Microwave-assisted synthesis in aqueous medium of new quinazoline derivatives as anticancer agent precursors

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Fast and eco-friendly microwave-irradiated reactions permitting the "green synthesis" of new 2-substituted quinazoline derivatives in aqueous medium *via* *S*-alkylation or $S_{RN}1$ reaction from 2-chloromethyl-3-methylquinazolin-4(3*H*)-one derivatives with different benzenesulfinic acids and nitronate anions, are reported herein.

Introduction

Within the last few years, green chemistry has become a major interest for the chemistry community.[1] The investigations and applications of green chemistry principles have led to the development of cleaner and more benign chemical processes, many new technologies being developed each year.[2]

In most chemical processes, major adverse effects towards the environment are due mainly to the consumption of energy for heating. To overcome this problem it is highly desirable to develop efficient methods that use alternative energy sources such as microwave irradiation, to facilitate chemical reactions. At the same time, water can undoubtedly be considered as the cleanest solvent available for chemists.

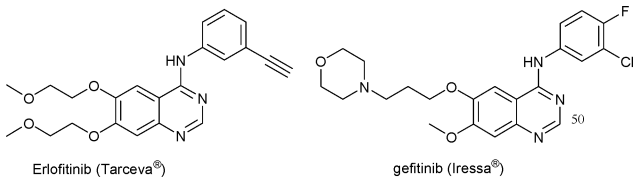
Recently, the combination of these two prominent green chemistry principles, "microwaves" and "water", has become very popular and received substantial interest.[3]

On the other hand, quinazoline derivatives have shown a remarkable activity as antitubercular, anti-fungal, antimalarial and anticancer agents.[4] Indeed, quinazoline derivatives have been shown to be efficient and highly selective inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) *via* a competitive mechanism with the binding of ATP. These compounds are of potential interest as anticancer drugs, because EGFR is known to be over-expressed in many clinical cancers, and its overexpression is associated with poor prognosis.[5]

Characterization of molecules which are likely to interact with the EGFR and to inhibit selectively this tyrosine kinase activity, such as gefitinib (Iressa®) or erlofitinib (Tarceva®), has given rise to important hopes for both patients and clinitians (Scheme 1).

The growing medicinal importance of these heterocycles perpetuates to provide strong international effort for the development of synthetic methods for their preparation.

We have recently developed a new microwave-assisted method for synthesizing compounds in water.[6] The biological activity of the quinazoline derivatives led us to develop the synthesis of new



Scheme 1

2-subtituted quinazolines, under microwave irradiation, in aqueous medium. Substituents were selected with different electronic and solubility characteristics, with the aim of investigating the substituent effects at the 2-position.

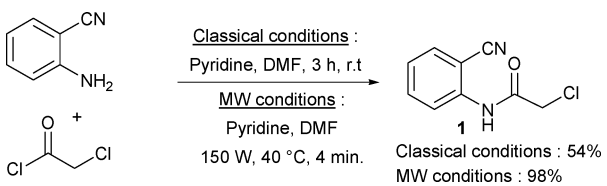
Results and discussion

The majority of synthetic routes to 2-substituted quinazolin-4(3*H*)-ones is based on Niementowski's reaction, which involves the fusion (130–150 °C) of anthranilic acid analogues with amides, proceeding *via* an *o*-amidobenzamide intermediate.[7] The reaction yield in such conditions is variable and sometimes, complicated mixtures of carbonaceous compounds and impurities are formed, requiring a purification step with chromatography column.

For the above mentioned reasons, we studied extensively the synthesis of 2-chloromethylquinazolin-4(3*H*)-one **2** under microwave irradiation by various methods.

Conventional synthesis of **2** involves two steps, condensation of 2-aminobenzonitrile with an excess of chloroacetylchloride, affording 2-chloro-*N*-(2-cyanophenyl)acetamide **1**,[8] followed by Radziszewski's reaction using UHP (urea hydrogen peroxide) as a mild, safe and non-hazardous oxidizing agent, leading to 2-chloromethylquinazolin-4(3*H*)-one **2**.[9]

We initialy started by conducting the first step in both classical and microwave-assisted conditions (Scheme 2).



Scheme 2

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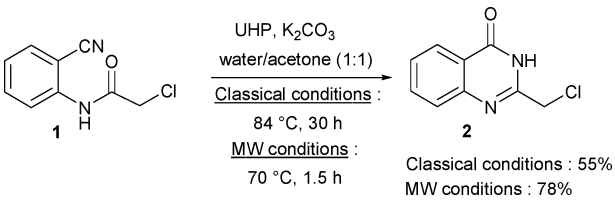
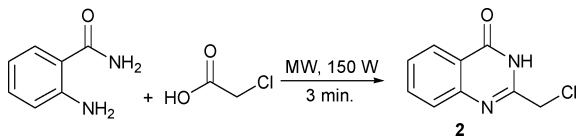
In classical conditions, the product **1** is obtained in 54% yield after 3 h reaction time, whereas under microwave irradiation, the same product is isolated in 98% yield after only 4 minutes reaction time. We then compared classical conditions *versus* microwave-assisted conditions toward a second reaction step.

In classical conditions (30 h at 84 °C), the derivative **2** is obtained in 55% yield, and under microwave irradiation (1.5 h reaction time at 70 °C, measured by an infrared detector), the same product **2** is prepared in 78% yield (Scheme 3).



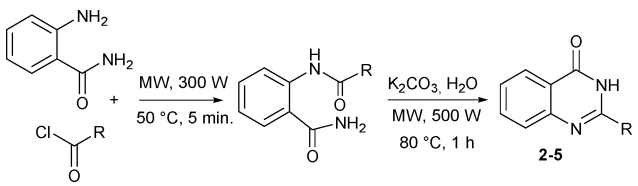
Scheme 3

Recently in the literature,[10] another method described the one pot solvent-free synthesis of **2**, from 2-aminobenzamide and 2-chloroacetic acid, under microwave irradiation (Scheme 4). This method consists in the fusion of 2-chloroacetic acid with 2-aminobenzamide. After several tests, we could not isolate the desired compound, using this method.



