

Synthesis of New 1*H*-Tetrazoles and 1,2,3-Triazoles via Reactions of 3(,5)-(di)chloro-2*H*-1,4-(benz)oxazin-2-ones with Sodium Azide or Diazocompounds.

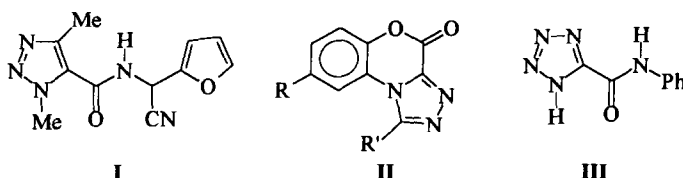
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Abstract: 3,5-dichloro-2*H*-1,4-oxazin-2-ones and 3-chloro-2*H*-1,4-benzoxazin-2-ones are reacted with bifunctional reagents as sodium azide and diazocompounds to yield bi(tri)cyclic tetrazolo- or triazolo fused intermediates *via* an intramolecular cyclisation reaction. Conversion of these lactone inter-mediate with various nucleophiles generates new substituted 1*H*-tetrazoles or 1,2,3-triazoles useful for pharmacological screening and for further elaboration *via* the α -chloroketone substituent at N-1. Copyright © 1996 Elsevier Science Ltd

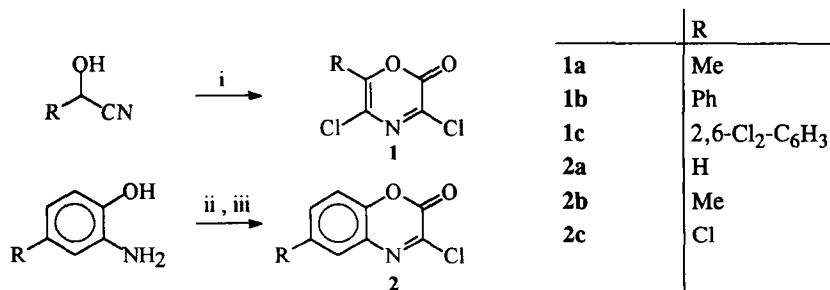
INTRODUCTION

In a previous communication, we reported a novel two-step procedure towards 1,5-substituted tetrazoles and 1,2,3-triazoles.¹ These compounds are readily available *via* reaction of the imidoyl chloride function in 3(,5)-(di)chloro-2*H*-1,4-(benz)oxazin-2-ones **1** and **2** with diazocompounds or sodium azide, followed by cleavage of the intermediate bi(tri)cyclic lactone with nucleophiles. Since tetrazoles and (fused) triazoles have widespread use as fungicides (**I**)² and anti-allergic compounds (**II**³ en **III**⁴), we applied the method to get new tetrazolo- or [1,2,3]triazolo(benz)oxazinones and the corresponding title compounds characterised by a carboxylic group in 5-position and an α -chloroketone substituent or an *ortho*-hydroxyphenyl group at N-1. We intended also to use both electrophilic centers of the α -chloroketone for elaboration into other heterocycles.



RESULTS AND DISCUSSION

3,(5)-(di)chloro-2*H*-1,4-(benz)oxazin-2-ones **1** and **2** are easily prepared *via* a one-pot synthetic method using oxalyl chloride and the appropriate cyanohydrins⁵ or *ortho*-amino phenols.⁶

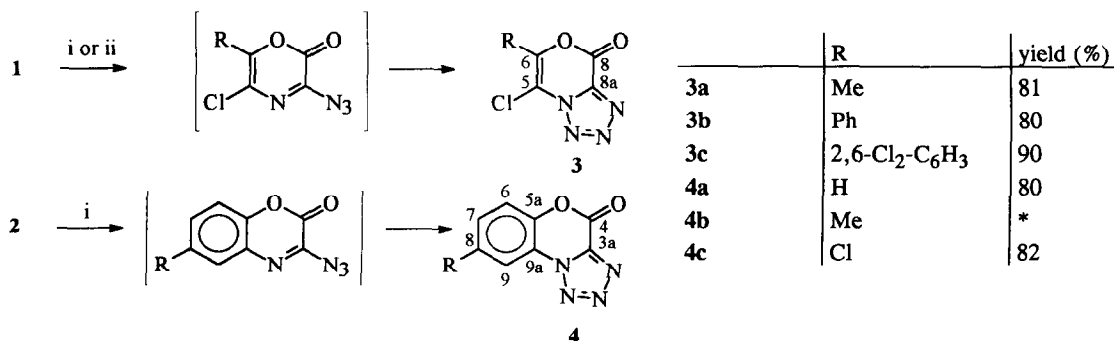


Reagents and conditions: i, oxalyl chloride (4 equiv.), NEt₃·HCl (0.5 equiv.), chlorobenzene, 4 h, 90 °C; ii, oxalyl chloride (1.4 equiv.), chlorobenzene, 3 h, 120 °C; iii, DMF (0.01 equiv.), SOCl₂ (1.4 equiv.), 1 h, 120 °C

*Synthesis of tetrazolo[5,1-*c*][1,4]oxazin-8-ones **3** and the corresponding fused benzoxazin-4-ones **4**.*

In a typical procedure, the (benz)oxazinones **1a-c** and **2a-c** were treated with NaN₃ in CH₃CN or DMF to yield compounds **3a-c** and **4a-c** after work up. We assume that the latter are generated by substitution of the imidoyl chloride function followed by ring closure *via* the azidoimino-tetrazolo equilibrium.⁷ The absence of an IR azido-absorption at 2100 cm⁻¹ is a strong indication for the tetrazolo structure. Moreover, the additional ring creates a deshielding effect demonstrated by the appearance of H-9 as a doublet x doublet at 8.30 ppm or as a multiplet at 8.40 ppm in the ¹H-NMR spectra of the crude compounds **4a** and **4c** respectively.

Table 1: tetrazolo[5,1-*c*][1,4]oxazin-8-ones **3** and -benzoxazin-4-ones **4**.



* Compound **4b** has not been purified but was used as such in the next step of our procedure.

Reagents and conditions: i, NaN₃ (2 equiv.), CH₃CN or DMF, 10 - 12 h, r.t.; ii, NaN₃ (1.1 equiv.), DMF, 2 h, r.t.

Little effect on the resonance values was noticed when changing the substituent in position 6 of the stable compounds **3**: typical ^{13}C -values are found at 110 (± 3) ppm (C-5), 144 (± 4) ppm (C-6), 146 (± 2) ppm (C-8) and 140.5 (± 1) ppm (C-8a). The IR lactone-carbonyl stretching appears at 1800 (± 20) cm^{-1} . The tetrazolobenzoxazinone **4b** is very sensitive to hydrolysis and has been used in the next step without any purification. The IR spectra of the crude compounds **4a** and **4c** show strong absorptions at 1605 (± 5) cm^{-1} (C=N) and at 1770 (± 5) cm^{-1} (lactone). Typical ^{13}C -absorptions are found at 116.4 (± 0.1) ppm (C-9), 143.0 (± 0.8) ppm (C-3a and C-6) and at 149.6 (± 0.2) ppm (lactone). Mass spectral analyses of compounds **3** and **4** show significant loss of N_2 .

*Synthesis of [1,2,3]triazolo[5,1-c][1,4]oxazin-4-ones **5** and the corresponding fused benzoxazin-4-ones **6**.*

An ethereal solution of **1** and **2** was treated with excess of diazocompound. Selective attack on the imidoyl chloride function followed by ring closure after proton abstraction yielded [1,2,3]triazolo[5,1-c][1,4](benz)oxazin-4-ones **5a-e** and **6a-e** via the diazoimino-triazolo equilibrium.⁸ Reaction with diazomethane gave higher yields (68 - 91 %) than reaction with diazoethane or diazopropane (41 - 52 %) presumably due to the unstability or lower reactivity of the diazoalkanes. The absence of an IR-absorption at 2100 cm^{-1} excludes the diazo-structure. With exception of **5d**, **e** all compounds were purified and fully characterised.

Table 2: [1,2,3]triazolo[5,1-c][1,4]oxazin-4-ones **5** and the corresponding fused benzoxazin-4-ones **6**.

1						
			5a	Me	H	91
			5b	Ph	H	81
			5c	2,6-Cl ₂ -C ₆ H ₃	H	72
			5d	2,6-Cl ₂ -C ₆ H ₃	Me	*
2						
			6a	H	H	75
			6b	Me	H	71
			6c	Cl	H	68
			6d	H	Me	52
6e	Cl	Et	41			

* Compounds **5d**, **e** were obtained as impure oils and were used as such in the next step of our procedure.

