2-(Benzoylimino)thiazolidin-4-ones: Formation by an Alternative Ring Closure and Analysis of Rotational Barriers

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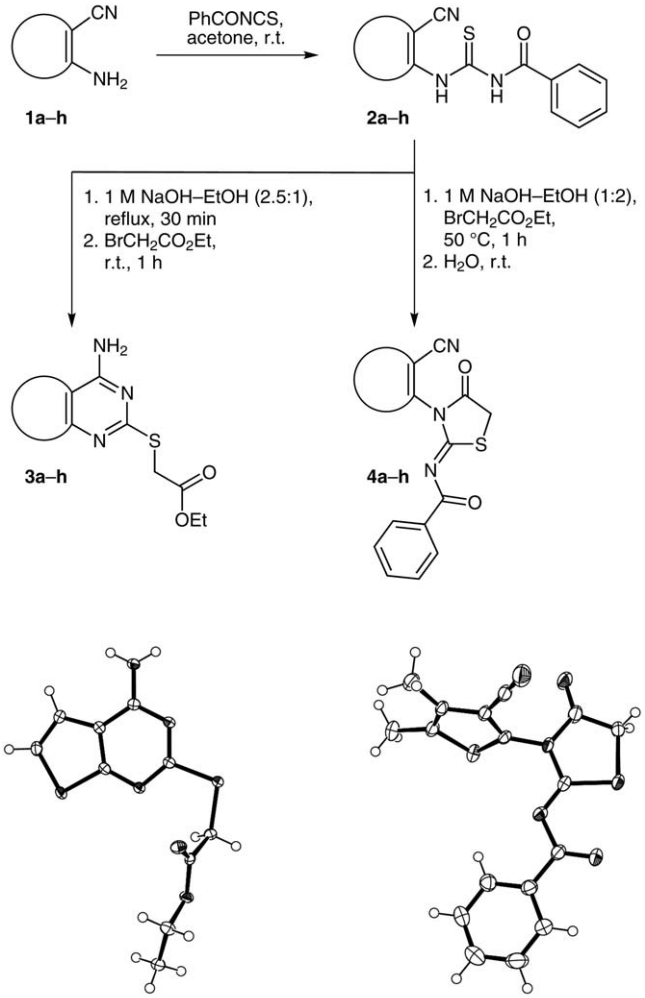
Abstract: The reactions of *N*-benzoyl-*N*′-(*o*-cyanoaryl)thioureas with ethyl bromoacetate under alkaline conditions led to the formation of either fused 2-(alkylsulfanyl)-4-aminopyrimidines or 2-(benzoylimino)-3-(*o*-cyanoaryl)thiazolidin-4-ones. The accurate application of slightly different reaction conditions allowed us to adjust the balance between the formation of the pyrimidine or thiazolidine heterocycles. Atropisomerism in the 3-(*o*-cyanoaryl)thiazolidin-4-ones was influenced by the size of the *o*-cyanoaryl ring, which was investigated by means of NMR measurements and theoretical calculations.

Key words: atropisomerism, ring closure, regioselectivity, thiazolidin-4-ones, DFT calculations

2-(Alkylsulfanyl)-substituted 4-aminothieno[2,3-*d*]pyrimidines exhibit biological activity, e.g. as ligands for serotonin receptor subtypes[1,2] or modulators of P-glycoprotein.[3] Several 2-(alkylsulfanyl)-4-aminothieno[2,3-*d*]pyrimidines are accessible by thermal ring closure of 2-(benzoylthioureido)thiophene-3-carbonitriles effected by sodium hydroxide in an ethanol–water mixture, followed by the addition of alkyl halides.[4] However, when this one-pot procedure is applied in the reaction of benzoylthiourea **2b** with ethyl bromoacetate as the alkylating agent, a side product was formed in addition to the expected thienopyrimidine **3b** (Scheme 1, Table 1). As NMR and IR spectra of the side product revealed an unaffected nitrile function, the presence of a benzoyl group, and the loss of ethanol, an alternative heterocyclization to a 2-iminothiazolidin-4-one was assumed. To elucidate which nitrogen of the starting thiourea was incorporated into the five-membered ring, crystals of the side product were subjected to X-ray diffraction analysis, and structure **4b** was determined (Scheme 1).[5] The formation of **4b** includes alkylation of the thiourea sulfur *prior* to acylation of the nitrogen atom bound to the thiophene ring. In reactions of unsymmetrical thioureas with α-halo esters, regiocontrol in the cyclization step was influenced by electronic factors and by a possible conjugative stabilization of the isothiourea imine through a (hetero)aryl substituent and could be promoted by hydrogen bond interactions.[6,7] The finding that the aryl-substituted, and not the electron-poor, benzoylated nitrogen atom was incorporated into heterocycle **4b** is in accordance with literature reports.[8–10]



Scheme 1 Formation of **3** and **4**; ORTEP diagrams of **3a** and **4b**[5]

Various biological effects of 2-iminothiazolidin-4-ones have been reported.[11–17] FR171113, for example, a 2-(aroylimino)-3-arylthiazolidin-4-one derivative, is a thrombin receptor antagonist with potent antiplatelet activity.[18] Therefore, we generated a small library of both heterocycles **3** and **4** starting from various thiophenes **1a–f**, as well as two anthranilonitrile derivatives **1g**,**h** (Table 1).

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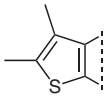
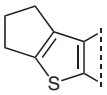
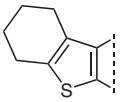
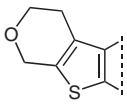
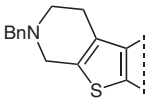
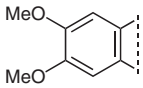
Table 1 Substitution Patterns of the Target Compounds **3** and **4** with Corresponding Yields

	3	Yield[a] (%)	**4**	Yield[a] (%)
	**3a**	58	**4a**	71
	**3b**	42	**4b**	63
	**3c**	65	**4c**	66
	**3d**	48	**4d**	58
	**3e**	74	**4e**	72
	**3f**	49	**4f**	19[b]
	**3g**	55	**4g**	70
	**3h**	68	**4h**	66

[a] Yields of products after recrystallization.
[b] Yield after purification by column chromatography.

Slightly different reaction conditions led to heterocycles **3** and **4** (Scheme 1). The direct addition of ethyl bromoacetate, a lowered temperature, an increased amount of ethanol, and the reduction of sodium hydroxide suppressed the formation of **3** in favor of **4**. Closely following either procedure, the target compounds **3** and **4** could be purified by a single recrystallization step and were obtained in mostly good yields. Conversion of **2** into **4** did not affect the nitrile function, whereas different behavior was obvious for thiazolidin-4-ones with an unsubstituted imino function in position 2.[19] When such compounds were formed as intermediates, they underwent a pyrimidine cyclization, and subsequent ethanolysis of the thiazolidin-4-one ring produced 4-aminopyrimidines of type **3**. In this way, Gewald et al. have prepared fused pyrimidines **3b**, **3d**, and **3g** from aromatic *o*-(chloroacetylamino)nitriles.[19]

