

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

Bart P. Medaer and Georges J. Hoornaert*

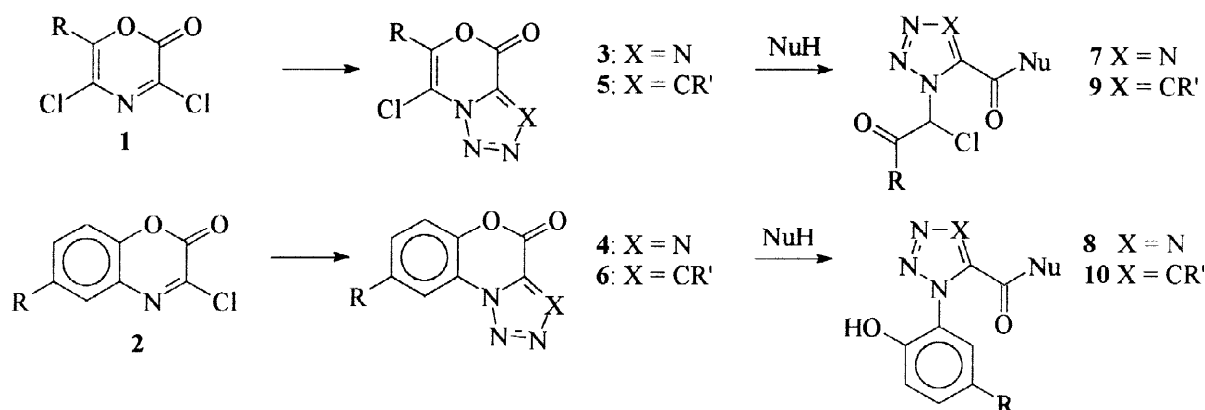
Laboratorium voor Organische Synthese, Department of Chemistry, K. U. Leuven, Celestijnenlaan 200 F, B-3001 Heverlee, Belgium

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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. © 1999 Elsevier Science Ltd. All rights reserved.

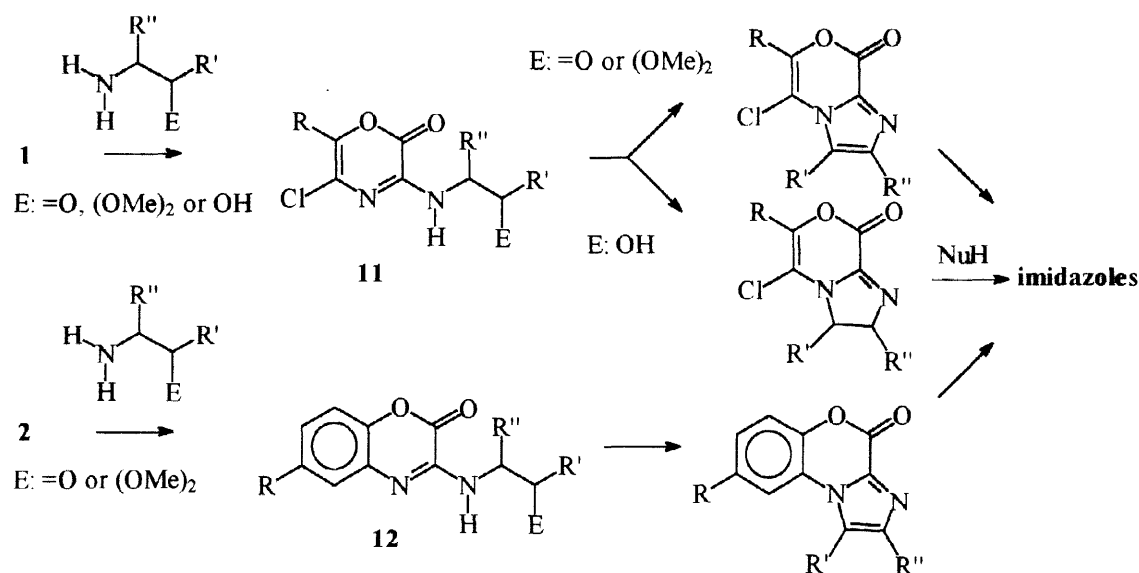
INTRODUCTION

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-benzoxazin-2-ones **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** ($\text{X} = \text{N}$) or **5** and **6** ($\text{X} = \text{CR}'$) via an electron shift towards the electrophilic part. The lactone function of these intermediates could easily be cleaved with different nucleophiles such as water ($\text{NuH} = \text{HOH}$), alcohols ($\text{NuH} = \text{ROH}$) and amines ($\text{NuH} = \text{RNH}_2$, R_2NH) yielding tetrazoles **7** and **8** or 1,2,3-triazoles **9** and **10**.



Scheme 1

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).

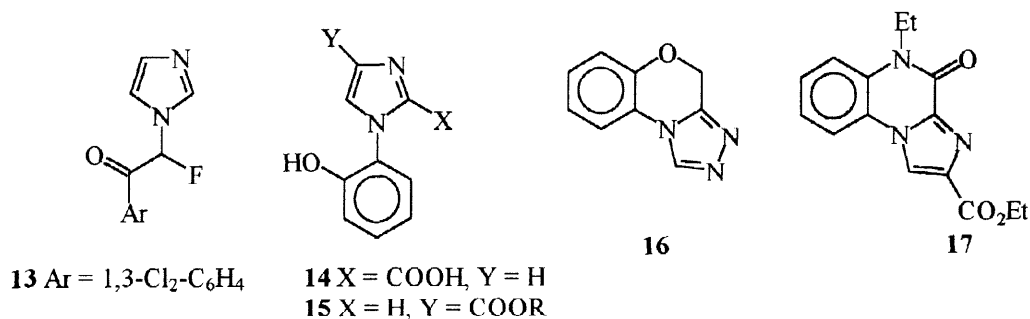
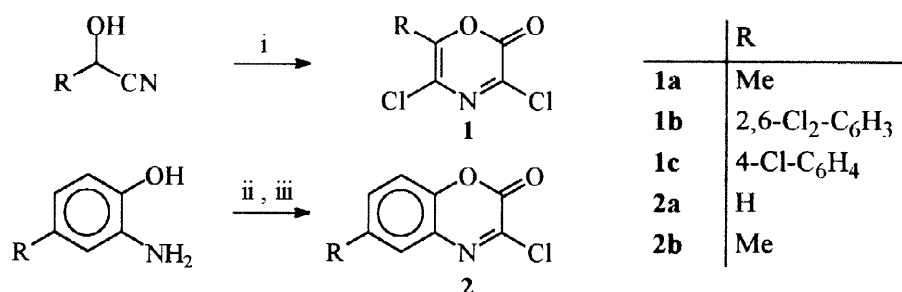


Figure 1

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.

