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AN EFFICIENT THREE-COMPONENT SYNTHESIS OF NOVEL SPIRO-[PYRAZOLE-4,2′-QUINAZOLINE] DERIVATIVES

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Abstract – A simple, efficient, and three-component xprocedure has been developed for the synthesis of a series of spiropyrazol-3-one derivatives containing dihydroquinazoline moiety by the reaction of 1*H*-pyrazole-4,5-diones, 2-aminobenzophenones, and ammonium acetate in moderate to good yields. This method provides several advantages such as operational simplicity, shorter reaction time, and higher yields. All the synthesized compounds were characterized by spectroscopic analysis.

Quinazoline and its derivatives are an important class of heterocycles found in a wide range of natural products and pharmaceuticals. They exhibit several biological activities including antibacterial,[1a] antitumor,[1b] anti-inflammatory,[1c] antiviral,[1d] and anti-oxidant[1e] activities. Quinazoline scaffold is also the building block for many naturally occurring alkaloids such as *Bacillus cereus*,[2a] *Bouchardatia neurococca*,[2b] *Dichroa febrifuga*,[2c] and *Peganum nigellastrum*.[2d] Therefore, the development of quinazoline-based drugs has renewed the interest in developing new synthetic strategies for the synthesis of quinazoline derivatives.[3] The growing importance of quinazolines in medicine is highlighted by the huge sales of the drugs Erlotinib, which is used in the treatment of several types tumors, and Prazosin, an α-adrenergic blocker. Likewise, Iressa, an epidermal growth factor receptor inhibitor, was recently approved by the U.S. Food and Drug Administration for the treatment of lung cancer (Figure 1).[4]

Among nitrogen-containing heterocyclic compounds, the pyrazole unit is also an important pharmacophore, which is found in a large number of biologically active molecules. Pyrazole and its derivatives are known to exhibit a wide spectrum of biological activities such as antipyretic, antimicrobial, hypoglycemic, antihypertensive, anti-oxidant, and antitumor activities.[5] For the reasons given above, a large number of general methods for the preparation of pyrazole derivatives have recently been reported.[6]

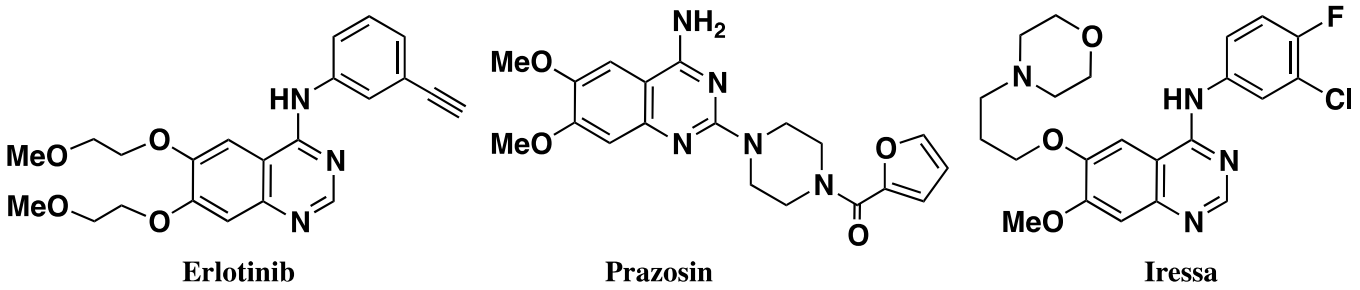
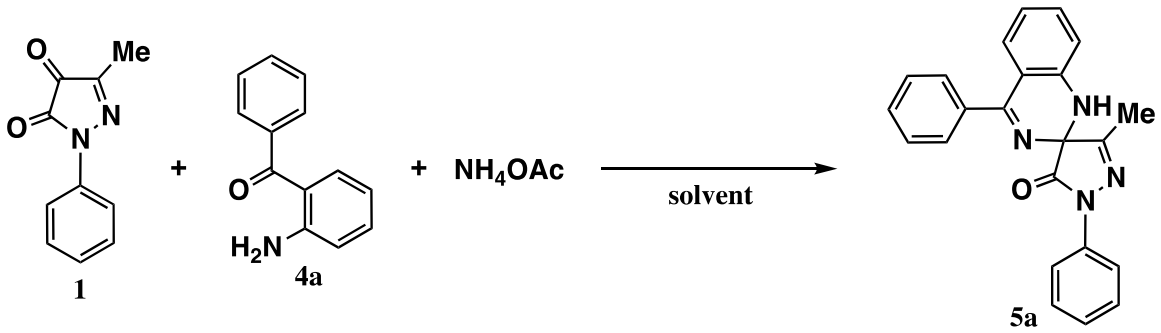


Figure 1. Popular drugs containing quinazoline unit

Spiro compounds are well known to possess varied biological activities and hence their synthesis has always been a challenge and of attraction to organic chemists.[7] In the course of our interest to develop new methods for the synthesis of spiro pyrazole derivatives,[8] we herein report a simple, efficient, and three-component synthesis of spiro[pyrazole-4,2′-quinazoline] derivatives, which might have useful biological activities, using 1*H*-pyrazole-4,5-diones, 2-aminobenzophenones, and ammonium acetate.

For the synthesis of the desired spiro[pyrazole-4,2′-quinazoline] derivative **5a**, we examined the optimization process of the three-component reaction with 1*H*-pyrazole-4,5-dione **1**, 2-aminobenzophenone **4a**, and ammonium acetate as model reactants (Table 1). The substrate **1** could be easily prepared according to the method reported procedure.[9] We carried out several experiments on **5a**, testing different reaction conditions, *e.g.* the ratio of the substrate **1** to **4a** and ammonium acetate, solvents, reaction temperature, and reaction time. When this transformation was carried out using various solvents such as in refluxing MeCN, EtOH, and MeOH conditions, the desired transformation was accomplished in 30, 77, and 67%, respectively (entries 4, 6, and 8). Therefore, EtOH was found to be a suitable solvent. In addition, the results suggested that a lower reaction temperature such as at room temperature could lead to somewhat lower 45% yield of **5a** with a longer reaction time whereas conducting the reaction under stronger reaction conditions such as in boiling solvent proved increase to the yield of **5a** with a shorter reaction time (entries 2 and 3). Furthermore, it was observed that this transformation proceeded smoothly in the presence of an excess amount of ammonium acetate as a nitrogen source (entries 5–7).[10] On the basis of these results, the optimized reaction conditions of 1 equiv. of 2-aminobenzophenones and 4 equiv. of ammonium acetate in refluxing EtOH were used for further investigation (entry 6).

Table 1. Optimization of the reaction conditions[a]



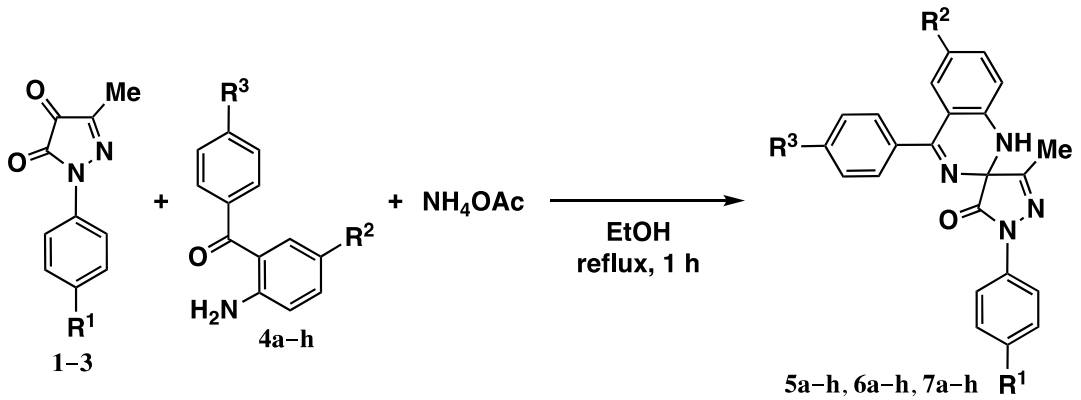
Entry	**4a**	NH_4OAc	Solvent	Temp.	Time (h)	Yield (%)[b]
1	1 equiv.	1 equiv.	EtOH	reflux	2	40
2	1 equiv.	2 equiv.	EtOH	reflux	2	57
3	1 equiv.	2 equiv.	EtOH	rt	24	45
4	1 equiv.	2 equiv.	MeCN	reflux	5	30
5	1 equiv.	3 equiv.	EtOH	reflux	1	65
6	1 equiv.	4 equiv.	EtOH	reflux	1	77
7	1 equiv.	5 equiv.	EtOH	reflux	1	75
8	1 equiv.	4 equiv.	MeOH	reflux	1	67

[a] Reactions were carried out with **1** (1 mmol) as the substrate. [b] Isolated yield.

