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Synthesis of Multifunctionalized 2-Iminothiazolidin-4-ones and Their 2-Arylimino Derivatives

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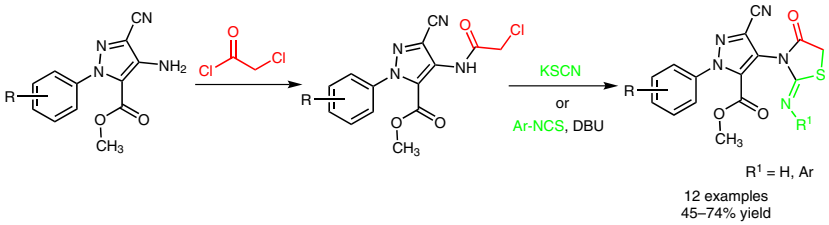

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Abstract Multifunctionalized 2-imino-3-(pyrazol-4-yl)thiazolidin-4-ones and 2-arylimino-3-(pyrazol-4-yl)thiazolidin-4-ones were prepared according to an efficient four-step procedure. The key step of the synthetic pathway involved the cyclization of 2-chloro-*N*-(pyrazol-4-yl)acetamide intermediate using KSCN or aryl isothiocyanate, respectively. The structure of the title compounds was confirmed on the basis of NMR data and ^{15}N-labeling.

Key words thiazolidin-4-ones, pyrazoles, cyclization, heterocycles, regioselectivity

Present in natural or synthetic products, five-membered heterocyclic rings are privileged scaffolds for the design of therapeutic agents. Among them, the 1,3-thiazolidin-4-one core has been widely explored due to its versatile biological properties.[1–3] In particular, 2-iminothiazolidin-4-ones **I** (Figure 1) display antifungal,[4–6] anti-inflammatory,[7,8] anticonvulsant,[9,10] hypnotic,[11] and antibacterial[6,12] activities. On the other hand, pyrazole scaffolds have also been largely exploited by medicinal chemists, leading to the development of valuable bioactive compounds.[13,14]

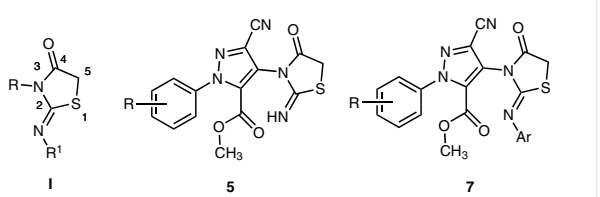
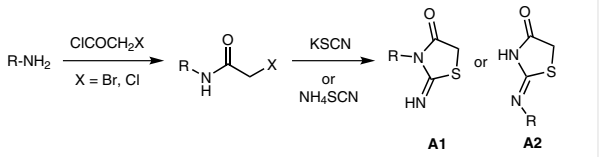


Figure 1 General structures of 2-iminothiazolidin-4-ones **I** and target compounds **5** and **7**

In continuation of our ongoing programs dedicated to the synthesis of new pyrazole and thiazolidin-4-one derivatives endowed with biological properties,[15,16] we became interested in the design of new hybrid compounds combining these two scaffolds. Such compounds have already demonstrated inhibitory activities toward VHR phosphatase, histone acetyltransferases, ADAMTS-5, and the TNF-α-TNFRc1 interaction as well as anti-inflammatory and antimicrobial properties.[17]

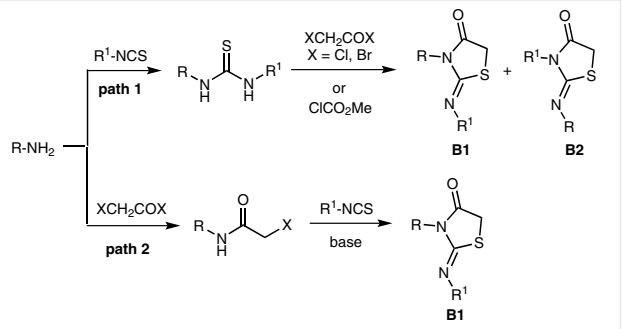
To our knowledge, despite a large diversity of reported 2-iminothiazolidine-4-ones, there is no example of derivatives bearing a pyrazole moiety at the position 3 of the thiazolidinone ring (Figure 1). Yet, the substituent R (Figure 1) has been chosen among the alkyl[7] and heteroaryl groups, the latter mainly including substituted phenyl,[18] thiazolyl,[4,19] and naphthyl[20] derivatives. Thus, we report herein the regioselective synthesis of two new series of 2-iminothiazolidin-4-ones, including the 2-imino-3-(pyrazol-4-yl)-thiazolidin-4-ones **5** and their 2-arylimino derivatives **7** (Figure 1). To unambiguously confirm the structure of the latter compounds, a ^{15}N-labeled 2-aryliminothiazolidin-4-one was synthesized.

A convenient method for the preparation of 2-iminothiazolidin-4-ones **A1** involves the reaction of 2-haloacetamides in the presence of potassium thiocyanate[4,5,19,20] or ammonium thiocyanate (Scheme 1).[21,22] It has been reported that this cyclization process can lead to the formation of the regioisomer **A2** using either NH_4SCN[23–25] or KSCN.[26]



Scheme 1 Synthesis of 2-iminothiazolidin-4-ones **A1** and **A2**

To get access to substituted 2-iminothiazolidin-4-ones of general structures **B1**/**B2**, two synthetic routes are commonly reported in the literature including, either the cyclization of 1,3-disubstituted thioureas with a haloacetic acid derivative (Path 1, Scheme 2)[7,27–32] or the condensation of 2-haloacetamides with alkyl or aryl isothiocyanates (Path 2, Scheme 2).[18,27,28] A major drawback of the first method is its lack of selectivity potentially leading to the formation of two regioisomers with unsymmetrical thioureas. This limitation prompted us to explore the second approach (Path 2, Scheme 2).

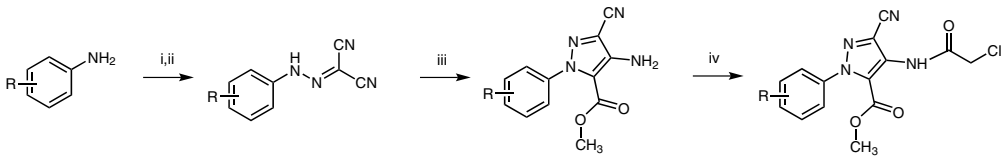


Scheme 2 General synthetic routes to 2-iminothiazolidin-4-ones **B1** and **B2**

Examination of these synthetic schemes reveals that the target compounds **5** and **7** could be synthesized from the 2-haloacetamides as a common precursor. Hence, the 2-chloro-3-(pyrazol-4-yl)acetamides **4** were prepared in a three-step procedure. Commercially available anilines **1a–h** were converted into the corresponding *N*-arylhydrazones **2a–h** and subsequent cyclization with methyl 2-bromoacetate led to the 4-amino-3-cyano-*N*-arylpyrazoles **3a–h** as previously described (Scheme 3).[15] New compounds **2e–h** and **3e–h** bearing a chlorine or a fluorine atom at the *meta* or *para* position of the phenyl ring were formed with slightly lower or similar yield to the known compounds **2a–d** and **3a–d**. The 2-chloro-*N*-(pyrazol-4-yl)acetamides **4a–h** were obtained by reacting the 2-aminopyrazoles **3a–h** with chloroacetyl chloride in DMF at room temperature in good to very good yields (80–86%, Scheme 3) except for compound **4f** (44% yield).

Cyclization of 2-chloroacetamides **4a–h** performed with KSCN in acetone at room temperature gave imines **5a–h** in yields ranging from 49 to 74% (Table 1). The α-thiocyanatoamide intermediate could not be isolated and spontaneously cyclized to furnish product **5** (Scheme 4). The structure of **5** was confirmed by analysis of the ^{1}H NMR spectral data showing a signal for the imine proton at 9.75 ppm. In addition, the IR spectra of compounds **5a–h** revealed an absorption band at 3300 cm^{-1} in agreement with an imine function. Under our reaction conditions, the formation of the regioisomer **6** was never observed (Scheme 4).

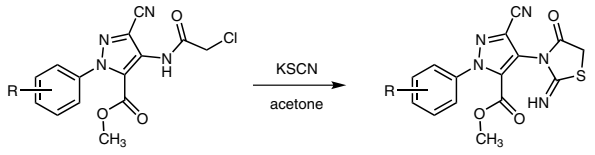
Access to the new thiazolidin-4-ones **7** can be envisaged by the condensation reaction of 2-chloroacetamides **4** with aryl isothiocyanates in the presence of a base such as K_2CO_3[18,28] or NaH.[29] Generally, these conditions lead to the desired products in a moderate yield. To validate the feasibility of the cyclization reaction, we performed our optimization study with pyrazole **4c** and phenyl isothiocyanate using THF as solvent (Table 2). In a first assay, using the conditions reported in the literature for our multifunctionalized scaffold,[18] acetamide **4c** was treated with 1 equivalent of phenyl isothiocyanate in the presence of 1 equivalent of the inorganic base K_2CO_3 to afford after stirring for 4 days, the desired product **7a** in a 17% NMR yield (Table 2, entry 1). It is noteworthy that only partial consumption of **4c** was observed. In order to improve the conversion rate, the nature of the base was screened (Table 2). The use of a strong base such as *t*-BuOK (1 equiv) allowed to reduce the reaction time and to increase the NMR yield up to 29% (entries



1a–e	2a–h	3a–h	4a–h
1a: R= H	**2a** (99%)	**3a** (70%)	**4a** (84%)
1b: R = 3-OCH$_3$	**2b** (91%)	**3b** (80%)	**4b** (80%)
1c: R= 3-Br	**2c** (97%)	**3c** (60%)	**4c** (81%)
1d: R = 4-Br	**2d** (94%)	**3d** (55%)	**4d** (80%)
1e: R= 3-Cl	**2e** (75%)	**3e** (68%)	**4e** (80%)
1f: R= 4-Cl	**2f** (67%)	**3f** (57%)	**4f** (44%)
1g: R = 3-F	**2g** (75%)	**3g** (72%)	**4g** (81%)
1h: R = 4-F	**2h** (74%)	**3h** (64%)	**4h** (86%)

Scheme 3 *Reagents and conditions*: (i) $NaNO_2$, HCl, 0 °C; (ii) $CH_2(CN)_2$, NaOAc, 0 °C; (iii) $BrCH_2CO_2Me$ (7.5 equiv), K_2CO_3 (2.7 equiv), toluene or 1,4-dioxane, 90 W, 110 °C; (iv) $ClCH_2COCl$ (1.1 equiv), DMF, r.t.

