Synthesis of Novel α-(Acyloxy)-α-(quinolin-4-yl)acetamides by a Three-Component Reaction between an Isocyanide, Quinoline-4-carbaldehyde, and Arenecarboxylic Acids

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Novel α-(acyloxy)-α-(quinolin-4-yl)acetamides were synthesized by the *Passerini* three-component reaction between an isocyanide, quinoline-4-carbaldehyde, and arenecarboxylic acids in H_2O. The reactions were carried out in one pot at room temperature with quantitative yields.

Introduction. – Multicomponent reactions (MCRs) are important for generating high levels of diversity, as they allow more than two building blocks to be combined in practical and time-saving one-pot operations that give rise to complex structures by simultaneous formation of two or more bonds [1]. MCRs contribute to the requirements for environmentally friendly processes by reducing synthetic steps, energy consumption, and waste production.

The high potential of isocyanides for MCRs lies in the diversity of bond-forming processes available, in their functional group tolerance, and in the high levels of chemo-, regio-, and stereoselectivity often observed [2–5]. Isocyanide-based MCRs are particularly useful in drug discovery and total syntheses of biologically relevant natural products [6–11].

The quinoline scaffold is prevalent in a variety of pharmacologically active synthetic and natural compounds [12]. Quinolines are historically among the most important antimalarial drugs ever used [13].

The *Passerini* reactions involve an oxo component, an isocyanide, and a nucleophile. In continuation of our recent studies on isocyanide chemistry [14–21], we report here the *Passerini* MCR between quinoline-4-carbaldehyde (**1**), an isocyanide **2**, and arenecarboxylic acids **3** (*Scheme 1*).

Results and Discussion. – Quinoline-4-carbaldehyde (**1**), isocyanide derivatives **2**, and aromatic acids **3** in a 1:1:1 ratio were allowed to react at room temperature in H_2O to yield α-(acyloxy)-α-(quinolin-4-yl)acetamides **4a**–**4v** (*Scheme 1* and *Table 1*). The one-pot reaction proceeded smoothly and cleanly under mild conditions in H_2O, and is, therefore, considered to be an almost waste-free method. The products were crystallized from MeOH/H_2O or EtOH/H_2O, without any further purification, in quantitative yield in one-pot reactions.

Scheme 1. *Preparation of α-(Acyloxy)-α-(quinolin-4-yl)acetamides* **4a**–**4v** *from Quinoline-4-carbaldehyde* (**1**)*, Isocyanide Derivatives* **2***, and Arenecarboxylic Acids* **3** *in* H_2O

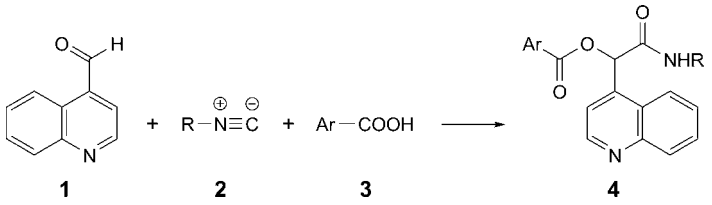


Table 1. *Synthesis of α-(Acyloxy)-α-(quinolin-4-yl)acetamides* **4a**–**4v**

Entry	Product	R	Ar	Reaction time [h]	Yield [%]
1	**4a**	cHex[a])	Ph	1	99
2	**4b**	cHex	4-^{t}Bu–C_6H_4	2	96
3	**4c**	cHex	4-Me–C_6H_4	2	96
4	**4d**	cHex	4-Cl–C_6H_4	1	97
5	**4e**	cHex	3-Cl–C_6H_4	1	97
6	**4f**	cHex	4-F–C_6H_4	1	98
7	**4g**	cHex	4-Br–C_6H_4	1	97
8	**4h**	cHex	4-I–C_6H_4	1	96
9	**4i**	cHex	4-CN–C_6H_4	2	97
10	**4j**	cHex	Naphthalen-1-yl	3	88
11	**4k**	^{t}Bu	Ph	1	98
12	**4l**	^{t}Bu	4-^{t}Bu–C_6H_4	2	96
13	**4m**	^{t}Bu	4-Cl–C_6H_4	1	97
14	**4n**	^{t}Bu	3-Cl–C_6H_4	1	97
15	**4o**	^{t}Bu	4-F–C_6H_4	1	98
16	**4p**	^{t}Bu	4-Br–C_6H_4	1	95
17	**4q**	^{t}Bu	4-CN–C_6H_4	2	96
18	**4r**	^{t}Bu	Naphthalen-1-yl	3	87
19	**4s**	2,6-Me_2–C_6H_3	Ph	2	96
20	**4t**	2,6-Me_2–C_6H_3	4-^{t}Bu–C_6H_4	2	95
21	**4u**	2,6-Me_2–C_6H_3	4-Cl–C_6H_4	2	96
22	**4v**	2,6-Me_2–C_6H_3	Naphthalen-1-yl	3	94

[a]) cHex, Cyclohexyl.

