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Diels–Alder reactions of 3-(1*H*-tetrazol-5-yl)-nitrosoalkenes: synthesis of functionalized 5-(substituted)-1*H*-tetrazoles

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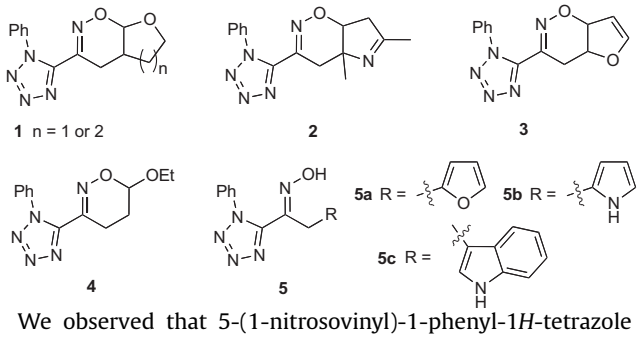
ABSTRACT

A general route to 1,2-oxazines and open chain oximes bearing a 1*H*-tetrazolyl substituent via Diels–Alder reaction of 3-(tetrazol-5-yl)-nitrosoalkenes is reported. It was also demonstrated that reduction of these adducts followed by deprotection of the tetrazolyl group give 5-(1-aminoalkyl)-1*H*-tetrazoles, α-amino acid analogues.

1. Introduction

Over the past decades it has been well established that 5-substituted-1*H*-tetrazoles are effective bioisosteres of the carboxylic acid functionality. The acidity of N–H is similar to that of carboxylic O–H at physiological pH, both exhibit planar structures, tetrazoles being more lipophylic—key factor when crossing cell membranes—than the corresponding carboxylic analogues.[1] It is also generally accepted that tetrazole moieties exhibit stronger metabolic stability. In fact, several literature works report the enhanced biological activity and metabolical stability of compounds in which the carboxylate group has been substituted by tetrazole.[1c,2] Thus, the tetrazole ring has been successfully incorporated into pharmacological drug formulations namely cardiovascular or hypertension drugs.[3] Furthermore, 1,5-disubstituted tetrazoles are conformational mimics of a cis-blocked peptide bond, like those found in a wide variety of biologically important peptides.

We have recently disclosed a hetero-Diels–Alder approach to 5-(substituted)-1*H*-tetrazoles via unprecedented reactions of 5-(1-nitrosovinyl)-1-phenyl-1*H*-tetrazole with electron rich alkenes and heterocycles, which gave new tetrahydro-3-tetrazolyl-1,2-oxazines **1**–**4** and open chain oximes bearing the tetrazole functionality **5**.[4] In fact, the Diels–Alder reaction of conjugated nitrosoalkenes has been successfully explored as an effective synthetic strategy for a large number of 1,2-oxazines and open chain oximes.[5,6] These adducts and cycloadducts have proved to be invaluable substrates for organic chemists due to their wide and versatile use as synthetic intermediates or useful building blocks for the synthesis of amino-carboxylic, -phosphonic and -phosphinic acids, pyrroles, proline analogues, pyrrolidizine alkaloids, amongst many other compounds of great chemical and biological interest.[6k,7] The use of 3-(tetrazol-5-yl)-nitrosoalkenes opened the way to a new class of compounds combining the 1,2-oxazine or the open chain oxime substructures with the tetrazol-5-yl substituent.



We observed that 5-(1-nitrosovinyl)-1-phenyl-1*H*-tetrazole **7** can be generated in situ from the corresponding bromooxime **6** under very mild reaction conditions and acts as an electron-deficient heterodiene in the presence of electron rich alkenes and heterocycles.[4] Reductive transformations of two of these adducts gave access to 5-(1-aminoalkyl)-1-phenyl-1*H*-tetrazoles namely to the tryptophan analogue **8** (Scheme 1).

The [4+2] cycloaddition of 5-(1-nitrosovinyl)-1-phenyl-1*H*-tetrazole **7** was selected as the model reaction since it was known that generally 1-phenyl-1*H*-tetrazoles are very stable and frequently crystalline compounds.[8] This choice proved to be important and precious on the course of the synthetic pathway the drawback being the impossibility of carrying out tetrazole deprotection in latter stages. Nevertheless, 1,5-disubstituted tetrazoles are also interesting molecules and indeed pharmaceutical formulations of this type of derivatives are known.[9]

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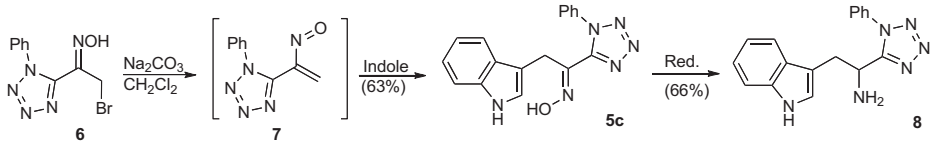
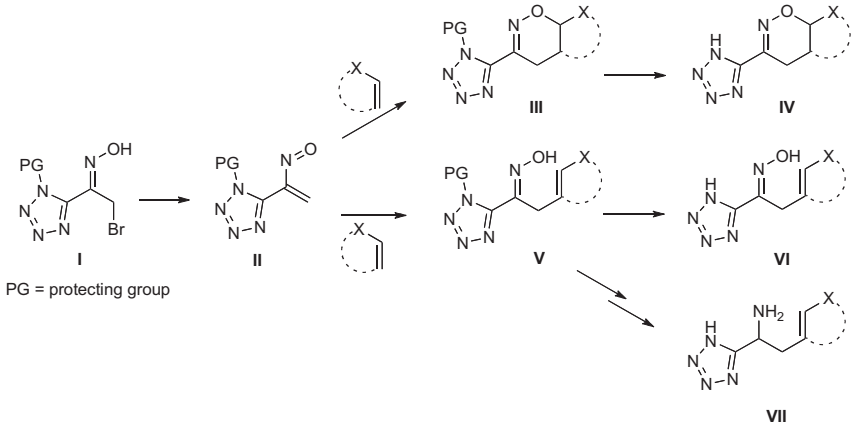


Scheme 1.

As a continuation of our work, we now describe the generation and Diels–Alder reactions of 5-(3-tetrazol-5-yl)-nitrosoalkenes, such as **II**, in which the N–H tetrazole is blocked by an easily removable protecting group, as a way to obtain a general route to 1,2-oxazines, open chain oximes bearing an unprotected tetrazolyl substituent and 5-(1-aminoalkyl)-1*H*-tetrazoles (Scheme 2).

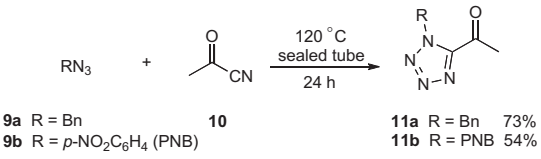


Scheme 2.