Reagents and conditions: i, excess of diazocompound, ether, 4 d, 4 °C (when diazoethane or diazopropane was used, the initial temperature was -78 °C)

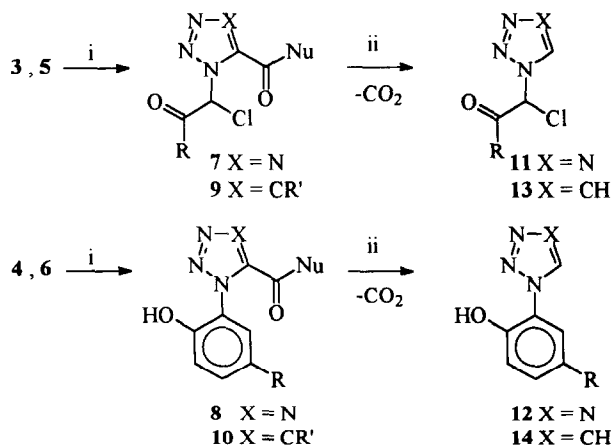
^1H -NMR spectra show a singlet at 8.7 (± 0.2) ppm (**5a-c** and **6a**, **c**) or 7.52 ppm (**6b**) assigned to the triazole proton H-3 and a doublet (**6b**, **c**, **e**) or a doublet x doublet (**6a**, **d**) at 8.2 (± 0.2) ppm for the deshielded proton H-9. In the ^{13}C NMR-spectra C-3 gives a signal at 136 (± 1) ppm (**5a-c** and **6a-c**), 149.1 ppm (**6d**) and 155.1 ppm (**6e**) whereas the absorption of C-3a is found at 123 (± 1) ppm (**5a-c** and **6a-c**), 121.1 ppm (**6d**) and at 117.9 ppm (**6e**). The lactone carbon atom absorbs at 152 (± 1) ppm and the lactone

IR carbonyl absorption is found at $1775 (\pm 15) \text{ cm}^{-1}$. Mass spectral analyses indicate significant loss of N_2 and CO.

Lactone cleavage of [1,2,3]triazolo- and tetrazolo[5,1-c](benz)oxazin-4-ones 3-6.

Ring cleavage at the lactone function of compounds **3-6** with nucleophiles such as water, amines and alcohols led to new tetrazoles and 1,2,3-triazoles which are characterised by an α -chloroketone or an *ortho*-hydroxyphenyl substituent at N-1 and a carboxylic group (derivative) at C-5. This method complements the most common generation method for 1,2,3-triazoles using the 1,3-dipolar cycloaddition of azides to unsymmetrical acetylenic compounds. However this procedure gives mainly the C-4 isomer. Other methods providing an electron withdrawing group in 5-position are limited by low yields and/or complicated multistep reactions.⁹ Moreover, the direct generation of the α -chloroketone substitution pattern of compounds **7**, **9**, **11** and **13** is rather unusual.

The lactone bridge of the tetrazolo[5,1-c](benz)oxazinones **3** and **4** is easily cleaved with ethanol (15 min reflux) and amines (15-30 min at 0°C) yielding tetrazoles **7** and **8**; for the comparable transformation with [1,2,3]triazolo[5,1-c](benz)oxazinones **5** and **6** into 1,2,3-triazoles **9** and **10** larger periods were required: (12 hours reflux in ethanol and one hour at room temperature with amines). On treatment with water, the acids **7** and **8** ($\text{Nu} = \text{OH}$) spontaneously decarboxylated yielding the final compounds **11** and **12**. Treatment of **5** and **6** with water yielded new 1,2,3-triazole acids **9** and **10** ($\text{Nu} = \text{OH}$) but decarboxylation to the triazoles **13** and **14** required heating at 130°C . The easy loss of CO_2 by the tetrazole-5-carboxylic acids and the relative stability of the analogous 1,2,3-triazole-5-carboxylic acids can be explained by the presence (or absence) of a neighbouring N-atom in 4-position of the heterocyclic ring which can act as a intramolecular base.¹⁰



Reagents and conditions: i, methanol, ethanol or $\text{H}_2\text{O}/\text{CH}_3\text{CN}$: 15 min, reflux (**7**, **8**); 12 h, reflux (**9**, **10**); propylamine or diethylamine: 30 min, 0°C (**7** and **8**); 1 h, r.t. (**9** and **10**); aniline: AlCl_3 (0.5 equiv.), 1,2-dichloroethane, 2 h, r.t. (**7d**); 3 h, reflux (**9f** and **10d**); ii, **11** and **12**: spontaneous decarboxylation from **7** and **8** ($\text{Nu} = \text{OH}$); **13**, **14**: chlorobenzene, 12 h, reflux: from **9g** and **10f** ($\text{Nu} = \text{OH}$).

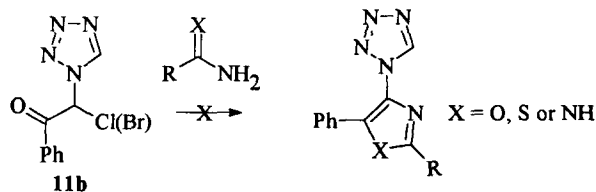
Table 3: tetrazoles and 1,2,3-triazoles 7 - 14.

	R	Nu	yield (%)		R	R'	Nu	yield (%)
7a	Me	OEt	95	9a	Me	H	OMe	95
7b	Ph	OMe	87	9b	Ph	H	OMe	80
7c	Ph	NEt ₂	78	9c	Me	H	NEt ₂	87
7d	Ph	NHPh	60	9d	Me	Et	OMe	28*
7e	2,6-Cl ₂ -C ₆ H ₃	NHPr	82	9e	2,6-Cl ₂ -C ₆ H ₃	Me	OMe	25*
8a	H	OEt	77	9f	2,6-Cl ₂ -C ₆ H ₃	H	NHPh	84
8b	Cl	NEt ₂	80	9g	Me	H	OH	55
11a	Me		85	10a	Cl	H	OMe	75
11b	Ph		83	10b	Cl	Et	OMe	60
12a	H		60	10c	Cl	Et	NHPr	76
12b	Me		63	10d	Me	H	NHPh	59
12c	Cl		70	10e	H	H	NEt ₂	60
				10f	H	H	OH	58
				13	Me	H		76
				14	H	H		68

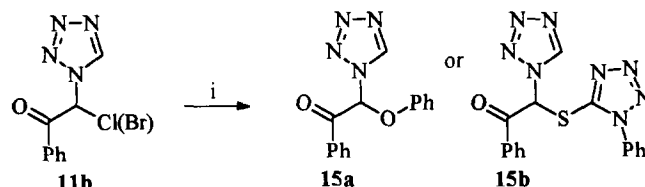
* overall yields starting from 1c or 1a

The α -chloroketone substituent on N-1 of compounds 7, 9, 11 and 13 shows two ¹³C-absorptions at 68.7 ($\pm$ 2.5) ppm (CHCl) and 190 ($\pm$ 5) ppm (ketone) whereas the *o*-hydroxyphenyl substituent of compounds 8, 10, 12 and 14 is characterised by a typical value of 150 ($\pm$ 2) ppm (C_{ar}-OH). The carbon absorption of the carboxylic group in the tetrazoles and 1,2,3-triazoles 7-10 is found around 156 ($\pm$ 3) ppm. ¹H-NMR spectra of compounds 7, 9, 11 and 13 show a singlet at 8 ($\pm$ 1) ppm (CHCl) whereas the absorption of the tetrazole proton H-5 of products 11 and 12 appears at 9.5 ($\pm$ 0.5) ppm. The triazole proton H-4 in compounds 9a-c, f and g, 10a, d-f, 13 and 14 gives a signal at 8 ($\pm$ 0.5) ppm. The carbonyl stretching of the ketone, ester or amide in the tetrazoles and 1,2,3-triazoles 7-11 and 13 is found around 1700 cm⁻¹ whereas IR-spectra of products 8, 10, 12 and 14 show intensive absorption at >3000 cm⁻¹ due to the Ar-OH stretching. Because of the easy loss of CO or N₂, mass spectral data show only low intensity peaks for the molecular ions.

We explored also the chemistry of these peculiar α -haloketones characterised by two electrophilic centers.¹¹ However, numerous attempts using bifunctional reagents such as amidines and (thio)amides did not give the expected heterocycles. These reactions failed also when using comparable α -bromoketone derivatives, prepared by alkylation of tetrazole and subsequent bromination.