The structures of the products were deduced from their IR, ^{1}H- and ^{13}C-NMR, and mass spectra. The mass spectra of the products displayed molecular-ion peaks at the appropriate *m*/*z* values. The ^{1}H-NMR spectrum of **4a** exhibited distinct signals for cyclohexyl CH_2 (δ(H) 1.15–1.94), N–CH (3.81–3.91), CH–O (6.98), NH (6.19), and aromatic CH groups (7.50–8.98). The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 21 distinct resonances arising from cyclohexyl CH_2 (δ(C) 24.68–32.85), N–CH (48.66), and CH–O (72.7) groups, aromatic C-atoms (120.1–149.8), and an ester C=O (164.88), and an amide C=O group (166.18).

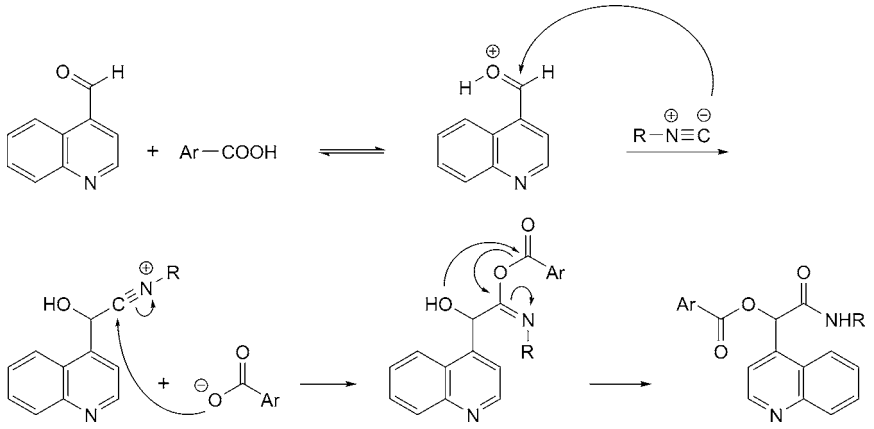
Finally, the structure of **4d** was confirmed unambiguously by X-ray single-crystal analysis (*Fig. 1*). Centrosymmetric crystals of **4d** were formed by exploiting convection from hexane at 65° (branch tube method) [22].

A plausible mechanism for the formation of **4a**–**4v** is proposed in *Scheme 2*. The acid **3** protonates carboxaldehyde **1** to form an intermediate, which is then attacked by the isocyanide **2**, leading to the formation of **4** (*Scheme 2*) [23].

Crystal Structure of **4d**. The centrosymmetric space group *C*2/*c* indicates that the crystal contains racemic **4d**. The molecular structure of the (*S*)-enantiomer is shown in *Fig. 1*. The conditions for the data collection and the structure refinement parameters for **4d** are given in the *Exper. Part*. The selected geometrical parameters are compiled in *Table 2*.

In **4d**, both COOR and CONHR groups are planar, and the whole 2-(cyclohexylamino)-2-oxoethyl 4-chlorobenzoate moiety adopts the extended conformation, as confirmed by the values of C(12)–N(2)–C(11)–C(10), O(2)–C(10)–C(11)–N(2), and C(10)–O(2)–C(18)–C(19) torsion angles, which are close to 180° (see

Scheme 2. *Proposed Mechanism for the Formation of* **4a**–**4v**



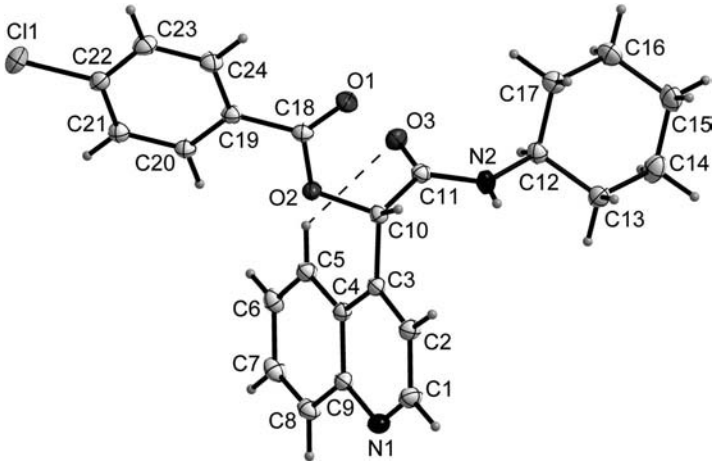


Fig. 1. *X-Ray crystal structure of one enantiomer of* **4d** (displacement ellipsoids at 50% probability level). Dashed line indicates the intramolecular C–H···O contact forming *S*(7) motif.

Table 2. *Selected Interatomic Distances, Bond Angles, and Torsion Angles of* **4d**

