DOI: 10.1002/ejoc.200900421

Synthesis of Original 2-Substituted 4-Arylquinazolines by Microwave-Irradiated Suzuki–Miyaura Cross-Coupling Reactions

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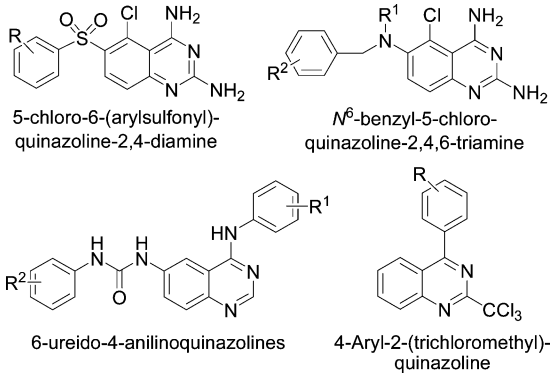
Keywords: Boron / Microwave chemistry / Cross-coupling / Nitrogen heterocycles

Original 2-substituted 4-arylquinazolines have been synthesized by using a microwave-assisted Suzuki–Miyaura cross-coupling approach. The optimization and generalization of the Suzuki–Miyaura cross-coupling reaction between 2-substituted 4-chloroquinazolines and various boronic acids are described herein.

Introduction

The palladium-catalysed cross-coupling reactions of arylboronic acids with aryl halides in the presence of a base, a Suzuki-type reaction, provides a convenient method for forming carbon–carbon bonds, in particular, in the synthesis of biaryl compounds.[1] In recent years various modifications to this reaction have been made involving the nature of catalysts, solvents, bases, reaction conditions and synthetic techniques that have permitted the use of organoboron compounds that are thermally stable and inert to water and oxygen.[2] At the same time, microwave heating has also been used to promote Suzuki reactions.[3] The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially when conventional methods require forcing conditions or prolonged reaction times.[4]



Scheme 1.

As a continuation of our previous studies[5] directed towards the preparation of new azaheterocyclic compounds and the evaluation of their anti-infectious activity, we have synthesized a series of new quinazoline derivatives substituted by a variety of groups at the 2-position by a microwave-assisted Suzuki–Miyaura cross-coupling reaction. Quinazoline derivatives are an important class of compounds and have shown interesting activity as antimalarial agents (Scheme 1).[6]

Results and Discussion

We have recently developed a microwave-assisted synthesis of 2-(chloromethyl)quinazolin-4(3*H*)-one (**1**).[7] This compound can easily be nitrated by using a HNO_3/H_2SO_4 mixture to give 2-(chloromethyl)-6-nitroquinazolin-4(3*H*)-one (**2**) in 80% yield (Scheme 2). To substitute the 2-position of **2**, we applied microwave technology in combination with $S_{RN}1$ or S_N2 reactions.[8] Thus, compound **2** was treated with the lithium salt of 2-nitropropane (**3**) to afford nitroquinazolinone **4**. The intermediate *C*-alkylated product was not isolated due to very rapid nitrous acid elimination in alkaline medium because of the acidity of the methylene protons.

In view of our pharmacomodulation goals, we initially substituted a methoxy group for the chlorine atom (compound **5**), as shown in Scheme 2.

We have previously described a "green chemistry procedure" that allows the substitution of a chlorine atom by a sulfone group.[7] This ecofriendly methodology in the aqueous phase, using microwave technology to ensure respect of the environment, was developed for the preparation of *S*-alkylated products **6** and **7** in high yields (Scheme 2).

4-Chloroquinazoline derivatives **8**–**11** were obtained after microwave-assisted chlorination of **4**–**7** by treatment with

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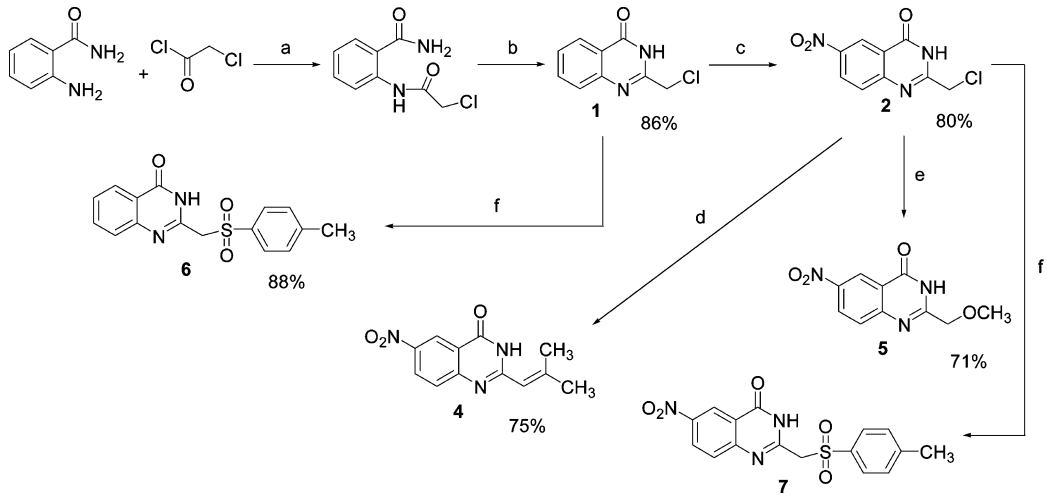
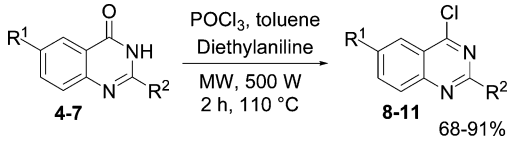


Scheme 2. Preparation of quinazolines **1**–**7**. Reagents and conditions: (a) MW, 300 W, 50 °C, 5 min; (b) K_2CO_3, H_2O, MW, 500 W, 80 °C, 1 h; (c) H_2SO_4, HNO_3, room temp., 4 h; (d) $(CH_3)_2NO_2C^-$ Li^+ (**3**), MW, 500 W, 70 °C, 2 h, CH_3OH; (e) CH_3OH, NaOH, MW, 500 W, 70 °C, 2 h; (f) *p*-CH_3PhSO_2Cl, $NaHCO_3$, Na_2SO_3, H_2O, MW, 300 W, 100 °C, 1 h.

$POCl_3$, as shown in Scheme 3 and Table 1. It appears that in the presence of a nitro group at the 6-position, the chlorination yield is lower. Deactivation of the quinazoline cycle most probably accounts for this result.



Scheme 3.

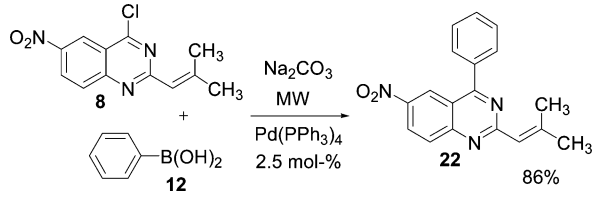
Table 1. Results of the chlorination reactions of 2-methylquinazolin-4(3*H*)-one derivatives **4**–**7**.

	R^1	R^2	Yield [%]
8	NO_2	$CH=C(CH_3)_2$	75
9	NO_2	CH_2OCH_3	68
10	NO_2	$CH_2SO_2Ph(pCH_3)$	74
11	H	$CH_2SO_2Ph(pCH_3)$	91

Compounds **8**–**11**, obtained in good yields, present the advantage of being functionalizable at the 4-position. We therefore investigated the possibility of using 4-chloroquinazoline derivatives **8**–**11** as substrates for Suzuki–Miyaura cross-coupling reactions. To optimize the operating conditions we studied the reaction with compound **8** and phenylboronic acid (**12**) by using the procedure described by Guiry and co-workers, but with significant modifications (Scheme 4).[9]

Various reaction parameters were tested and the best conditions were finally defined (Table 2), permitting the synthesis of quinazoline **8** in 86% yield in 3 h.