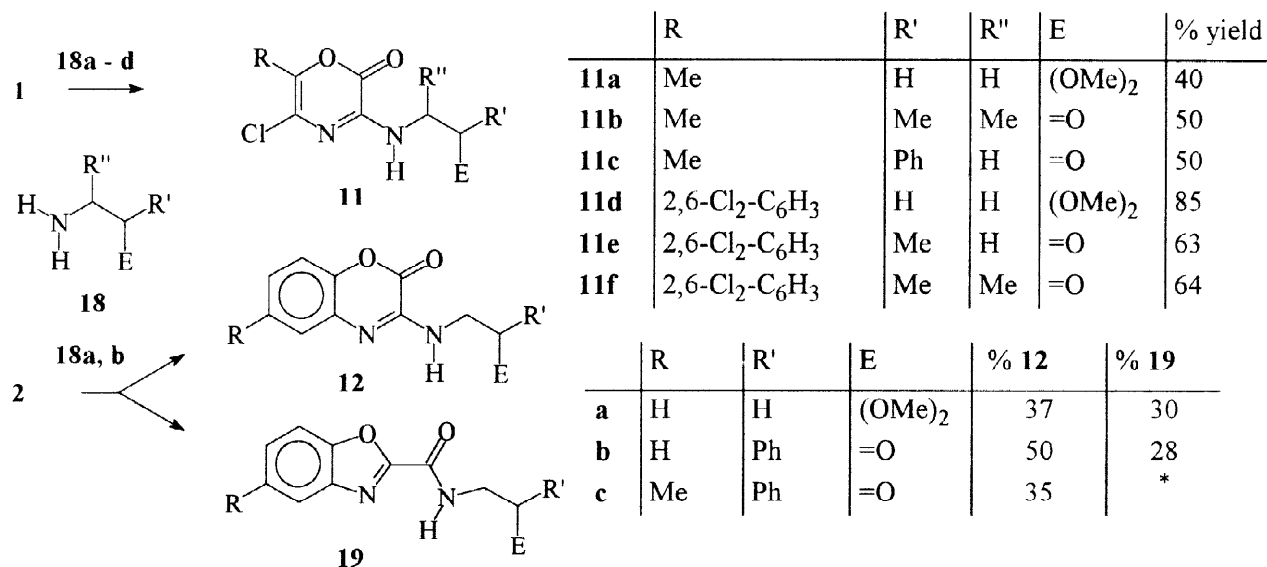


Reagents and conditions: i, oxalyl chloride (4 equiv.), Et₃N.HCl (0.5 equiv.), chlorobenzene, 4 h, 90 °C (compound **1c** was not separated and used as such); ii, oxalyl chloride (1.4 equiv.), chlorobenzene, 3 h, 120 °C; iii, DMF (0.01 equiv.), SOCl₂ (1.4 equiv.), 1 h, 120 °C

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}

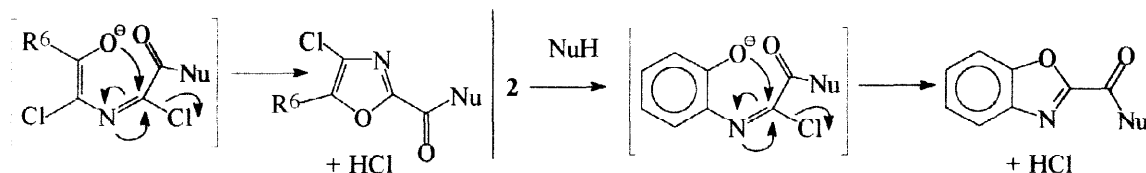


Reagents and conditions: **18**, EtOAc, Et₃N, 2 h, reflux; *: yield undetermined

Scheme 4

Reaction of these α -aminoketones with compounds **1** in the presence of Et₃N 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 cleavage¹⁰ (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 authors¹¹ - 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.

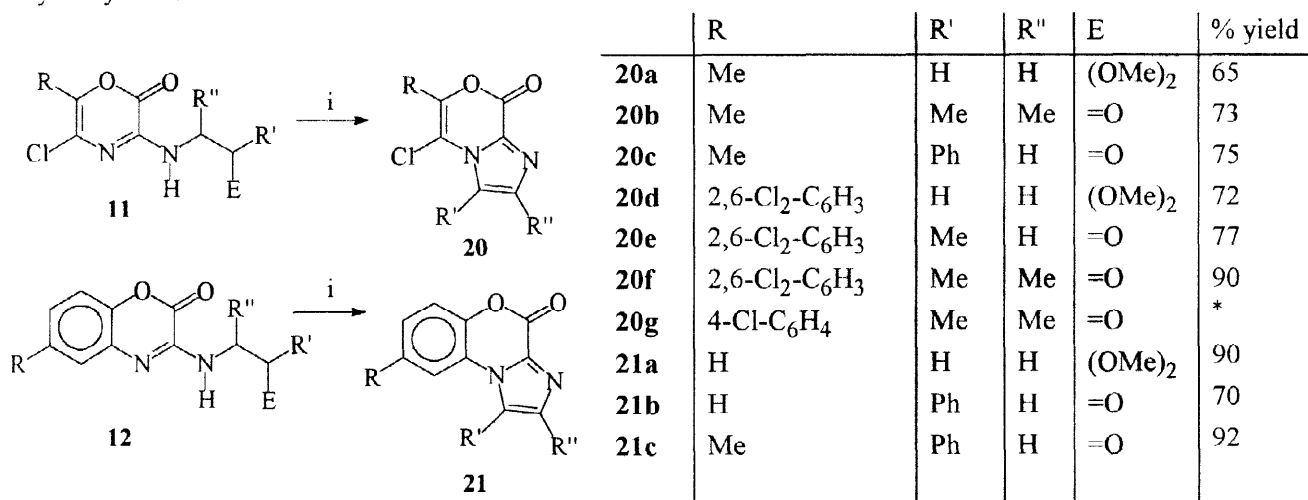


Scheme 5

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



*: 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.

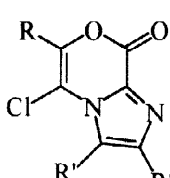
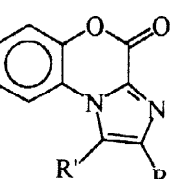
Scheme 6

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
					
20					
					
21					
22a	Me	H	H	OMe	84
22b	Me	Me	Me	OMe	81
22c	Me	Ph	H	OMe	90
22d	2,6-Cl ₂ -C ₆ H ₃	Me	H	OMe	79
22e	Me	Me	Me	NEt ₂	86
22f	2,6-Cl ₂ -C ₆ H ₃	H	H	NEt ₂	90
22g	2,6-Cl ₂ -C ₆ H ₃	Me	Me	NEt ₂	87
22h	2,6-Cl ₂ -C ₆ H ₃	Me	H	NHPh	90
22i	4-Cl-C ₆ H 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**.