The structures of compounds **3** and **4** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. In contrast to the ^{1}H NMR spectra of thiophene derivatives **4a**–**f**, those of benzonitriles **4g**,**h** showed splitting of the thiazolidin-4-one methylene signal into two doublets with a coupling constant of 18.6 Hz. This could be attributed to hindered rotation around the N–C_{aryl} bond, thus leading to atropisomerism.[20] The diastereotopic nature of the protons gave rise to geminal coupling in the spectra. Atropisomerism about *N*-aryl bonds, e.g. in thiazolidines or thiazolidin-4-ones, where an *ortho* substituent of the aryl group accounted for steric hindrance, was recently reported.[21,22] In contrast to these investigations focusing on the dimension and electronic properties of that *ortho* substituent, in our case the size of the aryl moiety seemed to be crucial for the occurrence of atropisomerism. Increasing the aryl size from a five-membered thiophene to a six-membered benzene ring led to a reduction of the gap between the *o*-nitrile function and the carbonyl and benzoylimino groups of the adjacent thiazolidin-4-one.[23] This is illustrated by comparison of the angles θ in the crystal structures[5] of **4a** and **4b** (125.9°, 124.2°) with that of **4g** (120.1°) as representatives of the two ring sizes (Figure 1). In the three structures, the benzoylimino groups are almost in plane with the thiazolidin-4-one system. Compounds **4a**, **4b**, and **4g** display a *Z*-configuration about the C=N bonds and an *s-cis* conformation about the N_{imine}–$C_{carbonyl}$ bonds. The nonbonded intramolecular distance between the thiazolidin-4-one sulfur and the benzoyl oxygen atoms of 2.61–2.65 Å indicates a polar interaction between the O and S atoms.[24,25]

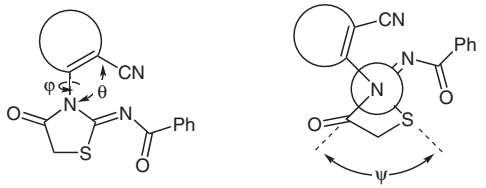


Figure 1 Thiazolidin-4-ones **4a**, **4b**, and **4g** with the rotation angle φ. The compounds differ with respect to the angle θ defining how close the nitrile is bent towards the thiazolidin-4-one and with respect to ψ. The dihedral angle ψ is defined by the bond vectors connecting the four atoms C(=O)–N–C(=N)–S of the thiazolidin-4-one moiety.

Next, DFT calculations for which Gaussian03[26] was used were performed to affirm the hypothesis that an internal rotational barrier between the nitrile group and the carbonyl and acylimino function of the thiazolidin-4-one led to atropisomers in case of the anthranilonitrile derivatives **4g**,**h**. On the basis of their crystal structures, *Z*-configured **4a**,**b**,**g** were used for a relaxed potential energy surface (PES) scan at BP86/LANL2DZ level, where a 5° stepwise complete rotation of the dihedral angle φ regarding the C–N bond connecting the cyanoarene and the thiazolidin-4-one was applied (Figure 2).

Rotamers close to the transition state were identified from PES scans and subsequently subjected to transition state optimization at the B3LYP/6-311G** level of theory or additional PES scans at the B3LYP/6-311G** level, if no transition state was reached. Frequency calculations were then carried out for transition states and B3LYP/6-311G** optimized maxima as well as minima to provide free energy values for the rotational barriers. Minima ob-

Table 2 RMSD Values of Optimized Minima and Crystal Structures, as well as Relevant Bond Angles, Internal Rotational Barriers and Corresponding Energies of Compounds **4a**, **4b**, and **4g** as Estimated by B3LYP/6-311G** DFT Calculations

Compound	RMSD (Å)	Bond angles (°)			Internal rotational barriers (°, kJ/mol)		
		θ	ψ	$\varphi_{carbonyl}$	$\Delta G^{\ddagger}_{rot,\ carbonyl}$	φ_{imine}	$\Delta G^{\ddagger}_{rot,\ imine}$
4a	0.512	125.9	2.7	198	64	350	59
4b	0.459	124.2	6.0	199	66	350	67
4g	0.438	120.1	1.4	187	87	348	95

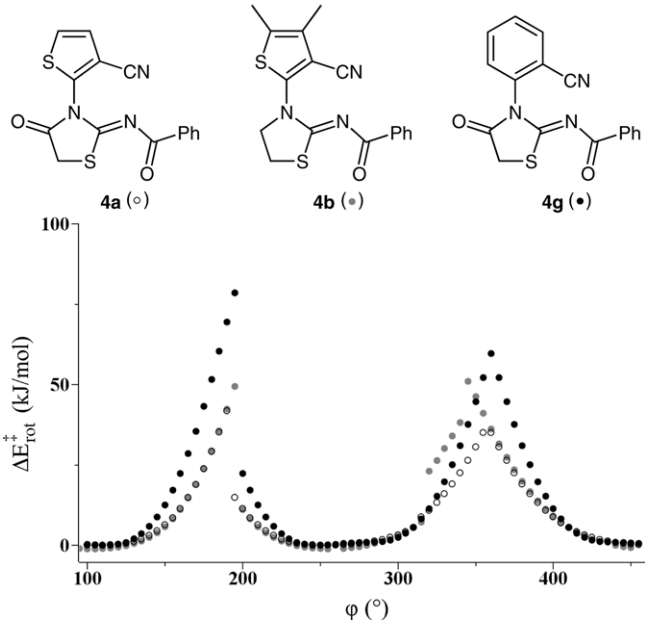


Figure 2 Rotational barrier energies (BP86/LANL2DZ) for rotamers of **4a**, **4b**, and **4g** as a function of the dihedral angle φ with respect to the C–N bond between the cyanoarene and the thiazolidin-4-one. The dihedral angle φ is defined by the four atoms C(CN)–C–N–C(=N). The observed energy gap at 320° torsion of compound **4b** can be explained by a flip of the benzoylimino moiety relative to the thiazolidin-4-one plane.

tained by DFT optimization closely resembled the crystal structures with RMSD values lower than 1 Å (Table 2).

Two rotational barriers were observed, at φ ~ 190° and φ ~ 350°, corresponding to the steric proximity of the cyano and carbonyl group and a clash between the cyano and imine group, respectively. A minor shift of the rotational barriers was observed when **4a**, **4b**, and **4g** were compared. This might be attributed to a slight tilt of the thiazolidin-4-one ring, defined by the dihedral angle ψ. The combination of the three angles φ, θ, and ψ describes the vicinity of the nitrile and carbonyl/imine moieties, and thus serves as a measure of how close the functional groups are to each other (Figure 1).

Compared to **4a** and **4b**, the corresponding $\Delta G^{\ddagger}_{rot}$ values of compound **4g** increased significantly (64/59 and 66/67 versus 87/95 kJ/mol). This was mainly attributed to the decreased θ value for **4g** (124.2 and 125.9 versus 120.1°), thus resulting in hindered rotation of **4g**. Calculated rotational barriers of **4g** were in accordance with literature data. For 2-(arylimino)-4-methyl-3-(*o*-substituted phenyl)-thiazolines, DFT calculations as well as racemization studies using HPLC on chiral support resulted in $\Delta G^{\ddagger}_{rot}$ values between 85 and 122 kJ/mol.[21] Enantiomers of 2-(arylimino)thiazolidin-4-ones with an *o*-tolyl, *o*-methoxyphenyl, *o*-chlorophenyl, or α-naphthyl substituent at position 3 were resolved and subjected to thermal racemization to obtain rotational barriers between 98 and 114 kJ/mol.[22]

The calculations for **4a**, **4b**, and **4g** were consistent with the spectroscopic data of the thiazolidin-4-ones. On the one hand, the five-membered cyanothienyl derivatives **4a**–**f** did not form stable atropisomers at room temperature, since the larger angle θ allowed the substituents to pass each other. On the other hand, the six-membered cyanophenyl derivatives **4g**,**h** with smaller θ values had sufficient steric repulsion for hindered rotation and were axially chiral racemates (Figure 3). Accordingly, **4g**,**h** had diastereotopic methylene protons in their ^{1}H NMR spectra. NMR experiments showed that rotation in **4a** could not be restricted at lower temperatures down to –40 °C, and that, vice versa, rotation was not allowed in **4g** at higher temperatures up to 70 °C.