The best yield of the coupled product was obtained when the reaction was stirred at 85 °C with 1.9 equiv. of boronic acid in a microwave oven (300 W) for 3 h with DME used as solvent. As expected, it was more convenient to carry out the Suzuki reaction in a microwave reactor, the reaction



Scheme 4.

Table 2. Parameters studied for the optimization of the Suzuki–Miyaura reaction between quinazoline **8** and phenylboronic acid (**12**).

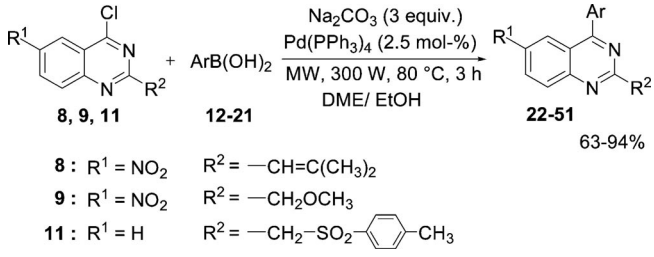
Solvent	Time [h]	Conditions[a]	*T* [°C]	Boronic acid [equiv.]	Yield [%]
DME	1.5	MW/150 W	85	1.2	50
DME	2	MW/300 W	85	1.2	54
DME	2	MW/300 W	85	1.5	58
Dioxane	2	MW/300 W	100	1.5	46
DMF	2	MW/300 W	150	1.5	52
DME	3	MW/300 W	85	1.9	86
H_2O	3	MW/300 W	100	1.9	<5
DME	24	Oil bath	85	1.9	35
DME	48	Oil bath	85	1.9	49
DME	72	Oil bath	85	1.9	55

[a] Microwave instrumentation: the temperature was measured with an infrared detector and the microwave pulsed power was regulated by the software of terminal 320 for Ethos start, Milestone Inc. Catalytic conditions: 3 equiv. Na_2CO_3 and 2.5 mol-% $[Pd(PPh_3)_4]$.

time being reduced from 72 to 3 h. The development of water-compatible transition-metal reagents for use in an aqueous solvent system has been proved to simplify catalyst/product separation and to increase catalyst activity.[10] Therefore we tried to employ water as a solvent in conjunction with microwave heating. All the reaction trials realized with water as solvent led to a poor yield of coupling product **22**, probably due to poor solubility of the starting material. An alternative method, described by Leadbeater, was

to use phase-transfer agent tetrabutylammonium bromide (TBAB) to increase the solvation of the organic substrates.[11]

Based on a number of reports regarding the Suzuki–Miyaura reaction and on our optimization work, reported in Table 2, we decided to use Na_2CO_3 as the base (3 equiv.) and $[Pd(PPh_3)_4]$ as the catalyst.[12] We first started to work with the 6-nitrated derivatives. Unfortunately, compound **10** presented poor reactivity towards the Suzuki–Miyaura cross-coupling reaction. We observed a high percentage of remaining starting material and significant difficulties in purification, probably due to a lack of solubility. A mixture of 4-chloroquinazoline derivative **8**, **9** or **11**, arylboronic acid, $[Pd(PPh_3)_4]$ and Na_2CO_3 was stirred at 80 °C in a microwave oven for 3 h (Scheme 5, Table 3). The disappearance of the starting materials was monitored by TLC. By using the microwave-assisted optimized operating procedure we prepared a series of 2-substituted 4-arylquinazolines (**22**–**51**) by varying the boronic acid (Table 3). The best result (94%) was obtained by using phenylboronic acid (**12**) with substrate **11**. The lowest yield (63%) was observed when treating 5-methylthiophen-2-ylboronic acid (**16**) with substrate **9**. Generally, the yields obtained seem to be more influenced by the nature of the boronic acid than by the nature of the quinazoline substituent at the 2-position.



Scheme 5.

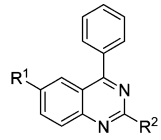
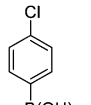
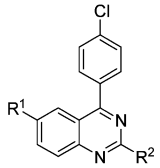
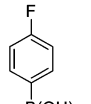
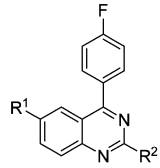
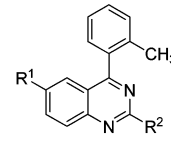
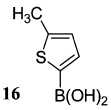
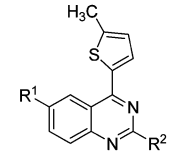
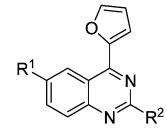
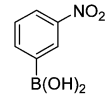
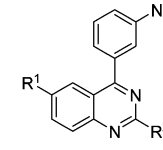
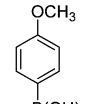
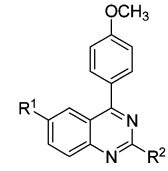
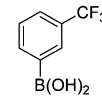
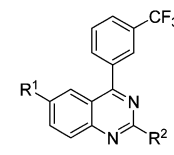
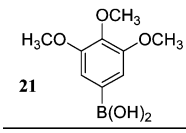
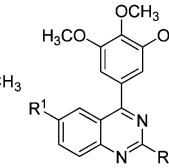
Conclusions

We have described herein an efficient route to original 2-substituted 4-arylquinazolines using a microwave-assisted Suzuki–Miyaura cross-coupling approach. The microwave-assisted process, in contrast to conventional heating, gives the desired compounds in higher overall yields in shorter reaction times. This work confirms that microwave-irradiated reactions allow easy and rapid access to original aza-heterocyclic compounds with potential antiplasmodial activities. In view of our pharmacomodulation goals, the next step of our research program involves analysing the antiplasmodial activities.

Experimental Section

General: Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Elemental analyses were performed by the Microanalyses Center of the University of Aix-Marseille 3, France. Both ^1H and ^{13}C NMR spectra were determined with a

Table 3. Optimal synthetic conditions and corresponding yields of Suzuki–Miyaura reactions in the three distinct series.

Boronic acid	Product	Yield **A**[a]	Yield **B**[a]	Yield **C**[a]
12 		86% **22**	88% **32**	94% **42**
13 		77% **23**	75% **33**	91% **43**
14 		64% **24**	76% **34**	79% **44**
15 		67% **25**	82% **35**	70% **45**
16 		78% **26**	63% **36**	78% **46**
17 		89% **27**	80% **37**	91% **47**
18 		75% **28**	67% **38**	72% **48**
19 		64% **29**	87% **39**	67% **49**
20 		76% **30**	83% **40**	74% **50**
21 		66% **31**	80% **41**	70% **51**

[a] **A**: $R^1 = NO_2$; $R^2 = CH{=}C(CH_3)_2$. **B**: $R^1 = NO_2$; $R^2 = CH_2OCH_3$. **C**: $R^1 = H$; $R^2 = CH_2SO_2Ph(pCH_3)$.

Bruker ARX 200 spectrometer. The ^1H chemical shifts are reported as ppm downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts are referenced to the solvent peak: $CDCl_3$ (δ =76.9 ppm) or [D_6]DMSO (δ =39.5 ppm). Solvents were dried by conventional methods. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 × 10 cm aluminium plates coated with silica gel 60F-254 (Merck) in an appropriate solvent.

Microwave Instrumentation: Multimode reactors: ETHOS Synth Lab station and MicroSYNTH Lab terminal 1024 (Ethos start, Milestone Inc.). The multimode microwave has a twin magnetron (2 × 800 W, 2.45 GHz) with a maximum delivered power of 1000 W in 10 W increments (pulsed irradiation). Built-in magnetic stirring (Teflon-coated stirring bar) was used in all operations. During the experiments, the time, temperature and power were measured with the "easy WAVE" software package. The temperature was measured throughout the reaction and evaluated by an infrared detector or an optical fibre (ATC-FO 300).

