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Reaction between (*Z*)-Arylchlorooximes and α-Isocyanoacetamides: A Procedure for the Synthesis of Aryl-α-ketoamide Amides

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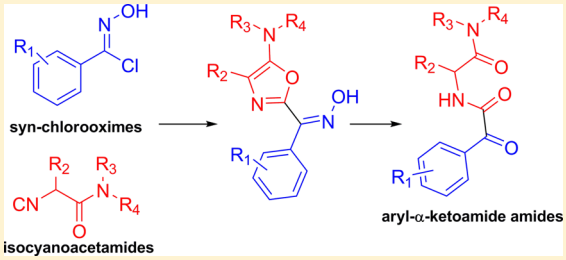
Supporting Information

ABSTRACT: (*Z*)-Arylchlorooximes and α-isocyanoacetamides undergo a smooth reaction to produce 1,3-oxazol-2-oxime derivatives in good yields. Opening of the oxazole ring and deoximation reaction give a facile access to aryl-α-ketoamide amides, a class of privileged scaffolds in medicinal chemistry and important synthetic intermediates in organic chemistry.

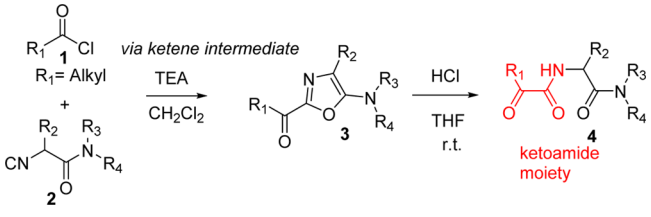


INTRODUCTION

It is clear for all the organic chemists involved in the search for novel isocyanide-mediated organic reactions[1] that the discovery of new suitable electrophilic partners for isocyanides can give a direct access to novel two- or multicomponent transformations[2] and consequently to an innovative way to synthesize known molecular scaffolds or give access to unknown molecular frameworks.

In this context, it is interesting to highlight the use of α-isocyanoacetamides **2** along with acyl chlorides[3] **1** or diazocarbonyl esters[4] to give substituted 2-acyl-5-amino-oxazoles **3**. As 5-aminooxazoles are not stable under acid conditions,[5] the 2-acyl-5-aminooxazoles can be hydrolyzed to give α-ketoamide amides **4** (Scheme 1).

Scheme 1. Reaction between Acyl Chlorides and α-Isocyanoacetamides



The latter are warhead scaffolds in medicinal chemistry due to their activity as inhibitors, since they can react with the key cysteine or lysine residues in protease,[6] lipase,[7] and histone deacetylase,[8] or to the fact that they constitute useful intermediates for a variety of transformations in organic chemistry.[9]

A drawback of the reaction between acyl chlorides and α-isocyanoacetamides[3] was the lack of reactivity of the latter with aroyl chlorides due to the concomitant reduced nucleophilicity of the isocyano group and the reduced electrophilicity of the aroyl chloride coupled with the impossibility for the latter to generate the ketene intermediate.[3]

Any attempts (higher temperatures, neat conditions, MW heating) to react, in a productive way, an aroyl chloride with an α-isocyanoacetamides failed.

Herein, we fill the gap by presenting our results on the reaction between (*Z*)-chlorooximes[10] and α-isocyanoacetamides and its potential in the synthesis of medicinal relevant aryl α-ketoamide amides.

RESULTS AND DISCUSSION

Our recent finding that nitrile *N*-oxide species (generated via base dehydrochlorination of (*Z*)-chlorooximes **5**, Huisgen's in situ method)[11] are able to react in a stereoselective way with isocyanides **7** under mild reaction conditions (TEA, room temperature, dichloromethane) to give a nitrilium ion **8**, which can be further intercepted by a third nucleophile,[12,13] has paved the way for an extensive use of this reaction which, to our surprise, has eluded chemists (Scheme 2).

A possible explanation of this missed opportunity might be found in a 1965 paper[14] where it was documented that nitrile *N*-oxides **10** and isocyanides **11** react to give isocyanates **12** and nitriles **13** according to the reaction reported in Scheme 3.

As no mechanism for this reaction was reported, we propose the following scenario: the isocyanide **11** attacks, in a stereoselective way,[15,16] the electrophilic carbon of the nitrile

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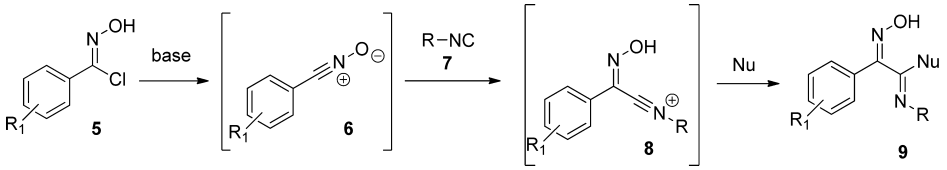
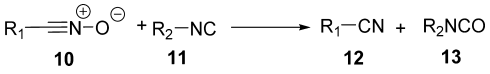
Scheme 2. Proposed Scheme for the Formation of Novel MCRs via Nitrile *N*-Oxide Species



Scheme 3. Reported Reaction between Nitrile *N*-Oxides and Isocyanides



N-oxide **10** to give the intermediate **a**. This intermediate is then intramolecularly intercepted by the oxygen of the nitrile *N*-oxide to give the highly unstable 4*H*-1,2-oxazet-4-imine derivative **b**[17] which, by a retro [2 + 2] cycloaddition, provides the corresponding cyanide **12** and isocyanate **13** (Scheme 4).

It appears evident, therefore, that the presence of a third nucleophile in the reaction mixture can preclude the formation of the high energy content 4*H*-1,2-oxazet-4-imine derivative[17] **b** driving the reaction toward another synthetic pathway as reported by us.[12,13,18]

In addition, it is reasonable to assume that an isocyanide containing an internal nucleophile can intramolecularly intercept the nitrilium ion species generating a novel molecular framework (Figure 1).

Inspired by pioneering work by Zhu, who demonstrated that α-isocyanoacetamides **2** can take part in a three-component reaction with aldehydes **15** and primary or secondary amines **16** to afford 5-aminooxazoles **17** (through interception of the nitrilium ion by the oxygen atom of the amide),[19] we reasoned that α-isocyanoacetamides could, in principle, react with the nitrile *N*-oxides and then intermolecularly intercept the nascent nitrilium species (Figure 2).

As a starting point for our study, we chose the reaction between (*Z*)-phenylchlooroxime **19** and the 4-(isocyanoacetyl)morpholine **20**. The reaction was carried out without TEA and with 1 equiv of TEA in dichloromethane at room temperature. To our delight, the reaction with 1 equiv of TEA was complete after 2 h giving the desired compound **21** in 74% yield after column chromatography (Scheme 5).

Not surprisingly, when the reaction was carried out without TEA we did not notice the formation of the desired product **21** and the *syn*-phenylchlorooxime **19** was recovered after column chromatography.

