Parallel Microwave Synthesis of 2-Styrylquinazolin-4(3*H*)-ones in a High-Throughput Platform Using HPLC/GC Vials as Reaction Vessels

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Received February 27, 2009

The application of a high-throughput reaction platform for performing parallel microwave synthesis in sealed HPLC/GC vials contained in a strongly microwave-absorbing silicon carbide plate is described. The use of aluminum crimp caps with PTFE coated silicone septa in combination with an appropriate plate sealing mechanism allows processing of reaction volumes from 0.5−1.5 mL at temperatures of ∼250 °C and pressures of up to ∼20 bar. A library of 39 2-styrylquinazolin-4(3*H*)-one derivatives was prepared in a two-step/one-pot parallel fashion involving the initial three-component condensation of four anthranilic acids with acetic anhydride and ammonium acetate at 250 °C for 30 min. This was followed by catalyst-free condensation of the resulting 2-methylquinazolinones with a selection of 15 aromatic aldehydes. Compared to single-mode sequential microwave synthesis, the overall processing times for library synthesis could be significantly reduced.

Introduction

The quinazolin-4(3*H*)-one moiety (**1**) constitutes an important class of heterocycles and is part of ∼150 naturally occurring alkaloids and drug molecules.[1] Quinazolin-4(3*H*)-ones exhibit a variety of biological activities, including antibacterial,[2] antimalarial,[3] anticonvulsant,[4] antidiabetic,[5] and anticancer.[6] Not surprisingly, these types of *N*-heterocycles are popular templates for drug discovery and have been used as scaffolds for the generation of combinatorial libraries (see Figure 1).[7] Of particular interest are 2-styryl-substituted derivatives of type **2** as they are associated with inhibitory effects on tubulin polymerization and the growth of L1210 murine leukemia cells (e.g., **3**).[8] In addition, *N*3-aryl-substituted analogs have been shown to exhibit potent anticonvulsant activity (piriqualone, **4**).[9]

Although there are several publications describing the synthesis of functionalized 4(3*H*)-quinazolinones,[10] there are only a few reports on the preparation of 2-styryl-substituted quinazolin-4(3*H*)-ones.[8−13] The general method for the synthesis of these heterocycles is the Knoevenagel condensation of 2-methyl-substituted quinazolinones with aromatic aldehydes under basic[9,11] or acidic[8,12] conditions. However, many of the protocols for the initial generation of the quinazolinone core and/or preparation of 2-styrylquinazolinones suffer from drawbacks such as requiring multistep procedures, harsh reaction conditions, long reaction times, or low yields.[8,9,11,12] Therefore, in the past decade, considerable effort has been directed to the combinatorial/high-throughput synthesis of *N*-heterocycles of type **2** for effective lead discovery and optimization.[13] Very recently a one-pot/two-step protocol for the synthesis of 2-styrylquinazolin-4(3*H*)-ones **2** was described.[14] In this method, isatoic anhydride, triethylorthoacetate, and ammonium acetate were heated at 80 °C in the presence of an ionic liquid for 5 h. In the second step, an aromatic aldehyde was added and the resulting mixture heated for an additional 7 h. Although this protocol allows for the preparation of the desired 2-styrylquinazolin-4(3*H*)-ones **2** in high yields, it is of restricted use for the generation of compound libraries in a combinatorial fashion because of the limited availability of substituted isatoic anhydrides and the long reaction times.

Herein, we describe the rapid and catalyst-free synthesis of 2-styrylquinazolinone compound libraries **8**. In a two-step/one-pot sequence, commercially available anthranilic acids **5** are converted into quinazolin-4(3*H*)-ones **6** which are subsequently transformed to 2-styrylquinazolinones **8** via condensation with aromatic aldehydes (Scheme 1). Importantly, both steps are performed in a recently disclosed high-throughput synthesis platform for parallel microwave chem-

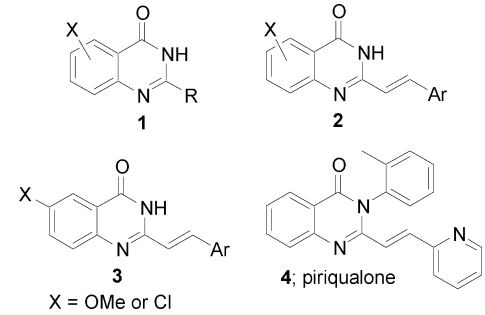

Figure 1. Quinazolinone and 2-styrylquinazolinones.

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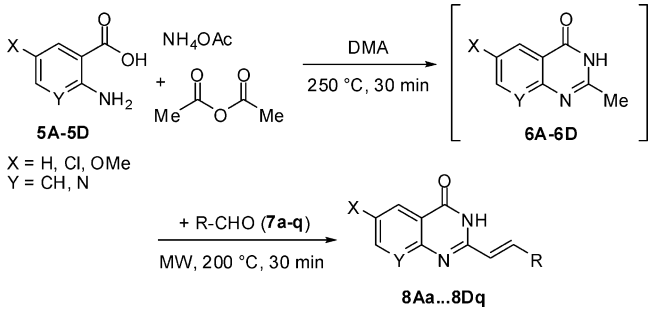
10.1021/cc900036a CCC: $40.75
Published on Web 05/11/2009

Scheme 1. Two-Step/One-Pot Synthesis of 2-Styrylquinazolinones **8**[a]



[a] For building blocks, see Figures 3 and 4.

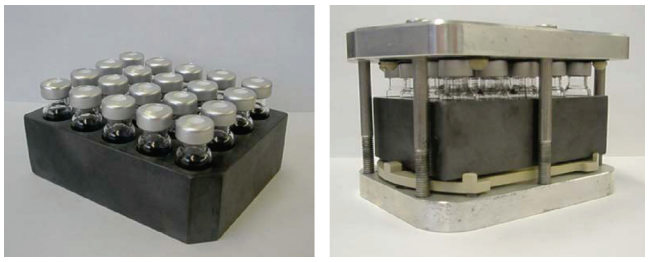


Figure 2. High-throughput synthesis platform for parallel microwave chemistry in silicon carbide plates. The left image shows the experimental setup for low pressure applications utilizing HPLC/GC vials with aluminum crimp tops for reaction temperatures of ~250 °C (max pressure ~8 bar). The right image shows the high pressure setup utilizing an aluminum sealing plate for achieving the reaction temperatures of 250 °C (max pressure 20 bar) used in this work. For further details, see ref 15.

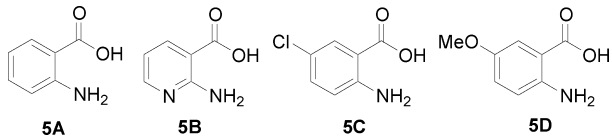


Figure 3. Anthranilic acid-type building blocks for library synthesis.