Scheme 4

From the same 2-aminobenzamide, reacting with an excess of chloroacetylchloride under microwave irradiation, we formed the intermediate *N*-(2-aminophenyl)-2-chloroacetamide. The crude product was isolated and directly engaged in a cyclization, with K_2CO_3 in water, under microwave irradiation, leading to the expected product **2**, as shown in Scheme 5.



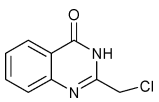
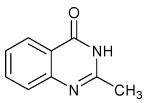
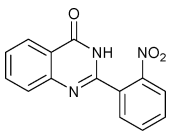
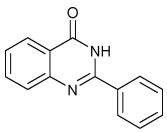
Scheme 5

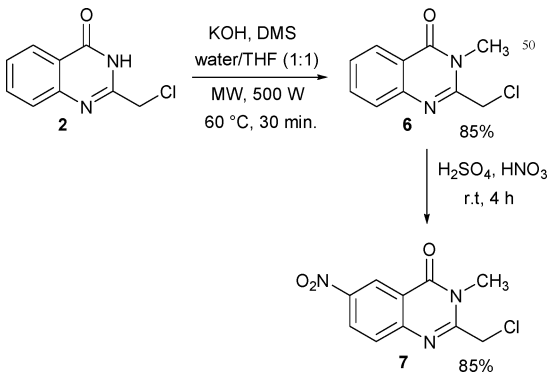
This method was generalized with various acid chlorides, enabling us to obtain compounds **2–5** in good yields (Table 1).

The 2-chloromethylquinazolin-4(3*H*)-one **2** can be methylated by using dimethylsulfate (DMS) in a water/THF (1:1) mixture and then, nitrated using the HNO_3–H_2SO_4 mixture, leading to 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one **7** in 63% global yield (Scheme 6).

Aiming at avoiding the last nitration step, we investigated another synthetic procedure for the preparation of 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one **7**, starting from the 2-amino-5-nitrobenzonitrile. Unfortunately, the yields we

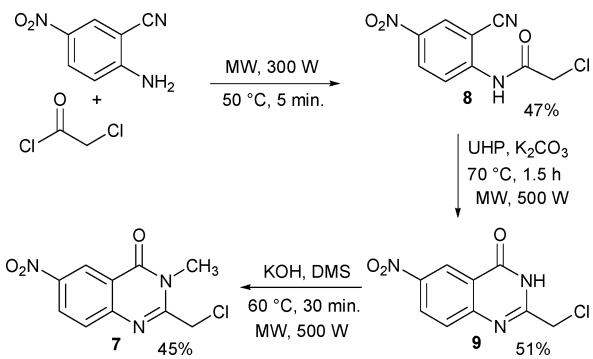
Table 1 Reactions of 2-aminobenzamide with various acid chlorides

N°	Product	Yield
2		87
3		81
4		83
5		72



Scheme 6

obtained, were appreciably lower than those previously observed (Scheme 7). However, this method permitted us to confirm the position of the nitro group on the quinazoline ring, firstly determined by NMR study.

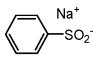
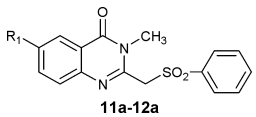
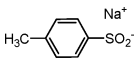
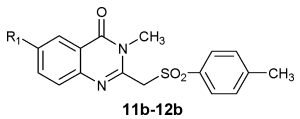
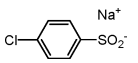
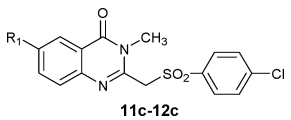
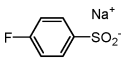
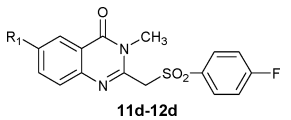
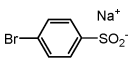
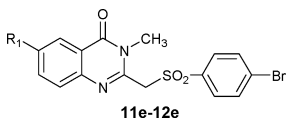
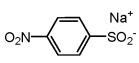
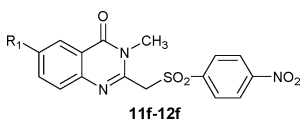
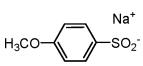
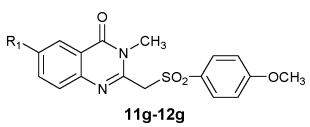
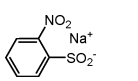
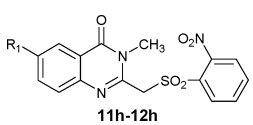
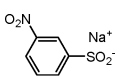
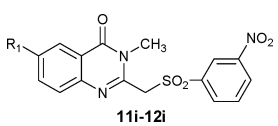
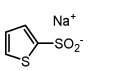
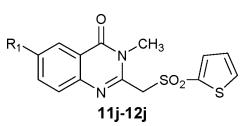


Scheme 7

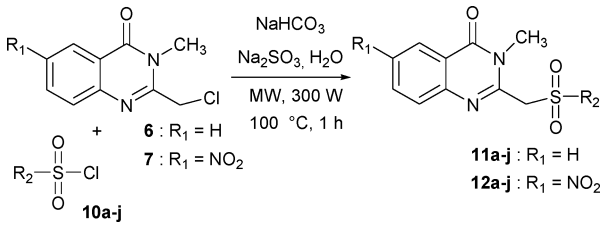
Recently, we described a "green chemistry procedure" allowing the substitution of a chloride atom by a sulfone group.[6] This

ecofriendly methodology in aqueous phase using microwave technology to ensure respect of the environment, was developed for the preparation of new 2-substituted quinazolines (Table 2). Experimentaly, a simple addition of both 2-chloromethyl-3-methylquinazolin-4(3*H*)-one derivatives **6**, **7** and the sodium salt of benzenesulfinic acid **10a–j** in an aqueous solution gave the corresponding *S*-alkylated product **11a–j** and **12a–j** in high yields (Scheme 8).