Replacement of one *ortho* substituent by hydrogen in tri-*o*-substituted biaryls mostly results in the loss of axial chirality.[20] We prepared the truncated compounds **5** and **6** (Figure 3). As expected, the ethylene protons of **5** showed a simple coupling pattern of two triplets (^3J = 7.7 Hz). Diastereotopic protons in the spectrum of **6** were not observed either, and the two methylene groups gave rise to

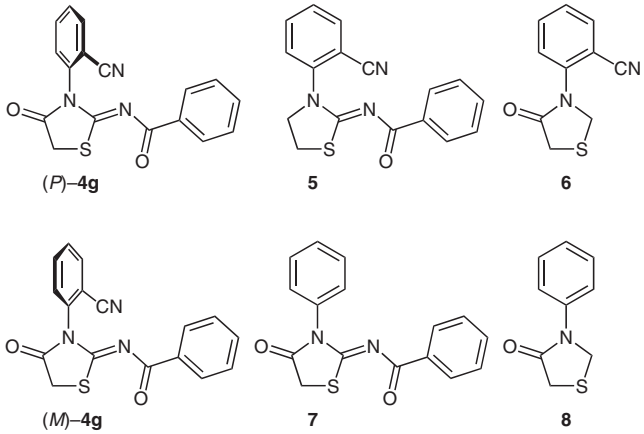


Figure 3 The two stereoisomers of **4g**, not interconvertible at room temperature, and the truncated structures **5**–**8**

two triplets (^4J = 1.0 Hz). This can be explained by long-range coupling through the eclipsing lone pair of the sulfur atom.[27–32] The long-range coupling in the spectrum of **6** is independent of the presence of the cyano group, since it was also found for compound **8** (^4J = 1.0 Hz).

Thiazolidin-4-ones **6** and **8** were obtained by the reaction of anthranilonitrile or aniline with thioglycolic acid and aqueous formaldehyde according to patent literature.[33,34] Compound **5** was prepared from *N*-benzoyl-*N*′-(2-cyanophenyl)thiourea (**2g**) and 1,2-dibromoethane in *N*,*N*-dimethylformamide in the presence of sodium acetate at room temperature. Thiazolidin-4-one derivative **7** could be synthesized by virtually the same reaction conditions as those used for **4a**–**h**. In both **5** and **7**, the aniline nitrogen was incorporated into the five-membered ring. This could be confirmed by ^{13}C NMR spectroscopy, in particular when the influence of the (benzoylimino)thiazolidine substituent on the *ipso* position in benzene or benzonitrile was considered.

An alternative method to prepare 2-iminothiazolidin-4-ones, the treatment of thioureas with haloacetyl halides,[6,12,16] was applied for the conversion of **2g** into **4g**. However, the reaction did not proceed uniformly as reported for other *N*-aroyl-*N*′-arylthioureas.[16] Klika et al. have proposed a mechanism for the reaction of *N*-(anthracen-9-yl)-*N*′-ethylthiourea with bromoacetyl bromide involving S-acylation, acetyl migration, and S-alkylation to produce two isomeric 2-iminothiazolidin-4-ones.[6]

In summary, we have elaborated optimized reaction conditions for the selective preparation of either fused pyrimidines **3** or substituted thiazolidin-4-ones **4**. Both products were obtained from the reaction of *N*-benzoyl-*N*′-(*o*-cyanoaryl)thioureas **2** with ethyl bromoacetate. In view of the diverse biological activities of thiazolidin-4-ones, compounds **4** might also be useful for further chemical transformations of the cyano group to produce bioactive heterocycles. This will be the subject of future investigations in our laboratories. Whereas the size of sterically demanding substituents has frequently been reported to influence atropisomerization,[20–22] we investigated the less common influence of ring size by means of NMR measurements and theoretical calculations. In contrast to (*o*-cyanothienyl)-substituted thiazolidin-4-ones **4a**–**f**, (*o*-cyanophenyl)-substituted derivatives **4g**,**h** cannot overcome internal rotational barriers at room temperature and were characterized as axially chiral racemates.

Solvents and reagents were obtained from Acros (Geel, Belgium), Fluka (Taufkirchen, Germany), or Sigma (Steinheim, Germany) if commercially available. 2-Aminothiophene-3-carbonitrile (**1a**) was prepared from 1,4-dithiane-2,5-diol and malononitrile following the conditions reported by Hallas et al.[35] Aminothiophenes **1b**–**f** were obtained by Gewald synthesis starting from appropriate ketones.[36] TLC was carried out on Merck aluminum sheets coated with silica gel 60 F_{254}. Preparative column chromatography was performed on Merck silica gel 60 (70–230 mesh). Melting points were determined on a Boëtius melting point apparatus (PHMK, VEB Wägetechnik Rapido, Radebeul, Germany) and are uncorrected. IR spectra were obtained on a Bruker Tensor 27 FTIR spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were acquired on a Bruker Avance DRX 500 spectrometer. Chemical shifts are relative to the solvent peaks used as reference [$CDCl_3$: δ_H = 7.26, δ_C = 77.0; DMSO-d_6: δ_H = 2.49, δ_C = 39.7]. Temperature-dependent NMR measurements were performed in $CDCl_3$ for **4a**, and in DMSO-d_6 for **4g**. Elemental analyses were carried out with a Vario EL apparatus.

N-Benzoyl-*N*′-(*o*-cyanoaryl)thioureas 2; General Procedure

BzCl (8.43 g, 6.96 mL, 60.0 mmol) was added dropwise to a stirred soln of NH_4SCN (5.18 g, 68.0 mmol) in anhyd acetone (20 mL) at 0 °C. The mixture was refluxed for 5 min and then cooled to r.t., and the precipitated NH_4Cl was removed by suction filtration. Subsequently, the resulting BzNCS soln was cooled (ice) and a soln of the appropriate (*o*-aminoaryl)carbonitrile **1** (50.0 mmol) in acetone was added dropwise. Upon complete addition, the reaction mixture was allowed to warm to r.t. and stirred for 3 h. The precipitated product was collected by filtration and washed with acetone (–20 °C, 30 mL). Additional material was obtained by cooling the remaining soln overnight (8 °C). The material was used without further purification.

N-Benzoyl-*N*′-(3-cyano-2-thienyl)thiourea (2a)

Pale yellow solid; yield: 11.9 g (83%); mp 199–202 °C; R_f = 0.56 (PE–EtOAc, 2:1).

IR (KBr): 3231, 3114, 2217, 1673 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.28 (d, J = 5.7 Hz, 1 H, H-4′/5′), 7.33 (d, J = 5.7 Hz, 1 H, H-4′/5′), 7.53–7.57 (m, 2 H, H-3/5), 7.66–7.69 (m, 1 H, H-4), 8.00–8.02 (m, 2 H, H-2/6), 12.26 (br s, 1 H, NH), 14.50 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 97.10, 114.20, 120.04, 124.64, 128.60, 129.06, 131.65, 133.64, 150.07, 169.51, 176.09.

Anal. Calcd for $C_{13}H_9N_3OS_2$: C, 54.34; H, 3.16; N, 14.62. Found: C, 53.80; H, 3.16; N, 14.53.

N-Benzoyl-*N*′-(3-cyano-4,5-dimethyl-2-thienyl)thiourea (2b)

Off-white solid; yield: 12.9 g (82%); mp 208–210 °C (Lit.[4] 208–210 °C); R_f = 0.59 (toluene–EtOAc, 4:1).

IR (KBr): 3274, 2917, 2217, 1672 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.16 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 7.53–7.58 (m, 2 H, H-3/5), 7.65–7.71 (m, 1 H, H-4), 7.97–8.03 (m, 2 H, H-2/6), 12.19 (br s, 1 H, NH), 14.40 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.18, 12.26, 99.13, 114.14, 126.17, 128.60, 128.98, 129.06, 131.68, 133.63, 145.96, 169.57, 175.43.

Anal. Calcd for $C_{15}H_{13}N_3OS_2$: C, 57.12; H, 4.15; N, 13.32. Found: C, 56.50; H, 4.38; N, 12.75.