2. Results and discussion

Two diverse pathways could be envisaged in order to obtain the required 5-acetyl-1-protected-1*H*-tetrazole, precursor of the bromooxime **I**. In fact, 1,5-disubstituted-1*H*-tetrazoles can be obtained via intermolecular [3+2] cycloaddition of organic azides and nitriles[10a] or by the initial synthesis of the 5-substituted-1*H*-tetrazole and subsequent *N*-alkylation. The latter may suffer from the disadvantage of lack of selectivity with the formation of both 1,5-disubstituted-1*H*-tetrazole and 2,5-disubstituted-2*H*-tetrazole derivatives.[2e,11] Thus, the click chemistry approach of organic azides was selected as the route to the target *N*-protected-1*H*-tetrazoles **11**. The neat sealed tube thermolysis of benzyl or nitrobenzyl azides with pyruvonitrile gave after purification the corresponding 1*H*-tetrazoles **11** in 73% and 54% yield, respectively. The crude products were dissolved in a 1:1 mixture of ethyl acetate/hexane and run down a short plug of silica gel. The 5-acetyl-1-(*p*-nitrobenzyl)-1*H*-tetrazole (**11b**) was further purified by recrystallization whereas 1*H*-tetrazole **11a**[10] was dissolved in ethyl acetate, washed with a 10% $NaHCO_3$ aqueous solution and isolated as an oil (Scheme 3).

The bromination was brought about by the reaction of the acetyltetrazoles **11** with bromine–dioxane complex in diethyl ether. In the case of the benzyl derivative **11a** the halogenation reaction was carried out at room temperature for 19 h, using 1 equiv of bromine, giving the 5-bromoacetyl-1-benzyl-1*H*-tetrazole (**12a**) in 52% yield. However, bromination attempts of *p*-nitrobenzyl derivative **11b** using these reaction conditions led only to the recovery of the starting material. Thus, 1*H*-tetrazole **11b** was reacted with 2 equiv of bromine at 50 °C for 20 h affording the 5-bromoacetyl-1-(*p*-nitrobenzyl)-1*H*-tetrazole (**12b**) in 87% yield. The desired oximes **13** were obtained as nice crystalline solids by the reaction of 5-bromoacetyl-1*H*-tetrazoles **12** with hydroxylamine hydrochloride in CH_2Cl_2/MeOH. Difference in reactivity was again observed between the 1-benzyl-1*H*-tetrazole and the 1-(*p*-nitrobenzyl)-1*H*-tetrazole derivatives. Oxime **13a** could be obtained in high yield carried out the reaction at room temperature, whereas in the synthesis of oxime **13b** higher temperature and the use of a larger excess of hydroxylamine hydrochloride was required (Table 1).



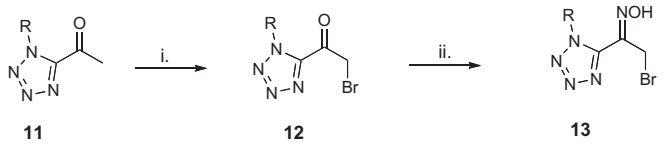
Scheme 3.

Nitrosoalkenes **14** were generated in situ, from the corresponding bromooximes **13** by treatment with sodium carbonate, whose small solubility in dichloromethane ensured a slow rate of dehydrobromination and consequently a low concentration of the heterodienes. Their reactivity towards dienophiles, present in the reaction media, was then examined (Table 2).

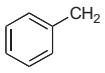
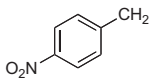
The reaction of **13a** with activated enol ether dienophiles, such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran provided the expected 1,2-oxazines in good yields (Table 2, entries 1 and 2). Striking and rather unexpected was the prolonged time necessary for the complete transformation of the oxime **13a** into the transient 5-(1-nitrosovinyl)-1-benzyl-1*H*-tetrazole **14a** (TLC control) when compared with the previous reported 5-(1-nitrosovinyl)-1-phenyl-1*H*-tetrazole generation.[4] The required longer reaction time may account for the partial isomerisation of 1,2-oxazine **16** into the open chain oxime **17** (the latter also detected by NMR of the crude mixture, prior to column chromatography).

The Diels–Alder reactions of nitrosoalkene **14a** were then extended to electron rich aromatic heterocycles. With furan and 2,5-dimethylpyrrole the 5,6-dihydro-4*H*-1,2-oxazines **18** and **19** were

Table 1
Oximes of 1-substituted-5-bromoacetyl-1*H*-tetrazoles



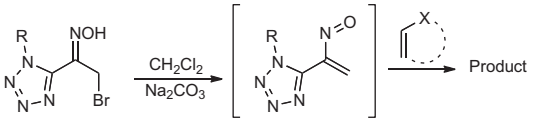
11 **12** **13**

R	i.	Yield	ii.	Yield
	Dioxane/diethyl ether Br_2 (1 equiv) rt, 19 h	**12a** 52%	$H_2NOH·HCl$ (3 equiv) CH_2Cl_2/MeOH rt, 72 h	**13a** 89%
	Dioxane/diethyl ether Br_2 (2 equiv) 50 °C, 20 h	**12b** 87%	$H_2NOH·HCl$ (12 equiv) CH_2Cl_2/MeOH 50 °C, 24 h	**13b** 89%
			$H_2NOH·HCl$ (6 equiv) CH_2Cl_2/MeOH 50 °C, 72 h	**13b** 83%

isolated in good yields (Table 2, entries 3 and 4) while with pyrrole and indole the corresponding open chain oximes **20a** and **21a** were obtained regioselectively (Table 2, entries 5 and 7). The formation of these end products can be rationalized considering the rearomatisation of the primarily formed 1,2-oxazines. No evidences of other isomers could be detected or isolated, namely either 3-pyrrole and/or 2-indole derivatives. Similar reactivity was observed when 5-bromoacetyl-1-(*p*-nitrobenzyl)-1*H*-tetrazole (**13b**) was reacted with pyrrole and indole in the presence of sodium carbonate (Table 2, entries 6 and 8).

At this stage we also looked at the chemical behaviour of 3-(1-benzyl-1*H*-tetrazol-5-yl)-5-vinylnitroso (**14a**) towards cumulated double bonds (Scheme 4). Reactions of vinylnitroso compounds with alkoxy and/or sugar-derived allenes have been reported before,[7g,12] but described as unsuccessful with phenyl- and trimethylsilyl-allenes.[12d] To the best of our knowledge, there are no examples of reactions of nitrosoalkenes involving aryloxy or phenyloxy allenes. However, it was observed that nitrosoalkene **14a** reacts with phenoxyallene at room temperature for 26 h to originate regioselectively cycloadduct **22**, although isolated in low yield (Scheme 4). Carrying out the reaction for a longer reaction time compound **23** was isolated in 16% yield resulting from the tautomerization of the initially formed Diels–Alder cycloadduct. Attempts to react nitrosoalkene **14a** with allenoates did not lead to isolable cycloadducts.