The scope and generality of the present protocol were then examined by employing various substituted 1*H*-pyrazole-4,5-diones **1**–**3** and 2-aminobenzophenones **4a**–**h**. The results are summarized in Table 2. The reaction tolerates both electron donating as well as electron withdrawing substituents (4-Me and 4-Cl) on the pyrazole component without any significant deviation in yields. Additionally, the reaction with 2-aminobenzophenones having both electron withdrawing as well as electron donating substituents (F, Cl, Br, and Me) proceeded smoothly to afford the desired products in moderate to good yields.

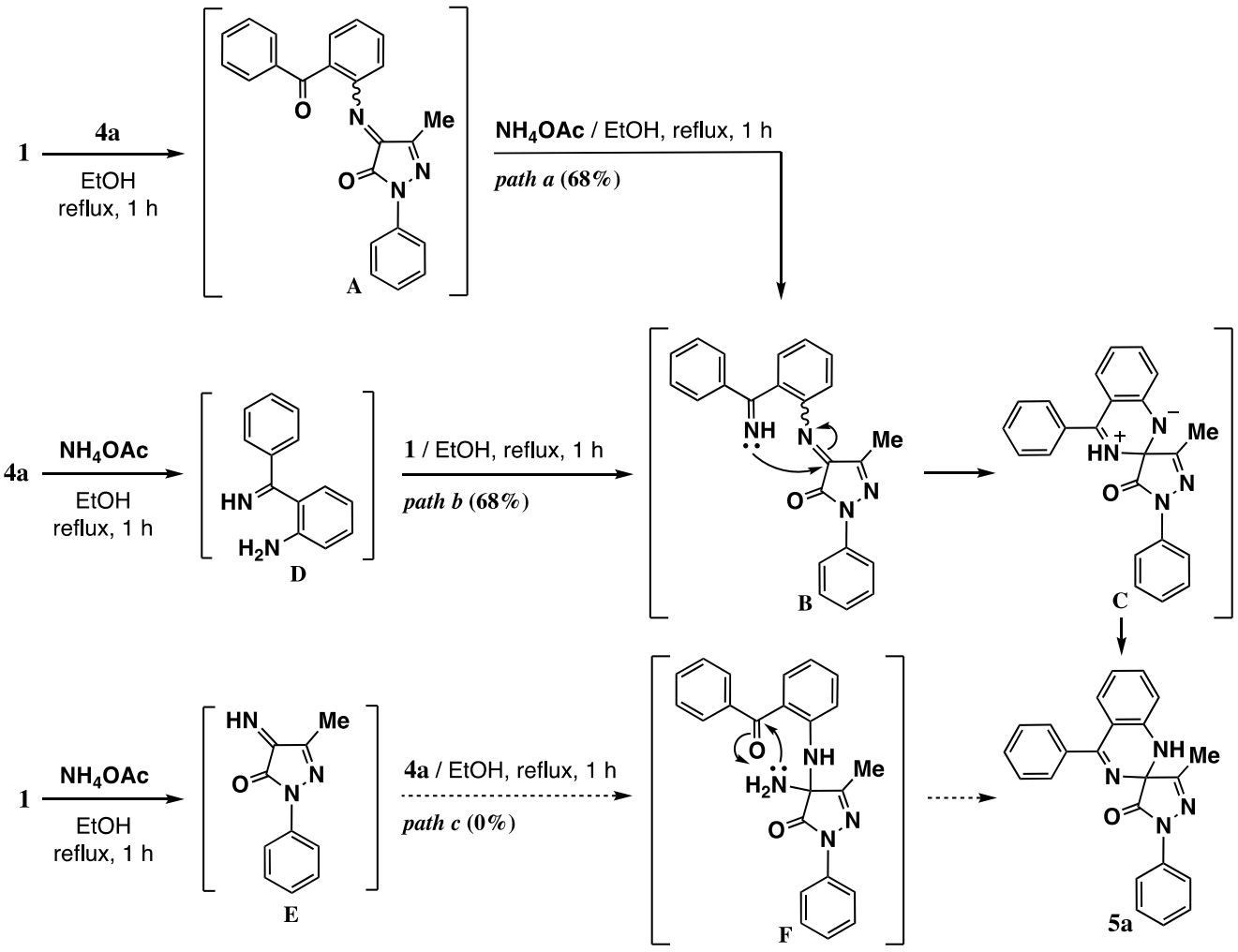
These products **5**–**7** gave satisfactory elemental analyses and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and MS) consistent with their assigned structures (see experimental section). For example, IR spectrum of **5a** displays bands a band at 3276 cm^{-1} because of a secondary amino group and a band at 1717 cm^{-1} because of a carbonyl group. The ^{1}H NMR spectrum of **5a** exhibits a three-proton singlet at δ 2.15 assignable to the methyl protons and a D_2O exchangeable one-proton broad singlets at δ 4.49 assignable to the secondary amino proton. The ^{13}C NMR spectrum of **5a** shows a signal at δ 13.7 because of the methyl carbon, a signal at δ 79.0 because of the spiro carbon, and a signal at δ 170.7 because of the carbonyl carbon.

Table 2. Substrate scope of the three-component reaction for spiro compounds **5**–**7**[a]



Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)[b]
1	**1**	H	H	H	**5a**	77
2	**1**	H	Cl	H	**5b**	67
3	**1**	H	Br	H	**5c**	62
4	**1**	H	Me	H	**5d**	81
5	**1**	H	H	F	**5e**	78
6	**1**	H	H	Cl	**5f**	76
7	**1**	H	H	Br	**5g**	70
8	**1**	H	H	Me	**5h**	71
9	**2**	Me	H	H	**6a**	76
10	**2**	Me	Cl	H	**6b**	65
11	**2**	Me	Br	H	**6c**	58
12	**2**	Me	Me	H	**6d**	87
13	**2**	Me	H	F	**6e**	77
14	**2**	Me	H	Cl	**6f**	77
15	**2**	Me	H	Br	**6g**	76
16	**2**	Me	H	Me	**6h**	79
17	**3**	Cl	H	H	**7a**	63
18	**3**	Cl	Cl	H	**7b**	48
19	**3**	Cl	Br	H	**7c**	43
20	**3**	Cl	Me	H	**7d**	72
21	**3**	Cl	H	F	**7e**	58
22	**3**	Cl	H	Cl	**7f**	57
23	**3**	Cl	H	Br	**7g**	49
24	**3**	Cl	H	Me	**7h**	62

[a] Reactions were carried out with **1**–**3** (1 mmol), **4** (1 mmol), and NH_4OAc (4 mmol). [b] Isolated yield.