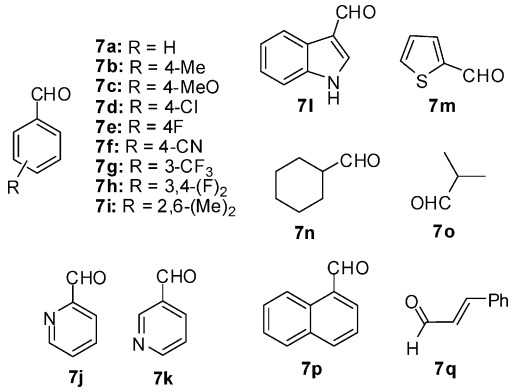


Figure 4. Aldehyde building blocks for library synthesis.

istry using standard HPLC/GC auto sampler vials as reaction vessels.[15] The platform consists of a block of silicon carbide (SiC) with a 5 × 4 deep well matrix in which the HPLC/GC vials are placed and can operate at a maximum temperature of 250 °C and 20 bar pressure (Figure 2).[15]

Results and Discussion

Reaction Optimization. According to the general strategy outlined in Scheme 1, the synthesis of the required 2-styrylquinazolinones **8** commenced with the preparation of 2-methylquinazolinone precursors of type **6**. Although several methods for the synthesis of 2-methylquinazolinones have been reported in the literature,[10] for the current library project we decided to use the three-component condensation of anthranilic acids, acetic anhydride (Ac_2O), and ammonium acetate (NH_4OAc) as a starting point (Scheme 1).[16] In an initial set of experiments anthranilic acid (**5A**, X = H, Y = CH) was chosen as a model substrate to optimize the reaction conditions with respect to solvent, reaction time and temperature, and molar ratio of starting materials. The optimization studies were performed in a single mode microwave instrument with appropriate robotics to increase throughput (Optimizer 60 EXP, Biotage).[17] Our first experiments involved 0.5 mmol of anthranilic acid, 1.5 mmol of Ac_2O, and 1.0 mmol of NH_4OAc in 0.5 mL of dimethylacetamide (DMA). A solvent screen further established that DMA was indeed one of the best solvents to perform the condensation reaction, with results using other solvents such as DMF, DMSO, ethanol, methanol, or acetonitrile showing inferior conversions under otherwise identical conditions. Along similar lines, it was quickly established that 0.5 mL of solvent for 0.5 mmol of substrate proved to be optimal for obtaining high conversions in a comparatively short time frame. The highest yields (HPLC-UV conversion >90%) were obtained at a reaction temperature of 250 °C after 30 min, and the optimum ratio of anthranilic acid/Ac_2O/NH_4OAc was ultimately derived to be 1:4:3. At temperatures <220 °C, almost no conversion to 2-methylquinazolinone **6A** (X = H, Y = CH) was observed by HPLC-UV monitoring, and reaction times below 20 min led to significantly reduced yields. Product isolation involved precipitation of the quinazolinone with ice water and provided the desired 2-methylquinazolinone **6A** consistently in isolated yields of ~75% as a pure solid (HPLC-UV purity at 215 nm >99%).

In a subsequent step, we studied the Knoevenagel condensation of 2-methylquinazolinone **6A** with benzaldehyde (**7a**)—as a representative of an aromatic aldehyde—to produce the desired 2-styrylquinazolinone **8Aa**. Gratifyingly, we discovered that the 2-methylquinazolinone intermediate **6A** did not need to be isolated and that in fact higher overall yields of the final 2-styrylquinazolinone **8Aa** were obtained when the aldehyde component was added directly to the crude reaction mixture resulting from the condensation of anthranilic acid (**5A**) with Ac_2O and NH_4OAc after cooling. Under these conditions the desired product **8Aa** was obtained within 30 min (for step 2) in reproducibly high overall yields of ~75%. It has to be emphasized that, in contrast to pervious reports,[8,9,11,12,14] the Knoevenagel condensation step here is performed under catalyst-free conditions and provides a high product yield in a comparatively short reaction time.

Library Validation—Scope and Limitations. Having optimized conditions for the synthesis of 2-styrylquinazolinone **8Aa** in hand, we next investigated the scope and limitations of both steps of the planned library synthesis. We have therefore chosen three additional anthranilic acid-type building blocks **5B**−**D** (Figure 3) for the condensation with Ac_2O and NH_4OAc (**5** → **6**). The selection of anthranilic acids was made based on commercial availability and on

the known biological activity associated with the quinazolinone derivatives resulting from these aromatic scaffolds (Figure 1).[8] As anticipated, the 2-methylquinazolinones **6B**−**D** were formed in good yields (66−78%) applying the previously optimized conditions for **6A** using single-mode microwave irradiation (see the Experimental Section for details).

For the second step (Knoevenagel condensation), we wanted to utilize our recently developed high-throughput synthesis platform that allows parallel microwave chemistry to be performed in standard sealed HPLC/GC autosampler vials contained in a silicon carbide microtiter-type plate (Figure 2).[15] In combination with an aluminum sealing plate, this setup can be used for microwave processing reaction volumes from 0.5−1.5 mL at a maximum temperature/pressure limit of 250 °C/20 bar. The parallel reaction platform has been shown to display excellent temperature and reaction homogeneity and has been used successfully for high-throughput reaction optimization studies.[15] In order to rapidly evaluate the scope in aldehyde diversity for the reaction step **6** → **8** (Scheme 1), we have setup a parallel microwave plate experiment involving 2-methylquinazolinones **6A** and **6B** and a selection of 15 aromatic, heteroaromatic, and aliphatic aldehyde building blocks **7a**−**o** (Figure 4). The nicotinic acid-derived building block **5B** was chosen for an initial evaluation since preliminary experiments in a single-mode microwave reactor on 0.5 mmol scale (180−250 °C, 15−60 min) have demonstrated that the lowest yields were typically experienced with this aza-anthranilic acid derivative.

In order to increase synthetic efficiency and to simplify the weighing/handling of individual HPLC/GC vials, the preparation of the 2-methylquinazolinone intermediates **6A** and **6B** (Scheme 1) was performed on a 10.0 mmol scale (∼15 mL reaction volume) utilizing single-mode microwave heating in 20 mL reaction vials (Initiator EXP, Biotage) using the optimized synthetic procedure described above (DMA, 250 °C, 30 min). After cooling the reaction vials to ∼40 °C, 0.75 mL aliquots of the crude reaction mixtures containing ∼0.5 mmol of **6A** and **6B**, respectively, were each dispensed into 10 HPLC/GC vials containing the appropriate amount of aldehydes **7a**−**o** (0.5 mmol) together with a magnetic stir bar. After crimping the vials and sealing the plate setup with an aluminum top,[15] the synthesis platform was placed in a dedicated multimode microwave instrument (Synthos 3000, Anton Paar GmbH) and processed at 200 °C for 30 min. Analysis of the screening results based on isolated yields of the precipitated products and/or HPLC-UV analysis of the crude reaction mixtures quickly revealed that while aromatic and heteroaromatic aldehydes provided moderate to high overall isolated yields of the 2-styrylquinazolinones **8**, aliphatic aldehydes were not able to undergo the anticipated Knoevenagel condensation in a preparatively useful manner (Table 1). Although the formation of the corresponding 2-styrylquinazolinones **8** (R = alkyl) could be confirmed by MS analysis, attempts to find improved conditions for the Knoevenagel condensation of aliphatic aldehydes with 2-methylquinazolinones of type **6** remained unsuccessful.

Table 1. Parallel Reactivity Screening of Aldehydes **7a**−**o** in the Knoevenagel Condensation with 2-Methylquinazolinones **6A** and **6B** (Scheme *1*)[a]

product	yield (%)[b]	product	yield (%)[b]
8Ab	80	**8Bb**	37 [44][c]
8Ae	78	**8Ba**	35
8Ao		**8Bk**	33
8Ah	68	**8Bg**	39
8Ai	47	**8Bd**	41
8Ac	75 [69][c]	**8Bo**	
8An		**8Bn**	
8Aj	52 [47][c]	**8Bf**	37
8Al	62	**8Bh**	40
8Ak	68	**8Bm**	32

[a] Reaction conditions: multimode sealed-vessel microwave irradiation using the 5 × 4 silicon carbide high-throughput synthesis reaction platform (0.5 mmol scale, DMA, 200 °C, 30 min). For details, see the *Experimental Section*. [b] Yields refer to overall isolated yields of crude products (>90% purity by HPLC-UV at 215 nm) after precipitation with water based on anthranilic acids **5**. Products were characterized by ^{1}H/^{13}C NMR spectroscopy and MS analysis. [c] Yields obtained under single-mode conditions (0.5 mmol, same reaction temperatures/times as in the multimode experiments; see the *Experimental Section*).

