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A hetero-Diels–Alder approach to functionalized 1*H*-tetrazoles: synthesis of tetrazolyl-1,2-oxazines, -oximes and 5-(1-aminoalkyl)-1*H*-tetrazoles

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ABSTRACT

This work describes the first and unprecedented examples of inverse electron demand Diels–Alder reactions of 5-(1-nitrosovinyl)-1-phenyl-1*H*-tetrazole, generated in situ from the corresponding bromooxime, with electron rich alkenes and heterocycles, providing in good overall yields tetrazolyl-1,2-oxazines and -oximes. Upon subsequent reduction these allowed the access to 5-(1-aminoalkyl)-1*H*-tetrazoles, paving the way for a new entry into this important class of compounds, bioisosteres of α-amino acids.

1. Introduction

In recent years inverse electron demand Diels–Alder reactions of conjugated nitrosoalkenes, with electron rich heterocycles or nucleophilic olefins, have emerged as a successful and effective strategy to a large number of new 1,2-oxazines and open chain oximes.[1] Since the efficiency of the cycloaddition is associated with the electrophilic character of the heterodiene, nitrosoalkenes bearing electron withdrawing substituents at 3- and/or 4-positions such as aryl, trifluoromethyl, acyl, alkoxycarbonyl and phosphorus groups have been used. These 1,2-oxazines and oximes have proved to be useful targets, due to their wide and versatile use as synthetic intermediates. Specifically, reduction of the 3-ethoxycarbonyl derivatives allows access to a great variety of nonproteinogenic amino acids, proline analogues and pyrroles.[2] Similarly, if the heterodiene carries a phosphorus substituent at the 3- or 4-position,[3] the reduction of the corresponding adducts and cycloadducts affords α- and/or β-amino-phosphinic and -phosphonic acids, considered analogues or surrogates of amino acids, with the ability of regulating various important biological functions.[4]

The isosteric similarities of tetrazole and carboxylate anions have recently been provided by computational evidence,[5] but over the past decades it has as well been established that 5-substituted-1*H*-tetrazoles are effective bioisosteres of the carboxylic acid functionality.[6] The acidity of N–H is similar to that of O–H at physiological pH, both exhibit planar structures, tetrazoles being more lipophylic—key factor when crossing cell membranes—than the corresponding carboxylic analogues.[6d,f] It is also generally accepted that tetrazole moieties exhibit stronger metabolic stability.[7] Some studies, nevertheless, have shown that 1-substituted-1*H*-tetrazoles can likewise be effective.[8] 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.[9]

Pharmaceutical formulations, either of 5-substituted-1*H*- or 1,5-disubstituted-tetrazoles, have been used as anti-inflammatory, antiulcer, analgesic, HIV and in cephalosporin antibiotics, being the anti-hypertensive Losartan the most successful example.[10]

For the preparation of 5-substituted tetrazoles containing the amino functionality, the most common strategy reported in literature appears to be the [3+2] cycloaddition reaction of an azide with the *N*-protected α-amino nitrile producing the corresponding protected amino tetrazole.[11] However, this procedure cannot be regarded as general, due to the limited availability of the starting α-amino nitrile and/or the α-amino acid or α-amino amide, used as the nitrile precursor.

As a continuation of our work, we envisaged that a conjugated nitrosoalkene like **II**, carrying a tetrazole moiety at the 3-position, would be intercepted by a large range of electron rich olefins, heterocycles and nucleophiles producing a vast number of adducts and cycloadducts (Scheme 1). The reduction of these products would provide the α-amino tetrazole derivatives, circumventing the above mentioned limitations.

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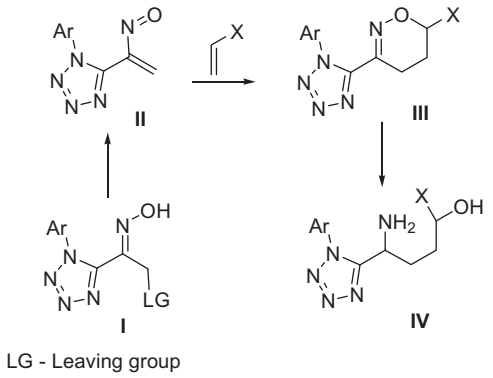


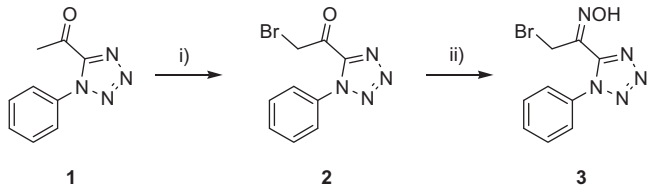
Scheme 1. Basis of the synthetic strategy.

