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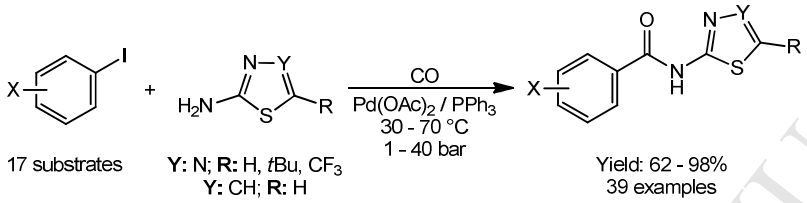
Graphical abstract



Aminothiazoles and Aminothiadiazoles as Nucleophiles in Aminocarbonylation of Iodobenzene Derivatives.

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Abstract: Various 2-, 3- and 4-substituted iodobenzenes were aminocarbonylated using aminothiazole and aminothiadiazole derivatives in palladium-catalysed reaction. The reaction is chemospecific toward the corresponding carboxamides. Consequently, the application of the above *N*-nucleophiles provided the *N*-1,3-thiazol-2-yl- and *N*-1,3,4-thiadiazol-2-ylcarboxamides in moderate to high yields. Due to the facile work-up of the reaction mixture isolated yields of 90% or higher were obtained in most cases.

Key-words: palladium, iodoarene, thiazole, carbonylation, carbon monoxide, carboxamide

1. Introduction

Among heterocycles, thiazoles and especially 1,3,4-thiadiazoles represent families of biological importance.[1] Functionalized 1,3,4-thiadiazole derivatives provided pharmacological effect in a wide spectrum, and several compounds have found applications in material science.[2]

Therefore, the facile synthetic procedures targeting these heterocycles are still in the focus. The synthetic approaches and medical significance of 1,3,4-thiadizoles were reviewed recently.[3]

One of the most efficient homogeneous catalytic reactions of practical importance is the palladium-catalysed aminocarbonylation, *i.e.*, the carbonylation of iodo- or bromoarenes (or their synthetic surrogates, aryl triflates) in the presence of *N*-nucleophiles ('Heck-carbonylation').[4] During the past three decades the efficiency and applicability of this reaction have been proved for the wide variety of compounds including the structure of both the substrates and nucleophiles. The influence of the reaction conditions (CO pressure,

temperature, base added) on the chemoselectivity, *i.e.*, the ratio of carboxamides and 2-ketocarboxamides formed in single and double CO insertion, respectively, was also investigated in detail.[5] It has to be added that the analogous substrates, iodoalkenes (or their synthetic surrogates, enol triflates) can be aminocarbonylated mainly with high chemoselectivity toward the corresponding carboxamides.[6]

The synthesis of several thiadiazole-based carboxamides, as well as their biological investigations were published. The introduction of carboxamide functionality into the thiazole and thiadiazole ring is of practical importance because there are several families of compounds possessing pharmacological effect. For instance, carboxamides of aminothiadiazole derivatives have shown good antagonist activity for human EP_3.[7] Among other substituents, the introduction of amide-functionalities into various positions of benzothiazoles and benzothiadiazoles leads to compounds of antioxidant and radioprotective effects.[8] The antiproliferative activity of *N*-substituted 2-amino-1,3,4-thiadiazoles[9], as well as their cytotoxicity were studied.[10] Starting from 4-hydroxy-3-methoxybenzaldehyde novel thiadiazole-based TRPV1 antagonists were synthesised.[11]

To the best of our knowledge, there are only sporadic results for the application of homogeneous catalytic approaches for the functionalization of thiadiazole nucleus. As an example of synthetic interest, C-H arylation in Pd/Cu-catalysed reaction should be mentioned.[12]

Since the above functionalizations of thiazole and thiadiazole nuclei were carried out mainly by using conventional synthetic methodologies, we were prompted to investigate some catalytic approaches. In this way, the high-yielding catalytic aminocarbonylation of various iodoaromatics with aminothiazole and aminothadiazole nucleophiles was carried out.

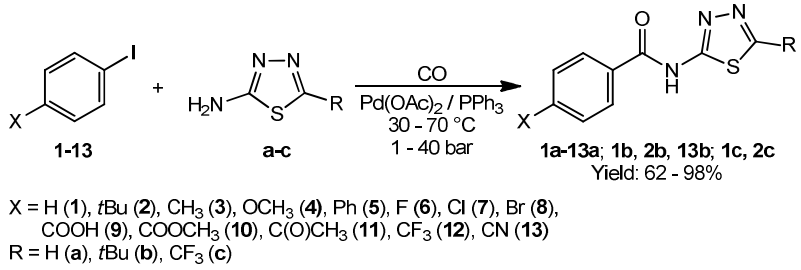
2. Results and discussion

*2.1. Aminocarbonylation of 4-substituted iodobenzenes with 2-amino-1,3,4-thiadiazole derivatives (**a-c**) under atmospheric carbon monoxide pressure*

Iodobenzene (**1**) and 4-substituted iodobenzenes (**2-13**) were aminocarbonylated using 2-amino-1,3,4-thiadiazole derivatives (**a-c**), *i.e.*, the parent 2-amino-1,3,4-thiadiazole (**a**) and the *tert*-butyl- (**b**) and trifluoromethyl-substituted (**c**) *N*-nucleophiles (*Scheme 1*). The aminocarbonylation was carried out at low (atmospheric) and high (40 bar) pressure of carbon monoxide at various temperatures (30, 50 and 70 ^{o}C) (*Table 1*). A well-known, widely applied palladium(0) catalyst, formed *in situ* from palladium(II) acetate and triphenylphosphine, was used. Both the mechanistic details including the catalytic cycles [5] and the formation of palladium(0) species were discussed.[13]

The aminocarbonylation is highly chemoselective toward carboxamides. No other products, for instance 2-ketocarboxamide type derivatives, were detected. These compounds are typically formed in the aminocarbonylation of aromatic iodides using primary and secondary amines as nucleophiles.[14] The aminothiadiazole nucleophiles (**a-c**) gave the characteristic carboxamide-specific reaction of aryl amines.

Similarly to those reactions carried out with aniline derivatives[15] no 2-ketocarboxamide formation due to double CO insertion was observed with **a-c** even under 40 bar CO pressure.



Scheme 1. Aminocarbonylation of 4-substituted iodobenzenes (**1-13**) with 2-amino-1,3,4-thiadiazol derivatives (**a-c**)

It was revealed by detailed analysis of the samples taken after 2, 6, 12 and 24 h reaction time, that the increase in the temperature, while the CO pressure was kept at 1 bar, resulted in increased reactivity (*Table 1, entries 1-3, Fig.1 (upper)*). Similar tendencies were observed with nucleophiles **b** and **c** (*entries 7,8 and 9, 10*, respectively). Carrying out the aminocarbonylation with **a** under 40 bar CO pressure, no increased activity was observed (*entries 4-6, Fig. 1 (bottom)*). In turn, negligible activity was observed at 30 ^{o}C.

The aminocarbonylation of the *t*Bu- and CN-substituted iodobenzenes (**2** and **13**, respectively) showed similar features (*entries 11-16 and 17-20, Fig. 2*). The only exception was the aminocarbonylation of **13** (possessing an electron-withdrawing group, CN) with nucleophile **c** (possessing an electron-withdrawing group, CF_3) where the desired product **13c** was formed in traces only even at 50 and 70 ^{o}C, therefore its full characterization was failed. Comparing the amine nucleophiles (**a-c**), similar reactivities were obtained in the aminocarbonylation of **1** (*Fig. 3*).

Under optimized conditions all carboxamides (**1a-13a**, **1b**, **2b**, **13b**, **1c**, **2c**) were obtained with practically full conversion and isolated in good to excellent yields (*Figure 1*).Not only 4-substituted iodoarenes but 2-iodoanisole (**14**) and 2-iodothiophene (**15**), as well as selected 3-substituted iodobenzenes (**16** and **17**) were aminocarbonylated efficiently.

Table 1. Aminocarbonylation of 4-substituted iodobenzenes (**1**, **2**, **13**) and 3-substituted iodobenzenes (**16**, **17**) in the presence of $Pd(OAc)_2$/2 PPh_3 *'in situ'* catalyst using 2-amino-1,3,4-thiadiazol derivatives (**a-c**)[a)]

Entry	Substrate	Amine	Time [h]	p(CO) [bar]	Temp. [°C]	Conv. [b] [%]
1	**1**	**a**	24	1	30	51
2	**1**	**a**	24	1	50	87
3	**1**	**a**	6	1	70	>98
4	**1**	**a**	24	40	30	<1
5	**1**	**a**	24	40	50	82
6	**1**	**a**	12	40	70	>98
7	**1**	**b**	24	1	50	88
8	**1**	**b**	6	1	70	>98
9	**1**	**c**	24	1	50	81
10	**1**	**c**	24	1	70	98
11	**2**	**a**	24	1	50	68
12	**2**	**a**	6	1	70	>98
13	**2**	**b**	24	1	50	82
14	**2**	**b**	6	1	70	>98
15	**2**	**c**	24	1	50	69
16	**2**	**c**	24	1	70	84
17	**13**	**a**	6	1	50	34
18	**13**	**a**	6	1	70	>98
19	**13**	**b**	6	1	50	19
20	**13**	**b**	6	1	70	>98
21	**13**	**c**	24	1	50	<1
22	**13**	**c**	24	1	70	<1
23	**16**	**a**	2	1	70	>98
24	**17**	**a**	2	1	70	>98

a) Reaction conditions: 1 mmol substrate (**1**, **2**, **13**, **16** or **17**), 1.2 mmol 2-amino-1,3-thiazole nucleophile (**a**, **b** or **c**); 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol of PPh_3, 0.5 mL of Et_3N, 10 ml of DMF.
b) Determined by GC and GC–MS.