In order to confirm the validity of the parallel plate concept, the synthesis of a few selected 2-styrylquinazolinones (**8Ac**, **8Aj**, **8Bb**) was repeated using single-mode microwave technology on the same reaction scale (0.5 mmol). Gratifyingly, the isolated yields obtained using this method were similar to the results achieved using multimode parallel microwave technology (Table 1). It should be emphasized that the parallel reactivity screening for different aldehydes in the Knoevenagel condensation **6** → **8** was performed in a single microwave irradiation experiment. The overall processing time for this experiment performed at 200 °C for 30 min including ramp and cooling times was ∼50 min. In order to obtain the same information using sequential microwave processing, having to irradiate each reaction vessel individually, a time frame of >12 h would be required.

Library Production. Having a reliable protocol for the rapid generation of 2-styrylquinazolinones of type **8** in hand, we decided to generate a 40 member library of this scaffold irradiating two silicon carbide plates containing 20 HPLC/GC reaction vials each simultaneously.[15,18] The limited solubility of 2-methylquinazolinones **6** derived from substituted anthranilic acids **5C** and **5D**, however, required a modification of the originally chosen processing scheme. Instead of preparing the 2-methylquinazolinone intermediates **6A**−**D** under single-mode microwave conditions and subsequently dispensing stock solutions into HPLC/GC vials containing the aldehyde building blocks **7**, both synthetic steps were now performed in the silicon carbide plates. For the initial three-component condensation step **5** → **6**, solutions of the corresponding anthranilic acids **5A**−**D** (0.5 mmol) in DMA containing the appropriate amounts of Ac_2O (2.0 mmol) and NH_4OAc (1.5 mmol) were filled into the corresponding 40 HPLC/GC vials (2 plates of 20 each). After sealing and microwave processing at 250 °C for 30 min, the plates were cooled down to ambient conditions. For the second reaction step (**6** → **8**), 0.5 mmol of the appropriate aldehyde building blocks **7** were added neat to the HPLC/GC vials. For the current library project, this was done by decrimping/recrimping of the HPLC/GC vials although in principle the aldehydes could also have been dispensed as

Table 2. Parallel Microwave-Assisted Library Synthesis of 2-Styrylquinazolines **8** Using a High-Throughput Synthesis Platform (Scheme *1*)[a]

product	yield (%)[b]	product	yield (%)[b]
8Ab	79	**8Ce**	60
8Ae	67	**8Cb**	60
8Ap	65	**8Ca**	67
8Ah	64	**8Ch**	57
8Ai	55	**8Ci**	25
8Ac	82	**8Cd**	60
8Aq	35	**8Ck**	52
8Aj	60	**8Cm**	57
8Al	67	**8Cl**[c]	71
8Ak	76	**8Cq**	
8Bb	39	**8Da**	58
8Ba	40	**8Db**	59
8Bk	36	**8Dd**	59
8Bg	35	**8Dg**	47
8Bd	40	**8Dk**	55
8Bc	45	**8Dc**[c]	67
8Be	40	**8Dm**	59
8Bf	30	**8Df**[c]	45
8Bh	41	**8Dh**	62
8Bm	37	**8De**[c]	62

[a] Reaction conditions: multimode sealed-vessel microwave irradiation using the 5 × 4 silicon carbide high-throughput synthesis reaction platform [(step 1 (**5** → **6**)) 0.5 mmol scale, DMA, 250 °C, 30 min; (step 2) 200 °C, 30 min). For details, see the *Experimental Section*. [b] Yields refer to overall isolated yields of crude products (>90% purity by HPLC-UV at 215 nm) after precipitation with water based on anthranilic acids **5**. Products were characterized by ^{1}H/^{13}C NMR spectroscopy and MS analysis. [c] HPLC purity (215 nm) of **8Cl** 52%; **8Dc** 80%; **8Df** 66%; **8De** 80%.

stock solutions through the silicone/PTFE septa.[15] Subsequent microwave processing at 200 °C for 30 min provided the desired 2-styrylquinazolinones **8**. Workup of the reaction mixtures in all cases involved addition of water and filtration of the precipitated solids, followed by washing with water. In the majority of cases, the crude purity of the obtained heterocycles was >90% as judged from HPLC-UV (215 nm) and/or ^{1}H NMR analysis, with only four examples showing a lower purity (see Table 2). The main impurity in all cases consisted of unreacted intermediates **6A**−**D** and of the corresponding aldehyde building blocks **7**, indicating that the Knoevenagel step was not reaching completion under these reaction conditions. Analytically pure samples were obtained by recrystallization from EtOH (see the Experimental Section for details).

The results of the library synthesis are shown in Table 2. Four types of anthranilic acids (**5A**−**D**, Figure 3) and fifteen aromatic and heteroaromatic aldehydes **7a**−**m**,**p**,**q** (Figure 4) were selected. Since our validation experiments indicated that aliphatic aldehydes (i.e., **7n** and **o**) were not suitable for the Knoevenagel condensation step **6** → **7**, those were omitted from the library synthesis. Each of the four anthranilic acid building blocks was reacted with ten aldehydes in two silicon carbide plates. Gratifyingly, all 40 two-step/one-pot transformations were successful and led to the desired 2-styrylquinazolinones **8** in moderate to high yields (25−82%, average yield 54%). The only exception was compound **8Cq** derived from cinnammaldehyde which did not lead to any Knoevenagel-derived isolated product. Apart from this example, the combination of anthranilic acids **5A**−**D** with a wide variety of aromatic aldehydes **7** including electron-donating (OMe, Me) and -withdrawing substituents (CF_3, CN), in addition to sterically demanding aldehydes (2,6-dimethylphenyl, 1-naphthyl), was successful. The use of heteroaromatic aldehydes such as indole-, thiophene-, and pyridine-derived substrates was equally efficient (Table 2). The low to moderate yields obtained for some analogs were mainly a consequence of poor crystallization (in particular for compounds derived from aza-anthranilic acid **5B**), in some cases also a result of incomplete Knoevenagel condensations.

Of particular interest were 2-styrylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones of type **8B** derived from nicotinic acid analog **5B**. While a significant number of papers have been published describing different approaches to 2-styrylquinazolinones,[9−13] the aza-analogs 2-styrylpyrido[2,3-*d*]pyrimidines have attracted far less attention.[19]

The required microwave processing time for the two-step generation of this 39 member library was ∼2 h, taking into account heating and cooling cycles, as well as the time needed for the assembly of the silicon carbide platforms. Preparing all 40 compounds via automated sequential microwave processing would require at least 50 h.

Conclusion

In conclusion, we have demonstrated that the generation of compound libraries can be efficiently performed in a high-throughput synthesis platform consisting of 20 standard disposable HPLC/GC autosampler vials contained in a block of silicon carbide. The use of aluminum crimp caps with PTFE coated silicon septa in combination with an appropriate plate sealing mechanism allows processing of reaction volumes from 0.5−1.5 mL at temperatures of ∼250 °C and pressures of up to ∼20 bar. In the current example, the two-step/one-pot parallel microwave synthesis of a library of 39 2-styrylquinazolinones **8** was achieved in two plates within ∼2 h microwave processing time. Compared to conventional library generation methods using automated sequential microwave processing, this constitutes a considerable increase in efficiency. With the possibility of performing 80 reactions in parallel in the current design (four plates),[15] the HPLC/GC microwave reaction vial platform can be used as an efficient tool for high-throughput synthesis, either by rapidly validating the reactivity of building blocks (scope and limitation studies) or by synthesizing compound libraries in parallel on a small scale (10−100 mg).

Experimental Section

General and Materials. All chemicals were purchased from commercial sources and used without further purification. The details of the silicon carbide reaction platform have been previously reported.[15]

HPLC-UV Analysis. Analytical HPLC analysis (Shimadzu LC 20) was carried out on a C 18 reversed-phase analytical column (150 × 4.6 mm, particle size 5 μm) using mobile phases A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 0.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 9 min, hold at 100% solution B for 2 min.