2. Results and discussion

The generation of the 5-(1-nitrosovinyl)-1*H*-tetrazoles would require the initial preparation of halogenated oximes such as **3**. The 5-acetyl-1-phenyl-1*H*-tetrazole (**1**) was prepared following a known synthetic procedure[12a] and the subsequent bromination allowed the synthesis of 5-bromoacetyl-1-phenyl-1*H*-tetrazole (**2**). Although being described in the literature,[12b] the bromination step was troublesome and satisfactory results were only obtained when the acetyltetrazole was submitted to the action of bromine in dioxane/ethyl ether. The target oxime could be synthesized from the reaction of tetrazole **2** and hydroxylamine.[13] The oximation went smoothly, but the solvent must be carefully chosen since attempts to carry out the reaction in MeOH/H_2O led to the formation of the product of bromide displacement by methanol (Scheme 2).

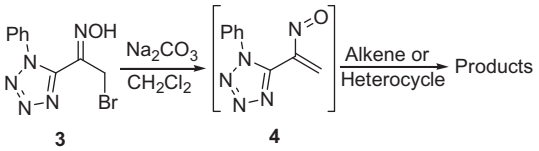
By treatment with sodium carbonate in dichloromethane at room temperature, oxime **3** was converted into the transient 5-(1-nitrosovinyl)-1-phenyl-1*H*-tetrazole (**4**) and this was trapped in situ by ethyl vinyl ether or heterocycles affording new tetrahydro 3-(1-phenyl-1*H*-tetrazol-5-yl)-1,2-oxazines or 5-(1-hydroxyiminoethyl)-1-phenyl-1*H*-tetrazole derivatives[14] (Table 1).

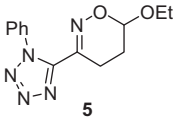
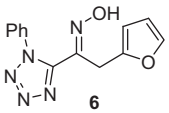
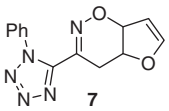
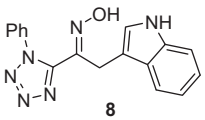
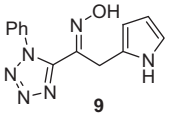
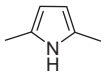
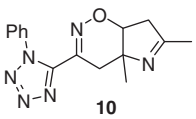
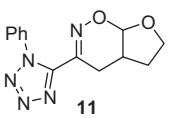
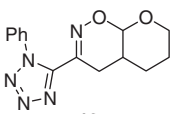
With acyclic and cyclic ethers such as ethyl vinyl ether, 2,3-dihydrofuran and 2,3-dihydropyran, cycloadducts were isolated, as a result of [4+2] cycloaddition reaction with inverse electron demand. With heterocycles possessing higher aromatic character such as pyrrole and indole, open chain oximes were isolated. Although it was not unquestionably established that the products isolated always resulted from a formal [4+2] cycloaddition reaction, we assume analogously with our previous work and discussions with nitrosovinyl-acrylate[15] and -phosphonates[3a] that these oximes are the result of rearomatization of the firstly formed cycloadducts, that is, in all cases a cycloaddition is occurring and not a conjugate addition or alkylation reaction. Indeed further support for this assumption may come from the interesting observation that cycloadduct **7** isolated initially as the sole product (TLC control and IR data), underwent isomerization to a mixture 3.5/1 of adduct/cycloadduct during the time elapsed between isolation and



Scheme 2. Synthesis of bromooxime **3** precursor of 5-(1-nitrosovinyl)-1-phenyl-1*H*-tetrazole **4**. Reagents and conditions: (i) Br_2 in dioxane/ethyl ether (30:70), rt, 4 h (75%); (ii) $NH_2OH{\cdot}HCl$ in CH_2Cl_2/MeOH (60:40), rt, 48 h (83%).