Table 2 Reactions of 2-chloromethyl-3-methyl quinazolin-4(3*H*)-one derivatives **6**, **7** with benzenesulfinic acid anions **10a–j**[a]

Anion	Product	Yield $R_1 = H$	Yield $R_1 = NO_2$
 **10a**	 **11a-12a**	68	95
 **10b**	 **11b-12b**	71	91
 **10c**	 **11c-12c**	66	71
 **10d**	 **11d-12d**	67	67
 **10e**	 **11e-12e**	67	69
 **10f**	 **11f-12f**	60	63
 **10g**	 **11g-12g**	—	75
 **10h**	 **11h-12h**	—	59
 **10i**	 **11i-12i**	57	—
 **10j**	 **11j-12j**	54	—

[a] Microwave instrumentation: the temperature was measured by an infrared detector, and the microwave pulsed power was regulated by the software of terminal 320 for Ethos start, Milestone Inc. Reaction conditions: 1 h, microwave power 300 W, 100 °C.

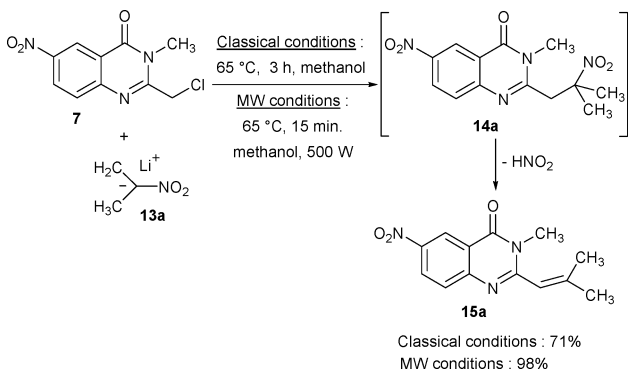


Scheme 8

When the same reaction was carried out under classical conditions (24 h, 100 °C), 2-chloromethyl-3-methyl quinazolin-4(3*H*)-one **6** reacted with the benzenesulfonyl chloride, leading to the same product **11a**, with a lower yield (70%).

The above results show the activation of the *S*-alkylation reaction by microwave heating.

In order to extend the chemical variability in position 2, we applied the microwave technology to the $S_{RN}1$ reaction in the quinazoline series. Thus, compound **7** was treated with 2-nitropropane anion **13a** to afford the ethylenic derivative **15a** as shown in Scheme 9.



Scheme 9

The *C*-alkylated product **14a** was not isolated because the nitrous acid elimination is very rapid in basic medium, due to the acidity of the methylene protons.

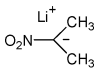
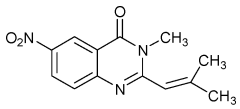
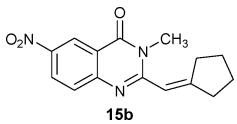
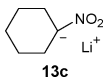
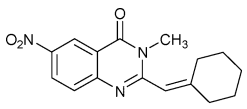
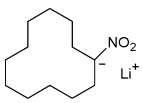
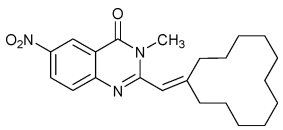
The best reaction yield (98%) of **15a** was obtained when the reaction was carried out under 500 W microwave power, during 15 minutes, in methanol using 3 equivalents of 2-nitropropane anion **13a**. The electron transfer mechanism was confirmed by complete inhibition studies.[11]

From these interesting results, we sought to generalize this $S_{RN}1$ reaction in the quinazoline series to various nitronate anions **13b–d** (Table 3).

It was described that the thermal effects and specific effects induced by the microwave field can be observed for polar mechanisms when the polarity is increased during the reaction, from the ground state (GS) towards the transition state (TS).[12]

We recently observed that the TS for *S*-alkylation reaction (S_N2 mechanism) involves loose ion pairs as a charge delocalised

Table 3 Reactions of 2-chloromethyl-3-methylquinazolin-4(3*H*)-one derivatives **7** with several nitronate anions **13a–d**[a]

Anion	Product	Yield
 **13a**	 **15a**	98
 **13b**	 **15b**	97
 **13c**	 **15c**	95
 **13d**	 **15d**	93

[a] Microwave instrumentation: the temperature was measured by an infrared detector, and the microwave pulsed power was regulated by the software of terminal 320 for Ethos start, Milestone Inc. Reaction conditions: 15 min, microwave power 500 W, 65 °C.

(soft) anion,[6] whereas the GS involves a neutral electrophile and tighter ion pair. During the course of the reaction, ionic dissociation is increased and that way, polarity is enhanced from GS to TS. Thus, a favourable microwave effect can be observed. It is the same for the $S_{RN}1$ reactions using charged species such as the nitroalkane lithium salts and radicals or radical anions derived from **7**.

All the quinazoline derivatives obtained are to be screened for their antitumor activity. Their cytotoxicity is under evaluation in triplicate on colon adenocarcinoma cell line (HT29 and SW620) and vulvar epidermoid carcinoma cell line (A431), in order to evaluate the activity of the prepared 2-substituted quinazolines on the EGFR signaling.

Conclusion

In the present study, we have investigated the preparation of new anticancer agent precursors in a quinazoline series. Using dedicated microwave irradiation in aqueous medium, the Niementowski reaction could be easily and rapidly performed, affording the intermediate 2-chloromethyl-6-nitroquinazolin-4(3*H*)-one **9** in very good yield. This compound served as a substrate for the synthesis of several new quinazolines, bearing various substituents in position 2. The present synthetic method is a simple, efficient, inexpensive and green approach for the preparation of 2-substituted quinazolines *via* *S*-alkylation or $S_{RN}1$ reactions in aqueous medium.

These new quinazoline derivatives could be employed as intermediates in the synthesis of more complex quinazolines, properly substituted in position 4, as potential inhibitors of the EGFR.

Experimental

General experimental

Melting points were determined on a Büchi B-540 and are uncorrected. Elemental analyses were performed by the Microanalyses center of the University of Aix-Marseille 3, France. Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker ARX 200 spectrometer. The ^{1}H chemical shifts are reported as ppm downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvent peak: $CDCl_3$ (76.9 ppm) or DMSO-d_6 (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 were performed on 5 cm × 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 experiments, 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 fiber (ATC-FO 300).