Table 2
Reactions of nitrosoalkenes **14** with cyclic enol ethers and heterocycles



13a R = Bn
13b R = PNB

14a R = Bn
14b R = PNB

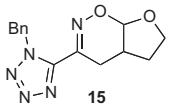
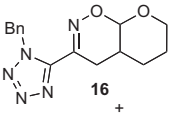
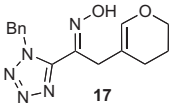
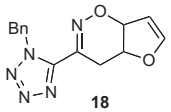
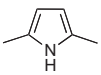
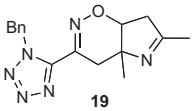
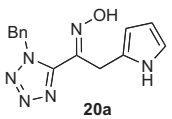
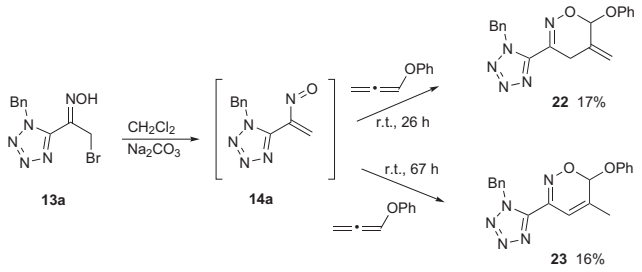
Entry	Oxime	Dienophile (reaction conditions)	Product	Isolated yield
1	**13a**	 (r.t., 50 h)	 **15**	65%
2	**13a**	 (r.t., 70 h)	 **16** +  **17**	65% 9%
3	**13a**	 (r.t., 48 h)	 **18**	69%
4	**13a**	 (r.t., 24 h)	 **19**	51%
5	**13a**	 (r.t., 48 h)	 **20a**	85%

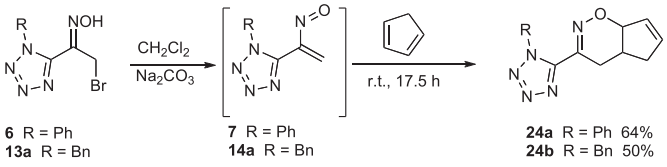
Table 2 (*continued*)

Entry	Oxime	Dienophile (reaction conditions)	Product	Isolated yield
6	**13b**	(r.t., 48 h)	**20b**	79%
7	**13a**	(r.t., 48 h)	**21a**	64%
8	**13b**	(r.t., 24 h)	**21b**	68%



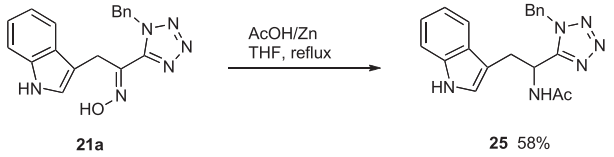
Scheme 4.

Finally cycloaddition of nitrosoalkenes **7** and **14a** with cyclopentadiene was studied in order to establish the reactivity pattern as 4π or 2π reaction component (Scheme 5). Cycloadducts **24** were obtained in good yield and regioselectivity confirming that the heterodienes acted as the 4π component. This is the commonly mode of reactivity[12d,13] although some exceptions are known,[5f,i,14] in which the nitrosoalkenes react with cyclopentadiene preferentially as the 2π counterpart, particularly with β,β-dihalo- and β-halo-β-alkyl-nitrosoalkenes and β-phosphorylated nitrosoalkenes.



Scheme 5.

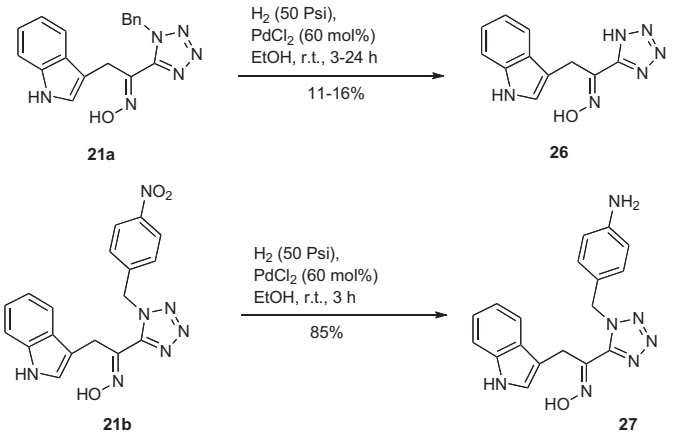
We have previously demonstrated that 5-(1-aminoalkyl)-1-phenyl-1*H*-tetrazoles, bioisosteres of α-amino acids, could be obtained from the corresponding oximes by the action of aluminium amalgam in moist THF[4] (see Scheme 1). Therefore, attempts were made to carry out the reduction of oxime **21a** under these reaction conditions, but only starting material was recovered. The same out come was observed following a reported general procedure for the conversion of oximes to amines under Zn/HCOOH reductive conditions.[15] However, the reduction of oxime **21a** was achieved by using Zn/AcOH at reflux affording 5-(*N*-acetylaminoalkyl)-1*H*-tetrazole **25** in 58% yield (Scheme 6).



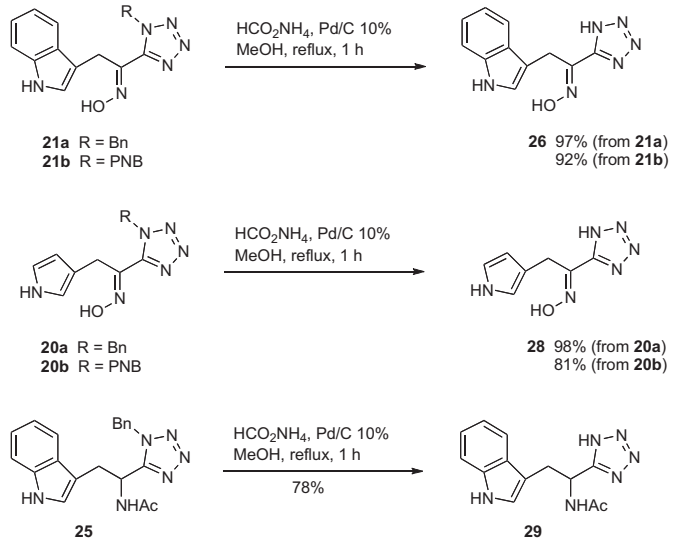
Scheme 6.