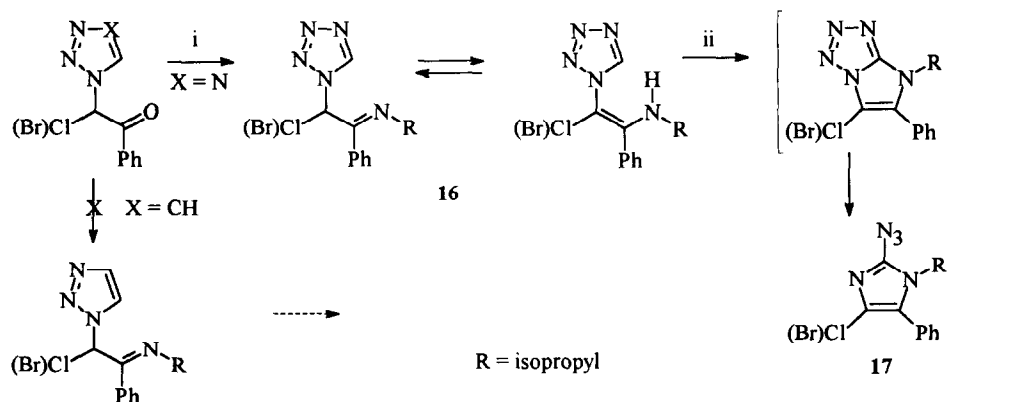


Later on, we noticed that a selective halogenide substitution could only be achieved with relatively weak nucleophiles such as phenols and thiocompounds as 1-phenyl-1*H*-tetrazole-5-thiol; in this way tetrazole **11b** was converted into compounds **15a** and **b**. The CHCl₃ ¹³C-value shifted from 62.8 ppm (**11b**) to 83.8 ppm (C-OR) or 66.0 ppm (C-SR) in compounds **15a** and **15b**. ¹H-NMR spectra of these tetrazoles show 2 singlets at 7.90 ppm (CHOR) and 9.06 ppm (H-tetrazole) and at 8.75 ppm (CHSR) and 9.06 ppm (H-tetrazole). Reaction with other nucleophiles (CN⁻, MeO⁻, SCN⁻ and N₃⁻) gave complex reaction mixtures.



Reagents and conditions: i, phenol or 1-phenyl-1*H*-tetrazole-5-thiol (1.1 equiv.), NaH (1.3 equiv.), CH₃CN, 15 min, r.t.

An α -chlorimine **16** could be generated by selective reaction of the ketone function of compound **11b** with 5 equivalents isopropyl amine and 0.3 equivalents TiCl₄ in diethyl ether at 0 °C.¹² Its IR absorption at 1619 cm⁻¹ is in agreement with the imine structure but ¹H-NMR spectral data in CDCl₃ indicate the imine-enamine equilibrium. Surprisingly this compound could be transformed into the azidoimidazole **17** which was isolated after reaction with 2 equivalents NBS in CCl₄ at reflux temperature. The IR-spectrum of compound **17** shows a strong azide absorption at 2141 cm⁻¹. Typical ¹³C-NMR values are 138.3 ppm (C-2) and 124.3 ppm (C-4). The formation of **17** presumably proceeds *via* an intramolecular attack of an intermediate radical species on the heterocycle. However we did not succeed to create efficiently comparable imines using other amines or a 1,2,3-triazole as heterocycle.



Reagents and conditions: i, isopropylamine (5 equiv.), TiCl₄ (0.5 equiv.), dry diethyl ether, 24 h, r.t.; ii, NBS (2 equiv.), benzoyl peroxide (cat), CCl₄, 5 min, reflux.

CONCLUSION

The reaction of 3,(5)-(di)chloro-2*H*-1,4-(benz)oxazin-2-ones **1** and **2** with sodium azide or diazoalkanes and the subsequent cleavage of the lactone is shown to be a very general method for the generation of 1*H*-tetrazoles and 1*H*-1,2,3-triazoles with a carboxylic acid group (or derivative) in 5-position. The substituent on N-1 is determined by the oxazinone: using 3,5-dichloro-2*H*-1,4-oxazin-2-ones an α -chloroketone substituent can be introduced whereas 3-chloro-2*H*-1,4-benzoxazin-2-ones yield *o*-hydroxyphenyl substituted tetrazoles or 1,2,3-triazoles. However, the exploration of the chemistry of this peculiar α -chloroketone system shows a limited number of applications.

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 5-chloro-8*H*-tetrazolo[5,1-*c*][1,4]oxazin-8-ones **3a-c and 4*H*-tetrazolo[5,1-*c*][1,4]-benzoxazin-4-ones **4a-c**.**

A solution of compounds **1** or **2** (10 mmol) and NaN_3 (20 mmol) in CH_3CN (150 ml) was kept at 0 °C for 0.5 hours and then brought to room temperature. When the oxazinone fluorescence (366 nm) had disappeared (10 - 12 hours), the mixture was filtered and the solvent was evaporated to give the crude products **3a-c** and **4a-c**. 5-Chloro-8*H*-tetrazolo[5,1-*c*][1,4]oxazin-8-ones **3a-c** and **4a, c** could be recrystallised from CHCl_3 /Hexane. The 4*H*-tetrazolo[5,1-*c*][1,4]benzoxazin-4-one **4b** was unstable and could not be purified.

5-Chloro-6-methyl-8*H*-tetrazolo[5,1-*c*][1,4]oxazin-8-one (3a**).** Yield: 81%; m.p.: 209 °C; IR (KBr cm^{-1}) 1650, 1790; ^1H -NMR (250 MHz, $\text{DMSO}-d_6$): δ 2.38 (s, 3H, 6- CH_3); ^{13}C -NMR (250 MHz, $\text{DMSO}-d_6$): δ 149.5, 144.0, 141.6, 108.0, 15.2; MS [m/z (%)]: 186 (100): M^+ , 158 (4); HRMS calcd. for $\text{C}_5\text{H}_3\text{ClN}_4\text{O}_2$: 185.9945; found: 185.9945; anal. calcd. for $\text{C}_5\text{H}_3\text{ClN}_4\text{O}_2$: C 32.19, H 1.62, N 30.03; found: C 32.04, H 1.51, N 30.27

5-Chloro-6-phenyl-8*H*-tetrazolo[5,1-*c*][1,4]oxazin-8-one (3b**).** Yield: 80%; m.p.: 158 °C; IR (KBr cm^{-1}) 1629, 1788; ^1H -NMR (250 MHz, CDCl_3): δ 7.65 (m, 3H, PhH), 8.96 (m, 2H, PhH); ^{13}C -NMR (250 MHz, CDCl_3): δ 147.6, 144.4, 139.6, 132.1, 129.0, 128.7, 126.3, 109.2; MS [m/z (%)]: 248 (9): M^+ , 220 (4), 105 (100): PhCO^+ , 77 (81); HRMS calcd. for $\text{C}_{10}\text{H}_5\text{ClN}_4\text{O}_2$: 248.0101; found: 248.0096; anal. calcd. for $\text{C}_{10}\text{H}_5\text{ClN}_4\text{O}_2$: C 48.31, H 2.03, N 22.53; found: C 48.19, H 1.93, N 22.55

5-Chloro-6-(2,6-dichlorophenyl)-8*H*-tetrazolo[5,1-*c*][1,4]oxazin-8-one (3c**).** Yield: 90%; m.p.: 150 °C; IR (KBr cm^{-1}) 1650, 1807; ^1H -NMR (250 MHz, CDCl_3): δ 7.60 (m, 3H, ArH); ^{13}C -NMR (250 MHz, CDCl_3): δ 147.4, 140.0, 139.9, 136.3, 133.7, 128.6, 125.6, 113.5; MS [m/z (%)]: 316 (4): M^+ , 173 (100): Cl_2PhCO^+ ; HRMS calcd. for $\text{C}_{10}\text{H}_3\text{Cl}_3\text{N}_4\text{O}_2$: 315.9322; found: 315.9326; anal. calcd. for $\text{C}_{10}\text{H}_3\text{Cl}_3\text{N}_4\text{O}_2$: C 37.83, H 0.95, N 17.65; found: C 37.80, H 0.87, N 17.51

4H-tetrazolo[5,1-c][1,4]benzoxazin-4-one (4a). Yield: 80 %; m.p.: 244 °C; IR (KBr cm^{-1}): 1610, 1773; ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.57 (m, 1H, H-6), 7.70 (m, 2H, H-7, 8), 8.28 (dxd, 1H, H-9); ^{13}C -NMR (400 MHz, $\text{DMSO}-d_6$): 149.8, 143.5, 142.2, 130.8, 126.1, 120.2, 117.8, 116.5; MS [m/z (%)] : 188 (26): M^+ , 160 (83), 116 (100): $\text{M}^+ - \text{N}_2$, $-\text{CO}_2$; HRMS calcd. for $\text{C}_8\text{H}_4\text{N}_4\text{O}_2$: 188.0334; found: 188.0340; anal. calcd. for $\text{C}_8\text{H}_4\text{N}_4\text{O}_2$: C 51.07, H 2.14, N 29.78; found: C 51.17, H 2.02, N 29.61

8-Chloro-4H-tetrazolo[5,1-c][1,4]benzoxazin-4-one (4c). Yield: 82 %; m.p.: 180 °C; IR (KBr cm^{-1}): 1605, 1768; ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.80 (m, 2H, H-6, 7), 8.40 (m, 1H, H-9); ^{13}C -NMR (400 MHz, $\text{DMSO}-d_6$): 149.5, 142.4, 142.3, 130.7, 130.0, 121.0, 119.6, 116.4; MS [m/z (%)] : 222 (10): M^+ , 194 (32), 194 (53); HRMS calcd. for $\text{C}_8\text{H}_3\text{ClN}_4\text{O}_2$: 221.9945; found: 221.9951

General procedure for the synthesis of 7-chloro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-4-ones 5a-e and 4H-[1,2,3]triazolo-[5,1-c][1,4]benzoxazin-4-ones 6a-e.