N-Benzoyl-*N*′-(3-cyano-5,6-dihydro-4*H*-cyclopenta[*b*]-2-thienyl)thiourea (2c)

Pale yellow solid; yield: 15.3 g (93%); mp 213–214 °C; R_f = 0.71 (toluene–EtOAc, 4:1).

IR (KBr): 2859, 2216, 1670 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.49 (quint, J = 7.3 Hz, 2 H, H-5′), 2.90 (tt, J = 7.3, 1.6 Hz, 2 H, H-4′), 2.95 (tt, J = 7.3, 1.6 Hz, 2 H, H-6′), 7.56–7.60 (m, 2 H, H-3/5), 7.68–7.72 (m, 1 H, H-4), 7.95–7.80 (m, 2 H, H-2/6), 9.14 (br s, 1 H, NH), 14.20 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.08, 28.11, 29.55, 94.42, 113.97, 127.72, 129.30, 130.88, 134.14, 136.32, 141.69, 151.58, 167.08, 173.90.

Anal. Calcd for $C_{16}H_{13}N_3OS_2$: C, 58.69; H, 4.00; N, 12.83. Found: C, 58.65; H, 4.17; N, 12.74.

_N_-Benzoyl-_N′_-(3-cyano-4,5,6,7-tetrahydro-1-benzo-2-thienyl)-thiourea (2d)

Yellow solid; yield: 15.9 g (93%); mp 219–220 °C (Lit.[4] 214–216 °C); R_f = 0.89 (toluene–EtOAc, 4:1).

IR (KBr): 3289, 2921, 2212, 1670 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 1.79–1.86 (m, 4 H, H-5′/6′), 2.62–2.68 (m, 4 H, H-4′/7′), 7.51–7.55 (m, 2 H, H-3/5), 7.63–7.66 (m, 1 H, H-4), 7.90–7.93 (m, 2 H, H-2/6), 9.12 (br s, 1 H, NH), 14.16 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.01, 22.99, 23.86, 24.07, 98.61, 113.71, 127.68, 129.23, 129.75, 130.79, 131.80, 134.07, 146.83, 167.04, 174.02.

Anal. Calcd for $C_{17}H_{15}N_3OS_2$: C, 59.80; H, 4.43; N, 12.31. Found: C, 59.69; H, 4.62; N, 12.15.

_N_-Benzoyl-_N′_-(3-cyano-4,7-dihydro-5_H_-thieno[2,3-_c_]pyran-2-yl)thiourea (2e)

Pale yellow solid; yield: 16.7 g (97%); mp 218–220 °C; R_f = 0.66 (toluene–EtOAc, 4:1).

IR (KBr): 3312, 2841, 2217, 1672 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.67 (tt, J = 5.7, 1.6 Hz, 2 H, H-4′), 3.89 (t, J = 5.7 Hz, 2 H, H-5′), 4.66 (t, J = 1.6 Hz, 2 H, H-7′), 7.53–7.57 (m, 2 H, H-3/5), 7.66–7.70 (m, 1 H, H-4), 7.99–8.02 (m, 2 H, H-2/6), 12.25 (br s, 1 H, NH), 14.48 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.90, 63.86, 63.91, 96.85, 113.36, 126.66, 128.60, 129.06, 129.08, 131.64, 133.66, 148.08, 169.60, 175.64.

Anal. Calcd for $C_{16}H_{13}N_3O_2S_2$: C, 55.96; H, 3.82; N, 12.24. Found: C, 55.59; H, 3.95; N, 12.09.

_N_-Benzoyl-_N′_-(6-benzyl-3-cyano-4,5,6,7-tetrahydrothieno[2,3-_c_]pyridin-2-yl)thiourea (2f)

Off-white solid; yield: 19.3 g (89%); mp 138–140 °C; R_f = 0.56 (PE–EtOAc, 2:1).

IR (KBr): 3287, 2830, 2219, 1668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.76 (t, J = 5.4 Hz, 2 H, H-4′), 2.84 (t, J = 5.6 Hz, 2 H, H-5′), 3.55 (t, J = 1.6 Hz, 2 H, H-7′), 3.71 (s, 2 H, CH_2), 7.25–7.28 (m, 1 H, H-4″), 7.31–7.35 (m, 4 H, H-2″/3″/5″/6″), 7.51–7.55 (m, 2 H, H-3/5), 7.63–7.66 (m, 1 H, H-4), 7.90–7.93 (m, 2 H, H-2/6), 9.16 (br s, 1 H, NH), 14.23 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.07, 49.39, 50.72, 61.69, 98.01, 113.48, 127.21, 127.41, 127.72, 128.44, 129.03, 129.26, 130.36, 130.74, 134.15, 137.69, 147.64, 167.16, 174.07.

Anal. Calcd for $C_{23}H_{20}N_4OS_2$: C, 63.86; H, 4.66; N, 12.95. Found: C, 63.58; H, 4.86; N, 12.67.

_N_-Benzoyl-_N′_-(2-cyanophenyl)thiourea (2g)

White solid; yield: 11.1 g (79%); mp 169–172 °C (Lit.[37] 172–173 °C); R_f = 0.64 (toluene–EtOAc, 4:1).

IR (KBr): 3120, 2229, 1675 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.48–7.52 (m, 1 H, H-4′/5′/6′), 7.53–7.57 (m, 2 H, H-3/5), 7.65–7.69 (m, 1 H, H-4), 7.74–7.80 (m, 2 H, H-4′/5′/6′), 7.89–7.91 (m, 1 H, H-3′), 7.99–8.03 (m, 2 H, H-2/6), 11.85 (br s, 1 H, NH), 12.56 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 110.64, 116.56, 127.90, 128.64, 128.93, 132.03, 133.24, 133.45, 133.85, 141.32, 168.37, 181.54.

Anal. Calcd for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.01; H, 4.03; N, 14.72.

_N_-Benzoyl-_N′_-(2-cyano-4,5-dimethoxyphenyl)thiourea (2h)

Yellow solid; yield: 16.4 g (96%); mp 201–204 °C; R_f = 0.55 (toluene–EtOAc, 4:1).

IR (KBr): 3073, 2229, 1761, 1676 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 3.83 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 7.40 (s, 1 H, H-3′/5′), 7.42 (s, 1 H, H-3′/5′), 7.53–7.57 (m, 2 H, H-3/5), 7.65–7.69 (m, 1 H, H-4), 7.98–8.01 (m, 2 H, H-2/6), 11.83 (br s, 1 H, NH), 12.47 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 56.28, 56.31, 101.58, 114.38, 116.86, 128.64, 128.89, 132.06, 133.43, 135.90, 147.77, 168.50, 181.57.

Anal. Calcd for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31. Found: C, 59.79; H, 4.64; N, 12.18.

4-Aminothieno[2,3-_d_]pyrimidines and 4-Aminoquinazolines 3; General Procedure

The appropriate _N_-benzoyl-_N′_-(_o_-cyanoaryl)thiourea **2** (3.00 mmol) was refluxed for 30 min in a mixture of EtOH (3.0 mL) and 1 M NaOH (7.5 mL). The soln was cooled to r.t. and ethyl bromoacetate (601 mg, 399 μL, 3.60 mmol) was slowly added. After 1 h, the solid was removed by suction filtration, washed with H_2O (100 mL) and dried under reduced pressure. Pure material was obtained by recrystallization from EtOH.

Ethyl [(4-Aminothieno[2,3-_d_]pyrimidin-2-yl)sulfanyl]acetate (3a)

Colorless plates; yield: 468 mg (58%); mp 116–117 °C (EtOH); R_f = 0.45 (PE–EtOAc, 2:1).