Subsequently, deprotection of the tetrazolyl substituent was studied. Initially, general procedures reported for debenzylation of *N*-benzy-1*H*-tetrazoles via hydrogenolysis in ethanol solution at room temperature using Pd/C as catalyst[16] or in the presence of an acid[2f] were used aiming to convert oxime **21a** into the corresponding derivatives with unprotected tetrazolyl substituent. However, the target compound could not be obtained. The hydrogenolysis using a combination of Pd/C and $Pd(OH)_2/C$ in THF/isopropanol, described as an efficient methodology for deprotection of aryl and alkyl ethers,[17] also failed when applied to the cleavage of the *N*-benzyl-1*H*-tetrazoles. The hydrogenolysis with Pd/C in 600 wt % for 48 h at 20 °C has been described for the removal of all four benzyl protecting group of a tetrakis(tetrazolylmethyl)-1,2-ethanodiamine derivative.[18] However, these reaction conditions did not lead to the deprotection of oxime **21a**. The target compound **26** was obtained in low yield from the hydrogenolysis of oxime **21a** using $PdCl_2$ as catalyst in ethanol, methodology reported for debenzylation of *N*-benzyl-1*H*-tetrazole derivatives.[19] The same reaction conditions led to the conversion of oxime **21b** into derivative **27** in 85% yield, instead of the desired deprotection of the tetrazolyl group (Scheme 7).

After the preceding disappointing results we were happy to find that deprotection of compounds **21** could be carried out efficiently following a reported general procedure for the debenzylation of *N*-benzylamines and 1-benzyl-1*H*-imidazoles using ammonium formate as catalytic hydrogen transfer agent.[20] Thus, a suspension of compound **21a** or **21b** and 10% Pd/C in methanol was treated with an excess of ammonium formate and the mixture was refluxed for 1 h giving the target compound **26** in high yield. This methodology was also applied successfully to deprotection of the 1*H*-tetrazolyl group of oximes **20**. Finally, it was also demonstrated that the optimized deprotection reaction conditions allows the conversion of 5-(*N*-acetylaminoalkyl)-1*H*-tetrazole **25** into derivative **29** bearing the unprotected tetrazolyl group (Scheme 8).



Scheme 7.



Scheme 8.

3. Conclusion

Hetero-Diels–Alder reaction of nitrosoalkenes bearing a *N*-protected-1*H*-tetrazole substituent at C-3 with enol ethers, phenoxyallene, cyclopentadiene and electron rich heterocycles gave access to a new class of compounds combining the 1,2-oxazine or open chain oxime substructures with the tetrazol-5-yl substituent. It was demonstrated that the tetrazolyl moiety can be efficiently deprotected.

The reduction of an oxime derivative followed by deprotection gave the corresponding 5-(1-aminoalkyl)-1*H*-tetrazole showing that the reported methodology can be used for the synthesis of α-amino acid analogues.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded on an instrument operating at 300 or at 400 MHz ^{13}C NMR spectra were recorded on an instrument operating at 100 MHz. The solvent is deuteriochloroform except where indicated otherwise. Chemical shifts are expressed in parts per million related to internal TMS, and coupling constants (*J*) are in hertz. IR spectra were recorded on a Nicolet 6700 FTIR spectrometer. Mass spectra were recorded under electrospray ionization (ESI). HRMS spectra were recorded on a Finnigan MAT95 S instrument. Melting points were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

*4.1.1. 1-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)ethanone (**11b**).* A vial was charged with a stir bar, azide (8.42 mmol), and pyruvonitrile (84.2 mmol) and tightly capped. The reagents were stirred in an oil bath set to 120 °C, neat, for 24 h. The reaction mixture was then cooled, and dissolved in ethyl acetate (25 mL). Hexane (25 mL) was added and the mixture was run through a short plug of silica gel. The silica plug was washed with an equal amount and composition of solvent. The solvent was evaporated off. The compound **11b** was purified by crystallization in ethyl acetate in 54% yield (1.114 g). Mp 117.7–118.6 °C (from ethyl acetate); IR (KBr) 729, 1123, 1341, 1522, 1709, 3080 cm^{-1}; ^{1}H NMR 2.84 (s, 3H), 5.99 (s, 2H), 7.56 (d, 2H, *J*=8.8 Hz), 8.21 (d, 2H, *J*=8.8 Hz); ^{13}C NMR 28.8, 51.9, 124.2, 129.5, 140.0, 148.3, 148.8, 188.4; MS (ESI) *m*/*z* 270 (MNa^+, 100%) and 248 (MH^+, 70%); HRMS (ESI) *m*/*z* 248.07704 ($C_{10}H_{10}N_5O_3$ [MH^+], 248.07782).

*4.1.2. 1-(1-Benzyl-1H-tetrazol-5-yl)-2-bromoethanone (**12a**).* To a solution of 1-benzyl-5-acetyltetrazole (0.01 mol) in a mixture of diethyl ether/dioxane (70:30) (70 mL) was added bromine (0.01 mol). The reaction mixture was stirred at room temperature for 19 h and then poured onto a mixture of water/ice and was extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated off. The compound **12a** was purified by crystallization in diethyl ether, as a white solid in 52% yield (1.462 g). Mp 66.1–67.9 °C (from diethyl ether); IR (KBr) 725, 987, 1381, 1726, 2940 cm^{-1}; ^{1}H NMR 4.71 (s, 2H), 5.89 (s, 2H), 7.34–7.39 (m, 5H, Ar*H*); ^{13}C NMR 32.1, 53.1, 128.6, 129.1, 129.3, 132.9, 147.1, 181.5; MS (ESI) *m*/*z* 281 (MH^+, 100%), 277 (34), 270 (49), 255 (23), 248 (30) and 203 (21); HRMS (ESI) *m*/*z* 281.00310 ($C_{10}H_{10}BrN_4O$ [MH^+], 281.00325).

*4.1.3. 2-Bromo-1-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)ethanone (**12b**).* To a solution of 1-benzyl-5-acetyltetrazole (0.01 mol) in a mixture of diethyl ether/dioxane (70:30) (70 mL) was added bromine (0.02 mol). The reaction mixture was stirred at room temperature for 24 h. The reaction was poured onto a mixture of water/ice and was extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated off. The compound **12b** was purified by crystallization in diethyl ether, as a white solid in 87% yield (2.837 g). Mp 129.9–132.2 °C (from diethyl ether); IR (KBr) 675, 726, 1348, 1516, 1721, 2937 cm^{-1}; ^{1}H NMR 4.72 (s, 2H), 6.00 (s, 2H), 7.56 (d, 2H, *J*=8.4 Hz, Ar*H*), 8.23 (d, 2H, *J*=8.4 Hz, Ar*H*); ^{13}C NMR 31.7, 52.1, 124.4, 129.5, 139.4, 147.2, 148.4, 181.8; MS (ESI) *m*/*z* 325 (MH^+, 8%), 259 (32) and 203 (66); HRMS (ESI) *m*/*z* 325.98801 ($C_{10}H_9BrN_5O_3$ [MH^+], 325.98833).

