: C, 45.31; H, 2.85; N, 6.60. Found: C, 45.22; H, 2.93; N, 6.54.

4.1.9.6. 6,7,8-Trimethoxy-2-phenethyl-3*H*-quinazolin-4-thione (13g). Brown solid. Yield: 98%. Mp >250 °C. ^{1}H NMR (200 MHz, DMSO-d_6) : 2.87 (2H, t, J = 8.0 Hz), 3.04 (2H, t, J = 8.0 Hz), 3.88 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 7.25–7.27 (5H, m), 7.77 (1H, s), 13.72 (1H, br s). MS (CI) m/z 357.0 ([M+H],$^+$ 100). Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86. Found: C, 64.23; H, 5.78; N, 7.74.

4.1.10. Synthesis of 4-(1*H*-tetrazol-5-yl)biphenyl methylsulfanyl substituted quinazolines (3).

Starting from corresponding 3*H*-quinazolin-4-thione **13a–g** (0.5 mmol), in the presence of corresponding protected bromomethyl-biphenyl-1*H*-tetrazole (**5g–i**) (0.557 g, 1.0 mmol) the reaction was carried out as described in the preparation of compounds **1a–d**.

4.1.10.1. 4-[3′-(1*H*-Tetrazol-5-yl)-biphenyl-4-ylmethyl sulfanyl]-quinazoline (3a). White solid. Yield: 25%. Mp 213–215 °C. IR (KBr): 4323, 2919, 1613, 1566, 1487, 1323, 998, 762 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74 (2H, s), 7.47–8.13 (11H, m), 8.30 (1H, s), 9.07 (1H, s). Anal. Calcd for $C_{22}H_{16}N_6S$: C, 66.65; H, 4.07; N, 21.20. Found: C, 66.35; H, 4.25; N, 20.85.

4.1.10.2. 4-[4′-(1*H*-Tetrazol-5-yl)-biphenyl-4-ylmethyl sulfanyl]-quinazoline (3b). White solid. Yield: 16%. Mp >250 °C. IR (KBr): 3416, 2360, 1615, 1566, 1488, 1322, 1162, 996, 762, 668 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74 (2H, s), 7.20–7.35 (3H, m), 7.70–7.80 (9H, m), 9.06 (1H, s). Anal. Calcd for $C_{22}H_{16}N_6S$: C, 66.65; H, 4.07; N, 21.20. Found: C, 66.42; H, 4.18; N, 20.99.

4.1.10.3. 2-Methyl-4-[2′-(1-*H*-tetrazol-5-yl)-biphenyl-4-yl methylsulfanyl]-quinazoline (3c). White solid. Yield: 78%. Mp 207–209 °C. IR (KBr): 3415, 2976, 1629, 1569, 1482, 1355, 1093, 976, 762 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.50 (3H, s), 4.62 (2H, s), 7.03 (2H, d, J = 8.0 Hz), 7.48–7.70 (5H, m), 7.83 (1H, d, J = 8.1 Hz), 7.89 (1H, dt, J = 8.3 and 1.4 Hz), 8.02 (1H, d, J = 8.1 Hz). Anal. Calcd for $C_{23}H_{18}N_6S$: C, 69.84; H, 4.42; N, 20.47. Found: C, 69.59; H, 4.32; N, 20.37.

4.1.10.4. 2-Methyl-4-[3′-(1-*H*-tetrazol-5-yl)-biphenyl-4-yl methylsulfanyl]-quinazoline (3d). Yellow solid. Yield: 48%. Mp 219–221 °C. IR (KBr): 3414, 1628, 1565, 1339, 1293, 761 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.48 (3H, s), 4.70 (2H, s), 7.66–7.86 (7H, m), 7.90–8.00 (3H, m) 8.03 (1H, t, J = 8.7 Hz), 8.31 (1H, s). Anal. Calcd for $C_{23}H_{18}N_6S$: C, 69.84; H, 4.42; N, 20.47. Found: C, 70.09; H, 4.23; N, 20.15.

4.1.10.5. 2-Methyl-4-[4′-(1-*H*-tetrazol-5-yl)-biphenyl-4-yl methylsulfanyl]-quinazoline (3e). White solid. Yield: 61%. Mp 246–247 °C. IR (KBr): 3413, 1616, 1548, 1448, 1338, 835, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.75 (3H, s), 4.67 (2H, s), 7.50–7.60 (8H, m), 7.70–7.90 (2H, m), 7.92–8.10 (2H, m). Anal. Calcd for $C_{23}H_{18}N_6S$: C, 69.84; H, 4.42; N, 20.47. Found: C, 69.99; H, 4.26; N, 20.57.

