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CONVERSION OF 2-THIOXO-2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES TO *N*(3)-UNSUBSTITUTED 2-(HET)ARYLQUINAZOLIN-4(3*H*)-ONES BY COPPER-MEDIATED Pd-CATALYSED CROSS-COUPLING REACTIONS

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Dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday

Abstract – With the purpose of searching for new heterocyclic building blocks, a new method to access *N*(3)-unsubstituted 2-(het)arylquinazolin-4(3*H*)-ones from 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one derivatives was developed. The synthetic protocol was based on the copper-mediated palladium-catalysed cross-coupling reactions of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones with (het)arylstannanes or their *S*-benzylated derivatives with (het)arylboronic acids, using CuBr·Me_2S and CuMeSal as promoters, respectively. A similar transformation was applied for the preparation of 2-aryl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones.

INTRODUCTION

The quinazolin-4(3*H*)-one ring system is an important structural unit of many synthetically produced or naturally occurring[1,2] biologically active compounds, with some well-known drugs among them.[3,4] Examples include the *β*-glucuronidase enzyme inhibitor 2-(3,4-dimethoxyphenyl)quinazolin-4(3*H*)-one (**1**)[5] and 2,3-disubstituted derivatives of quinazolin-4(3*H*)-one such as Diproqualone (**2**), which exhibits sedative and analgesic properties,[6] as well as Afloqualone (**3**), which is known for its muscle-relaxant effects.[7-9] Tiprinast (**4**), which is based on the isosteric thieno[2,3-*d*]pyrimidin-4(3*H*)-one ring system, is a potent non-steroidal anti-allergy agent.[10] Moreover, the [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one **5**, which is structurally related to compound **4**, has been screened as an inhibitor for the Pim family of kinases.[11]

The most common approach for the construction of the quinazolin-4(3*H*)-one ring system is based on cyclization reactions of various 2-aminobenzoic acid derivatives including 2-aminobenzamides.[12,13] The recent examples for the synthesis of 3-substituted quinazolin-4(3*H*)-ones from 2-aminobenzamides comprise coupling the latter amide with benzaldehydes,[5] acid chlorides,[14] aryl halides in the presence of isocyanide,[15] and methylarenes.[16] Another recently developed synthetic pathway is based on the Pd-catalysed cyclization reaction of 2-halobenzoates with amidines.[17]

We have recently shown[18,19] that *N*(3)-benzyl 2-substituted quinazolin-4(3*H*)-one derivatives easily form with good yields when *N*(3)-benzyl 2-(benzylsulfanyl)quinazolin-4(3*H*)-ones are subjected to Suzuki- type Liebeskind-Srogl copper 3-methylsalicylate (CuMeSal) mediated palladium-catalysed cross-coupling reactions,[20] while the corresponding Stille-type reactions with (het)aryl tri-*n*-butylstannanes, are successfully completed in the presence of copper(I) thiophene-2-carboxylate (CuTC). However, the presence of a benzyl substituent at the *N*(3) atom of the products obtained, potentially prevents further functionalization of the heterocyclic system at this site of the molecule. Therefore, the main aim of the present work was to develop a method to access *N*(3)-unprotected 2-(het)arylquinazolin-4(3*H*)-ones from 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one derivatives. Such a synthetic protocol could also be useful in the preparation of diverse fused-pyrimidine libraries,[21,22] while it would provide a method for the convenient conversion of the 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one structural unit to the 2-substituted quinazolin-4(3*H*)-one moiety.

