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Novel series of 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones via two Niementowski condensations

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Abstract—Efficient microwave-assisted multi-step synthesis of 8*H*-quinazolino[4,3-*b*]quinazolin-8-one was investigated. The synthesis involved two Niementowski condensations from anthranilic acids. Homogeneous or heterogeneous conditions were studied with the aim to develop convenient syntheses of the desired compounds.

1. Introduction

The quinazoline ring skeleton is widely found in alkaloids and many biologically active compounds.[1] Among this class of molecules, 4-aminoquinazolines **1** are useful as fungicides, anti-inflammatory, anticancer, antimicrobial and antihypertensive agents.[2,3] Other natural fused heterocycles such as Rutaecarpine **2**, which has intrinsic hypertensive, diuretic and uterotonic properties,[4] and Luotonine A **3**, which has antitumor activity,[5] possess a quinazolinone moiety fused with indolopyrido and pyrrolloquinoline ring systems, respectively (Fig. 1). In search of new polyheterocyclic compounds with potential pharmaceutical value and in association with our work on the application of microwaves in organic chemistry, we planned to prepare novel tetracyclic 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **4**, from anthranilic acids, by fusing the quinazolinone and the quinazoline rings. The synthesis of various congeners was performed via two Niementowski condensations, inspired by our recent work on the preparation of fused polyheterocycles.[6]

Microwave-assisted reactions are now well established and have gained popularity as indicated by the large number of papers currently published on this topic since 1986.[7] The beneficial effects of microwave irradiation are finding an increased role in process chemistry,[8] especially in cases when usual methods require forcing conditions or prolonged reaction times. Microwaves have also shown an advantage where processes involve sensitive reagents or when products may decompose under prolonged reaction conditions. The possibilities offered by this technology are particularly attractive for multi-step synthesis[9] and drug discovery process[10] where high yielding protocols and avoidance or facility of purification are highly desirable. In this paper the multi-step synthesis of the 8*H*-quinazolino[4,3-*b*]quinazolin-8-one ring was realised under microwave irradiation with the aim to develop original and environmentally friendly procedures.

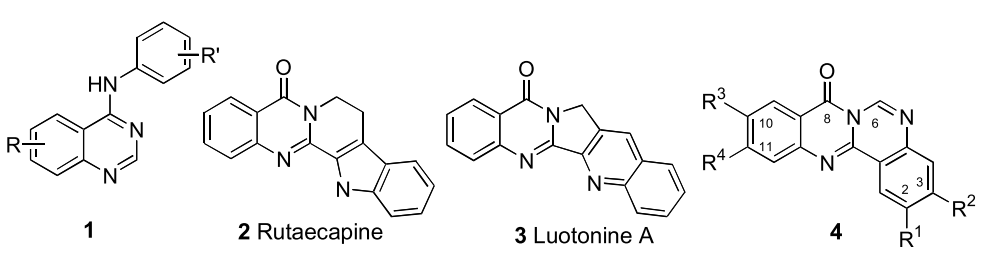

Figure 1.

Keywords: nitrogen heterocycles; fused ring systems; microwave-assisted multi-steps synthesis; cyclisation.
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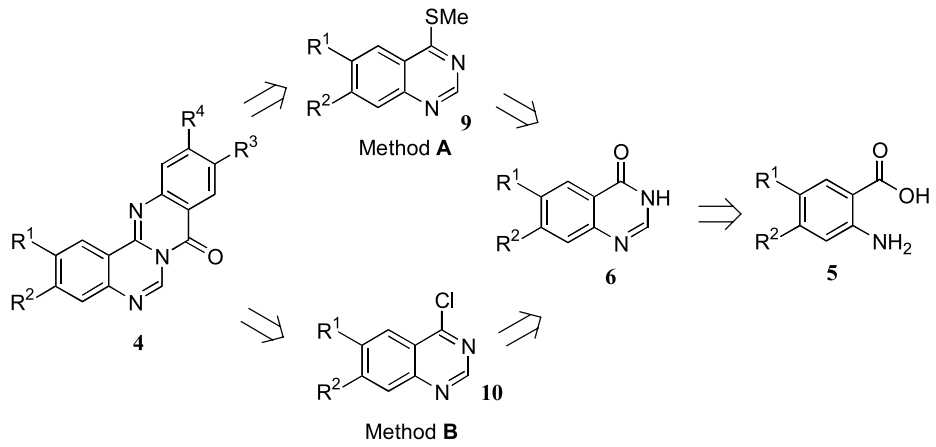


Scheme 1. Retrosynthetic pathways.