4.1.10.6. 4-[2′-(1*H*-Tetrazol-5-yl)-biphenyl-4-ylmethyl sulfanyl]-2-trichloromethyl-quinazoline (3f). Brown solid. Yield: 59%. Mp >250 °C. IR (KBr): 3414, 2938, 1605, 1480, 1402, 1252, 1125, 752 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.72 (2H, s), 7.02 (2H, d, J = 8.0 Hz), 7.46–7.67 (6H, m), 7.80–7.89 (1H, m), 8.01–8.15 (2H, m), 8.20 (1H, d, J = 8.4 Hz). Anal. Calcd for $C_{23}H_{15}Cl_3N_6S$: C, 53.76; H, 2.94; N, 16.36. Found: C, 53.78; H, 2.66; N, 16.40.

4.1.10.7. 2-Isopropil-4-[2′-(1-*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl-quinazoline (3g). Brown solid. Yield: 72%. Mp 221–223 °C. IR (KBr): 3413, 2965, 2918, 1615, 1563, 1486, 1301, 763 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.35 (6H, d, J = 6.8 Hz) 3.31–3.35 (1H, m), 4.72 (2H, s), 7.58–7.63 (3H, m), 7.70 (2H, d, J = 7.3 Hz), 7.81–7.93 (4H, m), 8.02 (1H, d, J = 7.9 Hz). Anal. Calcd for $C_{25}H_{22}N_6S$: C, 68.47; H, 5.06; N, 19.16. Found: C, 68.12; H, 5.25; N, 19.36.

4.1.10.8. 2-Isopropyl-4-[3′-(1*H*-tetrazol-5-yl)-biphenyl-4ylmethylsulfanyl-quinazoline (3h). White solid. Yield: 57%. Mp 206–208 °C. IR (KBr): 3414, 2965, 1615, 1550, 1302, 756 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.37 (6H, d, J = 7.1 Hz) 3.31 (1H, hep, J = 7.1 Hz), 4.75 (2H, s), 7.62–7.76 (6H, m), 7.82–7.95 (3H, m), 7.99–8.06 (2H, m), 8.31 (1H, s). Anal. Calcd for $C_{25}H_{22}N_6S$: C, 68.47; H, 5.06; N, 19.16. Found: C, 68.78; H, 5.03; N, 19.36.

4.1.10.9. 2-(4-Chloro-phenyl)-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl]-quinazoline (3i). Brown solid. Yield: 69%. Mp 248–250 °C. IR (KBr): 3414, 2940, 1637, 1560, 1483, 1309, 1253, 1091, 763 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.82 (2H, s), 7.06 (2H, d, J = 8.2 Hz), 7.47 (2H, d, J = 8.2 Hz), 7.50–7.57 (2H, m), 7.64 (2H, d, J = 8.6 Hz), 7.66–7.81 (3H, m), 7.99–8.01 (2H, m), 8.11 (1H, d, J = 8.2 Hz), 8.58 (2H, d, J = 8.6 Hz). Anal. Calcd for $C_{28}H_{19}ClN_6S$: C, 66.33; H, 3.78; N, 16.58. Found: C, 66.03; H, 4.04; N, 16.80.

4.1.10.10. 5,7-Dibromo-2-phenethyl-4-[3′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl]-quinazoline (3j). Brown solid. Yield: 68%. Mp 213–215 °C. IR (KBr): 3194, 2922, 1655, 1481, 1243, 993, 795,763 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6) δ: 2.01–2.04 (2H, m), 2.05–2.06 (2H, m), 4.69 (2H, s), 7.25–7.29 (4H, m), 7.50 (1H, d, J = 8.0 Hz), 7.65–7.80 (6H, m), 7.87 (1H, d, J = 8.6 Hz), 7.66–7.81 (3H, m), 7.99–8.01 (2H, m), 8.11 (1H, d, J = 7.9 Hz), 8.04 (1H, d, J = 2.2 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.40 (1H, s). Anal. Calcd for $C_{30}H_{22}Br_2N_6S$: C, 54.73; H, 3.37; N, 12.76. Found: C, 54.55; H, 3.25; N, 12.47.