Using these already optimized conditions (1 equiv of TEA, rt, DCM), the scope and limitations of this novel reaction were explored. (*Z*)-Phenylchloroxime (**19**) or (*Z*)-phenylchloroximes bearing electron-withdrawing (**22**, **26**, **27**, **28**, **29**) or electron-donating (methyl- or methoxy-, **23** and **24**, respectively) substituents on the *para* position were chosen, as well as one (*Z*)-heteroarylchloroxime with a thiophene ring (**25**). α-Isocyanoacetamides (**20**, **30**−**37**) exhibit two points of

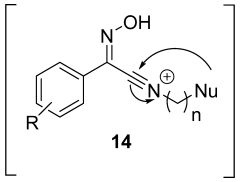


Figure 1. Intramolecular trapping of the nascent nitrilium ion.

diversity: the amide function derived from cyclic secondary amines (as for **20**, **30**−**32**, **36**, **37**) or noncyclic secondary amine (as for **35**) and the α-substitution (methyl- or benzyl, **30** and **31**, **32**, respectively) (Figure 3).

Arylchlorooximes were synthesized by chlorination of the corresponding oximes with *N*-chlorosuccinimide,[20] while α-isocyanoacetamides were easily accessible by amidation of the corresponding α-isocyanomethyl ester using the Dömling procedure;[21] to obtain the α-substituted α-isocyanoacetamides the alkylation was carried out in the presence of cesium hydroxide.[22]

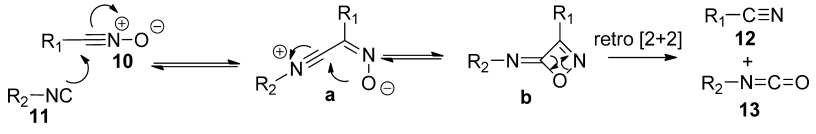
The reaction appeared to be quite general, not depending on electronic factors, as (*Z*)-arylchloroximes bearing both electron-withdrawing and electron-donating substituents reacted smoothly with the different isocyanoacetamides giving the desired 1,3-oxazol-2-oxime derivatives (**38**−**54**) in good yields (ranging from 32% to 88%) (Figure 4).

When isocyanoacetamide **36** was used, TEA was not necessary, as the basic nitrogen of piperazine was able to trigger the formation of the nitrile *N*-oxide species. The reaction failed when a secondary amide was present such as in the isocyanoacetamides (**33** and **34**); anyway this behavior was not unexpected as it was already reported by Zhu.[19,23]

1,3-Oxazol-2-oximes were not stable molecules with isomerization of the oxime, especially when the oxazole ring was substituted at the 4-position, and formation of decomposition products. Although we have fully characterized them, they cannot be stored for long time (even at 0 °C).

At the beginning, we attempted a one-pot procedure for the conversion of 1,3-oxazol-2-oximes into aryl-α-ketoamides. Hydrolysis of these intermediates in the presence of HCl, at room temperature, afforded the oxime−dipeptide analogue **55**, favoring, at the same time, the partial isomerization of the oxime. When the reaction was heated, we did observe the hydrolysis of the oxime and also the formation of several byproducts, which decrease the yield and make difficult the chromatographic purification. For these reasons, we opted to use milder catalysts as a Lewis acid, and we identified the

Scheme 4. Proposed Mechanism for the Formation of Isocyanates and Cyanides Starting from Nitrile *N*-Oxides and Isocyanides



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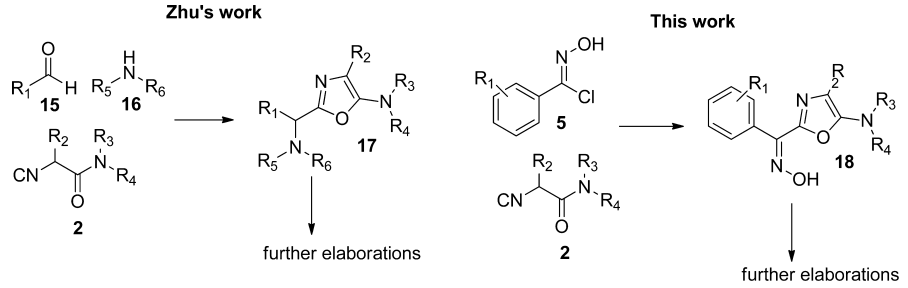
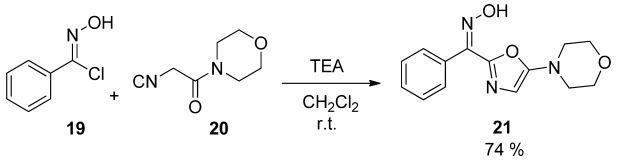


Figure 2. Comparison between Zhu's work and the reaction described in this work.

Scheme 5. Reaction between (*Z*)-Phenylchlorooxime and 4-(Isocyanoacetyl)morpholine



copper(II) chloride[24] as the reagent of choice. After the aminooxazole ring was opened with HCl,[25] the deoximation reaction in the presence of copper(II) chloride was carried out. Both reactions proceeded well and only a purification step was required (Scheme 6).

By using this protocol, we prepared different aryl-α-ketoamide amides (**57**–**73**) in good yields (Figure 5).

CONCLUSIONS

In conclusion a general and straightforward methodology to prepare structurally diverse aryl α-ketoamide amides has been demonstrated. It is important to highlight that the entire sequence of reactions is realized under mild reaction conditions avoiding the use of expensive coupling agents and using simple and easily available starting materials ((*Z*)-arylchlorooximes and α-isocyanoacetamides). This method is complementary to those previously reported for the synthesis of alkyl α-ketoamide amides.[3]

We believe that this new protocol can find application in the synthesis of tailored aryl α-ketoamide amides given their importance in both organic and medicinal chemistry.

EXPERIMENTAL SECTION

General Methods. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 Å). When necessary, the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^1H and ^{13}C APT NMR were recorded on a 300 MHz. Mass spectrometry was equipped with an ESI source and an ion-trap detector. HRMS were recorded on ORBITRAP mass spectrometer equipped with an ESI source. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin-layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (silica gel 60 F254). When necessary, they were developed with $KMnO_4$. Elemental analysis (C, H, N) of all of the new compounds were within ±0.4% of the calculated values. Chloroximes **19** and **22**–**29** are not new, and they were prepared following literature procedure.[20] Isocyanoacetamides **20** and **33**–**36** were prepared following Dömling's procedure,[21] while isocyanoacetamides **30**–**32** were prepared following Zhu's procedure.[22]

Synthesis of 4-Benzyl-1-(isocyanoacetyl)piperidine (37). Methyl isocyanoacetate (1 equiv) was reacted with 4-benzylpiperidine (1 equiv) overnight under neat conditions. The solution was evaporated and the crude was purified by column chromatography Ex/EtOAc 7:3 to give 37 as amorphous solid (yield 75%): ^1H NMR