In order to compare microwave irradiation with conventional heating, the reactions were performed under similar experimental conditions (amount of reactants and temperature) using a thermostated 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.

Experimental procedure

2-Chloro-*N*-(2-cyanophenyl)acetamide 1

Classical method.[8]

Microwave method. To a solution of 2-aminobenzonitrile (5 g, 42.2 mmol) in pyridine (10.2 mL, 126.7 mmol), chloroacetylchloride (5.7 mL, 71.8 mmol) diluted in DMF (48 mL) was added dropwise at 0 °C. The reaction mixture was irradiated in a microwave oven at 40 °C, for 4 min. at a power of 150 W. After cooling, 100 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave 8.05 g (98%) of white solid, mp 116 °C (Lit.[8] 115–116 °C). δ_H (200 MHz; $CDCl_3$) 4.26 (s, 2H, CH_2Cl), 7.21–7.28 (m, 1H, H ar), 7.59–7.67 (m, 2H, H ar), 8.38 (d, J = 8.8 Hz, 1H, H ar), 8.86 (bs, 1H, NH). δ_C (50 MHz; $CDCl_3$) 42.9, 102.9, 115.8, 121.1, 125.1, 132.4, 134.2, 139.3, 164.3.

2-Chloromethylquinazolin-4(*3H*)-one 2

To a mixture of **1** (5.76 g, 29.6 mmol) and acetone/H_2O (v/v 1:1, 160 mL) was added K_2CO_3 (0.8 g, 5.8 mmol) and UHP (5.6 g, 59.2 mmol). The reaction mixture was irradiated in a microwave oven at 70 °C, for 1.5 h at a power of 500 W. After cooling, 100 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave 4.49 g (78%) of white solid, mp 249–250 °C (Lit.[9] 247–248 °C). δ_H (200 MHz; DMSO-d_6) 4.55 (s, 2H, CH_2Cl), 7,51–7.58 (m, 1H, H ar), 7.68 (d, $J = 8.1$ Hz, 1H, H ar), 7.80–7.87 (m, 1H, H ar), 8.12 (d, $J = 8.1$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 43.4, 121.4, 126.0, 127.4, 134.8, 148.4, 152.5, 161.7.

General procedure for the synthesis of 2-chloromethylquinazolin-4(3*H*)-one 2–5, from 2-aminobenzamide, *via* the corresponding 2-amidobenzamide derivatives

First step: a mixture of 2-aminobenzamide (1 g, 7.40 mmol) and corresponding acid chloride derivative (6 eq) was irradiated in a microwave oven at 50 °C, for 5 min. at a power of 300 W. After cooling, 50 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). A white solid was obtained and directly engaged in the second step.

Second step: a mixture of the corresponding intermediate compound and K_2CO_3 (0.5 eq) in water (40 mL), was irradiated in a microwave oven at 80 °C for 1 h at a power of 500 W. After cooling, 60 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave the expected compound **2–5**.

2-Methylquinazolin-4(3*H*)-one 3

Light yellow solid, mp 230–231 °C, (Lit.[13] 229–230 °C). δ_H (200 MHz; $CDCl_3$) 2.26 (s, 3H, CH_3), 7.43–7.62 (m, 2H, H ar), 7.66–7.82 (m, 1H, H ar) 8.24 (d, $J = 8.1$ Hz, 1H, H ar), 11.09 (bs, 1H, NH). δ_C (50 MHz; $CDCl_3$) 24.1,126.9, 128.9, 130.0, 131.9, 135.0, 147.8, 154.5, 163.2.

2-(2-Nitrophenyl)quinazolin-4(3*H*)-one 4

Light yellow solid, mp 212 °C, (Lit.[14] 210–212 °C). δ_H (200 MHz; DMSO-d_6) 7.49–7.61 (m, 2H, H ar), 7.65 (d, $J = 8.4$ Hz, 1H, H ar) 7.81–7.95 (m, 4H, H ar), 8.21 (t, $J = 8.1$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 121.1, 124.4, 125.9, 127.0, 127.2, 129.2, 131.3, 131.7, 134.1, 134.7, 147.5, 148.5, 151.6, 161.5.

2-Phenylquinazolin-4(3*H*)-one 5

Light yellow solid, mp 241 °C, (Lit.[13] 241–242 °C). δ_H (200 MHz; $CDCl_3$) 7.48–7.60 (m, 4H, H ar), 7.78–7.91 (m, 2H, H ar), 8.24–8.35 (m, 3H, H ar). δ_C (50 MHz; $CDCl_3$) 120.8, 126.4, 126.8, 127.5, 127.5, 127.9, 129.0, 129.0, 131.7, 132.7, 134.9, 149.4, 151.8, 163.8.

2-Chloromethyl-3-methylquinazolin-4(3*H*)-one 6

2-Chloromethylquinazolin-4(3*H*)-one **2** (1.56 g, 8.02 mmol), dimethyl sulfate (1.52 ml, 16.04 mmol) and potassium hydroxide (0.78 g, 13.9 mmol) were intimately mixed in a solution THF/H_2O (v/v 1:1, 40 mL). The reaction mixture was irradiated in a microwave oven, at 60 °C, for 30 min. at a power of 500 W. After cooling, 60 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). The product was recrystallized from 2-propanol gave 1.43 g (85%) of yellow solid, mp 185 °C (Lit.[15] 182 °C), δ_H (200 MHz; $CDCl_3$) 3.77 (s, 3H, N-CH_3), 4.65 (s, 2H, CH_2Cl), 7,48–7.56 (m, 1H, H ar), 7.66–7.81 (m, 2H, H ar), 8.29 (dd, $J = 2.4$ Hz, $J = 8.2$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 30.7, 44.4, 120.8, 126.9, 127.4, 134.4, 146.6, 151.6, 162.1.

The same method was used to prepare compound **7** from **9**, by methylation.