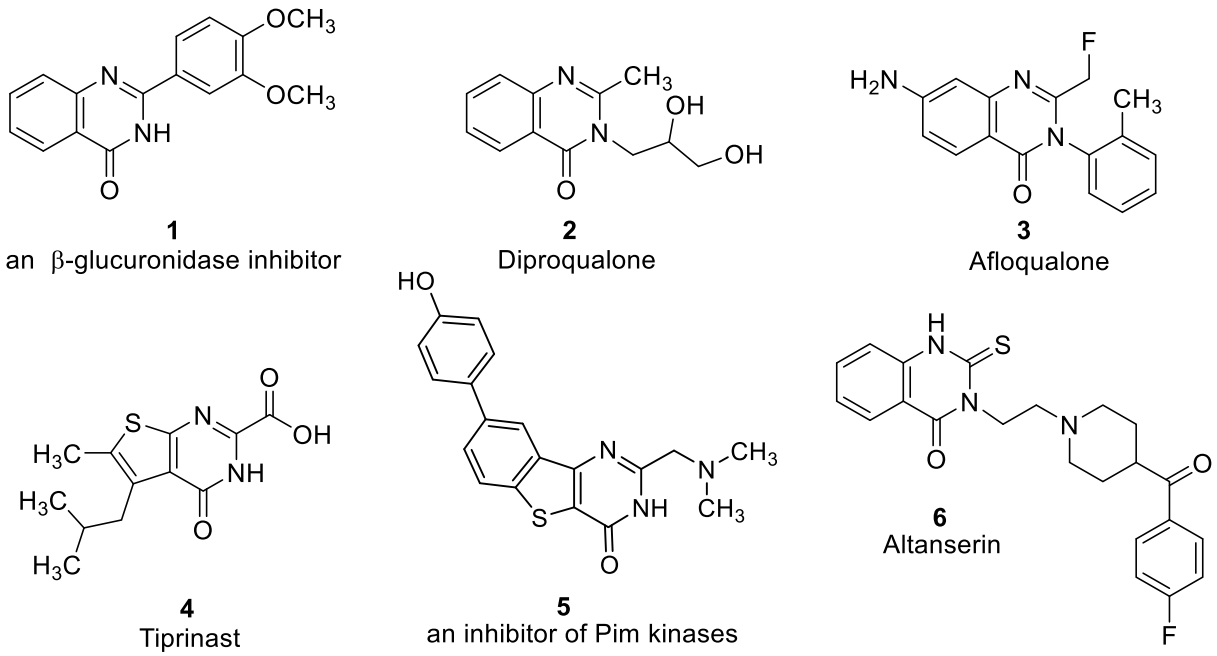


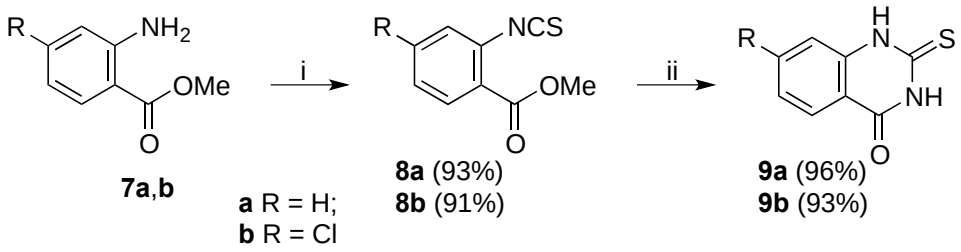
Figure 1. Biologically active molecules derived from quinazolin-4(3*H*)-one and its thieno-analogues

It has to be mentioned that 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones are easily accessible compounds.

Examples of their synthesis include the base-catalysed intramolecular cyclization of 2-[(carbamothioyl)amino]benzoates[18] and 1-(2-haloaroyl)-3-aryl thioureas,[23] the reaction of 2-aminobenzamides with phenyl isothiocyanate,[24] or aromatic ring annulation onto 2-thiobarbituric acid.[25] It was also shown that various derivatives of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one exhibit interesting biological activities and have found practical applications as diacylglycerol kinases inhibitors[26] and serotonin antagonists.[27-29] For example, the [^{18}F]-form of Altanserin **6** is the preferred radiotracer for in vivo labelling of serotonin 2A receptors by positron emission tomography (PET).[30]

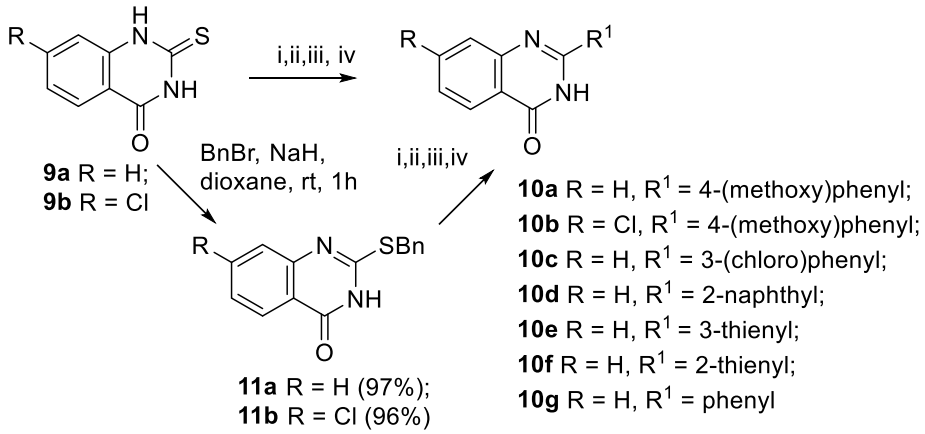
RESULTS AND DISCUSSION

The synthetic pathway for the preparation of the starting 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones **9a**,**b** is depicted in Scheme 1. The required precursor methyl 2-isothiocyanatobenzoate **8a** was obtained in good yield by reacting the corresponding methyl anthranilate **7a** with thiophosgene as previously reported.[18] The 4-chloro derivative **8b** was analogously prepared. Stirring of **8a**,**b** in toluene saturated with gaseous ammonia resulted in the formation of compounds **9a**,**b** in 96% and 93% yield, respectively.



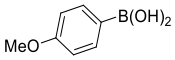
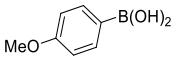
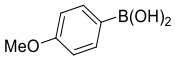
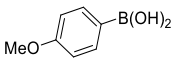
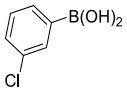
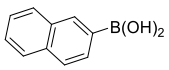
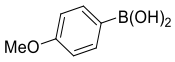
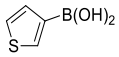
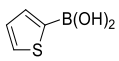
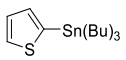
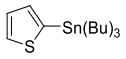
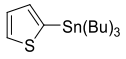
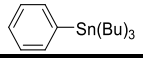
Scheme 1. *Reagents and conditions:* (i) $CSCl_2$, $CHCl_3$, $NaHCO_3$, H_2O, rt, 40 min, then corresponding amine, rt, 8 h; (ii) NH_3, toluene, pyridine, -34 °C to rt, 2 bar, 1 h

Having the key precursor **9a** in hand, we further tested its Suzuki-type cross-coupling under Liebeskind-Srogl Pd-catalysed reaction conditions.[20] 4-Methoxyphenylboronic acid was selected as a coupling counterpart, for the reason that the expected 2-(4-methoxyphenyl)quinazolin-4(3*H*)-one **10a** is known as a potent *β*-glucuronidase enzyme inhibitor.[5] However, the reaction of compound **9a** with 4-methoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ as catalyst and CuMeSal as promoter[31] in THF gave the target product **10a** in only a low isolated yield of 18% (Table 1, entry 1). Heating of the reaction mixture under microwave irradiation (MW) did not significantly improve the yield (Table 1, entry 2).