To compare the microwave irradiation with conventional heating, the reactions were performed under similar experimental conditions (amount of reactants and temperature) using a thermostatted oil bath. The temperature was measured by the insertion of a Quick digital thermometer into the reaction mixture and the rate of the temperature rise was adjusted to be the same as measured under microwave irradiation.

2-(2-Methylprop-1-enyl)-6-nitroquinazolin-4(3*H*)-one (4): 2-(Chloromethyl)-6-nitroquinazolin-4(3*H*)-one (**2**; 0.5 g, 2.08 mmol) was added to a solution of the lithium salt of the 2-nitropropane anion (**3**; 0.8 g, 8.32 mmol) in methanol (20 mL). The reaction mixture was irradiated in a microwave oven at 70 °C for 2 h at a power of 500 W. After evaporation of the methanol, the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried with magnesium sulfate and the solvent was removed under vacuum. A yellow solid was obtained that was recrystallized from 2-propanol to give **4** (0.38 g, 75%), m.p. 253 °C. ^1H NMR (200 MHz, [D_6]DMSO, 22 °C): δ = 1.98 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 6.07 (s, 1 H, vinylic H), 7.72 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, 9-H), 8.46 (dd, $^4J_{H,H}$ = 2.7 Hz, $^3J_{H,H}$ = 9.0 Hz, 1 H, 7-H), 8.72 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO, 22 °C): δ = 21.5 (CH_3), 28.6 (CH_3), 117.4 (CH), 120.9 (C), 122.3 (CH), 128.7 (CH), 129.1 (CH), 144.6 (C), 153.7 (C), 154.9 (C), 155.5 (C), 161.6 (C) ppm. $C_{12}H_{11}N_3O_3$ (245.23): calcd. C 58.77, H 4.52, N 17.13; found C 58.59, H 4.61, N 17.14.

2-(Methoxymethyl)-6-nitroquinazolin-4(3*H*)-one (5): A mixture of 2-(chloromethyl)-6-nitroquinazolin-4(3*H*)-one (**2**; 0.5 g, 2.08 mmol) and sodium hydroxide (0.2 g, 6.24 mmol) dissolved in methanol (40 mL) was heated at 70 °C for 2 h in the microwave, irradiating with 500 W. After evaporation of the methanol, water was added and the solution was neutralized with 2 N H_2SO_4. The aqueous layer was extracted with chloroform, the combined organic extracts were dried with magnesium sulfate and the solvents evaporated. A yellow solid was obtained that was recrystallized from 2-propanol (0.35 g, 71%), m.p. 229 °C. ^1H NMR (200 MHz, [D_6]DMSO, 22 °C): δ = 3.39 (s, 3 H, OCH_3), 4.39 (s, 2 H, CH_2), 7.82 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, 8-H), 8.51 (dd, $^4J_{H,H}$ = 2.7 Hz, $^3J_{H,H}$ = 8.9 Hz, 1 H, 7-H), 8.75 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO, 22 °C): δ = 59.1 (OCH_3), 71.8 (CH_2), 122.0 (C), 122.4 (CH), 128.8 (CH), 129.2 (CH), 145.4 (C), 152.9 (C), 158.3 (C), 161.3 (C) ppm. $C_{10}H_9N_3O_4$ (235.20): calcd. C 51.07, H 3.86, N 17.87; found C 51.24, H 3.93, N 17.67.

2-(Tosylmethyl)quinazolin-4(3*H*)-one (6): 2-(Chloromethyl)quinazolin-4(3*H*)-one (**1**; 1 g, 5.14 mmol) was added to a solution of 4-methylbenzenesulfonyl chloride (1.96 g, 10.28 mmol), $NaHCO_3$ (0.86 g, 10.28 mmol) and Na_2SO_3 (1.29 g, 10.28 mmol) in water (30 mL). The reaction mixture was irradiated in a microwave oven at 100 °C for 1 h at a power of 300 W. The precipitate was filtered, washed with water (3 × 20 mL) and dried in vacuo in a drying oven (desiccator cabinet). The product required was recrystallized from 2-propanol to give **6** (1.42 g, 88%), m.p. 249 °C. ^1H NMR (200 MHz, [D_6]DMSO, 22 °C): δ = 2.41 (s, 3 H, CH_3), 4.65 (s, 2 H, CH_2), 7.41–7.57 (m, 4 H, Ar-H), 7.69–7.84 (m, 3 H, Ar-H), 8.10 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, [D_6]-DMSO, 22 °C): δ = 21.3 (CH_3), 60.7 (CH_2), 121.3 (C), 125.9 (CH), 127.2 (CH), 127.4 (CH), 128.4 (2 CH), 129.8 (2 CH), 134.8 (CH), 136.0 (C), 145.0 (C), 146.4 (C), 148.3 (C), 161.4 (C) ppm. $C_{16}H_{14}N_2O_3S$ (314.36): calcd. C 61.13, H 4.49, N 8.91; found C 60.78, H 4.58, N 8.79.

6-Nitro-2-(tosylmethyl)quinazolin-4(3*H*)-one (7): 2-(Chloromethyl)-6-nitroquinazolin-4(3*H*)-one (**2**; 1 g, 4.17 mmol) was added to a solution of 4-methylbenzenesulfonyl chloride (1.59 g, 8.34 mmol), $NaHCO_3$ (0.7 g, 8.34 mmol) and Na_2SO_3 (1.05 g, 8.34 mmol) in water (30 mL). The reaction mixture was irradiated in a microwave oven at 100 °C for 1 h at a power of 300 W. The precipitate was filtered, washed with water (3 × 20 mL) and dried in vacuo in a drying oven (desiccator cabinet). The product required was recrystallized from 2-propanol to give **7** (1.39 g, 93%), m.p. 281 °C. ^1H NMR (200 MHz, [D_6]DMSO, 22 °C): δ = 2.42 (s, 3 H, CH_3), 4.71 (s, 2 H, CH_2), 7.44 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 3′,5′-H), 7.64 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 8-H), 7.73 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2′,6′-H), 8.53 (dd, $^4J_{H,H}$ = 2.6 Hz, $^3J_{H,H}$ = 8.7 Hz, 1 H, 7-H), 8.78 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO, 22 °C): δ = 21.6 (CH_3), 61.3 (CH_2), 121.7 (C), 122.4 (CH), 128.8 (2 CH), 129.1 (CH), 129.3 (CH), 130.2 (2 CH), 136.2 (C), 145.5 (C), 145.8 (C), 150.6 (C), 152.6 (C), 161.1 (C) ppm. $C_{16}H_{13}N_3O_5S$ (359.36): calcd. C 53.48, H 3.65, N 11.69; found C 53.62, H 3.51, N 11.61.

4-Chloro-2-(2-methylprop-1-enyl)-6-nitroquinazoline (8): 2-(2-Methylprop-1-enyl)-6-nitroquinazolin-4(3*H*)-one (0.3 g, 1.22 mmol) was dissolved in toluene (20 mL). Diethylaniline (0.58 mL, 3.67 mmol) and phosphorus oxychloride (0.23 mL, 2.44 mmol) were added. The mixture was heated at 110 °C in the microwave oven irradiating with 500 W for 2 h. After cooling and hydrolysis with water (100 mL), the mixture was extracted with dichloromethane. The combined organic extracts were washed with water (3 × 60 mL), dried with magnesium sulfate and the solvents evaporated. Purification by column chromatography [silica gel, eluent: dichloromethane/petroleum ether (1:1)] afforded 0.24 g (75%) of **8** as a brown solid, m.p. 140 °C. ^1H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.10 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 6.58 (s, 1 H, vinylic H), 8.08 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, 8-H), 8.62 (dd, $^4J_{H,H}$ = 2.3 Hz, $^3J_{H,H}$ = 9.5 Hz, 1 H, 7-H), 9.09 (d, $^4J_{H,H}$ = 2.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.1 (CH_3), 28.8 (CH_3), 120.5 (C), 122.8 (CH), 123.4 (CH), 128.1 (CH), 130.1 (CH), 145.8 (C), 153.6 (C), 154.3 (C), 163.4 (C), 163.7 (C) ppm. $C_{12}H_{10}ClN_3O_2$ (263.68): calcd. C 54.66, H 3.82, N 15.94; found C 54.29, H 3.86, N 15.66.