IR (KBr): 3388, 3162, 2903, 1735, 1647 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 1.19 (t, J = 7.1 Hz, 3 H, CH_3), 3.95 (s, 2 H, CH_2), 4.11 (q, J = 7.1 Hz, 2 H, CH_2), 7.37 (d, J = 6.0 Hz, 1 H, H-5′/6′), 7.47 (d, J = 6.0 Hz, 1 H, H-5′/6′), 7.57 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.23, 32.82, 60.88, 113.23, 119.69, 120.69, 158.06, 164.46, 166.89, 169.36.

Anal. Calcd for $C_{10}H_{11}N_3O_2S_2$: C, 44.59; H, 4.12; N, 15.60. Found: C, 44.41; H, 4.17; N, 15.47.

Ethyl [(4-Amino-5,6-dimethylthieno[2,3-_d_]pyrimidin-2-yl)sulfanyl]acetate (3b)

Colorless plates; yield: 375 mg (42%); mp 149–151 °C (EtOH) (Lit.[19] 148–151 °C); R_f = 0.17 (toluene–EtOAc, 4:1).

IR (KBr): 3506, 3298, 3140, 2978, 1733, 1644 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 3.93 (s, 2 H, CH_2), 4.10 (q, J = 7.1 Hz, 2 H, CH_2), 6.98 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.95, 13.89, 14.25, 32.75, 60.88, 113.49, 124.82, 126.23, 157.91, 162.97, 165.40, 169.38.

Anal. Calcd for $C_{12}H_{15}N_3O_2S_2$: C, 48.46; H, 5.08; N, 14.13. Found: C, 47.97; H, 5.22; N, 13.84.

Ethyl [(4-Amino-6,7-dihydro-5_H_-cyclopenta[4,5]thieno[2,3-_d_]pyrimidin-2-yl)sulfanyl]acetate (3c)

Colorless plates; yield: 599 mg (65%); mp 180–182 °C (EtOH); R_f = 0.19 (toluene–EtOAc, 4:1).

IR (KBr): 3490, 3290, 3119, 2906, 1734, 1641 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 2.34–2.39 (m, 2 H, H-6′), 2.85–2.89 (m, 2 H, H-5′/7′), 2.96–2.99

(m, 2 H, H-5′/7′), 3.94 (s, 2 H, CH_2), 4.10 (q, J = 7.1 Hz, 2 H, CH_2), 6.96 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.25, 27.34, 28.81, 29.11, 32.81, 60.90, 109.55, 134.63, 136.02, 157.39, 163.09, 169.38, 171.42.

Anal. Calcd for $C_{13}H_{15}N_3O_2S_2$: C, 50.46; H, 4.89; N, 13.58. Found: C, 50.20; H, 4.94; N, 13.44.

Ethyl [(4-Amino-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-2-yl)sulfanyl]acetate (3d)

White needles; yield: 468 mg (48%); mp 139–140 °C (EtOH) (Lit.[19] 138–141 °C); R_f = 0.22 (toluene–EtOAc, 4:1).

IR (KBr): 3511, 3296, 3130, 2930, 1740, 1632 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 1.75–1.79 (m, 4 H, H-6′/7′), 2.69–2.70 (m, 2 H, H-5′/8′), 2.83–2.84 (m, 2 H, H-5′/8′), 3.93 (s, 2 H, CH_2), 4.10 (q, J = 7.1 Hz, 2 H, CH_2), 6.86 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.26, 22.06, 22.37, 24.83, 32.76, 60.88, 112.45, 126.96, 129.48, 157.76, 163.09, 166.09, 169.37.

Anal. Calcd for $C_{14}H_{17}N_3O_2S_2$: C, 51.99; H, 5.30; N, 12.99. Found: C, 51.69; H, 5.57; N, 12.59.

Ethyl [(4-Amino-5,8-dihydro-6*H*-pyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-2-yl)sulfanyl]acetate (3e)

Colorless blocks; yield: 726 mg (74%); mp 192–193 °C (EtOH); R_f = 0.40 (toluene–EtOAc, 4:1).

IR (KBr): 3489, 3294, 3161, 2968, 1727, 1631 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 2.95 (tt, J = 5.5, 1.9 Hz, 2 H, H-5′), 3.91 (t, J = 5.5 Hz, 2 H, H-6′), 3.95 (s, 2 H, CH_2), 4.10 (q, J = 7.1 Hz, 2 H, CH_2), 4.71 (t, J = 1.9 Hz, 2 H, H-8′), 6.97 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.25, 26.02, 32.80, 60.90, 63.94, 64.58, 111.89, 124.86, 127.23, 157.81, 163.60, 166.60, 169.32.

Anal. Calcd for $C_{13}H_{15}N_3O_3S_2$: C, 47.98; H, 4.65; N, 12.91. Found: C, 47.89; H, 4.64; N, 12.86.

Ethyl [(4-Amino-7-benzyl-5,6,7,8-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-2-yl)sulfanyl]acetate (3f)

Yellow needles; yield: 611 mg (49%); mp 143–144 °C (EtOH); R_f = 0.24 (toluene–EtOAc, 4:1).

IR (KBr): 3501, 3283, 3107, 2911, 1741, 1634 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.19 (t, J = 7.1 Hz, 3 H, CH_3), 2.77 (t, J = 5.7 Hz, 2 H, H-5′/6′), 2.94 (t, J = 5.7 Hz, 2 H, H-5′/6′), 3.60 (s, 2 H, H-8′), 3.70 (s, 2 H, CH_2), 3.96 (s, 2 H, CH_2), 4.11 (q, J = 7.1 Hz, 2 H, CH_2), 6.94 (br s, 2 H, NH_2), 7.26–7.30 (m, 1 H, H-4″), 7.33–7.38 (m, 4 H, H-2″/3″/5″/6″).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.25, 25.65, 32.78, 48.97, 51.39, 60.75, 60.89, 111.95, 125.61, 127.11, 127.23, 128.40, 128.94, 138.29, 157.80, 163.44, 166.43, 169.33.

Anal. Calcd for $C_{20}H_{22}N_4O_2S_2$: C, 57.95; H, 5.35; N, 13.52. Found: C, 57.70; H, 5.56; N, 13.35.

Ethyl [(4-Aminoquinazolin-2-yl)sulfanyl]acetate (3g)

White needles; yield: 438 mg (55%); mp 153–154 °C (EtOH) (Lit.[19] 151–152 °C); R_f = 0.88 (EtOAc).

IR (KBr): 3406, 3173, 2973, 1735, 1646 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.19 (t, J = 7.0 Hz, 3 H, CH_3), 3.98 (s, 2 H, CH_2), 4.11 (q, J = 7.0 Hz, 2 H, CH_2), 7.36 (ddd, J = 8.2, 6.9, 1.3 Hz, 1 H, H-6′), 7.45 (dd, J = 8.2, 1.3 Hz, 1 H, H-8′), 7.69 (ddd, J = 7.9, 7.1, 1.6 Hz, 1 H, H-7′), 7.85 (br s, 2 H, NH_2), 8.13 (dd, J = 8.2, 1.6 Hz, 1 H, H-5′).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.26, 32.79, 60.86, 112.70, 123.92, 124.55, 126.09, 133.41, 150.04, 161.34, 165.58, 169.54.

Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.45; H, 5.10; N, 15.54.

Ethyl [(4-Amino-6,7-dimethoxyquinazolin-2-yl)sulfanyl]acetate (3h)

White needles; yield: 659 mg (68%); mp 178–181 °C (EtOH); R_f = 0.27 (toluene–EtOAc, 4:1).

IR (KBr): 3108, 2888, 1725, 1661 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.20 (t, J = 7.0 Hz, 3 H, CH_3), 3.01 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 3.97 (s, 2 H, CH_2), 4.12 (q, J = 7.0 Hz, 2 H, CH_2), 6.87 (s, 1 H, H-5′/8′), 7.51 (br s, 2 H, NH_2), 7.52 (s, 1 H, H-5′/8′).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.25, 32.65, 55.76, 56.09, 60.81, 103.34, 105.87, 106.01, 147.13, 147.56, 154.49, 160.32, 163.25, 169.66.