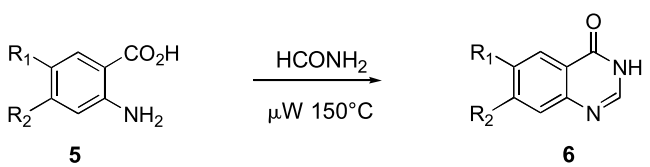
2. Results and discussion

2.1. Synthesis of (3*H*)-quinazolin-4-ones

The 6-unsubstituted 8*H*-quinazolino[4,3-*b*]quinazolin-8-one skeleton was rarely published, only compound **4a** (Table 4) has been previously described.[11,12] The first descriptions of such a ring involved condensation between methyl anthranilate and 2-chloroquinazoline followed by thermolysis.[11] The second method described dehydrogenation of 9,10,11,12-tetrahydroquinazolino[4,3-*b*]quinazolin-8-one.[12]

The retrosynthetic pathway (Scheme 1) suggests that generation of various quinazolinoquinazolines may start with a Niementowski reaction between formamide and anthranilic acids. Two routes were then identified from the intermediate quinazolin-4-one **6**. The first one was inspired by recent works on base-modified nucleosides[13] or indoloquinazolines[6] and involved a modified Niementowski condensation. The second path is more common and suggests to prepare 4-chloroquinazolines **10** before condensation with anthranilic acid derivatives.

The first step of the two routes studied involves preparation of 4-(3*H*)-quinazolinones **6** via a traditional Niementowski condensation[14] (Scheme 2). This old reaction, which consist of the fusion between anthranilic acids **5** and various amides or thioamides (in dry media or with solvents), was recently re-investigated under microwave irradiation.[15] Condensation of formamide with various anthranilic acids afforded substituted quinazolinones **6** in high yields and in short reaction times (15–40 min) (Table 1).



Scheme 2. Synthesis of the (3*H*)-quinazolines-4-ones **6**[15] under microwave conditions (μW).

Table 1.

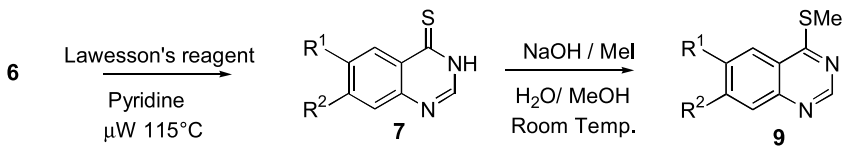
Compound	R^1	R^2	Time (min)	Yield of **6** (%)
5a	H	H	20	90
5b	Me	H	15	75
5c	Br	H	20	75
5d	MeO	MeO	40	70

Formation of **4** was firstly investigated by a shorter route which consists of condensation of the quinazolin-4-ones **6** and anthranilic acids. This strategy was rapidly judged non-feasible in comparison with methods which favour the first nucleophilic attack of the amino group of anthranilic acid by introduction of a good leaving group on carbon 4 of the quinazoline ring. Two strategies were identified: the first one (method A) suggest a selective *S*-alkylation of a mercapto group, whilst, the second pathway (method B) consist of introduction of a chlorine at the appropriate position.

2.2. Method A

Thionation of quinazolinones **6** was performed under microwave irradiation using Lawesson's reagent in the presence of pyridine[16] (Scheme 3, Table 2). Microwave assisted transformations of **6a–c** into **7a–c** were completed in 15–40 min instead of 18 h using classical heating (oil bath). Curiously, treatment of **6d** with Lawesson's reagent afforded the unexpected phenylthioformamide **8** in 56% yield as the sole product (Scheme 4). The attempted quinazolinethione **7d** was synthesised from **6d** using P_2S_5 in pyridine under microwave irradiation in a 70% yield. Inspired by a recent microwave heterogeneous thionation methods,[17,18] an alternative approach to the thionation reaction was studied using Lawesson's reagent under solvent-free conditions on solid support (graphite). In the best case, only 40% of the attempted product **7a** was obtained and the method generated a lot of technical problems (hazardous electric arcs and important elevation of temperature).