4-Chloro-2-(methoxymethyl)-6-nitroquinazoline (9): 2-(Methoxymethyl)-6-nitroquinazolin-4(3*H*)-one (**5**; 1 g, 4.24 mmol) was dissolved in toluene (60 mL). Diethylaniline (2 mL, 12.72 mmol) and phosphorus oxychloride (0.8 mL, 8.48 mmol) were added. The mixture was heated at 110 °C in the microwave oven, irradiating with 500 W for 2 h. After cooling and hydrolysis with water (100 mL), the mixture was extracted with dichloromethane. The combined organic extracts were washed with water (3 × 100 mL),

dried with magnesium sulfate and the solvents evaporated. Purification by column chromatography [silica gel, eluent: dichloromethane/petroleum ether (2:1)] afforded 0.73 g (68%) of **9** as a purple solid, m.p. 119 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.62 (s, 3 H, OCH_3), 4.85 (s, 2 H, CH_2), 8.26 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, 8-H), 8.69 (dd, $^4J_{H,H}$ = 2.7 Hz, $^3J_{H,H}$ = 8.9 Hz, 1 H, 7-H), 9.15 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 59.5 (OCH_3), 74.7 (CH_2), 122.0 (C), 122.6 (CH), 128.4 (CH), 130.9 (CH), 146.5 (C), 153.4 (C), 164.6 (C), 165.8 (C) ppm. $C_{10}H_8ClN_3O_3$ (253.64): calcd. C 47.35, H 3.18, N 13.98; found C 47.13, H 3.14, N 13.92.

4-Chloro-6-nitro-2-(tosylmethyl)quinazoline (10): 6-Nitro-2-(tosylmethyl)quinazolin-4(3*H*)-one (**7**; 1 g, 2.65 mmol) was dissolved in toluene (60 mL). Diethylaniline (1.26 mL, 7.95 mmol) and phosphorus oxychloride (0.5 mL, 5.3 mmol) were added. The mixture was heated at 110 °C in the microwave oven, irradiating with 500 W for 2 h. After cooling and hydrolysis with water (100 mL), the mixture was extracted with dichloromethane. The combined organic extracts were washed with water (3 × 100 mL), dried with magnesium sulfate and the solvents evaporated. Purification by column chromatography [silica gel, eluent: dichloromethane then dichloromethane/ethyl acetate (95:5)] afforded 0.78 g (74%) of **10** as a beige solid, m.p. 228 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.47 (s, 3 H, CH_3), 4.86 (s, 2 H, CH_2), 7.34 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 3′,5′-H), 7.72 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2′,6′-H), 8.17 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, 8-H), 8.72 (dd, $^4J_{H,H}$ = 2.7 Hz, $^3J_{H,H}$ = 8.9 Hz, 1 H, 7-H), 9.16 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.7 (CH_3), 65.6 (CH_2), 121.9 (C), 122.6 (CH), 128.6 (3 CH), 129.8 (2 CH), 131.1 (CH), 135.9 (C), 145.4 (C), 147.0 (C), 153.3 (C), 158.1 (C), 164.7 (C) ppm. $C_{16}H_{12}ClN_3O_4S$ (377.80): calcd. C 50.87, H 3.20, N 11.12; found C 50.46, H 3.12, N 10.93.

4-Chloro-2-(tosylmethyl)quinazoline (11): 2-(Tosylmethyl)quinazolin-4(3*H*)-one (**6**; 1 g, 3.18 mmol) was dissolved in toluene (60 mL). Diethylaniline (1.52 mL, 9.54 mmol) and phosphorus oxychloride (0.6 mL, 6.36 mmol) were added. The mixture was heated at 110 °C in the microwave oven, irradiating with 500 W for 2 h. After cooling and hydrolysis with water (100 mL), the mixture was extracted with dichloromethane. The combined organic extracts were washed with water (3 × 100 mL), dried with magnesium sulfate and the solvents evaporated. Purification by column chromatography [silica gel, eluent: dichloromethane/petroleum ether (2:1)] afforded 0.96 g (91%) of **11** as a beige solid, m.p. 153 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.45 (s, 3 H, CH_3), 4.82 (s, 2 H, CH_2), 7.30 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 3′,5′-H), 7.68–7.79 (m, 3 H, Ar-H), 7.96–8.00 (m, 2 H, Ar-H), 8.22–8.27 (m, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.6 (CH_3), 65.6 (CH_2), 122.5 (C), 125.7 (CH), 128.7 (3 CH), 129.5 (CH), 129.6 (2 CH), 135.3 (CH), 136.1 (C), 145.0 (C), 151.2 (C), 154.7 (C), 162.7 (C) ppm. $C_{16}H_{13}ClN_2O_2S$ (332.80): calcd. C 57.74, H 3.94, N 8.42; found C 57.53, H 3.92, N 8.24.

General Procedure for the Cross-Coupling Reaction: 4-Chloroquinazoline derivatives **8**–**11** (0.76 mmol) and tetrakis(triphenylphosphane)palladium(0) (2.5 mol-%) were dissolved in DME (15 mL) under nitrogen and stirred for 1 h at room temperature. Arylboronic acid (1.9 equiv.) in ethanol (2 mL) and sodium carbonate (2.28 mmol) were added. The mixture was placed in the microwave oven irradiating with 300 W, heating at reflux for 3 h. After addition of water (60 mL), the solution was extracted into dichloromethane. The organic layer was washed with water, dried with sodium sulfate and the solvents evaporated. The crude product was purified by column chromatography [silica gel, eluent: dichloromethane/petroleum ether (1:4)].

2-(2-Methylprop-1-enyl)-6-nitro-4-phenylquinazoline (22): Yield: 86% (0.20 g). Yellow solid, m.p. 129 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.10 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 6.70 (s, 1 H, vinylic H), 7.62–7.65 (m, 3 H, 3′,4′,5′-H), 7.79–7.84 (m, 2 H, 2′,6′-H), 8.11 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 8-H), 8.59 (dd, $^4J_{H,H}$ = 2.6 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, 7-H), 8.98 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 20.9 (CH_3), 28.5 (CH_3), 119.2 (C), 124.1 (CH), 124.8 (CH), 126.7 (CH), 129.0 (2 CH), 130.0 (2 CH), 130.3 (CH), 130.7 (CH), 136.3 (C), 145.1 (C), 151.7 (C), 154.1 (C), 164.3 (C), 169.8 (C) ppm. $C_{18}H_{15}N_3O_2$ (305.33): calcd. C 70.81, H 4.95, N 13.76; found C 70.63, H 4.98, N 13.74.

4-(4-Chlorophenyl)-2-(2-methylprop-1-enyl)-6-nitroquinazoline (23): Yield: 77% (0.20 g). Yellow solid, m.p. 218 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.10 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 6.69 (s, 1 H, vinylic H), 7.61 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 3′,5′-H), 7.77 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 2′,6′-H), 8.11 (d, $^3J_{H,H}$ = 9.7 Hz, 1 H, 8-H), 8.60 (dd, $^4J_{H,H}$ = 2.5 Hz, $^3J_{H,H}$ = 9.7 Hz, 1 H, 7-H), 8.92 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 20.9 (CH_3), 28.5 (CH_3), 119.0 (C), 123.6 (CH), 124.7 (CH), 126.9 (CH), 129.4 (2 CH), 130.6 (CH), 131.3 (2 CH), 134.7 (C), 137.3 (C), 145.2 (C), 152.1 (C), 154.2 (C), 164.3 (C), 168.6 (C) ppm. $C_{18}H_{14}ClN_3O_2$ (339.78): calcd. C 63.63, H 4.15, N 12.37; found C 63.42, H 4.15, N 12.22.