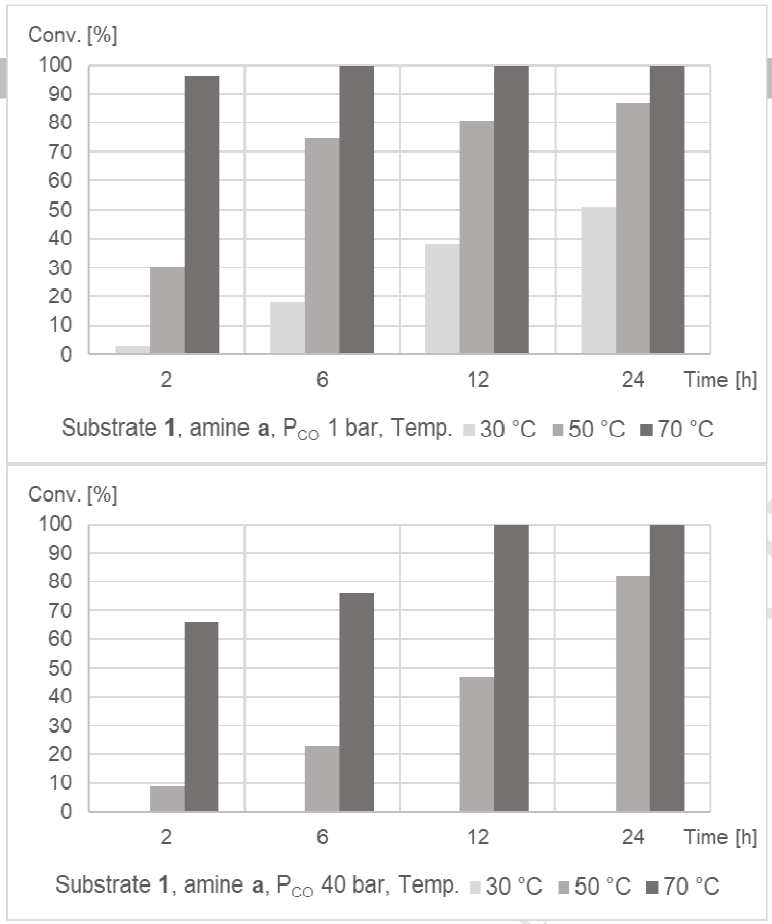


Fig. 1. Conversion *vs* reaction time diagrams of the aminocarbonylation of **1** in the presence of **a** nucleophile at various temperatures (under atmospheric CO pressure (upper diagram) and 40 bar CO pressure (bottom diagram))

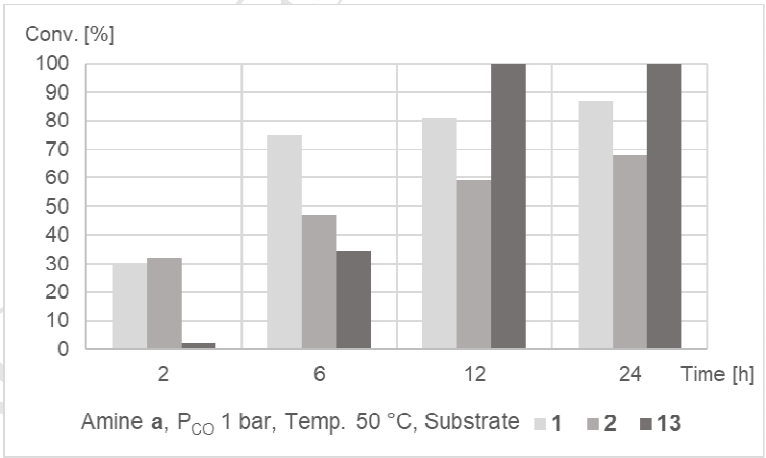


Fig. 2 Conversion *vs* reaction time diagrams of the aminocarbonylation of **1**, **2** and **13** in the presence of **a** nucleophile at 50 ^{o}C under atmospheric CO pressure

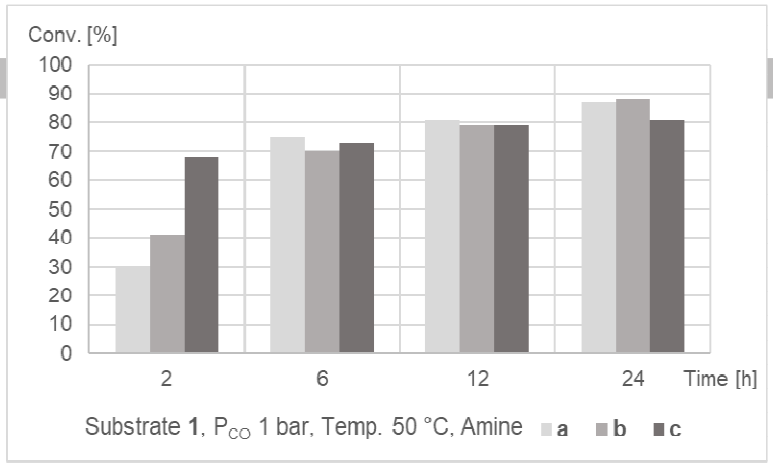


Fig. 3. Conversion vs reaction time diagrams of the aminocarbonylation of **1** in the presence of **a-c** nucleophiles at 50 ^{o}C under atmospheric CO pressure

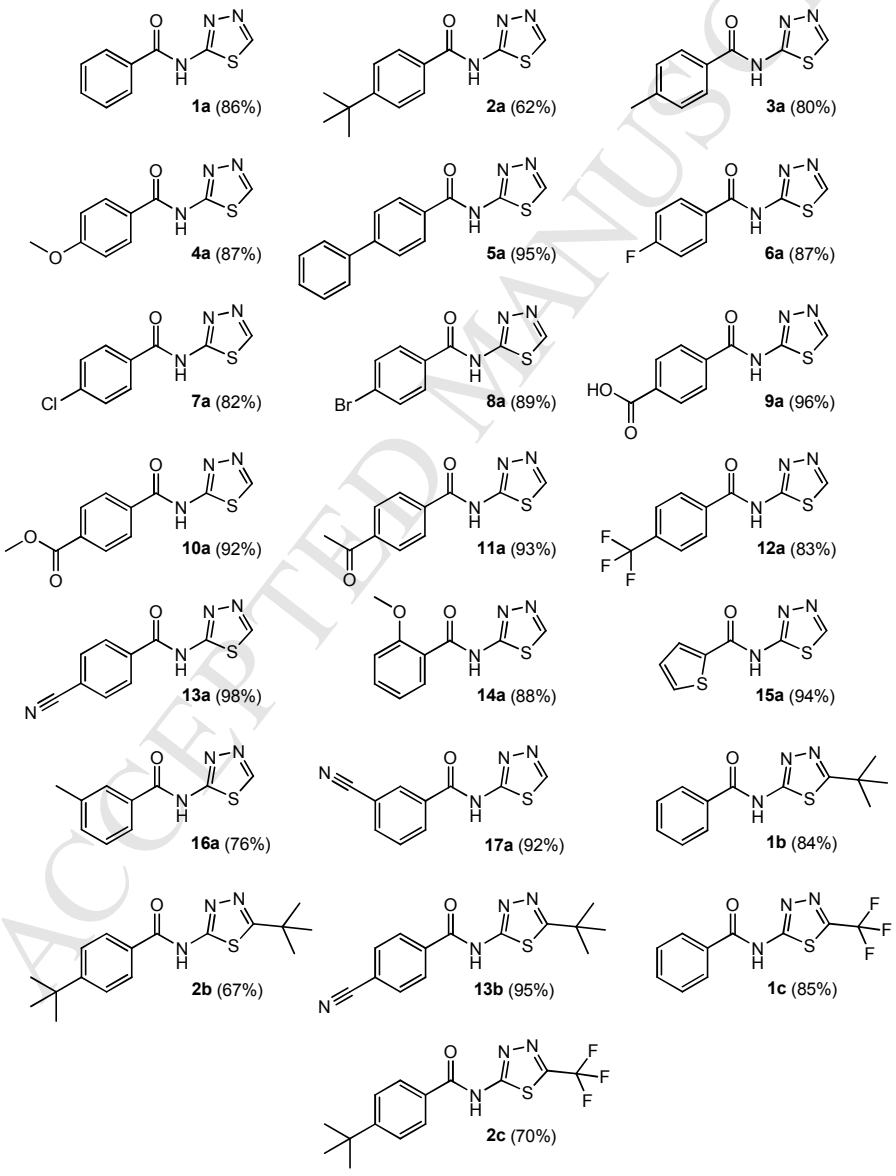
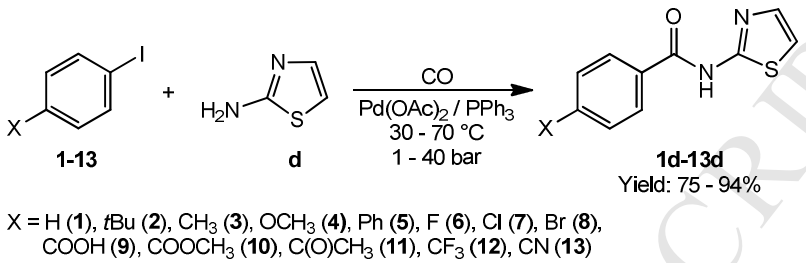


Figure 4. Products obtained (isolated yields in brackets) in the aminocarbonylation of **1**-**17** using 2-amino-1,3,4-thiadiazol derivatives (**a-c**) as nucleophiles

*2.2. Aminocarbonylation of 4-substituted iodobenzenes (**1-13**) with 2-amino-1,3-thiiazole (**d**)*

The set of 4-substituted iodobenzenes were aminocarbonylated using 2-amino-1,3-thiiazol (**d**) under various conditions (*Scheme 2*). As above, the reaction was found perfectly chemoselective and the corresponding carboxamides (**1d-13d**) were isolated in 75-94% yields. In addition, four further substrates (**14**, **15**, **16** and **17**) were aminocarbonylated and the isolated carboxamides (**14d**, **15d**, **16d** and **17d**) were fully characterized (*Figure 7*).



Scheme 2. Aminocarbonylation of 4-substituted iodobenzenes (**1**-**13**) with 2-amino-1,3-thiazole (**d**)

By the variation of the reaction conditions, similar features as in case of nucleophile **a**-**c** were observed. The use of higher reaction temperature (70 ^{o}C) resulted in increase in conversion (*Table 2, entries 1-3; Fig. 5 (upper diagram)*). A specially high reactivity was observed with **13** (*entries 6,7*), The application of high pressure (*entries 10-12, Figure 5 (bottom diagram)*) resulted in similar conversions to those obtained at atmospheric pressure. In some cases the conversion is even lower (compare *entries 5 and 13*) especially at low temperature (compare *entries 1 and 10*).