Anal. Calcd for $C_{14}H_{17}N_3O_4S$: C, 52.00; H, 5.30; N, 12.99. Found: C, 52.14; H, 5.30; N, 13.00.

***N*-[3-(*o*-Cyanoaryl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamides 4; General Procedure**

The appropriate *N*-benzoyl-*N*′-(*o*-cyanoaryl)thiourea **2** (1.00 mmol) was dissolved in a mixture of EtOH (3.0 mL) and 1 M NaOH (1.5 mL). The soln was heated to 50 °C and ethyl bromoacetate (200 mg, 133 μL, 1.20 mmol) was added within 1 min. If turbidity was observed, a few drops of 1 M NaOH were added to prevent precipitation. After heating at 50 °C for 1 h, the mixture was cooled to r.t. and H_2O (5 mL) was added, and the precipitate was removed by suction filtration, washed with H_2O (50 mL), and dried in vacuo. Pure material was obtained by recrystallization from EtOH.

***N*-[3-(3-Cyano-2-thienyl)-4-oxo-1,3-thiazolidin-2-ylidene]-benzamide (4a)**

White needles; yield: 245 mg (71%); mp 191–192 °C (EtOH); R_f = 0.40 (PE–EtOAc, 2:1).

Material for X-ray crystallography was recrystallized from EtOAc.

IR (KBr): 3111, 2970, 2234, 1755, 1648 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.29 (s, 2 H, H-5′), 7.46–7.51 (m, 2 H, H-3/5), 7.59–7.63 (m, 2 H, H-4/4″/5″), 7.93–7.96 (m, 2 H, H-2/6), 7.99 (d, J = 5.7 Hz, 1 H, H-4″/5″).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 33.58, 109.71, 113.25, 127.15, 128.86, 129.52, 129.77, 133.71, 134.61, 143.04, 171.48, 172.66, 176.12.

Anal. Calcd for $C_{15}H_9N_3O_2S_2{\cdot}H_2O$: C, 52.16; H, 3.21; N, 12.17. Found: C, 52.25; H, 3.25; N, 12.18.

***N*-[3-(3-Cyano-4,5-dimethyl-2-thienyl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamide (4b)**

Pale yellow plates; yield: 223 mg (63%); mp 218–221 °C (EtOH); R_f = 0.62 (toluene–EtOAc, 4:1).

IR (KBr): 2230, 1751, 1649 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.26 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 4.27 (s, 2 H, H-5′), 7.48–7.52 (m, 2 H, H-3/5), 7.60–7.62 (m, 1 H, H-4), 7.96–7.98 (m, 2 H, H-2/6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.56, 13.24, 33.44, 111.67, 113.24, 128.89, 129.57, 132.05, 133.68, 134.60, 136.16, 138.21, 171.49, 172.41, 176.25.

Anal. Calcd for $C_{17}H_{13}N_3O_2S_2$: C, 57.45; H, 3.69; N, 11.82. Found: C, 57.02; H, 3.92; N, 11.53.

***N*-[3-(3-Cyano-5,6-dihydro-4*H*-cyclopenta[*b*]-2-thienyl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamide (4c)**
Colorless needles; yield: 243 mg (66%); mp 175–176 °C (EtOH); R_f = 0.49 (PE–EtOAc, 2:1).

IR (KBr): 2934, 2224, 1746, 1654 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.40–2.47 (m, 2 H, H-5″), 2.87–2.92 (m, 2 H, H-4″/6″), 3.01–3.06 (m, 2 H, H-4″/6″), 4.27 (s, 2 H, H-5′), 7.48–7.51 (m, 2 H, H-3/5), 7.60–7.62 (m, 1 H, H-4), 7.96–7.99 (m, 2 H, H-2/6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.37, 27.82, 30.04, 33.43, 105.62, 113.08, 128.87, 129.58, 133.68, 134.57, 143.32, 143.39, 144.16, 171.56, 172.43, 176.28.

Anal. Calcd for $C_{18}H_{13}N_3O_2S_2$: C, 58.84; H, 3.57; N, 11.44. Found: C, 58.87; H, 3.60; N, 10.97.

***N*-[3-(3-Cyano-4,5,6,7-tetrahydro-1-benzo-2-thienyl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamide (4d)**
Colorless plates; yield: 223 mg (58%); mp 194–197 °C (EtOH); R_f = 0.76 (toluene–EtOAc, 4:1).

IR (KBr): 2934, 2227, 1754, 1642 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 1.82–1.86 (m, 4 H, H-5″/6″), 2.65–2.69 (m, 2 H, H-4″/7″), 2.80–2.84 (m, 2 H, H-4″/7″), 4.27 (s, 2 H, H-5′), 7.48–7.52 (m, 2 H, H-3/5), 7.60–7.64 (m, 1 H, H-4), 7.97–7.99 (m, 2 H, H-2/6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.54, 22.46, 23.88, 24.35, 33.43, 109.84, 112.77, 128.88, 129.60, 133.67, 133.98, 134.56, 138.61, 139.28, 171.43, 172.17, 176.27.

Anal. Calcd for $C_{19}H_{15}N_3O_2S_2$: C, 59.82; H, 3.96; N, 11.02. Found: C, 59.92; H, 4.18; N, 10.82.

***N*-[3-(3-Cyano-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-2-yl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamide (4e)**
Colorless needles; yield: 277 mg (72%); mp 181–182 °C (EtOH); R_f = 0.42 (toluene–EtOAc, 4:1).

IR (KBr): 2926, 2230, 1756, 1645 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.75–2.83 (m, 2 H, H-4″), 3.98 (t, J = 5.4 Hz, 2 H, H-5″), 4.28 (s, 2 H, H-5′), 4.81 (t, J = 1.6 Hz, 2 H, H-7″), 7.48–7.52 (m, 2 H, H-3/5), 7.61–7.63 (m, 1 H, H-4), 7.97–8.00 (m, 2 H, H-2/6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.28, 33.50, 63.87, 64.30, 109.88, 112.41, 128.88, 129.61, 131.78, 133.68, 134.55, 136.26, 140.61, 171.40, 172.31, 176.24.

Anal. Calcd for $C_{18}H_{13}N_3O_3S_2$: C, 56.38; H, 3.42; N, 10.96. Found: C, 56.30; H, 3.66; N, 10.70.

***N*-[3-(6-Benzyl-3-cyano-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamide (4f)**
The compound was purified by column chromatography (silica gel, PE–EtOAc, 2:1).

Orange solid; yield: 105 mg (19%); mp 86–89 °C; R_f = 0.40 (toluene–EtOAc, 4:1).

IR (KBr): 2924, 2228, 1756, 1646 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.73–2.89 (m, 4 H, H-4″/5″), 3.69–3.81 (m, 4 H, H-7″, CH_2), 4.27 (s, 2 H, H-5′), 7.26–7.30 (m, 1 H, H-4‴), 7.33–7.38 (m, 4 H, H-2‴/3‴/5‴/6‴), 7.48–7.51 (m, 2 H, H-3/5), 7.60–7.63 (m, 1 H, H-4), 7.97–8.00 (m, 2 H, H-2/6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.84, 33.48, 48.62, 50.71, 60.45, 109.41, 112.58, 127.36, 128.47, 128.87, 129.00, 129.60, 132.59, 133.68, 134.57, 136.09, 137.88, 140.17, 171.42, 172.26, 176.26.

Anal. Calcd for $C_{25}H_{20}N_4O_2S_2$·EtOAc: C, 62.12; H, 5.03; N, 9.99. Found: C, 62.02; H, 5.19; N, 9.69.

***N*-[3-(2-Cyanophenyl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamide (4g)**
Yellow plates; yield: 226 mg (70%); mp 196–198 °C (EtOH); R_f = 0.51 (toluene–EtOAc, 4:1).