4.1.10.11. 6,7,8-Trimethoxy-2-phenethyl-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethylsulfanyl]-quinazoline (3k). Brown solid. Yield: 68%. Mp >250 °C. IR (KBr): 3414, 2938, 1605, 1480, 1402, 1252, 1125, 752 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.18 (2H, q, J = 7.5 Hz), 3.26 (2H, q, J = 7.5 Hz), 3.89 (3H, s), 3.90 (3H, s), 3.97 (3H, s), 4.59 (2H, s), 6.98 (1H, s), 7.03 (2H, d, J = 8.2 Hz), 7.12–7.22 (5H, m), 7.40 (2H, d, J = 8.2 Hz), 7.49 (1H, d, J = 7.5 Hz), 7.55 (1H, d, J = 7.2 Hz), 7.62–7.67 (2H, d, J = 8.6 Hz). Anal. Calcd for $C_{33}H_{30}N_6O_3S$: C, 67.10; H, 5.12; N, 14.23. Found: C, 67.01; H, 5.09; N, 13.98.

4.1.11. Synthesis of biphenylcarbonitrile, and biphenylmetoxycarbonyl methylsulfany 2-substituted quinazolines (4a–j).

Corresponding starting material **11a–c** or **13a–d** (0.6 mmol) was dissolved in anhydrous DMF (5 mL), and then K_2CO_3 (0.165 g, 1.2 mmol) and corresponding bromomethyl-2-biphenyl derivative (**5d–f**) (0.6 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. Afterwards the crude reaction was poured into distilled water (10 mL), and extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$, saturated solution of NaCl, dried (Na_2SO_4) and concentrated under vacuum. The residue obtained was purified by column chromatography (silica gel hexane/EtOAc 7:3) and crystallized from toluene.

4.1.11.1. 4-(Quinazolin-4-ylsulfanylmethyl)-biphenyl-2-carbonitrile (4a). Yellow solid. Yield: 91%. Mp 246–248 °C. IR (KBr): 3414, 2218, 1613, 1561, 1484, 1411, 1258, 998, 679 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 4.71 (2H, s), 7.43 (1H, dt, J = 7.3 and 1.3 Hz), 7.46–7.66 (8H, m), 7.76 (1H, dd, J = 7.9 and 1.4 Hz), 7.86 (1H, dt, J = 8.5 and 1.4 Hz, 1H), 7.97 (1H, dd, J = 8.4 and 1.4 Hz). Anal. Calcd for $C_{22}H_{15}N_3S$: C, 74.76; H, 4.28; N, 11.89. Found: C, 74.89; H, 4.56; N, 11.65.

4.1.11.2. 4-(2-Methyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-2-carbonitrile (4b). Yellow solid. Yield: 75%. Mp 195–198 °C. IR (KBr): 3413, 3062, 2223, 1613, 1562, 1550, 1480, 1336, 919, 642 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.84 (3H, s), 4.67 (2H, s), 7.38–7.55 (5H, m), 7.56–7.64 (3H, m), 7.73 (1H, d, J = 7.2 Hz), 7.79 (1H, dd, J = 7.2 and 1.1 Hz), 7.86 (1H, d, J = 8.2 Hz), 8.00 (1H, d, J = 8.2 Hz). Anal. Calcd for $C_{23}H_{17}N_3S$: C, 75.18; H, 4.66; N, 11.43. Found: C, 75.09; H, 4.56; N, 11.40.

4.1.11.3. 4-(2-Trichloromethyl-quinazolin-4-yl sulfanylmethyl)-biphenyl-2-carbonitrile (4c). Brown solid. Yield: 65%. Mp 231–233 °C. IR (KBr): 3415, 2981, 2220, 1611, 1561, 1478, 1349, 1258, 960, 683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.77 (2H, s), 7.40–7.53 (4H, m), 7.59–7.76 (4H, m), 7.86–7.98 (2H, m), 8.08–8.13 (2H, m). Anal. Calcd for $C_{23}H_{14}Cl_3N_3S$: C, 58.68; H, 3.00; N, 8.93. Found: C, 58.98; H, 3.23; N, 8.76.