The *in situ* formation of palladium-dicarbonyl and tricarbonyl complexes might be responsible for this break-down effect of increased carbon monoxide pressure. The coordinatively highly unsaturated $Pd(PPh_3)(CO)(solvent)_n$ complexes are supposed to be responsible for the high activity. However, under high carbon monoxide pressure the formation of $Pd(PPh_3)(CO)_n$ (n=2-3) coordinatively saturated species are supposed hindering the activation of the aryl iodides via oxidative addition.

In addition to the above selected 4-substtituted iodobenzenes the aminocarbonylation of some 3-substituted derivatives was also carried out. While 3-methyliodobenzene (**16**) show lower (compare *entries 3 and 8*), the 3-cyano derivative (**17**) (compare *entries 3 and 9*) similar reactivity to the parent iodobenzene.

The selected substrates (**1**, **2** and **13**) showed similar reactivity in the aminocarbonylation with **d** nucleophile (*Fig. 6*). The carboxamide products (**1d-17d**) were isolated in high yields when the substrates were practically fully converted (*Fig. 7*). The scale-up experiments carried out at higher substrate to catalyst ratio (400:1) resulted in higher isolated yields. It is worth noting that yields can be improved by 5-8% when gram-scale experiments were carried out.

Table 2. Aminocarbonylation of 4-substituted iodobenzenes (**1**, **2**, **13**) and 3-substituted iodobenzenes (**16**, **17**) in the presence of $Pd(OAc)_2$/2 PPh_3 'in situ' catalyst using 2-amino-1,3-thiazole (**d**)[a)]

Entry	Substrate	Time [h]	p(CO) [bar]	Temp. [°C]	Conv. [b] [%]
1	**1**	24	1	30	67
2	**1**	24	1	50	>98
3	**1**	6	1	70	>98
4	**2**	6	1	50	>98
5	**2**	6	1	70	>98
6	**13**	2	1	50	58
7	**13**	2	1	70	>98
8	**16**	12	1	70	>98
9	**17**	6	1	70	>98
10	**1**	24	40	30	18
11	**1**	24	40	50	94
12	**1**	6	40	70	>98
13	**2**	6	40	70	86
14	**13**	6	40	70	>98

a) Reaction conditions: 1 mmol of substrate (**1**, **2**, **13**, **16** or **17**), 1.2 mmol of 2-amino-thiazole (**d**); 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol of PPh_3, 0.5 mL of Et_3N, 10 ml of DMF.
b) Determined by GC and GC–MS.

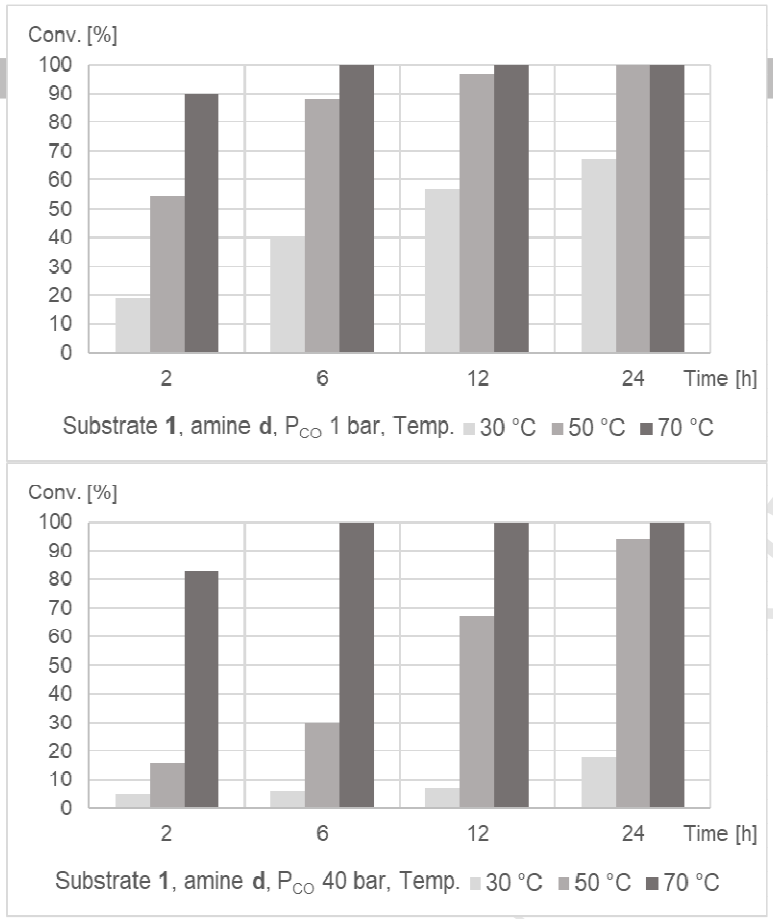


Fig. 5 Conversion *vs* reaction time diagrams of the aminocarbonylation of **1** in the presence of **d** nucleophiles at different temperatures under atmospheric CO pressure (upper) and 40 bar CO pressure (bottom)

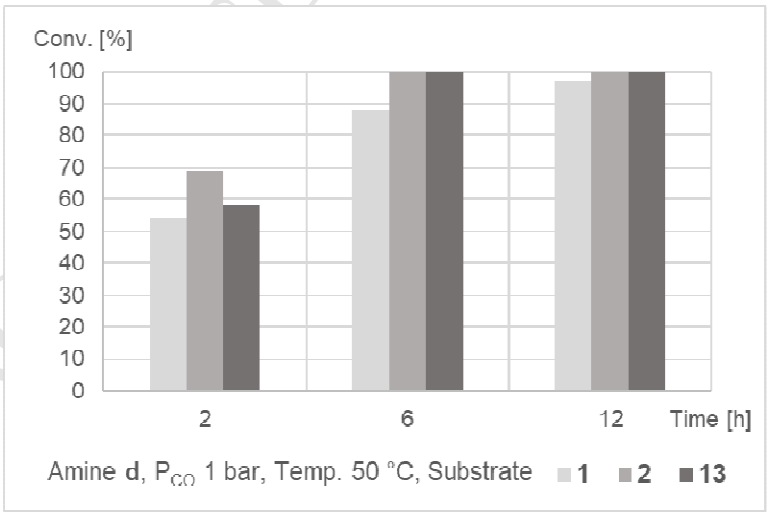


Fig. 6 Conversion vs reaction time diagrams of the aminocarbonylation of **1**, **2** and **13** in the presence of **d** nucleophiles at 50 °C under atmospheric CO pressure

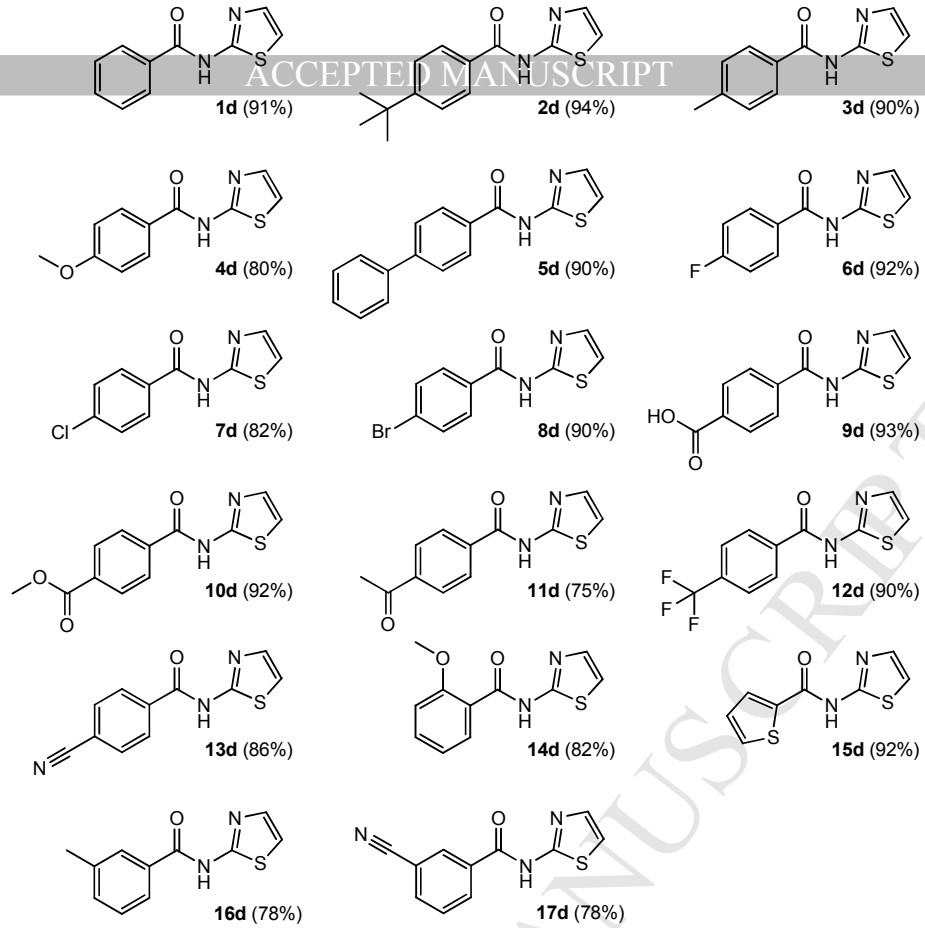
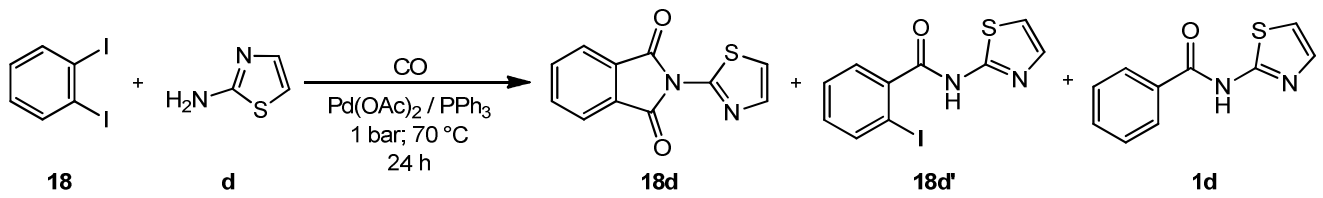


Figure 7. Products obtained (isolated yields in brackets) in the aminocarbonylation of **1**-**17** using 2-amino-1,3-thiazole (**d**) as nucleophile

*2.3. Investigation of the aminocarbonylation of 1,2-diiodobenzene (**18**) with 2-amino-1,3-thiiazole (**d**)*

One of the amine nucleophiles (**d**) was tested in the aminocarbonylation of 1,2-diiodobenzene with the aim of producing the corresponding phthalimide derivative. The reation resulted in a rather complex mixture of compounds (*Scheme 3*). A conversion lower than 20% was obtained at 70 ^{o}C in 24 h. The expected phthalinide product (**18d**) and 2-iodobenzamide (**18d'**) derivatives were formed in less than 5% and 10% , respectively. According to GC-MS investigations the deiodination of the latter compound also took place, leading to the benzamide derivative (**1d**). Based on our previous experiments,[17] the low-yielding formation of the phthalimide product using amine of low basicity is not surprising. As the high chemoselectivity toward carboxamides, the low imide formation can also be explained by the aromatic amine nucleophile (**d**) showing similar behavior to aniline.