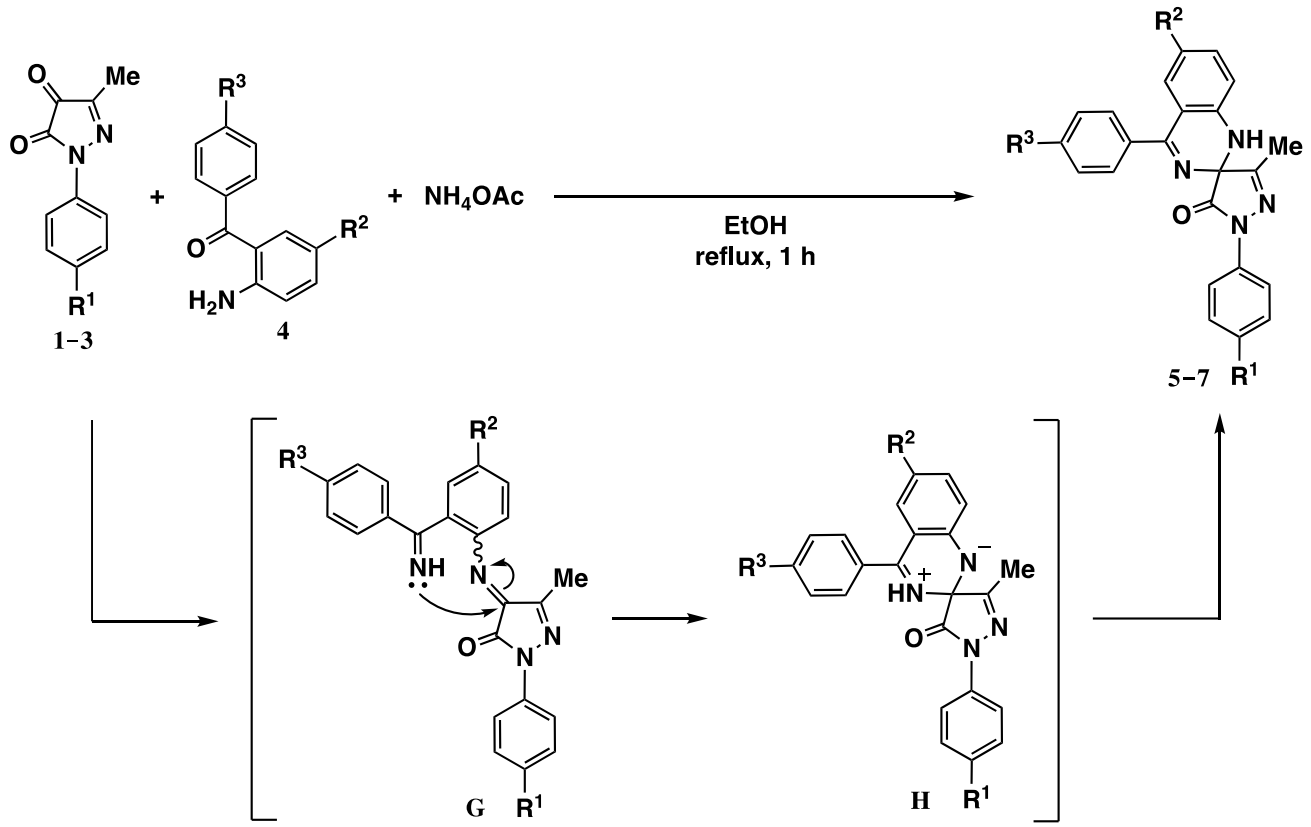


Scheme 1

Mechanistically, there are three possible pathways by which the reactants can come together to form the observed intermediates **A**–**F** in the three-component reaction with 1*H*-pyrazole-4,5-dione **1**, 2-amino-benzophenone **4a**, and ammonium acetate (Scheme 1). As the first pathway, the reaction is presumed to proceed with the formation of the ketoimine **A** from **1** and **4a**. Later ammonium acetate reacts with the carbonyl group of **A** to give the diimine **B** with the expulsion of water and acetic acid. An intramolecular nucleophilic addition of the adjacent nitrogen atom to the imine carbon of **B** occurs and then **5a** would be produced from **C** *via* a proton migration (*path a*). As the second pathway, **4a** can form the imine **D** by reacting with ammonium acetate. Later **1** reacts with **D** to give the diimine **B** (*path b*). As the third pathway, the reaction of **1** with ammonium acetate provides the imine **E**. Later an intermolecular nucleophilic addition of the nitrogen atom of **4a** to the imine carbon of **E** occurs and then **5a** would be produced from **F** *via* an intramolecular dehydration condensation (*path c*). To gain more insight into the mechanism of this process, three experiments were investigated according to three possible pathways. Thus, when a mixture of **1** and **4a** in refluxing EtOH for 1 h and then the reaction mixture was treated

with ammonium acetate in refluxing EtOH for 1 h, the desired **5a** was obtained in 68% yield (*path a*). Alternatively, when a mixture of **4a** and ammonium acetate in refluxing EtOH for 1 h and then the resulting mixture was treated with **1** in refluxing EtOH for 1 h, **5a** was obtained in 68% yield (*path b*). On the other hand, when a mixture of **1** and ammonium acetate in refluxing EtOH for 1 h and then the reaction mixture was treated with **4a** in refluxing EtOH for 1 h, **5a** was not obtained at all (*path c*).

On the basis of the aforementioned results, a plausible reaction mechanism was proposed as shown in Scheme 2 to explain the formation of products **5**–**7**. 1*H*-Pyrazole-4,5-diones **1**–**3** would be reacted with 2-aminobenzophenones **4** and ammonium acetate to give the key intermediate diimines **G** with the expulsion of water and acetic acid. The intramolecular cyclization of **G** easily occurs *via* a nucleophilic addition of the adjacent nitrogen atom to the imine carbon and then the corresponding **5**–**7** would be produced from **H** *via* a proton migration.



Scheme 2

In conclusion, we have developed new one-pot three-component reaction for the synthesis of spiro[pyrazole-4,2′-quinazoline] derivatives using 1*H*-pyrazole-4,5-diones, 2-aminobenzophenones, and ammonium acetate. The diimine intermediates formed in situ by the three-component reaction play a key role in the formation of spiropyrazol-3-ones containing dihydroquinazoline moiety. Pyrazole and quinazoline are important building blocks for the preparation of biologically active compounds with

interest in medicinal chemistry. Further synthetic applications for novel spiropyrazole derivatives containing heterocyclic skeleton are in progress.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Thermo Fisher Scientific Nicolet iS5 FT-IR spectrometer equipped with an iD7 diamond ATR accessory. The ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-ECZ600R/S1 spectrometer at 600.17 and 150.91 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard. Positive FAB MS spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer. The substrates **1**–**3** were prepared in this laboratory according to the method reported procedure.[9]

General procedure for the preparation of spiro compounds 5a–h, 6a–h, and 7a–h from 1–3, 4a–h, and ammonium acetate. A mixture of **1**–**3** (1.0 mmol), **4a**–**h** (1.0 mmol), and ammonium acetate (0.308 g, 4.0 mmol) in EtOH (10 mL) was refluxed for 1 h. After removal of the solvent *in vacuo*, cold H_2O was added to the residue. The resulting mixture was extracted with $CHCl_3$ (60 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give **5a**–**h**, **6a**–**h**, and **7a**–**h**.

3-Methyl-1,4′-diphenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5a): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-aminobenzophenone (**4a**) (0.197 g, 1.0 mmol). Yellow needles (0.283 g, 77%), mp 207–208 °C (acetone/petroleum ether); IR (ATR): ν 3276 (NH), 1717 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, pyrazole 3-Me), 4.49 (s, 1H, NH), 6.66 (d, *J* = 6.9 Hz, 1H, quinazoline 8′-H), 6.71–6.74 (m, 1H, quinazoline 6′-H), 7.14–7.16 (m, 1H, quinazoline 5′-H), 7.17–7.19 (m, 1H, Ph-H), 7.20–7.25 (m, 1H, quinazoline 7′-H), 7.35–7.47 (m, 5H, Ph-H), 7.53–7.55 (m, 2H, Ph-H), 7.88–7.90 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 79.0 (spiro C), 114.9 (quinazoline C-8′), 116.4 (quinazoline C-4′a), 118.9 (Ph-C), 119.5 (quinazoline C-6′), 125.2, 128.4, 128.9, 129.0 (Ph-C), 129.3 (quinazoline C-5′), 130.0 (Ph-C), 133.8 (quinazoline C-7′), 137.3, 137.9 (Ph-C), 143.5 (quinazoline C-8′a), 160.5 (pyrazole C-3), 169.1 (quinazoline C-4′), 170.7 (pyrazole C-5); MS: *m/z* 367 $[M+H]^+$. Anal. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.36; H, 4.95; N, 15.29.

6′-Chloro-3-methyl-1,4′-diphenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5b): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-amino-5-chlorobenzophenone (**4b**) (0.231 g, 1.0 mmol). Yellow needles (0.269 g, 67%), mp 208–209 °C (acetone/petroleum ether); IR (ATR): ν 3361 (NH), 1696 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H, pyrazole 3-Me), 4.73 (s, 1H, NH), 6.56–6.60 (m, 1H, quinazoline 8′-H), 7.10–7.13 (m, 2H, quinazoline 5′- and 7′-H), 7.15–7.18 (m, 1H, Ph-H), 7.33–7.38 (m,

2H, Ph-H), 7.44–7.52 (m, 5H, Ph-H), 7.83–7.85(m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.6 (pyrazole 3-Me), 79.1 (spiro C), 116.2 (quinazoline C-8′), 117.1 (quinazoline C-4′a), 118.9 (Ph-C), 124.0 (quinazoline C-6′), 125.4, 128.6 (Ph-C), 128.7 (quinazoline C-5′), 128.9, 129.0, 130.3 (Ph-C), 133.6 (quinazoline C-7′), 136.6, 137.7 (Ph-C), 142.2 (quinazoline C-8′a), 160.4 (pyrazole C-3), 168.1 (quinazoline C-4′) 170.5 (pyarazole C-5); MS: *m/z* 401 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}ClN_4O$: C, 68.91; H, 4.27; N, 13.98. Found: C, 68.97; H, 4.31; N, 13.93.