2-Chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one 7

To a solution of 2-chloromethyl-3-methylquinazolin-4(3*H*)-one **6** (1.18 g, 5.65 mmol) in concentrated sulfuric acid (12.7 mL), fuming nitric acid (1.3 mL) was added dropwise at 0 °C. The reaction mixture was stirred at the room temperature for 4 h, poured into crushed ice (100 mL). A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave 1.22 g (85%) of yellow solid, mp 178–179 °C, (Found: C, 47.05; H, 3.24; N, 16.90. $C_{10}H_8ClN_3O_3$ requires C, 47.35; H, 3.18; N, 16.57%). δ_H (200 MHz; $CDCl_3$) 3.80 (s, 3H, N-CH_3), 4.66 (s, 2H, CH_2Cl), 7,82 (d, $J = 9.1$ Hz, 1H, H ar), 8.55 (dd, $J = 2.5$, $J = 9.1$ Hz, 1H, H ar), 9.15 (d, $J = 2.5$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 31.1, 44.1, 121.0, 123.6, 128.5, 129.2, 146.3, 150.6, 154.8, 161.1.

2-Chloro-*N*-(2-cyano-4-nitrophenyl)acetamide 8

A mixture of 2-amino-5-nitrobenzonitrile (1 g, 6.13 mmol) and corresponding acid chloride (6 eq) was irradiated in a microwave oven at 50 °C, for 5 min. at a power of 300 W. After cooling, 50 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in vacuum drying oven (dessicator cabinet). A brown solid was obtained in 47% yield and directly engaged in the second step, mp 159 °C (Lit.[16] 157–159 °C).

2-Chloromethyl-6-nitroquinazolin-4(3*H*)-one 9

To a mixture of 2-chloro-*N*-(2-cyano-4-nitrophenyl)acetamide **8** (0.5 g, 2.08 mmol) and acetone/H_2O (v/v 1:1, 20 mL) was added K_2CO_3 (0.06 g, 0.42 mmol) and UHP (0.4 g, 4.16 mmol). The reaction mixture was irradiated in a microwave oven at 70 °C, for 1.5 h at a power of 500 W. After cooling, 50 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). The product required was recrystallized from 2-propanol gave 0.25 g (51%) of yellow solid, mp 235 °C, (Found: C, 44.81; H, 2.61; N, 17.64. $C_9H_6ClN_3O_3$ requires C, 45.11; H, 2.52; N, 17.54%). δ_H (200 MHz; DMSO-d_6) 4.61 (s, 2H, CH_2Cl), 7.89 (d, $J = 8.9$ Hz, 1H, H ar), 8.57 (dd, $J = 2.7$,

$J = 8.9$ Hz, 1H, H ar), 8.81 (d, $J = 2.7$ Hz, 1H, H ar) δ_C (50 MHz; DMSO-d_6) 43.4, 121.9, 122.4, 129.0, 129.5, 145.8, 152.9, 156.5, 161.3.

General procedure for the synthesis of the sulfonylmethyl-quinazolin-4(3*H*)-one derivatives (11a–j and 12a–j)

The sodium salts were commercially available or prepared as previously described.[17]

Conventional conditions. To a solution of benzenesulfonyl chloride (2 eq), $NaHCO_3$ (0.34 g, 1.92 mmol), Na_2SO_3 (2 eq) in water (30 mL) at 100 °C, was added 2-chloromethyl-3-methylquinazolin-4(3*H*)-one **6** (0.2 g, 0.96 mmol). The reaction mixture was heated at 100 °C for 24 h and filtered. The precipitate was filtered, washed with 3 × 20 mL of water and dried in a low pressure drying oven. The product required **11a** was recrystallized from 2-propanol.

Microwave irradiation conditions. To a solution of substituted sulfonyl chloride (2 eq), $NaHCO_3$ (2 eq), Na_2SO_3 (2 eq) in water (30 mL) was added 2-chloromethyl-3-methylquinazolin-4(3*H*)-one **6** (0.2 g, 0.96 mmol) or 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one **7** (0.2 g, 0.79 mmol). 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 a vacuum drying oven (dessicator cabinet). The product required was recrystallized from 2-propanol.

3-Methyl-2-(phenylsulfonylmethyl)quinazolin-4(3*H*)-one 11a

White solid, mp 186 °C, (Found: C, 61.19; H, 4.47; N, 8.93. $C_{16}H_{14}N_2O_3S$ requires C, 61.13; H, 4.49; N, 8.91%). δ_H (200 MHz; $CDCl_3$) 3.85 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 7.34 (d, $J = 8.3$ Hz, 1H, H ar), 7.45–7.56 (m, 3H, H ar), 7.64–7.73 (m, 2H, H ar), 7.84 (m, 2H, H ar), 8.26 (dd, $J = 2.3$ Hz, $J = 8.3$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 32.0, 62.1, 120.7, 127.0, 127.1, 127.7, 128.7, 129.2, 134.2, 134.3, 138.0, 146.2, 146.3, 162.0.

3-Methyl-2-(tosylmethyl)quinazolin-4(3*H*)-one 11b

White solid, mp 178 °C, (Found: C, 62.15; H, 5.00; N, 8.54. $C_{17}H_{16}N_2O_3S$ requires C, 62.18; H, 4.91; N, 8.53%). δ_H (200 MHz; $CDCl_3$) 2.44 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 7.30 (d, $J = 8.5$ Hz, 2H, H ar), 7.38 (d, $J = 8.5$ Hz, 1H, H ar), 7.44–7.54 (m, 1H, H ar), 7.65–7.74 (m, 3H, H ar), 8.27 (dd, $J = 2.4$ Hz, $J = 8.5$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 21.3, 32.1, 62.0, 120.6, 126.8, 127.0, 127.8, 128.8, 129.8, 134.4, 135.2, 145.6, 146.0, 146.6, 161.8.