Previous experience of the Niementowski reaction[6] showed us that direct condensation of thioamides with anthranilic acids may be very difficult, or unsuccessful, and require the transformation of the mercapto group of thioquinazolines **7** into a better leaving group. *S*-Methylation of

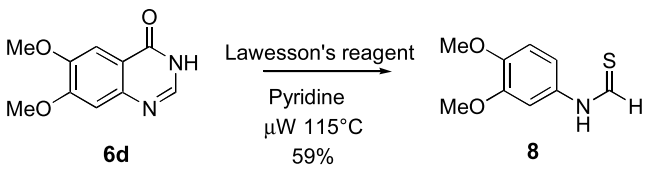


Scheme 3. Thionation of quinazolinones **6** and *S*-alkylation of quinazolinethiones **7**.

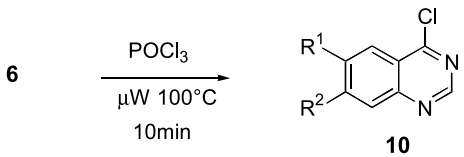
Table 2.

Compound	R^1	R^2	Time (min)	Yield of **7** (%)	Time (min)	Yield of **9** (%)
6a	H	H	20	93[a]	20	85
6b	Me	H	15	87	15	78
6c	Br	H	20	84	20	74
6d	MeO	MeO	20	75[b]	20	70

[a] Same experiment using traditional heating (pyridine at reflux) gave **7a** in 18 h and 92% yield.
[b] Using P_2S_5 in pyridine.



Scheme 4.



Scheme 5. Synthesis of 4-chloroquinazolines **10** under microwave conditions.

Table 3.

Compound	R^1	R^2	Yield of **10** (%)
6a	H	H	85
6b	Me	H	90
6c	Br	H	90
6d	MeO	MeO	70

quinazolinethiones **7** was easily carried out with iodomethane in the presence of sodium hydroxide in a mixture of water and methanol at room temperature according to known procedures (Table 2).[19]

Graphite is one of the solids most efficiently heated by microwaves and is also known for its adsorbing properties of organic molecules.[20] Thus, as we described before in the synthesis of indoloquinazolines,[6] the best method for the preparation of 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **4** consists of microwave irradiation (150°C, 60 W) of a mixture of the 4-(thiomethyl)quinazoline **9** and an excess of anthranilic acid (6 equiv.), adsorbed on graphite (Scheme 6). This procedure led to the cyclised compounds **4** in good yields and in a shorter time than for the purely thermal procedures (Table 4) (the yields observed are in accordance with the reactivity of such anthranilic acids in similar reactions).

2.3. Method B

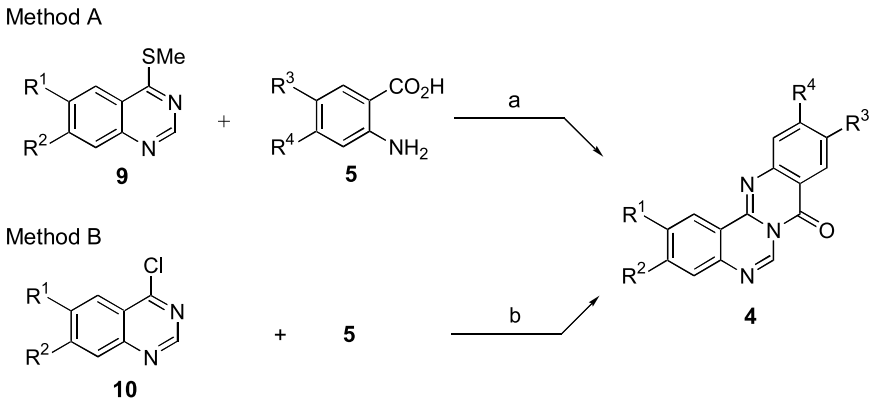
Reviewing literature, we decided to investigate an alternative to the preceding method and we performed microwave assisted final cyclisation reactions in which chlorine is the leaving group (instead of thiomethyl group).[21] Short exposure (10 min) of a mixture of the intermediate quinazolinones **6** with phosphoryl chloride to microwaves led to 4-chloroquinazolines **10** in very good yields (Scheme 5, Table 3). Under similar experimental conditions, with the same quantity of starting materials, several hours are needed by conventional heating to give the same yields.