MS Analysis. For MS investigations, an HP 1100 combined with a HP LC/MSD fitted with an Atmospheric

Pressure Chemical Ionization (APCI) ion source was used. The chromatographic conditions were as follows: flow injection analysis (FIA) mode (no column). The flow rate was set to 0.7 mL/min, and the injection volume was 5 μL. The mobile phase consisted of 75% acetonitrile, 20% water/acetonitrile (9:1), and 5% methanol. The MS conditions were as follows: positive and negative ions were generated using APCI (3000 V capillary voltage for positive and negative ion mode, respectively). The nebulizer was set to 60 psig, and the drying gas flow, to 5 L/min. The drying gas flow temperature and the vaporizer temperature were set to 350 °C, respectively. The current of the Corona was 5 μA for positive and 20 μA for negative ionization. The peak width was set to 0.1 min, and the fragmentor was set to 50, 100, 150, and 200 V, respectively.

General Procedure for the Preparation of Quinazolin-4(3*H*)-ones 6A−D (Single-Mode). A microwave vial (0.5−2 mL) was equipped with a magnetic stir bar, 0.5 mmol of the appropriate anthranilic acid **5A−D**, 2 mmol (190 μL) of Ac_2O, 1.5 mmol (116 mg) of NH_4OAc, and 0.5 mL of DMA. The microwave vial was crimped, inserted into the microwave cavity (Initiator EXP, Biotage), and the reaction mixture was irradiated for 30 min (hold time) at 250 °C. After the reaction mixture was cooled to ∼40 °C with compressed air (∼5 min), the quinazolinone products **6A−D** were obtained as colorless solids by precipitation with cold water (∼7 mL) and filtration in a preweight glass frit (>99% purity by HPLC at 215 nm).

2-Methylquinazolin-4(3*H*)-one (6A). 75% yield, mp 235−236 °C, literature[20a] mp 238−239 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.35 (s, 3H), 7.42−7.48 (m, 1 H), 7.57 (d, J = 7.8 Hz, 1 H), 7.74−7.80 (m, 1 H), 8.08 (dd, J = 7.8, 1.2 Hz, 1 H), 12.20 (brs, 1 H, NH).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.9, 121.1, 126.1, 126.2, 127.0, 134.7, 149.4, 154.7, 162.1. MS (neg. APCI) *m/z:* 159.2 [M − H$^+$], (M = 160.17).

2-Methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (6B). 68% yield, mp 257−259 °C, literature[20b] mp 262−264 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.40 (s, 3 H), 7.46−7.50 (m, 1 H), 8.45 (dd, J = 8.0, 1.8 Hz, 1 H), 8.90 (dd, J = 4.5, 1.8 Hz, 1 H), 12.49 (brs, 1 H, NH).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 22.2, 116.1, 122.1, 135.8, 156.2, 158.3, 159.3, 162.7. MS (neg. APCI) *m/z:* 160.2 [M − H$^+$], (M = 161.16).1.

6-Chloro-2-methylquinazolin-4(3*H*)-one (6C). 72% yield, mp 280−281 °C, literature[20a] mp 282−283 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.35 (s, 3 H), 7.59 (d, J = 9.0 Hz, 1 H), 7.79 (dd, J = 9.0, 2.7 Hz, 1 H), 8.0 (d, J = 2.7 Hz, 1 H), 12.38 (brs, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.9, 122.3, 125.1, 129.3, 130.5, 134.8, 148.2, 155.4, 161.2. MS (neg. APCI) *m/z:* 193.2 [M − H$^+$], (M = 194.62).

6-Methoxy-2-methylquinazolin-4(3*H*)-one (6D). 78% yield, mp 271−272 °C, literature[20c] mp 270 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.32 (s, 3 H), 3.85 (s, 3 H), 7.37 (dd, J = 9.0, 3.0 Hz, 1 H), 7.46 (d, J = 3.0 Hz, 1 H), 7.52 (d, J = 8.7 Hz, 1 H), 12.14 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.6, 55.9, 106.1, 121.8, 124.1, 128.7, 143.9, 152.2, 157.5, 162.0. MS (neg. APCI) *m/z:* 189.3 [M − H$^+$], (M = 190.20).

General Procedure for the Preparation of 2-Styrylquinazolin-4(3*H*)-ones 8 (One Pot, Single-Mode). To obtain the desired 2-styrylquinazolin-4(3*H*)-ones **8**, the microwave vials from the reaction step **5** → **6** (see above) were decrimped after the cooling process and 0.5 mmol of the appropriate aldehyde building blocks **7** (Figure 4) were added. After crimping, the vials were inserted into the microwave cavity (Initiator EXP, Biotage) and irradiated for additional 30 min at 200 °C. After cooling, the crude products were obtained by precipitation with ∼7 mL of water and filtration into preweight glass frits. After drying the products overnight at 50 °C, the purities were determined by HPLC-UV analysis (215 nm, see Table 2 for yields and purities).

Parallel Microwave Synthesis of 2-Styrylquinazolin-4(3*H*)-ones 8 (Validation Plate, Table 1). For the initial formation of the intermediate **6A** (Scheme 1), a 20 mL microwave vial (Initiator EXP, Biotage) equipped with a stir bar was filled with 10 mmol (1.36 g) of anthranilic acid **5A**, 40 mmol (3.8 mL) of Ac_2O, 30 mmol (2.32 g) of NH_4OAc, and 10 mL of DMA. The reaction mixture was heated for 30 min at 250 °C and subsequently cooled to ∼40 °C with compressed air. An analogous procedure was performed for anthranilic acid **5B** (10 mmol, 1.38 g). After generating the 2-methylquinazolin-4(3*H*)-one intermediates **6A** and **6B** in the single-mode instrument, 0.75 mL aliquots of the crude reaction mixtures containing ∼0.5 mmol of **6A** and **6B** were dispensed into 20 HPLC/GC vials (10 for each intermediate) containing the appropriate preweighed amount of aldehydes **7a−o** (0.5 mmol) and a magnetic stir bar. The HPLC/GC vials were sealed with aluminum crimp caps in combination with PTFE-coated silicone septa to ensure pressure and heat resistance. Additionally the pressure resistance was increased by the use of an aluminum top plate fixed with six stainless bolts.[15] Microwave-assisted processing using a previously described high-throughput experimentation platform was carried out in a Synthos 3000 multimode microwave reactor (Anton Paar GmbH) using a dedicated rotor inside the cavity of the Synthos 3000 (temperature measured with an IR-sensor on the bottom of the SiC plate).[15] The second step (Knoevenagel condensation) was performed heating the reaction mixtures for 30 min at 200 °C. After cooling to room temperature, the crude products were obtained by precipitation with ∼7 mL of water and subsequent filtration using preweight glass frits. After drying in an oven at 50 °C overnight 16 styrylquinazolinones were obtained in moderate to high yields (Table 1). Analytically pure samples for NMR spectroscopy were obtained by recrystallization from EtOH.

Parallel Microwave Synthesis of 2-Styrylquinazolin-4(3*H*)-ones 8 (Library Production, Table 2). For the 40 member library production, both steps were performed in the SiC plates. Therefore 0.5 mmol of **5A** (68 mg), **5B** (69 mg), **5C** (86 mg), and **5D** (84 mg), respectively, were dispensed in 40 HPLC/GC vials (10 vials for each anthranilic acid) and mixed with 2 mmol (190 μL) of Ac_2O, 1.5 mmol (116 mg) of NH_4OAc, and 0.5 mL of DMA. A stir bar was put in each of the vials and the vials were sealed with aluminum crimp tops and an aluminum top plate as described

above. The initial reaction step **5** → **6** was performed at 250 °C for 30 min. After cooling with the built-in fan (∼10 min), the HPLC/GC vials were opened and the appropriate aldehyde building blocks **7a**−**m**,**p**,**q** (0.5 mmol, Figure 4) were added. After crimping/sealing as described above, the second reaction step (**6** → **8**, Knoevenagel condensation) was performed as described for the validation plate. Workup as discussed for the validation plate provided 39 2-styrylquinazolin-4(3*H*)-ones **8** (for yields and purities; see Table 2). Analytically pure samples for NMR spectroscopy were obtained by recrystallization from EtOH. All 2-styrylquinazolinones were identified either by comparison with authentic samples or in the case of novel structures by ^{1}H/^{13}C NMR spectroscopy in addition to MS analysis.

