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TETRAHEDRON

Synthesis of New 1*H*-Imidazoles *via* Reactions of 3(,5)-(Di)chloro-2*H*-1,4-(benz)oxazin-2-ones with α-Aminoketones

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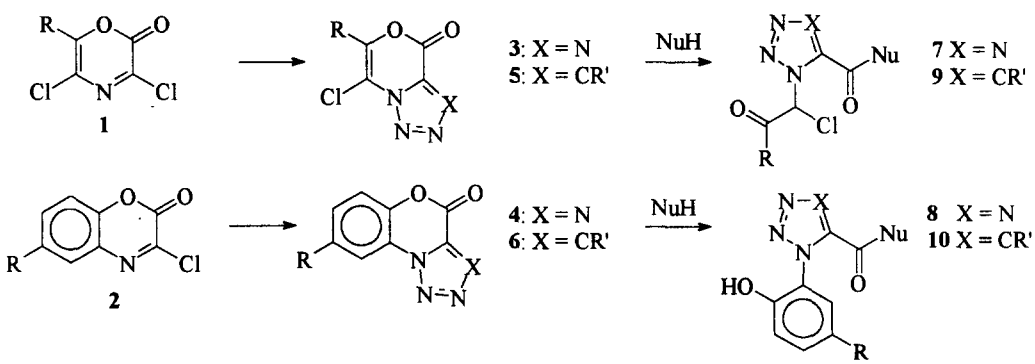
Abstract: 3,5-Dichloro-2*H*-1,4-oxazin-2-ones **1** and 3-chloro-2*H*-1,4-benzoxazin-2-ones **2** react with α-aminoketones to yield bi- and tricyclic imidazo-fused intermediates *via* an intramolecular cyclisation reaction. Reaction of these lactone intermediates with various nucleophiles generates new substituted 1*H*-imidazoles useful for pharmacological screening. Reactions of compounds **1** with β-amino-alcohols followed by treatment with $SOCl_2$ provides 2,3-dihydro-8*H*-imidazo[2,1-*c*]-1,4-oxazin-8-ones but lactone cleavage resulted in the formation of some unidentified decomposition products.

INTRODUCTION

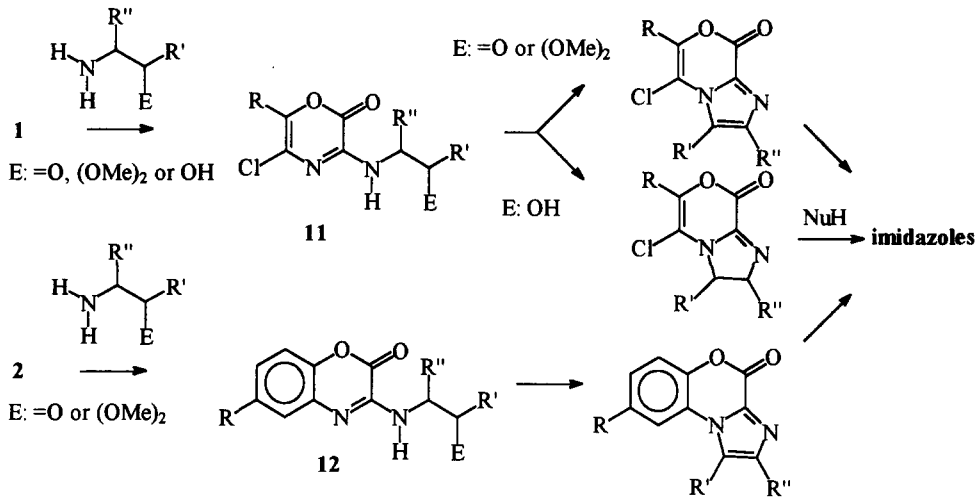
In previous papers[1a,b] we described a convenient and high yielding sequence for the synthesis of specifically substituted tetrazoles and 1,2,3-triazoles with a carboxylic group in the 5-position and an α-chloro ketone substituent or an *ortho*-hydroxyphenyl group at N-1. These compounds could easily be obtained from readily available 3,5-dichloro-2*H*-1,4-oxazin-2-ones **1** and 3-chloro-2*H*-1,4-benzoxazinons **2** *via* a two-step procedure (Scheme 1). Selective reaction of the imidoyl chloride function with NaN_3 or diazocompounds followed by an intramolecular ring closure gave bi- and tricyclic tetrazolo[5,1-*c*]- and [1,2,3]triazolo[5,1-*c*]-fused ring systems **3** and **4** (X = N) or **5** and **6** (X = CR') *via* an electron shift towards the electrophilic part. The lactone function of these intermediates could easily be cleaved with different nucleophiles such as water (NuH = HOH), alcohols (NuH = ROH) and amines (NuH = RNH_2, R_2NH) yielding tetrazoles **7** and **8** or 1,2,3-triazoles **9** and **10**.



Scheme 1

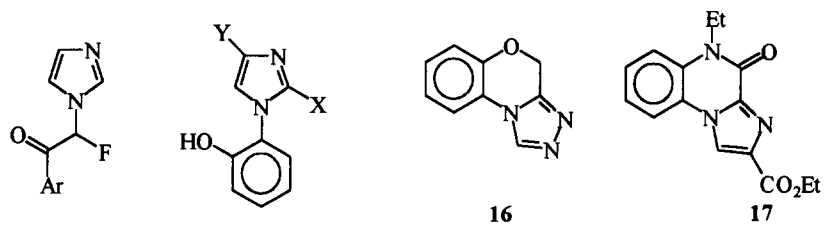
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00087-3

We here deal with a comparable methodology using other bifunctional reagents such as α-aminoketones or the corresponding dimethyl acetals (E = O or $(OMe)_2$) and β-amino-alcohols (E = OH). We have studied their reaction with compounds **1** and **2** to yield 3-amino-substituted compounds **11** and **12** which could possibly be converted into bi- and tricyclic products. Their cleavage with nucleophiles could provide new specifically substituted imidazoles (Scheme 2).



Scheme 2

Various imidazoles have been described to possess various pharmacological properties such as fungicidal (**13**)[2], cardiovascular (**14**)[3] , psychopharmacological (**15**)[4] and anti-allergic (16[5] , 17[6]) activity (Figure 1).



13 Ar = 1,3-Cl_2-C_6H_4

14 X = COOH, Y = H
15 X = H, Y = COOR

16

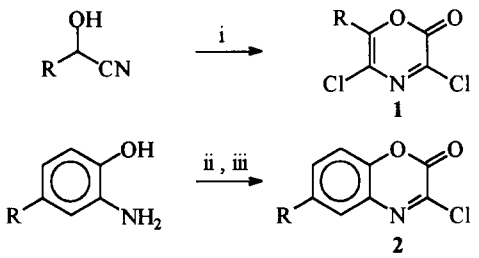
17

Figure 1

RESULTS AND DISCUSSION

The 3,5-dichloro-2*H*-1,4-oxazin-2-ones **1a-c**[7] and 3-chloro-2*H*-1,4-benzoxazin-2-ones **2a,b**[8] were easily prepared *via* a one-pot synthetic method using oxalyl chloride and the appropriate cyanohydrins or *ortho*-amino phenols (Scheme 3). These compounds (**1** and **2**) are characterised by two electrophilic sites: an

imidoyl chloride and a lactone group. Their selective reactions with bifunctional reagents such as α-aminoketones and β-amino alcohols were tested.



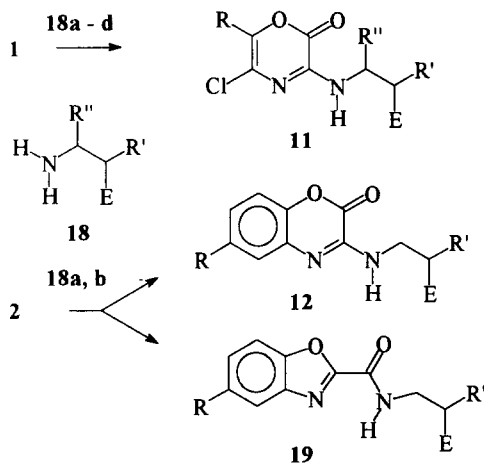
	R
1a	Me
1b	2,6-Cl_2-C_6H_3
1c	4-Cl-C_6H_4
2a	H
2b	Me

Reagents and conditions: i, oxalyl chloride (4 equiv.), Et_3N.HCl (0.5 equiv.), chlorobenzene, 4 h, 90 °C (compound **1c** was not separated and used as such); ii, oxalyl chloride (1.4 equiv.), chlorobenzene, 3 h, 120 °C; iii, DMF (0.01 equiv.), $SOCl_2$ (1.4 equiv.), 1 h, 120 °C

Scheme 3

Reactivity of compounds 1 and 2 towards α-aminoketones

The α-aminoaldehydes or ketones were purchased (**18a**: R' = R'' =H, E = $(OMe)_2$) or prepared using the Délépine (**18b** : R' = Ph, R'' = H, E =O)[9a] or the Gabriel procedure (**18c**: R' = Me, R'' = H, E =O; **18d**: R', R'' = Me, E =O)[9b]



	R	R'	R''	E	% yield
11a	Me	H	H	$(OMe)_2$	40
11b	Me	Me	Me	=O	50
11c	Me	Ph	H	=O	50
11d	2,6-Cl_2-C_6H_3	H	H	$(OMe)_2$	85
11e	2,6-Cl_2-C_6H_3	Me	H	=O	63
11f	2,6-Cl_2-C_6H_3	Me	Me	=O	64

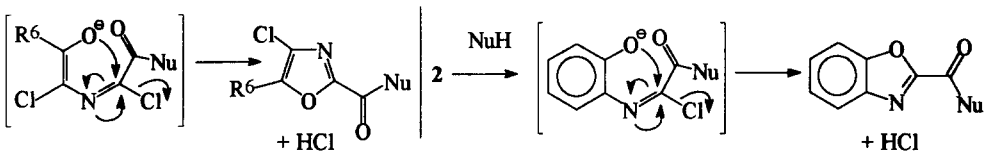
	R	R'	E	% 12	% 19
a	H	H	$(OMe)_2$	37	30
b	H	Ph	=O	50	28
c	Me	Ph	=O	35	*

Reagents and conditions: **18**, EtOAc, Et_3N, 2 h, reflux; *: yield undetermined

Scheme 4

Reaction of these α-aminoketones with compounds **1** in the presence of Et_3N in refluxing ethyl acetate gave selective attack on the imidoyl chloride function yielding 3-amino-substituted compounds **11a-f** (Scheme 4) in moderate to good yields. Oxazole formation *via* lactone cleavage[10] (Scheme 5) in reactions of aminoketones with compounds **1** could be avoided by working at higher temperatures. However, a similar formation of benzoxazoles - also observed by other authors[11] - could not be avoided. Numerous attempts

(higher temperatures, presence of Lewis acids, replacement of the imidoyl chloride by fluoride, iodide, cyanide) failed to improve the selectivity of the reaction. 3-Amino-substituted compounds **12a-c** (by reaction with the imidoyl chloride) as well as benzoxazoles **19a-c** (*via* lactone cleavage) were isolated by chromatography, the benzoxazoles being more polar.