*4.1.4. 1-(1-Benzyl-1H-tetrazol-5-yl)-2-bromoethanone oxime (**13a**).* 1-(1-Benzyl-1*H*-tetrazol-5-yl)-2-bromoethanone (**12a**) (0.873 g, 3.1 mmol) was dissolved in a mixture of CH_2Cl_2/CH_3OH (60:40) (16.5 mL) and hydroxylamine hydrochloride (3 equiv, 0.646 g, 5.64 mmol) was added. The reaction mixture was stirred at room temperature for 72 h. The solvent was removed and the substrate dissolved in water, and extracted with ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The compound **13a** was obtained as a white solid in 89% yield (0.816 g). Mp 90.1–91.9 °C (from dichloromethane); IR (KBr) 724, 991, 1461, 1534, 2836, 3030 cm^{-1}; ^{1}H NMR 4.66 (s, 2H), 5.76 (s, 2H), 7.16–7.22 (m, 5H, Ar*H*), 10.21 (s, 1H, O*H*); ^{13}C NMR 31.8, 52.9, 128.1, 128.8, 128.9, 133.6, 144.7, 148.7; MS (ESI) *m*/*z* 296 (MH^+, 7%), 284 (25), 270 (26), 256 (67),

252 (100) and 234 (66); HRMS (ESI) *m/z* 296.01421 ($C_{10}H_{11}BrN_5O$ [MH^+], 296.01415).

*4.1.5. 2-Bromo-1-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)ethanone oxime (**13b**).* 2-Bromo-1-(1-(4-nitrobenzyl)-1*H*-tetrazol-5-yl)ethanone (**12b**) (0.700 g, 2.15 mmol) was dissolved in a mixture of CH_2Cl_2/CH_3OH (60:40) (30.8 mL) and hydroxylamine hydrochloride (12 equiv, 1.792 g, 25.8 mmol) was added. The reaction mixture was stirred at 50 °C for 24 h. The solvent was removed and the substrate dissolved in water, and the extraction was made with ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The compound **13b** was obtained as a white solid in 89% yield (0.651 g). Mp 150.2–152.5 °C (from chloroform); IR (KBr) 731, 995, 1347, 1518, 3187 cm^{-1}; ^1H NMR (DMSO-d_6) 4.71 (s, 2H), 6.03 (s, 2H), 7.47 (d, 2H, *J*=8.4 Hz, Ar*H*), 8.23 (d, 2H, *J*=8.4 Hz, Ar*H*), 13.36 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 32.4, 51.5, 123.8, 128.8, 141.9, 143.0, 147.2, 149.1; MS (ESI) *m/z* 340 (MH^+, 5%), 319 (50), 297 (100), 285 (13) and 263 (41); HRMS (ESI) *m/z* 340.99904 ($C_{10}H_{10}BrN_6O_3$ [MH^+], 340.99923).

4.2. General procedure for the Diels–Alder reaction

To a solution of oxime **6**, **13a** or **13b** (0.68 mmol) in CH_2Cl_2 (30 mL) and the appropriate dienophile (6.8 mmol), Na_2CO_3 (3.4 mmol) was added and the reaction mixture stirred at room temperature. The mixture was then filtered through Celite and the Celite pad washed with dichloromethane. The solvent was evaporated off and the product purified by flash chromatography.

*4.2.1. 3-(1-Benzyl-1H-tetrazol-5-yl)-4a,5,6,7a-tetrahydro-4H-furo[3,2-e][1,2]oxazine (**15**).* Ethyl acetate/hexane (1:2), white solid, 0.126 g, 65% yield. Mp 86.9–88.0 °C (from ethyl acetate/hexane); IR (KBr) 697, 718, 981, 1094, 1457, 2976 cm^{-1}; ^1H NMR 1.94–2.20 (m, 3H), 4.03 (approx. t, 2H, *J*=6.8 Hz), 4.66 (approx. t, 2H, *J*=11.6 Hz), 5.83–5.92 (m, 3H), 7.33 (br s, 5H, Ar*H*); ^{13}C NMR 23.3, 30.8, 32.7, 52.9, 68.5, 108.4, 128.4, 128.6, 128.8, 133.8, 144.6, 148.2; MS (ESI) *m/z* 286 (MH^+, 6%), 252 (100), 234 (8) and 218 (14); HRMS (ESI) *m/z* 286.12996 ($C_{14}H_{16}N_5O_2$ [MH^+], 286.12985).

*4.2.2. 3-(1-Benzyl-1H-tetrazol-5-yl)-4,4a,5,6,7,8a-hexahydropyrano[3,2-e][1,2]oxazine (**16**).* Ethyl acetate/hexane (1:2), white solid, 0.133 g, 65% yield. Mp 73.3–74.5 °C (from ethyl acetate/hexane); IR (KBr) 726, 899, 1033, 1157, 1456, 1604, 2950 cm^{-1}; ^1H NMR 1.47–1.56 (m, 1H), 1.62–1.77 (m, 3H), 2.21–2.24 (m, 1H), 2.77–2.90 (m, 2H), 3.72–3.77 (m, 1H), 3.97–4.03 (m, 1H), 5.23 (d, 1H, *J*=2.0 Hz), 5.87 (d, 1H, *J*=14.4 Hz), 5.91 (d, 1H, *J*=14.4 Hz), 7.31–7.34 (m, 5H, Ar*H*); ^{13}C NMR 22.7, 24.4, 26.7, 27.6, 52.9, 63.6, 96.8, 128.5, 128.6, 128.8, 134.0, 145.0, 149.1; MS (ESI) *m/z* 300 (MH^+, 100%), 256 (6) and 203 (5); HRMS (ESI) *m/z* 300.14630 ($C_{15}H_{18}N_5O_2$ [MH^+], 300.14550).

*4.2.3. 1-(1-Benzyl-1H-tetrazol-5-yl)-2-(3,4-dihydro-2H-pyran-5-yl) ethanone oxime (**17**).* Ethyl acetate/hexane (1:2), white solid, 0.019 g, 9% yield. Mp 146.5–148.5 °C (from ethyl acetate/hexane); IR (KBr) 726, 983, 1150, 1667, 2925, 3216 cm^{-1}; ^1H NMR 1.62–1.68 (m, 2H), 1.72–1.75 (m, 2H), 3.55 (s, 2H), 3.73 (t, 2H, *J*=4.8 Hz), 5.83 (s, 2H), 6.26 (s, 1H), 7.19–7.20 (m, 2H, Ar*H*), 7.29–7.30 (m, 3H, Ar*H*), 8.24 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 21.7, 22.9, 29.4, 51.8, 64.4, 106.5, 127.7, 128.2, 128.7, 134.8, 141.1, 145.5, 150.0; MS (ESI) *m/z* 300 (MH^+, 100%), 259 (6), 256 (7), 219 (9), 203 (15), 189 (7) and 171 (6); HRMS (ESI) *m/z* 300.14501 ($C_{15}H_{18}N_5O_2$ [MH^+], 300.14550).