4-(4-Fluorophenyl)-2-(2-methylprop-1-enyl)-6-nitroquinazoline (24): Yield: 64% (0.16 g). Yellow solid, m.p. 194 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.10 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 6.68 (s, 1 H, vinylic H), 7.28–7.36 (m, 2 H, 3′,5′-H), 7.79–7.86 (m, 2 H, 2′,6′-H), 8.10 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 8-H), 8.58 (dd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 9.2 Hz, 1 H, 7-H), 8.92 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 20.9 (CH_3), 28.5 (CH_3), 116.3 (2 CH), 119.1 (C), 123.8 (CH), 124.8 (CH), 126.9 (CH), 130.5 (CH), 132.1 (2 CH), 132.5 (C), 145.2 (C), 152.0 (C), 154.2 (C), 164.3 (C), 164.4 (C), 168.7 (C) ppm. $C_{18}H_{14}FN_3O_2$ (323.32): calcd. C 66.87, H 4.36, N 13.00; found C 66.52, H 4.40, N 12.81.

2-(2-Methylprop-1-enyl)-6-nitro-4-(*o*-tolyl)quinazoline (25): Yield: 67% (0.16 g). Brown solid, m.p. 181 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.09 (s, 3 H, CH_3), 2.19 (s, 3 H, tolyl CH_3), 2.45 (s, 3 H, CH_3), 6.70 (s, 1 H, vinylic H), 7.31–7.53 (m, 4 H, 3′,4′,5′,6′-H), 8.11 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 8-H), 8.51–8.61 (m, 2 H, 5,7-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 19.9 (CH_3), 20.9 (CH_3), 28.5 (CH_3), 120.3 (C), 124.0 (CH), 124.9 (CH), 126.0 (CH), 126.9 (CH), 129.5 (CH), 129.9 (CH), 130.4 (CH), 131.1 (CH), 135.5 (C), 136.1 (C), 145.1 (C), 151.9 (C), 153.6 (C), 164.3 (C), 171.4 (C) ppm. $C_{19}H_{17}N_3O_2$ (319.36): calcd. C 71.46, H 5.37, N 13.16; found C 71.85, H 5.29, N 12.86.

2-(2-Methylprop-1-enyl)-4-(5-methylthiophen-2-yl)-6-nitroquinazoline (26): Yield: 78% (0.19 g). Yellow solid, m.p. 172 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.09 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 2.63 (s, 3 H, thiophenyl CH_3), 6.61 (s, 1 H, vinylic H), 6.98–7.01 (m, 1 H, 4′-H), 7.74 (d, $^3J_{H,H}$ = 4.1 Hz, 1 H, 3′-H), 8.02 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 8-H), 8.56 (dd, $^4J_{H,H}$ = 2.5 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 7-H), 9.36 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 15.5 (CH_3), 20.8 (CH_3), 28.4 (CH_3), 117.6 (C), 123.1 (CH), 124.5 (CH), 126.4 (CH), 127.4 (CH), 130.2 (CH), 132.5 (CH), 138.2 (C), 145.0 (C), 147.4 (C), 151.4 (C), 154.5 (C), 161.3 (C), 163.9 (C) ppm. $C_{17}H_{15}N_3O_2S$ (325.38): calcd. C 62.75, H 4.65, N 12.91; found C 62.46, H 4.65, N 12.90.

4-(Furan-2-yl)-2-(2-methylprop-1-enyl)-6-nitroquinazoline (27): Yield: 89% (0.20 g). Yellow solid, m.p. 169 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.10 (s, 3 H, CH_3), 2.46 (s, 3 H,

CH_3), 6.62 (s, 1 H, vinylic H), 6.71–6.73 (m, 1 H, 4′-H), 7.66 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 3′-H), 7.90 (m, 1 H, 5′-H), 8.01 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 8-H), 8.56 (dd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 7-H), 9.87 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 20.8 (CH_3), 28.5 (CH_3), 112.8 (CH), 116.9 (C), 117.3 (CH), 124.3 (CH), 124.8 (CH), 126.7 (CH), 130.2 (CH), 145.2 (C), 147.0 (CH), 151.1 (C), 153.3 (C), 154.8 (C), 156.3 (C), 164.3 (C) ppm. $C_{16}H_{13}N_3O_3$ (295.29): calcd. C 65.08, H 4.44, N 14.23; found C 65.06, H 4.43, N 14.20.

2-(2-Methylprop-1-enyl)-6-nitro-4-(3-nitrophenyl)quinazoline (28): Yield: 75% (0.20 g). Yellow solid, m.p. 217 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.12 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 6.71 (s, 1 H, vinylic H), 7.80–7.88 (m, 1 H, Ar-H), 8.11–8.19 (m, 2 H, 8-H, Ar-H), 8.49–8.53 (m, 1 H, Ar-H), 8.64 (dd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 9.4 Hz, 1 H, 7-H), 8.70–8.72 (m, 1 H, Ar-H), 8.85 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.0 (CH_3), 28.6 (CH_3), 118.8 (C), 122.9 (CH), 124.5 (CH), 124.9 (CH), 125.3 (CH), 127.3 (CH), 130.1 (CH), 130.9 (CH), 135.5 (CH), 138.0 (C), 145.4 (C), 148.8 (C), 152.9 (C), 154.2 (C), 164.3 (C), 167.3 (C) ppm. $C_{18}H_{14}N_4O_4$ (350.33): calcd. C 61.71, H 4.03, N 15.99; found C 61.53, H 4.03, N 15.94.

4-(4-Methoxyphenyl)-2-(2-methylprop-1-enyl)-6-nitroquinazoline (29): Yield: 64% (0.16 g). Yellow solid, m.p. 175 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.09 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 3.94 (s, 3 H, OCH_3), 6.68 (s, 1 H, vinylic H), 7.14 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 3′,5′-H), 7.81 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 2′,6′-H), 8.08 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 8-H), 8.56 (dd, $^4J_{H,H}$ = 2.7 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 7-H), 9.01 (d, $^4J_{H,H}$ = 2.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 20.9 (CH_3), 28.5 (CH_3), 55.6 (OCH_3), 114.6 (2 CH), 119.1 (C), 124.3 (CH), 124.8 (CH), 126.7 (CH), 128.8 (C), 130.2 (CH), 131.9 (2 CH), 145.0 (C), 151.7 (C), 154.2 (C), 162.0 (C), 164.2 (C), 169.3 (C) ppm. $C_{19}H_{17}N_3O_3$ (335.36): calcd. C 68.05, H 5.11, N 12.53; found C 67.61, H 5.17, N 12.42.

2-(2-Methylprop-1-enyl)-6-nitro-4-[3-(trifluoromethyl)phenyl]quinazoline (30): Yield: 76% (0.22 g). Yellow solid, m.p. 152 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.11 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 6.71 (s, 1 H, vinylic H), 7.73–7.81 (m, 1 H, Ar-H), 7.89–8.00 (m, 2 H, Ar-H), 8.11 (s, 1 H, Ar-H), 8.15 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 8-H), 8.62 (dd, $^4J_{H,H}$ = 2.2 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 7-H), 8.88 (d, $^4J_{H,H}$ = 2.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 20.9 (CH_3), 28.6 (CH_3), 119.0 (CH), 123.3 (CH), 124.6 (CH), 126.9 (CH), 127.1 (CH), 127.4 (CH), 129.1 (C), 129.5 (CH), 130.7 (CH), 131.9 (C), 133.1 (C), 137.2 (C), 145.3 (C), 152.5 (C), 154.2 (C), 164.3 (C), 168.3 (C) ppm. $C_{19}H_{14}F_3N_3O_2$ (373.33): calcd. C 61.13, H 3.78, N 11.26; found C 61.10, H 3.79, N 11.28.