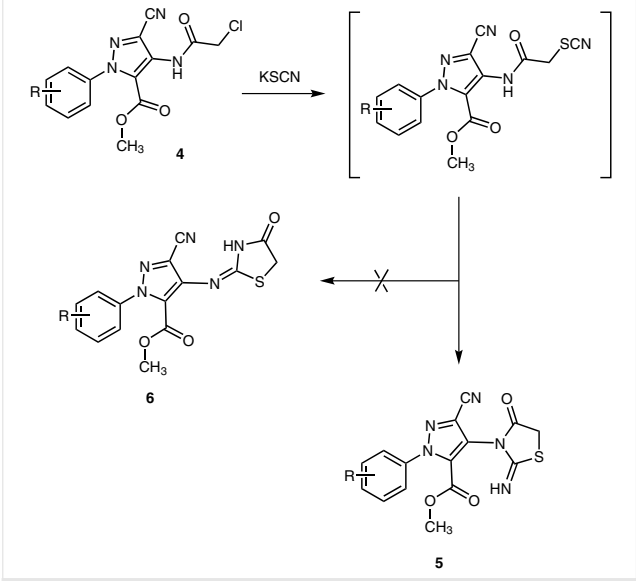
Table 1 Preparation of 2-Imino-3-(pyrazol-4-yl)thiazolidin-4-ones **5a–h**



4 5

Entry	R	Product[a]	Yield (%)[b]
1	H	**5a**	55
2	3-CH_3O	**5b**	70
3	3-Br	**5c**	67
4	4-Br	**5d**	49
5	3-Cl	**5e**	72
6	4-Cl	**5f**	49
7	3-F	**5g**	49
8	4-F	**5h**	74

[a] Reaction conditions: compound **4** (1 equiv), KSCN (4 equiv), acetone, r.t., 48 h.
[b] Isolated yield.

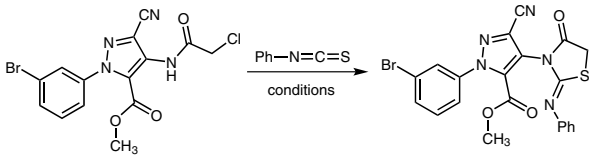


Scheme 4 Formation of the α-thiocyanatoamide intermediate during the transformation of compound **4** to **5**

2, 3). The formation of **7a** did not occur in the presence of nitrogen-containing bases such as DMAN, DABCO, or TMG (entries 4–6). Interestingly, using TMG as the base gave the 2-aminothiazole **8** in 56% NMR yield according to Jalani et al. (see Supporting Information).[33] An encouraging result was obtained with DBU (1 equiv) leading to compound **7a** in 34% NMR yield after only 4 hours of reaction (entry 7).

Further optimizations related to the amounts of DBU and phenyl isothiocyanate (entries 8–10) showed that the use of 3 equivalents of phenyl isothiocyanate allowed a significant improvement of the NMR yield (54%, entry 9). Afterwards, the dilution effect was examined (entries 11–14). Optimal conditions using 0.1 M pyrazole **4c**, DBU (1 equiv), and phenyl isothiocyanate (3 equiv) led to **7a** in an improved 70% NMR yield and 45% isolated yield (entry 12).

Table 2 Screening of the Reaction Conditions[a]



4c 7a

Entry	**4c** (mol·L^{-1})	Base[b]	Base (equiv)	PhNCS (equiv)	Time (h)	Yield (%)[c]
1	0.19	K_2CO_3	1	1	96	17[d]
2	0.19	*t*-BuOK	1	1	28	29
3	0.19	*t*-BuOK	1	2	16	27
4	0.19	DABCO	1	1	24	0
5	0.19	DMAN	1	1	4	0[e]
6	0.19	TMG	1	1	4	0
7	0.19	DBU	1	1	4	34
8	0.19	DBU	1	2	4	44
9	0.19	DBU	1	3	4	54
10	0.19	DBU	2	3	4	7
11	0.10	DBU	1	1	24	55
12	**0.10**	**DBU**	**1**	**3**	**4**	**70 (45)[f]**
13	0.10	DBU	2	3	4	33
14	0.05	DBU	1	3	6	60
15	0.10	DBN	1	1	24	34

[a] Reaction conditions: compound **4c** (0.13 mmol), phenyl isothiocyanate (1–3 equiv), base (1–2 equiv), THF, r.t.
[b] DABCO: 1,4-Diazabicyclo[2.2.2]octane; DMAN: 1,8-bis(dimethylamino)naphthalene; TMG: 1,1,3,3-tetramethylguanidine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN: 1,5-diazabicyclo[4.3.0]non-5-ene.
[c] ^{1}H NMR yields determined by comparison with butadiene sulfone as an internal standard.
[d] Partial consumption.
[e] No reaction.
[f] Isolated yield.

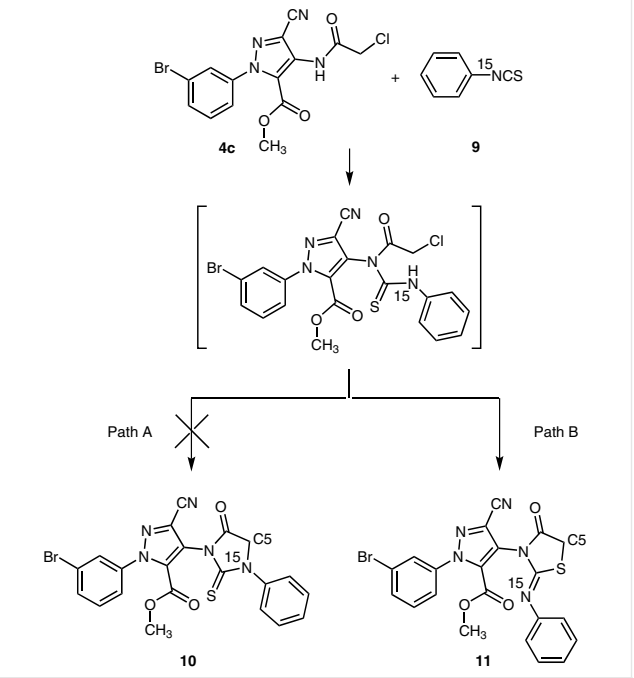
Replacement of DBU by DBN caused a significant drop of the NMR yield (34%, Table 2, entry 15). Finally, a few solvents were screened using our best conditions (entry 12). 1,4-Dioxane gave a comparable yield to THF (66%, Table 3, entry 2) while the use of DME, toluene, or acetonitrile resulted in a reduced NMR yield ranging from 26 to 60% (entries 3–5).

Table 3 Solvent Effect[a]

Entry	Solvent	Yield (%)[b]
1	THF	70
2	1,4-dioxane	66
3	DME[c]	60
4	MeCN	26
5	toluene	50

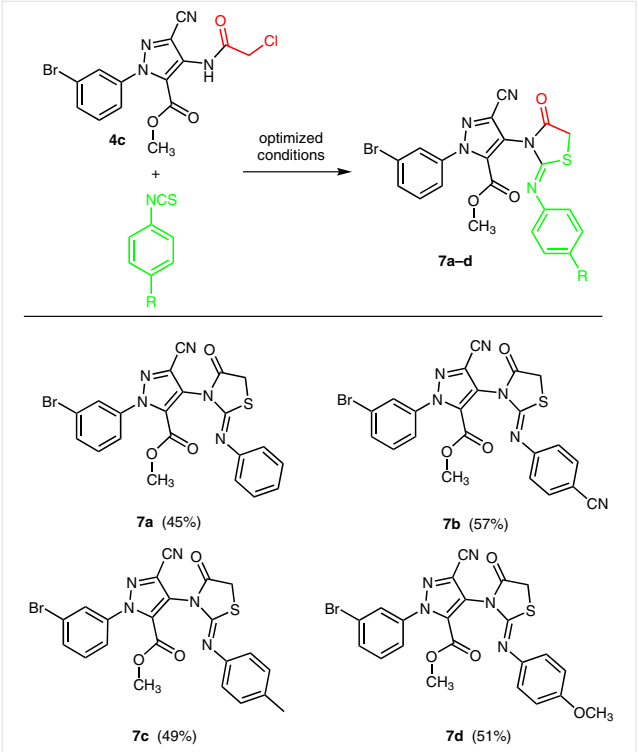
[a] Reaction conditions: pyrazole **4c** (0.13 mmol), DBU (1 equiv), PhNCS (3 equiv), solvent (1.3 mL), r.t., 4 h.
[b] ^{1}H NMR yields determined by comparison with butadiene sulfone as an internal standard.
[c] DME: Dimethoxyethane.