Diazomethane, diazoethane and diazopropane were obtained *via* reaction of KOH with *N*-alkyl-*N*-nitrosoarene derivatives using the procedure of F. Arndt in *Organic Synthesis*, John Wiley and Sons Inc., New York, 1945 Coll. Vol II, 161.

Compounds **1** and **2** (10 mmol) were slowly added to a diisopropyl ether solution of a 4-fold excess of diazoethane or diazopropane at -78 °C to avoid violent reaction. In the case of diazomethane, diethyl ether was used as solvent (0 °C). Afterwards the temperature was brought to 4 °C. After stirring for 3 days the excess of diazocompound and the solvent was evaporated. Then the residue was recrystallised from a mixture of CHCl_3 /hexane (except for compounds **5d** and **5e**).

7-Chloro-6-methyl-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-4-one (5a). Yield: 91%; m.p.: 136 °C; IR (KBr cm^{-1}) 1655, 1780; ^1H -NMR (250 MHz, CDCl_3): δ 2.46 (s, 3H, 6- CH_3), 8.50 (s, 1H, H-3); ^{13}C -NMR (250 MHz, CDCl_3): δ 151.2, 142.1, 136.9, 122.4, 110.5, 15.6; MS [m/z (%)] : 185 (10): M^+ , 129 (16), 43 (100): CH_3CO^+ ; HRMS calcd. for $\text{C}_6\text{H}_4\text{ClN}_3\text{O}_2$: 184.9992; found: 184.9991; anal. calcd. for $\text{C}_6\text{H}_4\text{ClN}_3\text{O}_2$: C 38.83, H 2.17, N 22.64; found: C 38.79, H 2.18, N 22.39

7-Chloro-6-phenyl-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-4-one (5b). Yield: 81%; m.p.: 112 °C; IR (KBr cm^{-1}): 1630, 1760; ^1H -NMR (250 MHz, CDCl_3): δ 7.55 (m, 3H, PhH), 7.85 (m, 2H, PhH), 8.57 (s, 1H, H-3); ^{13}C -NMR (250 MHz, CDCl_3): δ 151.0, 142.2, 136.9, 131.4, 129.1, 128.9, 127.9, 122.5, 110.7; MS [m/z (%)] : 247 (22): M^+ , 219 (5), 105 (100): PhCO^+ ; HRMS calcd. for $\text{C}_{11}\text{H}_6\text{ClN}_3\text{O}_2$: 247.0148; found: 247.0147; anal. calcd. for $\text{C}_{11}\text{H}_6\text{ClN}_3\text{O}_2$: C 53.35, H 2.44, N 16.97; found: C 52.96, H 2.38, N 16.85

7-Chloro-6-(2,6-dichlorophenyl)-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-4-one (5c). Yield: 72%; m.p.: 135 °C; IR (KBr cm^{-1}): 1654, 1770; ^1H -NMR (250 MHz, CDCl_3): δ 7.50 (s, 3H, ArH), 8.60 (s, 1H, H-3); ^{13}C -NMR (250 MHz, CDCl_3): δ 150.8, 137.8, 137.2, 136.4, 133.5, 128.5, 126.5, 122.7, 114.6; MS [m/z (%)] : 315 (11): M^+ , 259 (6): M^+ , 173 (100): Cl_2PhCO^+ ; HRMS calcd. for $\text{C}_{11}\text{H}_4\text{Cl}_3\text{N}_3\text{O}_2$: 314.9369; found: 314.9379; anal. calcd. for $\text{C}_{11}\text{H}_4\text{Cl}_3\text{N}_3\text{O}_2$: C 41.74, H 1.27, N 13.28; found: C 41.59, H 1.22, N 13.21

4H-[1,2,3]triazolo[5,1-c][1,4]benzoxazin-4-one (6a). Yield: 75%; m.p.: 197 °C; IR (KBr cm^{-1}): 1630, 1760; ^1H -NMR (250 MHz, CD_3CN): δ 7.58 (m, 3H, H-6, 7, 8), 8.34 (dxd, 1H, H-9), 8.58 (s, 1H, H-3); ^{13}C -NMR (250 MHz, CD_3CN): δ 152.8, 143.8, 137.0, 131.0, 126.8, 124.1, 122.0, 118.6, 116.8; MS [m/z (%)] : 187 (37): M^+ , 159 (42), 131 (27), 103 (100): $\text{M}^+ - \text{N}_2$, $-\text{CO}$, $-\text{CO}$; HRMS calcd. for $\text{C}_9\text{H}_5\text{N}_3\text{O}_2$: 187.0382; found: 187.0383; anal. calcd. for $\text{C}_9\text{H}_5\text{N}_3\text{O}_2$: C 57.76, H 2.69, N 22.45; found: C 57.82, H 2.60, N 22.67

8-Methyl-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazin-4-one (6b). Yield: 71%; m.p.: 180 °C; IR (KBr cm^{-1}): 1645, 1763; $^1\text{H-NMR}$ (250 MHz, $\text{DMSO-}d_6$): δ 2.45 (s, 3H, 8- CH_3), 7.42 (dxd, 1H, H-7), 7.50 (d, 1H, H-6), 7.52 (s, 1H, H-3), 8.11 (d, 1H, H-9); $^{13}\text{C-NMR}$ (250 MHz, $\text{DMSO-}d_6$): δ 152.1, 140.9, 136.1, 135.6, 130.5, 123.8, 120.5, 117.4, 115.5, 20.3, MS [m/z (%): 201 (35): M^+ , 173 (28), 145 (17), 117 (100): $\text{M}^+ - \text{N}_2$, -CO, -CO; HRMS calcd. for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2$: 201.0538; found: 201.0549; anal. calcd. for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2$: C 59.70, H 3.51, N 20.89; found: C 59.68, H 3.40, N 20.87

8-Chloro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazin-4-one (6c). Yield: 68%; m.p.: 221 °C; IR (KBr cm^{-1}): 1616, 1751. $^1\text{H-NMR}$ (250 MHz, $\text{DMSO-}d_6$): δ 7.70 (m, 2H, H-6, 7), 8.36 (d, 1H, H-9), 8.87 (s, 1H, H-3); $^{13}\text{C-NMR}$ (250 MHz, $\text{DMSO-}d_6$): δ 151.7, 141.9, 141.9, 136.2, 129.7, 129.4, 121.7, 119.6, 115.4; MS [m/z (%): 221 (31): M^+ , 193 (26), 165 (23), 137 (100): $\text{M}^+ - \text{N}_2$, -CO, -CO; HRMS calcd. for $\text{C}_9\text{H}_4\text{ClN}_3\text{O}_2$: 220.9992; found: 220.9996; anal. calcd. for $\text{C}_9\text{H}_4\text{ClN}_3\text{O}_2$: C 48.78, H 1.82, N 18.96; found: C 48.43, H 1.66, N 18.85

3-Methyl-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazin-4-one (6d). Yield: 52%; m.p.: 161 °C; IR (KBr cm^{-1}): 1616, 1764; $^1\text{H-NMR}$ (250 MHz, CDCl_3): δ 2.70 (s, 3H, 3- CH_3), 7.45 (m, 3H, H-6, 7, 8), 8.28 (dxd, 1H, H-9); $^{13}\text{C-NMR}$ (250 MHz, CDCl_3): δ 152.3, 149.1, 142.7, 129.8, 125.8, 121.1, 118.5, 117.8, 116.1, 11.2; MS [m/z (%): 201 (4): M^+ , 173 (3), 145 (100): $\text{M}^+ - \text{N}_2$, -CO; HRMS calcd. for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2$: 201.0538; found: 201.0536; anal. calcd. for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2$: C 59.70, H 3.51; found: 20.96, H 59.75, N 3.40

8-Chloro-3-ethyl-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazin-4-one (6e). Yield: 41%; m.p.: 125 °C; IR (KBr cm^{-1}): 1613, 1760; $^1\text{H-NMR}$ (250 MHz, CDCl_3): δ 1.40 (t, 3H, CH_3), 3.15 (q, 2H, CH_2), 7.42 (d, 1H, H-6), 7.50 (dxd, 1H, H-7), 8.32 (d, 1H, H-9); $^{13}\text{C-NMR}$ (250 MHz, CDCl_3): δ 155.1, 151.8, 141.3, 131.6, 130.0, 121.7, 119.3, 117.9, 116.4, 19.3, 13.1; MS [m/z (%): 249 (2): M^+ , 221 (9), 193 (88), 63 (100): C_5H_3 ; HRMS calcd. for $\text{C}_{11}\text{H}_8\text{ClN}_3\text{O}_2$: 249.0305; found: 249.0303; anal. calcd. for $\text{C}_{11}\text{H}_8\text{ClN}_3\text{O}_2$: C 52.92, H 3.23, N 16.83; found: 52.97, H 3.15, N 16.84

General procedure for the lactone cleavage of compounds 3 - 6 with alcohols, amines and water.