Bond lengths [Å]			
O(1)–C(18)	1.2060(11)	N(2)–C(11)	1.3388(12)
O(2)–C(18)	1.3499(10)	N(2)–C(12)	1.4636(13)
O(2)–C(10)	1.4369(11)	C(10)–C(11)	1.5452(13)
O(3)–C(11)	1.2240(11)		
Bond angles [°]			
C(18)–O(2)–C(10)	115.36(7)	O(3)–C(11)–C(10)	122.24(8)
C(11)–N(2)–C(12)	123.91(8)	N(2)–C(11)–C(10)	112.20(7)
O(2)–C(10)–C(3)	107.24(7)	O(1)–C(18)–O(2)	123.52(8)
O(2)–C(10)–C(11)	110.70(7)	O(1)–C(18)–C(19)	125.50(8)
C(3)–C(10)–C(11)	112.79(7)	O(2)–C(18)–C(19)	110.96(7)
O(3)–C(11)–N(2)	125.53(8)		
Torsion angles [°]			
C(18)–O(2)–C(10)–C(3)	162.12(7)	O(2)–C(10)–C(11)–O(3)	– 18.03(11)
C(18)–O(2)–C(10)–C(11)	– 74.46(9)	C(3)–C(10)–C(11)–O(3)	102.13(9)
C(4)–C(3)–C(10)–O(2)	52.28(10)	O(2)–C(10)–C(11)–N(2)	163.81(7)
C(4)–C(3)–C(10)–C(11)	– 69.84(10)	C(11)–N(2)–C(12)–C(13)	– 153.44(9)
C(12)–N(2)–C(11)–C(10)	176.27(8)	C(10)–O(2)–C(18)–C(19)	– 177.46(7)

Table 2). The molecule has the $C{=}O_{amide}$,$C{-}O_{ester}$ *syn*-periplanar conformation (O(2)–C(10)–C(11)–O(3) amounting to $-18.03(11)^\circ$). As seen from the torsion angle C(18)–O(2)–C(10)–C(11) (–74.46(9)°), the α-(acyloxy)acetamide fragment is twisted at the O(2)–C(10) bond, with the ester and amide C=O C-atoms in *sc* orientation to each other. The orientation of the quinolin-4-yl (QN) moiety in relation to the α-(acyloxy)acetamide (defined by the C(4)–C(3)–C(10)–O(2) and C(4)–C(3)–C(10)–C(11) torsion angles; *Table 2*) is accompanied by the intramolecular $C{-}H_{QN}\cdots O{=}C_{amide}$ contact (forming *S*(7) motif), as shown in *Fig. 1*.

In the crystal lattice of **4d**, the adjacent molecules related by the action of the glide plane ((*S*) and (*R*)-isomers) are joined to each other by N(2)–H···N(1) H-bonds (*Table 3*) to form chains running down the *c*-axis (*Fig. 2*). The interchain contacts are provided by weak C–H···O bonds and $\pi\cdots\pi$ interactions (centroid···centroid distance, 3.6672(11) Å; centroid···plane perpendicular distance, 3.5310(4) Å), as well as by the halogen Cl···Cl interactions (3.302(1) Å), giving rise to a 3D network.

Table 3. *Proposed H-Bonds and Close Contacts for* **4d**

D–H···A[a])	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
N(2)–H···N(1)^{i})	0.85(2)	2.24(2)	3.0647(13)	163(2)
C(5)–H···O(3)	0.95	2.57	3.2906(14)	133
C(14)–H···O(3)^{ii})	0.99	2.54	3.4349(14)	151
C(20)–H···O(1)^{iii})	0.95	2.58	3.1566(14)	119
C(21)–H···O(1)^{iii})	0.95	2.44	3.0829(14)	125

[a]) Symmetry codes: ^{i}) $x, -y+2, z-1/2$; ^{ii}) $-x+3/2, -y+3/2, -z+1$; ^{iii}) $x, -y+1, z+1/2$.

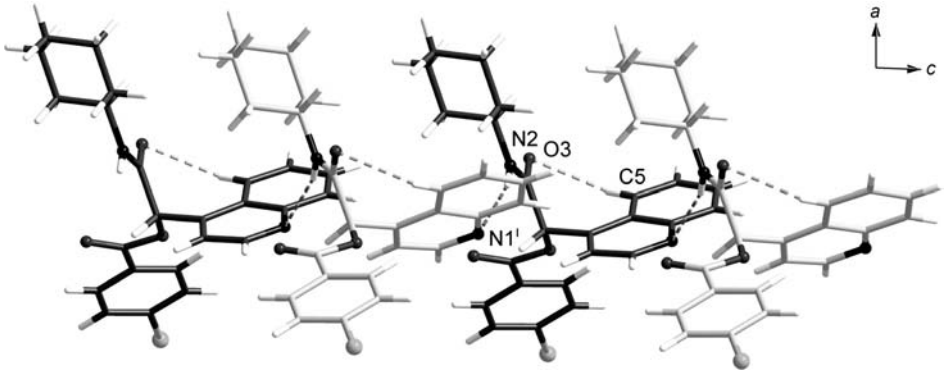


Fig. 2. *The molecules of* **4d** *joined to each other* via *the N–H ··· N contacts* (dashed lines)*, forming chains down the* c*-axis.* Intramolecular C–H ··· O contacts are also shown. Different enantiomers are indicated by light and dark grey. Viewed down the *b*-axis. Symmetry code is given in *Table 3*.

Conclusions. – We have synthesized and characterized novel α-(acyloxy)-α-quinolin-4-yl)acetamides by the *Passerini* three-component reaction between quinoline-4-carbaldehyde (**1**), an isocyanide **2**, and arenecarboxylic acids **3** in H_2O. This procedure offers significant advantages such as operational simplicity, mild reaction conditions, enhanced rates, ease of isolation of products, cleaner reaction profiles, and H_2O as medium, rendering it a useful protocol for the synthesis of these compounds.