Heating the 4-chloroquinazolines **10** and anthranilic acids (2 equiv.) in acetic acid allowed the synthesis of the expected quinazolino[4,3-*b*]quinazoline ring in very good yields (Scheme 6, Table 4). The reaction is completed within 20 min under microwave irradiation and needed 1 h with classical heating. Under the same conditions (same quantity of starting materials), a preliminary study of this reaction showed that transposition of such experiments in sealed tube (pressure monitored by the microwave apparatus) gave shorter times (10 min) and comparable yields. A short exploration of this reaction at atmospheric pressure under solvent-free conditions, with graphite as solid support, gave unsatisfactory results (decomposition of starting material).

Although method A can be considered as a convenient solventless procedure, method B afforded a more straightforward access to 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **4** and gave better yields than method A. Method B, which was realised in solvents, is offering the possibility to explore the interest of associating solid-phase synthesis and microwave heating, as it has been recently demonstrated in our group.[22] Such a strategy is currently in course and will be described latter.

3. Conclusion

In conclusion, we have described an efficient microwave-assisted multi-step synthesis of 8*H*-quinazolino[4,3-*b*]-quinazolin-8-ones **4** via two Niementowski condensations from anthranilic acids. This work demonstrates the real benefit of using focussed microwave irradiation in multi-step procedures, with commercially available reactors under either homogeneous or heterogeneous conditions. In contrast to conventional heating, it gave the desired compounds in higher overall yield with shorter reaction times and products that are more amenable for purification. The



Scheme 6. *Reagents and conditions*: (a) *S*-methyl derivative **9**, **5** (6 equiv.), graphite, μW (P 60 W) 150°C, 30 min; (b) chloroquinazolinone **10**, **5** (2 equiv.), CH_3CO_2H, atmopheric pressure, μW (P 100 W) 105°C, 20 min or sealed tube, μW (P 100 W) 130°C, 10 min.

Table 4. Synthesis of 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones **4**

Compound	R^1	R^2	R^3	R^4	Yield (%)	
					Method A	Method B
4a	H	H	H	H	79	82
4b	Me	H	H	H	58	70
4c	Br	H	H	H	21	54
4d	MeO	MeO	H	H	34	62
4e	H	H	Me	H	53	85
4f	H	H	Br	H	50	76
4g	H	H	MeO	MeO	29	41
4h	MeO	MeO	MeO	MeO	/	65

experimental microwave conditions described in this paper are now well established and could be safely and beneficially scaled up to multigram level with similar yields, a strategy which is particular developed in our group.

4. Experimental

4.1. General

Commercial reagents were used as received without additional purification. Melting points were measured using a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Paragon 1000PC FT-IR instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a JEOL JNM LA400 spectrometer. Chemical shifts (δ values) are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants (J) are expressed in Hertz. Mass spectra were recorded on Spectrometer simple quad platform LC micromass, electrospray. Thin-layered chromatography (TLC), was performed on 0.2 mm pre-coated plates of silica gel 60F-264 (Merk). Visualisation was made with ultraviolet light. Column chromatography was performed by using Merck silica gel (70–230 mesh). Elemental analyses for new compounds were performed at Centre Commun d'Analyses (University of La Rochelle). High-resolution mass measurments were performed on a Varian MAT 311 in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Université de Rennes). Focused microwave irradiations were carried out with CEM Discover™ focused microwave reactor (300 W, monomode system) which has in situ magnetic stirrer, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control. Manipulations were performed at atmospheric pressure or under pressure in pressure-rated reaction tubes with continuous pressure measurement.

Quinazolin-4(3*H*)-one **6a–d** were obtained according to the procedure previously described.[15]

4.2. Synthesis of 4(3*H*)-quinazolinethione derivatives 7 and *N*-(3,4-dimethoxyphenyl)thioformamide 8: general procedure

A solution of quinazolin-4(3*H*)-one **6** (1.7 mmol) and Lawesson's reagent (0.8 equiv., 1.37 mmol) (or P_2S_5 for **6d**, 2 equiv.) in pyridine(8.5 mL) was irradiated at 115°C (power input: 60 W) until completion (TLC monitoring, 20 min). After cooling, the solvent was removed under reduced pressure. The residue was then poured into boiling water and was filtered off. The collected yellow solid was dissolved into 1 M NaOH solution and the solution was filtered again. The filtrate was neutralised with a saturated NH_4Cl solution until complete crystallisation occurred. After filtration compound **7a** as yellow solid was dried until constant weight.