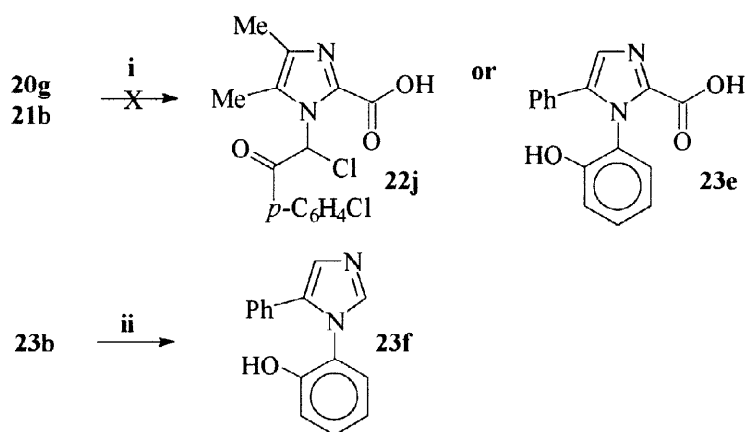
Reagents and conditions: i, MeOH (or EtOH in case of **22i**), 1 week, reflux (**22a-d**, **23a,b**); propylamine, diethylamine, 45 min, R.T. (**22e-g**, **23c,d**); in case of **22h**: 1,2-dichloroethane, aniline, AlCl_3 , 24 h, R.T.

Scheme 7

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

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.

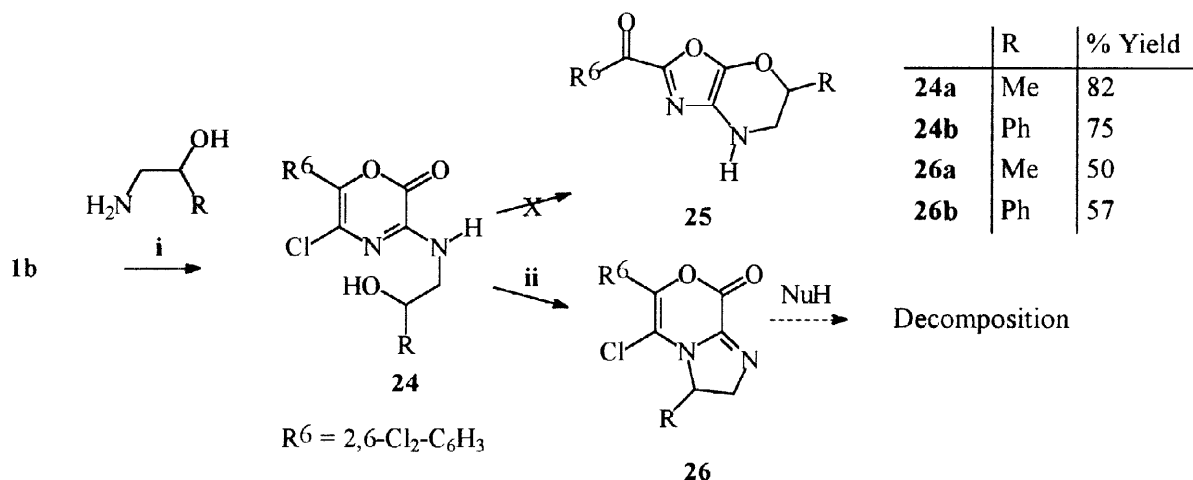
Scheme 8

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 $\text{DMSO-}d_6/\text{D}_2\text{SO}_4$. 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-2H-1,4-oxazin-2-ones **1** with β -amino alcohols. Reflux of compound **1b** in EtOAc with amino alcohols in the presence of Et₃N gave selectively 3-amino-substituted-2H-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 CH₂Cl₂ giving a compound with strong IR-absorptions at 1720 cm⁻¹ (lactone) and 3440 cm⁻¹ (OH, NH). Typical ¹³C NMR signals for the oxazinone part of the molecule appeared around 152 ($\pm$ 1) ppm (C-2), 145 ($\pm$ 1) ppm (C-3), 128.2 ($\pm$ 0.3) ppm (C-5) and 132.4 ($\pm$ 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 SOCl₂. A rapid substitution of OH by Cl was immediately followed by an intramolecular ring closure. The lactone gave a strong IR-band at 1750 ($\pm$ 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 ¹³C NMR spectra, the signal of C-2 is deshielded from 48 ppm to 63 ($\pm$ 2) ppm. However cleavage of the lactone function of these 2,3-dihydro-5-chloro-8H-imidazo[2,1-c][1,4]oxazin-8-ones with several nucleophiles was not successful: complex reaction mixtures were obtained.



Reagents and conditions: i, β -amino alcohol, EtOAc, Et₃N, 2 h, reflux; ii, xylene, SOCl₂, 3 h, 90 °C

Scheme 9

CONCLUSION

We can conclude that in addition to the previously examined reagents NaN₃ 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. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The ^1H 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/UV₂₅₄) 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 $\text{Et}_3\text{N}\cdot\text{HCl}$ 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 , $\text{CH}_2\text{Cl}_2/\text{EtOAc}$)

5-Chloro-3-(2,2-dimethoxyethylamino)-6-methyl-2H-1,4-oxazin-2-one (11a): Yield: 70 %; m.p.: 56 °C; IR (KBr cm^{-1}): 1603 and 1630 (s): $\nu_{\text{C}=\text{N}}$, 1736 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2987 (s): $\nu_{\text{CH aliph}}$, 3348 (s): ν_{NH} ; ^1H NMR (250 MHz, CDCl_3): δ 2.25 (s, 3H, 6- CH_3), 3.40 (s, 6H, 2xOCH₃), 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^+ , 217 (2): $\text{M}^+ - \text{OCH}_3$, 75 (100): $(\text{CH}_3\text{O})_2\text{CH}^+$; HRMS calcd. for $\text{C}_9\text{H}_{13}\text{ClN}_2\text{O}_4$: 248.0562; found: 248.0559