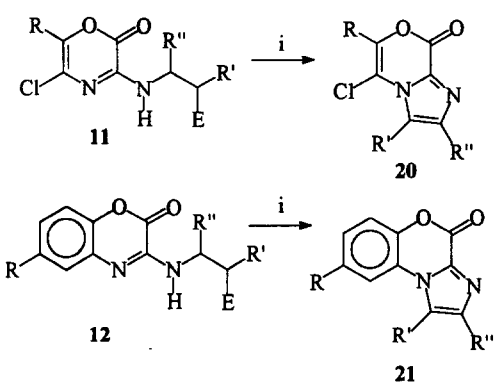


Scheme 5

Compounds **11** show strong IR-absorptions around 3350 (± 70) cm^{-1} (NH) and 1740 (± 10) cm^{-1} (lactone/ ketone). Typical ^{13}C-signals for 3-amino-substituted oxazin-2-ones appear at 152 (± 1) ppm (C-2), 144 (± 2) ppm (C-3), 126 (± 3) ppm (C-5) and 135 (± 3) ppm (C-6). The aliphatic carbonyl signal appears at 202 (± 5) ppm (**11b,e** and **f**) and 192.5 (± 0.3) ppm (**11c**) while the absorption of the acetal in compounds **11a** and **11d** is found around 101.7 (± 0.3) ppm. The N-H signal is found in ^1H NMR-spectra as a broad singlet or triplet at 6.7 (± 0.4) ppm. Compounds **12** and **19** were differentiated on the basis of their ^{13}C NMR-signals: 151.7 (± 0.2) ppm (C-2), 144.7 (± 0.6) ppm (C-3), and 116.0 (± 0.3) ppm (C-8) for the former and 155.5 (± 0.15) ppm (C-2, amide) and 113 (± 3) ppm (C-7) for the latter.

Cyclisation of compounds 11 and 12: generation of 8H-imidazo[2,1-c][1,4]oxazin-8-ones 20a-f and 4H-imidazo[2,1-c][1,4]benzoxazin-4-ones 21a-c

Ring closure of compounds **11** or **12** was realised by stirring them in a 2/1 mixture of acetic anhydride/trifluoroacetic acid (2/1) for 3 to 5 h giving 8*H*-imidazo[2,1-*c*][1,4]oxazin-8-ones **20a-f** and 4*H*-imidazo[2,1-*c*][1,4]benzoxazin-4-ones **21a-c** in good yields (Scheme 6). These compounds were purified by recrystallisation.



	R	R'	R''	E	% yield
20a	Me	H	H	$(OMe)_2$	65
20b	Me	Me	Me	=O	73
20c	Me	Ph	H	=O	75
20d	2,6-Cl_2-C_6H_3	H	H	$(OMe)_2$	72
20e	2,6-Cl_2-C_6H_3	Me	H	=O	77
20f	2,6-Cl_2-C_6H_3	Me	Me	=O	90
20g	4-Cl-C_6H_4	Me	Me	=O	*
21a	H	H	H	$(OMe)_2$	90
21b	H	Ph	H	=O	70
21c	Me	Ph	H	=O	92

*: **compound 20g was not separated but used as such in the next step of the procedure.**
Reagents and conditions: **i, acetic anhydride/trifluoroacetic acid (2/1), 3-5 h, 60 °C.**

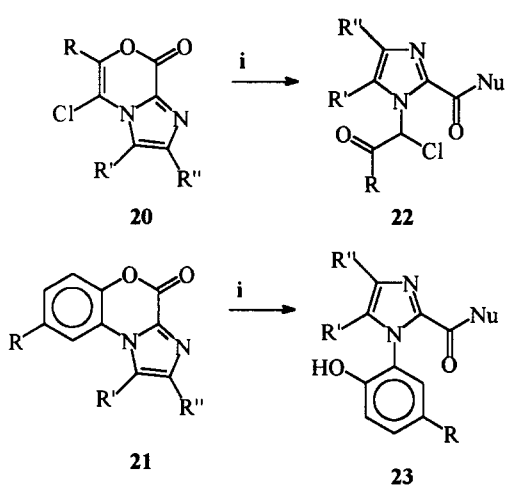
Scheme 6

Formation of the imidazo-fused ring systems **20** and **21** is characterised by the disappearance of the N-H stretching in the IR spectra. The lactone gives a ^{13}C NMR absorption around 150 ppm. Other typical values are found at 112 (± 3) ppm (C-5) and 131 (± 2) ppm (C-8a) for compounds **20** and at 134 (± 1) ppm (C-2), 141 (± 1) ppm (C-5a) and 121 (± 1) ppm (C-9a) for compounds **21**. ^1H NMR-spectra show signals for the imidazole part at 7.6 (± 0.3) ppm.

*Lactone cleavage of 8H-imidazo[2,1-c][1,4]oxazin-8-ones **20a-f** and 4H-imidazo[2,1-c][1,4]benzoxazin-4-ones **21a-c** with alcohols and amines*

The lactone function of compounds **20** and **21** could be cleaved with various nucleophiles such as amines and alcohols yielding imidazoles. The latter are characterised respectively by an α-chloro ketone or an *ortho*-hydroxyphenyl substituent at N-1 and a carboxylic group (derivative) at C-5. These substitution patterns are almost undescribed in the literature.

When comparing the reactivity of the lactone of the tetrazolo (**3** and **4**), [1,2,3]triazolo (**5** and **6**) and imidazo fused compounds (**20** and **21**) towards nucleophiles, we noticed an increasing stability: lactone cleavage with alcohols yielding compounds **22a-d** and **23a,b** required up to one week of reflux (instead of 15 minutes or 12 h for the tetrazolo or triazolo compounds respectively)[1a,b]. When using amines (diethylamine and *iso*-propylamine), we obtained the imidazoles **22e-g** and **23c,d** after stirring for 45 minutes at room temperature (15 to 30 minutes for the tetrazolo or triazolo compounds)[1a,b]. Cleavage of the lactone with aniline to yield the imidazole **22h** was only possible by using $AlCl_3$ in 1,2-dichloroethane as solvent (Scheme 7).



	R	R'	R''	Nu	% yield
22a	Me	H	H	OMe	84
22b	Me	Me	Me	OMe	81
22c	Me	Ph	H	OMe	90
22d	2,6-Cl_2-C_6H_3	Me	H	OMe	79
22e	Me	Me	Me	NEt_2	86
22f	2,6-Cl_2-C_6H_3	H	H	NEt_2	90
22g	2,6-Cl_2-C_6H_3	Me	Me	NEt_2	87
22h	2,6-Cl_2-C_6H_3	Me	H	NHPh	90
22i	4-Cl- C_6H_4	Me	Me	OEt	86*
23a	H	H	H	OMe	46
23b	H	Ph	H	OMe	90
23c	Me	Ph	H	NHPr	65
23d	H	Ph	H	NEt_2	80

*: overall yield starting from compound **1c**.

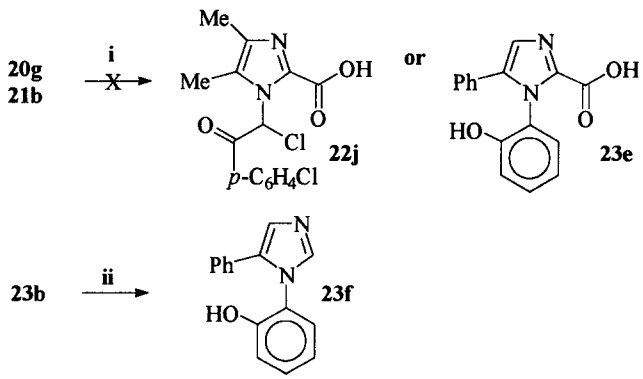
Reagents and conditions: i, MeOH (or EtOH in case of **22i**), 1 week, reflux (**22a-d, 23a,b**); propylamine, diethylamine, 45 min, R.T. (**22e-g, 23c,d**); in case of **22h**: 1,2-dichloroethane, aniline, $AlCl_3$, 24 h, R.T.

Scheme 7

The carbonyl stretching of the ketone, ester or amide in the imidazoles **22** and **23** is found around 1720 (± 20) cm^{-1} and 1640 (± 20) cm^{-1}. IR-spectra of imidazoles **23** show additional strong absorptions at > 3000 cm^{-1} due to the Ar-OH stretching. The α-chloro ketone substituent of compounds **22** shows two ^{13}C-absorptions at 68 (± 2) ppm (CHCl) and 196 (± 1.2) ppm (**22a-c,e**) or 188 (± 2) ppm (ketone) (**22d, f-i**). The *o*-hydroxyphenyl substituent of imidazoles **23** is characterised by a typical C-Ar-OH absorption value of 152 (± 2) ppm. The ester or amide gives a signal around 158 (± 2) ppm. The resonance values of the imidazole carbon atoms of compounds **22** and **23** are strongly substituent dependent: C-2 gives an absorption at 134 (± 2) ppm or 138.8 (± 1) ppm in the esters **22a-d,i** or the amides **22e-h** respectively; these values are deshielded by about 3 ppm in the analogous compounds **23**. The signals for C-4 and C-5 are found around 129 (± 2) ppm and 122.5 (± 2) ppm respectively (H- or Ph-substituted) or at 136 (± 2) ppm and 131.5 (± 5) ppm (Me-substituted). The (H-4 or H-5) in the imidazole part of compounds **22** and **23** absorbs in ^1H NMR spectra around 7.3 (± 0.5) ppm whereas the CHCl of the α-chloro ketone substituent of compounds **22** is found around 8 (± 1.7) ppm.

Lactone cleavage of 8H-imidazo[2,1-c][1,4]oxazin-8-ones 20 and 4H-imidazo[2,1-c][1,4]benzoxazin-4-ones 21 with water

On treatment of tetrazolo and [1,2,3]triazolo fused compounds **20** and **21** with water, decarboxylated tetrazoles and more stable 1,2,3-triazole-5-carboxylic acids were obtained. We tried this reaction also with the imidazo-fused ring systems **20g** and **21b**. (Scheme 8) A complex reaction mixture was obtained instead of the desired imidazole-2-carboxylic acids **22j** and **23e**.