4.2.1. 4(3*H*)-Quinazolinethione (7a). 93% Yield; yellow solid; mp (H_2O) >260°C (lit.[23] 312–314°C); IR (KBr) ν 3200–2500, 1597, 1247, 869, 763 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 7.61 (t, J=7.6 Hz, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.89 (td, J=8.0, 1.6 Hz, 1H), 8.17 (s, 1H), 8.56 (dd, J=8.0, 1.6 Hz, 1H), 13.87 (brs, 1H); ^{13}C NMR (d_6-DMSO) δ 123.3, 123.5, 124.1, 124.4, 130.6, 139.0, 139.5, 180.8; MS (ESI, EI$^+$) m/z=163 (MH^+); HRMS: calcd for $C_8H_6N_2S$, 162.0252; found, 162.0250.

4.2.2. 6-Methyl-4(3*H*)-quinazolinethione (7b). 87% Yield; yellow solid; mp (H_2O) >260°C (lit.[24] >300°C); IR (KBr) ν 3200–2500, 1625, 1570, 1257, 865, 821, 691, 502 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 2.52 (t, J=1.2 Hz, 3H), 7.65 (d, J=8.2 Hz, 1H), 7.75 (dd, J=8.2, 1.2 Hz, 1H), 8.14 (s, 1H), 8.38 (s, 1H), 13.86 (brs, 1H); ^{13}C NMR (d_6-DMSO) δ 21.0, 127.9, 128.4, 128.6, 136.8, 138.1, 142.4, 143.1,

185.2; MS (ESI, El$^+$) m/z=177 (MH$^+$); HRMS: calcd for $C_9H_8N_2S$, 176.0408; found, 176.0403.

4.2.3. 6-Bromo-4(3*H*)-quinazolinethione (7c). 84% Yield; yellow solid; mp (H_2O) >260°C; IR (KBr) ν 3200–2500, 1621, 1286, 821, 698, 623 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 7.68 (d, J=8.8 Hz, 1H), 8.33 (dd, J=8.8, 2.4 Hz, 1H), 8.21 (s, 1H), 8.64 (d, J=2.4 Hz, 1H), 14.08 (brs, 1H); ^{13}C NMR (d_6-DMSO) δ 121.1, 130.3, 130.6, 130.9, 138.0, 143.3, 146.1, 184.4; MS (ESI, El$^-$) m/z=239–241 (M−H$^+$); HRMS: calcd for $C_8H_5BrN_2S$, 239.9357; found, 239.9357.

4.2.4. 6,7-Dimethoxy-4(3*H*)-quinazolinethione (7d). 75% Yield; yellow solid; mp (H_2O) >260°C; IR (KBr) ν 3200–2500, 1609, 1492, 1359, 1206, 880, 556 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 3.89 (s, 3H), 3.94 (s, 3H), 7.16 (s, 1H), 7.91 (s, 1H), 8.10 (s, 1H), 13.67 (brs, 1H); ^{13}C NMR (d_6-DMSO) δ 55.7, 56.2, 107.6, 107.8, 123.2, 141.0, 142.5, 149.9, 155.9, 182.0; MS (ESI, El$^+$) m/z=223 (MH$^+$); HRMS: calcd for $C_{10}H_{10}N_2O_2S$, 222.0463; found, 222.04605.

4.2.5. *N*-(3,4-Dimethoxyphenyl)thioformamide (8). Compound purified by chromatography on silica gel; (CH_2Cl_2/EtOAc 8:2); 59% yield; yellow solid; mp ($CHCl_3$) 152–154°C; IR (KBr) ν 3200–2800, 1624, 1580, 1278, 1027, 976, 806, 622 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.89 (s, 3H),6.74 (m, 2H), 6.85 (d, J=8.4 Hz, 1H), 9.67 and 9.70 (2×s, 1H, NHC=S and N=CSH), 10.24 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 56.1, 56.2, 102.3, 110.1, 111.8, 123.4, 147.8, 149.9, 186.9; MS (ESI, El$^+$) m/z=197 (MH$^+$); HRMS: calcd for $C_9H_{11}NO_2S$, 197.0477; found, 197.0474.