To confirm the structure of the cyclization product **7a**, we chose to synthetize its ^{15}N-labeled analogue by reacting **4c** and phenyl isothiocyanate-^{15}N **9**[34] under our optimized conditions (Table 2, entry) and performed NMR studies (Scheme 5). Although the presence of the nitrogen and sulfur nucleophilic centers of the reactive intermediate could give rise to the formation of the labeled thiohydantoin **10** (Scheme 5, path A) or 2-iminothiazolidin-4-one **11** (Scheme 5, path B), an exclusive cyclization process triggered by the sulfur atom was observed leading to the regioselective formation of compound **11**. Indeed, the position of the ^{15}N atom in the reaction product was determined through analysis of its ^{1}H and ^{13}C NMR spectra. In particular, the C5 thiazolidinone carbon gave a ^{13}C singlet (32.8 ppm) whereas splitting of resonance due to ^{15}N–C coupling is expected in compound **10**. In addition, the IR spectrum shows a strong band at about 1640 cm^{-1} characteristic of C=N functionality.



Scheme 5 Mechanism pathways for the reaction of 2-chloro-*N*-(pyrazol-4-yl)acetamide **4c** with phenyl isothiocyanate-^{15}N **9**

With the optimized conditions in hand, the protocol was applied to a set of commercially available aryl isothiocyanates bearing substituents in the *para* position. The results are shown in Scheme 6. For this limited series of functionalized 2-(arylimino)thiazolidin-4-ones, three additional products **7b–d** were obtained with isolated yields between 49 and 57% underlying that the reaction tolerates electron-donating or -withdrawing groups in the *para* position of the phenyl ring.



Scheme 6 The scope of the reaction of pyrazole **4c** and aryl isothiocyanates

In summary, we have reported the regioselective synthesis of two new series of highly functionalized 2-imino-3-(pyrazol-4-yl)thiazolidin-4-ones and 2-(arylimino)-3-(pyrazol-4-yl)thiazolidin-4-ones. Interestingly for the latter family, DBU proved to be an efficient base for the formation of the thiazolidin-4-one core. The structure of these compounds was established by ^{15}N labeling and NMR spectroscopy. In the future, the reactivity of the methylene, ester, and nitrile groups as well as the presence of the halogen atoms will be exploited to extend the molecular diversity and lead to new compounds of potential biological interest.

All reagents were obtained from commercial suppliers and used without further purification. Aniline-^{15}N (CAS 7022-92-6) and butadiene sulfone (CAS 77-79-2) were purchased from Aldrich. Silica gel 60F 254 plates (Merck) were used for analytical TLC. Flash column chromatography was performed on silica gel 60 (40–63 µm, Merck) or basic Al_2O_3 (Brockmann I). All microwave-assisted reactions were carried out in a single-mode focused microwave reactor (CEM Discover Benchmate) in open vessel mode. The reaction temperature was monitored with the external surface sensor. Heating time was included in the measurement of reaction time. Melting points were determined on a Kofler hot bench and are uncorrected. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded at 300 K in DMSO-d_6 on a Bruker Avance or Avance II. Chemical shifts (δ) are expressed in ppm relative to the solvent resonance and coupling constants (*J*) are in Hertz (Hz). Multiplicities are reported using standard abbreviations. Peak assignments were made according to COSY, HSQC, and HMBC spectra. IR spectra were recorded on a PerkinElmer Spectrum one FT-IR Spectrophotometer (ATR), and the wavelengths are reported in cm^{-1}. Low-resolution mass spectra were obtained on a LCQ Advantage spectrometer (ThermoElectron). High-resolution mass spectra were recorded with a TOF mass analyzer. Isotopes used for the mass spectra are ^{35}Cl and ^{79}Br. Compounds **2a–d** and **3a–d** were prepared according to the literature procedures as described below.[15]

Aryl Hydrazones 2; General Procedure I (GP I)[15]

To an ice-cold solution of the aniline **1** (95.70 mmol, 1 equiv) in H_2O (5 mL·mmol^{-1}) were successively added dropwise 37% aq HCl (11 equiv) and 1 M aq $NaNO_2$ (1 equiv). The mixture was stirred for 30 min and then added dropwise to a solution of malononitrile (143,55 mmol, 1.5 equiv) and NaOAc (31 equiv) in H_2O (8.5 mL·mmol^{-1} of aniline) with continuous stirring at 0 °C. After 2 h, the insoluble hydrazone was collected by filtration and washed with H_2O. The precipitate was dissolved in EtOAc and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel afforded the expected aryl hydrazone **2**.

Pyrazoles 3; General Procedure II (GP II)[15]

A mixture of hydrazone **2** (1 equiv), K_2CO_3 (2.7 equiv), methyl bromoacetate (7.5 equiv) in the respective anhyd solvent (3 mL·mmol^{-1}) was irradiated at 110 °C (power input: 90 W) until the starting material was consumed (TLC control). After cooling to r.t., the reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Chromatographic purification on silica gel afforded the expected pyrazole **3**.

2-Chloroacetamidopyrazoles 4; General Procedure III (GP III)

To a stirred solution of the pyrazole **3** (1 equiv) in DMF was added chloroacetyl chloride (1.1 equiv) and the mixture was stirred at r.t. After total consumption of the starting material (TLC control), EtOAc (15 mL·mmol^{-1}) was added, and the organic phase was washed with H_2O and brine (3 × 15 mL·mmol^{-1}), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography on silica gel afforded the expected compound **4**.

2-Iminothiazolidin-4-ones 5; General Procedure IV (GP IV)

To a solution of the 2-chloroacetamidopyrazole **4** (1 equiv) in acetone was added KSCN (4 equiv) and the mixture was stirred at r.t. for 48 h. The solvent was removed under reduced pressure. The crude product was dissolved in CH_2Cl_2, and washed with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL·mmol^{-1}). The organic layers were combined, washed with brine (3 × 15 mL·mmol^{-1}), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography on silica gel afforded the expected thiazolidin-4-one **5**.

2-(Arylimino)thiazolidin-4-ones 7; General Procedure V (GP V)

To a solution of the 2-chloroacetamidopyrazole **4** (1 equiv) in THF (10 mL·mmol^{-1}) was added DBU (1 equiv) and the corresponding aryl isothiocyanate (3 equiv). The mixture was stirred at r.t. for 3–4 h and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography on silica gel or basic Al_2O_3 afforded the title product **7**.

2-[(3-Chlorophenyl)hydrazono]malononitrile (2e)

According to GP I, hydrazone **2e**[35] was synthesized from 3-chloroaniline (12.21 g, 95.71 mmol). Flash chromatography (cyclohexane/EtOAc, 3:1) followed by recrystallization from EtOH gave **2e** as a yellow solid (14.66 g, 75%); mp 146–148 °C; R_f = 0.42 (cyclohexane/EtOAc, 3:1).

^{1}H NMR: δ = 12.99 (br s, 1 H, NH), 7.50–7.38 (m, 3 H, H-2, H-5, H-6), 7.27–7.20 (m, 1 H, H-4).

^{13}C NMR (125 MHz): δ = 142.7 (C-1), 133.9 (C-3), 131.2 (C-5), 125.3 (C-4), 116.1 (C-2), 115.0 (C-6), 113.9, 109.6 (2 × C≡N), 85.9 (C=N).

2-[(4-Chlorophenyl)hydrazono]malononitrile (2f)

According to GP I, hydrazone **2f** was synthesized from 4-chloroaniline (12.21 g, 95.71 mmol). Flash chromatography (cyclohexane/EtOAc, 3:1) followed by recrystallization from EtOH gave **2f** as a yellow solid (13.1 g, 67%); mp 174–176 °C. NMR spectral data are in agreement with the literature.[36]

2-[(3-Fluorophenyl)hydrazono]malononitrile (2g)

According to GP I, hydrazone **2g**[37] was synthesized from 3-fluoroaniline (10.64 g, 95.75 mmol). Flash chromatography (cyclohexane/EtOAc, 3:1) followed by recrystallization from EtOH gave **2g** as a yellow solid (13.55 g, 75%); mp 176–178 °C; R_f = 0.39 (cyclohexane/EtOAc, 2:1).

^{1}H NMR: δ = 13.02 (br s, 1 H, NH), 7.48–7.40 (m, 1 H, H-5), 7.33–7.27 (m, 1 H, H-6), 7.26–7.21 (m, 1 H, H-2), 7.06–6.99 (m, 1 H, H-4).

^{13}C NMR: δ = 162.57 (C-3, $J_{C,F}$ = 244.0 Hz), 143.1 (C-1, $J_{C,F}$ = 10.0 Hz), 131.3 (C-5, $J_{C,F}$ = 10.0 Hz), 113.9 (C≡N), 112.4 (C-6), 112.2 (C-4, $J_{C,F}$ = 21.0 Hz), 109.6 (C≡N), 103.5 (C-2, $J_{C,F}$ = 27.0 Hz), 85.8 (C=N).