5-Chloro-6-(2,6-dichlorophenyl)-3-(2,2-dimethoxyethylamino)-2H-1,4-oxazin-2-one (11d): Yield: 85 %; m.p.: 148 °C; IR (KBr cm^{-1}): 1602 and 1631 (s): $\nu_{\text{C}=\text{N}}$, 1752 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2973 and 2997 (m): $\nu_{\text{CH aliph}}$, 3037 (w): $\nu_{\text{CH arom}}$, 3293 (s): ν_{NH} ; ^1H NMR (250 MHz, CDCl_3): δ 3.45 (s, 6H, 2xOCH₃), 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^+ , 347 (3): $\text{M}^+ - \text{OCH}_3$, 75 (100): $(\text{CH}_3\text{O})_2\text{CH}^+$; HRMS calcd. for $\text{C}_{14}\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_4$: 377.9941; found: 377.9939

3-(2,2-Dimethoxyethylamino)-2H-1,4-benzoxazin-2-one (12a): Yield: 37 %; m.p.: 95 °C; IR (KBr cm^{-1}): 1581 and 1618 (s): $\nu_{\text{C}=\text{N}}$, 1730 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2905 and 2939 (m): $\nu_{\text{CH aliph}}$, 3048 (m): $\nu_{\text{CH arom}}$, 3372 (s): ν_{NH} ; ^1H NMR (250 MHz, CDCl_3): δ 3.40 (s, 6H, 2xOCH₃), 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, $^3J_{\text{H}_5, \text{H}_6} = 6.5$ 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^+ , 219 (57): $\text{M}^+ - \text{CH}_3\text{O}$, 187 (23): $\text{M}^+ - \text{CH}_3\text{O}$, - CH_3OH , 75 (100): $(\text{CH}_3\text{O})_2\text{CH}^+$; HRMS calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4$: 250.0954; found: 250.0955

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

6H, 2xOCH₃), 3.70 (t, 2H, NHCH₂, 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); ¹³C NMR (250 MHz, CDCl₃): 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⁺, 219 (12): M⁺-CH₃O, 187 (7): M⁺-CH₃O, -CH₃OH, 75 (100): (CH₃O)₂CH⁺; HRMS calcd. for C₁₂H₁₄N₂O₄: 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 Et₃N (3g, 30 mmol) in EtOAc (100 ml) was slowly added. After stirring for 2 h the mixture was cooled on an ice-bath and Et₃N.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 (SiO₂, EtOAc; CH₂Cl₂) and afterwards recrystallised from CH₂Cl₂.

5-Chloro-6-methyl-3-(3-oxo-2-butylamino)-2H-1,4-oxazin-2-one (11b): Yield: 50 %; m.p.: 88 °C; IR (KBr cm⁻¹): 1602 and 1615 (s): ν_{C=N}, 1735 (s): ν_{C=O} (ketone, lactone), 2986 and 2099 (w): ν_{CH aliph}, 3386 (s): ν_{NH}; ¹H NMR (250 MHz, CDCl₃): δ 1.50 (d, 3H, CHCH₃, ³J = 6.4 Hz), 2.20 (s, 3H, CH₃CO or 6-CH₃), 2.30 (s, 3H, CH₃CO or 6-CH₃), 4.60 (m, 1H, CHCH₃), 6.70 (broad d, 1H, NH, ³J = 4.0 Hz); ¹³C NMR (250 MHz, CDCl₃): 15.8, 16.4, 26.4, 55.7, 124.3, 136.5, 143.2, 152.1, 205.5; MS [m/z (%): 230 (2): M⁺, 187 (12): M⁺-CH₃CO, 43 (100): CH₃CO⁺; HRMS calcd. for C₉H₁₁ClN₂O₃: 230.0458; found: 230.0459

5-Chloro-6-methyl-3-(2-phenyl-2-oxoethylamino)-2H-1,4-oxazin-2-one (11c): Yield: 50 %; m.p.: 120 °C; IR (KBr cm⁻¹): 1597 and 1620 (s): ν_{C=N}, 1687 (s): ν_{C=O} (ketone), 1736 (s): ν_{C=O} (lactone), 2907 (w): ν_{CH aliph}, 3060 (w): ν_{CH arom}, 3403 (s): ν_{NH}; ¹H NMR (250 MHz, CDCl₃): δ 2.25 (s, 3H, CH₃), 4.82 (d, 2H, NHCH₂, 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); ¹³C NMR (250 MHz, CDCl₃): 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⁺, 250 (2): M⁺-CO, 173 (7): M⁺-PhCO, 105 (100): PhCO⁺; HRMS calcd. for C₁₃H₁₁ClN₂O₃: 278.0458; found: 278.0454

5-Chloro-6-(2,6-dichlorophenyl)-3-(2-oxopropylamino)-2H-1,4-oxazin-2-one (11e): Yield: 63 %; m.p.: 140 °C; IR (KBr cm⁻¹): 1608 (s): ν_{C=N}, 1746 (s): ν_{C=O} (ketone, lactone), 2956 (w): ν_{CH aliph}, 3050 (w): ν_{CH arom}, 3416 (s): ν_{NH}; ¹H NMR (250 MHz, CDCl₃): δ 2.30 (s, 3H, CH₃CO), 4.35 (d, 2H, NHCH₂, ³J = 4.2 Hz), 7.00 (broad t, 1H, NH, ³J = 4.2 Hz), 7.40 (m, 3H, ArH); ¹³C NMR (250 MHz, CDCl₃): 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⁺, 275 (94): M⁺-CH₃COCH₂NH, 43 (100): CH₃CO⁺; HRMS calcd. for C₁₃H₉Cl₃N₂O₃: 345.9679; found: 345.9686

5-Chloro-6-(2,6-dichlorophenyl)-3-(1-methyl-2-oxopropylamino)-2H-1,4-oxazin-2-one (11f): Yield: 64 %; m.p.: 85 °C; IR (KBr cm⁻¹): 1603 and 1629 (s): ν_{C=N}, 1746 (s): ν_{C=O} (ketone, lactone), 2933 and 2978 (w): ν_{CH aliph}, 3082 (m): ν_{CH arom}, 3382 (s): ν_{NH}; ¹H NMR (250 MHz, CDCl₃): δ 1.55 (d, 3H, CHCH₃, ³J = 6.0 Hz), 2.30 (s, 3H, CH₃CO), 4.70 (m, 1H, CHCH₃), 7.10 (d, 1H, NH, ³J = 5.0 Hz), 7.40 (m, 3H, ArH); ¹³C NMR (250 MHz, CDCl₃): 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⁺, 317 (64): M⁺-CH₃CO, 43 (100): CH₃CO⁺; HRMS calcd. for C₁₄H₁₁Cl₃N₂O₃: 359.9835; found: 359.9830