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Experimental Part

General. Starting materials and solvents were purchased from *Merck* (Germany), *Fluka* (Switzerland), and *Acros* (USA), and were used without further purification. The reactions were monitored by TLC and NMR techniques, which indicated that there were no side-products. M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Mattson-1000* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker 400* spectrometer; 400 and 100 MHz for ^1H and ^{13}C, resp.; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-MAT 8430* mass spectrometer; at 20 eV; in *m*/*z* (rel. %).

General Procedure for the Syntheses of **4a** – **4v**. Isocyanide **2** (0.2 mmol) was added to a magnetically stirred soln. of quinoline-4-carbaldehyde (**1**; 0.2 mmol) and arenecarboxylic acids **3** (0.2 mmol) in H_2O (5 ml) at r.t. over 5 min. The mixture was stirred at r.t. for the time specified in *Table 1*, after which single-spot products were obtained by TLC. H_2O was removed under reduced pressure, and the products were purified by TLC and then crystallized.

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl Benzoate (**4a**). Yield: 99%. Colorless crystals. M.p. 157 – 159°. IR (KBr): 3419, 3280, 2930, 2855, 1719, 1660, 1565, 1269, 1097. ^1H-NMR: 1.15 – 1.94 (*m*, 5 CH_2); 3.81 – 3.91 (*m*, N–CH); 6.19 (*d*, *J* = 8, NH); 6.98 (*s*, CH–O); 7.50 – 8.98 (*m*, 11 arom. H). ^{13}C-NMR: 24.68 – 32.85 (5 CH_2); 48.66 (N–CH); 72.70 (CH–O); 120.13, 124.05, 127.46, 128.80, 129.79, 129.88, 133.99, 149.83 (11 arom. CH); 126.19, 130.09, 141.48, 148.47 (4 C); 164.88 (ester C=O); 166.18 (amide C=O). EI-MS: 388 (8), 263 (42), 158 (91), 130 (11), 105 (100), 77 (38), 55 (35).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 4-(1,1-Dimethylethyl)benzoate (**4b**). Yield: 97%. Colorless crystals. M.p. 167 – 169°. IR (KBr): 3420, 3298, 2932, 2852, 1723, 1658, 1555, 1272, 1099. ^1H-NMR: 1.14 – 1.41 (*m*, 2 $CH_2(\beta)$); 1.36 (*s*, 3 Me); 1.61 – 1.73 (*m*, 2 $CH_2(\alpha)$); 1.91 – 1.97 (*m*, $CH_2(\gamma)$); 3.81 – 3.91 (*m*, N–CH); 6.28 (*d*, *J* = 8, NH); 7.00 (*s*, CH–O); 7.52 – 8.96 (*m*, 10 arom. H). ^{13}C-NMR: 31.06