(*E*)-2-(4-Methylstyryl)quinazolin-4(3*H*)-one (8Ab). mp 280−282 °C, literature[14] mp 285−287 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.34 (s, 3 H), 6.95 (d, J = 18 Hz, 1 H), 7.27 (d, J = 8.1 Hz, 2 H), 7.45−7.48 (m, 1 H), 7.55 (d, J = 8.1 Hz, 2 H), 7.68 (d, J = 7.8 Hz, 1 H), 7.78−7.80 (m, 1 H), 7.93 (d, J = 18 Hz, 1 H), 8.12 (dd, J = 7.8, 1.2 Hz, 1 H), 12.30 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.4, 120.4, 121.5, 126.3, 126.5, 127.5, 128.0, 130.1, 132.7, 134.9, 138.7, 140.0, 149.5, 152.0, 162.2. MS (pos. APCI) *m/z:* 263.3 [M + H$^+$], MS (neg. APCI) *m/z:* 261.2 [M − H$^+$], (M = 262.31).

(*E*)-2-(4-Fluorostyryl)quinazolin-4(3*H*)-one (8Ae). mp 284−286 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.96 (d, J = 16.2 Hz, 1 H), 7.27−7.33 (m, 2 H), 7.45−7.51 (m, 1 H), 7.66−7.84 (m, 4 H), 7.95 (d, J = 16.2 Hz, 1 H), 8.12 (dd, J = 7.8, 1.2 Hz, 1 H), 11.70 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.4, 116.7, 121.5, 126.3, 126.7, 127.5, 130.2, 130.3, 132.1, 132.1, 134.9, 137.5, 149.4, 151.8, 161.6, 162.2, 164.9. MS (pos. APCI) *m/z:* 267.2 [M + H$^+$], MS (neg. APCI) *m/z:* 265.1 [M − H$^+$], (M = 266.27).

(*E*)-2-(2-(Naphthalen-1-yl)vinyl)quinazolin-4(3*H*)-one (8Ap). mp 240−242 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.10 (d, J = 16.2 Hz, 1 H), 7.49−7.75 (m, 5 H), 7.81−7.87 (m, 1 H), 7.98−8.03 (m, 3 H), 8.17 (dd, J = 8.1 Hz, 1.2 Hz, 1 H), 8.49 (d, J = 8.1 Hz, 1 H), 8.76 (d, J = 16.2 Hz, 1 H), 12.59 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 121.6, 124.0, 124.5, 124.8, 126.3, 126.3, 126.7, 127.3, 127.7, 129.1, 130.4, 131.4, 132.5, 133.8, 134.8, 134.9, 149.4, 151.9, 162.3. MS (pos. APCI) *m/z:* 299.3 [M + H$^+$], MS (neg. APCI) *m/z:* 297.2 [M − H$^+$], (M = 298.34).

(*E*)-2-(3,4-Difluorostyryl)quinazolin-4(3*H*)-one (8Ah). mp 308−310 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.00 (d, J = 16.2 Hz, 1 H), 7.47−7.55 (m, 3 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.76−7.93 (m, 3 H), 8.12 (d, J = 7.8 Hz, 1 H), 12.34 (brs, 1 H, NH). MS (pos. APCI) *m/z:* 285.2 [M + H$^+$], MS (neg. APCI) *m/z:* 283.1 [M − H$^+$], (M = 284.26).

(*E*)-2-(2,6-Dimethylstyryl)quinazolin-4(3*H*)-one (8Ai). mp 214−216 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.37 (s, 6 H), 6.57 (d, J = 16.8 Hz, 1 H), 7.11−7.16 (m, 3 H), 7.47−7.52 (m, 1 H), 7.70 (d, J = 7.8 Hz, 1 H), 7.81 (t, J = 8.1 Hz, 1 H), 8.04 (d, J = 16.8 Hz, 1 H), 8.13 (dd, J = 8.1, 1.2 Hz, 1 H), 12.39 (brs, 1 H, NH).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.4, 121.6, 126.3, 126.7, 127.1, 127.7, 127.8, 128.4, 128.7, 130.0, 134.8, 134.9, 136.9, 136.9, 149.4, 151.7, 162.3. MS (pos. APCI) *m/z:* 277.1 [M + H$^+$], MS (neg. APCI) *m/z:* 275.3 [M − H$^+$], (M = 276.33).

(*E*)-2-(4-Methoxystyryl)quinazolin-4(3*H*)-one (8Ac). mp 277−279 °C, literature[14] mp 276−278 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.81 (s, 3 H), 6.86 (d, J = 16.2 Hz, 1 H), 7.03 (d, J = 8.7 Hz, 1 H), 7.64 (t, J = 7.3 Hz, 1 H), 7.60−7.67 (m, 3 H), 7.77−7.82 (m, 3 H), 7.92 (d, J = 16.2 Hz, 1 H), 8.10 (d, J = 6.9 Hz, 1 H), 12.25 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 55.8, 115.0, 118.9, 121.4, 126.3, 126.4, 127.4, 128.0, 129.7, 134.9, 138.5, 149.6, 152.2, 161.1, 162.2. MS (neg. APCI) *m/z:* 277.3 [M − H$^+$], (M = 278.31).

2-((1*E*,3*E*)-4-Phenylbuta-1,3-dienyl)quinazolin-4(3*H*)-one (8Aq). mp 241−243 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.01 (d, J = 15.3 Hz, 1 H), 7.13−7.21 (m, 1 H), 7.29−7.46 (m, 4 H), 7.57−7.63 (m, 3 H), 7.69−7.78 (m, 2 H), 8.07 (dd, J = 7.9, 1.2 Hz, 1 H), 12.28 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 121.4, 124.6, 126.3, 126.5, 127.5, 127.6, 127.9, 129.2, 129.2, 134.9, 136.7, 139.1, 139.7, 149.5, 151.9, 162.2. MS (neg. APCI) *m/z:* 273.3 [M − H$^+$], (M = 274.32).

(*E*)-2-(2-(Pyridin-2-yl)vinyl)quinazolin-4(3*H*)-one (8Aj). mp 212−213 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.38−7.42 (m, 1 H), 7.46−7.53 (m, 2 H), 7.65−7.72 (m, 2 H), 7.81−7.91 (m, 2 H), 7.99 (d, J = 15.7 Hz, 1 H), 8.13 (d, J = 7.9 Hz, 1 H), 8.68 (d, J = 4.5 Hz, 1 H), 12.46 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 121.7, 124.6, 124.9, 125.0, 126.3, 126.9, 127.7, 134.9, 137.7, 138.0, 149.3, 150.4, 151.5, 153.3, 162.1. MS (neg. APCI) *m/z:* 248.3 [M − H$^+$], (M = 249.27).

(*E*)-2-(2-(1*H*-Indol-3-yl)vinyl)quinazolin-4(3*H*)-one (8Al). mp 215−216 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.98 (d, J = 15.9 Hz, 1 H), 7.19−7.26 (m, 2 H), 7.37−7.51 (m, 2 H), 7.63 (d, J = 8.1, 1 H), 7.73−7.79 (m, 1 H), 7.92 (d, J = 2.7 Hz, 1 H), 8.00−8.10 (m, 2 H), 8.20 (d, J = 15.9 Hz, 1 H), 11.72 (s, 1 H, NH), 12.13 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 112.9, 113.2, 114.7, 120.5, 121.1, 121.1, 122.9, 125.3, 125.6, 126.3, 127.1, 131.5, 133.7, 134.8, 137.9, 150.0, 153.3, 162.3. MS (neg. APCI) *m/z:* 286.3 [M − H$^+$], (M = 287.32).