*4.2.4. 3-(1-Benzyl-1H-tetrazol-5-yl)-4a,7a-dihydro-4H-furo[2,3-e][1,2]oxazine (**18**).* Ethyl acetate/hexane (1:2), oil, 0.133 g, 69% yield; IR (film) 722, 1012, 1411, 1457, 1606, 3035, 3286 cm^{-1}; ^1H NMR 2.92 (dd, 1H, J_1=15.6 Hz and J_2=4.8 Hz), 3.47 (dd, 1H, J_1=15.6 Hz and J_2=3.2 Hz), 5.13 (s, 1H), 5.19–5.23 (m, 1H), 5.40 (dd, 1H, J_1=8.0 Hz and J_2=1.6 Hz), 5.88 (d, 1H, *J*=14.4 Hz), 5.93 (d, 1H, *J*=14.4 Hz), 6.37 (d, 1H, *J*=2.0 Hz), 7.27–7.31 (m, 5H, Ar*H*); ^{13}C NMR 25.1, 53.0, 79.8, 82.9, 100.5, 128.4, 128.7, 128.8, 133.8, 148.7, 152.8, 157.8; MS (ESI) *m/z* 284 (MH^+, 100%), 240 (1) and 218 (5); HRMS (ESI) *m/z* 284.11545 ($C_{14}H_{14}N_5O_2$ [MH^+], 284.11420).

*4.2.5. 3-(1-Benzyl-1H-tetrazol-5-yl)-4a,6-dimethyl-4,4a,7,7a-tetrahydropyrrolo[2,3-e][1,2]oxazine (**19**).* Ethyl acetate/hexane (3:1), oil, 0.108 g, 51% yield; IR (film) 723, 1115, 1411, 1647, 2968, 3421 cm^{-1}; ^1H NMR 1.22 (s, 3H), 1.97 (s, 3H), 2.78 (d, 1H, *J*=18.8 Hz), 2.94 (d, 1H, *J*=16.0 Hz), 2.97–3.03 (m, 1H), 3.12 (d, 1H, *J*=16.0 Hz), 4.10 (d, 1H, *J*=6.4 Hz), 5.88 (d, 1H, *J*=14.8 Hz), 5.94 (d, 1H, *J*=14.8 Hz), 7.27–7.33 (m, 5H, Ar*H*); ^{13}C NMR 19.6, 25.7, 32.3, 52.9, 76.4, 84.0, 128.3, 128.7, 128.8, 133.9, 148.7, 158.4, 172.3; MS (ESI) *m/z* 311 (MH^+, 100%); HRMS (ESI) *m/z* 311.16118 ($C_{16}H_{19}N_6O$ [MH^+], 311.16149).

*4.2.6. 1-(1-Benzyl-1H-tetrazol-5-yl)-2-(1H-pyrrol-2-yl)ethanone oxime (**20a**).* Ethyl acetate/hexane (1:2), grey solid, 0.164 g, 85% yield. Mp 111.3–113.2 °C (from ethyl acetate/hexane); IR (KBr) 719, 965, 1063, 1531, 3027, 3214, 3442 cm^{-1}; ^1H NMR 4.27 (s, 2H), 5.77 (s, 2H), 6.05–6.06 (m, 2H), 6.62 (d, 1H, *J*=1.2 Hz), 7.06–7.29 (m, 5H, Ar*H*), 8.89 (br s, 1H, N*H*), 9.25 (s, 1H, O*H*); ^{13}C NMR 24.9, 52.9, 107.9, 108.2, 117.6, 124.0, 127.9, 128.6, 128.9, 133.8, 147.2, 149.9; MS (ESI) *m/z* 283 (MH^+, 100%) and 218 (6); HRMS (ESI) *m/z* 283.13018 ($C_{14}H_{15}N_6O$ [MH^+], 283.13019).

*4.2.7. 1-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-2-(1H-pyrrol-2-yl) ethanone oxime (**20b**).* Ethyl acetate/hexane (1:1), grey solid, 0.176 g, 79% yield. Mp 152.4–154.3 °C (from chloroform); IR (KBr) 718, 981, 1064, 1348, 1524, 3228, 3430 cm^{-1}; ^1H NMR (DMSO-d_6) 4.14 (s, 2H), 5.61 (s, 1H), 5.82 (s, 1H), 6.01 (s, 2H), 6.54 (s, 1H), 7.40 (d, 2H, *J*=8.0 Hz, Ar*H*), 8.19 (d, 2H, *J*=8.0 Hz, Ar*H*), 10.51 (br s, 1H, N*H*), 12.62 (br s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 24.6, 51.3, 105.8, 107.3, 116.7, 123.8, 124.2, 128.8, 142.1, 145.0, 147.2, 150.5; MS (ESI) *m/z* 328 (MH^+, 100%) and 263 (15); HRMS (ESI) *m/z* 328.11561 ($C_{14}H_{14}N_7O_3$ [MH^+], 328.11526).

*4.2.8. 1-(1-Benzyl-1H-tetrazol-5-yl)-2-(1H-indol-3-yl)ethanone oxime (**21a**).* Ethyl acetate/hexane (1:2), light brown solid, 0.145 g, 64% yield. Mp 189.6–191.3 °C (from ethyl acetate/hexane); IR (KBr) 698, 745, 976, 1458, 1522, 3213, 3364 cm^{-1}; ^1H NMR (DMSO-d_6) 4.31 (s, 2H), 5.79 (s, 2H), 6.94–7.37 (m, 8H, Ar*H*), 7.61 (d, 1H, *J*=8.0 Hz, Ar*H*), 10.83 (br s, 1H, N*H*), 12.67 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 22.1, 51.6, 107.7, 111.4, 118.4, 118.5, 121.0, 124.0, 126.8, 127.6, 128.0, 128.5, 134.7, 135.9, 146.4, 150.2; MS (ESI) *m/z* 355 (MNa^+, 100%), 333 (MH^+, 96%), 233 (10), 210 (17), 203 (29) and 171 (16); HRMS (ESI) *m/z* 333.14592 ($C_{18}H_{17}N_6O$ [MH^+], 333.14584).

*4.2.9. 1-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-2-(1H-indol-3-yl)ethanone oxime (**21b**).* Ethyl acetate/hexane (1:1), light brown solid, 0.174 g, 68% yield. Mp 192.0–193.6 °C (from chloroform); IR (KBr) 756, 975, 1056, 1348, 1523, 3223, 3400 cm^{-1}; ^1H NMR (DMSO-d_6) 4.33 (s, 2H), 5.98 (s, 2H), 6.95 (t, 1H, *J*=7.6 Hz, Ar*H*), 6.97 (br s, 2H, Ar*H*), 7.20 (d, 2H, *J*=8.4 Hz, Ar*H*), 7.34 (d, 1H, *J*=8.0 Hz, Ar*H*), 7.56 (d, 1H, *J*=8.0 Hz, Ar*H*), 8.01 (d, 2H, *J*=8.4 Hz, Ar*H*), 10.89 (br s, 1H, N*H*), 12.67 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 22.0, 51.1, 107.5, 111.3, 118.3, 118.4, 120.9, 123.5, 124.1, 126.6, 128.4, 135.8, 141.8, 146.2, 146.9, 150.4; MS (ESI) *m/z* 378 (MH^+, 100%), 304 (8) and 263 (27); HRMS (ESI) *m/z* 378.12973 ($C_{18}H_{16}N_7O_3$ [MH^+], 378.13091).