(3 Me); 24.70, 24.72, 25.39, 32.83, 32.91 (5 CH_2); 35.26 (C_q of ^{t}Bu); 48.58 (N–CH); 72.47 (CH–O); 120.02, 124.12, 125.58, 127.42, 129.76, 129.80, 130.07, 157.98 (10 arom. CH); 125.90, 126.25, 141.71, 148.47, 149.80 (5 C); 164.47 (ester C=O); 166.30 (amide C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 4-Methylbenzoate (**4c**). Yield: 95%. Colorless crystals. M.p. 141–143°. IR (KBr): 3450, 3301, 2928, 2852, 1720, 1660, 1550, 1260, 1110. ^{1}H-NMR: 1.11–1.97 (*m*, 5 CH_2); 2.45 (*s*, Me); 3.82–3.89 (*m*, N–CH); 6.23 (*d*, *J* = 7.2, NH); 6.99 (*s*, CH–O); 7.29–8.96 (*m*, 10 arom. H). ^{13}C-NMR: 21.79 (Me); 24.66, 24.69, 25.37, 32.78, 32.86 (5 CH_2); 48.59 (N–CH); 72.47 (CH–O); 120.02, 124.11, 125.96, 127.44, 129.53, 129.79, 129.92, 130.00, 149.77 (10 arom. CH); 126.24, 129.02, 141.72, 145.00, 148.39 (5 C); 164.86 (ester C=O); 166.29 (amide C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 4-Chlorobenzoate (**4d**). Yield: 97%. Colorless crystals. M.p. 187–189°. IR (KBr): 3445, 3271, 2932, 2851, 1734, 1700, 1569, 1253, 1095. ^{1}H-NMR: 1.13–1.69 (*m*, 5 CH_2); 3.81–3.90 (*m*, N–CH); 6.116 (*d*, *J* = 8, NH); 6.968 (*s*, CH–O); 7.29–8.98 (*m*, 10 arom. H). ^{13}C-NMR: 24.66–32.84 (5 CH_2); 48.75 (N–CH); 72.94 (O–CH); 120.31, 123.89, 127.61, 129.16, 130.13, 131.26, 149.81 (10 arom. CH); 126.10, 127.20, 140.57, 141.14, 148.43 (5 C); 164.19 (ester C=O); 165.94 (amid C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-Chlorobenzoate (**4e**). Yield: 97%. Colorless crystals. M.p. 171–173°. IR (KBr): 3432, 3276, 2929, 2852, 1728, 1656, 1563, 1247, 1129. ^{1}H-NMR: 1.12–1.96 (*m*, 5 CH_2); 3.80–3.90 (*m*, N–CH); 6.122 (*d*, *J* = 8, NH); 6.96 (*s*, CH–O); 7.29–8.97 (*m*, 10 arom. H). ^{13}C-NMR: 24.65–32.82 (5 CH_2); 48.77 (N–CH); 73.02 (CH–O); 120.28, 123.83, 127.62, 128.02, 129.89, 129.92, 130.10, 130.22, 133.99, 149.92 (10 arom. CH); 126.06, 130.52, 134.96, 140.89, 148.56 (5 C); 163.89 (ester C=O); 165.86 (amide C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 4-Fluorobenzoate (**4f**). Yield: 98%. Colorless crystals. M.p. 178–180°. IR (KBr): 3430, 3271, 2923, 2851, 1734, 1655, 1568, 1255, 1085. ^{1}H-NMR: 1.08–1.97 (*m*, 5 CH_2); 3.81–3.90 (*m*, N–CH); 6.08 (*d*, *J* = 8, NH); 6.96 (*s*, CH–O); 7.16–8.98 (*m*, 10 arom. H). ^{13}C-NMR: 24.66–32.84 (5 CH_2); 48.72 (N–CH); 72.88 (CH–O); 115.92, 116.14, 120.31, 123.89, 127.50, 129.78, 130.26, 132.51, 132.60, 149.95 (10 arom. CH); 125.04, 126.11, 141.03, 148.63, 165.02 (5 C); 164.04 (ester C=O); 166.06 (amide C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 4-Bromobenzoate (**4g**). Yield: 97%. Colorless crystals. M.p. 167–169°. IR (KBr): 3435, 3295, 2928, 2854, 1732, 1658, 1554, 1254, 1098. ^{1}H-NMR: 1.07–1.95 (*m*, 5 CH_2); 3.79–3.88 (*m*, N–CH); 6.241 (*d*, *J* = 8, NH); 6.93 (*s*, CH–O); 7.57–8.94 (*m*, 10 arom. H). ^{13}C-NMR: 24.66–32.83 (5 CH_2); 48.75 (N–CH); 72.98 (CH–O); 120.36, 123.86, 127.53, 127.68, 129.80, 131.35, 132.14, 149.98 (10 arom. CH); 126.07, 129.24, 130.27, 140.87, 148.64 (5 C); 164.37 (ester C=O); 165.97 (amide C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 4-Iodobenzoate (**4h**). Yield: 96%. Colorless crystals. M.p. 146–148°. IR (KBr): 3438, 3277, 2930, 2853, 1728, 1656, 1562, 1247, 1129. ^{1}H-NMR: 1.23–1.97 (*m*, 5 CH_2); 3.82–3.89 (*m*, N–CH); 6.06 (*d*, *J* = 8, NH); 6.98 (*s*, CH–O); 7.29–9.00 (*m*, 10 arom. H). ^{13}C-NMR: 24.65–32.82 (5 CH_2); 48.79 (N–CH); 73.01 (CH–O); 120.27, 123.86, 127.67, 128.02, 129.92, 129.98, 130.10, 130.51, 133.99, 134.96, 149.78 (10 arom. CH); 126.09, 131.18, 138.18, 141.11, 148.37 (5 C); 163.88 (ester C=O); 165.83 (amide C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 4-Cyanobenzoate (**4i**). Yield: 97%. Yellow crystals. M.p. 189–190°. IR (KBr): 3426, 3302, 2931, 2854, 2232, 1736, 1658, 1550, 1251, 1104. ^{1}H-NMR: 1.03–1.95 (*m*, 5 CH_2); 3.79–3.88 (*m*, N–CH); 6.04 (*d*, *J* = 8, NH); 6.92 (*s*, CH–O); 7.58–8.96 (*m*, 10 arom. H). ^{13}C-NMR: 24.64–32.80 (5 CH_2); 48.93 (N–CH); 73.52 (CH–O); 120.72, 123.68, 127.74, 129.98, 130.39, 130.42, 132.50, 149.99 (10 arom. CH); 117.22, 117.71, 125.95, 132.69, 140.30, 148.67 (6 C); 163.67 (ester C=O); 165.57 (amide C=O).

2-(Cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl Naphthalene-1-carboxylate (**4j**). Yield: 88%. Yellow crystals. M.p. 163–165°. IR (KBr): 3420, 3236, 2851, 1721, 1670, 1526, 1250, 1138. ^{1}H-NMR: 1.15–1.97 (*m*, 5 CH_2); 3.85–3.92 (*m*, N–CH); 6.29 (*d*, *J* = 8, NH); 7.13 (*s*, CH–O); 7.55–9.00 (*m*, 10 arom. H). ^{13}C-NMR: 24.71–32.88 (5 CH_2); 48.68 (N–CH); 72.69 (CH–O); 120.12, 124.07, 124.54, 125.44, 126.67, 127.58, 128.37, 128.77, 129.92, 130.08, 130.56, 134.50, 149.81 (13 arom. CH); 125.54, 126.23, 131.41, 133.87, 141.70, 148.42 (6 C); 165.50 (ester C=O); 166.29 (amide C=O).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl Benzoate (**4k**). Yield: 98%. Colorless crystals. M.p. 207–209°. IR (KBr): 3426, 3304, 2964, 2925, 1720, 1664, 1557, 1252, 1111. ^{1}H-NMR: 1.39 (*s*,