(*E*)-2-(2-(Pyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (8Ak). mp 247−249 °C, literature[11] mp 240−241 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.13 (d, J = 16.2 Hz, 1 H), 7.47−7.53 (m, 2 H), 7.70 (d, J = 7.8 Hz, 1 H), 7.80−7.85 (m, 1 H), 7.98 (d, J = 16.2 Hz, 1 H), 8.08−8.15 (m, 2 H), 8.60 (dd, J = 4.5, 1.2 Hz, 1 H), 8.82 (d, J = 2.1 Hz, 1 H), 12.39 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 121.6, 123.5, 124.5, 126.3, 126.9, 127.6, 131.2, 134.3, 135.0, 135.3, 149.3, 149.7, 150.7, 151.5, 162.1. MS (neg. APCI) *m/z:* 248.3 [M − H$^+$], (M = 249.27).

(*E*)-2-(4-Methylstyryl)pyrido[2,3-d]pyrimidin-4(3*H*)-one (8Bb). mp 255−257 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.35 (s, 3 H), 6.98 (d, J = 15.9 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.45−7.49 (m, 1 H), 7.58 (d, J = 8.1 Hz, 2 H), 8.02 (d, J = 15.9 Hz, 1 H), 8.46 (dd, J = 7.8, 1.8 Hz, 1 H), 8.93−8.94 (m, 1 H), 12.58 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.5, 116.7, 120.0,

122.1, 128.3, 130.2, 132.5, 135.8, 140.3, 140.5, 154.9, 156.5, 159.5, 162.9. MS (neg. APCI) *m/z:* 262.3 [M − H^+], (M = 263.29).

(*E*)-2-Styrylpyrido[2,3-d]pyrimidin-4(3*H*)-one (8Ba). Mp 256−258 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.06 (d, *J* = 15.9 Hz, 1 H), 7.44−7.51 (m, 4 H), 7.68−7.71 (m, 2 H), 8.06 (d, *J* = 15.9 Hz, 1 H), 8.48 (dd, *J* = 7.8, 1.8 Hz, 1 H), 8.94−8.96 (m, 1 H), 12.63 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.7, 121.1, 122.2, 128.3, 129.5, 130.5, 135.2, 135.8, 140.3, 154.8, 156.5, 159.4, 162.8. MS (neg. APCI) *m/z:* 248.3 [M − H^+], (M = 249.27).

(*E*)-2-(2-(Pyridin-3-yl)vinyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (8Bk). mp 269−271 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.53 (d, *J* = 15.3 Hz, 1 H), 7.05 (d, *J* = 15.6 Hz, 1 H), 7.16−7.25 (m, 1 H), 7.32−7.49 (m, 4 H), 7.61−7.73 (m, 3 H), 7.77−7.82 (m, 2 H), 8.08−8.11 (m, 1 H), 12.32 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 121.4, 124.6, 126.3, 126.5, 127.5, 127.6, 127.9, 129.2, 129.2, 134.9, 136.7, 139.1, 139.7, 149.5, 151.9, 162.2. MS (neg. APCI) *m/z:* 249.3 [M − H^+], (M = 250.26).

(*E*)-2-(3-(Trifluoromethyl)styryl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (8Bg). mp 259−261 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.18 (d, *J* = 16.2 Hz, 1 H), 7.48−7.52 (m, 1 H), 7.69−7.80 (m, 2 H), 8.00 (d, *J* = 10.8 Hz, 2 H), 8.11 (d, *J* = 16.2 Hz, 1 H), 8.48 (dd, *J* = 7.8, 2.1 Hz, 1 H), 8.95 (dd, *J* = 4.5, 2.1 Hz, 1 H), 12.61 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.9, 122.4, 122.6, 123.3, 124.6, 124.7, 126.2, 126.6, 126.7, 130.1, 130.5, 130.6, 131.9, 135.8, 136.3, 138.4, 154.4, 156.5, 159.3, 162.7. MS (neg. APCI) *m/z:* 316.3 [M − H^+], (M = 317.27).

(*E*)-2-(4-Chlorostyryl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (8Bd). mp 285−286 °C, literature[20b] mp 285 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.03 (d, *J* = 16.2 Hz, 1 H), 7.46−7.54 (m, 3 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 8.02 (d, *J* = 16.2 Hz, 1 H), 8.46 (dd, *J* = 7.8, 1.8 Hz, 1 H), 8.93−8.95 (m, 1 H), 12.62 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.8, 121.9, 122.2, 129.6, 129.9, 134.1, 135.0, 135.8, 138.8, 154.6, 156.5, 159.3, 162.8. MS (neg. APCI) *m/z:* 282.3 [M − H^+], (M = 283.71).

(*E*)-2-(4-Methoxystyryl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (8Bc). mp 255−257 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.82 (s, 3 H), 6.89 (d, *J* = 15.9 Hz, 1 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 7.44−7.48 (m, 1 H), 7.64 (d, *J* = 8.7 Hz, 2 H), 8.01 (d, *J* = 15.9 Hz, 1 H), 8.45 (dd, *J* = 7.8, 2.1 Hz, 1 H), 8.92 (dd, *J* = 4.5, 1.8 Hz, 1 H), 12.53 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 55.8, 115.0, 116.5, 118.4, 121.9, 127.8, 130.0, 135.8, 140.1, 155.1, 156.4, 159.5, 161.3, 162.9. MS (neg. APCI) *m/z:* 278.3 [M − H^+], (M = 279.29).

(*E*)-2-(4-Fluorostyryl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (8Be). mp 274−276 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.99 (d, *J* = 16.2 Hz, 1 H), 7.32 (t, *J* = 9 Hz, 2 H), 7.46−7.51 (m, 1 H), 7.73−7.78 (m, 2 H), 8.05 (d, *J* = 16.2 Hz, 1 H), 8.47 (dd, *J* = 7.8, 2.1 Hz, 1 H), 8.93 (dd, *J* = 4.5, 1.8 Hz, 1 H), 12.61 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.4, 116.7, 121.0, 122.2, 130.5, 130.6, 131.8, 131.8, 135.8, 139.1, 154.8, 156.4, 159.4, 161.8, 162.8, 165.1. MS (neg. APCI) *m/z:* 266.3 [M − H^+], (M = 267.26).

(*E*)-4-(2-(4-Oxo-3,4-dihydropyrido[2,3-*d*]pyrimidin-2-yl)vinyl)benzonitrile (8Bf). mp 340−342 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.18 (d, *J* = 16.5 Hz, 1 H), 7.50−7.53 (m, 1 H), 7.89−8.11 (m, 5 H), 8.49 (d, *J* = 6.9 Hz, 1 H), 8.96 (brs, 1 H), 12.69 (brs, 1 H, NH). MS (neg. APCI) *m/z:* 273.3 [M − H^+], (M = 274.28).

(*E*)-2-(3,4-Difluorostyryl)pyrido[2,3-d]pyrimidin-4(3*H*)-one (8Bh). mp 298−300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.02 (d, *J* = 16.2 Hz, 1 H), 7.47−7.54 (m, 3 H), 7.76−7.83 (m, 1 H), 8.01 (d, *J* = 16.2 Hz, 1 H), 8.47 (dd, *J* = 7.8, 2.1 Hz, 1 H), 8.94 (dd, *J* = 4.5, 1.8 Hz, 1 H), 12.61 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.7, 116.8, 117.0, 118.5, 118.8, 122.3, 122.6, 125.5, 125.5, 125.6, 125.6, 133.1, 133.1, 133.2, 135.8, 138.0, 148.5, 148.6, 149.0, 149.1, 151.7, 151.9, 152.3, 152.4, 154.4, 156.5, 159.3, 162.8. MS (neg. APCI) *m/z:* 284.3 [M − H^+], (M = 285.25).