*4.2.10. 3-(1-Benzyl-1H-tetrazol-5-yl)-5-methylene-6-phenoxy-5,6-dihydro-4H-1,2-oxazine (**22**).* Ethyl acetate/hexane (1:2), white solid, 0.039 g, 17% yield. Mp 104.9–107.0 °C (from ethyl acetate/hexane); IR (KBr) 694, 929, 1033, 1207, 1490, 1591, 3039 cm^{-1}; ^1H NMR 3.68 (d, 1H, *J*=20.8 Hz), 3.75 (d, 1H, *J*=20.8 Hz), 5.30 (s, 1H), 5.39 (d, 1H, *J*=1.6 Hz), 5.84 (d, 1H, *J*=14.4 Hz), 5.88 (d, 1H,

J=14.4 Hz), 6.02 (s, 1H), 7.06–7.34 (m, 10H, Ar*H*); ^{13}C NMR 27.3, 53.0, 97.7, 114.9, 117.3, 123.4, 128.6, 128.6, 128.8, 129.7, 131.5, 133.7, 147.8, 148.4, 155.9; MS (ESI) *m*/*z* 348 (MH^+, 100%), 320 (6), 292 (9) and 254 (1); HRMS (ESI) *m*/*z* 348.14609 ($C_{19}H_{18}N_5O_2$ [MH^+], 348.14550).

*4.2.11. 3-(1-Benzyl-1H-tetrazol-5-yl)-5-methyl-6-phenoxy-6H-1,2-oxazine (**23**).* Ethyl acetate/hexane (1:3), white solid, 0.038 g, 16% yield. Mp 129.3–130.8 °C (from ethyl acetate/hexane); IR (KBr) 726, 755, 947, 1218, 1489, 1663, 3078 cm^{-1}; ^{1}H NMR 2.17 (s, 3H), 5.93 (s, 2H), 6.14 (s, 1H), 6.91 (d, 1H, J=0.8 Hz), 7.11–7.16 (m, 3H, Ar*H*), 7.21–7.38 (m, 7H, Ar*H*); ^{13}C NMR 19.1, 53.0, 95.3, 111.9, 117.7, 123.6, 128.6, 128.7, 128.8, 129.8, 133.7, 136.8, 145.5, 147.9, 156.6; MS (ESI) *m*/*z* 370 (MNa^+, 53%), 348 (MH^+, 100%), 322 (31), 254 (65) and 252 (12); HRMS (ESI) *m*/*z* 348.14569 ($C_{19}H_{18}N_5O_2$ [MH^+], 348.14550).

*4.2.12. 3-(1-Phenyl-1H-tetrazol-5-yl)-4,4a,5,7a-tetrahydrocyclopenta[e][1,2]oxazine (**24a**).* Ethyl acetate/hexane (1:2), white solid, 0.116 g, 64% yield. Mp 110.1–112.5 °C (from ethyl acetate/hexane); IR (KBr) 697, 760, 1362, 1495, 1593, 2947, 3071 cm^{-1}; ^{1}H NMR 2.28–2.33 (m, 1H), 2.61–2.66 (m, 1H), 2.70–2.77 (m, 1H), 2.94–3.02 (m, 1H), 3.07–3.13 (m, 1H), 4.95 (d, 1H, J=7.6 Hz), 5.76–5.77 (m, 1H), 6.09–6.11 (m, 1H), 7.43–7.53 (m, 5H, Ar*H*); ^{13}C NMR 26.5, 35.3, 39.4, 85.2, 125.9, 129.0, 129.2, 129.3, 130.5, 134.8, 137.6, 149.7, 156.5; MS (ESI) *m*/*z* 268 (MH^+, 100%); HRMS (ESI) *m*/*z* 268.12018 ($C_{14}H_{14}N_5O$ [MH^+], 268.11929).

*4.2.13. 3-(1-Benzyl-1H-tetrazol-5-yl)-4,4a,5,7a-tetrahydrocyclopenta[e][1,2]oxazine (**24b**).* Ethyl acetate/hexane (1:2), white solid, 0.095 g, 50% yield. Mp 63.8–65.6 °C (from ethyl acetate/hexane); IR (KBr) 695, 720, 905, 1111, 1437, 2905 cm^{-1}; ^{1}H NMR 2.16–2.22 (m, 1H), 2.61–2.72 (m, 2H), 2.93–2.99 (m, 1H), 3.01–3.07 (m, 1H), 5.01 (d, 1H, J=7.2 Hz), 5.82–5.84 (m, 1H), 5.89 (d, 1H, J=14.4 Hz), 5.94 (d, 1H, J=14.4 Hz), 6.05–6.06 (m, 1H), 7.24–7.31 (m, 5H, Ar*H*); ^{13}C NMR 25.8, 35.2, 39.3, 52.9, 85.4, 128.5, 128.7, 128.8, 128.9, 133.9, 137.9, 149.1, 157.6; MS (ESI) *m*/*z* 304 (MNa^+, 100%), 282 (MH^+, 80%), 247 (7) and 203 (14); HRMS (ESI) *m*/*z* 282.13422 ($C_{15}H_{16}N_5O$ [MH^+], 282.13494).

*4.2.14. N-(1-(1-Benzyl-1H-tetrazol-5-yl)-2-(1H-indol-3-yl)ethyl) acetamide (**25**).* Zinc (0.235 g, 3.6 mmol) was added to a solution of 1-(1-Benzyl-1*H*-tetrazol-5-yl)-2-(1*H*-indol-3-yl)ethanone oxime (**21a**) (0.1 g, 0.30 mmol) in acetic acid (5 mL). The resulting mixture was stirred under reflux for 27 h. The reaction mixture was cooled at room temperature and the zinc salts was removed by filtration through a Celite pad, which was then washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure and the residue dissolved in ethyl acetate and neutralized with aqueous NaOH (1 M). The organic layer was dried over Na_2SO_4 and the solvent evaporated. The compound **25** was purified by flash chromatography [ethyl acetate (100%)] and obtained as a white solid in 58% yield (0.063 g). Mp 135.0–136.1 °C (from ethyl acetate/hexane); IR (KBr) 725, 746, 1457, 1532, 1674, 3033, 3292, 3395, 3415 cm^{-1}; ^{1}H NMR 1.93 (s, 3H), 3.31 (dd, 1H, J_1=14.0 Hz and J_2=9.2 Hz), 3.36 (dd, 1H, J_1=14.0 Hz and J_2=6.0 Hz), 5.16 (d, 1H, J=15.2 Hz), 5.39 (d, 1H, J=15.2 Hz), 5.55 (approx. q, 1H, J=6.8 Hz), 6.74 (br d, 1H, J=1.2 Hz, N*H*) 6.90 (d, 2H, J=7.2 Hz, Ar*H*), 7.00 (d, 1H, J=8.0 Hz, Ar*H*), 7.07 (t, 1H, J=7.6 Hz, Ar*H*), 7.13–7.20 (m, 4H, Ar*H*), 7.29–7.33 (m, 2H, Ar*H*), 8.13 (s, 1H, N*H*); ^{13}C NMR 22.8, 30.1, 44.2, 50.7, 109.4, 111.4, 118.2, 120.0, 122.4, 123.3, 126.9, 127.5, 128.6, 128.9, 133.3, 136.0, 156.0, 170.2; MS (ESI) *m*/*z* 383 (MNa^+, 100%), 361 (MH^+, 95%), 258 (21), 203 (20) and 171 (12); HRMS (ESI) *m*/*z* 361.17643 ($C_{20}H_{21}N_6O$ [MH^+], 361.17714).