3-(2-Phenyl-2-oxoethylamino)-2H-1,4-benzoxazin-2-one (12b): Yield: 50 %; m.p.: 162–164 °C; IR (KBr cm^{-1}): 1578 and 1619 (s): $\nu_{\text{C}=\text{N}}$, 1688 (s): $\nu_{\text{C}=\text{O}}$ (ketone), 1748 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 3064 (w): $\nu_{\text{CH arom}}$, 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, $^3J_{\text{H}5,\text{H}6} = 6.0$ 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^+ , 175 (44): $\text{M}^+ - \text{PhCO}$, 105 (100): PhCO^+ , 77 (60): C_6H_5^+ , 51 (36): C_4H_3^+ ; HRMS calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$: 280.0848; found: 280.0844

6-Methyl-3-(2-phenyl-2-oxoethylamino)-2H-1,4-benzoxazin-2-one (12c): Yield: 35 %; m.p.: 142–144 °C; IR (KBr cm^{-1}): 1578 and 1621 (s): $\nu_{\text{C}=\text{N}}$, 1688 (s): $\nu_{\text{C}=\text{O}}$ (ketone), 1741 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2918 (m): $\nu_{\text{CH aliph}}$, 3040 (w): $\nu_{\text{CH arom}}$, 3387 (s): ν_{NH} ; ^1H NMR (250 MHz, CDCl_3): δ 2.35 (s, 3H, 6- CH_3), 4.90 (d, 2H, CH_2NH , $^3J = 4.0$ Hz), 6.95 (d, 1H, H-7, $^3J_{\text{H}7,\text{H}8} = 8.0$ Hz), 7.05 (d, 1H, H-8, $^3J_{\text{H}8,\text{H}7} = 8.0$ Hz), 7.10 (broad t, 1H, CH_2NH , $^3J = 4.0$ 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^+ , 189 (75): $\text{M}^+ - \text{PhCO}$, 105 (92): PhCO^+ , 77 (100): Ph^+ , 51 (46): C_4H_3^+ ; HRMS calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$: 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): $\nu_{\text{C}=\text{N}}$, 1678 and 1704 (s): $\nu_{\text{C}=\text{O}}$ (amide, ketone), 1704 (s): $\nu_{\text{C}=\text{O}}$ (ketone), 2911 (w): $\nu_{\text{CH aliph}}$, 3090 (w): $\nu_{\text{CH arom}}$, 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, $^3J_{\text{H}4,\text{H}5} = 7.0$ 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^+ , 175 (33): $\text{M}^+ - \text{PhCO}$, 105 (100): PhCO^+ , 77 (67): C_6H_5^+ , 51 (28): C_4H_3^+ ; anal. calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$: 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 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

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-8H-imidazo[2,1-c][1,4]oxazin-8-one (20a): Yield: 65 %; m.p.: 180 °C; IR (KBr cm^{-1}): 1664 (s): $\nu_{\text{C}=\text{N}}$, 1753 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2958 (w): $\nu_{\text{CH aliph}}$, 3136 and 3157 (w): $\nu_{\text{CH imidazole}}$; ^1H NMR (250 MHz, CDCl_3): δ 2.38 (s, 3H, CH_3), 7.55 (d, 1H, H-2, $^3J_{\text{H}2,\text{H}3} = 1.1$ Hz), 7.61 (d, 1H, H-3, $^3J_{\text{H}3,\text{H}2} = 1.1$ 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^+ , 43 (100): CH_3CO^+ ; HRMS calcd. for $\text{C}_5\text{H}_5\text{ClN}_2\text{O}_2$: 184.0040; found: 184.0043

5-Chloro-2,3,6-trimethyl-8H-imidazo[2,1-c][1,4]oxazin-8-one (20b): Yield: 73 %; m.p.: 178 °C; IR (KBr cm^{-1}): 1659 (s): $\nu_{\text{C}=\text{N}}$, 1753 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2923 (m): $\nu_{\text{CH aliph}}$; ^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^+ , 43 (100): CH_3CO^+ ; HRMS calcd. for $\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2$: 212.0353; found: 212.0354; anal. calcd. for $\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2$: 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-8H-imidazo[2,1-c][1,4]oxazin-8-one (20c): Yield: 75 %; m.p.: 203 °C; IR (KBr cm^{-1}): 1653 (s): $\nu_{\text{C}=\text{N}}$, 1749 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2957 (w): $\nu_{\text{CH aliph}}$, 3031 and 3054 (m): $\nu_{\text{CH arom}}$, 3107 (s): $\nu_{\text{CH imidazole}}$; ^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^+ , 77 (17): Ph^+ , 43 (100): CH_3CO^+ ; HRMS calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}_2$: 260.0353; found: 260.0354; anal. calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}_2$: 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)-8H-imidazo[2,1-c][1,4]oxazin-8-one (20d): Yield: 72 %; m.p.: 163 °C; IR (KBr cm^{-1}): 1672 (m): $\nu_{\text{C}=\text{N}}$, 1766 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 3077 (w): $\nu_{\text{CH arom}}$, 3122 and 3138 (s): $\nu_{\text{CH imidazole}}$; ^1H NMR (250 MHz, CD_3CN): δ 7.58 (m, 3H, ArH), 7.65 (d, 1H, H-2, $^3J_{\text{H}_2,\text{H}_3} = 1.0$ Hz), 7.82 (d, 1H, H-3, $^3J_{\text{H}_3,\text{H}_2} = 1.0$ 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^+ , 279 (4): $\text{M}^+ - \text{Cl}$, 251 (36): $\text{M}^+ - \text{Cl}$, -CO, 173 (100): $\text{Cl}_2 - \text{C}_6\text{H}_3 - \text{CO}^+$; HRMS calcd. for $\text{C}_{12}\text{H}_5\text{Cl}_3\text{N}_2\text{O}_2$: 313.9417; found: 313.9416; anal. calcd. for $\text{C}_{12}\text{H}_5\text{Cl}_3\text{N}_2\text{O}_2$: 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-8H-imidazo[2,1-c][1,4]oxazin-8-one (20e): Yield: 77 %; m.p.: 192 °C; IR (KBr cm^{-1}): 1656 (s): $\nu_{\text{C}=\text{N}}$, 1752 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2979 and 2999 (w): $\nu_{\text{CH aliph}}$, 3067 (m): $\nu_{\text{CH arom}}$, 3124 (w): $\nu_{\text{CH imidazole}}$; ^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^+ , 293 (2): $\text{M}^+ - \text{Cl}$, 265 (23): $\text{M}^+ - \text{Cl}$, -CO, 173 (100): $\text{Cl}_2 - \text{C}_6\text{H}_3 - \text{CO}^+$; HRMS calcd. for $\text{C}_{13}\text{H}_7\text{Cl}_3\text{N}_2\text{O}_2$: 327.9573; found: 327.9580