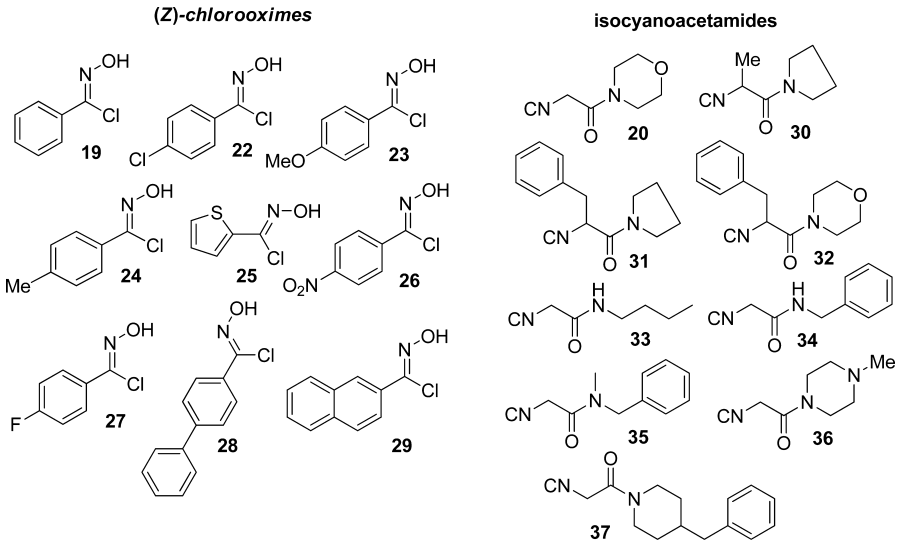


Figure 3. Structure of (*Z*)-chlorooximes and α-isocyanoacetamides.

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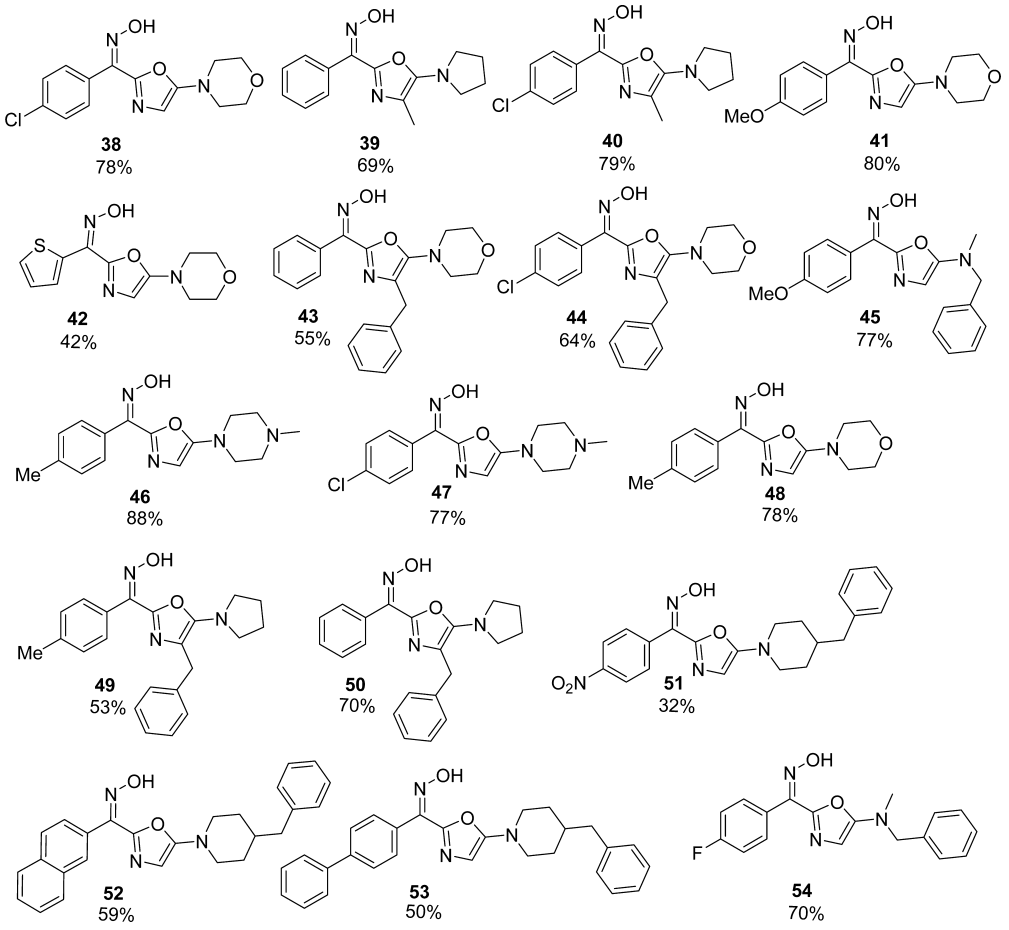
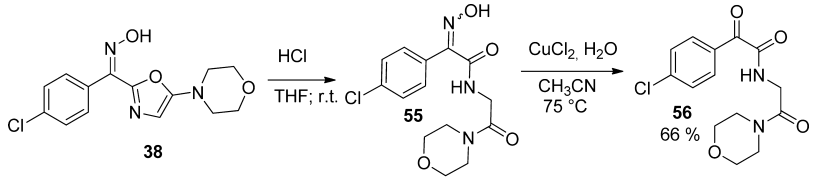


Figure 4. Synthesized 1,3-oxazol-2-oxime derivatives.

Scheme 6. Acid Hydrolysis and Deoximation of 1,3-Oxazol-2-oximino Derivatives



(400 MHz, $CDCl_3$) δ 7.26–7.09 (m, 5H), 4.45 (br d, 1H), 4.24 (br d, 2H), 3.45 (br d, 1H), 2.93 (br t, 1H), 2.51–2.49 (m, 3H), 1.73–1.64 (m, 3H), 1.17–1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 160.4, 139.7, 129.1, 128.3, 126.1, 45.6, 44.6, 42.8, 42.6, 37.7, 32.0, 31.3; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{15}H_{18}N_2O$ 242.1419, found 242.1422.

General Preparation of 1,3-Oxazol-2-oximes (21, 38–54). The chlorooxime (1 equiv) was dissolved in dry dichloromethane, and α-isocyanoacetamide (1 equiv) was added dropwise or portionwise at room temperature. Finally, TEA (1 equiv) was added dropwise (the reaction is slightly exothermic and on a large scale the addition should be done at 0 °C), and the reaction was stirred at room temperature under a nitrogen atmosphere until all the chlorooxime was consumed (typically 2–3 h as judged by TLC). The reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography.

*(Z)-(5-Morpholinooxazol-2-yl)phenylmethanone Oxime (**21**).* Starting material: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 148 mg (0.96 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 195 mg of product as yellow solid (yield 74%): ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.66–7.62 (m, 2H), 7.44–7.40 (m, 3H), 6.26 (br s, 1H), 3.78 (br t, 4H), 3.16 (br t, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 156.2, 146.9, 141.9, 133.0, 129.5, 128.4 (2C), 101.5, 65.8, 47.3; HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{14}H_{15}N_3NaO_3$ 296.1011, found 296.1012.