2-[(4-Fluorophenyl)hydrazono]malononitrile (2h)

According to GP I, hydrazone **2h** was synthesized from 4-fluoroaniline (10.6 g, 95.7 mmol). Flash chromatography (cyclohexane/EtOAc, 3:1) followed by recrystallization from EtOH gave **2h** as a yellow solid (13.3 g, 74%); mp 190–192 °C. NMR spectral data are in agreement with the literature.[38]

Methyl 4-Amino-1-(3-chlorophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3e)

According to GP II, pyrazole **3e** was synthesized from hydrazone **2e** (500 mg, 2.44 mmol) and methyl bromoacetate (1.69 mL, 18.3 mmol) in 1,4-dioxane within 13 min. Flash chromatography (CH_2Cl_2) followed by recrystallization from EtOH afforded **3e** as a white solid (461 mg, 68%); mp 240–242 °C (EtOH); R_f = 0.25 (CH_2Cl_2).

IR (ATR): 3475, 3369 (NH_2), 2238 (C≡N), 1724 (ester C=O), 1620 (C=N), 1560, 1509, 1433 (CH_3), 1356 (C–N), 1300, 1220, 1136, 1009 cm^{-1}.

^{1}H NMR: δ = 7.67–7.62 (m, 1 H, H-2′), 7.59–7.54 (m, 1 H, ArH), 7.53–7.44 (m, 2 H, ArH, H-5′), 6.11 (br s, 2 H, NH_2), 3.72 (s, 3 H, CO_2CH_3).

^{13}C NMR: δ = 158.6 (CO_2CH_3), 142.4 (C_{pyr}), 140.7 (C-1′), 132.6 (C-3′), 130.1 (C-5′), 129.0 (CH), 125.8 (C-2′), 124.6 (CH), 116.4 (C_{pyr}), 113.5, 113.0 (C≡N, C_{pyr}), 51.6 (OCH_3).

MS (ESI): *m*/*z* = 299 [M + Na]$^+$.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}{}^{35}ClN_4O_2$: 277.0498; found: 277.0501.

Methyl 4-Amino-1-(4-chlorophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3f)

According to GP II, pyrazole **3f** was synthesized from hydrazone **2f** (2.0 g, 9.77 mmol) and methyl bromoacetate (6.76 mL, 73.3 mmol) in toluene within 20 min. Flash chromatography (CH_2Cl_2) followed by recrystallization from EtOH afforded **3f** as a white solid (1.54 g, 57%); mp 248–250 °C (EtOH); R_f = 0.27 (CH_2Cl_2).

IR (ATR): 3473, 3368 (NH_2), 2231 (C≡N), 1728 (ester C=O), 1617, 1564 (C=N, C=C), 1493 (CH_3), 1429, 1355 (C–N), 1298 (C–O), 1136, 1091, 1005 cm^{-1}.

^{1}H NMR: δ = 7.58–7.49 (m, 4 H, ArH), 6.10 (br s, 2 H, NH_2), 3.70 (s, 3 H, CO_2CH_3).

^{13}C NMR: δ = 158.7 (CO_2CH_3), 142.5 (C_{pyr}), 138.5 (C_q), 133.5 (C_q), 128.5 (CH), 127.5 (CH), 116.3 (C_{pyr}), 113.3, 113.0 (C≡N, C_{pyr}), 51.6 (OCH_3).

MS (ESI): *m*/*z* = 277 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}{}^{35}ClN_4O_2$: 277.0498; found: 277.0492.

Methyl 4-Amino-1-(3-fluorophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3g)

According to GP II, pyrazole **3g** was synthesized from hydrazone **2g** (500 mg, 2.65 mmol) and methyl bromoacetate (1.84 mL, 19.9 mmol) in 1,4-dioxane within 13 min. Flash chromatography (cyclohexane/EtOAc, 2:1) followed by recrystallization from EtOH afforded **3g** as a yellow solid (500 mg, 72%); mp (dec.) (EtOH); R_f = 0.22 (CH_2Cl_2).

IR (ATR): 3439, 3350 (NH_2), 3007, 2970, 2942, 2233 (C≡N), 1738 (ester C=O), 1439 (CH_3), 1365 (C–N), 1228, 1216 cm^{-1}.

^{1}H NMR: δ = 7.67–7.63 (m, 1 H, H-2′), 7.59–7.54 (m, 1 H, ArH), 7.53–7.44 (m, 2 H, ArH, H-5′), 6.11 (br s, 2 H, NH_2), 3.72 (s, 3 H, OCH_3).

^{13}C NMR: δ = 161.3 (C-3′, $J_{C,F}$ = 244.0 Hz), 158.9 (CO_2CH_3), 142.4 (C_{pyr}), 140.9 (C-1′, $J_{C,F}$ = 10.0 Hz), 130.1 (C-5′, $J_{C,F}$ = 9.0 Hz), 121.9 (C-6′), 116.4 (C_{pyr}), 115.9 (C-4′, $J_{C,F}$ = 21.0 Hz), 113.4 (2 C, C_{pyr}, C-2′, $J_{C,F}$ = 25.0 Hz), 113.0 (C≡N), 51.6 (OCH_3).

MS (ESI): *m*/*z* = 261 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}FN_4O_2$: 261.0782; found: 261.0788.

Methyl 4-Amino-1-(4-fluorophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3h)

According to GP II, pyrazole **3h** was synthesized from hydrazone **2h** (2 g, 10.63 mmol) and methyl bromoacetate (7.36 mL, 79.7 mmol) in toluene within 25 min. Flash chromatography (CH_2Cl_2) followed by recrystallization from EtOH afforded **3g** as a white solid (1.78 g, 64%); mp 234–236 °C (EtOH); R_f = 0.16 (CH_2Cl_2).

IR (ATR): 3473, 3364 (NH_2), 3076, 2957, 2918, 2228 (C≡N), 1723 (ester C=O), 1637 (C=N), 1509 (C=C), 1431 (CH_3), 1356 (C–N), 1299, 1220, 1136, 1006 cm^{-1}.

^{1}H NMR: δ = 7.61–7.48 (m, 2 H, H-3′, H-5′), 7.39–7.25 (m, 2 H, H-2′, H-6′), 6.09 (br s, 2 H, NH_2), 3.69 (s, 3 H, OCH_3).

^{13}C NMR: δ = 161.8 (C-4′, $J_{C,F}$ = 251.0 Hz), 158.7 (CO_2CH_3), 142.4 (C_{pyr}), 136.1 (C-1′), 128.1 (2 C, C-2′, C-6′, $J_{C,F}$ = 9.0 Hz), 116.5 (C_{pyr}), 115.3 (2 C, C-3′, C-5′, $J_{C,F}$ = 24.0 Hz), 113.1 (C_q), 113.0 (C_q), 51.5 (OCH_3).

MS (ESI): *m*/*z* = 261 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}FN_4O_2$: 261.0782; found: 261.0787.

Methyl 4-(2-Chloroacetamido)-3-cyano-1-phenyl-1*H*-pyrazole-5-carboxylate (4a)

According to GP III, pyrazole **4a** was synthesized from **3a** (244 mg, 1.0 mmol) in DMF (3 mL) within 3 h. Flash chromatography (cyclohexane/EtOAc, 2:1 to 1:1) afforded compound **4a** as a white solid (267 mg, 84%); mp 168–170 °C; R_f = 0.28 (cyclohexane/EtOAc, 1:1).

IR (ATR): 3344 (NH), 3022, 2961, 2925, 2241 (C≡N), 1733 (ester C=O), 1643 (amide C=O, C=N), 1574, 1429, 1280, 1200, 1140, 1023 cm^{-1}.

^{1}H NMR: δ = 10.47 (s, 1 H, NH), 7.59–7.51 (m, 5 H, ArH), 4.42 (s, 2 H, CH_2), 3.72 (s, 3 H, OCH_3).

^{13}C NMR: δ = 165.3 (CONH), 157.6 (CO_2CH_3), 138.9 (C-1′), 129.8 (C-4′), 129.0 (2 C, C-3′, C-5′), 127.7, 126.6 (2 C, C_{pyr}), 125.6 (2 C, C-2′, C-6′), 121.2 (C_{pyr}), 112.0 (C≡N), 52.6 (OCH_3), 42.3 (CH_2).

MS (ESI): *m*/*z* = 317 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{10}{}^{35}ClN_4O_3$: 317.0447; found: 317.0444.

Methyl 1-(3-Methoxyphenyl)-4-(2-chloroacetamido)-3-cyano-1*H*-pyrazole-5-carboxylate (4b)

According to GP III, pyrazole **4b** was synthesized from **3b** (964 mg, 3.54 mmol) in DMF (11 mL) within 3 h. Flash chromatography (cyclohexane/EtOAc, 1:1) afforded compound **4b** as a yellow solid (984 mg, 80%); mp 221–223 °C; R_f = 0.30 (cyclohexane/EtOAc, 1:1).

IR (ATR): 3007 (NH), 2959, 2244 (C≡N), 1734 (ester C=O), 1670 (amide C=O, C=N), 1610, 1570, 1474, 1270, 1134, 1033 cm^{-1}.

^{1}H NMR: δ = 10.45 (s, 1 H, NH), 7.48–7.40 (m, 1 H, H-5′), 7.19–7.07 (m, 3 H, H-2′, H-4′, H-6′), 4.42 (s, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 3.73 (s, 3 H, CO_2CH_3).

^{13}C NMR: δ = 165.3 (CONH), 159.4 (C-3′), 157.6 (CO_2CH_3), 139.9 (C-1′), 129.7 (C-5′), 127.3 (C_{pyr}), 126.5 (C_{pyr}), 121.1 (C_{pyr}), 117.7 (C-6′), 115.7 (C-4′), 111.9 (C≡N), 111.3 (C-3′), 55.6 (OCH_3), 52.6 (CO_2CH_3), 42.3 (CH_2).