Table 1
Cycloaddition reactions of 5-(1-nitrosovinyl)-1*H*-tetrazole **4**

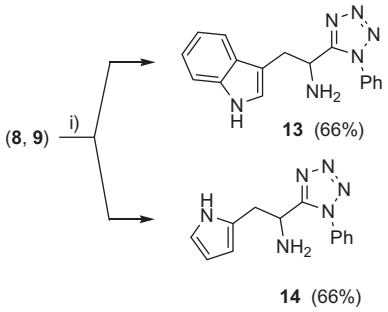


Alkene or heterocycles	Product	Yield (%)
	 **5**	73
	 **6** (3.5)	30
	 **7** (1)	
	 **8**	63
	 **9**	70
	 **10**	40
	 **11**	60
	 **12**	47

NMR analysis. Similar isomerization of an tetrahydro 1,2-oxazine cycloadduct obtained with furan to open chain oxime has been reported.[16]

With 2,5-dimethylpyrrole the expected imine[15] was isolated as the end result of enamine-imine tautomerism (the low yield observed may reflect a slower rate of isomerization to the imine, allowing further additions to the enamine leading to complicated mixtures and/or degradation products). In this case a stepwise alkylation followed by cyclization may not be unequivocally ruled out[17] but this is very unlikely since it is well established that 2,5-disubsituted pyrroles are alkylated at 3- and/or 4-positions.[18] The other products were isolated in generally good yields, and all compounds as single regioisomers, no other isomers being detected or isolated from the reaction media.

Subsequently, we were happy to find that compounds **8** and **9**, by the action of aluminium amalgam in moist THF at room temperature,[19] were smoothly converted into the corresponding α-aminotetrazoles **13** and **14**, respectively (Scheme 3). It should be noted that **13** is a tryptophan analogue.



Scheme 3. Reduction to 5-(1-aminoalkyl)-1*H*-tetrazoles. Reagents and conditions: (i) Al/Hg; THF/10% H_2O; rt.

3. Conclusions

Herein, the first examples of Diels–Alder reactions of 5-(1-nitrosovinyl)-1*H*-tetrazole **4**, generated in situ from the corresponding bromooxime **3**, with electron rich alkenes and heterocycles are reported. The products are obtained with high selectivity, the yields being comparable or somewhat higher than those reported for nitrosoalkenes bearing a 3-ethoxycarbonyl substituent and better than those carrying a phosphonate group at the same position. Furthermore, it was demonstrated that the reduction of these adducts allows access to 5-(1-aminoalkyl)-1*H*-tetrazoles. Thus, the present work may be regarded as the opening door to a novel synthetic methodology to this important class of compounds, bioisosteres of α-aminoacids.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.095.