*(Z)-(4-Chlorophenyl)(5-morpholinooxazol-2-yl)methanone Oxime (**38**).* Starting material: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 122 mg (0.79 mmol). The crude material was purified by column chromatography (PE/EtOAc 6:4) to give 187 mg of product as a yellow solid (yield 78%): ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.60–7.56 (m, 2 H, AA′XX′), 7.44–7.36 (m, 2 H, AA′XX′), 6.26 (br s, 1H), 3.80–3.77 (m, 4H), 3.18–3.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 156.2, 146.5, 141.0, 135.6, 131.5, 129.7, 128.7, 101.6, 65.7, 47.2; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{14}H_{14}ClN_3O_3$ 307.0724, found 307.0727.

*(Z)-(4-Methyl-5-(pyrrolidin-1-yl)oxazol-2yl)phenylmethanone Oxime (**39**).* Starting material: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 147 mg (0.96 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 180 mg of product as yellow solid (yield 69%): ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.69–7.66 (m, 2H), 7.40–7.38 (m, 3H), 3.42–3.38 (m, 4H), 2.27 (s, 3H), 1.95–1.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 150.2,

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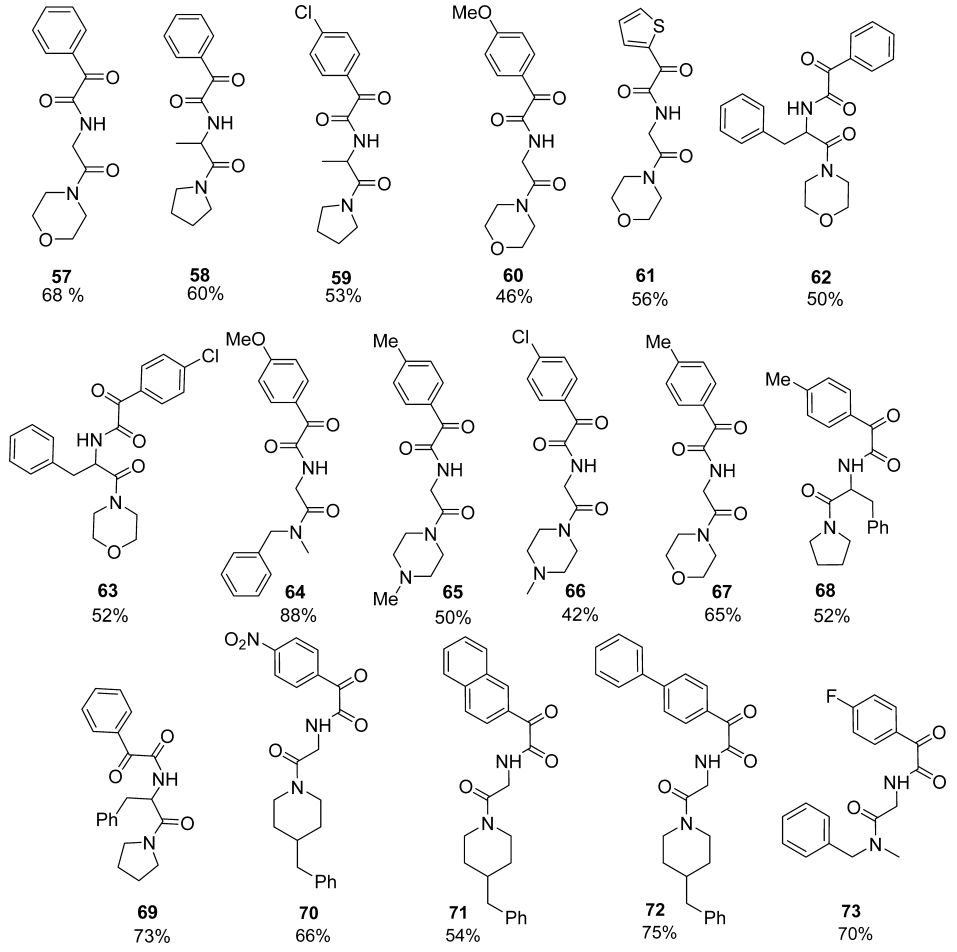

Figure 5. Synthesized aryl-α-ketoamides.

143.9, 141.4, 133.3, 129.2, 128.4, 128.3, 108.4, 48.8, 25.4, 11.7; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{15}H_{17}N_3O_2$ 271.1321, found 271.1321.

*(Z)-(4-Chlorophenyl)(4-methyl-5-(pyrrolidin-1-yl)oxazol-2-yl)-methanone Oxime (**40**).* Starting material: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 120 mg (0.79 mmol). The crude material was purified by column chromatography (PE/EtOAc 6:4) to give 190 mg of product as orange solid (yield 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.65−7.62 (m, 2H, AA′XX′), 7.40−7.37 (m, 2H, AA′XX′), 3.45−3.43 (m, 4H), 2.29 (s, 3H), 1.98−1.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 150.3, 143.7, 140.5, 135.3, 131.9, 129.8, 128.6, 108.5, 48.9, 25.5, 11.7; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{15}H_{16}ClN_3O_2$ 305.0931, found 305.0933.

*(Z)-(4-Methoxyphenyl)(5-morpholinooxazol-2-yl)methanone Oxime (**41**).* Starting material: chlorooxime 150 mg (0.81 mmol), isocyanoacetamide 125 mg (0.81 mmol). The crude material was purified by column chromatography (PE/EtOAc 5:5) to give 196 mg of product as yellow solid (yield 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60−7.56 (m, 2H, AA′XX′), 6.97−6.91 (m, 2H, AA′XX′), 6.25 (br s, 1H), 3.81−3.78 (m, 7H), 3.17−3.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 160.6, 156.1, 147.1, 141.5, 129.7, 125.5, 113.8, 101.5, 65.8, 55.4, 47.3; HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{15}H_{17}N_3NaO_4$ 326.1117, found 326.1120.

*(E)-(5-Morpholinooxazol-2-yl)(thiophene-2-yl)methanone Oxime (**42**).* Starting material: chlorooxime 150 mg (0.93 mmol), isocyanoacetamide 143 mg (0.93 mmol). The crude material was purified by column chromatography (PE/EtOAc 6:4) to give 108 mg of product as brown solid (yield 42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60−7.58 (m, 1H), 7.36−7.34 (m, 1H), 7.10−7.06 (m, 1H), 6.26 (br s, 1H), 3.87−3.83 (m, 4H), 3.28−3.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 156.2, 146.1, 137.1, 135.6, 127.6, 127.3, 127.2, 101.4, 65.8, 47.3; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{12}H_{13}N_3O_3S$ 279.0678, found 279.0677.

*(Z)-(4-Benzyl-5-morpholinooxazol-2-yl)phenylmethanone Oxime (**43**).* Starting material: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 236 mg (0.96 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 169 mg of product as yellow oil (yield 55%). Mixture of E/Z isomers; signals are referred to the main isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.69−7.66 (m, 2H), 7.45−7.39 (m, 3H), 7.35−7.21 (m, 5H), 3.94 (s, 2H), 3.75−3.71 (m, 4H), 3.10−3.06 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.2, 148.3, 141.9, 138.3, 132.8, 129.5, 128.7, 128.4, 128.3, 128.0, 126.7, 121.4, 66.5, 49.9, 31.80; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{21}H_{21}N_3O_3$ 363.1583, found 363.1583.