Scheme 3. Aminocarbonylation of 1,2-diiodobenzene (**18**) with 2-amino-1,3-thiazole (**d**)

2.3. Conclusions

In summary, novel carboxamides possessing *N*-1,3-thiazol-2-yl- and *N*-1,3,4-thiadiazol-2-yl moieties were obtained under mild conditions. The two types of nucleophiles, *i.e.*, 2-amino-1,3,4-thiadiazole and 2-amino-1,3-thiazole derivatives behave as aromatic amines in the aminocarbonylation of iodoaromatics providing carboxamides exclusively. The high chemoselectivity and full conversion enabled facile isolation of the target compounds in high yields. No characteristic influence of the 4-substituents of the iodobenzene series on reactivity was observed. The only example when the target carboxamide was obtained in negligible conversion, was the aminocarbonylation of a substrate possessing electron-withdrawing group with a nucleophile possessing a substituent of similar properties. In accordance with our previous findings, the increase in the carbon monoxide pressure resulted in lower carbonylation activity. The mechanistic details were already discussed.[16]

The high selectivity, excellent isolated yields and facile work-up of the catalytic mixtures, as well as the presence of thiazole or thiadiazole rings make this reaction of both synthetic and pharmacological importance.

3. Experimental

3.1. General procedures

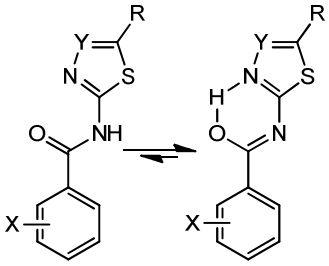
^{1}H, ^{19}F and ^{13}C NMR spectra were recorded in DMSO on a Bruker Avance III 500 spectrometer at 500, 470.4 and 125.7 MHz, respectively. Chemical shifts δ are reported in ppm relative to DMSO (2.50 and 39.50 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. The FT-IR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400-4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was *ca*. 0.5 mg. Mass spectrometry data have been obtained using a GC-MS system consisting of a Perkin Elmer AutoSystem XL gas-chromatograph. Melting points are uncorrected and were measured with a Büchi apparatus. TLC plates (silica gel on TLC Al foils with fluorescence indicator 254 nm) were purchased from Sigma-Aldrich. The eluents used in thin-layer chromatography are specified below.

Substrates (iodoaromatics, **1**-**18**) and nucleophiles (**a**-**d**) were purchased from Sigma-Aldrich and were used without further purification.

The characterization of the carboxamides **1a**,[18,19] **1c**,[20] **1d**,[21] **3d**,[21] **4a**,[19] **6d**,[22] **7a**[19] and **7d**[21] , which were synthesised by conventional (acylation) reactions, was already published. The compounds isolated in this work gave practically identical spectra. However, due to some further analytical details (for instance detailed description of NMR spectra) the full characterization is given below for all compounds (*3.4.*)

It is worth noting that the analytical investigations have shown an amide–imidic acid tautomerism of the target carboxamides. For instance, the extremely large downfield shift of one proton (typically in the

range of 11.8-13.8 ppm) reflects to the hydrogen bridging between the oxygen atom of the imidic acid tautomer and nitrogen atom of the thiadiazole and thiazole moieties (*Scheme 4*).



Scheme 4. The amide–imidic acid tautomerism of *N*-1,3-thiazol-2-yl- (Y=CH) and *N*-1,3,4-thiadiazol-2-yl (Y=N) benzamides

*3.2. Aminocarbonylation of iodobenzene derivatives in the presence of 2-amino-1,3,4-thiadiazoles (**a**-**c**) and 2-amino-1,3-thiazole (**d**) under an atmospheric pressure of carbon monoxide (preparation of the target carboxamides)*

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.1 mg, 0.05 mmol), iodobenzene (**1**) (or an other iodoaromatics, **2**-**18**) (1.0 mmol), and 2-amino-1,3,4-thiadiazol (**a**) (or its 5-substituted derivatives, **b** or **c**, or 2-amino-1,3-thiazole, **d**) (121.4 mg, 1.2 mmol) and triethylamine (0.5 mL) were dissolved in DMF (10 mL) under argon in a 100 mL three-necked flask equipped with reflux condenser connected to a balloon filled with argon. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 70 ^{o}C and analyzed by TLC and GC-MS. The cooled reaction mixture was then concentrated and evaporated to dryness under reduced pressure.

Method **A**. (**2a**, **14a**, **1d**-**8d**, **10d**, **14d**-**16d**): The residue was dissolved in chloroform (15 mL) and washed three times with water (30 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to a solid material. Aforesaid compounds were subjected to column chromatography (Silicagel 60 (Merck), 0.063-0.200 mm), EtOAc/$CHCl_3$ eluent mixtures (the exact ratios are specified in Characterization for each compound; isolated yields are not optimized).

Method **B**. (**1a**, **3a**-**13a**, **15a**-**17a**, **1b**, **2b**, **13b**, **1c**, **2c**, **9d**, **11d**-**13d, 17d**): Toluene (15 mL) was added to the residue, the insoluble material (product) was filtered, washed with water on the filter and dried. The off-white powder-like material was dissolved in methanol, the palladium-black was filtered off and methanol was evaporated.

*3.3. Aminocarbonylation of iodobenzene derivatives in the presence of 2-amino-1,3,4-thiadiazoles (**a**-**c**) and 2-amino-1,3-thiiazole (**d**) under 40 bar pressure of carbon monoxide*

In a typical experiment $Pd(OAc)_2$, triphenylphosphine, iodobenzene (**1**) (or an other iodoaromatics, **2**-**15**) (1 mmol), 2-amino-1,3,4-thiadiazol (**a**) (or its 5-substituted derivatives, **b** or **c**, or 2-amino-1,3-thiazole,

d) and triethylamine were used in the same amount as above (*3.2.*) and were dissolved in DMF under argon in a 100 mL autoclave. The autoclave was pressurized to 40 bar with carbon monoxide. (Caution: High pressure carbon monoxide should only be used with adequate ventilation (hood) using CO sensors as well.) The reaction was conducted for the given reaction time upon stirring at 30 ^{o}C (or at 50 °C or 70 ^{o}C) and analyzed by GC and GC-MS. The work-up of the reaction mixture was identical to that discussed above.

3.4. Characterization of the products

N-(1,3,4-Thiadiazol-2-yl)benzamide (**1a**). Yield: 175.5 mg (86%), pale yellow powder, mp 216-217 °C; [Found: C, 52.47; H, 3.50; N, 20.35; $C_9H_7N_3OS$ requires C, 52.67; H, 3.44; N, 20.47%]; R_f (10% EtOAc, 90% $CHCl_3$) 0.87; δ_H (500 MHz, DMSO) 13.09 (1H, br s, N-H-O), 9.25 (1H, s, CH (thiadiazole)), 8.14 (2H, d, 7.3 Hz, CH_{ortho}(Ph)), 7.68 (1H, t, 7.4 Hz, CH_{para}(Ph)), 7.58 (2H, t, 7.6 Hz, CH_{meta}(Ph)); δ_C (125.7 MHz, DMSO) 165.7, 159.9, 149.5, 133.4, 132.1, 129.1, 128.9. IR (KBr ν (cm^{-1})) 3158 (NH), 1672 (CON), 1536 and 1323 (thiadiazole ring); MS m/z (rel int.): 205 (8, M^+), 204 (13), 177 (21), 105 (100), 77 (71).

N-(5-(tert-Butyl)-1,2,4-thiadiazol-2-yl)benzamide (**1b**). Yield: 219.0 mg (84%), white powder, mp 237-238 °C; [Found: C, 59.77; H, 5.88; N, 16.01; $C_{13}H_{15}N_3OS$ requires C, 59.75; H, 5.79; N, 16.08%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.44; δ_H (500 MHz, DMSO) 12.95 (1H, br s, N-H-O), 8.12 (2H, d, 7.4 Hz, H_{ortho}(Ph)), 7.66 (1H, t, 7.3 Hz, H_{para}(Ph)), 7.56 (2H, t, 7.7 Hz, H_{meta}(Ph)), 1.44 (9H, s, CH_3); δ_C (125.7 MHz, DMSO) 174.1, 165.7, 159.6, 133.3, 132.3, 129.1, 128.8, 35.9, 31.0. IR (KBr ν (cm^{-1})) 3132 (NH), 1669 (CON), 1533 and 1310 (thiadiazole ring); MS m/z (rel int.): 261 (10, M^+), 260 (18), 233 (18), 105 (100), 77 (40).

N-(5-(Trifluoromethyl)-1,2,4-thiadiazol-2-yl)benzamide (**1c**). Yield: 233.0 mg (85%), white powder, mp 256-257 °C; [Found: C, 43.87; H, 2.70; N, 24.05; $C_{10}H_6N_3OSF_3$ requires C, 43.96; H, 2.63; N, 24.33%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.80; δ_H (500 MHz, DMSO) 13.76 (1H, br s, N-H-O), 8.17 (2H, d, 7.7 Hz, H_{ortho}(Ph)), 7.72 (1H, t, 7.3 Hz, H_{para}(Ph)), 7.61 (2H, t, 7.6 Hz, H_{meta}(Ph)); δ_F (470.4 MHz, DMSO): -58.23 (3F, s, CF_3); δ_C (125.7 MHz, DMSO) 166.3, 162.9, 151.4 (q, J_{C-F} 37.4 Hz), 134.0, 131.1, 129.3, 129.1, 120.6 (q, J_{C-F} 272.0 Hz). IR (KBr ν (cm^{-1})) 3217 (NH), 1675 (CON), 1518 and 1302 (thiadiazole ring), 1302, 1176 and 1145 (CF); MS m/z (rel int.): 273 (4, M^+), 105 (100), 77 (56), 51 (18).