Reagents and conditions: i, water, CH_3CN, 12 h, reflux; ii, THF, Me_3SiOK, 2 h, R.T.

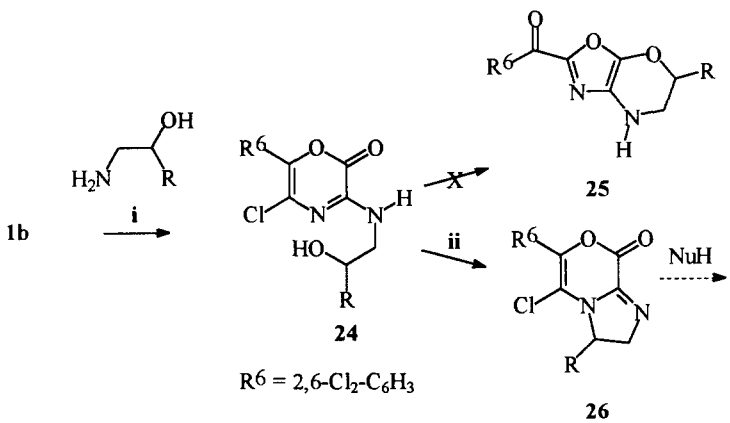
Scheme 8

An alternative way *via* hydrolysis of the ester **23b** was also tested. Treatment of compound **23b** with Me_3SiOK in refluxing THF gave the decarboxylated imidazole **23f** which was identified by NMR-spectral data in DMSO-d_6/D_2SO_4. Typical ^{13}C-absorptions were found at 138.2 ppm (C-2) and at 118.0 ppm (C-4).The ^1H NMR spectrum shows two singlets at 9.5 ppm (H-2) and 8.0 ppm (H-4).

Reactivity of 3-chloro-2H-1,4-oxazin-2-ones 1 towards β-amino-alcohols and ring closure to 5-chloro-2,3-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-ones

Further, we studied the reaction of 3-chloro-2*H*-1,4-oxazin-2-ones **1** with β-amino alcohols. Reflux of compound **1b** in EtOAc with amino alcohols in the presence of Et_3N gave selectively 3-amino-substituted-2*H*-1,4-oxazin-2-ones **24a** and **24b** in good yield. Surprisingly, these compounds were remarkably stable: no intramolecular reaction of the alcohol function with the lactone (leading to morpholino-fused oxazoles of type **25**) occurred. Purification was performed by recrystallisation from CH_2Cl_2 giving a compound with strong IR-absorptions at 1720 cm^{-1} (lactone) and 3440 cm^{-1} (OH, NH). Typical ^{13}C NMR signals for the oxazinone part of the molecule appeared around 152 (± 1) ppm (C-2), 145 (± 1) ppm (C-3), 128.2 (± 0.3) ppm (C-5) and 132.4 (± 0.5) ppm (C-6). The N-H absorption was observed as a triplet in the ^1H NMR spectra of compounds **24a** and **24b** at 8.25 ppm and 7.03 ppm respectively.

In the next step of our procedure, we obtained the desired bicyclic compounds **26a** and **26b** in moderate yields by heating compounds **24a** and **24b** (Scheme 9) in xylene at 90 °C for 3 h with $SOCl_2$. A rapid substitution of OH by Cl was immediately followed by an intramolecular ring closure. The lactone gave a strong IR-band at 1750 (± 30) cm^{-1}. Further evidence for the ring closed system was found in the NMR-spectral data showing the disappearance of the N-H absorption; the ABX-pattern of the dihydro part of the molecule was found between 3.8 ppm and 5.5 ppm. In the ^{13}C NMR spectra, the signal of C-2 is deshielded from 48 ppm to 63 (± 2) ppm. However cleavage of the lactone function of these 2,3-dihydro-5-chloro-8*H*-imidazo[2,1-c][1,4]oxazin-8-ones with several nucleophiles was not successful: complex reaction mixtures were obtained.



	R	% Yield
24a	Me	82
24b	Ph	75
26a	Me	50
26b	Ph	57

Reagents and conditions: i, β-amino alcohol, EtOAc, Et_3N, 2 h, reflux; ii, xylene, $SOCl_2$, 3 h, 90 °C

Scheme 9

CONCLUSION

We can conclude that in addition to the previously examined reagents NaN_3 and diazocompounds, the bifunctional α-aminoketones and β-amino alcohols proved to be useful reagents in the synthesis of new imidazo and dihydro-imidazo fused bi- and tricyclic ring systems. Lactone cleavage by treatment of the imidazo fused oxazinones and benzoxazinones with some nucleophiles yielded new imidazoles with a carboxylic acid function on C-2 and an α-chloro-ketone or an *o*-hydroxyphenyl substituent on N-1. However this lactone cleavage could not be successfully achieved with the dihydro imidazo-fused analogues.

EXPERIMENTAL

Infrared spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier transform spectrometer. The mentioned IR-absorptions were observed as strong bands. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. For chromatography analytical TLC plates (Alugram Sil G/UV$_{254}$) and 70-230 mesh silica gel 60 (E.M. Merck) were used. Melting points were taken using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106.

General procedure for the synthesis of compounds 11a, 11d, 12a and 19a *via* reaction of compounds 1 or 2 with aminoacetaldehyde dimethylacetal 18a

A mixture of aminoacetaldehyde dimethylacetal **18a** (1.36 g, 13 mmol) and Et_3N (3g, 30 mmol) in EtOAc (50 ml) was slowly added to a solution of compounds **1** or **2** (10 mmol) in EtOAc (150 ml) at reflux temperature. After refluxing for 2 h, the mixture was cooled on an ice-bath and Et_3N.HCl was filtered off. The solvent was evaporated and the crude mixture was purified by recrystallisation (**11a,d**; CH_2Cl_2) or by chromatography: (**12a**, **19a**; SiO_2, CH_2Cl_2/EtOAc)

5-Chloro-3-(2,2-dimethoxyethylamino)-6-methyl-2*H*-1,4-oxazin-2-one (11a): Yield: 70 %; m.p.: 56 °C; IR (KBr cm^{-1}): 1603 and 1630 (s): $\nu_{C=N}$, 1736 (s): $\nu_{C=O}$ (lactone), 2987 (s): $\nu_{CH\ aliph}$, 3348 (s): ν_{NH} ; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.25 (s, 3H, 6-CH_3), 3.40 (s, 6H, 2xOCH_3), 3.52 (t, 2H, NHCH_2, ^3J = 4.4 Hz), 4.50 (t, 1H, O-CH-O, ^3J = 4.4 Hz), 6.20 (broad t, 1H, NH, ^3J = 4.4 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 15.9, 42.5, 54.2, 101.9, 124.7, 136.4, 144.4, 152.5; MS [m/z (%)]: 248 (2): $M^{+\cdot}$, 217 (2): $M^{+\cdot}$-OCH_3, 75 (100): $(CH_3O)_2CH^+$; HRMS calcd. for $C_9H_{13}ClN_2O_4$: 248.0562; found: 248.0559

5-Chloro-6-(2,6-dichlorophenyl)-3-(2,2-dimethoxyethylamino)-2*H*-1,4-oxazin-2-one (11d): Yield: 85 %; m.p.: 148 °C; IR (KBr cm^{-1}): 1602 and 1631 (s): $\nu_{C=N}$, 1752 (s): $\nu_{C=O}$ (lactone), 2973 and 2997 (m): $\nu_{CH\ aliph}$, 3037 (w): $\nu_{CH\ arom}$, 3293 (s): ν_{NH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.45 (s, 6H, 2xOCH_3), 3.70 (t, 2H, NHCH_2, ^3J = 4.4 Hz), 4.55 (t, 1H, O-CH-O, ^3J = 4.4 Hz), 6.50 (broad t, 1H, NH, ^3J = 4.4 Hz), 7.40 (m, 3H, ArH); ^{13}C NMR (250 MHz, $CDCl_3$): 42.7, 54.4, 101.6, 128.2, 128.6, 128.7, 132.1, 132.4, 137.2, 145.6, 152.0; MS [m/z (%)]: 378 (2): $M^{+\cdot}$, 347 (3): $M^{+\cdot}$-OCH_3, 75 (100): $(CH_3O)_2CH^+$; HRMS calcd. for $C_{14}H_{13}Cl_3N_2O_4$: 377.9941; found: 377.9939

3-(2,2-Dimethoxyethylamino)-2*H*-1,4-benzoxazin-2-one (12a): Yield: 37 %; m.p.: 95 °C; IR (KBr cm^{-1}): 1581 and 1618 (s): $\nu_{C=N}$, 1730 (s): $\nu_{C=O}$ (lactone), 2905 and 2939 (m): $\nu_{CH\ aliph}$, 3048 (m): $\nu_{CH\ arom}$, 3372 (s): ν_{NH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.40 (s, 6H, 2xOCH_3), 3.70 (t, 2H, NHCH_2, ^3J = 4.4 Hz), 4.60 (t, 1H, O-CH-O, ^3J = 4.4 Hz), 6.40 (broad t, 1H, NH, ^3J = 4.4 Hz), 7.20 (m, 3H, H-6, 7, 8), 7.45 (d, 1H, H-5, $^3J_{H5,H6}$ = 6.5 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 42.2, 53.9, 101.7, 115.7, 124.6, 125.4, 132.2, 143.5, 145.3, 151.7; MS [m/z (%)]: 250 (54): $M^{+\cdot}$, 219 (57): $M^{+\cdot}$-CH_3O, 187 (23): $M^{+\cdot}$-CH_3O, -CH_3OH, 75 (100): $(CH_3O)_2CH^+$; HRMS calcd. for $C_{12}H_{14}N_2O_4$: 250.0954; found: 250.0955

***N*-(2,2-dimethoxyethyl)-2-benzoxazolecarboxamide (19a)**: Yield: 30 %; m.p.: 117 °C; IR (KBr cm^{-1}): 1606 (s): $\nu_{C=N}$, 1680 (s): $\nu_{C=O}$ (amide), 2953 (m): $\nu_{CH\ aliph}$, 3340 (s): ν_{NH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.40 (s,

6H, 2xOCH$_3$), 3.70 (t, 2H, NHCH_2, ^3J = 4.3 Hz), 4.58 (t, 1H, O-CH-O, ^3J = 4.3 Hz), 7.40 (m, 2H, H-5, 6), 7.60 (dd, 1H, H-7, $^3J_{H7,H6}$ = 7.5 Hz, $^4J_{H7,H5}$ = 1.3 Hz), 7.71 (broad t, 1H, NH, ^3J = 4.3 Hz), 7.76 (dd, 1H, H-4, $^3J_{H4,H5}$ = 7.5 Hz, $^4J_{H4,H6}$ = 1.3 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 40.9, 53.9, 101.6, 111.3, 120.9, 125.0, 126.9, 139.8, 151.2, 155.0, 155.5, MS [m/z (%)]: 250 (0.5): $M^{+\cdot}$, 219 (12): $M^{+\cdot}$-CH_3O, 187 (7): $M^{+\cdot}$-CH_3O, -CH_3OH, 75 (100): $(CH_3O)_2CH^+$; HRMS calcd. for $C_{12}H_{14}N_2O_4$: 250.0954; found: 250.0951

General procedure for the synthesis of compounds 11b,c,e,f, 12b,c and 19b *via* reaction of compounds 1 or 2 with the α-aminoketones 18b-d

To a mixture of compounds **1** or **2** (10 mmol) and the hydrochloride salt of the appropriate α-aminoketone **18b-d**[9a-b] (13 mmol) in ethyl acetate (150 ml) at reflux temperature a solution of Et_3N (3g, 30 mmol) in EtOAc (100 ml) was slowly added. After stirring for 2 h the mixture was cooled on an ice-bath and Et_3N.HCl was filtered off. The solvent was evaporated and the crude mixture was purified by crystallisation. In case of reactions with compounds **2**, compounds **12** and **19** were initially separated by chromatography (SiO_2, EtOAc; CH_2Cl_2) and afterwards recrystallised from CH_2Cl_2.