MS (ESI): *m*/*z* 347 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{12}{}^{35}ClN_4O_4$: 347.0542; found: 347.0540.

Methyl 1-(3-Bromophenyl)-4-(2-chloroacetamido)-3-cyano-1*H*-pyrazole-5-carboxylate (4c)

According to GP III, pyrazole **4c** was synthesized from **3c** (614 mg, 1.9 mmol) in DMF (6 mL) within 3 h. Flash chromatography (cyclohexane/EtOAc, 2:1) afforded compound **4c** as a white solid (635 mg, 81%); mp 168–170 °C; R_f = 0.14 (cyclohexane/EtOAc, 2:1).

IR (ATR): 3372 (NH), 2956, 2248 (C≡N), 1732 (ester C=O), 1695 (amide C=O, C=N), 1570, 1478, 1462, 1444, 1406, 1357, 1278, 1232, 1143, 1038 cm^{-1}.

^{1}H NMR: δ = 10.45 (s, 1 H, NH), 7.90 (s, 1 H, H-2′), 7.79 (d, *J* = 8.0 Hz, 1 H, H-4′), 7.62 (d, *J* = 8.0 Hz, 1 H, H-6′), 7.50 (t, *J* = 8.0 Hz, 1 H, H-5′), 4.43 (s, 2 H, CH_2), 3.75 (s, 3 H, OCH_3).

^{13}C NMR: δ = 165.3 (CONH), 157.5 (CO_2CH_3), 140.0 (C-1′), 132.7 (C-4′), 130.7 (C-5′), 128.7 (C-2′), 127.1 (C_{pyr}), 126.8 (C_{pyr}), 125.1 (C-6′), 121.5 (C_{pyr}), 121.1 (C-3′), 111.9 (C≡N), 52.6 (OCH_3), 42.3 (CH_2).

MS (ESI): *m*/*z* = 395, 397 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9{}^{79}Br^{35}ClN_4O_3$: 394.9552; found: 394.9537.

Methyl 1-(4-Bromophenyl)-4-(2-chloroacetamido)-3-cyano-1*H*-pyrazole-5-carboxylate (4d)

According to GP III, pyrazole **4d** was synthesized from **3d** (200 mg, 0.62 mmol) in DMF (2 mL) within 48 h. Flash chromatography (cyclohexane/EtOAc, 2:1) afforded compound **4d** as a white solid (200 mg, 80%); mp 210–212 °C; R_f = 0.16 (cyclohexane/EtOAc, 2:1).

IR (ATR): 3283 (NH), 2958, 2245 (C≡N), 1732 (ester C=O), 1668 (amide C=O, C=N), 1574, 1515, 1496, 1475, 1435, 1409, 1356, 1294, 1202, 1175, 1142, 1069, 1040, 1014 cm^{-1}.

^{1}H NMR: δ = 10.45 (s, 1 H, NH), 7.75 (d, *J* = 8.5 Hz, 2 H, H-3′, H-5′), 7.55 (d, *J* = 8.5 Hz, 2 H, H-2′, H-6′), 4.42 (s, 2 H, CH_2), 3.74 (s, 3 H, OCH_3).

^{13}C NMR: δ = 165.3 (CONH), 157.5 (CO_2CH_3), 138.1 (C-1′), 131.9 (2 C, C-3′, C-5′), 127.8 (2 C, C-2′, C-6′), 127.1 (C_{pyr}), 126.8 (C_{pyr}), 122.9 (C-4′), 121.5 (C_{pyr}), 111.9 (C≡N), 52.6 (OCH_3), 42.3 (CH_2).

MS (ESI): *m*/*z* = 395, 397 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9{}^{79}Br^{35}ClN_4O_3$: 394.9552; found: 394.9541.

Methyl 1-(3-Chlorophenyl)-4-(2-chloroacetamido)-3-cyano-1*H*-pyrazole-5-carboxylate (4e)

According to GP III, pyrazole **4e** was synthesized from **3e** (964 mg, 3.54 mmol) in DMF (11 mL) within 3 h. Flash chromatography (cyclohexane/EtOAc, 2:1) afforded compound **4e** as a yellow solid (984 mg, 80%); mp 221–223 °C; R_f = 0.30 (cyclohexane/EtOAc, 1:1).

IR (ATR): 3248 (NH), 3003, 2970, 2942, 2245 (C≡N), 1735 (ester C=O), 1692 (amide C=O, C=N), 1575, 1478, 1446, 1365, 1297, 1204, 1147, 1047, 993 cm^{-1}.

^{1}H NMR: δ = 10.46 (s, 1 H, NH), 7.85–7.76 (m, 1 H, H-5′), 7.69–7.62 (m, 1 H, ArH), 7.61–7.55 (m, 2 H, ArH), 4.44 (s, 2 H, CH_2), 3.76 (s, 3 H, OCH_3).

^{13}C NMR: δ = 165.3 (CONH), 157.5 (CO_2CH_3), 140.0 (C-1′), 133.0 (C-3′), 130.5 (C-5′), 129.8 (C_q), 127.2 (C_{pyr}), 126.8 (C_{pyr}), 126.0 (C-2′), 124.8 (C_q), 121.6 (C_{pyr}), 111.9 (C≡N), 52.6 (OCH_3), 42.3 (CH_2).

MS (ESI): *m*/*z* = 351 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9{}^{35}Cl_2N_4O_3$: 351.0057; found. 351.0053.

Methyl 1-(4-Chlorophenyl)-4-(2-chloroacetamido)-3-cyano-1*H*-pyrazole-5-carboxylate (4f)

According to GP III, pyrazole **4f** was synthesized from **3f** (200 mg, 0.72 mmol) in DMF (4.5 mL) within 16 h. Flash chromatography (cyclohexane/EtOAc, 2:1) afforded compound **4f** as a yellow solid (111 mg, 44%); mp 221–223 °C; R_f = 0.14 (cyclohexane/EtOAc, 2:1).

IR (ATR): 3275 (NH), 2957, 2243 (C≡N), 1732 (ester C=O), 1668 (amide C=O, C=N), 1574, 1498, 1475, 1434, 1296, 1142, 1090, 1038 cm^{-1}.

^{1}H NMR: δ = 10.51 (s, 1 H, NH), 7.61 (br s, 4 H, ArH), 4.43 (s, 2 H, CH_2), 3.74 (s, 3 H, OCH_3).

^{13}C NMR: δ = 165.2 (CONH), 157.5 (CO_2CH_3), 137.7 (C-1′), 134.3 (C-4′), 128.9 (2 C, CH), 127.5 (2 C, CH), 127.2 (C_{pyr}), 126.7 (C_{pyr}), 121.5 (C_{pyr}), 111.9 (C≡N), 52.6 (OCH_3), 42.3 (CH_2).

MS (ESI): *m*/*z* = 351 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9{}^{35}Cl_2N_4O_3$: 351.0057; found: 351.0054.

Methyl 1-(3-Fluorophenyl)-4-(2-chloroacetamido)-3-cyano-1*H*-pyrazole-5-carboxylate (4g)

According to GP III, pyrazole **4g** was synthesized from **3g** (200 mg, 0.77 mmol) in DMF (2.5 mL) within 3 h. Flash chromatography (cyclohexane/EtOAc, 2:1) afforded compound **4g** as a white solid (210 mg, 81%); mp 162–164 °C; R_f = 0.11 (cyclohexane/EtOAc, 2:1).

IR (ATR): 3290, 3260 (NH), 3081, 3032, 2243 (C≡N), 1728 (ester C=O), 1686 (amide C=O, C=N), 1604, 1577, 1490, 1429, 1352, 1295, 1270, 1221, 1201, 1120, 1043 cm^{-1}.

^{1}H NMR: δ = 10.45 (s, 1 H, NH), 7.61–7.57 (m, 2 H, ArH), 7.46–7.43 (m, 2 H, ArH), 4.42 (s, 2 H, CH_2), 3.74 (s, 3 H, OCH_3).

^{13}C NMR: δ = 165.1 (CONH), 160.3 (d, $J_{C,F}$ = 245.0 Hz, C-3′), 157.3 (CO_2CH_3), 139.9 (d, $J_{C,F}$ = 10.0 Hz, C-1′), 130.5 (d, $J_{C,F}$ = 9.0 Hz, C-5′), 127.0 (C_{pyr}), 126.6 (C_{pyr}), 122.0 (C-6′), 121.4 (C_{pyr}), 116.7 (d, $J_{C,F}$ = 20.0 Hz, C-4′), 113.4 (d, $J_{C,F}$ = 25.5 Hz, C-2′), 111.7 (C≡N), 52.5 (OCH_3), 42.2 (CH_2).

MS (ESI): *m*/*z* = 335 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9{}^{35}ClFN_4O_3$: 335.0353; found: 335.0355.

Methyl 1-(4-Fluorophenyl)-4-(2-chloroacetamido)-3-cyano-1*H*-pyrazole-5-carboxylate (4h)

According to GP III, pyrazole **4h** was synthesized from **3h** (220 mg, 0.84 mmol) in DMF (3.5 mL) within 3 h. Flash chromatography (cyclohexane/EtOAc, 2:1) afforded compound **4h** as a beige solid (242 mg, 86%); mp 194–196 °C; R_f = 0.11 (cyclohexane/EtOAc, 2:1).