3 Me); 6.18 (*s*, NH); 6.93 (*s*, CH–O); 7.49–9.00 (*m*, 11 arom. H). ^{13}C-NMR: 28.64 (3 Me); 52.06 (Me_3C); 72.74 (CH–O); 120.14, 124.04, 127.54, 128.76, 128.83, 129.86, 129.96, 134.01, 149.72 (11 arom. CH); 126.30, 128.31, 141.93, 148.31 (5 C); 164.80 (ester C=O); 166.17 (amide C=O).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 4-(1,1-Dimethylethyl)benzoate (**4l**). Yield: 84%. Colorless crystals. M.p. 159–161°. IR (KBr): 3460, 3346, 2962, 2869, 1720, 1670, 1538, 1264, 1116. ^{1}H-NMR: 1.36 (*s*, 3 Me); 1.40 (*s*, 3 Me); 6.24 (*s*, NH); 6.93 (*s*, CH–O); 7.51–8.97 (*m*, 10 arom. H). ^{13}C-NMR: 28.66 (3 Me); 31.06 (3 Me); 35.25 (Me_3C); 51.98 (C–NH); 72.56 (CH–O); 120.06, 124.09, 125.84, 127.40, 129.72, 129.76, 130.09, 149.81 (10 arom. CH); 125.94, 126.32, 141.95, 148.48, 157.94 (5 C); 164.72 (ester C=O); 166.36 (amide C=O).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 4-Chlorobenzoate (**4m**). Yield: 97%. Colorless crystals. M.p. 124–126°. IR (KBr): 3434, 3224, 3077, 2968, 1720, 1676, 1581, 1265, 1096. ^{1}H-NMR: 1.38 (*s*, 3 Me); 6.09 (*s*, NH); 6.92 (*s*, CH–O); 7.48–9.01 (*m*, 10 arom. H). ^{13}C-NMR: 28.61 (3 Me); 52.14 (C–NH); 72.99 (CH–O); 120.41, 123.81, 127.55, 128.59, 129.16, 129.81, 130.29, 131.24, 150.01 (10 arom. CH); 126.15, 127.24, 140.54, 141.09, 148.67 (5 C); 164.17 (ester C=O); 166.01 (amide C=O).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 3-Chlorobenzoate (**4n**). Yield: 97%. Colorless crystals. M.p. 158–160°. IR (KBr): 3434, 3315, 3069, 2975, 1727, 1663, 1551, 1246, 1129. ^{1}H-NMR: 1.38 (*s*, 3 Me); 6.00 (*s*, NH); 6.89 (*s*, CH–O); 7.43–9.00 (*m*, 10 arom. H). ^{13}C-NMR: 28.61 (3 Me); 57.17 (C–NH); 73.08 (CH–O); 120.34, 123.83, 127.64, 127.99, 129.91, 130.10, 133.96, 134.95, 149.84 (10 arom. CH); 126.15, 130.18, 130.54, 141.23, 148.47 (5 C); 163.85 (ester C=O); 165.84 (amide C=O).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 4-Fluorobenzoate (**4o**). Yield: 98%. Colorless crystals. M.p. 178–180°. IR (KBr): 3430, 3308, 2979, 2963, 1720, 1667, 1560, 1260, 1114. ^{1}H-NMR: 1.38 (*s*, 3 Me); 6.034 (*s*, NH); 6.89 (*s*, CH–O); 7.15–8.98 (*m*, 10 arom. H). ^{13}C-NMR: 28.61 (3 Me); 52.11 (C–NH); 72.92 (CH–O); 115.93, 116.15, 120.36, 123.88, 127.54, 129.83, 130.22, 132.48, 132.58, 149.90 (10 arom. CH); 125.06, 126.19, 141.35, 148.56, 165.02, 167.56 (5 C); 163.99 (ester C=O); 166.06 (amide C=O). EI-MS: 380 (7), 281 (34), 158 (100), 123 (71), 95 (27), 75 (13), 57 (67).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 4-Bromobenzoate (**4p**). Yield: 95%. Colorless crystals. M.p. 177–179°. IR (KBr): 3439, 3222, 3076, 2967, 1719, 1675, 1589, 1265, 1096. ^{1}H-NMR: 1.37 (*s*, 3 Me); 6.00 (*s*, NH); 6.88 (*s*, CH–O); 7.59–8.98 (*m*, 10 arom. H). ^{13}C-NMR: 28.61 (3 Me); 52.14 (C–NH); 73.01 (CH–O); 120.38, 123.84, 127.59, 129.88, 130.19, 131.32, 132.16, 149.87 (10 arom. CH); 126.16, 127.69, 129.25, 141.26, 148.51 (5 C); 164.31 (ester C=O); 165.95 (amide C=O).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 4-Cyanobenzoate (**4q**). Yield: 96%. Yellow crystals. M.p. 117–119°. IR (KBr): 3444, 3228, 3076, 2967, 2232, 1720, 1677, 1596, 1270, 1103. ^{1}H-NMR: 1.35 (*s*, 3 Me); 5.83 (*s*, NH); 6.86 (*s*, CH–O); 7.63–9.00 (*m*, 10 arom. H). ^{13}C-NMR: 28.58 (3 Me); 52.32 (C–NH); 73.55 (CH–O); 117.25, 123.71, 127.86, 130.13, 130.42, 132.51, 132.69, 149.75 (10 arom. CH); 117.70, 120.73, 126.10, 130.21, 140.87, 148.50 (6 C); 163.61 (ester C=O); 165.48 (amide C=O).