5-Chloro-6-methyl-3-(3-oxo-2-butylamino)-2*H*-1,4-oxazin-2-one (11b): Yield: 50 %; m.p.: 88 °C; IR (KBr cm^{-1}): 1602 and 1615 (s): $\nu_{C=N}$, 1735 (s): $\nu_{C=O}$ (ketone, lactone), 2986 and 2099 (w): $\nu_{CH\ aliph}$, 3386 (s): ν_{NH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.50 (d, 3H, CHCH_3, ^3J = 6.4 Hz), 2.20 (s, 3H, CH_3CO or 6-CH_3), 2.30 (s, 3H, CH_3CO or 6-CH_3), 4.60 (m, 1H, CHCH$_3$), 6.70 (broad d, 1H, NH, ^3J = 4.0 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 15.8, 16.4, 26.4, 55.7, 124.3, 136.5, 143.2, 152.1, 205.5; MS [m/z (%)]: 230 (2): $M^{+\cdot}$, 187 (12): $M^{+\cdot}$-CH_3CO, 43 (100): CH_3CO^+; HRMS calcd. for $C_9H_{11}ClN_2O_3$: 230.0458; found: 230.0459

5-Chloro-6-methyl-3-(2-phenyl-2-oxoethylamino)-2*H*-1,4-oxazin-2-one (11c): Yield: 50 %; m.p.: 120 °C; IR (KBr cm^{-1}): 1597 and 1620 (s): $\nu_{C=N}$, 1687 (s): $\nu_{C=O}$ (ketone), 1736 (s): $\nu_{C=O}$ (lactone), 2907 (w): $\nu_{CH\ aliph}$, 3060 (w): $\nu_{CH\ arom}$, 3403 (s): ν_{NH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 4.82 (d, 2H, NHCH_2, ^3J = 4.3 Hz), 7.10 (broad t, 1H, NH, ^3J = 4.3 Hz), 7.50 (t, 2H, ArH-3, 5, ^3J = 7.5 Hz), 7.70 (t, 1H, ArH-4, ^3J = 7.5 Hz), 8.0 (d, 2H, ArH-2, 6, ^3J = 7.5 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 16.0, 47.7, 124.5, 128.0, 128.9, 134.3, 136.7, 144.1, 152.2, 192.7; MS [m/z (%)]: 278 (10): $M^{+\cdot}$, 250 (2): $M^{+\cdot}$-CO, 173 (7): $M^{+\cdot}$-PhCO, 105 (100): $PhCO^+$; HRMS calcd. for $C_{13}H_{11}ClN_2O_3$: 278.0458; found: 278.0454

5-Chloro-6-(2,6-dichlorophenyl)-3-(2-oxopropylamino)-2*H*-1,4-oxazin-2-one (11e): Yield: 63 %; m.p.: 140 °C; IR (KBr cm^{-1}): 1608 (s): $\nu_{C=N}$, 1746 (s): $\nu_{C=O}$ (ketone, lactone), 2956 (w): $\nu_{CH\ aliph}$, 3050 (w): $\nu_{CH\ arom}$, 3416 (s): ν_{NH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3CO), 4.35 (d, 2H, NHCH_2, ^3J = 4.2 Hz), 7.00 (broad t, 1H, NH, ^3J = 4.2 Hz), 7.40 (m, 3H, ArH); ^{13}C NMR (250 MHz, $CDCl_3$): 27.3, 51.0, 128.0, 128.1, 128.4, 132.0, 132.4, 136.9, 144.9, 151.4, 200.7; MS [m/z (%)]: 346 (32): $M^{+\cdot}$, 275 (94): $M^{+\cdot}$-CH_3COCH_2NH, 43 (100): CH_3CO^+; HRMS calcd. for $C_{13}H_9Cl_3N_2O_3$: 345.9679; found: 345.9686

5-Chloro-6-(2,6-dichlorophenyl)-3-(1-methyl-2-oxopropylamino)-2*H*-1,4-oxazin-2-one (11f): Yield: 64 %; m.p.: 85 °C; IR (KBr cm^{-1}): 1603 and 1629 (s): $\nu_{C=N}$, 1746 (s): $\nu_{C=O}$ (ketone, lactone), 2933 and 2978 (w): $\nu_{CH\ aliph}$, 3082 (m): $\nu_{CH\ arom}$, 3382 (s): ν_{NH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.55 (d, 3H, CHCH_3, ^3J = 6.0 Hz), 2.30 (s, 3H, CH_3CO), 4.70 (m, 1H, CHCH$_3$), 7.10 (d, 1H, NH, ^3J = 5.0 Hz), 7.40 (m, 3H, ArH); ^{13}C NMR (250 MHz, $CDCl_3$): 16.4, 26.4, 56.0, 128.0, 132.0, 128.4, 132.4, 136.9, 144.4, 151.5, 205.0; MS [m/z (%)]: 360 (15): $M^{+\cdot}$, 317 (64): $M^{+\cdot}$-CH_3CO, 43 (100): CH_3CO^+; HRMS calcd. for $C_{14}H_{11}Cl_3N_2O_3$: 359.9835; found: 359.9830

3-(2-Phenyl-2-oxoethylamino)-2*H*-1,4-benzoxazin-2-one (12b): Yield: 50 %; m.p.: 162-164 °C; IR (KBr cm^{-1}): 1578 and 1619 (s): $\nu_{C=N}$, 1688 (s): $\nu_{C=O}$ (ketone), 1748 (s): $\nu_{C=O}$ (lactone), 3064 (w): $\nu_{CH\ arom}$, 3399 (s): ν_{NH}; ^1H NMR (250 MHz, $CDCl_3$): δ 4.90 (d, 2H, CH_2CO, ^3J = 4.0 Hz), 7.20 (m, 4H, H-6, 7, 8 and NH), 7.45 (d, 1H, H-5, $^3J_{H5,H6}$ = 6.0 Hz), 7.55 (t, 2H, COPhH-3', 5', ^3J = 7.3 Hz), 7.65 (t, 1H, COPhH-4', ^3J = 7.3 Hz), 8.05 (d, 2H, ArH-2', 6', ^3J = 7.3 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 47.7, 116.2, 125.1, 125.6, 128.0, 128.9, 132.3, 134.2, 134.5, 143.9, 145.1, 151.6, 193.1; MS [m/z (%)]: 280 (14): $M^{+\cdot}$, 175 (44): $M^{+\cdot}$-PhCO, 105 (100): $PhCO^+$, 77 (60): $C_6H_5^+$, 51 (36): $C_4H_3^+$; HRMS calcd. for $C_{16}H_{12}N_2O_3$: 280.0848; found: 280.0844

6-Methyl-3-(2-phenyl-2-oxoethylamino)-2*H*-1,4-benzoxazin-2-one (12c): Yield: 35 %; m.p.: 142-144 °C; IR (KBr cm^{-1}): 1578 and 1621 (s): $\nu_{C=N}$, 1688 (s): $\nu_{C=O}$ (ketone), 1741 (s): $\nu_{C=O}$ (lactone), 2918 (m): $\nu_{CH\ aliph}$, 3040 (w): $\nu_{CH\ arom}$, 3387 (s): ν_{NH}; ^1H NMR (250 MHz, $CDCl_3$): δ 2.35 (s, 3H, 6-CH_3), 4.90 (d, 2H, C*H*$_2$NH, ^3J = 4.0 Hz), 6.95 (d, 1H, H-7, $^3J_{H7,H8}$ = 8.0 Hz), 7.05 (d, 1H, H-8, $^3J_{H8,H7}$ = 8.0 Hz), 7.10 (broad t, 1H, CH_2N*H*, ^3J = 4.0 Hz), 7.21 (s, 1H, H-5), 7.50 (t, 2H, COPhH-3', 5', ^3J = 6.7 Hz), 7.62 (t, 1H, COPhH-4', ^3J = 6.7 Hz), 8.05 (d, 2H, COPhH-2', 6', ^3J = 6.7 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 20.8, 47.7, 115.7, 125.7, 125.9, 128.0, 128.9, 131.9, 134.2, 134.5, 135.5, 141.9, 145.2, 151.8, 193.2; MS [m/z (%)]: 294 (22): $M^{+\cdot}$, 189 (75): $M^{+\cdot}$-PhCO, 105 (92): $PhCO^+$, 77 (100): Ph^+, 51 (46): $C_4H_3^+$; HRMS calcd. for $C_{17}H_{14}N_2O_3$: 294.1004; found: 294.1007

***N*-(2-phenyl-2-oxoethyl)-2-benzoxazolecarboxamide (19b)**: Yield: 28 %; m.p.: 178 °C; IR (KBr cm^{-1}): 1599 (s): $\nu_{C=N}$, 1678 and 1704 (s): $\nu_{C=O}$ (amide, ketone), 1704 (s): $\nu_{C=O}$ (ketone), 2911 (w): $\nu_{CH\ aliph}$, 3090 (w): $\nu_{CH\ arom}$, 3400 (s): ν_{NH}; ^1H NMR (250 MHz, $CDCl_3$): δ 5.00 (d, 2H, CH_2CO, ^3J = 4.2 Hz), 7.50 (m, 4H, H-5, 6 and COPhH-3', 5'), 7.65 (m, 2H, H-7 and COPhH-4'), 7.85 (d, 1H, H-4, $^3J_{H4,H5}$ = 7.0 Hz), 8.05 (d, 2H, COPhH-2', 6', ^3J = 7.8 Hz), 8.30 (broad t, 1H, NH, ^3J = 4.2 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 46.5, 111.8, 121.6, 128.0, 128.1, 129.0, 129.1, 134.1, 134.5, 140.4, 151.2, 155.0, 155.7, 192.9; MS [m/z (%)]: 280 (5): $M^{+\cdot}$, 175 (33): $M^{+\cdot}$-PhCO, 105 (100): $PhCO^+$, 77 (67): $C_6H_5^+$, 51 (28): $C_4H_3^+$; anal. calcd. for $C_{16}H_{12}N_2O_3$: C 68.57, H 4.32, N 9.99; found: C 68.48, H 4.12, N 9.99.