*4.2.15. 1-(1-(4-Aminobenzyl)-1H-tetrazol-5-yl)-2-(1H-indol-3-yl) ethanone oxime (**27**).* A solution of 1-(1-(4-nitrobenzyl)-1*H*-tetrazol-5-yl)-2-(1*H*-indol-3-yl)ethanone oxime (**21b**) (0.082 g, 0.22 mmol) in absolute ethanol (15 mL) was shaken at room temperature with $PdCl_2$ (60 mol %, 0.040 g, 0.13 mmol) at an initial hydrogen pressure of 50 psi for 3 h. The catalyst was removed by filtration through a Celite pad, which was then washed with ethanol. The combined filtrates were concentrated under reduce pressure. The compound **27** was purified by crystallization in diethyl ether in 85% yield (0.065 g). Mp 148.6–149.8 °C (from diethyl ether); IR (KBr) 755, 973, 1521, 1617, 3204, 3377, 3466 cm^{-1}; ^{1}H NMR (DMSO-d_6) 4.29 (s, 2H), 5.12 (br s, 2H, NH_2), 5.56 (s, 2H), 6.37 (d, 2H, J=8.0 Hz, Ar*H*), 6.81 (d, 2H, J=8.0 Hz, Ar*H*), 6.97–7.06 (m, 3H, Ar*H*), 7.32 (d, 2H, J=8.0 Hz, Ar*H*), 7.62 (d, 2H, J=7.6 Hz, Ar*H*), 10.84 (s, 1H, N*H*), 12.66 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 22.1, 51.6, 107.8, 111.4, 113.5, 118.4, 118.5, 121.0, 121.3, 124.0, 126.8, 129.2, 135.9, 146.5, 148.7, 149.7; MS (ESI) *m*/*z* 348 (MH^+, 100%) and 333 (3); HRMS (ESI) *m*/*z* 348.15653 ($C_{18}H_{18}N_7O$ [MH^+], 348.15673).

4.3. General procedure for N-deprotection of compounds 20a, 20b, 21a, 21b and 25

To a stirred suspension of compounds **20a**, **20b**, **21a**, **21b** or **25** (0.35 mmol) and an equal weight of 10% Pd/C in methanol (10 mL), anhydrous ammonium formate (3.5 mmol) was added in a single portion under nitrogen. The resulting mixture was stirred under reflux for 1 h. The reaction mixture was cooled at room temperature and the catalyst was removed by filtration through a Celite pad, which was then washed with methanol. The combined filtrates were concentrated under reduced pressure and the residue dissolved in ethyl acetate and washed with aqueous HCl (1 M). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated.

*4.3.1. 2-(1H-Indol-3-yl)-1-(1H-tetrazol-5-yl)ethanone oxime (**26**).* Crystallization in diethyl ether, white solid, 0.082 g, 97% yield; decomposes >160 °C (from diethyl ether); IR (KBr) 745, 978, 1063, 1458, 1570, 2469, 2857, 3220, 3397 cm^{-1}; ^{1}H NMR (DMSO-d_6) 4.30 (s, 2H), 7.02 (t, 1H, J=7.6 Hz, Ar*H*), 7.10 (t, 1H, J=7.2 Hz, Ar*H*), 7.18 (s, 1H), 7.36 (d, 1H, J=8.4 Hz, Ar*H*), 7.70 (d, 1H, J=8.0 Hz, Ar*H*), 10.91 (s, 1H, N*H*), 12.42 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 21.4, 108.0, 111.3, 118.4, 118.5, 120.9, 124.1, 126.8, 135.8, 145.9; MS (ESI) *m*/*z* 243 (MH^+, 77%), 203 (100), 189 (46), 171 (32) and 152 (19); HRMS (ESI) *m*/*z* 243.09860 ($C_{11}H_{11}N_6O$ [MH^+], 243.09889).

*4.3.2. 2-(1H-Pyrrol-2-yl)-1-(1H-tetrazol-5-yl)ethanone oxime (**28**).* Crystallization in diethyl ether, white solid, 0.055 g, 81% yield; decomposes >150 °C (from diethyl ether); IR (KBr) 744, 1047, 1418, 1560, 2882, 3179, 3407 cm^{-1}; ^{1}H NMR (DMSO-d_6) 4.16 (s, 2H), 5.73 (s, 1H), 5.89 (d, 1H, J=2.0 Hz), 6.61 (s, 1H), 10.57 (br s, 1H, N*H*), 12.40 (s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) 24.0, 105.7, 107.3, 116.6, 124.6, 144.6; MS (ESI) *m*/*z* 193 (MH^+, 77%) and 192 (50); HRMS (ESI) *m*/*z* 193.08320 ($C_7H_9N_6O$ [MH^+], 193.08324).

*4.3.3. N-(2-(1H-Indol-3-yl)-1-(1H-tetrazol-5-yl)ethyl)acetamide (**29**).* Crystallization in diethyl ether, white solid, 0.074 g, 78% yield; decomposes >210 °C (from diethyl ether); IR (KBr) 744, 1053, 1545, 1641, 2682, 3068, 3325 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6) 1.95 (s, 3H), 3.38–3.49 (m, 2H), 5.65 (approx. q, 1H, J=7.2 Hz), 6.86 (s, 1H), 7.01 (t, 1H, J=7.6 Hz, Ar*H*), 7.10 (t, 1H, J=7.2 Hz, Ar*H*), 7.33 (d, 1H, J=8.0 Hz, Ar*H*), 7.46 (d, 1H, J=8.0 Hz, Ar*H*), 7.84 (br d, 1H, J=4.8 Hz, N*H*), 10.11 (s, 1H, N*H*), 15.61 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$/DMSO-d_6) 27.7, 34.8, 50.0, 114.0, 116.3, 123.0, 123.8, 126.2, 128.4, 132.2, 141.1, 174.9.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.051.

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