4.3. Synthesis of 4-(methylsulfanyl)quinazoline derivatives 9: general procedure

To a solution of **7** (3.8 mmol) and 1 M NaOH (5.3 mL) in a 1:1 mixture of MeOH and water (20 mL), was added CH_3I (260 μL, 4.2 mmol) at room temperature. The reaction mixture was stirred until completion (TLC monitoring, 20 min). MeOH was then evaporated under reduced pressure and the remaining aqueous layer was extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc 9:1) to furnish **9** as a white solid.

4.3.1. 4-(Methylsulfanyl)quinazoline (9a). 85% Yield; white solid; mp (EP/EtOAc) 62°C (lit.[23] 65°C); IR (KBr) ν 3000, 2927, 1614, 1570, 999, 755, 679, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3H), 7.59 (dt, J=8.4, 1.6 Hz, 1H), 7.85 (td, J=8.0, 1.0 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H), 9.01 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.6, 123.8, 124.0, 127.3, 128.8, 133.6, 147.7, 153.6, 171.9; MS (ESI, El$^+$) m/z=177 (MH$^+$); HRMS: calcd for $C_9H_8N_2S$, 176.0408; found, 176.0403.

4.3.2. 6-Methyl-4-(methylsulfanyl)quinazoline (9b). 78% Yield; cream/white solid; mp (CH_2Cl_2) 72°C (lit.[24] 96–98°C); IR (KBr) ν 3022, 2930, 1536, 799, 685, 500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 2.70 (s, 3H), 7.66 (dd, 1H, J=8.4, 2.0 Hz, 1H), 7.82 (d, J=2.0 Hz, 1H), 7.84 (d, J=8.4 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 21.7, 122.6, 123.8, 128.3, 135.6, 137.5, 146.0, 152.8, 170.7; MS (ESI, El$^+$) m/z=191 (MH$^+$); HRMS: calcd for $C_{10}H_{10}N_2S$, 190.0565; found, 190.0561.

4.3.3. 6-Bromo-4-(methylsulfanyl)quinazoline (9c). 74% Yield; white solid, mp (CH_2Cl_2) 163°C; IR (KBr) ν 3071, 2926, 1557, 1481, 829, 618, 494 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.72 (s, 3H), 7.83 (d, J=8.8 Hz, 1H), 7.91 (dd, J=8.8, 2.0 Hz, 1H), 8.23 (d, J=2.0 Hz, 1H), 9.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 120.9, 124.9, 126.2, 130.5, 137.1, 146.4, 153.8, 171.0; MS (ESI, El$^+$) m/z=255/257 (MH$^+$); HRMS: calcd for $C_9H_7BrN_2S$, 253.9513; found, 253.9487.

4.3.4. 6,7-Dimethoxy-4-(methylsulfanyl)quinazoline (9d). 70% Yield; white solid, mp ($CHCl_3$) 160°C; ^{1}H NMR ($CDCl_3$): δ 2.72 (s, 3H), 4.03 (s, 3H), 4.04 (s, 3H), 7.20 (s, 1H), 7.25 (s, 1H), 8.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 56.2, 56.3, 101.4, 107.1, 119.1, 145.3, 149.9, 152.5, 155.4, 167.8; MS (ESI, El$^+$) m/z=237 (MH$^+$); HRMS: calcd for $C_{11}H_{12}N_2O_2S$, 236. 0619; found, 236.0619.

4.4. Synthesis of 4-chloroquinazoline derivatives 10: general procedure

The quinazolinone **6** (4.42 mmol) and $POCl_3$ (6 mL) were irradiated at 100°C (maximum power input 70 W) until completion (TLC monitoring, 10 min). $POCl_3$ was evaporated in vacuo and the residue was dissolved in EtOAc. The organic phase was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated in vacuo to furnish the compound **10** as a white/grey solid which was used without further purification in the next.

4-Chloroquinazoline (**10a**, 85% yield)[25], 4-chloro-6-methylquinazoline (**10b**, 90% yield)[26], 6-bromo-4-chloroquinazoline (**10c**, 90% yield)[27], 4-chloro-6,7-dimethoxyquinazoline (**10d**, 70% yield)[27] gave spectroscopic data in accordance with those previously described.