6′-Bromo-3-methyl-1,4′-diphenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5c): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-amino-5-bromobenzophenone (**4c**) (0.275 g, 1.0 mmol). Yellow needles (0.275 g, 62%), mp 209–211 °C (acetone/petroleum ether); IR (ATR): ν 3334 (NH), 1693 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, pyrazole 3-Me), 4.65 (s, 1H, NH), 6.54 (d, *J* = 8.9 Hz, 1H, quinazoline 8′-H), 7.16–7.18 (m, 1H, Ph-H), 7.25–7.29 (m, 2H, quinazoline 5′- and 7′-H), 7.34–7.38 (m, 2H, Ph-H), 7.44–7.53 (m, 5H, Ph-H), 7.82–7.86 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.6 (pyrazole 3-Me), 79.0 (spiro C), 111.0 (quinazoline C-4′a), 116.5 (quinazoline C-8′), 117.6 (quinazoline C-6′), 118.9, 125.4, 128.6, 128.9, 129.0, 130.3 (Ph-C), 131.6 (quinazoline C-5′), 136.4 (quinazoline C-7′), 136.6, 137.7 (Ph-C), 142.6 (quinazoline C-8′a), 160.3 (pyrazole C-3), 168.0 (quinazoline C-4′), 170.4 (pyrazole C-5); MS: *m/z* 445 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}BrN_4O$: C, 62.03; H, 3.85; N, 12.58. Found: C, 62.08; H, 3.88; N, 12.51.

3,6′-Dimethyl-1,4′-diphenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5d): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-amino-5-methylbenzophenone (**4d**) (0.197 g, 1.0 mmol). Yellow needles (0.309 g, 81%), mp 198–199 °C (acetone/petroleum ether); IR (ATR): ν 3337 (NH), 1687 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3H, pyrazole 3-Me), 2.18 (s, 3H, quinazoline 6′-Me), 4.29 (s, 1H, NH), 6.60 (d, *J* = 7.5 Hz, 1H, quinazoline 8′-H), 6.96 (s, 1H, quinazoline 5′-H), 7.04–7.09 (m, 1H, quinazoline 7′-H), 7.15–7.18 (m, 1H, Ph-H), 7.35–7.39 (m, 2H, Ph-H), 7.42–7.48 (m, 3H, Ph-H), 7.53–7.55 (m, 2H, Ph-H), 7.89–7.91 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.8 (pyrazole 3-Me), 20.7 (quinazoline 6′-Me), 79.0 (spiro C), 115.2 (quinazoline C-8′), 116.8 (quinazoline C-4′a), 118.9, 125.1, 128.3, 128.9 (Ph-C), 129.0 (Ph-C and quinazoline C-6′), 129.4 (quinazoline C-5′), 129.9 (Ph-C), 134.5 (quinazoline C-7′), 137.4, 137.9 (Ph-C), 141.0 (quinazoline C-8′a), 160.6 (pyrazole C-3), 169.2 (quinazoline C-4′), 170.8 (pyrazole C-5); MS: *m/z* 381 $[M+H]^+$. Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.74; H, 5.41; N, 14.76.

4′-(4-Fluorophenyl)-3-methyl-1-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5e): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-amino-4′-fluorobenzophenone (**4e**) (0.215 g, 1.0 mmol). Yellow needles (0.300 g, 78%), mp 203–204 °C (acetone/petroleum ether); IR (ATR): ν 3361

(NH), 1704 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H, pyrazole 3-Me), 4.48 (s, 1H, NH), 6.66 (d, *J* = 8.2 Hz, 1H, quinazoline 8′-H), 6.73–6.76 (m, 1H, 6′-H), 7.09–7.14 (m, 3H, Ph-H and quinazoline 5′-H), 7.16–7.18 (m, 1H, Ph-H), 7.22–7.25 (m, 1H, quinazoline 7′-H), 7.36–7.39 (m, 2H, Ph-H), 7.53–7.57 (m, 2H, Ph-H), 7.88–7.90 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazle 3-Me), 78.9 (spiro C), 115.0 (quinazoline C-8′), 115.3, 115.5 (Ph-C), 116.3 (quinazoline C-4′a), 118.9 (Ph-C), 119.6 (quinazoline C-6′), 125.3, 128.9 (Ph-C), 129.1 (quinazoline C-5′), 131.1, 131.2, 133.32, 133.34 (Ph-C), 133.9 (quinazoline C-7′), 137.8 (Ph-C), 143.6 (quinazoline C-8′a), 160.4 (pyrazole C-3), 163.1, 164.7 (Ph-C), 168.1 (quinazoline C-4′), 170.6 (pyrazole C-5); MS: *m/z* 385 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}FN_4O$: C, 71.86; H, 4.46; N, 14.57. Found: C, 71.80; H, 4.51; N, 14.61.

4′-(4-Chlorophenyl)-3-methyl-1-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5f): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-amino-4′-chlorobenzophenone (**4f**) (0.231 g, 1.0 mmol). Yellow needles (0.303 g, 76%), mp 208–209 °C (acetone/petroleum ether); IR (ATR): ν 3363 (NH), 1703 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.14 (s, 3H, pyrazole 3-Me), 4.45 (s, 1H, NH), 6.66 (d, *J* = 8.2 Hz, 1H, quinazoline 8′-H), 6.73–6.76 (m, 1H, quinazoline 6′-H), 7.12 (d, *J* = 7.6 Hz, 1H, quinazoline 5′-H), 7.16–7.18 (m, 1H, Ph-H), 7.23–7.26 (m, 1H, quinazoline 7′-H), 7.35–7.41 (m, 4H, Ph-H), 7.49–7.51 (m, 2H, Ph-H), 7.88–7.90 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 78.9 (spiro C), 115.0 (quinazoline C-8′), 116.2 (quinazoline C-4′a), 118.9 (Ph-C), 119.6 (quinazoline C-6′), 125.3, 128.6, 128.9 (Ph-C), 129.0 (quinazoline C-5′), 130.5 (Ph-C), 134.0 (quinazoline C-7′), 135.6, 136.2, 137.8 (Ph-C), 143.6 (quinazoline C-8′a), 160.4 (pyrazole C-3), 168.1 (quinazoline C-4′), 170.5 (pyrazole C-5); MS: *m/z* 401 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}ClN_4O$: C, 68.91; H, 4.27; N, 13.98. Found: C, 69.01; H, 4.35; N, 13.94.

4′-(4-Bromophenyl)-3-methyl-1-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5g): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-amino-4′-bromobenzophenone (**4g**) (0.275 g, 1.0 mmol). Yellow needles (0.310 g, 70%), mp 207–209 °C (acetone/petroleum ether); IR (ATR): ν 3367 (NH), 1703 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.14 (s, 3H, pyrazole 3-Me), 4.46 (s, 1H, NH), 6.66 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 6.73–6.75 (m, 1H, quinazoline 6′-H), 7.11 (d, *J* = 7.6 Hz, 1H, quinazoline 5′-H), 7.16–7.18 (m, 1H, Ph-H), 7.23–7.25 (m, 1H, quinazoline 7′-H), 7.36–7.39 (m, 2H, Ph-H), 7.42–7.45 (m, 2H, Ph-H), 7.55–7.57 (m, 2H, Ph-H), 7.87–7.89 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 78.9 (spiro C), 115.0 (quinazoline C-8′), 116.1 (quinazoline C-4′a), 118.9 (Ph-C), 119.6 (quinazoline C-6′), 124.5, 125.3 (Ph-C), 129.0 (Ph-C and quinazoline C-5′), 130.7, 131.6 (Ph-C), 134.0 (quinazoline C-7′), 136.1, 137.8 (Ph-C), 143.6 (quinazoline C-8′a), 160.4 (pyrazole C-3), 168.1 (quinazoline C-4′), 170.5 (pyrazole C-5); MS: *m/z* 445 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}BrN_4O$: C, 62.03;

H, 3.85; N, 12.58. Found: C, 62.09; H, 3.87; N, 12.58.

3-Methyl-4′-(4-methylphenyl)-1-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (5h): Reaction was carried out with **1** (0.188 g, 1.0 mmol) and 2-amino-4′-methylbenzophenone (**4h**) (0.211 g, 1.0 mmol). Yellow needles (0.269 g, 71%), mp 178–179 °C (acetone/petroleum ether); IR (ATR): ν 3341 (NH), 1702 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, pyrazole 3-Me), 2.39 (s, 3H, 4-*Me*-C_6H_4), 4.42 (s, 1H, NH), 6.66 (d, *J* = 7.6 Hz, 1H, quinazoline 8′-H), 6.72–6.74 (m, 1H, quinazoline 6′-H), 7.15–7.19 (m, 2H, Ph-H and quinazoline 5′-H), 7.21–7.25 (m, 3H, Ph-H and quinazoline 7′-H), 7.35–7.38 (m, 2H, Ph-H), 7.42–7.46 (m, 2H, Ph-H), 7.88–7.90 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.5 (4-*Me*-C_6H_4), 78.9 (spiro C), 114.9 (quinazoline C-8′), 116.6 (quinazoline C-4′a), 118.9 (Ph-C), 119.5 (quinazoline C-6′), 125.2, 128.9, 129.0, 129.1 (Ph-C), 129.3 (quinazoline C-5′), 133.6 (quinazoline C-7′), 134.5, 137.9, 140.2 (Ph-C), 143.5 (quinazoline C-8′a), 160.6 (pyrazole C-3), 169.0 (quinazoline C-4′), 170.8 (pyrazole C-5); MS: *m/z* 381 $[M+H]^+$. Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.79; H, 5.32; N, 14.65.