Scheme 2. *Reagents and conditions:* see Table 1

Table 1. Pd-catalysed reaction conditions using various coupling agents

Entry	Starting substrate	Coupling counterpart	Reaction conditions*	Product	Yield
1.	**9a**		i	**10a**	18%
2.	**9a**		ii	**10a**	24%
3.	**11a**		i	**10a**	96%
4.	**11b**		i	**10b**	66%
5.	**11a**		i	**10c**	73%
6.	**11a**		i	**10d**	95%
7.	**11a**		ii	**10a**	97%
8.	**11a**		ii	**10e**	93%
9.	**11a**		ii	**10f**	49%
10.	**9a**		iii	**10f**	79%
11.	**11a**		iii	**10f**	29%
12.	**11a**		iv	**10f**	80%
13.	**11a**		iv	**10g**	91%

*(i) Coupling counterpart (2.2 eqiv.), $Pd(PPh_3)_4$ (0.01 eqiv.), CuMeSal (2.2 eqiv.), THF, reflux, 48 h; (ii) coupling counterpart (2.2 eqiv.), CuMeSal (2.2 eqiv.), $Pd(PPh_3)_4$ (0.01 eqiv.), THF, MW, 100 ºC, 1 h; (iii) coupling counterpart (2.2 eqiv.), $CuBr{\cdot}Me_2S$ (2.2 eqiv.), $Pd(PPh_3)_4$ (0.01 eqiv.), THF, reflux, 48 h; (iv) coupling counterpart (2.2 eqiv.), $CuBr{\cdot}Me_2S$ (2.2 eqiv.), $Pd(PPh_3)_4$ (0.01 eqiv.), THF, MW, 100 ºC, 1 h

Next, we decided to activate the starting substrate by *S*-benzylation thereby forming the benzylsulfanyl moiety as a more effective leaving group, which was the strategy used in our previous work on the arylation of *N*(3)-protected 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones.[18,19] However, it is worth noting that the applicability of this two-step approach for the arylation of **9a**,**b** was uncertain due to the recent findings of Guillaumet et al. showing that the Suzuki-type Liebeskind-Srogl reaction of thiouracils with phenylboronic acid provides a successful outcome only for the corresponding *N*(3)-protected substrates.[32]

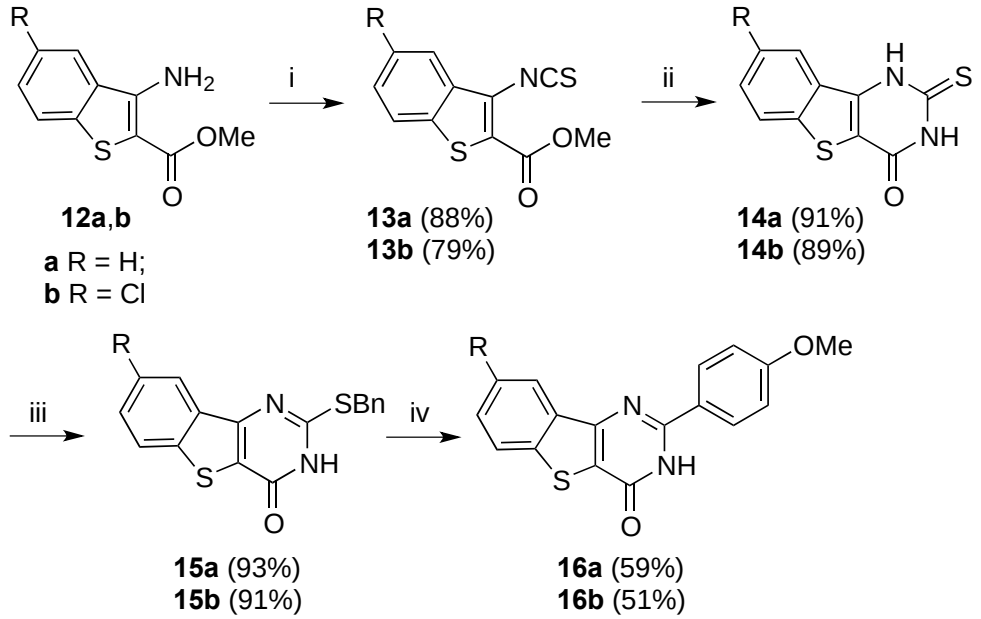
To prepare the required starting *N*(3)-unprotected 2-(benzylsulfanyl)quinazolin-4(3*H*)-ones **11a**,**b** as coupling substrates, we investigated the reaction of compounds **9a**,**b** with benzyl bromide. Recently, Sanchez et al. reported that the reaction of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **9a** with benzyl bromide in dry DMF in the presence of K_2CO_3 at rt afforded the *S*-benzylated product **11a**.[33] However, it was previously reported by Yun et al. that a similar benzylation **9a**, carried out in the presence of KOH, provided a mixture of *S*- and *N*-benzylated products.[34] When we treated 7-chloro-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one **9b** with benzyl bromide according to Sanchez's protocol (DMF, K_2CO_3, rt),[33] the formation of a complex mixture of *S*-monoalkylated, *S*/*N*-dialkylated and *S*/*O*-dialkylated products (NMR spectroscopy data) took place, from which the required **11b** could only be separated in a poor yield of 3%. However, when replacing DMF by dioxane and using sodium hydride as the base, the benzylation furnished 7-chloro-2-(benzylsulfanyl)quinazolin-4(3*H*)-one **11b** as the sole product in 96% isolated yield. Subsequently, compound **11a** was similarly obtained in 97% yield.

Treatment of 2-(benzylsulfanyl)quinazolin-4(3*H*)-ones **11a,b** with 4-methoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ and CuMeSal in refluxing THF for 48 h, afforded the target compounds **10a**,**b** in 96% and 66% yield, respectively (Table 1, entries 3 and 4). The coupling of **11a** with 3-chlorophenyl- and 2-naphthylboronic acids afforded 2-arylquinazolin-4(3*H*)-ones **10c** and **10d** (Table 1, entries 5 and 6). An excellent yield (97%) of compound **10a** was also obtained when the corresponding reaction mixture was heated in a closed vessel at 100 C under MW irradiation, allowing the reaction time to be significantly reduced (Table 1, entry 7).