4.5. Synthesis of 8*H*-quinazolino[4,3-*b*]quinazolin-8-one 4: general procedures

Method A. A mixture of compound **9** (0.57 mmol) and anthranilic acid (3.4 mmol) was adsorbed (with AcOEt) on graphite (1 g) and was placed in a microwave oven in a quartz vial. The irradiation was programmed at a fixed temperature 150°C (maximum power input 60 W) and the powder was stirred for 30 min. After cooling, the graphite powder was filtered off and washed with dichloromethane. The solution was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallisation from ethanol or DMF afforded compound **4**.

Method B. A mixture of compound **10** (0.61 mmol) and anthranilic acid (467 mg, 3.4 mmol) in CH_3CO_2H (2 mL) was introduced in a pressure-rated reaction tube. The tube was irradiated at 130°C (maximum power input 100 W) for 10 min. After reaction, solvent was evaporated under reduced pressure. Recrystallisation from ethanol or purification by chromatography on silica gel (CH_2Cl_2/EtOAc 95:5) afforded compound **4**.

4.5.1. 8*H*-Quinazolino[4,3-*b*]quinazolin-8-one (4a). 79% Yield from **9a** (method A) and 82% yield from **10a** (method

B); white solid; mp (EtOH) 198°C (lit.[11,12] 197°C); ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 1H), 7.66 (m, 1H), 7.86 (m, 4H), 8.45 (d, J=8.0 Hz, 1H), 8.84 (d, 1H, J=8.0 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 118.7, 121.4, 125.8, 126.5, 127.5, 127.7, 128.1, 128.9, 128.9, 133.6, 135.8, 137.7, 143.0, 144.3, 147.5, 159.1; HRMS: calcd for $C_{15}H_9N_3O$, 247.0745; found, 247.0743. Anal. calcd for $C_{15}H_9N_3O$: C 72.87, H 3.67, N 16.99. Found: C 72.93, H 3.66, N 16.89.

4.5.2. 2-Methyl-8*H*-quinazolino[4,3-*b*]quinazolin-8-one (4b). 58% Yield from **9b** (method A) and 70% yield from **10b** (method B); white solid; mp (DMF) 179°C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 7.55 (dt, J=7.6, 1.2 Hz, 1H), 7.67 (m, 2H), 7.79 (d, J=8.0 Hz, 1H), 7.93 (dt, J=7.6, 1.2 Hz, 1H), 8.27 (dd, J=8.0, 1.2 Hz, 1H), 8.47 (s, 1H), 9.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 118.7, 120.9, 124.9, 126.4, 127.0, 127.3, 127.6, 135.0, 135.9, 137.3, 138.9, 141.0, 144.4, 147.2, 158.8; HRMS: calcd for $C_{16}H_{11}N_3O$, 261.0902; found, 261.0900. Anal. calcd for $C_{16}H_{11}N_3O$: C 73.55, H 4.24, N 16.08. Found: C 73.24, H 4.22, N 15.96.

4.5.3. 2-Bromo-8*H*-quinazolino[4,3-*b*]quinazolin-8-one (4c). 21% Yield from **9c** (method A) and 54% yield from **10c** (method B); white solid; mp (DMF) 234°C; ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 1H), 7.78 (d, J=8.8 Hz, 1H), 8.00 (m, 1H), 8.06 (dd, J=8.8, 2.4 Hz, 1H), 8.33 (d, J=8.4 Hz, 1H), 8.79 (d, J=2.0 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 118.9, 121.6, 123.2, 126.9, 127.1, 127.4, 127.5, 130.0, 136.1, 136.6, 138.9, 142.0, 143.3, 146.8, 158.6; HRMS: calcd for $C_{15}H_8BrN_3O$, 324.9851; found, 324.9865. Anal. calcd for $C_{15}H_8BrN_3O$: C 55.24, H 2.47, N 12.88. Found: C 55.19, H 2.53, N 12.72.

4.5.4. 2,3-Dimethoxy-8*H*-quinazolino[4,3-*b*]quinazolin-8-one (4d). 34% Yield from **9d** (method A) and 62% yield from **10d** (method B); white solid; mp (DMF) >260°C; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H), 4.13 (s, 3H), 7.24 (s, 1H), 7.49 (m, 1H), 7.85 (m, 2H), 8.14 (s, 1H), 8.40 (d, J=8.4 Hz, 1H); 9.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.4, 56.5, 105.4, 109.0, 114.7, 118.0, 125.9, 127.3, 127.6, 135.8, 136.6, 139.3, 144.3, 148.0, 150.4, 154.4, 159.3; HRMS: calcd for $C_{17}H_{13}N_3O_3$, 307.0957; found, 309.0963. Anal. calcd for $C_{17}H_{13}N_3O_3$: C 66.44, H 4.26, N 13.67. Found: C 65.80, H 4.15, N 13.53.