4-(tert-Butyl)-N-(1,3,4-thiadiazol-2-yl)benzamide (**2a**). Yield: 163.2 mg (62%), pale yellow crystal, mp 179-180 °C; [Found: C, 59.67; H, 5.90; N, 15.95; $C_{13}H_{15}N_3OS$ requires C, 59.75; H, 5.79; N, 16.08%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.41; δ_H (500 MHz, DMSO) 13.01 (1H, br s, N-H-O), 9.24 (1H, s, CH(thiadiazole)), 8.09 (2H, d, 8.5 Hz, CH(Ph)), 7.59 (2H, d, 8.5 Hz, CH(Ph)), 1.33 (9H, s, CH_3); δ_C (125.7 MHz, DMSO) 165.5, 160.0, 156.5, 149.4, 129.3, 128.8, 126.0, 35.3, 31.3. IR (KBr ν (cm^{-1})) 3141 (NH), 1668

(CON), 1530 and 1296 (thiadiazole ring); MS m/z (rel int.): 261 (6, M^+), 260 (6), 161 (100), 146 (10), 118 (11), 91 (9).

4-(tert-Butyl)-N-(5-(tert-Butyl)-1,2,4-thiadiazol-2-yl)benzamide (**2b**). Yield: 211.3 mg (67%), white powder, mp 292-293 °C; [Found: C, 64.37; H, 7.44; N, 13.12; $C_{17}H_{23}N_3OS$ requires C, 64.32; H, 7.30; N, 13.24%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.70; δ_H (500 MHz, DMSO) 12.85 (1H, br s, N-H-O), 8.07 (2H, d, 8.0 Hz, CH(Ph)), 7.58 (2H, d, 8.0 Hz, CH(Ph)), 1.44 (9H, s, CH_3), 1.33 (9H, s, CH_3); δ_C (125.7 MHz, DMSO) 174.0, 165.3, 159.5, 156.4, 129.4, 128.7, 125.9, 35.9, 35.3, 31.3, 31.0. IR (KBr ν (cm^{-1})) 3168 (NH), 1669 (CON), 1529 and 1299 (thiadiazole ring); MS m/z (rel int.): 317 (8, M^+), 316 (18), 289 (13), 161 (100), 146 (7), 130 (8), 118 (9), 91 (6).

4-(tert-Butyl)-N-(5-(trifluoromethyl)-1,2,4-thiadiazol-2-yl)benzamide (**2c**). Yield: 230.9 mg (70%), delicate pink powder, mp 238-239 °C; [Found: C, 51.17; H, 4.32; N, 12.51; $C_{14}H_{14}N_3OSF_3$ requires C, 51.06; H, 4.28; N, 12.76%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.96; δ_H (500 MHz, DMSO) 13.68 (1H, br s, N-H-O), 8.12 (2H, d, 8.4 Hz, CH(Ph)), 7.61 (2H, d, 8.4 Hz, CH(Ph)), 1.33 (9H, s, CH_3); δ_F (470.4 MHz, DMSO): -58.27 (3F, s, CF_3); δ_C (125.7 MHz, DMSO) 165.9, 162.9, 157.2, 151.3 (q, $J_{C\text{-}F}$ 37.4 Hz), 129.0, 128.3, 126.1, 120.6 (q, $J_{C\text{-}F}$ 272.0 Hz), 35.4, 31.2. IR (KBr ν (cm^{-1})) 3172 (NH), 1673 (CON), 1521 and 1297 (thiadiazole ring), 1297, 1182 and 1149 (CF); MS m/z (rel int.): 329 (3, M^+), 314 (3), 163 (14), 161 (100), 146 (9), 118 (10), 91 (8).

4-Methyl-N-(1,3,4-thiadiazol-2-yl)benzamide (**3a**). Yield: 174.5 mg (80 %), pale yellow powder, mp 237-238 °C; [Found: C, 54.67; H, 4.30; N, 19.02; $C_{10}H_9N_3OS$ requires C, 54.78; H, 4.14; N, 19.16%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.26; δ_H (500 MHz, DMSO) 13.00 (1H, br s, N-H-O), 9.24 (1H, s, CH(thiadiazole)), 8.04 (2H, d, 8.1 Hz, CH(Ph)), 7.38 (2H, d, 8.1 Hz, CH(Ph)), 2.41 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 165.5, 159.9, 149.4, 143.8, 129.7, 129.2, 128.9, 21.6. IR (KBr ν (cm^{-1})) 3192 (NH), 1665 (CON), 1529 and 1316 (thiadiazole ring); MS m/z (rel int.): 219 (7, M^+), 218 (9), 191 (10), 119 (100), 91 (50), 65 (20).

4-Methoxy-N-(1,3,4-thiadiazol-2-yl)benzamide (**4a**). Yield: 204.1 mg (87%), white powder, mp 242-243 °C; [Found: C, 51.27; H, 3.90; N, 17.75; $C_{10}H_9N_3O_2S$ requires C, 51.05; H, 3.86; N, 17.86%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.18; δ_H (500 MHz, DMSO) 12.90 (1H, br s, N-H-O), 9.22 (1H, s, CH(thiadiazole)), 8.15 (2H, d, 8.9 Hz, CH(Ph)), 7.10 (2H, d, 8.9 Hz, CH(Ph)), 3.86 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 164.9, 163.5, 160.0, 149.3, 131.0, 124.0, 114.4, 56.0. IR (KBr ν (cm^{-1})) 3217 (NH), 1662 (CON), 1534 and 1309 (thiadiazole ring), 1259 and 1174 (C-O); MS m/z (rel int.): 235 (7, M^+), 135 (100), 107 (10), 92 (16), 77 (18).

N-(1,3,4-Thiadiazol-2-yl)-[1,1'-biphenyl]-4-carboxamide (**5a**). Yield: 265.8 mg (95%), pale yellow powder, mp 283-284 °C; [Found: C, 64.17; H, 3.83; N, 14.75; $C_{15}H_{11}N_3OS$ requires C, 64.04; H, 3.94; N, 14.94%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.28; δ_H (500 MHz, DMSO) 13.13 (1H, br s, N-H-O), 9.26 (1H, s, CH(thiadiazole)), 8.24 (2H, d, 8.4 Hz, CH(Ph)), 7.88 (2H, d, 8.4 Hz, CH(Ph)), 7.79 (2H, d, 7.4 Hz, CH_{ortho}(Ph)), 7.53 (2H, t, 7.4 Hz, CH_{meta}(Ph)), 7.45 (1H, t, 7.4 Hz, CH_{para}(Ph)); δ_C (125.7 MHz, DMSO) 165.4, 159.9, 149.5, 144.9, 139.3, 129.6, 129.5, 128.9, 127.5, 127.3. IR (KBr ν (cm^{-1})) 3150 (NH), 1655 (CON), 1526 and 1298 (thiadiazole ring); MS m/z (rel int.): 281 (11, M^+), 253 (6), 181 (100), 152 (49), 76 (6).

4-Fluoro-N-(1,3,4-thiadiazol-2-yl)benzamide (**6a**). Yield: 194.1 mg (87%), white powder, mp 285-286 °C; [Found: C, 48.57; H, 2.81; N, 18.69; $C_9H_6N_3OSF$ requires C, 48.43; H, 2.71; N, 18.82%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.21; δ_H (500 MHz, DMSO) 13.13 (1H, br s, N-H-O), 9.25 (1H, s, CH(thiadiazole)), 8.22 (2H, dd, $J_{H\text{-}F}$ 8.9 Hz, $J_{H\text{–}H}$ 5.4 Hz, CH(Ph)), 7.41 (2H, dd, $J_{H\text{-}F}$ 8.9 Hz, $J_{H\text{-}H}$ 8.9 Hz, CH(Ph)); δ_F (470.4 MHz, DMSO): -106.38 (1F, br s, CF(Ph)); δ_C (125.7 MHz, DMSO) 165.3 (d, $J_{C\text{-}F}$ 251.1 Hz), 164.8, 160.0, 149.5, 131.8 (d, $J_{C\text{-}F}$ 9.3 Hz), 128.7, 116.2 (d, $J_{C\text{-}F}$ 22.0 Hz). IR (KBr ν (cm^{-1})) 3159 (NH), 1682 (CON), 1548 and 1320 (thiadiazole ring), 1236 (CF); MS m/z (rel int.): 223 (6, M^+), 222 (11), 195 (16), 123 (100), 95 (52), 75 (20).

4-Chloro-N-(1,3,4-thiadiazol-2-yl)benzamide (**7a**). Yield: 196.7 mg (82%), white powder, mp 275-276 °C; [Found: C, 45.15; H, 2.59; N, 17.27; $C_9H_6N_3OSCl$ requires C, 45.10; H, 2.52; N, 17.53%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.26; δ_H (500 MHz, DMSO) 13.19 (1H, br s, N-H-O), 9.25 (1H, s, CH(thiadiazole)), 8.14 (2H, d, 7.9 Hz, CH(Ph)), 7.65 (2H, d, 7.9 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 164.9, 160.0, 149.5, 138.3, 131.0, 130.8, 129.2. IR (KBr ν (cm^{-1})) 3132 (NH), 1673 (CON), 1548 and 1321 (thiadiazole ring); MS m/z (rel int.): 240 (6, M^+), 238 (13, M^+), 213 (7), 211 (19), 141 (32), 139 (100), 113 (14), 111 (45), 75 (27).

4-Bromo-N-(1,3,4-thiadiazol-2-yl)benzamide (**8a**). Yield: 253.6 mg (89%), white powder, mp 285-286 °C; [Found: C, 38.26; H, 2.25; N, 14.67; $C_9H_6N_3OSBr$ requires C, 38.05; H, 2.13; N, 14.79%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.26; δ_H (500 MHz, DMSO) 13.19 (1H, br s, N-H-O), 9.25 (1H, s, CH(thiadiazole)), 8.06 (2H, d, 7.9 Hz, CH(Ph)), 7.79 (2H, d, 7.9 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 165.0, 159.9, 149.5, 132.2, 131.4, 130.9, 127.4. IR (KBr ν (cm^{-1})) 3132 (NH), 1673 (CON), 1539 and 1321 (thiadiazole ring); MS m/z (rel int.): 285 (8, M^+), 284 (16), 283 (8, M^+), 282 (15), 257 (21), 255 (18), 185 (100), 183 (100), 157 (42), 155 (44), 76 (31).