General procedure for the synthesis of 8*H*-imidazo[2,1-*c*][1,4]oxazin-8-ones 20a-f and 4*H*-imidazo [2,1-*c*][1,4]benzoxazin-4-ones 21a-c

A solution of compounds **11** or **12** (10 mmol) in acetic anhydride/trifluoroacetic acid (2/1) was stirred for 3-5 h at 60 °C. After cooling, the solvent was evaporated and the crude product was subjected to chromatographic purification (SiO_2, EtOAc; CH_2Cl_2) and recrystallisation from a mixture of CH_2Cl_2/hexane.

5-Chloro-6-methyl-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (20a): Yield: 65 %; m.p.: 180 °C; IR (KBr cm^{-1}): 1664 (s): $\nu_{C=N}$, 1753 (s): $\nu_{C=O}$ (lactone), 2958 (w): $\nu_{CH\ aliph}$, 3136 and 3157 (w): $\nu_{CH\ imidazole}$; ^1H NMR (250 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 7.55 (d, 1H, H-2, $^3J_{H2,H3}$ = 1.1 Hz), 7.61 (d, 1H, H-3, $^3J_{H3,H2}$ = 1.1 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 15.8, 109.1, 117.1, 131.1, 134.3, 140.2, 150.7; MS [m/z (%)]: 184 (76): $M^{+\cdot}$, 43 (100): CH_3CO^+; HRMS calcd. for $C_5H_5ClN_2O_2$: 184.0040; found: 184.0043

5-Chloro-2,3,6-trimethyl-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (20b): Yield: 73 %; m.p.: 178 °C; IR (KBr cm^{-1}): 1659 (s): $\nu_{C=N}$, 1753 (s): $\nu_{C=O}$ (lactone), 2923 (m): $\nu_{CH\ aliph}$; ^1H NMR (250 MHz, $CDCl_3$): δ 2.33 (s, 6H, 2-CH_3 and 6-CH_3), 2.60 (s, 3H, 3-CH_3); ^{13}C NMR (250 MHz, $CDCl_3$): 11.8, 13.0, 15.9, 109.6, 126.0, 129.6, 138.8, 142.3, 150.9; MS [m/z (%)]: 212 (9): $M^{+\cdot}$, 43 (100): CH_3CO^+; HRMS calcd. for $C_9H_9ClN_2O_2$: 212.0353; found: 212.0354; anal. calcd. for $C_9H_9ClN_2O_2$: C 50.84, H 4.27, N 13.17; found: C 50.60, H 4.17, N 12.91

5-Chloro-3-phenyl-6-methyl-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (20c): Yield: 75 %; m.p.: 203 °C; IR (KBr cm^{-1}): 1653 (s): $\nu_{C=N}$, 1749 (s): $\nu_{C=O}$ (lactone), 2957 (w): $\nu_{CH\ aliph}$, 3031 and 3054 (m): $\nu_{CH\ arom}$, 3107 (s): $\nu_{CH\ imidazole}$; ^1H NMR (250 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 7.45 (m, 6H, H-2 and ArH); ^{13}C NMR (250 MHz, $CDCl_3$): 16.2, 109.8, 128.1, 129.9, 131.2, 132.2, 133.6, 135.3, 140.3, 151.6; MS [m/z (%)]: 260 (13): $M^{+\cdot}$, 77 (17): Ph^+, 43 (100): CH_3CO^+; HRMS calcd. for $C_{13}H_9ClN_2O_2$: 260.0353; found: 260.0354; anal. calcd. for $C_{13}H_9ClN_2O_2$: C 59.90, H 3.48, N 10.75; found: C 60.10, H 3.43, N 10.82

5-Chloro-6-(2,6-dichlorophenyl)-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (20d): Yield: 72 %; m.p.: 163 °C; IR (KBr cm^{-1}):1672 (m): $\nu_{C=N}$, 1766 (s): $\nu_{C=O}$ (lactone), 3077 (w): $\nu_{CH\ arom}$, 3122 and 3138 (s): $\nu_{CH\ imidazole}$; ^1H NMR (250 MHz, CD_3CN): δ 7.58 (m, 3H, ArH), 7.65 (d, 1H, H-2, $^3J_{H2,H3}$ = 1.0 Hz), 7.82 (d, 1H, H-3, $^3J_{H3,H2}$ = 1.0 Hz); ^{13}C NMR (250 MHz, CD_3CN): 113.1, 118.0, 126.6, 128.1, 130.8, 132.9, 133.8, 135.2, 135.5, 150.2; MS [m/z (%)]: 314 (40): $M^{+\cdot}$, 279 (4): $M^{+\cdot}$-Cl, 251 (36): $M^{+\cdot}$-Cl, -CO, 173 (100): Cl_2-C_6H_3-CO^+; HRMS calcd. for $C_{12}H_5Cl_3N_2O_2$: 313.9417; found: 313.9416; anal. calcd. for $C_{12}H_5Cl_3N_2O_2$: C 45.68, H 1.60, N 8.88; found: C 45.29, H 1.50, N 8.66

5-Chloro-6-(2,6-dichlorophenyl)-3-methyl-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (20e): Yield: 77 %; m.p.: 192 °C; IR (KBr cm^{-1}): 1656 (s): $\nu_{C=N}$, 1752 (s): $\nu_{C=O}$ (lactone), 2979 and 2999 (w): $\nu_{CH\ aliph}$, 3067 (m): $\nu_{CH\ arom}$, 3124 (w): $\nu_{CH\ imidazole}$; ^1H NMR (250 MHz, $CDCl_3$): δ 2.70 (s, 3H, 3-CH_3), 7.39 (s, 1H, H-2), 7.45 (m, 3H, ArH); ^{13}C NMR (250 MHz, $CDCl_3$): 12.8, 114.2, 127.8, 128.4, 131.1, 132.1, 132.8, 135.0, 135.8, 136.4, 150.7; MS [m/z (%)]: 328 (32): $M^{+\cdot}$, 293 (2): $M^{+\cdot}$-Cl, 265 (23): $M^{+\cdot}$-Cl, -CO, 173 (100): Cl_2-C_6H_3-CO^+; HRMS calcd. for $C_{13}H_7Cl_3N_2O_2$: 327.9573; found: 327.9580

5-Chloro-6-(2,6-dichlorophenyl)-2,3-dimethyl-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (20f): Yield: 90 %; m.p.: 197 °C; IR (KBr cm^{-1}): 1658 (m): $\nu_{C=N}$, 1767 (s): $\nu_{C=O}$ (lactone), 2960 and 2983 (w): $\nu_{CH\ aliph}$, 3067 (w): $\nu_{CH\ arom}$; ^1H NMR (250 MHz, DMSO-d_6): δ 2.30 (s, 3H, 2-CH_3), 2.70 (s, 3H, 3-CH_3), 7.65 (m, 3H, ArH); ^{13}C NMR (250 MHz, DMSO-d_6): 11.1, 12.4, 113.6, 127.2, 127.4, 128.5, 129.2, 133.5, 134.5, 135.2, 142.2, 148.7; MS [m/z (%)]: 342 (43): $M^{+\cdot}$, 307 (2): $M^{+\cdot}$-Cl, 279 (18): $M^{+\cdot}$-Cl, -CO, 173 (100): Cl_2-C_6H_3-CO^+; HRMS calcd. for $C_{14}H_9Cl_3N_2O_2$: 341.9730; found: 341.9732; anal. calcd. for $C_{14}H_9Cl_3N_2O_2$: C 48.94, H 2.64, N 8.15; found: C 49.01, H 2.55, N 8.10

4*H*-Imidazo[2,1-*c*][1,4]benzoxazin-4-one (21a): Yield: 70 %; m.p.: 192 °C; IR (KBr cm^{-1}): 1781 (s): $\nu_{C=O}$ (lactone); ^1H NMR (250 MHz, DMSO-d_6): δ 7.42 (m, 3H, H-6, 7, 8), 7.70 (d, 1H, H-2, $^3J_{H2,H1}$ = 1.0 Hz), 8.10 (dd, 1H, H-9, $^3J_{H9,H8}$ = 7.0 Hz, $^4J_{H9,H7}$ = 3.0 Hz), 8.60 (d, 1H, H-1, $^3J_{H1,H2}$ = 1.0 Hz); ^{13}C NMR (250 MHz, DMSO-d_6): 116.3, , 117.3, 117.5, 121.8, 125.0, 127.5, 131.0, 134.0, 142.9, 150.8; MS [m/z (%)]: 186 (100): $M^{+\cdot}$, 158 (7): $M^{+\cdot}$-CO, 76 (41): $C_6H_4^+$; HRMS calcd. for $C_{10}H_6N_2O_2$: 186.0429; found: 186.0409

1-Phenyl-4*H*-imidazo[2,1-*c*][1,4]benzoxazin-4-one (21b): Yield: 90 %; m.p.: 154 °C; IR (KBr cm^{-1}): 1744 (s): $\nu_{C=O}$ (lactone); ^1H NMR (250 MHz, $CDCl_3$): δ 7.02 (ddd, 1H, H-8, $^3J_{H8,H7,\ H8.H9}$ = 8.5 Hz, $^4J_{H8,H6}$ = 2.0 Hz), 7.17 (dd, 1H, H-9, $^3J_{H9,H8}$ = 8.5 Hz, $^4J_{H9,H7}$ = 2.0 Hz), 7.30 (td, 1H, H-7, $^3J_{H7,H8,\ H7.H6}$ = 8.5 Hz, $^4J_{H7,H9}$ = 2.0 Hz), 7.35 (dd, 1H, H-6, $^3J_{H6,H7}$ = 8.5 Hz, $^4J_{H6,H8}$ = 2.0 Hz), 7.48 (s, 1H, H-2), 7.59 (m, 5H, PhH); ^{13}C NMR (250 MHz, $CDCl_3$): 116.3, 117.9, 122.2, 124.2, 127.2, 128.1, 128.8, 129.5, 129.7, 131.8, 132.8, 134.6, 142.8, 150.5, MS [m/z (%)]: 262 (100): $M^{+\cdot}$, 218 (81): $M^{+\cdot}$-CO_2, 77 (42): Ph^+, 51 (45): $C_4H_3^+$; HRMS calcd. for $C_{16}H_{10}N_2O_2$: 262.0742; found: 262.0747; anal.calcd. for $C_{16}H_{10}N_2O_2$: C 73.27, H 3.84, N 10.68; found: C 73.31, H 3.76, N 10.72