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13. *5-Bromoacetyl-1H-1-phenyltetrazole*, **2**. To a solution of 5-acetyl-1-phenyltetrazole (0.188 g, 0.01 mol) in a mixture of diethyl ether/dioxane (70:30) was added bromine (0.160 g, 0.01 mol). The reaction mixture was stirred at room temperature for 4 h and poured onto a mixture of water/ice and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated off. The compound was obtained as a white solid in 79% yield. Mp 82.5–84.3 °C (diethyl ether). IR (KBr) 769, 979, 1503, 1722, 1736 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 4.75 (s, 2H); 7.49–7.64 (m, 5H). ^{13}C NMR (100 MHz) $CDCl_3$ δ 32.4, 125.2, 129.5, 131.1, 133.6, 147.7, 180.3.
5-(2-Bromo-1-hydroxyiminoethyl)-1H-1-phenyltetrazole, **3**. The 5-Bromoacetyl-1*H*-1-phenyltetrazole (1.88 mmol) was dissolved in a mixture of CH_2Cl_2/CH_3OH (60:40) and hydroxylamine hydrochloride (0.392 g, 5.64 mmol) was added. The reaction mixture was stirred at room temperature for 48 h. The solvents removed and the substrate dissolved in water and ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The compound was obtained as a white solid in 83% yield. Mp 143.2–144.5 °C (from dichloromethane). IR (KBr) 687, 770, 979, 1023, 1376, 1495, 3268 cm^{-1}. ^1H NMR (400 MHz) DMSO-d_6 δ 4.70 (s, 2H), 7.57–7.62 (m, 5H, Ar*H*), 13.07 (s, 1H, O*H*). ^{13}C NMR (100 MHz) DMSO-d_6 δ 33.7, 126.3, 129.8, 130.0, 130.3, 130.9, 135.3, 142.5, 149.8
14. *General procedure for Diels–Alder reactions*. To a solution of oxime (0.71 mmol) in CH_2Cl_2 (20 mL) and the appropriate diene (7.1 mmol), Na_2CO_3 (3.6 mmol) was added at room temperature and the mixture was stirred for 16 h. The solvent was evaporated and the product was purified by flash chromatography [ethyl acetate/hexane (1:2)].
6-Ethoxy-3-(1-phenyl-1H-tetrazol-5-yl)-5,6-dihydro-4H-1,2-oxazine, **5**. White solid, 73% yield, mp 143.7–144.4 °C (from ethyl acetate/hexane). IR (KBr) 766, 889, 1108, 1495, 2922, 3451 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 1.14 (t, J = 7.1 Hz, 3H), 1.91–2.06 (m, 1H, 5-H), 2.05–2.20 (m, 1H, 5-H), 2.66–2.94 (m, 2H, 4-H), 3.48–3.61 (m, 1H, CH_2–ethoxy), 3.66–3.74 (m, 1H, CH_2–ethoxy), 5.14 (s, 1H, 6-H), 7.34–7.59 (m, 5H, Ar-H). ^{13}C NMR (100 MHz) $CDCl_3$ δ 14.9, 18.0, 22.9, 64.1, 95.8, 125.6, 129.2, 130.2, 135.0, 147.1, 150.0. MS (ESI) m/z 274 $[M+H]^+$ (81%), 233 (11), 203 (35), 201 (23), 189 (15) and 171 (15). HRMS (ESI) calcd for $C_{13}H_{16}N_5O_2$ $[M+H]^+$: 274.13092; found: 274.12985.

2-(Furan-2-yl)-1-(1-phenyl-1H-tetrazol-5-yl)ethanone oxime **6** *and 3-(1-Phenyl-1H-tetrazol-5-yl)-4a,7a-dihydro-4H-furo[2,3-e][1,2]oxazine* **7**. Oil, mixture of isomers (3.5:1), 30% yield. IR (film) 738, 1045, 1266, 1421, 1499, 1731, 3330 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ *Major component* δ 4.38 (s, 2H), 6.15–6.16 (m, 1H, 3-H of furan), 6.28–6.30 (m, 1H, 4-H of furan), 7.28–7.34 (m, 1H, 5-H of furan), 7.43–7.65 (m, 4H, Ar-H), 7.71–7.75 (m, 1H, Ar-H), 8.07 (s, 1H, O–H). *Minor component* δ 3.01 (dd, J_1 = 15.0 Hz and J_2 = 6.0 Hz, 1H, 4-H), 3.42 (dd, J_1 = 15.0 Hz and J_2 = 6.0 Hz, 1H, 4-H), 5.11 (t, J = 3.0 Hz, 1H, H-4a), 5.22–5.28 (m, 1H, 7a-H), 5.31–5.36 (m, 1H, 7-H), 6.04 (d, J = 3.0 Hz, 1H, 6-H), 7.27–7.59 (m, 5H, Ar-H). MS (ESI) m/z 270 $[M+H]^+$ (61%), 201 (18), 181 (11), 169 (29) and 147 (34). HRMS (ESI) calcd for $C_{13}H_{12}N_5O_2$ $[M+H]^+$: 270.09800; found: 270.09855.

2-(1H-Indol-3-yl)-1-(1-phenyl-1H-tetrazol-5-yl)ethanone oxime, **8**. White solid 63% yield, Mp 193.0–194.5 °C (from dichloromethane). IR (KBr) 746, 972, 1421, 1496, 3428 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$/DMSO δ 4.40 (s, 2H), 6.94–7.05 (m, 4H, Ar-H), 7.10–7.14 (m, 1H, Ar-H), 7.24–7.28 (m, 2H, Ar-H), 7.33–7.39 (m, 2H, Ar*H*), 7.56–7.61 (m, 1H, Ar-H), 10.09 (br s, 1H, O–H), 11.99 (s, 1H, N–H). ^{13}C NMR (100 MHz) $CDCl_3$/DMSO δ 23.0, 107.9, 111.5, 118.9, 121.6, 124.3, 125.0, 127.0, 129.1, 129.6, 134.8, 136.3, 145.6, 150.9. MS (ESI) m/z 319 $[M+H]^+$ (100%), 226 (51), 204 (31), 169 (77) and 147 (84). HRMS (ESI) calcd for $C_{17}H_{15}N_6O$ $[M+H]^+$: 319.12944; found: 319.13019.

