Bioorganic & Medicinal Chemistry 19 (2011) 7318–7337

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Arylcyanoacrylamides as inhibitors of the Dengue and West Nile virus proteases

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ARTICLE INFO

Article history:
Received 20 September 2011
Revised 18 October 2011
Accepted 19 October 2011
Available online 25 October 2011

Keywords:
Dengue virus
West Nile virus
Flavivirin
NS2B-NS3 protease
Nitrile
Aldol condensation

ABSTRACT

The 3-aryl-2-cyanoacrylamide scaffold was designed as core pharmacophore for inhibitors of the Dengue and West Nile virus serine proteases (NS2B-NS3). A total of 86 analogs was prepared to study the structure–activity relationships in detail. Thereby, it turned out that the electron density of the aryl moiety and the central double bond have a crucial influence on the activity of the compounds, whereas the influence of substituents of the amide residue is less relevant. The *para*-hydroxy substituted analog was found to be the most potent inhibitor in this series with a K_i-value of 35.7 μM at the Dengue and 44.6 μM at the West Nile virus protease. The aprotinin competition assay demonstrates a direct interaction of the inhibitor molecule with active centre of the Dengue virus protease. The target selectivity was studied in a counterscreen with thrombin and found to be 2.8:1 in favor of DEN protease and 2.3:1 in favor of WNV protease, respectively.

1. Introduction

Dengue fever, West Nile fever and other infectious diseases caused by flaviviruses are of growing interest in pharmaceutical research. The number of flaviviral infections, especially in the northern hemisphere, has increased in the last decade.[1] Infections with the Dengue (DEN) or West Nile viruses (WNVs) are currently neither preventable by immunization nor treatable by chemotherapeutics. Against this background, the viral serine protease NS2B-NS3 is an attractive target to develop new therapeutics against DEN, WNV and other flaviviral infections.[2] Because of its role in the posttranslational processing of the viral polyprotein, the NS2B-NS3 protease is essential for the viral life cycle and replication mechanism. Therefore, inhibition of this enzyme is expected to interfere with virus replication in the human host cells. Primarily for the DEN protease there are currently no reports of drug-like small molecule inhibitors with sufficient potency for advanced preclinical studies.

The oxygen nucleophile in serine and threonine proteases can be targeted by various electrophiles, which results in a covalent-reversible or covalent-irreversible inhibition of the enzyme. Quite frequently, peptidyl-aldehydes are used to inhibit serine proteases (also DEN and WNV) in the context of crystallographic studies.[3] Other electrophiles include halomethylketones and similar functional groups. These electrophiles can be useful for in vitro studies, but are too reactive for any type of advanced biological experiment or clinical use. Fortunately, the reactivity of the electrophile can be tuned to match the requirements of the target while maintaining a high degree of selectivity and stability. It has therefore been possible to apply the strategy of covalent inhibition of serine proteases in the development of inhibitors of the proteasome (bortezomib, a boronic acid derivative),[4] hepatitis C virus protease (telaprevir and other ketoamides),[5] and most recently dipeptidyl peptidase IV (vildagliptin and other nitriles).[6] These prominent examples clearly demonstrate that the integration of suitable electrophiles into the design considerations for inhibitors of serine proteases, is an advantageous approach that has considerable clinical significance.

We previously identified the cinnamyl moiety as a valuable fragment which, in connection with the ketoamide electrophile, yields potent inhibitors of the DEN and WNV proteases.[7] This work also demonstrated the benefit of a possible additional covalent mode of inhibition to obtain inhibitors with sufficient potency and selectivity whose antiviral activity could also be shown in a cell-culture experiment of DEN replication.

The design approach for the inhibitors described in the present work was to combine the promising cinnamyl moiety with an alternative electrophile, the nitrile group. The resulting 3-aryl-2-cyanoacrylamides, whose general chemical structure is shown in Figure 1, are drug-like compounds. We assume that the cinnamyl structure, with an aryl substituent in R^1 and a proton or small aliphatic substituent in R^2, interacts with the S_1 pocket of the NS2B-NS3 protein. The nitrile may act as an electrophilic trap for the catalytic serine to induce a dipole-dipole interaction or to create a reversible covalent bond between inhibitor and protease (Fig. 1).[8] An amide residue serves to complete a peptidomimetic structure and may interact with the S_1' recognition elements of the enzyme.

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doi:10.1016/j.bmc.2011.10.061

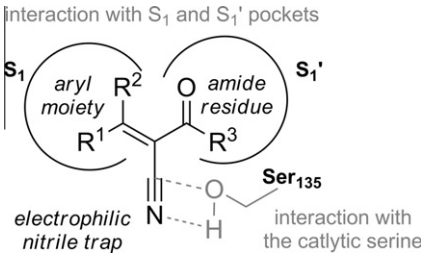


Figure 1. Pharmacophoric model and possible molecular interactions. R^1 = aryl, R^2 = H or alkyl, R^3 = amine, S_1 and S_1' describe enzyme pockets, Ser_{135} is the serine residue of the catalytic triad.

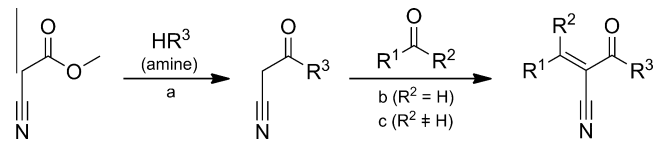
2. Results and discussion

2.1. Synthesis

For the synthesis of 3-aryl-2-cyanoacrylamides a one- or two-step approach was used as shown in Scheme 1. If unsubstituted 2-cyanoacetamide was used ($R^3 = NH_2$), step (b) in Scheme 1 was employed to obtain 3-aryl-2-cyanoacrylamide derivatives. Otherwise the N-substituted 2-cyanoacetamide had to be synthesized in a previous reaction step from methyl 2-cyanoacetate in an efficient direct treatment with the required amine without solvent at room temperature (step (a) in Scheme 1).[9] In some cases the carbonyl component (mostly aromatic aldehydes) had to be synthesized from other, commercially available compounds. The aldol condensation with aromatic aldehydes was carried out in methanol with *N*-methylpiperazine as catalyst leading in a mostly selective and quantitative fashion to the *trans*-olefin product. The *trans*-geometry of the products was verified by the crystal structure of compound **14**.[10] Only in a few cases a small amount of *cis*-olefin was obtained (detected by LC–MS). However, the use of ketones instead of aldehydes gave mixtures of *cis* and *trans* isomers (Table 1). By X-ray crystal structural analysis of compound **3b**[10] and NMR correlation, we were able to determine the absolute structure of all compounds. The approach towards the cyclic *N*-arylamines **55**–**63**, **70** and **71** depends on the desired *N*-aryl-connection in *ortho*, *meta* or *para* position. The *para*-substituted compounds **55**–**60** are available via a one pot/three component reaction of the corresponding cyanoacetamide, the 4-fluorobenzaldehyde and the secondary cyclic amine as shown in Scheme 2.[11] We were also able to transfer this reaction to 2-fluorobenzaldehyde to obtain the *ortho*-substituted derivative **63**. Pentafluorobenzaldehyde as starting material for derivative **61** reacted selectively in *para*-position at room temperature. The *meta*-substituted derivative **62** and the heterocyclic compounds **70** and **71** were available by a copper catalyzed coupling reaction of the cyclic amine with the corresponding bromoarylaldehyde.[12]

The aromatic amide derivatives **64**–**66** were available by amide coupling reaction of the desired amine and the aromatic carboxylic acids **37**–**39**.

The double bond of compounds **40**, **20**, **57**, **54**, **69** and **67** could be reduced selectively with sodium borohydride in methanol to obtain the saturated analogs **76**–**81**.



Scheme 1. Synthetic approach for simple 3-aryl-2-cyanoacrylamides. Reagents and conditions: (a) no solvent, rt, 20 h; (b) *N*-methylpiperazine, MeOH, rt, 20 h; (c) NH_4OAc/AcOH, toluene, reflux, 2–5 h.

2.2. Structure–activity relationships

The compounds were screened against the DEN and WNV proteases (NS2B-NS3) and thrombin (as a counterscreen for selectivity studies). The results at the different targets are shown in Table 1. The best activities against DEN and WNV proteases were observed for the *para*-hydroxy derivatives **21** and **23**–**27**. Some of those derivatives show inhibition values of more than 50% at 50 μM inhibitor and substrate concentration at DEN and WNV proteases. In general it can be observed that an aromatic system with an electron withdrawing group resulted in low activity, whereas electron donor groups like hydroxy or amine substituents gave best results. *Para*-substituted aromatic systems showed better activity than *meta*-substituted and *para*,*meta*-disubstituted systems. There is a loss of nearly 40% of activity if the hydroxy substituent is positioned in *meta* (**28**) and not in *para* position (**21**). Various halogen, amine or methoxy substituents in the *para*-position were unable to maintain the activity of the hydroxy-substituted analogs. However, non-functionalized aliphatic chains like methyl (**5**) or isopropyl (**6**–**9**) gave satisfying results. Various heterocycles, also shown in Table 1, did not result in increased activity. In contrast to the importance of the aryl moiety we only found a limited influence of the amide residue (Table 1). Attempts to mimic the substrate more closely by attaching a serine residue (for S_1' pocket interaction) in compounds **16** and **17** were unsuccessful. Apparently, the S_1 and S_2 pockets are most important for molecular recognition at the DEN and WNV proteases. We assume that the aryl moiety interacts with the S_1 pocket of the enzyme, probably combined with an interaction of the electrophilic nitrile and the adjacent catalytic serine (Fig. 1).

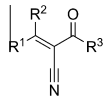
An enlargement of inhibitor molecules towards the S_2 pocket can be expected to increase the activity and selectivity of the compounds. Therefore, we synthesized molecules which are able to create additional interactions in the direction of the S_2 pocket. An extension of the compounds without modification of the underlying arylacrylonitrile pharmacophore is only possible at the olefinic R^2 position or at the aromatic system. Non-hydrogen substituents at R^2 caused a pronounced decrease in activity. An additional methyl group at R^2 (as in compound **22a**) leads to a decrease of activity of more than 30% in comparison to **21** at all targets. The geometry of the double bond is apparently not critical in all tested R^1- and R^2-disubstituted compounds (**2a**/**b**, **3a**/**b**, **4a**/**b**, **22a**/**b**).

Various extensions of the aromatic system were also evaluated. The *para*-benzyloxy substituted derivative **72** was an initial test for a possible occupation of the S_2 pocket. This attempt resulted in an inactive molecule at both tested viral targets in comparison to its analog **32**. Next we evaluated cyclic systems with restricted flexibility. For this we synthesized substituted cyclic *N*-arylamines (**55**–**63**).

The evaluation of the cyclic *N*-arylamine derivatives showed, in accordance with the results described before, that *para*-substituted aromatic systems gave best activity results, whereas *ortho*- or *meta*-substitution resulted in decreased activities. Best results showed compounds **59** and **60** with good activities at the DEN and WNV protease. The perfluorinated compound **61** shows a decline in activity in comparison to the non-fluorinated derivatives **59** and **60**. This is also in correlation with the results described before for the simple substituted aryl moieties. In general, it therefore seems obvious that an aromatic system with high electron density is needed for an effective interaction with the target. The 4-hydroxy substituted derivatives remained the most active compounds in this series. Different aromatic amide derivatives **64**–**66** were not able to increase activity. The same unsatisfying results were observed with the less drug-like double-unsaturated compounds **67**–**69**.

Because of the apparent structural analogy of the explored compounds with the known catecholamine *O*-methyl transferase

Table 1
Activity of substituted arylacrylamides against the Dengue and West Nile virus proteases in comparison to thrombin.



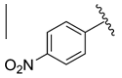
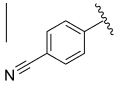
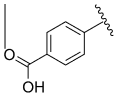
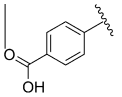
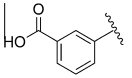
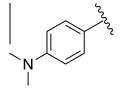
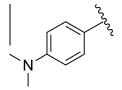
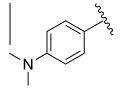
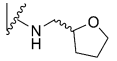
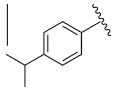
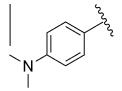
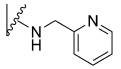
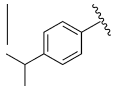
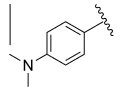
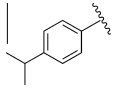
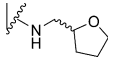
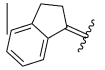
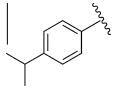
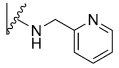
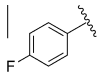
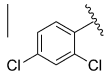
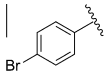
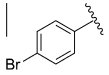
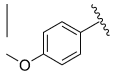
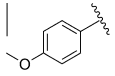
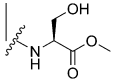
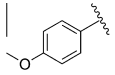
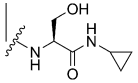
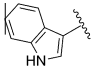
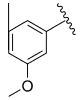
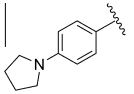
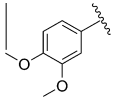
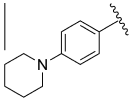
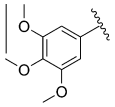
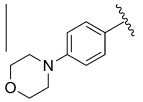
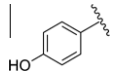
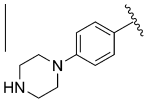
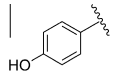
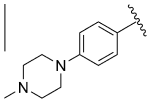
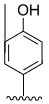
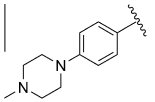
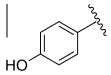
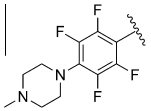
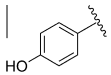
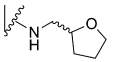
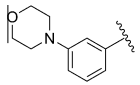
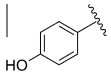
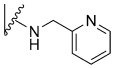
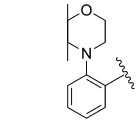
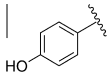
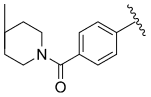
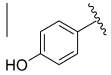
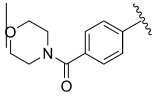
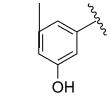
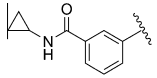
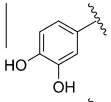
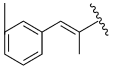
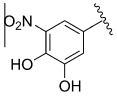
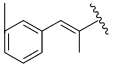
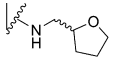
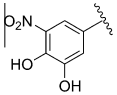
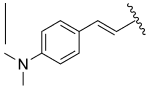
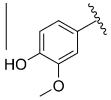
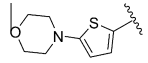
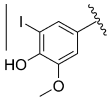
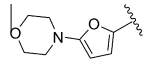
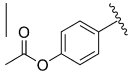
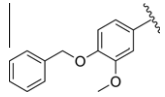
No.	R^1	R^2	R^3	DEN[a]	WNV[b]	F2[c]	No.	R^1	R^2	R^3	DEN[a]	WNV[b]	F2[c]
1		H	NH_2	15.0 ± 1.6	9.3 ± 4.9	12.5 ± 5.2	**35**		H	NH_2	n.i.	10.5 ± 2.2	n.i.
2a		Me	NH_2	n.i.	13.7 ± 1.1	7.3 ± 3.9	**36**		H	NH_2	13.3 ± 1.9	20.0 ± 6.3	10.6 ± 5.1
2b	Me		NH_2	9.0 ± 2.1	18.4 ± 3.2	9.7 ± 2.6	**37**		H	NH_2	17.1 ± 1.6	23.8 ± 2.5	13.2 ± 5.1
3a		*i*-Pr	NH_2	n.i.	n.i.	16.7 ± 9.7	**38**		H		20.0 ± 1.2	31.0 ± 1.1	15.9 ± 1.5
3b	*i*-Pr		NH_2	n.i.	13.8 ± 4.6	10.1 ± 2.9	**39**		H		20.2 ± 2.2	20.1 ± 5.2	11.9 ± 2.4
4a		Pr	NH_2	6.7 ± 1.8	15.3 ± 4.0	11.1 ± 1.1	**40**		H	NH_2	35.1 ± 2.4	46.0 ± 0.9	21.6 ± 0.7
4b	Pr		NH_2	7.6 ± 2.7	16.0 ± 1.7	6.9 ± 0.9	**41**		H		22.6 ± 0.8	33.2 ± 3.1	23.7 ± 2.5
5		H	NH_2	32.2 ± 5.4	22.8 ± 3.7	n.i.	**42**		H		23.3 ± 3.8	28.1 ± 3.7	19.8 ± 3.5
6		H	NH_2	23.0 ± 3.3	24.6 ± 3.3	19.4 ± 5.2	**43**		H		25.3 ± 4.5	21.3 ± 3.5	n.i.
7		H		18.2 ± 4.5	22.2 ± 4.2	17.9 ± 5.4	**44**		H		43.3 ± 2.7	38.1 ± 2.0	25.1 ± 2.9
8		H		28.2 ± 1.2	46.3 ± 1.0	14.4 ± 6.0	**45**			NH_2	23.2 ± 3.1	24.1 ± 2.5	10.3 ± 2.1
9		H		24.9 ± 1.3	39.5 ± 1.7	11.6 ± 4.1	**46**		H	NH_2	n.i.	n.i.	n.i.
10		H	NH_2	22.1 ± 2.4	21.7 ± 0.8	8.7 ± 1.2	**47**			NH_2	n.i.	n.i.	n.i.