IR (ATR): 3266 (NH), 3075, 3014, 2246 (C≡N), 1728 (ester C=O), 1670 (amide C=O, C=N), 1577, 1518, 1474, 1435, 1295, 1267, 1228, 1037 cm^{-1}.

^{1}H NMR: δ = 10.45 (s, 1 H, NH), 7.68–7.61 (m, 2 H, H-2′, H-6′), 7.42–7.34 (m, 2 H, H-3′, H-5′), 4.42 (s, 2 H, CH_2), 3.73 (s, 3 H, OCH_3).

^{13}C NMR: δ = 165.0 (CONH), 162.1 (d, $J_{C,F}$ = 248.0 Hz, C-4′), 157.4 (CO_2CH_3), 135.2 (C-1′), 128.0 (d, $J_{C,F}$ = 9.0 Hz, 2 C, C-2′, C-6′), 127.0 (C_{pyr}), 126.5 (C_{pyr}), 121.1 (C_{pyr}), 115.6 (d, $J_{C,F}$ = 23.0 Hz, 2 C, C-3′, C-5′), 111.8 (C≡N), 52.4 (OCH_3), 42.2 (CH_2).

MS (ESI): *m*/*z* 335 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9{}^{35}ClFN_4O_3$: 335.0353; found: 335.0349.

Methyl 3-Cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1-phenyl-1*H*-pyrazole-5-carboxylate (5a)

According to GP IV, thiazolidin-4-one **5a** was obtained from pyrazole **4a** (200 mg, 0.63 mmol) in acetone (3 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5a** as a white solid (119 mg, 55%); mp 82–84 °C; R_f = 0.17 (cyclohexane/EtOAc, 3:2).

IR (ATR): 3300 (NH), 2928, 2248 (C≡N), 1740 (estr C=O), 1633, 1619 (amide C=O, C=N), 1493, 1439, 1369, 1290, 1241, 1199, 1179, 1137, 1112, 1038, 1018 cm^{-1}.

^{1}H NMR: δ = 9.75 (s, 1 H, NH), 7.65–7.53 (m, 5 H, ArH), 4.38 (s, 2 H, H-5″), 3.70 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.4 (C-4″), 156.7 (CO_2CH_3), 155.8 (C-2″), 138.6 (C-1′), 130.8 (C_{pyr}), 130.1 (C-4′), 129.1 (2 C, C-3′, C-5′), 125.5 (2 C, C-2′, C-6′), 124.0 (C_{pyr}), 123.4 (C_{pyr}), 111.2 (C≡N), 53.0 (OCH_3), 33.6 (C-5″).

MS (ESI): m/z = 342 $[M + H]^+$.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{15}H_{10}N_5O_3S$: 340.0510; found: 340.0503.

Methyl 1-(3-Methoxyphenyl)-3-cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1*H*-pyrazole-5-carboxylate (5b)

According to GP IV, thiazolidin-4-one **5b** was obtained from pyrazole **4b** (80 mg, 0.23 mmol) in acetone (1.2 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5b** as a yellow solid (60 mg, 70%); mp (dec.); R_f = 0.14 (cyclohexane/EtOAc, 1:1).

IR (ATR): 3300 (NH), 2952, 2923, 2248 (C≡N), 1740 (ester C=O), 1631 (amide C=O, C=N), 1607, 1493, 1369, 1295, 1233, 1127, 1026 cm^{-1}.

^1H NMR: δ = 9.74 (s, 1 H, NH), 7.49–7.43 (m, 1 H, H-5′), 7.26–7.22 (m, 1 H, H-2′), 7.19–7.12 (m, 2 H, H-4′, H-6′), 4.38 (s, 2 H, H-5″), 3.82 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.4 (C-4″), 159.5 (C-3′), 156.7 (CO_2CH_3), 155.8 (C-2″), 139.6 (C-1′), 130.9 (C_{pyr}), 129.9 (C-5′), 123.9 (C_{pyr}), 123.3 (C_{pyr}), 117.8 (C-6′), 116.2 (C-4′), 111.2 (2 C, C-2′, C≡N), 55.7 (OCH_3), 53.0 (CO_2CH_3), 33.7 (C-5″).

MS (ESI): m/z = 372 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_5O_4S$: 372.0761; found: 372.0753.

Methyl 1-(3-Bromophenyl)-3-cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1*H*-pyrazole-5-carboxylate (5c)

According to GP IV, thiazolidin-4-one **5c** was obtained from pyrazole **4c** (150 mg, 0.38 mmol) in acetone (2.4 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5c** as a white solid (106 mg, 67%); mp 158–160 °C; R_f = 0.18 (cyclohexane/EtOAc, 3:2).

IR (ATR): 3300 (NH), 2926, 2251 (C≡N), 1742 (ester C=O), 1619 (amide C=O, C=N), 1480, 1371, 1270, 1197, 1144, 1120, 1040 cm^{-1}.

^1H NMR: δ = 9.76 (s, 1 H, NH), 7.99 (t, J = 2.0 Hz, 1 H, H-2′), 7.80 (dd, J = 8.0, 2.0 Hz, 1 H, H-4′), 7.67 (dd, J = 7.5, 2.0 Hz, 1 H, H-6′), 7.52 (dd, J = 8.0, 7.5 Hz, 1 H, H-5′), 4.38 (s, 2 H, H-5″), 3.71 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.4 (C-4″), 156.6 (CO_2CH_3), 155.7 (C-2″), 139.7 (C-1′), 133.1 (C-4′), 130.9 (C_{pyr}), 130.8 (C-5′), 128.6 (C-2′), 125.1 (C-6′), 124.3 (C_{pyr}), 123.4 (C_{pyr}), 121.3 (C-3′), 111.1 (C≡N), 53.0 (OCH_3), 33.7 (C-5″).

MS (ESI): m/z = 420, 422 $[M + H]^+$.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{15}H_9{}^{79}BrN_5O_3S$: 417.9615; found: 417.9623.

Methyl 1-(4-Bromophenyl)-3-cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1*H*-pyrazole-5-carboxylate (5d)

According to GP IV, thiazolidin-4-one **5d** was obtained from pyrazole **4d** (100 mg, 0.25 mmol) in acetone (1.5 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5d** as a white solid (51 mg, 49%); mp 182–184 °C; R_f = 0.21 (cyclohexane/EtOAc, 3:2).

IR (ATR): 3289 (NH), 2927, 2252 (C≡N), 1735 (ester C=O), 1616 (amide C=O, C=N), 1492, 1440, 1372, 1295, 1247, 1201, 1142, 1110, 1070, 1034, 1011 cm^{-1}.

^1H NMR: δ = 9.75 (s, 1 H, NH), 7.77 (d, J = 8.5 Hz, 2 H, H-3′, H-5′), 7.55 (d, J = 8.5 Hz, 2 H, H-2′, H-6′), 4.38 (s, 2 H, H-5″), 3.71 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.4 (C-4″), 156.7 (CO_2CH_3), 155.7 (C-2″), 137.8 (C-1′), 132.0 (2 C, C-2′, C-6′), 130.8 (C_{pyr}), 127.8 (2 C, C-3′, C-5′), 124.2 (C_q), 123.5 (C_q), 123.3 (C_q), 111.1 (C≡N), 53.0 (OCH_3), 33.7 (C-5″).

MS (ESI): m/z = 420, 422 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{11}{}^{79}BrN_5O_3S$: 419.9760; found: 419.9753.

Methyl 1-(3-Chlorophenyl)-3-cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1*H*-pyrazole-5-carboxylate (5e)

According to GP IV, thiazolidin-4-one **5e** was obtained from pyrazole **4e** (100 mg, 0.28 mmol) in acetone (1.8 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5e** as a white solid (77 mg, 72%); mp (dec.); R_f = 0.13 (cyclohexane/EtOAc, 1:1).

IR (ATR): 3320 (NH), 2248 (C≡N), 1721 (ester C=O), 1634 (amide C=O, C=N), 1587, 1552, 1481, 1347, 1310, 1240, 1130, 1043 cm^{-1}.

^1H NMR: δ = 9.76 (s, 1 H, NH), 7.91–7.86 (m, 1 H, H-2′), 7.71–7.56 (m, 3 H, H-4′, H-5′, H-6′), 4.37 (s, 2 H, H-5″), 3.71 (s, 3 H, CO_2CH_3).

^{13}C NMR: δ = 170.4 (C-4″), 156.6 (CO_2CH_3), 155.7 (C-2″), 139.6 (C-1′), 133.2 (C-3′), 130.9 (C_{pyr}), 130.6 (CH), 130.2 (CH), 125.9 (C-2′), 124.7 (C-6′), 124.3 (C_{pyr}), 123.4 (C_{pyr}), 111.1 (C≡N), 53.0 (OCH_3), 33.7 (C-5″).

MS (ESI): m/z = 376 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{11}{}^{35}ClN_5O_3S$: 376.0266; found: 376.0261.

Methyl 1-(4-Chlorophenyl)-3-cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1*H*-pyrazole-5-carboxylate (5f)

According to GP IV, thiazolidin-4-one **5f** was obtained from pyrazole **4f** (81 mg, 0.23 mmol) in acetone (3.5 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5f** as a white solid (42 mg, 49%); mp 174–176 °C; R_f = 0.19 (cyclohexane/EtOAc, 3:2).

IR (ATR): 3313 (NH), 2926, 2850, 2251 (C≡N), 1741 (ester C=O), 1619 (amide C=O, C=N), 1495, 1441, 1371, 1293, 1243, 1181, 1138, 1035, 1013 cm^{-1}.