1-(1-Phenyl-1H-tetrazol-5-yl)-2-(1H-pyrrol-2-yl)ethanone oxime, **9**. White solid 70% yield. Mp 108.6–109.9 °C (from dichloro-metane). IR (film) 708, 963, 1413, 1495, 3425 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 4.23 (s, 2H), 6.03 (s, 1H, 3-H of pyrrole), 6.08 (d, J = 2.8 Hz, 1H, 4-H of pyrrole), 6.67 (br s, 1H, 5-H of pyrrole), 7.19 (d, 2H, J = 7.2 Hz, Ar-H), 7.42–7.52 (m, 3H, Ar-H), 8.62 (s, 1H, N–H), 8.84 (br s, 1H, O–H). ^{13}C (100 MHz) $CDCl_3$ δ 25.6, 108.1, 108.4, 117.8, 123.8, 125.6, 130.3, 134.8, 146.3, 150.2. MS (ESI) m/z 269 $[M+H]^+$ (88%), 201 (19), 169 (6) and 147 (6). HRMS (ESI) calcd for $C_{13}H_{13}N_6O$ $[M+H]^+$: 269.11373; found: 269.11454.

4a,6-Dimethyl-3-(1-phenyl-1H-tetrazol-5-yl)-4,4a,7,7a-tetrahydropyrrolo[2,3-e]-[1,2]oxazine, **10**. Eluent [ethyl acetate/dichloromethane (1:1)], oil 40% yield. IR (film) 690, 764, 1017, 1414, 1496, 1646 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 1.30 (s, 3H, 4a-Me), 2.00 (s, 3H, 6-Me), 2.71 (d, J = 18.8 Hz, 1H, 4-H), 2.92–2.99 (m, 2H, 4′-H and 7-H), 3.13 (d, J = 16.0 Hz, 1H, 7′-H), 4.12 (d, J = 6.4 Hz, 1H, 7a-H), 7.43–7.55 (m, 5H, ArH). ^{13}C NMR (100 MHz) $CDCl_3$ δ 19.6, 25.7, 33.0, 45.3, 76.4, 83.8, 125.9, 129.3, 130.6, 134.7, 149.5, 157.4, 172.7. MS (ESI) m/z 297 $[M+H]^+$ (100%), 201 (7) and 162 (6). HRMS (ESI) calcd. for $C_{15}H_{17}N_6O$ $[M+H]^+$: 297.14588; found: 297.14584.

3-(1-Phenyl-1H-tetrazol-5-yl)-4a,5,6,7a-tetrahydro-4H-furo[3,2-e][1,2]oxazine, **11**. White solid, 60% yield. Mp 160.2–161.9 °C (from ethyl acetate/hexane). IR (KBr) 770, 888, 1008, 1123, 1494 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 1.72–1.82 (m, 1H), 2.21–2.29 (m, 1H), 2.79–2.87 (m, 1H), 2.99–3.14 (m, 2H), 3.95–3.97 (m, 1H, 6-H), 4.01–4.12 (m, 1H, 6′-H), 5.46 (d, J = 4.8 Hz, 1H, 7a-H), 7.44–7.54 (m, 5H, ArH). ^{13}C NMR (100 MHz) $CDCl_3$ δ 24.9, 29.0, 34.7, 68.7, 101.2, 126.0, 129.2, 130.5, 134.8, 148.4, 149.7. MS (ESI) m/z 272 $[M+H]^+$ (100%), 200 (11). HRMS (ESI) calcd for $C_{13}H_{14}N_5O_2$ $[M+H]^+$: 272.11404; found: 272.11420.