Next, we explored the Pd-catalysed Suzuki-type coupling of 2-(benzylsulfanyl)quinazolin-4(3*H*)-one **11a** with 3- and 2-thienylboronic acids. The MW-assisted reaction of **11a** with 3-thienylboronic acid was carried out in analogous conditions to those for the aforementioned couplings with arylboronic acids and furnished product **10e** in 93% yield (Table 1, entry 8), while the reaction with 2-thienylboronic acid afforded the target product **10f** in only 49% yield (Table 1, entry 9). To increase the yield of **10f**, we decided to investigate cross-coupling reactions of substrates **9a** and **11a** with 2-(tributylstannyl)thiophene under Stille reaction conditions. Guillaumet et al. have recently shown that 2-thiouracil derivatives displaying an unprotected acyl thiourea moiety underwent a Stille-type palladium-catalysed cross-coupling with (het)arylstannanes when copper(I) bromide-dimethyl sulphide complex ($CuBr{\cdot}Me_2S$) was used as

promoter.[32] Indeed, treatment of substrate **9a** with 2-(tributylstannyl)thiophene in the presence of $Pd(PPh_3)_4$ and $CuBr{\cdot}Me_2S$ as metal cofactor in refluxing THF gave the desired compound **10f** with an acceptable yield of 79% (Table 1, entry 10). The yield of the analogous coupling of the *S*-benzylated substrate **11a** was less than 30% (Table 1, entry 11), but it could be increased to 80% by MW irradiation heating of the reaction mixture (Table 1, entry 12). The MW-assisted reaction of **11a** with tributylphenylstannane provided 2-phenylquinazolin-4(3*H*)-one **10g** with a good yield of 91% (Table 1, entry 13).

To estimate the synthetic versatility of those methods, we further moved our attention to a Suzuki arylation of 2-thioxo-2,3-dihydro[1]benzothieno[3,2-*d*]pyrimidin-4(1*H*)-ones **14a**,**b**. The starting compounds **12a** and **12b** were obtained by reacting methyl 2-mercaptoacetate with 2-nitrobenzonitrile or 4-chloro-2-fluorobenzonitrile, respectively, according to published methods.[11,35] The reaction of **12a** with thiophosgene in acetone as described in the literature[36] gave **13a** in 70% yield. However, when carried out in the presence of $NaHCO_3$ in a binary chloroform–water mixture, the reaction of **12a**,**b** with thiophosgene afforded the isothiocyanates **13a** and **13b** with yields of 88% and 79%, respectively. Treatment of **13a** and **13b** with ammonia under pressure in a mixture of pyridine and toluene at rt afforded the target compounds **14a**,**b** in 91% and 89% yield, respectively.



12a,**b**
a R = H;
b R = Cl

13a (88%)
13b (79%)

14a (91%)
14b (89%)

15a (93%)
15b (91%)

16a (59%)
16b (51%)

Scheme 3. *Reagents and conditions:* (i) $CSCl_2$, $CHCl_3$, $NaHCO_3$, H_2O, rt, 24 h; (ii) NH_3, pyridine, toluene, -34 °C to rt, 2 bar, 1 h; (iii) BnBr, NaH, dioxane, rt, 1 h; (iv) 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, CuMeSal, THF, reflux, 48 h

The conversion of compounds **14a**,**b** to the corresponding 2-aryl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones was tested using the synthetic protocol described above.

Thioxo derivatives **14a**,**b** were selectively alkylated to the corresponding *S*-benzyl derivatives **15a**,**b** by reaction with benzyl bromide in dioxane solution in the presence of NaH. The 2-(benzylsulfanyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **15a**,**b** were further submitted to the cross-coupling reaction with 4-methoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ and CuMeSal in refluxing THF (Scheme 3). Flash column chromatography purification of crude products was not feasible, due to their low solubility in common organic solvents. However, pure target compounds **16a**,**b** could be readily obtained via sublimation under high vacuum.

In summary, we have demonstrated that *N*(3)-unsubstituted 2-arylquinazolin-4(3*H*)-ones can be directly obtained from 2-thioxo-2,3-dihydroquinazolin-4(1*H*)ones in good to excellent yields by Stille-type $CuBr{\cdot}Me_2S$ promoted Liebeskind-Srogl reactions with (het)arylstannanes or by a two-step procedure *via* their *S*-benzylated derivatives applying CuMeSal promoted Suzuki-type Liebeskind-Srogl reactions with arylboronic acids. Selective *S*-benzylation of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones can be performed with excellent yields by their reaction with benzyl bromide in dioxane in the presence of sodium hydride.

EXPERIMENTAL

Uncorrected melting points (ºC) were determined using a Büchi Melting Point M-560 apparatus. Elemental analysis was performed with an Exeter Analytical CE-440 elemental analyser. IR spectra (KBr disk or neat) were measured on a Perkin-Elmer Paragon 1000 PC or a Bruker Vertex V70 spectrophotometer. NMR spectra were recorded on a 300 MHz Varian Unity Inova instrument, a 400 MHz Bruker Avance spectrometer or a 700 MHz Bruker Avance spectrometer using TMS as the internal standard. Chemical shifts are reported in parts per million (ppm). Low-resolution mass spectra were recorded on a Perkin-Elmer Micromass ZQ System apparatus for the positive chemical ionization (APCI) mode, or a Shimadzu LCMS-2020 spectrometer for the positive electrospray ionization (ESI) mode. High-resolution mass spectra (HRMS) were recorded with a Bruker microTOF-QIII spectrometer in the ESI mode. Analytical thin layer chromatography (TLC) was performed on aluminum foil backed plates (Merck Kieselgel 60 F_{254}). Visualization of the compounds was effected by UV light (254 nm). Column chromatography was performed using silica gel SI 60 (43-60 μm, E. Merck). Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 150 W. The reaction was performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by

means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon coated magnetic stirring bar in the vessel.

Starting Materials. Compounds **8a**[18], **12a**,**b**[11,35] and **13a**[18] were prepared according to previously reported procedures. All other starting chemicals used in this study were commercially available.