Table 1 (*continued*)

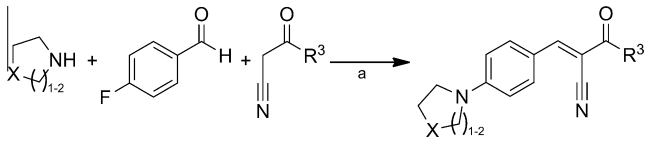
No.	R^1	R^2	R^3	DEN[a]	WNV[b]	F2[c]	No.	R^1	R^2	R^3	DEN[a]	WNV[b]	F2[c]
11		H	NH_2	22.5 ± 7.4	16.0 ± 2.1	7.9 ± 5.5	**48**		H	NH_2	28.4 ± 7.9	23.9 ± 2.5	15.7 ± 3.7
12		H	NH_2	14.7 ± 2.3	10.7 ± 3.0	8.5 ± 2.1	**49**		H	NH_2	22.0 ± 7.3	23.8 ± 3.8	27.9 ± 1.3
13		H	NH_2	11.6 ± 2.0	15.9 ± 2.0	13.6 ± 8.2	**50**		H	NH_2	20.2 ± 2.9	19.2 ± 0.8	26.3 ± 0.8
14		H		10.9 ± 0.6	22.6 ± 2.1	n.i.	**51**		H		n.i.	10.5 ± 2.1	17.9 ± 2.2
15		H	NH_2	19.7 ± 1.0	23.4 ± 0.9	16.7 ± 7.8	**52**		H	NH_2	18.4 ± 1.4	19.3 ± 1.0	10.1 ± 6.9
16		H		20.3 ± 1.3	21.1 ± 1.5	21.4 ± 4.7	**53**		H		15.6 ± 3.7	23.9 ± 3.7	26.9 ± 0.7
17		H		23.0 ± 1.7	31.7 ± 2.8	23.3 ± 6.0	**54**		H	NH_2	23.7 ± 0.6	33.4 ± 2.8	16.4 ± 2.0
18		H	NH_2	16.3 ± 5.8	12.3 ± 1.7	9.6 ± 7.6	**55**		H	NH_2	24.3 ± 8.7	24.6 ± 2.1	17.7 ± 5.8
19		H	NH_2	19.2 ± 2.7	22.0 ± 2.2	20.0 ± 3.3	**56**		H	NH_2	14.0 ± 4.1	24.2 ± 5.4	20.0 ± 7.2
20		H	NH_2	15.6 ± 2.9	19.3 ± 2.5	17.8 ± 6.5	**57**		H	NH_2	28.2 ± 5.8	35.3 ± 3.5	19.2 ± 3.1
21		H	NH_2	51.7 ± 1.0	55.0 ± 4.6	24.4 ± 4.9	**58**		H	NH_2	28.6 ± 3.9	45.0 ± 1.8	26.1 ± 6.5
22a		Me	NH_2	16.8 ± 1.4	21.9 ± 5.7	n.i.	**59**		H	NH_2	32.3 ± 1.1	40.9 ± 2.4	22.0 ± 3.0
22b	Me		NH_2	13.2 ± 1.6	22.7 ± 1.9	n.i	**60**		H		37.4 ± 1.1	47.8 ± 2.5	21.8 ± 3.0

(*continued on next page*)

Table 1 (*continued*)

No.	R^1	R^2	R^3	DEN[a]	WNV[b]	F2[c]	No.	R^1	R^2	R^3	DEN[a]	WNV[b]	F2[c]
23		H		44.7 ± 0.7	57.3 ± 5.8	18.8 ± 1.7	**61**		H	NH_2	19.2 ± 2.6	31.9 ± 2.7	28.5 ± 3.8
24		H		46.4 ± 0.1	44.4 ± 1.0	16.8 ± 0.6	**62**		H		18.5 ± 4.8	20.5 ± 1.7	9.7 ± 4.6
25		H		46.6 ± 4.9	41.8 ± 1.7	18.9 ± 3.5	**63**		H	NH_2	10.4 ± 3.0	7.7 ± 2.1	7.4 ± 0.3
26		H		32.2 ± 7.9	49.9 ± 4.9	18.0 ± 1.9	**64**		H	NH_2	22.3 ± 8.5	24.0 ± 6.0	n.i.
27		H		35.4 ± 2.7	35.1 ± 1.7	20.8 ± 7.7	**65**		H		22.9 ± 2.2	23.0 ± 0.3	9.0 ± 1.3
28		H	NH_2	15.7 ± 1.8	18.1 ± 2.4	9.8 ± 9.7	**66**		H		10.8 ± 1.8	19.1 ± 1.8	8.0 ± 2.9
29		H	NH_2	34.9 ± 2.0	28.8 ± 1.7	18.4 ± 9.7	**67**		H	NH_2	30.2 ± 1.1	34.6 ± 0.8	20.5 ± 1.3
30		H	NH_2	24.3 ± 1.7	28.2 ± 0.4	22.5 ± 2.0	**68**		H		36.8 ± 3.4	30.1 ± 2.6	28.7 ± 2.1
31		H		21.0 ± 1.7	32.4 ± 0.7	21.9 ± 6.2	**69**		H		10.3 ± 0.9	17.1 ± 1.3	16.2 ± 7.8
32		H	NH_2	43.2 ± 6.3	42.9 ± 3.6	17.4 ± 4.7	**70**		H	NH_2	23.2 ± 3.8	29.1 ± 1.4	38.6 ± 8.1
33		H	NH_2	30.5 ± 3.1	43.8 ± 3.7	23.0 ± 3.7	**71**		H		10.5 ± 5.0	24.0 ± 0.5	47.0 ± 4.0
34		H	NH_2	43.1 ± 0.1	28.8 ± 3.9	24.4 ± 6.7	**72**		H	NH_2	n.i.	n.i.	16.0 ± 2.4

[a] % Inhibition of the Dengue Virus (DEN) NS2B-NS3 protease (enzyme: 100 nM; inhibitor 50 μM; substrate 50 μM).
[b] % Inhibition of the West Nile Virus (WNV) NS2B-NS3 protease (enzyme: 150 nM; inhibitor 50 μM; substrate 50 μM).
[c] % Inhibition of thrombin (F2) (enzyme: 10 nM; inhibitor 25 μM; substrate 50 μM).



Scheme 2. Three component reaction. Reagents and conditions: X = CH_2, O, NH, NMe: (a) EtOH, microwave: 20 min, 160 °C.

(COMT) inhibitor entacapone, we also tested this substance. Similar to all our explored compounds bearing a hydroxy function in *para*-position, entacapone (**31**) shows activity at both tested viral targets. However, the second hydroxy and the nitro group in *meta*-position caused a loss of activity in comparison to the only *para*-hydroxy substituted derivatives.

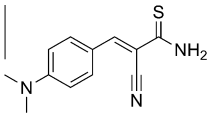
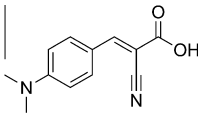
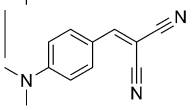
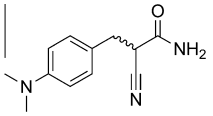
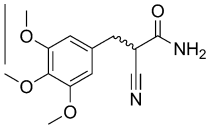
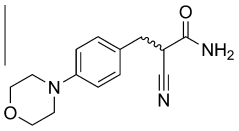
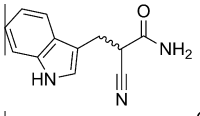
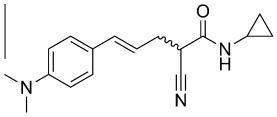
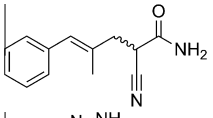
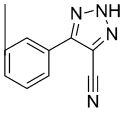
In addition to the aryl moiety and the amide residue we explored alternative structures of the acrylamide skeleton. For this we synthesized different analogs which are shown in Table 2. A replacement of the carbonyl oxygen by sulfur leads to the thioacrylamide compound **73** and to a total loss of activity at the tested viral proteases. The implementation of a second nitrile function in compound **75** causes a near-complete loss of activity. The acrylic acid **74** shows activity in a similar range as the analogous acrylamide compound **40**. One may speculate about the necessity of a hydrogen bond between the amide or acid residue and the target protein. This could explain the observation that the double nitrile derivative **75** is not very potent, whereas its carboxylic acid analog **74** shows good activity. The acid may in this case act as a bioisosteric replacement of the unsubstituted amide functionality.

In addition, we explored the necessity of the double bond by selective reduction. In nearly all cases we observed a significant dependence of the activity on the acrylamide double bond (compounds **76**–**81**, Table 2).

Although the double bond is very important for activity, there was no evidence for a 1,4-electrophilic attack at the catalytic serine. To exclude a potential 'Michael reactivity' of the α,β-unsaturated system, the most active compounds **8**, **21**, **40** and **71** were incubated with glutathione as a representative biological nucleophile and the resulting mixture was studied by HPLC. These experiments clearly indicated that the compounds are inert to 1,4-addition (data not shown).

The planar geometry of the unsaturated side-chain with limited degrees of rotational freedom appears to be important for the non-covalent recognition of the inhibitor. Only at compound **80** we found a satisfying activity at the WNV protease. This derivative carries an amine substituent in *para*-position and double bond in benzyl position, without a Michael-reactive functionality. This further verifies the conclusion that a Michael-reactive group is not a critical necessity in this compound class. Finally, the exotic derivative **82** did not show relevant activity.

Table 2
Activity of derivatives without acrylamide structure.

No.	Structure	DEN[a]	WNV[b]	F2[c]
73		n.i.	n.i.	13.7 ± 3.2
74		38.7 ± 1.1	46.5 ± 1.5	13.3 ± 3.2
75		8.7 ± 3.8	8.8 ± 3.1	16.3 ± 3.7
76		7.1 ± 3.2	16.2 ± 2.0	n.i.
77		n.i.	n.i.	n.i.
78		n.i.	7.9 ± 3.8	n.i.
79		n.i.	n.i.	n.i.
80		9.0 ± 2.8	37.0 ± 2.1	6.7 ± 3.5
81		n.i.	n.i.	n.i.
82		n.i.	11.2 ± 1.2	n.i.

[a] % Inhibition of the Dengue Virus (DEN) NS2B-NS3 protease (enzyme 100 nM; inhibitor 50 μM; substrate 50 μM).
[b] % Inhibition of the West Nile Virus (WNV) NS2B-NS3 protease (enzyme 150 nM; inhibitor 50 μM; substrate 50 μM).
[c] % Inhibition of thrombin (F2) (enzyme 10 nM; inhibitor 25 μM; substrate 50 μM).

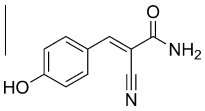
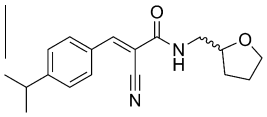
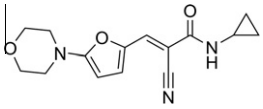
2.3. K_i-values, target selectivities and aprotinin competition assay

The evaluation at the DEN and WNV NS2B-NS3 proteases was performed using an established fluorescence assay with an internally quenched FRET substrate as described by Steuer et al.[13] For the initial exploration of the new compounds and to search for lead structures, the evaluation was usually restricted to single-concentration experiments, performed in triplicate (percentage of inhibition at [inhibitor] = 50 μM). Selected compounds with pronounced activity or selectivity were assayed in more detail. Table 3 shows the K_i-values and target selectivities of these compounds.

The most active compound **21** has a K_i-value of 35.7 μM at DEN and 44.6 μM at WNV protease. The seeming contradiction between percentage inhibition against DEN and WNV protease (Table 1) and the respective K_i-values (Table 3) can be explained by a lower K_m-value for the substrate of DEN protease. Compound **21** shows selectivity for the flaviviral proteases. In comparison to thrombin the selectivity ratio for this compound was 2.8:1 in favor of DEN protease and 2.3:1 of WNV protease respectively. Quite interestingly, compound **71** was identified as a thrombin inhibitor with a K_i-value in the low micromolar range for thrombin and very low affinity for the flaviviral proteases.

The K_i-value of compound **21** at the DEN protease is in the range of various published peptidyl-aldehyde inhibitors for this target.[3] Other non-peptidic inhibitors, like the recently published anthracene derivatives from Tomlinson et al., show activities in the micromolar range.[14] There might be a general difficulty to create

Table 3
K_i-values and target selectivities of selected compounds.

No.	Structure	K_i DEN[a] (μM)	K_i WNV[b] (μM)	K_i F2[c] (μM)
21		35.7	44.6	102
8		98.1	101	165
71		184	>200	23.4

[a] K_i-value against DEN protease.
[b] K_i-value against WNV protease.
[c] K_i-value against thrombin (F2).

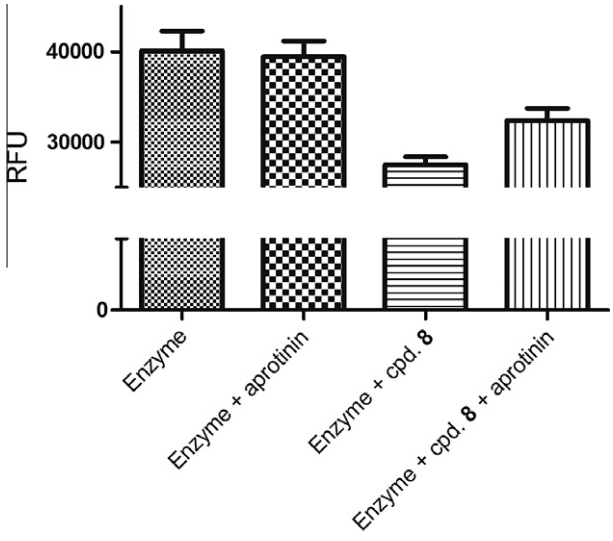


Figure 2. Aprotinin assay results of compound **8**.

high affinities with small molecule inhibitors at the DEN protease target.

The aprotinin competition assay described by Bodenreider et al. can be used to identify compounds that bind to the active site of DEN protease.[15] The intrinsic fluorescence of Trp_{50}, which is located near the transition of S_1 to S_2 pocket is quenched by UV-absorbing compounds binding to the active site. The fluorescence of Trp_{50} is partially restored if the compounds are displaced by the known competitive inhibitor aprotinin. Because of its advantageous spectroscopic properties (no inherent fluorescence at relevant wavelength and an absorption maximum near 330 nm), compound **8** with a K_i-value of 98.1 μM was used for this experiment. The results are shown in Figure 2 and indicate that aprotinin can at least partially displace compound **8** from the active site of the enzyme. This indicates a direct interaction of the inhibitor **8** with the catalytic center of the protein.

To exclude the possibility of an unspecific or promiscuous binding mode, the solutions (100 μM) of some of the most potent inhibitors in KH_2PO_4 buffer (pH 7) were analyzed by dynamic light scattering (data not shown), without any hints of aggregate formation. In addition, the compounds were practically inactive against a number of other, unrelated enzyme targets that are routinely tested in our laboratory (*Escherichia coli* methionine aminopeptidase, *Homo sapiens* methionine aminopeptidase 1, *E. coli* MurA).

3. Conclusion

3-Aryl-2-cyanoacrylamides were discovered as a new class of nitrile-containing inhibitors of the DEN and WNV NS2B-NS3 proteases. The most relevant structural features for high activity are a *para*-substituted aromatic system with high electron density, an amide or acid residue and a planar molecule geometry. Consequently, the most active molecule was the hydroxy derivative **21** with affinities in the range of other known inhibitor classes, mainly for the DEN target with a K_i-value of 35.7 μM. With a very low molecular weight, these compounds have a high ligand efficiency (LE = 23.6 for compound **21**)[16] and the potential to become lead structures for further development. With respect to selectivity, compound **21** has pronounced affinity towards the viral targets, whereas compound **71** shows activity against thrombin but only marginal activity at the viral enzymes. The latter compound may have some relevance for the development of thrombin inhibitors. Future work will aim at the development of inhibitors that bind to additional substrate recognition sites, in particular the S_2–S_4 pockets of the protease, to increase the potency and selectivity.

4. Experimental section

4.1. Biological methods

4.1.1. Substrate synthesis

The internally quenched DEN NS2B-NS3 protease substrate Abz-NleKRRS-3-(NO_2)Y was synthesized by solid-phase synthesis on Rink amide resin according to the Fmoc-protocol. It was purified by preparative HPLC using an ÄKTA Purifier, GE Germany, with a RP-18 chromatography column (Lobar, Merck, Germany, 40–63 μm, 25 × 310 mm). The mobile phase consisted of MeOH/0.1% TFA and H_2O/0.1% TFA following a gradient of 20–100% MeOH in water with a flow rate of 1.5 ml/min. The internally quenched substrate for the WNV assay (Abz-GLKRGG-3-(NO_2)Y) was synthesized and purified as described above. The purity of both substrates was assessed by HPLC and found to be higher than 95%. The identity was confirmed by MALDI-TOF-MS.

4.1.2. Expression and purification of DEN and WNV proteases

The DEN NS2B-NS3 gene, with the hydrophilic cofactor NS2B connected to the protease domain NS3pro via a flexible glycine linker, was synthesized by a commercial supplier. The expression plasmid pET28a (Novagen) with the inserted gene was used to transform *E. coli* BL 21 λ (DE3) cells. Overnight cultures of the

transformed cells were grown at 37 °C in standard LB-medium containing 50 μg/ml kanamycin. After the OD of 0.6–0.8 at 600 nm was reached, the expression was induced by addition of IPTG to a final concentration of 1 mM. The cells were grown at 30 °C for further 4 h and then collected by centrifugation at 4500 *g*. The pellet was resuspended in buffer A (lysis buffer: 50 mM Tris–HCl pH 7.9, 100 mM NaCl, 5% glycerol and 5 mM imidazole) and passed through a cell disruptor (One Shot, Constant Systems). Afterwards the solution was centrifuged at 18,500*g* and 4 °C for 40 min. The supernatant was then purified by Ni^{2+}-affinity chromatography. The protein was eluted by increasing the imidazole concentration from 5 mM to 250 mM. Stocks of purified protein were stored at −70 °C in 100 mM Tris–HCl pH 7.9, 50 mM NaCl and 50% glycerol. The expression and purification protocol for the WNV protease was similar to the one given for DEN.