1-Phenyl-8-methyl-4*H*-imidazo[2,1-*c*][1,4]benzoxazin-4-one (21c): Yield: 92 %; m.p.: 190 °C; IR (KBr cm^{-1}) : 1617 (s): $\nu_{C=N}$, 1747 (s): $\nu_{C=O}$ (lactone), 3102 (s): $\nu_{CH\ imidazole}$; ^1H NMR (250 MHz, $CDCl_3$): δ 2.1 (s, 3H,

8-CH_3), 6.90 (d, 1H, H-9, $^4J_{H9,H7}$ = 2.0 Hz), 7.09 (dd, 1H, H-7, $^3J_{H7,H6}$ = 8.8 Hz, $^4J_{H7,H9}$ = 2.0 Hz), 7.23 (d, 1H, H-6, $^3J_{H6,H7}$ = 8.8 Hz), 7.30 (s, 1H, H-2), 7.60 (m, 5H, PhH); ^{13}C NMR (250 MHz, $CDCl_3$): 20.8, 116.8, 117.8, 122.0, 128.4, 128.1, 128.9, 129.8, 130.0, 132.2, 132.9, 134.5, 134.8, 140.9, 151.0; MS [m/z (%)]: 276 (100): $M^{+\cdot}$, 232 (25): $M^{+\cdot}$-CO_2, 77 (88): Ph^+, 51 (80): $C_4H_3^+$; HRMS calcd. for $C_{17}H_{11}N_2O_2$: 276.0899; found: 276.0904; anal. calcd. for $C_{17}H_{11}N_2O_2$: C 73.90, H 4.38, N 10.14; found: C 73.61, H 4.33, N 9.97

General procedure for the lactone cleavage of compounds 20 and 21 with alcohols and amines

Compounds **20** or **21** (10 mmol) were dissolved in 50 ml of the appropriate alcohol or amine. When alcohols were used, the solution was brought to reflux temperature and the solvent was evaporated after 1 week. In the case of diethylamine and propylamine, the solvent was evaporated after 45 minutes. Further purification was performed by crystallisation from a mixture of $CHCl_3$/hexane.

(±)-Methyl 1-(1-chloro-2-oxopropyl)-1*H*-imidazole-2-carboxylate (22a): Yield: 84 %; m.p.: 70 °C; IR (KBr cm^{-1}): 1718 (s): $\nu_{C=O}$ (ketone, ester), 2917 and 2963 (s): $\nu_{CH\ aliph}$, 3109 and 3127 (w): $\nu_{CH\ imidazole}$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.45 (s, 3H, $COCH_3$), 3.90 (s, 3H, OCH_3), 7.20 (d, 1H, H-4, $^3J_{H4,H5}$ = 1.2 Hz), 7.38 (d, 1H, H-5, $^3J_{H5,H4}$ = 1.2 Hz), 7.54 (s, 1H, CHCl); ^{13}NMR (250 MHz, $CDCl_3$): 25.9, 52.7, 67.5, 124.3, 130.4, 135.8, 159.9, 194.9; MS [m/z (%)]: 217 (100): MH^+, 174 (75): [$M^{+\cdot}$- CH_3CO]H, 43 (78): CH_3CO^+; HRMS calcd. for $C_8H_9ClN_2O_3$: 216.0302; found: 216.0299

(±)-Methyl 1-(1-chloro-2-oxopropyl)-4,5-dimethyl-1*H*-imidazole-2-carboxylate (22b): Yield: 81 %; m.p.: 71 °C; IR (KBr cm^{-1}): 1726 (s): $\nu_{C=O}$ (ketone, ester), 2941 (s): $\nu_{CH\ aliph}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 and 2.22 (2xs, 6H, 4-CH_3 and 5-CH_3), 2.43 (s, 3H, $COCH_3$), 3.93 (s, 3H, OCH_3), 7.80 (s, 1H, CHCl); ^{13}C NMR (400 MHz, $CDCl_3$): 9.8, 12.5, 26.3, 52.4, 68.6, 129.7, 133.4, 137.3, 159.4, 195.8; MS [m/z (%)]: 244 (38): $M^{+\cdot}$, 209 (22): $M^{+\cdot}$- Cl, 43 (100): CH_3CO^+; HRMS calcd. for $C_{11}H_{13}ClN_2O_3$: 244.0615; found: 244.0618

(±)-Methyl 1-(1-chloro-2-oxopropyl)-5-phenyl-1*H*-imidazole-2-carboxylate (22c): Yield: 90 %; m.p.: 157 °C; IR (KBr cm^{-1}): 1720 and 1738 (s): $\nu_{C=O}$ (ketone, ester), 2929 and 2955 (m): $\nu_{CH\ aliph}$, 3010 and 3067 (w): $\nu_{CH\ arom}$, 3120 (w): $\nu_{CH\ imidazole}$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.50 (s, 3H, $COCH_3$), 3.95 (s, 3H, OCH_3), 6.30 (s, 1H, CHCl), 7.20 (s, 1H, H-4), 7.50 (m, 5H, ArH); ^{13}C NMR (250 MHz, $CDCl_3$): 26.7, 52.6, 67.0, 127.2, 128.9, 129.1, 129.5, 129.7, 135.6, 138.6, 159.1, 196.8; MS [m/z (%)]: 292 (37): $M^{+\cdot}$, 249 (78): $M^{+\cdot}$-CH_3CO, 43 (100): CH_3CO^+; anal. calcd. for $C_{14}H_{13}ClN_2O_3$: C 57.45, H 4.48, N 9.57; found: C 57.49, H 4.45, N 9.58

(±)-Methyl 1-[1-chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-5-methyl-1*H*-imidazole-2-carboxylate (22d): Yield: 79 %; m.p.: 140 °C; IR (KBr cm^{-1}): 1703 (s): $\nu_{C=O}$ (ketone, ester), 2961 (m): $\nu_{CH\ aliph}$, 3034 and 3074 (m): $\nu_{CH\ arom}$, 3128 (m): $\nu_{CH\ imidazole}$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.45 (s, 3H, 5-CH_3), 3.95 (s, 3H, OCH_3), 7.05 (s, 1H, H-4), 7.40 (s, 3H, ArH), 9.10 (s, 1H, CHCl); ^{13}C NMR (250 MHz, $CDCl_3$): 11.9, 52.6, 67.2, 130.3, 128.4, 131.9, 134.8, 135.6, 135.8, 159.6, 189.2; MS [m/z (%)]: 360 (4): $M^{+\cdot}$, 173 (100): Cl_2-C_6H_3-CO^+; HRMS calcd. for $C_{14}H_{11}Cl_3N_2O_3$: 359.9835; found: 359.9838; anal. calcd. for $C_{14}H_{11}Cl_3N_2O_3$: C 46.50, H 3.07, N 7.75; found: C 46.50, H 2.99, N 7.69

(±)-1-(1-Chloro-2-oxopropyl)-4,5-dimethyl-*N*,*N*-diethyl-1*H*-imidazole-2-carboxamide (22e): Yield: 86 %; m.p.: 70 °C; IR (KBr cm^{-1}): 1610 (s): $\nu_{C=O}$ (amide), 1729 (s): $\nu_{C=O}$ (ketone), 2955 and 2980 (m): $\nu_{CH\ aliph}$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 [m, 6H, $N(CH_2CH_3)_2$], 2.10 and 2.20 (2xs, 6H, 4-CH_3 and 5-CH_3), 2.40 (s, 3H, $COCH_3$), 3.75 [m, 4H, $N(CH_2CH_3)_2$], 7.40 (s, 1H, CHCl); ^{13}C NMR (250 MHz, $CDCl_3$): 9.3, 12.4, 12.5, 14.3, 26.0, 40.7, 43.5, 69.9, 125.5, 134.7, 138.3, 159.9, 196.0; MS [m/z (%)]: 286 (21): MH^+, 214 (29):

$[M^+-NEt_2]H$, 72 (100): NEt_2^+; HRMS calcd. for $C_{13}H_{20}ClN_3O_2$: 285.1244; found: 285.1248; anal. calcd. for $C_{13}H_{20}ClN_3O_2$: C 54.64, H 7.05, N 14.70; found: C 54.61, H 7.09, N 14.69

(±)-1-[1-Chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-*N,N*-diethyl-1*H*-imidazole-2-carboxamide (22f): Yield: 90 %; m.p.: 78°C; IR (KBr cm^{-1}): 1617 (s): $\nu_{C=O}$ (amide), 1729 (s): $\nu_{C=O}$ (ketone), 2963 (m): $\nu_{CH\ aliph}$, 3070 (m): $\nu_{CH\ arom}$, 3114 and 3154 (s): $\nu_{CH\ imidazole}$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 [m, 6H, $N(CH_2CH_3)_2$], 3.50 [m, 4H, $N(CH_2CH_3)_2$], 7.13 (d, 1H, H-4, $^3J_{H4,H5}$ = 1.1 Hz), 7.43 (m, 3H, ArH), 7.50 (d, 1H, H-5, $^3J_{H5,H4}$ = 1.1 Hz), 8.37 (s, 1H, CHCl); ^{13}C NMR (400 MHz, $CDCl_3$): 12.4, 14.3, 40.8, 43.4, 67.6, 121.1, 128.0, 128.4, 131.4, 131.8, 135.0, 139.8, 159.0, 189.5; MS [m/z (%)]: 388 (1): MH^+, 316 (1): $[M^+-NEt_2]H$, 173 (100): $Cl_2-C_6H_3-CO^+$; anal. calcd. for $C_{16}H_{16}Cl_3N_3O_2$: C 49.44, H 4.15, N 10.81; found: C 49.25, H 4.14, N 10.59