4.1.11.4. 4-(2-Isopropyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-2-carbonitrile (4d). Brown solid. Yield: 77%. Mp 225–226 °C. IR (KBr): 2967, 2223, 1561, 1444, 1340, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44 (6H, d, J = 6.9 Hz), 3.31 (1H, hep, J = 6.9 Hz) 4.73 (2H, s), 7.40–7.56 (5H, m), 7.58–7.66 (3H, m), 7.75 (1H, dd, J = 7.7 and 1.1 Hz), 7.81 (1H, dd, J = 7.0 and 1.5 Hz), 7.90 (1H, d, J = 8.4 Hz), 8.03 (1H, d, J = 8.2 Hz). Anal. Calcd for $C_{25}H_{21}N_3S$: C, 75.92; H, 5.35; N, 10.62. Found: C, 75.98; H, 5.68; N, 10.93.

4.1.11.5. 4-(2-Benzylsulfanyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-2-carbonitrile (4e). Yellow solid. Yield: 69%. Mp 201–203 °C. IR (KBr): 3435, 2223, 1612, 1559, 1479, 1336, 1173, 993, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.55 (2H, s), 4.60 (2H, s), 7.24–7.46 (3H, m). Anal. Calcd for $C_{29}H_{21}N_3S_2$: C, 73.23; H, 4.45; N, 8.83. Found: C, 72.98; H, 4.34; N, 9.00.

4.1.11.6. 4-[2-(4-Fluoro-benzylsulfanyl)-quinazolin-4-yl sulfanylmethyl]-biphenyl-2-carbonitrile (4f). Yellow solid. Yield: 94%. Mp 225–227 °C. IR (KBr): 3414, 2916, 222, 1611, 1506, 1409, 1338, 993, 682 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.51 (2H, s), 4.60 (2H, s), 6.98 (2H, t, J = 8.6 Hz), 7.40–7.58 (9H, m), 7.63 (1H, dt, J = 8.2 and 2.3 Hz), 7.72–7.80 (3H, m), 7.93 (1H, d, J = 8.2 Hz), 7.90 (1H, d, J = 8.4 Hz), 8.03 (1H, d, J = 8.2 Hz). Anal. Calcd for $C_{29}H_{20}FN_3S_2$: C, 70.56; H, 4.08; N, 8.51. Found: C, 70.86; H, 4.26; N, 8.42.

4.1.11.7. 4-[2-(4-Nitro-benzylsulfanyl)-quinazolin-4-yl sulfanylmethyl]-1,1′-biphenyl-2-carbonitrile (4g). Yellow solid. Yield: 60%. Mp >250 °C. IR (KBr): 3414, 2913, 2229, 1612, 1509, 1442, 1340, 994, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.57 (2H, s), 4.59 (2H, s), 7.41–7.56 (7H, m), 7.63 (1H, dd J = 7.8 and 1.4 Hz), 7.68 (2H, d, J = 8.8 Hz), 7.75–7.80 (3H ,m), 7.97 (1H, d, J = 8.2 Hz), 8.15 (2H, d, J = 8.8 Hz). Anal. Calcd for $C_{29}H_{21}N_4O_2S_2$: C, 66.77; H, 4.06; N, 12.29. Found: C, 66.12; H, 4.09; N, 10.87.

4.1.11.8. 4-(2-Isopropyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-2-carboxylic acid methyl ester (4h). White solid. Yield: 67%. Mp 162–164 °C. IR (KBr): 2964, 1732, 1614, 1558, 1484, 1302, 1088, 994, 844, 761, 637 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (6H, d, J = 6.8 Hz), 3.31 (1H, hep, J = 6.8 Hz), 3.64 (3H, s), 4.74 (2H, s), 7.25–7.58 (8H, m), 7.76–7.84 (2H, m), 7.91 (1H, d, J = 8.4 Hz), 8.03 (1H, d, J = 8.2 Hz). Anal. Calcd for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54. Found: C, 73.21; H, 5.25; N, 6.81.

4.1.11.9. 4-(2-Isopropyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-3-carboxylic acid methyl ester (4i). White solid. Yield: 58%. Mp 157–159 °C. IR (KBr): 2964, 1678, 1593, 1561, 1301, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (6H, d, J = 6.8 Hz), 3.43 (1H, hep, J = 6.8 Hz), 3.94 (3H, s), 4.72 (2H, s), 7.42–7.58 (6H, m), 7.72–7.81 (2H, m), 7.91–8.03 (3H, m), 8.27 (1H, s). Anal. Calcd for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54. Found: C, 72.44; H, 5.23; N, 6.87.