Methyl 4-chloro-2-isothiocyanatobenzoate (8b). A solution of thiophosgene (0.84 mL, 11.03 mmol) in $CHCl_3$ (10 mL) was treated dropwise with a solution of $NaHCO_3$ (0.72 g, 8.62 mmol) in water (5 mL) over 30 min at room temperature. After 10 min vigorous stirring, a solution of methyl 5-chloroanthranilate (1.60 g, 8.62 mmol) in $CHCl_3$ (15 mL) was added, followed by 8 h stirring at room temperature. The workup consisted of a dilution with $CHCl_3$ (50 mL) followed by washing sequentially with water (2×50 mL) and brine (100 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluent: Hex/EtOAc 97:3) provided product **8b** (1.96 g, 91%) as white needles; mp 75–78 ºC (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 7.52 (dd, 1H, J = 1.8, 8.6 Hz, H-5), 7.35 (d, 1H, J = 1.8 Hz, H-3), 7.93 (d, 1H, J = 8.6 Hz, H-6). ^{13}C NMR (75 MHz, DMSO-d_6): δ 52.7 (OCH_3), 124.6, 127.8, 127.9 (CH-Ar), 130.4, 132.7, 134.8 (C_{IV}-Ar), 138.1 (C=S), 163.5 (C=O). IR (KBr): ν 3096, 2148 (NCS), 1710 (C=O), 1591, 1430, 1289, 1112 cm^{-1}. MS (APCI): *m/z* 228 $[M + H]^+$. *Anal.* Calcd for $C_9H_6ClNO_2S$: C, 47.48; H, 2.66; N, 6.15. Found: C, 47.41; H, 2.77; N, 6.11.

2-Thioxo-2,3-dihydroquinazolin-4(1*H*)-one (9a). A solution of methyl 2-isothiocyanatobenzoate (**8a**) (2.15 g, 11.16 mmol) in dry toluene (10 mL) and pyridine (1.35 mL, 16.74 mmol) was placed in a 15 mL pressure tube (reactor) under argon atmosphere. After the solution was cooled to -34 ºC, ammonium gas was added in excess at a rate that kept the solution below -34 ºC. The tube was carefully sealed, and the solution was stirred at rt for 1 h (pressure 2 bar). The white precipitate obtained was collected by filtration, washed with toluene, and recrystallized from MeOH to afford compound **9a** (1.91 g, 96%) as white needles; mp 296–297 ºC (lit.[37] mp 300 ºC).

7-Chloro-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (9b). Prepared from isothiocyanate **8b** (2.13 g, 9.35 mmol) as described for the preparation of **9a**; yield 1.85 g (93%); white needles; mp 305–306 ºC (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32–7.36 (m, 2H), 7.91 (d, 1H, J = 8.3 Hz), 12.56 (br s, 1H, NH), 12.72 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.2, 115.3, 124.4, 128.9, 139.7, 141.3, 159.0 (C=O), 174.8 (C=S). IR (KBr): ν 3086 (br, 2×NH), 1710 (C=O), 1618, 1561, 1426, 1289, 1166 cm^{-1}. *Anal*. Calcd for $C_8H_5ClN_2OS$: C, 45.18; H, 2.37; N, 13.17. Found: C, 45.37; H, 2.39; N, 13.49.

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (10a). *Method A. Thermal heating.* To a solution of **9a** (0.14 g, 0.79 mmol) or **11a** (0.12 g, 0.45 mmol) in dry THF (6 mL), CuMeSal (0.37 g, 1.73 mmol or 0.21 g, 0.98 mmol, respectively) and *p*-methoxyphenylboronic acid (0.26 g, 1.73 mmol or 0.15 g, 0.98 mmol,

respectively) were added. After stirring at rt for 10 min, tetrakis(triphenylphosphine) palladium (9 mg, 0.0079 mmol or 5 mg, 0.0045 mmol, respectively) was added, then the mixture was stirred under reflux for 48 h. After removal of the solvent *in vacuo*, the crude product was purified *via* column chromatography (eluent: Hex/EtOAc 7:3). The obtained white solid was recrystallized from MeOH to afford compound **10a** (0.03 g, 18% or 0.11 g, 96%, respectively); white needles; mp 247–248 ºC (lit.[37] mp 245–247 ºC).

Method B. Microwave heating. To a solution of compound **9a** (0.12 g, 0.67 mmol) or compound **11a** (0.12 g, 0.45 mmol) in dry THF (6 mL), CuMeSal (0.32 g, 1.48 mmol or 0.21 g, 0.98 mmol, respectively) and *p*-methoxyphenylboronic acid (0.22 g, 1.48 mmol or 0.15 g, 0.98 mmol, respectively) were added. After stirring at rt for 10 min, tetrakis(triphenylphosphine) palladium (8 mg, 0.007 mmol or 5 mg, 0.0045 mmol, respectively) was added, then the mixture was heated in a microwave reactor at 100 °C for 1 h. After removal of the solvent *in vacuo*, the crude product was purified *via* column chromatography (eluent: Hex/EtOAc 7:3). The obtained white solid was recrystallized from MeOH to afford compound **10a** (0.04 g, 24% or 0.11 g, 97%, respectively) as white needles.

7-Chloro-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (10b). This compound was prepared from **11b** (0.11 g, 0.37 mmol) in a similar manner as described for the preparation of **10a** (*method A*); yield 0.07 g (66%); white needles; mp 316–317 ºC (MeOH); (lit.[38] mp 310–312 ºC). ^{1}H NMR (300 MHz, $CDCl_3$:CF_3COOD, 1:1): δ 3.78 (s, 3H, OCH_3), 7.03 (d, 2H, J = 9.0 Hz), 7.55 (dd, 1H, J = 1.8 Hz, J = 8.6 Hz), 7.71 (d, 1H, J = 1.8 Hz), 8.85 (d, 2H, J = 9.0 Hz), 8.14 (d, 1H, J = 8.6 Hz), 11.57 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$:CF_3COOD, 1:1): δ 56.3 (OCH_3), 114.5, 116.0, 116.9 (2×CH), 120.0, 129.8, 131.4 (2×CH), 131.6, 138.9, 146.7, 157.4, 161.7, 168.1 (C=O). IR (Neat): *v* 3173 (NH), 1664 (C=O), 1598, 1250, 1186 cm^{-1}. MS (APCI): *m/z* 287 $[M + H]^+$. *Anal.* Calcd for $C_{15}H_{11}ClN_2O_2$: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.98; H, 3.90; N, 9.82.