4.1.3. Flourimetric DEN and WNV protease assay

The DEN protease assay was performed as described previously (Steuer et al.).[13] In short, continuous enzymatic assays were performed on a BMG Labtech Fluostar OPTIMA microtiter fluorescence plate reader using black 96 well V-bottom plates from Greiner. The excitation wavelength was 320 nm and the emission was monitored at 405 nm. The inhibitor concentration was 50 μM. The inhibitors were preincubated for 15 min with the enzyme (100 nM). Afterwards, the reaction was initiated by the addition of the substrate to a final concentration of 50 μM. The activity of the enzyme was determined as the slope per second (RFU/s) and monitored for 15 min. Experiments were performed in triplicate ($n = 3$) and the experimental values were averaged. The WNV protease assay was performed in analogy to the DEN protease assay. Final concentration of the enzyme was 150 nM.

4.1.4. Thrombin assay

The thrombin assay was performed as a continuous fluorimetric assay on a BMG Labtech Fluostar OPTIMA microtiter fluorescence plate reader. The excitation wavelength was 355 nm and the emission wavelength was 460 nm. The protease was assayed against the substrate Boc-VPR-AMC (Bachem, Germany). The final concentrations of the enzyme and substrate were 10 and 50 μM respectively. The inhibitors were preincubated with the enzyme for 15 min at a concentration of 25 μM. The cleavage reaction was initiated by addition of the substrate. The assay buffer consisted of 50 mM Tris–HCl pH 7.5, 150 mM NaCl and 0.05% Tween 20.[17] The activity of the enzyme was determined as the slope per second (RFU/s) and monitored for 10 min.

4.1.5. K_i-value determination

K_i-values were determined by duplicate experiments using eight different substrate concentrations (25, 50, 75, 100, 150, 200, 300, 400 μM) at three different inhibitor concentrations (25, 50, 100 μM) and without inhibitor. K_m-values of the different substrates are 104 μM (DEN protease—Abz-NleKRRS-3-(NO_2)Y), 211 μM (WNV protease—Abz-GLKRGG-3-(NO_2)Y) and 15.9 μM (thrombin—Boc-VPR-AMC). The calculation was done using Prism 5.0 (GraphPad Software, Inc.).

4.1.6. Tryptophan quenching assay

This assay was performed as described by Bodenreider et al.[15]

4.2. Chemistry

All chemicals were obtained from Sigma-Aldrich (Germany) and Alfa Aesar, Johnson Matthey (Germany) and were of analytical grade. No further purification steps were performed unless indicated. All solvents were used as obtained from the commercial sources. Solvents were dried using standard procedures. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on Varian Mercury Plus (300 MHz) and Varian NMR System 500 (500 MHz) instruments at 300 K in $CDCl_3$, acetone-d_6, DMSO-d_6, CD_3OD or D_2O. Chemical shifts given in parts per million (δ, ppm) and the residuals of non-deuterated solvents were use as internal standard (^1H NMR: $CDCl_3$: $\delta = 7.25$ ppm, acetone-d_6: $\delta = 2.04$ ppm, DMSO-d_6: $\delta = 2.49$ ppm, CD_3OD: $\delta = 3.30$ ppm, D_2O: $\delta = 4.75$ ppm; ^{13}C NMR: $CDCl_3$: $\delta = 77.00$ ppm, acetone-d_6: $\delta = 29.80$ ppm, DMSO-d_6: $\delta = 39.50$ ppm, CD_3OD: $\delta = 49.00$ ppm). Coupling constants (J) are given in hertz (Hz). Multiplicity is reported as s (singlet), d (doublet), t (triplet), quart (quartet), sept (septet), dd (doublet-doublet), ddd (doublet-doublet-doublet), dt (doublet-triplet), td (triplet-doublet), m (multiplet) and br (broad), respectively. IR spectra were recorded on a Jasco FT-IR spectrometer (FT/IR-4100) with a Pike MIRacle ATR module and are reported in reciprocal centimeters (cm^{-1}). Mass spectra were measured on Finnigan MAT 8200 (EI), Bruker micrOTOF-Q II (HR-ESI) and Bruker BIFLEX III (MALDI-TOF) instruments. Combustion elemental analysis was performed by double determination using a Foss Heraeus Vario EL analyzer. Flash chromatography was performed on a Biotage Isolera One purification system using silica gel (0.060–0.200 mm) cartridges (KP-Sil) and UV monitoring. The reaction progress was determined by thin layer chromatography on Merck Silica Gel plates 60 F_{254} (UV detection). Microwave synthesis was performed using a Monowave 300 synthesis reactor from Anton Paar. Purity of the compounds used in biological assays was determined by combustion elemental analysis (to an accuracy of within ± 0.4%) and HPLC. HPLC was performed using an Agilent 1200 HPLC system on a xTerra MS C_{18} (2.5 μm) 2.1 × 50 mm column. Detection was conducted at 285 and 320 nm. The system conditions were A: H_2O (0.1% TFA), B: CH_3CN (0.1% TFA), flow rate: 0.3 ml/min, gradient: 10% B (1 min), 95% B (9 min), 95% B (11 min), 10% B (11.1 min), 10% B (20 min).

4.2.1. General procedure for the preparation of compounds 1, 5–15, 18–21, 23–33, 35–44, 46–54, 61, 62, 65, 67–69, 72–75, 92

A solution of arylaldehyde (1 equiv), 2-cyanoacetamide or derivative (1.0–1.5 equiv) and *N*-methylpiperazine (0.05–1.05 equiv) in methanol (2–10 ml) was stirred at room temperature overnight. After addition of an equivalent volume of water/methanol (1:1) or 1 N HCl/methanol (1:1) for acidic products, the precipitate was collected by filtration and washed with water/methanol (1:1). If precipitation did not occur, the mixture was evaporated and the residue was purified by flash chromatography.

4.2.1.1. (*E*)-2-Cyano-3-phenylacrylamide (1). Starting from benzaldehyde (2.12 g, 20.0 mmol) and 2-cyanoacetamide (2.14 g, 25.5 mmol) compound **1** was obtained after precipitation as a colorless solid (2.25 g, 65%). ^1H NMR (300 MHz, acetone-d_6): $\delta = 7.20$ (br m, 2H), 7.59 (m, 3H), 8.01 (m, 2H), 8.24 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): $\delta = 106.5$, 117.2, 130.0, 131.1, 133.0, 133.2, 152.4, 162.9 ppm; IR (neat): 3395, 3154, 2219, 1686, 1595, 1573, 1495, 1447, 1368, 1289, 1208, 1183, 1105, 952, 765, 741, 682 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 172.1 (77) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_9N_2O$: 173.0709, found: 173.0701. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.64; H, 4.88; N, 16.26.

4.2.1.2. (*E*)-2-Cyano-3-(4-methylphenyl)acrylamide (5). Starting from 4-methylbenzaldehyde (240 mg, 2.0 mmol) and 2-cyanoacetamide (211 mg, 2.51 mmol) compound **5** was obtained after precipitation as a colorless solid (220 mg, 59%). ^1H NMR (300 MHz, acetone-d_6): $\delta = 2.41$ (s, 3H), 7.13 (br m, 2H), 7.38 (m, 2H), 7.92 (m, 2H), 8.19 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): $\delta = 21.6$, 105.2, 117.5, 130.4, 130.7, 131.3, 144.3, 152.3, 162.9 ppm; IR (neat): 3381, 3145, 2218, 1692, 1588, 1507, 1366, 1213, 1181, 1105,

815 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 186.1 (93) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0866, found: 187.0869. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.86; H, 5.42; N, 15.00.

4.2.1.3. (*E*)-2-Cyano-3-(4-isopropylphenyl)acrylamide (6). Starting from 4-isopropylbenzaldehyde (148 mg, 1.0 mmol) and 2-cyanoacetamide (93 mg, 1.11 mmol) compound **6** was obtained after precipitation as a colorless solid (95 mg, 44%). ^1H NMR (300 MHz, acetone-d_6): δ = 1.27 (d, *J* = 7.0 Hz, 6H), 3.01 (sept, *J* = 6.9 Hz, 1H), 7.10 (br m, 2H), 7.46 (m, 2H), 7.96 (m, 2H), 8.20 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 23.8, 34.9, 105.3, 117.5, 128.1, 130.8, 131.5, 152.3, 155.0, 162.9 ppm; IR (neat): 3413, 3203, 2958, 2212, 1685, 1588, 1508, 1462, 1421, 1362, 1283, 1211, 1189, 1053, 829 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 214.1 (78) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1183. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.67; H, 6.66; N, 12.92.

4.2.1.4. (*E*)-2-Cyano-*N*-cyclopropyl-3-(4-isopropylphenyl)acrylamide (7). Starting from 4-isopropylbenzaldehyde (148 mg, 1.0 mmol) and **84** (137 mg, 1.10 mmol) compound **7** was obtained after precipitation and recrystallization from methanol/acetone/water as a colorless solid (140 mg, 55%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.64 (m, 2H), 0.88 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 6H), 2.87 (m, 1H), 2.96 (sept, *J* = 6.9 Hz, 1H), 6.42 (br m, 1H), 7.33 (m, 2H), 7.86 (m, 2H), 8.29 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.8, 23.5, 23.6, 34.3, 102.3, 117.3, 127.4, 129.5, 131.0, 152.9, 154.7, 161.7 ppm; IR (neat): 3329, 3012, 2961, 2871, 2221, 1668, 1592, 1558, 1511, 1420, 1363, 1273, 1204, 1096, 1014, 993, 959, 840, 824 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 254.1 (40) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}N_2O$: 255.1492, found: 255.1494. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.26; H, 7.20; N, 10.94.

4.2.1.5. (*E*)-2-Cyano-3-(4-isopropylphenyl)-*N*-(tetrahydrofuran-2-ylmethyl)acrylamide (8). Starting from 4-isopropylbenzaldehyde (148 mg, 1.0 mmol) and **85** (185 mg, 1.10 mmol) compound **8** was obtained after precipitation and recrystallization from acetone/water as a colorless solid (150 mg, 50%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.9 Hz, 6H), 1.59 (m, 1H), 1.93 (m, 2H), 2.03 (m, 1H), 2.96 (sept, *J* = 6.9 Hz, 1H), 3.37 (m, 1H), 3.69 (m, 1H), 3.79 (m, 1H), 3.91 (m, 1H), 4.05 (m, 1H), 6.68 (br s, 1H), 7.33 (m, 2H), 7.87 (m, 2H), 8.28 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 25.9, 28.7, 34.3, 44.1, 68.3, 77.1, 102.7, 117.1, 127.4, 129.5, 130.9, 152.9, 154.6, 160.7 ppm; IR (neat): 3368, 2957, 2867, 2214, 1673, 1595, 1520, 1463, 1427, 1269, 1211, 1057, 918, 828 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 298.1 (23) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{23}N_2O_2$: 299.1754, found: 299.1771. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.05; H, 7.39; N, 9.35.

4.2.1.6. (*E*)-2-Cyano-3-(4-isopropylphenyl)-*N*-(pyridin-2-ylmethyl)acrylamide (9). Starting from 4-isopropylbenzaldehyde (148 mg, 1.0 mmol) and **86** (193 mg, 1.10 mmol) compound **9** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a colorless solid (110 mg, 36%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.9 Hz, 6H), 2.97 (sept, *J* = 6.9 Hz, 1H), 4.72 (d, *J* = 4.8 Hz, 2H), 7.22 (m, 1H), 7.28 (m, 1H), 7.34 (m, 2H), 7.68 (td, *J* = 7.6, 1.8 Hz, 1H), 7.76 (br m, 1H), 7.89 (m, 2H), 8.32 (s, 1H), 8.60 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 34.3, 45.1, 102.8, 117.1, 121.9, 122.6, 127.4, 129.6, 131.0, 136.8, 149.3, 152.8, 154.6, 155.2, 160.6 ppm; IR (neat): 3370, 2956, 2217, 1663, 1590, 1523, 1472, 1434, 1413, 1288, 1270, 1209, 1194, 830, 749 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 305.2 (9) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}N_3O$: 306.1601, found: 306.1599; HPLC purity >96%.

4.2.1.7. (*E*)-2-Cyano-3-[4-(hydroxymethyl)phenyl]acrylamide (10). Starting from **93** (409 mg, 3.0 mmol) and 2-cyanoacetamide (280 mg, 3.33 mmol) compound **10** was obtained after precipitation as a colorless solid (420 mg, 69%). ^1H NMR (300 MHz, acetone-d_6): δ = 4.45 (t, *J* = 5.8 Hz, 1H), 4.73 (d, *J* = 5.8 Hz, 2H), 7.56 (m, 2H), 7.99 (m, 2H), 8.22 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 64.1, 105.7, 117.4, 127.7, 131.2, 131.6, 148.6, 152.3, 162.8 ppm; IR (neat): 3501, 3328, 3153, 2218, 1697, 1592, 1382, 1209, 1111, 1024, 1011, 956, 938, 829, 804, 679 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0815, found: 203.0821. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.47; H, 5.08; N, 13.68.

4.2.1.8. (*E*)-2-Cyano-3-(4-fluorophenyl)acrylamide (11). Starting from 4-fluorobenzaldehyde (248 mg, 2.0 mmol) and 2-cyanoacetamide (215 mg, 2.56 mmol) compound **11** was obtained after precipitation as a colorless solid (190 mg, 50%). ^1H NMR (300 MHz, acetone-d_6): δ = 7.15 (br m, 2H), 7.36 (m, 2H), 8.11 (m, 2H), 8.23 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 106.3, 117.0 + 117.3 (d, $^2J_{CF}$ = 22.2 Hz), 117.2, 129.7 + 129.7 (d, $^4J_{CF}$ = 3.2 Hz), 133.8 + 133.9 (d, $^3J_{CF}$ = 9.2 Hz), 151.1, 162.6, 163.9 + 167.3 (d, $^1J_{CF}$ = 253 Hz) ppm; IR (neat): 3468, 3158, 2216, 1697, 1585, 1502, 1414, 1381, 1301, 1234, 1163, 1113, 956, 834 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 190.1 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_8FN_2O$: 191.0615, found: 191.0618. Anal. Calcd for $C_{10}H_7FN_2O$: C, 63.16; H, 3.71; N, 14.73. Found: C, 62.98; H, 3.89; N, 14.57.

4.2.1.9. (*E*)-2-Cyano-3-(2,4-dichlorophenyl)acrylamide (12). Starting from 2,4-dichlorobenzaldehyde (350 mg, 2.0 mmol) and 2-cyanoacetamide (210 mg, 2.50 mmol) compound **12** was obtained after precipitation as a colorless solid (252 mg, 52%). ^1H NMR (300 MHz, acetone-d_6): δ = 7.31 (br m, 2H), 7.61 (ddd, *J* = 8.5, 2.1, 0.6 Hz, 1H), 7.71 (d, *J* = 2.1 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.48 (t, *J* = 0.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 111.0, 116.2, 128.9, 130.5, 130.7, 131.6, 136.9, 138.6, 147.3, 161.8 ppm; IR (neat): 3388, 3168, 2229, 1708, 1604, 1584, 1469, 1379, 1206, 1144, 1108, 1050, 923, 862 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 240.0 (6) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_7Cl_2N_2O$: 240.9930, found: 240.9927. Anal. Calcd for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62. Found: C, 49.64; H, 2.75; N, 11.46.

4.2.1.10. (*E*)-3-(4-Bromophenyl)-2-cyanoacrylamide (13). Starting from 4-bromobenzaldehyde (185 mg, 1.0 mmol) and 2-cyanoacetamide (93 mg, 1.11 mmol) compound **13** was obtained after precipitation as a colorless solid (235 mg, 94%). ^1H NMR (300 MHz, acetone-d_6): δ = 7.18 (br m, 2H), 7.78 (m, 2H), 7.94 (m, 2H), 8.20 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 107.3, 116.2, 125.9, 131.1, 131.7, 132.3, 149.3, 162.5 ppm; IR (neat): 3437, 3142, 2215, 1694, 1600, 1578, 1488, 1374, 1205, 1185, 1115, 1071, 1006, 954, 808 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 249.9 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_8BrN_2O$: 250.9815, found: 250.9814. Anal. Calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16. Found: C, 47.79; H, 2.98; N, 10.88.

4.2.1.11. (*E*)-3-(4-Bromophenyl)-2-cyano-*N*-cyclopropylacrylamide (14). Starting from 4-bromobenzaldehyde (185 mg, 1.0 mmol) and **84** (137 mg, 1.10 mmol) compound **14** was obtained after precipitation as a colorless solid with pure crystals used for X-ray analysis (50 mg, 17%). ^1H NMR (300 MHz, acetone-d_6): δ = 0.67 (m, 2H), 0.76 (m, 2H), 2.88 (m, 1H), 7.56 (br m, 1H),

7.75 (m, 2H), 7.91 (m, 2H), 8.16 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 6.4, 24.3, 107.7, 116.7, 127.0, 132.3, 132.7, 133.2, 150.3, 162.3 ppm; IR (neat): 3325, 3016, 2221, 1669, 1582, 1509, 1274, 1197, 1074, 1009, 991, 835, 816 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{13}H_{12}BrN_2O$: 291.0128, found: 291.0128. Anal. Calcd for $C_{13}H_{11}BrN_2O$: C, 53.63; H, 3.81; N, 9.62. Found: C, 53.62; H, 3.87; N, 9.59.

4.2.1.12. (*E*)-2-Cyano-3-(4-methoxyphenyl)acrylamide (15). Starting from anisaldehyde (272 mg, 2.0 mmol) and 2-cyanoacetamide (210 mg, 2.50 mmol) compound **15** was obtained after precipitation as a colorless solid (364 mg, 90%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.84 (s, 3H), 7.12 (m, 2H), 7.72 (br m, 2H), 7.95 (m, 2H), 8.10 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.6, 102.9, 114.8, 117.1, 124.4, 132.4, 150.1, 162.6, 163.1 ppm; IR (neat): 3444, 3166, 2208, 1693, 1579, 1508, 1385, 1364, 1309, 1259, 1176, 1024, 961, 824 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 202.0 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0815, found: 203.0817. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.21; H, 5.02; N, 13.73.