4-((1,3,4-Thiadiazol-2-yl)carbamoyl)benzoic acid (**9a**). Yield: 239.1 mg (96%), brown solid, mp 309-310 °C; [Found: C, 48.30; H, 2.90; N, 16.74; $C_{10}H_7N_3O_3S$ requires C, 48.19; H, 2.83; N, 16.86%]; R_f (10%

EtOAc, 90% $CHCl_3$) 0.19; δ_H (500 MHz, DMSO) 13.31 (2H, br s, COOH; N-H-O), 9.26 (1H, s, CH(thiadiazole)), 8.21 (2H, d, 8.3 Hz, CH(Ph)), 8.09 (2H, d, 8.3 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 167.1, 165.4, 160.0, 149.6, 135.9, 134.8, 129.9, 129.1. IR (KBr ν (cm^{-1})) 3163 (NH), 2505 (OH), 1677 (CO (acid), CON), 1557 and 1330 (thiadiazole ring), 1295 (C-O).

Methyl 4-((1,3,4-thiadiazol-2-yl)carbamoyl)benzoate (**10a**). Yield: 242.8 mg (92%), white solid, mp 278-279 °C; [Found: C, 53.49; H, 3.81; N, 16.86; $C_{11}H_9N_3O_3S$ requires C, 53.43; H, 3.67; N, 16.99%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.19; δ_H (500 MHz, DMSO) 13.32 (1H, br s, N-H-O), 9.26 (1H, s, CH(thiadiazole)), 8.23 (2H, d, 8.5 Hz, CH(Ph)), 8.11 (2H, d, 8.5 Hz, CH(Ph)), 3.91 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 166.0, 165.3, 160.1, 149.6, 136.3, 133.6, 129.7, 129.3, 53.0. IR (KBr ν (cm^{-1})) 3192 (NH), 1723 (CO (ester)), 1711 (CON), 1535 and 1325 (thiadiazole ring), 1290 and 1112 (C-O); MS m/z (rel int.): 263 (6, M^+), 262 (11), 235 (19), 163 (100), 135 (23), 103 (15), 76 (15).

4-Acetyl-N-(1,3,4-thiadiazol-2-yl)benzamide (**11a**). Yield: 230.1 mg (93%), yellow powder, mp 263-264 °C; [Found: C, 53.49; H, 3.58; N, 16.84; $C_{11}H_9N_3O_2S$ requires C, 53.43; H, 3.67; N, 16.99%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.13; δ_H (500 MHz, DMSO) 13.29 (1H, br s, N-H-O), 9.27 (1H, s, CH(thiadiazole)), 8.24 (2H, d, 8.2 Hz, CH(Ph)), 8.11 (2H, d, 8.2 Hz, CH(Ph)), 2.66 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 198.2, 165.2, 159.9, 149.6, 140.3, 135.9, 129.2, 128.7, 27.5. IR (KBr ν (cm^{-1})) 3150 (NH), 1677 (CO (keto); CON), 1530 and 1326 (thiadiazole ring); MS m/z (rel int.): 247 (8, M^+), 246 (13), 219 (27), 147 (100), 119 (15), 100 (11), 91 (23), 76 (15).

N-(1,3,4-Thiadiazol-2-yl)-4-(trifluoromethyl)benzamide (**12a**). Yield: 225.6 mg (83%), white powder, mp 264-265 °C; [Found: C, 43.86; H, 2.28; N, 15.15; $C_{10}H_6N_3OSF_3$ requires C, 43.96; H, 2.21; N, 15.38%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.34; δ_H (500 MHz, DMSO) 13.36 (1H, br s, N-H-O), 9.28 (1H, s, CH(thiadiazole)), 8.31 (2H, d, 8.1 Hz, CH(Ph)), 7.95 (2H, d, 8.1 Hz, CH(Ph)); δ_F (470.4 MHz, DMSO): -61.58 (3F, s, CF_3); δ_C (125.7 MHz, DMSO) 165.0, 159.9, 149.6, 136.1, 132.9 (q, $J_{C\text{-}F}$ 32.0 Hz), 129.8, 126.0 (q, $J_{C\text{-}F}$ 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ 272.5 Hz). IR (KBr ν (cm^{-1})) 3168 (NH), 1674 (CON), 1533 and 1299 (thiadiazole ring), 1299, 1152 and 1118 (CF); MS m/z (rel int.): 273 (10, M^+), 272 (18), 245 (23), 173 (100), 145 (71), 95 (10), 75 (9).

4-Cyano-N-(1,3,4-thiadiazol-2-yl)benzamide (**13a**). Yield: 226.6 mg (98%), pale brown solid, mp 310-311 °C; [Found: C, 52.30; H, 2.51; N, 24.20; $C_{10}H_6N_4OS$ requires C, 52.17; H, 2.63; N, 24.33%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.14; δ_H (500 MHz, DMSO) 13.36 (1H, br s, N-H-O), 9.28 (1H, s, CH(thiadiazole)), 8.25 (2H, d, 8.3 Hz, CH(Ph)), 8.06 (2H, d, 8.3 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 164.8, 159.9, 149.7,

136.1, 133.1, 129.7, 118.6, 115.5. IR (KBr ν (cm^{-1})) 3137 (NH), 2225 (CN), 1674 (CON), 1544 and 1328 (thiadiazole ring); MS m/z (rel int.): 230 (3, M^+), 299 (22), 202 (24), 130 (100), 102 (60), 75 (16).

N-(5-(tert-Butyl)-1,2,4-thiadiazol-2-yl)-4-cyanobenzamide (**13b**). Yield: 273.1 mg (95%), white powder, mp 287-288 °C; [Found: C, 51.78; H, 4.99; N, 19.43; $C_{14}H_{14}N_4OS$ requires C, 51.72; H, 4.93; N, 19.57%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.34; δ_H (500 MHz, DMSO) 13.29 (1H, br s, N-H-O), 8.23 (2H, d, 8.4 Hz, CH(Ph)), 8.04 (2H, d, 8.4 Hz, CH(Ph)), 1.44 (9H, s, CH_3); δ_C (125.7 MHz, DMSO) 174.1, 165.1, 160.1, 136.7, 133.0, 129.6, 118.6, 115.3, 36.0, 30.9. IR (KBr ν (cm^{-1})) 3150 (NH), 2226 (CN), 1671 (CON), 1534 and 1301 (thiadiazole ring); MS m/z (rel int.): 286 (31, M^+), 285 (76), 271 (27), 258 (29), 199 (16), 184 (27), 130 (100), 102 (54).

2-Methoxy-N-(1,3,4-thiadiazol-2-yl)benzamide (**14a**). Yield: 206.3 mg (88%), yellow needle crystal, mp 115-116 °C; [Found: C, 51.19; H, 3.90; N, 17.61; $C_{10}H_9N_3O_2S$ requires C, 51.05; H, 3.86; N, 17.86%]; R_f (50% EtOAc, 50% $CHCl_3$) 0.37; δ_H (500 MHz, DMSO) 12.36 (1H, br s, N-H-O), 9.24 (1H, s, CH(thiadiazole)), 7.71 (1H, d, 7.6, CH(Ph)), 7.59 (1H, t, 7.9 Hz, CH(Ph)), 7.23 (1H, d, 8.5 Hz, CH(Ph)), 7.11 (1H, t, 7.5 Hz, CH(Ph)), 3.93 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 164.9, 158.9, 157.7, 149.5, 134.0, 130.7, 122.1, 121.1, 112.7, 56.5. IR (KBr ν (cm^{-1})) 3319 (NH), 1668 (CON), 1517 and 1299 (thiadiazole ring), 1228 and 1019 (C-O); MS m/z (rel int.): 235 (<1, M^+), 204 (50), 135 (100), 92 (19), 77 (31).

N-(1,3,4-Thiadiazol-2-yl)thiophene-2-carboxamide (**15a**). Yield: 198.1 mg (94%), white powder, mp 260-261 °C; [Found: C, 39.77; H, 2.44; N, 19.74; $C_7H_5N_3OS_2$ requires C, 39.80; H, 2.39; N, 19.89%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.23; δ_H (500 MHz, DMSO) 13.21 (1H, br s, N-H-O), 9.22 (1H, s, CH(thiadiazole)), 8.31 (1H, br s, CH(thiophene)), 8.01 (1H, d, 4.9 Hz, CH(thiophene), 7.28 (1H, t, 4.3 Hz, CH(thiophene)); δ_C (125.7 MHz, DMSO) 160.3, 159.9, 149.4, 137.2, 134.6, 132.1, 129.1. IR (KBr ν (cm^{-1})) 3199 (NH), 1649 (CON), 1548 and 1303 (thiadiazole ring); MS m/z (rel int.): 211 (12, M^+), 183 (25), 111 (100).

N-(thiazol-2-yl)benzamide (**1d**). Yield: 185.2 mg (91%), white crystal, mp 140–141°C; [Found: C, 58.87; H, 3.81; N, 13.65; $C_{10}H_8N_2OS$ requires C, 58.81; H, 3.95; N, 13.72%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.64; δ_H (500 MHz, DMSO) 12.03 (1H, br s, N-H-O), 8.03 (2H, d, 8.2 Hz, CH_{ortho}(Ph)), 7.66 (1H, t, 7.5 Hz, CH_{para}(Ph)), 7.55 (2H, t, 7.7 Hz, CH_{meta}(Ph)), 7.12 (1H, d, 3.6 Hz, NCH, 6.98 (1H, d, 3.6 Hz, SCH); δ_C (125.7 MHz, DMSO) 165.5, 159.8, 137.3, 132.8, 132.7, 128.9, 127.9, 113.6. IR (KBr ν (cm^{-1})) 3145 (NH), 1677 (CON), 1552 (thiazole ring); MS m/z (rel int.): 204 (16, M^+), 176 (18), 105 (100), 77 (59).