2-(2-Methylprop-1-enyl)-6-nitro-4-(3,4,5-trimethoxyphenyl)quinazoline (31): Yield: 66% (0.2 g). Yellow solid, m.p. 191 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.11 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 3.95 (s, 6 H, OCH_3), 3.99 (s, 3 H, OCH_3), 6.70 (s, 1 H, vinylic H), 7.05 (s, 2 H, 2′,6′-H), 8.11 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, 8-H), 8.59 (dd, $^4J_{H,H}$ = 2.5 Hz, $^3J_{H,H}$ = 9.5 Hz, 1 H, 7-H), 9.11 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 20.9 (CH_3), 28.5 (CH_3), 56.4 (2 OCH_3), 61.1 (OCH_3), 107.6 (2 CH), 119.1 (C), 124.1 (CH), 124.9 (CH), 126.7 (CH), 130.4 (CH), 131.5 (C), 140.6 (C), 145.1 (C), 151.7 (C), 153.7 (2 C), 154.3 (C), 164.2 (C), 169.3 (C) ppm. $C_{21}H_{21}N_3O_5$ (395.41): calcd. C 63.79, H 5.35, N 10.63; found C 63.41, H 5.29, N 10.22

2-(Methoxymethyl)-6-nitro-4-phenylquinazoline (32): Yield: 88% (0.19 g). Rose solid, m.p. 164 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.67 (s, 3 H, OCH_3), 4.98 (s, 2 H, CH_2), 7.63–7.66 (m, 3 H, 3′,4′,5′-H), 7.78–7.83 (m, 2 H, 2′,6′-H), 8.33 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 8-H), 8.65 (dd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 9.2 Hz, 1 H, 7-H), 9.05 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 59.5 (OCH_3), 75.5 (CH_2), 120.8 (C), 124.1 (CH), 127.1 (CH), 129.1 (2 CH), 130.0 (2 CH), 130.9 (CH), 131.0 (CH), 135.7 (C), 145.9 (C), 153.7 (C), 165.9 (C), 170.9 (C) ppm. $C_{16}H_{13}N_3O_3$ (295.29): calcd. C 65.08, H 4.44, N 14.23; found C 65.05, H 4.34, N 14.34.

4-(4-Chlorophenyl)-2-(methoxymethyl)-6-nitroquinazoline (33): Yield: 75% (0.18 g). Grey solid, m.p. 209 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.67 (s, 3 H, OCH_3), 4.98 (s, 2 H, CH_2), 7.64 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 3′,5′-H), 7.77 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 2′,6′-H), 8.38 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, 8-H), 8.68 (dd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 9.4 Hz, 1 H, 7-H), 9.01 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 59.5 (OCH_3), 75.5 (CH_2), 120.6 (C), 123.6 (CH), 127.3 (CH), 129.5 (2 CH), 131.1 (CH), 131.4 (2 CH), 134.1 (C), 137.7 (C), 146.0 (C), 153.8 (C), 165.9 (C), 169.7 (C) ppm. $C_{16}H_{12}ClN_3O_3$ (329.74): calcd. C 58.28, H 3.67, N 12.74; found C 58.58, H 3.72, N 12.63.

4-(4-Fluorophenyl)-2-(methoxymethyl)-6-nitroquinazoline (34): Yield: 76% (0.18 g). Grey solid, m.p. 208 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.67 (s, 3 H, OCH_3), 4.97 (s, 2 H, CH_2), 7.30–7.39 (m, 2 H, 3′,5′-H), 7.80–7.89 (m, 2 H, 2′,6′-H), 8.34 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 8-H), 8.68 (dd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7-H), 9.01 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 59.5 (OCH_3), 75.5 (CH_2), 116.4 (2 CH), 120.7 (C), 123.8 (CH), 127.3 (CH), 131.0 (CH), 131.9 (C), 132.3 (2 CH), 146.0 (C), 153.8 (C), 164.6 (C), 165.9 (C), 169.7 (C) ppm. $C_{16}H_{12}FN_3O_3$ (313.28): calcd. C 61.34, H 3.86, N 13.41; found C 61.32, H 3.95, N 13.47.

2-(Methoxymethyl)-6-nitro-4-(*o*-tolyl)quinazoline (35): Yield: 82% (0.19 g). Rose solid, m.p. 104 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.17 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 4.98 (s, 2 H, CH_2), 7.31–7.53 (m, 4 H, 3′,4′,5′,6′-H), 8.33 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 8-H), 8.59 (d, $^4J_{H,H}$ = 2.3 Hz, 1 H, 5-H), 8.66 (dd, $^4J_{H,H}$ = 2.3 Hz, $^3J_{H,H}$ = 9.2 Hz, 1 H, 7-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 19.9 (CH_3), 59.5 (OCH_3), 75.5 (CH_2), 121.9 (C), 124.0 (CH), 126.2 (CH), 127.4 (CH), 129.5 (CH), 130.3 (CH), 130.9 (CH), 131.3 (CH), 134.9 (C), 136.2 (C), 145.9 (C), 153.2 (C), 166.0 (C), 172.5 (C) ppm. $C_{17}H_{15}N_3O_3$ (309.32): calcd. C 66.01, H 4.89, N 13.58; found C 65.99, H 4.97, N 13.68.

2-(Methoxymethyl)-4-(5-methylthiophen-2-yl)-6-nitroquinazoline (36): Yield: 63% (0.15 g). Yellow solid, m.p. 181 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.64 (s, 3 H, thiophenyl CH_3), 3.66 (s, 3 H, OCH_3), 4.90 (s, 2 H, CH_2), 7.01 (d, $^3J_{H,H}$ = 3.6 Hz, 1 H, 4′-H), 7.78 (d, $^3J_{H,H}$ = 3.6 Hz, 1 H, 3′-H), 8.25 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 8-H), 8.64 (dd, $^4J_{H,H}$ = 2.1 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 7-H), 9.43 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 15.7 (CH_3), 59.4 (OCH_3), 75.3 (CH_2), 119.4 (C), 123.4 (CH), 126.9 (CH), 127.7 (CH), 130.9 (CH), 133.3 (CH), 137.4 (C), 146.0 (C), 148.4 (C), 154.2 (C), 162.5 (C), 165.8 (C) ppm. $C_{15}H_{13}N_3O_3S$ (315.35): calcd. C 57.13, H 4.16, N 13.33; found C 57.10, H 4.16, N 13.30.

4-(Furan-2-yl)-2-(methoxymethyl)-6-nitroquinazoline (37): Yield: 80% (0.17 g). Yellow solid, m.p. 152 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.66 (s, 3 H, OCH_3), 4.90 (s, 2 H, CH_2), 6.73–6.75 (m, 1 H, 4′-H), 7.75 (d, $^3J_{H,H}$ = 3.5 Hz, 1 H, 3′-H), 7.92 (m, 1 H, 5′-H), 8.22 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, 8-H), 8.63 (dd, $^4J_{H,H}$ = 2.1 Hz, $^3J_{H,H}$ = 9.1 Hz, 1 H, 7-H), 9.91 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 59.4 (OCH_3), 75.4 (CH_2), 113.0 (CH), 118.3 (CH), 118.4 (C), 124.3 (CH), 127.0 (CH), 130.7 (CH), 145.9 (C), 147.5 (CH), 152.7 (C), 154.4 (C),

157.0 (C), 165.9 (C) ppm. $C_{14}H_{11}N_3O_4$ (285.25): calcd. C 58.95, H 3.89, N 14.73; found C 58.75, H 3.97, N 14.67.