2-[(4-Chlorophenylsulfonyl)methyl]-3-methylquinazolin-4(3*H*)-one 11c

White solid, mp 207 °C, (Found: C, 55.03; H, 3.72; N, 7.98. $C_{16}H_{13}ClN_2O_3S$ requires C, 55.09; H, 3.76; N, 8.03%). δ_H (200 MHz; $CDCl_3$) 3.84 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 7.29 (d, $J = 8.4$ Hz, 1H, H ar), 7.44–7.54 (m, 3H, H ar), 7.65–7.75 (m, 3H, H ar), 8.26 (dd, $J = 2.2$ Hz, $J = 8.4$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 32.0, 61.9, 120.6, 126.8, 127.0, 127.9, 129.4, 130.3, 134.5, 136.4, 141.3, 146.0, 146.2, 161.8.

2-[(4-Fluorophenylsulfonyl)methyl]-3-methylquinazolin-4(3*H*)-one 11d

White solid, mp 184 °C, (Found: C, 57.88; H, 3.96; N, 8.43. $C_{16}H_{13}FN_2O_3S$ requires C, 57.82; H, 3.94; N, 8.43%). δ_H (200 MHz; $CDCl_3$) 3.84 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 7.12–7.21 (m, 2H, H ar), 7.28 (d, $J = 8.9$ Hz, 1H, H ar), 7.45–7.53 (m, 1H, H ar), 7.64–7.72 (m, 1H, H ar), 7.76–7.84 (m, 2H, H ar), 8.26 (dd, $J = 2.1$ Hz, $J = 8.9$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 32.0, 62.0, 116.6, 120.6, 120.7, 126.9, 127.0, 127.9, 131.7, 131.9, 133.9, 134.5, 146.1, 146.3, 161.9, 163.7, 166.3.

2-[(4-Bromophenylsulfonyl)methyl]-3-methylquinazolin-4(3*H*)-one 11e

White solid, mp 217 °C, (Found: C, 48.46; H, 3.28; N, 6.83. $C_{16}H_{13}BrN_2O_3S$ requires C, 48.87; H, 3.33; N, 7.12%). δ_H (200 MHz; $CDCl_3$) 3.84 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 7.29 (d, $J = 8.2$ Hz, 1H, H ar), 7.46–7.55 (m, 1H, H ar), 7.64–7.74 (m, 5H, H ar), 8.26 (dd, $J = 2.9$ Hz, $J = 8.2$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 32.0, 62.0, 120.7, 126.9, 128.0, 129.9, 130.3, 132.4, 134.5, 135.3, 137.0, 146.1, 146.2, 162.0.

3-Methyl-2-[(4-nitrophenylsulfonyl)methyl]quinazolin-4(3*H*)-one 11f

White solid, mp 273 °C, (Found: C, 53.54; H, 3.61; N, 11.32. $C_{16}H_{13}N_3O_5S$ requires C, 53.48; H, 3.65; N, 11.69%). δ_H (200 MHz; DMSO-d_6) 3.68 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 7.32 (d, $J = 8.5$ Hz, 1H, H ar), 7.49–7.56 (m, 1H, H ar), 7.72–7.80 (m, 1H, H ar), 8.11 (d, $J = 8.5$ Hz, 1H, H ar), 8.19 (d, $J = 9.1$ Hz, 2H, H ar), 8.41 (d, $J = 9.1$ Hz, 2H, H ar). δ_C (50 MHz; DMSO-d_6) 31.8, 60.2, 120.6, 124.7, 126.8, 127.2, 128.1, 131.0, 135.1, 144.7, 146.5, 147.7, 151.2, 161.6.

3-Methyl-2-[(3-nitrophenylsulfonyl)methyl]quinazolin-4(3*H*)-one 11i

White solid, mp 233 °C, (Found: C, 53.52; H, 3.65; N, 11.58. $C_{16}H_{13}N_3O_5S$ requires C, 53.48; H, 3.65; N, 11.69%). δ_H (200 MHz; $CDCl_3$) 3.86 (s, 3H, CH_3), 4.74 (s, 2H, CH_2), 7.18 (d, $J = 8.7$ Hz, 1H, H ar), 7.46–7.54 (m, 1H, H ar), 7.62–7.75 (m, 2H, H ar), 8.06–8.15 (m, 1H, H ar), 8.27 (dd, $J = 2.3$ Hz, $J = 8.7$ Hz, 1H, H ar), 8.50–8.55 (m, 1H, H ar), 8.71 (m, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 31.9, 61.6, 120.7, 124.5, 126.7, 127.2, 128.1, 128.7, 130.3, 134.4, 134.6, 140.0, 145.8, 146.0, 148.3, 161.7.

3-Methyl-2-[(thiophen-2-ylsulfonyl)methyl]quinazolin-4(3*H*)-one 11j

White solid, mp 189 °C, (Found: C, 52.55; H, 3.86; N, 8.70. $C_{14}H_{12}N_2O_3S_2$ requires C, 52.48; H, 3.78; N, 8.74%). δ_H (200 MHz; $CDCl_3$) 3.84 (s, 3H, CH_3), 4.83 (s, 2H, CH_2), 7.12–7.16 (m, 1H, H ar), 7.43–7.55 (m, 2H, H ar), 7.66–7.76 (m, 3H, H ar), 8.28 (d, $J = 8.6$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 32.0, 63.0, 120.6, 127.0, 127.8, 128.0, 134.4, 135.4, 135.8, 138.4, 146.2, 146.3, 161.8.

3-Methyl-6-nitro-2-(phenylsulfonylmethyl)quinazolin-4(3*H*)-one 12a

Yellow solid, mp 202 °C, (Found: C, 53.17; H, 3.71; N, 11.70. $C_{16}H_{13}N_3O_5S$ requires C, 53.48; H, 3.65; N, 11.69%). δ_H (200 MHz; $CDCl_3$) 3.87 (s, 3H, CH_3), 4.71 (s, 2H, CH_2), 7.41 (d, $J = 8.9$ Hz, 1H, H ar), 7.51–7.58 (m, 2H, H ar), 7.67–7.74 (m, 1H, H ar), 7.82–7.86 (m, 2H, H ar), 8.44 (dd, $J = 2.1$ Hz, $J = 8.9$ Hz, 1H, H ar), 9.10 (d, $J = 2.1$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 32.4, 62.2, 120.8, 123.7, 128.4, 128.7, 129.3, 134.6, 137.9, 146.1, 149.8, 150.1, 154.2, 160.8.