4-(tert-Butyl)-N-(thiazol-2-yl)benzamide (**2d**). Yield: 245.1 mg (94%), White needle crystal, mp 166–167°C; [Found: C, 64.67; H, 6.28; N, 10.55; $C_{14}H_{16}N_2OS$ requires C, 64.59; H, 6.19; N, 10.76%]; R_f (20%

EtOAc, 80% $CHCl_3$) 0.88; δ_H (500 MHz, DMSO) 12.58 (1H, br s, N-H-O), 8.06 (2H, d, 8.5 Hz, CH(Ph)), 7.58 – 7.55 (3H, m, CH(Ph); NCH), 7.29 (1H, d, 3.5 Hz, SCH), 1.33 (9H, s, CH_3); δ_C (125.7 MHz, DMSO) 165.3, 159.2, 156.0, 138.1, 129.8, 128.5, 125.9, 114.2, 35.3, 31.3. IR (KBr ν (cm^{-1})) 3151 (NH), 1664 (CON), 1553 (thiazole ring); MS m/z (rel int.): 260 (12, M^+), 161 (100), 146 (11), 118 (13), 91 (8).

4-Methyl-N-(thiazol-2-yl)benzamide (**3d**). Yield: 195.6 mg (90%), pale yellow powder, mp 213–214 °C; [Found: C, 60.59; H, 4.66; N, 12.70; $C_{11}H_{10}N_2OS$ requires C, 60.53; H, 4.62; N, 12.83%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.70; δ_H (500 MHz, DMSO) 12.52 (1H, br s, N-H-O), 8.01 (2H, d, 6.2 Hz, CH(Ph)), 7.56 (1H, br s, NCH), 7.35 (2H, d, 6.2 Hz, CH(Ph)), 7.27 (1H, br s, SCH), 2.40 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 165.4, 159.2, 143.2, 138.1, 129.9, 129.6, 128.6, 114.2, 21.5. IR (KBr ν (cm^{-1})) 3150 (NH), 1665 (CON), 1539 (thiazole ring); MS m/z (rel int.): 218 (16, M^+), 190 (7), 119 (100), 91 (46), 65 (19).

4-Methoxy-N-(thiazol-2-yl)benzamide (**4d**). Yield: 187.8 mg (80%), white powder, mp 214–215°C; [Found: C, 56.49; H, 4.41; N, 11.74; $C_{11}H_{10}N_2O_2S$ requires C, 56.40; H, 4.30; N, 11.96%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.56; δ_H (500 MHz, DMSO) 12.47 (1H, br s, N-H-O), 8.12 (2H, d, 8.9 Hz, CH(Ph)), 7.56 (1H, d, 3.5 Hz, NCH), 7.26 (1H, d, 3.5 Hz, SCH), 7.08 (2H, d, 8.9 Hz, CH(Ph)), 3.86 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 164.8, 163.1, 159.4, 138.0, 130.7, 124.7, 114.3, 114.1, 56.0. IR (KBr ν (cm^{-1})) 3145 (NH), 1672 (CON), 1543 (thiazole ring), 1255 and 1020 (C-O); MS m/z (rel int.): 234 (13, M^+), 135 (100), 107 (10), 92 (13), 77 (17).

N-(Thiazol-2-yl)-[1,1'-biphenyl]-4-carboxamide (**5d**). Yield: 252.6 mg (90%), pale brown powder, mp 208–209 °C; [Found: C, 68.46; H, 4.20; N, 9.84; $C_{16}H_{12}N_2OS$ requires C, 68.55; H, 4.31; N, 9.99%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.77; δ_H (500 MHz, DMSO) 12.71 (1H, br s, N-H-O), 8.21 (2H, d, 8.5 Hz, CH(Ph)), 7.87 (2H, d, 8.5 Hz, CH(Ph)), 7.79 (2H, d, 7.5 Hz, CH(Ph)), 7.59 (1H, d, 3.5 Hz, NCH), 7.53 (2H, t, 7.5 Hz, CH(Ph)), 7.45 (1H, t, 7.5 Hz, CH(Ph)), 7.31 (1H, d, 3.5 Hz, SCH); δ_C (125.7 MHz, DMSO) 165.2, 159.2, 144.4, 139.4, 138.1, 131.4, 129.6, 129.3, 128.8, 127.4, 127.2, 114.3. IR (KBr ν (cm^{-1})) 3150 (NH), 1668 (CON), 1544 (thiazole ring); MS m/z (rel int.): 280 (15, M^+), 181 (100), 153 (47).

4-Fluoro-N-(thiazol-2-yl)benzamide (**6d**). Yield: 203.6 mg (92%), white powder, mp 194–195°C; [Found: C, 54.17; H, 3.04; N, 12.50; $C_{10}H_7N_2OSF$ requires C, 54.05; H, 3.17; N, 12.61%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.65; δ_H (500 MHz, DMSO) 12.68 (1H, br s, N-H-O), 8.19 (2H, dd, J_{H-H} 8.9 Hz, J_{H-F} 5.5 Hz, CH(Ph)), 7.58 (1H, d, 3.6 Hz, NCH), 7.40 (2H, dd, J_{H-H} 8.9 Hz, J_{H-F} 8.9 Hz, CH(Ph)), 7.30 (1H, d, 3.6 Hz, SCH); δ_F (470.4 MHz, DMSO): -107.20 (1F, br s, CF(Ph)); δ_C (125.7 MHz, DMSO) 165.1 (d, J_{C-F} 250.3 Hz), 164.6, 159.2, 138.1, 131.5 (d, J_{C-F} 9.5 Hz), 129.3, 116.1 (d, J_{C-F} 22.0 Hz), 114.3. IR (KBr ν (cm^{-1})) 3150

(NH), 1672 (CON), 1543 (thiazole ring), 1230 (CF); MS m/z (rel int.): 222 (16, M^+), 194 (13), 123 (100), 95 (44), 75 (14).

4-Chloro-N-(thiazol-2-yl)benzamide (**7d**). Yield: 195.4 mg (82%),pale brown powder, mp 216–217 °C; [Found: C, 50.45; H, 2.82; N, 11.60; $C_{10}H_7N_2OSCl$ requires C, 50.32; H, 2.96; N, 11.74%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.63; δ_H (500 MHz, DMSO) 12.72 (1H, br s, N-H-O), 8.11 (2H, d, 8.6 Hz, CH(Ph)), 7.62 (2H, d, 8.6 Hz, CH(Ph)), 7.57 (1H, d, 3.5 Hz, NCH, 7.30 (1H, d, 3.5 Hz, SCH); δ_C (125.7 MHz, DMSO) 164.7, 159.3, 137.9, 133.0, 130.5, 129.4, 129.1, 114.4. IR (KBr ν (cm^{-1})) 3152 (NH), 1671 (CON), 1552 (thiazole ring); MS m/z (rel int.): 240 (33, M^+), 238 (100, M^+), 113 (19), 111 (52), 75 (36).

4-Bromo-N-(thiazol-2-yl)benzamide (**8d**). Yield: 255.2 mg (90%), pale brown powder, mp 213–214 °C; [Found: C, 42.47; H, 2.33; N, 9.80; $C_{10}H_7N_2OSBr$ requires C, 42.42; H, 2.49; N, 9.89%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.72; δ_H (500 MHz, DMSO) 12.72 (1H, br s, N-H-O), 8.03 (2H, d, 8.5 Hz, CH(Ph)), 7.76 (2H, d, 8.5 Hz, CH(Ph)), 7.57 (1H, d, 3.5 Hz, NCH, 7.29 (1H, d, 3.5 Hz, SCH); δ_C (125.7 MHz, DMSO) 164.9, 159.3, 137.9, 132.1, 132.0, 130.7, 126.9, 114.4. IR (KBr ν (cm^{-1})) 3152 (NH), 1668 (CON), 1549 (thiazole ring); MS m/z (rel int.): 284 (17, M^+), 282 (17, M^+), 256 (16), 254 (16), 185 (100), 183 (100), 157 (32), 155 (32), 76 (23).

4-(thiazol-2-ylcarbamoyl)benzoic acid (**9d**). Yield: 230.5 mg (93%),pale brown solid, mp 332-333 °C; [Found: C, 53.27; H, 3.34; N, 11.10; $C_{11}H_8N_2O_3S$ requires C, 53.22; H, 3.25; N, 11.28%]; R_f (10% EtOAc, 90% $CHCl_3$) 0.14; δ_H (500 MHz, DMSO) 13.05 (2H, br s, N-H-O; COOH), 8.19 (2H, d, 8.3 Hz, CH(Ph)), 8.08 (2H, d, 8.3 Hz, CH(Ph)), 7.59 (1H, d, 3.6 Hz, NCH), 7.31 (1H, d, 3.6 Hz, SCH); δ_C (125.7 MHz, DMSO) 167.1, 165.2, 159.3, 137.8, 136.5, 134.5, 129.8, 128.9, 114.4. IR (KBr ν (cm^{-1})) 3186 (NH), 3079 (OH), 1674 (CO (acid), CON), 1566 (thiazole ring).

Methyl 4-((thiazol-2-yl)carbamoyl)benzoate (**10d**). Yield: 241.3 mg (92%), white crystal, mp 247–248 °C; [Found: C, 54.88; H, 3.80; N, 10.55; $C_{12}H_{10}N_2O_3S$ requires C, 54.95; H, 3.84; N, 10.68%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.53; δ_H (500 MHz, DMSO) 12.87 (1H, br s, N-H-O), 8.21 (2H, d, 8.6 Hz, CH(Ph)), 8.10 (2H, d, 8.6 Hz, CH(Ph)), 7.60 (1H, d, 3.6 Hz, NCH), 7.33 (1H, d, 3.6 Hz, SCH), 3.91 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 166.1, 165.0, 159.1, 138.3, 136.9, 133.2, 129.7, 129.1, 114.5, 53.0. IR (KBr ν (cm^{-1})) 3147 (NH), 1712 (CO (ester)), 1674 (CON), 1545 (thiazole ring), 1276 and 1111 (C-O); MS m/z (rel int.): 262 (14, M^+), 234 (20), 163 (100), 135 (22), 120 (7), 103 (12), 76 (12).

4-Acetyl-N-(thiazol-2-yl)benzamide (**11d**). Yield: 185.4 mg (75%), white powder, mp 221–222°C; [Found: C, 58.60; H, 4.00; N, 11.23; $C_{12}H_{10}N_2O_2S$ requires C, 58.52; H, 4.09; N, 11.37%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.32; δ_H (500 MHz, DMSO) 12.83 (1H, br s, N-H-O), 8.21 (2H, d, 7.2 Hz, CH(Ph)), 8.09 (2H,

d, 7.2 Hz, CH(Ph)), 7.59 (1H, br s, NCH), 7.32 (1H, br s, SCH), 2.66 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 198.2, 165.1, 158.9, 139.9, 138.2, 136.5, 129.0, 128.7, 114.5, 27.5. IR (KBr ν (cm^{-1})) 3150 (NH), 1673 (CO, CON), 1544 (thiazole ring); MS m/z (rel int.): 246 (16, M^+), 218 (25), 147 (100), 119 (18), 104 (10), 91 (20), 76 (16).