3-Methyl-1-(4-methylphenyl)-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6a): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-aminobenzophenone (**4a**) (0.197 g, 1.0 mmol). Yellow needles (0.290 g, 76%), mp 210–211 °C (acetone/petroleum ether); IR (ATR): ν 3353 (NH), 1709 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, pyrazole 3-Me), 2.34 (s, 3H, 4-*Me*-C_6H_4), 4.52 (s, 1H, NH), 6.66 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 6.71–6.74 (m, 1H, quinazoline 6′-H), 7.13–7.17 (m, 3H, Ph-H and quinazoline 5′-H), 7.21–7.25 (m, 1H, quinazoline 7′-H), 7.41–7.47 (m, 3H, Ph-H), 7.53–7.55 (m, 2H, Ph-H), 7.75–7.77 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.1 (4-*Me*-C_6H_4), 78.8 (spiro C), 114.9 (quinazoline C-8′), 116.3 (quinazoline C-4′a), 118.9 (Ph-C), 119.4 (quinazoline C-6′), 128.4, 129.1 (Ph-C), 129.38 (quinazoline C-5′), 129.43, 130.1 (Ph-C), 133.9 (quinazoline C-7′), 134.9, 135.4, 137.1 (Ph-C), 143.6 (quinazoline C-8′a), 160.3 (pyrazole C-3), 169.1 (quinazoline C-4′), 170.4 (pyrazole C-5); MS: *m/z* 381 $[M+H]^+$. Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.75; H, 5.38; N, 14.65.

6′-Chloro-3-methyl-1-(4-methylphenyl)-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6b): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-amino-5-chlorobenzophenone (**4b**) (0.231 g, 1.0 mmol). Yellow needles (0.271 g, 65%), mp 231–232 °C (acetone/petroleum ether); IR (ATR): ν 3316 (NH), 1694 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, pyrazole 3-Me), 2.33 (s, 3H, 4-*Me*-C_6H_4), 4.51 (s, 1H, NH), 6.61 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 7.13 (d, *J* = 2.1 Hz, 1H, quinazoline 5′-H), 7.16–7.19 (m, 3H, Ph-H and quinazoline 7′-H), 7.43–7.53 (m, 5H, Ph-H), 7.73–7.75 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.6 (pyrazole 3-Me), 21.0 (4-*Me*-C_6H_4), 78.9 (spiro C), 116.2

(quinazoline C-8′), 117.4 (quinazoline C-4′a), 118.9 (Ph-C), 124.2 (quinazoline C-6′), 128.6 (Ph-C), 128.8 (quinazoline C-5′), 128.9, 129.5, 130.3 (Ph-C), 133.5 (quinazoline C-7′), 135.1, 135.3, 136.6 (Ph-C), 142.1 (quinazoline C-8′a), 160.2 (pyrazole C-3), 168.1 (quinazoline C-4′), 170.1 (pyrazole C-5); MS: *m/z* 415 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}ClN_4O$: C, 69.48; H, 4.62; N, 13.51. Found: C, 69.43; H, 4.68; N, 13.42.

6′-Bromo-3-methyl-1-(4-methylphenyl)-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6c): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-amino-5-bromobenzophenone (**4c**) (0.275 g, 1.0 mmol). Yellow needles (0.268 g, 58%), mp 231–232 °C (acetone/petroleum ether); IR (ATR): ν 3314 (NH), 1694 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, pyrazole 3-Me), 2.33 (s, 3H, 4-*Me*-C_6H_4), 4.45 (s, 1H, NH), 6.56 (d, *J* = 8.9 Hz, 1H, quinazoline 8′-H), 7.16–7.18 (m, 2H, Ph-H), 7.25–7.27 (m, 1H, quinazoline 5′-H), 7.32–7.34 (m, 1H, quinazoline 7′-H), 7.44–7.53 (m, 5H, Ph-H), 7.73–7.75 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.0 (4-*Me*-C_6H_4), 78.8 (spiro C), 111.2 (quinazoline C-6′), 116.5 (quinazoline C-8′), 117.9 (quinazoline C-4′a), 118.9, 128.6, 128.9, 129.5, 130.3 (Ph-C), 131.6 (quinazoline C-5′), 135.1, 135.3 (Ph-C), 136.4 (quinazoline C-7′), 136.6 (Ph-C), 142.6 (quinazoline C-8′a), 160.1 (pyrazole C-3), 167.9 (quinazoline C-4′), 170.0 (pyrazole C-5); MS: *m/z* 459 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}BrN_4O$: C, 62.75; H, 4.17; N, 12.20. Found: C, 62.77; H, 4.27; N, 12.11.

3,6′-Dimethyl-1-(4-methylphenyl)-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6d): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-amino-5-methylbenzophenone (**4d**) (0.197 g, 1.0 mmol). Yellow needles (0.342 g, 87%), mp 203–205 °C (acetone/petroleum ether); IR (ATR): ν 3339 (NH), 1691 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, pyrazole 3-Me), 2.18 (s, 3H, quinazoline 6′-Me), 2.33 (s, 3H, 4-*Me*-C_6H_4), 4.30 (s, 1H, NH), 6.59 (d, *J* = 8.2 Hz, 1H, quinazoline 8′-H), 6.95 (s, 1H, quinazoline 5′-H), 7.05–7.08 (m, 1H, quinazoline 7′-H), 7.16–7.19 (m, 2H, Ph-H), 7.42–7.48 (m, 3H, Ph-H), 7.53–7.55 (m, 2H, Ph-H), 7.75–7.77 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 20.7 (quinazoline 6′-Me), 21.0 (4-*Me*-C_6H_4), 78.9 (spiro C), 115.2 (quinazoline C-8′), 116.8 (quinazoline C-4′a), 118.9, 128.3 (Ph-C), 128.9 (quinazoline C-6′), 129.0, 129.4, 129.9 (Ph-C), 134.5 (quinazoline C-7′), 134.8, 135.5, 137.5 (Ph-C), 141.1 (quinazoline C-8′a), 160.5 (pyrazole C-3), 169.2 (quinazoline C-4′), 170.7 (pyrazole C-5); MS: *m/z* 395 $[M+H]^+$. Anal. Calcd for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.35; H, 5.73; N, 14.13.

4′-(4-Fluorophenyl)-3-methyl-1-(4-methylphenyl)spiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6e): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-amino-4′-fluorobenzophenone (**4e**) (0.215 g, 1.0 mmol). Yellow needles (0.305 g, 77%), mp 208–209 °C (acetone/petroleum ether); IR

(ATR): ν 3300 (NH), 1687 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, pyrazole 3-Me), 2.33 (s, 3H, 4-*Me*-C_6H_4), 4.48 (s, 1H, NH), 6.65 (d, *J* = 8.9 Hz, 1H, quinazoline 8′-H), 6.72–6.75 (m, 1H, quinazoine 6′-H), 7.09–7.13 (m, 3H, Ph-H and quinazoline 5′-H), 7.15–7.19 (m, 2H, Ph-H), 7.21–7.26 (m, 1H, quinazoline 7′-H), 7.53–7.56 (m, 2H, Ph-H), 7.74–7.76 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.0 (4-*Me*-C_6H_4), 78.8 (spiro C), 115.0 (quinazoline C-8′), 115.3, 115.5 (Ph-C), 116.3 (quinazoline C-4′a), 118.9 (Ph-C), 119.5 (quinazoline C-6′), 129.0 (quinazoline C-5′), 129.5, 131.1, 131.2, 133.4 (Ph-C), 133.9 (quinazoline C-7′), 134.9, 135.4 (Ph-C), 143.6 (quinazoline C-8′a), 160.3 (pyrazole C-3), 163.1, 164.7 (Ph-C), 168.0 (quinazoline C-4′), 170.5 (pyrazole C-5); MS: *m/z* 399 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}FN_4O$: C, 72.35; H, 4.81; N, 14.06. Found: C, 72.42; H, 4.82; N, 14.03.