4.2.1.13. (*E*)-2-Cyano-3-(3-methoxyphenyl)acrylamide (18). Starting from 3-methoxybenzaldehyde (272 mg, 2.0 mmol) and 2-cyanoacetamide (210 mg, 2.50 mmol) compound **18** was obtained after precipitation as a colorless solid (198 mg, 49%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.87 (m, 3H), 7.15 (m, 1H), 7.19 (br m, 2H), 7.47 (m, 1H), 7.58 (m, 2H), 8.21 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 55.8, 106.8, 115.7, 117.3, 119.3, 123.7, 131.1, 134.3, 152.4, 160.9, 162.6 ppm; IR (neat): 3453, 3331, 2213, 1611, 1574, 1497, 1468, 1447, 1426, 1371, 1308, 1254, 1177, 1027, 956, 858, 778 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 202.0 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0815, found: 203.0816. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.22; H, 4.99; N, 13.79.

4.2.1.14. (*E*)-2-Cyano-3-(3,4-dimethoxyphenyl)acrylamide (19). Starting from 3,4-dimethoxybenzaldehyde (1.16 g, 6.98 mmol) and 2-cyanoacetamide (810 mg, 9.64 mmol) compound **19** was obtained after precipitation as a colorless solid (1.47 g, 90%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.88 (s, 3H), 3.92 (s, 3H), 7.03 (br m, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.60 (ddd, *J* = 8.4, 2.2, 0.5 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 8.15 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 56.1, 56.2, 102.7, 112.4, 113.2, 118.1, 125.7, 126.9, 150.3, 152.4, 154.2, 163.1 ppm; IR (neat): 3386, 3186, 3003, 2222. 1713, 1667, 1632, 1586, 1513, 1448, 1380, 1272, 1248, 1019, 956, 850 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 232.2 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{13}N_2O_3$: 233.0921, found: 233.0923. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.01; H, 5.35; N, 12.00.

4.2.1.15. (*E*)-2-Cyano-3-(3,4,5-trimethoxyphenyl)acrylamide (20).
Starting from 3,4,5-trimethoxybenzaldehyde (1.37 g, 6.98 mmol) and 2-cyanoacetamide (795 mg, 9.46 mmol) compound **20** was obtained after precipitation as a colorless solid (1.73 g, 94%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.83 (s, 3H), 3.89 (s, 6H), 7.14 (br m, 2H), 7.41 (s, 2H), 8.16 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.3, 61.1, 101.3, 108.3, 117.5, 126.7, 142.6, 153.3, 153.9, 162.0 ppm; IR (neat): 3406, 3133, 2224, 1711, 1690, 1596, 1575, 1502, 1466, 1450, 1415, 1384, 1355, 1323, 1302, 1256, 1240, 1188, 1155, 1116, 991, 832 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 262.2 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{13}H_{15}N_2O_4$: 263.1026, found: 263.1026. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.43; H, 5.50; N, 10.63.

4.2.1.16. (*E*)-2-Cyano-3-(4-hydroxyphenyl)acrylamide (21). Starting from 4-hydroxybenzaldehyde (611 mg, 5.0 mmol) and 2-cyanoacetamide (560 mg, 6.66 mmol) compound **21** was obtained after precipitation as a pale yellow solid (850 mg, 90%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.00 (br m, 2H), 7.01 (m, 2H), 7.96 (m, 2H), 8.13 (s, 1H), 9.40 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 101.5, 116.2, 117.3, 122.9, 132.9, 150.5, 161.7, 163.3 ppm; IR (neat): 3449, 3362, 3159, 2227, 1651, 1599, 1569, 1511, 1412, 1374, 1287, 1229, 1179, 930, 835, 810 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 188.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{10}H_9N_2O_2$: 189.0659, found: 189.0657. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.65; H, 4.40; N, 14.68.

4.2.1.17. (*E*)-2-Cyano-*N*-cyclopropyl-3-(4-hydroxyphenyl)acrylamide (23). Starting from 4-hydroxybenzaldehyde (122 mg, 1.0 mmol) and **84** (135 mg, 1.09 mmol) compound **23** was obtained after precipitation as a pale yellow solid (200 mg, 88%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 0.66 (m, 2H), 0.73 (m, 2H), 2.87 (m, 1H), 7.00 (m, 2H), 7.36 (br m, 1H), 7.92 (m, 2H), 8.09 (s, 1H), 9.41 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7, 23.4, 101.6, 116.2, 117.1, 122.9, 132.7, 149.9, 161.6, 163.0 ppm; IR (neat): 3324, 3015, 2217, 1643, 1609, 1562, 1516, 1442, 1285, 1201, 1161, 830 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{13}H_{13}N_2O_2$: 229.0972, found: 229.0963. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.34; H, 5.41; N, 12.29.

4.2.1.18. (*E*)-2-Cyano-3-(4-hydroxyphenyl)-*N*-(tetrahydrofuran-2-ylmethyl)acrylamide (24). Starting from 4-hydroxybenzaldehyde (183 mg, 1.50 mmol) and **85** (265 mg, 1.58 mmol) compound **24** was obtained after precipitation as a colorless solid (360 mg, 88%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.62 (m, 1H), 1.81–2.03 (m, 3H), 3.36 (m, 1H), 3.50 (m, 1H), 3.69 (m, 1H), 3.83 (m, 1H), 4.03 (m, 1H), 7.00 (m, 2H), 7.23 (br m, 1H), 7.95 (m, 2H), 8.14 (s, 1H), 9.45 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.1, 28.5, 43.6, 67.1, 76.7, 101.1, 116.2, 117.2, 122.9, 132.8, 150.3, 161.6, 161.7 ppm; IR (neat): 3349, 3150, 2211, 1652, 1539, 1507, 1440, 1286, 1210, 1169, 1069, 833 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1234, found: 273.1234. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.98; H, 5.90; N, 10.29.

4.2.1.19. (*E*)-2-Cyano-3-(4-hydroxyphenyl)-*N*-(pyridin-2-ylmethyl)acrylamide (25). Starting from 4-hydroxybenzaldehyde (183 mg, 1.50 mmol) and **86** (276 mg, 1.58 mmol) compound **25** was obtained after precipitation as a colorless solid (260 mg, 62%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.51 (d, *J* = 5.6 Hz, 2H), 6.93 (m, 1H), 7.28 (m, 2H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.90 (m, 2H), 8.11 (s, 1H), 8.51 (m, 1H), 8.85 (m, 1H), 10.59 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.0, 100.8, 116.2, 117.2, 121.0, 122.2, 122.9, 132.9, 136.7, 148.8, 150.7, 157.9, 161.7, 161.8 ppm; IR (neat): 3372, 2203, 1675, 1591, 1569, 1526, 1508, 1444, 1386, 1297, 1244, 1202, 1171, 1011, 831 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 279.1 (17) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{16}H_{14}N_3O_2$: 280.1081, found: 280.1074. Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.49; H, 4.84; N, 15.02.

4.2.1.20. (*E*)-3-(4-Hydroxyphenyl)-2-(morpholin-4-ylcarbonyl)acrylonitrile (26). Starting from 4-hydroxybenzaldehyde (183 mg, 1.50 mmol) and **87** (243 mg, 1.58 mmol) compound **26** was obtained after precipitation as a pale yellow solid (200 mg, 52%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.67 (m, 8H), 6.99 (m, 2H), 7.61 (s, 1H), 7.89 (m, 2H), 9.33 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 67.1, 102.8, 116.9, 117.6, 125.2, 133.2,

151.2, 162.1, 164.2 ppm; IR (neat): 3270, 2958, 2217 1634, 1588, 1516, 1426, 1276, 1205, 1178, 1105, 1065, 1028, 1008, 839 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1077, found: 259.1076. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.73; H, 5.59; N, 10.69.

4.2.1.21. (*E*)-3-(4-Hydroxyphenyl)-2-[(4-methylpiperazin-1-yl)-carbonyl]acrylonitrile hydrochloride (27). Starting from 4-hydroxybenzaldehyde (244 mg, 2.0 mmol) and **88** (360 mg, 2.15 mmol) the crude product was obtained after precipitation. After resolving in methanol an excess of aqueous hydrochloric acid was added, which resulted in precipitation of compound **27** as a colorless solid (95 mg, 15%). ^1H NMR (300 MHz, CD_3OD): δ = 2.96 (s, 3H), 3.22 (br m, 2H), 3.45 (br m, 2H), 3.57 (br m, 2H), 4.48 (br m, 2H), 6.90 (m, 2H), 7.75 (s, 1H), 7.90 (m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 41.9, 51.7, 99.6, 116.1, 117.0, 123.1, 132.5, 150.9, 161.7, 163.4 ppm; IR (neat): 3069, 2671, 2596, 2464, 2201, 1659, 1606, 1576, 1510, 1406, 1284, 1235, 1212, 1167, 976, 844 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}N_3O_2$: 272.1394, found: 272.1394; HPLC purity >98%.

4.2.1.22. (*E*)-2-Cyano-3-(3-hydroxyphenyl)acrylamide (28). Starting from 3-hydroxybenzaldehyde (1.83 g, 15.0 mmol) and 2-cyanoacetamide (1.61 g, 19.1 mmol) compound **28** was obtained after precipitation as a colorless solid (2.41 g, 85%). ^1H NMR (300 MHz, acetone-d_6): δ = 7.07 (m, 1H), 7.19, (br m 2H), 7.41 (m, 2H), 7.52 (m, 1H), 8.15 (s, 1H), 8.89 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 106.3, 115.9, 116.4, 119.7, 121.5, 130.3, 133.1, 150.7, 157.8, 162.9 ppm; IR (neat): 3406, 3202, 2217, 1670, 1578, 1448, 1389, 1285, 1230, 1116, 996, 956, 862 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 188.1 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_9N_2O_2$: 189.0659, found: 189.0653; HPLC purity >98%.

4.2.1.23. (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)acrylamide (29). Starting from 3,4-dihydroxybenzaldehyde (415 mg, 3.0 mmol) and 2-cyanoacetamide (333 mg, 3.96 mmol) compound **29** was obtained after precipitation as a pale brown solid (350 mg, 57%). ^1H NMR (300 MHz, acetone-d_6): δ = 6.98 (d, *J* = 8.4 Hz, 1H), 7.00 (br m, 2H), 7.38 (ddd, *J* = 8.4, 2.2, 0.5 Hz, 1H), 7.68 (d, *J* = 2.2 Hz, 1H), 8.05 (s, 1H), 8.70 (bs, 1H), 8.90 (bs, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 101.6, 116.6, 116.8, 118.0, 125.2, 126.8, 146.3, 151.1, 152.5, 163.4 ppm; IR (neat): 3461, 3410, 3313, 2603, 2208, 1675, 1567, 1446, 1391, 1293, 1262, 1194, 1167, 1122, 869, 794 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 204.1 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_9N_2O_3$: 205.0608, found: 205.0608. Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.70; H, 4.04; N, 13.58.

4.2.1.24. (*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide (30). Starting from **95** (183 mg, 1.0 mmol) and 2-cyanoacetamide (110 mg, 1.31 mmol) compound **30** was obtained after precipitation and recrystallization in acetone/water (containing hydrochloric acid) as a yellow solid (150 mg, 60%). ^1H NMR (300 MHz, DMSO-d_6): δ = 7.60–8.00 (m, 4H), 8.04 (s, 1H), 10.88 (br m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 104.7, 116.4, 188.0, 119.2, 122.1, 137.3, 145.4, 148.1, 148.8, 162.8 ppm; IR (neat): 3432, 3406, 3257, 2234, 1655, 1606, 1537, 1484, 1398, 1360, 1288, 1250, 1129, 941, 887, 866, 765 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_8N_3O_5$: 250.0458, found: 250.0457; HPLC purity >98%.

4.2.1.25. (*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylacrylamide (31). Starting from **95** (183 mg, 1.0 mmol) and **89** (175 mg, 1.25 mmol) compound **31** was obtained after precipitation and recrystallization from methanol/acetone/water (containing hydrochloric acid) as a yellow solid (40 mg, 13%). ^1H NMR (300 MHz, acetone-d_6): δ = 1.21 (br m, 6H), 3.51 (br m, 4H), 7.60 (s, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 8.18 (d, *J* = 2.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.8, 24.7, 104.7, 116.2, 117.6, 118.4, 122.7, 137.2, 144.8, 147.1, 148.0, 162.6 ppm; IR (neat): 2983, 2210, 1629, 1607, 1537, 1440, 1310, 1244, 1139, 945, 871, 764 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}N_3O_5$: 306.1084, found: 306.1079; HPLC purity >98%.

4.2.1.26. (*E*)-2-Cyano-3-(4-hydroxy-3-methoxyphenyl)acrylamide (32). Starting from vanillin (761 mg, 5.0 mmol) and 2-cyanoacetamide (550 mg, 6.54 mmol) compound **32** was obtained after precipitation as a colorless solid (900 mg, 83%). ^1H NMR (300 MHz, acetone-d_6): δ = 3.91 (s, 3H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.02 (br m, 2H), 7.55 (ddd, *J* = 8.4, 2.2, 0.5 Hz, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 8.13 (s, 1H), 8.73 (bs, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 56.3, 101.9, 113.7, 116.5, 118.2, 125.1, 127.2, 148.6, 152.2, 152.6, 163.3 ppm; IR (neat): 3469, 3364, 2211, 1681, 1563, 1508, 1433, 1404, 1285, 1163, 1130, 1018, 849 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 218.1 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_2O_3$: 219.0764, found: 219.0760. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.46; H, 4.72; N, 12.73.

4.2.1.27. (*E*)-2-Cyano-3-(4-hydroxy-3-iodo-5-methoxyphenyl)-acrylamide (33). Starting from 4-hydroxy-3-iodo-5-methoxybenzaldehyde (1.39 g, 5.0 mmol) and 2-cyanoacetamide (526 mg, 6.26 mmol) compound **33** was obtained after precipitation and recrystallization from acetone as a pale yellow solid (1.25 g, 73%). ^1H NMR (300 MHz, DMSO-d_6): δ = 3.85 (s, 3H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.76 (br m, 2H), 7.93 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 10.60 (br m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.1, 84.8, 103.0, 112.8, 117.1, 125.0, 133.9, 146.8, 149.3, 150.5, 162.9 ppm; IR (neat): 3459, 3343, 3323, 2215, 1669, 1572, 1551, 1494, 1473, 1415, 1328, 1302, 1263, 1246, 1163, 1130, 1035, 970, 844, 761 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 344.0 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{10}IN_2O_3$: 344.9731, found: 344.9721; HPLC purity >97%.

4.2.1.28. (*E*)-2-Cyano-3-(4-nitrophenyl)acrylamide (35). Starting from 4-nitrobenzaldehyde (151 mg, 51.0 mmol) and 2-cyanoacetamide (93 mg, 1.10 mmol) compound **35** was obtained after precipitation as a brown solid (120 mg, 55%). ^1H NMR (300 MHz, acetone-d_6): δ = 7.30 (br m, 2H), 8.23 (m, 2H), 8.36 (s, 1H), 8.42 (m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 110.6, 115.7, 124.2, 131.0, 138.1, 148.3, 148.8, 162.1 ppm; IR (neat): 3429, 3340, 2224, 1686, 1591, 1378, 1341, 1295, 1201, 1106, 854, 768 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 217.0 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_8N_3O_3$: 218.0560, found: 218.0558. Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.14; H, 3.48; N, 19.03.

4.2.1.29. (*E*)-2-Cyano-3-(4-cyanophenyl)acrylamide (36). Starting from 4-formylbenzonitrile (131 mg, 1.0 mmol) and 2-cyanoacetamide (105 mg, 1.25 mmol) compound **36** was obtained after precipitation as a colorless solid (95 mg, 48%). ^1H NMR (300 MHz, acetone-d_6): δ = 7.27 (br m, 2H), 7.98 (m, 2H), 8.16 (m, 2H), 8.30 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 110.0, 113.8, 115.8, 118.2, 130.3, 132.9, 136.3, 148.7, 162.1 ppm; IR (neat): 3422, 3171, 2226, 1699, 1684, 1597, 1503, 1374, 1296, 1205, 1114, 1016, 936, 826 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 197.0 (77) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_8N_3O$: 198.0662, found: 198.0658. Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 66.72; H, 3.79; N, 21.40.

4.2.1.30. 4-[(*E*)-3-Amino-2-cyano-3-oxoprop-1-en-1-yl]benzoic acid (37). Starting from 4-formylbenzoic acid (2.40 g, 16.0 mmol) and 2-cyanoacetamide (1.48 g, 17.6 mmol) compound **37** was obtained after precipitation as a colorless solid (2.98 g, 86%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.83 (bs, 1H), 7.99 (m, 3H), 8.07 (m, 2H), 8.23 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 108.9, 116.0, 129.9, 130.0, 133.4, 135.8, 149.4, 162.4, 166.5 ppm; IR (neat): 3389, 3218, 2227, 1709, 1677, 1620, 1581, 1416, 1281, 1208, 1193, 1119, 1103, 974, 856, 769 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 216.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{11}H_9N_2O_3$: 217.0608, found: 217.0611; HPLC purity >98%.

4.2.1.31. 4-[(*E*)-2-Cyano-3-(cyclopropylamino)-3-oxoprop-1-en-1-yl]benzoic acid (38). Starting from 4-formylbenzoic acid (380 mg, 2.53 mmol) and **84** (335 mg, 2.69 mmol) compound **38** was obtained after precipitation and recrystallization from acetone/water (containing hydrochloric acid) as a colorless solid (260 mg, 40%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.59 (m, 2H), 0.69 (m, 2H), 2.78 (m, 1H), 7.98 (m, 2H), 8.07 (m, 2H), 8.14 (s, 1H), 8.58 (d, *J* = 4.0 Hz, 1H), 13.27 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7, 12.4, 108.8, 115.9, 129.9, 129.9 133.4, 135.8, 148.9, 162.1, 166.5 ppm; IR (neat): 2833, 2217, 1681, 1607, 1575, 1505, 1427, 1288, 1249, 1203, 1108, 1013, 928, 851 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{14}H_{13}N_2O_3$: 257.0921, found: 257.0916; HPLC purity >97%.