(*E*)-2-(2-(Thiophen-2-yl)vinyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (8Bm). mp 232−234 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.76 (d, *J* = 15.6 Hz, 1 H), 7.17−7.20 (m, 1 H), 7.46−7.48 (m, 1 H), 7.54 (d, *J* = 3.3 Hz, 1 H), 7.73 (d, *J* = 5.1 Hz, 1 H), 8.23 (d, *J* = 15.6 Hz, 1 H), 8.45 (dd, *J* = 7.8, 2.1 Hz, 1 H), 8.92 (dd, *J* = 4.5, 2.1 Hz, 1 H), 12.51 (brs, 1 H, NH).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 116.6, 119.4, 122.0, 129.1, 129.8, 132.2, 133.4, 135.8, 140.3, 154.8, 156.4, 159.2, 163.0. MS (neg. APCI) *m/z:* 254.2 [M − H^+], (M = 255.30).

(*E*)-6-Chloro-2-(4-fluorostyryl)quinazolin-4(3*H*)-one (8Ce). mp 335−337 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.96 (d, *J* = 16.2 Hz, 1 H), 7.30 (t, *J* = 9 Hz, 2 H), 7.67−7.75 (m, 3 H), 7.83 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.96 (d, *J* = 16.2 Hz, 1 H), 8.03 (d, *J* = 2.4 Hz, 1 H), 10.15 (brs, 1 H, NH).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 100.0, 116.4, 116.7, 122.7, 125.4, 129.7, 130.3, 130.4, 130.8, 135.1, 138.0, 148.2, 152.4, 161.4. MS (neg. APCI) *m/z:* 299.3 [M − H^+], (M = 300.71).

(*E*)-6-Chloro-2-(4-methylstyryl)quinazolin-4(3*H*)-one (8Cb). mp 326−328 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.92 (d, *J* = 16.2 Hz, 1 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.54 (d, *J* = 8.1 Hz, 2 H), 7.67 (d, *J* = 8.7 Hz, 1 H), 7.81 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.91 (d, *J* = 16.2 Hz, 1 H), 8.02 (d, *J* = 2.7 Hz, 1 H), 12.45 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.5, 120.1, 122.7, 125.3, 128.1, 129.7, 130.1, 130.7, 132.6, 135.0, 139.2, 140.2, 148.2, 152.5, 161.2. MS (pos. APCI) *m/z:* 297.2 [M + H^+], MS (neg. APCI) *m/z:* 295.1 [M − H^+], (M = 296.75).

(*E*)-6-Chloro-2-styrylquinazolin-4(3*H*)-one (8Ca). mp 318−320 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.00 (d, *J* = 16.2 Hz, 1 H), 7.42−7.50 (m, 3 H), 7.65−7.71 (m, 3 H), 7.83 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.96 (d, *J* = 16.2 Hz, 1 H), 8.02 (d, *J* = 2.4 Hz, 1 H), 12.51 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 121.2, 122.8, 125.3, 128.1, 129.5, 129.8, 130.4, 130.8, 135.0, 135.3, 139.2, 148.2, 152.3, 161.2. MS (neg. APCI) *m/z:* 281.3 [M − H^+], (M = 282.72).

(*E*)-6-Chloro-2-(3,4-difluorostyryl)quinazolin-4(3*H*)-one (8Ch). mp 315−317 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.98 (d, *J* = 16.2 Hz, 1 H), 7.50−7.55 (m, 1 H), 7.68 (d, *J* = 8.7 Hz, 1 H), 7.77−7.92 (m, 3 H), 8.03

(d, J = 2.7 Hz, 1 H), 11.21 (brs, 1 H, NH). MS (neg. APCI) *m/z:* 317.3 [M − H^+], (M = 318.71).

(*E*)-6-Chloro-2-(2,6-dimethylstyryl)quinazolin-4(3*H*)-one (8Ci). mp 270−272 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.37 (s, 6 H), 6.57 (d, J = 16.5 Hz, 1 H), 7.09−17 (m, 3 H), 7.71 (d, J = 8.7 Hz, 1 H), 7.82 (dd, J = 8.7, 2.4 Hz, 1 H), 8.02−8.08 (m, 2 H), 12.55 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.3, 122.8, 125.3, 126.7, 128.5, 128.7, 129.9, 130.9, 134.7, 135.0, 136.7, 137.4, 148.1, 152.1, 161.3. MS (neg. APCI) *m/z:* 309.3 [M − H^+], (M = 310.78).

(*E*)-6-Chloro-2-(4-chlorostyryl)quinazolin-4(3*H*)-one (8Cd). mp >350 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.02 (d, J = 16.2 Hz, 1 H), 7.54 (d, J = 8.4 Hz, 2 H), 7.69−7.72 (m, 3 H), 7.85 (dd, J = 8.7, 2.7 Hz, 1 H), 7.95 (d, J = 16.2 Hz, 1 H), 8.06 (d, J = 2.4 Hz, 1 H), 12.52 (brs, 1 H, NH). MS (neg. APCI) *m/z:* 316.5 [M − H^+], (M = 317.17).

(*E*)-6-Chloro-2-(2-(pyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (8Ck). mp 304−306 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.09 (d, J = 16.2 Hz, 1 H), 7.46−7.50 (m, 1 H), 7.69 (d, J = 8.7 Hz, 1 H), 7.82 (dd, J = 8.7, 2.4 Hz, 1 H), 7.93−8.09 (m, 3 H), 8.58 (dd, J = 4.8, 1.2 Hz, 1 H), 8.81 (d, J = 1.2 Hz, 1 H), 12.55 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 122.8, 123.2, 124.5, 125.3, 129.8, 131.1, 131.1, 134.3, 135.1, 135.8, 148.0, 149.7, 150.9, 151.9, 161.1. MS (neg. APCI) *m/z:* 282.3 [M − H^+], (M = 283.71).

(*E*)-6-Chloro-2-(2-(thiophen-2-yl)vinyl)quinazolin-4(3*H*)-one (8Cm). mp 308−309 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.72 (d, J = 15.6 Hz, 1 H), 7.15−7.18 (m, 1 H), 7.49 (d, J = 3.3 Hz, 1 H), 7.66 (d, J = 8.7 Hz, 1 H), 7.70 (d, J = 5.1 Hz, 1 H), 7.81 (dd, J = 8.7, 2.7 Hz, 1 H), 8.01 (d, J = 2.4 Hz, 1 H), 8.13 (d, J = 15.6 Hz, 1 H), 12.42 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 119.5, 122.6, 125.3, 129.1, 129.4, 129.6, 130.6, 131.7, 132.4, 135.0, 140.4, 148.2, 152.1, 161.1. MS (neg. APCI) *m/z:* 287.2 [M − H^+], (M = 288.75).

(*E*)-2-(2-(1*H*-Indol-3-yl)vinyl)-6-chloroquinazolin-4(3*H*)-one (8Cl). mp 288−290 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 6.96 (d, J = 15.9 Hz, 1 H), 7.20−7.27 (m, 2 H), 7.48−7.51 (m, 1 H), 7.58−7.65 (m, 1 H), 7.78 (td, J = 8.7, 2.7 Hz, 1 H), 7.93 (d, J = 2.7 Hz, 1 H), 8.00−8.02 (m, 2 H), 8.19 (d, J = 15.9 Hz, 1 H), 11.75 (brs, 1 H, NH), 12.28 (brs, 1 H, NH). MS (neg. APCI) *m/z:* 320.3 [M − H^+], (M = 321.76).