4.5.5. 10-Methyl-8*H*-quinazolino[4,3-*b*]quinazolin-8-one (4e). 53% Yield from **9a** (method A) and 85% yield from **10a** (method B); white solid; mp (DMF) 211°C; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 7.66 (dt, J=8.2, 1.2 Hz, 1H), 7.72 (dd, J=8.2, 1.2 Hz, 1H), 7.78–7.86 (m, 3H), 8.24 (s, 1H), 8.84 (dd, J=7.6, 1.2 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 118.5, 121.6, 125.8, 126.8, 127.6, 128.1, 128.9, 133.5, 137.0, 137.6, 137.9, 143.0, 143.8, 145.7, 159.3; HRMS: calcd for $C_{16}H_{11}N_3O$, 261.0902; found, 261.0900. Anal. calcd for $C_{16}H_{11}N_3O$: C 73.55, H 4.24, N 16.08. Found: C 72.65, H 4.24, N 15.71.

4.5.6. 10-Bromo-8*H*-quinazolino[4,3-*b*]quinazolin-8-one (4f). 50% Yield from **9a** (method A) and 76% yield from **10a** (method B); white solid; mp (DMF) 229°C; ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 1H), 7.76 (d, J=8.8 Hz, 1H), 7.87 (m, 2H), 7.97 (d, J=8.4 Hz, 1H), 8.58 (s, 1H), 8.84 (d, J=8.4 Hz, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 119.99, 120.01, 121.2, 125.9, 128.3, 129.2, 129.5, 129.9, 134.0, 137.5, 139.0, 143.1, 144.8, 146.5, 158.2; HRMS: calcd for $C_{15}H_8BrN_3O$, 324.9851; found, 324.9849. Anal. calcd for $C_{15}H_8BrN_3O$: C 55.24, H 2.47, N 12.88. Found: C 55.33, H 2.53, N 13.06.

4.5.7. 10,11-Dimethoxy-8*H*-quinazolino[4,3-*b*]quinazolin-8-one (4g). 29% Yield from **9a** (method A) and 41% yield from **10a** (method B); yellow solid; mp (DMF) >260°C. ^{1}H NMR ($CDCl_3$): δ 4.07 (s, 3H), 4.11 (s, 3H), 7.25 (s, 1H), 7.65 (dt, J=6.8, 1.6 Hz, 1H), 7.71 (s, 1H), 7.80 (dt, J=6.8, 1.6 Hz, 1H), 7.86 (dd, J=8.0, 1.2 Hz, 1H), 8.78 (dd, J=8.0, 1.2 Hz, 1H), 9.51 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 56.4, 56.5, 105.9, 107.9, 111.9, 121.4, 125.4, 128.1, 128.8, 133.3, 137.9, 142.9, 143.6, 144.4, 149.1, 156.5, 158.2; HRMS: calcd for $C_{17}H_{13}N_3O_3$, 307.0957; found, 309.0963. Anal. calcd for $C_{17}H_{13}N_3O_3$: C 66.44, H 4.26, N 13.67. Found: C 66.21, H 4.38, N 13.89.

4.5.8. 2,3,10,11-Tetramethoxy-8*H*-quinazolino[4,3-*b*]quinazolin-8-one (4h). 65% Yield from **10d** (method B); light yellow solid; mp (DMF) >260°C; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H), 4.06 (s, 3H), 4.09 (s, 3H), 4.14 (s, 3H), 7.24 (s, 1H), 7.28 (s, 1H), 7.69 (s, 1H), 8.13 (s, 1H), 9.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.39, 56.42, 56.43, 56.49, 104.9, 105.9, 107.5, 108.9, 114.9, 136.8, 139.0, 143.5, 144.9, 150.3, 154.0, 156.5, 158.4; HRMS: calcd for $C_{19}H_{17}N_3O_5$, 367.1168; found, 367.1173. Anal. calcd for $C_{19}H_{17}N_3O_5$: C 62.12, H 4.66, N 11.44. Found: C 61.63, H 4.89, N 11.54.

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