4.2.1.32. 3-[(*E*)-2-cyano-3-(cyclopropylamino)-3-oxoprop-1-en-1-yl]benzoic acid (39). Starting from 3-formylbenzoic acid (250 mg, 1.67 mmol) and 2-cyanoacetamide (227 mg, 2.70 mmol) compound **39** was obtained after precipitation as a colorless solid (194 mg, 45%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 0.68 (m, 2H), 0.76 (m, 2H), 2.89 (m, 1H), 7.61 (br m, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 8.20 (m, 2H), 8.27 (s, 1H), 8.62 (m, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 6.4, 24.2, 108.4, 116.5, 130.4, 132.0, 132.4, 133.6, 133.6, 134.9, 150.6, 166.6 ppm; IR (neat): 3350, 2222, 1675, 1597, 1509, 1457, 1415, 1362, 1286, 1203, 1170, 933, 750 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 256.0 (80) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{14}H_{13}N_2O_3$: 257.0921, found: 257.0919; HPLC purity >98%.

4.2.1.33. (*E*)-2-Cyano-3-[4-(dimethylamino)phenyl]acrylamide (40). Starting from 4-(dimethylamino)benzaldehyde (1.52 g, 10.2 mmol) and 2-cyanoacetamide (850 mg, 10.2 mmol) compound **40** was obtained after precipitation as an orange solid (1.62 g, 75%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.11 (s, 6H), 6.83 (m, 2H), 6.84 (br m, 2H), 7.92 (m, 2H), 8.04 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 40.0, 97.3, 112.4, 119.1, 120.2, 133.8, 152.4, 154.3, 164.1 ppm; IR (neat): 3398, 3143, 2198, 1676, 1608, 1558, 1518, 1440, 1358, 1235, 1166, 943, 808 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 215.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{14}N_3O$: 216.1131, found: 216.1137. Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.61; H, 6.35; N, 19.18.

4.2.1.34. (*E*)-2-Cyano-*N*-cyclopropyl-3-[4-(dimethylamino)-phenyl]acrylamide (41). Starting from 4-(dimethylamino)benzaldehyde (450 mg, 3.02 mmol) and **84** (395 mg, 3.18 mmol) compound **41** was obtained after precipitation as a yellow solid (590 mg, 77%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 0.64 (m, 2H), 0.72 (m, 2H), 2.85 (m, 1H), 3.11 (s, 6H), 6.82 (m, 2H), 7.16 (br m, 1H), 7.89 (m, 2H), 8.01 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7, 23.3, 39.5, 97.4, 111.6, 118.0, 118.7, 132.5, 149.8, 152.8, 163.6 ppm; IR (neat): 3294, 2915, 2207, 1606, 1571, 1525, 1437, 1382, 1361, 1328, 1286, 1254, 1174, 950, 825 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 255.1 (54) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{18}N_3O$: 256.1444, found: 216.1458. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.25; H, 6.78; N, 16.31.

4.2.1.35. (*E*)-2-Cyano-3-[4-(dimethylamino)phenyl]-*N*-(tetrahydrofuran-2-ylmethyl)acrylamide (42). Starting from 4-(dimethylamino)benzaldehyde (373 mg, 2.50 mmol) and **85** (459 mg, 2.73 mmol) compound **42** was obtained after precipitation as an orange solid (681 mg, 91%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.62 (m, 1H), 1.82–2.00 (m, 3H), 3.11 (s, 6H), 3.36 (m, 1H), 3.49 (m, 1H), 3.68 (m, 1H), 3.83 (m, 1H), 4.02 (m, 1H), 6.83 (m, 2H), 7.04 (br m, 1H), 7.91 (m, 2H), 8.05 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 26.3, 40.0, 44.6, 68.4, 78.1, 97.4, 110.9, 112.4, 119.0, 120.3, 133.8, 152.0, 154.3, 162.4 ppm; IR (neat): 3409, 2973, 2927, 2870, 2832, 2194, 1651, 1610, 1569, 1505, 1444, 1378, 1324, 1285, 1234, 1176, 1080, 1010, 945, 817 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 299.1 (86) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{17}H_{22}N_3O_2$: 300.1707, found: 300.1719. Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.04; H, 7.15; N, 13.91.

4.2.1.36. (*E*)-2-Cyano-3-[4-(dimethylamino)phenyl]-*N*-(pyridin-2-ylmethyl)acrylamide (43). Starting from 4-(dimethylamino)benzaldehyde (150 mg, 1.0 mmol) and **86** (193 mg, 1.10 mmol) compound **43** was obtained after precipitation as an orange solid (300 mg, 98%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.05 (s, 6H), 4.50 (d, *J* = 5.7 Hz, 2H), 6.82 (m, 2H), 7.25 (m, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H), 7.88 (m, 2H), 8.03 (s, 1H), 8.50 (m, 1H), 8.66 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 39.5, 44.9, 96.4, 111.6, 118.2, 118.7, 120.9, 122.1, 132.8, 136.7, 148.8, 150.7, 153.0, 158.1, 162.3 ppm; IR (neat): 3377, 2913, 2196, 1649, 1609, 1565, 1503, 1440, 1415, 1374, 1289, 1169, 995, 813, 749 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 306.1 (71) [M]$^+$; HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{18}H_{18}N_4NaO$: 329.1373, found: 329.1365. Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.26; H, 6.03; N, 18.33.

4.2.1.37. (*E*)-3-[4-(Dimethylamino)phenyl]-2-(morpholin-4-ylcarbonyl)acrylonitrile (44). Starting from 4-(dimethylamino)benzaldehyde (300 mg, 2.01 mmol) and **87** (310 mg, 2.01 mmol) compound **44** was obtained after precipitation as a yellow solid (250 mg, 44%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.09 (s, 6H), 3.65 (m, 8H), 6.80 (m, 2H), 7.57 (s, 1H), 7.87 (m, 2H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 40.0, 46.5, 67.1, 98.3, 112.3, 118.6, 120.7, 133.2, 152.2, 154.0, 165.1 ppm; IR (neat): 2954, 2911, 2862, 2197, 1633, 1604, 1561, 1521, 1425, 1363, 1323, 1266, 1232, 1169, 1111, 1021, 950, 827 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 285.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{16}H_{20}N_3O_2$: 286.1550, found: 286.1557. Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.26; H, 6.71; N, 14.59.

4.2.1.38. (*E*)-2-Cyano-3-pyridin-4-ylacrylamide (46). Starting from isonicotinaldehyde (421 mg, 3.93 mmol) and 2-cyanoacetamide (430 mg, 5.12 mmol) compound **46** was obtained after precipitation as a colorless solid (235 mg, 35%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.30 (br m, 2H), 7.82 (m, 2H), 8.22 (s, 1H), 8.80 (m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 111.5, 115.5, 122.9, 139.1, 148.2, 150.7, 161.9 ppm; IR (neat): 3426, 3027, 2216, 1696, 1639, 1598, 1546, 1415, 1359, 1239, 1204, 1059, 1004, 974, 853, 806 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 173.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_9H_8N_3O$: 174.0662, found: 174.0653. Anal. Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.24; H, 4.17; N, 24.21.

4.2.1.39. (*E*)-2-Cyano-3-pyridin-3-ylacrylamide (47). Starting from nicotinaldehyde (214 mg, 2.0 mmol) and 2-cyanoacetamide (210 mg, 2.50 mmol) compound **47** was obtained after precipitation as a colorless solid (205 mg, 59%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.60 (dd, J = 8.1, 4.8 Hz, 1H), 7.85 (br m, 1H), 7.98 (br m, 1H), 8.23 (s, 1H), 8.36 (m, 1H), 8.72 (dd, J = 4.8, 1.6 Hz, 1H), 8.97 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 108.9, 116.1, 124.1, 128.1, 135.9, 147.7, 151.2, 152.3, 162.1 ppm; IR (neat): 3127, 2217, 1712, 1675, 1637, 1593, 1490, 1414, 1371, 1255, 1223, 1193, 1137, 1097, 1028, 967, 803 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 173.1 (85) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_9H_8N_3O$: 174.0662, found: 174.0662. Anal. Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.18; H, 4.18; N, 24.11.

4.2.1.40. (*E*)-2-Cyano-3-(2-thienyl)acrylamide (48). Starting from thiophene-2-carbaldehyde (337 mg, 3.0 mmol) and 2-cyanoacetamide (333 mg, 3.96 mmol) compound **48** was obtained after precipitation as a pale orange solid (365 mg, 58%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.11 (br m, 2H), 7.31 (m, 1H), 7.90 (m, 1H), 8.01 (m, 1H), 8.40 (m, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 102.4, 117.4, 129.3, 135.1, 137.2, 138.1, 144.9, 162.8 ppm; IR (neat): 3467, 3296, 3133, 2206, 1696, 1616, 1573, 1417, 1375, 1355, 1301, 1242, 1215, 1107, 1081, 1048, 858, 738 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 178.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_8H_7N_2OS$: 179.0274, found: 179.0273. Anal. Calcd for $C_8H_6N_2OS$: C, 53.92; H, 3.39; N, 15.72. Found: C, 53.77; H, 3.52; N, 15.59.

4.2.1.41. (*E*)-3-(5-Chloro-2-thienyl)-2-cyanoacrylamide (49). Starting from 5-chlorothiophene-2-carbaldehyde (160 mg, 1.10 mmol) and 2-cyanoacetamide (115 mg, 1.37 mmol) compound **49** was obtained after precipitation as a pale brown solid (110 mg, 47%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.11 (br m, 2H), 7.28 (d, J = 4.1 Hz, 1H), 7.76 (d, J = 4.1 Hz, 1H), 8.30 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 102.4, 116.5, 128.4, 134.8, 136.7, 138.1, 143.2, 162.1 ppm; IR (neat): 3393, 3159, 2207, 1683, 1583, 1509, 1422, 1377, 1290, 1246, 1210, 1071, 1005, 943, 804 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 212.1 (57) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_8H_6ClN_2OS$: 212.9884, found: 212.9879. Anal. Calcd for $C_8H_5ClN_2OS$: C, 45.18; H, 2.37; N, 13.17. Found: C, 45.12; H, 2.53; N, 13.04.

4.2.1.42. (*E*)-3-(5-Bromo-2-thienyl)-2-cyanoacrylamide (50). Starting from 5-bromothiophene-2-carbaldehyde (382 mg, 2.0 mmol) and 2-cyanoacetamide (215 mg, 2.56 mmol) compound **50** was obtained after precipitation as a pale yellow solid (150 mg, 29%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.12 (br m, 2H), 7.40 (d, J = 4.1 Hz, 1H), 7.71 (dd, J = 4.1, 0.6 Hz, 1H), 8.32 (d, J = 0.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 102.6, 116.6, 121.2, 131.9, 137.4, 138.6, 142.9, 162.2 ppm; IR (neat): 3426, 3170, 2209, 1682, 1578, 1504, 1413, 1365, 1283, 1238, 1204, 1113, 1077, 1058, 976, 941, 805 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_8H_6BrN_2OS$: 256.9379, found: 256.9378. Anal. Calcd for $C_8H_5BrN_2OS$: C, 37.37; H, 1.96; N, 10.90. Found: C, 37.05; H, 2.22; N, 10.80.

4.2.1.43. (*E*)-3-(5-Bromo-2-thienyl)-2-cyano-*N*-cyclopropylacrylamide (51). Starting from 5-bromothiophene-2-carbaldehyde (1.0 g, 5.23 mmol) and **84** (720 mg, 5.80 mmol) compound **51** was obtained after precipitation as a pale yellow solid (1.48 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.58 (m, 2H), 0.66 (m, 2H), 2.76 (m, 1H), 7.45 (d, J = 4.1 Hz, 1H), 7.68 (dd, J = 4.1, 0.4 Hz, 1H), 8.26 (d, J = 0.4 Hz, 1H), 8.41 (br m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7, 23.4, 102.5, 116.4, 121.0, 131.8, 137.4, 138.5, 142.4, 161.9 ppm; IR (neat): 3317, 3064, 3009, 2219, 1659, 1578, 1517, 1502, 1415, 1265, 1242, 1205, 1165, 1098, 1046, 1018, 977, 955, 852, 809 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{11}H_{10}BrN_2OS$: 296.9692, found: 296.9696. Anal. Calcd for $C_{11}H_9BrN_2OS$: C, 44.46; H, 3.05; N, 9.43. Found: C, 44.39; H, 3.29; N, 9.47.

4.2.1.44. (*E*)-3-(3-Bromo-2-thienyl)-2-cyanoacrylamide (52). Starting from 3-bromothiophene-2-carbaldehyde (192 mg, 1.0 mmol) and 2-cyanoacetamide (105 mg, 1.25 mmol) compound **52** was obtained after precipitation as a pale brown solid (220 mg, 86%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.19 (br m, 2H), 7.38 (d, J = 5.4 Hz, 1H), 8.12 (dd, J = 5.4, 1.0 Hz, 1H), 8.47 (d, J = 1.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 104.3, 116.9, 122.8, 131.7, 132.3, 134.9, 142.4, 162.2 ppm; IR (neat): 3468, 3114, 2211, 1696, 1615, 1581, 1475, 1412, 1374, 1304, 1236, 1115, 937, 876, 735 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 256.0 (2) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_8H_6BrN_2OS$: 256.9379, found: 256.9376. Anal. Calcd for $C_8H_5BrN_2OS$: C, 37.37; H, 1.96; N, 10.90. Found: C, 37.46; H, 2.11; N, 10.82.

4.2.1.45. (*E*)-3-(5-Bromo-2-furyl)-2-cyano-*N*-cyclopropylacrylamide (53). Starting from 5-bromo-2-furaldehyde (528 mg, 3.0 mmol) and **84** (410 mg, 3.30 mmol) compound **53** was obtained after precipitation as a yellow solid (410 mg, 49%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 0.67 (m, 2H), 0.74 (m, 2H), 2.86 (m, 1H), 6.83 (dd, J = 3.7, 0.3 Hz, 1H), 7.35 (dd, J = 3.7, 0.6 Hz, 1H), 7.45 (br m, 1H), 7.90 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7, 23.4, 101.5, 115.7, 116.0, 123.3, 128.8, 134.0, 150.3, 162.0 ppm; IR (neat): 3306, 3105, 3039, 2225, 1662, 1605, 1517, 1453, 1362, 1283, 1262, 1200, 1091, 1019, 946, 927, 803 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{11}H_{10}BrN_2O_2$: 280.9920, found: 280.9911. Anal. Calcd for $C_{11}H_9BrN_2O_2$: C, 47.00; H, 3.23; N, 9.97. Found: C, 46.79; H, 3.43; N, 9.96.

4.2.1.46. (*E*)-2-Cyano-3-(1*H*-indol-3-yl)acrylamide (54). Starting from 1*H*-indole-3-carbaldehyde (726 mg, 5.0 mmol) and 2-cyanoacetamide (535 mg, 6.37 mmol) compound **54** was obtained after precipitation as a pale yellow solid (700 mg, 66%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 6.90 (br m, 2H), 7.28 (m, 2H), 7.59 (m, 1H), 7.95 (m, 1H), 8.58 (m, 2H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 98.1, 111.3, 113.4, 119.1, 119.4, 122.6, 124.3, 128.5, 131.0, 137.3, 144.0, 164.1 ppm; IR (neat): 3471, 3371, 3110, 2210, 1684, 1584, 1563, 1512, 1485, 1459, 1422, 1373, 1329, 1298, 1228, 1130, 1112, 1061, 752 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 211.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{10}N_3O$: 212.0818, found: 212.0819. Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.00; H, 4.55; N, 19.67.

4.2.1.47. (*E*)-2-Cyano-3-[2,3,5,6-tetrafluoro-4-(4-methylpiperazin-1-yl)phenyl]acrylamide (61). Starting from Pentafluorobenzaldehyde (197 mg, 1.0 mmol), 2-cyanoacetamide (105 mg, 1.25 mmol) and *N*-methylpiperazine (0.11 ml, 1.0 mmol) compound **61** was obtained after precipitation and recrystallization from methanol/water as a pale yellow solid (12 mg, 4%). ^{1}H NMR (300 MHz, CD3OD): δ = 2.35 (s, 3H), 2.59 (m, 4H), 3.44 (m, 4H), 8.07 (m, 1H) ppm; ^{19}F NMR (282 MHz, CD_3OD): δ = −153.2, −138.6 ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.8, 50.1, 54.8, 103.4, 114.1, 114.8, 132.7, 136.9 139.9, 141.9, 143.6, 145.6, 161.3 ppm; IR (neat): 3500, 3400, 2806, 2226, 1702, 1643, 1604, 1486, 1455, 1384, 1351, 1289, 1273, 1187, 1160, 1140, 980 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 342.4 (51) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{15}F_4N_4O$: 343.1177, found: 343.1175; HPLC purity >98%.

4.2.1.48. (*E*)-2-Cyano-*N*-cyclopropyl-3-(3-morpholin-4-ylphenyl)acrylamide (62). Starting from **97** (75 mg, 0.39 mmol) and **84** (62 mg, 0.5 mmol) compound **62** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a yellow oil (18 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.65 (m, 2H), 0.89 (m, 2H), 2.86 (m, 1), 3.20 (m, 4H), 3.87 (m, 4H), 6.42 (br m, 1H), 7.07 (m, 1H), 7.36 (m, 2H), 7.47 (m, 1H), 8.29 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.9, 23.6, 48.8, 66.7, 103.4, 116.4, 117.2, 120.0, 122.6, 129.9, 132.6, 151.6, 153.7, 161.5 ppm; IR (neat): 2962, 2850, 2210, 1671, 1600, 1522, 1447, 1263, 1242, 1118, 1069, 1027, 996, 887, 780, 683 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{17}H_{20}N_3O_2$: 298.1550, found: 298.1548; HPLC purity >93%.