*(Z)-(4-Benzyl-5-morpholinooxazol-2-yl)(4-chlorophenyl)-methanone Oxime (**44**).* Starting material: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 193 mg (0.79 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 200 mg of product as white solid (yield 64%). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.65−7.58 (m, 2H), 7.43−7.36 (m, 2H), 7.32−7.18 (m, 5H), 3.96 (s, 2H), 3.75−3.67 (m, 4H), 3.09−3.06 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.3, 147.7, 141.2, 138.3, 135.5, 131.4, 129.6, 128.8, 128.59, 128.32, 126.65, 121.3, 66.6, 49.8, 31.81; HRMS (ESI) m/z $(M + H)^+$calcd for $C_{21}H_{20}ClN_3O_3$ 397.1193, found 397.1197.

*(Z)-(5-(Benzylmethylamino)oxazol-2-yl)(4-methoxyphenyl)-methanone Oxime (**45**).* Starting material: chlorooxime 150 mg (0.81 mmol), isocyanoacetamide 152 mg (0.81 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 210 mg product as yellow solid (yield 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.61−7.56 (m, 2H, AA′XX′), 7.37−7.27 (m, 3H), 7.25−7.19 (m, 2H), 6.94−6.90 (m, 2H, AA′XX′), 6.15 (br s, 1H), 4.37 (s, 2H), 3.85

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(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 160.5, 156.1, 145.8, 141.3, 136.1, 129.7, 128.8, 127.9, 127.7, 125.6, 113.7, 55.5, 55.3, 36.6; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{19}H_{19}N_3O_3$ 337.1426, found 337.1426.

*(Z)-(5-(4-Methylpiperazin-1-yl)oxazol-2-yl)(p-tolyl)methanone Oxime (**46**).* Starting materials: chlorooxime 150 mg (0.88 mmol), isocyanoacetamide 147 mg (0.88 mmol). The crude material was purified by column chromatography (DCM/MeOH 95:5) to give 232 mg product as yellow solid (88% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 (d, J = 7.8 Hz, 2H), 7.23 (m, 2H) partially overlapped to the solvent, 6.23 (s, 1H), 3.22 (br t, 4H), 2.50 (br t, 4H), 2.39 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.2, 146.7, 142.0, 139.3, 130.4, 128.9, 128.1, 101.4, 53.6, 46.9, 46.0, 21.3; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{16}H_{20}N_4O_2$ 300.1586, found 300.1590.

*(Z)-(4-Chlorophenyl)-(5-(4-methylpiperazin-1-yl)oxazol-2-yl)-methanone Oxime (**47**).* Starting materials: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 132 mg (0.79 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellow solid (195 mg, 77% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57−7.55 (m, 2H, AA′XX′), 7.36−7.34 (m, 2H, AA′XX′), 6.23 (s, 1H), 3.23 (br t, 4H), 2.52 (br t, 4H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.3, 146.2, 141.2, 135.3, 131.9, 129.5, 128.5, 101.7, 53.6, 46.9, 46.0; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{15}H_{17}ClN_4O_2$ 320.1040, found 320.1042.

*(Z)-(5-Morpholinooxazol-2-yl)-p-tolylmethanone Oxime (**48**).* Starting materials: chlorooxime 150 mg (0.88 mmol), isocyanoacetamide 136 mg (0.88 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as yellow solid (197 mg, 78% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (m, 2H, AA′XX′), 7.23 (m, 2H, AA′XX′), 6.26 (s, 1H), 3.80 (m, 4H), 3.17 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.0, 147.0, 141.7, 139.4, 130.0, 129.0, 128.2, 101.3, 65.7, 47.2, 21.3; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{15}H_{17}N_3O_3$ 287.1270, found 287.1268.

*(4-Benzyl-5-(pyrrolidin-1-yl)oxazol-2-yl)-p-tolylmethanone Oxime (**49**).* Starting materials: chlorooxime 150 mg (0.88 mmol), isocyanoacetamide 202 mg (0.88 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as yellow solid (168 mg, 53% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (m, 2H, AA′XX′), 7.31−7.22 (m, 7H) partially overlapped to the solvent, 3.99 (s, 2H), 3.42 (br t, 4H), 2.40 (s, 3H), 1.93 (br t, 4H); ^{13}C NMR (100 MHz, CDCl3) δ_C 150.3, 144.3, 141.3, 140.0, 139.1, 130.3, 128.9, 128.6, 128.2, 128.1, 126.3, 110.7, 48.8, 31.8, 25.3, 21.3; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{22}H_{23}N_3O_2$ 361.1790, found 361.1793.

*(Z)-(4-Benzyl-5-(pyrrolidin-1-yl)oxazol-2-yl)phenylmethanone Oxime (**50**).* Starting materials: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 219 mg (0.96 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as yellow solid (233 mg, 70% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (br d, 2H), 7.63−7.57 (m, 1H), 7.43−7.41 (m, 3H), 7.33−7.20 (m, 4H) partially overlapped to the solvent, 4.00 (s, 2H), 3.41 (br t, 4H), 1.92 (br t, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 150.3, 144.1, 141.4, 140.0, 133.2, 129.1, 128.6, 128.3, 128.2, 128.1, 126.3, 110.7, 48.7, 31.8, 25.3; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{21}H_{21}N_3O_2$ 347.1634, found 347.1637.

*(Z)-(5-(4-Benzylpiperidin-1-yl)oxazol-2-yl)(4-nitrophenyl)-methanone Oxime (**51**).* Starting materials: chlorooxime 150 mg (0.75 mmol), isocyanoacetamide 182 mg (0.75 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 9:1) to give the product as bright yellow solid (97 mg, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.28 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.6 Hz, 2H), 7.29−7.12 (m, 6H), 6.23 (s, 1H), 3.54 (br d, 2H), 2.83 (br t, 2H), 2.58 (br d, 2H), 1.77−1.73 (m, 3H), 1.39−1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5, 148.2, 145.2, 139.9, 139.5, 139.2, 129.1, 129.0, 128.3, 126.1, 123.5, 100.7, 47.5, 42.8, 37.3, 30.7; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{22}H_{22}N_4O_4$ 406.1641, found 406.1646.

*(Z)-(5-(4-Benzylpiperidin-1-yl)oxazol-2-yl)(naphthalen-2-yl)-methanone Oxime (**52**).* Starting materials: chlorooxime 150 mg (0.73 mmol), isocyanoacetamide 178 mg (0.73 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 9:1) to give the product as yellow solid (177 mg, 59% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.18 (s, 1H), 7.89−7.85 (m, 3H), 7.79 (br d, 1H), 7.52−7.50 (m, 2H), 7.30−7.25 (m, 3H), 7.21 (br d, 1H), 7.13 (br d, 2H), 6.23 (s, 1H), 3.54 (br d, 2H), 2.79 (br t, 2H), 2.56 (br d, 2H), 1.72−1.70 (m, 3H), 1.38−1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5, 146.2, 141.7, 139.7, 133.6, 133.0, 130.5, 129.1, 128.5, 128.3, 128.2, 127.9, 127.6, 126.8, 126.4, 126.1, 125.6, 100.6, 47.5, 42.8, 37.3, 30.7; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{26}H_{25}N_3O_2$ 411.1947, found 411.1950.