N-(Thiazol-2-yl)-4-(trifluoromethyl)benzamide (**12d**). Yield: 243.8 mg (90%), white crystal, mp 232–233 °C; [Found: C, 48.46; H, 2.51; N, 10.14; $C_{11}H_7N_2OSF_3$ requires C, 48.53; H, 2.59; N, 10.29%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.60; δ_H (500 MHz, DMSO) 12.90 (1H, br s, N-H-O), 8.28 (2H, d, 8.2 Hz, CH(Ph)), 7.93 (2H, d, 8.2 Hz, CH(Ph)), 7.59 (1H, d, 3.6 Hz, NCH, 7.33 (1H, d, 3.6 Hz, SCH; δ_F (470.4 MHz, DMSO) -61.48 (3F, s, CF_3); δ_C (125.7 MHz, DMSO) 164.8, 159.4, 137.8, 136.8, 132.5 (q, $J_{C\text{-}F}$ 31.7 Hz), 129.6, 125.9 (q, $J_{C\text{-}F}$ 3.8 Hz), 124.3 (q, $J_{C\text{-}F}$ 272.8 Hz), 114.5. IR (KBr ν (cm^{-1})) 3142 (NH), 1672 (CON), 1544 (thiazole ring), 1297, 1157 and 1109 (CF); MS m/z (rel int.): 272 (18, M^+), 244 (34), 173 (100), 145 (73).

4-Cyano-N-(thiazol-2-yl)benzamide (**13d**). Yield: 196.8 mg (86%), pale yellow powder, mp 237–238°C; [Found: C, 57.58; H, 3.20; N, 18.15; $C_{11}H_7N_3OS$ requires C, 57.63; H, 3.08; N, 18.33%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.36; δ_H (500 MHz, DMSO) 12.91 (1H, br s, N-H-O), 8.23 (2H, d, 8.1 Hz, CH(Ph)), 8.03 (2H, d, 8.1 Hz, CH(Ph)), 7.60 (1H, d, 7.5 Hz, NCH, 7.33 (1H, d, 7.5 Hz, SCH); δ_C (125.7 MHz, DMSO) 164.7, 159.5, 137.5, 137.0, 133.0, 129.4, 118.6, 115.1, 114.5. IR (KBr ν (cm^{-1})) 3161 (NH), 2227 (CN), 1671 (CON), 1547 (thiazole ring); MS m/z (rel int.): 229 (16, M^+), 201 (37), 130 (100), 102 (56), 75 (12).

2-Methoxy-N-(thiazol-2-yl)benzamide (**14d**). Yield: 191.1 mg (82%), brown crystal, mp 98–99 °C; [Found: C, 56.49; H, 4.40; N, 11.75; $C_{11}H_{10}N_2O_2S$ requires C, 56.40; H, 4.30; N, 11.96%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.59; δ_H (500 MHz, DMSO) 11.80 (1H, br s, N-H-O), 7.75 (1H, d, 6.7 Hz, CH(Ph)), 7.58 (1H, br s, CH(Ph)), 7.53 (1H, br s, NCH), 7.29 (1H, br s, SCH), 7.23 (1H, d, 7.6 Hz, CH(Ph)), 7.11 (1H, br s, CH(Ph)), 3.95 (3H, s, OCH_3); δ_C (125.7 MHz, DMSO) 164.2, 158.1, 157.6, 138.3, 133.9, 130.8, 122.1, 121.2, 114.4, 112.8, 56.6. IR (KBr ν (cm^{-1})) 3307 (NH), 1655 (CON), 1539 (thiazole ring), 1226 and 1014 (C-O); MS m/z (rel int.): 234 (7, M^+), 203 (29), 135 (100), 92 (18), 77 (28).

N-(Thiazol-2-yl)thiophene-2-carboxamide (**15d**). Yield: 193.9 mg (92%), white crystal, mp 158–159°C; [Found: C, 45.77; H, 2.11; N, 13.24; $C_8H_6N_2OS_2$ requires C, 45.72; H, 2.08; N, 13.34%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.59; δ_H (500 MHz, DMSO) 12.75 (1H, br s, N-H-O), 8.25 (1H, br s, CH(thiophene)), 7.97 (1H, d, 4.9 Hz, CH(thiophene)), 7.57 (1H, d, 3.5 Hz, NCH), 7.29 (1H, d, 3.5 Hz, SCH), 7.26 (1H, dd, 4.9 Hz, 3.9 Hz, CH(thiophene)); δ_C (125.7 MHz, DMSO) 160.2, 158.9, 138.2, 137.9, 133.9, 131.2, 129.0, 114.3. IR (KBr ν (cm^{-1})) 3153 (NH), 1655 (CON), 1544 (thiazole ring); MS m/z (rel int.): 210 (22, M^+), 182 (9), 111 (100), 83 (10).

3-Methyl-N-(1,3,4-thiadiazol-2-yl)benzamide (**16a**). Yield: 166.1 mg (76%), pale brown powder, mp 185-186 °C; [Found: C, 54.61; H, 4.22; N, 19.01; $C_{10}H_9N_3OS$ requires C, 54.78; H, 4.14; N, 19.16%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.31; δ_H (500 MHz, DMSO) 13.01 (1H, br s, NH), 9.25 (1H, s, CH(thiadiazole)), 7.98 (1H, s, CH(Ph)), 7.93 (1H, d, 7.3 Hz, CH(Ph)), 7.50-7.44 (2H, m, CH(Ph)), 2.41 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 165.8, 159.9, 149.4, 138.5, 134.0, 132.1, 129.4, 129.0, 126.0, 21.4. IR (KBr ν (cm^{-1})) 3170 (NH), 1663 (CON), 1524 and 1309 (thiadiazole ring); MS m/z (rel int.): 219 (8, M^+), 218 (10), 191 (13), 119 (100), 91 (58), 65 (19).

3-Cyano-N-(1,3,4-thiadiazol-2-yl)benzamide (**17a**). Yield: 210.7 mg (92%), pale brown powder, mp 305-306 °C; [Found: C, 52.30; H, 3.75; N, 24.23; $C_{10}H_6N_4OS$ requires C, 52.17; H, 3.63; N, 24.33%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.15; δ_H (500 MHz, DMSO) 13.29 (1H, br s, NH), 9.28 (1H, s, CH(thiadiazole)), 8.56 (1H, s, CH(Ph)), 8.39 (1H, d, 7.9 Hz, CH(Ph)), 8.14 (1H, d, 7.9 Hz, CH(Ph)), 7.80 (1H, t, 7.9 Hz, CH(Ph)); δ_C (125.7 MHz, DMSO) 164.3, 159.8, 149.7, 136.6, 133.5, 133.4, 132.7, 130.5, 118.5, 112.3. IR (KBr ν (cm^{-1})) 3152 (NH), 2233 (CN), 1670 (CON), 1537 and 1325 (thiadiazole ring); MS m/z (rel int.): 230 (14, M^+), 229 (29), 202 (21), 130 (100), 102 (58), 75 (15).

3-Methyl-N-(1,3-thiazol-2-yl)benzamide (**16d**). Yield: 170.3 mg (78%), brown solid, mp 143-144 °C; [Found: C, 60.50; H, 4.74; N, 12.72; $C_{11}H_{10}N_2OS$ requires C, 60.53; H, 4.62; N, 12.83%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.67; δ_H (500 MHz, DMSO) 12.58 (1H, br s, NH), 7.95 (1H, s, CH(Ph)), 7.90 (1H, d, 7.3 Hz, CH(Ph)), 7.57 (1H, d, 3.7 Hz, CH(thiazole)), 7.47-7.42 (2H, m, CH(Ph)), 7.29 (1H, d, 3.7 Hz, CH(thiazole)), 2.41 (3H, s, CH_3); δ_C (125.7 MHz, DMSO) 165.6, 159.2, 138.4, 138.1, 133.6, 132.6, 129.1, 128.9, 125.7, 114.3, 21.4. IR (KBr ν (cm^{-1})) 3152 (NH), 1673 (CON), 1540 and 1318 (thiazole ring); MS m/z (rel int.): 218 (15, M^+), 190 (11), 119 (100), 91 (54), 65 (19).

3-Cyano-N-(1,3-thiazol-2-yl)benzamide (**17d**). Yield: 178.9 mg (78%), brown powder, mp 223-224 °C; [Found: C, 57.52; H, 3.14; N, 18.20; $C_{11}H_7N_3OS$ requires C, 57.63; H, 3.08; N, 18.33%]; R_f (20% EtOAc, 80% $CHCl_3$) 0.40; δ_H (500 MHz, DMSO) 12.86 (1H, br s, NH), 8.54 (1H, t, 1.5 Hz, CH(Ph)), 8.37 (1H, dt, 7.8 Hz, 1.5 Hz, CH(Ph)), 8.11 (1H, d, 7.8 Hz, CH(Ph)), 7.78 (1H, t, 7.8 Hz, CH(Ph)), 7.60 (1H, d, 3.7 Hz, CH(thiazole)), 7.33 (1H, d, 3.7 Hz, CH(thiazole)); δ_C (125.7 MHz, DMSO) 164.2, 159.3, 137.7, 136.2, 134.1, 133.3, 132.4, 130.4, 118.6, 114.6, 112.2. IR (KBr ν (cm^{-1})) 3158 (NH), 2227 (CN), 1670 (CON), 1543 and 1324 (thiazole ring); MS m/z (rel int.): 229 (18, M^+), 201 (29), 130 (100), 102 (59), 75 (13).

N-(1,3-thiazol-2-y)lphthalimide (**18d**): MS m/z (rel int.): 230 (100, M^+), 202 (10), 172 (6), 104 (62), 76 (45).

2-Iodo-N-(1,3-thiazol-2-yl)benzamide (**18d'**): MS m/z (rel int.): 330 (9, M^+), 302 (7), 231 (100), 203 (79), 105 (8), 76 (34).

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