Compounds 3 - 6 (10 mmol) were dissolved in 50 ml of the appropriate alcohol, amine or a 50/50 mixture of H_2O and CH_3CN . When alcohols or water was used, the solution was brought to reflux temperature and the solvent was evaporated after 15 minutes (3 and 4) or 12 hours (5 and 6). In the case of diethyl amine and propylamine, the solvent was evaporated after 10 minutes (3 and 4) while compounds 5 and 6 were reacted for one hour at room temperature. Reactions with aniline were carried out in presence of 0.5 equivalents AlCl_3 in 50 ml 1,2-dichloroethane (3: 2 hours, room temperature; 5 and 6: 3 hours, reflux). Further purification was performed by recrystallisation from a mixture of CHCl_3 /hexane. Compounds 7d, 7e, 9c and 9d were additionally subjected to chromatographic purification (SiO_2 , CH_2Cl_2 /EtOAc).

($\pm$)-Ethyl 1-(1-chloro-2-oxopropyl)-1*H*-tetrazole-5-carboxylate (7a). Yield: 95%; m.p.: 55 °C; IR (KBr cm^{-1}): 1750; $^1\text{H-NMR}$ (250 MHz, CDCl_3): δ 1.47 (t, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.53 (q, 2H, CH_2), 7.30 (s, 1H, CHCl); $^{13}\text{C-NMR}$ (250 MHz, CDCl_3): δ 193.6, 156.1, 145.7, 68.9, 64.3, 26.1, 13.9; MS [m/z (%): 233 (11): MH^+ , 89 (100); anal. calcd. for $\text{C}_7\text{H}_9\text{ClN}_4\text{O}_3$: C 36.14, H 3.90, N 24.08; found: 36.16, H 3.79, N 24.30

($\pm$)-Methyl 1-(1-chloro-2-phenyl-2-oxoethyl)-1*H*-tetrazole-5-carboxylate (7b). Yield: 87%; m.p.: 92 °C; IR (KBr cm^{-1}): 1737; $^1\text{H-NMR}$ (250 MHz, CDCl_3): δ 4.00 (s, 3H, CH_3), 7.50 (dxd, 2H, PhH-3, 5), 7.65 (dxd, 1H, PhH-4), 8.00 (d, 2H, PhH-2, 6), 8.32 (s, 1H, CHCl); $^{13}\text{C-NMR}$ (250 MHz, CDCl_3): δ 184.7, 156.5, 145.5, 134.9, 131.5, 129.0, 66.2, 54.1; MS [m/z (%): 281 (45): MH^+ , 105 (100): PhCO^+ ; HRMS calcd. for $\text{C}_9\text{H}_5\text{ClN}_4\text{O}$ ($\text{M-CH}_3\text{OCO}$): 220.0109; found: 220.0105

(±)-1-(1-Chloro-2-phenyl-2-oxoethyl)-*N,N*-diethyl-1*H*-tetrazole-5-carboxamide (7c). Yield: 78%; m.p.: 107 °C; IR (KBr cm⁻¹): 1708; ¹H-NMR (250 MHz, CDCl₃): δ 1.20 and 1.30 [2xt, 6H, N(CH₂CH₃)₂], 3.50 and 3.90 [2xq, 4H, N(CH₂CH₃)₂], 7.55 (m, 3H, PhH-3, 4, 5), 8.00 (d, 2H, PhH-2, 6), 8.30 (s, 1H, CHCl); ¹³C-NMR (250 MHz, CDCl₃): δ 184.6, 155.7, 148.0, 134.8, 132.4, 129.3, 129.2, 67, 41.7, 44.1, 14.5, 12.5; MS [m/z (%): 322 (1): MH⁺, 105 (100): PhCO⁺; HRMS calcd. for C₁₄H₁₇ClN₅O₂ (MH⁺): 322.1070; found: 322.1062; anal. calcd. for C₁₄H₁₆ClN₅O₂: C 52.26, H 5.01, N 21.77; found: C 51.84, H 5.12, N 21.77

(±)-1-(1-Chloro-2-phenyl-2-oxoethyl)-*N*-phenyl-1*H*-tetrazole-5-carboxamide (7d). Yield: 60%; m.p.: oil; IR (NaCl cm⁻¹): 1600, 1693, 3377; ¹H-NMR (250 MHz, CDCl₃): 7.15 (dxd, 1H, NPh), 7.30 (dxd, 2H, NPh), 7.50 (dxd, 2H, NPh), 7.60 (m, 3H, COPhH-3, 4, 5), 8.00 (d, 2H, COPhH-2, 6), 8.60 (s, 1H, CHCl), 9.38 (s, 1H, CONH); ¹³C-NMR (250 MHz, CDCl₃): δ 185.0, 152.3, 135.5, 134.7, 131.8, 129.0, 128.9, 126.0, 120.4, 66.2; MS [m/z (%): 341 (1): M⁺, 105 (100): PhCO⁺; HRMS calcd. for C₁₆H₁₂ClN₅O₂: 341.0680; found: 341.0680

(±)-1-[1-Chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-*N*-propyl-1*H*-tetrazole-5-carboxamide (7e). Yield: 82%; m.p.: oil; IR (NaCl cm⁻¹): 1734, 3388; ¹H-NMR (250 MHz, CDCl₃): δ 1.00 (t, 3H, NHCH₂CH₂CH₃), 1.70 (txq, 2H, NHCH₂CH₂CH₃), 3.50 (dxt, 2H, NHCH₂CH₂CH₃), 7.40 (s, 3H, ArH), 8.32 (t, 1H, NH), 8.80 (s, 1H, CHCl); ¹³C-NMR (250 MHz, CDCl₃): δ 187.6, 154.1, 146.9, 134.1, 132.2, 131.6, 128.1, 67.7, 41.5, 22.2, 11.1; MS [m/z (%): 376 (6): MH⁺, 347 (2): M⁺, 173 (100): Cl₂PhCO⁺; HRMS calcd. for C₁₃H₁₂Cl₃N₃O₂ (M-N₂): 346.9995; found: 346.9982; anal. calcd. for C₁₃H₁₂Cl₃N₅O₂: C 41.46, H 3.21, N 18.59; found: C 41.40, H 3.14, N 18.73

Ethyl 1-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxylate (8a). Yield: 77%; m.p.: 110 °C; IR (KBr cm⁻¹): 1752, >3000; ¹H-NMR (250 MHz, CD₃CN): δ 1.20 (t, 3H, CH₂CH₃), 4.30 (q, 2H, CH₂CH₃), 7.12 (m, 2H, ArH-4, 6), 7.50 (m, 2H, ArH-3, 5), 7.90 (s, 1H, OH); ¹³C-NMR (250 MHz, CD₃CN): 156.8, 151.8, 148.8, 133.2, 127.9, 123.2, 121.5, 117.6, 64.1, 14.0; MS [m/z (%): 234 (1): M⁺, 160 (59); HRMS calcd. for C₁₀H₁₀N₄O₃: 234.0753; found: 234.0743; anal. calcd. for C₁₀H₁₀N₄O₃: C 51.28, H 4.30, N 23.92; found: 51.08, H 4.08, N 24.30

1-(5-Chloro-2-hydroxyphenyl)-*N,N*-diethyl-1*H*-tetrazole-5-carboxamide (8b). Yield: 80%; m.p.: 157 °C; IR (KBr cm⁻¹): 1650, >3000; ¹H-NMR (250 MHz, CD₃CN): δ 1.10 and 1.30 [2xt, 6H, N(CH₂CH₃)₂], 3.45 [m, 4H, N(CH₂CH₃)₂], 7.05 (d, 1H, ArH-3), 7.41 (dxd, 1H, ArH-4), 7.52 (d, 1H, ArH-6), 8.10-8.80 (br, 1H, OH); ¹³C-NMR (250 MHz, CD₃CN): δ 155.8, 149.4, 148.9, 131.0, 125.8, 123.6, 122.0, 117.5, 42.6, 39.2, 12.8, 10.8; MS [m/z (%): 253 (11): [M⁺-NEt]H, 72 (100): NEt₂⁺; anal. calcd. for C₁₂H₁₄ClN₅O₂: C 48.74, H 4.77, N 23.68; found: C 49.15, H 4.77, N 23.92