*(Z)-[1,1′-Biphenyl]-4-yl(5-(4-benzylpiperidin-1-yl)oxazol-2-yl)-methanone Oxime (**53**).* Starting materials: chlorooxime 150 mg (0.65 mmol), isocyanoacetamide 158 mg (0.73 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 9:1) to give the product as yellowish solid (142 mg, 50% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (br d, 2H), 7.67−7.63 (m, 4H), 7.47−7.44 (m, 3H), 7.38 (br d, 1H), 7.31−7.27 (m, 2H), 7.22 (br d, 1H), 7.14 (br d, 2H), 6.22 (s, 1H), 3.56 (br d, 2H), 2.81 (br t, 2H), 2.58 (br d, 2H), 1.75−1.72 (m, 3H), 1.41−1.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5, 146.2, 142.0, 141.4, 140.3, 139.7, 132.0, 129.1, 128.8, 128.7, 128.3, 127.6, 127.1, 127.0, 126.1, 100.6, 47.6, 42.9, 37.4, 30.7; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{26}H_{25}N_3O_2$ 411.1947, found 411.1948.

*(Z)-(5-(Benzylmethylamino)oxazol-2-yl)(4-fluorophenyl)-methanone Oxime (**54**).* Starting material: chlorooxime 150 mg (0.87 mmol), isocyanoacetamide 163 mg (0.81 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 198 mg product as yellow solid (yield 70%). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.65−7.53 (m, 3H), 7.37−7.19 (m, 3H), 7.10−7.02 (m, 3H), 6.18 (br s, 1H), 4.38 (s, 2H), 2.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.9, 161.7, 156.2, 140.8, 136.0, 131.8, 130.3, 128.7, 128.6, 127.8, 115.4, 99.5, 55.3, 36.6; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{18}H_{16}FN_3O_2$ 325.1227, found 325.1229.

General Preparation of Aryl-α-ketoamide Amides 56−73. The 1,3-oxazol-2-oxime was dissolved in THF (0.8 M), concentrated HCl (1 equiv; 2 equiv for oxazoles **46** and **47**) was added, and the reaction was stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with EtOAc (×3). The organic phase was washed with $NaHCO_3$ standard solution (×1) and brine (×1), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude was dissolved in acetonitrile (0.25 M), and water (55 equiv) and copper(II) chloride (2 equiv) were added. The solution was stirred for 1 h at 75 °C. The reaction mixture was diluted with water and extracted with EtOAc (×2). The organic phase was washed with brine (×1), dried over sodium sulfate, filtered, and concentrated under reduced pressure, and the crude material was purified by column chromatography.

*2-(4-Chlorophenyl)-N-(2-morpholino-2-oxoethyl)-2-oxoacetamide (**56**).* Starting material: 1,3-oxazol-2-oxime 150 mg (0.49 mmol). The crude material was purified by column chromatography (PE/EtOAc 2:8) to give 100 mg of product as white solid (yield 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.21−8.18 (m, 2H, AA′XX′), 8.03 (br s, NH), 7.41−7.38 (m, 2H, AA′XX′), 4.12 (d, J = 4.6 Hz, 2H), 3.65−3.59 (m, 6H), 3.44.3.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 185.8, 165.8, 161.9, 141.1, 132.4, 131.6, 128.9, 66.6, 66.3, 44.9, 42.4, 40.9; m/z 311 $(M + H)^+$; IR ν_{max}/cm^{-1} (KBr) 3239, 3096, 1670, 1652, 1533, 1465, 1246, 855; mp 122−123 °C. Anal. Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.12; H, 4.87; N, 9.02. Found: C, 53.95; H, 4.80; N, 9.31.

*N-(2-Morpholino-2-oxoethyl)-2-oxo-2-phenylacetamide (**57**).* Starting materials: 1,3-oxazol-2-oxime 150 mg (0.55 mmol). The crude material was purified by column chromatography (*n*-hexane/EtOAc 5:5) to give the product as yellowish solid (103 mg, 68% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.28 (br d, 2H), 7.93 (br s, NH), 7.62 (br t, 1H), 7.47 (br t, 2H), 4.18 (d, J = 4.0 Hz, 2H), 3.72−3.66 (m, 6H), 3.47−3.45 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ_C 187.1, 165.8, 162.2, 134.4, 133.1, 130.9, 128.5, 66.6, 66.3, 44.9, 42.3, 40.8; MS m/z 277 $(M + H)^+$; IR ν_{max}/cm^{-1} (KBr) 3380, 1687, 1667, 1642, 1505, 1474, 1275, 745; mp 164−165 °C. Anal. Calcd for

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$C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.95; H, 5.97; N, 10.01.

N-(1-Morpholino-1-oxopropan-2-yl)-2-oxo-2-phenylacetamide (**58**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.55 mmol). The crude material was purified by column chromatography (PE/EtOAc 3:7) to give 92 mg of product as yellow oil (yield 60%). Mixture of rotamers, signals are referred to the main rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.20−8.17 (m, 2H), 8.03 (br d, NH), 7.56−7.38 (m, 3H), 4.80−4.72 (m, 1H), 3.64−3.35 (m, 4H), 1.98−1.78 (m, 4H), 1.39 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 187.5, 169.9, 161.6, 134.2, 133.23, 130.9, 128.4, 46.9, 46.4, 46.2, 26.0, 24.1, 17.9; MS m/z 275 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3253, 3062, 1638, 1667, 1510, 1449, 1264, 715. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.66; H, 6.65; N, 10.25.

2-(4-Chlorophenyl)-N-(1-morpholino-1-oxopropan-2-yl)-2-oxoacetamide (**59**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.49 mmol). The crude material was purified by column chromatography (PE/EtOAc 4:6) to give 80 mg of product as colorless oil (yield 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.25−8.23 (m, 2H, AA′XX′), 7.97 (br d, NH), 7.43−7.40 (m, 2H, AA′XX′), 4.77−4.72 (m, 1H), 3.66−3.39 (m, 4H), 2.03−1.83 (m, 4H), 1.42 (d, J = 7.0 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ_C 186.1, 169.9, 161.0, 141.1, 132.6, 131.8, 129.0, 47.1, 46.5, 46.3, 26.2, 24.2, 18.1; MS m/z 309 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3239, 3062, 1670, 1668, 1586, 1455, 856. Anal. Calcd for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; N, 9.07. Found: C, 58.23; H, 5.21; N, 9.2.