2-[(1,1-Dimethylethyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl Naphthalene-1-carboxylate (**4r**). Yield: 87%. Yellow crystals. M.p. 154–156°. IR (KBr): 3501, 3228, 3075, 2972, 1720, 1676, 1569, 1270, 1059. ^{1}H-NMR: 1.40 (*s*, 3 Me); 6.22 (*s*, NH); 7.03 (*s*, CH–O); 7.54–9.00 (*m*, 13 arom. H). ^{13}C-NMR: 28.67 (3 Me); 52.10 (C–NH); 72.79 (CH–O); 120.15, 124.04, 124.55, 125.42, 126.66, 127.57, 128.36, 128.78, 129.88, 130.12, 130.54, 134.51, 149.85 (13 arom. CH); 125.52, 126.31, 131.42, 133.88, 141.89, 148.47 (6 C); 165.45 (ester C=O); 166.35 (amide C=O).

2-[(2,6-Dimethylphenyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl Benzoate (**4s**). Yield: 96%. Colorless crystals. M.p. 197–199°. IR (KBr): 3427, 3250, 3030, 2923, 1726, 1666, 1535, 1263, 1116. ^{1}H-NMR: 2.09 (*s*, 2 Me); 7.21 (*s*, CH–O); 7.65 (*s*, NH); 7.02–9.02 (*m*, 14 arom. H). ^{13}C-NMR: 18.28 (2 Me); 73.18 (CH–O); 119.86, 124.17, 127.79, 128.33, 128.65, 128.86, 129.97, 134.13, 135.38, 149.96 (14 arom. CH); 125.95, 127.61, 130.23, 132.39, 140.98, 148.62 (7 C); 165.10 (ester C=O); 165.53 (amide C=O). EI-MS: 410 (5), 263 (25), 158 (40), 130 (8), 105 (100), 91 (7), 77 (44), 51 (14).

2-[(2,6-Dimethylphenyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 4-(1,1-Dimethylethyl)benzoate (**4t**). Yield: 95%. Colorless crystals. M.p. 162–164°. IR (KBr): 3422, 3262, 2964, 2867, 1723, 1660, 1530, 1268, 1113. ^{1}H-NMR: 1.37 (*s*, Me_3C); 2.11 (*s*, 2 Me); 7.22 (*s*, CH–O); 7.66 (*s*, NH); 7.03–9.01 (*m*, 13 arom. H). ^{13}C-NMR: 18.30 (2 Me); 31.07 (Me_3C); 35.28 (Me_3C); 73.01 (CH–O); 119.77, 124.29, 125.88, 127.76,

128.32, 129.90, 130.01, 135.38, 149.71 (13 arom. CH); 125.78, 126.02, 127.61, 132.42, 141.50, 148.33, 158.10 (8 C); 160.01 (ester C=O); 165.60 (amide C=O).

2-[(2,6-Dimethylphenyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl 4-Chlorobenzoate (**4u**). Yield: 96%. Colorless crystals. M.p. 212–214°. IR (KBr): 3447, 3252, 3031, 1733, 1663, 1591, 1255, 1117. ^{1}H-NMR: 2.06 (*s*, 2 Me); 7.18 (*s*, CH–O); 7.54 (*s*, NH); 7.02–9.04 (*m*, 13 arom. H). ^{13}C-NMR: 18.25 (2 Me); 73.36 (CH–O); 120.00, 124.09, 125.93, 127.89, 127.92, 128.38, 129.26, 129.90, 130.32, 131.34, 132.26, 135.33, 149.58 (13 arom. CH); 127.04, 128.73, 128.91, 131.43, 140.77, 141.23, 148.11 (8 C); 164.37 (ester C=O); 165.16 (amide C=O).

2-[(2,6-Dimethylphenyl)amino]-2-oxo-1-(quinolin-4-yl)ethyl Naphthalene-1-carboxylate (**4v**). Yield: 94%. Yellow crystals. M.p. 193–195°. IR (KBr): 3435, 3260, 3030, 2922, 1712, 1669, 1591, 1243, 1164. ^{1}H-NMR: 2.12 (*s*, 2 Me); 7.35 (*s*, CH–O); 7.55 (*s*, NH); 7.02–9.05 (*m*, 16 arom. H). ^{13}C-NMR: 18.33 (2 Me); 73.10 (CH–O); 119.84, 124.17, 124.54, 125.46, 126.70, 127.74, 127.84, 128.36, 128.47, 128.80, 130.09, 130.81, 134.71, 135.42, 149.87 (16 arom. CH); 125.29, 126.00, 130.18, 130.49, 132.38, 133.91, 141.27, 148.50 (9 C); 165.63 (ester C=O); 165.72 (amide C=O).