(±)-Methyl 1-(1-chloro-2-oxopropyl)-1*H*-1,2,3-triazole-5-carboxylate (9a). Yield: 95%; m.p.: 70 °C; IR (KBr cm⁻¹): 1740; ¹H-NMR (250 MHz, CDCl₃): δ 2.55 (s, 3H, COCH₃), 3.95 (s, 3H, OCH₃), 7.48 (s, 1H, CHCl), 8.17 (s, 1H, H-4); ¹³C-NMR (250 MHz, CDCl₃): δ 194.2, 185.1, 138.0, 127.6, 70.3, 52.8, 26.3; MS [m/z (%): 218 (27): MH⁺, 175 (43), 43 (100): CH₃CO⁺; HRMS calcd. for C₇H₉ClN₃O₃: 218.0332; found: 218.0350; anal. calcd. for C₇H₈ClN₃O₃: C 38.64, H 3.71, N 19.31; found: C 38.30, H 3.55, N 19.17

(±)-Methyl 1-(1-chloro-2-phenyl-2-oxoethyl)-1*H*-1,2,3-triazole-5-carboxylate (9b). Yield: 80%; m.p.: 80 °C; IR (KBr cm⁻¹): 1723; ¹H-NMR (CDCl₃): δ 3.90 (s, 3H, OCH₃), 7.35 (m, 2H, PhH-3, 5), 7.50 (m, 1H, PhH-4), 7.86 (m, 2H, PhH-2, 6), 8.11 (s, 1H, H-4), 8.31 (s, 1H, CHCl); ¹³C-NMR (250 MHz, CDCl₃): δ 184.7, 158.4, 137.9, 134.1, 132.5, 128.8, 128.6, 127.6, 68.2, 52.8; MS [m/z (%): 279 (1): M⁺, 105 (100): PhCO⁺; HRMS calcd. for C₁₂H₁₀ClN₃O₃: 279.0411; found: 279.0406; anal. calcd. for C₁₂H₁₀ClN₃O₃: C 51.53, H 3.60, N 15.02; found: C 51.11, H 3.47, N 14.76

(±)-1-(1-Chloro-2-oxopropyl)-*N,N*-diethyl-1*H*-1,2,3-triazole-5-carboxamide (9c). Yield: 87%; m.p.: oil; IR (KCl cm⁻¹): 1750; ¹H-NMR (250 MHz, CDCl₃): δ 1.28 (m, 6H, 2xCH₃), 2.41 (m, 3H, CH₃CO), 3.52 (m, 4H, 2xCH₂), 7.18 (s, 1H, CHCl), 7.89 (s, 1H, H-4); ¹³C-NMR (250 MHz, CHCl₃): δ 193.6, 157.9, 132.3, 130.7, 70.8, 43.2, 40.2, 25.9, 14.2, 12.1; MS [m/z (%]): 258 (1): M⁺, 100 (100): Et₂NCO⁺; HRMS calcd. for C₁₀H₁₅ClN₄O₂: 258.0884; found: 258.0887

(±)-Methyl 1-(1-chloro-2-oxopropyl)-4-ethyl-1*H*-1,2,3-triazole-5-carboxylate (9d). Yield: 28%; m.p.: oil; IR (KCl cm⁻¹): 1729; ¹H-NMR (CDCl₃): δ 1.35 (t, 3H, CH₂CH₃), 2.50 (s, 3H, COCH₃), 3.00 (q, 2H, CH₂CH₃), 3.95 (s, 3H, OCH₃), 7.19 (s, 1H, CHCl); ¹³C-NMR (250 MHz, CDCl₃): δ 194.4, 159.1, 154.2, 123.4, 71.2, 52.6, 26.4, 19.9, 13.3 MS [m/z (%]): 246 (25): MH⁺, 43 (100): CH₃CO⁺; HRMS calcd. for C₉H₁₂ClN₃O₃-CH₃CO: 202.0271; found: 202.0384

(±)-Methyl 1-[1-chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-4-methyl-1*H*-1,2,3-triazole-5-carboxylate (9e). Yield: 25%; m.p.: 139-141 °C; IR (KBr cm⁻¹): 1740; ¹H-NMR (250 MHz, CDCl₃): δ 2.60 (s, 3H, CH₃), 4.00 (s, 3H, OCH₃), 7.45 (s, 3H, ArH), 8.40 (s, 1H, CHCl); ¹³C-NMR (250 MHz, CDCl₃): δ 188.2, 159.3, 148.2, 134.8, 132.0, 131.8, 128.3, 124.9, 69.2, 52.8, 12.4; MS [m/z (%]): 361 (1): M⁺, 173 (100): Cl₂PhCO⁺; HRMS calcd. for C₁₃H₁₀Cl₃N₃O₃: 360.9788; found: 360.9799; anal. calcd. for C₁₃H₁₀Cl₃N₃O₃: C 43.06, H 2.78, N 11.59; found: C 43.01, H 2.69, N 11.48

(±)-1-[1-Chloro-2-(2,6-dichlorophenyl)-2-oxoethyl]-*N*-phenyl-1*H*-1,2,3-triazole-5-carboxamide (9f). Yield: 84%; m.p.: 135 °C; IR (KBr cm⁻¹): 1730; ¹H-NMR (250 MHz, CDCl₃): δ 7.15 (m, 6H, ArH, NPhH-3, 4, 5), 7.75 (m, 2H, NPhH-2, 6), 8.25 (s, 1H, H-4), 8.75 (s, 1H, CHCl), 9.50 (s, 1H, NH); ¹³C-NMR (250 MHz, CDCl₃): δ 188.8, 155.4, 136.3, 134.4, 133.5, 132.1, 132.0, 131.5, 128.1, 125.5, 121.2, 68.5; MS [m/z (%]): 408 (1): M⁺, 173 (100): Cl₂PhCO⁺; HRMS calcd. for C₁₇H₁₁Cl₃N₄O₂: 407.9948; found: 407.9948; anal. calcd. for C₁₇H₁₁Cl₃N₄O₂: C 49.84, H 2.71, N 13.68; found: C 49.74, H 2.66, N 13.69

(±) 1-(1-Chloro-2-oxopropyl)-1*H*-1,2,3-triazole-5-carboxylic acid (9g). Yield: 55%; IR (KCl cm⁻¹): 1740, >3000; ¹H-NMR (250 MHz, DMSO-*d*₆): δ 2.30 (s, 3H, CH₃), 7.80 (s, 1H, CHCl), 8.40 (s, 1H, H-4); ¹³C-NMR (250 MHz, DMSO-*d*₆): δ 194.4, 158.7, 138.2, 129.2, 71.2, 26.2; MS [m/z (%]): 204 (1): MH⁺, 161 (1), 43 (100): CH₃CO⁺; HRMS calcd. for C₄H₄ClN₃O₂ (M⁺-CH₃CO)H: 160.9992; found: 160.9984

Methyl 1-(5-chloro-2-hydroxyphenyl)-1*H*-1,2,3-triazole-5-carboxylate (10a). Yield: 75%; m.p.: 204 °C; IR (KBr cm⁻¹): 1760, >3000; ¹H NMR (250 MHz, DMSO-*d*₆): δ 3.75 (s, 3H, OCH₃), 7.05 (d, 1H, ArH-3), 7.47 (dxd, 1H, ArH-4), 7.58 (d, 1H, ArH-6), 8.43 (s, 1H, H-4), 10.6 (s, 1H, OH); ¹³C NMR (250 MHz, DMSO-*d*₆): 157.7, 150.9, 136.6, 131.0, 130.1, 126.9, 125.0, 122.1, 117.7, 52.4; MS [m/z (%]): 253 (7): M⁺, 221 (15), 193 (26), 165 (31), 137 (91); HRMS calcd. for C₁₀H₈ClN₃O₃: 253.0254; found: 253.0254; anal. calcd. for C₁₀H₈ClN₃O₃: C 47.35, H 3.18, N 16.57; found: C 47.02, H 3.15, N 16.41

Methyl 1-(5-chloro-2-hydroxyphenyl)-4-ethyl-1*H*-1,2,3-triazole-5-carboxylate (10b). Yield: 60%; m.p.: 150 °C; IR (KBr cm⁻¹): 1752, >3000; ¹H-NMR δ (250 MHz, DMSO-*d*₆): δ 1.30 (t, 3H, CH₂CH₃), 2.90 (q, 2H, CH₂CH₃), 3.75 (s, 3H, COOCH₃), 7.05 (d, 1H, ArH-3), 7.43 (dxd, 1H, ArH-4), 7.52 (d, 1H, ArH-6), 10.60 (s, 1H, OH); ¹³C-NMR (250 MHz, DMSO-*d*₆): δ 158.6, 151.2, 150.7, 130.7, 126.7, 126.1, 125.7, 122.1, 117.7, 52.2, 18.9, 13.2; MS [m/z (%]): 281 (1): M⁺, 221 (12), 193 (100): M⁺-CH₃OH, -N₂, -CO; HRMS calcd. for C₁₂H₁₂ClN₃O₃: 281.0567; found: 281.0549