^1H NMR: δ = 9.75 (s, 1 H, NH), 7.72–7.68 (m, 2 H, H-2′, H-6′), 7.66–7.62 (m, 2 H, H-3′, H-5′), 4.38 (s, 2 H, H-5″), 3.71 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.4 (C-4″), 156.7 (CO_2CH_3), 155.7 (C-2″), 137.4 (C-1′), 134.7 (C-4′), 130.9 (C_{pyr}), 129.1 (2 C, C-2′, C-6′), 127.6 (2 C, C-3′, C-5′), 124.2 (C_{pyr}), 123.5 (C_{pyr}), 111.9 (C≡N), 53.0 (OCH_3), 33.7 (C-5″).

MS (ESI): m/z = 376 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{11}{}^{35}ClN_5O_3S$: 376.0266; found: 376.0261.

Methyl 1-(3-Fluorophenyl)-3-cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1*H*-pyrazole-5-carboxylate (5g)

According to GP IV, thiazolidin-4-one **5g** was obtained from pyrazole **4g** (190 mg, 0.56 mmol) in acetone (3.5 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5g** as a white solid (99 mg, 49%); mp 144–146 °C; R_f = 0.17 (cyclohexane/EtOAc, 3:2).

IR (ATR): 3305 (NH), 3086, 2924, 2246 (C≡N), 1738 (ester C=O), 1633 (amide C=O, C=N), 1611, 1490, 1460, 1437, 1371, 1297, 1258, 1216, 1197, 1124, 1110, 1037, 903, 734 cm^{-1}.

^1H NMR: δ = 9.75 (s, 1 H, NH), 7.72–7.67 (m, 1 H, H-2′), 7.64–7.57 (m, 1 H, H-5′), 7.52–7.43 (m, 2 H, H-6′, H-4′), 4.37 (s, 2 H, H-5″), 3.71 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.4 (C-4″), 161.5 (d, $J_{C,F}$ = 246.0 Hz, C-3′), 156.6 (CO_2CH_3), 155.8 (C-2″), 139.7 (d, $J_{C,F}$ = 11.0 Hz, C-1′), 131.0 (C_{pyr}), 130.8 (d, $J_{C,F}$ = 9.0 Hz, C-5′), 124.3 (C_{pyr}), 123.5 (C_{pyr}), 122.1 (C-6′), 117.2 (d, $J_{C,F}$ = 21.0 Hz, C-4′), 113.6 (d, $J_{C,F}$ = 26.5 Hz, C-2′), 111.7 (C≡N), 53.5 (OCH_3), 33.7 (C-5″).

MS (ESI): m/z = 358 $[M - H]^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_9FN_5O_3S$: 358.0416; found: 358.0406.

Methyl 1-(4-Fluorophenyl)-3-cyano-4-(2-imino-4-oxothiazolidin-3-yl)-1*H*-pyrazole-5-carboxylate (5h)

According to GP IV, thiazolidin-4-one **5h** was obtained from pyrazole **4h** (182 mg, 0.54 mmol) in acetone (4.5 mL). Flash chromatography (cyclohexane/EtOAc, 1:1) afforded **5h** as a white solid (143 mg, 74%); mp 178–180 °C; R_f = 0.17 (cyclohexane/EtOAc, 3:2).

IR (ATR): 3311 (NH), 2925, 2254 (C≡N), 1747 (ester C=O), 1614 (amide C=O, C=N), 1515, 1444, 1374, 1292, 1241, 1143, 1123 cm^{-1}.

^{1}H NMR: δ = 9.74 (s, 1 H, NH), 7.74–7.67 (m, 2 H, H-2′, H-6′), 7.43–7.36 (m, 2 H, H-3′, H-5′), 4.38 (s, 2 H, H-5″), 3.70 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.3 (C-5″), 162.3 (d, $J_{C,F}$ = 248.0 Hz, C-4′), 156.5 (CO_2CH_3), 155.7 (C-2″), 134.9 (C-1′), 130.8 (C_{pyr}), 128.1 (d, $J_{C,F}$ = 9.0 Hz, 2 C, C-2′, C-6′), 123.9 (C_{pyr}), 123.3 (C_{pyr}), 115.9 (d, $J_{C,F}$ = 23.5 Hz, 2 C, C-3′, C-5′), 111.0 (C≡N), 52.9 (OCH_3), 33.6 (C-5″).

MS (ESI): *m*/*z* = 358 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_9FN_5O_3S$: 358.0416; found: 358.0407.

Methyl 1-(3-Bromophenyl)-3-cyano-4-[4-oxo-2-(phenylimino)thiazolidin-3-yl]-1*H*-pyrazole-5-carboxylate (7a)

According to GP V, thiazolidin-4-one **7a** was obtained from pyrazole **4c** (70 mg, 0.18 mmol) and phenyl isothiocyanate (63 µL, 0.51 mmol). Flash chromatography on Al_2O_3 (cyclohexane/EtOAc, 4:1) afforded **7a** as a white solid (39 mg, 45%); mp (dec.); R_f = 0.15 (cyclohexane/EtOAc, 7:3).

IR (ATR): 2980, 2248 (C≡N), 1738 (ester C=O), 1639 (amide C=O, C=N), 1592, 1350, 1261, 1241, 1149, 1063, 1041 cm^{-1}.

^{1}H NMR: δ = 8.06–8.02 (m, 1 H, H-2′), 7.84–7.79 (m, 1 H, H-4′), 7.74–7.69 (m, 1 H, H-6′), 7.55–7.50 (m, 1 H, H-5′), 7.42–7.36 (m, 2 H, H-3‴, H-5‴), 7.20–7.14 (m, 1 H, H-4‴), 6.97–6.91 (m, 2 H, H-2‴, H-6‴), 4.42 (s, 2 H, H-5″), 3.78 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.0 (C-4″), 156.7 (CO_2CH_3), 153.4 (C-2″), 147.0 (C-1‴), 139.7 (C-1′), 133.1 (C-4′), 130.8 (2 C, C_{pyr}, C-5′), 129.4 (2 C, C-3‴, C-5‴), 128.7 (C-2′), 125.2 (C-6′), 124.8 (C-4‴), 123.9 (C_{pyr}), 122.9 (C_{pyr}), 121.3 (C-3′), 120.5 (2 C, C-2‴, C-6‴), 111.3 (C≡N), 53.2 (OCH_3), 32.8 (C-5″).

MS (ESI): *m*/*z* = 496, 498 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}{}^{79}BrN_5O_3S$: 496.0073; found: 496.0059.

Methyl 1-(3-Bromophenyl)-3-cyano-4-{2-[(4-cyanophenyl)imino]-4-oxothiazolidin-3-yl}-1*H*-pyrazole-5-carboxylate (7b)

According to GP V, thiazolidin-4-one **7b** was obtained from pyrazole **4c** (70 mg, 0.18 mmol) and 4-cyanophenyl isothiocyanate (84 mg, 0.51 mmol). Flash chromatography on silica gel (cyclohexane/EtOAc, 4:1) afforded **7b** as a white solid (52 mg, 57%); mp (dec.); R_f = 0.15 (cyclohexane/EtOAc, 3:2).

IR (ATR): 2987, 2901, 2250, 2227 (C≡N), 1742 (ester C=O), 1640 (amide C=O, C=N), 1596, 1480, 1393, 1367, 1353, 1241, 1154, 1066 cm^{-1}.

^{1}H NMR: δ = 8.05–8.02 (m, 1 H, H-2′), 7.89–7.85 (m, 2 H, H-3‴, H-5‴), 7.83–7.79 (m, 1 H, ArH), 7.73–7.69 (m, 1 H, ArH), 7.55–7.49 (m, 1 H, H-5′), 7.14–7.08 (m, 2 H, H-2‴, H-6‴), 4.47 (s, 2 H, H-5″), 3.78 (s, 3 H, OCH_3).

^{13}C NMR: δ = 169.9 (C-4″), 156.6 (CO_2CH_3), 155.2 (C-2″), 151.2 (C-1‴), 139.7 (C-1′), 133.9 (2 C, C-3‴, C-5‴), 133.1 (C-4′), 130.9 (C_{pyr}), 130.8 (C-5′), 128.7 (C-2′), 125.2 (C-6′), 123.8 (C_{pyr}), 122.6 (C_{pyr}), 121.7 (2 C, C-2‴, C-6‴), 121.3 (C-3′), 118.7 (C≡N), 111.3 (C≡N), 107.2 (C-4‴), 53.2 (OCH_3), 33.2 (C-5″).

MS (ESI): *m*/*z* = 519, 521 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{22}H_{11}{}^{79}BrN_6O_3S$: 518.9880; found: 518.9891.

Methyl 1-(3-Bromophenyl)-3-cyano-4-[4-oxo-2-(*p*-tolylimino)thiazolidin-3-yl]-1*H*-pyrazole-5-carboxylate (7c)

According to GP V, thiazolidin-4-one **7c** was obtained from pyrazole **4c** (70 mg, 0.18 mmol) and *p*-tolyl isothiocyanate (76 mg, 0.51 mmol). Flash chromatography on Al_2O_3 (cyclohexane/EtOAc, 4:1) afforded **7c** as a white solid (44 mg, 49%); mp (dec.); R_f = 0.18 (cyclohexane/EtOAc, 7:3).

IR (ATR): 2923, 2825, 2249 (C≡N), 1736 (ester C=O), 1637 (amide C=O, C=N), 1607, 1588, 1482, 1352, 1265, 1180, 1152, 1040 cm^{-1}.