5-Chloro-6-(2,6-dichlorophenyl)-2,3-dimethyl-8H-imidazo[2,1-c][1,4]oxazin-8-one (20f): Yield: 90 %; m.p.: 197 °C; IR (KBr cm^{-1}): 1658 (m): $\nu_{\text{C}=\text{N}}$, 1767 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2960 and 2983 (w): $\nu_{\text{CH aliph}}$, 3067 (w): $\nu_{\text{CH arom}}$; ^1H NMR (250 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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^+ , 307 (2): $\text{M}^+ - \text{Cl}$, 279 (18): $\text{M}^+ - \text{Cl}$, -CO, 173 (100): $\text{Cl}_2 - \text{C}_6\text{H}_3 - \text{CO}^+$; HRMS calcd. for $\text{C}_{14}\text{H}_9\text{Cl}_3\text{N}_2\text{O}_2$: 341.9730; found: 341.9732; anal. calcd. for $\text{C}_{14}\text{H}_9\text{Cl}_3\text{N}_2\text{O}_2$: C 48.94, H 2.64, N 8.15; found: C 49.01, H 2.55, N 8.10

4H-Imidazo[2,1-c][1,4]benzoxazin-4-one (21a): Yield: 70 %; m.p.: 192 °C; IR (KBr cm^{-1}): 1781 (s): $\nu_{\text{C}=\text{O}}$ (lactone); ^1H NMR (250 MHz, $\text{DMSO}-d_6$): δ 7.42 (m, 3H, H-6, 7, 8), 7.70 (d, 1H, H-2, $^3J_{\text{H}_2,\text{H}_1} = 1.0$ Hz), 8.10 (dd, 1H, H-9, $^3J_{\text{H}_9,\text{H}_8} = 7.0$ Hz, $^4J_{\text{H}_9,\text{H}_7} = 3.0$ Hz), 8.60 (d, 1H, H-1, $^3J_{\text{H}_1,\text{H}_2} = 1.0$ Hz); ^{13}C NMR (250 MHz, $\text{DMSO}-d_6$): 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^+ , 158 (7): $\text{M}^+ - \text{CO}$, 76 (41): C_6H_4^+ ; HRMS calcd. for $\text{C}_{10}\text{H}_6\text{N}_2\text{O}_2$: 186.0429; found: 186.0409

1-Phenyl-4H-imidazo[2,1-c][1,4]benzoxazin-4-one (21b): Yield: 90 %; m.p.: 154 °C; IR (KBr cm^{-1}): 1744 (s): $\nu_{\text{C}=\text{O}}$ (lactone); ^1H NMR (250 MHz, CDCl_3): δ 7.02 (ddd, 1H, H-8, $^3J_{\text{H}_8,\text{H}_7} = 8.5$ Hz, $^4J_{\text{H}_8,\text{H}_6} = 2.0$ Hz), 7.17 (dd, 1H, H-9, $^3J_{\text{H}_9,\text{H}_8} = 8.5$ Hz, $^4J_{\text{H}_9,\text{H}_7} = 2.0$ Hz), 7.30 (td, 1H, H-7, $^3J_{\text{H}_7,\text{H}_8} = 8.5$ Hz, $^4J_{\text{H}_7,\text{H}_9} = 2.0$ Hz), 7.35 (dd, 1H, H-6, $^3J_{\text{H}_6,\text{H}_7} = 8.5$ Hz, $^4J_{\text{H}_6,\text{H}_8} = 2.0$ 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^+ , 218 (81): $\text{M}^+ - \text{CO}_2$, 77 (42): Ph^+ , 51 (45): C_4H_3^+ ; HRMS calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2$: 262.0742; found: 262.0747; anal. calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2$: C 73.27, H 3.84, N 10.68; found: C 73.31, H 3.76, N 10.72