IR (KBr): 2240, 1758, 1632 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 4.26 (d, J = 18.6 Hz, 1 H, H-5′), 4.42 (d, J = 18.6 Hz, 1 H, H-5′), 7.40–7.46 (m, 2 H, H-3/5), 7.55–7.59 (m, 1 H, H-4), 7.76–7.79 (m, 2 H, H-4″/6″), 7.80–7.83 (m, 2 H, H-2/6), 7.95–7.99 (m, 1 H, H-5″), 8.12–8.15 (m, 1 H, H-3″).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 33.75, 111.84, 115.80, 128.79, 129.35, 130.26, 130.52, 133.58, 133.74, 134.67, 134.75, 137.50, 172.34, 173.03, 176.11.

Anal. Calcd for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.27; H, 3.41; N, 12.90.

***N*-[3-(2-Cyano-4,5-dimethoxyphenyl)-4-oxo-1,3-thiazolidin-2-ylidene]benzamide (4h)**
Orange cubes; yield: 251 mg (66%); mp 216–218 °C (EtOH); R_f = 0.29 (toluene–EtOAc, 4:1).

IR (KBr): 2940, 2225, 1755, 1642 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 4.22 (d, J = 18.6 Hz, 1 H, H-5′), 4.40 (d, J = 18.6 Hz, 1 H, H-5′), 7.41 (s, 1 H, H-3″/6″), 7.44–7.47 (m, 2 H, H-3/5), 7.57–7.59 (m, 1 H, H-4), 7.65 (s, 1 H, H-3″/6″), 7.86–7.89 (m, 2 H, H-2/6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 33.50, 56.50, 103.21, 113.11, 114.78, 116.17, 128.81, 129.42, 131.95, 133.54, 134.76, 149.38, 153.10, 172.37, 172.93, 176.27.

Anal. Calcd for $C_{19}H_{15}N_3O_4S$: C, 59.83; H, 3.96; N, 11.02. Found: C, 59.81; H, 3.98; N, 11.63.

***N*-[3-(2-Cyanophenyl)-1,3-thiazolidin-2-ylidene]benzamide (5)**
A mixture of *N*-benzoyl-*N*′-(2-cyanophenyl)thiourea (**2g**; 281 mg, 1.00 mmol) and NaOAc (197 mg, 2.40 mmol) in DMF (10 mL) was treated dropwise with 1,2-dibromoethane (225 mg, 103 μL, 1.20 mmol). The mixture was stirred overnight at r.t. A precipitate was removed by filtration and the filtrate was evaporated in vacuo. The crude material was purified by column chromatography (silica gel, toluene–EtOAc, 4:1).

White solid; yield: 85 mg (28%); mp 130–132 °C; R_f = 0.28 (toluene–EtOAc, 4:1).

IR (KBr): 3059, 2231, 1617 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 3.43 (t, J = 7.7 Hz, 2 H, H-5′), 4.19 (t, J = 7.7 Hz, 2 H, H-4′), 7.36–7.40 (m, 2 H, H-3/5), 7.47–7.51 (m, 1 H, H-4), 7.59–7.63 (m, 1 H, H-4″), 7.72 (dd, J = 8.2, 1.0 Hz, 1 H, H-6″), 7.84–7.89 (m, 3 H, H-2/6/5″), 8.02–8.05 (dd, J = 7.9, 1.6 Hz, 1 H, H-3″).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.66, 51.76, 111.44, 116.66, 127.13, 128.35, 128.58, 129.09, 132.36, 133.71, 134.58, 136.03, 142.75, 172.38, 174.45.

Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.23; H, 4.19; N, 13.65.

2-(4-Oxo-1,3-thiazolidin-3-yl)benzonitrile (6)
Compound **6** was prepared by a method according to Brouwer et al.:[33] an aq formaldehyde soln (37 wt%, 4.5 mL) was added dropwise to a soln of anthranilonitrile (5.91 g, 50.0 mmol) and thioglycolic acid (4.61 g, 3.48 mL, 50.0 mmol) in EtOH (15 mL). After stirring for 4 h at r.t., the mixture was poured into ice water (75 mL).

Precipitated 2-[(2-cyanophenylamino)methylsulfanyl]acetic acid (9.85 g, 44.3 mmol) was recovered by suction filtration, washed with H_2O (100 mL), and dried under reduced pressure. It was then redissolved in *p*-xylene (60 mL) and refluxed for 6 h using a water trap. The resulting soln was filtered and the solvent was removed under reduced pressure. Recrystallization from EtOH afforded **6**.

White needles; yield: 3.47 g (43%, 2 steps); mp 124–126 °C (EtOH) (Lit.[33] 120–122 °C); R_f = 0.21 (toluene–EtOAc, 4:1).

IR (KBr): 2233, 1683 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.73 (t, *J* = 1.0 Hz, 2 H, H-5′), 4.85 (t, *J* = 1.0 Hz, 2 H, H-2′), 7.53–7.57 (m, 1 H, H-5), 7.62 (dd, *J* = 8.2, 1.0 Hz, 1 H, H-3), 7.78–7.82 (m, 1 H, H-4), 7.93 (dd, *J* = 7.9, 1.6 Hz, 1 H, H-6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.70, 48.86, 111.12, 116.41, 127.52, 128.62, 133.80, 134.50, 141.11, 170.98.

Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.72. Found: C, 58.92; H, 3.97; N, 13.73.

N-(4-Oxo-3-phenyl-1,3-thiazolidin-2-ylidene)benzamide (7)

N-Benzoyl-*N*′-phenylthiourea[38] (256 mg, 1.00 mmol) was dissolved in a mixture of EtOH (5.0 mL) and 1 M NaOH (1.5 mL). The soln was heated to 50 °C and ethyl bromoacetate (200 mg, 133 μL, 1.20 mmol) was added within 1 min. After heating at 50 °C for 1 h, the mixture was cooled to r.t., H_2O (8 mL) was added, and the precipitate was removed by suction filtration, washed with H_2O (50 mL), and dried in vacuo. Recrystallization from EtOAc afforded **7**.

Colorless needles; yield: 255 mg (86%); mp 221–222 °C (EtOAc) (Lit.[8] 224 °C); R_f = 0.54 (PE–EtOAc, 2:1).

IR (KBr): 2968, 1733, 1637 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.16 (s, 2 H, H-5′), 7.40–7.45 (m, 4 H, H-3/5/2′/6′), 7.49–7.59 (m, 4 H, H-4/3′/4′/5′), 7.83–7.86 (m, 2 H, H-2/6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 33.57, 128.32, 128.67, 129.01, 129.08, 129.36, 133.30, 135.07, 135.39, 173.04, 173.88, 176.24.

Anal. Calcd for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45. Found: C, 64.56; H, 4.04; N, 9.41.

3-Phenyl-1,3-thiazolidin-4-one (8)

Compound **8** was prepared by a procedure of Kay et al.:[34] thioglycolic acid (5.68 g, 4.29 mL, 61.7 mmol) was added within 1 min to a soln of aniline (5.75 g, 5.62 mL, 61.7 mmol) in toluene (120 mL). After 10 min, the soln was treated dropwise with an aq formaldehyde soln (37 wt%, 4.8 mL), and addition of PTSA·H_2O (10 mg, 53 μmol) followed. The mixture was refluxed for 4 h using a water trap. After the mixture had cooled to r.t. and been washed with sat. aq $NaHCO_3$ (2 × 50 mL), the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, toluene–EtOAc, 4:1).

White solid; yield: 6.01 g (54%); mp 110–112 °C (EtOH) (Lit.[39] 110–114 °C, Lit.[33] 116–119 °C); R_f = 0.35 (PE–EtOAc, 4:1).