2-(Methoxymethyl)-6-nitro-4-(3-nitrophenyl)quinazoline (38): Yield: 67% (0.17 g). Rose solid, m.p. 171 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.67 (s, 3 H, OCH_3), 4.98 (s, 2 H, CH_2), 7.82–7.90 (m, 1 H, Ar-H), 8.11–8.15 (m, 1 H, Ar-H), 8.37 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, 8-H), 8.49–8.54 (m, 1 H, Ar-H), 8.69–8.74 (m, 2 H, 7-H, Ar-H), 8.91 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 59.5 (OCH_3), 75.4 (CH_2), 120.4 (C), 122.9 (CH), 125.0 (CH), 125.6 (CH), 127.7 (CH), 130.3 (CH), 131.4 (CH), 135.6 (CH), 137.4 (C), 146.2 (C), 148.8 (C), 153.8 (C), 166.1 (C), 168.3 (C) ppm. $C_{16}H_{12}N_4O_5$ (340.29): calcd. C 56.47, H 3.55, N 16.46; found C 56.21, H 3.53, N 16.43.

2-(Methoxymethyl)-4-(4-methoxyphenyl)-6-nitroquinazoline (39): Yield: 87% (0.21 g). Brown solid, m.p. 148 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.66 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.96 (s, 2 H, CH_2), 7.15 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 3′,5′-H), 7.81 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 2′,6′-H), 8.28 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 8-H), 8.64 (dd, $^4J_{H,H}$ = 3.4 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 7-H), 9.09 (d, $^4J_{H,H}$ = 3.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 55.6 (OCH_3), 59.5 (OCH_3), 75.6 (CH_2), 114.7 (2 CH), 120.7 (C), 124.3 (CH), 126.9 (CH), 128.2 (C), 130.8 (CH), 132.0 (2 CH), 145.8 (C), 154.0 (C), 162.2 (C), 165.9 (C), 170.2 (C) ppm. $C_{17}H_{15}N_3O_4$ (325.32): calcd. C 62.76, H 4.65, N 12.92; found C 62.39, H 4.64, N 13.01.

2-(Methoxymethyl)-6-nitro-4-[3-(trifluoromethyl)phenyl]quinazoline (40): Yield: 83% (0.22 g). Rose solid, m.p. 105 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.68 (s, 3 H, OCH_3), 4.99 (s, 2 H, CH_2), 7.75–7.83 (m, 1 H, Ar-H), 7.91–8.00 (m, 2 H, Ar-H), 8.10 (br. s, 1 H, Ar-H), 8.36 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, 8-H), 8.70 (dd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 9.4 Hz, 1 H, 7-H), 8.94 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 59.5 (OCH_3), 75.5 (CH_2), 120.6 (C), 123.4 (CH), 126.9 (CH), 127.5 (CH), 127.7 (CH), 129.1 (C), 129.6 (CH), 131.3 (CH), 131.9 (C), 133.2 (CH), 136.5 (C), 146.1 (C), 153.8 (C), 166.0 (C), 169.3 (C) ppm. $C_{17}H_{12}F_3N_3O_3$ (363.29): calcd. C 56.20, H 3.33, N 11.57; found C 56.06, H 3.39, N 11.42.

2-(Methoxymethyl)-6-nitro-4-(3,4,5-trimethoxyphenyl)quinazoline (41): Yield: 80% (0.23 g). Rose solid, m.p. 173 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 3.68 (s, 3 H, OCH_3), 3.95 (s, 6 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.98 (s, 2 H, CH_2), 7.02 (s, 2 H, 2′,6′-H), 8.33 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, 8-H), 8.67 (dd, $^4J_{H,H}$ = 2.8 Hz, $^3J_{H,H}$ = 9.1 Hz, 1 H, 7-H), 9.16 (d, $^4J_{H,H}$ = 2.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 56.5 (2 OCH_3), 59.5 (OCH_3), 61.1 (OCH_3), 75.5 (CH_2), 107.7 (2 CH), 108.1 (C), 120.7 (C), 124.2 (CH), 127.2 (CH), 130.8 (C), 131.0 (CH), 132.1 (C), 145.9 (C), 153.8 (C), 153.9 (C), 165.9 (C), 170.5 (C) ppm. $C_{19}H_{19}N_3O_6$ (385.37): calcd. C 59.22, H 4.97, N 10.90; found C 59.08, H 5.04, N 10.82.

4-Phenyl-2-(*p*-tosylmethyl)quinazoline (42): Yield: 94% (0.27 g). Yellow solid, m.p. 156 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.43 (s, 3 H, tosyl CH_3), 4.96 (s, 2 H, CH_2), 7.26 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, tosyl 3,5-H), 7.53 (br. s, 5 H, 2′,3′,4′,5′,6′-H), 7.59–7.63 (m, 1 H, Ar-H), 7.69 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, tosyl 2,6-H), 7.89–7.96 (m, 1 H, Ar-H), 8.06–8.13 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.6 (CH_3), 66.1 (CH_2), 121.5 (C), 127.0 (CH), 128.3 (CH), 128.5 (2 CH), 128.8 (3 CH), 129.5 (2 CH), 130.1 (2 CH), 130.3 (CH), 134.1 (CH), 136.4 (C), 136.5 (C), 144.6 (C), 151.4 (C), 155.2 (C), 168.8 (C) ppm. $C_{22}H_{18}N_2O_2S$ (374.46): calcd. C 70.57, H 4.85, N 7.48; found C 70.21, H 4.76, N 7.39.

4-(4-Chlorophenyl)-2-(*p*-tosylmethyl)quinazoline (43): Yield: 91% (0.28 g). Yellow solid, m.p. 160 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.43 (s, 3 H, tosyl CH_3), 4.93 (s, 2 H, CH_2), 7.25 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, tosyl 3,5-H), 7.50 (br. s, 4 H, Ar-H), 7.60–7.70 (m, 3 H, Ar-H), 7.89–7.96 (m, 1 H, Ar-H), 8.05–8.09 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.6 (CH_3), 66.0 (CH_2), 121.3 (C), 126.5 (CH), 128.5 (CH), 128.7 (2 CH), 128.8 (2 CH), 128.9 (CH), 129.5 (2 CH), 131.4 (2 CH), 134.3 (CH), 134.9 (C), 136.4 (C), 136.8 (C), 144.7 (C), 151.4 (C), 155.2 (C), 167.5 (C) ppm. $C_{22}H_{17}ClN_2O_2S$ (408.90): calcd. C 64.62, H 4.19, N 6.85; found C 64.37, H 4.46, N 6.57.

4-(4-Fluorophenyl)-2-(*p*-tosylmethyl)quinazoline (44): Yield: 79% (0.24 g). Yellow solid, m.p. 150 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.43 (s, 3 H, tosyl CH_3), 4.94 (s, 2 H, CH_2), 7.17–7.28 (m, 4 H, Ar-H), 7.55–7.65 (m, 3 H, Ar-H), 7.67–7.71 (m, 2 H, Ar-H), 7.89–7.97 (m, 1 H, Ar-H), 8.06–8.10 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.6 (CH_3), 65.8 (CH_2), 115.5 (CH), 116.0 (CH), 121.4 (C), 126.7 (CH), 128.5 (CH), 128.6 (CH), 128.8 (2 CH), 129.6 (2 CH), 132.3 (2 CH), 132.5 (C), 134.4 (CH), 136.4 (C), 144.7 (C), 151.1 (C), 155.0 (C), 164.2 (C), 167.8 (C) ppm. $C_{22}H_{17}FN_2O_2S$ (392.45): calcd. C 67.33, H 4.37, N 7.14; found C 66.96, H 4.48, N 7.07.

4-(*o*-Tolyl)-2-(*p*-tosylmethyl)quinazoline (45): Yield: 70% (0.21 g). Yellow solid, m.p. 122 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.03 (s, 3 H, tolyl CH_3), 2.38 (s, 3 H, tosyl CH_3), 4.94 (s, 2 H, CH_2), 7.10–7.44 (m, 6 H, Ar-H), 7.50–7.70 (m, 4 H, Ar-H), 7.87–7.92 (m, 1 H, Ar-H), 8.05 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 19.6 (CH_3), 21.5 (CH_3), 66.1 (CH_2), 122.4 (C), 125.5 (CH), 126.9 (CH), 128.1 (CH), 128.5 (2 CH), 128.6 (CH), 129.2 (CH), 129.3 (CH), 129.4 (2 CH), 130.6 (CH), 134.1 (CH), 135.8 (C), 136.1 (C), 136.3 (C), 144.5 (C), 150.9 (C), 155.1 (C), 170.3 (C) ppm. $C_{23}H_{20}N_2O_2S$ (388.48): calcd. C 71.11, H 5.19, N 7.21; found C 70.88, H 5.32, N 6.95.