4.2.1.49. (*E*)-2-Cyano-*N*-cyclopropyl-3-[4-(morpholin-4-ylcarbonyl)phenyl]acrylamide (65). Starting from **96** (220 mg, 1.0 mmol) and **84** (137 mg, 1.10 mmol) compound **65** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a pale yellow oil (70 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (m, 2H), 0.90 (m, 2H), 2.89 (m, 1H), 3.34–3.86 (br m, 8H), 6.44 (br m, 1H), 7.51 (m, 2H), 7.95 (m, 2H), 8.33 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.9, 23.7, 38.6, 66.8, 105.2, 116.7, 127.9, 130.7, 133.0, 139.1, 151.6, 161.0, 168.9 ppm; IR (neat): 3277, 2218, 1666, 1619, 1525, 1458, 1438, 1274, 1203, 1155, 1114, 1067, 1029, 1011, 932, 838 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{18}H_{20}N_3O_3$: 326.1499, found: 326.1493; HPLC purity >91%.

4.2.1.50. (2*E*,4*E*)-2-Cyano-4-methyl-5-phenylpenta-2,4-dienamide (67). Starting from (*E*)-2-methyl-3-phenylacrylaldehyde (1.46 g, 10.0 mmol) and 2-cyanoacetamide (1.07 mg, 12.7 mmol) compound **67** was obtained after precipitation as a colorless solid (1.33 g, 63%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.39 (d, *J* = 1.3 Hz, 3H), 7.04 (br m, 2H), 7.31 (bs, 1H), 7.36–7.54 (m, 5H), 7.95 (d, *J* = 1.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 15.5, 104.6, 117.5, 129.4, 129.7, 130.8, 134.0, 136.7, 146.5, 157.6, 163.2 ppm; IR (neat): 3464, 3291, 3150, 2206, 1681, 1571, 1373, 1211, 1111, 1078, 1010, 962, 756 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 212.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{13}H_{13}N_2O$: 213.1022, found: 213.1021. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.45; H, 5.85; N, 13.15.

4.2.1.51. (2*E*,4*E*)-2-Cyano-4-methyl-5-phenyl-*N*-(tetrahydrofuran-2-ylmethyl)penta-2,4-dienamide (68). Starting from (*E*)-2-methyl-3-phenylacrylaldehyde (390 mg, 2.67 mmol) and **85** (490 mg, 2.91 mmol) compound **68** was obtained after precipitation as a colorless solid (300 mg, 38%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.62 (m, 1H), 1.80–2.01 (m, 3H), 2.39 (d, *J* = 1.2 Hz, 3H), 3.35 (m, 1H), 3.49 (m, 1H), 3.68 (m, 1H), 3.83 (m, 1H), 4.02 (m, 1H), 7.23 (br m, 2H), 7.31 (bs, 1H), 7.35–7.54 (m, 5H), 7.96 (m, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 15.6, 26.3, 29.4, 44.7, 68.4, 77.9, 104.7, 117.5, 129.4, 129.7, 130.8, 134.0, 136.7, 146.5, 157.2, 161.6 ppm; IR (neat): 3375, 2977, 2937, 2874, 2209, 1658, 1567, 1523, 1278, 1258, 1207, 1084, 1015, 959, 757 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 296.1 (32) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{18}H_{21}N_2O_2$: 297.1598, found: 297.1609. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.79; H, 6.85; N, 9.35.

4.2.1.52. (2*E*,4*E*)-2-Cyano-*N*-cyclopropyl-5-[4-(dimethylamino)-phenyl]penta-2,4-dienamide (69). Starting from (*E*)-3-[4-(dimethylamino)phenyl]acrylaldehyde (180 mg, 1.03 mmol) and **84** (150 mg, 1.21 mmol) compound **69** was obtained after precipitation as a red solid (225 mg, 78%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 0.63 (m, 2H), 0.71 (m, 2H), 2.85 (m, 1H), 3.05 (s, 6H), 6.77 (m, 2H), 6.99 (dd, *J* = 15.0, 11.7 Hz, 1H), 7.22 (br m, 1H), 7.32 (d, *J* = 15.0 Hz, 1H), 7.55 (m, 2H), 7.91 (d, *J* = 11.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 6.5, 24.1, 40.1, 103.4, 112.8, 116.6, 118.5, 118.6, 123.7, 131.0, 149.2, 153.2, 153.5 ppm; IR (neat): 3325, 2206, 1663, 1588, 1504, 1443, 1369, 1284, 1231, 1193, 1151, 987, 942, 811 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 281.1 (56) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{17}H_{20}N_3O$: 282.1601, found: 282.1605. Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.45; H, 6.78; N, 14.74.

4.2.1.53. (*E*)-3-[4-(Benzyloxy)-3-methoxyphenyl]-2-cyanoacrylamide (72). Starting from **98** (242 mg, 1.0 mmol) and 2-cyanoacetamide (105 mg, 1.25 mmol) compound **72** was obtained after precipitation as a colorless solid (190 mg, 62%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.90 (s, 3H), 5.26 (s, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.31–7.45 (m, 3H), 7.50 (m, 1H), 7.52 (m, 1H), 7.59 (ddd, *J* = 8.4, 2.2, 0.5 Hz, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 8.15 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.5, 69.9, 103.0, 112.6, 113.2, 117.2, 124.7, 125.2, 128.0, 128.1, 128.5, 136.3, 148.9, 150.5, 151.5, 163.0 ppm; IR (neat): 3166, 2209, 1659, 1640, 1586, 1508, 1457, 1425, 1377, 1334, 1269, 1242, 1173, 1143, 1023, 978, 854, 749 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 308.2 (7) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234, found: 309.1237. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.02; H, 5.31; N, 8.72.

4.2.1.54. (*E*)-2-Cyano-3-[4-(dimethylamino)phenyl]prop-2-enethioamide (73). Starting from 4-(dimethylamino)benzaldehyde (230 mg, 1.54 mmol) and 2-cyanoethanethioamide (165 mg, 1.65 mmol) compound **73** was obtained after precipitation as a red solid (265 mg, 74%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.14 (s, 6H), 6.85 (m, 2H), 7.97 (m, 2H), 8.32 (br m, 1H), 8.43 (s, 1H), 8.92 (br m, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 40.0, 102.9, 112.6, 118.4, 120.1, 134.5, 154.4, 154.6, 194.7 ppm; IR (neat): 3327, 3283, 3150, 2215, 1638, 1605, 1560, 1516, 1409, 1365, 1229, 1194, 1169, 1117, 1061, 943, 905, 806 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 231.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{14}N_3S$: 232.0903, found: 232.0902. Anal. Calcd for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17. Found: C, 62.06; H, 5.65; N, 18.02.

4.2.1.55. (*E*)-2-Cyano-3-[4-(dimethylamino)phenyl]acrylic acid (74). Starting from 4-(dimethylamino)benzaldehyde (746 mg, 5.0 mmol) and cyanoacetic acid (638 mg, 7.5 mmol) compound **74** was obtained after precipitation as an orange solid (600 mg, 56%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.06 (s, 6H), 6.82 (m, 2H), 7.93 (m, 2H), 8.06 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 39.6, 93.4, 111.7, 117.9, 118.4, 133.5, 153.5, 153.8, 164.8 ppm; IR (neat): 2215, 1657, 1609, 1561, 1516, 1433, 1384, 1330, 1284, 1248, 1166, 1090, 1063, 941, 812, 709 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{13}N_2O_2$: 217.0972, found: 217.0978; HPLC purity >98%.

4.2.1.56. [4-(Dimethylamino)benzylidene]malononitrile (75). Starting from 4-(dimethylamino)benzaldehyde (373 mg, 2.50 mmol) and malononitrile (250 mg, 3.78 mmol) compound **75** was obtained after precipitation as an orange solid (465 mg, 94%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.18 (s, 6H), 6.87 (m, 2H), 7.84 (s, 1H), 7.91 (m, 2H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 40.1, 71.2, 112.5, 116.0, 116.7, 120.1, 134.5, 155.5, 159.3 ppm; IR (neat): 2921, 2206, 1607, 1561, 1514, 1385, 1357, 1259, 1174, 942, 929, 815 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 197.1 (97) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{12}N_3$: 198.1026, found: 198.1027. Anal. Calcd for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30. Found: C, 72.95; H, 5.69; N, 21.13.

4.2.1.57. (*E*)-2-Cyano-3-(4-methoxyphenyl)acrylsäure (92). Starting from anisaldehyde (816 mg, 6.0 mmol) and cyanoacetic acid (638 mg, 7.50 mmol) compound **92** was obtained after precipitation as a colorless solid (761 mg, 62%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.85 (s, 3H), 7.11 (m, 2H), 8.01 (m, 2H), 8.16 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.6, 102.4, 114.7, 117.4, 124.4, 132.7, 152.0, 162.6, 164.0 ppm; MS (EI, 70 eV): *m/z* (%): 203.0 (100) $[M]^+$.

4.2.1.58. Methyl *N*-[(*E*)-2-cyano-3-(4-methoxyphenyl)prop-2-enoyl]-L-serinate (16). To a solution of **92** (305 mg, 1.50 mmol), methyl L-serinate (245 mg, 1.58 mmol) and HATU (627 mg, 1.65 mmol) in dry DMF (5 ml) was added DIPEA (0.78 ml, 4.50 mmol) slowly. After 2 h the reaction was quenched with water and the mixture was extracted with ethyl acetate. After drying over $MgSO_4$ the solvent was evaporated and the residue was purified by flash chromatography (cyclohexane/ethyl acetate). Compound **16** was obtained as a colorless solid (288 mg, 63%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.74 (s, 3H), 3.92 (s, 3H), 3.97 (m, 1H), 4.04 (m, 1H), 4.67 (m, 1H), 7.13 (m, 2H), 7.42 (br m, 1H), 8.04 (m, 2H), 8.21 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 52.6, 56.1, 56.4, 62.5, 102.1, 115.6, 117.7, 125.5, 133.8, 152.3, 161.4, 164.4, 171.2 ppm; IR (neat): 3385, 2954, 2214, 1735, 1645, 1611, 1579, 1514, 1462, 1436, 1374, 1314, 1258, 1212, 1177, 1093, 1054, 1024, 958, 847 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 304.1 (18) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_5$: 305.1132, found: 305.1133; HPLC purity >98%.

4.2.1.59. N^2-[(*E*)-2-Cyano-3-(4-methoxyphenyl)prop-2-enoyl]-N^1-cyclopropyl-L-serinamide (17). To a solution of **92** (305 mg, 1.50 mmol), **91** (284 mg, 1.58 mmol) and HATU (627 mg, 1.65 mmol) in dry DMF (5 ml) was added DIPEA (0.78 ml, 4.50 mmol) slowly. After 2 h the reaction was quenched with water and the mixture was extracted with ethyl acetate. After drying over $MgSO_4$ the solvent was evaporated and the residue was purified by flash chromatography (cyclohexane/ethyl acetate). Compound **17** was obtained as a colorless solid (240 mg, 48%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 0.48 (m, 2H), 0.66 (m, 2H), 2.73 (m, 1H), 3.82 (m, 1H), 3.91 (m, 1H), 3.92 (s, 3H), 4.45 (m, 1H), 7.12 (m, 2H), 7.48 (br m, 1H), 8.03 (m, 2H), 8.18 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 6.4, 23.3, 56.1, 56.5, 63.0, 102.5, 115.6, 117.8, 125.6, 133.7, 151.9, 161.3, 164.3, 171.3 ppm; IR (neat): 3545, 3426, 3266, 3079, 2204, 1652, 1590, 1510, 1425, 1254, 1173, 1067, 1015, 835 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 329.2 (6) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}N_3O_4$: 330.1448, found: 330.1447; HPLC purity >98%.

4.2.1.60. 4-[(*E*)-3-Amino-2-cyano-3-oxoprop-1-en-1-yl]phenyl acetate (34). A solution of **21** (188 mg, 1.0 mmol), triethylamine (3.0 ml, 21.6 mmol) and acetic anhydride (5.0 ml, 52.9 mmol) in acetone (5 ml) and dichloromethane (5 ml) was stirred for 30 min. After quenching with water and evaporation of the solvent the residue was purified by flash chromatography (cyclohexane/ethyl acetate). Compound **34** was obtained as a colorless solid (105 mg, 46%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.30 (s, 3H), 7.15 (br m, 2H), 7.35 (m, 2H), 8.07 (m, 2H), 8.23 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 21.0, 106.4, 117.2, 123.6, 130.6, 132.6, 151.3, 154.8, 162.6, 169.3 ppm; IR (neat): 3410, 3152, 2218, 1760, 1692, 1595, 1507, 1418, 1380, 1364, 1294, 1199, 1166, 1116, 1014, 971, 946, 907, 841, 790 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{11}N_2O_3$: 231.0764, found: 231.0750. Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.62; H, 4.53; N, 12.05.

4.2.2. Genreal procedure for the preparation of compounds 2a–4b, 22a/b

A solution of arylketone (1 equiv), cyanoacetamide (1.0–1.5 equiv), NH_4OAc (0.25 equiv) and acetic acid (0.75 equiv) in toluene (10–25 ml) was refluxed at a Dean-Stark apparatus for 2–5 h. After cooling to room temperature crystallization occurred in the case of **2a** and **4b**. The crystals were washed with diethyl ether and water. The remaining mixture was evaporated and the residue was purified by flash chromatography (cyclohexane/ethyl acetate) to isolate the *cis* and *trans* isomers.

4.2.2.1. (*E*)-2-Cyano-3-phenylbut-2-enamide (2a) and (*Z*)-2-cyano-3-phenylbut-2-enamide (2b). Starting from acetophenone (1.80 g, 15.0 mmol) and 2-cyanoacetamide (1.39 g, 16.5 mmol) compound **2a** (470 mg, 17%) and **2b** (450 mg, 16%) were obtained as colorless solids.

4.2.2.1.1. (*E*)-2-Cyano-3-phenylbut-2-enamide (2a). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.48 (s, 3H), 7.06 (br m, 1H), 7.36 (br m, 1H), 7.43–7.53 (m, 5H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.0, 108.5, 116.9, 127.1, 128.6, 129.7, 139.3, 160.8, 163.5 ppm; IR (neat): 3371, 3176, 2215, 1655, 1590, 1491, 1429, 1380, 1121, 793, 764, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0866, found: 187.0867. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.90; H, 5.55; N, 14.96.

4.2.2.1.2. (*Z*)-2-Cyano-3-phenylbut-2-enamide (2b). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.44 (s, 3H), 6.78 (br m, 2H), 7.40 (m, 5H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.0, 109.2, 116.7, 127.1, 128.3, 129.5, 138.1, 158.7, 163.4 ppm; IR (neat): 3371, 3176, 2217, 1644, 1591, 1491, 1381, 1279, 1086, 794, 764, 696 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0866, found: 187.0864; HPLC purity 70% (containing 30% **2a**).

4.2.2.2. (*E*)-2-Cyano-4-methyl-3-phenylpent-2-enamide (3a) and (*Z*)-2-cyano-4-methyl-3-phenylpent-2-enamide (3b). Starting from isobutyrophenone (5.0 g, 33.7 mmol) and 2-cyanoacetamide (2.84 g, 33.8 mmol) compound **3a** (40 mg, 0.5%) and **3b** (425 mg, 6%) were obtained as colorless solids with pure crystals of **3b** used for X-ray analysis.

4.2.2.2.1. (*E*)-2-Cyano-4-methyl-3-phenylpent-2-enamide (3a). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.02 (d, J = 6.9 Hz, 6H), 3.61 (sept, J = 6.9 Hz, 1H), 7.07 (br m, 2H), 7.22 (m, 2H), 7.45 (m, 3H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 20.9, 32.8, 110.9, 116.7, 128.5, 129.0, 129.3, 137.5, 164.0, 171.9 ppm; IR (neat): 3357, 3158, 2967, 2223, 1687, 1631, 1581, 1489, 1460, 1440, 1371, 989, 800, 758, 704 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1169. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.70; H, 6.59; N, 12.99.

4.2.2.2.2. (*Z*)-2-Cyano-4-methyl-3-phenylpent-2-enamide (3b). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.08 (d, J = 6.9 Hz, 6H), 3.32 (sept, J = 6.9 Hz, 1H), 6.57 (br m, 2H), 7.21 (m, 2H), 7.41 (m, 3H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): δ = 20.7, 36.5, 111.1 116.3, 128.6, 128.8, 129.3, 136.0, 163.6 169.5 ppm; IR (neat): 3454, 3403, 3188, 2973, 2936, 2271, 1672, 1604, 1410, 1378, 1263, 926, 852, 795, 755, 709 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1188; HPLC purity >98%.

4.2.2.3. (*E*)-2-Cyano-3-phenylhex-2-enamide (4a) and (*Z*)-2-cyano-3-phenylhex-2-enamide (4b). Starting from butyrophenone (2.22 g, 15.0 mmol) and 2-cyanoacetamide (1.68 g,

20.0 mmol) compound **4a** (315 mg, 10%) and **4b** (295 mg, 9%) were obtained as colorless solids.

4.2.2.3.1. (*E*)-2-Cyano-3-phenylhex-2-enamide (4a). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.3 Hz, 3H), 1.41 (m, 2H), 3.09 (m, 2H), 5.64 (br m, 1H), 6.22 (br m, 1H), 7.36 (m, 2H), 7.45 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.8, 37.0, 105.9, 117.7, 127.2, 128.7, 130.1, 139.3, 162.8, 175.4 ppm; IR (neat): 3410, 3322, 2962, 2220, 2025, 1975, 1697, 1660, 1565, 1440, 1362, 1080, 777, 739, 697 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1180. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.99; H, 6.72; N, 13.01.

4.2.2.3.2. (*Z*)-2-Cyano-3-phenylhex-2-enamide (4b). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.4 Hz, 3H), 1.42 (m, 2H), 2.81 (m, 2H), 5.37 (br m, 1H), 5.82 (br m, 1H), 7.20 (m, 2H), 7.41 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 20.9, 41.5, 108.8, 116.1, 126.8, 128.9, 129.8, 136.9, 163.0, 168.7 ppm; IR (neat): 3383, 3147, 2962, 2209, 1691, 1593, 1443, 1374, 1292, 1159, 1069, 802, 759, 695 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1180. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 73.07; H, 6.69; N, 13.04.