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

8-CH₃), 6.90 (d, 1H, H-9, $^4J_{\text{H9,H7}} = 2.0$ Hz), 7.09 (dd, 1H, H-7, $^3J_{\text{H7,H6}} = 8.8$ Hz, $^4J_{\text{H7,H9}} = 2.0$ Hz), 7.23 (d, 1H, H-6, $^3J_{\text{H6,H7}} = 8.8$ Hz), 7.30 (s, 1H, H-2), 7.60 (m, 5H, PhH); ^{13}C NMR (250 MHz, CDCl₃): 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⁺, 232 (25): M⁺-CO₂, 77 (88): Ph⁺, 51 (80): C₄H₃⁺; HRMS calcd. for C₁₇H₁₁N₂O₂: 276.0899; found: 276.0904; anal. calcd. for C₁₇H₁₁N₂O₂: 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 CHCl₃/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): ν_{C=O} (ketone, ester), 2917 and 2963 (s): ν_{CH aliph}, 3109 and 3127 (w): ν_{CH imidazole}; ^1H NMR (250 MHz, CDCl₃): δ 2.45 (s, 3H, COCH₃), 3.90 (s, 3H, OCH₃), 7.20 (d, 1H, H-4, $^3J_{\text{H4,H5}} = 1.2$ Hz), 7.38 (d, 1H, H-5, $^3J_{\text{H5,H4}} = 1.2$ Hz), 7.54 (s, 1H, CHCl); ^{13}C NMR (250 MHz, CDCl₃): 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⁺-CH₃CO]H, 43 (78): CH₃CO⁺; HRMS calcd. for C₈H₉ClN₂O₃: 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): ν_{C=O} (ketone, ester), 2941 (s): ν_{CH aliph}; ^1H NMR (400 MHz, CDCl₃): δ 2.18 and 2.22 (2xs, 6H, 4-CH₃ and 5-CH₃), 2.43 (s, 3H, COCH₃), 3.93 (s, 3H, OCH₃), 7.80 (s, 1H, CHCl); ^{13}C NMR (400 MHz, CDCl₃): 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⁺, 209 (22): M⁺-Cl, 43 (100): CH₃CO⁺; HRMS calcd. for C₁₁H₁₃ClN₂O₃: 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): ν_{C=O} (ketone, ester), 2929 and 2955 (m): ν_{CH aliph}, 3010 and 3067 (w): ν_{CH arom}, 3120 (w): ν_{CH imidazole}; ^1H NMR (250 MHz, CDCl₃): δ 2.50 (s, 3H, COCH₃), 3.95 (s, 3H, OCH₃), 6.30 (s, 1H, CHCl), 7.20 (s, 1H, H-4), 7.50 (m, 5H, ArH); ^{13}C NMR (250 MHz, CDCl₃): 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⁺, 249 (78): M⁺-CH₃CO, 43 (100): CH₃CO⁺; anal. calcd. for C₁₄H₁₃ClN₂O₃: 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): ν_{C=O} (ketone, ester), 2961 (m): ν_{CH aliph}, 3034 and 3074 (m): ν_{CH arom}, 3128 (m): ν_{CH imidazole}; ^1H NMR (250 MHz, CDCl₃): δ 2.45 (s, 3H, 5-CH₃), 3.95 (s, 3H, OCH₃), 7.05 (s, 1H, H-4), 7.40 (s, 3H, ArH), 9.10 (s, 1H, CHCl); ^{13}C NMR (250 MHz, CDCl₃): 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⁺, 173 (100): Cl₂-C₆H₃-CO⁺; HRMS calcd. for C₁₄H₁₁Cl₃N₂O₃: 359.9835; found: 359.9838; anal. calcd. for C₁₄H₁₁Cl₃N₂O₃: 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): ν_{C=O} (amide), 1729 (s): ν_{C=O} (ketone), 2955 and 2980 (m): ν_{CH aliph}; ^1H NMR (250 MHz, CDCl₃): δ 1.25 [m, 6H, N(CH₂CH₃)₂], 2.10 and 2.20 (2xs, 6H, 4-CH₃ and 5-CH₃), 2.40 (s, 3H, COCH₃), 3.75 [m, 4H, N(CH₂CH₃)₂], 7.40 (s, 1H, CHCl); ^{13}C NMR (250 MHz, CDCl₃): 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⁺-NEt₂]H, 72 (100): NEt₂⁺; HRMS calcd. for C₁₃H₂₀ClN₃O₂: 285.1244; found: 285.1248; anal. calcd. for C₁₃H₂₀ClN₃O₂: 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-1H-imidazole-2-carboxamide (**22f**): Yield: 90 %; m.p.: 78 °C; IR (KBr cm⁻¹): 1617 (s): ν_{C=O} (amide), 1729 (s): ν_{C=O} (ketone), 2963 (m): ν_{CH aliph}, 3070 (m): ν_{CH arom}, 3114 and 3154 (s): ν_{CH imidazole}; ¹H NMR (400 MHz, CDCl₃): δ 1.20 [m, 6H, N(CH₂CH₃)₂], 3.50 [m, 4H, N(CH₂CH₃)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); ¹³C NMR (400 MHz, CDCl₃): 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⁺-NEt₂]H, 173 (100): Cl₂-C₆H₃-CO⁺; anal. calcd. for C₁₆H₁₆Cl₃N₃O₂: 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-1H-imidazole-2-carboxamide (**22g**): Yield: 87 %; oil; IR (KCl cm⁻¹): 1616 (s): ν_{C=O} (amide), 1733 (s): ν_{C=O} (ketone), 2934 and 2971 (s): ν_{CH aliph}, 3082 (w): ν_{CH arom}; ¹H NMR (250 MHz, CDCl₃): δ 1.15 [m, 6H, N(CH₂CH₃)₂], 2.10 (s, 3H, 4-CH₃ or 5-CH₃), 2.35 (s, 3H, 4-CH₃ or 5-CH₃), 3.50 [m, 4H, N(CH₂CH₃)₂], 7.25 (m, 3H, ArH), 8.35 (s, 1H, CHCl); ¹³C NMR (250 MHz, CDCl₃): 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): Cl₂-C₆H₃-CO⁺, 72 (100): NEt₂⁺; HRMS calcd. for C₁₈H₂₀Cl₃N₃O₂: 415.0621; found: 415.0630

(±)-1-[1-Chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-5-methyl-N-phenyl-1H-imidazole-2-carboxamide (**22h**): Yield: 90 %; m.p.: 168 °C; IR (KBr cm⁻¹): 1596, 1663, 1728 and 1793 (s): ν_{C=O} (ketone, amide), 2935 and 2973 (m): ν_{CH aliph}, 3016 and 3064 (m): ν_{CH arom}, 3136 (s): ν_{CH imidazole}, 3363 (s): ν_{NH}; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (400 MHz, CDCl₃): 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): Cl₂-C₆H₃-CO⁺; HRMS calcd. for C₁₉H₁₅Cl₃N₂O₃: 421.0152; found: 421.0206; anal. calcd. for C₁₉H₁₅Cl₃N₂O₃: 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-1H-imidazole-2-carboxylate (**22i**): Yield: 86 % (overall from **1c**); m.p.: 78 °C; IR (KBr cm⁻¹): 1685 (s): ν_{C=O} (ketone), 1718 (s): ν_{C=O} (ester), 2927 and 2079 (m): ν_{CH aliph}, 3020 (m): ν_{CH arom}; ¹H NMR (250 MHz, CDCl₃): δ 1.50 (t, 3H, COOCH₂CH₃, ³J = 7.2 Hz), 2.20 (s, 6H, 4-CH₃ and 5-CH₃), 4.50 (m, 2H, COOCH₂CH₃), 7.40 (d, 2H, 4-Cl-C₆H₄-H-3, 5, ³J = 8.0 Hz), 7.87 (d, 2H, 4-Cl-C₆H₄-H-2, 6, ³J = 8.0 Hz), 9.07 (s, 1H, CHCl); ¹³C NMR (400 MHz, CDCl₃): 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-C₆H₄-CO⁺; HRMS calcd. for C₁₆H₁₆Cl₂N₂O₃: 354.0538; found: 354.0547; anal. calcd. for C₁₆H₁₆Cl₂N₂O₃: C 54.10, H 4.54, N 7.89; found: C 54.10, H 4.36, N 7.84

Methyl 1-(2-hydroxyphenyl)-1H-imidazole-2-carboxylate (**23a**): Yield: 46 %; m.p.: 200 °C; IR (KBr cm⁻¹): 1727 (s) ν_{C=O} (ester), 2956 (w): ν_{CH aliph}, 3043 (m): ν_{CH arom}, 3125 and 3145 (s): ν_{CH imidazole}, >3000 (br): ν_{OH}; ¹H NMR (250 MHz, CDCl₃): δ 3.70 (s, 3H, OCH₃), 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); ¹³C NMR (250 MHz, CDCl₃): 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⁺-CH₃OH, 159 (53): M⁺-COOCH₃; HRMS calcd. for C₁₁H₁₀N₂O₃: 218.0691; found: 218.0674