3-Methyl-6-nitro-2-(tosylmethyl)quinazolin-4(3*H*)-one 12b

Yellow solid, mp 241 °C, (Found: C, 54.51; H, 4.07; N, 11.28. $C_{17}H_{15}N_3O_5S$ requires C, 54.68; H, 4.05; N, 11.25%). δ_H (200 MHz; DMSO-d_6) 2.46 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 7.34 (d, $J = 8.9$ Hz, 2H, H ar), 7.53 (d, $J = 9.3$ Hz, 1H, H ar), 7.73 (d, $J = 8.9$ Hz, 2H, H ar), 8.48 (dd, 1H, $J = 2.3$ Hz, $J = 9.3$ Hz, 1H, H ar), 9.11 (d, $J = 2.3$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 21.6, 32.3, 61.2, 120.5, 122.9, 128.9, 129.1, 130.1, 136.2, 145.5, 145.9, 150.5, 151.6, 161.0.

2-[(4-Chlorophenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3*H*)-one 12c

Yellow solid, mp 260 °C, (Found: C, 48.49; H, 3.07; N, 10.52. $C_{16}H_{12}ClN_3O_5S$ requires C, 48.80; H, 3.07; N, 10.67%). δ_H (200 MHz; DMSO-d_6) 3.71 (s, 3H, CH_3), 5.29 (s, 2H, CH_2), 7.56 (d, $J = 9.4$ Hz, 1H, H ar), 7.70 (d, $J = 8.3$ Hz, 2H, H ar), 7.93 (d, $J = 8.3$ Hz, 2H, H ar), 8.52 (dd, $J = 2.8$ Hz, $J = 9.4$ Hz, 1H, H ar), 8.80 (d, $J = 2.8$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.3, 60.7, 120.6, 122.7, 129.0, 129.7, 131.1, 137.8, 139.9, 146.0, 150.4, 151.6, 161.0.

2-[(4-Fluorophenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3*H*)-one 12d

Yellow solid, mp 234 °C, (Found: C, 50.69; H, 3.26; N, 10.91. $C_{16}H_{12}FN_3O_5S$ requires C, 50.93; H, 3.21; N, 11.14%). δ_H (200 MHz; DMSO-d_6) 3.69 (s, 3H, CH_3), 5.24 (s, 2H, CH_2), 7.42 (d, $J = 9.1$ Hz, 1H, H ar), 7.52 (d, $J = 9.6$ Hz, 2H, H ar), 7.95 (m, 2H, H ar), 8.49 (dd, $J = 2.4$ Hz, $J = 9.1$ Hz, 1H, H ar), 8.77 (d, $J = 2.4$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 31.9, 60.5, 116.5, 120.2, 122.6, 128.7, 132.1, 134.9, 145.6, 150.1, 151.3, 160.7, 165.5.

2-[(4-Bromophenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3*H*)-one 12e

Yellow solid, mp 247 °C, (Found: C, 43.65; H, 2.69; N, 9.27. $C_{16}H_{12}BrN_3O_5S$ requires C, 43.85; H, 2.76; N, 9.59%). δ_H (200 MHz; DMSO-d_6) 3.71 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 7.57 (d, $J = 9.1$ Hz, 1H, H ar), 7.85 (m, 4H, H ar), 8.53 (dd, $J = 3.0$ Hz, $J = 9.1$ Hz, 1H, H ar), 8.80 (d, $J = 3.0$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.3, 60.7, 120.6, 122.9, 129.0, 131.1, 132.7, 137.3, 139.9, 146.0, 150.4, 151.6, 161.0.

3-Methyl-6-nitro-2-[(4-nitrophenylsulfonyl)methyl] quinazolin-4(3*H*)-one 12f

Yellow solid, mp 244 °C, (Found: C, 47.26; H, 2.91; N, 13.47. $C_{16}H_{12}N_4O_7S$ requires C, 47.53; H, 2.99; N, 13.86%). δ_H (200 MHz; DMSO-d_6) 3.70 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 7.52 (d, $J = 8.6$ Hz, 1H, H ar), 8.22 (d, $J = 8.9$ Hz, 2H, H ar), 8.42 (d, $J = 8.9$ Hz, 2H, H ar), 8.47 (dd, $J = 2.5$ Hz, $J = 8.6$ Hz, 1H, H ar), 8.77 (d, $J = 2.5$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.3, 60.2, 120.7, 123.0, 124.7, 129.1, 129.3, 131.1, 144.5, 146.1, 150.3, 151.3, 151.5, 161.0.

2-[(4-methoxyphenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3*H*)-one 12g

Yellow solid, mp 217 °C, (Found: C, 52.38; H, 3.94; N, 10.46 $C_{17}H_{15}N_3O_6S$ requires C, 52.44; H, 3.88; N, 10.79%). δ_H (200 MHz; DMSO-d_6) 3.68 (s, 3H, CH_3), 3.85 (s, 3H, CH_3) 5.15 (s, 2H, CH_2), 7.11 (d, $J = 8.7$ Hz, 2H, H ar), 7.58 (d, $J = 8.9$ Hz, 1H, H ar), 7.80 (d, $J = 8.7$ Hz, 2H, H ar), 8.51 (dd, $J = 2.6$ Hz, $J = 8.9$ Hz, 1H, H ar), 8.79 (d, $J = 2.6$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.0, 56.0, 61.1, 114.5, 120.2, 122.7, 128.6, 128.8, 130.1, 131.0, 145.6, 150.2, 151.5, 160.7, 163.9.