2-(4-Methoxyphenyl)-N-(2-morpholino-2-oxoethyl)-2-oxoacetamide (**60**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.49 mmol). The crude material was purified by column chromatography (PE/EtOAc 2:8) to give 70 mg of product as white solid (yield 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.33−8.8.30 (m, 2H, AA′XX′), 7.97 (br s, NH), 6.94−6.91 (m, 2H, AA′XX′), 4.16 (br d, 2H), 3.87 (s, 3H), 3.71−3.65 (m, 6H), 3.46−43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 185.3, 165.9, 164.8, 162.8, 133.8, 126.3, 114.0, 66.8, 66.4, 55.7, 45.0, 42.4, 41.0; MS m/z 307 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3349, 3078, 1682, 1647, 1594, 1474, 1257, 861; mp 169−169.5 °C. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.93; H, 6.24; N, 9.36.

N-(2-Morpholino-2-oxoethyl)-2-oxo-2-(thiophene-2-yl)-acetamide (**61**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.54 mmol). The crude material was purified by column chromatography (PE/EtOAc 2:8) to give 85 mg of product as white solid (yield 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.36 (d, J = 4.0 Hz, 1H), 8.19 (br s, NH), 7.80 (d, J = 4.8 Hz, 1H), 7.18−7.15 (m, 1H), 4.15 (d, J = 4.5 Hz, 2H), 3.71−3.66 (m, 6H), 3.53−3.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 177.6, 165.7, 161.0, 138.5, 138.0, 136.9, 128.4, 66.6, 66.40, 42.5, 41.1, 40.7; MS m/z 283 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3371, 3071, 1691, 1658, 1495, 1359, 1275, 737; mp 193−194 °C. Anal. Calcd for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92. Found: C, 51.34; H, 5.36; N, 10.10.

N-(1-Morpholino-1-oxo-3-phenylpropan-2-yl)-2-oxo-2-phenylacetamide (**62**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.41 mmol). The crude material was purified by column chromatography (PE/EtOAc 4:6) to give 76 mg of product as white solid (yield 50%). Mixture of rotamers, signals are referred to the main rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.21 (d, J = 8.2 Hz, 2H), 7.87 (br d, NH), 7.64−7.59 (br t, 1H), 7.52−7.38 (br t, 2H), 7.34−7.23 (m, 5H), 5.18 (br q, 1H), 3.62−3.44 (m, 6H), 3.16−2.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 187.4, 169.0, 161.6, 135.8, 134.5, 131.0, 129.7, 129.6, 128.8, 128.6, 127.4, 66.4, 66.0, 49.7, 46.1, 42.4, 39.8; MS m/z 367 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3277, 3027, 1665, 1642, 1524, 1486, 1211; mp 151.5−152 °C. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.95; H, 6.40; N, 7.34.

2-(3-Chlorophenyl)-N-(1-morpholino-1-oxo-3-phenylpropan-2-yl)-2-oxoacetamide (**63**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.38 mmol). The crude material was purified by column chromatography (PE/EtOAc 5:5) to give 78 mg of product as white solid (yield 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.19 (d, J = 8.1 Hz, 2H), 7.93 (br d, NH), 7.42 (br d, 2H), 7.34−7.22 (m, 5H), 5.16 (br q, 1H), 3.64−3.58 (m, 2H), 3.55−3.25 (m, 4H), 3.14−2.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 185.8, 169.0, 160.9, 141.3, 135.7, 132.6, 131.6, 129.7, 129.0, 128.9, 127.5, 66.5, 66.1, 49.8, 46.1, 42.4, 39.9; MS m/z 401 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3246, 3064, 1665, 1617, 1586, 1476, 1218, 858; mp 128−129 °C. Anal. Cacld for $C_{21}H_{21}ClN_2O_4$: C, 62.92; H, 5.28; N, 6.99. Found: C, 63.04; H, 5.46; N, 6.74.

N-Benzyl-2-(2-(4-methoxyphenyl)-2-oxoacetamido)-N-methylacetamide (**64**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.44 mmol). The crude material was purified by column chromatography (PE/EtOAc 5:5) to give 133 mg of product as colorless oil (yield 88%). Mixture of rotamers, signals are referred to the main rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.35−8.31 (m, 2H), 8.05 (br s, NH), 7.38−7.14 (m, 5H), 6.94−6.89 (m, 2H), 4.61 (s, 2H), 4.24−4.20 (br t, 2H), 3.85 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 185.4, 167.4, 164.7, 162.8, 136.4, 133.7, 129.2, 128.8, 127.8, 126.3, 113.9, 55.6, 51.3, 41.3, 33.7; MS m/z 341 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3387, 3300, 1646, 1653, 1511, 1453, 1263, 1028. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.14; H, 6.12; N, 8.46.

N-(2-(4-Methylpiperazin-1-yl)-2-oxoethyl)-2-oxo-2-p-tolylacetamide (**65**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.50 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellow solid (75 mg, 50% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.19 (br d, 2H, AA′XX′), 7.92 (br s, NH), 7.27−7.25 (m, 2H, AA′XX′) partially overlapped to the solvent, 4.17 (d, J = 4.2 Hz, 2H), 3.68 (br t, 2H), 3.47 (br t, 2H), 2.44 (br s, 7H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ_C 186.8, 165.5, 162.5, 145.5, 131.0, 130.7, 129.2, 54.6, 54.3, 45.8, 44.3, 41.9, 40.9, 21.8; MS m/z 304 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3351, 3000, 1669, 1642, 1504, 1475, 1276, 789; mp 97−98 °C. Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.67; H, 7.12; N, 14.12.

2-(4-Chlorophenyl)-N-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-2-oxoacetamide (**66**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.47 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellowish solid (64 mg, 42% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.23 (d, J = 8.4 Hz, 2H, AA′XX′), 7.98 (br s, NH), 7.41 (d, J = 8.4 Hz, 2H, AA′XX′), 4.12 (d,, J = 4.0 Hz 2H), 3.63 (br t, 2H), 3.43 (br t, 2H), 2.40−2.37 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ_C 185.7, 165.3, 161.7, 141.0, 132.4, 131.5, 128.8, 54.7, 54.4, 46.0, 44.4, 42.0, 40.9; MS m/z 324 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3344, 1673, 1645, 1586, 1443, 1273, 857; mp 127−128 °C. Anal. Calcd for $C_{15}H_{18}ClN_3O_3$: C, 55.64; H, 5.60; N, 12.98. Found: C, 55.54; H, 5.42; N, 12.78.

N-(2-Morpholino-2-oxoethyl)-2-oxo-2-p-tolylacetamide (**67**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.52 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellow solid (98 mg, 65% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.20 (d, J = 8.2 Hz, 2H), 7.92 (br s, NH), 7.28−7.25 (m, 2H) partially overlapped to the solvent, 4.17 (d, J = 4.0 Hz, 2H), 3.71−3.67 (m, 6H), 3.47−3.46 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ_C 186.6, 165.8, 162.4, 145.6, 131.1, 130.7, 129.2, 66.6, 66.3, 44.9, 42.3, 40.8, 21.8; MS m/z 291 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3430, 3423, 1695, 1660, 1494, 1276, 785; mp 83−84 °C. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.34; H, 6.43; N, 9.78.