Methyl 5-phenyl-1-(2-hydroxyphenyl)-1H-imidazole-2-carboxylate (**23b**): Yield: 90 %; m.p.: 159 °C; IR (KBr cm⁻¹): 1730 (s) ν_{C=O} (ester), >3000 (br): ν_{OH}; ¹H NMR (250 MHz, CDCl₃): δ 3.70 (s, 3H, OCH₃), 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^+ , 262 (100): $\text{M}^+ - \text{CH}_3\text{OH}$, 235 (40): $[\text{M}^+ - \text{CH}_3\text{OH}, -\text{CO}]^+$, 77 (22): C_6H_5^+ , 51 (18): C_4H_3^+ ; HRMS calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$: 294.1004; found: 294.1035; anal. calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$: 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): $\nu_{\text{C=O}}$ (amide II), 1651 (s): $\nu_{\text{C=O}}$ (amide I), 2967 (m): $\nu_{\text{CH aliph}}$, 3233 (s): ν_{NH} , >3000 (br): ν_{OH} ; ^1H NMR (250 MHz, CDCl_3): δ 0.80 (t, 3H, $\text{NHCH}_2\text{CH}_2\text{CH}_3$, $^3J = 5.3$ Hz), 1.40 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 2.05 (s, 3H, ArCH_3), 3.20 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 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^+ , 249 (100): $\text{M}^+ - \text{CH}_3\text{CH}_2\text{CH}_2\text{NHCO}$, 77 (7): C_6H_5^+ ; HRMS calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2$: 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): $\nu_{\text{C=O}}$ (amide), 2974 (w): $\nu_{\text{CH aliph}}$, 3167 (s): $\nu_{\text{CH imidazole}}$, >3000 (br): ν_{OH} ; ^1H NMR (250 MHz, CDCl_3): δ 0.95 and 1.10 [m, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 3.50 [m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 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^+ , 235 (69): $\text{M}^+ - \text{NEt}_2$, -CO, 72 (100): NEt_2^+ ; HRMS calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2$: 335.1634; found: 335.1638; anal. calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2$: 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 $\text{DMSO}-d_6$ and D_2SO_4 .

2-[(5-Phenyl)-1*H*-imidazol-1-yl]phenol (23f): Yield: 40 %; IR (KBr cm^{-1}): 3054 (m): $\nu_{\text{CH arom}}$, >3000 (br): ν_{OH} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$ 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, $\text{DMSO}-d_6$ 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^+ , 77 (28): Ph^+ , 51 (7): C_4H_3^+ ; HRMS calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}$: 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 $\text{Et}_3\text{N.HCl}$ 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)-2H-1,4-oxazin-2-one (24a): Yield: 82 %; oil, IR (NaCl cm^{-1}): 1576 (s): $\nu_{\text{C}=\text{N}}$, 1722 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2931 and 2974 (m): $\nu_{\text{CH aliph}}$, 3394 (s): ν_{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, $\text{NH}-\text{CH}_2-\text{CH}$), 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^+ , 173 (100): $\text{Cl}_2-\text{C}_6\text{H}_3-\text{CO}^+$

5-Chloro-6-(2,6-dichlorophenyl)-3-(2-hydroxy-2-phenylethylamino)-2H-1,4-oxazin-2-one (24b): Yield: 75 %; m.p.: 195 °C; IR (KBr cm^{-1}): 1577 (s): $\nu_{\text{C}=\text{N}}$, 1722 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2950 (m): $\nu_{\text{CH aliph}}$, 3040 (m): $\nu_{\text{CH arom}}$, 3422 (br): ν_{OH} and NH ; ^1H NMR (250 MHz, $\text{DMSO}-d_6$, 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, $\text{DMSO}-d_6$, 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^+ , 304 (100): M^+-PhCHOH , 173 (56): $\text{Cl}_2-\text{C}_6\text{H}_3-\text{CO}^+$; HRMS calcd. for $\text{C}_{18}\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_3$: 409.9992; found: 409.9984

General procedure for the synthesis of 5-chloro-2,3-dihydro-8H-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-8H-imidazo[2,1-c][1,4]oxazin-8-one (26a): Yield: 50 %; m.p.: 163 °C; IR (KBr cm^{-1}): 1631 (s): $\nu_{\text{C}=\text{N}}$, 1720 (s): $\nu_{\text{C}=\text{O}}$ (lactone); ^1H NMR (250 MHz, CDCl_3): δ 1.50 (d, 3H, CH_3CH , $^3J = 6.2$ Hz), 3.85 (dd, 1H, H_a , $^2J_{\text{H}_a,\text{H}_b} = 17.5$ Hz, $^3J_{\text{H}_a,\text{H}_3} = 5.0$ Hz), 4.25 (dd, 1H, H_b , $^2J_{\text{H}_b,\text{H}_a} = 17.5$ Hz, $^3J_{\text{H}_b,\text{H}_3} = 10.0$ Hz), 4.60 (m, 1H, H_3), 7.40 (m, 3H, ArH-3, 4, 5); ^{13}C NMR (250 MHz, $\text{DMSO}-d_6$): 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^+ , 173 (100): $\text{Cl}_2-\text{C}_6\text{H}_3-\text{CO}^+$; HRMS calcd. for $\text{C}_{13}\text{H}_9\text{Cl}_3\text{N}_2\text{O}_2$: 329.9729; found: 329.9845

5-Chloro-6-(2,6-dichlorophenyl)-2,3-dihydro-3-phenyl-8H-imidazo[2,1-c][1,4]oxazin-8-one (26b): Yield: 57 %; m.p.: 180 °C; IR (KBr cm^{-1}): 1621 and 1667 (s): $\nu_{\text{C}=\text{N}}$, 1768 (s): $\nu_{\text{C}=\text{O}}$ (lactone), 2928 (w): $\nu_{\text{CH aliph}}$, 3042 (w): $\nu_{\text{CH arom}}$; ^1H NMR (CDCl_3): δ 4.08 (dd, 1H, H_a , $^2J_{\text{H}_a,\text{H}_b} = 17.0$ Hz, $^3J_{\text{H}_a,\text{H}_3} = 6.0$ Hz), 4.62 (dd, 1H, H_b , $^2J_{\text{H}_b,\text{H}_a} = 17.0$ Hz, $^3J_{\text{H}_b,\text{H}_3} = 12.0$ Hz), 5.50 (dd, 1H, H_3 , $^3J_{\text{H}_3,\text{H}_a} = 6.0$ Hz, $^3J_{\text{H}_3,\text{H}_b} = 12.0$ 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^+ , 173 (79): $\text{Cl}_2-\text{C}_6\text{H}_3-\text{CO}^+$, 104 (100): $\text{Ph}-\text{CHCH}_2^+$; HRMS calcd. for $\text{C}_{18}\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}_2$: 391.9886; found: 391.9890

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