(*E*)-6-Methoxy-2-styrylquinazolin-4(3*H*)-one (8Da). mp 286−287 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.88 (s, 3 H), 6.98 (d, J = 16.2 Hz, 1 H), 7.40−7.48 (m, 4 H), 7.51 (d, J = 3 Hz, 1 H), 7.62−7.66 (m, 3 H), 7.89 (d, J = 16.2 Hz, 1 H), 12.30 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 56.0, 106.4, 121.6, 122.3, 124.4, 127.9, 129.3, 129.5, 130.0, 135.6, 137.6, 143.9, 149.7, 158.0, 161.9. MS (neg. APCI) *m/z:* 277.3 [M − H^+], (M = 278.31).

(*E*)-6-Methoxy-2-(4-methylstyryl)quinazolin-4(3*H*)-one (8Db). mp 290−292 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 2.34 (s, 3 H), 3.88 (s, 3 H), 6.91 (d, J = 16.2 Hz, 1 H), 7.26 (d, J = 8.1 Hz, 2 H), 7.41 (dd, J = 5.7, 3.0 Hz, 1 H), 7.50−7.54 (m, 3 H), 7.62 (d, J = 9.0 Hz, 1 H), 7.85 (d, J = 16.2 Hz, 1 H), 12.26 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.4, 56.0, 106.4, 120.5, 122.2, 124.4, 127.9, 129.2, 130.1, 132.8, 137.6, 139.8, 143.9, 149.9, 157.9, 161.9. MS (neg. APCI) *m/z:* 291.3 [M − H^+], (M = 292.33).

(*E*)-2-(4-Chlorostyryl)-6-methoxyquinazolin-4(3*H*)-one (8Dd). mp 314−316 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.88 (s, 3 H), 6.98 (d, J = 16.2 Hz, 1 H), 7.42 (dd, J = 5.7, 3.0 Hz, 1 H), 7.49−7.52 (m, 3 H), 7.62−7.68 (m, 3H), 7.86 (d, J = 16.2 Hz, 1 H), 12.30 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 56.1, 106.4, 122.4, 122.4, 124.5, 129.3, 129.5, 129.6, 134.4, 134.5, 136.2, 143.8, 149.5, 158.1, 161.9. MS (pos. APCI) *m/z:* 313.1 [M + H^+], MS (neg. APCI) *m/z:* 311.3 [M − H^+], (M = 312.75).

(*E*)-6-Methoxy-2-(3-(trifluoromethyl)styryl)quinazolin-4(3*H*)-one (8Dg). mp 265−266 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.88 (s, 3 H), 7.13 (d, J = 16.5 Hz, 1 H), 7.43 (dd, J = 9.0, 3.0 Hz, 1 H), 7.50−7.53 (m, 1 H), 7.63−7.77 (m, 3 H), 7.93−9.78 (m, 3H), 12.29 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 56.1, 100.0, 106.5, 122.5, 123.8, 124.3, 124.3, 124.5, 126.3, 129.4, 130.0, 130.6, 131.6, 135.9, 136.8, 143.7, 149.3, 158.2, 161.8. MS (pos. APCI) *m/z:* 347.1 [M + H^+], MS (neg. APCI) *m/z:* 345.3 [M − H^+], (M = 346.3).

(*E*)-6-Methoxy-2-(2-(pyridin-3-yl)vinyl)quinazolin-4(3*H*)-one (8Dk). mp 312−313 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.88 (s, 3 H), 7.09 (d, J = 16.5 Hz, 1 H), 7.44−7.53 (m, 3 H), 7.65 (d, J = 8.7 Hz, 1 H), 7.90 (d, J = 16.5 Hz, 1 H), 8.08 (d, J = 8.1 Hz, 1 H), 8.58 (d, J = 3.6 Hz, 1 H), 8.81 (s, 1 H), 12.35 (brs, 1 H, NH). MS (pos. APCI) *m/z:* 280.1 [M + H^+], MS (neg. APCI) *m/z:* 278.3 [M − H^+], (M = 279.29).

(*E*)-6-Methoxy-2-(4-methoxystyryl)quinazolin-4(3*H*)-one (8Dc). mp 285−287 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.81 (s, 3 H), 3.87 (s, 3 H), 6.83 (d, J = 15.9 Hz, 1 H), 7.35−7.62 (m, 7 H), 7.84 (d, J = 15.9 Hz, 1 H), 12.22 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 56.0, 106.4, 115.0, 119.0, 122.1, 124.1, 124.4, 128.2, 129.5, 137.4, 150.1, 157.5, 157.8, 160.9, 162.0. MS (pos. APCI) *m/z:* 309.2 [M + H^+], MS (neg. APCI) *m/z:* 307.3 [M − H^+], (M = 308.33).

(*E*)-6-Methoxy-2-(2-(thiophen-2-yl)vinyl)quinazolin-4(3*H*)-one (8Dm). mp 220−221 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.87 (s, 3 H), 6.71 (d, J = 15.9 Hz, 1 H), 7.14−7.17 (m, 1 H), 7.38−7.50 (m, 3 H), 7.60 (d, J = 9.0 Hz, 1 H), 7.66 (d, J = 5.7 Hz, 1 H), 8.06 (d, J = 15.9 Hz, 1 H), 12.22 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.7, 56.0, 106.4, 120.0, 122.2, 124.1, 124.4, 128.8, 128.9, 130.8, 130.9, 140.6, 143.9, 149.4, 157.9, 161.8. MS (pos. APCI) *m/z:* 285.1 [M + H^+], (M = 284.33).

(*E*)-4-(2-(6-Methoxy-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)benzonitrile (8Df). mp 322−324 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.88 (s, 3 H), 7.04−7.05 (m, 1 H), 7.41−7.45 (m, 1 H), 7.52 (d, J = 3.0 Hz, 1 H), 7.63−7.72 (m, 2 H), 7.82 (d, J = 9.6 Hz, 1 H), 7.89−7.94 (m, 3 H), 12.37 (brs, 1 H, NH).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 56.1, 106.5, 111.8, 119.2, 122.6, 124.6, 125.2, 127.7, 128.6, 129.6, 133.4, 135.7, 140.2, 143.7, 149.2,

158.3, 161.8. MS (pos. APCI) *m/z:* 304.1 [M + H^+], MS (neg. APCI) *m/z:* 302.3 [M − H^+], (M = 303.31).

(*E*)-2-(3,4-Difluorostyryl)-6-methoxyquinazolin-4(3*H*)-one (8Dh). mp 330−332 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.88 (s, 3 H), 6.95−7.01 (m, 1 H), 7.50−7.62 (m, 5 H), 7.74−7.86 (m, 2 H), 12.30 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 21.6, 56.0, 106.1, 106.5, 121.8, 124.2, 124.5, 128.7, 129.4, 143.9, 149.4, 152.2, 157.6, 162.0. MS (pos. APCI) *m/z:* 315.1 [M + H^+], MS (neg. APCI) *m/z:* 313.3 [M − H^+], (M = 314.29).

(*E*)-2-(4-Fluorostyryl)-6-methoxyquinazolin-4(3*H*)-one (8De). mp 313−315 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 3.88 (s, 3 H), 6.93 (m, J = 16.5 Hz, 1 H), 7.29 (t, J = 8.8 Hz, 2 H), 7.41 (dd, J = 9.0, 3.0 Hz, 1 H), 7.51 (d, J = 3.0 Hz, 1 H), 7.63 (d, J = 9.0 Hz, 1 H), 7.68−7.73 (m, 2 H), 7.87 (d, J = 16.2 Hz, 1 H), 11.23 (brs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 56.0, 106.4, 116.3, 116.6, 121.6, 122.3, 124.4, 129.2, 130.0, 130.1, 132.1, 136.4, 143.8, 149.7, 158.0, 161.9. MS (pos. APCI) *m/z:* 297.2 [M + H^+], MS (neg. APCI) *m/z:* 295.3 [M − H^+], (M = 296.30).

Acknowledgment. This work was supported by a grant from the Christian Doppler Research Society (CDG). We thank Anton Paar GmbH (Graz, Austria) for technical assistance and advice with microwave instrumentation.

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CC900036A