^{1}H NMR: δ = 8.05–8.01 (m, 1 H, H-2′), 7.83–7.78 (m, 1 H, H-4′), 7.73–7.69 (m, 1 H, H-6′), 7.55–7.49 (m, 1 H, H-5′), 7.23–7.16 (m, 2 H, H-3‴, H-5‴), 6.87–6.80 (m, 2 H, H-2‴, H-6‴), 4.41 (s, 2 H, H-5″), 3.77 (s, 3 H, OCH_3), 1.99 (CH_3).

^{13}C NMR: δ = 170.1 (C-4″), 156.7 (CO_2CH_3), 153.0 (C-2″), 144.4 (C-1‴), 139.7 (C-1′), 133.9 (C-4‴), 133.1 (C-4′), 130.8 (2 C, C-5′, C_{pyr}), 129.9 (2 C, C-3‴, C-5‴), 128.7 (C-2′), 125.2 (C-6′), 123.9 (C_{pyr}), 123.0 (C_{pyr}), 121.3 (C-3′), 120.3 (2 C, C-2‴, C-6‴), 111.3 (C≡N), 53.2 (OCH_3), 32.8 (C-5″), 20.4 (CH_3).

MS (ESI): *m*/*z* = 510, 512 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}{}^{79}BrN_5O_3S$: 510.0250; found: 512.0229.

Methyl 1-(3-Bromophenyl)-3-cyano-4-{2-[(4-methoxyphenyl)imino]-4-oxothiazolidin-3-yl}-1*H*-pyrazole-5-carboxylate (7d)

According to GP V, thiazolidin-4-one **7d** was obtained from pyrazole **4c** (70 mg, 0.18 mmol) and 4-methoxyphenyl isothiocyanate (87 mg, 0.53 mmol). Flash chromatography on Al_2O_3 (cyclohexane/EtOAc, 4:1) afforded **7d** as a white solid (47 mg, 51%); mp 182–184 °C; R_f = 0.11 (cyclohexane/EtOAc, 7:3).

IR (ATR): 2251 (C≡N), 1741 (ester C=O), 1637 (amide C=O, C=N), 1584, 1507, 1352, 1242, 1187, 1138, 1029 cm^{-1}.

^{1}H NMR: δ = 8.05–8.01 (m, 1 H, H-2′), 7.84–7.78 (m, 1 H, H-4′), 7.73–7.68 (m, 1 H, H-6′), 7.55–7.50 (m, 1 H, H-5′), 6.98–6.93 (m, 2 H, H-3‴, H-5‴), 6.92–6.87 (m, 2 H, H-2‴, H-6‴), 4.41 (s, 2 H, H-5″), 3.77 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.0 (C-4″), 156.8, 156.4 (C-4‴, CO_2CH_3), 152.7 (C-2″), 139.9, 139.7 (C-1′, C-1‴), 133.1 (C-4′), 130.9 (2 C, C-5′, C_{pyr}), 128.7 (C-2′), 125.2 (C-6′), 123.9 (C_{pyr}), 123.1 (C_{pyr}), 121.6 (2 C, C-2‴, C-6‴), 121.3 (C-3′), 114.6 (2 C, C-3‴, C-5‴), 111.3 (C≡N), 53.2 (OCH_3), 53.1 (CO_2CH_3), 32.8 (C-5″).

MS (ESI): *m*/*z* = 526, 528 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}{}^{79}BrN_5O_4S$: 526.0179; found: 526.0192.

Methyl 1-(3-Bromophenyl)-3-cyano-4-({[4-(dimethylamino)-2-(phenylamino)-1,3-thiazol-5-yl]carbonyl}amino)-1*H*-pyrazole-5-carboxylate (8)

To a solution of pyrazole **4c** (50 mg, 0.13 mmol) in THF (0.7 mL) was added phenyl isothiocyanate (45 µL, 0.39 mmol) and TMG (17 µL, 0.13 mmol). The mixture was stirred at r.t. for 4 h, then H_2O (15 mL) was added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (cyclohexane/ EtOAc, 2:3) afforded compound **8** as a yellow solid (40 mg, 56%); mp (dec.); R_f = 0.45 (cyclohexane/EtOAc, 3:7).

IR (ATR): 3327 (NH), 2240 (C≡N), 1743 (ester C=O), 1713, 1650 (amide C=O, C=N), 1599, 1587, 1561, 1542, 1465, 1425, 1363, 1250, 1216, 1074, 1040 cm^{-1}.

^1H NMR: δ = 10.77 (s, 1 H, NHCO), 10.48 (s, 1 H, NH), 7.91–7.89 (m, 1 H, H-2′), 7.80–7.74 (m, 1 H, H-4′), 7.67–7.59 (m, 3 H, H-2‴, H-6‴, H-6′), 7.54–7.47 (m, 1 H, H-5′), 7.42–7.34 (m, 2 H, H-3‴, H-5‴), 7.10–7.03 (m, 1 H, H-4‴), 3.76 (s, 3 H, OCH_3), 2.93 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR: δ = 163.7 (C-2″), 162.0 (C-4″), 158.4 (CONH), 157.9 (CO_2CH_3), 140.4 (C-1′), 139.9 (C-1‴), 132.5 (C-4′), 130.6 (C-5′), 129.1 (3 C, C-3‴, C-5‴, C_{pyr}), 128.8 (C-2′), 125.2 (C-6′), 123.7 (C_{pyr}), 122.8 (C-4‴), 121.0 (C_q), 120.0 (C_q), 118.1 (2C, C-2‴, C-6‴), 112.9 (C≡N), 52.6 (OCH_3), 43.6 [2 C, $N(CH_3)_2$].

MS (ESI): *m*/*z* = 566, 568 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{21}{}^{79}BrN_7O_3S$: 566.0604; found: 566.0586.

Phenyl Isothiocyanate-^{15}N (9)

This compound was synthesized according to the following literature procedure.[34] To aniline-^{15}N (0.38 mL, 4.40 mmol) in absolute EtOH (4 mL) were added CS_2 (3.34 g, 44 mmol, 10.0 equiv) and Et_3N (0.44 g, 1.0 equiv) at r.t. After stirring for 30 min, the resulting dithiocarbamate was cooled in an ice bath. Boc_2O (950 mg, 4.36 mmol) in absolute EtOH (1 mL) and DMAP (8 mg, 0.065 mmol, 1.5 mol%) in absolute EtOH (1 mL) were added and the reaction mixture was kept in the ice bath for 5 min before being allowed to reach r.t. After stirring for 30 min, the mixture was concentrated in vacuo to afford the crude product, which was used without further purification; yellow oil (570 mg).

^1H NMR (250 MHz): δ = 7.54–7.33 (m, 5 H, ArH).

^{13}C NMR (62.5 MHz): δ = 133.4 (d, $J_{C,N}$ = 49.9 Hz, C-7), 130.1 (C-1), 129.8 (d, $J_{C,N}$ = 2.2 Hz, 2 C, C-3, C-5), 127.9 (C-4), 125.8 (d, $J_{C,N}$ = 1.5 Hz, 2 C, C-2, C-6).

^{13}C NMR spectrum was in agreement with the literature.[39]

Methyl 1-(3-Bromophenyl)-3-cyano-4-[4-oxo-2-(phenylimino-^{15}N)thiazolidin-3-yl]-1*H*-pyrazole-5-carboxylate (11)

According to GP V, ^{15}N-labeled compound **11** was obtained from pyrazole **4c** (300 mg, 0.75 mmol) and phenyl isothiocyanate-^{15}N (**9**; 306 mg, 2.25 mmol). Flash chromatography on Al_2O_3 (cyclohexane/EtOAc, 4:1) afforded **11** as a yellow solid (215 mg, 57%); mp (dec.); R_f = 0.24 (cyclohexane/EtOAc, 4:1).

IR (ATR): 2980, 2248 (C≡N), 1738 (ester C=O), 1639 (amide C=O, C=N), 1592, 1350, 1261, 1241, 1149, 1063, 1041 cm^{-1}.

^1H NMR: δ = 8.06–8.02 (m, 1 H, H-2′), 7.84–7.79 (m, 1 H, H-4′), 7.74–7.69 (m, 1 H, H-6′), 7.55–7.50 (m, 1 H, H-5′), 7.42–7.36 (m, 2 H, H-3‴, H-5‴), 7.20–7.14 (m, 1 H, H-4‴), 6.97–6.91 (m, 2 H, H-2‴, H-6‴), 4.42 (s, 2 H, H-5″), 3.78 (s, 3 H, OCH_3).

^{13}C NMR: δ = 170.0 (C-4″), 156.7 (CO_2CH_3), 153.4 (d, $J_{C,N}$ = 13.0 Hz, C-2″), 147.0 (d, $J_{C,N}$ = 5.0 Hz, C-1‴), 139.7 (C-1′), 133.1 (C-4′), 130.8 (2 C, C_{pyr}, C-5′), 129.4 (2 C, C-3‴, C-5‴), 128.7 (C-2′), 125.2 (C-6′), 124.8 (C-4‴), 123.9 (C_{pyr}), 123.0 (C_{pyr}), 121.3 (C-3′), 120.5 (2 C, C-2‴, C-6‴), 111.3 (C≡N), 53.2 (OCH_3), 32.8 (C-5″).

MS (ESI): *m*/*z* = 495, 497 $[M - H]^-$.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{21}H_{13}{}^{79}BrN_4{}^{15}NO_3S$: 494.9898; found: 494.9917.

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Supporting Information

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