3-(1-Phenyl-1H-tetrazol-5-yl)-4,4a,5,6,7,8a-hexahydro-pyrano[3,2-e][1,2]oxazine, **12**. White solid, 47% yield. Mp 147.2–148.6 °C (from ethyl acetate/hexane). IR (KBr) 767, 901, 1032, 1158, 1494 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 1.59–1.81 (m, 4H), 2.25 (br s, 1H), 2.91–2,92 (m, 2H), 3.67–3.71 (m, 1H, 7-H), 3.92–3.97 (m, 1H, 7′-H), 5.18 (d, J = 2.0 Hz, 1H, 8a-H), 7.44–7.53 (m, 5H, ArH). ^{13}C NMR (100 MHz) $CDCl_3$ δ 22.7, 24.5, 27.2, 27.7, 63.5, 96.7,126.0, 129.2, 130.4, 135.0, 144.0, 149.8 MS (ESI) m/z 286 $[M+H]^+$ (100%), 281 (20), 258 (12), 209 (6). HRMS (ESI) calcd for $C_{14}H_{16}N_5O_2$ $[M+H]^+$: 286.12967; found: 286.12985.

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19. *General procedure for reduction of oximes*. The aluminium amalgam used in these reductions was freshly prepared as follows. Aluminium foil was cut into small pieces. The pieces were then washed successively with: diethyl ether, ethanol, 2% mercuric chloride solution, ethanol and finally with ether. Each washing lasted for ten seconds. The strips were added immediately to a solution of the oxime (0.31 mmol) in moist tetrahydrofuran (7 mL, 10% H_2O), and the mixture was stirred at room temperature with TLC control. The mixture was then filtered through celite, the celite pad was washed well with THF and diethyl ether and the combined filtrates were reduced in volume. Dichloromethane was added, the solution was dried over Na_2CO_3, solvent was evaporated off and the product was purified by flash chromatography.

2-(1H-Indol-3-yl)-1-(1-phenyl-1H-tetrazol-5-yl)ethanamine, **13**. Eluent [CH_2Cl_2/MeOH (9:1)], white solid 66% yield. Mp 151.9–153.7 °C (from diethyl ether). IR (KBr) 694, 742, 1070, 1495, 3302 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 1.80 (br s, 2H, NH_2), 3.32 (dd, 1H, J_1 = 14.0 Hz and J_2 = 7.2 Hz), 3.37 (dd, 1H, J_1 = 14.0 Hz and J_2 = 7.2 Hz), 4.43 (approx. t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J = 1.6 Hz), 6.97–7.021 (m, 3H, Ar*H*), 7.15–7.21 (m, 2H, Ar*H*), 7.29–7.41 (m, 3H, Ar*H*), 7.43–7.45 (m, 1H, Ar*H*), 8.11 (br s, 1H, N*H*). ^{13}C NMR (100 MHz) $CDCl_3$ δ 34.3, 47.4, 110.7, 111.3, 118.1, 119.8, 122.3, 123.1, 125.2, 127.0, 129.5, 130.3, 133.3, 136.2, 158.6. MS (ESI) m/z 305 $[M+H]^+$ (15%), 281 (28), 260 (100), 207 (13). HRMS (ESI): Calcd for $C_{17}H_{16}N_6$ $[M+H]^+$: 305.15082, found 305.15092.

1-(1-phenyl-1H-tetrazol-5-yl)-2-(1H-pyrrol-2-yl)ethanamine, **14**. Eluent [CH_2Cl_2/MeOH (9:1))], oil, 50% yield. IR (film) 692, 764, 1653, 3418 cm^{-1}. ^1H NMR (400 MHz) $CDCl_3$ δ 3.20 (dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz, 1H, 2-H), 3.28 (dd, J_1 = 14.4 Hz, J_2 = 5.6 Hz, 1H, 2′-H), 3.56 (bt, J = 4.4 Hz, 2H, N–H$_2$), 4.05 (dd, J_1 = 8.4 Hz, J_2 = 5.6 Hz, 1H, 1-H), 5.77 (s, 1H, 3-H of pyrrole), 6.06 (d, J = 0.8 Hz, 1H, 4-H of pyrrole), 6.62 (d, J = 0.8 Hz, 1H, 5-H of pyrrole), 7.02 (d, J = 7.6 Hz, , 2H, Ar-H), 7.47–7.57 (m, 3H, Ar-H), 8.75 (br s, 1H, N–H).