3-Methyl-6-nitro-2-[(2-nitrophenylsulfonyl)methyl] quinazolin-4(3*H*)-one 12h

Yellow solid, mp 232 °C, (Found: C, 47.79; H, 2.96; N, 13.46. $C_{16}H_{12}N_4O_7S$ requires C, 47.53; H, 2.99; N, 13.86%). δ_H (200 MHz; DMSO-d_6) 3.72 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 7.47 (d, $J = 9.2$ Hz, 1H, H ar), 7.85–7.92 (m, 1H, H ar), 7.98–8.11 (m, 3H, H ar), 8.48 (dd, $J = 2.6$ Hz, $J = 9.2$ Hz, 1H, H ar), 8.80 (d, $J = 2.6$ Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.1, 61.4, 120.4, 122.6, 125.1, 128.7, 130.7, 132.7, 133.1, 136.5, 145.7, 148.8, 150.1, 150.9, 155.0, 160.7.

General procedure for the synthesis of the 6-nitroquinazolin-4(3*H*)-one derivatives (15a–d)

The lithium salts were prepared as previously described.[18]

Classical conditions. To a solution of lithium salt of nitronate anion **13a** (3 eq) in methanol (20 mL) was added 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one **7** (0.2 g, 0.79 mmol). The reaction mixture was heated (oil bath), to 65 °C, for 3 h. After evaporation of methanol, the residue was dissolved in ethyl acetate and washed with water (3 × 30 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. Then, the product **15a** was recrystallized from 2-propanol and dried in a vacuum drying oven (dessicator cabinet).

Microwave conditions. To a solution of lithium salt of nitronate anion **13a–d** (3 eq) in methanol (20 mL) was added 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one **7** (0.2 g, 0.79 mmol). The reaction mixture was irradiated in a microwave oven, at 65 °C, for 15 min. at a power of 500 W. After evaporation of methanol, the residue was dissolved in ethyl acetate and washed with water (3 × 30 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. Then, the corresponding product **15a–d** was recrystallized from

2-propanol and dried in a vacuum drying oven (dessicator cabinet).

3-Methyl-2-(2-methylprop-1-enyl)-6-nitroquinazolin-4(3*H*)-one 15a

Yellow solid, mp 145 °C, (Found: C, 60.13; H, 5.01; N, 16.17. $C_{13}H_{13}N_3O_3$ requires C, 60.22; H, 5.05; N, 16.21%). δ_H (200 MHz; $CDCl_3$) 2.06 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 6.18 (s, 1H, CH), 7.76 (d, $J = 8.8$ Hz, 1H, H ar), 8.48 (dd, $J = 2.8$ Hz, $J = 8.8$ Hz, 1H, H ar), 9.13 (d, $J = 2.8$ Hz, 1H, Har). δ_C (50 MHz; $CDCl_3$) 20.7, 27.1, 31.7, 117.4, 120.1, 123.6, 128.1, 128.5, 145.4, 150.7, 151.3, 156.2, 161.4.

2-(Cyclopentylidenemethyl)-3-methyl-6-nitroquinazolin-4(3*H*)-one 15b

Yellow solid, mp 175 °C, (Found: C, 62.98; H, 5.35; N, 14.68. $C_{15}H_{15}N_3O_3$ requires C, 63.15; H, 5.30; N, 14.73%). δ_H (200 MHz; $CDCl_3$) 1.80 (m, 4H, $2CH_2$), 2.63 (t, $J = 7.4$ Hz, 2H, CH_2), 2.94 (t, $J = 7.4$ Hz, 2H, CH_2), 3.66 (s, 3H, CH_3), 6.40 (s, 1H, CH), 7.73 (d, $J = 9.1$ Hz, 1H, H ar), 8.46 (dd, $J = 2.8$ Hz, $J = 9.1$ Hz, 1H, H ar), 9.12 (d, $J = 2.8$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 25.5, 26.5, 31.1, 33.5, 36.9, 111.8, 119.7, 123.7, 128.0, 128.4, 145.0, 151.6, 156.0, 161.5, 167.3.

2-(Cyclohexylidenemethyl)-3-methyl-6-nitroquinazolin-4(3*H*)-one 15c

Yellow solid, mp 154 °C, (Found: C, 63.92; H, 5.79; N, 14.03. $C_{16}H_{17}N_3O_3$ requires C, 64.20; H, 5.72; N, 14.04%). δ_H (200 MHz; $CDCl_3$) 1.67 (m, 6H, $3CH_2$), 2.39 (t, $J = 6.3$ Hz, 2H, CH_2), 2.59 (t, $J = 6.3$ Hz, 2H, CH_2), 3.64 (s, 3H, CH_3), 6.10 (s, 1H, CH), 7.77 (d, $J = 9.5$ Hz, 1H, H ar), 8.48 (dd, $J = 2.6$ Hz, $J = 9.5$ Hz, 1H, H ar), 9.14 (d, $J = 2.6$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 26.1, 26.5, 31.1, 33.5, 36.9, 111.8, 119.7, 123.7, 128.0, 128.4, 145.0, 151.6, 156.0, 161.5, 167.3.

2-(Cyclododecylidenemethyl)-3-methyl-6-nitroquinazolin-4(3*H*)-one 15d

Yellow solid, mp 130 °C, (Found: C, 68.56; H, 7.76; N, 10.83. $C_{22}H_{29}N_3O_3$ requires C, 68.90; H, 7.62; N, 10.96%). δ_H (200 MHz; $CDCl_3$) 1.35 (m, 14H, $7CH_2$), 1.57 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 2.38 (t, $J = 6.3$ Hz, 2H, CH_2), 2.56 (t, $J = 6.3$ Hz, 2H, CH_2), 3.64 (s, 3H, CH_3), 6.26 (s, 1H, CH), 7.75 (d, $J = 8.4$ Hz, 1H, H ar), 8.49 (dd, $J = 2.5$ Hz, $J = 8.4$ Hz, 1H, H ar), 9.14 (d, $J = 2.5$ Hz, 1H, H ar). δ_C (50 MHz; $CDCl_3$) 22.5, 23.2, 23.9, 24.1, 24.4, 24.5, 24.6, 24.7, 24.9, 29.9, 31.9, 33.2, 117.9, 120.2, 123.6, 128.1, 128.7, 145.3, 151.5, 156.5, 156.8, 161.5.

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