2-(3-Chlorophenyl)quinazolin-4(3*H*)-one (10c). Prepared from **11a** (0.16 g, 0.60 mmol) as described for the preparation of **10a** (*method A*); yield (0.11 g, 73%); white needles; mp 297–300 ºC (lit.[39] mp 297–298 ºC). ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.39 (d, 1H, J = 7.0 Hz), 7.66 (d, 1H, J = 7.0 Hz), 7.76–7.78 (m, 1H), 7.86 (t, 1H, J = 7.0 Hz), 8.09–8.14 (m, 1H), 8.15–8.17 (m, 2H), 8.25 (d, 1H, J = 2.1 Hz), 12.62 (s, 1H, NH). ^{13}C NMR (176 MHz, DMSO-d_6): δ 118.9, 126.3, 126.9, 128.0, 128.2, 129.2, 131.0, 131.9, 132.0, 135.2, 136.7, 149.0, 151.5, 160.2 (C=O). IR (KBr): *v* 3162 (NH), 1678 (C=O), 1610, 1450, 1230 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2O$: 257.0476, found: 257.0476.

2-(Naphthalen-2-yl)quinazolin-4(3*H*)-one (10d). Prepared from **11a** (0.20 g, 0.74 mmol) as described for the preparation of **10a** (*method A*); yield 0.19 g (95%); pale yellow needles; mp 284.5–285.4 ºC (MeOH); (lit.[40] mp 212 ºC). ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.55 (t, 1H, J = 7.0 Hz), 7.62–7.66 (m, 2H), 7.80 (d, 1H, J = 7.0 Hz), 7.87 (t, 1H, J = 7.0 Hz), 8.01 (d, 1H, J = 7.0 Hz), 8.06–8.08 (m, 2H),

8.18–8.19 (m, 1H), 8.32–8.33 (m, 1H), 8.82 (s, 1H), 12.66 (s, 1H, NH). ^{13}C NMR (176 MHz, DMSO-d_6): δ 121.5, 125.0, 126.4 (2xCH), 127.1, 127.4, 128.0, 128.1, 128.6, 128.7, 129.4, 130.4, 132.8, 134.6, 135.1, 149.3, 152.7, 162.7 (C=O). IR (KBr): *v* 3193 (NH), 1671 (C=O), 1603, 1562, 1470, 1305 cm^{-1}. MS (ESI): *m/z* 273 $[M + H]^+$.

2-(Thiophen-3-yl)quinazolin-4(3*H*)-one (10e). Prepared from **11a** (0.12 g, 0.45 mmol) as described for the preparation of **10a** (*method B*); yield 0.09 g (93%); pale yellow needles; mp 259–261 ºC (MeOH). ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.50 (t, 1H, J = 7.0 Hz), 7.68–7.73 (m, 2H), 7.82 (t, 1H, J = 7.0 Hz), 7.88 (d, 1H, J = 7.0 Hz), 8.13 (d, 1H, J = 7.0 Hz), 8.60 (d, 1H, J = 1.7 Hz), 12.46 (s, 1H, NH). ^{13}C NMR (176 MHz, DMSO-d_6): δ 121.0, 125.5, 126.4, 127.0, 127.4, 127.7, 128.6, 134.6, 135.4, 148.3, 148.9, 162.0 (C=O). IR (KBr): *v* 3172 (NH), 1669 (C=O), 1597, 1468, 1287 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_9N_2OS$: 229.0430, found: 229.0430.

2-(Thiophen-2-yl)quinazolin-4(3*H*)-one (10f). *Method A.* Prepared from **11a** (0.12 g, 0.45 mmol) as described for the preparation of **10a** (*method B*); yield 0.50 g (49%); pale yellow needles; mp 285–287 ºC (MeOH); (lit.[41] mp 275–276 ºC).

Method B. To a solution of compound **9a** (0.20 g, 1.12 mmol) or compound **11a** (0.15 g, 0.56 mmol) in dry THF (10 mL), CuBr·Me_2S (0.51 g, 2.47 mmol or 0.25 g, 1.23 mmol, respectively) and 2-(tributylstannyl)thiophene (0.78 mL, 2.47 mmol or 0.39 mL, 1.23 mmol, respectively) were added. After stirring at rt for 10 min, tetrakis(triphenylphosphine)palladium (13 mg, 0.011 mmol or 6 mg, 0.005 mmol, respectively) was added, then the mixture was stirred under reflux for 48 h. After removal of the solvent *in vacuo*, the crude product was purified *via* column chromatography (eluent: Hex/EtOAc 7:3 → 1:1). The obtained white solid was recrystallized from MeOH to afford compound **10f** (0.20 g, 79% or 0.04 g, 29%, respectively).

Method C. To a solution of compound **11a** (0.15 g, 0.56 mmol) in dry THF (10 mL), CuBr·Me_2S (0.25 g, 1.23 mmol) and 2-(tributylstannyl)thiophene (0.39 mL, 1.23 mmol) were added. After stirring at rt for 10 min, tetrakis(triphenylphosphine) palladium (6 mg, 0.005 mmol) was added, then the mixture was heated in a microwave reactor at 100 ºC for 1 h. After removal of the solvent *in vacuo*, the crude product was purified *via* column chromatography (eluent: Hex/EtOAc 7:3 → 1:1). The obtained white solid was recrystallized from methanol to afford compound **10f** (0.10 g, 80%).