4′-(4-Chlorophenyl)-3-methyl-1-(4-methylphenyl)spiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6f): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-amino-4′-chlorobenzophenone (**4f**) (0.231 g, 1.0 mmol). Yellow needles (0.319 g, 77%), mp 225–226 °C (acetone/petroleum ether); IR (ATR): ν 3324 (NH), 1693 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, pyrazole 3-Me), 2.33 (s, 3H, 4-*Me*-C_6H_4), 4.48 (s, 1H, NH), 6.65 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 6.72–6.77 (m, 1H, quinazoline 6′-H), 7.11 (d, *J* = 7.5 Hz, 1H, quinazoline 5′-H), 7.14–7.17 (m, 2H, Ph-H), 7.21–7.25 (m, 1H, quinazoline 7′-H), 7.39–7.41 (m, 2H, Ph-H), 7.48–7.50 (m, 2H, Ph-H), 7.74–7.76 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.1 (4-*Me*-C_6H_4), 78.9 (spiro C), 115.0 (quinazoline C-8′), 116.2 (quinazoline C-4′a), 118.9 (Ph-C), 119.5 (quinazoline C-6′), 128.6 (Ph-C), 128.9 (quinazoline C-5′), 129.5, 130.5 (Ph-C), 134.0 (quinazoline C-7′), 134.9, 135.4, 135.7, 136.2 (Ph-C), 143.6 (quinazoline C-8′a), 160.3 (pyrazole C-3), 168.0 (quinazoline C-4′), 170.4 (pyrazole C-5); MS: *m/z* 415 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}ClN_4O$: C, 69.48; H, 4.62; N, 13.50. Found: C, 69.50; H, 4.63; N, 13.52.

4′-(4-Bromophenyl)-3-methyl-1-(4-methylphenyl)spiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6g): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-amino-4′-bromobenzophenone (**4g**) (0.275 g, 1.0 mmol). Yellow needles (0.351 g, 76%), mp 225–226 °C (acetone/petroleum ether); IR (ATR): ν 3320 (NH), 1695 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, pyrazole 3-Me), 2.33 (s, 3H, 4-*Me*-C_6H_4), 4.48 (s, 1H, NH), 6.65 (d, *J* = 7.6 Hz, 1H, quinazoline 8′-H), 6.72–6.74 (m, 1H, quinazoline 6′-H), 7.10 (d, *J* = 7.6 Hz, 1H, quinazoline 5′-H), 7.14–7.17 (m, 2H, Ph-H), 7.21–7.26 (m, 1H, quinazoline 7′-H), 7.39–7.43 (m, 2H, Ph-H), 7.55–7.57 (m, 2H, Ph-H), 7.74–7.76 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.1 (4-*Me*-C_6H_4), 78.9 (spiro C), 115.0 (quinazoline C-8′), 116.1 (quinazoline C-4′a), 118.9 (Ph-C), 119.5 (quinazoline C-6′), 124.5 (Ph-C), 128.9 (quinazoline C-5′), 129.5, 130.7, 131.6 (Ph-C), 134.0 (quinazoline C-7′), 135.0, 135.4, 136.1 (Ph-C), 143.6 (quinazoline C-8′a), 160.3 (pyrazole C-3), 168.1 (quinazoline C-4′), 170.3 (pyrazole C-5); MS: *m/z* 459 $[M+H]^+$. Anal.

Calcd for $C_{24}H_{19}BrN_4O$: C, 62.75; H, 4.17; N, 12.20. Found: C, 62.74; H, 4.14; N, 12.16.

3-Methyl-1,4′-bis(4-methylphenyl)spiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (6h): Reaction was carried out with **2** (0.202 g, 1.0 mmol) and 2-amino-4′-methylbenzophenone (**4h**) (0.211 g, 1.0 mmol). Yellow needles (0310 g, 79%), mp 210–211 °C (acetone/petroleum ether); IR (ATR): ν 3288 (NH), 1706 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H, pyrazole 3-Me), 2.33 [s, 3H, pyrazole 1-(4-*Me*-C_6H_4)], 2.39 [s, 3H, quinazoline 4′-(4-*Me*-C_6H_4)], 4.47 (s, 1H, NH), 6.65 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 6.71–6.74 (m, 1H, quinazoline 6′-H), 7.16–7.19 (m, 3H, Ph-H and quinazoline 5′-H), 7.21–7.25 (m, 3H, Ph-H and quinazoline 7′-H), 7.41–7.45 (m, 2H, Ph-H), 7.73–7.77 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.0 [pyrazole 1-(4-*Me*-C_6H_4)], 21.5 [quinazoline 4′-(4-*Me*-C_6H_4)], 78.7 (spiro C), 114.9 (quinazoline C-8′), 116.6 (quinazoline C-4′a), 118.9 (Ph-C), 119.4 (quinazoline C-6′), 129.0, 129.1 (Ph-C), 129.40 (quinazoline C-5′), 129.42 (Ph-C), 133.7 (quinazoline C-7′), 134.3, 134.8, 135.5, 140.2 (Ph-C), 143.6 (quinazoline C-8′a), 160.4 (pyrazole C-3), 169.0 (quinazoline C-4′), 170.5 (pyrazole C-5); MS: *m/z* 395 $[M+H]^+$. Anal. Calcd for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.14; H, 5.63; N, 14.16.

1-(4-Chlorophenyl)-3-methyl-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7a): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-aminobenzophenone (**4a**) (0.197 g, 1.0 mmol). Yellow needles (0.253 g, 63%), mp 214–215 °C (acetone/petroleum ether); IR (ATR): ν 3280 (NH), 1717 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, pyrazole 3-Me), 4.50 (s, 1H, NH), 6.65 (d, *J* = 6.9 Hz, 1H, quinazoline 8′-H), 6.72–6.75 (m, 1H, quinazoline 6′-H), 7.15 (d, *J* = 8.2 Hz, 1H, quinazoline 5′-H), 7.21–7.25 (m, 1H, quinazoline 7′-H), 7.30–7.33 (m, 2H, Ph-H), 7.40–7.47 (m, 3H, Ph-H), 7.53–7.55 (m, 2H, Ph-H), 7.84–7.87 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 79.0 (spiro C), 114.9 (quinazoline C-8′), 116.4 (quinazoline C-4′a), 119.6 (quinazoline C-6′), 119.9, 128.4, 128.95, 128.98 (Ph-C), 129.4 (quinazoline C-5′), 130.1, 130.6 (Ph-C), 133.9 (quinazoline C-7′), 136.5, 137.2 (Ph-C), 143.4 (quinazoline C-8′a), 160.8 (pyrazole C-3), 169.2 (quinazoline C-4′), 170.7 (pyrazole C-5); MS: *m/z* 401 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}ClN_4O$: C, 68.91; H, 4.27; N, 13.98. Found: C, 69.05; H, 4.27; N, 14.05.

6′-Chloro-1-(4-chlorophenyl)-3-methyl-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7b): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-amino-5-chlorobenzophenone (**4b**) (0.231 g, 1.0 mmol). Yellow needles (0.210 g, 48%), mp 226–227 °C (acetone/petroleum ether); IR (ATR): ν 3286 (NH), 1694 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, pyrazole 3-Me), 4.50 (s, 1H, NH), 6.61 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 7.12–7.16 (m, 1H, quinazoline 5′-H), 7.18–7.20 (m, 1H, quinazoline 7′-H), 7.31–7.34 (m, 2H, Ph-H), 7.44–7.53 (m, 5H, Ph-H), 7.83–7.85 (m, 2H, Ph-H); ^{13}C

NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 78.9 (spiro C), 116.2 (quinazoline C-8′), 117.3 (quinazoline C-4′a), 119.9 (Ph-C), 124.4 (quinazoline C-6′), 128.6 (Ph-C), 128.9 (Ph-C and quinazoline C-5′), 129.0, 130.4 (Ph-C), 133.7 (quinazoline C-7′), 136.3, 136.5 (Ph-C), 141.9 (quinazoline C-8′a), 160.3 (pyrazole C-3), 168.2 (quinazoline C-4′), 170.2 (pyrazole C-5); MS: *m/z* 435 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}Cl_2N_4O$: C, 63.46; H, 3.70; N, 12.87. Found: C, 63.42; H, 3.66; N, 12.92.