X-Ray Crystal-Structure Determination of **4d** (*Fig. 1*)[1]). The crystallographic measurement for **4d** was performed on a *Kuma KM4CCD* κ-geometry four-circle diffractometer with graphite-monochromatized MoK_α radiation. The data were collected at 100(2) K using an *Oxford Cryosystems* cooler. Data were corrected for *Lorentz* and polarization effects. Data collection, cell refinement, and data reduction and analysis were carried out with the KM4CCD software, CRYSALIS CCD and CRYSALIS RED, resp. [24]. Empirical absorption correction was applied to the data with the use of CRYSALIS RED. The structure was solved by direct methods with the SHELXS-97 program [25] and refined by a full-matrix least-squares technique based on F^2 using SHELXL-2013 [25] with anisotropic thermal parameters for the non-H-atoms. The H-atoms were found in difference *Fourier* maps, and, in the final refinement cycles, the C-bonded H-atoms were repositioned in their calculated positions and refined using a riding model, with C–H of 0.95–1.00 Å, and with $U_{iso}(H) = 1.2\ U_{eq}(C)$. The figures were made using DIAMOND program [26].

Crystallographic Data for **4d**. $C_{24}H_{23}ClN_2O_3$, M_r 422.89; colorless bloc; crystal size, $0.50 \times 0.30 \times 0.20$ mm; monoclinic; space group *C*2/*c* (No. 15); $a = 33.010(9)$, $b = 11.261(3)$, $c = 11.380(3)$ Å, $\beta = 92.12(3)°$, $V = 4227(2)$ Å^3, $T = 100(2)$ K, $Z = 8$, $\rho_{calc} = 1.329$ g cm^{-3}, $\mu = 0.21$ mm^{-1} (for MoK_α, $\lambda = 0.71073$ Å), $T_{min} = 0.857$, $T_{max} = 1.000$; 36202 reflections measured, 10168 unique ($R_{int} = 0.035$), 7626 observed ($I > 2\sigma(I)$); θ range, 3.11–36.96°, parameters, 275, restraints, 0; $R_1 = 0.048$, $wR_2 = 0.134$ (observed refl.); goodness-of-fit, *S*, 1.06; largest difference in peak and hole, $\Delta\rho_{max}$ and $\Delta\rho_{min}$, 0.64 and -0.24 e Å^{-3}, resp.

REFERENCES

[1] M. C. Bagley, J. W. Dale, J. Bower, *J. Chem. Commun.* **2002**, 1682; C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957; Y. J. Huang, F. Y. Yang, C. J. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16386.

[2] I. Ugi, *Angew. Chem., Int. Ed.* **1962**, *1*, 8.

[3] J. Sapi, J. Y. Laronze, *Arkivoc* **2004**, *vii*, 208.

[4] J. Zhu, H. Bienayme, 'Multi-component Reactions', Wiley-VCH, Weinheim, 2005.

[5] M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 126.

[6] A. Domling, I. Ugi, *Angew. Chem., Int. Ed.* **2000**, *39*, 3169.

[7] M. Murakami, *Angew. Chem., Int. Ed.* **2003**, *42*, 718.

[8] C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51.

[9] A. Domling, *Chem. Rev.* **2006**, *106*, 17.

[10] C. C. Musonda, D. Taylor, J. Lehman, J. Gut, P. J. Rosenthal, K. Chibale, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3901.

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[1]) CCDC-966112 contains the supplementary crystallographic data for **4d**. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk.

[11] I. Akritopoulou-Zanze, *Curr. Opin. Chem. Biol.* **2008**, *12*, 324.
[12] T. Eicher, S. Hauptmann, 'The Chemistry of Heterocycles', 2nd edn., Wiley-VCH, Weinheim, 2003, pp. 316 – 336.
[13] K. Kaur, M. Jain, R. P. Reddy, R. Jain, *Eur. J. Med. Chem.* **2010**, *45*, 3245.
[14] A. Souldozi, A. Ramazani, N. Bouslimani, R. Welter, *Tetrahedron Lett.* **2007**, *48*, 2617.
[15] A. Souldozi, A. Ramazani, *Tetrahedron Lett.* **2007**, *48*, 1549.
[16] A. R. Kazemizadeh, A. Ramazani, *J. Braz. Chem. Soc.* **2009**, *20*, 309.
[17] A. R. Kazemizadeh, A. Ramazani, *Arkivoc* **2008**, *xv*, 159.
[18] A. Ramazani, A. Tofangchi Mahyari, M. Rouhani, A. Rezaei, *Tetrahedron Lett.* **2009**, *50*, 5625.
[19] A. Ramazani, A. Rezaei, A. Tofangchi Mahyari, M. Rouhani, M. Khoobi, *Helv. Chim. Acta* **2010**, *93*, 2033.
[20] A. Ramazani, M. Rouhani, A. Rezaei, N. Shajari, A. Souldozi, *Helv. Chim. Acta* **2011**, *94*, 282.
[21] E. Vessally, A. Ramazani, E. Yaaghubi, *Monatsh. Chem.* **2011**, *142*, 1143.
[22] A. Tofangchi Mahyari, N. Shajari, A. R. Kazemizadeh, K. Ślepokura, T. Lis, A. Ramazani, *Z. Naturforsch., B* **2007**, *62*, 829.
[23] R. H. Baker, D. Stanonis, *J. Am. Chem. Soc.* **1951**, *73*, 699.
[24] CRYSALIS CCD and CRYSALIS RED in KM4CCD Software, Oxford Diffraction Ltd, Abingdon, England, 2010.
[25] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112.
[26] K. Brandenburg, DIAMOND, Ver. 3.0d, Crystal Impact GbR, Bonn, Germany, 2005.

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