2-Phenylquinazolin-4(3*H*)-one (10g). Prepared from **11a** (0.12 g, 0.45 mmol) as described for the preparation of **10f** (*method B*); yield **10g** (0.09 g, 91%); white needles; mp 218–222 ºC (MeOH); (lit.[42] mp 220–222 ºC). The NMR data are in good agreement with the literature.[37,42] HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{14}H_{11}N_2O$ 223.0866, found 223.0866.

2-(Benzylsulfanyl)quinazolin-4(3*H*)-one (11a). To a solution of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-

one (**9a**) (0.50 g, 2.81 mmol) in dry dioxane (12 mL) were added NaH (0.12 g, 3.09 mmol) and benzyl bromide (0.33 mL, 0.48 g, 2.81 mmol) and the reaction mixture was stirred at rt for 1 h under argon atmosphere. After removal of the solvent *in vacuo*, the crude was recrystallized from methanol to afford compound **11a** (0.73 g, 97%) as white needles; mp 216–218 ºC (lit.[34] mp 212–213 ºC). ^{1}H NMR (300 MHz, $CDCl_3$:DMSO-d_6, 1:1): δ 4.47 (s, 2H, SCH_2), 7.18–7.39 (m, 4H, 7-H, Ar-H), 7.44 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.55 (d, 1H, *J* = 8.1 Hz, 8-H), 7.57–7.74 (m, 1H, 6-H), 8.01 (d, 1H, *J* = 8.0 Hz, 5-H), 12.47 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$:DMSO-d_6, 1:1): δ 33.6 (SCH_2), 99.4, 120.0, 125.3, 125.7, 125.9, 127.0, 128.2 (2×CH), 128.9 (2×CH), 134.2, 137.1, 148.2, 161.3 (C-2). IR (neat): *v* 3156 (NH), 1666 (C=O) 1577, 1468, 1263, 1169 cm^{-1}. MS (APCI): *m/z* 291 $[M + Na]^+$. *Anal.* Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 66.89; H, 4.67; N, 10.39.

2-(Benzylsulfanyl)-7-chloroquinazolin-4(3*H*)-one (11b). Prepared from **10b** (0.20 g, 0.93 mmol) as described for the preparation of **11a**; yield 0.27 g (96%); white needles; mp 195–196 ºC (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.48 (s, 2H, SCH_2), 7.22–7.34 (m, 3H, Ar-H), 7.44 (dd, 1H, *J* = 2.0 Hz, *J* = 8.5 Hz, 6-H), 7.48 (d, 2H, *J* = 6.8 Hz, Ar-H), 7.65 (d, 1H, *J* = 2.0 Hz, 8-H), 8.00 (d, 1H, *J* = 8.5 Hz, 5-H), 12.73 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.6 (SCH_2), 118.8, 125.2, 125.9, 127.3, 128.1, 128.5 (2×CH), 129.3 (2×CH), 137.3, 139.2, 149.3, 157.2 (C=O), 160.6 (C-2). IR (neat): *v* 3025 (NH), 1657 (C=O), 1604, 1572, 1446, 1261, 116 cm^{-1}. MS (APCI): *m/z* 303 $[M + H]^+$. *Anal*. Calcd for $C_{15}H_{11}ClN_2OS$: C, 59.50; H, 3.66; N, 9.25. Found: C, 59.62; H, 3.91; N, 9.12.

Methyl 5-chloro-3-isothiocyanato[1]benzothiophene-2-carboxylate (13b). Prepared from **12b** (0.20 g, 0.80 mmol) as described for the preparation of **8b**. Purification of the crude product by flash chromatography on silica gel (eluent: Hex/EtOAc 95:5) provided compound **13b** (0.18 g, 79%) as white needles; mp 146–147 ºC ($CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.91 (s, 3H, CH_3), 7.65 (dd, 1H, *J* = 2.1, 8.7 Hz, 6-H), 7.89 (d, 1H, *J* = 2.1 Hz, 4-H), 8.12 (d, 1H, *J* = 8.7 Hz, 7-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.7 (CH_3), 100.2, 122.4, 124.9, 126.3, 128.2, 129.7, 132.1, 135.6, 136.5 (C=S), 161.3 (C=O). IR (KBr): *v* 2134 (NCS), 1721 (C=O), 1524, 1431, 1353, 1267, 1142 cm^{-1}; MS (APCI): *m/z* 283.5 $[M + H]^+$. *Anal.* Calcd for $C_{11}H_6ClNO_2S_2$: C, 46.56; H, 2.13; N, 4.94. Found: C, 46.73; H, 2.35; N, 4.89.

2-Thioxo-2,3-dihydro[1]benzothieno[3,2-*d*]pyrimidin-4(1*H*)-one (14a). Prepared from **13a** (0.20 g, 0.80 mmol) as described for the preparation of **9a**; yield 0.17 g (91%); white needles; mp 318–319 ºC (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54–7.60 (m, 1H, 8-H), 7.66 (t, 1H, *J* = 7.5 Hz, 7-H), 8.13 (d, 1H, *J* = 8.1 Hz, 9-H), 8.61 (d, 1H, *J* = 7.9 Hz, 6-H), 12.80 (br s, 1H, NH), 13.65 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.0, 124.0 (2xC), 125.6, 127.9, 129.3, 140.4, 141.9, 157.2 (C=O), 175.1 (C=S). IR (KBr): *v* 3053 (NH), 1669 (C=O), 1556, 1181 cm^{-1}. MS (APCI): *m/z* 235 $[M + H]^+$. *Anal.* Calcd for $C_{10}H_6N_2OS_2$: C, 51.26; H, 2.58; N, 11.96. Found: C, 50.98; H, 2.61; N, 11.65.