(±)-1-[1-Chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-4,5-dimethyl-*N,N*-diethyl-1*H*-imidazole-2-carboxamide (22g): Yield: 87 %; oil; IR (KCl cm^{-1}): 1616 (s): $\nu_{C=O}$ (amide), 1733 (s): $\nu_{C=O}$ (ketone), 2934 and 2971 (s): $\nu_{CH\ aliph}$, 3082 (w): $\nu_{CH\ arom}$; ^1H NMR (250 MHz, $CDCl_3$): δ 1.15 [m, 6H, $N(CH_2CH_3)_2$], 2.10 (s, 3H, 4-CH_3 or 5-CH_3), 2.35 (s, 3H, 4-CH_3 or 5-CH_3), 3.50 [m, 4H, $N(CH_2CH_3)_2$], 7.25 (m, 3H, ArH), 8.35 (s, 1H, CHCl); ^{13}C NMR (250 MHz, $CDCl_3$): 10.4, 12.4, 12.5, 14.3, 40.5, 43.5, 67.8, 128.2, 126.8, 131.5, 131.6, 134.7, 134.9, 138.4, 159.9, 189.6; MS [m/z (%)]: 416 (5): MH^+, 173 (44): $Cl_2-C_6H_3-CO^+$, 72 (100): NEt_2^+; HRMS calcd. for $C_{18}H_{20}Cl_3N_3O_2$: 415.0621; found: 415.0630

(±)-1-[1-Chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-5-methyl-*N*-phenyl-1*H*-imidazole-2-carboxamide (22h): Yield: 90 %; m.p.: 168 °C; IR (KBr cm^{-1}): 1596, 1663, 1728 and 1793 (s): $\nu_{C=O}$ (ketone, amide), 2935 and 2973 (m): $\nu_{CH\ aliph}$, 3016 and 3064 (m): $\nu_{CH\ arom}$, 3136 (s): $\nu_{CH\ imidazole}$, 3363 (s): ν_{NH}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 1H, H-4), 7.11 (t, 1H, NHArH-4, ^3J = 6.7 Hz), 7.35 (m, 5H, COArH-3, 4, 5 and NHArH-3, 5), 7.65 (d, 2H, NHArH-2, 6, ^3J = 6.7 Hz), 9.30 (broad s, 1H, NH), 9.60 (s, 1H, CHCl); ^{13}C NMR (400 MHz, $CDCl_3$): 12.0, 67.4, 119.9, 124.5, 128.3, 128.4, 129.0, 131.8, 132.0, 135.1, 137.2, 138.2, 156.8, 190.0; MS [m/z (%)]: 421 (9): M^+, 173 (100): $Cl_2-C_6H_3-CO^+$; HRMS calcd. for $C_{19}H_{15}Cl_3N_2O_3$: 421.0152; found: 421.0206; anal. calcd. for $C_{19}H_{15}Cl_3N_2O_3$: C 53.99, H 3.34, N 9.94; found: C 54.01, H 3.22, N 9.92

(±)-Ethyl 1-[1-chloro-2-(4-chlorophenyl)-2-oxoethyl]-4,5-dimethyl-1*H*-imidazole-2-carboxylate (22i): Yield: 86 % (overall from **1c**); m.p.: 78 °C; IR (KBr cm^{-1}): 1685 (s): $\nu_{C=O}$ (ketone), 1718 (s) $\nu_{C=O}$ (ester), 2927 and 2079 (m): $\nu_{CH\ aliph}$, 3020 (m): $\nu_{CH\ arom}$; ^1H NMR (250 MHz, $CDCl_3$) δ 1.50 (t, 3H, $COOCH_2CH_3$, ^3J = 7.2 Hz), 2.20 (s, 6H, 4-CH_3 and 5-CH_3), 4.50 (m, 2H, $COOCH_2CH_3$), 7.40 (d, 2H, 4-Cl-C_6H_4-H-3, 5, ^3J = 8.0 Hz), 7.87 (d, 2H, 4-Cl-C_6H_4-H-2, 6, ^3J = 8.0 Hz), 9.07 (s, 1H, CHCl); ^{13}C NMR (400 MHz, $CDCl_3$) 10.3, 12.4, 13.9, 61.7, 66.4, 129.0, 130.0, 130.3, 131.0, 133.1, 137.6, 140.5, 159.7, 186.0; MS [m/z (%)]: 354 (2): M^+, 319 (9): M^+- Cl, 139 (100): Cl-C_6H_4-CO^+; HRMS calcd. for $C_{16}H_{16}Cl_2N_2O_3$: 354.0538; found: 354,0547; anal. calcd. for $C_{16}H_{16}Cl_2N_2O_3$: C 54.10, H 4.54, N 7.89; found: C 54.10, H 4.36, N 7.84

Methyl 1-(2-hydroxyphenyl)-1*H*-imidazole-2-carboxylate (23a): Yield: 46 %; m.p.: 200 °C; IR (KBr cm^{-1}): 1727 (s) $\nu_{C=O}$ (ester), 2956 (w): $\nu_{CH\ aliph}$, 3043 (m): $\nu_{CH\ arom}$, 3125 and 3145 (s): $\nu_{CH\ imidazole}$, >3000 (br): ν_{OH}; ^1H NMR (250 MHz, $CDCl_3$): δ 3.70 (s, 3H, OCH_3), 6.85 (t, 1H, 1-ArH-5, ^3J = 7.0 Hz), 7.00 (d, 1H, 1-ArH-3, ^3J = 7.0 Hz), 7.20 (d, 1H, H-4, $^3J_{H4,H5}$ = 1.0 Hz), 7.25 (m, 2H, 1-ArH-4, 6), 7.45 (d, 1H, H-5, $^3J_{H5,H4}$ = 1.0 Hz), 10.00 (s, 1H, OH); ^{13}C NMR (250 MHz, $CDCl_3$): 51.5, 116.1, 118.9, 125.7, 126.6, 126.8, 128.9, 129.5, 137.1, 151.7, 158.5; MS [m/z (%)]: 218 (17): M^+, 186 (100): M^+-CH_3OH, 159 (53): M^+-$COOCH_3$; HRMS calcd. for $C_{11}H_{10}N_2O_3$: 218.0691; found: 218.0674

Methyl 5-phenyl-1-(2-hydroxyphenyl)-1*H*-imidazole-2-carboxylate (23b): Yield: 90 %; m.p.: 159 °C; IR (KBr cm^{-1}): 1730 (s) $\nu_{C=O}$ (ester), >3000 (br): ν_{OH}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.70 (s, 3H, OCH_3), 6.79 (td, 1H, 1-ArH-5, ^3J = 7.4 Hz, ^4J = 1.1 Hz), 6.95 (dd, 1H, 1-ArH-3, ^3J = 7.4 Hz, ^4J = 1.1 Hz), 7.05 (dd, 1H,

1-ArH-6, ^3J = 7.4 Hz, ^4J = 1.1 Hz), 7.22 (m, 6H, 1-ArH-4 and 5-PhH), 7.45 (s, 1H, H-4), 10.00 (s, 1H, OH); ^{13}C NMR (250 MHz, $CDCl_3$): 51.7, 116.2, 119.0, 124.5, 127.9, 128.2, 128.4, 128.6, 128.7, 128.9, 130.2, 135.1, 137.7, 137.8, 153.1, 158.3; MS [m/z (%)]: 294 (38): $M^{+\cdot}$, 262 (100): $M^{+\cdot}$-CH_3OH, 235 (40): [$M^{+\cdot}$-CH_3OH, -CO]H, 77 (22): $C_6H_5^+$, 51 (18): $C_4H_3^+$; HRMS calcd for $C_{17}H_{14}N_2O_3$: 294.1004; found: 294.1035; anal calcd. for for $C_{17}H_{14}N_2O_3$: C 69.38, H 4.79, N 9.52; found: C 68.99, H 4.72, N 9.50

5-Phenyl-1-(2-hydroxy-5-methylphenyl)-*N*-propyl-1*H*-imidazole-2-carboxamide (23c): Yield: 65 %; m.p.: 177 °C; IR (KBr cm^{-1}): 1561 (s): $\nu_{C=O}$ (amide II), 1651 (s): $\nu_{C=O}$ (amide I), 2967 (m): $\nu_{CH\ aliph}$, 3233 (s): ν_{NH}, >3000 (br): ν_{OH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.80 (t, 3H, $NHCH_2CH_2CH_3$, ^3J = 5.3 Hz), 1.40 (m, 2H, $NHCH_2CH_2CH_3$), 2.05 (s, 3H, $ArCH_3$), 3.20 (m, 2H, $NHCH_2CH_2CH_3$), 6.50 (m, 1H, 1-ArH-6), 6.85 (d, 1H, 1-ArH-3, ^3J = 7.3 Hz), 7.00 (d, 1H, 1-ArH-4, ^3J = 7.3 Hz), 7.12 (s, 1H, H-4), 7.15 (m, 5H, 5-PhH), 7.55 (t, 1H, NH, ^3J = 5.3 Hz); ^{13}C NMR (250 MHz, $CDCl_3$): 11.2, 20.2, 22.5, 41.0, 118.2, 125.4, 126.8, 127.9, 128.4, 128.0, 128.3, 128.6, 129.5, 130.8, 138.2, 141.3, 150.8, 158.8; MS [m/z (%)]: 335 (23): $M^{+\cdot}$, 249 (100): $M^{+\cdot}$-$CH_3CH_2CH_2NHCO$, 77 (7): $C_6H_5^+$; HRMS calcd. for $C_{20}H_{21}N_3O_2$: 335.1634; found: 335.1641

5-Phenyl-1-(2-hydroxyphenyl)-*N*,*N*-diethyl-1*H*-imidazole-2-carboxamide (23d): Yield: 80 %; m.p.: 175 °C; IR (KBr cm^{-1}): 1623 (s): $\nu_{C=O}$ (amide), 2974 (w): $\nu_{CH\ aliph}$, 3167 (s): $\nu_{CH\ imidazole}$, >3000 (br): ν_{OH}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.95 and 1.10 [m, 6H, $N(CH_2CH_3)_2$], 3.50 [m, 4H, $N(CH_2CH_3)_2$], 6.70 (dd, 1H, 1-ArH-5, ^3J = 7.5 Hz, ^4J = 1.2 Hz), 6.90 (m, 2H, 1-ArH-3, 6), 7.20 (m, 7H, H-4, 1-ArH-4 and 5-PhH), 10.05 (broad s, 1H, OH); ^{13}C NMR (250 MHz, $CDCl_3$): 12.0, 13.9, 39.5, 43.4, 117.8, 119.5, 124.0, 125.6, 127.4, 127.5, 128.0, 128.8, 128.9, 130.2, 135.1, 135.5, 142.9, 161.1; MS [m/z (%)]: 335 (42): $M^{+\cdot}$, 235 (69): $M^{+\cdot}$-NEt_2, -CO, 72 (100): NEt_2^+; HRMS calcd. for $C_{20}H_{21}N_3O_2$: 335.1634; found: 335.1638; anal. calcd. for $C_{20}H_{21}N_3O_2$: C 71.62, H 6.31, N 12.53; found: C 71.53, H 6.42, N 12.55

Synthesis of compound 23f

Me_3SiOK (20 mmol) was added to a solution of compound **23b** (10 mmol) in dry THF (50 ml). After 2 h of stirring at reflux temperature the reaction mixture was poured in 3N HCl (50 ml). After removal of the THF layer and extraction of the aqueous phase with CH_2Cl_2 (3x 100 ml), the combined organic layers were dried and evaporated. The crude residue was immediately taken up in a mixture of DMSO-d_6 and D_2SO_4.