6′-Bromo-1-(4-chlorophenyl)-3-methyl-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7c): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-amino-5-bromobenzophenone (**4c**) (0.275 g, 1.0 mmol). Yellow needles (0.206 g, 43%), mp 222–223 °C (acetone/petroleum ether); IR (ATR): ν 3290 (NH), 1695 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, pyrazole 3-Me), 4.65 (s, 1H, NH), 6.54 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 7.25–7.32 (m, 4H, Ph-H, quinazoline 5′- and 7′-H), 7.44–7.52 (m 5H, Ph-H), 7.80–7.83 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 79.0 (spiro C), 111.2 (quinazoline C-6′), 116.5 (quinazoline C-8′), 117.6 (quinazoline C-4′a), 119.9, 128.6, 128.9, 129.0, 130.4 (Ph-C), 131.6 (quinazoline C-5′), 136.3 (Ph-C), 136.47 (quinazoline C-7′), 136.50 (Ph-C), 142.4 (quinazoline C-8′a), 160.6 (pyrazole C-3), 168.1 (quinazoline C-4′), 170.3 (pyrazole C-5); MS: *m/z* 479 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}BrClN_4O$: C, 57.58; H, 3.36; N, 11.68. Found: C, 57.57; H, 3.34; N, 11.67.

1-(4-Chlorophenyl)-3,6′-dimethyl-4′-phenylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7d): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-amino-5-methylbenzophenone (**4d**) (0.197 g, 1.0 mmol). Yellow needles (0.299 g, 72%), mp 215–216 °C (acetone/petroleum ether); IR (ATR): ν 3293 (NH), 1716 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.14 (s, 3H, pyrazole 3-Me), 2.18 (s, 3H, quinazoline 6′-Me), 4.40 (s, 1H, NH), 6.61 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 6.96 (s, 1H, quinazoline 5′-H), 7.06–7.08 (m, 1H, quinazoline 7′-H), 7.30–7.34 (m, 2H, Ph-H), 7.41–7.49 (m, 3H, Ph-H), 7.51–7.54 (m, 2H, Ph-H), 7.84–7.88 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.8 (pyrazole 3-Me), 20.7 (quinazoline 6′-Me), 78.8 (spiro C), 115.3 (quinazoline C-8′), 116.7 (quinazoline C-4′a), 119.9, 128.4, 128.9, 129.1 (Ph-C), 129.2 (quinazoline C-6′), 129.6 (quinazoline C-5′), 130.1, 130.2 (Ph-C), 134.8 (quinazoline C-7′), 136.5, 137.1 (Ph-C), 141.0 (quinazoline C-8′a), 160.7 (pyrazole C-3), 169.5 (quinazoline C-4′), 170.6 (pyrazole C-5); MS: *m/z* 415 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}ClN_4O$: C, 69.48; H, 4.62; N, 13.50. Found: C, 69.55; H, 4.63; N, 13.48.

1-(4-Chlorophenyl)-4′-(4-fluorophenyl)-3-methylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7e): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-amino-4′-fluorobenzophenone (**4e**) (0.215 g, 1.0 mmol). Yellow needles (0.242 g, 58%), mp 225–226 °C (acetone/petroleum ether); IR (ATR): ν 3310 (NH), 1711 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, pyrazole 3-Me), 4.42 (s, 1H, NH),

6.67 (d, *J* = 6.9 Hz, 1H, quinazoline 8′-H), 6.75–6.78 (m, 1H, quinazoline 6′-H), 7.10–7.15 (m, 3H, Ph-H and quinazoline 5′-H), 7.25–7.28 (m, 1H, quinazoline 7′-H), 7.32–7.34 (m, 2H, Ph-H), 7.53–7.56 (m, 2H, Ph-H), 7.85–7.88 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 78.8 (spiro C), 115.0 (quinazoline C-8′), 115.4, 115.5 (Ph-C), 116.4 (quinazoline C-4′a), 119.8 (quinazoline C-6′), 119.9, 129.0 (Ph-C), 129.1 (quinazoline C-5′), 130.3, 131.1, 131.2, 133.2 (Ph-C), 134.0 (quinazoline C-7′), 136.4 (Ph-C), 143.4 (quinazoline C-8′a), 160.7 (pyrazole C-3), 163.1, 164.8 (Ph-C), 168.2 (quinazoline C-4′), 170.5 (pyrazole C-5); MS: *m/z* 419 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}ClFN_4O$: C, 65.95; H, 3.85; N, 13.38. Found: C, 66.04; H, 3.92; N, 13.35.

1,4′-Bis(4-chlorophenyl)-3-methylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7f): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-amino-4′-chlorobenzophenone (**4f**) (0.231 g, 1.0 mmol). Yellow needles (0.249 g, 57%), mp 229–231 °C (acetone/petroleum ether); IR (ATR): ν 3310 (NH), 1703 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, pyrazole 3-Me), 4.34 (s, 1H, NH), 6.68 (d, *J* = 6.9 Hz, 1H, quinazoline 8′-H), 6.76–6.79 (m, 1H, quinazoline 6′-H), 7.13 (d, *J* = 7.6 Hz, 1H, quinazoline 5′-H), 7.26–7.29 (m, 1H, quinazoline 7′-H), 7.32–7.35 (m, 2H, Ph-H), 7.40–7.43 (m, 2H, Ph-H), 7.48–7.52 (m, 2H, Ph-H), 7.85–7.89 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 78.8 (spiro C), 115.0 (quinazoline C-8′), 116.3 (quinazoline C-4′a), 119.86 (quinazoline C-6′), 119.93, 128.6, 129.0 (Ph-C), 129.1 (quinazoline C-5′), 130.3, 130.5 (Ph-C), 134.1 (quinazoline C-7′), 135.5 (Ph-C), 136.3 (Ph-C), 136.4 (Ph-C), 143.4 (quinazoline C-8′a), 160.6 (pyrazole C-3), 168.2 (quinazoline C-4′), 170.3 (pyrazole C-5); MS: *m/z* 435 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}Cl_2N_4O$: C, 63.46; H, 3.70; N, 12.87. Found: C, 63.54; H, 3.84; N, 12.90.

4′-(4-Bromophenyl)-1-(4-chlorophenyl)-3-methylspiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7g): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-amino-4′-bromobenzophenone (**4g**) (0.275 g, 1.0 mmol). Yellow needles (0.236 g, 49%), mp 234–235 °C (acetone/petroleum ether); IR (ATR): ν 3304 (NH), 1704 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, pyrazole 3-Me), 4.37 (s, 1H, NH), 6.67 (d, *J* = 7.5 Hz, 1H, quinazoline 8′-H), 6.75–6.78 (m, 1H, quinazoline 6′-H), 7.13 (d, *J* = 7.6 Hz, 1H, quinazoline 5′-H), 7.25–7.28 (m, 1H, quinazoline 7′-H), 7.32–7.35 (m, 2H, Ph-H), 7.42–7.44 (m, 2H, Ph-H), 7.56–7.59 (m, 2H, Ph-H), 7.85–7.88 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 78.8 (spiro C), 115.0 (quinazoline C-8′), 116.2 (quinazoline C-4′a), 119.8 (quinazoline C-6′), 119.9, 124.6, 129.00 (Ph-C), 129.04 (quinazoline C-5′), 130.3, 130.7, 131.6 (Ph-C), 134.1 (quinazoline C-7′), 136.0, 136.4 (Ph-C), 143.4 (quinazoline C-8′a), 160.6 (pyrazole C-3), 168.3 (quinazoline C-4′), 170.3 (pyrazole C-5); MS: *m/z* 479 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}BrClN_4O$: C, 57.58; H, 3.36; N, 11.68. Found: C, 57.45; H, 3.39; N, 11.65.

1-(4-Chlorophenyl)-3-methyl-4′-(4-methylphenyl)spiro[pyrazole-4,2′(1′*H*)-quinazolin]-5(1*H*)-one (7h): Reaction was carried out with **3** (0.222 g, 1.0 mmol) and 2-amino-4′-methylbenzophenone (**4h**) (0.211 g, 1.0 mmol). Yellow needles (0.255 g, 62%), mp 228–229 °C (acetone/petroleum ether); IR (ATR): ν 3298 (NH), 1705 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, pyrazole 3-Me), 2.39 (s, 3H, 4-*Me*-C_6H_4), 4.47 (s, 1H, NH), 6.64 (d, *J* = 8.3 Hz, 1H, quinazoline 8′-H), 6.72–6.75 (m, 1H, quinazoline 6′-H), 7.19 (d, *J* = 7.5 Hz, 1H, quinazoline 5′-H), 7.21–7.25 (m, 3H, Ph-H and quinazoline 7′-H), 7.30–7.33 (m, 2H, Ph-H), 7.41–7.46 (m, 2H, Ph-H), 7.84–7.87 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.7 (pyrazole 3-Me), 21.5 (4-*Me*-C_6H_4), 78.9 (spiro C), 114.9 (quinazoline C-8′), 116.6 (quinazoline C-4′a), 119.6 (quinazoline C-6′), 119.9, 128.9, 129.0 (Ph-C), 129.4 (quinazoline C-5′), 130.2 (Ph-C), 133.7 (quinazoline C-7′), 134.4, 136.5, 140.3 (Ph-C), 143.4 (quinazoline C-8′a), 160.9 (pyrazole C-3), 169.1 (quinazoline C-4′), 170.7 (pyrazole C-5); MS: *m/z* 415 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}ClN_4O$: C, 69.48; H, 4.62; N, 13.50. Found: C, 69.62; H, 4.85; N, 13.53.