1-(5-Chloro-2-hydroxyphenyl)-4-ethyl-*N*-propyl-1*H*-1,2,3-triazole-5-carboxamide (10c). Yield: 76%; m.p.: 145 °C; IR (KBr cm⁻¹): 1741, >3000; ¹H-NMR (250 MHz, DMSO-*d*₆): δ 0.75 (t, 3H, NHCH₂CH₂CH₃), 1.30 (t, 3H, CH₂CH₃), 1.45 (txq, 2H, NHCH₂CH₂CH₃), 2.80 (q, 2H,

CH_2CH_3), 3.10 (dxt, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 7.00 (d, 1H, ArH-3), 7.38 (dxd, 1H, ArH-4), 7.45 (d, 1H, ArH-6), 8.41 (t, 1H, NH); ^{13}C -NMR (250 MHz, $\text{DMSO}-d_6$): δ 158.5, 151.1, 146.2, 131.4, 130.3, 127.0, 125.3, 121.5, 117.8, 40.6, 22.0, 18.3, 13.2, 11.2; MS [m/z (%): 265 (2): M^+ , 237 (1), 43 (100): $\text{CH}_3\text{CH}_2\text{CH}_2^+$; HRMS calcd. for $\text{C}_{14}\text{H}_{17}\text{ClN}_4\text{O}_2$: 308.1040; found: 308.1046

1-(2-Hydroxyphenyl)-*N*-phenyl-1*H*-1,2,3-triazole-5-carboxamide (10d). Yield: 59%, m.p.: 207 °C; IR (KBr cm^{-1}): 1666, >3000; ^1H -NMR (250 MHz, CDCl_3): δ 2.25 (s, 3H, CH_3), 6.85 (d, 1H, ArH-3), 7.10 (dxd, 1H, NPhH-4), 7.15 (dxd, 1H, ArH-4), 7.25 (d, 1H, ArH-6), 7.33 (dxd, 2H, NPhH-3, 5), 7.65 (d, 2H, NPhH-2, 6), 8.35 (s, 1H, H-4), 10.0 (s, 1H, OH or NH), 10.60 (1H, OH or NH); ^{13}C -NMR (250 MHz, CDCl_3): δ 156.1, 148.9, 138.4, 133.8, 133.6, 131.0, 128.7, 128.0, 127.9, 124.3, 124.1, 120.0, 116.1, 19.8; MS [m/z (%): 294 (7): M^+ , 266 (18), 93 (100): $\text{C}_6\text{H}_7\text{N}^+$; HRMS calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_2$: 294.1117; found: 294.1110

1-(2-Hydroxyphenyl)-*N,N*-diethyl-1*H*-1,2,3-triazole-5-carboxamide (10e). Yield: 60%; m.p.: 155 °C; IR (KBr cm^{-1}): 1637, >3000; ^1H -NMR (250 MHz, $\text{DMSO}-d_6$): δ 1.10 and 1.21 [2xt, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 3.30 [m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 6.95 (dxdxd, 1H, ArH-5), 7.10 (dxd, 1H, ArH-3), 7.35 (m, 2H, ArH-4, 6), 8.10 (s, 1H, H-4), 10.30 (s, 1H, OH); ^{13}C -NMR (250 MHz, CHCl_3): δ 158.9, 151.0, 133.7, 131.1, 130.7, 127.0, 123.9, 119.0, 116.3, 42.6, 39.5, 13.8, 12.0; MS [m/z (%): 260 (1): M^+ , 232 (1), 72 (100): NEt_2^+ ; HRMS calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_2$: 260.1273; found: 260.1268; anal. calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_2$: C 59.99, H 6.20, N 21.52; found: 59.83, H 6.23, N 21.63

1-(2-Hydroxyphenyl)-1*H*-1,2,3-triazole-5-carboxylic acid (10f). Yield: 58%; IR (KCl cm^{-1}): >2500, 1713; ^1H -NMR (250 MHz, $\text{DMSO}-d_6$): δ 6.60 (s, 1H, OH), 7.00 (m, 2H, ArH-3, 5), 7.35 (m, 2H, ArH-4, 6), 8.30 (s, 1H, H-4), 10-13 (br s, 1H, COOH); ^{13}C -NMR (250 MHz, $\text{DMSO}-d_6$): δ 158.8, 151.9, 136.5, 131.7, 127.3, 124.8, 118.9, 116.4; MS [m/z (%): 205 (2): M^+ , 187 (72), 103 (100); HRMS calcd. for $\text{C}_9\text{H}_7\text{N}_3\text{O}_3$: 205.0487; found: 205.0479

($\pm$)-1-Chloro-1-(1*H*-tetrazol-1-yl)-2-propanone (11a). Yield: 85%; m.p.: 70 °C; IR (KBr cm^{-1}): 1750; ^1H -NMR (250 MHz, CDCl_3): δ 2.63 (s, 3H, CH_3), 7.05 (s, 1H, CHCl), 9.05 (s, 1H, H-5); ^{13}C -NMR (250 MHz, CDCl_3): δ 192.5, 142.9, 66.6, 25.9; MS [m/z (%): 161 (6): MH^+ , 118 (100): [$\text{M}^+ - \text{CH}_3\text{CO}$]H; HRMS calcd. for $\text{C}_4\text{H}_6\text{ClN}_4\text{O}$ (MH): 161.0230; found: 161.0320; anal. calcd. for $\text{C}_4\text{H}_5\text{ClN}_4\text{O}$: C 29.92, H 3.14, N 34.89; found: C 29.83, H 3.00, N 34.88

($\pm$)-2-Chloro-1-phenyl-2-(1*H*-tetrazol-1-yl)ethanone (11b). Yield: 83%; m.p.: 86 °C; IR (KBr cm^{-1}): 1703; ^1H -NMR (250 MHz, CDCl_3): δ 7.60 (m, 2H, PhH-3, 5), 7.75 (m, 1H, PhH-4), 7.88 (s, 1H, CHCl), 8.10 (dxd, 2H, PhH-2, 6), 9.28 (s, 1H, H-5); ^{13}C -NMR (250 MHz, CDCl_3): δ 184.8, 143.6, 135.7, 131.0, 129.5, 129.4, 62.8; MS [m/z (%): 223 (1): MH^+ , 105 (100): PhCO^+ , 77 (51), 51 (17); HRMS calcd. for $\text{C}_9\text{H}_8\text{ClN}_4\text{O}$ (MH): 223.0389; found: 223.0392; anal. calcd. for $\text{C}_9\text{H}_7\text{ClN}_4\text{O}$: C 48.56, H 3.17, N 25.17; found: 48.22, H 3.14, N 25.08

2-(1*H*-tetrazol-1-yl)phenol (12a). Yield: 60%; m.p.: 135 °C; IR (KBr cm^{-1}): >3000; ^1H -NMR (250 MHz, $\text{DMSO}-d_6$): δ 6.97 (dxdxd, 1H, H-4), 7.14 (dxd, 1H, H-6), 7.37 (dxdxd, 1H, H-5), 7.60 (dxd, 1H, H-3), 7.75 (s, 1H, H-tetrazole), 8.50-11.50 (s, 1H, OH); ^{13}C -NMR (250 MHz, $\text{DMSO}-d_6$): δ 150.7, 144.4, 131.1, 125.3, 121.5, 119.2, 117.2; MS [m/z (%): 162 (8): M^+ , 134 (48); anal. calcd. for $\text{C}_7\text{H}_6\text{N}_4\text{O}$: C 51.85, H 3.73, N 34.55; found: 51.90, H 4.12, N 34.13

4-Chloro-2-(1*H*-tetrazol-1-yl)phenol (12b). Yield: 63%; m.p.: 195 °C; IR (KBr cm^{-1}): >3000;; ^1H -NMR (250 MHz, $\text{DMSO}-d_6$): δ 6.19 (d, 1H, H-6), 7.48 (dxd, 1H, H-5), 7.78 (d, 1H, H-3), 9.85 (s, 1H, H-tetrazole), 10.20-12.30 (br, 1H, OH); ^{13}C -NMR (250 MHz, $\text{DMSO}-d_6$): δ 149.4, 144.5, 130.9, 125.1, 122.7, 122.2, 118.6; MS [m/z (%): 196 (4): M^+ , 128 (30); anal. calcd. for $\text{C}_8\text{H}_8\text{N}_4\text{O}$: C 54.54, H 4.58, N 31.80; found: 54.56, H 4.49, N 31.83

4-Methyl-2-(1*H*-tetrazol-1-yl)phenol (12c). Yield: 70%; m.p.: 155 °C; IR (KBr cm⁻¹): >3000; ¹H-NMR (250 MHz, DMSO-*d*₆): δ 2.27 (s, 3H, 4-CH₃), 7.03 (d, 1H, H-6), 7.21 (dxd, 1H, H-5), 7.41 (d, 1H, H-3), 9.73 (s, 1H, H-tetrazole), 10.54 (s, 1H, OH); ¹³C-NMR (250 MHz, DMSO-*d*₆): δ 147.8, 144.4, 128.7, 131.6, 125.5, 121.0, 116.9, 19.8; MS [*m/z* (%): 176 (5): M⁺, 148 (100): M⁺-N₂; anal. calcd. for C₅H₇ClN₄O: C 42.77, H 2.56, N 28.50; found: C 42.64, H 2.47, N 28.49

Decarboxylation of the acids 9g and 10f: synthesis of compounds 13 and 14.