4.2.2.4. (*E*)-2-Cyano-3-(4-hydroxyphenyl)but-2-enamide (22a) and (*Z*)-2-Cyano-3-(4-hydroxyphenyl)but-2-enamide (22b). Starting from 4-hydroxyacetophenone (2.04 g, 15.0 mmol) and 2-cyanoacetamide (1.39 g, 16.5 mmol) compound **22a** (250 mg, 8%) was obtained as colorless crystalline solid and **22b** (240 mg, 8%) as a pale yellow solid.

4.2.2.4.1. (*E*)-2-Cyano-3-(4-hydroxyphenyl)but-2-enamide (22a). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.46 (s, 3H), 6.92 (m, 2H), 6.94 (br m, 1H), 7.26 (br m, 1H), 7.43 (m, 2H), 8.83 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 22.2, 107.2, 116.1, 118.3, 130.1, 132.0, 159.8, 160.0, 164.1 ppm; IR (neat): 3435, 3193, 2224, 1656, 1609, 1587, 1513, 1433, 1370, 1274, 1220, 1178, 1144, 1118, 837 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0815, found: 203.0813; HPLC purity >98%.

4.2.2.4.2. (*Z*)-2-Cyano-3-(4-hydroxyphenyl)but-2-enamide (22b). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.41 (s, 3H), 6.75 (br m, 2H), 6.85 (m, 2H), 7.30 (m, 2H), 8.79 (bs, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 24.4, 108.8, 116.1, 117.5, 130.1, 131.9, 159.9, 164.1, 164.9 ppm; IR (neat): 3240, 2224, 1651, 1605, 1566, 1514, 1362, 1268, 1234, 1189, 850, 831 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0815, found: 203.0815; HPLC purity >95% (containing <5% **22a**).

4.2.2.5. 2-Cyano-2-(2,3-dihydro-1*H*-inden-1-ylidene)acetamide (45). A solution of 1-indanone (397 mg, 3.0 mmol), 2-cyanoacetamide (252 mg, 3.0 mmol), NH_4OAc (58 mg, 0.75 mmol) and *N*-methylpiperazine (15 mg, 0.15 mmol) was stirred in ethanol (5 ml) at 60 °C overnight. After the evaporation of the solvent the residue was purified by flash chromatography (cyclohexane/ethyl acetate). Compound **45** was obtained as a pale brown solid (30 mg, 5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.08 (m, 2H), 3.57 (m, 2H), 5.81 (br m, 1H), 6.34 (br m, 1H), 7–34–7.54 (m, 3H), 8.53 (d, J = 8.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3, 34.2, 94.7, 110.0, 118.4, 125.8, 127.4, 133.5, 137.3, 153.3, 164.3, 174.6 ppm; IR (neat): 3450, 3361, 3297, 3157, 2203, 1683, 1613, 1567, 1469, 1429, 1396, 1352, 1307, 1206, 1097, 764 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{11}N_2O$: 199.0866, found: 199.0867; HPLC purity >93%.

4.2.3. General procedure for the preparation of compounds 55–60, 63

A solution of fluorobenzaldehyde (1 equiv), cyanoacetamide or derivative (1.05–1.1 equiv) and cyclic amine (2.5–10 equiv) in ethanol (5–10 ml) was reacted in a microwave reactor for 20 min at 160 °C. After cooling to room temperature precipitation occurred and the precipitate was collected by filtration and washed with ethanol/water (1:1). If precipitation did not occur, the mixture was evaporated and the residue was purified by flash chromatography.

4.2.3.1. (*E*)-2-Cyano-3-(4-pyrrolidin-1-ylphenyl)acrylamide (55). Starting from 4-fluorobenzaldehyde (372 mg, 3.0 mmol), 2-cyanoacetamide (265 mg, 3.15 mmol) and pyrrolidine (534 mg, 7.51 mmol) compound **55** was obtained after precipitation and recrystallization from acetone as an orange solid (280 mg, 39%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.05 (m, 5H), 3.42 (m, 4H), 6.67 (m, 2H), 6.79 (br m, 2H), 7.91 (m, 2H), 8.02 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.9, 47.3, 96.4, 111.8, 118.3, 118.4, 132.8, 150.4, 150.6, 164.0 ppm; IR (neat): 3395, 3151, 2517, 2159, 2029, 1976, 1660, 1604, 1568, 1523, 1479, 1443, 1396, 1344, 1245, 1157, 957, 807 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{16}N_3O$: 242.1288, found: 242.1287; HPLC purity >98%.

4.2.3.2. (*E*)-2-Cyano-3-(4-piperidin-1-ylphenyl)acrylamide (56). Starting from 4-fluorobenzaldehyde (400 mg, 3.22 mmol), 2-cyanoacetamide (300 mg, 3.57 mmol) and piperidine (686 mg, 8.06 mmol) compound **56** was obtained after precipitation as an orange solid (350 mg, 43%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.66 (m, 6H), 3.48 (m, 4H), 6.86 (br m, 2H), 7.02 (m, 2H), 7.90 (m, 2H), 8.03 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.0, 24.9, 47.5, 98.1, 113.4, 118.0, 119.6, 132.7, 150.2, 153.1, 163.8 ppm; IR (neat): 3392, 3174, 2939, 2852, 2220, 1662, 1604, 1573, 1518, 1442, 1395, 1354, 1271, 1242, 1197, 1123, 918, 805 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{18}N_3O$: 256.1444, found: 256.1445; HPLC purity >96%.

4.2.3.3. (*E*)-2-Cyano-3-(4-morpholin-1-ylphenyl)acrylamide (57). Starting from 4-fluorobenzaldehyde (621 mg, 5.0 mmol), 2-cyanoacetamide (441 mg, 5.25 mmol) and morpholine (1.09 g, 12.5 mmol) compound **57** was obtained after precipitation as a yellow solid (340 mg, 26%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.33 (m, 4H), 3.72 (m, 4H), 7.05 (m, 2H), 7.59 (br m, 2H), 7.86 (m, 2H), 8.00 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.5, 65.8, 99.5, 113.5, 117.8, 121.1, 132.4, 150.2, 153.4, 163.6 ppm; IR (neat): 3135, 2208, 1675, 1605, 1569, 1515, 1434, 1361, 1275, 1254, 1232, 1193, 1115, 1071, 1031, 928, 811 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{16}N_3O_2$: 258.1237, found: 258.1217; HPLC purity >98%.

4.2.3.4. (*E*)-2-Cyano-3-(4-piperazin-1-ylphenyl)acrylamide (58). Starting from 4-fluorobenzaldehyde (372 mg, 3.0 mmol), 2-cyanoacetamide (265 mg, 3.15 mmol) and piperazine (2.58 g, 30.0 mmol) compound **58** was obtained after precipitation as an orange solid (320 mg, 42%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.92 (m, 4H), 3.37 (m, 4H), 6.88 (br m, 2H), 7.04 (m, 2H), 7.92 (m, 2H), 8.05 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.3, 47.4, 98.6, 113.4, 117.9, 120.3, 132.5, 150.2, 153.6, 163.7 ppm; IR (neat): 3382, 3264, 2926, 2213, 1681, 1632, 1605, 1561, 1513, 1434, 1362, 1255, 1233, 1189, 1125, 1017, 966, 910, 814 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_4O$: 257.1397, found: 257.1320; HPLC purity >90%.

4.2.3.5. (*E*)-2-Cyano-3-[4-(4-methylpiperazin-1-yl)phenyl]acrylamide (59). Starting from 4-fluorobenzaldehyde (372 mg, 3.0 mmol), 2-cyanoacetamide (265 mg, 3.15 mmol) and *N*-methyl-

piperazine (751 mg, 7.5 mmol) compound **59** was obtained after precipitation as an orange solid (300 mg, 37%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.26 (s, 3H), 2.48 (m, 4H), 3.44 (m, 4H), 6.88 (br m, 2H), 7.05 (m, 2H), 7.92 (m, 2H), 8.05 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.6, 46.1, 54.1, 99.0, 113.6, 117.9, 120.5, 132.4, 150.2, 153.2, 163.6 ppm; IR (neat): 3116, 2807, 2208, 1683, 1607, 1572, 1517, 1448, 1362, 1291, 1254, 1234, 1194, 1145, 1079, 1001, 925, 810, 791 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{19}N_4O$: 271.1553, found: 271.1542; HPLC purity >90%.

4.2.3.6. (*E*)-2-Cyano-*N*-cyclopropyl-3-[4-(4-methylpiperazin-1-yl)phenyl]acrylamide (60). Starting from 4-fluorobenzaldehyde (372 mg, 3.0 mmol), **84** (391 mg, 3.15 mmol) and *N*-methylpiperazine (751 mg, 7.5 mmol) compound **60** was obtained after precipitation and recrystallization from methanol/water as an orange solid (180 mg, 19%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.56 (m, 2H), 0.66 (m, 2H), 2.20 (s. 3H), 2.41 (m, 4H), 2.75 (m, 1H), 3.37 (m, 4H), 7.04 (m, 2H), 7.83 (m, 2H), 7.90 (s, 1H), 8.20 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7, 23.3, 45.7, 46.2, 54.2, 99.1, 113.6, 117.6, 120.6, 132.4, 149.6, 153.1, 163.4 ppm; IR (neat): 3323, 2937, 2842, 2794, 2218, 1665, 1606, 1574, 1509, 1449, 1377, 1359, 1277, 1232, 1192, 1008, 920, 819 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{18}H_{23}N_4O$: 311.1866, found: 311.1854; HPLC purity >94%.

4.2.3.7. (*E*)-2-Cyano-3-(2-morpholin-4-ylphenyl)acrylamide (63). Starting from 2-fluorobenzaldehyde (372 mg, 3.0 mmol), 2-cyanoacetamide (265 mg, 3.15 mmol) and morpholine (653 mg, 7.5 mmol) compound **63** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a yellow solid (60 mg, 8%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.97 (m, 4H), 3.81 (m, 4H), 7.12 (br m, 2H), 7.21 (m, 2H), 7.55 (m, 1H), 8.03 (m, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (125 MHz, acetone-d_6): δ = 42.9, 66.8, 110.9, 116.7, 116.9, 121.2, 125.9, 129.7, 135.5, 143.7, 161.1, 163.2 ppm; IR (neat): 3370, 3145, 2211, 1696, 1591, 1481, 1447, 1373, 1346, 1298, 1227, 1111, 1068, 937, 768 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 257.1 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{14}H_{16}N_3O_2$: 258.1237, found: 258.1227; HPLC purity >94%.

4.2.4. General procedure for the preparation of compounds 70, 71, 97

A solution of arylbromide (1 equiv), morpholine (1.5 equiv), L-proline (0.2 equiv), CuI (0.1 equiv) and K_2CO_3 (2 equiv) in DMSO (1.5–3 ml) was stirred under a nitrogen atmosphere for 4–20 h at 80 °C. After cooling to room temperature water was added and the mixture was extracted with ethyl acetate. After evaporation of the solvent the residue was purified by flash chromatography.

4.2.4.1. (*E*)-2-Cyano-3-(5-morpholin-4-yl-2-thienyl)acrylamide (70). Starting from **50** (129 mg, 0.5 mmol) compound **70** was obtained after flash chromatography (cyclohexane/ethyl acetate) as an orange crystalline solid (50 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.39 (m, 4H), 3.84 (m, 4H), 6.14 (d, *J* = 4.5 Hz, 1H), 7.45 (d, *J* = 4.5 Hz, 1H), 8.17 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 49.3, 65.2, 90.8, 105.2, 118.5, 119.7, 142.7, 144.0, 164.0, 167.0 ppm; IR (neat): 3472, 3103, 2194, 1691, 1573, 1510, 1472, 1442, 1396, 1374, 1357, 1310, 1282, 1243, 1154, 1111, 1086, 1027, 934, 893, 849, 762 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 263.0 (100) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{14}N_3O_2S$: 264.0801, found: 264.0798. Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.57; H, 5.30; N, 15.75.

4.2.4.2. (*E*)-2-Cyano-*N*-cyclopropyl-3-(5-morpholin-4-yl-2-furyl)acrylamide (71). Starting from **53** (281 mg, 1.0 mmol) compound **71** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a yellow crystalline solid (270 mg, 94%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.53 (m, 2H), 0.61 (m, 2H), 2.71 (m, 1H), 3.44 (m, 4H), 3.71 (m, 4H), 5.77 (d, *J* = 4.0 Hz, 1H), 7.34 (d, *J* = 4.0 Hz, 1H), 7.52 (s, 1H), 7.77 (d, *J* = 4.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.8, 23.3, 45.6, 65.2, 88.4, 89.7, 118.4, 132.3, 139.6, 162.4, 164.0 ppm; IR (neat): 3345, 3119, 3023, 2964, 2863, 2188, 1644, 1614, 1542, 1488, 1445, 1408, 1366, 1348, 1319, 1261, 1236, 1173, 1116, 1048, 984, 884, 764, 690, 657 cm^{-1}; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{18}N_3O_3$: 288.1343, found: 288.1346. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.67; H, 6.11; N, 14.56.

4.2.4.3. 3-Morpholin-4-ylbenzaldehyde (97). Starting from 2-bromobenzaldehyde (925 mg, 5.0 mmol) compound **97** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a pale yellow oil (140 mg, 15%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20 (m, 4H), 3.85 (m, 4H), 7.14 (m, 1H), 7.37 (m, 3H), 9.93 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.7, 66.6, 114.5, 121.5, 122.2, 129.7, 137.2, 151.6, 192.6 ppm; MS (EI, 70 eV): *m/z* (%): 194.1 (86) [M]$^+$.

4.2.4.4. (*E*)-2-Cyano-3-[4-(piperidin-1-ylcarbonyl)phenyl]acrylamide (64). To a solution of **37** (432 mg, 2.0 mmol), HOAt (300 mg, 2.20 mmol) and HATU (912 mg, 2.40 mmol) in dry DMF (3 ml) was added DIPEA (1.10 ml, 6.0 mmol) slowly at 0 °C. After 30 min the mixture was allowed to warm up to room temperature and piperidine (0.19 ml, 2.3 mmol) was added. After 4 h the reaction was quenched with water and the mixture was extracted with ethyl acetate. After drying over $MgSO_4$ the solvent was evaporated and the residue was purified by flash chromatography (ethyl acetate/methanol). Compound **64** was obtained as a pale yellow solid (345 mg, 61%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.55 (br m, 6H), 3.24 (br m, 2H), 3.58 (br m, 2H), 7.53 (m, 2H), 7.80 (br m, 1H), 7.94 (br m, 1H), 7.96 (m, 2H), 8.20 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.0, 25.2, 25.9, 42.3, 47.9, 107.5, 116.3, 127.3, 130.1, 132.5, 139.9, 149.7, 162.5, 167.7 ppm; IR (neat): 3360, 3160, 2944, 2856, 2219, 1694, 1610, 1592, 1440, 1376, 1272, 1206, 1117, 1090, 1005, 948, 842 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 283.0 (67) [M]$^+$; HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{16}H_{18}N_3O_2$: 284.1394, found: 284.1395; HPLC purity >98%.

4.2.4.5. 3-[(*E*)-2-Cyano-3-(cyclopropylamino)-3-oxoprop-1-en-1-yl]-*N*-cyclopropylbenzamide (66). To a solution of **39** (128 mg, 0.50 mmol), HOAt (75 mg, 0.55 mmol) and HATU (228 mg, 0.60 mmol) in dry DMF (3 ml) was added DIPEA (0.28 ml, 1.5 mmol) slowly at 0 °C. After 30 min the mixture was allowed to warm up to room temperature and cyclopropylamine (33 mg, 0.58 mmol) was added. After 4 h the reaction was quenched with water and the mixture was extracted with ethyl acetate. After drying over $MgSO_4$ the solvent was evaporated and the residue was purified by flash chromatography (ethyl acetate/methanol). Compound **66** was obtained as a colorless solid (75 mg, 51%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.58 (m, 4H), 0.70 (m, 4H), 2.78 (m, 1H), 2.85 (m, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.95 (m, 1H), 8.07 (m, 1H), 8.13 (s, 1H), 8.28 (m, 1H), 8.55 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7, 23.1, 23.4, 107.6, 115.9, 129.1, 129.5, 130.3, 131.4, 132.0, 135.3, 149.4, 162.2, 166.5 ppm; IR (neat): 3355, 3293, 2219, 1678, 1633, 1604, 1530, 1360, 1313, 1265, 1227, 1207, 1053, 1023, 965, 849, 683 cm^{-1};

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_2$: 296.1394, found: 296.1392; HPLC purity >95%.

4.2.5. General procedure for the preparation of compounds 76–81

To a stirring solution of arylcyanoacrylamide (1 equiv) in methanol (5–10 ml) was added $NaBH_4$ (5 equiv) at 0 °C. After 1 h the reaction was quenched by the addition of an equivalent volume of water. If precipitation occurred, the precipitate was collected by filtration and washed with water/methanol (1:1). If precipitation did not occur, the mixture was evaporated and the residue was purified by flash chromatography.

4.2.5.1. 2-Cyano-3-[4-(dimethylamino)phenyl]propanamide (76). Starting from **40** (646 mg, 3.0 mmol) compound **76** was obtained after precipitation as a colorless solid (400 mg, 61%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.85 (s, 6H), 2.86–3.08 (m, 2H), 3.81 (m, 1H), 6.67 (m, 2H), 7.09 (m, 2H), 7.42 (br m, 1H), 7.72 (br m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.6, 40.0, 40.1, 112.3, 118.6, 124.0, 129.5, 149.5, 166.5 ppm; IR (neat): 3410, 3182, 2915, 2796, 2254, 1660, 1614, 1521, 1475, 1442, 1408, 1331, 1287, 1219, 1188, 1163, 1128, 1057, 945, 814, 743, 710 cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{12}H_{15}N_3NaO$: 240.1107, found: 240.1095. Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.18; H, 7.07; N, 19.16.