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REFERENCES

1. (a) R. Tiwari and G. Chhabra, *Asian J. Chem.*, 2010, **22**, 5981; (b) M. N. Noolvi, H. M. Patel, V. Bhardwaj, and A. Chauhan, *Eur. J. Med. Chem.*, 2011, **46**, 2327; (c) C. Balakumar, P. Lamba, D. P. Kishore, B. L. Narayana, K. V. Rao, K. Rajwinder, A. R. Rao, B. Shireesha, and B. Narsaiah, *Eur. J. Med. Chem.*, 2010, **45**, 4904; (d) T.-C. Chien, C.-S. Chen, F.-H. Yu, and J.-W. Chern, *Chem. Pharm. Bull.*, 2004, **52**, 1422; (e) A. Kumar, P. Sharma, P. Kumari, and B. L. Kalal. *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4353.
2. (a) S. Yoshida, T. Aoyagi, S. Harada, N. Mastuda, T. Ikeda, H. Naganawa, M. Hamada, and T. Takeuchi, *J. Antibiot.*, 1991, **44**, 111; (b) C. Wattanapiromsakul, P. I. Forster, and P. G. Waterman, *Phytochemistry*, 2003, **64**, 609; (c) Y. Deng, R. Xu, and Y. Yang, *J. Chin. Pharm. Sci.*, 2000, **9**, 116; (d) Z.-Z. Ma, Y. Hano, T. Nomura, and Y.-J. Chen, *Heterocycles*, 1997, **46**, 541.
3. (a) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii, and H. Ohno, *Org. Lett.*, 2010, **12**, 3963; (b) R. Alonso, A. Caballero, P. J. Campos, D. Sampedro, and M. A. Rodríguez, *Tetrahedron*, 2010, **66**, 4469; (c) F. Portela-Cubillo, J. S. Scott, and J. C. Walton, *J. Org. Chem.*, 2009, **74**, 4934; (d) Z.-H. Zhang, X.-N. Zhang, L.-P. Mo, Y.-X. Li, and F.-P. Ma, *Green Chem.*, 2012, **14**, 1502; (e) K. Karnakar, J. Shankar, S. N. Murthy, K. Ramesh, and Y. V. D. Nageswar, *Synlett*, 2011, 1089; (f) V. L. Truong and M. Morrow, *Tetrahedron Lett.*, 2010, **51**, 758.

4. (a) R. Gundla, R. Kazemi, R. Sanam, R. Muttineni, J. A. R. P. Sarma, R. Dayam, and N. Neamati, *J. Med. Chem.*, 2008, **51**, 3367; (b) J. F. M. da Silva, M. Walters, S. Al-Damluji, and C. R. Ganellin, *Bioorg. Med. Chem.*, 2008, **16**, 7254; (c) G. W. Rewcastle, B. D. Palmer, A. J. Bridges, H. D. H. Showalter, L. Sun, J. Nelson, A. McMichael, A. J. Kraker, D. W. Fry, and W. A. Denny, *J. Med. Chem.*, 1996, **39**, 918; (d) A. Luth and W. Lowe, *Eur. J. Med. Chem.*, 2008, **43**, 1478.

5. (a) P. D. Sauzem, G. D. S. Sant'Anna, P. Machado, M. M. M. F. Duarte, J. Ferreira, C. F. Mello, P. Beck, H. G. Bonacorso, N. Zanatta, M. A. P. Martins, and M. A. Rubin, *Eur. J. Pharmacol.*, 2009, **616**, 91; (b) H.-V. Eduardo, A.-O. Rodrigo, R.-E. J. Jose, E.-S. Samuel, and H.-L. Francisco, *Eur. J. Med. Chem.*, 2013, **69**, 10; (c) H. Y. Lo, C. C. Man, R. W. Fleck, N. A. Farrow, R. H. Ingraham, A. Kukulka, J. R. Proudfoot, R. Betageri, T. Kirrane, U. Patel, R. Sharma, M. A. Hoermann, A. Kabcenell, and S. D. Lombaert, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6379; (d) D.-M. Shen, E. J. Brady, M. R. Candelore, Q. Dallas-Yang, V. D.-H. Ding, W. P. Feeney, G. Jiang, M. E. McCann, S. Mock, S. A. Qureshi, R. Saperstein, X. Shen, X. Tong, L. M. Tota, M. J. Wright, X. Yang, S. Zheng, K. T. Chapman, B. B. Zhang, J. R. Tata, and E. R. Parmee, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 76; (e) L.-W. Zheng, L.-L. Wu, B.-X. Zhao, W.-L. Dong, and J.-Y. Miao, *Bioorg. Med. Chem.*, 2009, **17**, 1957.

6. (a) G. Varvounis, Y. Fiamegos, and G. Pilidis, *Adv. Heterocycl. Chem.*, 2001, **80**, 73; (b) G. Varvounis, Y. Fiamegos, and G. Pilidis, *Adv. Heterocycl. Chem.*, 2004, **87**, 141; (c) G. Varvounis, Y. Fiamegos, and G. Pilidis, *Adv. Heterocycl. Chem.*, 2008, **95**, 27; (d) G. Varvounis, *Adv. Heterocycl. Chem.*, 2009, **98**, 143; (e) S. Fustero, M. Sánchez-Roselló, P. Barrio, and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984; (f) S. Kumari, S. Paliwal, and R. Chauhan, *Synth. Commun.*, 2014, **44**, 1521.

7. (a) T. C. McMorris, M. D. Staake, and M. J. Kelner, *J. Org. Chem.*, 2004, **69**, 619; (b) C. Laroche, J.-B. Behr, J. Szymoniak, P. Bertus, C. Schütz, P. Vogel, and R. Plantier-Royon, *Bioorg. Med. Chem.*, 2006, **14**, 4047; (c) S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton, and A. H. White, *Tetrahedron*, 2007, **63**, 1191; (d) A. Nakazaki and S. Kobayashi, *Synlett*, 2012, **23**, 1427; (e) M. Xia and R.-Z. Ma, *J. Heterocycl. Chem.*, 2014, **51**, 539; (f) M. A. Borad, M. N. Bhoi, N. P. Prajapati, and H. D. Patel, *Synth. Commun.*, 2014, **44**, 897; (g) J. Xie, X.-Y. Xing, F. Sha, Z.-Y. Wu, and X.-Y. Wu, *Org. Biomol. Chem.*, 2016, **14**, 8346; (h) L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen, and D. Enders, *Angew. Chem. Int. Ed.*, 2016, **55**, 11110; (i) J. Zhou, W.-J. Huang, and G.-F. Jiang, *Org. Lett.*, 2018, **20**, 1158.

8. (a) H. Maruoka, N. Kashige, T. Eishima, F. Okabe, R. Tanaka, T. Fujioka, F. Miake, and K. Yamagata, *J. Heterocycl. Chem.*, 2008, **45**, 1883; (b) E. Masumoto, F. Okabe, T. Fujioka, K. Yamagata, and H. Maruoka, *Heterocycles*, 2014, **89**, 2572; (c) E. Masumoto, H. Maruoka, F. Okabe, T. Fujioka, and K. Yamagata, *J. Heterocycl. Chem.*, 2015, **52**, 48; (d) E. Masumoto, E. Shirouzu, N.

Kashige, F. Okabe-Nakahara, F. Miake, K. Yamagata, and H. Maruoka, *Heterocycles*, 2018, **96**, 1289.

9. (a) P. Chauhan, S. Mahajan, U. Kaya, A. Peuronen, K. Rissanen, and D. Enders, *J. Org. Chem.*, 2017, **82**, 7050; (b) F. Vetica, P. Chauhan, S. Mahajan, G. Raabe, and D. Enders, *Synthesis*, 2018, **50**, 1039.
10. (a) S. I. Bhat, U. K. Das, and D. R. Trivedi, *J. Heterocycl. Chem.*, 2015, **52**, 1253; (b) X. Yang, X. Guo, M. Qin, X. Yuan, H. Jing, and B. Chen, *Org. Biomol. Chem.*, 2018, **16**, 3104.