Compounds **9g** or **10f** (10 mmol) were dissolved in chlorobenzene (100 ml) and refluxed for 12 hours. Then, the solvent was evaporated and the residue was recrystallised from a mixture of CHCl₃/hexane to yield **13** and **14** respectively.

(±) 1-(1-Chloro-2-oxopropyl)-1*H*-1,2,3-triazole (13). Yield: 76%; m.p.: 55 °C; IR (KBr cm⁻¹) 1747; ¹H-NMR (250 MHz, CDCl₃): δ 2.50 (s, 3H, CH₃), 7.05 (s, 1H, CHCl), 7.80 (s, 1H, H-4), 7.95 (s, 1H, H-5); ¹³C-NMR (250 MHz, CDCl₃): δ 193.7, 134.6, 124.1, 69.1, 25.8; anal. calcd. for C₅H₆ClN₃O: C 37.64, H 3.79, N 26.33; found: C 37.51, H 3.74, N 26.22

2-[1*H*-1,2,3-triazol-1-yl]phenol (14). Yield: 68%; m.p.: 154 °C; IR (KBr cm⁻¹) >2500; 7.03 (dxdxd, 1H, H-4), 7.20 (dxd, 1H, H-6), 7.30 (dxdxd, 1H, H-5), 7.43 (dxd, 1H, H-3), 7.90 (d, 1H, triazole-H-4), 8.50 (d, 1H, H-triazole-5); ¹³C-NMR (250 MHz, CDCl₃): δ 149.8, 133.0, 132.9, 129.9, 126.3, 119.4, 117.0; MS [*m/z* (%): 161 (54): M⁺, 133 (45), 78 (100): C₆H₄; HRMS calcd. for C₈H₇N₃O: 161.0589; found: 161.0583;

Preparation of compounds 15a and 15b.

To a stirred mixture of phenol or 1-phenyl-1*H*-tetrazole-5-thiol (3 mmol) and NaH (3 mmol) in CH₃CN (50 ml) compound **11b** (3 mmol) was added. After 15 minutes, the solvent was evaporated and the residue was subjected to chromatography (SiO₂, CH₂Cl₂/ hexane) and crystallised from a mixture of CHCl₃/hexane.

(±)-2-Phenoxy-1-phenyl-2-(1*H*-tetrazol-1-yl)ethanone (15a). Yield: 83%; m.p.: 150 °C; IR (KBr cm⁻¹): 1714; ¹H-NMR (250 MHz, CDCl₃): δ 7.05 (d, 1H, OPhH-2), 7.13 (dxd, 1H, OPhH-4), 7.31 (dxd, 2H, OPhH-3, 5), 7.52 (dxdxd, 2H, COpH-3, 5), 7.68 (dxdxd, 1H, COpH-4), 7.90 (s, 1H, CHOPh), 8.03 (dxd, 2H, COpH-2, 6), 9.06 (s, 1H, H-5) ¹³C-NMR (250 MHz, CDCl₃): δ 186.4, 154.8, 143.1, 135.3, 132.3, 130.3, 129.4, 129.3, 124.6, 83.8; MS [*m/z* (%): 281 (49): M⁺, 239 (1), 211 (100): M⁺-N₃, -CO; anal. calcd. for: C₁₅H₁₂N₄O₂: C 64.28, H 4.34, N 19.99; found: C 63.99, H 4.18, N 20.08

(±)-1-Phenyl-2-[(1-phenyl-1*H*-tetrazol-5-yl)thio]-2-(1*H*-tetrazol-1-yl)ethanone (15b). Yield: 80%; m.p.: 156 °C; IR (KBr cm⁻¹): 1694; ¹H-NMR (250 MHz, CDCl₃): δ 7.48 (m, 7H, NPhH, COpH-3, 5), 7.61 (dxd, 1H, COpH-4), 8.00 (d, 2H, COpH-2, 6), 8.75 (s, 1H, CHS), 9.06 (s, 1H, H-5); ¹³C-NMR (250 MHz, CDCl₃): δ 186.1, 150.2, 144.1, 135.6, 132.6, 131.7, 131.0, 130.2, 129.5, 129.3, 124.0, 66.0 MS [*m/z* (%): 365 (100): MH⁺, 189 (92), 105 (76); anal. calcd. for C₁₆H₁₂N₈OS: C 52.74, H 3.32, N 30.75; found: C 52.33, H 3.10, N 30.47

Synthesis of (±)-*N*-(isopropyl)-2-chloro-1-(2,6-dichlorophenyl)-2-(1*H*-tetrazol-1-yl)ethanimine (16).

Isopropyl amine (14 mmol) was added to a mixture of compound **11b** (3 mmol) in dry diethyl ether (50 ml) at 0 °C followed by dropwise addition of TiCl₄ (1 mmol). After addition, the reaction mixture was stirred for 24 hours at room temperature. Then, the reaction mixture was poured into 50 ml of an aqueous 0.5 - 1 N NaOH solution. After removal of the diethyl ether layer and extraction of the aqueous phase with

diethyl ether, the combined ether fractions were dried with CaCO_3 and evaporated. The residue was kept at low temperature to avoid decomposition.

($\pm$)-*N*-(isopropyl)-2-Chloro-1-(2,6-dichlorophenyl)-2-(1*H*-tetrazol-1-yl)ethanimine (**16**). Yield: 82 %; m.p.: 104 - 105 °C; IR (KBr cm^{-1}): 1619, 3400; ^1H -NMR (250 MHz, CDCl_3): imine: δ 0.95 and 1.25 (2xd, 6H, $\text{CH}(\text{CH}_3)_2$), 3.50 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 9.20 (s, 1H, H-5); enamine: 1.15 (d, 6H, $\text{CH}(\text{CH}_3)_2$), 3.17 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 4.38 (d, 1H, NH), 8.25 (s, 1H, H-5); enamine and imine: 7.0 - 7.6 (m, 10H, PhH); ^{13}C -NMR (250 MHz, CDCl_3): imine: 159.0, 143.6, 132.2, 129.9, 129.0, 127.1, 69.3, 53.0, 23.2, 23.1; enamine: 147.4, 145.1, 130.5, 129.7, 128.7, 128.4, 90.1, 46.0, 24.1; MS [m/z (%)]: 264 (57): MH^+ , 104 (100): Ph-CN^+ ; HRMS calcd. for $\text{C}_{12}\text{H}_{14}\text{ClN}_5$: 263.0938; found: 263.0941

Synthesis of 2-azido-4-chloro-1-isopropyl-5-phenyl-imidazole (**17**).

Compound **16** (3 mmol), NBS (6 mmol) and a catalytic amount of benzoyl peroxide were dissolved in CCl_4 (50 ml) and brought to reflux temperature. After 5 minutes, the reaction mixture was cooled and the precipitate was removed. After evaporation of the solvent, the residue was subjected to chromatographic purification (SiO_2 , CH_2Cl_2 /hexane) and crystallised from a mixture of CHCl_3 /hexane.

2-Azido-4-chloro-1-isopropyl-5-phenyl-imidazole (**17**). Yield: 60 %; m.p.: 102 °C; IR (KBr cm^{-1}): 2141; ^1H -NMR (250 MHz, CDCl_3): δ 1.41 (d, 6H, $\text{CH}(\text{CH}_3)_2$), 4.17 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 7.39 (m, 5H, PhH); ^{13}C -NMR (250 MHz, CDCl_3): δ 138.3, 130.3, 128.8, 128.7, 127.9, 126.1, 124.3, 48.6, 21.3; MS [m/z (%)]: 261 (57): M^+ , 104 (100); HRMS calcd. for $\text{C}_{12}\text{H}_{12}\text{ClN}_5$: 261.0781; found: 261.0780

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