IR (KBr): 3058, 1677 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.70 (t, *J* = 1.0 Hz, 2 H, H-2/5), 4.89 (t, *J* = 1.0 Hz, 2 H, H-2/5), 7.21–7.25 (m, 1 H, H-4′), 7.38–7.42 (m, 2 H, H-3′/5′), 7.48–7.52 (m, 2 H, H-2′/6′).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 32.66, 48.71, 122.57, 125.84, 128.94, 139.05, 170.40.

Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.25; H, 5.36; N, 7.86.

DFT Calculations

3D coordinates of compounds **4a**,**b**,**g** were retrieved from their corresponding crystal structures. Relaxed potential energy surface (PES) scans were carried out applying a 5° (BP86/LANL2DZ) stepwise rotation around the C–N bond connecting the cyanoarene and the thiazolidin-4-one. Transition state optimization was done at the B3LYP/6-311G** level of theory. If no transition state was reached (carbonyl and imine barrier in case of **4a**, carbonyl barrier in case of **4b**), additional PES scans at the B3LYP/6-311G** level were carried out, providing 1° and subsequent 0.1° stepwise rotations in close range to rotational barriers discovered at BP86/LANL2DZ level. Coordinates and corresponding energies of each optimized step were extracted using a custom PERL script,[40] and submitted to transition state optimization. All transition states were pre-optimized at the BP86/LANL2DZ level before final geometries were obtained using the DFT hybrid B3LYP/6-311G**. All B3LYP/6-311G** maxima, as well as transition state optimizations, were accompanied by frequency calculations to ensure maxima or first-order saddle point identification and to retrieve free energy values. All measurements, e.g. bond angles and dihedrals, and RMSD calculations were performed using PyMOL.[41]

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References

(1) Modica, M.; Santagati, M.; Santagati, A.; Russo, F.; Cagnotto, A.; Goegan, M.; Mennini, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1089.
(2) Modica, M.; Romeo, G.; Materia, L.; Russo, F.; Cagnotto, A.; Mennini, T.; Gáspár, R.; Falkay, G.; Fülöp, F. *Bioorg. Med. Chem.* **2004**, *12*, 3891.
(3) Kondratov, R. V.; Komarov, P. G.; Becker, Y.; Eweson, A.; Gudkov, A. V. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 14078.
(4) Leistner, S.; Gütschow, M.; Wagner, G. *Arch. Pharm.* **1989**, *322*, 227.
(5) Complete bond length and angles, coordinates, and displacement parameters of **3a**, **4a**, **4b**, and **4g** have been deposited at the Cambridge Crystallography Data Centre (CCDC numbers 706312, 706313, 706314, and 706315).
(6) Klika, K. D.; Janovec, L.; Imrich, J.; Suchár, G.; Kristian, P.; Sillanpää, R.; Pihlaja, K. *Eur. J. Org. Chem.* **2002**, 1248.
(7) St. Laurent, D. R.; Gao, Q.; Wu, D.; Serrano-Wu, M. H. *Tetrahedron Lett.* **2004**, *45*, 1907.
(8) Wobig, D. *Liebigs Ann. Chem.* **1992**, 415.
(9) Peng, Y.; Song, G.; Liu, L. *Org. Prep. Proced. Int.* **2004**, *36*, 151.
(10) Peng, Y.; Song, G.; Huang, F. *J. Chem. Res.* **2004**, 676.
(11) Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175.
(12) Ottaná, R.; Maccari, R.; Barreca, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Di Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G. *Bioorg. Med. Chem.* **2005**, *13*, 4243.
(13) Rostom, S. A. F. *Bioorg. Med. Chem.* **2006**, *14*, 6475.
(14) Vicini, P.; Geronikaki, A.; Incerti, M.; Zani, F.; Dearden, J.; Hewitt, M. *Bioorg. Med. Chem.* **2008**, *16*, 3714.

(15) Zhou, H.; Wu, S.; Zhai, S.; Liu, A.; Sun, Y.; Li, R.; Zhang, Y.; Ekins, S.; Swaan, P. W.; Fang, B.; Zhang, B.; Yan, B. *J. Med. Chem.* **2008**, *51*, 1242.
(16) Saeed, A.; Abbas, N.; Flörcke, U. *J. Braz. Chem. Soc.* **2007**, *18*, 559.
(17) Hamama, W. S.; Ismail, M. A.; Shaaban, S.; Zoorob, H. H. *J. Heterocycl. Chem.* **2008**, *45*, 939.
(18) Kato, Y.; Kita, Y.; Nishio, M.; Hirasawa, Y.; Ito, K.; Yamanaka, T.; Motoyama, Y.; Seki, J. *Eur. J. Pharmacol.* **1999**, *384*, 197.
(19) Gewald, K.; Schäfer, H.; Eckert, K.; Jeschke, T. *J. Prakt. Chem.* **1996**, *338*, 206.
(20) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem.* **2005**, *117*, 5518.
(21) Roussel, C.; Vanthuyne, N.; Bouchekaram, M.; Djarfri, A.; Elguero, J.; Alkorta, I. *J. Org. Chem.* **2008**, *73*, 403.
(22) Erol, S.; Dogan, I. *J. Org. Chem.* **2007**, *72*, 2494.
(23) Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076.
(24) Ángyán, J. G.; Poirier, R. A.; Kucsmán, A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1987**, *109*, 2237.
(25) Gütschow, M.; Leistner, S.; Pink, M. *J. Heterocycl. Chem.* **1992**, *29*, 279.
(26) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, revision D.01*; Gaussian Inc.: Wallingford, CT, **2004**.
(27) Diurno, M. V.; Mazzoni, O.; Piscopo, E.; Calignano, A.; Giordano, F.; Bolognese, A. *J. Med. Chem.* **1992**, *35*, 2910.
(28) Jayalakshmi, K.; Mahendra, M.; Basappa Doreswamy, B. H.; Sridhar, M. A.; Shashidhara Prasad, J.; Rangappa, K. S. *J. Chem. Crystallogr.* **2005**, *35*, 67.
(29) Allingham, Y.; Cookson, R. C.; Crabb, T. A. *Tetrahedron* **1968**, *24*, 1989.
(30) Cunico, W.; Capri, L. R.; Gomes, C. R. B.; Sizilio, R. H.; Wardell, S. M. S. V. *Synthesis* **2006**, 3405.
(31) Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. *Org. Biomol. Chem.* **2004**, *2*, 2809.
(32) Hickel, D.; Leger, J. M.; Capry, A.; Vigorita, M. G.; Chimirri, A.; Grasso, S. *Acta Crystallogr., Sect. C* **1983**, *39*, 240.
(33) Brouwer, W. G.; Blem, A. R. Patent Application EP 200415, **1986**; *Chem. Abstr.* **1987**, *107*, 39793.
(34) Kay, I. T.; Barton, J. E. D.; Collins, D. J.; Kowalczyk, B.; Mitchell, G.; Shribbs, J. M.; Cox, J. M.; Barnes, N. J.; Smith, S. C. Patent Application WO 9413652, **1994**; *Chem. Abstr.* **1995**, *122*, 81373.
(35) Hallas, G.; Towns, A. D. *Dyes Pigm.* **1997**, *33*, 319.
(36) Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94.
(37) Pazdera, P.; Potůček, E.; Nováček, E.; Kalviňš, I.; Trapencieris, P.; Poguvics, O. *Chem. Pap.* **1991**, *45*, 527.
(38) Rasmussen, C. R.; Villani, F. J.; Weaner, L. E.; Reynolds, B. E.; Hood, A. R.; Hecker, L. R.; Nortey, S. O.; Hanslin, A.; Costanzo, M. J.; Powell, E. T.; Molinari, A. J. *Synthesis* **1988**, 456.
(39) Pacha, W.; Erlenmeyer, H. *Helv. Chim. Acta* **1956**, *39*, 1156.
(40) See: http://pwe.no-ip.org/other/pes-results (July 28, 2008).
(41) PyMOL Molecular Graphics System 0.99: http://www.pymol.org (February 12, 2008).