4.1.11.10. 4-(2-Isopropyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-4-carboxylic acid methyl ester (4j). White solid. Yield 80%. Mp 131–132 °C. IR (KBr): 2964, 1679, 1603, 1562, 1301, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (6H, d, J = 6.8 Hz), 3.33 (1H, hep, J = 6.8 Hz), 3.94 (3H, s), 4.73 (2H, s), 7.50 (1H, t, J = 8.2 Hz), 7.59–7.63 (4H, m), 7.70 (2H, d, J = 7.3 Hz), 7.80 (1H, t, J = 6.9 Hz), 7.91 (1H, d, J = 8.2 Hz), 8.03 (1H, d, J = 8.2 Hz), 8.09 (2H, d, J = 8.0 Hz),. Anal. Calcd for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54. Found: C, 72.81; H, 5.60; N, 6.95.

4.1.12. Synthesis of biphenylcarboxylic acid methylsulfany 2-isopropyl quinazolines (4k–m).

A mixture of the corresponding carboxylic acid methyl ester (**4h–j**) (128 mg, 0.3 mmol), a solution of LiOH 2.5 N (0.5 mL), distilled water (3 mL) and THF (3 mL) was stirred at room tempera-

ture for 6 h. Afterwards the reaction was acidified with 1 N HCl (pH 3) and the solid formed was filtered off, washed with hexane and dried under vacuum. The crystalline product obtained was recrystallised from methanol.

4.1.12.1. 4-(2-Isopropyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-2-carboxylic acid (4k). White solid. Yield: 72%. Mp 226–228 °C. IR (KBr): 3431, 1971, 1694, 1567, 1486, 1306, 1134, 761, 641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.42 (6H, d, J = 6.7 Hz), 3.28 (1H, hep, J = 6.7 Hz), 4.73 (2H, s), 7.26–7.35 (4H, m), 7.40–7.52 (4H, m), 7.55–7.84 (2H, m), 7.94 (1H, d, J = 7.8 Hz), 8.05 (1H, d, J = 8.6 Hz). Anal. Calcd for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.82; H, 5.54; N, 6.56.

4.1.12.2. 4-(2-Isopropyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-3-carboxylic acid (4l). White solid. Yield: 69%. Mp 163–165 °C. IR (KBr): 3414, 2965, 2925, 1694, 1564, 1303, 1236, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (6H, d, J = 6.8 Hz), 3.33 (1H, hep, J = 6.8 Hz), 4.74 (2H, s), 7.48-7.57 (2H, m), 7.58–7.61 (4H, m), 7.77–7.84 (2H, m), 7.98 (1H, d, J = 8.4 Hz), 8.04 (1H, d, J = 8.3 Hz), 8.11 (1H, d, J = 7.9 Hz), 8.36 (1H, s). Anal. Calcd for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.82; H, 5.56; N, 6.53.

4.1.12.3. 4-(2-Isopropyl-quinazolin-4-ylsulfanylmethyl)-biphenyl-4-carboxylic acid (4m). White solid. Yield: 89%. Mp 221–223 °C. IR (KBr): 3414, 2965, 1694, 1564, 1303, 1236, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (6H, d, J = 6.9 Hz), 3.43 (1H, hep, J = 6.9 Hz), 4.73 (2H, s), 7.53–7.68 (7H, m), 7.84 (1H, t, J = 7.1 Hz), 7.99–8.06 (2H, m), 8.15 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.66; H, 5.30; N, 6.87.

4.2. Phosphodiesterase inhibition assay

Compounds **1**–**4** are resuspended in DMSO at a stock concentration of 10 mM. The compounds are tested at concentrations ranging from 1 mM to 1 nM in order to calculate an IC_{50}. All dilutions are performed in 96 well plates.

For each reaction 10 μL of the diluted compounds are poured into 'low binding' assay plates. 80 μL of a reaction mixture containing 50 mM Tris pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EGTA, and 15 nM 3′,5′ [3H]-cAMP (around 150,000 dpm) are added to each well. The reaction is initiated by adding 10 μL of a solution containing PDE7 to the reaction mixture. The plate is then incubated under stirring for 1 h at room temperature. After incubation the reaction is stopped with 50 μL (0.89 mg) of PDE SPA beads (Amersham Pharmacia Biotech RPNQ0150), and the resulting mixture is allowed to settle for 20 min before counting in a microlitre plate counter.

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