4.2.5.2. 2-Cyano-3-(3,4,5-trimethoxyphenyl)propanamide (77). Starting from **20** (525 mg, 2.0 mmol) compound **77** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a colorless solid (400 mg, 76%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.08 (m, 1H), 3.21 (m, 1H), 3.69 (s, 3H), 3.79 (s, 6H), 3.93 (m, 1H), 6.66 (s, 2H), 6.83 (br m, 1H), 7.21 (br m, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 37.0, 40.7, 56.4, 60.4, 107.4, 118.8, 133.3, 138.3, 154.3, 167.2 ppm; IR (neat): 3395, 3308, 2941, 2835, 2248, 1670, 1618, 1590, 1507, 1460, 1422, 1402, 1339, 1311, 1239, 1185, 1153, 1123, 1008, 974, 807 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 264.1 (38) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}N_2O_4$: 265.1183, found: 265.1182. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.07; H, 5.95; N, 10.49.

4.2.5.3. 2-Cyano-3-(4-morpholin-4-ylphenyl)propanamide (78). Starting from **57** (128 mg, 0.5 mmol) compound **78** was obtained after flash chromatography (cyclohexane/ethyl acetate) as a colorless solid (70 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10–3.24 (m, 6H), 3.57 (m, 1H), 3.84 (m, 4H), 5.68 (br m, 1H), 5.98 (br m, 1H), 6.87 (m, 2H), 7.19 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.9, 40.6, 49.1, 66.9, 115.8, 117.9, 126.4, 130.0, 150.7, 165.9 ppm; IR (neat): 3423, 3170, 2969, 2857, 2813, 2257, 1674, 1613, 1516, 1448, 1379, 1330, 1301, 1263, 1233, 1193, 1119, 1067, 1050, 927, 807 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{18}N_3O_2$: 260.1394, found: 260.1392. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.55; H, 6.71; N, 16.14.

4.2.5.4. 2-Cyano-3-(1*H*-indol-3-yl)propanamide (79). Starting from **54** (211 mg, 1.0 mmol) compound **79** was obtained after precipitation as a colorless solid (140 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44 (m, 1H), 3.51 (m, 1H), 3.71 (m, 1H), 5.40 (br m, 1H), 5.91 (br m, 1H), 7.12–7.24 (m, 3H), 7.39 (m, 1H), 7.64 (m, 1H), 8.11 (br m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.0, 39.1, 109.4, 111.5, 118.4, 118.5, 118.9, 121.1, 123.9, 126.7, 136.1, 166.8 ppm; IR (neat): 3401, 3354, 3176, 2927, 2257, 1661, 1455, 1420, 1325, 1228, 1119, 1097, 1008, 927, 846, 809, 754 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}N_3O$: 214.0975, found: 214.0963; HPLC purity >98%.

4.2.5.5. (*E*)-2-Cyano-*N*-cyclopropyl-5-[4-(dimethylamino)-phenyl]pent-4-enamide (80). Starting from **69** (141 mg, 0.5 mmol) compound **80** was obtained after precipitation as a pale orange solid (110 mg, 78%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.39 (m, 2H), 0.62 (m, 2H), 2.62 (m, 2H), 2.88 (s, 6H), 3.65 (t, *J* = 7.3 Hz, 1H), 5.85 (dt, *J* = 15.7, 7.2 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.66 (m, 2H), 7.20 (m, 2H), 8.38 (d, *J* = 4.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.5, 5.8, 22.6, 33.5, 37.9, 40.0, 112.2, 118.4, 119.2, 124.4, 127.0, 133.1, 149.9, 165.7 ppm; IR (neat): 3287, 2898, 2247, 2189, 1648, 1611, 1523, 1345, 1292, 1226, 1192, 1166, 1063, 1024, 967, 813 cm^{-1}; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{21}N_3NaO$: 306.1577, found: 306.1570; HPLC purity >98%.

4.2.5.6. (*E*)-2-Cyano-4-methyl-5-phenylpent-4-enamide (81). Starting from **67** (213 mg, 1.0 mmol) compound **81** was obtained after precipitation as a colorless solid (155 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93 (s, 3H), 2.74 (m, 1H), 2.88 (m, 1H), 3.60 (m, 1H), 5.90 (br m, 1H), 6.24 (br m, 1H), 6.49 (s, 1H), 7.18–7.39 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 37.6, 40.5, 117.8, 126.8, 128.2, 128.9, 129.9, 132.2, 137.1, 166.3 ppm; IR (neat): 3362, 3184, 2930, 2255, 1662, 1490, 1415, 1314, 1247, 1167, 1111, 1022, 916, 806, 748, 692 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1176; HPLC purity >92%.

4.2.5.7. 5-Phenyl-1,2,3-triazole-4-carbonitrile (82). To a stirring solution of sodium azide (200 mg, 3.08 mmol) in DMF (2 ml) was added a solution of **83** (255 mg, 2.0 mmol) in DMF (0.8 ml) drop wise at 90 °C under a nitrogen atmosphere. After 1.5 h the reaction was quenched by the addition of an equivalent volume of water. The precipitated product was filtered off and washed with water and diethyl ether. Compound **83** was obtained as a pale brown solid (280 mg, 82%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.58 (m, 3H), 7.97 (m, 2H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 113.7, 127.4, 127.6, 130.1, 130.2, 130.9, 150.9 ppm; IR (neat): 3076, 3000, 2948, 2904, 2812, 2241, 1610, 1496, 1484, 1273, 1220, 1101, 1024, 984, 914, 865, 834, 773, 715, 684 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 170.1 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_9H_7N_4$: 171.0665, found: 171.0665. Anal. Calcd for $C_9H_6N_4$: C, 63.52; H, 3.55; N, 32.92. Found: C, 63.46; H, 3.80; N, 32.72.

4.2.5.8. 3-Phenylprop-2-ynenitrile (83). To a stirring solution of copper cyanide (7.16 g, 80.0 mmol), sodium iodide (400 mg, 2.67 mmol) and phenylacetylene (2.93 ml, 26.7 mmol), in DMSO (50 ml), acetonitrile (13.3 ml) and water (0.72 ml) was added trimethylsilyl chloride (10.1 ml, 79.6 mmol) over 1 h at room temperature under a nitrogen atmosphere. After the addition, the reaction was warmed up to 50 °C and was stirred at this temperature for 100 h. After addition of water the mixture was extracted with dichloromethane. The extract was washed with sodium bicarbonate solution and brine. After evaporation of the solvent, the residue was purified by flash chromatography (cyclohexane/ethyl acetate) to get compound **83** as a colorless crystalline solid (850 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (m, 2H), 7.53 (m, 1H), 7.60 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.1, 82.9, 105.5, 117.5, 128.9, 131.9, 133.5 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for C_9H_6N: 128.0494, found: 128.0504.

4.2.6. General procedure for the preparation of compounds 84–88

A mixture of methyl cyanoacetate (1 equiv) and amine (1–1.05 equiv) was stirred 1 h at 0 °C and at room temperature overnight. If precipitation occurred, the precipitate was filtered off and washed with diethyl ether. If precipitation did not occur, the mixture was evaporated and the residue was washed with diethyl ether.

4.2.6.1. 2-Cyano-*N*-cyclopropylacetamide (84). Starting from Cyclopropylamine (1.4 ml, 20.0 mmol) and methyl cyanoacetate (1.98, 20.0 mmol) compound **84** was obtained after precipitation as a colorless solid (2.13 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.58 (m, 2H), 0.82 (m, 2H), 2.72 (m, 1H), 3.33 (s, 2H), 6.33 (br m, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 6.2, 23.6, 25.9, 115.9, 163.8 ppm; MS (EI, 70 eV): *m/z* (%): 124.0 (29) $[M]^+$.

4.2.6.2. 2-Cyano-*N*-(tetrahydrofuran-2-ylmethyl)acetamide (85). Starting from 1-(tetrahydrofuran-2-yl)methanamine (3.1 ml, 30.0 mmol) and methyl cyanoacetate (3.00, 30.3 mmol) compound **85** was obtained after addition of water (5 drops) and precipitation as a pale rose solid (4.55 g, 90%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.54 (m, 1H), 1.79–1.98 (m, 3H), 3.20 (m, 1H), 3.35 (m, 1H), 3.58 (s, 2H), 3.65 (m, 1H), 3.78 (m, 1H), 3.89 (m, 1H), 7.41 (br m, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 25.9, 26.3, 29.3, 44.2, 44.3, 68.3, 78.0, 116.1, 162.8 ppm; MS (EI, 70 eV): *m/z* (%): 169.0 (2) $[M+H]^+$.

4.2.6.3. 2-Cyano-*N*-(pyridin-2-ylmethyl)acetamide (86). Starting from 1-pyridin-2-ylmethanamine (1.08 g, 10.0 mmol) and methyl cyanoacetate (990 mg, 10.0 mmol) compound **86** was obtained after evaporation and washing procedure as a colorless solid (1.79 g, quant.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 2H), 4.38 (d, *J* = 5.9 Hz, 2H), 7.29 (m, 2H), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H), 8.50 (m, 1H), 8.81 (br m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.3, 44.6, 116.2, 121.2, 122.3, 136.8, 148.9, 157.6, 162.4 ppm; MS (MALDI-TOF): *m/z*: 176.2 $[M+H]^+$.

4.2.6.4. 3-Morpholin-4-yl-3-oxopropanenitrile (87). Starting from morpholine (3.50 ml, 40.2 mmol) and methyl cyanoacetate (3.96 g, 40.0 mmol) compound **87** was obtained after addition of diethyl ether and precipitation as a pale brown solid (5.53 g, 90%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.50 (m, 4H), 3.63 (m, 4H), 3.87 (m, 2H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 43.1, 47.0, 66.9, 115.8, 162.1 ppm; MS (MALDI-TOF): *m/z*: 155.1 $[M+H]^+$.

4.2.6.5. 3-(4-Methylpiperazin-1-yl)-3-oxopropanenitrile (88). Starting from *N*-methylpiperazine (2.0 g, 20.0 mmol) and methyl cyanoacetate (1.98 g, 20.0 mmol) compound **88** was obtained after precipitation as a pale rose solid (2.69 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.16 (s, 3H), 2.21–2.32 (m, 4H), 3.28–3.46 (m, 4H), 4.01 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.7, 41.5, 45.2, 45.5, 54.0, 54.3, 116.1, 161.4 ppm; MS (EI, 70 eV): *m/z* (%): 167.1 (64) $[M]^+$.

4.2.6.6. 2-Cyano-*N*,*N*-diethylacetamide (89). A mixture of methyl cyanoacetate (1.5 g, 15.1 mmol) and diethylamine (3.0 ml, 29.0 mmol) was stirred 1 h at 0 °C and at room temperature overnight. Dichloromethane was added, the precipitate was filtered and discarded; the organic layer was washed with 1 N hydrochloric acid and sodium bicarbonate solution and dried over $MgSO_4$. After evaporation of the solvent, compound **89** was obtained as a pale red oil (630 mg, 30%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.07 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 3.35 (m, 4H), 3.81 (s, 2H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 13.1, 14.2, 25.1, 41.1, 43.0, 116.1, 162.3 ppm; MS (MALDI-TOF): *m/z*: 141.1 $[M+H]^+$.

4.2.6.7. N^2-(*tert*-Butyloxycarbonyl)-N^1-cyclopropylserineamide (90). To a solution of *N*-(*tert*-butoxycarbonyl)-L-serine (2.00 g, 9.75 mmol) and HATU (4.08 g, 10.7 mmol) in dry DMF (15 ml) were added cyclopropylamine (0.71 ml, 10.2 mmol) and DIPEA (5.09 ml, 29.3 mmol) slowly. After 2 h the reaction was quenched with water and the mixture was extracted with ethyl acetate. After drying over $MgSO_4$ the solvent was evaporated and the residue was purified by flash chromatography (dichloromethane/methanol). Compound **90** was obtained as a colorless solid (896 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.49 (m, 2H), 0.77 (m, 2H), 1.44 (s, 9H), 2.71 (m, 1H), 3.01 (br m, 1H), 3.19 (m, 1H), 3.62 (m, 1H), 4.06 (m, 1H), 5.55 (br m, 1H), 6.78 (br m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.4, 6.5, 22.5, 28.2, 54.8, 62.8, 80.5, 156.2, 172.8 ppm; MS (EI, 70 eV): *m/z* (%): 224.2 (1) $[M]^+$.

4.2.6.8. N^1-Cyclopropylserineamide hydrochloride (91). To a solution of **90** (628 mg, 2.57 mmol) in ethyl acetate (15 ml) was added a 2 N solution of HCl in diethyl ether (5 ml, 10.0 mmol) slowly. After 24 h at 4 °C the precipitate was collected by filtration and washed with diethyl ether. Compound **91** was obtained as a colorless solid (337 mg, 73%). ^{1}H NMR (300 MHz, D_2O): δ = 0.54 (m, 2H), 0.75 (m, 2H), 2.63 (m, 1H), 3.83–4.04 (m, 3H) ppm; ^{13}C NMR (75 MHz, D_2O): δ = 5.3, 22.0, 54.4, 60.1, 169.1 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_6H_{13}N_2O_2$: 145.0972, found: 145.0978.

4.2.6.9. 4-(Hydroxymethyl)benzaldehyde (93). A solution of terephthalaldehyde (7.5 g, 56 mmol) in THF (50 ml) was cooled to 0 °C. Sodium borohydride (750 mg, 19.8 mmol) was added and the mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was taken up in ethyl acetate and the solution was washed with water and brine and dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by flash chromatography (cyclohexane/ethyl acetate) to obtain **93** as a white solid (3.85 g, 50%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 4.49 (t, *J* = 5.3 Hz, 1H), 4.74, (d, *J* = 4.4 Hz, 2H), 7.58 (m, 2H), 7.88 (m, 2H), 10.01 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 64.1, 127.5, 130.2, 136.5, 150.4, 192.6 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_8H_9O_2$: 137.0597, found: 137.0612.

4.2.6.10. 4-Hydroxy-3-methoxy-5-nitrobenzaldehyde (94). To a solution of vanillin (5.0 g, 32.9 mmol) in acetic acid (50 ml) was added nitric acid (60%, 2.6 ml) slowly at 0 °C. Afterwards the solution was warmed up to room temperature and allowed to stir for another 30 min. The precipitate was filtered off and washed with cold water, to give compound **94** as a yellow solid (5.40 g, 83%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.95 (s, 3H), 7.61 (d, *J* = 1.8 Hz, 1H), 8.08 (d, *J* = 1.9 Hz, 1H), 9.85 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.8, 112.5, 120.8, 126.8, 137.0, 147.7, 150.0, 190.4 ppm; HRMS (ESI): *m/z* $[M-H]^-$ calcd for $C_8H_6NO_5$: 196.0251, found: 196.0277.

4.2.6.11. 3,4-Dihydroxy-5-nitrobenzaldehyde (95). A solution of **94** (3.5 g, 17.8 mmol) in hydrobromic acid (48%, 32 ml) was refluxed for 4 h. After cooling to room temperature and addition of water and ice, the precipitate was filtered off and washed with cold water, to give compound **95** as a brown solid (1.62 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.46 (d, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 1.9 Hz, 1H), 9.79 (s, 1H), 10.52 (br m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 115.8, 119.6, 127.0, 137.2, 147.2, 148.3, 190.5 ppm; HRMS (ESI): *m/z* $[M-H]^-$ calcd for $C_7H_4NO_5$: 182.0059, found: 182.0088.

4.2.6.12. 4-(Morpholin-4-ylcarbonyl)benzaldehyde (96). To a solution of 4-formylbenzoic acid (750 mg, 5.0 mmol), HOAt (750 mg, 5.50 mmol) and HATU (2.28 g, 6.0 mmol) in dry dichloromethane (15 ml) was added DIPEA (2.70 ml, 15.0 mmol) slowly at 0 °C. After 30 min the mixture was allowed to warm up to room temperature and morpholine (0.50 ml, 5.75 mmol) was added. After 2 h the solvent of the reaction mixture was evaporated and the residue was purified by flash chromatography (cyclohexane/ethyl acetate) to obtain compound **96** as a pale yellow oil (950 mg, 87%). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.31–3.79 (m, 8H), 7.63 (m, 2H), 7.99 (m, 2H), 10.09 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d_6): δ = 38.7, 67.2, 128.6, 130.3, 138.0, 142.6, 169.1, 192.5 ppm; MS (EI, 70 eV): *m/z* (%): 219.1 (64) $[M]^+$.

4.2.6.13. 4-(Benzyloxy)-3-methoxybenzaldehyde (98). A solution of vanillin (1.52 g, 10.0 mmol), K_2CO_3 (5 g, 36.2 mmol) and benzylbromide (2.5 ml, 21.0 mmol) in acetone (20 ml) was refluxed for 1 h. After cooling to room temperature and addition of water the emerging oil was extracted with hexane and separated. After removal of the solvent and drying compound **98** was obtained as a pale yellow solid (2.14 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94 (s, 3H), 5.24 (s, 2H), 6.98 (d, J = 8.2 Hz, 1H), 7.78–7.46 (m, 7H), 9.83 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1, 70.9, 109.3, 112.4, 126.6, 127.2, 128.2, 128.7, 130.3, 136.0, 150.1, 153.6, 190.9 ppm; MS (MALDI-TOF): m/z: 243.1 $[M+H]^+$.

Acknowledgements

Christoph Nitsche acknowledges funding by a fellowship of the Studienstiftung des deutschen Volkes. Christian Steuer acknowledges funding by a fellowship of the Konrad Adenauer Stiftung. We thank Franziska Schenk and Florian Mulks for assisting in the synthesis of some compounds. We thank Dr. Frank Rominger (Chemistry Department, University of Heidelberg) for performing the small-molecule X-ray analysis.

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