2-Oxo-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-2-p-tolylacetamide (**68**). Starting material: 1,3-oxazol-2-oxime 150 mg (0.41 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as a light yellow solid (78 mg, 52% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (d, J = 8.0 Hz, 2H), 7.79 (br d, NH), 7.28−7.23 (m, 7H), 4.95 (br q, 1H), 3.47−3.30 (m, 3H), 3.09 (d, J = 7.4 Hz, 2H), 2.69−2.63 (m, 1H), 2.40 (s, 3H), 1.80−1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ_C 186.8, 168.6, 161.7, 145.5, 136.1, 132.0, 131.1, 130.7, 129.5, 128.5, 127.1, 52.4, 46.3, 45.8, 39.5, 25.8, 23.9, 21.8; MS m/z 365 (M + H)$^+$; IR ν_{max}/cm^{-1} (KBr) 3239, 3062, 1680, 1662, 1624, 1454, 1228, 763; mp 88−89 °C. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.52; H, 6.65; N, 7.65.

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*2-Oxo-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-2-phenylacetamide (**69**).* Starting material: 1,3-oxazol-2-oxime 150 mg (0.43 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as a yellowish solid (110 mg, 73% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 7.8 Hz, 2H), 7.76 (br d, NH), 7.60 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.31−7.25 (m, 6H), 4.96 (br q, 1H), 3.49−3.36 (m, 3H), 3.10 (d, J = 7.4 Hz, 2H), 2.70−2.64 (m, 1H), 1.81−1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers δ_C 187.4, 168.6, 161.6, 136.0, 134.2, 133.2, 130.8, 129.4, 128.8, 128.5, 128.4, 128.4, 127.0, 52.4, 46.3, 45.8, 39.4, 25.7, 23.9; MS m/z 351 $(M + H)^+$; IR ν_{max}/cm^{-1} (KBr) 3240, 3062, 1682, 1664, 1621, 1555, 1454, 1222; mp 118−119 °C. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.21; H, 6.12; N, 8.21.

*N-(2-(4-Benzylpiperidin-1-yl)-2-oxoethyl)-2-(4-nitrophenyl)-2-oxoacetamide (**70**).* Starting material: 1,3-oxazol-2-oxime 150 mg (0.37 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 5:5) to give the product as a yellowish solid (100 mg, 66% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.48 (d, J = 8.6 Hz, 2H), 8.31 (d, J = 8.8 Hz, 2H), 8.08 (br s, NH), 7.31−7.12 (m, 5H), 4.59 (br d, 1H), 4.17−4.14 (m, 2H), 3.72 (br d, 1H), 3.02 (br t, 1H), 2.58−2.55 (m, 2H), 1.83−1.76 (m, 3H), 1.21−1.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 185.5, 164.8, 160.8, 150.8, 139.6, 137.9, 132.1, 129.0, 128.4, 126.2, 123.4, 44.8, 42.8, 42.6, 41.0, 38.0, 32.2, 31.5; MS m/z 410 $(M + H)^+$; IR ν_{max}/cm^{-1} (KBr) 3280, 1665, 1651, 1602, 1519; mp 78−79 °C. Anal. Calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.78; H, 5.84; N, 10.02.

*N-(2-(4-Benzylpiperidin-1-yl)-2-oxoethyl)-2-(naphthalen-2-yl)-2-oxoacetamide (**71**).* Starting material: 1,3-oxazol-2-oxime 150 mg (0.36 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 5:5) to give the product as a sticky solid (81 mg, 54% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.06 (s, 1H), 8.18 (br d, AA′XX′, 1H), 8.06 (br s, NH), 7.98 (d, J = 8.1 Hz, 1H), 7.90−7.85 (m, 2H), 7.64−7.60 (m, 1H), 7.56−7.53 (m, 1H), 7.31−7.19 (m, 3H), 7.13 (br d, 2H), 4.60 (br d, 1H), 4.22−4.19 (m, 2H), 3.75 (br d, 1H), 3.01 (br t, 1H), 2.61−2.55 (m, 2H), 1.82−1.72 (m, 3H), 1.25−1.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 186.9, 165.1, 162.3, 139.6, 136.1, 134.5, 132.3, 130.5, 130.2, 129.2, 129.0, 128.3, 128.3, 127.7, 126.7, 126.1, 125.1, 44.8, 42.8, 42.6, 41.0, 38.0, 32.2, 31.5; MS m/z 415 $(M + H)^+$; IR ν_{max}/cm^{-1} (KBr) 3280, 1665, 1651, 1602, 1519. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.36; H, 6.46; N, 6.73.

*2-([1,1′-Biphenyl]-4-yl)-N-(2-(4-benzylpiperidin-1-yl)-2-oxoethyl)-2-oxoacetamide (**72**).* Starting material: 1,3-oxazol-2-oxime 150 mg (0.34 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 5:5) to give the product as a white solid (112 mg, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.38 (br d, AA′XX′, 2H), 8.01 (br s, NH), 7.70 (br d, AA′XX′, 2H), 7.64 (br d, AA′XX′, 2H), 7.49−7.38 (m, 3H), 7.31−7.19 (m, 3H), 7.13 (br d, AA′XX′, 2H), 4.60 (br d, 1H), 4.24−4.12 (m, 2H), 3.74 (br d, 1H), 3.01 (br t, 1H), 2.64−2.55 (m, 3H), 1.82−1.75 (m, 3H), 1.25−1.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 186.7, 165.16, 162.3, 146.9, 139.7, 139.6, 132.0, 131.6, 129.0, 128.9, 128.4, 128.3, 127.3, 127.1, 126.1, 44.8, 42.8, 42.6, 41.0, 38.0, 32.2, 31.5; MS m/z 441 $(M + H)^+$; IR ν_{max}/cm^{-1} (KBr) 3364, 2919, 1682, 1628, 1475; mp 140−141 °C. Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.29; H, 6.42; N, 6.78.

*N-Benzyl-2-(2-(4-fluorophenyl)-2-oxoacetamido)-N-methylacetamide (**73**).* Starting material: 1,3-oxazol-2-oxime 150 mg (0.46 mmol). The crude material was purified by column chromatography (PE/EtOAc 5:5) to give 106 mg of product as yellow oil (yield 70%). Mixture of rotamers, signals are referred to the main rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.37−8.29 (m, 2H), 8.11 (br s, NH), 7.34−7.21 (m, 4H), 7.19−7.05 (m, 3H), 4.59 (s, 2H), 4.20 (d, J = 4 Hz, 2H), 2.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 185.4, 167.2, 164.8, 162.1, 136.4, 134.1, 129.7, 128.7, 128.1, 127.7, 115.9, 51.3, 41.2, 33.6; MS m/z 329 $(M + H)^+$; IR ν_{max}/cm^{-1} (KBr) 3377, 2926, 1647, 1595, 1230, 1089. Anal. Calcd for $C_{18}H_{17}FN_2O_3$: C, 65.84; H, 5.22; N, 8.53. Found: C, 65.52; H, 4.98; N, 8.76.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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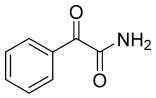

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