2-[(5-Phenyl)-1*H*-imidazol-1-yl]phenol (23f): Yield: 40 %; IR (KBr cm^{-1}): 3054 (m): $\nu_{CH\ arom}$, >3000 (br): ν_{OH}; ^{1}H NMR (400 MHz, DMSO-d_6 and D_2SO_4): 6.86 (dd, 1H, 1-ArH-5, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 6.95 (d, 1H, 1-ArH-3, ^3J = 8.0 Hz, ^4J = 1.0 Hz), 7.07 (d, 1H, 1-ArH-6, ^3J = 8.0 Hz), 7.23 (m, 6H, 5-PhH and 1-ArH-4), 8.08 (s, 1H, H-4), 9.43 (s, 1H, H-2); ^{13}C NMR (400 MHz, DMSO-d_6 and D_2SO_4): 117.5, 118.1, 120.3, 121.7, 126.7, 128.7, 129.3, 129.4, 130.2, 132.8, 135.1, 135.4, 138.2; MS [m/z (%)]: 236 (100): $M^{+\cdot}$, 77 (28): Ph^+, 51 (7): $C_4H_3^+$; HRMS calcd. for $C_{15}H_{12}N_2O$: 236.0950; found: 236.0955

General procedure for the synthesis of compounds 24a,b *via* reaction of compounds 1 with β-amino-alcohols

A mixture of the appropriate β-amino alcohol (13 mmol) and Et_3N (3g, 30 mmol) in EtOAc (50 ml) was slowly added to a solution of compounds **1** (10 mmol) in EtOAc (150 ml) at reflux temperature. After refluxing for 1 h, the mixture was cooled on an ice-bath and Et_3N.HCl was filtered off. The solvent was evaporated and the crude mixture was purified by crystallisation (CH_2Cl_2).

5-Chloro-6-(2,6-dichlorophenyl)-3-(2-hydroxypropylamino)-2*H*-1,4-oxazin-2-one (24a): Yield: 82 %; oil; IR (NaCl cm^{-1}): 1576 (s): $\nu_{C=N}$, 1722 (s): $\nu_{C=O}$ (lactone), 2931 and 2974 (m): $\nu_{CH\ aliph}$, 3394 (s): $\nu_{OH\ and\ NH}$; ^1H NMR (250 MHz, $CDCl_3$): δ 1.24 (d, 3H, CH_3CH, ^3J = 6.5 Hz), 3.20 (s, 1H, OH), 3.35 and 3.64 (m, 2H, NH-CH_2-CH), 4.05 (m, 1H, $CHCH_3$), 7.03 (t, 1H, NH, ^3J = 5.9 Hz), 7.40 (m, 3H, ArH-3, 4, 5); ^{13}C NMR (250 MHz, $CDCl_3$): 20.9, 48.5, 66.2, 128.0, 128.5, 131.9, 136.9, 145.9, 152.0; MS [m/z (%)]: 348 (66): $M^{+\cdot}$, 173 (100): Cl_2-C_6H_3-CO^+

5-Chloro-6-(2,6-dichlorophenyl)-3-(2-hydroxy-2-phenylethylamino)-2*H*-1,4-oxazin-2-one (24b): Yield: 75 %; m.p.: 195 °C; IR (KBr cm^{-1}): 1577 (s): $\nu_{C=N}$, 1722 (s): $\nu_{C=O}$ (lactone), 2950 (m): $\nu_{CH\ aliph}$, 3040 (m): $\nu_{CH\ arom}$, 3422 (br): $\nu_{OH\ and\ NH}$; ^1H NMR (250 MHz, DMSO-d_6, 60 °C): δ 3.60 (m, 2H, CH_2CH), 4.95 (m, 1H, CH_2-CH), 5.55 (s, 1H, OH), 7.25 (m, 5H, PhH), 7.60 (m, 3H, 2,6-Cl_2-ArH), 8.25 (broad t, 1H, NH, ^3J = 6.0 Hz); ^{13}C NMR (250 MHz, DMSO-d_6, 60 °C): 48.8, 69.7, 125.7, 126.9, 127.8, 127.9, 128.2, 130.3, 132.8, 135.9, 145.6, 151.0; MS [m/z (%)]: 410 (5): $M^{+\cdot}$, 304 (100): $M^{+\cdot}$-PhCHOH, 173 (56): Cl_2-C_6H_3-CO^+; HRMS calcd. for $C_{18}H_{13}Cl_3N_2O_3$: 409.9992; found: 409.9984

General procedure for the synthesis of 5-chloro-2,3-dihydro-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-ones 26a, b

A solution of compounds **24a** or **24b** (10 mmol) in xylene (10 ml) and $SOCl_2$ (2 ml, 20 mmol) was stirred for 3 h at 90 °C. After cooling, the precipitate was filtered off, washed with cold hexane and recrystallised from a mixture of CH_2Cl_2/hexane.

5-Chloro-6-(2,6-dichlorophenyl)-2,3-dihydro-3-methyl-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (26a): Yield: 50 %; m.p.: 163 °C; IR (KBr cm^{-1}): 1631 (s): $\nu_{C=N}$, 1720 (s): $\nu_{C=O}$ (lactone); ^1H NMR (250 MHz, $CDCl_3$): δ 1.50 (d, 3H, CH_3CH, ^3J = 6.2 Hz), 3.85 (dd, 1H, H_a, $^2J_{Ha,Hb}$ = 17.5 Hz, $^3J_{Ha,H3}$ = 5.0 Hz), 4.25 (dd, 1H, H_b, $^2J_{Hb,Ha}$ = 17.5 Hz, $^3J_{Hb,H3}$ = 10.0 Hz), 4.60 (m, 1H, H_3), 7.40 (m, 3H, ArH-3, 4, 5); ^{13}C NMR (250 MHz, DMSO-d_6): 21.0, 56.6, 61.4, 117.3, 126.7, 128.1, 132.1, 137.2, 137.5, 145.4, 152.3; MS [m/z (%)]: 330 (86): $M^{+\cdot}$, 173 (100): Cl_2-C_6H_3-CO^+; HRMS calcd. for $C_{13}H_9Cl_3N_2O_2$: 329.9729; found: 329.9845

5-Chloro-6-(2,6-dichlorophenyl)-2,3-dihydro-3-phenyl-8*H*-imidazo[2,1-*c*][1,4]oxazin-8-one (26b): Yield: 57 %; m.p.: 180 °C; IR (KBr cm^{-1}): 1621 and 1667 (s): $\nu_{C=N}$, 1768 (s): $\nu_{C=O}$ (lactone), 2928 (w): $\nu_{CH\ aliph}$, 3042 (w): $\nu_{CH\ arom}$; ^1H NMR ($CDCl_3$): δ 4.08 (dd, 1H, H_a, $^2J_{Ha,Hb}$ = 17.0 Hz, $^3J_{Ha,H3}$ = 6.0 Hz), 4.62 (dd, 1H, H_b, $^2J_{Hb,Ha}$ = 17.0 Hz, $^3J_{Hb,H3}$ = 12.0 Hz), 5.50 (dd, 1H, H_3, $^3J_{H3,Ha}$ = 6.0 Hz, $^3J_{H3,Hb}$= 12.0 Hz), 7.30 (m, 8H, ArH-3, 4, 5 and PhH-2,3,4,5,6); ^{13}C NMR (250 MHz, $CDCl_3$): 64.1, 65.7, 117.9, 125.4, 126.6, 127.9, 128.0, 128.5, 129.0, 132.1, 137.3, 137.4, 140.5, 146.2, 152.3, MS [m/z (%)]: 392 (65): $M^{+\cdot}$, 173 (79): Cl_2-C_6H_3-CO^+, 104 (100): Ph-$CHCH_2^+$; HRMS calcd. for $C_{18}H_{11}Cl_3N_2O_2$: 391.9886; found: 391.9890

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REFERENCES

1a Medaer, B.; Van Aken, K.; Hoornaert, G. *Tetrahedron Lett.* **1994**, *66*, 9767.

1b Medaer, B.; Van Aken, K.; Hoornaert, G. *Tetrahedron* **1996**, *52 (26)*, 8813

2 Frick, W.; Meyer, A.; Nyfeler, R. Eur.Pat.Appl. EP 149,426 **1985**, CA 104: 5879q.

3 Jpn.Kokai Tokkyo Koho JP 59 13,762 **1984**, CA 101: 7156t.

4 Frazee, J.; Kaizer, C.; Kruze, L. Eur.Pat.Appl. EP 125,783 **1985**, CA 102: 132038c.

5 Georgiev, S.; Loev, B.; Musser, J. U.S. Patent, US 4,276,292 **1981**.

6 Westwood, R.; Ager, I.; Barnes, A.; Danswan, G.; Hairsine, P.; Kay, D.; Kennewell, P.; Matharu, S.; Miller, P.; Robson, P.; Rowlands, D.; Tully, W. *J. Med. Chem.* **1988**, *31*, 1098.

7 Meerpoel, L.; Hoornaert, G. *Synthesis* **1990**, 305.

8 Dickoré, K.; Sasse, K.; Bode, K.-D. *Liebigs Ann. Chem.* **1970**, *70*, 733.

9a Abdalla, G.; Sowell, J. *J. Heterocyclic Chem.* **1987**, *24*, 297

9b Prepared using the procedure described by Muller, H.; Rieck, G. in *J. Prakt. Chem.* **1959**, *9*, 30 and Kukolja, S.; Lammert, S. in *J. Am. Chem. Soc.* **1975**, *97*, 5582

10 Van Aken, K.; Hoornaert, G. *J. Chem. Soc., Chem. Commun.* **1992**, 895

11 Georgiev, V.; Kropp, P.; Carlson, R.; Van Inwegen, R. *Eur. J. Med. Chem.* **1989**, *24*, 639