4-(5-Methylthiophen-2-yl)-2-(*p*-tosylmethyl)quinazoline (46): Yield: 78% (0.27 g). Yellow solid, m.p. 135 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.38 (s, 3 H, tosyl CH_3), 2.55 (s, 3 H, thiophenyl CH_3), 4.85 (s, 2 H, CH_2), 6.86 (m, 1 H, 4′-H), 7.20–7.26 (m, 2 H, tosyl 3,5-H), 7.53–7.67 (m, 4 H, Ar-H), 7.81–7.89 (m, 1 H, Ar-H), 7.97 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H), 8.42 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 15.5 (CH_3), 21.5 (CH_3), 65.9 (CH_2), 120.1 (C), 125.9 (CH), 126.8 (CH), 128.2 (CH), 128.6 (2 CH), 128.9 (CH), 129.5 (2 CH), 132.2 (CH), 133.7 (CH), 136.1 (C), 137.9 (C), 144.4 (C), 146.6 (C), 151.7 (C), 154.9 (C), 160.5 (C) ppm. $C_{21}H_{18}N_2O_2S_2$ (394.51): calcd. C 63.93, H 4.60, N 7.10; found C 63.58, H 4.60, N 6.97.

4-(Furan-2-yl)-2-(*p*-tosylmethyl)quinazoline (47): Yield: 91% (0.22 g). Yellow solid, m.p. 149 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.40 (s, 3 H, tosyl CH_3), 4.87 (s, 2 H, CH_2), 6.59–6.61 (m, 1 H, 4′-H), 7.15 (d, $^3J_{H,H}$ = 3.6 Hz, 1 H, 3′-H), 7.24 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, tosyl 3,5-H), 7.61–7.97 (m, 6 H, Ar-H), 8.88 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.5 (CH_3), 66.0 (CH_2), 112.3 (CH), 116.8 (CH), 119.3 (C), 126.6 (CH), 128.4 (CH), 128.8 (3 CH), 129.4 (2 CH), 133.9 (CH), 136.3 (C), 144.4 (C), 146.2 (CH), 152.2 (C), 153.2 (C), 155.2 (2 C) ppm. $C_{20}H_{16}N_2O_3S$ (364.42): calcd. C 65.92, H 4.43, N 7.69; found C 65.59, H 4.58, N 7.42.

4-(3-Nitrophenyl)-2-(*p*-tosylmethyl)quinazoline (48): Yield: 72% (0.23 g). Yellow solid, m.p. 132 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.41 (s, 3 H, tosyl CH_3), 4.95 (s, 2 H, CH_2), 7.28 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, tosyl 3,5-H), 7.65–7.76 (m, 4 H, Ar-H), 7.92–8.02 (m, 3 H, Ar-H), 8.12 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, Ar-H), 8.37–8.41 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ =

21.6 (CH_3), 66.1 (CH_2), 121.1 (C), 124.8 (CH), 124.9 (CH), 125.9 (CH), 128.7 (2 CH), 129.1 (CH), 129.4 (CH), 129.6 (2 CH), 129.7 (CH), 134.6 (CH), 136.0 (CH), 136.3 (C), 138.2 (C), 145.1 (C), 148.4 (C), 151.8 (C), 155.4 (C), 165.9 (C) ppm. $C_{22}H_{17}N_3O_4S$ (419.45): calcd. C 63.00, H 4.09, N 10.02; found C 62.68, H 4.32, N 9.59.

4-(4-Methoxyphenyl)-2-(*p*-tosylmethyl)quinazoline (49): Yield: 67% (0.21 g). Yellow solid, m.p. 171 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.41 (s, 3 H, tosyl CH_3), 3.89 (s, 3 H, OCH_3), 4.92 (s, 2 H, CH_2), 7.01 (d, $^3J_{H,H}$ = 9.2 Hz, 2 H, 3′,5′-H), 7.24 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, tosyl 3,5-H), 7.52 (d, $^3J_{H,H}$ = 9.2 Hz, 2 H, 2′,6′-H), 7.56–7.60 (m, 1 H, Ar-H), 7.66 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, tosyl 2,6-H), 7.84–7.92 (m, 1 H, Ar-H), 8.02 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H), 8.13 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.5 (CH_3), 55.4 (OCH_3), 66.1 (CH_2), 113.9 (2 CH), 121.4 (C), 126.9 (CH), 127.9 (CH), 128.7 (2 CH), 128.8 (CH), 128.9 (C), 129.4 (2 CH), 131.8 (2 CH), 133.8 (CH), 136.4 (C), 144.5 (C), 151.6 (C), 155.1 (C), 161.4 (C), 168.0 (C) ppm. $C_{23}H_{20}N_2O_3S$ (404.48): calcd. C 68.30, H 4.98, N 6.93; found C 67.96, H 4.92, N 6.79.

2-(*p*-Tosylmethyl)-4-[3-(trifluoromethyl)phenyl]quinazoline (50): Yield: 74% (0.24 g). Yellow solid, m.p. 105 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.41 (s, 3 H, tosyl CH_3), 4.96 (s, 2 H, CH_2), 7.26 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, tosyl 3,5-H), 7.67–7.83 (m, 7 H, Ar-H), 7.92–8.03 (m, 2 H, Ar-H), 8.13 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.5 (CH_3), 66.0 (CH_2), 121.3 (C), 123.8 (C), 126.2 (CH), 126.6 (CH), 126.8 (CH), 128.7 (2 CH), 128.8 (CH), 129.0 (CH), 129.1 (CH), 129.5 (2 CH), 131.2 (C), 133.4 (CH), 134.4 (CH), 136.3 (C), 137.3 (C), 144.9 (C), 151.6 (C), 155.3 (C), 167.1 (C) ppm. $C_{23}H_{17}F_3N_2O_2S$ (442.45): calcd. C 62.44, H 3.87, N 6.33; found C 61.99, H 4.11, N 6.18.

2-(*p*-Tosylmethyl)-4-(3,4,5-trimethoxyphenyl)quinazoline (51): Yield: 70% (0.25 g). Yellow solid, m.p. 148 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 2.41 (s, 3 H, tosyl CH_3), 3.90 (s, 6 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.95 (s, 2 H, CH_2), 6.88 (s, 2 H, 2′,6′-H), 7.24–7.28 (m, 2 H, tosyl 3,5-H), 7.61–7.73 (m, 3 H, Ar-H), 7.89–7.96 (m, 1 H, Ar-H), 8.05 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H), 8.18 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = 21.6 (CH_3), 56.5 (2 OCH_3), 61.0 (OCH_3), 66.0 (CH_2), 107.8 (2 CH), 121.5 (C), 126.9 (CH), 128.2 (CH), 128.7 (2 CH), 128.8 (CH), 129.5 (2 CH), 131.8 (C), 134.1 (CH), 136.6 (C), 140.2 (C), 144.6 (C), 151.4 (C), 153.4 (2 C), 155.1 (C), 168.6 (C) ppm. $C_{25}H_{24}N_2O_5S$ (464.53): calcd. C 64.64, H 5.21, N 6.03; found C 64.41, H 5.36, N 6.11.

Acknowledgments

This work was supported by the Centre Nacional de la Recherche Scientifique (CNRS) and the University of Aix-Marseille II. The authors thank P. Verhaeghe for his cooperation, V. Remusat for recording the ^{1}H and ^{13}C NMR spectra and G. Lanzada for his technical support.

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Received: April 16, 2009
Published Online: July 8, 2009