8-Chloro-2-thioxo-2,3-dihydro[1]benzothieno[3,2-*d*]pyrimidin-4(1*H*)-one (14b). Prepared from **13b** (0.20 g, 0.71 mmol) as described for the preparation of **9a**; yield 0.17 g (89%); white needles; mp > 320 ºC (dec.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (dd, 1H, J = 2.0 Hz, J = 8.8 Hz, 7-H), 8.19 (d, 1H, J = 8.8 Hz, 6-H), 8.76 (d, 1H, J = 2.0 Hz, 9-H), 12.86 (s, 1H, NH), 13.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.5, 116.7, 123.4, 125.8, 129.3, 130.6, 138.9, 140.9, 157.1 (C=O), 175.1 (C=S). IR (KBr): v 3377 (NH), 3046 (NH), 1682 (C=O), 1559, 1423, 1169, 1152 cm^{-1}. MS (ESI): *m/z* 269 [M + H]$^+$. *Anal.* Calcd for $C_{10}H_5ClN_2OS_2$: C, 44.69; H, 1.88; N, 10.42. Found: C, 44.87; H, 1.93; N, 10.05.

2-(Benzylsulfanyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (15a). Prepared from **14a** (0.20 g, 0.86 mmol) as described for the preparation of **11a**; yield 0.26 g (93%); white needles; mp 280–282 ºC (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.60 (s, 2H, SCH_2), 7.24 (t, 1H, J = 7.2 Hz, 7-H), 7.29–7.34 (m, 2H, Ar-H), 7.54 (d, 2H, J = 7.3 Hz, Ar-H), 7.58–7.69 (m, 2H, Ar-H, 8-H), 8.12 (d, 1H, J = 7.7 Hz, 9-H), 8.32 (d, 1H, J = 7.2 Hz, 6-H), 13.11 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.0 (SCH_2), 118.9, 120.0, 123.4, 123.9, 125.6, 127.3, 128.5 (2×CH), 129.2 (2×CH), 133.7, 137.5, 140.4, 152.4, 158.3, 158.4 (C-2). IR (KBr): v 3061 (NH), 1659 (C=O), 1538, 1211 cm^{-1}. MS (APCI): *m/z* 325 [M + H]$^+$, 347 [M + Na]$^+$. *Anal.* Calcd for $C_{17}H_{12}N_2OS_2$: C, 62.94; H, 3.73; N, 8.63. Found: C, 62.94; H, 3.91; N, 8.76.

2-(Benzylsulfanyl)-8-chloro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (15b). Prepared from **14b** (0.20 g, 0.73 mmol) as described for the preparation of **11a**; yield 0.24 g, (91%); white needles; mp 278–281 ºC (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.62 (s, 2H, SCH_2), 7.31–7.35 (m, 3H, Ar-H), 7.53 (d, 2H, J = 7.2 Hz, Ar-H), 7.70 (dd, 1H, J = 2.1 Hz, J = 8.7 Hz, 7-H), 8.19 (d, 1H, J = 8.7 Hz, 6-H), 8.30 (d, 1H, J = 2.1 Hz, 9-H), 13.17 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.5 (SCH_2), 123.0, 126.3, 127.2, 127.8, 128.9 (2×CH), 129.6 (2×CH), 129.7, 131.1, 135.5, 137.8, 139.3, 151.8, 158.6, 159.1 (C-2). IR (KBr): v 3061 (NH), 1673 (C=O), 1538, 1495, 1211, 1077 cm^{-1}. MS (ESI): *m/z* 359 [M + H]$^+$, 381 [M + Na]$^+$. *Anal.* Calcd for $C_{17}H_{11}ClN_2OS_2$: C, 56.90; H, 3.09; N, 7.81. Found: C, 57.20; H, 3.28; N, 7.63.

2-(4-Methoxyphenyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (16a). Prepared from **15a** (0.11 g, 0.33 mmol) as described for the preparation of **10a** (*method A*). The crude product was purified by sublimation (200 ºC, 0.2 mbar), then the obtained solid was recrystallized from MeOH; yield 0.06 g (59%); white needles; mp 295–297 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 7.13 (d, 2H, J = 8.9 Hz, 2′-H, 6′-H), 7.59–7.69 (m, 2H, 7-H, 8-H), 8.16 (d, 1H, J = 7.5 Hz, 6-H), 8.28 (d, 2H, J = 8.9 Hz, 3′-H, 5′-H), 8.35 (d, 1H, J = 7.3 Hz, 9-H), 12.89 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.5 (OCH_3), 114.1 (2×CH), 120.0, 123.4, 123.9 (2×CH), 124.4, 125.4, 129.1, 129.6, 134.3, 140.5, 153.3, 154.6, 159.1, 161.9 (C=O). IR (neat): v 3152 (NH), 1662 (C=O), 1502, 1259, 1180 cm^{-1}. HRMS [M + H]$^+$ calcd for $C_{17}H_{13}N_2O_2S$: 309.0692, found: 309.0695.

8-Chloro-2-(4-methoxyphenyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (16b). Prepared from **15b** (0.10 g, 0.29 mmol) as described for the preparation of **10a** *(method A).* The crude product was purified by sublimation (200 °C, 0.2 mbar), then the obtained solid was recrystallized from MeOH; yield 0.05 g (51%); white crystals. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.89 (s, 3H, OCH_3), 7.15 (d, 2H, J = 8.9 Hz, 2′-H, 6′-H), 7.74 (dd, 1H, J = 2.2 Hz, J = 8.7 Hz, 7-H), 8.23 (d, 1H, J = 8.7 Hz, 6-H), 8.33 (d, 1H, J = 2.2 Hz, 9-H), 8.50 (d, 2H, J = 8.9 Hz, 3′-H, 5′-H), 12.91 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.6 (OCH_3), 114.2 (2×CH), 120.4, 123.6, 123.6 (2×CH), 124.0, 125.5, 129.2, 129.7, 134.4, 140.6, 153.3, 154.7, 159.2, 162.0 (C=O). IR (KBr): v 3158 (NH), 1672 (C=O), 1579, 1263, 1186 cm^{-1}; MS (APCI): *m/z* 343 $[M + H]^+$. *Anal.* Calcd for $C_{17}H_{11}ClN_2O_2S$: C, 59.56; H, 3.23; N, 8.17. Found: C, 59.89; H, 3.32; N, 8.01.

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